Review Article:
THE 22 PLEIOTROPIC PROPERTIES OF STATIN AND CARDIOVASCULAR DISEASES
The Roles of Atorvastatin with Its PPECCAT-GOMMESAAB Effects

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ABSTRACT

There are 22 possible pleiotropic atheroprotective effects of statin. Specifically, it was hypothesized that in addition to their beneficial lipid modulating activity, specific metabolites (but not the parent drug) of atorvastatin called ATM (ATorvastatin Metabolite). Atorvastatin is very effective in lowering LDL-C levels, and the clinical evidence-based data have been proved by the results of prominent studies, such as AVERT (Pitt et al 1999), ASAP (Smilde et al 2001), MIRACL (Schwartz et al 2001, Waters et al 2002), and GREACE (Athyros et al 2002), CARDS (Colhoun et al 2005), REVERSAL (Nissen 2005), PROVE IT-TIMI 22 (Sever et al 2005), ASCOT-LLA (Sever et al 2005), ARMYDA-3 (Patti et al 2006), TNT-Subgroup Analysis (Khus et al 2007), ASCOT-LLA Extension (Sever et al 2008), and SANDS (Howard et al 2008). The aim of this article is to describe shortly pleiotropic properties of statins (which in part = 16 components can be indicated as PPECCAT-GOMMESAAB) from basic to possible clinical application (focus on atorvastatin), to general practitioners, residents, internists, and other associated specialists.

Keywords: Atorvastatins, PPECCAT-GOMMESAAB, cardiovascular diseases.

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Abbreviations: ASAP = Atorvastatin versus Simvastatin on Atherosclerosis Progression; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; ATM = ATorvastatin hydroxy Metabolite; ATi-R = ATi-Receptor; AVERT = Atorvastatin Versus Revascularization Treatment; BP = Blood Pressure; CARDS = Collaborative Atorvastatin Diabetes Study; GREACE = The GREEk Atorvastatin and Coronary heart-disease Evaluation; LVM = Left Ventricle Mass; MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; PPECAAT–GOMMESAAB = Plaque stabilization, improved Platelet and Endothelial function, decreased CD40L, decreased CRP, decreased Atherothrombosis, Tissue factor, no impaired Glucose tolerance, suppressed Oxidized LDL, decreased Macrophage number, decreased MMPs, decreased Endothelin-1, suppressed SMC proliferation and migration, antioxidant effects of AT.M, suppressed ATi-Receptor, increased Apo-B degradation); PROVE IT-TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22; REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid Lowering; SANDS = Stop Atherosclerosis in Native Diabetes Study.

INTRODUCTION

The author (2000, 2001A,B, 2002A,B) summarized from several studies (Bernini et al 1993, 1995, Corsini et al 1993, 1996, 1998, Bellosta et al 1998, Hussein et al 1997, Huhle et al 1999, Blumenthal 2000) 22 possible pleiotropic atheroprotective effects of statin, which could be categorized into 3 sites of action, such as: the Pre-Endothelium (6 effects) Endothelium (4 effects), and in the Sub-Endothelium (12 effects). Sixteen (16) of the 22 components can be indicated as PPECCAT-GOMMESAAB (see abbreviation list).

Specifically, it was hypothesized that in addition to their beneficial lipid modulating activity, specific metabolites (but not the parent drug) of atorvastatin called AT.M (ATorvastatin Metabolite) and gemfibrozil might also reduce the atherogenic potential of lipoproteins through their anti-oxidant properties (Aviram et al 1998A, 1998B).

Summarized order of priorities for the treatment of diabetic dyslipidemia in adults recommended by American Diabetes Association (ADA 2003) are LDL Cholesterol lowering with the first choice drug statins, HDL-Cholesterol raising interventions such as weight loss, physical activity, smoking cessation, and fibrates as recommended drugs, triglyceride lowering programs: excellent glycemic control (first priority) and gemfibrozil or fibrates, and combined hyperlipidemia: improved glycemic control plus high-dose statin as the first choice of treatment.

