

## **Final Draft**

# **Best Practice Guidelines for Hypercholesterolemia**

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**For the Caribbean Cardiac Society**

### ***Preamble***

The basic principle underlying the issuance of guidelines or best practice statements is that the practitioner should be made aware of the importance of changes that have occurred within the medical literature and which impacts on the best practice of medicine so that he may be able to use these guidelines to improve patient care and management. Chronic Non Communicable Diseases have taken over from Infectious Diseases as the number one disease entity in the Caribbean region. The ICSHIB study along with the Jamaican National Healthy Lifestyle Survey has identified Obesity, Hypertension, Hyperlipidaemia and Diabetes as significant problems within the region. These studies also revealed that our females carry a disproportionately higher disease burden as they are more obese, have a higher prevalence of hypertension, diabetes and hyperlipidaemia and thus are at greater risk for the development of atherosclerotic vascular disease.

### ***Introduction***

The rationale for an aggressive approach to prevention of cardiovascular disease is due to the following observations:

- Cardiovascular disease has been the leading cause of death within the Caribbean region.
- Atherosclerosis is identified as the underlying pathology in both coronary artery disease, stroke and peripheral vascular disease.
- Sudden death occurs not infrequently from myocardial infarction and stroke.
- Cardiovascular disease is related to identifiable physiological factors and lifestyle.

- Risk factor eradication has been shown unequivocally to reduce cardiovascular morbidity and mortality. For example: smoking cessation, cholesterol reduction and lifestyle modifications.

In December 2002 the Adult Treatment Panel III (ATP III) recommendations of the National Council on Cholesterol Education Panel (NCEP) was published. This American guideline was followed by the Third Joint Task Force presentation of the European guidelines in September 2003. Both set of guidelines are relatively similar apart from minor differences such as the use of different risk score methods. Since that time seven major trials on lipid therapy have been published and this has prompted a call for the revision of these guidelines and leaves us to ask “How low should we go in reducing cholesterol levels?” We will briefly review these studies later and provide our recommendations for therapy.

### ***Classification***

The efforts at prevention are most successful when directed to those individuals who are at highest risk to develop disease. Like the ATP III guidelines, we have chosen to classify patients into the following risk categories:

- Individuals at very high risk. This includes patients with coronary artery disease or those who are coronary risk equivalent. Conditions classified as coronary risk equivalent includes Type 2 Diabetes Mellitus, Type 1 Diabetes Mellitus with microalbuminuria, atherosclerotic cerebrovascular disease and peripheral vascular disease.
- Moderately high risk category
- Moderate risk category
- Low risk category

Patients at moderate or high risk who have 2+ risk factors are also subdivided according to the Framingham Risk Score so as to triage them into three level of 10-year risk for hard Coronary Heart Disease (CHD) events (myocardial infarction + CHD death):

- Those with a >20% risk.

- Those with a 10 – 20% risk
- Those with a <10% risk

Those with 2+ risk factors and a 10-year risk of 20% of CHD are placed in the high risk category. Those with 2+ risk factors and a 10-year risk of CHD of 10 - 20% are placed in the moderately high risk category. Those with 2+ risk factors and a <10% 10-year risk of CHD are placed in the moderate risk category and those with 0 -1 risk factor are classified as low risk.

### ***Review of Clinical Trials***

The following clinical trial results will be summarized.

1. Heart Protection Study ( HPS MRC/BHF STUDY)
2. Progressive Study of Pravastatin in the Elderly at Risk ( PROSPER)
3. Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA)
4. Pravastatin or Atorvastatin Evaluation and Infection Therapy in Myocardial Infarction (PROVE IT – TIMI 22)
5. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease – Treating to New Targets ( TNT)
6. Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial
7. A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) Trial

The MRC/BHF Heart Protection Study was a randomized placebo controlled multicenter trial of 20,536 UK adults with established coronary artery disease, other arterial diseases or diabetes mellitus. The patients were randomly allocated to either simvastatin 40 mg or a matching placebo. The primary outcomes were mortality, fatal or non fatal vascular events.

