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Electron Beam CT and Coronary Calcium Score

To the Editors:

I read with enthusiasm the recent article by Secci et al.¹ This prospective study using electron beam CT (EBCT) and coronary calcium score was done in 326 mostly elderly (mean age, 66 ± 8 years) men (82%). Hypertension (50%) and family history of coronary disease (44%) were common, but lipids were average (LDL 144 ± 37 mg/dL, HDL 54 ± 14 mg/dL). The 10-year Framingham risk was $19 \pm 9\%$. Each was followed up for 32 months after EBCT or until documentation of a hard (death, infarction) or a soft (need for revascularization) event. Dividing results into quartiles of EBCT calcium score, Secci et al found a clear trend for more total events in those with scores above the median. When hard and soft events were separated, there were still significantly more soft events when the score was above the median. However, despite a greater total number of events for subjects with calcium scores in the highest quartile, especially compared with those with scores in the lowest quartile, there was no significant trend for hard events alone.

My comments relate to four important issues not raised in the discussion. First, the amount of calcified plaque correlates, albeit as an underestimation, with the total atherosclerotic plaque burden (lipid-rich, fibrotic, and calcified fibrotic plaques) as shown by histological^{2,3} and ultrasonic^{4,5} studies. The discussion by Secci et al of calcified plaque and acute coronary syndromes totally misses the point regarding total plaque burden and vulnerable plaques, calcification, and inflammation.⁶ Second, the data⁷ given in their reference 16 states an average 10-year risk for men between 60 and 70 years old of 21% to 30%. This would suggest that the cohort currently under discussion was likely average and not necessarily high risk, since age and male gender are particularly important determinants using the Framingham equations. In fact, the calcium scores given in Table 3 of the Secci study (3-mm protocol) are similar to those previously published in similar age groups by Janowitz for "average" asymptomatic adults.⁸ Third, the study is significantly underpowered ($n=326$) for hard cardiac events, and from the outset, a potentially weak but not necessarily significant relationship to calcium score would have been anticipated. By combining hard and soft events, they likely improved the power and were able to demonstrate a correlation to higher calcium scores (above the median and especially in the highest quartile). Fourth, the follow-up was actually short, less than 3 years, and arbitrary at best. Follow-up of a minimum of 5 years is the common time period for most prospective studies examining cardiac events. They need to continue follow-up for a more extended time period. Rather than decrying this as such a "negative" study, I find the results provocative, consistent with prior studies⁹⁻¹¹ in younger adults, and supportive of the notion that the EBCT calcium score, as a surrogate to total atherosclerotic plaque burden and thus extent of coronary disease, has the potential to become one of the most if not the most powerful noninvasive predictors of cardiac mortality and morbidity in adults at risk, irrespective of age and gender.

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Response

Rumberger responds to our report entitled "Electron Beam Computed Tomographic Coronary Calcium as a Predictor of Coronary Events: Comparison of Two Protocols." This report treated a preliminary study of the 326 members of our South Bay Heart Watch cohort of 1309 high-risk subjects. These 326 subjects were scanned multiple times using two different electron beam CT scanning protocols within a half-hour period in 1991. All 1309 subjects have now been followed up clinically for 3 years. The preliminary report to which Rumberger refers states three conclusions:

1. Calcium quantities from the 3-mm and more reproducible 6-mm scans are equally accurate for predicting coronary events.
2. Calcium is a weak predictor of coronary death and infarction.

3. The predictive accuracy of calcium for predicting revascularization is greater than that for predicting death or infarction.

Rumberger does not disagree with our conclusions but comments on their interpretation in our discussion. Specifically, he states that we "missed the point" regarding the monotonically increasing relationship between the amount of calcified plaque and the "total plaque burden" that he and others have noted in autopsied hearts.

We agree that the amount of calcific plaque, quantitated on radiographic studies, roughly reflects the total sum of atherosclerotic areas in segments of the coronary tree. However, what determines the probability of a coronary catastrophe is not only the amount of atherosclerosis but the propensity of individual plaque segments to rupture and collect blood elements that obstruct the arterial lumen.

The following mathematical diversion clarifies this point.

Here, $P(t)$ denotes the probability of plaque rupture somewhere in the coronary tree at time t , and dl is an infinitesimal segment length in that tree. $P(t)$ will be related to the plaque areas as follows:

$$P(t) = \int A(l,t) p(l,t) dl$$

The argument between the integral sign and dl is a product of two factors. The plaque area, $A(l,t)$, changes with location, l , in the coronary tree and also changes with time (progresses). This plaque area is what Rumberger has found to be roughly and directly related to the amount of calcium. The second factor in the argument, $p(l,t)$, is the plaque vulnerability function. This is the probability that plaque at location l will rupture at time t . This probability increases with the size of the lipid core.¹ It decreases with the thickness of the fibrous cap¹ and probably with the amount of calcium deposited in the plaque.² Thus, this factor will contribute to an inverse relationship between the probability of coronary death or infarction and the measured amount of calcification.

Cities are occasionally buried by volcanic eruptions. The chance that a city will be buried depends not only on the number of nearby peaks but also on the volcanic activity of each one. Indeed, Vesuvius is the only large mountain near Pompeii.

