A comparison of Canadian and American guidelines for lipid management using data from the National Cholesterol Education Program Evaluation Project Utilizing Novel E-technology (NEPTUNE) II survey

Kevin C Maki PhD, Michael H Davidson MD, Mary R Dicklin PhD

KC Maki, MH Davidson, MR Dicklin. A comparison of Canadian and American guidelines for lipid management using data from the National Cholesterol Education Program Evaluation Project Utilizing Novel E-technology (NEPTUNE) II survey. *Can J Cardiol* 2006;22(4):315-322.

BACKGROUND: The United States' National Cholesterol Education Program (NCEP) Adult Treatment Panel III and the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias (CWG) have each issued guidelines for the treatment of dyslipidemia.

OBJECTIVE: The present analysis compared the percentage of patients reaching target lipid levels according to NCEP and CWG guidelines among participants of the NCEP Evaluation Project Utilizing Novel E-technology (NEPTUNE) II, a survey performed in the United States.

METHODS: American physicians who were high prescribers of lipid-modifying medications (n=376) each enrolled 10 to 20 consecutive patients from February to September 2003. Medical information, laboratory measurements and treatment plans associated with a single office visit were entered into a personal digital assistant and uploaded to a central database via the Internet.

RESULTS: Under both sets of guidelines, treatment success was strongly related to risk category ($P < 0.001$). Treatment goal achievement in the low-risk (zero or one risk factor) and moderate-risk (two or more risk factors) categories was not substantially different between NCEP and CWG guidelines; however, in the high-risk category (coronary artery disease [CAD] and risk equivalents [RE]), CWG treatment goals were met less frequently than NCEP goals. NCEP combined low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol treatment goals were met by 39% of hypertriglyceridemic patients (27% in the CAD + CAD RE category). CWG combined low-density lipoprotein cholesterol and total cholesterol/high-density lipoprotein cholesterol ratio treatment goals were met by 38% of hypertriglyceridemic patients (19% in the CAD + CAD RE category).

CONCLUSIONS: These data indicate substantial underachievement of treatment goals by patients at high risk under both the CWG and NCEP guidelines. The lower frequency of treatment success in high-risk patients according to the CWG definition indicates that more aggressive treatment is needed to reach CWG goals.

Key Words: *Canadian Working Group; Cholesterol-lowering medications (or therapy); Low-density lipoprotein cholesterol; National Cholesterol Education Program guidelines*

Comparaison des lignes directrices sur la prise en charge des dyslipidémies au Canada et aux États-Unis à partir de données provenant de l'enquête *National Cholesterol Education Program Evaluation Project Utilizing Novel E-technology (NEPTUNE) II*

CONTEXTE : Le groupe de traitement *National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III* aux États-Unis et le groupe de travail canadien sur l'hypercholestérolémie et les autres dyslipidémies (GTC) ont tous deux publié des lignes directrices sur la prise en charge des troubles lipidiques.

BUT : La présente analyse visait à comparer le pourcentage de patients qui avaient atteint les valeurs cibles de traitement selon le NCEP ATP III et selon le GTC 2003 parmi les sujets qui avaient participé à l'enquête NCEP Evaluation Project Utilizing Novel E-technology (NEPTUNE) II, enquête menée aux États-Unis.

MÉTHODE : Les médecins aux États-Unis, qui étaient d'importants prescripteurs d'hypolipémiants ($n = 376$), ont chacun admis de 10 à 20 patients consécutifs (de février à septembre 2003) dans l'enquête. Les données médicales, les résultats de laboratoire et les plans de traitement associés à une seule consultation en cabinet ont été entrés dans un assistant numérique, puis téléchargés vers une base de données centrale par Internet.

RÉSULTATS : La réussite du traitement était fortement liée à la catégorie de risque ($P < 0,001$) pour les deux ensembles de lignes directrices. L'atteinte des valeurs cibles dans les groupes à faible risque (aucun ou un facteur de risque) et à risque modéré (deux facteurs de risque ou plus) était sensiblement la même pour les lignes directrices du NCEP et celles du GTC; par contre, dans le groupe à risque élevé (coronaropathie [CP] et risque équivalent [RE]), l'atteinte des valeurs cibles selon les lignes directrices du GTC était moins élevée que selon celles du NCEP. En effet, 39 % des patients hypertriglycéridémiques ont atteint les objectifs de traitement du NCEP pour le cholestérol à lipoprotéines de basse densité et le cholestérol à lipoprotéines non de haute densité, réunis (27 % dans les groupes de CP et de RE) contre 38 % des patients hypertriglycéridémiques pour le cholestérol à lipoprotéines de basse densité et le rapport cholestérol total/cholestérol à lipoprotéines de haute densité, réunis, selon les lignes directrices du GTC (19 % dans les groupes de CP et de RE).

CONCLUSIONS : Les données indiquent qu'un pourcentage important de patients à risque élevé n'atteignent pas les valeurs cibles de traitement, et ce, tant selon les lignes directrices du NCEP que selon celles du GTC. De plus, le taux de réussite plus faible chez les patients à risque élevé selon la définition du GTC appelle un traitement plus énergique pour permettre l'atteinte des objectifs établis par le groupe.

