believe that our conclusion suggesting that Lp(a) by itself is not a risk factor for ischemic heart disease (1) is erroneous. Although some prospective population-based studies have found Lp(a) to be an independent risk factor for ischemic heart disease (2,3), we must bear in mind that the bulk of the data supporting that conclusion is derived from case-control studies. The studies of Hopkins et al. (4) and Orth-Gomer et al. (5), which are mentioned by Drs. Enas and Metha, fall into that category. In the former, 160 young subjects with documented ischemic heart disease were matched to 165 control subjects. A subgroup of 27 patients and five control subjects with elevated Lp(a) and total cholesterol had a relative risk of 13.8 of developing ischemic heart disease (4). Although this may look extremely impressive when compared with our risk of 2.96 (1), I do not think that the two studies can be compared. Our study is prospective, population based with at least 215 subjects in each subgroup of analysis. These numbers alone can account for the differences. The latter study, also case-control, is a study of women younger than 65 years (5). Risk factors for this group are different than those for the men in our study. The inherent selection biases associated with case-control studies will favor the inclusion of subjects with altered lipid profiles as well as other ischemic heart disease risk factors. Therefore, these data should be interpreted with caution.

The PROCAM study is also a population-based prospective cohort; in the report of Assmann et al. (6) there is a significant risk of ischemic heart disease associated with elevated Lp(a). However, it must not be forgotten that in that particular report, only 863 of the 4381 participants included had Lp(a) measurements. I do not want to underestimate the importance Lp(a) may have in ischemic heart disease; it is clearly a risk factor when associated with other risk factors. However, I still think that there is a lack of prospective population-based studies supporting a role for Lp(a) as an independent risk factor. Considering this, I do not think that Lp(a) measurements should be carried out in a primary prevention setting.

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References

Functional Assessment of Coronary Stenoses
I read the article by Bech et al. regarding deferral of angioplasty on intermediate coronary stenoses based on measured coronary flow reserve with interest (1). The authors addressed an important issue, that of interventional revascularization procedures being performed on obstructive lesions of “intermediate” severity by angiography without objective evidence of ischemia and therefore uncertain influence on outcome.

I take issue, however, with the statement in the conclusion of their article, that deferral of PTCA based on FFR<0.75 is safe “irrespective of the noninvasive stress test result.” If the authors are considering stress ECG testing, their statement may be correct as it is known that abnormalities on treadmill tolerance tests do not correlate well with functional severity of coronary lesions. Stress nuclear perfusion scintigraphy, with either thallium or technetium based agents, however, is reflective of the functional significance of an underlying stenosis. Dr. N. Pijs (one of the authors of the present study), nicely demonstrated in an earlier paper the strong relationship between an FFR<0.75 and ischemia demonstrated either by stress thallium scintigraphy or dobutamine echocardiography (2). This study, in fact, used the noninvasive test results as the reference standard as three patients of 211 with FFR ≥0.75 were said to have “false negative results” as their stress tests were positive.

It is also widely appreciated that provocative testing with nuclear or echocardiographic imaging have quite good positive predictive values regarding future coronary events. An original study by K. Brown showed in a series of 100 patients that compared with clinical, stress ECG, and angiographic data, the best predictor of future events was the number of segments with reversible thallium defects (3).

Therefore, if the authors use the term “noninvasive stress test” includes the above-described imaging modalities, I would be interested in seeing more data before abandoning such diagnostic techniques. Although all noninvasive testing modalities for detecting coronary artery disease have less than optimal sensitivity and specificity depending on the patient population, I don’t feel the evidence is there to support the use of intracoronary pressure recording in favor of “stress testing”.

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References

Reply
We appreciate the comments of Dr. Miller, which give us the opportunity to clarify the use of coronary pressure and fractional flow reserve in case of intermediate stenosis.

Generally, we believe that a decision to perform myocardial revascularization should be based upon objective proof of inducible
myocardial ischemia. Ideally, such proof should be obtained before the patient is on the table for PTCA or surgery. Therefore, the first tools to confirm reversible myocardial ischemia as the cause of chest pain are noninvasive tests, of which exercise nuclear perfusion scintigraphy is probably most widely used. This implicates that in a patient with typical chest pain, a significant coronary artery stenosis, and a positive nuclear test, it is not necessary at all to do invasive physiologic assessment of that coronary lesion. In such cases, revascularization can be performed straightforward.

