

EXPERT OPINIONS.

CLINICAL IMPACT.

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faculty

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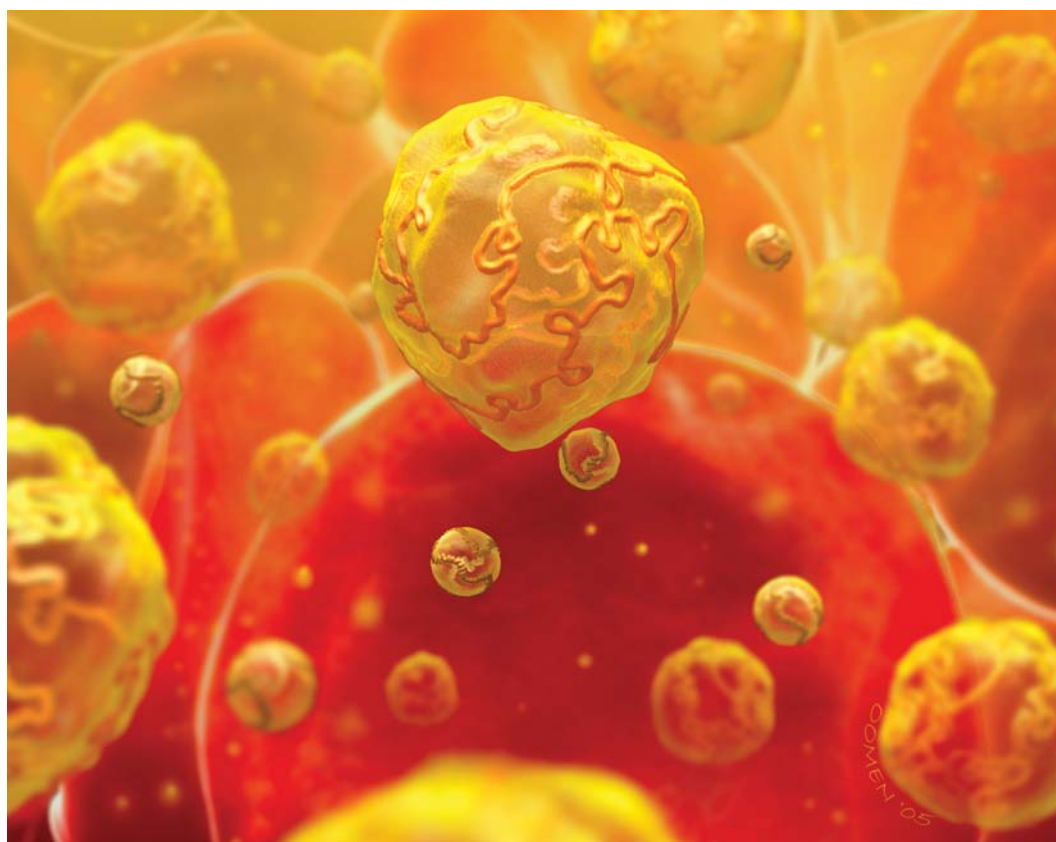
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Combination Therapy for the Hypertensive Patient with Multiple CV Risk Factors

The editors wish to acknowledge the major commitment to unbiased continuing education within the cardiovascular community demonstrated by Pfizer Canada Inc., whose financial contribution in the form of an unrestricted educational grant makes the publication of Expert Opinions Clinical Impact possible.

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In this issue of Expert Opinions Clinical Impact, Canadian experts provide compelling information about hypertension and hypercholesterolemia. The importance of global risk assessment is reviewed, explaining its importance in risk management. The frequent co-existence of hypertension and hypercholesterolemia in patients is then addressed, with mention of a promising new therapy that may help to treat such patients. A discussion on patient compliance with combination therapy follows, outlining the ways in which non-adherence can be combated. And finally, the results of the ASCOT-LLA trial are discussed, demonstrating the role of statins in treating global vascular risk for hypertensive patients. On behalf of the faculty, we hope that this issue provides you with information that will help you in your therapeutic decision-making.

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GLOBAL RISK ASSESSMENT IN 2005: Where Do We Stand?

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HIGHLIGHTS

- Risk factor identification and risk-lowering treatment could postpone or prevent the majority of CVD events
- Over time, clinicians have been presented with increasingly more sophisticated ways to assess risk
- Global risk assessment holds importance in its ability to assess the overall risk of a patient

Introduction

Canadians run a high risk of developing cardiovascular disease, as 8 out of 10 Canadians have at least one modifiable risk factor for cardiovascular disease, and 1 in 10 have three or more.¹ The percentage of the population that is overweight or obese is increasing at an alarming rate, as is the incidence of hypertension and diabetes. CVD risk factors are also appearing at much earlier ages in younger generations.¹ Because risk factors for CVD account for a large proportion of the burden of heart disease, risk factor identification and risk-lowering treatment could postpone or prevent the majority of CVD events.

Since the initiation of the Framingham Heart Study more than 50 years ago, our knowledge of CHD risk, and the benefit of risk modification, has grown considerably. The “traditional” risk factors outlined in the Framingham Study do not identify all CHD risk, but the absence of all these major risk factors does identify those individuals at very low risk. For high-risk patients, the major traditional risk factors account for between 50% and 80% of subsequent cardiovascular events.² Newer “novel” risk factors are now being identified and also taken into consideration, when calculating risk (see Table 1).³

Risk Factor Counting

The simplest approach to risk assessment is the simple numerical tally of risk factors. This is based on the observation that total

atherosclerotic risk does increase incrementally with each additional risk factor. This risk factor “tally” approach has been incorporated into several risk assessment algorithms, including that of the WHO-ISH hypertension guidelines. Although, this risk factor assessment system, which is the easiest to implement, is also the most prone to error. This is particularly true at both extremes of risk, i.e., in patients with more advanced grades of single risk factors, as well as those with marginal elevations of several risk factors.

