Diagnosing Essential Fatty Acid Deficiency

To the Editor:

Dr Gould and colleagues reported the effects of an intensive cholesterol-lowering program using mostly low-fat diets. To monitor essential fatty acid (EFA) status, they measured the ratio 20:3α/20:4α (triene/tetraene or T/T ratio). The authors stated that a ratio >0.4 in serum phospholipids indicates EFA deficiency (p 1532). In 1987, Siguel et al showed that measures of T/T currently in use were in error by a factor ≥10. The use of old technology, which had inadequate peak separation and erroneous peak integration, led to huge errors in measuring 20:3α and 20:3α when 20:3α was properly measured, T/T ratios >0.02 (in whole plasma) indicated EFA deficiency. For healthy people, T/T ratios in red blood cells (RBCs), RBC phospholipids, and serum phospholipids, which reflect the subject’s plasma levels, give reference values that are >10 times below the values reported by Dr Gould (Siguel, unpublished data, 1997). The T/T reference values used by Gould et al appear to be too high and would account for the statement that “no patient showed evidence of EFA deficiency.”

If we seek to detect abnormal cholesterol using a method that can only measure cholesterol >1000 mg/dL, most patients would be found to have normal cholesterol, and saturated fat and obesity would be found not to increase cholesterol.

Patients are unlikely to develop the severe EFA deficiencies that would have dramatic symptoms, such as substantial hair loss, overt clinical dermatitis, and T/T ratios >0.4; this would require severe depletion of EFAs over a period of many years. However, biochemical evidence of EFA deficiency can be detected in patients after several months on a low-fat diet when appropriate technology is used. Insufficient levels of EFAs, a condition I characterized as EFA insufficiency (EFAI), and imbalance of the α3/α6 ratios is associated with abnormal lipid levels, hypertension, coronary artery disease, and a higher-than-average probability of premature death as a result of heart disease. Patients who routinely follow low-fat diets deprived of EFAs are likely to develop EFAI and ought to be warned about the long-term consequences of EFA deficiency. Researchers can now monitor EFA status quite accurately and measure the biochemical onset of EFA deficiency over the duration of a study.

These issues have far greater implications for public health than a mere technical discussion on reference levels. The existence of EFA abnormalities affects both medical and food policy in the United States. Failure to diagnose EFA abnormalities may lead to expensive treatments for prevalent chronic diseases followed by unnecessary premature death. Billions of dollars are now spent on drug treatments and surgical procedures for conditions like high blood pressure, abnormal cholesterol ratios, and coronary artery disease, which respond quite well to conditions like high blood pressure, abnormal cholesterol and a higher-than-normal T/T ratios, and coronary artery disease, which respond quite well to conditions like high blood pressure, abnormal cholesterol and a higher-than-normal T/T ratios, and coronary artery disease, which respond quite well to conditions like high blood pressure, abnormal cholesterol and a higher-than-normal T/T ratios, and coronary artery disease, which respond quite well to conditions like high blood pressure, abnormal cholesterol and a higher-than-normal T/T ratios.

Corporations are now developing a wide range of fat substitutes and fat replacements. Replacing fat with fat substitutes (or substances that inhibit fat absorption) obviously reduces the amount of fat in the diet, which may help some patients, but also significantly reduces the amount of EFAs in the body, which can have disastrous consequences.

One obvious concern about the safety of these new products has been the likelihood that these food substitutes cause substantive EFA deficiency in the population. Companies engaged in the development and marketing of food substitutes would like to prove that their fat substitute (or related product) is healthful and does not lead to EFA deficiency. It is quite simple to prove that EFA deficiency does not exist by measuring EFA deficiency with a technology that can only detect severe EFA deficiency. By publishing articles, journals must be careful that they do not endorse, unintentionally, use of a technology that cannot detect EFA deficiency except in very rare and exceptional cases. Corporations could use this published information to state that subjects using their new products did not experience EFA depletion and that they used the same methods of measurement reported in the peer-reviewed journal. This is not a merely hypothetical issue; I have been told of at least one company that plans to show that its product does not cause EFA deficiency because the T/T ratios of subjects remained <0.4, citing articles that rely on outdated technology to support their contention.

A similar concern arises with regard to drug treatment for heart disease, particularly when combined with a diet high in monounsaturated fatty acids (MUFAs), as proposed by many public health organizations and popular books such as The Zone. For example, the Heart Owner’s Handbook states that MUFAs are better than PUFAs (p 33). However, MUFAs obviously cannot replace the PUFAs missing in low-fat foods. These matters are critical now that many new food products are either under government review or already approved for consumer use. Failure to use a sensitive blood test would obscure EFA deficiency caused by the extensive use of low-fat foods or foods high in MUFAs. Failure to diagnose and treat PUFAs abnormalities can cause unnecessary premature death.

Editors who publish articles involving the analysis of fatty acids should insist that authors provide the following information and reviewers be qualified to understand it: column used (ID, phase, length, etc), gas-liquid chromatograph (GLC) (brand model), injection method (split, splitless, etc), amount of injection, how fatty acid methyl esters were prepared, GLC method (eg, temperature run, duration, gases used, flows), how samples were integrated, software used (model, version, etc), quality control for peak integration, how the area of each peak was evaluated for integration errors, and how peaks were identified. Articles should include (for review, if not for publication) at least 2 representative chromatograms for subjects in each group showing peaks and integration: 1 that shows all peaks and 1 enlarged enough to see the baseline and noise levels. This is needed to evaluate the accuracy of the integration and the presence of artifacts or extra peaks that would affect the results. These data are simple to produce and readily available to the authors.

