UNIT NO. 2

RATIONALE FOR COMBINATION THERAPY IN LIPID MANAGEMENT STRATEGY

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ABSTRACT

Due to the increasing prevalence of obesity and Type II diabetes mellitus (DM), mixed dyslipidemia characterised by high triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C) and small dense low-density lipoprotein cholesterol (LDL-C) particles is becoming increasingly common [1].

The primary goal of lipid treatment is to reduce LDL-C to target levels. However, residual cardiovascular risk remains even after achievement LDL-C goal in high risk patients on statin treatment.

This residual risk may be due in part to persistently low HDL-C and high TG. Combination therapy of statins with fibrates, niacin or prescription omega-3 fatty acids may reduce this risk.

Keywords: Dyslipidemia; Combination Therapy; Residual cardiovascular risk

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INTRODUCTION

Mixed dyslipidemia (atherogenic dyslipidemia) characterised by high TG, low HDL-C and small dense LDL-C particles is the most common dyslipidemia in metabolic syndrome and Type II DM. ATP III recognises low HDL-C as a major risk factor and elevated TG and small dense LDL-C as emerging risk factors for cardiovascular disease (CVD) [2].

Patients with mixed dyslipidemia are at higher risk for CVD. In a post-hoc analysis of the 4S trial[3], patients in the lowest HDL-C (< 39mg/dL) and highest TG (> 159mg/dL) quartiles had the highest incidence of CVD in the placebo group and these patients had the largest benefit when treated with statin compared to the general 4S population. It is therefore important to consider additional therapies to reduce the CVD risk associated with mixed dyslipidemia.

PREVALENCE OF MIXED DYSLIPIDEMIA

With the adoption of Western lifestyles and increasing affluence, the twin global pandemics of obesity and Type II DM are on the rise in Asia. In Singapore, the prevalence of DM is about 9% [4]. Almost 50% of all adults in Singapore have a BMI above 23 kg/m^2 and 14% have a BMI of more than 27.5kg/m^2 [5]. Consequently, mixed dyslipidemia is fast becoming the predominant lipid abnormality in our population.

RESIDUAL CARDIOVASCULAR RISK

Statins have been shown to reduce CVD mortality in both primary and secondary prevention, mainly by lowering LDL-C [6, 7]. However, significant residual cardiovascular risk remains. In a meta-analysis by Baigent et al, 14.1% of patients treated with a statin, had further or recurrent CVD events over a 5-year period, and this risk was even higher in patients with established coronary artery disease (CAD) or CAD risk equivalents, such as DM [8].

Hence, there is a need for additional treatment of mixed dyslipidemia in high risk patients already on statins at target LDL-C. Lifestyle modification which includes interventions aimed at weight loss through diet and exercise, followed by weight maintenance that employs low saturated fat intake remains the cornerstone of management [9]. In high risk patients, adjunctive pharmacotherapy with fibrates, niacin or prescription omega-3 fatty acids may be beneficial.

While there are clearly defined targets for LDL-C (< 100mg/dL for high risk and < 70mg/dL for very high risk) 10, no specific targets for HDL- C and TG have been determined in clinical trials. The following have been suggested as desirable therapeutic targets: HDL-C > 40mg/dL (men) and > 50mg/dL (women) and TG < 150mg/dL.

FIBRATES

Fibrates are peroxisome proliferator-activated receptor (PPAR) alpha agonists. PPAR alpha is a nuclear transcription factor which binds to retinoid X receptor (RXR) to modulate gene expression that influences fatty acid oxidation, lipid metabolism and inflammation[11]. Fenofibrate and gemfibrozil decreases TG's by 20 to 30% and increases HDL-C by 5 to 10%, depending on baseline levels [12, 13].