Radiant Development, Chicago, Illinois, USA

Correspondence: Dr Michael H Davidson, Radiant Development, #2700 – 515 North State Street, Chicago, Illinois 60610, USA.

Telephone 312-494-2220, fax 312-494-2217, e-mail MichaelDavidson@RadiantResearch.com

Received for publication May 26, 2005. Accepted September 9, 2005

Cardiovascular disease is a leading cause of death and disability among North Americans in the United States (US) and Canada (1,2). Dyslipidemia, particularly elevated levels of low-density lipoprotein cholesterol (LDL-C), increases the risk of coronary artery disease (CAD) (3-11).

Clinical practice guidelines have been developed and regularly updated to provide physicians with tools to evaluate the risk of CAD and establish treatment goals to manage dyslipidemia. In 2001, the US National Cholesterol Education Program (NCEP) released the report of its third Adult Treatment Panel (ATP III) (1,12). In 2000, the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias (CWG) issued recommendations (13), which were subsequently updated in 2003 (14). This update harmonized the approach to cardiovascular risk assessment in the US and Canada (14-16) by adopting the Framingham global risk equations published in the NCEP ATP III report.

The CWG and NCEP recommendations are similar in many respects, including a focus on LDL-C as the primary target for dyslipidemia management. However, the CWG recommendations established target levels for the total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) ratio for all patients as a secondary goal of therapy. In contrast, the NCEP guidelines have established non-HDL-C goals for patients with elevated triglycerides (at least 2.25 mmol/L) without indicating a target for the TC/HDL-C ratio. The NCEP ATP III expressed the view that the treatment of ratios would "divert priority from specific lipoprotein fractions as targets of therapy" (12), whereas the CWG believed that the TC/HDL-C ratio is "a more sensitive and specific index" than non-HDL-C (15).

The present report describes a theoretical application of the CWG goals to a group of patients treated in the US under the 2001 NCEP ATP III guidelines. These analyses are useful for evaluating how the different approaches adopted by the CWG and NCEP ATP III influence the aggressiveness of lipid management required to achieve treatment targets under the two sets of guidelines.

METHODS

Study design

Prior to the recent NCEP writing group recommendations (16), the NCEP Evaluation Project Utilizing Novel E-technology (NEPTUNE) II, a nationwide survey performed in the US, was conducted to estimate the probability of NCEP ATP III goal achievement among patients in the US receiving treatment for dyslipidemia (17). This study was conducted in the US from February to September 2003, following approval of the protocol by an institutional review board (Schulman Associates IRB, USA). A list of 37,234 physicians who were among the 26% highest prescribers of statin drugs in 2002 was obtained with permission from IMS Health (Connecticut, USA). The list was stratified by region and specialty before a random sample of 13,555 primary care physicians (family practice, general practice or internal medicine) and 4731 subspecialist physicians (cardiology or endocrinology) were selected. These 18,286 US physicians were sent letters inviting them to participate in NEPTUNE II.

A total of 401 physicians obtained institutional review board approval (from a central institutional review board) and participated in the study. The original objective was to collect data from 500 physicians, who would each enroll 10 consecutive patients receiving treatment for dyslipidemia. However, because the number of physicians recruited was less than anticipated, a random

subset of 158 investigators was asked to enroll an additional 10 consecutive patients to ensure an adequate sample in each of the risk categories.

Before initiation of the survey, each physician attended a regional investigator meeting to review the NCEP ATP III guidelines and be trained on data collection procedures. Due to the methods used for data collection, physicians were required to have access to a computer compatible with personal digital assistant (PDA) software and with an Internet connection. Requisite study data (as described in the 'Data collected' section below) were obtained from each patient's medical history. The investigator or other trained clinic personnel entered patient data into a hand-held PDA (Palm Tungsten T, Palm Inc, USA) that was equipped with the NEPTUNE II software program for recording medical information, laboratory measurements and treatment plans. Data were uploaded periodically from the PDA to a central database server via the Internet. This central database was used for all analyses. Procedures for the protection of personal health information according to the US Health Insurance Portability and Accountability Act Privacy Rule were followed.

Patient enrollment

Participating physicians recruited patients for the study during regularly scheduled office visits. Men and women with dyslipidemia who were 20 to 75 years of age inclusive, and who had been treated with diet and/or drug therapy (stable dose) for at least three months, were eligible. Patients also had to have a fasting lipoprotein profile available that reflected their lipid status at the time of the clinic visit (within three months before and two weeks after).

Individuals with any of the following conditions were excluded from participation: a history (within the past three months) of major trauma, surgery requiring anesthesia or myocardial infarction; a history (within the past month) of acute infection requiring antibiotic therapy; a recent (within the past month) or abrupt change in their usual diet; pregnant women, women who were breastfeeding, women who were recently (within the past six months) pregnant; any known secondary cause of dyslipidemia; or any condition that the physician believed would interfere with patient evaluation.

