Although being measured with rather different analytical approaches, this new generation of promising biomarkers shares several clinical strengths with cardiospecific troponins, but also displays some further advantages such as their resistance against spurious degradation in serum or plasma combined with robustness against extremes of pH and temperature [3]. Indeed, we are still a long way from routine assessment and larger clinical studies are needed [14], but measurement of microRNAs may represent the down of a new era in AMI diagnostics.

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Low-density lipoprotein-dependent and independent effects of statins on prevention of major coronary events: Meta-regression of randomized placebo-controlled trials

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In a recent meta-analysis by Naci et al. [1] of 51 randomized trials, statin therapy was associated with a reduction in major coronary events. Although the authors detected a modest association between mean low-density lipoprotein (LDL) concentrations of patients at baseline and effects of statins, comparative effect estimates did not change after adjustment. Meanwhile, to ascertain the relations of different LDL metrics to outcomes, Kizer et al. [2] used meta-regression analysis of 20 large-scale randomized trials of statins. The absolute difference between achieved in-trial LDL in the control versus treatment group exhibited the strongest inverse association with relative reduction in coronary artery disease events. We performed meta-regression analyses of randomized placebo-controlled trials to determine whether the effects of statins on prevention of major coronary events were modulated by the absolute difference between LDL changes (= achieved LDL − baseline LDL) in the treatment versus control group (ΔLDL change = LDL change in the treatment group − LDL change in the control group).

Instead of systematic literature search, we selected 51 randomized placebo-controlled trials [3–53] enrolling participants with and without prior coronary heart disease (in the secondary and primary prevention setting), which were included in the meta-analysis by Naci et al. [1]. To be brief, the following studies were included: open-label and double-blind randomized controlled trials comparing one statin with control (placebo, diet, or usual care) for adults with, or at risk of developing, cardiovascular disease; trials of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin if they had more than 50 participants per trial arm, lasted longer than 4 weeks and reported major coronary events; and both fixed-dose and titration designs. We excluded merely one trial by Sahni et al. [53] from the 51 trials because no LDL data were available. In the Cochrane Handbook for Systematic Reviews of Interventions [54], meta-regression should generally not be considered when there are fewer than 10 studies in a meta-analysis. Accordingly, we performed meta-regression analyses not for simvastatin (5 trials), lovastatin (7 trials), rosuvastatin (4 trials) and fluvastatin (4 trials) but for all statins (50 trials), pravastatin (20 trials) and atorvastatin (10 trials). Data regarding LDL levels and incidence of major coronary events were abstracted from each individual study. For each study, data regarding LDL levels and incidence of major coronary events in both the statin and control groups were used to calculate ΔLDL change and to generate odds ratios (ORs) and 95% confidence intervals (CIs), respectively. The ΔLDL change was assigned a negative value when

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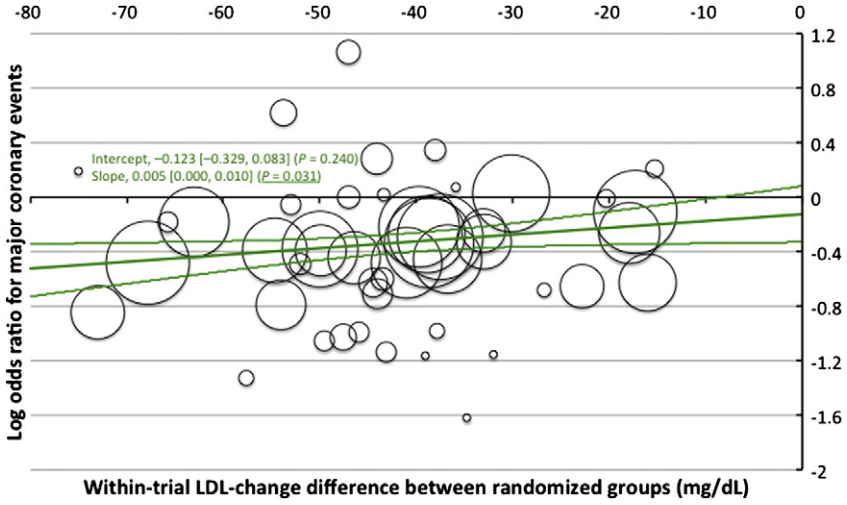

Fig. 1. Association of low-density lipoprotein (LDL) reduction with risk reduction for major coronary events in 50 trials of all statins. Black circles represent trials of all statins with the area of each circle inversely proportional to the variance of the log odds ratio. The green full line with curves (95% confidence interval) represents the summary meta-regression for major coronary events.

