Healthy Heart

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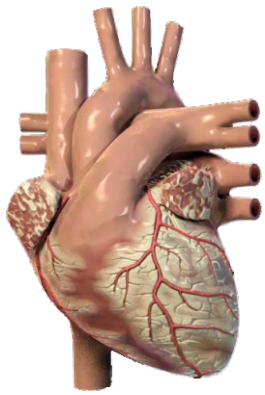

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From the desk of Editor:

There are many trials of importance, but I am presenting a few landmark trials which can change our day to day clinical practice or help us to understand the disease process. If you do not know the answers of the following, please read the full article :

(1) PROSPECT : In spite of aggressive secondary preventive therapy after PCI, approximately 20 % patients have recurrent Major Adverse Cardiac Event (MACE) within 1st 3 years. Why ? Who are at risk?

(2) EMPHASIS-HF : Aldosterone antagonist are useful in severe chronic heart failure (Spironolactone in RALES trial) and in post-MI LV-dysfunction (Eplerenone in EPHESUS trial). Is Eplerenone useful in mild heart failure ?

(3) HPS : Should every patient with CAD, Peripheral Vascular Disease (PVD), DM or HT receive statin regardless of LDL level? During course of disease, if we start statin lately to achieve ultimately similar lipid levels as of early starters, does it make any difference ?

(4) AIM-HIGH : Common lipid abnormality among Indians is low HDL level. Is addition of Niacin to statin ± Ezetimibe useful?

(5) SATURN : Atorvastatin 80 mg and Rosvivaitatin 40 mg are the most effective statin regimens for current treatment of atherosclerosis. Which is superior ?

Dr. Milan Chag

Clinically important late breaking Trials of 2011

1) PROSPECT:

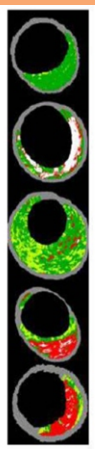
A Prospective Natural-History Study of Coronary Atherosclerosis

(Gregg W. Stone et al N Engl J Med 2011;364:226-35)

Atherosclerotic plaques that lead to ACS often occur at sites of angiographically mild coronary-artery stenosis. This study provides important information about contemporary event rates from culprit lesions and nonculprit lesions in patients undergoing Percutaneous Coronary Intervention (PCI) after an Acute Coronary Syndrome (ACS). The importance of this investigation is the prospective imaging evaluation of all mild to moderate lesions to determine lesion-related risk factors for future coronary events.

The findings are clinically relevant as the majority of patients were medically treated according to guidelines and revascularized. The main finding was that the 3-year cumulative cardiovascular event rates was 20.4%, with approximately half from the initial culprit lesion (12.9%) and half from the nonculprit lesions (11.6%) that were initially angiographically mild stenosis (diameter of stenosis 32.3±20.6%).

