Review Article and Clinical Experience:
PLEIOTROPIC PROPERTIES OF STATINS
(Potential Benefits of “PECA-GOMES” for the Elderly)

Askandar Tjokroprawiro

ABSTRACT

Five major risk factors that modify LDL-Goals are (ATP-III 2001): family history of premature CHD, age (men ≥ 45 years; women ≥ 55 years), hypertension (BP ≥ 140/90 mmHg or on antihypertensive medication), low-HDL-Chol (<40 mg/dl), and cigarette. Thus, it is obvious that the elderly can be included in one risk factor. In ATP-III, Diabetes Mellitus (DM) is regarded as a CHD risk equivalent. HDL-Chol ≥ 60 mg/dl counts as a “protective” factor; its presence removes one risk factor from the total count. Coronary Heart Disease (esp. for the elderly) remains a major therapeutic challenge in the world, and strategies aimed at cholesterol lowering from the primary target of treatment (LDL-Cholesterol < 100 mg/dl) for patients with CHD, DM, and “Double Jeopardy” (DM plus CHD). Decreased LDL size is mainly associated with premature CHD, but it is likely that LDL particle size is not a major risk factor in the elderly. Three categories of risk that modify LDL Chol (mg/dl). Goals are:CHD and CHD risk equivalent (LDL <100), Multiple (2+) risk factors (LDL <130), Zero to one risk factor (LDL <160). Statins (1st Gen: Lovastatin, Simvastatin, Pravastatin; 2nd Gen: Fluvastatin; 3rd Gen: Atorvastatin, Resuvastatin) have the primary effect to reduce LDL-Chol. However, emerging evidence indicate that Statins (f.e Atorvastatin in MIRACL, AVERT, ASAP-Clinical Trials) reduce the incidence of recurrent ischemic events, and slow the progression of atherosclerotic CHD. These clinical effects may be due to the pleiotropic effects (non-lipid mechanism) of Statins. Many of the pleiotropic properties (minimally 20 items) of the Statins have been compiled by the author, and 9 of 20 such beneficial effects can be abbreviated as PECA-GOMES (stimulate Plaque Stabilization, improve Endothelial and Platelet Function, Cellular Immunity, Anti inflammatory Response – No Glucose Intolerance Effect, lower Oxidized LDL, decrease Macrophage number, inhibit Endothelin production, suppress SMC Proliferation and Migration). It is most likely that these non-lipid properties may play pivotal roles in plaque stabilization and in improving endothelial and platelet function which then contribute to an antithrombotic effect. Conclusion: Taken together, the results of several studies indicate that the effects of Statins may extend beyond cholesterol lowering. PECA-GOMES effects of Statins may be of great therapeutical benefits for the elderly. The results of Atorvastatin Trials support the pleiotropic effect of Statins in clinical practice.

Keywords: statin, its pleiotropic effect, potential therapeutical benefits for the elderly

INTRODUCTION

The 2 major mechanisms of activity of statins are as follows: to inhibit the activity of HMG-CoA reductase (reduction of hepatic synthesis of Total Cholesterol=TC and LDL-C), and to enhance receptor-mediated clearance of LDL-C. It is generally accepted that elevated LDL-C is a major cause of CHD, and LDL-lowering therapy reduces risk for CHD. Diabetes Mellitus and CVD have been assumed as “Double Jeopardy” by International Diabetes Federation (IDF, 2001). Hence, ATP-III (May 2001) reported to continue ATP-II (1994) to identify elevated LDL-C (less than 100 mg/dl) as the primary target of Cholesterol-lowering therapy.

The author (2000, 2001, 2002) summarized 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) and resulted in 20 possible pleiotropic atheroprotective effects of statins, which could be categorized into 3, such as: Pre-Endothelium (6 effects), Endothelium (4 effects), and Sub-Endothelium (10 effects). Nine of these 20 effects can be abbreviated as PECA-GOMES (to be described on the next page).

Specifically, it was hypothesized (Pre-Endothelium Effect) that in addition to their beneficial lipid modulating activity, specific metabolites (but not the parent drug) of Atorvastatin and Gemfibrozil might also reduce the atherogenic potential effects of lipoproteins through their anti-oxidant properties (Aviram et al 1998A, 1998B).