In the Helsinki Heart Study[12], men with TG > 204mg/dL, HDL-C < 40mg/dL and body mass index (BMI) > 26kg/m^2 who were treated with gemfibrozil had a 78% relative risk reduction in CAD. Similarly, in the FIELD study [13], the greatest effect of fenofibrate on CVD risk was observed in subjects with mixed dyslipidemia, where there was a 27% relative risk reduction.

While there is efficacy data to suggest that combination treatment with statin and fibrate may have additional CVD benefit, until recently, there is no clinical outcome study to test this hypothesis. There is also a safety concern with the addition of fibrates to statins, as they both have skeletal muscle adverse

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effects. When used in combination with statins, the number of rhabdomyolysis reports was approximately 15 times lower for fenofibrate than for gemfibrozil [14]. Overall, it is much safer to combine fenofibrate with statin than with gemfibrozil.

The ACCORD-Lipid trial [15] published last year evaluated CVD outcomes in 5000 diabetic subjects randomised to receive either simvastatin plus fenofibrate or simvasatin plus placebo, in which all subjects were at LDL-C goal. The results showed that fenofibrate plus statins did not reduce CVD events more than statins alone. However, in the subgroup of patients with baseline levels of TG $\geq$204 mg/dL and HDL -C $\leq$34 mg/dL, there was a trend towards lower CVD event rates.

To further define the role of combination treatment with statin and fibrate, the FDA advisory panel recently recommended that a new trial of fenofibrate in diabetic patients who have met their LDL-C goal on a statin but still have high TG and low HDL -C, where patients should be randomised to fenofibrate plus a statin or placebo plus a statin should be conducted.

The combination of statin with ABT-335, which is the choline salt of fenofibrate is also currently being evaluated in a number of surrogate and clinical end-point trials.

NIACIN

Niacin is the most effective agent currently available for raising HDL-C. In addition to increasing HDL-C (20 to 25%), it also lowers LDL-C (10 to 15%), TG (15 to 25%) and lipoprotein (a)(15 to 20%) [16]. Niacin raises HDL-C by stimulating apo A1 production in the liver. The immediate release formulation of niacin was frequently associated with cutaneous flushing which limited its use. The introduction of extended release formulations (ER-niacin) and recently, formulations which contain the prostaglandin D2 receptor antagonist (laropiprant) has significantly reduced niacin-induced cutaneous flushing and improved its tolerability.

The Coronary Drug Project [17] is the only niacin monotherapy outcomes study, and was done in 1119 men with a previous MI randomised to niacin (immediate release formulation) or placebo. At the end of 5 years the niacin group had a 14% reduction in coronary death and non-fatal MI, and at the end of 9 years, an 11% reduction in all-cause mortality, due to a reduction in CAD mortality by 12%.

The HATS trial [18] was a randomised placebo controlled study which enrolled 160 patients with CAD and used quantitative coronary angiographic stenosis as the primary endpoint. It showed that in the placebo group, coronary stenosis progressed by 3.9% while in the simvastatin-niacin combination, there was regression by 0.4%.

The ARBITER-6 HALTS trial published in 2009 [19] was a randomised study which enrolled 360 patients with CAD and used regression of carotid-intima media thickness as the primary endpoint. It showed that while regression in the carotid-intima media thickness was seen in the simvastatin-niacin combination, no change was seen in the simvastatin-ezetimibe group.

However, the AIM-HIGH trial, which was the first randomised clinical outcome trial to compare ER-niacin combined with simvastatin versus simvastatin alone in 3,300 patients, with known CVD and mixed dyslipidemia was halted prematurely this year, 18 months ahead of schedule, because ER-niacin offered no additional protection against CVD events compared to simvastatin monotherapy in this patient population.

The HPS-2-THRIVE which is another large randomised clinical outcome trial comparing ER-niacin (plus laropiprant) combined with simvastatin versus simvastatin alone in 20,000 patients with known CVD (albeit a higher risk population than AIM-HIGH) and who are at LDL-C target is still ongoing, with results expected in 2013. It is hoped that the results of this trial would clarify the role of combination treatment of statin with niacin in high risk patients with mixed dyslipidemia.

