In reply—Regarding L-Carnitine and Cardiovascular Disease

We thank Thompson et al1 for their interest in our L-carnitine meta-analysis. Thompson et al claim that because the research performed by Davini et al2 was not blinded, it should not have been included in our meta-analysis. However, blinding was not an inclusion criterion for our meta-analysis. In addition, 2 recently approved cardiovascular medications that are recommended for the treatment of acute coronary syndrome and the prevention of stroke in patients with atrial fibrillation (ticagrelor and dabigatran, respectively) were not definitively blinded in their landmark trials. Indeed, the Food and Drug Administration documents indicated that at least 452 patients in the ticagrelor trial (Platelet Inhibition and Patient Outcomes trial) became unblinded before the database lock, and 20% of the dabigatran trial (Randomized Evaluation of Long-Term Anticoagulant Therapy [RE-LY]) documents reviewed by the adjudication core committee were noted to contain text that could have potentially unblinded reviewers.3,4

Thus, stating that the trial by Davini et al2 should not have been included in our meta-analysis does not seem relevant, especially because this trial was testing L-carnitine (a natural substance) and the study sponsor was not seeking approval for a potentially profitable branded medication (in which unblinding would undoubtedly be more of a concern).

In regard to including the trial by Singh et al,5 we discussed in detail the issues alluded to by the authors. Specifically, we performed a sensitivity analysis that excluded this trial, which revealed a similar reduction in all-cause mortality with L-carnitine (26% reduction [P = .07] vs the overall conclusions, which indicated a 27% reduction [P = .05]). Moreover, Thompson et al claim that combining so many small studies could result in misleading conclusions. However, when we excluded the smaller trials, a similar reduction in all-cause mortality was still found with L-carnitine (23% reduction; P = .09).

Also, we strongly disagree with the assertion that the trial by Iliceto et al6 should have been excluded because dropouts were nearly as high as deaths because dropouts have been significantly greater than deaths in large randomized controlled trials that have been used in the past as the foundation for approval of cardiovascular medications. Indeed, in the RE-LY trial, there was a significant and unequal dropout rate in both the dabigatran and warfarin groups (21% and 16.6%, respectively) that far exceeded the number of deaths.4

The authors also indicate that our meta-analysis on ventricular arrhythmias should not have included the trials by Martina et al7 and Rizzon et al8 because they used ventricular premature beats as end points, which Thompson et al stated are not considered severe arrhythmias. However, these 2 trials measured “high-grade” ventricular premature beats, which many would consider to be serious arrhythmias. Regardless, exclusion of both of those trials still indicates that L-carnitine causes a significant 59% reduction in ventricular arrhythmias (relative risk, 0.41; 95% CI, 0.20-0.85; P = .02). Nevertheless, we believe that our meta-analysis is considerably stronger regarding the mortality results compared with our findings on ventricular arrhythmias and angina, the latter of which, as we discussed, we would not be able to assess at all without including the trial by Singh et al.5

In summary, even after acknowledging the limitations that Thompson et al point out, L-carnitine still seems to offer potentially potent cardiovascular benefits, particularly regarding mortality benefits, in patients who have experienced an acute myocardial infarction. Although we appreciate the concerns regarding the limitations discussed by Thompson and colleagues, this debate cannot further be settled without an adequately powered, well-performed randomized controlled trial.

James J. DiNicolantonio, PharmD
Wegmans Pharmacy
Ithaca, NY
Mid America Heart Institute
University of Missouri
Kansas City, MO

James H. O’Keefe, MD
Mid America Heart Institute
University of Missouri
Kansas City, MO

Carl J. Lavie, MD
John Ochsner Heart and Vascular Institute
Ochsner Clinical School—The University of Quebec School of Medicine
New Orleans, LA

Pennington Biomedical Research Center
Baton Rouge, LA


Contra Contraception

To the Editor: The recent review article by Marnach et al1 asserts that contraception is a public health need because of the high rate of unintended pregnancies and the high rate of such pregnancies ending through abortion. This assertion is misleading on several fronts. First, “unintended” implies accidental, yet procreative potential is an essential element of the sexual act, not an accidental by-product. It is a disservice to the understanding and volitional capacity of most people who engage in an act inherently procreative to imply that they do not understand the nature of the act or do not exercise free choice when deciding whether or not to engage in it. Secondly, because most contraceptives can act as abortifacients, the increased use of oral contraceptives means more chemical abortions. Thirdly, the implication that contraceptives reduce induced abortion flies in the face of history and common sense. Contraception in the 1960s preceded widespread abortion in the 1970s. Contraception was not developed to prevent abortion but to prevent pregnancy. Abortion is back-up for failed contraception. Aside from their use for medical conditions such as menorrhagia, it is difficult to understand how pills and devices that increase promiscuity decrease abortions. Contraception, sterilization, and abortion are interrelated in that each reduces an act inherently procreative to one that is merely recreational.

The authors cited numerous risks associated with contraception but failed to mention that oral contraceptives are also associated with an increase in premenopausal breast cancer risk, which is an important consideration because breast cancer is the leading cause of cancer deaths in US women aged 20 to 59 years, and breast cancer rates have increased in recent decades.2

It is difficult to understand how interrupting normal procreative physiology is now viewed by many physicians as medical treatment, as if pregnancy were a disease. When the nutritional aspect of eating is sundered from the pleasurable aspect, it is called bulimia, a mental disorder. Yet when the procreative aspect of the sexual act is sundered from the pleasurable aspect, it is now called preventative medicine.

Thomas K. Nelson, MD
Mayo Clinic
Scottsdale, Arizona


In reply—Contra Contraception

We thank Dr Nelson for his interest in our article “Current Issues in Contraception,” published in the March 2013 issue of Mayo Clinic Proceedings,1 and for sharing his perspectives on this topic.

We respectfully disagree that contemporary oral contraceptives are linked with breast cancer. In our previous article,2 we analyzed key epidemiological studies and found no evidence that such a relationship exists with today’s low-dose estrogen oral contraceptive formulations. Of note, Kahlenborn and associates’ statements regarding breast cancer risk, contained in a July 2008 Letter to the Editor in Mayo Clinic Proceedings3 and referenced in Dr Nelson’s correspondence, were specifically refuted in our response to the latter.4 Further, the recent trends toward long-acting reversible contraception options (eg, contraceptive implants and intrauterine contraceptives) allow for long-term contraception without estrogen and without the need for daily actions by the user.5,6

Maternal death is still the sixth leading cause of mortality in reproductive-aged women in the United States.7 Pregnancy and the postpartum period pose a much greater risk of venous thromboembolic events, hemorrhage, infection, and cardiovascular complications than any method of contraception, including hormonal contraception.8 There are many medical conditions in which pregnancy is not advised and that can be frankly life threatening. Should we deny these women and their partners a healthy sex life, which has been shown to positively enhance quality of life and a sense of well-being for both men and women?9

With all due respect to Dr Nelson’s personal view on sexuality, 46% of adolescent high school females have been sexually active,10 82% of adolescent pregnancies are unplanned,11 and 68% of unintended pregnancies occur in women aged 20 to 34 years.12 Most reproductive-aged women and their partners do not espouse the philosophy on the beginnings of human life presented by Dr Nelson. Unplanned pregnancy is one of the highest-priority public health issues in the United States.