Mathematical models incorporating assessment of major CHD risk factors have been used to predict general levels of risk (e.g., low, intermediate, or high) and to estimate the yearly percentage risk (absolute risk) of future events. Estimates or scores derived from these models are now commonly known as “global” risk scores. Global risk scoring has been endorsed by a number of guideline committees to identify at-risk individuals. Over time, national guidelines have advanced, and as a result, clinicians have been presented with increasingly more sophisticated ways to assess risk.²

National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)

The NCEP ATP III risk assessment tool, or scoring system, for estimating 10-year risk of developing coronary heart disease (CHD) was developed using the Framingham Heart Study model as its basis (see Figure 1).⁴ Points are assigned based on the responses, and 10-year risk is calculated based on the scoring. The results are then interpreted by comparing them to the risk of an average person.⁶ Framingham calculations were designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes.⁶ The most recent NCEP ATP III “global risk” scoring system includes the following variables: age, gender, total cholesterol, high density lipoprotein (HDL) cholesterol, smoking status, SBP, and hypertension treatment (yes/no).⁴ The individual’s relevant CHD health information can be entered onto either a score sheet, or into an electronic calculator (available on the ATP III page of the NHLBI Website (www.nhlbi.nih.gov/guidelines/cholesterol)). The electronic calculators tend to be a bit more precise, as they use continuous variables, as opposed to the discreet cut-points used in the printed tables. The primary endpoint for this 10-year risk assessment is “hard CHD” (myocardial infarction + CHD death). Diabetes is not part of the ATP III risk algorithm, as the diagnosis of adult onset diabetes mellitus is itself considered a CHD risk equivalent ▶

“Traditional” risk factors	“Novel” risk factors
Cigarette smoking Hypertension High LDL-C Low HDL-C Diabetes mellitus Advancing age	Predisposing Obesity* Abdominal obesity* Physical inactivity Family history of premature CHD Ethnic characteristics Psychosocial factors
	Conditional Elevated serum triglycerides Small LDL particles Elevated serum homocysteine Elevated serum lipoprotein(a) Prothrombotic factors (e.g., fibrogen) Inflammatory markers (e.g., C-reactive protein)

Table 1. CHD risk factors.³ *Body weights are currently defined according to BMI as follows: normal weight 18.5-24.9 kg/m²; overweight 25-29 kg/m²; obesity >30.0 kg/m² (obesity class I 30.0-34.9 kg, class II 35.9-39.9, class III ≥50 kg/m²). Abdominal obesity is defined according to waist circumference men >102 cm (>40 in.) and women >88 cm (35 in.).

(high risk even without other risk factors or clinically evident CHD), thus having a 10-year risk of approximately 20%.⁴ Whether this assumption is justified, especially for those early after the diagnosis of diabetes, has been questioned.⁷ Framingham scoring has been undergoing modification over the past few years. Therefore, absolute risk estimation must be viewed as an evolving science. This is particularly the case as emerging risk factors and measures of sub-clinical atherosclerosis are added to risk assessment algorithms.⁴

PROCAM Scoring Scheme

The PROCAM scoring system was developed based on the 10-year follow-up of the cohort of middle-aged men from the large prospective epidemiological PROspective Cardiovascular Münster study in Europe.⁸ PROCAM is also a points-based scoring system, which takes the following risk factors into consideration: age, LDL-C, HDL-C, triglycerides, smoking, diabetes mellitus, family history of MI, and SBP. Similar to the Framingham model, points are assigned and the total is then calculated to give a 10-year percentage risk of acute coronary events. This model was compared to the NCEP ATP III model to determine the abilities of both methods for predicting the relative risk of an acute coronary event (see Figure 2).⁸

The area under the ROC curve derived from the Framingham score was significantly less than that achieved with the PROCAM method ($p < 0.001$). There are, however, significant differences between the models' data sets, particularly the lack of inclusion of family history of CHD, triglycerides or LDL-C in the Framingham model. As a result, the Framingham prediction function systematically overestimated risk in the PROCAM cohort.

European Society of Cardiology SCORE/HeartScore®

Due to difficulties in applying a Framingham-based risk scoring system to European populations, the European Society of Cardiology and the Second Joint Task Force of the European Societies on Coronary Prevention developed a system for risk stratification in the primary prevention of cardiovascular disease that would be applicable to European clinical practice.⁹ The result of this collaboration was the Systematic Coronary Risk Evaluation (SCORE) project. This risk scoring method is designed to estimate total cardiovascular risk, rather than risk of coronary heart disease, as with the NCEP ATP III method. The intention behind calculating total cardiovascular risk was that it would provide a better estimate of risk for the patient.⁹ In addition, non-coronary cardiovascular disease represents