CETP INHIBITORS

CETP inhibitors are a new class of drugs for raising HDL-C. CETP facilitates transfer of cholesterol from HDL to LDL and VLDL. Inhibition of CETP has been shown to increase HDL-C by 80 to 138% [20, 21].

The ILLUMINATE trial [20] was the first randomised clinical outcome trial with a CETP inhibitor. It compared torcetrapib combined with atorvastatin versus atorvastatin alone in 15,000 patients with known CVD, but was halted prematurely because of an increased CVD mortality in subjects who received torcetrapib, attributed to an off-target effect of torcetrapib on raising the blood pressure.

There has been renewed interest in CETP inhibitors after results of the DEFINE trial were published last year [21]. This was a randomised safety and efficacy trial which compared a new CETP inhibitor anacetrapib combined with simvastatin versus simvastatin alone in 1,623 patients with known CVD. The results showed that subjects who received anacetrapib had a 138% increase in HDL-C and a 36% decrease in LDL-C, but no increase in the blood pressure or CVD mortality.

The REVEAL HPS-3 TIMI 55 trial is an ongoing large randomised clinical outcome trial in 15,000 patients with known CVD to assess whether the combination of anacetrapib with simvastatin would reduce CVD events compared to simvastatin alone, with results expected in 2015.

PRESCRIPTION OMEGA-3 FATTY ACID

Omega-3 fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] are components of fish oil and the Mediterranean diet, and have been used to lower TG. Omega-3 fatty acids at pharmacologic doses (>2g/day) reduce VLDL concentration by unknown mechanisms. Fish oil reduces TG by

30%, but has minimal effects on other lipoproteins [22].

Although a recent Japanese study in patients with hypercholesterolemia reported a 19% reduction in CVD events, the data remain inconclusive and their clinical efficacy appears to be related to non-lipid effects [23].

CONCLUSIONS

The mixed dyslipidemia (atherogenic dyslipidemia) associated with DM and the metabolic syndrome (high TG, low HDL-C and small dense LDL-C) contributes to CVD risk. The primary goal of lipid therapy is to reduce LDL-C to targets with statins.

However, residual CVD risk remains after achievement of LDL-C goal in patients with CVD who are on statin treatment. This residual risk may be due to persistently low HDL-C and elevated TG. Combination lipid therapy of statins with fibrates, niacin or omega-3 fatty acids may reduce this risk, especially in high risk individuals.

To date, clinical trials are yet to demonstrate that combination lipid therapy could provide additional reduction of CVD events in high risk patients, compared to statin alone.

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LEARNING POINTS

- **Mixed dyslipidemia (high TG, low HDL-C and small dense LDL-C) is becoming increasingly common due to the increased prevalence of DM and metabolic syndrome, and is associated with a high CVD risk.**
- **The primary goal of lipid therapy is to reduce LDL-C to targets with statins [< 100mg/dL for high risk (established CAD or CAD risk equivalent e.g DM) and < 70mg/dL for very high risk (e.g acute coronary syndrome)].**
- **Treatment of mixed dyslipidemia may reduce the significant residual CVD risk that remains even after achievement of LDL-C goal in high risk patients on statin treatment.**
- **Lifestyle modification which includes interventions aimed at weight loss through diet and exercise, followed by weight maintenance that employs low saturated fat intake remains the cornerstone of management of mixed dyslipidemia.**
- **Combination lipid therapy is indicated in high risk patients on maximal doses of statins who have achieved the LDL-C goal, but have persistently low HDL-C and/or high TG, in spite of lifestyle modification.**
- **The choice of which drug to add on to the statin depends on which is the predominant lipid abnormality: If low HDL-C is predominant, niacin could be added; If high TG is predominant, either omega-3 fatty acids or fibrate could be added.**