Data collected

Physicians collected the following data and entered them into the PDA: sex; date of birth; race or ethnicity; LDL-C treatment goal; family history of CAD; history of left ventricular hypertrophy, atrial fibrillation and atherosclerotic disease; presence of hypertension; presence of diabetes mellitus; use of postmenopausal sex hormone therapy (including selective estrogen receptor modulators); cigarette smoking status; use of alcohol; height, weight and waist circumference; blood pressure; ankle blood pressure, if available; the patient's current fasting lipid profile (and a pretreatment lipid profile, if available); fasting glucose level; and high-sensitivity C-reactive protein level, if available.

According to the NCEP ATP III definitions for each risk category, LDL-C treatment goals were determined for each patient (Table 1). NCEP ATP III risk categories and their associated LDL-C treatment goals were defined as: zero to one risk factor – LDL-C goal of less than 4.13 mmol/L; two or more risk factors – LDL-C goal of less than 3.36 mmol/L; and CAD or CAD risk equivalents (RE) – LDL-C goal of less than 2.58 mmol/L. Risk factors included cigarette smoking, hypertension (blood pressure of 140/90 mmHg or above, or taking antihypertensive medication), family history of premature CAD, age (men 45 years of age or older; women 55 years of age or older), and low HDL-C (less than 1.03 mmol/L).

An HDL-C level of at least 1.55 mmol/L was considered to be a negative risk factor (ie, its presence removed one risk factor from the total count).

Data cleaning, query resolution and clinical monitoring

Data in the central database were verified through logic and edit checking. Any answer in the database that was identified as physiologically unlikely or outside the entry criteria prompted an electronic query. The appropriate investigative site was contacted to resolve each query, and the database was changed to reflect the corrected information. Data collection procedures were verified by a 100% data field audit performed at 42 of the sites.

Statistical analyses

SAS version 8.2 (SAS Institute, USA) was used for all analyses. The primary end point of the study was the proportion of patients who achieved their LDL-C treatment goals (success) as defined by the NCEP ATP III guidelines (1). Results of those analyses have been published elsewhere (17). A post hoc analysis of lipid goal achievement, as defined by the 2003 CWG update, was also performed (15).

NCEP ATP III and CWG risk categories and their respective lipid therapy treatment goals are shown in Table 1. Determination of risk category differs between NCEP ATP III and CWG guidelines. The steps followed to determine risk category by NCEP ATP III included first identifying CAD, diabetes or clinical atherosclerosis. If one of these diseases was present, then the patient was assigned to the CAD + CAD RE category. Next, patients with zero or one risk factor were identified. According to the NCEP ATP III recommendations (12), the Framingham risk score calculation is not needed routinely in this group. A Framingham risk score was calculated for patients with two or more risk factors; those with a 10-year risk over 20% were assigned to the CAD + CAD RE category, while those with a 20% or lower 10-year risk were assigned to the category of two or more risk factors.

Steps for determining risk category by CWG guidelines included first identifying patients with CAD, diabetes or clinical atherosclerosis. These patients were assigned to the CWG high-risk category. The Framingham risk score was calculated for all other patients. Patients with a 10-year risk of 20% or more were also assigned to the high-risk category, those with a 10-year risk of 11% to 19% were assigned to the moderate-risk category, and those with a 10-year risk of 10% or less were assigned to the low-risk category. For 24 patients, a Framingham 10-year risk score could not be calculated due to missing information regarding use of hypertension medication or smoking status. For 14 of these patients, risk category assignment was not affected by either assumption (use or nonuse of hypertension medication, smoker or nonsmoker). For the 10 remaining patients, risk categorization differed depending on hypertension medication use or smoking status. The physicians' assessments of risk category were used in those cases.

Achievement of the NCEP ATP III LDL-C goals, CWG LDL-C goals, and CWG combined TC/HDL-C ratio goals were determined for all patients. Achievement of the NCEP combined LDL-C and non-HDL-C treatment goals for patients with a triglyceride concentration of at least 2.25 mmol/L was also assessed. Means and standard deviations were calculated to describe continuous variables. Frequency counts and percentages were used for presentation of categorical data.

P values of 0.05 or less (two-tailed) were considered statistically significant. ANOVA and χ^2 tests were used to assess possible differences in characteristics with increasing risk categories. For

TABLE 1

Risk categories and lipid therapy goals* according to guidelines from the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III and the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias (CWG)

NCEP ATP III risk categories [†]	NCEP LDL-C goals	NCEP non-HDL-C goals (if TG $\geq$ 2.25 mmol/L)
0–1 risk factor	<4.13 mmol/L	<4.91 mmol/L
2+ risk factors, $\leq$ 20% 10-year risk	<3.36 mmol/L	<4.13 mmol/L
CAD + CAD RE, >20% 10-year risk	<2.58 mmol/L	<3.36 mmol/L
CWG risk categories [‡]	CWG LDL-C goals	CWG TC/HDL-C goals
Low (10% 10-year risk)	<4.5 mmol/L	<6.0 mmol/L
Moderate (11% to 19% 10-year risk)	<3.5 mmol/L	<5.0 mmol/L
High (CAD + CAD RE [§] or $\geq$ 20% 10-year risk)	<2.5 mmol/L	<4.0 mmol/L