Currently, seven statins are available, such as:
1. 1st Generation (Lovastatin, Simvastatin, Pravastatin),
2. 2nd Generation (Fluvastatin), and
3. 3rd Generation (Atorvastatin, Resuvastatin).

Five major risk factors that modify LDL-Goals are (ATP-III 2001): Family history of premature CHD, Age: Men ≥ 45 years – Women ≥ 55 years, Hypertension: ≥ 140/90 mmHg or on antihypertensive...
medication, Low HDL-Chol (< 40 mg/dl), and Cigarette Smoking. Thus, the elderly belongs to one of these risk factors that may represent one risk factor. Diabetes Mellitus is regarded as a CHD risk equivalent. Based on this short description, Statins with its pleiotropic effects beyond lipid lowering may be of therapeutic potential benefits for the elderly. This paper is aimed to give principle understanding on lipid, the roles of Statin, atherosclerosis, SYNDROME-36, and short report of the large trials, such as MIRACL, AVERT, and ASAP.

**LDL-CHESTEROL : THE PRIMARY TARGET OF THERAPY**

The NCEP periodically produces ATP clinical updates as warranted by advances in the science of cholesterol management.

1. ATP I outlined a strategy for primary prevention of CHD in persons with high levels of LDL-C ≥ 160 mg/dl or those with borderline-high LDL-C (130 – 159 mg/dl), and multiple (≥4) risk factors.

2. ATP II affirmed the importance of this approach and added a new feature: the intensive management of LDL-C in persons with established CHD. For CHD patients, ATP II set a new, low LDL-C goal of ≤ 100 mg/dl.

3. While ATP III maintains attention intensive treatment of patients, with CHD, its major new feature in a focus or primary prevention in persons with multiple risk factors, the New Features of ATP III (2001) can be listed as follows (ATP III, 2001):

   - According to ATP-III (2001), classification of LDL, Total and HDL cholesterol (mg/dl) can be summarized as seen in Table 1.
Table 1. ATP III Classification of LDL, Total, and HDL Cholesterol mg/dl (ATP III 2001)

<table>
<thead>
<tr>
<th>Lipid/Lipoprotein Metabolism</th>
<th>LDL Cholesterol</th>
<th>Total Cholesterol</th>
<th>HDL Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;100</td>
<td>&lt;200</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Near optimal/above optimal</td>
<td>100 – 129</td>
<td>200 – 239</td>
<td>60</td>
</tr>
<tr>
<td>Borderline high</td>
<td>130 – 159</td>
<td>Borderliner high</td>
<td></td>
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<tr>
<td>High</td>
<td>160 – 189</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>≥190</td>
<td>≥240</td>
<td>≥60</td>
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</tbody>
</table>

To reach NCEP target, several drugs affecting lipoprotein metabolism mentioned below (Table 2) can be used as a guideline in daily practice.

Table 2. Drugs Affecting Lipoprotein Metabolism (ATP III 2001)

<table>
<thead>
<tr>
<th>Drug Class, Agents and Daily Doses</th>
<th>Lipid/Lipoprotein Effects</th>
<th>Side Effects</th>
<th>Contraindications</th>
<th>Clinical Trial Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG CoA reductase Inhibitors (Statins)*</td>
<td>LDL ↓18-55%</td>
<td>Hyperlipidemia, Mypathy, Increased liver Enzymes</td>
<td>Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs†</td>
<td>Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality</td>
</tr>
<tr>
<td></td>
<td>HDL ↑5-15%</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>TG ↓7-30%</td>
<td></td>
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<tr>
<td>Bile acid Sequestrants‡</td>
<td>LDL ↓15-30%</td>
<td>Hyperlipidemia, Constipation</td>
<td>Absolute: • Dysbeta-lipoproteinemia Relative: • TG &gt;400 mg/dl</td>
<td>Reduced major Coronary events, and CHD deaths</td>
</tr>
<tr>
<td></td>
<td>HDL ↑3-5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TG No change</td>
<td>Decreased absorb of other drugs</td>
<td></td>
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<tr>
<td>Nicotinic AcidΨ</td>
<td>LDL ↓5-25%</td>
<td>Hyperlipidemia, Hyperglycemia, Hyperuricemia (gout), Upper GI distress Hepatotoxicity</td>
<td>Absolute: • Chr. Liver disease</td>
<td>Reduced major Coronary events, and possibly total mortality</td>
</tr>
<tr>
<td></td>
<td>HDL ↑15-35%</td>
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<td></td>
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<tr>
<td></td>
<td>TG ↓20-50%</td>
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<tr>
<td>Fibric AcidΩ</td>
<td>LDL ↓6-20% (may be increased in patients with high TG)</td>
<td>Hyperlipidemia, Mypathy, Unexplained non-CHD deaths in WHO study</td>
<td>Absolute: • Severe renal disease</td>
<td>Reduced major Coronary events</td>
</tr>
<tr>
<td></td>
<td>HDL ↑10-20%</td>
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<td>TG ↓20-50%</td>
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PLEIOTROPIC EFFECTS OF STATINS: PROMISING TREATMENT FOR Atherosclerosis