MEN					WOMEN					
Risk factor	Risk points				Risk factor	Risk points				
Age group, yr					Age group, yr					
20-34	-9				20-34	-7				
35-39	-4				35-39	-3				
40-44	0				40-44	0				
45-49	3				45-49	3				
50-54	6				50-54	6				
55-59	8				55-59	8				
60-64	10				60-64	10				
65-69	11				65-69	12				
70-74	12				70-74	14				
75-79	13				75-79	16				
Total cholesterol level, mmol/L	Age group, yr				Total cholesterol level, mmol/L	Age group, yr				
	20-39	40-49	50-59	60-69	70-79	20-39	40-49	50-59	60-69	70-79
<4.14	0	0	0	0	0	0	0	0	0	0
4.15-5.19	4	3	2	1	0	4	3	2	1	1
5.20-6.19	7	5	3	1	0	8	6	4	2	1
6.20-7.20	9	6	4	2	1	11	8	5	3	2
≥7.21	11	8	5	3	1	13	10	7	4	2
Smoker					Smoker					
No	0	0	0	0	0	0	0	0	0	0
Yes	8	5	3	1	1	9	7	4	2	1
HDL-C level, mmol/L					HDL-C level, mmol/L					
≥1.55	-1				≥1.55	-1				
1.30-1.54	0				1.30-1.54	0				
1.04-1.29	1				1.04-1.29	1				
<1.04	2				<1.04	2				
Systolic blood pressure, mm Hg	Untreated		Treated		Systolic blood pressure, mm Hg	Untreated		Treated		
<120	0		0		<120	0		0		
120-129	0		1		120-129	1		3		
130-139	1		2		130-139	2		4		
140-159	1		2		140-159	3		5		
≥160	2		3		≥160	4		6		
Total risk points	10-year risk, %				Total risk points	10-year risk, %				
<0	<1				<9	<1				
0-4	1				9-12	1				
5-6	2				13-14	2				
7	3				15	3				
8	4				16	4				
9	5				17	5				
10	6				18	6				
11	8				19	8				
12	10				20	11				
13	12				21	14				
14	16				22	17				
15	20				23	22				
16	25				24	27				
≥17	≥30				≥25	≥30				

Figure 1. Model for estimating the 10-year risk of coronary artery disease in a patient without diabetes mellitus or clinically evident cardiovascular disease.⁵



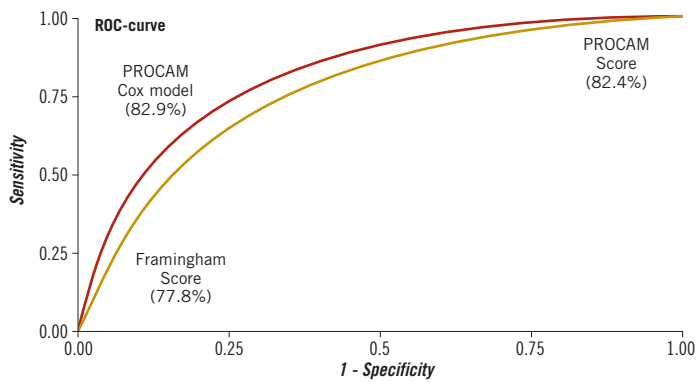


Figure 2. ROC curves showing performance of PROCAM and the Framingham scheme.⁸

a greater proportion of all cardiovascular risk in European regions with low rates of coronary heart disease. The risk charts used in this model estimate cardiovascular death based on age, sex, smoking habits, blood pressure and cholesterol (see Figure 2). Fatal atherosclerotic cardiovascular disease was selected as the endpoint for this method, due to the limitations in the availability of non-fatal endpoint data from clinical studies, and the non-uniformity in their definitions. Therefore, it was felt that this endpoint would allow the SCORE risk estimation system to be applicable at a national level in different European countries representing different rates and mixes (i.e., coronary and non-coronary) of cardiovascular disease.⁹ The SCORE system is currently applicable to the European population, and has not been tailored to all “local” conditions and, if applied in a Canadian context, would need to be adapted to the prevalence of CVD within our population.

HeartScore[®] is the electronic counterpart to the SCORE risk chart.¹⁰ It works with the same risk factors and endpoints, except that total risk is illustrated in a bar chart and the distribution of modifiable risk factors in a pie chart. The expected effect of intervention is also calculated, using large, randomized clinical trials in hypertension and hyperlipidemia.

Conclusion

Ultimately, the choice of the optimal approach for risk factor assessment must be based on three sets of considerations: 1) how easy the tool is to implement on a national/international basis, 2) how predictive an individual risk assessment tool is, and 3) (most importantly) which tool is most likely to positively impact on both the identification and management (i.e., reduction) in atherosclerotic risk for individual patients.

Global risk assessment holds importance in its ability to assess the overall risk of a patient, as it focuses on multiple risk factors and the multiplicative effect they have on each other. The use of global risk assessment is particularly valuable when assessing relative and absolute long-term risk in young and middle-aged adults. Short-term risk may not be high in younger patients who have multiple risk factors of moderate severity, but the long-term risk may be unacceptably high. As such, a clinician may only choose to treat a patient with moderately-high lipid levels with lifestyle modification, but initiate pharmacological therapy in another asymptomatic individual with lower lipids, because they are also male with mild hypertension, and a family history of CHD.

However, despite the availability of many risk assessment approaches, there remains a substantial gap in the detection of asymptomatic patients who ultimately develop CHD. Global risk assessment tools, even when optimally applied, would perpetuate this gap, as they are only moderately accurate in predicting the short- and long-term risk of manifesting a major coronary event in healthy populations. One must not overlook the role these tools play, however, in terms of risk management. They give clinicians the ability to refine the risk assessment process, initiate discussion with the patient regarding their level of risk, and thus better determine what risk reduction processes to initiate.