Atorvastatin is very effective in lowering LDL-C levels, and the clinical evidence-based data have been proved by the results of prominent studies, such as AVERT.
The 22 Pleiotropic Properties of Statin and Cardiovascular Diseases (Askandar Tjokroprawiro)

Minimally 22 pleiotropic properties of statins have been compiled (since 1997) and summarized in table 1 (Tjokroprawiro 2002A, 2000B, 2008). Besides, Hill et al (2001) demonstrated that atorvastatin prevented the enhanced uptake of Ca²⁺ by SR and non-SR Ca²⁺ in diabetic dyslipidemic pigs. They hypothesized that by preventing the uptake of Ca²⁺ into intracellular Ca²⁺ stores, atorvastatin may help prevent Ca²⁺ overload of intracellular organelles, and it is most likely vasodilatation may pursue.

The author (2002A; 2000B, 2008) summarized 16 of 22 lipid and non-lipid lowering effect of statins as PPECCAT-GOMMESAAB. There are plaque stabilization, glucose tolerance (improved), platelet function (improved), oxidation of LDL (inhibited), endothelial function (improved), MMPs expression (decreased), CRP expression (suppressed), Macrophage number (reduced), CD40-L expression (suppressed), endothelin-1 production (inhibited), atherothrombosis (suppressed), SMC migration and proliferation (inhibited), tissue factor (decreased), Atorvastatin metabolite as antioxidant, ATI-Receptor expression (suppressed), Apo-B degradation (increased).

The quality of PPECCAT-GOMMESAAB effects can be achieved by atorvastatin treatment. Nawrocki et al 1995 showed significant LDL-C reduction (p<0.05) across the 10 mg to 80 mg dose range of atorvastatin (compared with placebo) and its potency can be listed in sequence, as follows: 10 mg (-41% LDL-C reduction), 20 mg (-44%), 40 mg (-50%), and 80 mg (-61%). Comparative study (Newman et al 2006) on the safety of atorvastatin 80 mg vs 10 mg derived from analysis of
49 completed trials in 14,236 patients revealed that the incidence of treatment-associated adverse events for atorvastatin 80 mg was similar to that of atorvastatin 10 mg and placebo.

Mykkänen et al 1999 reported that decreased LDL size is mainly associated with premature CHD, however, it is likely that LDL particle size is not a major risk factor in the elderly. Most of patients (95%) taking atorvastatin reached LDL-C goals of ATP-III (LDL-C < 100 mg/dl) by week-54, all on monotherapy (Hunninghake et al 1999).

AS OVERVIEW: PLEIOTROPIC PROPERTIES OF ATORVASTATIN AND ITS LANDMARK STUDIES

Many beneficial pleiotropic properties (minimally 22) of statins (esp. atorvastatin) have been compiled by the author, and 16 of these 22 effects can be indicated as PPECAAT–GOMMESAAB (Plaque stabilization, improved Platelet and Endothelial function, decreased CD40L, decreased CRP, decreased Atherothrombosis, suppressed Tissue factor, no impaired Glucose tolerance, suppressed Oxidized LDL, decreased MMPs, decreased Endothelin-1, suppressed SMC proliferation and migration, antioxidant effects of AT.M, suppressed ATI-Receptor expression, and increased Apo-B degradation). It is most likely that these non-lipid properties of statin may play pivotal roles in plaque stabilization, improving endothelial and platelet functions which then contribute to an antiatherothrombotic effect and to suppress atherogenesis; hence, inhibition of diabetic vascular complication may pursue.

Importantly, atorvastatin showed potential effects in Phase-1 (lipid lowering effects on native LDL plasma), Phase-2 (beyond lipid lowering effects on ox-LDL in intima-media layer), and Phase-3 (beyond lipid lowering effect in plaque).