*To achieve NCEP ATP III treatment success, patients with a triglyceride (TG) concentration of less than 2.25 mmol/L need meet only the low-density lipoprotein cholesterol (LDL-C) goal. The NCEP ATP III non-high-density lipoprotein cholesterol (non-HDL-C) treatment goals apply only to patients with a TG concentration of 2.25 mmol/L or higher. To achieve treatment success by CWG guidelines, patients must meet both the LDL-C goal and the total cholesterol (TC)/HDL-C ratio goal. [†]Steps for determining risk category by NCEP ATP III guidelines include the following: (i) identify coronary artery disease (CAD), diabetes and clinical atherosclerosis. If present, assign to CAD + CAD risk equivalents (RE) category; (ii) identify those with zero to one risk factor. Framingham risk score (FRS) calculation is not needed routinely in this group; (iii) calculate FRS for those with two or more risk factors. If 10-year risk is over 20%, then assign to CAD + CAD RE category. Others stay in the two or more risk factor category. [‡]Steps for determining risk category by CWG guidelines include the following: (i) identify CAD, diabetes and clinical atherosclerosis. If present, then assign to high-risk category; (ii) calculate the FRS for everyone else. If the score is $\leq$ 10%, then assign to low-risk category; if 11% to 19%, then assign to moderate-risk category; and if $\geq$ 20%, then assign to high-risk category. [§]For diabetes mellitus, includes patients with chronic kidney disease and those undergoing dialysis

these analyses, P values for trend from the lowest to highest risk category are provided. The kappa statistic was used to test for disagreement (null hypothesis, kappa=1.0) between the classifications under the two sets of guidelines.

RESULTS

Investigator characteristics

A total of 401 investigators received institutional review board approval to participate in the survey. Of these, 376 physicians (94%) provided evaluable data. The participating physicians had a mean age of 49 years, were predominantly male (90%), and had been practicing medicine for a mean of 18 years. Most were board certified (90%) and had office-based practices (99%) in which they saw an average of 129 patients/week. Approximately equal numbers of investigators had specialties of general or family practice (42%) and internal medicine (40%). Fewer physicians had subspecialties of cardiology (15%) and endocrinology (2%). Less than 1% fell into other specialty categories. Most of the physicians (89%) indicated that they were at least somewhat familiar with PDAs before the training session required for study participation, while 11% said that they were not at all familiar with this type of device before the training.

Patient characteristics

A total of 4885 patients were evaluated in the NEPTUNE II survey. Characteristics of the patients according to NCEP

TABLE 2
Patient characteristics according to National Cholesterol Education Program Adult Treatment Panel III risk category definitions

Variable	0–1 risk factor	2+ risk factors	CAD + CAD RE	Total*
All patients, n (%)	859 (17.6)	1318 (27.0)	2708 (55.4)	4885 (100.0)
Men	354 (41.2)	738 (56.0)	1690 (62.4)	2782 (56.9)
45 years of age or older	205 (23.9)	655 (49.7)	1568 (57.9)	2428 (49.7)
Women	505 (58.8)	580 (44.0)	1018 (37.6)	2103 (43.1)
55 years of age or older	236 (27.5)	467 (35.4)	745 (27.5)	1448 (29.6)
Race or ethnicity, n (%)				
Non-Hispanic white	668 (77.8)	1100 (83.5)	2125 (78.5)	3893 (79.7)
African-American or black	68 (7.9)	86 (6.5)	254 (9.4)	408 (8.4)
Hispanic	49 (5.7)	40 (3.0)	128 (4.7)	217 (4.4)
Asian	38 (4.4)	29 (2.2)	81 (3.0)	148 (3.0)
Mixed	30 (3.5)	55 (4.2)	103 (3.8)	188 (3.8)
Other	6 (0.7)	8 (0.6)	17 (0.6)	31 (0.6)
Age, years (mean ± SD)	54.1±11.6	58.4±9.4	61.1±9.7	59.1±10.3
BMI, kg/m ² (mean ± SD)	29.0±5.8	30.0±5.6	31.6±6.7	30.7±6.3
Waist circumference, cm (mean ± SD)	94.3±14.0	98.9±13.6	103.6±15.7	100.7±15.3
Systolic blood pressure, mmHg (mean ± SD)	124.4±13.9	128.5±13.8	131.1±16.5	129.2±15.6
Diastolic blood pressure, mmHg (mean ± SD)	77.1±8.8	78.6±9.3	76.6±10.0	77.2±9.6

*Statistically significant trends from the lowest to highest risk categories for all variables ($P<0.001$). BMI Body mass index; CAD Coronary artery disease; RE Risk equivalents

TABLE 3
Patient characteristics according to Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias risk category definitions