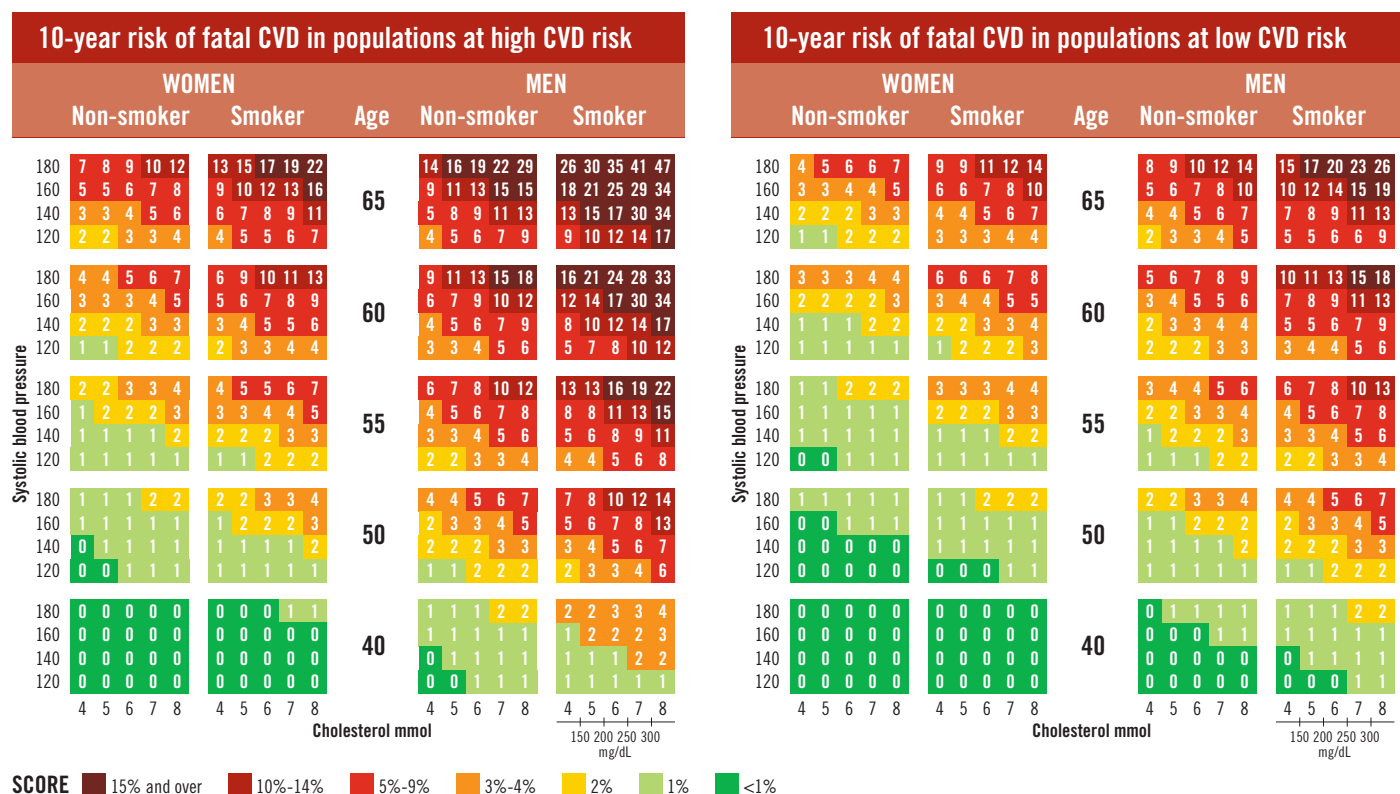


Figure 3. Ten-year risk of fatal cardiovascular disease in high- and low-risk populations based on total cholesterol.

HYPERTENSION AND HYPERCHOLESTEROLEMIA:

Co-existence and Interaction on Vascular Risk

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expert opinion

HIGHLIGHTS

- Dyslipidemia and hypertension are two of the major and most commonly modifiable risk factors for CV disease morbidity and mortality
- They are frequently present within the same patient
- A new combination pill offers patients the convenience of treating two CV conditions at once

Despite advances in treatment and detection, heart disease continues to represent the leading cause of death throughout the Western world.¹ As the size of the elderly population increases and the prevalence of obesity and diabetes rises, the burden of cardiovascular disease will continue to grow. The need for identifying and adequately treating susceptible individuals to prevent disease progression and to avoid unfavourable cardiovascular outcomes is crucial. Using current cardiovascular risk prediction algorithms, such as the Framingham Risk Score,² is a first step. Among the traditional cardiac risk factors, hypertension and hyperlipidemia are among the most prevalent and modifiable risk factors. Effective, proven medical treatment strategies exist for both conditions. With the upcoming introduction of *Caduet* to the Canadian market, a combination of amlodipine and atorvastatin, two different cardiac risk factors may be targeted using a single pill.

Dyslipidemia and hypertension are two of the major and most commonly modifiable risk factors for cardiovascular disease morbidity and mortality. Results from the Canadian Heart Health Surveys³ revealed that a significant number of older Canadians have one or more major risk factors for cardiovascular disease. Overall, 52% of participants were hypertensive (systolic or diastolic blood pressure, BP $\geq 160/90$ mm Hg) and 30% had hyperlipidemia (total cholesterol, total-C, level ≥ 6.2 mmol/L). Results from the Minnesota Heart Survey,⁴ a population-based surveillance of cardiovascular disease risk factors in adults aged 25 to 74 years, reveals a similar concern. This survey found that 21.2% of men and 19.3% of women had a serum total-C of ≥ 6.2 mmol/L, or were using cholesterol-lowering medication, while 25.8% of men and 17.9% of women were hypertensive (BP $\geq 140/90$ mmHg) or taking antihypertensive medications. Recently, the INTERHEART study⁵ confirmed the global epidemic of hypertension and hyperlipidemia, and assessed the contribution of these risk factors to cardiovascular disease worldwide. INTERHEART was a large, international, standardized, case-control study with 29,972 participants from 52 countries, designed to assess the importance of risk factors for coronary heart disease worldwide. The prevalence of hypertension among the control group (no previous diagnosis of

heart disease) was 21.9%. This was in contrast to the study group (presenting with a new myocardial infarction) that had a 39.0% prevalence of hypertension and a 33.5% prevalence of abnormal lipids (percentage in highest quintile of ApoB/ApoA1 ratio). Overall, the presence of abnormal lipids had the highest calculated population attributable risk (PAR) for acute myocardial infarction in both men (49.5%) and women (45.2%), with hypertension contributing 14.9% and 29.0% to the PAR in men and women, respectively.