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(Dr Siguel has a patent on a blood test to diagnose fatty acid abnormalities.)


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Response

In his letter about our study published in Circulation 3 years ago, 1 Dr Siguel raises essentially two concerns: (1) how to assay blood for essential fatty acid deficiency and (2) whether low-fat diets cause essential fatty acid deficiency. Both are addressed separately below.

There are two essential fatty acids, linoleic acid and alpha-linolenic acid, required for synthesis for arachidonic, eicosanoids, prostaglandins, thromboxanes, and leukotrienes that are important for cell membrane function. 2,4 With essential fatty acid deficiencies, an “abnormal” intermediate, eicosatrienoic acid (20:3n9), accumulates and the “normal” intermediate metabolite, arachidonic or an eicosatetraenoic acid (20:4n6), decreases such that the triene to tetraene ratio (20:3n9/20:4n6) or the T/T ratio increases. 2,6

Current texts of nutrition indicate that a T/T ratio of ≥ 0.4 is associated with clinical linoleic acid deficiency. 3,4 A criterion used in our 1993 study. Table 3 (page 666) of Dr Siguel’s 1987 study in the journal Metabolism shows an average T/T ratio of 0.45 in six patients with clinical essential fatty acid deficiency as the result of malabsorption syndromes or prolonged fat-free parenteral alimentation. 5 A normal reference group had a T/T ratio of 0.008, and a subset of subjects from the Framingham Study had values of 0.014. A patient with essential fatty acid deficiency corrected to a T/T ratio of 0.02, in the normal range, after intravenous infusion of adequate essential fatty acids. 5

In his second 1987 study, 6 Dr Siguel reports a T/T ratio in a normal reference group as 0.013±0.006. In 10 patients with clinical malabsorption syndromes, the T/T ratio was 0.30±0.61, with a value of $P=0.06$ for the difference, not statistically significant at the 0.05 level. The normal T/T ratio in older literature is reported as 0.1±0.07. 6 On the basis of these data, Dr Siguel claims in his letter that “measures of T/T currently in use were in error by a factor ≥ 10.” With his average value of the T/T ratio of 0.45 5 and 0.36 6 in patients with essential fatty acid deficiency by new technology 3 compared with 0.4 used traditionally, 3,4 his basis for this claim is questionable, particularly since his own value of 0.3 was not significantly different from his reference group at the $P=0.05$ level of probability. 6 His normal reference values for the T/T ratio of 0.013 compared with older literature of 0.1 6 do not redefine the criteria for clinical fatty deficiency, which are 0.3 to 0.45 by his own numbers, the same as traditionally used. Therefore, the criteria for our 1993 article in Circulation are the same as those traditionally used 3,4 and consistent with Dr Siguel’s own data. 5,6

In a publication of 1994, 7 Dr Siguel proposed a new intermediate stage of essential fatty acid insufficiency (as opposed to deficiency) with a number of other end point measures proposed as being more sensitive than the T/T ratio as indicators of essential fatty acid insufficiency. On the basis of fatty acid analyses in 47 patients with documented coronary artery disease, he reasoned that excessive dietary levels of saturated fatty acids saturate or disturb the transport of essential fatty acids, thereby producing a possible abnormal T/T ratio or other proposed biochemical markers of possible essential fatty acid deficiency despite apparently relatively normal diets in these patients. In this study, 7 the T/T ratio in the normal reference population was 0.013±0.001 and in the coronary artery disease patients was 0.016±0.001, a statistically significant difference of unclear biological importance, particularly in view of a T/T ratio of 0.3±0.61 in patients with clinical essential fatty acid deficiency that was not significantly different from normal at the $P=0.05$ level in his previous study. 5 By his T/T ratio criteria in the 1994 study, 5 9 of 47 patients were claimed to have deficiency of essential fatty acids without reference to the type of diet the patients were on. Dr Siguel then extrapolated this point of view to the more extended hypothesis that a low-fat diet causing essential fatty acid insufficiency may increase the risk of coronary artery disease. 7

In a 1996 study 8 and in his letter, this point of view is still further extrapolated to the more extended hypothesis that low-fat diets cause essential fatty acid deficiency and heart disease and that “billions of dollars are now spent on drug treatments and surgical procedures for conditions like high blood pressure, abnormal cholesterol ratios, and coronary artery disease, which respond quite well to correction of PUFA abnormalities.” His letter goes on to indict the low-fat food industry and “public health organizations” and concludes that “failure to diagnose and treat PUFA abnormalities can cause unnecessary premature death,” where “correcting PUFA abnormalities” apparently does not mean low-fat food or cholesterol-lowering drugs. The data documenting these extended hypotheses are not reported, to my knowledge. In fact, high intake of linoleic acid of > 12% of calories reportedly decreases HDL cholesterol that is associated with higher risk of atherosclerosis. 9,10