Interestingly, atorvastatin has many important properties such as, to reverse the elevated blood pressure response to Angiotensin-II (A-II) infusion and down regulated AT-1 receptor, to promote NO production by decreasing caveolin-1 expression in endothelial cells regardless of the level of extra cellular LDL-C; caveolin-1 may inhibit eNOS activity, to increase blood endothelial progenitor cells (EPCs) in patients with stable CAD; such an effect may contribute to ongoing endothelial repair, and to stabilize vascular oxidant stress via its antioxidant activity of ATM (ATorvastatin hydroxy Metabolite).

The rapid pleiotropic effects of statins on inflammation, endothelial function, and coagulation are likely to be particularly beneficial in patients with acute coronary syndrome (ACS) or type 2 diabetes mellitus (T2DM) with CVD in whom these systems are impaired. The long-term benefit of statin therapy across a spectrum of clinical presentations of CVD is related to both LDL-C reduction and non-lipid pleiotropic properties.

Rapid emergence of effect of atorvastatin on cardiovascular outcomes in CARDS, early (30 days), and late (from 6 months onward) benefits of high-dose atorvastatin on ACS in PROVE IT – TIMI 22, and atorvastatin intensive regimen which produces reductions in both LDL-C and hs CRP in REVERSAL are the new beneficial clinical findings of these three large studies on atorvastatin. In addition, other studies up to 2005 on atorvastatin (AVERT, ASAP, MIRAACL, GREACE, ESTABLISH, and ASCOT-LLA) indicate that atorvastatin reduced the incidence of recurrent ischemic events, and slow the progression of atherosclerotic CHD and also to be beneficial for prevention of coronary and stroke events.

One year later (in 2006), ARMYDA-3 concluded that treatment with atorvastatin 40 mg/day, initiated 7 (seven) days before surgery with cardio pulmonary bypass (CPB), significantly reduced the incident of post operative atrial fibrillation (AF) after elective cardiac surgery with CPB and shortened hospital stay. Recently (2008) ASCOT-LLA-Extension (2.2 years) reported almost all other endpoints (combined fatal CHD or non-fatal MI, etc), risk reductions also remained essentially unchanged (36% RRR in primary events favour of atorvastatin) and in the case of all cause mortality, the RRR of 15% now unachieved borderlines statistical significance.

Most recently the SANDS randomized 3 year trial to compare progression of subclinical atherosclerosis in patients with DM (n = 499) to reach agressive targets (LDL-C < 70 mg/dl and SBP < 115 mg Hg) vs standard targets (LDL-C < 100 mg/dl and SBP < 130 mg Hg). The study revealed that regression of CIMT and greater decrease in LV Mass (LVM) in diabetic patients of the aggressive targets.

Long-term (for a mean period of 3 years) treatment of established CHD patients with atorvastatin (from10 to 80 mg/day, mean: 24 mg/day) to achieve NCEP lipid targets significantly reduces total and coronary mortality, coronary morbidity and stroke, in comparison to patients receiving “usual” medical care. These clinical effects are due to the pleiotropic effects (non-lipid lowering effect) of atorvastatin.

Conclusions – There are minimally 22 beneficial pleiotropic properties belong to atorvastatin in which 16
of them can be indicated as PPECCAT-GOMMESAAB. Early and late clinical benefits of high-dose atorvastatin have been proven in several large studies. The very early benefits (at 30 days) of atorvastatin appeared to be correlated with CRP, and clinical outcomes are likely to be due to the improvements on inflammation, endothelial function, and coagulation. The long-term benefits of atorvastatin therapy are related to LDL reductions as well as to its pleiotropic effects. Due to the high event rates for CVD in diabetes, especially patients with ACS, should be started in-hospital and continued long-term on intensive statin therapy. Patients who have LDL-C levels of < 70 mg/dl (but not lower than 50 mg/dl), hs CRP levels < 1 mg/dl, and blood pressure < 115 mg Hg after atorvastatin therapy have regression of CIMT, greater decrease in LVM, and the lowest rate of recurrent events. In conclusion, the earlier (start early), the lower (aggressive target LDL-C < 70, BP < 115 mg Hg), and the longer (duration of treatment as long as possible) administration of atorvastatin may be the better therapeutic regimen for diabetic patients especially with subclinical cardiovascular complications.