Though hypertension and dyslipidemia are independent cardiovascular risk factors, they are frequently present within the same patient. An elevated total-C/HDL-C ratio was found to be significantly more common among hypertensive than non-hypertensive men and women of all ages.⁶ In fact, dyslipidemia is reported in 50% to 80% of hypertensive patients,⁷ and the co-occurrence of these conditions increases the risk of coronary heart disease more than the sum of the risks associated with these factors occurring alone.⁸ More alarming, is the finding that 9 of 10 dyslipidemic hypertensive adults have untreated or under-treated dyslipidemia.⁷ Current treatment guidelines suggest that blood pressure should be lowered to 140/90 mm Hg or less in all patients and 130/80 mm Hg or less in those with diabetes mellitus or renal disease.⁹ Target total-C/HDL-C ratio of <4.0 , <5.0 and <6.0 and LDL-C of <2.5 , <3.5 and <4.5 mmol/L are suggested for patients at high, moderate, or low cardiac risk respectively.¹⁰ Thus, the clustering of hyperlipidemia and the potential benefits of treatment among hypertensive adults highlights the need for screening and treating coexistent risk factors.

Numerous large-scale clinical trials have supported the use of CCBs and statins for cardiac risk factor modulation. Combining both drugs in a single pill (as with the *Caduet* formulation of amlodipine and atorvastatin) offers patients the convenience of treating two cardiovascular conditions at once, and would be expected to improve overall compliance rates, closing the care gap that currently exists in hypertensive or hyperlipidemic patients per se. ■

IS PATIENT COMPLIANCE BETTER WITH COMBINATION PHARMACOTHERAPY?

Simplifying Patient Management at Large

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expert opinion

HIGHLIGHTS

- The challenge of achieving tighter targets for patients at CV risk often becomes secondary to the difficulty of adherence
- Combination drugs now have more positive support
- Simple changes in prescribing choices and strategies can have a powerful impact in improving adherence

Alan is a 32-year-old man who is being treated by his family physician for treatment-resistant depression with psychotic features. Struggling with difficult environmental stresses, failure to show for appointments and an underlying reluctance to take medications, complicated his year-long struggle to obtain remission of symptoms. Eventually his mood disorder was well controlled on an SSRI and an atypical antipsychotic. His treatment was complicated by a 15-kg weight gain.

On a follow-up visit for a renewal of medications, he complains of thirst and nocturia which he attributes to side effects from the medication. A random blood sugar of 15.1 and a casual BP of 172/98 confirm that he now has another serious health problem.

As his family doctor, I look at this young man — already reluctant to take 3 pills per day — and wonder how I am now going to persuade him to take the 5 or 6 additional medications that he should be on to achieve control of his hypertension and diabetes.

The challenge of achieving tighter targets for patients at risk for cardiovascular disease often becomes secondary to the difficulty of adherence. We recommend lifestyle changes, but uptake on such interventions is minimal. There are effective and well-tolerated medications available, but there is often reluctance to accept pharmacotherapy, or poor adherence from patients. We know that the adherence rates at one year in naïve patients with all chronic disease is 50-80%. With cardiovascular medications, the adherence rate may be as low as 70%. Because of improper use, 30% to 50% of prescriptions fail to produce the desired therapeutic results in patients with chronic medical conditions.¹

Risk factors swim together. 91% of patients with hypertension have at least one other risk factor. Furthermore, risk factors are common. The Canadian Community Health Survey in 2000 reported that over 30% of Canadians have two or more risk factors for coronary artery disease.²


What facilitates improved adherence to medical therapy? What strategies can a family physician incorporate that will improve adherence?

- Adherence rates to therapies for established chronic diseases are higher than adherence rates to newly diagnosed diseases.

Given this finding, we should consider seeing patients with newly diagnosed cardiac risks more frequently, and soon after diagnosis, rather than having follow-up visits later. The optimum frequency to promote adherence is not known, but seeing newly diagnosed patients several times in the first six months after a diagnosis seems reasonable.

- There is an inverse relationship between number of doses per day and adherence. Patients who have to take medicine four times daily have compliance rates as low as 51% (see Figure 1).³

A simplified drug regime of once-daily medications improves adherence. Fortunately, many of the therapies we prescribe can be taken once daily.

- There is evidence that fixed-dose combination drugs improve compliance. 