The results showed that all cause mortality was significantly reduced in the simvastatin treated patients versus the placebo group (12.9% vs. 14.7%; p=0.0003). Coronary death rate was significantly reduced in the simvastatin group (RRR 18%; p=0.0005). There were also highly significant reductions in first event rate for nonfatal myocardial

infarction or coronary death, for nonfatal or fatal stroke and for coronary or non coronary revascularization ( $p < 0.0001$ ). The reduction of major vascular events were not significant in the first year but was found to be highly significant in the subsequent years under observation. The proportional reduction in event rates was similar in each subcategory studied. The simvastatin group showed improvement in event rates whether they had or were without coronary disease, cerebrovascular disease, peripheral arterial disease, diabetes, men or women, those either under or over 70 years at entry, or even those that presented with LDL cholesterol below 3.0 mmol/l or total cholesterol below 5.0 mmol/l.

The conclusion of this study was that the addition of simvastatin to existing treatments safely produces substantial benefits for a wide range of high risk patients, irrespective of their initial cholesterol concentration. This study demonstrated the effectiveness and benefits of cholesterol reduction in all subgroups. Subgroup analyses of the diabetic population in the HPS study confirmed that the benefits of cholesterol reduction extended to the high risk diabetic group even if they do not already have manifest coronary artery disease or high cholesterol concentrations.

The Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER trial) evaluated 5,804 high risk elderly patients between the ages of 70 and 82 years who had pre-existing vascular disease whether coronary, cerebral or peripheral. Their total cholesterol was between 4.0 to 9.0 mmol/l and they were randomized to either pravastatin 40 mg per day or a matching placebo. The average follow up was 3.2 years and the primary endpoints were a composite of coronary death, nonfatal myocardial infarction and fatal or nonfatal stroke. The primary endpoint was reduced from an absolute 16.1% in the placebo arm to 14.1% in the pravastatin arm ( $p = 0.014$ ). There was a significant reduction in combined cardiovascular death and myocardial infarction and cardiovascular death alone but no significant change in stroke. There was a safety concern in this study as there was an increased rate of new cancer in the pravastatin arm but a subsequent meta-analysis of statin randomized placebo controlled trials showed that treatment with pravastatin or any statin was not associated with an excess risk of cancer (hazard ratio 1.02,  $p = 0.32$ ). This was the first major study to show the benefit of cholesterol reduction in high risk elderly patients.

Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) was a randomized trial of 10,305 hypertensive patients with a total cholesterol of <251 mg/dl. The patients were randomized to atorvastatin 10 mg per day versus placebo with an aim to follow up for 5 years. This trial was stopped prematurely after 3.3 years because of significant treatment outcomes in the atorvastatin treatment arm. There was a 36% relative risk reduction in combined fatal and nonfatal myocardial infarction (p=0.0005) and a 45% relative risk reduction in nonfatal myocardial infarction alone. These event reductions were observed regardless of the baseline cholesterol results, again demonstrating the usefulness of statin therapy. The mean LDL cholesterol at baseline was 133 mg/dl and this was reduced by atorvastatin to 90 mg/dl at the end of follow up.

Pravastatin or Atorvastatin Evaluation and Infection Therapy in Myocardial Infarction (PROVE IT – TIMI 22) trial set out to evaluate whether statins are effective in reducing events in patients with the acute coronary syndrome and whether intensive LDL lowering would achieve a greater reduction in clinical events over standard LDL lowering therapy. This was a multi-center double blind randomized 2x2 factorial design study of 4,162 patients who had acute coronary syndrome and were enrolled <10 days from initial presentation. They were given standard medical therapy including aspirin and randomized to pravastatin 40 mg per day as standard LDL lowering therapy or atorvastatin 80 mg per day as intensive therapy. The primary endpoint was death, myocardial infarction, documented unstable angina requiring hospitalization, revascularization >30 days after randomization or stroke.

There was a significant reduction in LDL cholesterol in both groups with pravastatin achieving a median reduction of 95 mg/dl and atorvastatin 62 mg/dl. The intensive group reduced the risk of all cause mortality or major cardiac events by 16% (p=0.005) and the benefits emerged within 30 days post acute coronary syndrome event and there was continued benefit observed throughout the 2.5 years of follow-up. The benefits were consistent across all cardiovascular endpoints and most clinical subgroups except stroke.

Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease – Treating to New Targets ( TNT) trial analyzed 10,003 patients with stable coronary artery

disease who were aged between 35 and 75 years. The baseline LDL cholesterol ranged from 130 mg/dl to 250 mg/dl. All patients received atorvastatin 10 mg during a 8 week open labeled run in period and they were then randomized to atorvastatin 80 mg or atorvastatin 10 mg per day. The primary endpoint was a major cardiovascular event and this was defined as coronary heart disease death (CHD), nonfatal myocardial infarction, resuscitated cardiac arrest, and fatal or nonfatal stroke. Secondary endpoints were major coronary events, cerebrovascular events, hospitalization for congestive heart failure (CHF), all cause mortality, peripheral arterial disease, any cardiovascular event or any coronary event. The follow-up period was 5 years.

The primary composite endpoint of CHD death, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke was lower in the high dose atorvastatin group at a mean follow-up of 4.9 years (RRR 22%,  $p < 0.001$ ). The individual components of both the primary and secondary endpoints were lower or tended to be lower in the high dose group compared to the low dose group. The high dose group however had elevations in liver transaminase levels; treatment related adverse effects and study drug discontinuation due to adverse events suggesting that there may be a price to pay for aggressive lowering of LDL cholesterol using high dose statins.

The results of both PROVE-IT and TNT do suggest that aggressive lipid lowering to LDL levels  $< 75$  mg/dl ( $< 1.8$  mmol/l) reduces cardiovascular events in patients with unstable and stable coronary artery disease.

Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial was a randomized, double-blind, multicenter trial of aggressive lipid lowering using atorvastatin 80 mg per day compared to a moderate lipid lowering strategy using pravastatin 40 mg per day. 502 symptomatic coronary artery disease patients with elevated LDL cholesterol at baseline were subjected to intravascular ultrasound analysis at baseline and at 18 month follow-up. The primary endpoint was the percentage change in atheroma volume between baseline and follow-up examinations. The secondary endpoint was the absolute change in atheroma volume and the change in percent obstructive volume.

The median percentage change in atheroma volume was 2.7 for the moderate lipid lowering group versus -0.4 in the intensive lipid lowering group ( $p=0.02$ ). The median change in total atheroma volume was 4.4 cubic mm in the moderate lipid lowering group compared to -0.9 cubic mm in the intensive lipid lowering group ( $p=0.02$ ). The median percentage change in obstruction volume was 1.6 in the moderate group versus 0.2 in the intensive group ( $p=0.0002$ ). These results suggest that an aggressive lipid lowering strategy halts the progression of atherosclerosis.

A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) Trial. The goal of this trial was to evaluate the effect of treatment with intensive statin therapy on intravascular ultrasound with a hypothesis that high intensity rosuvastatin therapy (40 mg per day) will result in extremely low LDL cholesterol levels and elevate HDL cholesterol levels, and that this effect will result in regression of atherosclerosis. 349 patients were subjected to IVUS examination in this prospective, blinded open labeled trial. The primary endpoints were the change in percent atheroma volume and the change in nominal atheroma volume in the 10 mm sub-segment with the greatest disease severity at baseline. The secondary endpoint was a change in normalized total atheroma volume for the entire artery.

Rosuvastatin reduced the baseline mean LDL cholesterol from 130.4 mg/dl to 60.8 at follow-up, a mean reduction of 53.2% ( $p<0.001$ ). The mean HDL cholesterol increased from 43.1 mg/dl to 49.0 mg/dl, an increase of 14.7% ( $p<0.001$ ). The mean change in percent atheroma volume for the entire vessel was -0.98% with a median of -0.79% ( $p<0.001$ ). The mean change in atheroma volume in the most diseased 10 mm sub-segment was -6.1 cubic mm, with a median of -5.6 cubic mm ( $p<0.001$ ). The change in total atheroma volume showed a 6.8% median reduction with a mean reduction of -14.7 cubic mm and a median of -12.5 cubic mm ( $p<0.001$ ). Adverse events were infrequent. These results confirmed significant regression in all 3 pre-specified IVUS measures of disease burden thus showing that lowering of LDL cholesterol to low levels while raising HDL cholesterol can initiate regression of atherosclerosis.

