Best Practice Guidelines for Treatment of Hypercholesterolaemia

A Statement from the Caribbean Cardiac Society

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ABSTRACT

There is an increase prevalence of chronic non-communicable diseases in the Caribbean as the region undergoes an epidemiologic transition from infectious to chronic non-communicable diseases. Numerous studies have identified hypertension, obesity, diabetes mellitus and hyperlipidaemia as risk factors for the development of coronary atherosclerosis. The Caribbean Cardiac Society recognizes that there is an increased prevalence of these disease entities and in an effort to foster best practice guidelines for the region, implemented a consensus conference for the discussion of hypercholesterolaemia, hypertension, diabetes mellitus and obesity in 2005. This statement outlines the recommendations of the consensus group of the Caribbean Cardiac Society on the Best Practice Guidelines for the therapy of hypercholesterolaemia.

Las Mejores Guías Prácticas Para el Tratamiento de la Hipercolesterolemia

Una Declaración de la Sociedad Cardiológica del Caribe

EE Chung

RESUMEN

Existe una creciente prevalencia de enfermedades no transmisibles crónicas en el Caribe en la medida que la región experimenta una transición epidemiológica de enfermedades infecciosas a enfermedades crónicas no trasmisibles. Numerosos estudios han identificado la hipertensión, la obesidad, la diabetes mellitus y la hiperlipidemia como factores de riesgo en el desarrollo de la arterosclerosis coronaria. La Sociedad Cardiológica del Caribe reconoce que existe un aumento de la prevalencia de estas entidades y en un esfuerzo por fomentar las mejores guías prácticas para la región, organizó en 2005 una conferencia de consenso para el análisis de la hipercolesterolemia, la hipertensión, la diabetes mellitus y la obesidad. Esta declaración resume las recomendaciones del grupo de consenso de la Sociedad Cardiológica del Caribe, acerca de las mejores Guías Prácticas para la Terapia de la Hipercolesterolemia.

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BACKGROUND

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 impact on the best practice of medicine so that he/she 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 International Collaborative Study on Hypertension in Blacks (1) along with the Jamaican National Healthy Lifestyle Survey (2) has identified obesity, hypertension, hyperlipidaemia and diabetes mellitus as significant problems within the region. These studies also revealed that women carry a disproportionately higher disease burden as they are more obese, have a higher prevalence of hypertension, diabetes mellitus and hyperlipidaemia and thus are at greater risk for the development of atherosclerotic vascular disease.

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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 (3).
* Atherosclerosis is identified as the underlying pathology in both coronary artery disease, stroke and peripheral vascular disease (4).

* Sudden death occurs not infrequently from myocardial infarction and stroke (4, 5).
* Cardiovascular disease is related to identifiable physiological factors and lifestyle (4).
* Risk factor eradication (*eg* smoking cessation, cholesterol reduction and lifestyle modifications) has been shown unequivocally to reduce cardiovascular morbidity and mortality (6).

In December 2002, the Adult Treatment Panel III (ATP III) recommendations of the National Council on Cholesterol Education Panel (NCEP) was published (7). This American guideline was followed by the Third Joint Task Force presentation of the European guidelines in September 2003 (8). 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 one to ask "How low should we go in reducing cholesterol levels?" These studies will be reviewed later and we shall provide 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 (7), 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 include Type 2 diabetes mellitus, Type 1 diabetes mellitus with microalbuminuria, atherosclerotic cerebrovascular disease and peripheral vascular disease;
- moderately high risk category; moderate risk category and
- 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 levels of 10-year risk for hard coronary heart disease (CHD) events (myocardial infarction + CHD death) (9): those with a > 20% risk, between 10–20% risk and < 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) (10)
2. The Pravastatin in Elderly Individuals at risk of Vascular Disease *[PROSPER trial]* (11).
3. Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) (12).
4. Pravastatin or Atorvastatin Evaluation and Infection Therapy in Myocardial Infarction (PROVE IT – TIMI 22) (13).
5. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease – Treating to New Targets (TNT) (14).
6. Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial (15).
7. A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) Trial (16).

The MRC/BHF Heart Protection Study (10) was a randomized placebo controlled multicentre 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 and 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% *versus* 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 was 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 mellitus, 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 did not already have manifest coronary artery disease or high cholesterol concentrations.

The Pravastatin in Elderly Individuals at Risk of Vascular Disease [PROSPER trial] (11) evaluated 5804 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 to14.1% 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) (12) 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 five 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) (13) trial set out to evaluate whether statins were 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-centre double blind randomized 2 x 2 factorial design study of 4162 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 and 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 (14) 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 an eight-week open labelled 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 five 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 studies 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 (15) was a randomized, double-blind, multicentre trial of aggressive lipid lowering using atorvastatin 80 mg per day compared to a moderate lipid lowering strategy using pravastatin 40 mg per day. Five-hundred and two symptomatic coronary artery disease patients with elevated LDL cholesterol at baseline were subjected to intravascular ultrasound (IVUS) 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 per cent 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 (16). The goal of this trial was to evaluate the effect of treatment with intensive statin therapy using intravascular ultrasound (IVUS) 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. Three hundred and forty-nine patients were subjected to IVUS examination in this prospective, blinded open labelled trial. The primary endpoints were the change in per cent 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 per cent 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 three 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

Behavioural Risk Factors

Modification of behavioural 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 behaviour, health, exercise and disease. These efforts should be complimented by an effective follow-up programme which may involve other members of staff such as nurses, social workers and/or physiotherapist.

Healthy Food and Eating Habits

Healthy food choices are an integral part of a total risk management strategy. Advice should be given by the caregiver or with the assistance of a nutritionist. Emphasis on a proper diet is essential. It is important to educate the public that a proper diet will reduce risk by weight reduction, assist in lipid management, lower blood pressure and achieve glucose control in diabetic persons or those with impaired glucose tolerance. The diet should consist of: appropriate calories to maintain weight in those with a normal body mass index (BMI); modest caloric restriction for those who are overweight/obese; 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 and complex carbohydrates should partly replace saturated fats.

Exercise

Exercise should be encouraged. Steady and continuous physical activity of at least half hour three times per week is the minimum requirement. However individuals should be encouraged to exercise four to five times per week for 45 minutes to attain a target of 60 – 75% of the average maximal heart rate for age. Exercise not only enhances physical fitness but has been shown to alter lipids by elevating the HDL levels. Exercise should be undertaken in the form of walking, swimming or cycling. It is not essential for individuals to jog to attain cardiovascular fitness. A treadmill is very useful but expensive and is best used by those individuals who have a time restriction problem or limited access to parks, walking areas or swimming facilities.

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. Emphasis is placed on the

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

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

LDL level. Efforts should be made to reduce the LDL level in high risk individuals to < 1.8 mmol/L.

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 doses 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.

Monitoring of individuals should be done annually specifically looking for the development of any new atherosclerotic complications or co-morbid conditions which may change their risk status. The lipid panel should be repeated annually if the prior one was at target goals. Although complications are uncommon with statin and other lipid lowering therapy, individuals who are so treated should be reviewed periodically. Liver function tests (LFT) should be done at three months and if normal, there is no need for routinely repeating LFTs.

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