

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255-67. DOI: 10.1056/NEJMoa1107579.

Niacin Use in Cardiovascular Patients

Receiving Intensive Statin Therapy

The AIM-HIGH Investigators

Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides:

Impact on Global Health Outcomes (AIM-HIGH) Trial

Online Appendix

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Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria

Men and women aged 45 and older with established vascular disease and atherogenic dyslipidemia, defined in the following ways:

1. Established Vascular Disease satisfying at least one of the following:
 - a. Documented CHD with \geq one of the following:
 - i. Documented multi-vessel CHD, with one or more \geq 50% stenoses in \geq two major epicardial coronary arteries by angiography. Patients with prior successful percutaneous coronary intervention (PCI), even with no residual stenosis, were eligible.
 - ii. Documented prior MI satisfying \geq two of the following:
 - Characteristic ischemic chest pain or pain in associated referral areas
 - Elevation of CK (\geq twice the upper limit of normal) and/or CK-MB (\geq twice the upper limit of normal) and/or troponin T or I (\geq twice the upper limit of normal)
 - New Q waves in adjacent ECG leads, or new dominant R wave in V1
 - iii. Hospitalization for non-ST segment elevation acute coronary syndrome with objective evidence of ischemia (ST-segment deviation or biomarker positivity), stable \geq 4 weeks following hospital discharge.
 - b. Documented cerebrovascular or carotid disease with at least one of the following:
 - i. Documented ischemic stroke within the past 5 years but not $<$ 8 weeks prior to enrollment
 - ii. Symptomatic carotid artery disease with \geq 50% stenosis
 - iii. Asymptomatic carotid stenosis \geq 70%
 - iv. History of carotid revascularization (surgical or catheter based)

- c. Documented PAD with \geq one of the following:
 - i. Ankle-brachial index < 0.85 with or without claudication
 - ii. History of aorto-iliac or peripheral arterial intervention (surgical or catheter based)
- 2. AND Atherogenic Dyslipidemia defined as:
 - a. If off statins at entry, all of the following:
 - i. LDL-C ≤ 180 mg/dL (4.7 mmol/L)
 - ii. HDL-C ≤ 40 mg/dL (1.0 mmol/L) for men or ≤ 50 mg/dL (1.3 mmol/L) for women
 - iii. Triglycerides 150 – 400 mg/dL (1.7 – 4.5 mmol/L)
 - b. If on a statin with or without ezetimibe at entry, the equivalent lipid criteria satisfied¹:
 - i. Upper limit for LDL-C adjusted according to dose and published effect of particular statin
 - ii. HDL-C ≤ 42 mg/dL (1.1 mmol/L) for men or ≤ 53 mg/dL (1.4 mmol/L) for women
 - iii. Triglycerides 100 – 400 mg/dL (1.1 – 4.5 mmol/L)

Exclusion Criteria:

1. Hospitalization for acute coronary syndrome and discharge within 4 weeks prior to planned enrollment
2. Coronary Artery Bypass Graft (CABG) surgery within 1 year of planned enrollment (run-in phase), unless there has been a new, intercurrent acute coronary syndrome event or recurrent angina, associated with angiographic evidence of disease progression ($\geq 50\%$ stenosis) in 1 or more native vessels or bypass grafts, regardless of whether subsequently treated with PCI/stenting
3. Planned percutaneous coronary intervention (PCI) within 4 weeks prior to planned enrollment

¹ Except for statin and/or ezetimibe, all other drugs affecting lipid levels, such as fibrates, niacin, bile acid sequestrants, fish oils were washed out for ≥ 4 weeks prior to the baseline.

