thrombolysis in a developing nation. We found that those patients who were randomized to receive RIC upon arrival at the hospital and before thrombolytic therapy experienced a significant reduction in enzymatic MI size compared with the control group. The size of this cardioprotective effect was comparable to that observed in STEMI patients treated by PPCI, for which studies have reported 25% to 30% reductions in MI size as measured by myocardial single-photon emission computed tomography and cardiac magnetic resonance imaging (3–5). The limitations of our study include the following: 1) although tissue plasminogen activator (t-PA) is the most commonly used thrombolytic agent in developed countries, streptokinase (which costs 10-fold less than t-PA) continues to be used in developing nations; and 2) conducting a randomized control trial in a developing nation with very limited resources was challenging and explains in part why we were only able to obtain data on enzymatic MI size.

In conclusion, we have shown that RIC reduced MI size in STEMI patients treated with thrombolysis, making this noninvasive, easily applied, low-cost therapy an attractive option in developing nations where health care resources are limited and current therapy is not optimal.

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Are Phytosterols Responsible for the Low-Density Lipoprotein–Lowering Effects of Tree Nuts?

A Systematic Review and Meta-Analysis

Intake of tree nuts is associated with a lower risk of cardiovascular events in prospective cohorts and the PREDIMED (Prevención con Dieta Mediterránea) trial (1). Previous meta-analyses indicated that tree nut intake lowered low-density lipoprotein (LDL) cholesterol (2,3). However, few trials (≤13 studies) were included in these meta-analyses; pooled effects were not standardized to a common dose, which prevented conclusions about the magnitude of effects for a given intake of nuts, and specific constituents in tree nuts were not examined for their contributions to this LDL-lowering effect. Tree nuts are rich in phytosterols that displace cholesterol from intestinal micelles and reduce the pool of absorbable

cholesterol. Phytosterols also exhibit LDL-lowering effects in intact foods (4).

To investigate the role of phytosterols in the LDL-lowering effect of tree nuts, we conducted a systematic review and meta-analysis of controlled interventional trials. We included trials that provided nuts or dietary advice and that examined LDL cholesterol in adults (age ≥18 years) who were free of coronary heart disease or stroke.

Two investigators (M.F., K.L.) screened potentially eligible PubMed articles, adjudicated inclusion decisions, and extracted data. We calculated mean differences between tree nut intervention and control arms that were dose-standardized to one 1-oz (28.4 g) serving/day, using inverse variance fixed-effects meta-analysis. Phytosterol dose was determined by multiplying the daily nut intake by the phytosterol content of the specific nut types supplied (4), with and without adjustment for the overall dose of nuts. Meta-regression was used to evaluate the association of phytosterol intake with LDL cholesterol.

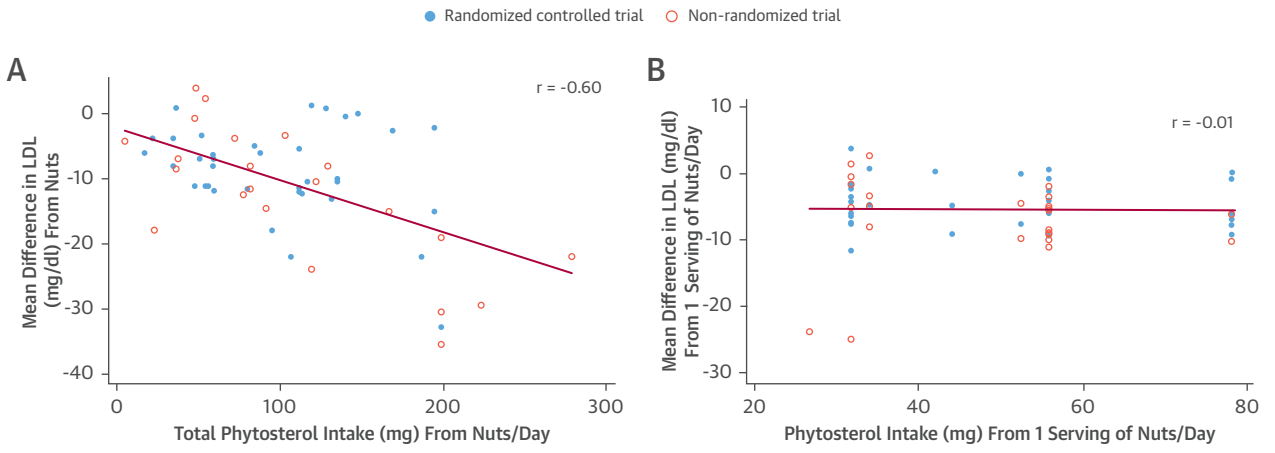
Of 1,301 potentially eligible articles, 61 trials met eligibility criteria (42 randomized, 18 nonrandomized), with a total of 2,582 unique participants. Interventions ranged from 3 to 26 weeks, with nut and phytosterol doses ranging from 0.2 to 3.5 servings and 4.8 to 279 mg/day, respectively. Across the 61 trials, the median baseline LDL cholesterol concentration was 131 mg/dl (range: 73 to 162 mg/dl). All of the trials directly provided nuts, rather than relying only on dietary advice. Fourteen trials included advice to maintain isocaloric balance; in the remaining 47 trials, participants were provided nuts on top of a common background diet. Compliance was generally assessed using self-reported dietary recalls or direct supervision of nut consumption. For meta-regression, trials of mixed nuts (in which the phytosterol content of specific nut types could not be ascertained) were excluded.

