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THE EFFECT OF LIPID-LOWERING PHARMACOTHERAPY ON CONCURRENT DIET AND EXERCISE BEHAVIORS

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ABSTRACT

Coronary Heart Disease (CHD) is the most common cause of mortality in both Canada and the United States. While dietary modification remains the cornerstone of CHD prevention strategies, it is becoming more and more at risk of being completely replaced because of the potency of pharmacologic therapy. In spite of this, the National Cholesterol Education Program Adult Treatment Panel II (NCEP ATP II) unequivocally advocates an initial trial of dietary modification in both primary and secondary prevention prior to the institution of pharmacotherapy. Perhaps the rationale for this delay rests in the inherent, yet unsubstantiated, fear among clinicians that lifestyle change will be compromised in the presence of concurrent pharmacotherapy. However, the question of adherence to diet and exercise interventions *following the initiation of lipid-lowering drug therapy* has seemingly never been addressed scientifically.

It was therefore hypothesized that pharmacologically-treated patients with untreated hypercholesterolemia started on a program of lifestyle modification would achieve relatively less reduction in dietary fat intake and body weight, and participate less often in physical activity, if a pharmacologic agent was simultaneously prescribed. This was tested by a protocol in which these and related variables were assessed in participants who thought they were taking a lipid-lowering medication at diagnosis, compared to conventional initial treatment of diet and exercise alone. Fifty-three patients with untreated hypercholesterolemia were recruited to participate in an 18-week prospective single-blind controlled study. During the first 12 weeks, 26 were randomized to receive a tablet that they thought was for cholesterol-lowering, but was a placebo. Twenty-seven matched participants received conventional therapy with no medication. During weeks 12-18, they received either simvastatin 10 mg daily (a standard lipid-lowering drug), or placebo. Data are presented for the first 12 weeks only, as the primary endpoint of the study was to identify changes occurring in the absence of an active drug. The two groups showed no significant differences initially in weight, % lean or fat mass, blood pressure, pulse, lipoprotein profiles (including total cholesterol [TC], triglycerides [TG], HDL-

cholesterol [HDL-C], LDL-cholesterol [LDL-C], total to HDL cholesterol ratio [TC:HDL-C]), physical activity levels, nutrient intakes, or reported "stage of change" classification for fruit and vegetable consumption, lower fat intake, weight loss, and exercise. Both groups improved over time, with significant intervention effects in weight, blood pressure, pulse, TC:HDL-C ratio, and intake of dietary and soluble fibers, while trends were observed for dietary cholesterol and starch. However it is remarkable that the groups did not differ in response. Based on these results, the hypothesis was disproved. The important implication of this is that in the type of patient studied, prescribing a lipid-lowering agent should not adversely affect adherence to the concurrently recommended lifestyle changes.

RÉSUMÉ

La maladie coronarienne (MCAS) est la cause la plus fréquente de mortalité au Canada et aux États-Unis. Bien que l'approche nutritionnelle demeure la pierre angulaire des stratégies préventives de la MCAS, elle risque de plus en plus d'être ignorée à cause de la puissance des thérapies pharmacologiques. Malgré tout, le *National Cholesterol Education Program Adult Treatment Panel II (NCEP ATP II)* recommande, sans équivoque, un essai initial de modification de la diète dans la prévention primaire et secondaire de la MCAS, avant l'institution d'un agent pharmacologique. Cette approche est basée en partie sur une crainte inhérente, bien que non-confirmée, parmi les cliniciens que tout changement du style de vie suggéré serait compromis par l'introduction concomitante d'une pharmacothérapie. Pourtant, cette question de l'adhérence aux interventions de diète et d'exercice lors de l'initiation *d'un agent hypolipidémiant* n'a apparemment jamais été étudiée scientifiquement.

L'hypothèse sous-jacente à cette étude est que les patients avec une hypercholestérolémie non traitée débutant un programme de modification du mode de vie réaliseront une diminution du poids et des ingestas de gras moindre, et feront moins d'activités physiques, si une médication est débutée simultanément. Cette hypothèse fut vérifiée en évaluant ces facteurs et d'autres reliés chez des participants croyant prendre une médication hypolipidémiante au diagnostic, par rapport à un traitement conventionnel de diète et exercice seuls. Cinquante-trois patients avec une hypercholestérolémie non-traitée furent recrutés pour participer à une étude prospective controlée à simple insu d'une durée de 18 semaines. Durant les premières 12 semaines, 26 furent randomisés pour recevoir un comprimé placebo qu'ils croyaient être un agent hypolipidémiant, les 27 autres participants suivirent une approche conventionnelle sans médication. Durant les semaines 12 à 18, les participants reçurent soit simvastatine 10 mg die (une médication hypolipidémiante couramment utilisée) ou un placebo. Les données sont présentées pour les premières 12 semaines seulement, puisque l'objectif principal était de décrire les changements survenant en l'absence de médication active. Les 2 groupes étaient semblables au début de l'étude pour le poids corporel, le % de masse maigre ou grasse, la

tension artérielle, le pouls, le profil lipidique (incluant le cholestérol-total [CT], -HDL, -LDL, les triglycérides, et le rapport CT:C-HDL), le niveau d'activité physique, l'apport nutritionnel, et la classification du stade de changement pour la consommation en fruits et légumes et en graisses alimentaires, la perte de poids, et l'exercice. Les deux groupes se sont améliorés durant l'étude, avec des effets significatifs de l'étude sur le poids corporel total, la tension artérielle, le pouls, le rapport CT:C-HDL, et la consommation en fibres alimentaires totales et solubles, alors que des tendances furent observées pour le cholestérol alimentaire et les féculents. Par contre, aucune différence ne fut notée entre les 2 groupes. L'hypothèse émise se trouve ainsi réfutée. L'implication importante de ce fait chez ce type de patient est que l'ordonnance d'un agent hypolipidémiant ne devrait pas compromettre les efforts de changements du style de vie.

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1.0 LITERATURE REVIEW

1.1 Introduction

Clinical trial evidence is continually accumulating to suggest that a more intensive approach to treatment of such conditions as hypercholesterolemia, diabetes mellitus, and hypertension may be warranted in future models describing standards of care. By reducing the rate of complications and the associated costs of managing these complications, intensive management appears attractive as a means by which to save health dollars and in possibly lengthening the number of quality years in a patient's life. While intensive management typically implies a multidisciplinary approach to caring for a patient and their disease, it is also associated with the institution of prescribed agents—often multiple medications—at a much earlier point in the disease process. When the tendency is to place a lot of value on the efficacy of medication in altering disease progression, how can one be assured that adjunctive measures such as lifestyle change, advocated as part of the total management plan for risk factor modification, is not compromised in the process? Despite similar concerns being raised by clinicians[1] and regulators[2], it would appear that no studies, to the best of our knowledge, have ever addressed this important and timely issue.

The following comprises a detailed review of the literature on hypercholesterolemia and coronary heart disease (CHD) with respect to its characterization and management, and to potential behavioral issues relating to medication and lifestyle change. Topics addressed include: epidemiology, risk factors, the National Cholesterol Education Program (NCEP), the Report of the Canadian Working Group, diagnosis and screening, primary prevention, secondary prevention, dietary intervention, physical activity promotion, drug therapy, physician prescribing behaviors, patient adherence behaviors, lifestyle promotion in the presence of drug therapy, and the Stages of Change model.

The intent of this review is to better acquaint the reader with the relevant background issues, which served as the basis for the rationale of this study. Following a

complete review of this manuscript, an assessment of the present study with regard to its contribution to the current body of knowledge in medication-taking and lifestyle behavior can then be made.

1.1.2 Epidemiology of Coronary Heart Disease (CHD)

Coronary heart disease (CHD) is a leading cause of mortality in North America, resulting in 500,000 deaths per year in the United States, and costing Americans between 50-100 billion dollars annually to treat[3]. It is both the number one cause of death in Canada[4] and the U.S.[5] [6], and figures prominently worldwide[7]. In Canada, two thirds of the population are at risk for CHD because they smoke or have high blood pressure increased serum cholesterol, or a combination of these risk factors[8].

1.1.3 Pathophysiology of CHD

Normally, blood flows unimpeded through the coronary vasculature. However, with alterations in the pattern of flow (i.e. through bifurcations), repeated shear forces amplified by the presence of hypertension, may lead to chronic physiological endothelial injury. In addition to hypertension, chemical or biochemical toxins from hypercholesterolemia, diabetes, or smoking, vasoactive, immunologic, or infective factors may also predispose the vasculature to endothelial injury. Endothelial dysfunction then allows the pathologic ingress of circulating lipoproteins, particularly LDL by virtue of their apolipoprotein B, into the intimal space. These lipoproteins then undergo oxidation, which triggers both an immunologic response in attracting circulating monocytes, and a local tissue response in the secretion of a chemotactic substance from the endothelium. The latter secretion facilitates adherence of monocytes to the endothelium and their subsequent penetration into the intimal layer. Once inside the intimal space, phagocytosis of oxidized LDL ensues by the monocytes having now been transformed into macrophages. Despite persistent phagocytosis, new LDL continues to penetrate the intima unabated. This results in the eventual saturation and expansion of macrophage cells with

cholesteryl ester, and their subsequent transformation into a foam cell. Eventually these foam cells burst, leaving a residual lipid-rich core, or a fatty streak, in the intimal space. Smooth muscle cells from the elastic lamina migrate into the intimal space, and become trapped in the lipid core or atheroma along with collagen and other fibrous material. This reorganization then leads to the formation of an atheromatous plaque, whose presence may be discerned intraluminally as a reduction in effective lumen diameter thereby creating an impedance to flow.

The vulnerability of plaques to rupture is dependent upon the relative amounts of lipid to fibrous material. The greater the lipid content, the more unstable the plaque, and thus, the more prone the plaque is to injury. Rupture may occur as a consequence of two independent processes: 1) passive or mechanical versus 2) active or enzymatic disruption.

Passive disruption takes place via mechanical forces, and is dependent upon the vulnerability of the fibrous cap (e.g. thickness, relative foam cell content), while active disruption involves destabilization by enzymatic degradation (e.g. plasminogen activators, matrix metalloproteinases). Regardless of the mechanism for plaque disruption, the occurrence of an intralesional fissure heralds the critical thrombotic event, exposing the procoagulant lipid core, and triggering an immunologic response. The infiltration of platelet cells to repare the injured tissue results in the formation of a thrombus. Both the size of the fissure and the relative occlusion of the coronary lumen to blood flow influence the extent to which myocardial perfusion is compromised.

Transient myocardial ischemia or chronic stable angina may occur where thrombus formation can lead to reduced oxygenation as a result of decreased perfusion. However, when the coronary lumen is rendered no longer patent due to the relative size of the thrombus, complete anoxia can occur, resulting in acute coronary syndromes such as unstable angina, acute myocardial infarction, or sudden death.

Controlled experiments examining plaque composition by tissue factor (TF) staining have demonstrated that the greatest thrombogenic potential arises from the lipid core, rich in cholesteryl ester. Therefore, in reducing the concentration of cholesteryl ester, the risk of plaque rupture may then be significantly attenuated. This is, in fact, the proposed mechanism by which cholesterol-lowering medications are believed to lower the

risk of progression to coronary artery disease, rather than through some particular property of the agents, themselves. It follows that non-pharmacologic interventions, such as improving diet and exercise habits, which elicit similar reductions in cholesterol levels, may afford similar protection[9] [10].

1.1.4 Relationship between Cholesterol and the Development of CHD

It has been well established that the greater the elevation in serum cholesterol levels, and particularly LDL-C[11], the greater the associated risk of progression to CHD[12]. Likewise, by lowering serum cholesterol, the associated risk of CHD and CHD-related mortality are reduced[13] [14] [15]. In fact, studies have shown that for every 1% reduction in total cholesterol, there is an associated 2% reduction in the risk of CHD[16].

1.1.5 Traditional Risk Factors for the Development of CHD

Development of CHD is associated with many non-modifiable non-lipid risk factors such as increasing age, male gender, or family history of premature cardiovascular death. However, the majority of CHD risk factors are considered modifiable (Table 1)[3]. They include hypertension (2X risk)[17], current smoking status (2-3X risk)[4], diabetes mellitus (2X risk)[18], and low HDL cholesterol (2X risk)[19]. Sedentary lifestyles (2X risk)[20], and obesity (1.5-2X risk)[21] are not recognized as major independent risk factors by the NCEP ATP II [21] [22]. Thus, based on these observations, the integral role of lifestyle modification in the initial management of hypercholesterolemia becomes apparent.

Table 1: Risk Factors Associated with Coronary Heart Disease[3]

POSITIVE†, NON-MODIFIABLE	POSITIVE†, MODIFIABLE
Age: *Male≥45 years* *Female≥55 years or premature Menopause without estrogen Replacement therapy*	**Current cigarette smoking**
	Hypertension *(≥ 140/90 mm Hg or on antihypertensive drugs)*
Family history of premature CHD *(definite MI, or sudden death before 55 years in father or other male 1st-degree relative or before 65 years in mother or other female 1st-degree relative)*	**Low HDL cholesterol** *(< 0.9 mmol/L)*
	Diabetes mellitus
	NEGATIVE‡, MODIFIABLE
	High HDL cholesterol *(≥ 1.6 mmol/L)*

[δ] These include risk factors other than elevated total or LDL cholesterol.
† Positive = a direct relationship between the risk factor and development of CHD
‡ Negative = an inverse relationship between the risk factor and development of CHD

1.1.6 Non-Traditional Risk Factors for the Development of CHD

While it is well established that high levels of LDL-C and low levels of HDL-C independently raise CHD risk, specific apolipoproteins have also been linked to CHD. Four apolipoproteins will be discussed: Apolipoprotein A1 (Apo A1), Apolipoprotein B-100 (Apo B), Lipoprotein(a) or Lp(a), and Apolipoprotein E (Apo E) genotype. Since other emerging biologic risk factors currently under study[23], such as fibrinogen, C-reactive protein, and homocysteine were not investigated at all in the present study, they will not be discussed, and as such, are only mentioned here for the sake of completeness. Furthermore, because guidelines have yet to address the aforementioned in dyslipidemia treatment recommendations, results in this paper will largely focus on the changes occurring in total cholesterol (TC), triglycerides, HDL-C, LDL-C, and TC:HDL-C ratio.

1.1.6.1 Apolipoprotein A1

Apo A1 is the main surface protein of HDL lipoproteins, and is also found in chylomicrons. Apo A1 concentrations can be correlated with the number of HDL particles in circulation. It is synthesized in both liver and small intestine, and is incorporated into nascent HDL_3 following recycling from remnant chylomicrons. Primarily involved in the exchange of cholesterol ester in the reverse cholesterol transport system, Apo A1 is considered antiatherogenic like HDL-C[24 25].

1.1.6.2 Apolipoprotein B

Apo B is a constituent protein located specifically on the surface coat of atherogenic VLDL, IDL, and LDL particles. Apo B concentrations relate mainly to the number of LDL particles in circulation. Whereas Apo A1 can be transferred from particle to particle (i.e. chylomicrons to HDL), Apo B remains fixed on the lipoprotein. Uniquely synthesized by the liver, this apoprotein acts as the specific ligand with hepatic receptors for LDL-C uptake. Both excess circulating LDL-C and Apo B are considered risk factors for CHD. During peroxidative processes affecting the LDL particle, Apo B can become modified, resulting in ectopic LDL deposition in the vascular endothelium. Consequently, this can lead to an immune response and subsequent cellular overload of cholesterol, ultimately giving rise to the formation of an atherosclerotic plaque[24 25].

1.1.6.3 Lipoprotein (a)

Lp(a) is a protein formed by the disulfide linkage of the apo(a), a protein found only on subpopulations of LDL, to Apo B. Levels of Lp(a) are largely genetically determined, and thus, its concentration in the circulation is subject to great variation. While high levels of Lp(a) are considered a risk factor for CHD in caucasian populations, they are not considered atherogenic among blacks[26]. Furthermore, the atherogenicity of Lp(a) may be mediated in part by high levels of LDL-C. Some studies have found that high levels of Lp(a) are only associated with a high CHD risk in the presence of

hypercholesterolemic levels of LDL-C. Due to the significant sequence homology shared with plasminogen, it is postulated that Lp(a)'s atherogenicity may arise from its interference with the fibrinolytic pathway. In addition, it is hypothesized that when present on LDL particles, Lp(a) may impair LDL-C uptake by receptors[24 27 28].

1.1.6.4 Apolipoprotein E

Apo E, like Apo A1 and B, is synthesized in the liver. It is located on all lipoproteins except LDL. However, unlike Apo B, it is not found on LDL particles. Genetically determined, isoforms of Apo E polymorphisms ascribe to 6 phenotypes: E2,2; E3,2; E4,2; E3,3; E4,3; and E4,4. Apo E3 is considered the normal population variant, in which there are no perturbations in LDL and VLDL metabolism[24]. The expression of a particular phenotype therefore influences, to some extent, the way in which the body handles cholesteryl ester. For example, alleles such as E2, may be associated with excessive LDL-C levels. Notwithstanding variations in metabolic handling, specific phenotypes may also modulate the responses to diets, such as interventional diets prescribed to hyperlipidemic patients. From the three phenotypes—E3,3; E3,4; E4,4—investigated in a study by Sarkkinen et al.[29], E4,4 was found to be the most responsive in terms of serum cholesterol to changes in diet[24 29 30].

1.2 Management of Hypercholesterolemias

Management of hypercholesterolemia is discussed with emphasis placed on clinical as opposed to population-based recommendations. Topics addressed include: the (American) National Cholesterol Education Program (NCEP), diagnosis and screening guidelines, primary and secondary prevention strategies.

Since the Report of the (Canadian) Working Group on Hypercholesterolemias and Other Dyslipidemias[23] has now been released, it is reviewed separately at the end of this section. Moreover, since the American recommendations constituted the most complete

set of guidelines available at the time this study was initiated, treatment and eligibility criteria were therefore based upon these NCEP practice recommendations.

1.2.1 The National Cholesterol Education Program

The National Cholesterol Education Program (NCEP) was initiated in 1985[31] in an effort to reduce the population mean serum cholesterol level through health promotion strategies and to identify and treat those people at increased risk for CHD in the United States[21]. Two Adult Treatment Panel (ATP) reports—ATP I and ATP II—have since been released providing guidelines for the detection, evaluation and treatment of hypercholesterolemia in adults[21,32] It should be noted that Canada was quick to follow the American lead, establishing guidelines from the report of the Canadian Consensus Conference on Cholesterol (CCCC) in 1988[33].

1.2.2 Diagnosis and Screening

It is recommended that all people over the age of 20 years be screened regularly for total cholesterol every 5 years. HDL-cholesterol should also be measured, resources permitting. In primary prevention, further need to undergo a lipoprotein analysis will be based on the results of the non-fasting total and HDL serum cholesterol, as well as the presence of CHD risk factors. In those with established CHD, intensity of intervention will be determined based on LDL-cholesterol obtained by fasting lipoprotein analysis (Table 2). Elevated LDL-cholesterol is recognized as the most atherogenic lipid moiety. Its concentration in the serum is highly correlated with that of total cholesterol, which provides the rationale for initial screening of total cholesterol, as well as for its use as a surrogate for treatment efficacy[21].

Table 2: Summary of NCEP ATP II Recommendations[3].

	DO A LIPOPROTEIN PROFILE IF TOTAL-C (mmol/L)	TREAT WITH DIET ALONE IF LDL-C (mmol/L)	TREAT WITH DIET & DRUGS IF LDL-C (mmol/L)
≤ 1 risk factor	> 6.2	4.1 - 4.9	> 4.9 (Goal 4.1)
≥ 2 risk factors	> 5.2	3.4 - 4.1	> 4.1 (Goal 3.0)
Secondary prevention	> 0	2.5 - 3.0	> 3.0 (Goal 2.5)
If HDL-C < 1 If TG > 2.3	SPECIFIC INTERVENTIONS		

1.2.3 Treatment Classification

Treatment classification of patients with hypercholesterolemia is based upon the absence (primary) or presence (secondary) of coronary heart disease, or other atherosclerotic disease such as peripheral arterial disease or symptomatic carotid artery disease[3].

1.2.3.1 Primary Prevention

Patients without CHD, whose serum total cholesterol can be characterized as either desirable or borderline-high (< 5.2 mmol/L or 5.2-6.2 mmol/L, respectively) undergo a subsequent lipoprotein analysis if there exist two or more CHD risk factors, or if serum HDL-cholesterol is already known to be < 0.9 mmol/L. By comparison, patients who initially present with high (> 6.2 mmol/L) serum total cholesterol necessarily proceed to a fasting lipoprotein analysis, regardless of HDL-C or presence of risk factors.

The decision to initiate lipid-lowering diet therapy is then based on the results of the LDL-C from the fasting lipoprotein analysis. Those patients who emerge with either an LDL-C between 3.4 - 4.1 mmol/L accompanied by two or more risk factors or with an LDL-C $\geq$ 4.1 mmol/L are candidates for an initial trial of diet therapy[3].

1.2.3.2 Secondary Prevention

In the presence of established CHD, a fasting lipoprotein analysis is performed, independent of any initial total cholesterol level determined by screening, for the purpose of estimating the LDL-cholesterol level. The analysis is performed twice over an 8-week period, and an average value is calculated. If the LDL-cholesterol is > 2.6 mmol/L, further evaluation ensues including clinical work-up, investigating for secondary causes and dyslipidemia classification. Intensity of treatment, in terms of dietary restriction and addition of drug therapy, is then based on these findings[3]. The thresholds for intervention are generally set at lower levels; several interventions have been shown effective, but are beyond the scope of this review.

1.2.3.3 Report of the (Canadian) Working Group

On May 16th, 2000, the long-awaited (Canadian) *Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias* was published in the Canadian Medical Association Journal[23]. These new guidelines are more intensive with respect to treatment intervention than both their Canadian[33 34] and American[21 32] predecessors. Moreover, they highlight the importance of ethnicity and family history in addition to other biochemical markers—such as Lp(a), homocysteine, fibrinogen, and C-reactive protein levels—as emerging non-traditional CHD surrogates in the overall risk assessment of hypercholesterolemic patients.

1.2.3.3.1 Distinct Features of the Canadian Report[23]

Four notable changes distinguish this set of recommendations from its forerunners. First is the apparent relegation of lifestyle modification to adjunctive therapy, in contrast to its previous role as the "cornerstone" of treatment. Second, more emphasis is placed on the full lipoprotein profile—in particular, LDL-cholesterol, triglycerides and Total:HDL-cholesterol ratio—as opposed to the previous focus on controlling LDL-cholesterol alone. Third is the contribution of gender to CHD risk, since women have a lower risk of CHD relative to men of the same age. Fourth is the intensity of treatment, which is guided by progression through an algorithm, based on data from the Framingham Heart Study for calculating a patient's 10-year risk of experiencing a CHD event (Appendix E.2.1).

1.2.3.3.2 Use of the Framingham Risk Assessment Algorithm[23]

In this risk algorithm, five factors are considered: age, total cholesterol, HDL-cholesterol, systolic blood pressure, and smoking status. Categories are grouped (i.e. age, total cholesterol, HDL-C, systolic blood pressure, and smoking status) and stratified according to a range of values (i.e. age: 55-59) for both males and females. Based on

patient data obtained, points are assigned for each category, which may increase or decrease in accordance with the component's relationship to CHD risk. For example, a rising systolic blood pressure (i.e. SBP of 146 mm Hg) is positively correlated with CHD risk, thus the points assigned will rise in concert (i.e. 2 points for a male and 2 points for a female). Conversely, a high HDL-cholesterol (i.e. HDL-C of 1.62 mmol/L) is negatively correlated with CHD risk, and therefore points will decline as a consequence (i.e. -2 points for a male and -3 points for a female).

Once all five components have been evaluated, the number of points from each category is summed, and a total score is achieved. This final score is then interpreted as an overall 10-year risk of CHD expressed as a percent. Based on this absolute risk (%), a corresponding risk category is determined: Low (<10% risk), Moderate (10-20% risk), High (20-30% risk), and Very High (>30% risk). Each risk category is accompanied by recommended target lipid values for LDL-cholesterol, triglycerides, and ratio lowering. (Appendix E2.2). For the "High" and "Very High" risk categories, drug therapy is now recommended as primary treatment *at diagnosis*. As patients with diabetes are at an especially high risk for CHD, they are classified as such, and thus drug therapy is initiated at once in all those in whom lipid concentrations are in excess of "Very High" target values.

While these guidelines represent an improvement over previous recommendations, clinicians are cautioned that the algorithm must not be used in guiding treatment decisions in familial dyslipidemias. Furthermore, the algorithm is not valid in patients whose age lies outside the defined boundaries (i.e. <30 years or >74 years).

1.2.3.3.3 Role of Pharmacotherapy

The conspicuously greater role of pharmacotherapy in cholesterol management has been attributed to the rising success of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins in reducing morbidity and mortality in both primary and secondary prevention trials[23 35 36 37 38 39]. Furthermore, the issue of cost-effectiveness or containment within a constrained healthcare system lends further support

to the wider use of these potent lipid-lowering agents in treating hyperlipidemia. Similar costs have been observed between non-pharmacologic (i.e. dietitian and monitoring) versus pharmacologic (i.e. drug therapy and monitoring) therapies in treating certain risk categories of patients. As this author acknowledged, unlike the statins, dietary intervention has yet to be shown to reduce all-cause mortality among patients with hypercholesterolemia[35]. In addition, the lipid-lowering in response to the statins is relatively predictable in contrast to the variability of response known to occur in patients treated by diet alone[35,40].