Reading the 1987 5,6 and 1994 7 articles of Dr Siguel suggests that he knows a great deal about measuring fatty acids and about their possible interactions, with thoughtful, provocative hypotheses about their potential biological importance. However, his own data do not support the claim of an error by a factor of 10 in the criteria of the T/T ratio indicating clinical essential fatty acid deficiency. His data actually support the current traditional criteria. The reader and Dr Siguel need to clearly separate documented criteria and conditions for clinical essential fatty acid deficiency supported by Dr Siguel’s own data 5,6 from a hypothesized, intermediate stage of essential fatty acid insufficiency in free-living people on undefined diets, on the basis of changes in fatty acid ratios of unknown significance, without defined clinical abnormalities, due to a hypothesized adverse effect on lipid profiles, by an undefined level of dietary polyunsaturated fatty acids. 7,8 These latter provocative hypotheses are just that—unconfirmed hypotheses. Furthermore, these hypotheses involve the effects of substantial amounts of dietary polyunsaturated fatty acids, particularly linoleic acid and alpha-linolenic acid, on lipid metabolism, not clinical deficiency of these essential fatty acids in the diet of well individuals without malabsorption syndromes or parental alimentation.

As to the second issue, do low fat-diets cause essential fatty acid deficiency? The Recommended Dietary Allowances (RDA) published by the National Research Council do not make recommendations on minimum daily requirements of essential fatty acids. The reason is a lack of data and the difficulty of identifying essential fatty acid deficiency in a free-living population other than patients with malabsorption syndromes or total parenteral alimentation. The United Kingdom Reference Nutrient Intakes suggest minimum consumption of 1% of calories from linoleic acid and 0.2% from alpha-linolenic acid. 3,4 For a 1500-calorie diet commonly needed to achieve lean body habitus, ~1.67 g of linoleic acid and 0.33 g of alpha-linolenic acid...
would be minimum requirements on the basis of these criteria. For an 1800-calorie diet, 2 g of linoleic acid and 0.4 g of alpha-linolenic acid would be the minimal requirements by these criteria.

Soybean oil, walnut oil, corn oil, grapeseed, sunflower, and cottonseed oil contain >50% linoleic acid. Soybean oil, walnut oil, canola, and rapeseed oil contain 7% to 11%, and linseed oil contains 53% alpha-linolenic acid.11-15 Only soybean and walnut oils have significant balanced amounts of both linoleic acid and alpha-linolenic acid in proportion to their essential requirements. Alternatively, the compounds synthesized from alpha-linolenic acid, docosahexanoic (DHA) and eicosapentenoic (EPA), can be acquired from seafood, specifically omega-3 fish oil. In view of the ubiquity of the two essential fatty acids in Western diets, essential fatty acid deficiency is considered rare in free-living adults if it occurs at all,3,4 being seen only and uncommonly in severe malnutrition, untreated malabsorption syndromes or prolonged incomplete fat-free intravenous alimentation.

However, I have seen 14 lean patients on self-imposed, well-documented diets of <5% of calories as fat for 1 to 3 years (less than my guidelines of 10% of calories as fat) who had clinical symptoms consistent with essential fatty acid deficiency. These symptoms included mild but definite temporary recent memory loss, difficulty concentrating, episodic somnolence during the day, visual scotoma, decreased visual acuity, and/or sexual dysfunction. One, several, or all of these symptoms first appeared on very low-fat diets and reverted to normal on increasing sources rich in essential fatty acids. In addition to these symptoms, 4 of these 14 subjects had their first episode of atrial fibrillation or tachyarrhythmia without alcohol exposure or identifiable cause and without recurrence after increasing essential fatty acid intake. Nine of these subjects had their first episode of overt vasovagal syncope preceded by symptoms of similar but less severe vasovagal reactions, all of which disappeared on increasing sources of essential fatty acids without other identifiable changes in food, weight, or medications. Two individuals developed flaking, soft nails that became normal after increased intake of essential fatty acid sources. None had the typical fatigue, elevated triglycerides, and low HDL commonly caused by excess carbohydrate and inadequate protein previously discussed in “Letters to the Editor” of JAMA in response to Dr Siguel.16 Therefore, clinically relevant essential fatty acid deficiency may occur in otherwise well-nourished, active, well individuals on very low-fat diets of <5% of calories as fat. Any treatment powerful enough to heal is also powerful enough to harm if misused or if its side effects are not understood. Very-low-fat food also has similar beneficial or bad potential and must be implemented properly with no less than 10% of calories as fat.

For individuals adherent to very-low-fat foods, I recommend specific sources of essential fatty acids. Soybean oil contains 51% linoleic acid and 6.8% alpha-linolenic acid.11-15 One teaspoon of soybean oil containing ~4.7 g of oil provides 2.4 g of linoleic acid and 0.38 g of alpha-linolenic acid, the minimum requirements to prevent clinical essential fatty acid deficiency on the basis of the criteria of the United Kingdom Reference Nutrient Intakes6,8 and consistent with discussion of the recommended dietary allowances of the US National Research Council.2 One form of soybean oil is soya lecithin,15 containing 1.2 g of oil per capsule, so that 4 capsules per day would provide this minimum requirement.

One teaspoon of walnut oil provides 2.4 g of linoleic acid and 0.25 g of alpha-linolenic acid. One to two teaspoons of walnut oil ingested per day provide the minimal requirements for essential fatty acids. It is the only oil besides soybean oil with balanced equivalent amounts of both linoleic and alpha linolenic acids in approximate proportion to their essential requirements.