Variable	Low risk	Moderate risk	High risk	Total*
All patients, n (%)	1472 (30.1)	546 (11.2)	2867 (58.7)	4885 (100.0)
Men	568 (38.6)	365 (66.8)	1849 (64.5)	2782 (56.9)
45 years of age or older	352 (23.9)	352 (64.5)	1724 (60.1)	2428 (49.7)
Women	904 (61.4)	181 (33.2)	1018 (35.5)	2103 (43.1)
55 years of age or older	541 (36.8)	162 (29.7)	745 (26.0)	1448 (29.6)
Race or ethnicity, n (%)				
Non-Hispanic white	1165 (79.1)	463 (84.8)	2265 (79.0)	3893 (79.7)
African-American or black	119 (8.1)	31 (5.7)	258 (9.0)	408 (8.4)
Hispanic	70 (4.8)	17 (3.1)	130 (4.5)	217 (4.4)
Asian	51 (3.5)	11 (2.0)	86 (3.0)	148 (3.0)
Mixed	58 (3.9)	20 (3.7)	110 (3.8)	188 (3.8)
Other	9 (0.6)	4 (0.7)	18 (0.6)	31 (0.6)
Age, years (mean ± SD)	54.2±10.6	62.0±8.4	61.1±9.6	59.1±10.3
BMI, kg/m ² (mean ± SD)	29.6±6.0	29.7±5.1	31.5±6.6	30.7±6.3
Waist circumference, cm (mean ± SD)	95.6±14.3	99.8±12.8	103.5±15.6	100.7±15.3
Systolic blood pressure, mmHg (mean ± SD)	124.3±13.0	131.7±14.6	131.3±16.4	129.2±15.6
Diastolic blood pressure, mmHg (mean ± SD)	77.5±9.0	78.7±9.6	76.8±9.9	77.2±9.6

*Statistically significant trends from the lowest to highest risk categories for all variables ($P<0.001$) with the exception of race or ethnicity. BMI Body mass index

ATP III and CWG risk categories are shown in Tables 2 and 3, respectively. More men (57%) than women (43%) participated in this survey. Patients were predominantly non-Hispanic white (80%), and had a mean age of 59 years and a mean body mass index of 31 kg/m². Notably, body mass index and waist circumference increased significantly from low- to moderate-risk and from moderate- to high-risk categories ($P<0.001$). Among women, 9.6% used postmenopausal estrogen or a selective estrogen receptor modulator.

Risk categorization

Of the 4885 patients, 18% had zero or one ATP III risk factor, 27% had at least two ATP III risk factors, and 55% had

ATP III-defined CAD or CAD RE (Table 2). Risk categorization using the CWG definitions resulted in classification of 30% of patients in the low-risk category, 11% in the moderate-risk category and 59% in the high-risk category (Table 3).

A 3×3 discordance analysis showed some differences ($P<0.001$) between the NCEP ATP III and CWG categorizations, specifically for the zero to one risk factor category (ATP III) versus the low-risk category (CWG), and for the two or more risk factor category (NCEP ATP III) versus the moderate-risk category (CWG). Of the 859 patients assigned to the zero to one risk factor category according to NCEP ATP III guidelines, 743 (86%) were also assigned to the low-risk CWG category. The remaining patients fell into the moderate-risk

TABLE 4

Achievement of lipid therapy goals of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III and the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias (CWG)

	CAD (number at goal/ total number of patients [%])	Diabetes (no CAD) (number at goal/ total number of patients [%])	Other* (no CAD) (number at goal/ total number of patients [%])
All patients in CAD + CAD RE or high-risk category			
NCEP			
Achieved LDL-C goal	819/1322 (62.0)	566/1030 (55.0)	144/356 (40.4)
CWG			
Achieved LDL-C goal	763/1322 (57.7)	516/1030 (50.1)	190/515 (36.9)
Achieved LDL-C and TC/HDL-C goals	548/1322 (41.5)	382/1030 (37.1)	129/515 (25.0)
Patients in CAD + CAD RE or high-risk category with triglycerides ≥ 2.25 mmol/L			
NCEP			
Achieved LDL-C goal	181/320 (56.6)	153/308 (49.7)	44/100 (44.0)
Achieved LDL-C and non-HDL-C goals	104/320 (32.5)	76/308 (24.7)	17/100 (17.0)
CWG			
Achieved LDL-C goal	177/320 (55.3)	142/308 (46.1)	60/140 (42.9)
Achieved LDL-C and TC/HDL-C goals	64/320 (20.0)	59/308 (19.2)	22/140 (15.7)

*Includes Framingham risk index score ≥ 20 , an ankle brachial index of <0.9 , and other forms of atherosclerosis such as transient ischemic attacks, cerebrovascular accidents, peripheral arterial disease and abdominal aortic aneurysms. CAD Coronary artery disease; HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol; RE Risk equivalents; TC Total cholesterol

(n=103) and high-risk CWG guideline categories (n=13). Of the 1318 patients in the two or more risk factor category according to NCEP ATP III guidelines, 443 (34%) were assigned to the moderate-risk CWG category. The remaining fell into the low-risk (n=729) and high-risk CWG guideline categories (n=146). All of the patients assigned to the CAD + CAD RE category of the NCEP ATP III guidelines were assigned to the high-risk category of the CWG guidelines.