1.2.4 Dietary Intervention

Dietary intervention in the context of hypercholesterolemia management is highlighted, prefaced by a review of the relationships between specific dietary fats and cholesterol in contributing to the development of CHD.

1.2.4.1 Relationship between CHD, Dietary Fats, and Cholesterol

Dietary fat is composed of triglycerides containing saturated (SFA) and unsaturated (UFA) fatty acids. It is the former, by virtue of raising LDL-C by reducing receptor-mediated clearance, which has been most often and consistently associated with CHD mortality. The most common saturated fatty acids (SFA) found in the diet include lauric (12:0), myristic (14:0), palmitic (16:0), and stearic (18:0) acids. While stearic acid may be considered as having no effect on lipids (i.e. lipid-neutral), the other three SFA's produce elevations in LDL-C with myristic generally regarded as the most atherogenic. In contrast, unsaturated fatty acids do not produce elevations in LDL-C. When substituted for SFA's, polyunsaturated fatty acids (PUFA) elicit reductions in LDL-C, whereas monounsaturated fatty acids (MUFA) have no effect or are mildly hypocholesterolemic. However, partially hydrogenated, *trans* unsaturated fatty acids, such as elaidic acid (18:1n9*trans*), are recognized to be highly atherogenic, resulting in both increased levels of LDL-C and reduced levels of HDL-C. Finally, excessive dietary cholesterol, like SFA,

has also been found to impair LDL-C removal, thereby resulting in increased circulating LDL-C concentrations, and subsequently increasing the risk for CHD[41 42 43 44].

1.2.4.2 American Heart Association (AHA) Step I and II Diets

Dietary therapy constitutes the cornerstone of any lipid-lowering treatment plan in both primary and secondary prevention of CHD. The initial diet to be prescribed is either an American Heart Association (AHA) Step I or Step II diet (Table 3), depending on baseline dietary intakes, the clinical status and severity of the hypercholesterolemia, and the magnitude of reduction in serum cholesterol desired. Based on the individual's pretreatment dietary fat intake as well as the level of commitment to change, a 25% reduction in total cholesterol level can be obtained through dietary modification alone[21 45]. However, individual responses are known to be highly subject to variation[45].

Table 3: Comparison of AHA Step I and II Lipid-Lowering Diets[21]

Dietary component	AHA Step I Diet	AHA Step II Diet
Total fat	< 30% of total energy	
Saturated fat	**< 10% of total energy**	**< 7% of total energy**
Polyunsaturated fat	≤ 10% of total energy	
Monounsaturated fat	10-15% of total energy	
Carbohydrate	50-60% of total energy	
Protein	10-20% of total energy	
Cholesterol	**< 300 mg per day**	**< 200 mg per day**
Total energy	To achieve and maintain desirable body weight	

1.2.4.2.1 Efficacy of AHA Step I Diet

The AHA Step I diet consists of the following recommendations: lowering total fat intake to <30% of total calories, saturated fat to <10% of total calories, and dietary cholesterol to < 300mg/day. (Table 3) According to 1996 AHA Conference Proceedings, the AHA Step I diet can generally be credited with accomplishing reductions in LDL-cholesterol of about 7-9%[45]. A more recent meta-analysis by Yu-Poth et al.[46] corroborates this dietary response. Dietary recommendations advocated in the Step I diet are similar in concept to those of the current public health guidelines in both Canada[47] and the U.S.[48] for disease prevention in the general population.

1.2.4.2.2 Efficacy of AHA Step II Diet

The AHA Step II diet consists of the slightly more intensive recommendations for limiting saturated fat and cholesterol intakes: saturated fat to <7% of total calories, and dietary cholesterol to < 200mg/day. (Table 3) According to 1996 AHA Conference Proceedings, the AHA Step II diet can generally be credited with accomplishing reductions in LDL-cholesterol of about 10-20%[45]. The recent meta-analysis by Yu-Poth et al.[46] also corroborates this dietary response.

1.2.5 Physical Activity

A sedentary lifestyle, defined as no reported physical activity[49], is associated with a twofold increase in the risk for CHD[20]. Regular exercise, depending on intensity and duration, can produce favorable alterations in lipid profiles, thereby helping to modify CHD risk[50]. However a staggering 40% of Canadians and Americans can be considered inactive[51]. Recognizing the importance of exercise in the prevention of CHD, the NCEP has subsequently included the participation of regular physical activity as a necessary constituent along with dietary intervention in its Second Report[21].

Although still controversial, increasing physical activity may be useful in reducing visceral depositions of adipose tissue, which concentrate around the abdominal region[52].

Such fat distribution has been associated with an increased risk of coronary heart disease[31]. The mechanism by which visceral adiposity may favor the development of CHD could relate to changes in lipoprotein metabolism, including the associated rises in both LDL-cholesterol and triglycerides, and lowered HDL-cholesterol[53]. Weight-loss initiatives in patients at risk for coronary sequelae are therefore geared at reducing total body weight as a means of achieving reductions in central adiposity. In further support of exercise, enhanced tissue oxygenation, reduced myocardial oxygen demand, improved cardiac function, and greater stability versus conduction disturbances may also contribute to the cardioprotective effect of exercise in addition to promoting healthier lipid profiles and weight status[54 55].

It is important to note that no lasting cardioprotection is afforded from sporadic engagement in physical activity. In a study by Paffenberger et al.[56] of Harvard alumni males, it was found that ex-varsity athletes who became inactive with age also became susceptible to the highest level of risk for CHD. By contrast, those alumni who had been previously inactive in university, but who later became active with age had levels of CHD risk as low as ex-varsity alumni who continued to be active with age. For clinicians, the evidence for cardioprotection resulting from increased physical activity, particularly if only initiated later in life by previously sedentary people is important information to bear in mind when discussing lifestyle modification with hypercholesterolemic patients.

Thus, for health promotion, the American College of Sports Medicine (ACSM) recommends that physical activity be performed at least 3 days per week for 20-60 minutes at a time. The activity should be of an aerobic nature, exercising large muscle groups, and approximating an intensity of 60-90% of maximal heart rate. However, it should be noted that the type of activity recommended requires special individualization for those patients with cardiovascular compromise or risk factors[57].

Canada's Physical Activity Guide[58], was released in the fall of 1998 as part of a joint initiative between Health Canada and the Canadian Society for Exercise Physiology to promote regular physical activity among Canadians. Like *Canada's Food Guide*[59], the Physical Activity Guide is presented as a rainbow, where the outermost arcs denote activities that should be performed most frequently, while the innermost arc represents

activities to limit in frequency. Three types of activities are promoted: 1) Endurance-type, which should be practised 4-7 times per week, 2) Flexibility-type, which should also be practised 4-7 times per week, and 3) Strength-type, which should be practised 2-4 times per week. Emphasis is placed on incorporating all types of physical activity into one's lifestyle, and in adopting what is often perceived as non-traditional forms of physical activities, such as taking the stairs instead of the elevator, vacuuming, carrying groceries, doing rigorous yardwork, etc, in addition to traditional varieties of activity like running, biking, swimming, and weight-training. Encouraging at least 60 minutes of activity per day on most days, the Guide highlights two important messages in endeavoring to meet this minimum daily physical activity requirement. First, activity is cumulative. A minimum of 10 minutes of continuous activity performed 6 times during a given day is advocated as a practical means by which to achieve the minimum 60-minute daily quota. Secondly, duration varies with intensity. The greater the effort (i.e. cross-country skiing), the less the time needed to maintain a given activity, while the lesser the effort (i.e. a leisurely walk), the longer one must persist with the activity in order to reap similar health benefits.

1.2.6 Drug Therapy

Despite dietary modification being traditionally regarded as the first line of treatment in hypercholesterolemia, by itself it often proves inadequate[45]. This apparent treatment failure in dietary behavioral change may largely stem from patient nonadherence.[60 61]. In general, if diet alone fails to achieve targeted lipid endpoints after 3-6 months, drug therapy is instituted[21].

1.2.6.1 Initiating Drug Therapy

For primary prevention in patients with $\leq$ 1 risk factor, drug therapy is generally initiated if LDL-C exceeds 4.9 mmol/L, while clinical judgement is used in cases of levels residing between 4.1 – 4.9 mmol/L. Patients without established CHD, who have $\geq$

2 risk factors, are considered for pharmacologic therapy once the LDL-C > 4.1 mmol/L, with clinical experience guiding decision-making for levels between 3.4 - 4.1 mmol/L. By comparison, a lipid-lowering agent is begun in secondary prevention when LDL-C persists above 3.4 mmol/L, while clinical judgement is reserved in the event of values between 2.6 - 3.4 mmol/L[3].

1.2.6.2 Choosing a Lipid-Lowering Agent

There are several major lipid-lowering agents from which to choose—bile acid sequestrants, HMG-CoA reductase inhibitors (statins), fibric acid derivatives, or niacin—each with varying degrees of efficacy against elevated triglycerides, total, or LDL cholesterol, and in raising HDL-cholesterol[62 63 64].

1.2.6.2.1 Bile Acid Sequesrants

Bile acid sequestrants, such as cholestyramine and colestipol, are classified as anion-exchange resins. By forming insoluble complexes with bile acids in the intestinal lumen, they interrupt the enterohepatic recirculation of cholesterol by causing an excretion of bile acids in the feces. This results in a depletion of bile acids, which then triggers both an increase in the conversion of cholesterol to bile acids, and an upregulation of LDL receptors. Circulating levels of cholesterol are thereby reduced as a consequence of increased uptake and removal of cholesteryl ester from the blood, and through depletion of hepatic cholesterol pools.

The primary indication for the use of bile acid sequestering agents is in the reduction of elevated total (12-25%) and LDL (15-30%) cholesterol. However, due to their adverse effects on Very Low Density Lipoprotein (VLDL)-cholesterol production, these agents may produce elevations in circulating levels of triglycerides in susceptible patients. Furthermore, patient acceptance, at least initially, may be lower in comparison to other available agents since gastrointestinal effects, such as constipation, are common with bile acid sequestrants[63 65].

1.2.6.2.2 Fibric Acid Derivatives

Although the precise mechanism of action of fibric acid derivatives or "fibrates" is unknown, they have been shown to exert their lipid-lowering effects principally through increasing lipolysis, which is thought to occur through both enhanced activity of lipoprotein lipase (LPL) and reduced hepatic expression of Apo C-III, an inhibitor of LPL activity. The induction of LPL is mediated by the activation of the nuclear transcription factor, peroxisome proliferator-activated receptor alpha ($PPAR_{\alpha}$), for which the fibrates are ligands. $PPAR_{\alpha}$ can be found in tissues, which metabolize large amounts of fatty acid, namely liver, kidney, heart, and muscle. Through increased lipolysis via LPL and depletion of Apo CIII, VLDL catabolism is increased, while hepatic VLDL production is reduced, resulting in decreased circulating levels of triglycerides. The concomitant rise in HDL-C concentrations that also occurs with the use of fibrates, is more likely the result of enhanced hepatic Apo A-I and A-II production[66].

The main indication for the use of fibrates is in the reduction of elevated triglycerides (40-50%). They are also able to modestly raise HDL-C levels (8-15%). As with the bile acid sequestrants, gastrointestinal effects comprise the most common adverse events reported [63 65]. However, the frequency of these untoward effects is similar to that of the well-tolerated statins[67].

1.2.6.2.3 Nicotinic Acid

Like the fibric acid derivatives, nicotinic acid or niacin exerts its hypolipemic effects through upregulation of lipoprotein lipase activity. Moreover, niacin lowers VLDL- and LDL-cholesterol directly by reducing hepatic biosynthesis.

Nicotinic acid is considered effective for lowering LDL-C (20-35%) and triglyceride (20-40%) levels, and in raising HDL-C (10-20%). Due to dose-related prostaglandin-mediated flushing, pruritis and rash, niacin may be a less acceptable therapeutic option. Furthermore, the use of niacin is associated with orthostatic hypotension, and increases in uric acid, and blood glucose levels, which may preclude their use in certain patient populations[63 65].

1.2.6.2.4 HMG-CoA Reductase Inhibitors

The most potent and well-tolerated agents for cholesterol reduction are the HMG-CoA reductase inhibitors or "statins". By inhibiting the step in cholesterol synthesis, at which HMG-CoA is converted to mevalonate by HMG-CoA reductase[63], the statins are able to elicit reductions in total and LDL-cholesterol in the range of 25% and 35%, respectively[68]. With a favorable side effect profile, and a once- to twice-daily dosing frequency, these statins are considered the agents of choice in treating elevated total and LDL cholesterol[23 62 63 64], and more recently, low HDL-C[63]. Nonetheless, the powerful lipid-lowering action of these drugs cannot and should not replace the efforts of diet and exercise[69] in helping individuals achieve and maintain healthy weights, change problem eating behaviors, manage stress, and improve cardiorespiratory fitness. Drug therapy, regardless of which agent is chosen, should be perceived as an important component of the overall therapeutic management plan in achieving optimal cardioprotection versus CHD.

1.3 Behavioral Issues in Medical Management

1.3.1 Implementation of the NCEP Guidelines

Since at least the inaugural NCEP ATP I guidelines published in 1988, it has been standard protocol when treating patients with hyperlipidemia, to delay the initiation of drug therapy until a "reasonable" trial of nonpharmacologic therapy failed to achieve eulipemia[32]. The convention to use dietary modification as first-line treatment versus the relatively more powerful pharmacotherapeutic agents like the HMG-CoA reductase inhibitors or "statins" is in accordance with the current NCEP guidelines[21]. Prescribing guidelines state that diet must invariably precede drug therapy, yet there is evidence from survey and other data [70 71 72 73] that suggests that the NCEP guidelines may not be as widely implemented into medical practice.

1.3.2 Characterization of Physician Prescribing Behaviors

O'Keefe et al.[71] surveyed a sample (n=633; response rate= 16%) of Midwestern doctors regarding their attitudes and practice patterns with respect to heart disease and diet counseling. Although more than 78% of physicians acknowledged deficient training in patient nutrition education, 1/3 downplayed the role of the dietitian in providing dietary counseling to their patients. Furthermore, an overwhelming majority identified numerous practical barriers, which negatively impacted on the time they were able to devote to nutritional advising, themselves.

Barriers to preventive lifestyle counseling were also examined by Pearson et al.[72] among cardiologists in a task force paper on implementing preventive cardiology. Time constraints, focus on acute interventions, inadequate skills training, and lack of communication among the health disciplines were identified as major barriers. In addition, it was recognized that practitioner roles and procedures in risk factor intervention need clarification in order to effect such preventive strategies.

Similarly, Stafford et al.[73] investigated the prevalence of non-clinical factors in determining the pattern of cholesterol management by surveying a sample of 2,912 physicians (response rate= 72%) taken from the National Ambulatory Medical Care Survey (NAMCS). Among the findings in the study, it was noted by the authors that the rate of preventive cholesterol screening in the general population determined in this survey to be 1 in 12 was well below the guideline set out by the NCEP of 1 in 5. As well, cholesterol counseling in these patients was more likely if they were aged 35-69 years, or if they presented with comorbidities. Patients with dyslipidemias who were obese were less likely to be tested, while those with cardiovascular disease (CVD) were no more likely to be tested.

Application of the NCEP guidelines for initiating drug therapy was investigated retrospectively by Barnard et al.[70] in 93 patients receiving lipid-lowering medication as part of an intensive diet and exercise intervention study. Patients were asked to indicate whether they received a trial of diet therapy prior to being placed on cholesterol-lowering medication, and if dietary change continued to be promoted once drug therapy was

instituted. Surprisingly, only 49% of primary care physicians had attempted a trial of diet therapy prior to adding a lipid-lowering agent, according to respondents. With the prescription of drug therapy, 29% of doctors were reported to offer no adjunctive dietary advice.

From these data, it would appear that the promotion and prescription of dietary change by physicians as part of comprehensive cholesterol management is less than optimal, and that the cause of these discrepant practices cannot be attributed to any single factor. However, there are two essential players in the provision of health care, the provider and the patient, such that one cannot overlook the contribution of patient factors in influencing therapeutic outcomes.

1.3.3 Characterization of Patient Adherence Behaviors

Patients, for example those who are newly diagnosed with hypercholesterolemia, likely face a variety of issues relating to change, not the least of which is their ability to make the requisite lifestyle changes advocated by their doctor. In a review article by Burke et al.[61], several key factors influencing a patient's level of adherence to a therapeutic regimen were identified. First of all, it is not sufficient for physicians or other health care professionals to assume the role of authoritarian in devising a treatment plan. Many patients not only want to be provided with an explanation of the reason for a treatment choice in relation to their disease, but they also need to be well acquainted with the skills incumbent on them in order to achieve desired outcomes with their treatment. Adherence will also be influenced by how confident the patient is in his or her ability to successfully implement these behavioral changes. Social support plays an important role in encouraging and reinforcing behavioral change. For example, a hostile attitude at home toward switching to a low-fat diet may present a considerable barrier to effecting and sustaining dietary change. Regimen complexity and duration ascribe to an inverse relationship with adherence; the greater the behavioral change required to follow a regimen, the greater the anticipated level of non-adherence. Finally, communication skills, manifested in the way in which the health professional relates to the patient can

also affect adherence levels. Burke also reviews the variable rates of adherence associated with diet (13-76%), exercise (attrition: 40-50% after 6-12 months), and drug therapy (82%). Such low levels of adherence associated with non-pharmacologic interventions can only leave one to sympathize with physicians regarding the distinct temptation they face to eschew a seemingly futile course of lifestyle modification in favor of more efficacious drug therapy.

1.3.4 Lifestyle Promotion in the Presence of Drug Therapy

What happens to lifestyle changes, like diet and exercise when drug therapy is needed to optimally manage the dyslipidemia? In cases where there has been a trial of diet and exercise before the consideration of drug therapy, do patients subsequently abandon their lower-fat diets and/or decrease their physical activity once a drug is added? Maybe they will assume the potency of the drug is such that it removes the need for any other supplementary efforts on their part.

The proposition that medication may exert an untoward effect on adherence to adjunctive lifestyle management is an important issue to address. An extensive literature review has failed to reveal previous work in this area, with one exception. In an open-labeled study by Stugaard et al.[74], the lipid-lowering efficacy of lovastatin (an HMG-CoA reductase inhibitor) alone or in combination with other hypolipemic agents was examined in addition to these drugs' effect on adherence to diet among patients with familial hypercholesterolemia. No effect of medication on diet was observed. The addition of lipid-lowering agents in these diet-treated patients did not influence adherence to the diet.

Two other studies investigating patterns of adherence in diabetes self-management likely provide useful models with which to predict behaviors occurring in lifestyle management of hypercholesterolemia. Both studies address self-management in terms of four common parameters: self-monitoring of blood glucose (SMBG), diet, exercise, and medication use.

In a study by Ruggiero et al.[5], the level of diabetes self-management was assessed by an independent national mailed survey completed by 2,056 American participants

(response rate=73.4%) who reported either Type 1 or 2 diabetes mellitus. Of most relevance, three items were used to investigate patterns of behavior associated with the four self-management parameters previously mentioned: 1) number of days during the past week where self-care was practised 2) number of behaviors practised during that week, and 3) an estimate for the past month on the frequency with which these four behaviors were practised. Analysis by chi-square revealed medication use with the highest reported rate of adherence, followed sequentially by SMBG, exercise, and diet. Due to sample size limitations and skewness of data, medication use was excluded in later sub-analyses looking at the effect of Type 1, Type 2 (no insulin), or Type 2 (with insulin) diabetes on self-care practices.

Similarly a Canadian study by Pham et al.[75] surveyed health beliefs about diabetes and its treatment in relation to reported levels of diabetes self-care behaviors practised among recent amputees with Type 2 diabetes. Letters of study invitation were mailed out to 231 patients from nine different centers who met inclusion criteria, of which 79 agreed to participate in the study. In addition to the four self-care behaviors evaluated, adherence to foot care was also assessed. Descriptive analyses included data from 76 volunteers, and yielded comparable results with those from the Ruggiero[5] study. That is, medication use emerged with the highest level of adherence, followed in succession by foot care, SMBG, diet, and exercise. However, since patients in this study were clearly a distinct sample within the population of patients with Type 2 diabetes, this observed level of self-care may not reflect that which would be seen in the larger population.

A particular concern raised among clinicians and regulators is that if patients were presented at diagnosis with a drug to correct their dyslipidemia, the patients may not make the effort to modify their unhealthy lifestyles[1,2]. In other words, there is a fear that patients may opt to rely solely on the medication to undo all their dietary improprieties and to supplant the need to become more physically active. This very opinion is highlighted in a recent review article by Pearson et al.—*There is continued concern that the prescription of a pharmacologic agent such as a lipid-lowering agent will cripple the patient's motivation for non-pharmacologic measures such as diet, exercise, and weight loss*[1]. A similar concern was highlighted in a recently released Food and Drug Consumer

(FDC) Tan Report issued by the U.S. Food and Drug Administration (FDA): *...would use of a cholesterol-lowering drug allow patients to ignore other needed interventions, such as smoking cessation, dietary discretion, and management of other risk factors?*[2]

Should this behavioral relationship truly exist, it would impart strong support to the NCEP[21] guidelines' current management approach of beginning initially with non-pharmacological (diet and exercise) intervention. In the absence of a clear rationale, it can be inferred, however, from these guidelines that the reasoning behind the precedence of diet over drug therapy rests on four basic issues. First, diet has not only been established as an effective means by which to improve lipemia, but it is also a relatively more accessible, lower risk therapeutic option. Secondly, patients who are prescribed lipid-lowering drugs are more than likely to remain on these agents for the rest of their lives. Given the fact that drug therapy can potentially be initiated as early as childhood in some genetic dyslipidemias, there is great concern over the long-term effects associated with chronic exposure to these drugs. Thirdly, management by dietary means may be a much more affordable way to treat hyperlipidemias where indicated, than by resorting to drug therapy. Finally, the enactment of certain lifestyle changes is able to provide additional cardioprotective benefits not derived from lipid-lowering medication.

1.3.5 The Transtheoretical Model for Stages of Change

The Transtheoretical Model or "Stages of Change" is a behavioral paradigm developed by Prochaska and colleagues in 1982 in an effort to describe behavioral change among patients attempting self-directed smoking cessation[76 77]. Visually, the model can be compared to a spiral staircase, where ascent up each flight of steps is associated with reaching a higher stage of change[78]. Movement, through the stages, however, can originate at any stage on the winding staircase and proceed in either direction. The goal is to have individuals progress through the stages, however backward movement or 'cycling' can occur. In fact, changing is a dynamic process, and cycling can be viewed as part of the process[77].

Since the inception of the Stages of Change model into the health psychology arena to analyze smoking cessation, its use has expanded dramatically to include explaining such diverse behaviors as: drug abuse, weight control, dietary fat consumption, exercise adoption, diabetes self-care practices, ultraviolet radiation exposure, responsible sex, mammography, and participation in a cholesterol intervention program[78 79 80 81 82 83 84 85 86].

Five discrete stages have been proposed to characterize a person's readiness to change a behavior[77 78]. Time-dependent in nature, they consist of Precontemplation, Contemplation, Preparation, Action, and Maintenance. Although most research to date has only examined the model from the perspective of strict stage dichotomization, this appears to be an area of current discussion. A person may exhibit characteristics of more than one stage at any one time. Furthermore, subtypes have been observed, reflecting the dynamic nature within each stage of change[87].

1.3.5.1 Stage Categorization

Five stages are used to classify readiness to change a behavior. They include: Precontemplation, Contemplation, Preparation, Action, and Maintenance. The first 3 stages are considered lower while the last two are higher stages of readiness to change behavior.

1.3.5.1.1 Precontemplation

Precontemplation can be described as the "Don't bother me" or "Leave me alone" stage. At this stage, the person neither has any intent of changing in the next 6 months, nor recognizes the problematic essence of continuing to adhere to the undesirable behavior. Because the individual has yet to personalize the risks inherent to the behavior, they cannot rationalize the purported need to change. Therefore, in the case of a patient newly-diagnosed with hypercholesterolemia, the task at this stage is to seek to raise the patient's level of awareness about the severity and consequences of the dyslipidemia.

Greater consciousness of their disease can help the patient to begin entertaining thoughts on the plausibility of change adoption[77 78].

1.3.5.1.2 Contemplation

Contemplation represents the next step up the staircase. People at this stage can be said to be thinking about changing sometime within the next 6 months. Discussing a person's motivation or reasons for changing, as well as the pros and cons for changing is essential. This is a critical stage, where the person can understand that their current behavior is unhealthy, but they are still hesitant about beginning to take steps to change. An equal-arm balance exists, where all the pros of changing are contained on one side and all the cons of not changing on the other side. The relative weight of the cons in excess of that of the pros is what is preventing the person to decide to change their dietary and exercise behaviors. For example, the patient with elevated LDL cholesterol may understand the benefits of changing to a low-fat diet and engaging in regular exercise on lowering their serum cholesterol and thus their risk of CHD. However, they remain resistant to adopting these healthier behaviors. What is essential, then, for the health professional is to help the patient identify the pros and cons, with the aim of increasing the weight of the pros while reducing that of the cons[77 78].