**SUMMARIZED LANDMARK STUDIES ON PLEIOTROPIC PROPERTIES OF ATORVASTATIN**

The reports of several selected Landmark Studies on the pleiotropic properties of atorvastatin are briefly summarized below.

**Atorvastatin VErsus Revascularization Treatment (AVERT)**

Study period is 18 months, n= 164 with atorvastatin, n = 177 with angioplasty. Aggressive lipid lowering with atorvastatin (80 mg/day) in stable CAD patients with results in a mean LDL-C level of 77 mg/dl and cardiovascular benefit was achieved, produced a 36% reduction in total ischemic events, and significantly delayed the time to the first ischemic event (Pitt et al. 1999).

**Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP)**

Study period is 2 years, n= 160 with atorvastatin and 165 with simvastatin. The results are carotid Intima Media Thickness (CIMT) regression in patients with Familial Hypercholesterolemia have implications for clinical practice and aggressive LDL-Cholesterol lowering with high dose Atorvastatin (40-80 mg) resulted in regression of CIMT, whereas conventional LDL-lowering was not (Smilde et al. 2001).

**Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL)**

Study period; 16 weeks, n= 3086, 1548 placebo, 1538 atorvastatin. The conclusion is early intensive lipid-lowering with Atorvastatin (80 mg/day) initiated during acute phase of Unstable Angina or Non-Q wave MI significantly reduces early recurrent ischemic events and atorvastatin reduced the incidence of recurrent ischemic events within 16 weeks (Schwartz et al. 2001, Waters et al. 2002).

![FIGURE-1. Results of GREACE STUDY : n =1600](image-url)

The GREek Atorvastatin and Coronary Heart Disease Evaluation (GREACE)

The GREek Atorvastatin and Coronary heart-disease Evaluation. The aim of this study is to assess the effect of atorvastatin on morbidity and mortality (total and coronary) of patients with established CHD; 1600 consecutive patients were randomized either to atorvastatin (dose from 10 to 80 mg/day, mean 24 mg/day) or to “usual” medical care, with NCEP Goal of LDL-C < 100 mg /dl (Athyros et al. 2002).

Mean period study was 3 years, with primary end points of the study is death, non-fatal myocardial infarction, unstable angina, CHF, revascularization (coronary morbidity: PTCA or CABG) and stroke. The results of GREACE study are summarized in figure 1. Long-term treatment of established CHD with atorvastatin (compared with “usual” care) to achieve NCEP lipid target (LDL-C < 100 mg/dl) significantly reduced several items as mentioned in figure 1, such as total mortality – 43% (p=0.0021), coronary mortality – 47% (p=0.0017), non-fatal MI – 59% (p=0.0001), unstable angina – 52% (p=0.0032), coronary morbidity – 51% (p=0.0011) (PTCA or CABG), CHF – 50% (p=0.021), and stroke – 47% (p=0.034).

The Collaborative Atorvastatin Diabetes Study (CARDS)

This study was a randomized, placebo-controlled trial of 2838 patients with T2DM comparing the effects of atorvastatin, 10 mg daily with dose of placebo on major cardiovascular disease (CVD) in patients with T2DM and no prior CVD history. Study period was 3.9 years but CARDS was terminated almost 2 years earlier than planned. Atorvastatin alters pathogenesis of CVD rapidly, such that the effects on cardiovascular events is apparent within months of initiation of therapy. These findings, and the high event rates for CVD in T2DM, emphasis that we should not delay in assessing the needs of patients with T2DM for such treatment (Colhoun et al. 2005).