One teaspoon of corn oil, grapeseed, sunflower, or cottonseed oil provides the same amount or more of linoleic acid, since all contain >50% linoleic acid. However, these oils lack the alpha-linolenic acid. Alpha-linolenic acid can be obtained from a teaspoon of linseed oil, rapeseed oil, or canola oil, containing ~2.4, 0.5, and 0.5 g of alpha-linolenic acid, respectively. Alternatively, instead of alpha-linolenic acid, fish consumption or fish oil could be used as sources of EPA and DHA instead of oils containing alpha-linolenic acid from which the body synthesizes these compounds.

In the study by Siscovick et al,17 quoted by Dr Siguel, one fish meal per week consisting of 5.5 g of N-3 fatty acids per month was associated with a 50% decrease in risk of primary cardiac arrest in patients without known heart disease after adjustment for confounding other risk factors. This level of intake is the equivalent of only 0.2 g of fish oil per day, not the “high intakes” of PUFA that Dr Siguel recommends in his 1996 study8 and implies in his letter. Although the Siscovick study17 has limitations, it suggests that very small amounts of fatty acids may be beneficial.

To keep this discussion with Dr Siguel in perspective, it is important to emphasize that low-fat or very-low-fat food, with adequate essential fatty acids, protein, and other nutrients and cholesterol-lowering drugs have been documented to stabilize or partially reverse coronary and cerebrovascular atherosclerosis with a profound decrease in cardiac and cerebrovascular events. Inadequate lowering of dietary fat or serum cholesterol in the management of patients with coronary artery disease because of extended, unvalidated hypotheses about potential essential fatty acid deficiency could be detrimental to optimal patient management.

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The fact that there is a threshold for the detection of coronary calcification by any method (and, in the case of a method as insensitive as fluoroscopy, a rather high threshold) implies first, that the greater the number of calcified vessels, the higher the coronary calcium score and second, that the sample of 326 high-risk subjects was too small to confirm what was already demonstrated in the larger study.

Two other studies of EBCT scanning in less-selected populations have reported unprecedented accuracy of the EBCT-derived coronary calcium score in the prediction of nonfatal MI and coronary death. When pooled with data from the South Bay Heart Watch, In the larger cohort of 1461 South Bay Heart Watch subjects, the risk of nonfatal myocardial infarction (MI) and coronary death is at odds with their own and other data and is probably the result of a critical flaw in the design of the South Bay Heart Watch.

In the larger cohort of 1461 South Bay Heart Watch subjects, the risk of nonfatal myocardial infarction and coronary death has been proportional to the number of calcified coronary arteries as determined by fluoroscopy. The fact that there is a threshold for the detection of coronary calcification by any method (and, in the case of a method as insensitive as fluoroscopy, a rather high threshold) implies first, that the greater the number of calcified vessels, the higher the coronary calcium score and second, that the sample of 326 high-risk subjects was too small to confirm what was already demonstrated in the larger study.

Two other studies of EBCT scanning in less-selected populations have reported unprecedented accuracy of the EBCT-derived coronary calcium score in the prediction of nonfatal MI and coronary death. When pooled with data from the South Bay Heart Watch, these studies yield odds ratios of 4.7 to 9.5 for nonfatal MI and coronary death for subjects with calcium scores in the upper third versus the lower two thirds of the population (P<0.001). These findings are consistent with autopsy evidence of calcification of the coronary arteries in victims of sudden cardiac death and fatal MI, as well as with results of a large study that reported 2 to 5 times as much calcium in the coronary arteries of victims of coronary heart disease (n=214) as persons dying of other diseases (n=1028).

Although Secci et al have reported MIs in several persons with coronary calcium scores of zero, this is undoubtedly a rare event. We have >1500 patient-years of documented follow-up in middle-aged men and women with coronary calcium scores of zero, with no coronary deaths and just 1 MI. That patient, a 58-year-old woman, had angiographically normal coronary arteries. Our favorable experience in asymptomatic persons with low coronary calcium scores is also consistent with the autopsy literature and correlations between EBCT and coronary angiographic findings. The majority of middle-aged victims of fatal MI have extensive coronary atherosclerosis, and although the culprit lesion is not necessarily calcified, calcified plaques are generally present elsewhere in the coronary arteries. Secci et al have concluded that a strategy of screening for coronary disease based on EBCT is flawed because "noncalcified plaques may be more likely to rupture than calcific plaques." Available evidence certainly supports the latter statement but, as cited above, also indicates just as clearly that coronary calcification is a marker for the presence of noncalcified plaque. A more likely explanation for the failure of the EBCT-derived coronary calcium score to predict nonfatal MI and coronary death in the South Bay Heart Watch is the nature of the population studied. In order to qualify, potential study participants were required to have a ≥10% risk of coronary heart disease events over the ensuing 8 years, which placed them at or above the 75th percentile in the population distribution. Bayes’ theorem predicts that the likelihood that a negative test result is a true negative is inversely proportional to the pretest probability of disease. Because the relationship between coronary calcification and the severity of underlying coronary atherosclerosis is imperfect, Bayes’ theorem applies to EBCT scanning. Thus, with respect to the phenomenon of coronary calcification, a high-risk population like that of the South Bay Heart Watch contains an unusually high prevalence of false-negative examinations. Similar results have been obtained in a cohort of symptomatic patients undergoing coronary arteriography, in which obstructive coronary disease was present in the majority of patients with angina pectoris and 4 or 5 risk factors for coronary artery disease regardless of the coronary calcium score.