1.3.5.1.3 Preparation

Preparation is a turning point in the Stages of Change model, bridging the lower (passive) stages to the higher (active) stages. It represents a decision by the patient to commit to change within the next 30 days. For example, the sedentary patient with low HDL-cholesterol not only recognizes the benefits of exercise on raising HDL-C levels, but also wants to begin a program of daily brisk walking. Patients at this stage are highly motivated and want to be equipped with the necessary tools that will help them succeed at changing their behavior. A person previously accustomed to consuming more than 30% of their calories as fat, will need to be taught how to lower the amount of fat in their diet. Adopting healthier eating behaviors would include instruction on how to label-read when

out grocery shopping, how to best prepare food at home, and how to select healthy dishes when dining out. Similarly, participation in regular physical activity necessitates development of time management skills. As well, to prevent injury and maintain a proper balance between intensity and duration of the activity, one must become familiar with physical abilities and limitations. Developing a change plan and establishing an intact social support system are key areas where the health care professional can provide assistance to increase the likelihood of success in adopting the healthy new behavior[77 78].

1.3.5.1.4 Action

Action is the stage of "the big leap", where the tools garnered from Preparation are now being employed to effect behavior change. A person can be considered to be functioning in the Action stage if they have been sustaining their behavioral change for less than 6 months. For example, the patient diagnosed with hypercholesterolemia has begun selecting low-fat food choices and is walking for a half-hour every morning. Nonetheless, the Action stage is a volatile, challenging period characterized by a great impetus to succeed, but also by a high vulnerability to cycle back to a previous stage. It is therefore incumbent upon family and friends to provide continued supportive feedback and reinforcement in order to assist in sustaining the new behavior. To help ease the patient's struggle to succeed, problem-solving strategies should be discussed. For example, gorging on a piece of rich chocolate cake could be countered with eating a low-fat chocolate brownie. In addition to partaking in a healthier alternative behavior, avoiding the source of temptation is another important action process termed "environmental control". To illustrate, the person subjected to the chocolate cake could also have chosen to leave the room and go for a walk outdoors, thereby controlling his or her environment. By building up a patient's self-confidence (self-efficacy) in their ability to change their behavior, a level of mastery in performing the new behavior can be realized, decreasing the patient's susceptibility of relapsing to a previous stage[77 78].

1.3.5.1.5 Maintenance

Maintenance is the period following Action, that is characterized by the successful adoption of behavior change, which has extended beyond 6 months in duration. This stage embodies 'behavior change for the long-term'. The patient with hypercholesterolemia, for example, has successfully adopted a diet containing less than 30% fat into their lifestyle for the past year, which has resulted in a reduction in their serum cholesterol. By reaching the maintenance phase, the patient has achieved a certain level of proficiency in performing the new behavior. Here, the keys to sustaining long-term behavioral change and resisting the tendency to relapse, are to ensure an intact social support network, and to provide continued positive reinforcement[77 78].

Ultimately, a sixth stage called 'Termination' may follow Maintenance[53]. Termination has been identified for some behaviors such as smoking cessation and alcohol abstinence. It describes individuals who have no problem in maintaining the new behavior[88]. They are no longer at risk of cycling back to an earlier stage, because they no longer feel tempted to return to the former behavior. In an ideal world, we would like every patient to achieve this highest stage of change. However, it should be noted that many individuals will not reach "Termination". Instead, the majority of individuals remain in Maintenance, where they must continue to make use of supportive techniques to protect their vulnerability toward enticement, which could send them spiraling back to their former behavior[77].

1.3.5.2 Applications of the Stages of Change in Dietary Research

Three studies are highlighted, which made use of the Stages of Change for the purpose of classifying people according to their readiness to consume 5 or more servings of fruits and vegetables per day[89], and in adopting a lower fat diet[90 91].

In the study by Van Duyn et al.[89], data were analyzed from the national *5 A Day for Better Health* program conducted among a representative sample of U.S. adults using the 1991 baseline survey data. The objectives of this study were twofold: 1) to develop an algorithm for classifying the participants into stages of change according to their current

fruit and vegetable intakes, and 2) to investigate predictors of reported fruit and vegetable intakes, including stages of change, demographic, and psychosocial factors.

The original survey was a random digit dial telephone poll, in which 2,811 respondents participated. The final sample consisted of 2,056 participants (response rate=42.8%) (42.3% male and 57.7% female), with an additional sample (n=755) of minority groups (African Americans and Hispanics). Fruit and vegetable intakes were assessed by food frequency questionnaires, in which intake was reported over the past year. Behavioral questions relating to fruit and vegetable consumption were of three types: 1) qualitative self-rating of intake, 2) behavioral intention to increase intake, and 3) self-efficacy or confidence to increase intake. Based on data from reported intakes and the responses to the behavioral questions, participants were classified into Precontemplation, Contemplation, Preparation, Action, and Maintenance stages. Results from this study showed that being female, older, and with more formal education were associated with eating 5 or more fruits and vegetables, and also being classified in the higher stages of change (Action, Maintenance). Stage of change classification was found to be a good predictor of fruit and vegetable intake, suggesting that use of this measure may be useful in targeting dietary behavior in population-based strategies as a means of preventing chronic disease.

The Australian study by McDonell et al.[90] investigated the use of the Stages of Change model to classify participants according to their intention to lower their dietary fat intakes. The sample consisted of 1081 full- and part-time university employees (response rate=58%). The survey included a questionnaire in which participants were assessed for their 1) dietary fat intakes, 2) nutrition knowledge, 3) stage of change for adopting a lower fat diet, 4) perceived benefits and barriers to adopting a low fat diet.

Dietary fat intake was assessed using the Short Fat questionnaire, which consisted of a 17-item food frequency survey of usual dietary intakes, focusing on saturated fat consumption. Nutrition knowledge was assessed by an 11-item multiple choice questionnaire, which examined knowledge of dietary fats and their interpretation on food labels. Classification of stage of change was based on selecting one of five possible statements, that best described current dietary fat behavior, and categorized individuals

into one of the 5 stages. Benefits and barriers for changing to a low fat diet were examined via a 17-item questionnaire.

Using multivariate analyses of variance, participants at each stage of change were compared on knowledge, fat intake, benefits, and barriers. Results indicated that individuals in the Precontemplation stage perceived fewer benefits, and individuals in the Maintenance stage perceived fewer barriers.

Finally, in a novel 18-month study by Greene et al.[91] investigating stage of change and reduction of dietary fat, stage of change classification for a low fat diet was contingent upon the corroboration of dietary fat intakes being $\leq$ 30% of total energy. The study investigated the effects of a single dietary feedback report on dietary fat reduction. The study was made up of two groups, one who received this baseline feedback, and the other who did not. Participants for this study were recruited randomly (n=614, response rate=32%) by mail throughout Rhode Island. Respondents who were already consuming a low fat diet ($\leq$ 30% of total energy), as well as pregnant or lactating women were excluded. The final sample (n=296) consisted predominantly of white, well-educated, male and female participants, who completed follow-ups at 6, 12, and 18 months.

In all participants fat intakes were found to decrease over time (~4%) while stage for reducing fat to $\leq$ 30% of total energy increased over the 18 weeks. Both dietary intakes and behavioral assessments corroborated these findings. However, there were no differences between the 2 study groups; those who received dietary feedback, and those who did not. Lack of more frequent feedback may have been the reason.

1.3.5.3 Relevance of the Stages of Change to the Present Study

The present study targeted patients with hypercholesterolemia, who were candidates for the AHA Step I diet (i.e. fat <30% of energy). Previous work with the Stages of Change model has been limited thus far in characterizing readiness to change behavior in people with chronic diseases. Therefore, the present study would represent a significant contribution to the growing body of knowledge in the application of the Stages

of Change model in both health research and in population and community-based health strategies for chronic disease prevention.

1.4 Rationale for the Present Study

Although our genetic background may set the stage, individual factors, such as diet, smoking, and other elements of lifestyle, are likely to determine the initiation and progression of CHD[92]. In a recent follow-up longitudinal study by Hu et al.[93], 85,941 women from the Nurses' Health Study were observed over 14 years for trends in the incidence of CHD. Among the outcome variables assessed, significant improvements in diet were identified as one of the major contributors to the 21% reduction in CHD incidence observed, accounting for 16% of this decrease. Alternatively, during the same follow-up period, Stampfer et al.[94] found that non-adherence with lifestyle modification was shown to account for 82% of coronary events within this same cohort.

Improving dietary habits has clearly been shown to be effective in lowering serum lipids, and in modifying CHD risk[95]. However, because of numerous behavioral issues that accompany dietary change, individuals may find changing eating habits very difficult because of the burden such habit-changing presents. Taking a lipid-lowering agent, which can accomplish the same or better outcomes on CHD risk, may seem like a more attractive option than investing the effort required to change lifestyle[160].

In the future, with the possible switch of certain low-dose statins from prescription- to over-the-counter (OTC) status in the U.S.[2] as an option to treat mild hypercholesterolemia, the temptation to ignore changing lifestyle behaviors will undoubtedly increase with the intensive direct-to-consumer (DTC) advertising sure to follow by pharmaceutical companies intent on marketing their product. This is likely to encourage a great number of people to self-treat by pharmacologic means, patients who would be traditionally and effectively managed by prescription of appropriate lifestyle change, such as the AHA Step I diet.

The benefits of lifestyle change in modifying CHD risk, the potential for additive therapeutic efficacy when both lifestyle and lipid-lowering drug therapies are combined,

and the possibility of using lower doses of pharmacologic agents provide a clear rationale for investigating the effects of medication on lifestyle behaviors. This study is the first trial of its kind to shed some light on this relationship, and should therefore contribute substantially to stimulating further research into this area.

2.0 STATEMENT OF PURPOSE

2.1 HYPOTHESIS

If prescribed a lipid-lowering medication upon diagnosis of hypercholesterolemia, patients will not improve their diet and exercise habits as much as a matched control group not prescribed medication.

2.2 OBJECTIVES

2.2.1 Primary Endpoints

2.2.1.1 Anthropometric

To determine whether the act of taking a lipid-lowering medication (i.e. placebo) at diagnosis affects changes in anthropometric outcomes (i.e. body weight, % fat and lean mass) as measured by total body weight, and bioelectrical impedance analysis when compared to patients treated conventionally by prescription of lifestyle modification alone.

2.2.1.2 Biochemical

To determine whether the act of taking a lipid-lowering medication (i.e. placebo) at diagnosis affects changes in biochemical outcomes (i.e. total cholesterol, triglycerides, HDL-C, LDL-C, TC:HDL-C), as measured by fasting lipoprotein analysis when compared to patients treated conventionally by prescription of lifestyle modification alone.

2.2.2 Secondary Endpoints

2.2.2.1 Dietary

To determine whether the act of taking a lipid-lowering medication (i.e. placebo) at diagnosis affects concomitant efforts to modify dietary habits, as measured by changes

in mean nutrient intakes (i.e. total energy, protein, total fat, saturated, polyunsaturated, omega-3, and monounsaturated fatty acids, dietary cholesterol, total carbohydrate, total sugars, total dietary, soluble, and insoluble fibers, total starches, and alcohol) when compared to patients treated conventionally by prescription of lifestyle modification alone.

2.2.2.2 Exercise

To determine whether the act of taking a lipid-lowering medication (i.e. placebo) at diagnosis affects concomitant efforts to modify exercise habits, as measured by changes in mean activity levels (i.e. Caltrac$_{TM}$ accelerometer daily activity counts, Bouchard 3-Day Physical Activity Record calculated daily energy expenditures) when compared to patients treated conventionally by prescription of lifestyle modification alone.

2.2.2.3 Stage of Behavioral Change

To determine whether the act of taking a lipid-lowering medication (i.e. placebo) at diagnosis affects stage of change for four lifestyle behaviors—1) readiness to consume 5 or more fruits and vegetables per day, 2) readiness to limit dietary fat intake, 3) readiness to lose excess body weight by changing diet and exercise habits, and 4) readiness to engage in regular exercise for at least 3 times or more per week for 20 minutes or longer—as assessed by questionnaire, when compared to patients treated conventionally by prescription of lifestyle modification alone.

3.0 METHODS AND PROCEDURES

For more detailed information on the timing and nature of clinical assessments, the reader is invited to refer to Table 4 for the *Clinical Assessment Time Frame: Sequence of Events*.

3.1 Design

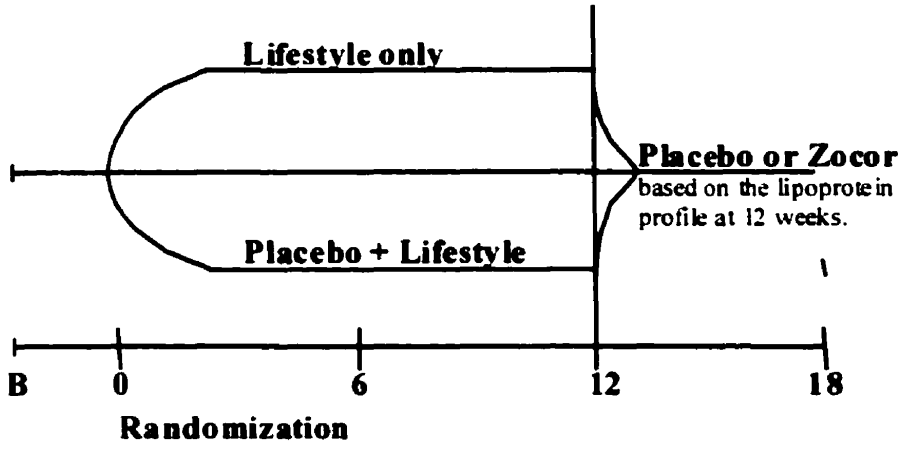
The study was a prospective single-blind placebo-controlled protocol, 18 weeks in duration, consisting of 4 visits at 6-week intervals. Stratified according to body mass index (BMI<30, >30) and serum LDL-cholesterol (LDL-C 3.4-4.7, 4.8-6.0), eligible patients were randomized to one of two groups: 1) *Treatment* group, who received a study medication at the initial medical consultation, and continued for the entire 18 weeks of the study + standard diet & exercise, or 2) *Control* group, who received standard diet & exercise alone for the first 12 weeks, followed by the addition of a study medication for the last 6 weeks of the study.

The study medication received by the treatment group for the first 12 weeks of the trial was always placebo. At week 12, based on the results of a fasting lipoprotein analysis, both groups of patients were either initiated or maintained on placebo, or initiated or switched to Zocor® (simvastatin 10 mg QD) for the final 6 weeks of the study. It is important to note that patients remained blinded to the identity of the study medication throughout the entire 18 weeks of the trial.

By ensuring the presence of a placebo during the first 12 weeks (treatment group) comparisons could be made between the two groups with regard to diet and exercise changes occurring over time, purely as a function of the effect of being on a "medication" for 12 weeks. More importantly, however, the use of a placebo instead of an actual lipid-lowering agent for the first 12 weeks permitted the examination of surrogates for lifestyle modification, such as changes in lipoprotein indices—one of the primary endpoints, which would not have been possible in the presence of a lipid-lowering agent. The

placebo further allowed us to attribute any observed changes in lipemic status to non-pharmacologic intervention alone.

Figure 1: Protocol Design



3.2 Inclusion and Exclusion Criteria

Patients included for this study were those who were newly diagnosed with hypercholesterolemia or previously untreated for the latter, who would be considered candidates for primary prevention of CHD. At least 35 years of age, eligible participants comprised both male and female patients, with BMI's greater than 25 kg/m^2, but not in excess of 40 kg/m^2. Fasting lipoprotein analyses at baseline yielded LDL-C levels between 3.4 and 6.0 mmol/L, and triglycerides not more than 6 mmol/L. In keeping with NCEP ATP II treatment guidelines, individuals presenting with baseline LDL-C levels below 4.1 mmol/L, but measuring at least 3.4 mmol/L were accepted into the study if they had 2 or more other risk factors for CHD (i.e. hypertension, smoking).

Patients whose dyslipidemias required more intensive treatment initially (i.e. pharmacologic) in order to achieve therapeutic targets, such as patients with established CHD (i.e. candidates for secondary prevention), or genetic dyslipidemias (i.e. homozygous or heterozygous familial hypercholesterolemia) were excluded. In addition, patients with secondary dyslipidemias (i.e. hypothyroidism, nephrotic syndrome) were excluded since the etiology of their hypercholesterolemia would not be considered as originating from a true (primary) lipid disorder. However, patients deemed clinically euthyroid presenting with persistent residual hypercholesterolemias following stable dosage of thyroxine replacement therapy were accepted into the study. Similarly, postmenopausal patients taking stable doses of estrogen or hormone replacement therapies were also accepted.

Other conditions, which precluded participation into the study were compromised liver function as evidenced by repeatedly abnormal liver function tests (>3xULN), partial ileal bypass, history of drug or alcohol abuse, hypersensitivity to HMG-CoA reductase inhibitors, prescription of anorexiants, systemic glucocorticoids or lipid-lowering agents, presence of tendon xanthomas, diabetes mellitus, or other serious disease. Previous counseling for hypercholesterolemia by a registered dietitian within approximately the last 3 years also precluded eligibility, if the patient exhibited a greater than average knowledge of the dietary principles found in the AHA Step I diet, as these same principles would be taught by the study's clinical dietitian. This decision to exclude on the basis of previous dietary knowledge was made most often by the research dietitian, or rarely by the author in consultation with the research dietitian.

3.3 Recruitment

Fifty-five patients with newly-diagnosed or untreated hypercholesterolemia were recruited over a period of 1 year from the Royal Victoria Hospital's (RVH) Community Clinic (CC), Internal Medicine Unit (IMU), and Endocrine Lipid (ENDO) clinics, St. Mary's Hospital Centre's Family Medicine Clinic (SMH FMC), and through public advertisement (i.e. Montreal's free *Mirror* and *ICI* newspapers; research posters displayed

on selected sites of the downtown McGill campus, McGill University Health Centre [MUHC], specifically the Royal Victoria and Montreal General Hospitals, and two major CLSC's [*centre local de services communautaires*]). Upon referral (from either self or physician), interested patients were contacted by phone, and invited to attend a small group information seminar (conducted in either French or English). Please refer to Figure 3 (in Chapter 6) for Recruitment Algorithm.

3.3.1 Recruitment by Physician Referral

Recruitment by physician referral was a strategy organized for execution in the aforementioned RVH and SMH clinics. The process initially consisted of generating a daily list of patients for each clinic, who were scheduled to be seen by clinic physicians for any medical consultation. From these daily lists, which included each patient's hospital registration number, a lipoprotein profile review by computer search through the respective hospitals' internal servers was conducted at least one day prior to the actual clinic day of interest. Profiles containing LDL-C levels at least 3.4 mmol/L were noted for further investigation by chart screen to assess for conformity to the study's eligibility criteria. Those profiles containing LDL-C values less than 3.4 mmol/L, or simply devoid of lipoprotein information, were discarded.

The next step was to perform a chart screen for all those patients whose LDL-C $\geq$ 3.4 mmol/L. This chart screen consisted of a manual search for at least 2 non-lipid CHD risk factors, if the patient's LDL-C was less than 4.1 mmol/L, in addition to being wary of exclusion criteria such as diabetes or lipid-lowering agents, which would preclude participation. Following this review, the charts of potential candidates were flagged by paperclip with a small (approximately 7 cm x 6 cm) lavender paper. The purpose of this identifying tag was to prompt the clinic physician to inquire of the patient's interest on becoming involved in the study during the scheduled consultation. Discussion of specific details relating to study participation were left to the author, so as to minimize the extent of the physician's involvement in non-clinic activities. Declaring the potential eligibility of the patient, this lavender paper also identified the name of the study, and the names and

extension numbers of the author and the study's physician. Space was provided at the bottom for the clinic physician to fill in the patient's name and telephone number for later follow-up by the author, if the patient expressed an interest in the study after having spoken with the physician. All completed lavender slips were deposited in a designated slotted "study box" located at the reception or common room for later collection and follow-up by the author. All uncompleted slips were discarded or reused. No patient was ever contacted whose name and telephone number were not supplied to the author, as this was interpreted as a refusal to participate in the study.

Patients who were referred to the study were later contacted by telephone. These patients were provided with general details of the study, and were interviewed briefly for the purpose of corroborating their eligibility criteria determined from the chart review. Upon successful completion of the interview, interested patients were invited to attend an upcoming small introductory group information seminar, the attendance of which was required for study participation.

Due to established procedures for chart delivery from the archives to the RVH CC, charts were reviewed each morning on-site prior to, or at the outset of the clinic day, as soon as the charts became available. For RVH IMU and SMH FMC clinics, charts were customarily pulled one day ahead of the clinic day of interest, which allowed for advanced screening, generally ensuring that all charts of interest were able to be examined without the concern of disruption to the physician or support staff's routines by same day review of charts. While it was initially hoped to include two Endocrine clinics from the RVH, it was soon realized that recruitment efforts would be inefficient in this milieu given the fact that the majority of Endocrine-referred patients were currently receiving lipid-lowering drug therapy—an exclusion criterion for the study—at the time of referral. Thus, recruitment in these clinics was soon halted in favor of focusing on the aforementioned more fruitful general practice clinics.

It should be stated that prior to beginning any screening in the targeted clinics, a presentation was always made by the author, almost always with the study's physician, to explain the study's rationale, design, and instruments to the clinic's physicians. This forum was usually scheduled as part of the clinic's grand rounds or monthly staff meeting

(SMH FMC). By proceeding in this manner, study personnel could be introduced, study objectives could be clarified, the role of the patient could be defined, and practical issues relating to recruitment in the specific clinic could be addressed. Physicians could therefore emerge more informed on the study and its risks to their patients, and confident with regard to the quality of care as facilitated by the multidisciplinary approach of the study.

3.3.2 Recruitment by Self-Referral

Recruitment by self-referral included all those study participants who were not referred by a health care professional, who may have learned about the study through a third person (i.e. spouse), or who responded to one of the public advertisements (i.e. poster, newspaper advertisement). One custom-designed ¼-page newspaper advertisement in French and one in English were run on two separate occasions in two complimentary Montreal newspapers—*Mirror* and *ICI*—during November 4-11 1999 and January 13-20, 2000 (Appendix B.1). The *Mirror* is an English language newspaper, which has an estimated total readership of 285,000 (56% male, 44% female), with 40 % of its readers residing in the age category of 35 years and above. A weekly circular, it is distributed across the entire island of Montreal. By comparison, *ICI* is a French language newspaper, which has an estimated total readership of 237,000 (59% male, 41% female), with 42 % of its readers aged at least 35 years old. Similar to the *Mirror* in content, style, and layout, this weekly circular is also distributed across the entire island of Montreal. Both papers attract a significant proportion of middle class, highly educated readers. In the *Mirror*, 47% of its readers are university-educated, with 45.5% reporting yearly incomes in excess of $ 50,000. By comparison, 63% of *ICI* readers are university-educated, while 41% collect a yearly income in excess of $ 50,000. Both periodicals are managed by the same firm, *Communications Gratte-Ciel Ltée*. (*Mirror*, *ICI* demographic information) Interested readers were provided with the McGill Nutrition and Food Science Centre telephone number in order to contact the author for further details. Due to an overwhelming response in the range of 50-55 callers on each of the two occasions the

advertisement was run, a secretary was asked to record the names and telephone numbers of the individual callers in a log book for follow-up by the author as soon as was convenient.

While these newspaper advertisements served as the primary means by which to recruit self-referred participants, 8.5" X 14" colored posters were also displayed at various sites within the MUHC and McGill University downtown campus, in addition to postings at two major CLSC's. These bright pink posters were an enlarged facsimile of the newspaper advertisements, except for the inclusion of tear-off tags at the bottom of the page, which provided the McGill Nutrition and Food Science Centre's telephone number along with the author's name as a contact person. Posters were displayed at designated sites at the following institutions: Royal Victoria Hospital, Montreal General Hospital, McIntyre Medical Building, Redpath Library, McGill Student Union Building, McGill Centre for Continuing Education, Guy Metro and Côte-des-Neiges CLSC's.

All respondents from both the newspaper and poster advertisements were interviewed by the author in a systematic manner, using a standard interview sheet devised to address all relevant inclusion and exclusion criteria. In addition, respondents were asked to provide the results of their most recent lipoprotein analysis and to describe any previous encounters with a dietitian if applicable, in order to assist in the initial determination of their eligibility (Appendix B.2). Like the physician-referred patients, self-referred respondents who were deemed initially eligible were also invited to attend a small introductory group information seminar, as was required for study participation.

3.4 Information Seminars

The objective of these meetings, which were held most often in the evening, (n=17: English=11, French=6) was to provide prospective participants with further details on their responsibilities as volunteers in the study, to instruct them on how they would report on their diet and physical activity habits, and to offer general cholesterol education by way of a short (5-minute) video presentation entitled *Atheromatosis*[96], along with introductory teaching on diet (by registered dietitian), exercise, and medication (by the

author, a registered pharmacist). Approximately 2 ½ to 3 hours in duration (including a short 10-15 minute nutrition break) depending on group size, all information seminars were led by the author, during which time all dietary teaching was conducted by the same research dietitian. Attendance of a single group information seminar was a prerequisite for study eligibility. Informed written consent was obtained at the conclusion of each presentation from all those patients who expressed an interest to participate in the study. Attendees who declined to participate were subsequently excused from the remaining portion of the seminar. The patients who had given consent were then measured for baseline weight, height, blood pressure, and asked to complete 3 questionnaires[‡] (Appendix C.1, C.4.1 and C.4.2). Caltrac$_{TM}$ accelerometers (1 each) and Bouchard 3-Day Physical Activity Records (3-DPAR, 1 set of 3) were distributed, along with assignment of dates for wear/reporting beginning the following day. Finally, laboratory appointments for fasting lipoprotein analyses were scheduled within approximately 2 weeks of an information seminar to both confirm eligibility and characterize baseline lipemic status.