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)

This study was a double-blind, randomized trial (n = 654) comparing the effects that 2 different statins (using pravastatin 40 mg or intensive treatment with atorvastatin 80mg), administered for 18 months, had on atherosclerotic burden measured by intravascular ultrasound (IVUS). For patients with CAD, intensive treatment with atorvastatin 80 mg reduced progression of coronary atherosclerosis compared with a more moderate regimen consisting of pravastatin 40 mg (Nissen 2005).

These differences are related to the greater reduction in atherogenic lipoproteins and CRP in intensively treated patients. Post hoc analysis demonstrated that greater reductions in both lipid levels and hs CRP were associated with slower disease progression.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 (PROVE IT_TIMI)

A total of 4162 patients with ACS were recruited in the PROVE IT-TIMI 22 trial. Patients were randomized to intensive statin therapy (atorvastatin 80 mg) or started therapy (pravastatin 40 mg). The composite triple endpoint of death, MI, or rehospitalization for recurrent ACS was determined in each group at 30 days. The composite triple and primary endpoints were assessed in stable patients from six months to the end of study, after censoring for clinical events before six months. Intensive atorvastatin therapy early after ACS leads to a reduction in clinical events at 30 days, consistent with greater early pleiotropic effects. In stable patients, intensive statin therapy provides long-term reduction in clinical events when compared with started therapy. Thus, treatment of patients with ACS should begin in-hospital with high-dose intensive statin therapy to achieve these early clinical benefits and should be continued long-term (Ray et al 2005).

The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA)

This trial determines the timing of cardiovascular risk reduction. In brief, 10305 adult out-patients with well-controlled hypertension and ≥ 3 additional cardiovascular risk factors were randomized to placebo or to a 10 mg/day dose of atorvastatin. The primary endpoint was nonfatal myocardial infarction and fatal CAD. Baseline total cholesterol concentrations were 6.5 mmol/L (Sever et al. 2005).

The trial was halted early after follow-up period of 3.3 years because CAD events in the atorvastatin treatment arm were reduced by 36% compared with placebo (p = 0.0005). In addition, the reduction in CAD events was accompanied by a 27% reduction in stroke events (p = 0.02).
Relative risk reductions in CAD events were large compared with placebo, becoming apparent at 30 days and significant within 3 months, but they tended to decrease with time. Risk reductions in stroke were also apparent at 30 days but remained constant throughout the trial. Significant differences in hazard ratio between atorvastatin and placebo occurred at 2-year follow-up. The differential effects on CAD and stroke events suggest the mechanisms of action for CAD and stroke prevention may be different.

These findings support the two hypotheses that CAD risk factor reduction may be an early benefit of statin treatment, and pleiotropic actions of atorvastatin may have contributed to early protection against CAD.

C-Reactive Protein Levels and Outcomes after Statin Therapy

This study evaluated relationships between the LDL-C and CRP levels achieved after treatment with 80 mg of atorvastatin or 40 mg of pravastatin per day and the risk of recurrent myocardial infarction or death from coronary causes among 3745 patients with acute coronary syndromes (ACSs). This study demonstrated that aggressive use of statin therapy to achieve target levels of both LDL-C and CRP decreases the risk of recurrent myocardial infarction or death from coronary causes among patients with ACS. Patients who had LDL-C levels of less than 70 mg/dl and CRP levels of less than 1 mg/dl after statin therapy had the lowest rate of recurrent events (Ridker et al 2005).