Stated differently, the design of the South Bay Heart Watch makes it difficult if not impossible to prove that the coronary calcium score predicts coronary events. Imagine trying to determine whether patients undergoing coronary vascular procedures such as stenting, angioplasty, or bypass surgery are better served by coronary calcium scoring. Could the observed increase in coronary calcium be interpreted as a marker for worse coronary disease or an indicator that stenting is unnecessary? This is not to say that coronary calcium is not related to adverse events. To the contrary, Secci and colleagues are to be commended for the integrity of their design. At the same time, left ventricular hypertrophy failed to predict need for coronary revascularization, raising the question of whether some of these deaths were the result of a primary (ie, hypertrophic) or secondary (hypertensive) cardiomyopathy rather than coronary atherosclerosis.

Although the balance of evidence demonstrates that EBCT predicts coronary death and nonfatal MI as well as coronary revascularization, there are still many questions about the pathogenesis of coronary artery disease. Unfortunately, it appears that the South Bay Heart Watch will provide few answers.
By guest on July 26, 2017

Correspondence


Response

Dr Guerci, Arad, and Agatston state (1) that the results of our preliminary report on the accuracy of EBCT in the South Bay Heart Watch are at odds with the results of our other reports regarding the accuracy of coronary calcium in predicting coronary events, (2) that our results are also at odds with the “unprecedented accuracy” of EBCT for predicting events reported by themselves, and (3) that differences between their results and our own are due to high pretest probability in the South Bay Heart Watch cohort.

1. Our 5-year follow-up of 1461 asymptomatic South Bay Heart Watch participants who had undergone digital fluoroscopy\(^1\) and our report of follow-up of 1196 of these subjects who underwent EBCT scanning\(^2\) both clearly demonstrate that there is a weak relationship between the presence and quantity of coronary calcium and subsequent coronary death and infarction. The preliminary report to which Guerci, Arad, and Agatston refer treats a subset of 326 of these subjects who had undergone both 3-mm and the more reproducible 6-mm scanning to determine if 1 of these scanning protocols was more accurate in predicting events. Since the primary purpose of this preliminary analysis was to compare protocols, it was not powered to detect weak associations between coronary calcium and future events. Therefore, there is no discrepancy between the conclusions of these 3 reports. Coronary calcium quantitated with EBCT predicts events about as well as standard risk factors.

2. There are indeed large differences between the “unprecedented accuracy” of the reports from Drs Guerci, Arad, and Agatston and the weak association found between calcium and coronary events in the South Bay Heart Watch participants. These may be due to methodological differences in cohort recruitment and analysis of scan results. The South Bay Heart Watch cohort was drawn from a population-based sample living in the Los Angeles, Calif, area. The Heart Watch had funding from government and private foundations and thus did not request payment from the subject volunteers, all of whom signed consent forms and understood that they were participating in a study of an unproven technology. The subjects participating in the studies of Drs Guerci, Arad, and Agatston were largely paying customers who were recruited through advertising campaigns directed at convincing them that the scan was a useful way of protecting their future health. A South Bay Heart Watch committee of adjudicators blindly assessed medical records to determine outcomes, whereas the method of assessment in the report of Arad et al\(^3\) is unclear. Thus, we agree with Drs Guerci, Arad, and Agatston that differences in study design might have affected results of either or both studies, though perhaps not in the way that they suggest.

3. Guerci, Arad, and Agatston attribute differences between their results and our own to a higher pretest probability of coronary events in our South Bay Heart Watch subjects. They criticize this aspect of the design of the South Bay Heart Watch study and believe that the weak relation between test results and coronary events is due to the relationship between pretest and posttest probabilities resulting from application of Bayes theorem.

Indeed, we chose our subjects to be at higher risk for 3 reasons: (1) higher risk would increase the number of coronary events and thus the power of the study; (2) higher-risk subjects would be subjects for whom risk factor reduction interventions would be appropriate and therefore for whom the results of an accurate screening test would be useful in making clinical decisions (eg, to treat with lipid-lowering medications); and (3) higher pretest probability (closer to 50% probability), according to Bayes theorem, increases rather than decreases information gained from diagnostic tests\(^4,5\) and would therefore increase, not decrease, the utility of coronary calcium screening. Indeed, Bayes theorem and most physicians would agree that coronary screening with any method applied to 25-year-old women without risk factors would not be useful.

Despite the fact that the South Bay Heart Watch cohort consisted of subjects who should be most appropriate for coronary calcium screening, this test was only as accurate for predicting outcomes as are the more easily verified and modifiable coronary risk factors. These research results should mandate an immediate moratorium on commercial coronary calcium screening of asymptomatic adults.

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Testing the Efficacy of Lipid-Lowering Therapy Versus Revascularization: The Time Has Come, or Is It Past Due?

To the Editor:

Small, lipid-rich, vulnerable plaques that are angiographically unimpressive and hemodynamically insignificant are responsible for most cases of fatal and nonfatal myocardial infarctions, whereas large, stable plaques that produce angiographically severe stenoses generally result in stable angina but rarely result in myocardial infarction. Accordingly, lipid-optimizing therapy, which stabilizes the vulnerable plaques, may have a major impact on prevention of myocardial infarction and death, whereas revascularization procedures, which are directed at severely
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stenotic lesions, may not. Therefore, I was particularly struck by the fascinating conclusion by Forrester and Shah1 in Circulation: “Coronary angiography does not identify, and consequently revascularization therapies do not treat, the lesions that lead to myocardial infarction.” Their conclusions, if proven correct, will have enormous implications for the management of coronary artery disease, since coronary angiography has been the gold standard for its diagnosis and revascularization its mainstay of treatment for decades.