Once the results of the blood test became known, patients were contacted, with those eligible being scheduled for their first official study appointment (Visit 1) with the study physician. The research dietitian was also concurrently apprised of the names and phone numbers of the eligible patients, so that a single baseline 24-hour recall could be conducted prior to the patient's first visit. All initial and follow-up laboratory and physical assessments were conducted at the Royal Victoria Hospital to ensure comparability of data.

3.5 Study Visits

Participants were followed at the RVH Metabolic Day Centre on 4 visits at 6-week intervals over the 18-week period, during which time, they had no contact with each other. They were randomized to one of the two groups at Visit 1. The author assessed total body weight, blood pressure, completion of Caltrac$_{TM}$ log sheets and activity records, body fat composition via bioelectrical impedance analysis (BIA; Visits 1, 3), Stage of

[‡] These questionnaires had all been previously tested for readability in Endocrine diabetes and lipid clinics.

Change (Visits 2, 4), and medication adherence (Visits 2-4). Medication tolerance was also assessed and followed over the course of the study (Visits 2-4). The initial visit (Visit 1) included primary medical work-up by the physician, who also reviewed them at Visits 1 and 3. In the event patients were not reachable by telephone for their food intakes during the 6 weeks between visits, they were seen in-person by the research dietitian at the time of their visit. This was to ensure the collection of the appropriate number of 24-hour recalls required for the given phase of the protocol.

3.6 Individual Consultation with a Registered Dietitian

It should be stated that there were two dietitians involved in the study: one dietitian functioned solely as a research dietitian, collecting 24-hour recall study data from the patients with the assistance of 2-dimensional food posters, while the other worked strictly as a clinician, developing and evaluating the patient's diet. They worked independently from each other, with no sharing of information throughout the entire duration. This was done on purpose for two reasons: 1) to prevent bias on the part of the dietitians, and 2) to increase the comfort level of patients.

Upon completion of Visit 1, randomized patients were subsequently contacted by phone by the clinical dietitian for scheduling of two individual diet consultations. The initial referral with the dietitian was approximately 60 minutes in duration, while the follow-up visit was about 20 minutes. Patients were encouraged to contact the dietitian by telephone as needed following the first visit. Initially assessed for medical and social history, in addition to current eating habits as estimated from a single 24-hour recall, all patients had an individualized sample meal plan developed for them based on principles from the American Heart Association (AHA) Step I diet. Published educational material on lowering dietary fat and cholesterol, *A Matter of Fat* (*I* and *II*)[97,98] and the *Becel*® *Healthy Heart Nutrition Guidelines*[99], were also provided.

3.7 Study Medication

3.7.1 Distribution

Patients randomized to the treatment group (i.e. receiving study medication for the entire 18 weeks) were initially provided with a 6-week supply† of placebo, followed by another 6-week supply of placebo at visit 2, and then by a final 6-week supply of either Zocor® (simvastatin 10 mg) or placebo at Visit 3. The control group, receiving study medication for weeks 12-18 only, were provided with a single 6-week supply of either Zocor® (simvastatin 10 mg) or placebo at Visit 3. Patients were instructed to take 1 tablet once daily in the evening with or without food. In addition, avoidance or lengthening of the time interval of grapefruit or grapefruit juice consumption in relation to the timing of medication administration was counseled in order to prevent significant dose magnification, which may occur as a result of combining simvastatin and grapefruit or its juice[100].

3.7.2 Contents

Zocor® 10 mg is a *peach-colored, shield-shaped, film-coated tablet, engraved 735 on one side and Z on the other*[63]. The following ingredients relate to the composition of Zocor®: simvastatin 10 mg (active ingredient), butylated hydroxyanisole (preservative), citric acid (buffer), hydroxypropyl cellulose (tablet coating agent), lactose (diluent), magnesium stearate (tablet lubricant), methylcellulose (suspending agent), microcrystalline cellulose (combination binder-disintegrant in tableting), pregelatinized starch (tablet disintegrant, filler, binder), red ferric oxide (pigment), talc (tablet excipient, filler), titanium dioxide (colorant), and yellow ferric oxide (pigment)[63 101].

Two different placebo tablets, varying slightly in physical appearance and chemical composition, were used due to the exhaustion of the manufacturer's supply of

† Patients who had planned to be away (i.e. vacation) for a period extending beyond the date of the next scheduled 6-week follow-up visit, were given extra tablets to prevent unintended medication-free intervals.

the initial tablet. The first placebo tablet was a hard-compressed white biconvex tablet completely devoid of identifying marks, which consisted of the following inactive ingredients: calcium hydrogen phosphate (buffer), microcrystalline cellulose (combination binder-disintegrant in tableting), highly dispersed silicon dioxide (anticaking agent), magnesium stearate (tablet lubricant), and maize starch (tablet disintegrant, filler, binder). The second placebo tablet used during the latter half of the study was a hard-compressed white oblong biconvex tablet devoid of identifying marks, and composed of the following inactive ingredients: lactose (diluent), microcrystalline cellulose (combination binder-disintegrant in tableting), and magnesium stearate (tablet lubricant)[101]. (Personal communication, Bayer, Dr. M. Seger, July 25, 2000)

3.7.3 Assessment of Adherence

In order to assess medication adherence, patients were asked to bring in their previous visit's medication vial including any leftover pills to the next visit. Patients who forgot to bring in their old medication vial were asked either to call a family member at home at the time of the visit, or to personally report back by telephone after the visit the number of tablets remaining in their bottle. Any remaining tablets were counted and recorded. Adherence was expressed as a percent of actual pills taken (i.e. 40/42 pills taken = 95%). To be considered adherent, patients would have taken 80% or more of the supply of tablets provided. In addition to pill counts, adherence to scheduled follow-up visits was used as a secondary indicator of medication adherence.

3.7.4 Adverse Events

Adverse events were reported to, and recorded by the author. Participants were informed of potential adverse effects associated with the use of simvastatin (Zocor®) during the initial Information Seminar. Moreover, each patient was provided with a study binder, that also contained a standard patient monograph on Zocor®, which included information on self-monitoring for possible adverse events. This monograph was similar

in content and presentation to that which would have been provided by the patient's community pharmacy.

3.8 Ethical Approval

3.8.1 Royal Victoria Hospital

The original study protocol was submitted for ethical review on June 1, 1998 to the Royal Victoria Hospital Research Ethics Board (RVH REB), and was subsequently approved on July 6, 1998. Three separate amendments were filed and subsequently approved by the RVH REB for their possible incorporation into the existing protocol; 1) Submitted: October 30, 1998; Approved: November 19, 1998: Special medication vial with an inconspicuously embedded microchip in the cap used for ascertaining medication adherence; 2) Submitted: January 26, 1999; Approved: February 16, 1999: Public advertisement prototypes (French and English) for newspaper and poster display, 3) Submitted April 12, 1999; Approved: May 18, 1999: Additional fasting blood sample for lipoprotein analysis at week 18. All three amendment submissions were approved, but due to excessive costs, only the last two were implemented.

3.8.2 Saint Mary's Hospital Centre

In an attempt to expand the existing pool of potential participants to include the Family Medicine Clinic at Saint Mary's Hospital (SMH FMC), a second complete protocol submission including a redesigned consent form according to SMH specifications was filed on August 16, 1999 for independent review by the SMH Research Ethics Committee (REC). The protocol, modified slightly from its original version by the implementation of the two aforementioned amendments, was also granted final approval by SMH REC on November 18, 1999. Recruitment at SMH FMC officially began January 11, 2000 and concluded March 6, 2000, since the required sample of participants had been achieved.

3.9 Financial Support for this Study

Funding for this project was made possible through a grant from the Royal Victoria Hospital Research Institute and through research funds from the McGill Nutrition and Food Science Centre. The study medications used in this project were generously donated by Merck Frosst (Zocor® 10mg) and Bayer (placebo tablets).

3.10 Debriefing Sessions

3.10.1 Procedure

Upon completion of the study, each participant was informed on how they had progressed in improving their lipemic control during the time they had participated in the study. Individual debriefing appointments were arranged approximately 2 weeks following the patient's final visit. Each patient's results were analyzed in terms of complete lipoprotein profile including apolipoproteins (Total-C, HDL-C, triglycerides, LDL-C, Total-C:HDL-C ratio, Apolipoprotein B, Apolipoprotein A1, Lp(a), and Apolipoprotein E) total body weight and body mass index, and blood pressure. Parameters were reported for 3 time points: Baseline (–2 weeks), Visit 3 (+12 weeks), and Visit 4 (+18 weeks). While the complete lipoprotein profile was documented in each report, apolipoprotein and Lp(a) levels were generally not discussed with the patient. This was done because targets for apolipoproteins are currently not addressed in practice guidelines. Therefore, these data were collected strictly for the purpose of scientific investigation.

3.10.2 Purpose

The purpose of these debriefing sessions was fourfold: 1) to provide the patients with feedback on their own progress in improving their lipoprotein profiles, 2) to ensure appropriate follow-up care with the patient's general practitioner by issuing him or her a

copy of the report, and 3) to determine the success of the blinding with regard to the study medication, and 4) to gauge the degree to which the patients were satisfied with the organization of the study.

3.10.3 Content

Debriefing may be considered as a type of unblinding process, which is used more often in psychological research, where deception may figure prominently. The debriefings were divided into two parts during a single appointment: 1) the feedback session, and 2) the progress report session.

All debriefings took place in-person on an individual basis with each patient (following protocol completion) save one case, where the feedback portion only was conducted over the telephone. Prior to the release of the latest Canadian guidelines, all treatment evaluation and post-study follow-up care recommendations were based upon the NCEP ATP II. Once the new Canadian guidelines became available, the progress reports were subsequently adapted to reflect this latest set of treatment recommendations.

3.10.3.1 Feedback

The feedback session consisted of a set of prepared questions, which ranged from issues relating to the patient's belief regarding the identity of the study medication they were taking to whether or not they would recommend the study to other patients. (Please refer to Appendix E for a copy of the questions posed.) Patients were seen for their feedback prior to meeting with the physician to discuss their progress. This was to ensure that the impressions they gave regarding the study medication's identity were not potentially confounded by *a priori* knowledge of the pill's identity, the revelation of which occurs during the progress report phase of the session. The majority of patients were interviewed by the author alone for their feedback, while a small minority were interviewed by the author in the presence of the study's physician.

3.10.3.2 Progress Report

The progress report session would then follow the feedback session, where the author would discuss the progress report with the patient in the presence of the study's physician, as well as reveal the identity of the study medication. Patients who had expressed concern over their apparent intolerance of a placebo were then able to be reassured by the physician.

4.0 APPARATUS AND MEASURES

4.1 Instruments and Assessments

In order to document changes in diet and exercise behaviors, a variety of direct and indirect instruments were employed including: mercury sphygmomanometer, digital scale, body fat analyzer, two-dimensional food models, Caltrac$_{TM}$ accelerometer, Bouchard 3-Day Physical Activity Record, and Stages of Change questionnaires. Lipoprotein profiles were analyzed at the Royal Victoria Hospital Biochemistry, Immunology, and Genetics Laboratories as applicable. Medication adherence was assessed by pill counts, taking into consideration time of follow-up presentation, the procedures for which are reviewed in Section 3.7.3

4.1.1 Blood Pressure Measurement

At each visit (Baseline, Visits 1-4), participants were assessed for seated blood pressure, and radial pulse. Two blood pressure readings were measured separated by a five-minute rest period using a free-standing mercury manometer (Baumanometer®, W.A. Baum Co., Inc., Copiague, NY) and stethoscope. These two measurements were then averaged for a mean seated blood pressure. The participant's radial pulse was also palpated for 15 seconds during the five-minute rest interval, and multiplied by 4 to achieve a pulse rate per minute. With the exception of the Information Seminar, all blood pressure and pulse measurements were taken by the author, who had been previously trained by a registered nurse for this purpose.

4.1.2 Total Body Weight

At each visit (Baseline, Visits 1-4), participants were weighed on a digital Seca® (Seca Corporation, Columbia, MD) scale (Maximum weight= 200 kg) in their street

clothes less their shoes. Weights were recorded to the nearest 0.1 kg. With the exception of the Information Seminar, all body weight assessments were performed by the author.

4.1.3 Body Composition

Using the Tanita® Body Fat Analyzer TBF-105 (Tanita Corporation, Tokyo, Japan), leg-to-leg bioelectrical impedance analysis (BIA) was used to estimate the percent body fat of each participant at two time points: weeks 0 (Visit 1) and 12 (Visit 3). To approximate the contribution of street clothing to the total body weight measured by the unit, 0.3 kg total body weight was systematically deducted for each participant. All bioelectrical impedance measurements were taken by the author.

Similar in appearance to a bathroom scale with the exception of steel-plated footpads, which serve as contact electrodes, patients mounted the body fat analyzer barefoot, and stood erect with arms at their sides while the measurement took place. Although the body fat analyzer will measure total body weight, it does require the input of both height and gender data.

4.1.3.1 Validation Studies

The principle of leg-to-leg BIA is based upon a two-compartment model of body composition for estimating total body water (TBW)—fat and fat-free mass. While the former consists almost entirely of fat, the latter compartment is more heterogenous in make-up, consisting of varying proportions of water, mineral, fat, and protein. Therefore, in order to successfully employ a two-compartment model, basic assumptions are made regarding the proportions in which these fat-free mass constituents exist[102]. The technology behind the leg-to-leg BIA involves the generation of a low frequency electrical current, which travels only through the person's lower limbs. Impedance to electrical flow is dependent on the relative amounts of fat to fat-free mass. The greater the proportion of fat-free mass—which supports conduction—the lesser the impedance to flow, while the greater the proportion of fat mass, the greater the resistance to flow.

Hence, TBW is estimated from the voltage drop measured across the four steel electrodes (i.e. the front and heel footpads).

The use of leg-to-leg BIA for assessing body composition has been previously validated against dual-energy X-ray absorbtiometry (DEXA) $r=0.94$, $p<0.001$ in a study by Rubiano et al.[103] using a sample of 39 volunteers (80% female) of mean age 55.4 $\pm$ 17.7 years, and BMI 28.6 $\pm$ 4.0 kg/m^2. In addition to this latter study, leg-to-leg BIA has also been shown to be comparable in performance to the conventional method of impedance measurement by tetrapolar BIA by Jebb et al.[102] in a study of 205 participants (males=104) aged 16-78 years with BMI's of 16-41 kg/m^2 evaluating the two-compartment BIA against a four-compartment model[102,103]. However, in a study by Bell et al.[104] that assessed foot-to-foot impedance in predicting TBW against the criterion measure, deuterium oxide dilution, among male and female participants (n=57) aged 19-56 years with mean BMI=24.9 kg/m^2, one caveat that was raised with respect to the use of leg-to-leg BIA was the potential for underestimation of absolute TBW as the latter rose. The author attributed this decrement in reliability to an error in the internal software program's prediction algorithm, which may present a limitation to the clinician in estimating percent body fat changes in those people with large TBW compartments. However, a threshold BMI beyond which the measurement became less reliable, was not offered.

4.1.4 Fasting Lipoprotein Analysis and Other Biochemical Testing

All laboratory indices were analyzed at the Royal Victoria Hospital (except for those of patient #29, whose data were assessed at the Centre Hospitalier de l'Université de Montréal). Total cholesterol, triglycerides, and HDL-C were analyzed using the Bayer DAX 96 analyzer, following which, LDL-C was calculated using the Friedewald equation[31]. Since all serum triglyceride measurements remained below 4.5 mmol/L, the use of this equation in this population is appropriate. The apolipoproteins, A1, B, and Lp(a), were all measured via immunological assay using the Beckman Image

nephelometer. Genotyping was performed to characterize Apolipoprotein E. (Personal communication, Dr. D. Blank, August 20, 2000)

4.1.4.1 Lipoprotein Profiles

All participants were measured at baseline, 12 (Visit 3), and 18 weeks (Visit 4) for fasting lipoprotein analysis. Each profile ordered consisted of the following: Total-C, triglycerides, HDL-C, LDL-C, Total-C: HDL-C, Apolipoprotein A1 [Apo A1], Apolipoprotein B [Apo B], Lipoprotein (a) [Lp(a)], and Apolipoprotein E genotype ([Apo E], Visit 3 only).

4.1.4.2 Thyroid Stimulating Hormone (TSH)

At baseline, a screening TSH was performed to rule out secondary dyslipidemia in all those patients who had never been previously screened for hypothyroidism as evidenced by RVH server information. Patients who were not registered at the RVH were also screened for hypothyroidism.

4.1.4.3 Creatine Kinase (CK) and Alanine Aminotransferase (ALT)

Included with the Visit 3 lipoprotein analysis orders were creatinine kinase (CK) and alanine aminotransferase (ALT). CK and ALT were measured to document baseline muscle and hepatic function respectively, and are considered standard monitoring practice prior to the initiation of lipid-lowering drug therapy. These measurements were subsequently repeated at Visit 4 in all those patients who had received simvastatin for the final 6 weeks of the study in order to evaluate any clinically significant changes that may have occurred in muscle and liver function during that interval.

4.1.5 Dietary Intake

4.1.5.1 24-Hour Recall with 2-Dimensional Food Models

Dietary assessment was accomplished through the collection of food data using 24-hour recalls with 2-dimensional food models (set of 2, black and white, 61 cm x 47 cm posters consisting of various geometrical shapes used to approximate food portion sizes) (Appendix C.2). The food posters served as a standardized reference through the use of which, both the participant and the research dietitian communicated over the telephone. All food recalls (n=416) were performed solely by the research dietitian with the exception of 2, which were done by the author. Recalls were executed in a random manner, for a total of 8 collection days over 18 weeks. The distribution of the recalls were divided as follows: 1 at Baseline (approximately 1 week prior to the initial physician visit), 2 between Visits 1-2, 3 between Visits 2-3, and 2 between Visits 3-4. Food intakes were typically collected by telephone interview. However, if the research dietitian experienced significant hardship in contacting the patient, an in-person recall was performed alternatively with the patient at the time of the follow-up visit.

A single baseline recall was conducted approximately 1 week prior to the first visit, while the 7 remaining recalls were performed after randomization during the active phase of the protocol. This self-report method has been validated previously[105], and has been shown to be reliable by itself in assessing dietary fat intake[106]. In order to approximate usual dietary fat intake, a minimum of six recalls is necessary[107]. Eight recalls were used, where one was conducted prior to randomization, five during the first 12 weeks, and two during the last 6 weeks of the study to allow between-group comparisons of dietary changes from baseline.

4.1.6 Physical Activity

4.1.6.1 Caltrac™ Accelerometer

The Caltrac™ accelerometer is an inexpensive, objective means of quantifying activity level performed on relatively flat terrain by both adults and children[108 109 110]. Designed to be worn fastened to the hip, it is an unobtrusive digital sensor, which measures total movement counts associated with vertical acceleration and deceleration from isotonic activity. It is not suitable for describing isometric activity, however, nor is it useful in quantifying non-weight-bearing exercise[109 110].

The Caltrac™ requires the input of the person's weight, height, age, and gender, and continuously accumulates their activity counts or calories unless the batteries are removed from the system. In addition, the device is capable of storing up to 19,999 activity counts before resetting itself to zero[111]. Besides quantifying movement, the accelerometer has the ability to give an estimate of the person's basal metabolic rate (BMR)[108 111]. The Caltrac™ accelerometer is available through *Muscle Dynamics Fitness Network Inc.*, located in Torrance, CA[109 111 112].

The validity of the Caltrac™ accelerometer has been assessed in adults using daily log books (r=0.11 - 0.37), the Stanford Seven-Day Physical Activity Recall questionnaire (r=0.12 - 0.37), observation of activity (r=.69), and the Large Scale Integrated Activity Monitor (LSI) (r=0.83). Test-retest for the Caltrac™ has also been assessed (r=0.35-0.54)[112].

Patients were asked to wear the Caltrac™ for five consecutive days during four occasions in this study. They were also asked to record their "daily total" in a log book at the end of each day, since accelerometers were only worn during waking hours.

4.1.6.2 Bouchard 3-Day Physical Activity Record

The Bouchard 3-Day Physical Activity Record (Appendix C.3.2) is a self-administered questionnaire designed to quantify physical activity expenditure using categories of grouped activities assigned an estimated caloric expenditure[6]. It presents as

a grid, such that activity data are entered in the framework of the 2400 hour clock with 15-minute time blocks. Validation of the activity questionnaire has been carried out previously in a sample of 150 adults and 150 children by Bouchard et al.[113]

The activity records were circulated four times during the study with the accelerometers. Patients were asked each time to complete the questionnaire for three designated days, during the five days they were assigned to wear the Caltrac™ accelerometer. Questionnaires and accelerometers were then returned to the hospital after the five-day period.

4.1.7 Behavioral Assessment

4.1.7.1 Stages of Change

The Stages of Change questionnaires were used to classify each patient into either Precontemplation, Contemplation, Preparation, Action, or Maintenance stages. This was accomplished by categorizing patients according to their responses to a set of questions relating to each of the four specific behaviors targeted: 1) consuming 5 or more fruits and vegetables per day, 2) reducing dietary fat consumption, 3) achieving a lower total body weight, and 4) engaging in regular exercise. All Stages of Change questionnaires were scored by the research assistant.

4.1.7.1.1. Dietary Intake

Stage of change for readiness to lower total fat intake to less than 30% of total energy was assessed using the questionnaire developed by Greene et al.[114] It consisted of five stage-oriented questions designed to classify people according to their intention or action to avoid consuming high fat foods. This was corroborated with actual dietary behaviors related to reducing fat intake.

4.1.7.1.2 Exercise

Readiness to incorporate a program of regular exercise into one's lifestyle was assessed using the questionnaire developed by Marcus et al.[84] Five fundamental questions regarding current exercise status are asked, each corresponding to one of the five stages of change. Differences between the questions relate to the projected time frame for adopting regular physical activity into one's daily routine, as determined by the patient's subjective evaluation.

5.0 DATA ANALYSIS

All data analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 10.0 (1999, Chicago, IL). Greenhouse-Geisser p-values were used for interpreting repeated measures analysis of variance (ANOVA).

5.1 Physical and Biochemical

Physical data such as total body weight, mean seated blood pressure (systolic, diastolic), lean body mass, fat body mass, and biochemical data such as lipoprotein levels (except Apo E) were analyzed for changes occurring over the first 12 weeks using repeated measures ANOVA. Since body composition was not measured until the first visit, changes in lean body mass and fat body mass were analyzed using Visit 1 as the baseline. Changes are reported as mean $\pm$ standard error of the mean (SEM).

5.2 24-Hour Recall Food Records

5.2.1 Procedure for Analysis of Food Records

All food recall data (n=416 records) were collected by the same research dietitian. These data were then analyzed using Genesis™ R&D software, Version 5.2 (ESHA Research, 1997, Salem, OR) by a team of 4 Dietetics students, and 1 clinical research assistant, all of whose work was evaluated by a single, independent research dietitian (henceforth referred to as the 'evaluating dietitian'). Two of the students (including the author) were graduate level students (M.Sc., Ph.D. candidates), while the other two were undergraduate level students, who had finished their third level stage. These food record analyses were completed over a period of 2 ½ months.

Two of the students were recruited following a 2-hour introductory seminar organized by the author, and animated by a registered dietitian with previous research experience (M.Sc.) in analyzing 24-hour recalls from two-dimensional food model data.

Eight interested undergraduate Dietetics students responding from a poster advertisement circulated to both the respective McGill University and Université de Montreal faculties attended this introductory meeting. The objectives of the seminar were threefold: 1) to teach the concepts behind the two-dimensional food posters for the purpose of translating 24-hour recall data, 2) to introduce the Genesis™ R&D software program as the database by which translated food data would be interpreted and analyzed, and 3) to evaluate and select the most competent candidates for analyzing the 24-hour recall data from the study, as assessed by the animator, the evaluating dietitian, and the author. Following the conclusion of the seminar, students were asked to complete two questionnaires evaluating the content of the program and the effectiveness of the animator. Feedback from the former served as an index of the level of general comprehension, permitting a follow-up review of difficult concepts with the selected students. Each student participating in the analysis of the 24-hour recalls was compensated with a $200 honorarium following the completed analysis of a predetermined number of food records. Six students (all of whom had completed their third level stage) were initially selected. However, due to the availability of higher wages elsewhere, four students declined to participate in the research project.

5.2.2 Analysis of Food Records

All food data were analyzed using computers at the McGill Nutrition and Food Science Centre. Students were asked to allocate as much of their time as feasible in order to complete the food records within a set time frame. Provided with an initial food standards list as a guideline in analyzing the food data, students were encouraged to consult with each other frequently to resolve difficulties in data translation. Functioning also as a resource person and supervisor, the author assisted the data analysis team in retrieving information on unlisted food items (i.e. recipes, ethnic foods), and in offering advice on the analysis of controversial items. Because Genesis™ R&D is an American-based program, several Canadian food items were not able to be appropriately coded from the list of food items provided in the database (i.e. non-hydrogenated margarines). For

this reason, new food items (i.e. Becel®) were entered into the database according to the nutrient composition data provided on the food labels. Moreover, some food record data necessitated recipe references in order to more precisely analyze their nutrient content. Most often, recipes were obtained on-line from major food recipe searchable databases, such as *Epicurious.com*. In other cases, conventional cookbooks were employed. All unlisted single-entity foods were always entered into the database as new food items by the author from either food label information, or on-line from nutrient composition data from the USDA Agricultural Research Service Nutrient Data Laboratory (www.nal.usda.gov/fnic/cgi-bin/nut_search.pl).