the LDL change (= achieved LDL − baseline LDL) was lower (i.e., the LDL reduction [= baseline LDL − achieved LDL] was greater) in the statin group compared with the control group. Percentage reductions in risk were estimated as [(1 − OR) × 100]. Random-effects meta-regression analyses were performed to determine whether the effects of all statins, pravastatin or atorvastatin were modulated by ΔLDL change. Meta-regression graphs depict the effect of statins on the outcome (plotted as a log OR on the *y*-axis) as a function of a given factor (plotted as a mean of that factor on the x-axis). Meta-regression coefficients (slopes of meta-regression lines) show the estimated increase in log OR per unit increase in the covariate. Since log OR > 0 corresponds to OR > 1 and log OR < 0 corresponds to OR < 1, a positive coefficient would indicate that as ΔLDL change decreases (i.e., statin therapy reduces LDL levels more) the OR decreases (i.e., statin therapy is more beneficial in reducing major coronary events). All statistical analyses were performed with the Open Meta-Analyst statistical software (http://www.cebm.brown.edu/open_meta).

For all statins (Fig. 1), the meta-regression coefficient (slope of the meta-regression line) was statistically significant (0.005; 95% CI =0.000–0.010; p = 0.031), but the intercept of the meta-regression line was not statistically significant (−0.123; 95% CI = −0.329 to 0.083; p = 0.240): i.e., overall, statin therapy achieved a 4.9% (95% CI = 0.0%–9.5%) reduction in the risk of major coronary events for each 10-mg/dL reduction in LDL levels. Similarly, for pravastatin (Fig. 2), the coefficient was statistically significant (0.007; 95% CI = 0.001–0.013; p = 0.025), but the intercept was not statistically significant (−0.023; 95% CI = −0.242 to 0.197; p = 0.839): i.e., pravastatin therapy achieved a 6.8% (95% CI = 1.0%–12.2%) reduction in the risk of major coronary events for each 10-mg/dL reduction in LDL levels. Meanwhile, for atorvastatin (Fig. 2), although the coefficient was not statistically significant (0.003; 95% CI = −0.005 to 0.011; p = 0.502), the intercept was statistically significant (−0.375; 95% CI = −0.747 to −0.004; p =0.048): i.e., at zero LDL reduction, the estimated relative risk reduction for major coronary events was 31.3% (95% CI = 0.4% − 52.6%) that corresponded to a 46-mg/dL reduction in LDL levels with pravastatin.

The present meta-regression analyses, based on the findings from 50 randomized placebo-controlled trials, show that the size of LDL

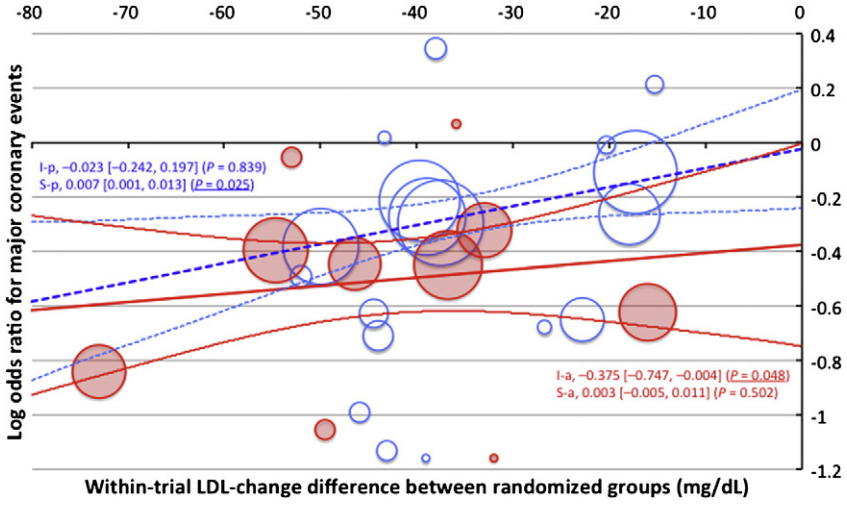

Fig. 2. Association of low-density lipoprotein (LDL) reduction with risk reduction for major coronary events in 20 trials of pravastatin and 10 trials of atorvastatin. Blue and shaded red circles represent trials of pravastatin and atorvastatin, respectively, with the area of each circle inversely proportional to the variance of the log odds ratio. The blue dashed (for pravastatin) and red full lines (for atorvastatin) with curves (95% confidence interval) represent the summary meta-regressions for major coronary events. I-p indicates intercept of the meta-regression line for pravastatin; S-p, slope (coefficient) of the meta-regression line for pravastatin; I-a, intercept of the meta-regression line for atorvastatin; S-a, slope (coefficient) of the meta-regression line for atorvastatin.