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## Q/ Does niacin decrease cardiovascular morbidity and mortality in CVD patients?

### EVIDENCE-BASED ANSWER

**A/ NO.** Niacin doesn't reduce cardiovascular disease (CVD) morbidity or mortality in patients with established disease (strength of recommendation [SOR]: **A**, meta-analyses of randomized

controlled trials [RCTs] and subsequent large RCTs).

Niacin may be considered as monotherapy for patients intolerant of statins (SOR: **B**, one well-done RCT).

### Evidence summary

Before the statin era, the Coronary Drug Project RCT (8341 patients) showed that niacin monotherapy in patients with definite electrocardiographic evidence of previous myocardial infarction (MI) reduced nonfatal MI to 8.9% compared with 12.2% for placebo ( $P=.002$ ).<sup>1</sup> (See TABLE.1-4) It also decreased long-term mortality by 11% compared with placebo ( $P=.0004$ ).<sup>5</sup>

Adverse effects such as flushing, hyperglycemia, gastrointestinal disturbance, and elevated liver enzymes interfered with adherence to niacin treatment (66.3% of patients were adherent to treatment with niacin vs 77.8% for placebo). The study was limited by the fact that flushing essentially unblinded participants and physicians.

### But adding niacin to a statin has no effect

A 2014 meta-analysis driven by the power of the large HPS2-Thrive study evaluated data from 35,301 patients primarily in secondary prevention trials.<sup>2,3</sup> It found that adding niacin to statins had no effect on all-cause mortality, coronary heart disease mortality, nonfatal MI, or stroke. The subset of 6 trials (N=4991) assessing niacin monotherapy did show a reduction in cardiovascular events

(odds ratio [OR]=0.62; confidence interval [CI], 0.54-0.82), whereas the 5 studies (30,310 patients) involving niacin with a statin demonstrated no effect (OR=0.94; CI, 0.83-1.06).

### No benefit from niacin/statin therapy despite an improved lipid profile

A 2011 RCT included 3414 patients with coronary heart disease on simvastatin who were randomized to niacin or placebo.<sup>4</sup> All patients received simvastatin 40 to 80 mg ± ezetimibe 10 mg/d to achieve low-density lipoprotein (LDL) cholesterol levels of 40 to 80 mg/dL.

At 3 years, no benefit was seen in the composite CVD primary endpoint (hazard ratio=1.02; 95% CI, 0.87-1.21;  $P=.79$ ) even though the niacin group had significantly increased median high-density lipoprotein (HDL) cholesterol compared with placebo and lower triglycerides and LDL cholesterol compared with baseline.

A nonsignificant trend toward increased stroke in the niacin group compared with placebo led to early termination of the study. However, multivariate analysis showed independent associations between ischemic stroke risk and age older than 65 years, history of stroke/transient ischemic attack/carotid artery disease, and elevated baseline cholesterol.<sup>6</sup>

TABLE

## Niacin for CVD: What the studies show

Study type	Population	Intervention	Comparison	Outcome	Comments
Meta-analysis <sup>2</sup> (11 studies)	35,301 patients in secondary prevention trials	Niacin alone or in combination with other cholesterol-lowering agents	Placebo or alternative cholesterol-lowering agent	No effect on: 1. All-cause mortality (OR=1.02; 95% CI, 0.92-1.15; P=.59) 2. Coronary heart disease mortality (OR=0.93; 95% CI, 0.76-1.12; P=.44) 3. Nonfatal myocardial infarction (OR=0.85; 95% CI, 0.72-1.01; P=0.07) 4. Stroke (OR=0.96; 95% CI, 0.75-1.22; P=.72)	
RCT HPS2-Thrive Collaborative Group <sup>3</sup>	25,673 patients ages 50-80 yrs with established CVD	Niacin/laropiprant 2 g/40 mg daily, in combination with statin ± ezetimibe; median follow-up 3.9 yrs	Placebo	No effect on: Major vascular events (13.2% vs 13.7%; rate ratio=0.96; 95% CI, 0.90-1.03; P=.29) <ul style="list-style-type: none"> <li>Major coronary events (rate ratio=0.96; 95% CI, 0.87-1.07; P=.51)</li> <li>Stroke (rate ratio=1; 95% CI, 0.88-1.13; P=.56)</li> </ul>	Laropiprant, used to suppress flushing, may be a contributing variable to the adverse effects seen with this study
RCT AIM-HIGH <sup>4</sup>	3414 patients ages ≥45 yrs with established CVD (85.2% male, 92.2% white)	All patients were treated with statins and then randomized to niacin 1.5-2 g/d for 36 mos or placebo	Placebo	No effect on major CVD events: 16.4% vs 16.2% (HR=1.02; 95% CI, 0.87-1.21; P=.79)	Study was discontinued early because of a trend toward increased ischemic stroke (HR=1.61; 95% CI, 0.89-2.91; P=.11)
RCT Coronary Drug Project <sup>1</sup>	8341 males ages 30-64 yrs with definite EKG evidence of MI	Niacin 3 g/d	Placebo	Reduction in nonfatal MI (8.9% vs 12.2%; P=.002)	

CI, confidence interval; CVD, coronary vascular disease; EKG, electrocardiogram; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio.

### Niacin combined with a statin increases the risk of adverse events

The largest RCT in the 2014 meta-analysis (HPS2-Thrive) evaluated 25,673 patients with established CVD receiving cholesterol-lowering therapy with simvastatin ± ezetimibe who were randomized to niacin or placebo for a median follow-up period of 3.9 years.<sup>3</sup> A pre-randomization run-in phase established effective cholesterol-lowering therapy with simvastatin ± ezetimibe.

Niacin didn't reduce the incidence of

major vascular events even though, once again, it decreased LDL and increased HDL more than placebo. Niacin increased the risk of serious adverse events 56% vs 53% (risk ratio [RR]=6; 95% CI, 3-8; number needed to harm [NNH]=35; 95% CI, 25-60), such as new onset diabetes (5.7% vs 4.3%; P<.001; NNH=71) and gastrointestinal bleeding/ulceration and other gastrointestinal disorders (4.8% vs 3.8%; P<.001; NNH=100).

A subsequent 2014 study examined the adverse events recorded in the AIM-HIGH<sup>4</sup>

study and found that niacin caused more gastrointestinal disorders (7.4% vs 5.5%;  $P=.02$ ; NNH=53) and infections and infestations (8.1% vs 5.8%;  $P=.008$ ; NNH=43) than placebo.<sup>7</sup> The overall observed rate of serious hemorrhagic adverse events was low, however, showing no significant difference between the 2 groups (3.4% vs 2.9%;  $P=.36$ ).

## Recommendations

As of November 2013, the Institute for Clinical Systems Improvement recommends against using niacin in combination with statins because of the increased risk of adverse events without a reduction in CVD outcomes. Niacin may be considered as monotherapy in patients who can't tolerate statins or fibrates based on results of the Coronary Drug Project and other studies completed before the era of widespread statin use.<sup>8</sup>

Similarly, American College of Cardiology/American Heart Association guidelines state that patients who are completely statin intolerant may use nonstatin cholesterol-lowering drugs, including niacin, that have

been shown to reduce CVD events in RCTs if the CVD risk-reduction benefits outweigh the potential for adverse effects.<sup>9</sup>

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