5.2.3 Assurance of Data Quality

Once a given patient's set of food records was completed (n=6-8), the records were printed, collated, packaged, labeled, and submitted to the author for delivery to the evaluating dietitian. The evaluating dietitian would then systematically review each set of food records to evaluate the quality of the data. Data were examined in terms of both accuracy and appropriateness in representing the patient's reported food intake. Any modifications recommended by the evaluating dietitian for improving the quality of the food record analyses, such as the selection of a more representative food item from the Genesis™ R&D database or a more appropriate portion weight, were indicated in writing on each printed report. All evaluated analyses were returned to the author for amendment by the latter and the research assistant. Following the correction of these food records, relevant sections were then reprinted, and resubmitted as an intact set to the evaluating dietitian for final verification and approval. The designated hard-drive file was then systematically reviewed by the author for verification that all the contained food records represented the "final approved" versions as updated from the initial set of diskettes. Statistical analyses were then conducted based on the analysis of these hard-drive records.

5.2.4 Precision among the Raters

To document the precision among the five raters in analyzing the food records, a single food record was selected by the research dietitian for analysis by each rater. None of the raters had been aware they were being tested, except the author, who had organized the testing procedure. Testing was conducted toward the end of the time frame allocated for the analysis of all the patient food records. To assure blindedness to the testing procedure, the food record was disguised by patient name, such that each rater received the test record as an inconspicuous component of an actual assigned batch of patient records.

5.2.5 Statistical Analyses

Food data were analyzed for changes occurring over the first 12 weeks (n=318 records) between the two groups using repeated measures ANOVA. Mean group intakes were initially determined according to the number of 24-hour recalls conducted within the visit time interval: Baseline to Visit 1 (1 recall); Visit 1 to Visit 2 (2 recalls), and Visit 2 to Visit 3 (3 recalls). Nutrients examined included: total energy, protein, total fat, saturated fat (SFA), polyunsaturated fat (PUFA) (including omega-3 fatty acids), monounsaturated fat (MUFA), cholesterol, total carbohydrate, sugars, starches, dietary fiber (including soluble and insoluble) and alcohol.

Precision among the raters was analyzed by descriptive statistics. Means and standard deviations for each nutrient were reported. Raw data for each rater is presented for comparison (Table 8). Coefficients of variation (CV) were calculated, and are presented as percentages in the table.

5.3 Caltrac$_{TM}$ Accelerometer Readings

Accelerometer data were analyzed according to daily activity count records maintained on a standard log sheet by the participant. A mean daily Caltrac$_{TM}$ activity

count was determined by simple addition of the total daily activity counts registered by the participant over the 5 consecutive days of wear. In cases of malfunction or omission to wear the machine, a mean daily activity count was calculated based upon the remaining eligible days of wear. The mean change in daily activity counts between groups was analyzed by repeated measures ANOVA for changes occurring between baseline to Visit 1 (2 weeks), Visit 1 to Visit 2 (6 weeks), Visit 2 to Visit 3 (6 weeks).

5.4 Bouchard 3-Day Physical Activity Records

Three-day Physical Activity Record (3-DPAR) data were analyzed according to recommendations by Bouchard[6] by summing the frequencies of performance of 9 levels of physical activity intensity (identified as 1-9 in the records) registered per 15-minute time block over the course of 3 x 24-hour time periods (3 x 96 x 15-minute time blocks). Each frequency was then multiplied by a provided energy expenditure equivalent (kcal/kg/15 min) known to correspond to the given activity intensity level. A mean total daily energy expenditure (kcal/kg/day) was then calculated for the 3 consecutive days when records were kept by the participants. In cases of unclassifiable data or omission to complete records at the time of assignment, a mean total daily energy expenditure was calculated based upon the remaining eligible days during which activity was recorded. The mean change in total daily energy expenditure between groups was analyzed by repeated measures ANOVA for changes occurring between baseline to Visit 1 (2 weeks), Visit 1 to Visit 2 (6 weeks), and Visit 2 to Visit 3 (6 weeks).

5.4.1 Scoring 'Unscorable' Data

The scoring of the activity records was performed by both the research assistant (primarily), and the author. Records, which were either devoid of data in whole or in part, or which contained notations other than the conventional numerical references used to denote activities performed, were considered "unscorable". All initially unscorable activity records, which were not completed according to the instructions given, were

deferred until all scorable records had been evaluated. These unscorable records were then systematically and simultaneously reviewed by both the author and the research assistant for consensus on appropriate activity categorization based on a provided list of activities, which corresponded to a specific intensity category.

5.5 Stages of Change Questionnaires

Individual stages of change were determined for 4 behaviors: 1) consumption of 5 or more fruits and vegetables per day, 2) reduction of dietary fat consumption, 3) achievement of a lower total body weight, and 4) engagement in regular exercise. ("Regular" being defined by the authors as at least 20 minutes of continuous exercise on 3 or more days per week)[84]. All Stages of Change questionnaires were scored by the research assistant.

Descriptive statistics were used to describe the number of individuals in each stage of change at Baseline and Visit 2 (Table 10). The Mann-Whitney Rank Sum Test was used to detect differences between groups at baseline and between baseline and Visit 2. Patients were reclassified for ease of reading into three categories (Decrease, No Change, Increase) according to the direction of their evolution across the stages of change (Table 11). Although not presented at this time, future analyses will seek to validate the observed stage of change against data from actual dietary intakes, activity levels, and demographic information.

5.6 Medication Adherence

Medication adherence was determined as the proportion of tablets taken from the initial supply of study medication provided. To be considered adherent, the participant would have taken at least 80% of the total number of doses provided.

Mean adherence rates were calculated for the placebo group for the interval between Visit 1-2, and Visit 2-3. The frequency of adherence rates of 80% or better was also analyzed. The change in mean adherence rates from Visits 1-2 to Visits 2-3 were

compared using paired sample t-tests between the mean adherence rate determined from Visits 1-2 and that from Visits 2-3. Pearson correlations were performed on medication adherence rates between Visits 1-2 and Visits 2-3, on mean adherence rates versus incidence of adverse effects. and on mean adherence rates and medication belief.

5.7 Adverse Events

The total incidence of adverse events occurring during the first 12 weeks (the time during which the placebo was taken), the most frequently affected organ system, and the total number of patients experiencing at least one adverse event during Visits 1-2 and Visits 2-3 was reported. Pearson correlations were performed between adverse event incidence and medication belief.

5.8 Achievement of NCEP ATP II Target for LDL-C Reduction

Comparison of the frequency of participants who achieved the NCEP ATP II target for LDL-C reduction at week 12 was analyzed by group using the chi-square statistic.

6.0 RESULTS

6.1 Recruitment and Randomization (Figures 2, 3)

6.1.1 Recruitment by Physician Referral

With respect to physician-referred patients, over 13,815 laboratory records were searched between the Royal Victoria and Saint Mary's Hospitals' clinics. Of these cases, approximately 10,809 were either rejected due to absence of lipoprotein data, or because results were outside the established lipemic boundaries for inclusion into the study. Chart-screening ensued in the 3,006 patients whose lipid profiles were initially within the study criteria parameters. Based on exclusionary medical histories and pharmacologic treatments, another 2,549 patients were rejected. Those patients remaining eligible following this chart review (n=457) were identified to the physicians as potentially suitable candidates for the study. Of this cohort, 52 were eventually recruited for the study. Reasons for the non-participation of the 405 patients identified for the study included principally: refusal to participate as evidenced by no contact information provided or ineligibility based on body mass index, as confirmed by telephone interview. (Figure 3)

6.1.2 Recruitment by Self-Referral

Over 110 persons responded to the public advertisements for participant recruitment. Of these 110, ten could not be reached by telephone, despite repeated attempts to contact them. Thus, 100 patients were successfully interviewed, with 26 respondents initially meeting the study's inclusion and exclusion criteria.

6.1.3 Randomization of Eligible Candidates

The physician- (n=52) and self-referred (n=26) study candidates attended the mandatory Study Information Seminar, after which 73/78 candidates provided written informed consent. These 73 candidates then underwent a screening lipoprotein analysis,

following which, another 19 patients became ineligible due to results falling outside the study's lipemic boundaries. The remaining 54 eligible patients were then randomized, with 27 assigned to the treatment (placebo) group, and 27 to the control group.

Figure 2: Cross-section of Participant Origins as Yielded from Recruitment resources

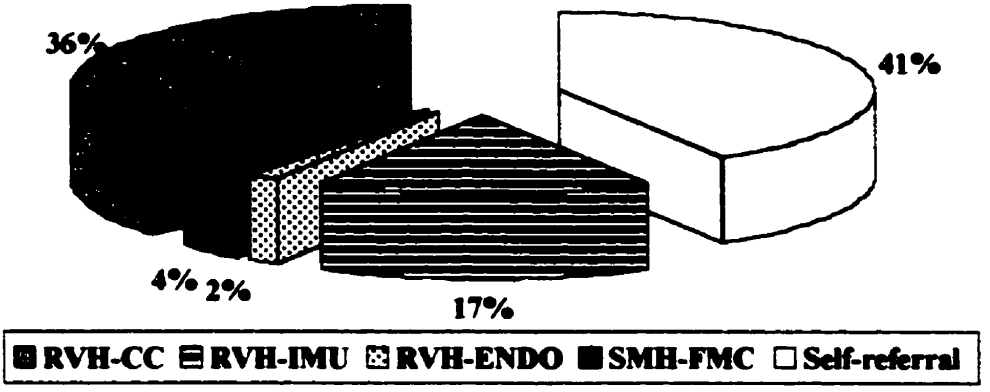
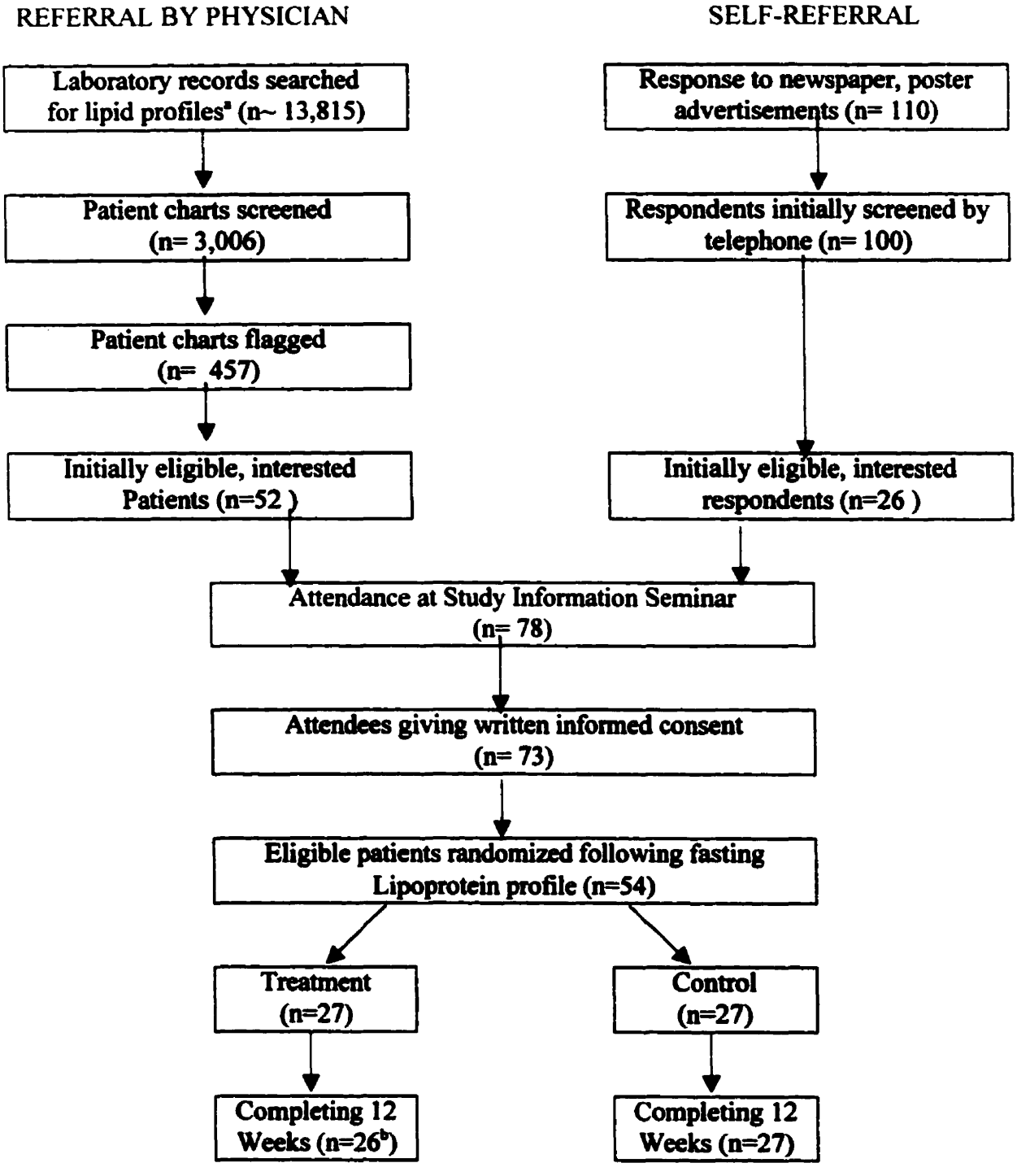


Figure 3: Algorithm of Recruitment and Randomization Procedure



[a] Includes Royal Victoria and Saint Mary's hospitals

[b] One patient discontinued the placebo within the first week of treatment due to intolerable visual disturbances. This patient was alternatively continued on the standard nonpharmacologic therapy (i.e. diet and exercise) alone.

6.2 Attrition

A total of 53/54 patients successfully completed 12 weeks of the 18-week protocol. One patient self-withdrew before even completing the first visit due to personal dissatisfaction with group assignment. (This patient had been randomized to the group which received study medication for the entire 18 weeks). Of the 53 patients, 1 patient who had initially completed Visits 1 and 2, had to be withdrawn due to an unrelated hospitalization for a pulmonary embolism. This patient was later restarted from Visit 1, and successfully completed the entire 18 weeks. Four other patients from the sample of 53 withdrew after 12 weeks. Of these four participants, 1 withdrew due to intolerable gastrointestinal effects attributed to the study medication (placebo). Another two withdrew due to personal crises unrelated to the study, while the fourth withdrawal was a loss to follow-up. This loss to follow-up occurred despite repeated attempts to contact the patient by telephone by the research dietitian, the author, and the study physician.

6.3 Baseline Participant Characteristics

One-way analysis of variance performed between the two groups for differences in baseline characteristics yielded no significant differences in age, body weight, % lean and fat masses, blood pressure, pulse, lipoprotein profiles, physical activity levels, or dietary nutrient intakes. Similarly, chi-square tests performed on gender, country of birth, Montreal Urban Community residency, university education, referral status, number of chronic medications, selected NCEP risk factors, overweight self-assessment, prior dietetic consultations, and number of weight loss attempts carried out in the past year yielded no significant differences between groups. Finally, independent sample t-tests were performed on weight 1 year ago, weight 5 years ago, maximum body weight, and age of maximum body weight produced no significant differences between groups, with the exception of weight 5 years ago. Participants in the placebo group were heavier 5 years ago than those in the control group (84.2 $\pm$ 3.1 kg vs. 75.2 $\pm$ 2.6 kg, p=0.031)

(Tables 5 and 6). However, the difference between groups disappeared when these weights were converted to body mass index (BMI).

Table 5: Baseline Physical and Biochemical Characteristics of Study Participants

Baseline characteristics[a]	Placebo group (n=26)	Control group (n=27)
Age (y)	58.0 + 1.9	56.8 + 2.0
Gender (% female)	12 (46.2)	16 (59.3)
Total body weight (kg)	88.7 + 2.6	82.9 + 2.6
Body mass index (kg/m^2)	30.7 + 0.6	31.1 + 0.8
Lean mass[b] (%)	65.9 + 1.6	63.7 + 1.7
Fat mass[b] (%)	35.0 + 1.9	36.3 + 1.7
Systolic Blood Pressure (mm Hg)[c]	137 + 2	139 + 4
Diastolic Blood Pressure (mm Hg)[c]	85 + 2	86 + 2
Pulse, radial (BPM)[d]	73 + 2	75 + 2
[illegible]		
Fasting plasma glucose (mmol/L)	5.0 + 0.1	5.1 + 0.1
Total cholesterol (mmol/L)	6.41 + 0.10	6.48 + 0.13
Triglycerides (mmol/L)	1.87 + 0.18	1.73 + 0.13
HDL-C (mmol/L)	1.27 + 0.05	1.33 + 0.06
LDL-C (mmol/L)	4.28 + 0.08	4.36 + 0.11
Total cholesterol: HDL-C ratio	5.19 + 0.18	5.05 + 0.20
Apolipoprotein A1 (mg/dL)	140 + 4	146 + 5
Apolipoprotein B (mg/dL)	133 + 3	131 + 4
Lipoprotein(a) (mg/dL)	38 + 7	51 + 12
Apolipoprotein E3/E3 genotype (%)	69.2	70.8
[illegible]		
Caltrac™ accelerometer (counts)	68 + 5	68 + 5[e]
Bouchard 3-DPAR (kcal/kg/day)	44.80 + 1.01[f]	43.64 + 1.02
[illegible]		
Total energy (kcal)	1875.77 + 160.98	1888.97 + 168.02
Protein (g)	82.28 + 8.66	79.32 + 8.35
% energy from protein	17.8 + 1.2	16.9 + 1.0
Total fat (g)	60.67 + 6.87	66.02 + 8.86
% energy from fat	28.4 + 1.6	30.3 + 2.3
SFA (g)	20.61 + 2.70	21.70 + 3.48
PUFA (g)	11.32 + 1.64	13.83 + 2.14
Omega-3 fatty acids (g)	1.09 + 0.18	1.15 + 0.14
MUFA (g)	23.90 + 2.62	23.40 + 3.59
Cholesterol (mg)	260.37 + 43.84	213.62 + 32.57
Total carbohydrate (g)	252.45 + 21.58	244.25 + 24.86
% energy from carbohydrate	54.2 + 2.0	53.3 + 2.8
Sugars (g)	94.68 + 9.71	91.00 + 9.92
Dietary fiber (g)	20.63 + 1.99	20.48 + 2.15
Soluble (g)	5.78 + 0.58	5.58 + 0.59
Insoluble (g)	11.84 + 1.19	11.62 + 1.18
Starches (g)	125.02 + 14.77	111.21 + 12.06
Alcohol (g)	3.54 + 1.20	4.97 + 2.73

[a] Means are reported as Mean ± SEM
[b] Estimated by leg-to-leg bioelectrical impedance analysis (BIA) at Visit 1
[c] Mean of two seated measurements spaced by 5-minute interval
[d] Palpated for 15 seconds and multiplied by 4
[e] n=26
[f] n=25

Table 6: Baseline Sociodemographic Characteristics

Baseline characteristics	Placebo group (n=26)	Control group (n=27)
Canadian-born (%)	15 (57.7)	18 (66.7)
MUC resident (%)	21 (80.8)	21 (77.8)
Married or equivalent	20 (76.9)	17 (63.0)
University education (%)	16 (61.5)	12 (44.4)
Recruited by MD referral (%)	16 (61.5)	18 (66.7)
≥ 1 Chronic Rx medications	15 (57.7)	21 (77.8)
≤ 2 CAD risk factors	22 (84.6)	22 (81.5)
LDL-C ≥ 4.1 (%)	22 (84.6)	18 (66.7)
Risk factor for age (%)[c]	22 (84.6)	20 (74.1)
Family history of premature CHD(%)	7 (26.9)	8 (29.6)
Diagnosed hypertension (%)	7 (26.9)	10 (37.0)
Smoking (%)	5 (19.2)	2 (7.4)
Consider self overweight	22 (84.6)	24 (88.9)
Prior dietetic consultation (%)[b]	11 (42.3)	15 (55.6)
≥ 1 weight loss attempts in past year	10 (38.5)	15 (57.7)
Weight 1 year ago	86.7 ± 2.7	80.7 ± 2.6
BMI 1 year ago	*29.9 ± 0.6*	*30.3 ± 0.8*
Weight 5 years ago	84.2 ± 3.1*	75.8 ± 2.5*
BMI 5 years ago	*28.9 ± 0.6*	*28.1 ± 0.6*
Maximum body weight (kg)	90.1 ± 2.9	85.2 ± 3.1
Maximum BMI	*31.1 ± 0.5*	*31.7 ± 0.8*
Age of maximum body weight (y)	53.2 ± 2.2	47.8 ± 2.6

[a] Means are reported either as Mean ± SEM or by frequency (%)

[b] Includes consultation for any reason

[c] Age: male ≥ 45 years; female ≥ 55 years or premature menopause without estrogen replacement therapy

* Significant p=0.041

MUC = Montreal Urban Community

6.3.1 Weight Loss History and Food and Supplement Activities

6.3.1.1 History of Weight Loss Methods

Additional information regarding specific methods used for the purpose of promoting weight loss was elicited from participants from the General Information questionnaire. Participants were queried as to the nature of the attempts made during both the past year and the past 5 years to lose weight. In all cases except one, (increasing physical activity level during the past 5 years, 51.9% in control group versus 23.1% in placebo group p=0.031) there were no statistically significant differences between groups.

In total, 7.5% and 15.1% of study participants reported having seen a dietitian for weight loss counseling during the past year and 5 years, respectively. Group meetings were attended by 11.3% during past year, and 13.2% during past 5 years. Specific diets were attempted infrequently with only 5.7% during past year, and 9.4% 5 years ago. Meal replacements were rarely used by 1.9% during both time frames. Skipping meals was reported by 11.3% at both 1 and 5 years ago. Eating less was a frequent method employed, with 37.7% and 45.3% having attempted this method during the past year and 5 years, respectively. Participants were also asked more specific questions on nutrient intakes: lowered intake of bread, cereals, and pasta: 24.5% at 1 year and 5 years ago; increased fruit and vegetable intake: 34.0% 1 year ago, 37.7% 5 years ago; lowered fat intake: 49.1% 1 year ago versus 56.6% 5 years ago. Increasing level of physical activity: 28.3% 1 year ago, and 37.7% 5 years ago. No participant reported having been on prescription weight-loss drugs in the previous year, while only 1 (1.9%) had 5 years ago. Herb or herbal supplement use for the purpose of weight loss was rare at 1.9% 1 year ago, while no usage was reported 5 years ago. Two patients (3.8%) reported having been treated by a physician for weight problem, while 3 (5.7%) had been treated 5 years ago. No participant either in the previous 1 or 5 years was ever treated at an obesity clinic.

6.3.1.2 Food and Supplement Activities

With regard to food-seeking behaviors, there were no significant differences between groups on any of the behaviors examined. In total, 92.3% of study participants reported doing the grocery shopping at least sometimes, while 44.2% were solely responsible for the preparation of food in their household. Label-reading for nutritional information when purchasing food was reported by 59.6% of the study participants. Although herbal use was infrequent at 15.4%, vitamin and mineral supplement consumption was reported by 55.8% of the patients.

6.4 Changes in Anthropometric, Lipoprotein, Physical Activity, and Dietary Intake Endpoints

The change in body weight during the study was –1.8 kg for the placebo group, and –1.5 kg for the control group. While the changes from baseline were significant, there were no significant differences between the groups.

The change in body composition suggests an increase in lean mass, and a decrease in fat mass: +1.1 kg lean mass, -2.0 kg fat mass for the placebo group; +0.2 kg lean mass, -0.2 kg fat mass for the control group. None of these differences were significant.

Blood pressure decreased significantly during the study, but there were no significant differences between the groups: -9/6 mm Hg in the placebo group; -12/7 mm Hg in the control group.

The changes in lipoproteins were small and non-significant: total cholesterol –0.04 $\pm$ 0.12 in the placebo group, -0.07 $\pm$ 0.11 in the control group; LDL-C –0.07 $\pm$ 0.11 in the placebo group, -0.06 $\pm$ 0.08 in the control group; HDL-C +0.04 $\pm$ 0.03 in the placebo group, +0.01 $\pm$ 0.03 in the control group; and triglycerides –0.01 $\pm$ 0.12 in the placebo group, -0.03 $\pm$ 0.09 in the control group. These small changes led to a significant improvement over time in the total cholesterol: HDL-C ratio (-0.19 $\pm$ 0.12 in the placebo group, -0.19 $\pm$ 0.11 in the control group), with again no significant difference between the two groups.

Repeated measures ANOVA revealed significant intervention effects in both groups for weight ($p<0.001$), systolic ($p<0.001$) and diastolic ($p<0.001$) blood pressures, pulse ($p<0.001$), TC:HDL-C ($p=0.019$), and total dietary ($p=0.028$) and soluble ($p=0.027$) fibers, while trends were observed for Apo A1 ($p=0.050$), and starch ($p=0.055$) and cholesterol ($p=0.079$) intakes. (Table 7)

A further analysis using only data from baseline and week 12 showed precisely the same significant outcomes as that which took account of the interval measurements: body weight ($p<0.001$), systolic ($p<0.001$) and diastolic ($p<0.001$) blood pressures, pulse ($p<0.001$), TC:HDL-C ratio ($p=0.019$), dietary cholesterol ($p=0.037$), and total dietary fiber ($p=0.016$).