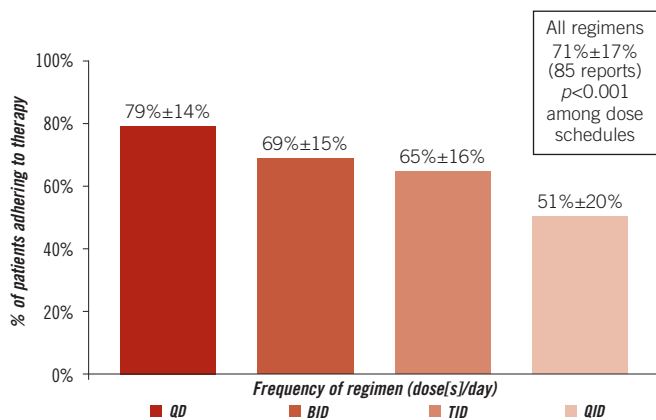


Figure 1. Adherence level according to the number of daily doses.³

Older dogma suggested that combination drugs should be avoided. The argument was that if you had side effects when a combination drug was prescribed, how could you determine which drug was responsible for the side effect? However, a more contemporary view provides more positive support for combination drugs. Data suggests that persistence rates are significantly improved when a single combination tablet is prescribed over two separate prescriptions for constituent molecules (see Figure 2).⁴ The tongue-in-cheek extension of this logic is the fabled ‘poly pill’ for patients with established CAD – a mythical single pill which would combine ASA, a statin, an ACEI and a beta-blocker.

- Combination of therapies may improve compliance.

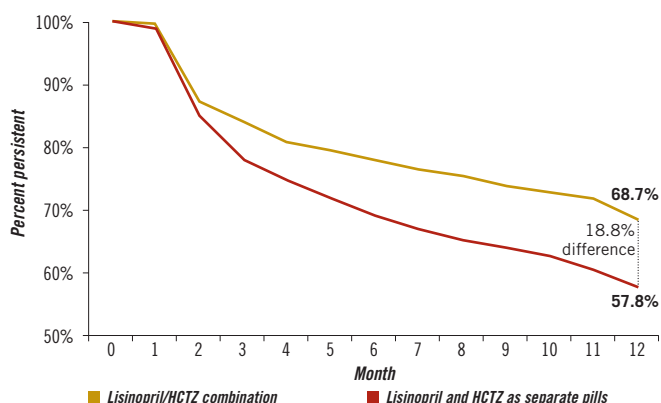


Figure 2. Persistence with fixed-dose antihypertensive combination.⁴ (lisinopril/HCTZ combination n=1,644, lisinopril and HCTZ as separate pills n=624) Statistical significance ($p<0.05$) demonstrated at months 6 and 12 for both comparisons.

Traditional approaches to treatment suggest a stepwise approach to therapy. Treat one condition, and then treat the second. Data exists, however, that suggests improved adherence when medications are given all at once, rather than introduced over time (see Figure 3).⁵

- Multiple changes in medications (also called “therapeutic turbulence”⁶) over a short period of time decrease persistence to therapy.

The concept of therapeutic turbulence⁶ suggests that patients are not receptive to changes in their medication regime. They perceive that the drug does not work and they see it as a failure. The more changes in therapy, the less likely patients are to persist with the therapy over time. Practically, this may mean starting with a more aggressive dosing level early in therapy. For example, in the case

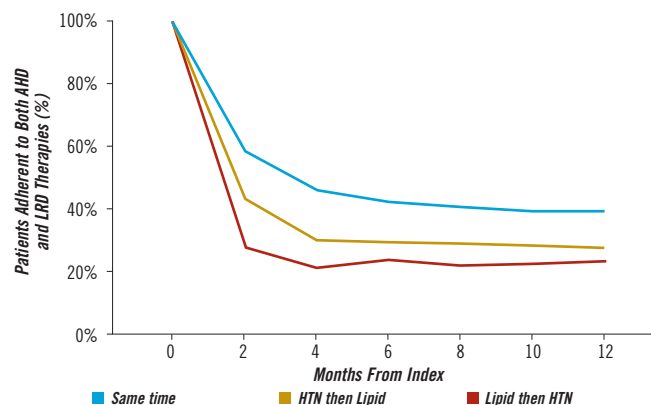


Figure 3. Simultaneous initiation of therapies improves patient adherence.⁵ HTN = antihypertensive drug therapy; Lipid = lipid-regulating drug therapy.

of our patient Alan, we know he will likely need more than one antihypertensive and more than one hypoglycemic agent to treat his BP and blood glucose. The initial choice of combination therapy for both conditions could be considered. (The current CDA guidelines do endorse the use of two agents as initial therapy for patients with marked hyperglycemia.)

There are other strategies which promote adherence to therapy. The use of dosettes will help patients keep track of medications and are particularly useful for those with complicated dosing schedules. Some pharmacies can even ‘blister pack’ medications so that ‘loading errors’ can be minimized. Reminder letters about overdue appointments and refill times can be utilized. Pharmacists can also monitor the frequency of refills and reinforce compliance. Brief telephone contact between pharmacists and patients can reinforce proper medication use and improve compliance. Involving the family in supporting a patient’s pill taking improves compliance. Finally, encouraging patients to build ‘pill taking’ into their daily routine encourages adherence.

Lack of compliance to medications has been described as the newest risk factor in treating patients with chronic diseases. For many physicians, non-compliance is a blind spot in our clinical questioning and decision making. Simple changes in our prescribing choices and strategies can have a powerful impact in improving adherence.