## ***Recommendations for the Management of CHD Risk Factors***

### **(1) Behavioral Risk Factors**

Modification of behavioral status and changes in lifestyle are important necessary adjustment to be adopted. Negative emotions such as anger, depression and hostility have to be recognized as important barriers. The physician should take time to explain the need for and effectiveness of lifestyle changes. This will require a therapeutic alliance with the patient so that the patient understands the importance of behavior, health, exercise and disease. These efforts should be complimented by an effective follow up program which may involve other members of staff such as nurses, social workers and/or physiotherapist.

### **(2) Healthy Food and Eating Habits**

Healthy food choices are an integral part of a total risk management strategy. Advice should be given by the care giver or with the assistance of a nutritionist. Emphasis on a proper diet is essential and the education that a proper diet will reduce risk by weight reduction; assist in lipid management, the lowering of blood pressure and glucose control in the diabetic or those with impaired glucose tolerance. The diet should consist of:

- no more than 30% of energy intake as total fat
- saturated fat intake should not exceed a third of total fat intake
- cholesterol intake should be less than 300 mg/day
- complex carbohydrates should partly replace saturated fats

### **(3) Exercise**

Exercise should be encouraged. Steady and continuous physical activity of at least one half hour 3 times per week is the minimum requirement. However individuals should be

encouraged to exercise 4 to 5 times per week for 45 minutes to attain a target of 60 – 75% of the average maximal heart rate for age.

#### **(4) Lipid Control**

LDL cholesterol remains the corner stone of dyslipidaemic therapy. There is a very strong association with atherosclerosis and CHD events. There is a log-linear relationship between LDL cholesterol levels and risk of CHD. Epidemiological studies have estimated that a 10% increase in LDL cholesterol will result in a 20% increase in CHD risk. Despite the recognition of this fact, most patients with elevated LDL cholesterol are untreated. When other risk factors are present, the 10-year risk of CHD events is increased substantially.

Recent randomized clinical trials have demonstrated the effectiveness of cholesterol reduction in reducing major cardiovascular events and more recently, either halting the progression or promoting regression of atherosclerosis. The consensus group of the Caribbean Cardiac Society, having reviewed the evidence, has recommended a scheme for initiating drug therapy based on the classification, risk assessment and level of LDL cholesterol. Table 1 outlines the details of this recommendation.

Although most clinical trials have used high dose statins to achieve the LDL goal reduction, we note that there is also a higher incidence of adverse effects with high dose statins. The consensus group feels that the achievement of LDL goal reduction may also be achieved by using lower dose of statin in combination with ezetimibe, thus reducing the risk of adverse drug effects. It should be emphasized that the dose of drug used should be that which attains the LDL goal and a fixed dosage is not being recommended.

**Table 1****Caribbean Cardiac Society Recommendations for LDL cholesterol cutoffs for lifestyle interventions and drug therapy in different risk categories**

<b>Risk category</b>	<b>LDL cholesterol goal</b>	<b>Initiate therapeutic lifestyle changes</b>	<b>Consider drug therapy</b>
<b>High risk: CHD or CHD risk equivalents (10-year risk &gt;20%)</b>	<b>&lt;1.8 mmol/l</b>	<b>≥1.8 mmol/l</b>	<b>≥1.8 mmol/l</b>
<b>Moderately high risk: two or more risk factors (10-year risk 10%-20%)</b>	<b>&lt;2.6 mmol/l</b>	<b>≥2.6 mmol/l</b>	<b>≥2.6 mmol/l (consider drug options if LDL-C 2.6 – 3.3 mmol/l)</b>
<b>Moderate risk: two or more risk factors (10-year risk &lt;10%)</b>	<b>&lt;3.4 mmol/l</b>	<b>≥3.4 mmol/l</b>	<b>&gt;4.1 mmol/l</b>
<b>Low risk: ≤1 risk factor</b>	<b>&lt;4.1 mmol/l</b>	<b>≥4.1 mmol/l</b>	<b>≥4.9 mmol/l (consider drug options if LDL-C 4.1-4.9 mmol/l)</b>