Repeated measures ANOVA was conducted between the two groups on measured anthropometric, lipoprotein, physical activity, and dietary intake endpoints during the first 12 weeks of the study. No significant differences between groups were found in any of the parameters investigated including total body weight, % lean and fat mass, blood pressure, pulse, total cholesterol, triglycerides, HDL-C, LDL-C, TC:HDL-C, and apolipoprotein concentrations. Likewise, changes occurring in accelerometer counts, calculated daily energy expenditures, and nutrient intakes including total energy, protein, total, saturated, polyunsaturated (PUFA), and monounsaturated (MUFA) fats, dietary cholesterol, total carbohydrate, sugars, total dietary, soluble, and insoluble fibers, starches, and alcohol remained similar between the two groups.

6.5 Power of the Study

With a standard deviation of 2.6, and a sample size of 26 participants per group, results from this study indicated that at a $p<0.05$, there was an 80% chance of detecting a 2.4-kg difference in total body weight between the two groups[115].

6.6 Evaluation of Inter-Rater Variability

Coefficients of variation were calculated to assess the extent of inter-rater variability in the analysis of the food records collected by 24-hour recall. Data from

individual raters are shown followed by group means and standard deviations for each nutrient evaluated (Table 8). Coefficients of variation (CV%) were then calculated by dividing the standard deviation by the mean, and multiplying by 100.

In general, precision was determined to be very good (CV% <15%) for total energy, protein, total, saturated, and monounsaturated (MUFA) fats, dietary cholesterol, total carbohydrate, and sugars. Other nutrients, which were associated with higher CV% were, in some cases, nutrients consumed in comparatively lesser amounts (i.e. omega-3 fatty acids). Thus, relatively small variations in rater decision-making in analyzing these nutrients would have resulted in a higher coefficient of variation.

Protein (g)	**82.28 + 8.66**	78.56 + 6.70	78.90 + 4.95	**79.32 + 8.35**	71.28 + 5.52	76.73 + 5.18
% protein energy	***17.8 + 1.2***	*17.1 + 0.8*	*17.3 + 0.7*	***16.9 + 1.0***	*17.1 + 0.9*	*18.0 + 0.7*
Total fat (g)	**60.67 + 6.87**	60.51 + 6.40	59.23 + 5.40	**66.02 + 8.86**	57.60 + 5.53	56.85 + 5.22
% fat energy	***28.4 + 1.6***	*28.6 + 1.5*	*27.9 + 1.3*	***30.3 + 2.3***	*29.8 + 1.4*	*28.6 + 1.0*
SFA (g)	**20.61 + 2.70**	20.24 + 2.42	18.25 + 1.86	**21.70 + 3.48**	17.91 + 1.82	17.40 + 1.61
% SFA energy	***9.5 + 0.8***	*9.4 + 0.7*	*8.5 + 0.5*	***9.9 + 0.9***	*9.4 + 0.6*	*8.7 + 0.4*
PUFA (g)	**11.32 + 1.64**	12.15 + 1.51	12.30 + 1.14	**13.83 + 2.14**	12.06 + 1.33	12.23 + 1.43
% PUFA energy	***5.3 + 0.6***	*5.8 + 0.5*	*5.9 + 0.4*	***6.3 + 0.7***	*6.2 + 0.4*	*6.1 + 0.4*
Omega-3 fatty acids (g)	**1.09 + 0.18**	1.17 + 0.15	1.25 + 0.13	**1.15 + 0.14**	1.11 + 0.17	1.09 + 0.11
MUFA (g)	**23.90 + 2.62**	23.24 + 2.53	23.38 + 2.24	**23.40 + 3.59**	22.75 + 2.68	21.82 + 2.19
% MUFA energy	***11.4 + 0.7***	*11.1 + 0.7*	*11.0 + 0.6*	***10.8 + 1.0***	*11.6 + 0.8*	*11.0 + 0.7*
Cholesterol (mg)	**260.37 + 43.84**	193.73 + 26.45	201.15 + 18.26	**213.62 + 32.57**	192.99 + 20.40	160.70 + 16.12
Total carbohydrate (g)	**252.45 + 21.58**	246.06 + 17.46	249.52 + 19.81	**244.25 + 24.86**	226.23 + 14.92	234.94 + 15.64
% carbohydrate energy	***54.2 + 2.0***	*54.4 + 1.9*	*53.4 + 1.5*	***53.3 + 2.8***	*54.8 + 1.8*	*54.7 + 1.5*
Sugars (g)	**94.68 + 9.71**	100.80 + 9.38	96.56 + 6.08	**91.00 + 9.92**	94.79 + 7.71	93.55 + 7.54
Dietary fiber (g)[1]	**20.63 + 1.99**	21.26 + 1.70	23.33 + 1.83	**20.48 + 2.15**	21.03 + 1.87	25.02 + 2.03
Soluble (g)[2]	***5.78 + 0.58***	*5.58 + 0.46*	*6.35 + 0.69*	***5.58 + 0.59***	*5.30 + 0.51*	*6.79 + 0.49*
Insoluble (g)	***11.84 + 1.19***	*11.75 + 1.08*	*12.95 + 1.04*	***11.62 + 1.18***	*11.38 + 1.21*	*13.57 + 0.99*
Starches (g)	**125.02 + 14.77**	103.26 + 9.00	95.82 + 8.26	**111.21 + 12.06**	94.37 + 9.04	102.41 + 9.17
Alcohol (g)	**3.54 + 1.20**	7.74 + 2.97	10.44 + 2.95	**4.97 + 2.73**	2.12 + 0.99	4.21 + 1.27

[a] Means are reported as Mean ± SEM

No significant differences between groups

[b] Assessed during the following intervals: Baseline to Visit 1, Visit 1-2, Visit 2-3.

[1] Treatment effect over time, p=0.028

[2] Treatment effect over time, p=0.027

Protein (g)	75.58	75.42	74.33	72.69	74.07	74.42 ± 1.17	1.6
Total fat (g)	24.65	25.35	24.04	22.23	27.05	24.26 ± 1.80	7.4
SFA (g)	5.64	5.83	5.55	5.56	6.28	5.77 ± 0.31	5.3
PUFA (g)	4.28	6.26	4.04	4.41	5.82	4.96 ± 1.01	20.3
Omega-3 fatty acids (g)	2.03	3.36	1.87	2.01	2.60	2.37 ± 0.62	26.0
MUFA (g)	12.08	10.71	11.99	10.30	12.17	11.45 ± 0.88	7.7
Cholesterol (mg)	119.92	120.74	119.90	94.42	99.54	110.90 ± 12.84	11.6
Total carbohydrate (g)	123.55	149.96	112.34	115.14	137.34	127.67 ± 15.81	12.4
Sugars (g)	64.16	63.94	52.71	65.35	64.71	61.77 ± 5.09	8.2
Dietary fiber (g)	13.25	16.85	11.51	10.63	15.62	13.57 ± 2.64	19.5
Soluble (g)	1.93	3.81	2.28	1.56	3.10	2.54 ± 0.91	36.0
Insoluble (g)	6.60	11.42	4.40	6.62	6.86	7.18 ± 2.57	35.8
Starches (g)	41.51	59.41	42.74	31.75	50.85	45.25 ± 10.42	23.0

[a] Mean intakes are reported as assessed by each rater, whose initial work was always subjected to the final evaluation and approval by the evaluating dietitian

6.7 Estimation of the Extent of Underreporting

In order to estimate the extent of underreporting, basal metabolic rates (BMR) were calculated for each participant using the WHO equation.[116] Each participant's total energy intake (EI) in kilojoules (KJ) was then divided by the calculated BMR, as outlined by Goldberg et al.[117] The EI/BMR fractions were subsequently compared to established minimum cut-points as determined by the number of participants being studied, and the number of days for which food data were collected. Repeated measures ANOVA performed between the EI/BMR ratios from Baseline to Visit 1, Visit 1 to Visit 2, and Visit 2 to Visit 3 revealed no significant differences between groups ($p=0.682$), and no significant effect of time on reporting tendencies ($p=0.500$). (Table 9)

Table 9: Estimation of the Extent of Underreporting Using the WHO[a] Energy Expenditure Equation for 30-60 Year-Old Adults

Recall period (*n* recalls)	Placebo group (n=26) EI/BMR (calc[a])	Control group (n=27) EI/BMR (calc[a])	Minimum Cut-off ratio[b]
Baseline (1)	1.32 ± 0.12	1.32 ± 0.13	1.39
Visit 1-2 (2)	1.29 ± 0.10	1.19 ± 0.09	1.41
Visit 2-3 (3)	1.32 ± 0.10	1.23 ± 0.09	1.43

[a] Men: EE (KJ) = 19.2 x weight (kg) + 66.9 x height (m) + 3769[116]
Women: EE (KJ) = 36.4 x weight (kg) – 104.6 x height (m) + 3619[116]
[b] EI/BMR (calc) = Energy intake/basal metabolic rate (calculated)[117]
No significant differences between or within groups
Mean weights were calculated for Baseline-Visit 1, Visits 1-2 and Visits 2-3.

6.8 Stage of Change

6.8.1 Baseline Stage of Change

Stage of change for each of the 4 lifestyle behaviors evaluated—1) readiness to consume 5 or more fruits and vegetables per day, 2) readiness to limit dietary fat intake, 3) readiness to lose excess body weight by changing diet and exercise habits, and 4) readiness to engage in regular exercise for at least 3 times or more per week for 20 minutes or longer—is reported at baseline and at Visit 2. (Table 10). No significant differences between groups were noted at baseline.

Table 10: Comparison of Change in Stage of Change between Groups Occurring from Baseline (-2 weeks) to Visit 2 (6 weeks)[a].

Stage of Change	Placebo group (n = 26)		Control group (n = 27)	
	Baseline	Visit 2	Baseline	Visit 2
Fruits & Vegetables[b]				
Precontemplation	5 (19.2)	4 (15.4)	3 (11.1)	2 (7.4)
Contemplation	6 (23.1)	6 (23.1)	4 (14.8)	6 (22.2)
Preparation	4 (15.4)	5 (19.2)	11 (40.7)	8 (29.6)
Action	2 (7.7)	2 (7.7)	—	5 (18.5)
Maintenance	9 (34.6)	9 (34.6)	9 (33.3)	6 (22.2)
Dietary Fat[c]				
Precontemplation	1 (3.8)	2 (7.7)	1 (3.7)	1 (3.7)
Contemplation	2 (7.7)	—	3 (11.1)	—
Preparation	5 (19.2)	1 (3.8)	5 (18.5)	1 (3.7)
Action	4 (15.4)	9 (34.6)	9 (33.3)	14 (51.9)
Maintenance	14 (53.8)	14 (53.8)	9 (33.3)	11 (40.7)
Weight loss[d]				
Precontemplation	1 (3.8)	2 (7.7)	3 (11.1)	2 (7.7)
Contemplation	6 (23.1)	1 (3.8)	5 (18.5)	2 (7.7)
Preparation	11 (42.3)	2 (7.7)	7 (25.9)	2 (7.7)
Action	3 (11.5)	9 (34.6)	4 (14.8)	12 (46.2)
Maintenance	5 (19.2)	12 (46.2)	8 (29.6)	8 (30.8)
Exercise[e]				
Precontemplation	5 (19.2)	—	—	1 (3.7)
Contemplation	3 (11.5)	6 (23.1)	5 (18.5)	2 (7.4)
Preparation	12 (46.2)	8 (30.8)	12 (44.4)	11 (40.7)
Action	1 (3.8)	6 (23.1)	1 (3.7)	4 (14.8)
Maintenance	5 (19.2)	6 (23.1)	9 (33.3)	9 (33.3)

[a] Stage of change is expressed as a frequency (%) within each group.
[b] Readiness to consume 5 or more servings of fruits and vegetables per day
[c] Readiness to limit dietary fat intake
[d] Readiness to lose excess body weight by changing diet and exercise habits
[e] Readiness to engage in regular exercise for at least 20 minutes 3 or more times per week
[f] Control group n = 26
No significant differences between groups

Table 11: Change in Stage of Change from Baseline to Visit 2

Change in Stage of Change [a]	Placebo group	Control group
	Frequency (%)	Frequency (%)
[illegible]		
Decrease	5 (19.2)	8 (29.6)
No change	15 (57.7)	12 (44.4)
Increase	6 (23.1)	7 (25.9)
Dietary Fat		
Decrease	5 (19.2)	2 (7.4)
No change	13 (50.0)	14 (51.9)
Increase	8 (30.8)	11 (40.7)
[illegible]		
Decrease	3 (11.5)	5 (19.2)
No change	8 (30.8)	11 (42.3)
Increase	15 (57.7)	10 (38.5)
[illegible]		
Decrease	6 (23.1)	1 (3.7)
No change	8 (30.8)	21 (77.8)
Increase	12 (46.2)	5 (18.5)

[a] All stages were transformed into categorical variables (1-5), as described in Section 6.8.2. Change scores were then obtained by subtracting the initial (i.e. baseline) stage from the stage of change observed upon retest (i.e. 6 weeks, visit 2). "Cycling" between stages was described by either positive (i.e. cycling forward) or negative (i.e. cycling backward) values, represented in the table as an increase or decrease in stage, respectively.

[b] Readiness to consume 5 or more servings of fruits and vegetables per day. (Range of change score: -3 to +4)

[c] Readiness to limit dietary fat intake. (Range of change score: -4 to +4)

[d] Readiness to lose excess body weight by changing diet and exercise habits. (Range of change score: -2 to +4)

[e] Readiness to engage in regular exercise for at least 20 minutes 3 or more times per week. (Range of change score: -2 to +4)

[f] Control group n = 26

No significant differences between groups by Rank Sum Mann-Whitney U Test

6.8.2 Changes in Stage of Change

For each of the four behaviors examined, rank scores of 1-5 were assigned to each of the five stages, where a score of 1 corresponded to the lowest stage (i.e.

Precontemplation), while a score of 5 represented the highest stage (i.e. Maintenance). For ease of interpretation only, Table 11 regroups derived change scores (i.e. stage of change at baseline subtracted from stage of change at visit 2) into three distinct categories of change evolution describing those participants whose stage decreased, did not change, or increased in comparison to their baseline stage of change. Non-parametric rank sum testing conducted on these initially ungrouped change scores using the Mann-Whitney U test revealed no significant differences between groups from baseline to Visit 2 in any of the 4 behaviors examined: fruit and vegetable consumption ($p=0.680$), dietary fat intake ($p=0.321$), weight loss ($p=0.191$), and exercise ($p=0.328$).

6.9 Adherence rates

Visit 1-2 (n=26): Mean adherence was 88.0 $\pm$ 3.3 % (SEM)
Visit 2-3 (n=25): Mean adherence was 89.5% $\pm$ 3.1 % (SEM)
Mean (Visit 1-2 & Visit 2-3) (n=25): 89.9% $\pm$ 2.3 % (SEM)

Adherence literature reports 80 % rate for lipid-lowering agents, but medication compliance in general decreases over time. Moreover, success with short-term adherence will predict success with long-term adherence[60]. There was a positive correlation ($r=0.373$) and a trend toward significance ($p=0.066$) in adherence rates between Visits 1-2 and Visits 2-3. Furthermore, there were no significant differences between adherence rates in Visits 1-2 and Visits 2-3 ($p=0.805$), with 21 (84%) of the participants achieving a medication adherence rate of 80% or greater during each time period. Among adherents in the placebo group with a mean adherence (Visits 1-2 and Visits 2-3) of 80% or greater ($n=19$), 9 (47.4%) had believed the study medication was the real drug, while 6 (31.6%) had been unsure as to the identity of the tablet.

Adherence rates were inversely related to the incidence of adverse effects, such that the more adverse events experienced, the less adherent the participant would be in taking the prescribed dose of medication. Although initially statistically insignificant ($r=$

-0.090. p=0.660) during Visits 1-2, the correlation became significant during Visit 2-3 (r= -0.776. p< 0.0001).

6.10 Adverse Events

During the first 12 weeks of the study, a total of 32 adverse events were reported. Within the placebo group, the highest number of untoward events noted (n=12) were of a digestive nature, such as nausea, dyspepsia, and flatulence. The frequency of gastrointestinal intolerances was followed closely by nervous system effects (n=11), which included dizziness, headache, and insomnia. Musculoskeletal-related (n=4) complaints, such as myalgia, completed the three most commonly reported adverse events. The placebo was ultimately discontinued in one patient who experienced intolerable visual disturbances within one week of initiating the study medication.

6.11 Achievement of NCEP ATP II Target for LDL-C Reduction

Number of participants who met their NCEP target LDL-C at 12 weeks (Visit 3):

Placebo group: 8 (30.8%)

Control group: 5 (18.5%)

Overall, 24.5% of all study participants were able to lower their LDL-C to the desired NCEP target level at 3 months by modifying their diet and exercise habits alone. The other participants required lipid-lowering medication (i.e. simvastatin 10 mg) at 3 months in order to elicit the desired reduction in their LDL-C.

6.12 Debriefing Questions

A series of post-study questions were asked to elicit patients' feedback as participants in the study upon their completion of the protocol. Included among these was whether they believed the study medication they were taking was the placebo or the real drug. Of the patients in the placebo group, 13/25 (52.0%) believed they were taking the

real drug, while 6 (24.0%) were unsure of the study medication's identity. Patients were asked if the fact of wearing the Caltrac$_{TM}$ accelerometer made them work harder on the days they wore it versus the days they did not wear it. While there were no significant differences between groups, 19 (37.3%) participants acknowledged that they were more physically active when wearing the accelerometer. When asked whether they thought two personal consultations with the dietitian had been sufficient, 82.4% of all patients interviewed had indicated two had been adequate, with no significant differences between groups.

Toward the end of the interview, patients were asked to comment on whether they had found the study demanding in general as a participant. The patients in the control group more frequently stated that the study had *not* been demanding in comparison to the patients in the placebo group. (25/26 [96.2%] versus 19/25 [76.0%]; p=0.037). Of the 50/51 patients who had provided feedback subsequent to having completed the study protocol, all 50 stated that they would recommend this study to other patients. (One patient had indicated he could not answer the question.) Moreover, all 51 patients interviewed stated that they would like to receive a lay-written mail-out of the study's major findings.

7.0 DISCUSSION

7.1 Purpose of the Study

The purpose of the present study was twofold: 1) to examine whether the prescription of a medication to treat hypercholesterolemia at diagnosis would impact upon the parallel efforts directed at improving diet and exercise habits as assessed by changes occurring in body weight, serum lipids, accelerometer counts, and food and activity records; and 2) to classify 'readiness' to change diet and exercise habits according to the Stages of Change. To the best of our knowledge, there exist no known studies, which have investigated this largely unchartered behavioral relationship between prescribed medication and lifestyle modification. Notwithstanding this absence of data, there seems to be a belief, nonetheless, among clinicians that to prescribe a medication at diagnosis would compromise the patient's diet and exercise change efforts. In fact, Pearson et al. underscores this in a recent review article discussing behavioral issues in the prevention of cardiovascular disease: *There is continued concern that the prescription of a pharmacologic agent such as a lipid-lowering agent will cripple the patient's motivation for non-pharmacologic measures such as diet, exercise, and weight loss*[1].

7.2 Hypothesis

The present study thus sought to illuminate whether a relationship actually existed between medication-taking and lifestyle change efforts. At the same time, however, it was postulated that patients *would* pay less attention to improving their diet and exercise habits, if they were concurrently prescribed a lipid-lowering agent. Contrary to our hypothesis, we believe that we have shown that the efforts directed at lifestyle modification among patients who are prescribed a lipid-lowering agent at diagnosis are no different from those of patients who are conventionally treated (i.e. by diet and exercise alone) for the first 3 months.

7.3 Effect of Initiation of Pharmacological Treatment on Lifestyle Modification

7.3.1 Results

In the present study, comparisons between the two groups (Table 7a and 7b) by repeated measures ANOVA yielded no significant differences in changes occurring over 12 weeks with respect to body weight, % lean and fat mass, blood pressure, lipoprotein profiles, physical activity levels, or nutrient consumption. Both groups showed a similar significant effect of the intervention over time in body weight, blood pressure, pulse rate, TC: HDL-C ratio, intake of total and soluble fibers, and a trend for Apo A1, and starch and dietary cholesterol intakes, as evidenced by incremental improvements occurring over the first 12 weeks of the study. The progression of the patients through the stages over time was also found to be no different between the two groups at the two time points measured during the first 12 weeks. What would be equally interesting to compare is actual intakes of nutrients and levels of activity against the corresponding observed stage of change as a validation of the Stage of Change questionnaires used. This sub-analysis will be performed on the study's data in future investigations of the Stages of Change.

7.3.2 Implications

In the recently released new Canadian guidelines for the treatment of hypercholesterolemia and other dyslipidemias[23], a more intensive approach to management is recommended than in previous guidelines. In fact, treatment intensification in not only dyslipidemia, but also in diabetes and hypertension management is becoming more and more the rule, rather than the exception. Medication is being initiated much earlier in the course of the given disorder, ultimately diminishing the time allotted for the evaluation of non-pharmacologic treatment efficacy alone. Because therapeutic targets are aiming for tighter and tighter control with the goal of reducing the risk of morbidity and mortality, non-pharmacologic therapies such as diet

and exercise are facing therapeutic ceilings with regard to their relative ability to elicit these more dramatic reductions required in cholesterol, blood pressure, and blood glucose. However, the purpose of a medication is not to gloss over lifestyle improprieties, such as excessive consumption of energy or saturated fat, or sedentary levels of physical activity; it is, and always should be considered another facet of the total therapeutic management strategy. Thus, regardless of how intensive treatment goals become, improving one's lifestyle in the context of risk factor management will always play a role in optimizing a patient's therapy. Therefore, to once again cite Pearson et al., *In reality, the two should work together (i.e. the diet, exercise, and weight control should allow minimalization of cost and side effects of drugs by requiring a lower dose of the cholesterol-lowering drug)*[1]. If these relationships hold over time, perhaps more progressive management will seek to reduce medication dosages, or even wean patients off medications altogether in the event clinically significant progress is realized from positive lifestyle change while taking a chronic medication.

7.4 Limitations

7.4.1 Power of the Study

A potential threat to a study's external validity, which could be raised, is the issue of insufficient power to be able to demonstrate an effect. The lack of significant differences with respect to changes in weight, blood pressure, lipid profiles, physical activity, and dietary intakes between the two groups may cause one to suspect lack of power to have played a role. Once again, we are very confident that inadequate power was not an issue in this study. While it is true the two groups appeared to have behaved as if mirror images of one another, closer examination of changes occurring within each group over time reveals a definite effect of the study intervention, with statistically significant improvements noted in weight, BMI, blood pressure (both systolic and diastolic), pulse, TC:HDL-C ratio, dietary fiber, soluble fiber, and a trends for cholesterol intake. The study's actual power to detect significant changes in total body weight was calculated to

be 2.4 kg. However, a significant intervention effect was nonetheless observed with a weight loss of 1.5 kg. This magnitude of total weight loss observed at the end of 12 weeks was found to be in agreement with the findings from previous interventional studies of similar duration, which also used the AHA Step I diet[46]. Moreover, studies included in this meta-analysis, whose duration extended beyond 12 weeks, were generally observed to be comparable in the magnitude of total weight loss achieved in comparison to interventions lasting 12 weeks or less. Finally, and perhaps most convincingly, the between-group p-values associated with the various parameters evaluated diverge in every instance from the original hypothesized direction.

7.4.2 Study Design

7.4.2.1 Single-Blinded Design

The present study was conducted under single-blinded conditions, where both the author and the study's physician were privy to the identity of the tablets assigned to the participants. The purpose of a double-blinded study is to prevent both participant and investigator bias from influencing the outcome of the endpoint being measured. While traditionally perceived as a methodological flaw in studies adopting a single-blinded design, we are very confident that the absence of a double-blind in this particular trial does not present a threat to the internal validity of the study's findings. There are two important reasons for this. First, a total of 32 adverse events, which the affected patients attributed to the study medication were reported. During the first 6 weeks, 9 (34.6%) patients reported experiencing adverse events, with 1/9 ceasing the placebo within the first week due to "intolerable" visual disturbances. While the number of patients reporting adverse events diminished slightly to 6 (24.0%) during the subsequent 6-week interval, intolerable side effects nonetheless resulted in another patient discontinuing the placebo, and in fact, stopping the trial at Visit 3. Secondly, during the debriefing sessions, all patients were asked as to whether they thought they had been taking the real drug or a placebo tablet during the study. Of the patients in the placebo group, more than half

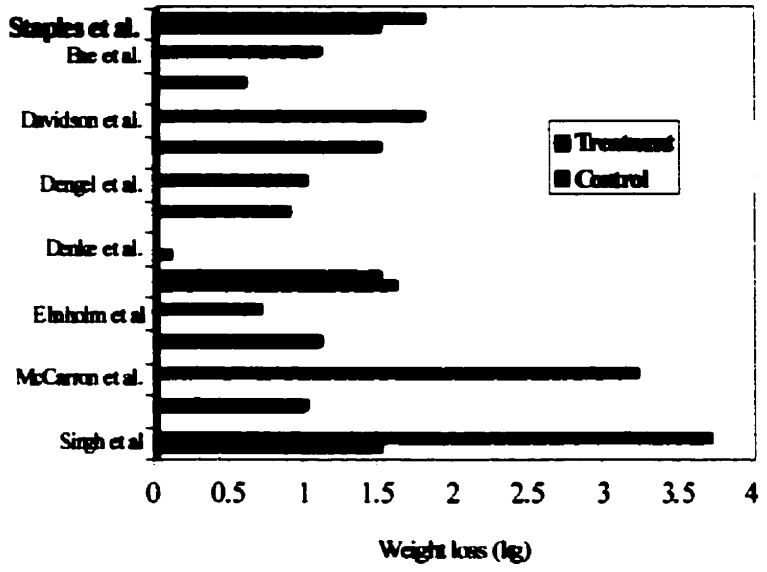
(52.0%) had been convinced they were taking the real drug, while another 24.0% had been unsure of the study medication's identity.