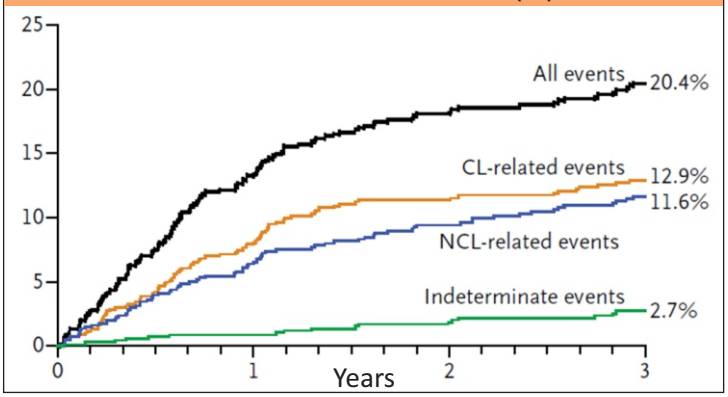
IVUS findings



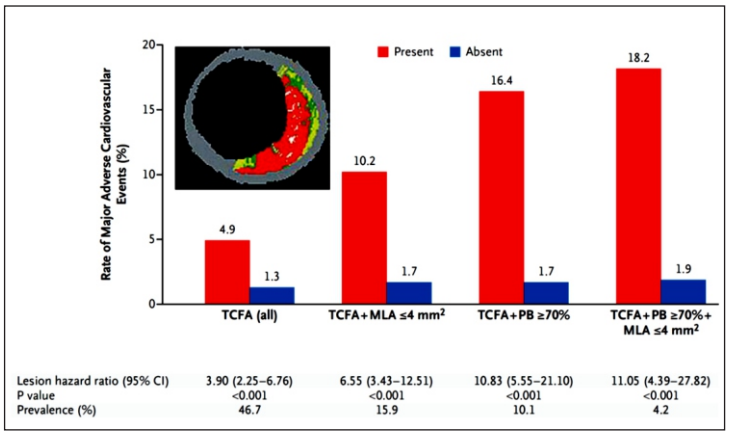
1. Fibrotic plaque
2. Fibrocalcific plaque
3. Pathological intimal thickening (PIT)
4. Thick-cap fibroatheroma (ThCFA)
5. Thin-cap fibroatheroma (TCFA)

From the intravascular imaging, the most important predictors of events in nonculprit lesions were plaque burden (>70%) with a hazard ratio of 5.03 (95% CI 2.52-10.11; p<0.001) and the minimal lumen area (<4.0mm2) with a hazard ratio of 3.21 (95% CI 1.61-6.42; p=0.001) or the presence of a thin cap fibroatheroma, with a hazard ratio of 3.35 (95% CI 1.77-6.36; p<0.001). The independent correlates or patient-level predictors of major adverse cardiovascular events related to nonculprit lesions were insulin-requiring diabetes, with a hazard ratio of 3.32 (95% CI 1.43-7.22; p=0.005), and previous PCI with a hazard ratio of 2.03 (95% CI 1.15-3.59; p=0.02). These patients with ACS were revascularized and treated with medical therapy including aspirin, thienopyridine, statin, beta blocker and Angiotensin Converting Enzyme (ACE) inhibitor or Angiotensin Receptor Blocker (ARB) use.

Cumulative Rate of MACE (%)



This landmark study will become a reference for future investigations using new therapies to reduce



Non-culprit Lesions : Risk Factors for MACE

Correlates	Hazard Ratio (95% CI)	P Value
Predictors of patient-level events†		
Insulin-requiring diabetes	3.32 (1.43–7.72)	0.005
Previous percutaneous coronary intervention	2.03 (1.15–3.59)	0.02
Predictors of events at individual lesion sites‡		
Plaque burden ≥70%	5.03 (2.51–10.11)	<0.001
Thin-cap fibroatheroma	3.35 (1.77–6.36)	<0.001
MLA ≤4.0 mm²	3.21 (1.61–6.42)	0.001

atherosclerosis and its complications. Imaging techniques at the time of PCI may help identify lesions at risk for future events and local or systemic therapy tested prospectively.

Take Home Message:

The findings from the PROSPECT trial suggest that destabilization of non-culprit lesions is dependent not only on systemic risk factors (IDDM and previous PCI) but also by identifying high-risk lesion characteristics (Thin cap fibro-atheroma, minimal lumen area < 4 sq mm, and plaque burden>70%). It remains to be proven that treating these thin cap fibroatheromas with high plaque burden or smaller lumen area may leads to a reduction in future events.