Achievement of lipid treatment goals

All patients: Success rates for LDL-C treatment goal achievement (NCEP and CWG guidelines) and TC/HDL-C goal achievement by risk category and for all patients are shown in Figure 1. Overall, 67% of patients were at their LDL-C treatment target according to both the NCEP and CWG guidelines. Under both sets of guidelines, treatment success was strongly related to risk category, with higher risk classification associated with a lower probability of goal achievement ($P<0.001$).

LDL-C treatment targets for each risk group are very similar between NCEP and CWG definitions, differing only by the desire of each organization to make treatment targets easy to remember in their country's commonly used units of lipid measurements (mg/dL versus mmol/L). Therefore, as expected, differences in LDL-C goal achievement by risk category between CWG and NCEP ATP III guidelines were small, reflecting the small differences in treatment targets.

The combined LDL-C and TC/HDL-C ratio treatment goals of the CWG guidelines were achieved by 57% of all patients. By risk category, the combined CWG goal was achieved by 91% of patients at low risk (target LDL-C less than 4.5 mmol/L and TC/HDL-C less than 6.0 mmol/L), 71% of patients at moderate risk (target LDL-C less than 3.5 mmol/L and TC/HDL-C less than 5.0 mmol/L), and 37% of patients at high risk (target LDL-C less than 2.5 mmol/L and TC/HDL-C less than 4.0 mmol/L).

Patients in the CAD + CAD RE group: Goal achievement within subgroups of the CAD + CAD RE and high-risk categories is shown in Table 4. Marked differences in goal

Figure 1) Percentages of the 4885 patients with evaluable data achieving National Cholesterol Education Program (NCEP) Adult Treatment Panel III low-density lipoprotein cholesterol (LDL-C) treatment goals, Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias (CWG) LDL-C treatment goals, and CWG combined LDL-C and total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio treatment goals according to risk category and overall. Numbers of patients in the NCEP zero to one risk factor, 2+ risk factor and coronary artery disease (CAD) + CAD risk equivalent (RE) categories were 859, 1318 and 2708, respectively. Numbers of patients in the CWG low-risk, moderate-risk and high-risk categories were 1472, 546 and 2867, respectively

achievement were observed between the two sets of guidelines, but it should be noted that the guidelines have different requirements for goal achievement: a single LDL-C target for the NCEP guidelines versus joint LDL-C and TC/HDL-C targets for the CWG guidelines. Whereas 62% of patients with

TABLE 5

Achievement of lipid therapy goals of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines and the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias (CWG) guidelines according to type of therapy received

Type of therapy	Number of patients at NCEP LDL-C goal/total number of patients (%)			
	0–1 risk factor	2+ risk factors	CAD + CAD RE	Total
Statin monotherapy	509/540 (94.3)	767/938 (81.8)	1170/1936 (60.4)	2446/3414 (71.6)
Nonstatin monotherapy	43/52 (82.7)	63/96 (65.6)	83/209 (39.7)	189/357 (52.9)
Combination drug therapy	35/41 (85.4)	83/101 (82.2)	199/326 (61.0)	317/468 (67.7)
No drug therapy	173/226 (76.5)	83/183 (45.4)	77/237 (32.5)	333/646 (51.5)
Type of therapy	Number of patients at CWG LDL-C and TC/HDL-C goals/total number of patients (%)			
	Low risk	Moderate risk	High risk	Total
Statin monotherapy	907/955 (95.0)	323/408 (79.2)	844/2051 (41.2)	2074/3414 (60.7)
Nonstatin monotherapy	84/102 (82.4)	13/28 (46.4)	46/227 (20.3)	143/357 (40.1)
Combination drug therapy	78/88 (88.6)	32/43 (74.4)	126/337 (37.4)	236/468 (50.4)
No drug therapy	266/327 (81.3)	22/67 (32.8)	43/252 (17.1)	331/646 (51.2)

CAD Coronary artery disease; HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol; RE Risk equivalents; TC Total cholesterol

Figure 2) Percentages of the 1231 patients with a triglyceride concentration of at least 2.25 mmol/L achieving National Cholesterol Education Program (NCEP) Adult Treatment Panel III low-density lipoprotein cholesterol (LDL-C) treatment goals, Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias (CWG) LDL-C treatment goals, NCEP combined LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) treatment goals, and CWG combined LDL-C and total cholesterol (TC)/HDL-C ratio treatment goals by risk category and overall. Numbers of patients in the NCEP zero to one risk factor category, 2+ risk factor category, and coronary artery disease (CAD) + CAD risk equivalent (RE) category were 163, 340 and 728, respectively. Numbers of patients in the CWG low-risk, moderate-risk and high-risk categories were 345, 118 and 768, respectively

CAD achieved the NCEP treatment goal of LDL-C values less than 2.58 mmol/L, 42% of patients achieved the combined CWG treatment goal of LDL-C values less than 2.5 mmol/L and TC/HDL-C values less than 4.0 mmol/L. Similar differences in goal achievement were observed between the NCEP ATP III and CWG goals for patients with diabetes in the absence of CAD (55% versus 37%, respectively) and in patients with other CAD RE (40% versus 25%, respectively).