However, in contrast to official guidelines, in many countries (among which the USA) PTCA is performed in many patients without documented proof of reversible schema (1). In those cases, noninvasive tests were negative, not conclusive, or just not performed. In such cases, in our opinion, it is mandatory to measure fractional flow reserve to justify subsequent PTCA.

The clinical problem sketched above is especially pronounced in case of intermediate stenosis or in patients with atypical chest pain. It is well known that in such patients, if they persist to complain, coronary angiography is often performed despite negative (nuclear) stress testing and that merely the visible presence of a stenosis in those cases triggers coronary intervention (oculo-stenotic reflex). Such a problem was present in the majority of the patient population described in our recent paper (2).

In the remaining 28 patients, a positive regular exercise test was present. In those cases coronary pressure measurements were performed because of the discrepancy between the positive exercise test and either the chest pain or the moderate severity of the coronary artery stenosis. We have argued that in such a population the incidence of false-positive exercise testing is rather high, and the favorable outcome of our patients after deferral of a PTCA supports that position. If in all these patients nuclear scintigraphy had been performed, probably many of these tests would have been (true) negative because of the higher specificity of nuclear exercise testing compared with exercise testing alone. It should be kept in mind, however, that especially in the case of intermediate stenosis, the accuracy of nuclear stress testing is not as high as desirable, as shown in our recent paper in the New England Journal of Medicine (3). In that paper it was shown that the diagnostic accuracy of invasive FFR determination was as high as the combined accuracy of exercise testing, nuclear scintigraphy, and stress-echo and higher than that of any noninvasive single test if performed alone.

In conclusion, we acknowledge the great value of nuclear stress testing for noninvasive assessment of coronary artery disease and emphasize that—with very few exceptions—objective evidence of reversible ischemia should be documented in any way before performing a revascularization procedure.

However, if that has not been done, as is often the case, or if the results of noninvasive tests are not conclusive or contrasting to other clinical data, justification of performing a PTCA on one hand or deferring the PTCA on the other hand can be found by measuring coronary pressure and fractional flow reserve just prior to the planned intervention.

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References

Familial Dilated Cardiomyopathy
Grüning et al. (1) have reported the results of their detailed examination of a large number of relatives of probands with dilated cardiomyopathy (DCM) and have concluded that up to 35% of patients with DCM may have an inherited disorder. Their work makes a valuable contribution to the area of inherited cardiac disease and emphasises the need for careful history taking and assessment of relatives in cases where the disease may, otherwise, appear to be sporadic in nature. However, there are several points that need to be addressed.

First, they report a family history and pedigree analysis negative for familial DCM in 289 of the 445 index patients. However, in this group, only 231 family members were examined—this means that in at least 58 cases familial disease cannot be definitely excluded and it would have been more appropriate to classify these as indeterminate rather than negative. Second, the definition of “suspected” DCM is rather loose and thereby creates the potential for mis-classification of familial disease. Third, the classification of the familial cases into six groups based on characteristic features and prognosis is helpful in defining patterns of disease. However, the authors do not attempt to address the issue of autosomal recessive disease (2).

Fourth, the description of the phenotype (from A to F) changes between Table 2 and Tables 3/4. Fifth, the inference from Table 2 is that all cases of phenotype A are caused by mutations in the dystrophin gene but, on perusal of the text, this has been validated for only one family.

Finally, there are numerous instances where the numbers quoted in the table do not agree with the text and careful examination of the pedigrees also reveals some discrepancies.

1. Figure 1: the number of cases classified as “suspected familial DCM” should read n = 108 (not n = 110).
2. Table 1: in the section under “functional status” the numbers under “course,” “transplantation,” and “death” do not add up correctly—are the groups mutually exclusive? The data set under “X-ray findings” is incomplete but no explanation is offered in the text.
3. Page 188: the numbers in the text “On examination, concomitant cardiac abnormalities, such as unspecific ECG changes....” do not add up to 120.
4. Table 3: the numbers in the section “functional status at diagnosis” do not add up correctly—no explanation is given in the text to account for missing data.
5. Figure 2: according to my interpretation of the pedigree IV-12 is the cousin and not the nephew of the index case IV-16. Three females are classified as affected but the text on page 189 reports depressed LV function in only two cases. This also leads on to difficulty with the numbers reported in Table 3 under Phenotype A.