These considerations explain why calcification, even if it correlated perfectly with the quantity of atherosclerosis, might not be a good predictor of coronary events. The relation between the amount of calcium and the probability of coronary events is much more complex than we might have desired.

Rumberger believes that as the power of our study grows with time and with the inclusion of all subjects in the cohort, we will see a relationship between coronary calcium amount and hard events. Indeed, we agree and have already seen this relationship.³ However, the relationship remains, as Rumberger has supposed, "weak." In fact, the discriminatory power of coronary calcium remains similar to that of the serum cholesterol, which is cheaper to obtain and can be modified.

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Alcohol Therapy for Hypertrophic Cardiomyopathy: Is It Time to Toast?

To the Editor:

We have read with interest the article by Knight et al¹ on the new technique of nonsurgical reduction as a therapeutic strategy in patients with hypertrophic obstructive cardiomyopathy

(HOCM). We congratulate the authors for obtaining excellent results in their series of 18 patients.

We have used the same technique at our center since early last year in a limited number of patients with excellent immediate reductions in left ventricular outflow tract (LVOT) gradients.^{2,3} However, we briefly discuss the course of our patients, highlighting the complications encountered.

Acute results: The authors, in their series of 18 patients, experienced the complication of transient complete heart block in only 4 patients, while a further 5 patients were on a permanent pacemaker before the septal ablation. However, both our patients developed complete heart block requiring implantation of a permanent dual-chamber pacemaker.

Furthermore, the authors did not develop any adverse results concerning the left ventricular performance of any of their patients. However, one of our patients developed recurrent episodes of pulmonary edema that stabilized only after initiation of the dual-chamber pacemaker and that may be related to stunned myocardium.²

Chronic results: Both our patients have completed more than 3 months of follow-up. The first patient has completed over 1 year. They have both been doing very well and remain asymptomatic, and their reductions in LVOT gradients have been maintained long term.

This elegant procedure of alcohol-induced septal infarction can be successfully used to reduce LVOT gradients in patients with HOCM. However, the possible complication of complete heart block requiring pacing and pulmonary edema needs to be borne in mind.

The combination of alcohol-induced septal reduction and dual-chamber pacing may be the best solution.

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Response

The letter by Bhargava et al raises an interesting point. The creation of complete AV block through injection of alcohol into one of the major septal branches is a distinct possibility. The reports of complete AV block after nonsurgical septal reduction in hypertrophic obstructive cardiomyopathy are conflicting. One series from the Methodist Hospital in Houston, Tex, describes an incidence of 30% of permanent AV block, but only 5% in the last 20 cases. Similar observations have been made by groups in Germany. It is not clear why there seem to be regional differences in the occurrence of this phenomenon.

Dr Bhargava suggests that nonsurgical septal reduction leading to complete AV block could well be a valid treatment. The combination of alcohol ablation and dual chamber pacing may indeed be the best solution for this disease. The occurrence of conduction abnormalities should be borne in mind when under-

taking this procedure, and it is mandatory to place a pacemaker electrode into the right ventricle before injecting alcohol into the septal coronary circulation.

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Effect of Warfarin on Rate of Restenosis After PTCA

To the Editor:

We disagree with Kastrati et al,¹ who state that warfarin has no effect on the rate of restenosis after PTCA. The ISAR trial compared the effect of two different antithrombotic regimens on restenosis after coronary stent placement and did not include a placebo group. One of the reasons for not including a group with placebo was the assumption that previous studies had shown that warfarin had no effect on restenosis after PTCA.¹

However, the effect of Coumadin on the short- and long-term results of PTCA is unknown. Only two studies have assessed this issue.^{2,3} Thornton et al² randomly assigned 248 patients after PTCA to aspirin or Coumadin for 6 months. Patients with acute complications during PTCA were excluded, and Coumadin was started immediately after PTCA. In that study, only 74% used Coumadin regularly, and an adequate prothrombin time was achieved in only 35%.² Urban et al³ included only 110 patients. In this study too, Coumadin was started after successful PTCA.³ In our opinion, these small numbers of patients with inadequate anticoagulation do not allow judgment of the role of Coumadin in the results of PTCA. Furthermore, we believe a preventive effect on restenosis can only be anticipated if Coumadin is started before PTCA and therefore before PTCA injury and mural thrombosis can lead to acute complications and restenosis. One of the possible reasons mentioned by Kastrati et al why ticlopidine failed to lower the restenosis rate was that it was started after PTCA, knowing its delayed onset. Surprisingly, they did not mention the same possible reason why warfarin did not affect the restenosis rate.¹

Since the effect of Coumadin on restenosis after PTCA and stent placement is unknown, we started the Balloon Angioplasty and Anticoagulation Study (BAAS), randomly assigning 1100 patients to aspirin or aspirin and Coumadin. The Coumadin is started long before PTCA, enabling patients to achieve adequate anticoagulation during PTCA.

