All participants of our study fasted overnight and consumed only a croissant without filling, thus limiting the influence of fat or any surrounding food matrix on the FMD response.

We fully agree with the authors that, in vivo, the endothelial cells lining the blood vessels would not be exposed to caseins or other milk proteins. This part of the study was conducted as a supplementary line of evidence to the in vivo measurements of FMD as proof of principle. We especially attempted to identify the individual milk proteins that could diminish the effects of tea on cellular level and on vasodilation in rat aortic rings. By adding each milk protein individually in equal amounts to tea, these experiments were able to show which of the various milk proteins were inhibiting the vasodilatory effects of tea on isolated aortic rings and on NO production on endothelial cells. Since only the group of caseins actually prevented the effects of tea in vitro, our experiments evidenced that caseins complexed the physiologically active compounds in tea, long before the beverage reached the digestive tract in the body.

References


Guidelines on the management of valvular heart disease

We have read with interest the recently published European guidelines on management valvular heart disease.1 Our attention was focussed on the section dealing with the management during pregnancy. In table 18 where general recommendations are listed, the medical therapy is favoured in most patients with regurgitant valve disease, even in symptomatic patients with a high level of evidence (IC). As it is reported beside, vasodilators should be used carefully especially in the case of angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers.

Under the 'management strategy' section, patients with symptomatic aortic/mitral regurgitation during pregnancy are treated medically using diuretics at the lowest dose possible to avoid impairing foetal perfusion and vasodilators.

In our point of view, guidelines should explain clearly the well-known increased risk of fetopathy related to the use of ACE-inhibitors not only during the second and third trimesters of pregnancy but also during the first trimester. When they are used in the second half of pregnancy, they can cause oligohydramnios, fetal growth retardation, pulmonary hypoplasia, joint contractures, hypocalvaria and neonatal renal failure, hypotension, and death.2,4

Infants with first-trimester exposure to ACE-inhibitors had an increased risk of major (cardiovascular and the central nervous system) congenital malformations.5 Because of its important clinical relevance, the use of ACE-inhibitors should be clearly avoided during pregnancy and guidelines should expose this fact so.

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Guidelines on the management of valvular heart disease: reply

We read with interest Dr Aiguar-Souto et al.’s comments regarding the recent Guidelines on the Management of Valvular Heart Disease.1 Medical management, including vasodilators, is recommended in patients with chronic regurgitant valve disease who are pregnant and have symptoms. We agree with the comment in the letter that ACE-inhibitors should be avoided during...
pregnancy and it is already clearly stated in the methods section of guidelines 'the use of vasodilators should take into account the contraindication of ACE-inhibitors and angiotensin receptor blockers'. We also agree with the reasons detailed in the letter, which, unfortunately, cannot be developed in a document of guidelines format.

More generally, if possible, patients with left ventricular ejection fraction <40% should probably be dissuaded from becoming pregnant due to the high risk of complications.

References

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Does cardiac resynchronization therapy reduce sudden cardiac deaths?

Rivero-Ayerza et al. report a meta-analysis of five trials comparing cardiac resynchronization therapy (CRT) with optimal medical treatment to determine if CRT affects total mortality, heart failure deaths, and sudden cardiac deaths (SCD). In three of the trials, the follow-up period was less than 6 months with a total of 30 overall mortality events which together only contributed <9% of statistical weights to the meta-analysis. The meta-analysis is dominated by data from CARE-HF demonstrating a favourable effect on all-cause mortality (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.48–0.85; P = 0.002) and COMPANION suggesting a favourable effect on all-cause mortality (HR, 0.76; CI, 0.58–1.01; P = 0.595). Since these two trials dominate the meta-analysis it is not surprising that it too found a favourable effect on all-cause mortality. CARE-HF alone provides level of evidence B for the efficacy of CRT on all-cause mortality. Do the authors contend that the findings from the meta-analysis raise this to level of evidence A?

The effects on mode of death are also presented. CRT favourably affects death due to progressive heart failure, but again this has been established to level of evidence B by CARE-HF. Individually, the five trials considered in the meta-analysis (including the CARE-HF main study) did not provide any evidence for an effect of CRT on SCD nor did the meta-analysis (OR, 1.04; 95% CI, 0.73–1.22). The CARE-HF trial extension phase did, however, find a beneficial effect of CRT on SCD (HR, 0.54; 95% CI, 0.35–0.84; P = 0.005). The fixed effects meta-analysis presented, incorporating the CARE-HF extension study, however did not demonstrate a benefit (OR, 0.86; 95% CI, 0.63–1.19). Although a random effects model is more appropriate (because of the presence of moderate statistical heterogeneity (X² = 8.25; df = 4; P = 0.08; I² = 51.5%), using such a model does not materially affect the result (OR, 1.01; 95% CI, 0.53–1.90; P = 0.99). Thus, the only evidence we have of a beneficial effect of CRT on SCD is derived from the CARE-HF trial extension phase. Given the established symptomatic and mortality benefits of CRT in this patient population (with NYHA Class III or IV heart failure symptoms) it would be unethical to conduct further trials of CRT against medical treatment. Thus, it is unlikely that we will ever get a more definitive answer as to whether CRT reduces the risk of SCD when compared with medical treatment alone.

References

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Does cardiac resynchronization therapy reduce sudden cardiac deaths?: reply

We thank Dr Lam and Dr Owen for their interest in our manuscript. We found it relevant to perform a meta-analysis evaluating the effects of cardiac resynchronization therapy (CRT) on overall mortality and mode of death mainly for two reasons. First, none of the randomized controlled trials comparing the effects of CRT vs. optimal medical therapy in patients with advanced systolic heart failure were powered to prove a survival benefit. Only the CARE-HF trial showed a reduction in...