4. Stroke within 8 weeks prior to enrollment
5. Fasting glucose >180 mg/dL (10 mmol/L) or hemoglobin A1C >9.0%
6. Inability or refusal to use a glucometer for home glucose monitoring (diabetic patients)
7. CHD associated with unstable angina and symptoms refractory to maximal medical therapy
8. Post MI course complicated by persistent rest angina, shock or persistent congestive heart failure, or if need for urgent revascularization is high
9. Patients with left main coronary disease $\geq 50\%$ and no prior CABG
10. Ejection fraction <30%
11. Cardiogenic shock, pulmonary edema or CHF unresponsive to standard medical therapy
12. Concomitant valvular heart disease likely to require surgery or adversely affect prognosis during follow-up
13. Congenital or primary cardiomyopathy likely to adversely affect prognosis during follow-up
14. Resuscitated out-of-hospital sudden death or symptomatic sustained or non-sustained ventricular tachycardia without an implantable cardioverter-defibrillator (ICD)
15. Significant systemic hypertension (blood pressure >200/100 mmHg) unresponsive to medical therapy
16. Active peptic ulcer disease
17. AST or ALT > 2 times upper limit of normal or active liver disease
18. Recent history of acute gout. (For patients with baseline uric acid > 7.0 mg/dL [415 umol/L], treatment with allopurinol is recommended but not mandated)
19. Chronic renal insufficiency with creatinine ≥ 2.5 mg/dL (220 umol/L)
20. Patients who cannot discontinue the following excluded concomitant medications:
 - Drugs with a high probability of increasing the risk for hepatotoxicity or myopathy, such as those predominantly metabolized by cytochrome P450 system 3A4, including, but not limited to:

cyclosporine, itraconazole, ketoconazole, HIV protease inhibitors, nefazodone, verapamil, amiodarone

- Lipid-lowering drugs (other than the investigational drugs), such as statins, bile-acid sequestrants, fish oils, cholesterol absorption inhibitors, fibrates
- High-dose, antioxidant vitamins (vitamins C, E, or beta-carotene)