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In their letter to the editor, we have the following comments to make:

Oral anticoagulation after stenting has been associated with severe hemorrhagic complications and a questionable effect in preventing early stent thrombosis.² Work from our institution has demonstrated that platelet activation was the determinant factor of thrombotic complications after stenting and that oral anticoagulation was unable to prevent it.³ Thus, the rationale of the ISAR trial was to assess the effects of a combined antiplatelet therapy with ticlopidine plus aspirin in the prevention of both thrombosis-induced and hemorrhagic events. Indeed, antiplatelet therapy started immediately after the procedure had an excellent effect on early thrombotic complications.⁴ Mural thrombus is considered to play a key role in restenosis after coronary interventions.⁵ On the basis of this theory, the statement of ten Berg and Plokker in their letter to the editor may be valid for each antithrombotic therapy: . . . a preventive effect on restenosis can only be anticipated if Coumadin is started . . . before PTCA injury and mural thrombosis can lead to acute complications and restenosis.⁶ Since we achieved a strong reduction of thrombus formation and subsequent clinical events with antiplatelet therapy given only at the end of the stenting procedure, we also anticipated a reduction of restenosis. But the results of the study in discussion¹ did not fulfill our expectation. We acknowledged in that study¹ that earlier administration of antiplatelet therapy (which was the therapy under testing) might have been more effective in preventing thrombus formation and restenosis. The same was stressed in the accompanying Editorial.⁶ We do not exclude that this may also be true for less-effective antithrombotic therapies such as Coumadin. For the moment, we relied on results already published on the effect of Coumadin on restenosis after balloon angioplasty.^{7,8} Despite the limitation that Coumadin was not administered before the end of the procedure, these studies may not be interpreted as stating the contrary of what was concluded.^{7,8}

We appreciate initiation by ten Berg and Plokker of the randomized trial about the effect on restenosis of an earlier administration of Coumadin. From a theoretical point of view, the ongoing study will further contribute to our knowledge about the role of thrombus in restenosis. From a practical point of view, however, the anticipated positive effect of Coumadin pretreatment on restenosis has to be strong enough to compensate for the cumbersome early complications associated with this therapy.

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Response

We thank Drs ten Berg and Plokker for their interest in our recently published study.¹ In response to the concerns expressed

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Potassium Channel-Blocking Actions of Nifedipine: A Cause for Morbidity at High Doses?

To the Editor:

In the last 2 years or so, the use of nifedipine, especially the short-acting form,^{1,2} has come under increasing scrutiny. It has been in wide use for almost two decades in the control of angina pectoris and hypertension but has been associated in a dose-dependent³ manner with unfavorable side effects like increased negative inotropy and hypotension, proarrhythmia, and in some studies, increased mortality,^{3,4} although this conclusion is not without controversy.⁵ The adverse actions of short-acting nifedipine in the acute situation in patients with hypertension¹ and/or preexisting coronary heart disease are more accepted,² and one important finding is T-wave inversion, which can be asymptomatic.⁶

We would like to highlight a possible underlying mechanism based on the sensitivity of myocardial potassium ion channels to calcium channel antagonists. The first-generation drugs (nifedipine, verapamil, and diltiazem) block calcium channels in myocardium with a relatively high affinity ($K_d=200$ to 300 nmol/L),⁷ but all three also block myocardial potassium channels, both in mammalian ventricular myocytes, with K_d s of 0.5 to 1 μ mol/L, and in cloned channels.^{8,9} The plateau phase of the cardiac action potential is normally terminated by repolarizing outward potassium fluxes so that block can prolong the action potential, causing a dispersion of refractoriness because these channels differ in their regional distribution across the myocardial wall¹⁰ and lead to instability of the resting potential of the ventricular muscle. Interestingly, one prominent effect is expected to be T-wave inversion related to preferential block of epicardial potassium currents responsible for the shorter epicardial action potential. Instability during the plateau or at the resting potential, in combination with raised catecholamine levels, may predispose to the generation of early or late afterdepolarizations, which can give rise to important ventricular arrhythmias.¹¹ One particular potassium current, I_{KUR} , a rapidly activating delayed rectifier present in¹² and cloned from human heart as hKv1.5,¹³ is particularly important in determining the plateau duration of the human cardiac action potential. Data exist showing that hKv1.5 is blocked by all three types of Ca^{2+} antagonists. We described block of hKv1.5 by verapamil in detail⁸ and suggested a mechanism of open channel block from the inner pore. Diltiazem and nifedipine block hKv1.5, and our recent data suggest that nifedipine is also an open channel blocker that acts predominantly at the external pore of hKv1.5 channels.⁹ Threshold effects of nifedipine on hKv1.5 were at 100 nmol/L, whereas sublingual and oral nifedipine, given as single doses, have been shown to

reach concentrations of 300 to 600 nmol/L,^{14,15} well within the range causing significant potassium channel blockade in vitro. Furthermore, these concentrations may well increase if significant renal impairment or hypoperfusion occurs. Due to the high-resistance nature of the cardiac action potential plateau, significant changes in duration could occur with only minor block of the current. It seems reasonable then to suggest that in situations where nifedipine is given acutely at high dose, in the compromised myocardium, and when catecholamine levels are high, such as during the stress of acute infarction, potassium channel block by nifedipine could exacerbate the likelihood of serious arrhythmias.

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