Atorvastatin for Reducing of MYocardial Dysrhythmia After cardiac surgery (ARMYDA-3)

Atrial fibrillation (AF) after cardiac surgery is associated with increased risk of complications, length of stay (LOS), and cost of care (COC). Usually, statin-treated patients who underwent operation had a incidence of post operative AF. Two hundred patients undergoing elective cardiac and cerebrovascular events, and post operative CRP variations. Atorvastatin treatment conferred a 61% reduction in risk of AF (p = 0.017), whereas high postoperative CRP levels were associated with increased risk (p = 0.01). The incidence of major adverse cardiac and cerebrovascular events at 30 days was similar in the2 (two) arms. Importantly, atorvastatin 40 mg/day, given 7 (seven) days before surgery, significantly reduced the incidence of post operative AF. These results are in favour of the therapeutic regimen with the administration atorvastatin minimally 7(seven) days before surgery (Patti et al 2006).

TNT – Subgroup Analysis

Subgroup analysis of the Treating to New Target (TNT) study on the effect of high-dose atorvastatin on hospitalizations for patients with heart failure (HF) reported compared with a lower dose (10mg/d), intensive treatment (80mg/d) with atorvastatin in patients with stable coronary disease significantly reduces hospitalizations for HF. This benefit was most pronounced in patients with a history of HF (Khush et al. 2007).

The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm-Trial (ASCOT-LLA Extension)

An extended observations 2.2 years. It is to determine the cardiovascular benefits of ASCOT-LLA. By the end of ASCOT-LLA, there was a 36% RRR in primary events in favor of atorvastatin (p = 0.0005). In this extended ASCOT-LLA, the Blood Pressure Lowering Arm of the SCOT-Trial (ASCOT-BPLA) compared 2 (two) different antihypertensive treatment strategies on cardiovascular outcomes.

At the end of ASCOT-BPLA, 2.2 years later, despite extensive crossover from and to statin usage, the RRR in primary events among those originally assigned to atorvastatin remained at 36% (p = 0.0001). For almost all other end points, risk reductions also remained essentially unchanged and in the case of all cause mortality, the risk reduction of 15% now achieved borderline statistical significant (p = 0.02). Carry-over benefits from those originally assigned atorvastatin but no longer taking the drug account for unchanged RRRs in most cardiovascular endpoints observed 2 years after ASCOT-LLA closed (Sever et al 2008).

Stop Atherosclerosis in Native Diabetics Study (SANDS)

This study was undertaken to compare progression of subclinical atherosclerotic disease, as evaluated by carotid ultrasound (by measuring CIMT), in American Indians with T2DM (3-year randomized, open-label, blinded-to end point clinical trial), randomly assigned to either aggressive targets (LDL-C < 70 mg/dl plus SBP < 115 mg Hg) or current standard targets (LDL-C < 100 mg/dl plus SBP < 130 mg Hg) (Howard et al. 2008).

The aggressive target LDL-C < 70 mg/dl plus SBP < 115 mg Hg resulted in aggressive in CIMT and greater decreased in left ventricular mass (LVM) of patients with T2DM (figure 2). Clinical events (fatal CHD or stroke, non-fatal MI or stroke, unstable angina, coronary revascularization, and carotid arterial revascularization)
were lower than expected and did not differ significantly between group. Howard et al (2008) suggested that further follow-up is needed to determine whether such improvement will result in lower long-term cardiovascular event rates and costs and favorable risk-benefit outcomes.

![Figure-2 Categorical Changes in CIMT and LVM Index by Treatment Group (SANDS, Howard et al 2008)](image)

**The Great Debate of 2008**

What are the take-home messages from SANDS? The “true believe”, these with a strong apriori conviction that more aggressive pharmacological treatment will reduce future cardiovascular events, and the “therapeutic nihilists”, those who require unequivocal proof before acceptance, are still in great debate (Peterson et al 2008). However, the results of SANDS showed that diabetic patients receiving intensive management had significant regression of carotid intimal medial thickness (CIMT) and reduce left ventricular mass (LVM) compared with those treated with standard therapies. Peterson et al (2008) concluded that SANDS is an important step forward in discovering whether lower goals are truly better primary prevention (Peterson et al 2008).

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