mortality was reduced towards zero (e.g. a reduction of 0·26% coronary heart disease risk per 1 g . day^{-1} of arginine, $P=0·53$, adjusted for saturated fatty acids and smoking; additional adjustment for flavonols was hampered by multicollinearity).

These results indicate that arginine is not clearly associated with coronary heart disease mortality at the population level. This is in agreement with our findings at the individual level[4]. In both study designs, arginine intake was strongly associated with the intake of energy and other nutrients through its widespread presence in animal and vegetable foods. The potential impact of arginine is therefore difficult to disentangle. Additional observational studies, preferably in populations with a relatively high range of intake, and including e.g. biomarkers for arginine intake, should be carried out to confirm the hypothesis of a protective effect of arginine on coronary heart disease as suggested by recent human and animal experiments.

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References

[1] Meyer EC, Palant A. Arginine consumption in coronary disease. (Letter). Eur Heart J 1998; 19: 970–1.
[2] Cooke JP, Singer AH, Tsao P, Zera P, Rowan RA, Billingham ME. Antiatherogenic effects of L-arginine in the hypercholesterolemic rabbit. J Clin Invest 1992; 90: 1168–72.
[3] Adams MR, McCredie R, Jessup W, Robinson J, Sullivan D, Celermajer DS. Oral L-arginine improves endothelium-dependent dilatation and reduces monocyte adhesion to endothelial cells in young men with coronary artery disease. Atherosclerosis 1997; 129: 261–9.
[4] Oomen CM, van Erk MJ, Feskens EJM, Kok FJ, Kromhout D. Arginine intake and the risk of coronary heart disease mortality in elderly men. Arterioscler Thromb Vasc Biol 2000; 20: 2134–9.
[5] Hertog MGL, Kromhout D, Aravanis C *et al.* Flavonoid intake and risk for coronary heart disease and cancer in the Seven Countries Study. Arch Intern Med 1995; 155: 381–6.

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Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms

We read with great interest the paper by English *et al.*[1] which demonstrated lower levels of androgens in men with coronary artery disease compared to those with normal coronary angiograms. We believe that this paper raises important questions on the still unresolved issue related to the effects of sex hormones on coronary atherosclerosis. We would like to make a few comments with regard to the results of this study, which we think are of special importance.

The subjects included in the study of English *et al.* differed in respect of age and body mass index, which can affect sex hormone levels. In support of this, they found no difference in total and free testosterone levels between either group after correcting for age and body mass index. However, the difference in bioavailable testosterone and free androgen index remained statistically significant, raising the question of low androgens as a risk factor in male atherosclerosis. We conducted a similar angiographic study of 337 age and body mass index matched men, which showed no significant difference with respect to oestrogen, free and total testosterone levels in patients with coronary artery disease compared to those with normal coronaries[2].

We believe that the relationship between male sex hormones and cardiovascular disease is still a matter of debate. The results of several studies related to the causative role of male sex hormones in coronary artery disease are conflicting and do not provide consistent evidence. The finding of low levels of endogenous testosterone in coronary artery disease has been shown mostly in case-control studies[3–6]. However, they are not proven with prospective studies, which indicated that baseline serum levels of testosterone were unrelated to the risk of subsequent coronary artery disease[7–9].

English *et al.* showed decreased levels of oestrogens in patients with coronary artery disease, a result which is contradictory to the results of most published studies, including ours which reported either normal or moderately increased oestrogen concentrations in patients with coronary artery disease[2,10–14]. We believe that their result is mostly due to methodological problems.

If low androgen status were a predisposing factor for coronary atherogenesis, we would expect the lowest androgen levels to be in patients with the most extensive disease. This finding was inconsistent in some recent studies[4,15]. On the contrary English *et al.* showed no association between plasma androgen levels and the degree of coronary atherosclerosis with regard to the number of diseased vessels. In our study, the extent of coronary artery disease was graded with the Gensini score[2]. However, similar to English *et al.* we found no correlation between age-adjusted sex hormone levels and the Gensini score in patients with coronary artery disease.

We believe that the role of sex steroids in male atherosclerosis, both the presence and extent, needs to be further clarified with large prospective studies before low testosterone levels can be claimed as a risk factor.

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References

[1] English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS.

Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. Eur Heart J 2000; 21: 890–4.
[2] Kabakci G, Yildirir A, Can I, Unsal I, Erbas B. Relationship between endogenous sex hormone levels, lipoproteins and coronary atherosclerosis in men undergoing coronary angiography. Cardiology 1999; 92: 221–5.
[3] Heller RF, Jacobs HS, Vermeulen A, Deslypere JP. Androgens, estrogens, and coronary heart disease. Br Med J 1981; 282: 438–9.
[4] Philips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 1994; 14: 701–6.
[5] Hauner H, Stangl K, Burger K, Busch U, Blomer H, Pfeiffer EF. Sex hormone concentrations in men with angiographically assessed coronary artery disease — relationship to obesity and body fat distribution. Klin Wochenschr 1991; 69: 664–8.
[6] Aksut SV, Aksut G, Karamehmetoglu A, Oram E. The determination of serum estradiol, testosterone and progesterone in acute myocardial infarction. Jpn Heart J 1986; 27: 825–37.
[7] Khaw KT, Barret-Conner E. Endogeneous sex hormones, high-density lipoprotein cholesterol, and other lipoprotein fractions in men. Arterioscler Thromb Vasc Biol 1991; 11: 489–94.
[8] Barrett-Connor E, Goodman-Gruen D. The epidemiology of DHEAS and cardiovascular disease. Ann NY Acad Sci 1995; 774: 259–70.
[9] Cauley SA, Gutai JP, Kuller LH, Dai S. Usefulness of sex steroid hormone levels in predicting coronary artery disease in men. Am J Cardiol 1987; 60: 771–7.
[10] Philips GB, Castelli WP, Abbott RD, McNamara PN. Association of hyperestrogenemia and coronary heart disease in men in the Framingham cohort. Am J Med 1983; 74: 863–6.
[11] Entrican JH, Beach C, Carroll D *et al.* Raised plasma oestradiol and oestrone levels in young survivors of myocardial infarction. Lancet 1978; 2(8088): 487–90.
[12] Takeda R, Ikeda M, Miyamori I *et al.* Relationship of plasma levels of estradiol to the severity of coronary arteriosclerosis. Atherosclerosis 1987; 68: 175–6.
[13] Chute CG, Baron JA, Plymate SR *et al.* Sex hormones and coronary artery disease. Am J Med 1987; 83: 853–9.
[14] Goldberg RJ, Gore JM, Ziwe M *et al.* Serum estradiol and coronary artery disease. Am J Med 1987; 82: 1–7.
[15] Rosano GMC, De Ziegler D, Pagnotta P *et al.* Plasma testosterone levels in male patients with coronary artery disease. Eur Heart J 1998; 19: 141A.

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A reply

Kabacki *et al.* raise some interesting points regarding our recent paper. These authors have published a similar study demonstrating no significant differences in hormone levels in men with and without coronary artery disease. The main difference between these two studies is the methods by which testosterone levels were assessed. The quantification of testosterone is notoriously problematic; most andrologists require the measurement of bio-available testosterone, and/or calculation of the free androgen index, feeling that the measurement of free and total testosterone alone is inadequate. Thus, we feel that the disparity in results between our own study and that of Kabacki *et al.* is more likely to be due to inadequate assessment of androgen levels, rather than the statistically corrected for slight differences in age and body mass index in our study population.

We would agree with Kabacki *et al.* that the relationship between male sex hormones and cardiovascular disease is still a matter for debate. Unfortunately, the necessary prospective measurements of bio-available testosterone are not available. However, to our knowledge, two of eight prospective studies, and 23 of 36 cross-sectional studies, have demonstrated increased rates of coronary artery disease in men with low androgen levels, whereas only one study of a total of 44 studies has demonstrated an association between coronary artery disease and increased androgen levels.

The authors also point out that the levels of oestrogen in our subjects were low, a finding which conflicts with much of the published data. This point must be treated with extreme caution, as (as stated in our paper) the accuracy of all the available oestrogen assays at the very low levels found in men is extremely poor, and any conclusions should be made with due regard for this.

Kabacki *et al.* suggest that if low androgen status were truly a predisposing factor for coronary atherogenesis, androgen levels should correlate with disease severity, a feature which our data did not display. This may be due to the small number of subjects, or, as we have stated in our paper, that the witnessed low levels of androgens may be a consequence of the disease process, or an epiphenomenon.

In their concluding paragraph, Kabacki *et al.* agree with our own concluding paragraph, suggesting that the role of sex steroids in atherogenesis needs to be 'further clarified with large prospective trials'. We fully support this suggestion, with the proviso that care must be taken to ensure adequate assessment of androgen levels. Only if these prospective studies are performed can real insight be gained into the role of androgens in atherosclerosis.

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Comment on the ESC/ACC redefinition of myocardial infarction by a consensus dissenter

Collaboration between the European Society and the American College of Cardiology is praiseworthy[1], but the joint attempt[2] to supplant the current WHO definition of myocardial infarction[3] is flawed in process and in outcome. The new definition[2], a manifesto for measurement of troponins, cannot work for many of the purposes for which a revised definition is needed. The two cardiological organizations should recognize that they have not succeeded, study what went wrong, and cooperate with the individuals and organizations who can ensure that the job is completed.

Diagnosis of coronary events, including myocardial infarction, has always been dependent on the availability, frequency and timing of corroborative tests — electrocardiographic or serological — the potential curtailment or censoring of these by death, and the almost arbitrary availability/non-availability of documentation and pathology in fatal cases[3–5]. In non-fatal cases the distinction between acute, and subacute or chronic, is difficult. The syndromes