The United States is home to only 5% of the world’s population but performs almost 50% of the invasive coronary procedures worldwide. Of a total of 900,000 coronary angioplasties performed worldwide in 1994, 404,000 were done in the United States, at an average cost of $21,700 each.2 Another 501,000 coronary bypass surgeries and 1.1 million coronary angiograms were done on Americans the same year, each at an average cost of $44,200 and $10,880, respectively. Revascularization procedures are done in 58% of all acute myocardial infarctions and account for about half the cost of hospital admission for this condition.3

Ironically, examination of regional, national, and international variations in the use of coronary revascularization before or after a myocardial infarction demonstrates no relation between these procedure rates and subsequent death and reinfarction.4 During a 19-year follow-up of the National Health And Nutrition Examination Survey (NHANES I), survival rates after the first myocardial infarction among whites and blacks were similar, although whites had a 6-fold higher rate of coronary revascularization.5 Among the participants of the Global Utilization of Streptokinase and TPA for Occluded arteries (GUSTO-1)6 and the Survival And Ventricular Enlargement (SAVE) studies, a 3-fold difference in the rate of revascularization between Canadian and American patients was observed with no significant difference in mortality or reinfarction at 1 year.7 In the largest comparison, involving 233,702 elderly patients with acute myocardial infarction, the relative rate of coronary revascularization was 4.6-fold higher in the United States than in Canada.8 However, the 1-year mortality rate was identical (34%). A similar observation was made in a large international study involving 8000 patients in 6 countries who had acute myocardial infarction without ST elevation. Although the United States and Brazil had a 3-fold higher rate of in-hospital coronary angioplasties and a 7-fold higher rate of bypass surgeries than Canada, Australia, Hungary, or Poland, there was no difference in rate of death or recurrent myocardial infarction in 6 months. An ominous finding in that study9 was the 3-fold higher rate of stroke and major bleeding requiring transfusion in Brazil and the United States, perhaps due to the aggressive coronary intervention. In that and many other studies, the use of invasive coronary procedures was determined by the availability of these procedures and not the severity or acuity of coronary artery disease.10,11

The benefits of revascularization are immediate but decrease steadily with time. After coronary angioplasty, restenosis occurs in 40% to 60% of vessels, usually within the first 6 months.12 During a 10-year follow-up of patients with successful coronary angioplasty, 35% had repeat coronary angioplasty, 31% had coronary bypass surgery, 14% suffered acute myocardial infarction, and 19% died.13 Yet, 53% had severe recurrent/persistent angina. In a 10-year follow-up of 1388 coronary bypass surgery patients, only 18% of the grafts were patent and non diseased.14 About half of the bypass patients will require repeat revascularization in 10 years.15 In large tertiary-care centers, up to one third of coronary angioplasty volume and one fourth of the surgical volume is performed on patients who had previously undergone coronary bypass procedures. Coronary bypass reoperation has a 5-fold higher perioperative mortality rate (6.4%) and considerably lower 10-year survival rate (69%) and event-free survival rate (41%).16

In sharp contrast to revascularization, the benefits of lipid-optimizing therapy are slow but steadily increase over time. Therefore, it may take 7 to 10 years to demonstrate significant differences in cost and outcome between revascularization procedures and lipid-lowering therapy. Surprisingly, a doubling in the rate of death or myocardial infarction (6.3% versus 3.3%) in 2.7 years was reported with coronary angioplasty compared with medical therapy in the second Randomized Intervention Treatment of Angina study (RITA-2).17 More importantly, the combined risk of death, myocardial infarction, or coronary bypass surgery was significantly lower in those randomized to medical therapy (7.1% versus 12.3%), even though only 12% of this group received lipid-lowering therapy. The result of the RITA-2 study provided no evidence to support the widely held belief that successful coronary angioplasty of a severe coronary stenosis reduces the risk of myocardial infarction.

Although angioplasty was superior to medical therapy in relieving angina, the benefit was confined to patients with severe angina or baseline exercise time of ≤ 9 minutes. The lack of survival benefit, along with possible excess morbidity and definite excess cost, associated with revascularization procedures underscores the need to temper our enthusiasm to invade all stenotic coronary lesions irrespective of the severity of angina or exercise intolerance.

Lipid-lowering therapy with “statins” saves money while saving lives. For example, the cost per year of life gained is $92,000 for coronary bypass surgery in left main disease and $91,500 for coronary angioplasty for 1-vessel disease18 compared with $70,000 for simvastatin in secondary prevention in middle-aged men with average serum cholesterol levels (213 mg/dL). The cost per year of life gained with simvastatin decreases to $21,000 when the indirect cost of lost wages is also included19 and becomes net cost savings in younger patients. It appears that the time for testing the efficacy of lipid-lowering therapy versus revascularization has not only come but is also past due.

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These less-stenotic lesions outnumber severe stenoses by more than 7:1. When it's fourth and long and you are deep in your own territory, prudence dictates you punt; yet this is perhaps the least of the difficulties encountered by Schmermund and colleagues; there are profound methodological deficiencies in both the design and analysis of their study that render such conclusions untenable. Some of these difficulties are familiar to us from our own investigations.