Patients with triglyceride concentrations of 2.25 mmol/L or higher

Frequencies of goal achievement for persons with triglyceride concentrations of 2.25 mmol/L or higher are shown in Figure 2. Of the 1231 hypertriglyceridemic patients, 13% had zero or one NCEP ATP III risk factor, 28% had at least two NCEP ATP III risk factors, and 59% had NCEP ATP III-defined CAD or CAD RE. Risk categorization using the CWG definitions resulted in 28%, 10% and 62% being categorized as low risk, moderate risk and high risk, respectively.

The frequencies of LDL-C goal achievement among patients with elevated triglycerides were 61% and 62% according to the NCEP and CWG guidelines, respectively. The NCEP combined LDL-C and non-HDL-Cs targets were met by 39% of hypertriglyceridemic patients. Success rates in the zero to one risk factor (target LDL-C less than 4.13 mmol/L and non-HDL-C less than 4.91 mmol/L), two or more risk factor (target LDL-C less than 3.36 mmol/L and non-HDL-C less than 4.13 mmol/L) and CAD + CAD RE (target LDL-C less than 2.58 mmol/L and non-HDL-C less than 3.36 mmol/L) categories were 64%, 52% and 27%, respectively. The CWG combined target of LDL-C and TC/HDL-C ratio was met by 38% of hypertriglyceridemic patients. Success rates in the low-risk (target LDL-C less than 4.5 mmol/L and TC/HDL-C less than 6.0 mmol/L), moderate-risk (target LDL-C less than 3.5 mmol/L and TC/HDL-C less than 5.0 mmol/L) and high-risk categories (target LDL-C less than 2.5 mmol/L and TC/HDL-C less than 4.0 mmol/L) were 78%, 48% and 19%, respectively.

Lipid-altering therapies and LDL-C goal achievement

Types of therapy for dyslipidemia were categorized into subgroups of statin monotherapy, nonstatin monotherapy, combination drug therapy and no drug therapy (Table 5). In the two lower risk categories, treatment success with the various lipid therapies was generally similar between NCEP and CWG guidelines. A total of 60% of the CAD + CAD RE patients receiving statin monotherapy achieved their NCEP LDL-C goal, compared with 41% of high-risk patients who achieved CWG LDL-C and TC/HDL-C ratio goals. Similar differences in CAD + CAD RE or high-risk category goal achievement

between NCEP and CWG guidelines were shown with non-statin monotherapy (40% NCEP versus 20% CWG), combination drug therapy (61% NCEP versus 37% CWG) and no drug therapy (33% NCEP versus 17% CWG).

DISCUSSION

Clinical policy regarding the detection and treatment of hypercholesterolemia is controversial. Guidelines and treatment algorithms differ among and within countries and professional/medical organizations. The NCEP ATP III guidelines (published in 2001) and CWG guidelines (developed by Health Canada in 2000 and updated in 2003) serve as comparable US and Canadian guidelines. The slightly different algorithms recommended in the two sets of guidelines resulted in significant differential categorization of patients in the low- and moderate-risk categories, with a larger percentage of subjects classified as moderate risk (two or more risk factors) under the NCEP ATP III system than under the CWG system (27% versus 11%, respectively).

Treatment targets between the guidelines differ primarily in their use of non-HDL-C versus the TC/HDL-C ratio as secondary goals. The practical implications of this difference are difficult to ascertain, except by comparing treatment results. The inclusion of a TC/HDL-C target is likely to lead to more aggressive treatment in many patients without hypertriglyceridemia, particularly in those with lower levels of HDL-C who will require greater reductions of non-HDL-C (and therefore, LDL-C) to reach this secondary goal. This is particularly evident in the present dataset for subjects in the highest risk group, in whom there was a 20% difference between the frequency of NCEP ATP III LDL-C goal achievement (57%) and the frequency of the combined CWG LDL-C and TC/HDL-C goal achievement (37%).

In contrast, among patients with a triglyceride concentration of 2.25 mmol/L or more, goal achievement rates differed by much less between the NCEP ATP III LDL-C plus non-HDL-C goals and the CWG LDL-C plus TC/HDL-C goals. This smaller difference is explained by the fact that both the NCEP and CWG guidelines specify combined lipid targets for these patients. Achievement of the combined targets was higher for the CWG group than for the NCEP ATP III group in the zero to one risk factor/low-risk category (78% versus 64%, respectively), but lower in the two or more risk factor/moderate-risk (48% versus 52%, respectively) and CAD + CAD RE/high-risk (19% versus 27%, respectively) categories. This suggests that more aggressive lipid management is often required to achieve treatment targets for higher risk hypertriglyceridemic patients using the CWG approach. In this regard, it should be noted that the NEPTUNE II survey was completed before the release of the NCEP ATP III Working Group report that recommended new, optional treatment targets for persons at very high risk for cardiovascular disease (LDL-C less than 1.81 mmol/L, non-HDL-C less than 2.58 mmol/L if TG is at least 2.25 mmol/L) (16). As reviewed by the NCEP ATP III Working Group, results of clinical trials published since 2001 have provided evidence demonstrating that cardiovascular event risk can be reduced further by lowering levels of atherogenic lipoproteins below previously established targets (16). Accordingly, more aggressive treatment would be expected to result in improved outcomes.

