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

References

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

References
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.5

References


Pr Alec Vahanian
Service de Cardiologie
Hôpital Bichat
46 rue Henri Huchard
75018 Paris
France
Tel: +33 1 40 25 67 35/60
Fax: +33 1 40 25 67 32
E-mail address: alec.vahanian@bch.aphp.fr
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Does cardiac resynchronization therapy reduce sudden cardiac deaths?

Rivero-Ayerza et al.1 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,2–4 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-HF3 (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 COMPANION4 (suggestive of a favourable effect on all-cause mortality (HR, 0.76; CI, 0.58–1.01; P = 0.059)). 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.5–7 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 phase2 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 (χ2 = 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 symptomatic2–4 and mortality5–7 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


Simon K.H. Lam
Heartland Medical Centre
PO Box 86485
Gillies Avenue
Hong Kong
Tel: +852 91928726
fax: +852 83445463
E-mail address: dr.skhlam@gmail.com

Andrew Owen
Department of Cardiology
Kent and Canterbury Hospital
Canterbury, Kent
UK
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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-HF2 trial showed a reduction in