Minimally 20 pleiotropic effects of Statins can be compiled as seen in TABLE-3 (Tjokroprawiro 2002). Besides, Hill et al (2001) demonstrated that Atorvastatin prevented the enhanced uptake of Ca^{2+} by SR and non-SR Ca^{2+} in diabetic dyslipidemic pigs. They hypothesized that by preventing the uptake of Ca^{2+} into intracellular Ca^{2+} stores, Atorvastatin may help prevent Ca^{2+} overload of intracellular organelles, and it is most likely that vasodilatation may pursue.

The author (2002) summarized 9 PECA-GOMES pleiotropic effects of Atorvastatin which stands for:
- **P**laque Stabilization (to promote)
- **E**ndothelial & Platelet Function (to improve)
- **C**ellular Immunity (immunosuppressive effect)
- **A**nti Inflammation (to suppress inflammatory response)
- **G**lucose Intolerance (to improve)
- **O**xidation of LDL (to inhibit)
- **M**acrophage number reduction
- **E**ndothelin Product inhibitor
- **S**MC migration and proliferation (to inhibit)

Beneficial effects of PECA-GOMES can be obtained by Statins 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), respectively, as follows: 10 mg (-41% LDL-C reduction), 20 mg (-44%), 40 mg (-50%), and 80 mg (-61%). Decreased LDL size is mainly associated with premature CHD, but it is likely that LDL particle size is not a major risk factor in the elderly (Mykkanen et al 1999). 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 1998).

LARGE CLINICAL TRIALS ON PLEIOTROPIC EFFECTS OF STATINS

The reports of 3 selected Large Clinical Trials on the pleiotropic effects of Statins have been published and each is shortly described below.

I. AVERT (Pitt et al 1999): Atorvastatin VErsus Revasculariation Treatment (Study period: 18 months, n= 164 with Atorvastatin, n= 177 with Angioplasty). Conclusion:
Over the 18-month study period, aggressive lipid lowering with Atorvastatin (80 mg/day) in Stable CAD patients:
1. results in a mean LDL-C level of 77 mg/dl and cardiovascular benefit was achieved.  
2. produced a 36% reduction in total ischemic events  
3. significantly delayed the time to the first ischemic event

II. MIRACL (Schwartz et al 2001): Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (Study period; 16 weeks, n= 3086, 1548 Placebo, 1538 Atorvastatin). Conclusion:  
1. 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  
2. Atorvastatin reduced the incidence of recurrent ischemic events within 16 weeks

III. ASAP (Smilde et al 2001): Atorvastatin versus Simvastatin on Atherosclerosis Progression (Study period: 2 years, n= 141 with Atorvastatin and 139 with Simvastatin)  
1. Carotid Intima Media Thickness (CIMT) regression in patients with Familial Hypercholesterolemia have implications for clinical practice  
2. Aggressive cholesterol lowering with high dose Atorvastatin (40-80 mg) resulted in regression of CIMT, whereas conventional LDL-lowering was not.

Taken together, such clinical evidences and trials shortly described above supported that Atorvastatin possessed clinical benefits beyond its cholesterol lowering capability.

1. MIRACL (Schwatz et al 1998): Reduced the incidence of recurrent ischemic events within 16 weeks  
2. AVERT (Pitt et al 1999): over the 18-months study period produced a 36% reduction in total ischemic events  
3. ASAP (Smilde et al 2001): High dose of Atorvastatin resulted in regression of CIMT within 2 years

NEW INSIGHTS INTO THE ROLES OF GENE REGULATOR  
(The Promising Treatment for Dyslipidemia and Atherosclerosis)

I. Acton et al (1999)  
As a consequence of the discovery of the HDL-receptor SR-B1, important progress has been made in the understanding of HDL metabolism and its role in Reverse Cholesterol Transport (“The Hero Pathway”). SR-B1 is strongly suggested has important role in the pathogenesis of atherosclerosis. Hence, SR-B1 modulator or activator by using gene-based therapy might be appealing therapeutic target for Coronary Heart Disease in Human (SR-B1 Modulator or Activator).