After explaining the diagnosis of Type 2 diabetes to Alan and sending him for diabetes education, he was more amenable to medical treatment for this diabetes and hypertension. He was started on combination therapy for his blood sugar, hypertension and dyslipidemia. His frequent visits allowed reinforcement of compliance and monitoring of his mood, blood pressure and glycemic control. Changes in therapy were made slowly over time to improve his persistence to therapy and reduce therapeutic turbulence. Over the next year, his medication regimen was stable and simplified to the point where he was taking two pills twice daily. ■

ASCOT-LLA TRIAL: Bridging the Hypertension and Dyslipidemia Guidelines

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expert opinion

HIGHLIGHTS

- ASCOT-LLA broadens the range of patients and serum cholesterol levels that warrant statin therapy
- A highly significant 36% RR on the primary endpoint was observed
- ASCOT-LLA reinforces the concept of treating global vascular risk rather than individual risk factors

Hypertension and hypercholesterolemia often co-exist in a large number of patients, exerting a multiplicative effect on cardiovascular risk. Although hypertensive patients have been included in previous lipid-lowering trials, the Lipid-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA) provides interesting evidence for the use of statins in primary prevention, specifically in hypertensive patients.¹ In addition, ASCOT-LLA extends the results of two other primary prevention lipid-lowering trials — WOSCOPS² and AFCAPS/TexCAPs³ — which confirmed the benefits of statins for the primary prevention of major coronary and cerebrovascular events. The ASCOT-LLA study broadens the range of patients and serum cholesterol levels that warrant statin therapy.

ASCOT enrolled 19,257 patients aged 40 to 79 years with hypertension (defined as untreated blood pressure $\geq 160/100$ mm Hg or treated blood pressure $\geq 140/90$ mm Hg). In addition, patients had to have at least 3 additional cardiovascular risk factors. The main study randomized patients to two different blood pressure-lowering strategies, the results of which have recently been published.⁴ In the lipid-lowering arm of ASCOT, 10,305 ASCOT patients with baseline total cholesterol levels ≤ 6.5 mmol/L (~ 250 mg/dL) were randomly assigned to receive atorvastatin 10 mg/day or placebo. In addition, these patients had at least three (average of 3.7) of the following risk factors: male gender, age ≥ 55 years, left ventricular hypertrophy or other electrocardiographic abnormality, smoking, family history of premature CVD, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischemic attack, microalbuminuria or proteinuria, and total-cholesterol to HDL-cholesterol ratio ≥ 6 . There was no total or LDL-cholesterol target in this study.

The primary objective of the study was to determine the effect of atorvastatin vs. placebo on the combined endpoint of nonfatal myocardial infarction (MI) and fatal CHD over a period of 5 years. However, the study was terminated prematurely at 3.3 years, due to a highly significant reduction in the primary endpoint of CHD events in patients receiving atorvastatin. In addition, a significant reduction in the incidence of stroke was also noted in patients receiving atorvastatin compared with placebo.

At study completion, LDL-C was 1.0 mmol/L lower with atorvastatin treatment compared to placebo, which represented a 29% relative reduction. A highly significant 36% risk reduction on the primary endpoint was observed with atorvastatin, a benefit that emerged very early in the trial ($p=0.0005$ vs placebo). Since hypertension is a stronger risk factor for stroke than hypercholesterolemia, the results of atorvastatin treatment on the incidence of stroke in this population were particularly compelling. Blood pressure control was similar between the treatment groups, with mean pressures of 138.3/80.4 mm Hg and 138.4/80.4 mm Hg for atorvastatin and placebo, respectively. However, atorvastatin treatment resulted in a 27% risk reduction in fatal/nonfatal stroke ($p=0.0236$), emphasizing that even in patients with good BP control, lowering of cholesterol further prevents both fatal and nonfatal stroke (see Figure 1).

The benefit of atorvastatin on the primary endpoint was assessed in the diabetic subgroup of patients ($n=2,532$), which represented 24.6% of the LLA patient population. These patients experienced a 16% risk reduction, which did not reach statistical significance ($p=0.4253$). This result was surprising, considering the potential benefits of lipid-lowering in these patients. However, the confidence intervals overlapped with those of the overall patient population, suggesting that this lack of observed benefit could have been due to an insufficient sample size. In addition, these results were ▶

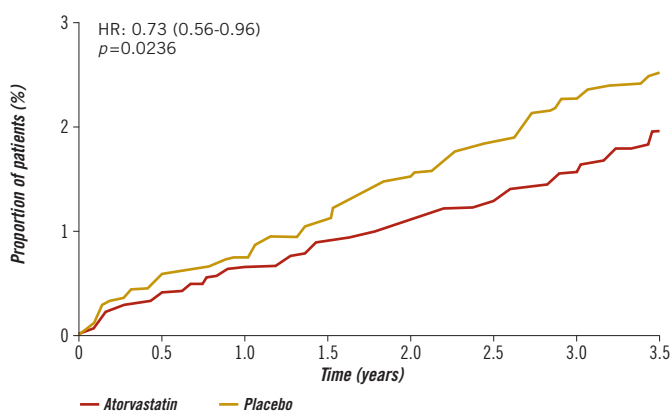


Figure 1. Cumulative incidence for fatal and non-fatal stroke.¹

substantiated with the larger CARDS study⁶ — a primary prevention study in 2,838 patients with diabetes without cardiovascular disease — which demonstrated that the ASCOT-LLA treatment regimen (atorvastatin 10 mg/day) did have a significant benefit in patients with diabetes. In CARDS, those patients on atorvastatin (mean LDL-C: 2.11 mmol/L) had a 37% lower rate of major cardiovascular events versus those patients taking placebo (mean LDL-C: 3.12 mmol/L) ($p=0.001$).