Another potential confounder in accepting a study's findings would be poor adherence rates to the study medication. If good medication adherence could not be assured, the external validity of the findings would be seriously questioned. In accordance with the behavioral literature on adherence with lipid-lowering medication[60], an acceptable level of medication adherence for this study was set at 80% or greater. No significant changes in adherence levels were found between Visits 1-2 and Visits 2-3, with 21 (84%) patients achieving adherence rates of at least 80% during each time interval.

7.4.2.2 Duration of the Study

The 3-month time period over the course of which, diet and exercise behaviors were examined, could also be viewed as a potential confounder in the interpretation of this study's findings. One might argue that the lack of significance observed between groups might have been the result of an insufficient time period allocated to document changes. Clearly, our data show no trends toward supporting the direction of the initial hypothesis. It has been shown that at least 4 weeks are required for lipid stabilization following dietary intervention[118]. Studies included in the meta-analysis by Yu-Poth et al.[46] specifically employing the Step I diet ranged in duration from as short as 4 weeks to as long as 4 years. Furthermore, both the NCEP ATP II and the new Canadian guidelines consider a minimum 3-month time frame sufficient for evaluating the efficacy of non-pharmacologic monotherapy as a means by which to achieve lipemic control. However, both the NCEP ATP II and the new Canadian guidelines also advocate up to 6 months of lifestyle modification in those patients classified as low risk for CAD before a decision is made on initiating a lipid-lowering agent. Therefore, future studies characterizing the relationship between longer-term medication-taking and lifestyle behavior change would therefore contribute greatly to the body of knowledge in this field.

Figure 4: Step I Dietary Intervention Studies ≤ 12 Weeks: Weight Loss Achieved



Yu-Poth et al., 1999

7.4.2.3 Assessment of Nutrient Intake

The interpretation and applicability of nutrient intake data as obtained from self-report measures, such as the 24-hour recall, have to take into account the findings from metabolic studies (i.e. doubly-labeled water) demonstrating underreporting with the use of these less objective instruments. Self-reported nutrient intakes from adult, female, or overweight populations have been found to be especially prone to underreporting[119,120]. The present study made use of the 24-hour recall to assess nutrient intake changes occurring over time, and reports on the results of the first 12 weeks only, during which, 6 recalls were conducted per patient. (The USDA advises a minimum of 6 recalls in order to adequately estimate absolute fat intakes between groups.[107]) In light of these issues, it should be reemphasized that the goal of this study was to detect relative changes. With respect to dietary intakes, examining relative as opposed to absolute nutrient intake

changes occurring between the groups was the intended purpose. However, the ability to interpret even relative changes is contingent upon the similarity of underreporting taking place between the two groups. For this reason, the extent of underreporting was estimated using the Goldberg[117] and WHO basal energy expenditure equations[116], subsequently followed by comparisons between the two groups for significant differences in underreporting (Table 9). Not only were the groups similar in their extent of underreporting, but the pattern within and between groups was also consistent over time. Thus, for the purposes of this study, we are confident that we were able to justifiably compare the relative nutrient intake changes occurring over time in the absence of more objective metabolic assessments that were not feasible in this study, mainly for reasons of cost.

7.4.2.4 Assessment of Physical Activity

Physical activity level changes assessed between the two groups were not only demonstrated to be similar, but were also shown to be resistant to significant improvement over time, underscoring the challenge clinicians face in motivating sedentary patients toward increased levels of physical activity. Activity levels were assessed using two novel, previously validated instruments. One was an accelerometer (Caltrac$_{TM}$), which provided an objective measure of the extent of participants' activity levels, while the other was a self-reported 3-day physical activity record. In having to wear the accelerometer for 5 days at a time, there was an inherent risk of sensitizing participants to the fact that they were being monitored (Hawthorne Effect). This awareness could then have resulted in the pursuit of physical activity levels unrepresentative of the participants' usual expenditures. To address and document the extent of this sensitization, participants were therefore asked upon completing the protocol whether they had been inclined to exert themselves to a greater extent on the days the instrument had been worn in comparison to the days in which it had not been assigned. Analyses revealed no significant differences between the groups with respect to the pattern of yes and no responses. Moreover, the participants who did indicate they had worked harder as a result of having to wear the machine represented only 37.3% of the

total sample. In previous unpublished work[121] documenting the change in accelerometer counts occurring over time, data suggested that an initial sensitization occurs acutely, while waning considerably over time, thereby suggesting a better estimation of usual activity levels with later use. In contrast to the accelerometer, the Bouchard 3-Day Physical Activity Record was entirely based upon self-reported physical activity. Despite its subjective nature, previous comparisons made with the more objective Caltrac™ revealed outcomes with the two instruments that were correlated[121]. Interestingly, the Bouchard had demonstrated less variability in reported activity over time when compared to the activity counts registered by the Caltrac™ (Data not shown). However, the Bouchard did have some limitations, despite the relative ease and lower cost of administration. The categorical list of activities provided, from which corresponding activity codes were selected, could have been improved to reflect more relevant activities that would be associated with urban living. In the present form, unlisted activities reported by a small number of participants had to be evaluated by study personnel, which could have introduced some minor inter-rater variability.

7.4.3 Generalizability of Results

7.4.3.1 Characteristics of Patients

The present study involved 53 patients of mean age 57.4 years (range 38-75) whose body mass index averaged 30.9 kg/m^2 (range: 25.3-38.9). Sixty-four percent were recruited by physician referral with the remaining 36% having been self-referred. Circumventing seasonal bias, small groups of patients were continually randomized and followed through the sequential phases of the protocol from April 7, 1999 to July 28, 2000. Genders were comparably represented in this trial, with female patients accounting for 52.8% of total participation. Cultural diversity was present with 37.7% born in countries other than Canada. Although the majority of participants lived within the 29 municipalities of the Montreal Urban Community, 39.6% reported living outside of the

MUC. Most participants (69.8%) reported being married or equivalent. A highly educated cohort, more than half (52.8%) reported having received some university education, while a similar number of participants (50.0%) acknowledged having consulted with a dietitian in the past for any reason.

In accordance with the Framingham risk stratification system adopted by the new Canadian guidelines, the majority of participants would be considered at Low (39.2 %) to Moderate (43.1%) risk for experiencing a CAD event within the next 10 years. Baseline medical evaluation had revealed concomitant risk factors for arterial hypertension in 32.1% of patients, active smoking in 13.2% (although a large proportion—35%—of patients were ex-smokers), and 28.3% with a family history of premature CAD. In addition, a large proportion (67.9%) of patients had reported taking at least one prescribed chronic medication at baseline.

Therefore, it is our opinion that the results from this study are highly generalizable to a very heterogeneous population of hypercholesterolemic patients. By convincingly disproving our original hypothesis, our results would alternatively suggest that prescribing a lipid-lowering medication at diagnosis does not adversely affect concurrent efforts directed at improving diet and exercise habits. Thus, the new Canadian guidelines, in shortening the time allotted for the evaluation of the efficacy of non-pharmacologic monotherapy, and in some cases initiating a lipid-lowering agent at once, are appropriate in the context of optimizing lipid therapy. As the trend toward tighter metabolic control continues, we would expect an updated version of the NCEP ATP III guidelines (Spring, 2001[122]) to reflect a version of this more intensive approach adopted by the Canadian Working Group in managing dyslipidemias.

7.4.3.2 Sub-Population Analysis

According to baseline data gathered to describe our sample population, several distinguishing characteristics emerged. Nonetheless, no significant between-group differences could be discerned with respect to the prevalence of these features at baseline. However, as a proportion of the total sample, 35.8% of patients had been recruited by

self-referral, 52.8% had received some university education, 67.9% had already been taking at least 1 chronic prescription medication at entry, and 49.1% had had a previous consultation (for any reason) with a dietitian. It could therefore be reasonably supposed that these features, if considered separately, could represent distinct subgroups, the contributions of which being presently eclipsed by the behaviors attributed to the two larger main groups. Therefore, sub-analyses were undertaken with the purpose of examining each of these 4 groups separately on the main outcome measures of body weight, total cholesterol, triglycerides, HDL-C, LDL-C, and TC: HDL-C.

Since these sub-analyses would theoretically lack sufficient power to be able to demonstrate significant outcome effects, caution is advised in their literal interpretation, as trends and directions of change were alternatively examined for corroboration with the results of the two main groups. In the case of self-referred (n=19), non-university educated (n=25), or prescription medication-naïve (n=17) patients there was little indication that these subgroups behaved any differently from the main pooled group. In the last cohort of patients who had had a previous encounter with a dietitian, consistent improvements were noted in weight, triglycerides, HDL-C, and TC:HDL-C . However, inconsistencies were observed in total cholesterol and LDL-C, where in both cases elevations occurred in the placebo group, while reductions took place in the control group. These could reflect chance findings, or ones that could be transitory, simply requiring more participants to enable concordant corroboration with the study's findings. In any event, based on the results of the 3 previous sub-analyses conducted, it may be reasonably concluded that the general tendency of these data is in the direction of the study's main findings. With regard to the fourth sub-analysis on previous dietetic consultation, the increases observed in total and LDL cholesterol may represent a limitation in the applicability of the findings to this subgroup of patients.

7.5 Conclusions

In a recent Food and Drug Consumer (FDC) Report released by the U.S. Food and Drug Administration, the potential switch from prescription to Over-the-Counter (OTC)

status of two currently marketed lipid-lowering agents—10 mg lovastatin (Mevacor®) and pravastatin (Pravachol®)—is discussed. One of the concerns raised in this report by the federal agency was the issue of appropriate therapeutic claims on OTC medication package labeling, with respect to such a claim's potential to impact upon consumer behaviors in concomitantly modifying unhealthy lifestyles: *Can prevention claims encourage ill-advised behavior...For example, would use of a cholesterol-lowering drug allow patients to ignore other needed interventions, such as smoking cessation, dietary discretion, and management of other risk factors?*[2]

We believe that we have answered this question, at least regarding concurrent ancillary diet and exercise interventions. In the present study, no significant differences were found in weight, % lean and fat mass, blood pressure, pulse, lipoprotein profiles, physical activity levels, or nutrient intakes between the groups. In other words, if a physician chooses to prescribe a lipid-lowering agent at diagnosis, there is no reason to suspect that patients would be less likely to modify their lifestyles (i.e. diet and exercise). With the possible exception of cases in which there was previous dietitian exposure, we believe our findings may be applied to a large population of hypercholesterolemic adults, who would be considered candidates for primary prevention.

In the absence of carefully designed studies it remains to be seen whether these relationships hold true in cases of familial dyslipidemias, established CAD, or in other chronic conditions, such as diabetes and hypertension. The difficulty, however, in elucidating such relationships, is that in most, if not all of the aforementioned conditions, the delay in pharmacotherapy is much shorter than in the treatment of most hypercholesterolemias. Thus, a different study design may be required if the standard of care is to be maintained.

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LIST OF APPENDICES

Appendix A

Consent Form

ROYAL VICTORIA HOSPITAL

Patient Information Sheet and Consent Form

The McGill Nutrition and Food Science Center is interested in comparing two different treatment schedules for people who are newly-diagnosed with hypercholesterolemia in the hopes of improving the overall efficacy of therapy for high blood cholesterol.

The aim of this study is to find out which of the two treatments best accomplishes the goals of cholesterol-lowering therapy: lowering dietary fat and cholesterol consumption, participating in regular physical activity, and improving lipid profiles.

Both treatment groups will be based on the same national practice guidelines for treating high blood cholesterol that doctors have been using for the past 5 years in both Canada and the United States. The length of this study will be a total of 18 weeks, after which time we would like to meet with every participant one-on-one at a convenient time so that we may get feedback about the study.

My participation in this study will involve the following:

1. I must attend the group information seminar, which will explain the details of the experiment to everyone. (Total time approximately 3 hours)

    a) At the beginning of this session, I will get my blood pressure and weight taken. My body fat composition will be analyzed by having me stand on a scale-like machine. I will also get some blood drawn to analyze my cholesterol for my doctor's appointment. I will then fill out three questionnaires about my eating and exercise habits. (1 hour)

    b) A registered dietitian will teach me how I can reduce the amount of fat and cholesterol in my diet. I will also be taught how to report food intake over the phone when a study technician calls me, using helpful two-dimensional food posters that will be given to me in order to make estimating portion sizes easier. (1 hour)

    c) A study investigator will explain to me how to incorporate more physical activity into my lifestyle, and will also show me how to record the amount of exercise I do. I will then observe a demonstration of a special meter that I will wear from time to time during the study, which will monitor my activity level. (1 hour)

    d) At the end of the session, I will be presented with a consent form, which I will sign if I choose to participate in this study.

2. After seeing my doctor (week=0), I will be randomly assigned to one of two treatment groups, where I will be asked to take a study medication either every day for 18 weeks, or every day for 6 weeks (weeks 12-18). The study medication I will take will either be a widely used cholesterol-lowering drug already on the market (simvastatin, Zocor®), or an inactive tablet (placebo).

3. During the period when I will be required to take a study medication as part of my comprehensive cholesterol-lowering therapy, I will bring in the vial along with any pills remaining in the vial at each 6 week follow-up visit. A study technician will then provide me with a new 6-week supply of pills.

4. After seeing my doctor (week 0), I will be expected to attend follow-up appointments every 6 weeks (at weeks 6, 12, 18).

5. At each 6-week follow-up visit, I will have my blood pressure and weight taken, and my body fat will be analyzed. Blood will also be drawn to monitor my progress in lowering my cholesterol.

6. Visits at weeks 6 and 18, will require me to fill out two questionnaires regarding my current diet and exercise habits (20 min)

7. I understand that a dietitian will call me randomly several times (approx 8 times) over the 18 weeks to find out what I ate in the previous 24 hours. Each time she calls, I will use the food posters I was given at the information session to help me estimate portion sizes. (20 min for each call)

8. As a participant in the study, I may be in the group which receives the Caltrac™ accelerometer after seeing my doctor at week 0. The Caltrac™ is a small (approx 7.5 x 7 x 2 cm^3), lightweight device, that is just a little bit larger than a pager. (Please see last page for picture of Caltrac™.) It will be used to record my physical activity. I will wear the Caltrac™ four times during the 18-week period at weeks 0 (or 2); 4 (or 6); 8 (or 10); 12 (or 16). Included with the Caltrac™ is a questionnaire on physical activity called the Bouchard 3-Day Physical Activity Record, that I will fill out for 3 consecutive days during the time I have the Caltrac™.

9. I understand that the Caltrac™ is meant to be worn all day, except during the night when I am sleeping. It must be worn at the waist, securely clipped onto a belt or waistband at a level in line with my armpit. I am aware that the Caltrac™ is not water-proof, so that if I take a shower or go swimming I must remove the device.

10. When I do receive the Caltrac™, I will be expected to wear it for a period of 5 days (including 2 weekend days). I will also keep track of the counts shown

on the screen by recording the count displayed in a logbook at the end of each day before I go to bed.

11. After 5 days of wearing the Caltrac™, I will return it to the Metabolic Day Center, so that the next person in the study may receive the device. I will also bring in my completed Bouchard 3-Day Physical Activity Record.

The <u>benefits</u> of participating in this study:

I understand that there are no direct benefits that can be guaranteed with my participation in this study. However, potential benefits that I may experience from having volunteered for this project could include weight loss/control, reduction in blood pressure, and improved lipid profiles. I may also emerge from this study with healthier eating habits, better physical fitness, and an overall increased quality of life.

The <u>risks</u> of participating in this study:

I am aware that I will be closely monitored at each visit. However, I may experience bruising at the site of venous blood sampling, or an adverse drug reaction. Adverse drug effects that I may encounter while taking Zocor®, although usually mild and infrequent (<3%), may include headache, digestive complaints (such as stomach pain, constipation, or gas), nausea, sleeplessness, and muscle pain.

Confidentiality:

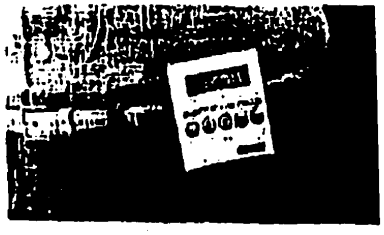
If I consent to participate in this study, I am aware that any information collected and analyzed will be kept strictly confidential. I also know that my name will not appear on any of the questionnaires, nor will it be used in any reports or publications.

Information:

If I have any further questions about the study or need any more explanation, I can contact Dr. Jean-François Yale at **843-1665**.
If I have any questions regarding my rights as a research participant, I may contact the Patient Representative at **842-1231, local 5655**.

Picture of *Caltrac*™ accelerometer:

Proper Position for Wearing Your Caltrac



Correct Horitontal Position

Correct "Below Armpit" Position

I have read and fully understand the implications of my participation in this study. I understand that I am free to refuse to participate or to withdraw from the study at any time for any reason, and that my decision will not affect my care at this institution.

I, _____ consent to be a participant in this
(Please print)
study.

Dated at Montreal, this _____ day of _____ 199__.

Participant _____
(Signature)

Investigator _____
(Signature)

Appendix B

Recruitment Material

B.1 Advertisement

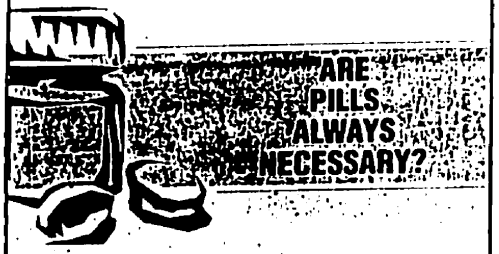
B.2 Initial Phone Call Questionnaire

McGill Nutrition & Food Science Centre
Royal Victoria Hospital

Clinical Study

Dr. Jean-François Yale, principal investigator

DO YOU HAVE HIGH CHOLESTEROL?



You may be eligible to be a part of an 18-week study to help improve the way cholesterol is treated if...

- ✔ You are at least 35 years old
- ✔ You were recently diagnosed with high cholesterol
- ✔ You are not on cholesterol-lowering medication
- ✔ You do not have diabetes

BENEFITS OF PARTICIPATION:

- Personal consultation with a registered dietitian
- Medical care with a lipid specialist
- FREE: Seminar on nutrition & physical activity

For more information, please call Heidi @ 514-843-1665

NAME: _____
PHONE NUMBER: _____
REFERRING MD: _____
DATE OF LAST CLINIC VISIT: _____
Date of initial phone call: _____
Date of "reminder" phone call: _____

McGill

McGill Nutrition and Food Science Centre
Centre de nutrition et des sciences de l'alimentation de l'université McGill

Initial Phone Call: Preliminary Assessment of Eligibility

CRITERIUM	PATIENT INPUT
Age (≥35 years old)	
Height	
Weight (25≤ BMI ≤ 40)	BMI = kg/m²
Presence of HTN?	❑ yes ❑ no
Presence of DM?	❑ yes ❑ no
Taking antilipemic meds?	❑ yes ❑ no
Other medications: (list) (Exclude: antilipemics, glucocorticoids, antidiabetics, anorexiants)	❑ yes ❑ no _____ _____ _____
Seen a dietitian before? TC = TG = HDL-C = LDL-C = date = _____	❑ yes ❑ no If "yes", when? _____ How many times? _____ Still using info? _____
Smoking status:	❑ smoker ❑ non-smoker
Family hx of premature CAD?	❑ yes ❑ no
Surgical hx: (e.g. G.I.)	❑ yes ❑ no _____
Hx of drug or alcohol abuse?	❑ yes ❑ no
Other serious disease(s)? (List) (Exclude: Renal dz, hepatic dz, active cancer)	❑ yes ❑ no _____ _____ _____

- Eligible for Dr. Yale's cholesterol study? ❑ yes ❑ no
- Date of next meeting: _____
- Have meal before coming…Short break + snack in between…Bring RVH hospital card…Room M9-29:Endocrine Conference Room…
  Duration: ≤ 3 hours or less, depending on group size, questions…

Appendix C

Study Tools

- C.1 General Information Questionnaire
- C.2 Nutrient Intake Assessment
- C.3 Physical Activity Assessment
  - C.3.1 Caltrac Log Sheet
  - C.3.2 Bouchard 3-Day Physical Activity Record
- C.4. Stages of Change Questionnaire
  - C.4.1 Fruit and Vegetables
  - C.4.2 Exercise

McGill Nutrition & Food Science Centre, H6
Royal Victoria Hospital
687 Pine Avenue West, Montreal, QC
H3A 1A1 (514) 843-1665

Patient name: _____
Study I.D. #: _____ Protocol # : _____
Visit # _____ Date: _____

General Information

Please answer the following questions.

ANTHROPOMETRIC INFORMATION		
1. What is your age?		
2. What is your current weight?		
3. What is your height?		
4. Are you male or female?	☐ male	☐ female

MEDICAL HISTORY		
5. Do you smoke?	☐ yes	☐ no
6. Do you have high blood pressure?	☐ yes	☐ no
7. Do you consider yourself overweight?	☐ yes	☐ no
8. Has your doctor prescribed any medication that you have to take long-term?	☐ yes	☐ no (go to # 11)
9. If "YES", please name the medications which were prescribed in the space provided below:		
10. Do you use any kind of system to help you remember to take your medication(s)?	☐ yes	☐ no
11. Do you have a family history of...		
a) heart disease?	☐ yes	☐ no
b) diabetes?	☐ yes	☐ no
c) obesity?	☐ yes	☐ no
12. Have you ever tried to lose weight during the past year?	☐ yes	☐ no (go to #14)
13. How many serious attempts have you made to lose weight during the past year?	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 or more	
14. What was your weight 1 year ago?		
15. What was your weight 5 years ago?		
16. What was your maximum weight during your life?		
17. At what age was your maximum weight?		
18. Have you ever seen a dietitian?	☐ yes	☐ no

McGill Nutrition & Food Science Centre, H6
Royal Victoria Hospital
687 Pine Avenue West, Montreal, QC
H3A 1A1 (514) 843-1665

Patient name: _____
Study I.D. #: _____ Protocol # : _____
Visit # _____ Date: _____

DIETING HISTORY

19. During the *past year*, what method(s) did you use (if any) to lose weight?

☐ **Did not try to lose weight**

Please check (√) all that apply:

☐ **Counseled by a dietitian**

☐ **Attended group meeting(s)**
(For example: Weight Watchers®, Overeaters Anonymous®)

☐ **Tried various diets. Please specify which diet(s) you have tried:**
_____
_____

☐ **Took meal replacement(s)**

☐ **Skipped meals**

☐ **Ate less**

☐ **Lowered my intake of bread, cereals, and pasta**

☐ **Increased my intake of fruits and vegetables**

☐ **Lowered my fat intake**

☐ **Increased my level of physical activity**

☐ **Was on prescription weight-loss drugs**

☐ **Took herbs/herbal supplements**

☐ **Treated by physician**

☐ **Treated at an obesity clinic**

☐ **Other (Please specify):** _____

McGill Nutrition & Food Science Centre, H6
Royal Victoria Hospital
687 Pine Avenue West, Montreal, QC
H3A 1A1 (514) 843-1665

Patient name: _____
Study I.D. #: _____ Protocol # :_____
Visit #: _____ Date: _____

DIETING HISTORY

20. During the *past 5 years*, what method(s) did you use (if any) to lose weight?

☐ **Did not try to lose weight**

Please check (√) all that apply:

☐ **Counseled by a dietitian**

☐ **Attended group meeting(s)**
(For example: Weight Watchers®, Overeaters Anonymous®)

☐ **Tried various diets. Please specify which diet(s) you have tried:**
_____
_____

☐ **Took meal replacement(s)**

☐ **Skipped meals**

☐ **Ate less**

☐ **Lowered my intake of bread, cereals, and pasta**

☐ **Increased my intake of fruits and vegetables**

☐ **Lowered my fat intake**

☐ **Increased my level of physical activity**

☐ **Was on prescription weight-loss drugs**

☐ **Took herbs/herbal supplements**

☐ **Treated by physician**

☐ **Treated at an obesity clinic**

☐ **Other (Please specify):**_____

McGill Nutrition & Food Science Centre, H6
Royal Victoria Hospital
687 Pine Avenue West, Montreal, QC
H3A 1A1 (514) 843-1665