2) EMPHASIS HF:

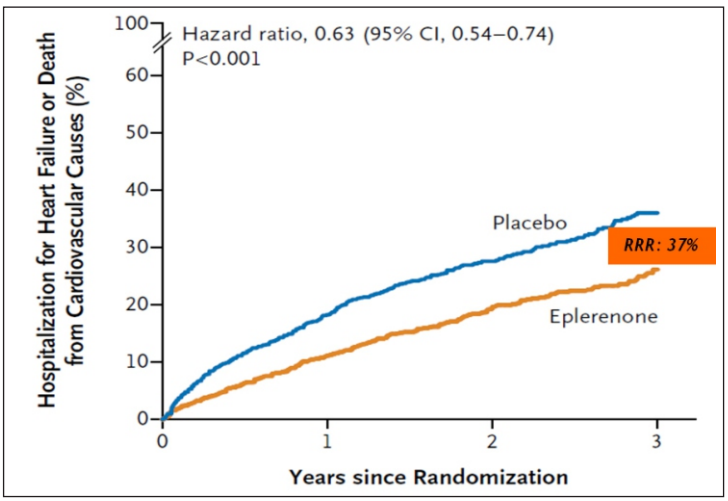
Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

(F.Zannad et al. N Engl J Med 2011;364:11-21)

Mineralocorticoid antagonists improve survival among patients with chronic, severe systolic heart failure and heart failure after myocardial infarction. EMPHASIS HF

group evaluated the effects of eplerenone in patients with chronic systolic heart failure and mild symptoms.

The EMPHASIS-HF study was a randomized, double-blind trial that enrolled 2737 patients with New York Heart Association class II heart failure and an ejection fraction of no more than 35% from 278 centers in 29 countries. The patients were randomized to receive eplerenone (up to 50 mg/day) or placebo, in addition to recommended therapy, with a primary endpoint of a composite of death from cardiovascular causes or a first hospitalization for HF. Secondary endpoints were hospitalization for HF or death from any cause. The trial was stopped prematurely after a median analysis at 21 months showed that those treated with eplerenone had a reduced risk of the primary endpoint.



The primary endpoint occurred in 18.3% of patients who received eplerenone compared with 25.9% in the placebo group (P<0.001). Death from any cause or hospitalization for HF occurred in 270 eplerenone patients (19.8%) compared to 376 placebo patients (27.4% reduction, P<0.001). The total number of hospitalizations was lower with eplerenone patients (750) compared to 961 placebo patients, for a 24% reduction (P<0.001), and hospitalization for HF had a 38% reduction (273 eplerenone patients vs. 429 placebo patients, P<0.001).

EMPHASIS-HF

Event	Adverse Event		
	Eplerenone (N=1360)	Placebo (N=1369)	P Value
	no. of patients (%)		
All events	979 (72.0)	1007 (73.6)	0.37
Hyperkalemia	109 (8.0)	50 (3.7)	<0.001
Hypokalemia	16 (1.2)	30 (2.2)	0.05
Renal failure	38 (2.8)	41 (3.0)	0.82
Hypotension	46 (3.4)	37 (2.7)	0.32
Gynecomastia or other breast disorders	10 (0.7)	14 (1.0)	0.54

Take Home Message:

Eplerenone significantly reduced the risk of death and hospitalization in patients with LVEF <35% and mild symptoms of heart failure(NYHA class-II). Patients should be watched for hyperkalemia

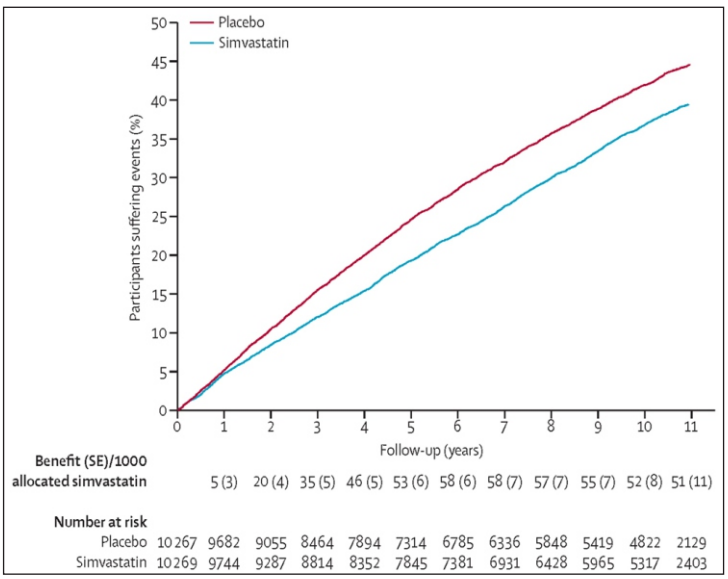
3) HPS:

Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomized controlled trial (Heart Protection Study Collaborative Group. The Lancet; November 23, 2011)

Heart Protection Study (HPS) assessed the effects of lowering LDL cholesterol on cause-specific mortality and major morbidity, not only during the study treatment period in HPS but also in the longer term, post-trial. The study was based on extended follow-up data from the HPS. In the original study, investigators randomized 20 536 high-risk patients (patients with CAD, PVD, DM or HT) between July 1994 and May 1997 to receive either 40 mg simvastatin daily or placebo for approximately five years. At final follow-up in 2001, investigators instructed patients to continue taking the statins unless there were any contraindications. During post-trial period, average 74% patients in both the groups were on statin. The absolute benefits of treatment continued during the initial five-year in-trial period and rose year after year, although they plateaued in the years after the trial. Post-trial follow-up lasted an average of 11 years.

The average decline in low-density lipoprotein cholesterol with statins in the initial five-year period that patients received them was 1.0 mmol/L, which was associated with a 23% proportional drop in major vascular events, compared with placebo-treated patients. At end of 11 years, cholesterol and LDL levels were similar between statin and placebo groups. The benefit persisted largely unchanged during the 11-year follow-up period, i.e. in spite of equal number of patients in both groups received statins and in spite of similar cholesterol and LDL levels in both groups, advantage of reduced MACE rates in original statin group persisted even after 11 years of follow up.

During the combined in-trial and post-trial periods, no significant differences were recorded in cancer incidence at all sites or any particular site, or in mortality attributed to cancer or to non-vascular causes.



Take Home Message:

If patient has high cardiovascular risk (CAD, PVD, DM or HT), regardless of baseline LDL level, and if one receives statin at the time of diagnosis, he/she remains in an advantageous position for MACE reduction for long-term as compared to the one who receives statin at a later date in his/her life-span. The benefit of early treatment with statin persists even after 11 years in spite of similar serum lipid levels among early versus late starters at 11 years.

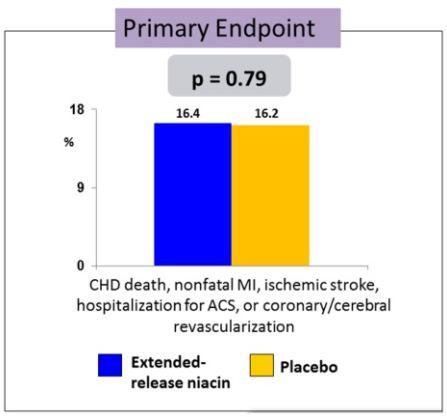
4) AIM-HIGH

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy

(AIM-HIGH Investigators- N Engl J Med 2011; Nov 15)

This study compared the use of extended-release niacin plus statin to statin alone in patients with established non-acute CVD and low levels of baseline HDL cholesterol. Study randomized 3414 patients with established heart disease, low HDL levels, and raised triglycerides to extended-release niacin (1500-2000 mg per day) or placebo. All patients also received simvastatin plus ezetimibe if needed to maintain LDL levels below 80 mg/dL (2.07 mmol/L).

At two years, niacin therapy had increased HDL levels from a median of 35 to 42 mg/dL, lowered triglyceride levels from 164 to 122 mg/dL, and lowered LDL levels from 74 to 62 mg/dL.



The primary end point—the first event of a composite of CHD death, nonfatal MI, ischemic stroke, hospitalization for ACS or symptom-driven coronary or cerebral revascularization—was similar in the two groups, occurring in 282 patients (16.4%) in the niacin group vs 274 patients (16.2%) on placebo. There was also no difference in two secondary composite end points.

In summary, among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg per deciliter (1.81 mmol per liter), there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels.