II. Brewer (2000)  
Brewer (2000) postulated the promising treatment for dyslipidemia and atherosclerosis, such as:  
SR-A and CD36 Blockers : to inhibit oxidized-LDL uptake  
ACAT-1 Inhibitors : to suppress foam-cell formation  
ABCA1 Activators : to activate cholesterol and phospholipids cellular efflux  
LCAT Modulators : to modulate the maturation of Nascent HDL

III. Ferber (2000)  
The researchers found that LG268 (Reximoid) ups production of ABCA1 in cells of the intestinal wall causing the lipid to pass right through the intestine without being absorbed. It is postulated that there are possible 3 ways to lower cholesterol. The drug LG268 fasters cholesterol elimination from the body by stimulating ABCA1-mediated export of the lipid from macrophages and intestinal cells and also by inhibiting CYP7A1, a key enzyme needed for bile acid formation by liver cells

IV. Van Heek (2001)  
Van Heek et al (2001) demonstrated that Ezetimibe, a potent cholesterol absorption inhibitor, normalized combined dyslipidemia in obese hyperinsulinemic Hamsters, and may be an effective therapy for ameliorating such a dyslipidemia in obese insulin-resistant and/or Type-2 Diabetic Humans.

V. Fruchart (2000)  
There are three distinct PPARs, α, β (δ), and γ, each encoded by a separate gene displaying different tissue and developmental expression patterns, have been identified. PPARα is preferentially in liver, heart, and kidney, while PPARγ is expressed at high level in adipose tissue. Activation of PPARα increases the catabolism of Fatty Acids at a different levels in the liver, and shows several effects, such as (Fruchart 2002):  
1. Increases Fatty Acid uptake and enhances β-oxidation  
2. Effects on Triglyceride rich lipoproteins through stimulation of LPL and repression of Apo-CIII expression  
3. Effects on HDL: dependent upon the regulation of Apo-A1 and Apo-AII.
PPARα and PPARγ are both expressed in human macrophages, whereas they have anti-inflammatory effects.

1. Activation of PPARγ may promote foam-cell formation by inducing expression of the macrophage scavenger receptor CD36.
2. PPARα and PPARγ activators induce the expression of the ABCA1 gene, a transporter that controls Apo A1-mediated cholesterol efflux from macrophages. This is due to an enhanced expression of the liver-X-receptor α, and oxysterol-activated nuclear receptor which induces ABCA1-promoter transcription.

CONCLUSION: Present and Future

Present

1. Statins (HMG-Co Reductase Inhibitors) and Fibrates (esp. Fenofibrate, PPAR Activator) play pivotal roles to counteract “The Villain (Atherogenic) and The Hero (Atheroprotective) Pathways”, respectively. In addition, 20 pleiotropic effects belong to statins may support the LDL-C goal (the primary target of therapy, ATP-III 2001) to reduce the risk for CHD.
2. Most of patients (95%), taking Atorvastatin (monotherapy) reached LDL-C goal (LDL<100 mg/dl) by week 54.
3. Nine of 20 pleiotropic effects of Atorvastatin can be abbreviated as PECA-GOMES (Plaque stabilization, Endothelial and platelet function, Cellular Immunity, Anti – Inflammation – Glucose intolerance, Oxidized-LDL, Macrophage number reducer, Endothelin product inhibitor, and SMC migration and proliferation inhibitors).

Hence, these 9 (nine) properties (PECA-GOMES) of Statins are most likely of great therapeutic potential benefits for the elderly.

Future

New insights into the Roles of Gene Regulating Lipoprotein Metabolisms and other research products may yield several promising drugs in the treatment of dyslipidemia and atherosclerosis, f.e:

1. CD36 Blocker
2. SR-A Blocker
3. ACAT1 Inhibitor
4. ABC1 Activator
5. LCAT Modulator
6. SR-B1 Modulator
7. LG-268
8. PPAR Activator
9. Ezetimibe
10. Etc.

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Pleiotropic Properties of Statins