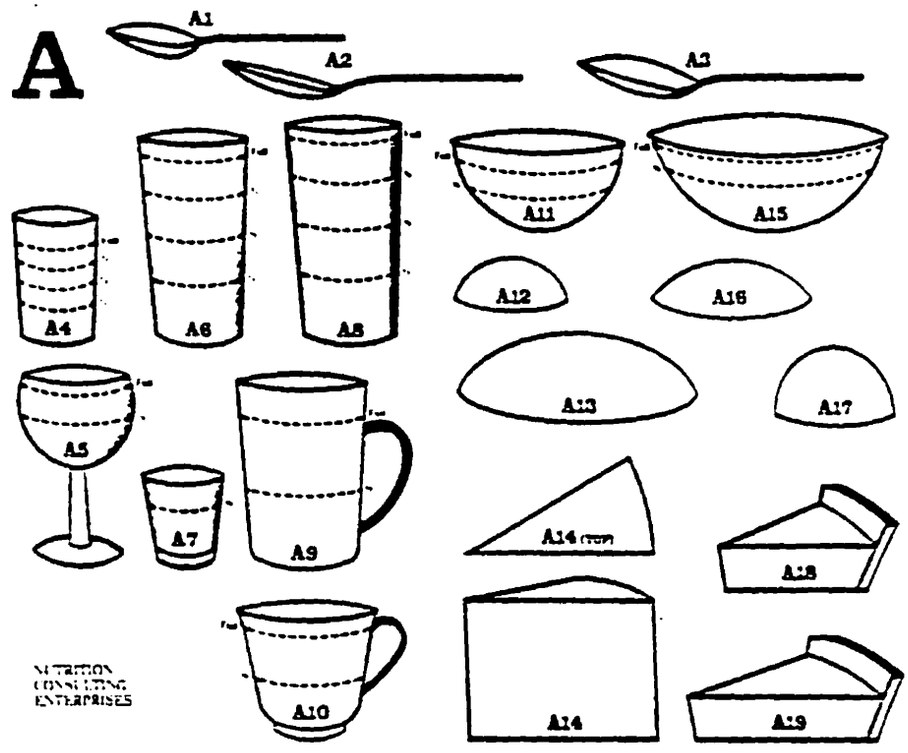
Patient name: _____
Study I.D. #: _____ Protocol # :_____
Visit #: _____ Date: _____

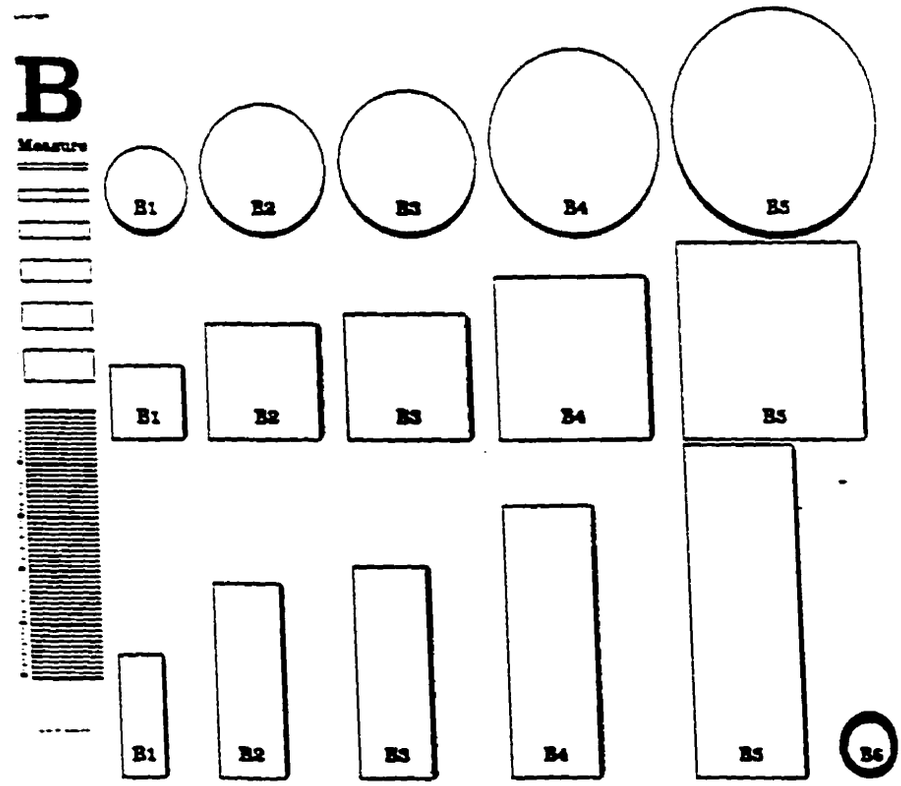
SOCIOECONOMIC INFORMATION

21. Are you employed?	☐ **yes**	☐ **no (go to #23)**	
22. If "YES", what is your occupation?			
23. What is the highest level of schooling you have completed?			
24. Are you married or equivalent?	☐ **yes**	☐ **no (includes: single, divorced, separated, widowed)**	
25. How many adults (age 18 or older) are there currently in your household?	☐ **1**	☐ **2**	☐ **3** ☐ **4** ☐ **more than 4**
26. How many children (under age 18) are there currently in your household?	☐ **0**	☐ **1**	☐ **2** ☐ **3** ☐ **4** ☐ **more than 4**
27. Do you do the grocery shopping?	☐ **yes**	☐ **no**	☐ **sometimes**
28. Who prepares the food in your household?	☐ **self**	☐ **other person**	☐ **both**
29. How much is usually spent per week on food in your household?	☐ **under $50**	☐ **$51-100**	☐ **$101-150** ☐ **$151-200** ☐ **over $200**
30. Do you read labels for nutritional information when you buy food?	☐ **yes**	☐ **no**	
31. Do you take nutritional supplements like vitamins or minerals? *If "YES", please specify:*_____	☐ **yes**	☐ **no**	
32. Do you take herbs or herbal supplements? *If "YES", please specify:*_____	☐ **yes**	☐ **no**	

Thank-you for completing this survey.

Figure 1
2D Food Portion Visual





Nom du Patient name:_____ I.D.#_____ Day/Jour_____
McGill Nutrition & Food Science Centre/Centre de nutrition et des sciences de l'alimentation, H6.72
Hôpital Royal Victoria Hospital, 687 Ave des Pins O/Pine Ave W, Montreal, QC, H3A 1A1, (514) 843-1665

CALTRAC™ log sheet/cahier de bord

Unit/unité # _____

Points to remember:

- Wear your Caltrac™ for 5 days in a row.
- Remove the Caltrac™ before bedtime, and when you take a shower or go swimming.
- At the end of the day, write down the number appearing in the "Cals used/ACTM" display in the chart below.
- At the end of the 5-day period, please return your Caltrac™, your completed log sheet, and your completed 3-day activity records to the Nutrition Centre.

Points à se rappeler:

- Portez votre Caltrac™ pour 5 jours consécutifs.
- Enlevez le Caltrac™ avant de vous coucher, et lorsque vous prenez une douche ou faites de la natation.
- À la fin de la journée, inscrivez sur le tableau ci-dessous le chiffre qui apparaît à l'écran au-dessous de "Cals used/ACTM".
- À la fin des 5 jours, SVP veuillez ramener votre Caltrac™, votre cahier de bord rempli, et vos formules d'enregistrement des activités physiques de 3 jours remplies au Centre de nutrition.

Date (dj/mm/ya)	"Cals used/ ACTM"
1.	
2.	
3.	
4.	
5.	

Nom du Patient name:_____ I.D. #_____ Day/Jour_____

McGill Nutrition & Food Science Centre/ Centre de nutrition et des sciences de l'alimentation, H6.72
Hôpital Royal Victoria Hospital, 687 Ave des Pins O/Pine Ave W, Montreal, QC, H3A 1A1, (514) 843-1665

Bouchard 3-Day Physical Activity Record

Instructions:

- In each box, write the number which corresponds to the activity which you have carried out during this 15 minute period.
- Please consult the activity cards that follow to establish the proper coding.
- If an activity is carried out over a long period (e.g. sleeping) you can draw a continuous line in the rectangular boxes which follow until such a time when there is a change in activity.

Minute / Hour	0 - 15	16 - 30	31 - 45	46 - 60
0				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				

Examples of daily physical activity:

Category of activity	Example of activity for each category
1	*Lying down:* - Sleeping - Resting in bed
2	*Seated:* - Listening in class - Eating - Writing by hand or typing - Reading - Listening to the radio or T.V. - Taking a bath
3	*Standing; light activity:* - Washing oneself - Shaving - Combing hair - Dusting - Cooking
4	Getting dressed Taking a shower Driving a car Taking a walk (strolling)
5	*Light manual work:* - Housework (washing windows, sweeping, etc.) - Tailor - Baker - Printer - Brewer - Cobbler - Mechanic - Electrician - Painter - Lab-work - Carpentry - Masonry - Driving a farm tractor - Cleaning trees - Working in the chemical or electric industries - Feeding animals on a farm - Doing the bed Riding a moped Moderately quick walking (going to school, shopping)
6	*Light sport or leisure activities:* - Light canoeing - Volleyball - Table tennis - Baseball (except the pitcher) - Golf -Rowing - Archery - Ninepins - Croquet - Sailing - Cycling (leisure)
7	*Moderate manual work:* - Machine operating (building industry) - Repairing a fence - Loading bags or boxes - Plantation work - Forest work (machine sawing and log handling) - Mine work - Shovelling snow
8	*Moderate sport or leisure activities:* - Baseball (pitcher) - Badminton - Canoeing - Cycling (race bike) - Dancing - Tennis - Jogging (slow running) - Horseback riding - Alpine skiing - Cross-country skiing (leisure) - Swimming - Gymnastics - Brisk walking
9	*Intense manual work:* - Felling a tree with an ax - Sawing with a hand-saw - Working with a pitchfork (on a farm) - Cutting tree branches *Intense sport or leisure activities:* - Running in a race - Boxing - Mountain-climbing - Squash - Cross-country skiing - Ice hockey - Basketball - Football - Racquetball

EXAMPLE FOR ENTERING DATA ABOUT DAILY PHYSICAL ACTIVITIES

Day 1

Date: 09 / 15 / 1996
day month year

Last name: Doe

First name: Jane

In each box, write the number which corresponds to the activity which you have carried out during this 15 minute period. Please consult the activity card that follows to establish the proper coding. If an activity is carried out over a long period (e.g. sleeping) you can draw a continuous line in the rectangular boxes which follow until such a time when there is a change in activity.

Hour \ Minute	0-15	16-30	31-45	46-60
0	2	—	—	1
1	—	—	—	—
2	—	—	—	—
3	—	—	—	—
4	—	—	—	—
5	—	—	—	—
6	—	—	—	—
7	—	—	—	—
8	—	—	—	—
9	3	4	3	4
10	5	—	—	—
11	—	—	—	—
12	—	—	—	2
13	—	—	5	—
14	—	—	—	—
15	—	—	2	—
16	—	—	—	—
17	—	—	4	2
18	—	—	4	—
19	2	—	—	—
20	—	—	—	—
21	8	—	—	4
22	—	—	2	—
23	—	—	—	1

Patient name:_____ I.D.#_____ Protocol #:____ Visit #:____ Date:_____
McGill Nutrition & Food Science Centre, H6.72, Royal Victoria Hospital, 687 Pine Ave W, Montreal, QC, H3A 1A1 (514) 843-1665

FRUITS AND VEGETABLES

Please answer the following questions.

1. How many *servings* of fruits and vegetables do you usually eat each day?
(1 serving = 1 medium size banana or apple, 1/2 cup of vegetables, ½ cup juice, 1 cup salad, etc.)

❒ 0	❒ 1	❒ 2	❒ 3	❒ 4	❒ 5	❒ 6 or more

(If you answered between "0 and 4" to question 1, go to question 2.) ↓

2. Do you intend to start eating 5 or more servings of fruits and vegetables a day in the next 6 months?

❒ No, I do NOT intend to in the NEXT SIX MONTHS.

❒ Yes, I intend to in the NEXT SIX MONTHS.

❒ Yes, I intend to in the NEXT 30 DAYS. ↓

Go to question # 4.

(If you answered "5" or "6 or more" to question 1, go to question 3.) ↓

3. Have you been eating 5 or more servings of fruits and vegetables a day for...

❒ Less than 6 months

❒ More than 6 months ↓

Go to question # 4.

Consistently avoiding high fat foods *involves regular use of fat reducing strategies such as substituting low fat foods for higher fat foods, eating high fat foods less often and in smaller amounts, using low fat cooking techniques (e.g. poaching, boiling, roasting, etc), and eating more fruits, vegetables, and grains. According to this definition...*

4. Do you *consistently avoid eating high fat foods*? (Please choose only ONE answer.)
❒ NO, and I do NOT intend to in the next 6 months.
❒ NO, but I intend to in the next 6 months.
❒ NO, but I intend to in the next 30 days.
❒ YES, and I have been, but for LESS than 6 months.
❒ YES, and I have been for MORE than 6 months.

Please answer "Yes" or "No" to each of the following questions.

	Yes	No
5. Do you USUALLY choose very lean meat such as skinless chicken or turkey, or extra lean meat? (If you do not eat meat or chicken, answer "Yes".)	❒ Yes	❒ No
6. Do you OFTEN eat low-fat cheese or limit cheese to cut down on fat?	❒ Yes	❒ No
7. Do you USUALLY substitute low-fat foods for high-fat foods? (This means you would choose to eat low-fat foods instead of high-fat foods.)	❒ Yes	❒ No
8. Do you ALMOST ALWAYS avoid fried foods like french fries?	❒ Yes	❒ No
9. Do you USUALLY eat at least two servings a day of vegetables like carrots, celery, corn, peppers, broccoli, etc?	❒ Yes	❒ No

Please place a checkmark (✓) beside the ONE statement below that best describes how you feel right now.

10. Do you intend to change what you are eating so you can answerYES to all five of the previous (#5 - #9) questions? (Please choose only ONE answer.)

- ❒ NO, and I do NOT intend to in the NEXT 6 MONTHS.
- ❒ YES, and I intend to in the NEXT 6 MONTHS.
- ❒ YES, and I intend to in the NEXT 30 days.
- ❒ I answered "Yes" to all five of the previous questions.

11. Do you consider yourself overweight?	❒ Yes	❒ No

12. Have you been *actively trying* to *lose weight* by changing your diet and exercise habits? (Please choose only ONE answer.)

❒ YES, I have been FOR THE PAST 30 DAYS.	❒ YES, I have been FOR THE PAST 6 MONTHS.	❒ NO, I have not been actively trying to lose weight.

If you answered "YES" to question 12, you have finished the questionnaire. STOP Thank-you.	*If you answered "NO" to question 12, go to question 13.* ↓

13. Are you seriously *considering* trying to *lose weight* by changing your diet and exercise habits? (Please choose only ONE answer.)

- ❒ YES, I intend to in THE NEXT 30 DAYS.
- ❒ YES, I intend to in THE NEXT 6 MONTHS.
- ❒ NO, I am not seriously considering trying to lose weight.

THANK-YOU FOR COMPLETING THIS SURVEY.

[redacted]

Please read each of the following 5 statements carefully.

Place a checkmark (√) beside the statement that best describes how you feel ***right now***. (Please choose only **ONE** statement.)

2. I currently do not exercise and I do not intend to start exercising in the next 6 months.	
3. I currently do not exercise, but I am thinking about starting to exercise in the next 6 months.	
4. I currently exercise some, but not regularly*.	
5. I currently exercise regularly*, but I have only begun doing so within the last 6 months.	
6. I currently exercise regularly*, and have done so for longer than 6 months.	

	Not at all Confident					Very Confident		Does not apply to me
7. When I am tired.	1	2	3	4	5	6	7	0
8. When I am not feeling well.	1	2	3	4	5	6	7	0
9. When I am in a bad mood.	1	2	3	4	5	6	7	0
10. When I feel I don't have time.	1	2	3	4	5	6	7	0
11. When I am on vacation.	1	2	3	4	5	6	7	0
12. When it is raining or snowing.	1	2	3	4	5	6	7	0

THANK-YOU FOR COMPLETING THIS SURVEY.

Appendix D

Patient Information Documents

D.1 Acti-Menu

D.2 Physical Activity Guide

D.3 Zocor® Information Sheet

June 1996

INFORMATION FOR THE PATIENT

ZOCOR® Tablets

The Product Monograph is available on request to the physician and pharmacist only.

ZOCOR® is the brand name of Merck Frosst Canada Inc. for the substance - simvastatin, available only on prescription from your physician. Simvastatin is one of a class of medicines known as HMG-CoA reductase inhibitors. They inhibit, in other words block, an enzyme that is necessary for the body to make cholesterol. In this way, less cholesterol is produced in the liver.

When it is necessary to lower cholesterol, physicians usually try to control the condition, known as hypercholesterolemia, with a carefully supervised diet. Also, your physician may recommend other measures such as exercise and weight control. Medicines like this one are prescribed along with, and not as a substitute for, a special diet and other measures. Simvastatin is used to lower the levels of cholesterol (particularly Low Density Lipoprotein (LDL) cholesterol) in the blood.

Elevated cholesterol can cause coronary heart disease (CHD) by clogging the blood vessels which carry oxygen and nutrients to the heart. If you have coronary heart disease (CHD) and elevated cholesterol levels, your physician has prescribed ZOCOR® to help prolong your life, to lessen the risk of a heart attack, and to decrease the risk of needing a surgical procedure to increase the blood flow to your heart. Although, you should be aware that the exact effects of ZOCOR® in the prevention of heart attack, blood vessel disease, or heart disease in patients who have never experienced these conditions, are not yet known. However, studies and investigations are proceeding.

Remember - This medicine is prescribed for the particular condition that you have. Do not give this medicine to other people, nor use it for any other condition.
Do not use outdated medicine.
Store your tablets in a tightly closed container away from heat and direct light.
Keep all medicines out of the reach of children.

Read the following information carefully. If you need any explanations, or further information, ask your physician or pharmacist.

BEFORE TAKING THIS MEDICINE

This medicine may not be suitable for certain people. So, tell your physician if you think any of the following applies to you:

- You have previously taken simvastatin or any other medication in the same class - example, fluvastatin (Lescol), lovastatin (MEVACOR®) or pravastatin (Pravachol) - and were allergic, or reacted badly to it.
- You are pregnant or intend to become pregnant. This medicine should not be used during pregnancy.
- You are breast-feeding or intend to breast-feed.
- You have liver disease.

Your physician also needs to know if you are taking any other medication, whether on prescription or otherwise. It is particularly important to inform your physician if you are taking:

- cyclosporine (Sandimmune), gemfibrozil (Lopid), lipid-lowering doses of niacin (nicotinic acid), corticosteroids, an anticoagulant (drugs that prevent blood clots, such as warfarin [WARFILONE®]), digoxin, erythromycin or antifungal agents (itraconazole)

The safety of this medicine has not been established in adolescents and children.

PROPER USE OF THIS MEDICINE

- Take this medicine exactly as your physician ordered. It is usually recommended as a single dose with the evening meal.

- If you miss taking a tablet at its usual time, take it as soon as possible. But, if it is too close to the time of your next dose, take only the prescribed dose at the appointed time. Do not take a double dose.

- Carefully follow any measures that your physician has recommended for diet, exercise or weight control.

- It is important to continue taking the tablets as instructed. **Do not alter the dosage or stop taking the medicine without consulting your physician.**

- Keep your appointments regularly with your physician so that your blood can be tested and your progress checked at proper intervals. Your physician may also arrange for periodic eye examinations by an ophthalmologist.

- Avoid drinking large quantities of alcohol.

MEVACOR® is a Trademark of Merck & Co., Inc.,
Merck Frosst Canada Inc., licensed user
WARFILONE® is a Trademark of Merck Frosst Canada Inc.

- Do not start taking any other medicines unless you have discussed the matter with your physician.
- Let your physician know if you suffer a severe injury, or severe infection.
- If you have to undergo any kind of surgery, tell your physician about the planned surgery; and also inform the physician in charge that you are taking this medicine.
- Store your tablets at room temperature (15°C - 30°C), in a tightly closed container, away from heat and direct light, and out of damp places, such as the bathroom or kitchen.

SIDE EFFECTS OF THIS MEDICINE - AND WHAT YOU SHOULD DO

Along with its intended action, any medication may cause unwanted effects. Most people do not have any problem when taking this medicine; but if you notice any of the following reactions, check with your physician as soon as possible:

Aching muscles, muscle cramps, tiredness or weakness
Fever
Blurred vision

Some other side effects that may occur, generally do not require medical attention, and may come and go during treatment. But if any of the following persist or become troublesome, do check with your physician or pharmacist:

Constipation, diarrhea, gas, stomach upset, nausea
Pain in the abdomen
Headache
Skin rash

Some people may have other reactions. If you notice any unusual effect, check with your physician or pharmacist.

Appendix E

Debriefing Material

- E.1 Feedback Questionnaire
- E.2 Feedback to Patient and Physician
- E.2.1 Framingham CHD Risk Assessment Table
- E.2.2 Target Lipid Values by Level of Risk

Parameters	Baseline Date: Nov 29/99	Target	VISIT # 3 Date: March 20/2000	Visit # 4 Date: May 1/2000
Lipoprotein profile				
Total cholesterol (mmol/L)	5.89	< 5.2	5.57	5.52
LDL-C (mmol/L)	3.41	<3.0	2.81	3.38
HDL-C (mmol/L)	1.17	≥ 0.9	1.48	1.17
Triglycerides (mmol/L)	2.88	< 2.0	2.81	2.14
Ratio (TC/HDL-C)	5.03	< 5	3.76	4.72
Apo A1 (mg/dL)	142	90-180	133	137
Apo B (mg/dL)	141	45-136	118	126
Apo E genotype	E3/E3	—	—	—
Lp(a) (mg/dL)	14	0-35	12.3	14.5
Physical assessment				
Weight (kg)	113.2	95.5-100	108.1	109.6
Body mass index (BMI) (kg/m^2)	34.3	—	32.7	33.2
Mean blood pressure; Seated, twice (mm Hg)	149/99	< 130/85	138/90	140/88

Down = 3.4kg (~8 lb)

End diet only

Framingham CHD Risk Assessment Table MEN & WOMEN[a]

STEP 1 AGE

Years	Men	Women
30-34	-1	-9
35-39	0	-4
40-44	1	0
45-49	2	3
50-54	3	6
55-59	(4)	7
60-64	5	8
65-69	6	8
70-74	7	8

STEP 2 TOTAL CHOLESTEROL

mmol/L	Men	Women
< 4.14	-3	-2
4.15 - 5.17	0	0
5.18 - 6.21	(1)	1
6.22 - 7.24	2	2
> 7.25	3	3

STEP 3 HDL-C

mmol/L	Men	Women
< 0.90	2	5
0.91 - 1.16	1	2
1.17 - 1.29	(0)	1
1.30 - 1.55	0	0
≥ 1.56	-2	-3

STEP 4 SYSTOLIC BLOOD PRESSURE

mm Hg	Men	Women
< 120	0	-3
120-129	0	0
130-139	1	1
140-159	(2)	2
≥ 160	3	3

STEP 5 SMOKER

	Men	Women
NO	0	0
YES	(2)	2

STEP 6 RISK (SUM 1-5)

	Points
Age	4
Total cholesterol	1
HDL-C	0
Blood pressure	2
Smoker	2
Total points	9

STEP 7 CALCULATE RISK

Risk Points	10 yr RISK Men	10 yr RISK Women
1	3%	2%
2	4%	3%
3	5%	3%
4	7%	4%
5	8%	4%
6	10%	5%
7	13%	6%
8	16%	7%
9	(20%)	8%
10	25%	10%
11	31%	11%
12	37%	13%
13	45%	15%
14	≥ 53%	18%
15	—	20%
16	—	24%
17	—	> 27%

STEP 8 COMPARE CHD RISK

Men		
Age	Average	Low
30-34	3%	2%
35-39	5%	3%
40-44	7%	4%
45-49	11%	4%
50-54	14%	6%
(55-59)	16%	7%
60-64	21%	9%
65-69	25%	11%
70-74	30%	14%

Women		
Age	Average	Low
30-34	< 1%	< 1%
35-39	< 1%	< 1%
40-44	2%	2%
45-49	5%	3%
50-54	8%	5%
55-59	12%	7%
60-64	12%	8%
65-69	13%	8%
70-74	14%	8%

[a] Table adapted from: Fodor JG, Frohlich JJ, Genest Jr JJG, et al. *Recommendations for the management and treatment of dyslipidemia.* CMAJ 2000; 162(10) 1441-7.

TARGET LIPID VALUES BY LEVEL OF RISK[a]

Level of risk (Definition)	Target values: LDL-C level, mmol/L	Total cholesterol: HDL-C ratio	Triglyceride level, mmol/L
☐ **Very High**[*] (10-year risk of CAD > 30%, or history of cardiovascular disease or diabetes)	**< 2.5**	**< 4**	**< 2.0**
☑ **High**[*] (10-year risk 20%-30%)	**< 3.0**	**< 5**	**< 2.0**
☐ **Moderate**[†] (10-year risk 10%-20%)	**< 4.0**	**< 6**	**< 2.0**
☐ **Low**[‡] (10-year risk < 10%)	**< 5.0**	**< 7**	**< 3.0**

[*] **Start medication and lifestyle changes concomitantly if values are above target values.**
[†] **Start medication if target values are not achieved after 3 months of lifestyle modification.**
[‡] **Start medication if target values are not achieved after 6 months of lifestyle modification.**

[a] Table adapted from: Fodor JG, Frohlich JJ, Genest Jr JJG, et al. *Recommendations for the management and treatment of dyslipidemia: Report of the working group on hypercholesterolemia and other dyslipidemias.* CMAJ 2000; 162(10) 1441-7.