Limitations and discussion:

- At entry in trial: 94% patients were on statin and 20% on Niacin. They already had plaque stabilizing effect
- "Placebo" arm also received 100-200 mg Niacin/day, 25 % of Niacin group stopped the drug prematurely
- Trial stopped prematurely at 3 years (instead of ~7 years) Supposedly achieved 12.5% lower event rate was just half of predicted 25% on which power calculations were based
- Unexpected 9.8% increase in HDL-C in placebo-arm minimized difference in event rate

Take Home Message:

- If we achieve LDL < 70 mg/dL or Non-HDL< 100 mg/dL with aggressive Statin ± Ezetimibe, addition of Niacin may not be helpful on short period (2-3 yr).
- If these goals are not achieved, or if patient is high risk (ACS, Post-MI, high TG, Lp(a)), Niacin (or Fibrate) may be added.

5) SATURN

Effect of Two Intensive Statin Regimens on Progression of Coronary Disease

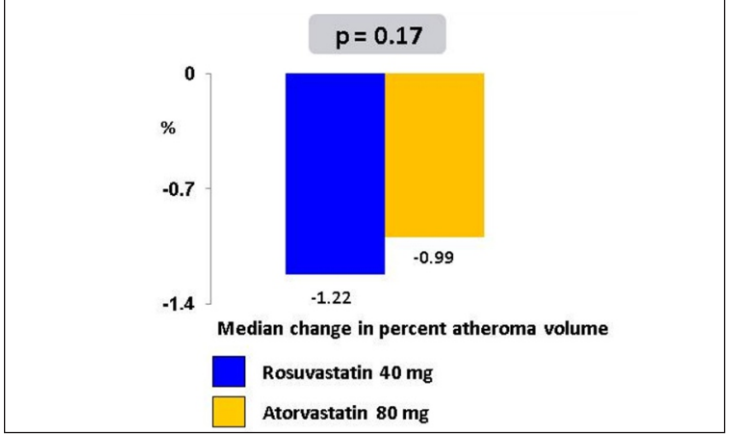
(Stephen J. Nicholls , Steven E. Nissen et al. Engl J Med 2011;365:2078-87)

SATURN study is a randomized, double-blind clinical trial designed to test the effectiveness of the maximum doses of rosuvastatin and atorvastatin to regress coronary atherosclerosis in 1385 patients with coronary artery disease. Prior to the study initiation, investigators hypothesized that the LDL-lowering effects of the statins would be similar but that rosuvastatin would likely raise HDL-cholesterol levels more than atorvastatin.

Over 104 weeks of therapy, treatment with rosuvastatin and atorvastatin resulted in low LDL-cholesterol levels (62.6 vs 70.2 mg/dL, respectively; p<0.001) and HDL cholesterol that approached levels considered acceptable for secondary prevention of cardiovascular events (48.6 vs 50.4 mg/dL, respectively; p=0.01).

The primary efficacy end point, percent atheroma volume (PAV), decreased 0.99% in atorvastatin-treated patients and 1.22% in rosuvastatin-treated patients, a nonsignificant difference. In terms of effect on normalized total atheroma volume (TAV), a secondary end point, there was a significant reduction of 6.39 mm3 in the rosuvastatin arm compared with a 4.42-mm3 reduction in the atorvastatin arm, a between-group difference that was statistically significant (p=0.02). Both agents had acceptable side-effect profiles, with a low incidence of laboratory abnormalities and cardiovascular events.

Median Change Percent Atheroma Volume



Take Home Message :

High-dose statin therapy with atorvastatin or rosuvastatin resulted in a significant regression of coronary atherosclerosis. Treatment with rosuvastatin 40 mg resulted in lower LDL- and higher HDL-cholesterol levels than atorvastatin 80 mg, but the effect on percent atheroma volume measured by intravascular ultrasound (IVUS) did not significantly differ. Subgroup analysis showed that among females and those with low HDL, rosuvastatin was better than atorvastatin for plaque regression.

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