Compared with control groups, each daily serving of tree nuts lowered LDL cholesterol (-4.8 mg/dl; 95% confidence interval: -5.5 to -4.2). Total phytosterol intake from nuts was correlated with nut dose ($r = 0.84$). In pooled analyses, total phytosterol dose from nuts was inversely correlated with a reduction in LDL ($r = -0.60$) (**Figure 1A**). However, this association was not independent of total nut dose: after standardization of nut dose, phytosterol content was no longer independently associated with LDL ($r = -0.01$; $p > 0.05$) (**Figure 1B**).

Potential limitations should be considered. Compliance was often assessed by self-report, and low compliance could cause underestimation of effects. Some trials were nonrandomized; however, similar findings were seen in randomized trials (data not shown). The relative variation in phytosterol dose, accounting for total nut dose, might be too small to be clinically meaningful.

In conclusion, our analysis demonstrates that the dose of phytosterol intake from tree nuts is associated

FIGURE 1 Associations of Phytosterol Intake From Nuts and Mean Difference in LDL



(A) Relation of total phytosterol intake (mg) from nuts and absolute mean difference in LDL. **(B)** Relation of phytosterol intake (standardized to 1 serving/day [28.4 g] of different nut types) and mean difference in LDL (standardized to 1 serving/day). Phytosterol-LDL associations were modeled using meta-regression. Total phytosterol intake was calculated by multiplying the daily nut intake dose for a given nut type from each trial by the phytosterol content of each nut type, given in Phillips et al. (4). Trials of mixed nuts were excluded. LDL = low-density lipoprotein.

with the LDL-lowering effect, but that this relationship is driven by the total daily dose of nuts, rather than by differences in phytosterol content between types of nuts.

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When to Call It Severe Mitral Regurgitation?

I read with great interest the article by Grayburn et al. (1), which defined "severe" secondary mitral regurgitation (MR). The investigators did a great job of explaining the mechanism and application of new guidelines in the evaluation of MR. The investigators proposed that classification of a patient with severe secondary MR should be deferred until guideline-directed medical therapy or interventions are optimized.

Current guidelines for valvular heart disease define the class of valvular heart disease by echocardiographic data and symptoms, asymptomatic severe MR (stage C), and symptomatic severe MR (stage D) (2). However, the severity of MR is primarily based on the echocardiographic findings, including color Doppler, vena contracta, effective regurgitant orifice, and regurgitant volume and/or fraction. It is well known that the severity of MR is dependent on the loading conditions (blood pressure and heart rate), and that there may be disparities among various parameters for the assessment of severity. The echocardiologist reading the study may not have any knowledge about the optimization of the medical therapy, and may find it difficult not to describe a patient with severe MR if the patient meets the echocardiographic diagnostic criteria for severe MR. It seems more logical to say that the decision to recommend surgical or other invasive procedures should be deferred until the guideline-directed therapy has been optimized and the severity of MR subsequently reassessed. However, more research is needed in this area to further define the duration of optimal therapy.

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REPLY: When to Call It Severe Mitral Regurgitation?

As stated in our review article, functional mitral regurgitation (MR) is notoriously dynamic and may change in severity depending on loading conditions (1). Dr. Sharma correctly points out that echocardiographers may be unaware of whether a given patient is appropriately treated or not, and therefore, they must base severity on the echocardiographic findings alone. We agree with Dr. Sharma that "the decision to recommend surgical or other invasive procedures should be deferred until the guideline-directed