Some years ago, while pondering the relationship between calcium and the probability of plaque rupture and subsequent clinical events, we conducted a pilot study to attempt to elucidate this relationship. We assessed coronary calcium with digital cinefluoroscopy in 24 patients referred for angiography within 2 or 3 days of acute Q-wave myocardial infarction. We identified the segment of the coronary artery responsible for the infarction and found that this segment had no detectable calcium in 16 (66.7%) of the cases, but nearly all patients had calcium somewhere in their coronary vasculature. Although intriguing, in the end we found these data meaningless. The primary reason was the obvious and overwhelming selection bias. A large number of patients who in fact had plaque rupture were simply excluded from the study, for a variety of reasons: they died before reaching the hospital, they died before angiography, they were not referred for angiography, they refused angiography, they did not have clear evidence either by ECG or symptoms of a myocardial infarction or unstable angina, the culprit lesion could not be identified with confidence, the symptoms of plaque rupture were unrecognized or misdiagnosed, or plaque rupture was symptomatically silent and they never sought medical attention. Given this enormous exclusion of patients who in fact had ruptured coronary lesions, no conclusion could possibly be drawn from such sponsored studies.

The authors conclude that “...EBCT identifies calcified plaques in the vast majority of patients with vulnerable atherosclerotic plaques” and that EBCT “seems a very promising method to identify patients at risk for future atherosclerosis-related coronary unstable events.” Unfortunately, however, this study was not only retrospective but examined patients with EBCT up to 18 months after their events. “Future” coronary events were simply not addressed. Yet this is perhaps the least of the difficulties encountered by Schmermund and colleagues; there are profound methodological deficiencies in both the design and analysis of their study that render such conclusions untenable. Some of these difficulties are familiar to us from our own investigations.

As avid football fans, we read with great interest the recent study by Schmermund et al in Circulation (“Coronary Artery Calcium in Acute Coronary Syndromes: A Comparative Study of Electron-Beam Computed Tomography, Coronary Angiography, and Intracoronary Ultrasound in Survivors of Acute Myocardial Infarction and Unstable Angina”). In the introduction, Dr Schmermund and colleagues suggest, as have we, the distinct possibility that the association of coronary calcium with subsequent events may be a consequence of higher numbers of rupture-prone lesions that may not be calcified in patients who have coronary lesions elsewhere in the coronary vasculature that are calcified. Any association of calcium with subsequent events may thus actually be a spurious one. We hasten to add, however, that as yet there is no direct evidence that addresses this question, and the study by Schmermund et al would seem to shed little light on the subject. The authors conclude that “...EBCT identifies calcified plaques in the vast majority of patients with vulnerable atherosclerotic plaques” and that EBCT “seems a very promising method to identify patients at risk for future atherosclerosis-related coronary unstable events.” Unfortunately, however, this study was not only retrospective but examined patients with EBCT up to 18 months after their events. “Future” coronary events were simply not addressed. Yet this is perhaps the least of the difficulties encountered by Schmermund and colleagues; there are profound methodological deficiencies in both the design and analysis of their study that render such conclusions untenable. Some of these difficulties are familiar to us from our own investigations.

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Ah, but the punt has taken a favorable bounce, rolls into the end zone, and is about to roll harmless past the end line, when Schmermund et al field the punt 9 yards deep in their own end zone and attempt to return it, with defenders converging rapidly.

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Coronary Calcium, Subsequent Events, and Selection Bias
To the Editor:
As avid football fans, we read with great interest the recent study by Schmermund et al in Circulation (“Coronary Artery Calcium in Acute Coronary Syndromes: A Comparative Study of Electron-Beam Computed Tomography, Coronary Angiography, and Intracoronary Ultrasound in Survivors of Acute Myocardial Infarction and Unstable Angina”).
The crowd can only gasp; Schmermund et al are mercilessly gang tackled by selection bias.

For it is precisely the selection bias encountered by us that plagues the study by Schmermund et al and similarly renders their data all but meaningless. The fact that 28 months was required to recruit 118 patients (an average of only 4 patients per month) likely is testimony to enormous exclusion. Therefore, their conclusion that “[t]he vast majority of patients with acute coronary syndromes and at least moderate angiographic disease have identifiable coronary calcium by EBCT” is neither supported nor excluded by their study; no statement whatsoever can be made regarding the “vast majority” because these were largely excluded from enrollment.

But the methodological difficulties do not end here. Although the authors do not explicitly state this one way or another, one can only surmise that those reading the EBCT scans were not blinded to angiographic or clinical data, introducing yet another source of bias (if one was needed); test-review bias. Furthermore, it is not known what change in coronary calcium may have occurred in the interval between the acute event and the EBCT scan, which was as long as 1½ years. Finally, given that a major problem with EBCT calcium scanning is not lack of sensitivity but rather lack of specificity, where was the control group? How would the sensitivity and specificity have been affected by including a large group of patients who, for instance, were admitted to rule out myocardial infarction, subsequently did have myocardial infarction ruled out, and were found to have angiographically normal coronary arteries? Plays may be executed to perfection during the pregame warm-up, but how effective they are when the opposing team is on the field determines whether points are scored.

What, then, might be the clinical implications of the results of the study by Schmermund et al? Patients in their study had all suffered at least 1 acute coronary event already (mostly myocardial infarction) and were referred for angiography “for further investigation corresponding to the recommendations by the American Heart Association” or acute myocardial infarction usually have extensive coronary disease. In this respect, the selection of patients in our study... [However,...] 