A notable finding in the present survey was the improvement in goal achievement compared with that observed in

previous studies (18-20). Surveys conducted under earlier lipid management guidelines (ATP II) indicated suboptimal success rates, particularly in patients with the most aggressive LDL-C treatment goal (18-20). Studies in Canada have also indicated discrepancies between guidelines and practice, and have shown that many at-risk individuals were undertreated (21-24). The increase in goal achievement is likely due to awareness of the body of trial data showing benefits of reducing cholesterol levels on cardiovascular events and mortality, as well as the availability of more efficacious lipid-altering therapies. Because NEPTUNE II sampled high prescribers of lipid drugs, it is likely that the physician sample was biased in favour of more aggressive clinicians. Thus, although substantial progress was apparent, significant treatment gaps were evident, particularly for patients in the highest risk group and those with hypertriglyceridemia.

During the past 25 years, North America has experienced an epidemic of obesity (14,25). Excess adiposity is associated with triglyceride elevation; thus, the regularity with which physicians encounter patients with hypertriglyceridemia has increased in recent years. The low frequency of achievement of the combined LDL-C and non-HDL-C or TC/HDL-C ratio goals among patients in the higher risk groups is alarming and underscores the need to target hypertriglyceridemic patients for more aggressive lipid management.

The present examination of lipid goal achievement according to two sets of national guidelines for the management of dyslipidemia suggests undertreatment of high-risk patients in the US, particularly in those with elevated triglyceride levels. Lower success rates according to the CWG definitions indicate that more aggressive treatment is often required to achieve these goals compared with the targets recommended by the NCEP ATP III. The authors favour the simplification of national guidelines and harmonization across North America in an attempt to increase treatment success and improve outcomes.

ACKNOWLEDGEMENTS: This study was funded by AstraZeneca Pharmaceuticals (Delaware, USA).

REFERENCES

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
2. Heart and Stroke Foundation of Canada. The Growing Burden of Heart Disease and Stroke in Canada 2003. <www.cvdinfobase.ca/cvdbook> (Version current at February 27, 2005).
3. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351-64.
4. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
5. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301-7.
6. Sacks FM, Pfeffer MA, Moye LA, et al; for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-9.
7. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. *Air Force/*

- Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615-22.
8. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
 9. Shepherd J, Blauw GJ, Murphy MB, et al; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. *Lancet* 2002;360:1623-30.
 10. Sever PS, Dahlof B, Poulter NR, et al; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT – LLA): A multicentre randomised controlled trial. *Lancet* 2003;361:1149-58.
 11. Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504. (Erratum in 2006;354:778).
 12. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.
 13. Fodor JG, Frohlich JJ, Genest JJ Jr, McPherson PR. Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *CMAJ* 2000;162:1441-7.
 14. Genest J, Frohlich J, Fodor G, McPherson R; Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: Summary of the 2003 update. *CMAJ* 2003;169:921-4. (Erratum in 2003;169:1149).
 15. Genest J, Frohlich J, Fodor G, McPherson R. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: Summary of the 2003 update. www.cmaj.ca/cgi/content/full/169/9/921. (Version current at February 27, 2006).
 16. Grundy SM, Cleeman JI, Merz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.
 17. Davidson MH, Maki KC, Pearson TA, et al. Results of the National Cholesterol Education Program (NCEP) Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. *Am J Cardiol* 2005;96:556-63.
 18. Schechtman G, Hiatt J. Drug therapy for hypercholesterolemia in patients with cardiovascular disease: Factors limiting achievement of lipid goals. *Am J Med* 1996;100:197-204.
 19. Schrott HG, Bittner V, Vittinghoff E, Herrington DM, Hulley S. Adherence to National Cholesterol Education Program Treatment goals in postmenopausal women with heart disease. The Heart and Estrogen/Progestin Replacement Study (HERS). The HERS Research Group. *JAMA* 1997;277:1281-6.
 20. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): A multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000;160:459-67.
 21. Grover SA, Dorais M, Paradis G, et al. Lipid screening to prevent coronary artery disease: A quantitative evaluation of evolving guidelines. *CMAJ* 2000;163:1263-9.
 22. MacLean DR, Petrasovits A, Connelly PW, Little JA, O'Connor B. Impact of different blood lipid evaluation and treatment guidelines on the proportion of Canadians identified and treated for elevated blood cholesterol. Canadian Heart Health Surveys Research Group. *Can J Cardiol* 1999;15:445-51.
 23. Olson KL, Tsuyuki RT. Patients' achievement of cholesterol targets: A cross-sectional evaluation. *Am J Prev Med* 2003;25:339-42.
 24. Joffres MR, Kamath TV, Williams GR, Casey J, Svenson LW. Impact of guidelines on health care use for the management of dyslipidemia in two Canadian provinces, Alberta and Nova Scotia, from 1990 to 2001. *Can J Cardiol* 2004;20:767-72.
 25. Manson JE, Skerrett PJ, Greenland P, VanItallie TB. The escalating pandemics of obesity and sedentary lifestyle. A call to action for clinicians. *Arch Intern Med* 2004;164:249-58.