21. Pregnant (or likely to become pregnant) women or pre-menopausal women not using adequate contraception

22. Significant co-morbidity likely to cause death in the 3-5 year follow-up

23. Patients with AIDS/active HIV infection, due to potential confounding drug interactions

24. Significant active history of substance abuse within 5 years

25. Unwillingness/inability to give informed consent or follow study protocol

26. Current participation in another clinical study or trial that involves a study drug or intervention

27. Unwillingness of patient's physician to allow participation in the study

Figure 1: Study Diagram

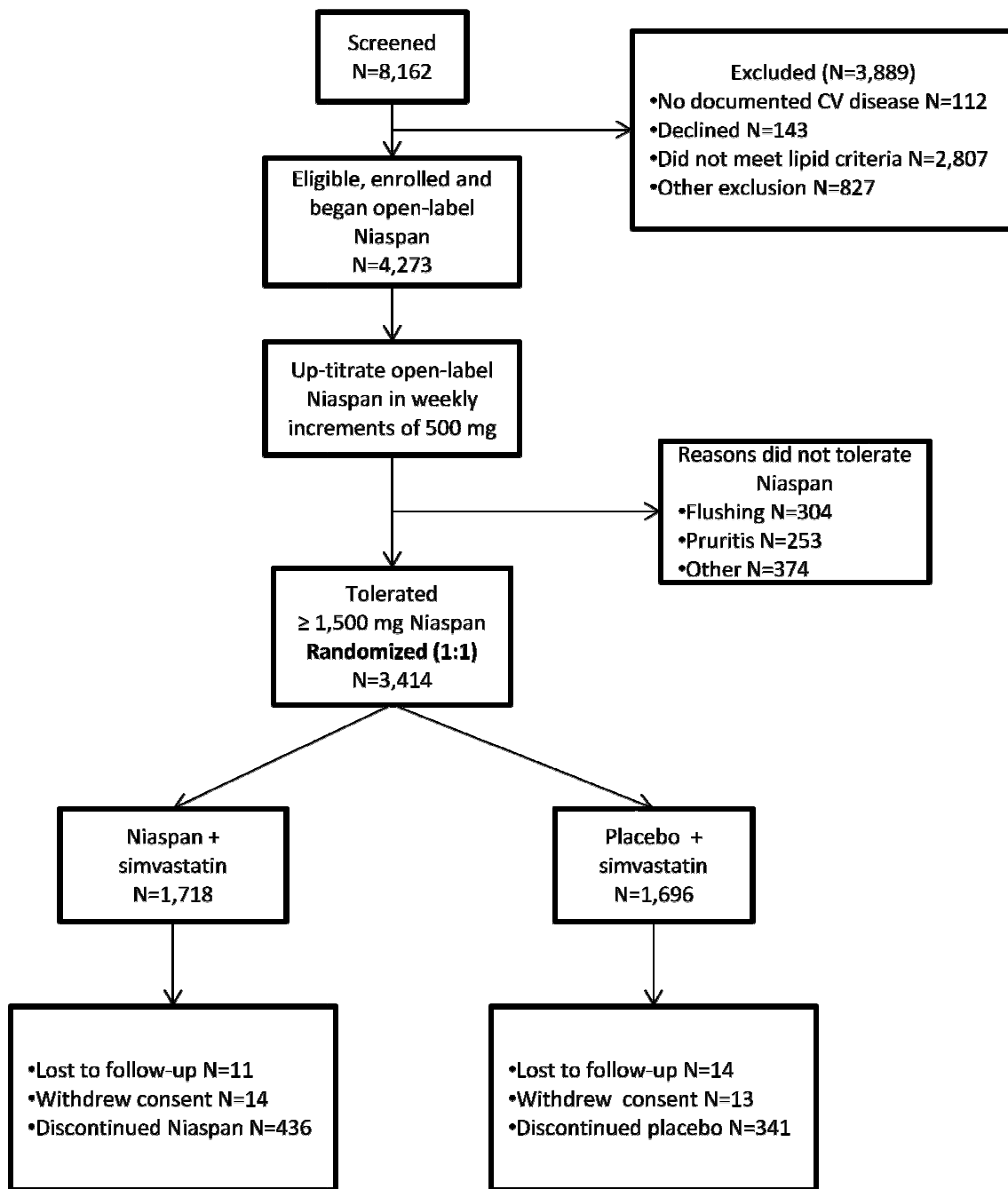
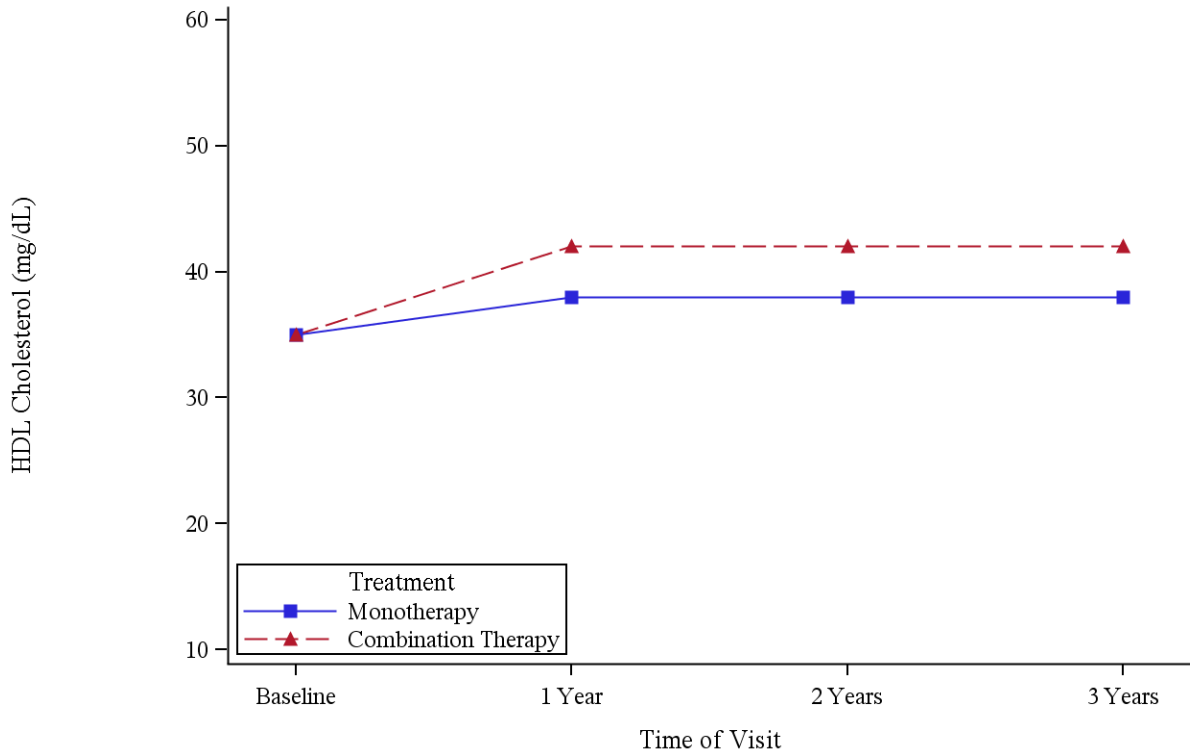