We applaud Schmermund and colleagues for their attempts, however ill fated, to elucidate the relationship between calcium in a lesion and the probability of that lesion to rupture and cause a clinical event. However, although we can well empathize with the methodological difficulties encountered by Schmermund et al, their conclusions are nevertheless completely unjustified on the basis of their data. Eventually, as the recent American Heart Association position paper has indicated, EBCT may well be shown to be of definite usefulness, in at least some patients with known or suspected coronary artery disease. For the time being, however, if EBCT calcium evaluation is “a very promising method,” one would never know it from the study by Schmermund et al. A sound strategy, in both science and football, is punt on fourth and long.

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Response

Although Drs Doherty and Detrano emphasize epidemiological questions regarding our study, we addressed a completely different issue. We presented the first report on the detection of coronary calcium with respect to coronary plaque morphology in patients with acute coronary syndromes based on clinical, coronary angiographic, and intracoronary ultrasound data. Contrary to Doherty and Detrano’s statement, we provided direct (morphological) evidence pertaining to the association of coronary calcium and acute coronary syndromes, even though we agree that many details remain to be learned. We used intracoronary ultrasound to examine coronary anatomy of culprit lesions. Intracoronary ultrasound allows classification of plaque formation corresponding to the recommendations by the American Heart Association and visualization of plaque rupture even at very early stages of the atherosclerotic disease process. In view of the diagnostic and clinical implications of negative calcium scans by electron-beam CT (EBCT) in some patients with acute coronary syndromes, it was critical to explain the mechanisms of acute ischemia in these patients. We state in our article that “... patients with low coronary plaque burden or mechanisms of unstable events that are not specifically related to atherosclerosis may be missed by EBCT calcium scanning. [However,...] EBCT reliably identified coronary calcific plaques in those patients who had moderate to severe coronary atherosclerotic disease.”

We never denied that there may have been an inherent selection bias, and in fact we clarify this in the article by stating “Most of [our] patients were referred by their physicians or other medical centers for further diagnosis and/or treatment at the University Clinic Essen.” One will never be able to examine a truly unselected population of patients with acute coronary syndromes due to the problems Doherty and Detrano explain in their letter. Our report included only patients with index myocardial infarctions or a first episode of unstable angina and no further events. They were a random sample of all eligible patients whom we were able to scan at a remote EBCT site, with scanner availability as the limiting factor. We sought to explain where calcium scanning works and where it may not work and why and to discuss the clinical implications. We found that coronary calcium was reliably detected in patients with acute coronary syndromes and moderate to severe plaque burdens. It has been known for more than a century that patients with unstable angina or acute myocardial infarction usually have extensive coronary disease. In this respect, the selection of patients in our study tended to play against calcium scanning, because a comparably...
large percentage (15 of 118 patients, or 13%) had no angiographically obstructive coronary lesions.

Our conclusions are therefore fully justified that “... EBCT seems a very promising method to identify patients at risk for future atherosclerosis-related coronary unstable events.”1 Our article clearly focused on sensitivity considerations. We purposely did not consider the issue of specificity, which is indeed very complex and needs to be addressed by much larger prospective studies in the general population.

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Lipoprotein Lipase Gene Variants and Coronary Risk

To the Editor:

In their paper concerning the Ser447-Stop substitution in the lipoprotein (Lp) lipase gene, Groenemeijer et al1 quoted only 2 publications by other groups when reporting associations of this mutation with lipid levels. When introducing their work, the authors stated that no studies had been reported in any substantial sample of subjects with angiographically defined coronary artery disease. We would like to recall our results published in 1995 from the ECTIM multicentric study including >600 patients with myocardial infarction and 700 matched controls.2 The Stop447 allele had a lowering effect on triglycerides (P<0.01) and apolipoprotein C-III (apoC-III) levels (P<0.001). These effects were consistently observed in the 4 populations included in the study (Belfast in Northern Ireland; Lille, Strasbourg, and Toulouse in France). The Stop447 allele was also associated with lower VLDL cholesterol (P<0.05), Lp E:B (P<0.01), and Lp C-III:B (P<0.05) levels and higher apoA-I levels (P<0.05). The Stop447 allele was weakly associated with a lower risk for myocardial infarction (odds ratio [CI]=0.81 [0.63 to 1.03], P=0.09, assuming a codominant model). A coronary angiogram was available for 412 French patients, and a coronary score was defined as the number of coronary arteries with >50% occlusion (range, 0 to 3). This score was not associated with the Ser447-Stop polymorphism. Although the rationale that led Groenemeijer et al1 to test the hypothesis of an interaction between β-blockers and the Ser447-Stop polymorphism was not evident to us, we reexamined our data to see if we could confirm this interaction. HDL cholesterol levels (mmol/L) were as follows (mean±SD): Stop447 absent, 1.20±0.33 (n=213) and 1.10±0.28 (n=295), no β-blockers versus with β-blockers; and Stop447 present, 1.15±0.34 (n=53) and 1.13±0.24 (n=67), no β-blockers versus with β-blockers, respectively. β-Blocker use lowered HDL cholesterol (P<0.001), but no interaction between β-blockers and the Ser447-Stop polymorphism was observed on HDL cholesterol. In β-blocker users, the increase in HDL cholesterol was marginal and not significant.

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Diagnosing Essential Fatty Acid Deficiency
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