Figure 2: Median Lipid Levels at Baseline and During Follow-up:

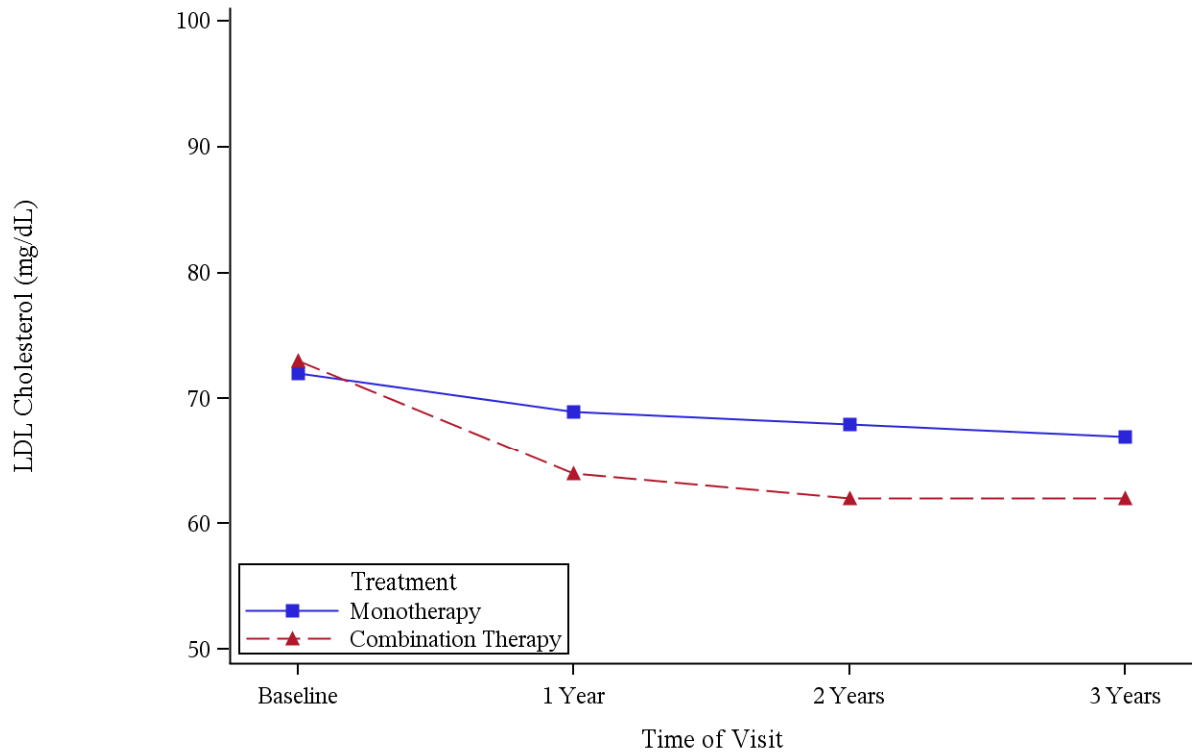
Figure 2A: Median HDL-C



No. of patients

Monotherapy	1695	1548	1326	873
Combination Therapy	1716	1559	1329	865

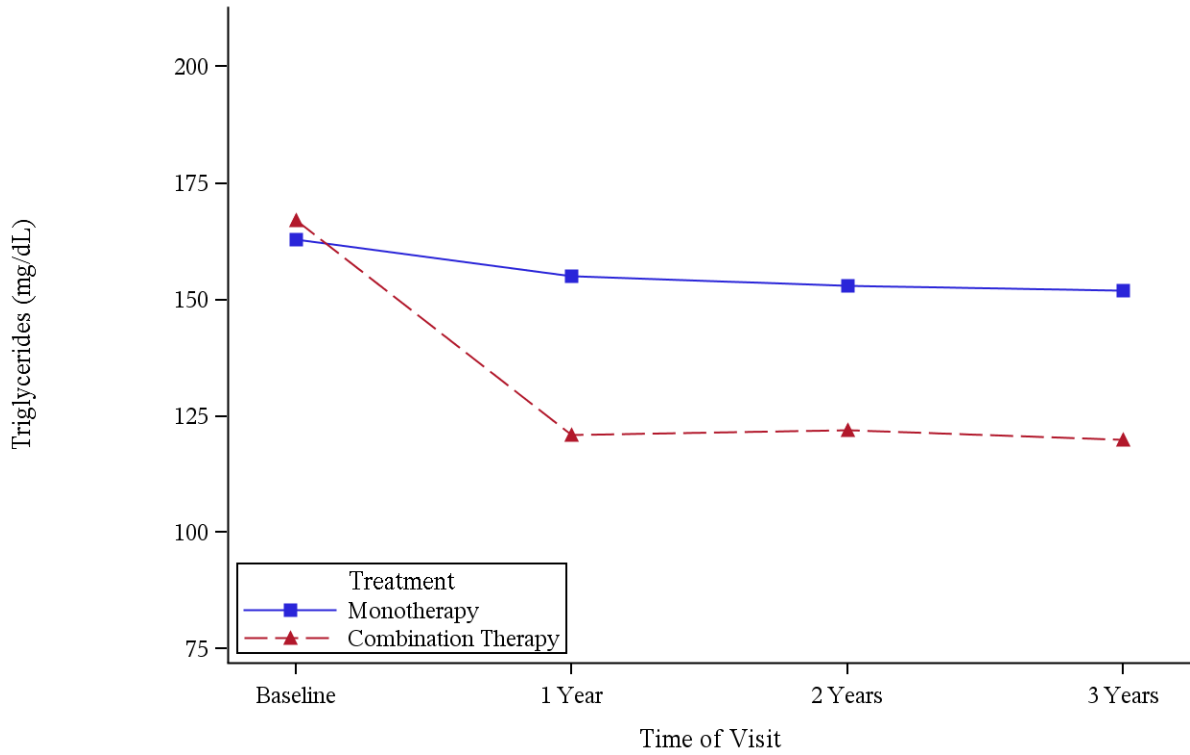
Figure 2B: Median LDL-C



No. of patients

	Baseline	1 Year	2 Years	3 Years
Monotherapy	1695	1544	1326	873
Combination Therapy	1716	1558	1329	865

Figure 2C: Triglycerides



No. of patients

	Baseline	1 Year	2 Years	3 Years
Monotherapy	1695	1553	1326	873
Combination Therapy	1716	1562	1329	865

Figure 3: Forest Plots

Panel A: Components of the Endpoint Constellation

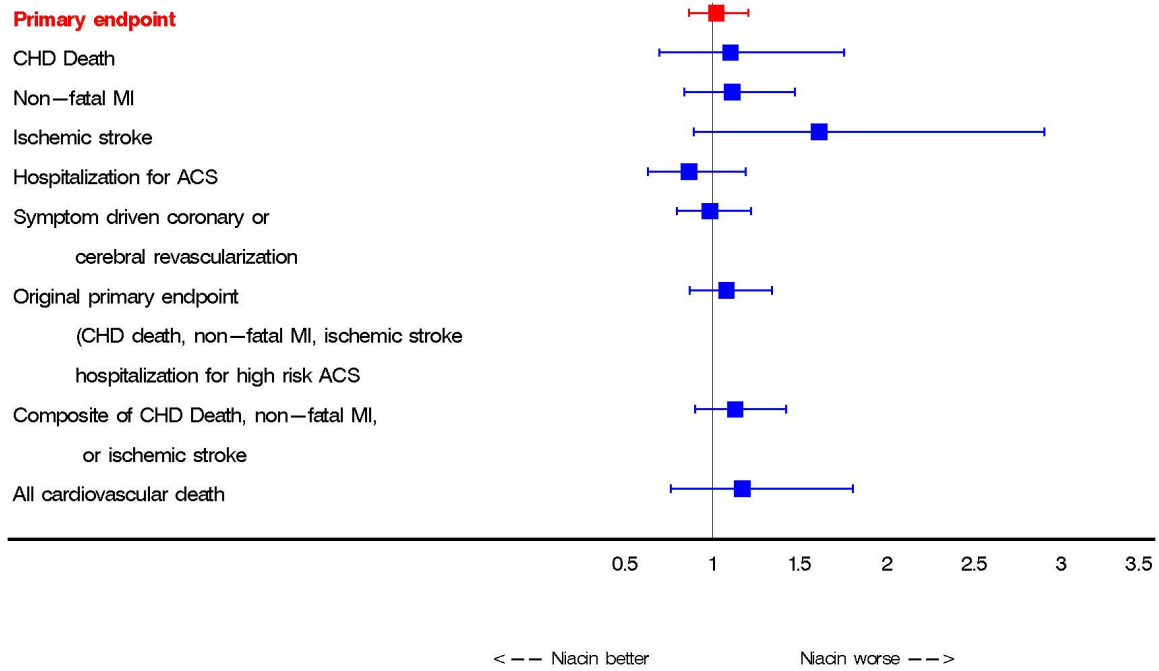


Chart shows hazard ratio (squares) and 95% CI (horizontal lines). For components of the primary outcome (CHD death, non-fatal MI, ischemic stroke, hospitalization for ACS or symptom-driven coronary or cerebral revascularization), the hazard ratio for all patients with that outcome is depicted.

Panel B: Pre-specified Subgroups

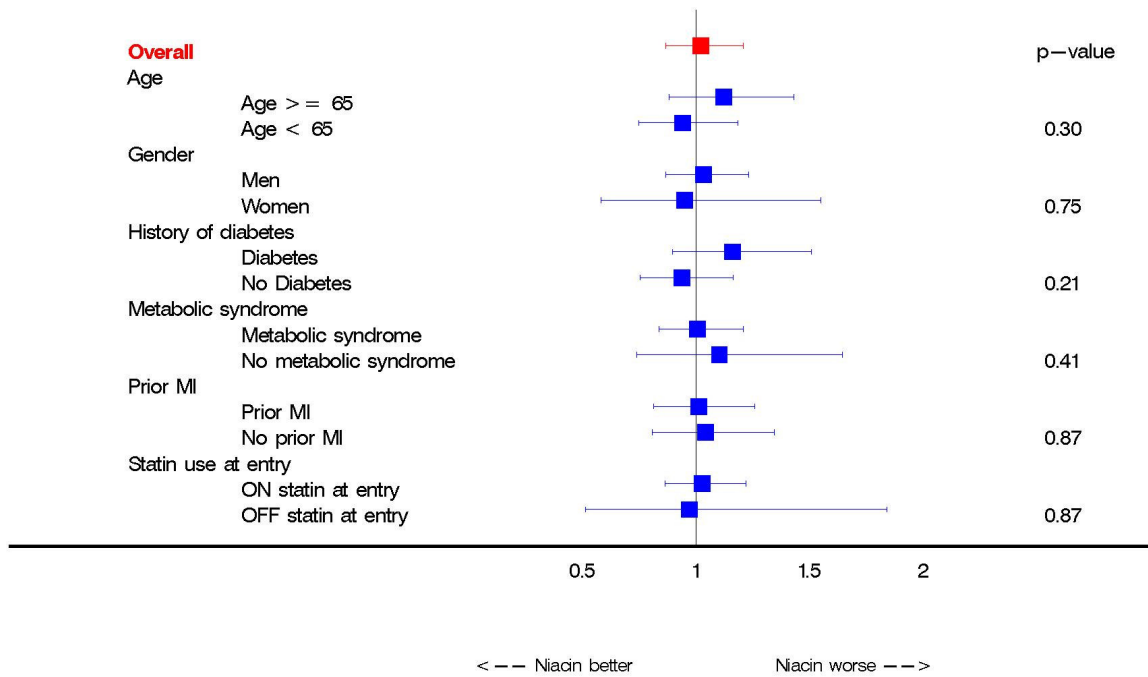


Chart shows hazard ratio (squares) and 95% CI for the primary endpoint over all patients randomized and in each subgroup. P-value is from a Cox proportional hazards model testing for the significance of the interaction between treatment assignment and the subgroup of interest, with no adjustment for multiplicity of comparisons.

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