In ASCOT-LLA, atorvastatin treatment was well tolerated, demonstrated by the fact that 87% of the patients originally assigned to the drug were still taking it after three years of follow-up. The number of serious adverse events and rates of liver-enzyme abnormalities were similar between atorvastatin- and placebo-treated patients.¹ Only one non-fatal case of rhabdomyolysis was reported in a male patient receiving atorvastatin, who had had a very high alcohol intake and a recent febrile illness.^{1,4}

The results of the ASCOT-LLA trial support the use of global risk assessment in determining which hypertensive patients may receive benefit from lipid-lowering therapy. The majority of patients in ASCOT did not have evident CHD or significantly elevated LDL-C, yet they were at increased risk due to hypertension and other CV risk factors (see Figure 2). ASCOT patients are therefore quite representative of patients seen in clinical practice. The ASCOT-LLA authors reported that the placebo group experienced the equivalent of a 9.4% 10-year coronary event rate (non-fatal MI and fatal CHD), which is considered a low-risk population. However, without the average BP reduction of 25/14 mm Hg achieved in the larger antihypertensive trial, the placebo group would have experienced a 10-year coronary risk of about 15%, which would have made them at least a moderate-risk population. These results reinforce the concept that the initiation of statin therapy should be considered based upon a patient's *global vascular risk*, rather than by the numeric value of a given risk factor, such as LDL-C or blood pressure. Notably, this conclusion has been reinforced by the Canadian Hypertension Education Program recommendations in support of statin treatment for all hypertensive patients that meet "ASCOT criteria".⁸

Based on the Canadian lipid guidelines,⁶ ASCOT patients would fall into the low or moderate risk categories. Low-risk patients have a 10-year risk of CHD of $\leq 10\%$, with an LDL-C target of < 4.5 mmol/L. Moderate-risk patients are those with a 10-year CAD risk of 11-19%, and their LDL-C target should be < 3.5 mmol/L. The results of ASCOT-LLA reinforce the trend of broadening the types of patients eligible for statin therapy; in this case, those with hypertension and average cholesterol levels. The post-hoc analysis of ASCOT-LLA lends further support to lowering lipid targets, as similar hazard ratios for the primary endpoint were shown across a range of baseline total cholesterol values (see Table 1).¹

Baseline total cholesterol	Hazard ratio	p-value
<5.0 mmol/L	0.63	0.098
5.0-5.99 mmol/L	0.62	0.011
≥ 6.0 mmol/L	0.69	0.084

Table 1. Hazard ratios for primary endpoint of ASCOT-LLA based on baseline total cholesterol values.¹

Based upon these findings, patients with hypertension and associated risk factors should be treated with statins, dosed to reduce LDL-C by 30%, as achieved by atorvastatin 10 mg in ASCOT-LLA. Such a treatment strategy, combined with optimal antihypertensive therapy, should result in clinical benefit of similar magnitude to what was observed in ASCOT.

As the pool of patients eligible for statin therapy widens, and as their absolute risk level falls, the issue of cost-efficacy must be considered. The ASCOT-LLA trial provides convincing evidence of benefit on hard endpoints, but in a relatively low-to-moderate risk population. The cost-effectiveness of atorvastatin in primary prevention has been evaluated in light of the ASCOT results, in relation to the German health system.⁹ The results illustrated that the cost-effectiveness of atorvastatin was 7,311 Euro (95% CI: 5197; 10,091) per life-year gained, certainly comparable to many other accepted therapies both in cardiovascular medicine and beyond. The authors concluded that the administration of atorvastatin in hypertensive patients in Germany would be cost-effective.

Thus, the ASCOT-LLA trial demonstrates the efficacy of atorvastatin 10 mg and a 30% reduction in LDL at reducing major cardiovascular events in patients with hypertension and other risk factors. Taken into context with other major lipid-lowering trials (see Figure 2), ASCOT-LLA clearly broadens the range of patients eligible for statin therapy, and reinforces the concept of treating global vascular risk rather than individual risk factors, in the pursuit of optimal vascular health. ■

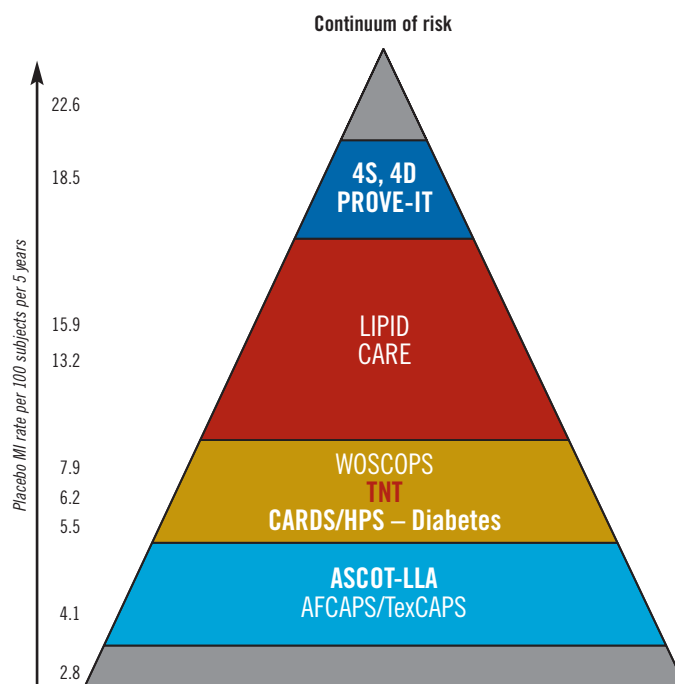


Figure 2. Lipid Reduction Studies: PROVE-IT, TNT, CARDS, HPS – Diabetes, ASCOT-LLA, 4D. This pyramid ranks major morbidity and mortality statin studies in primary and secondary prevention populations according to the type of patients that were included in each study. The ranking is according to the continuum of risk in the placebo group of the study based on the number of MI's per 100 patients over five years.



EOCI Case Study

Tim is a 57-year-old male patient of yours, who has come to see you for a follow-up visit. At his previous visit 6 months ago, he presented with hypertension, so you started him on amlodipine 5 mg/day. However, at this visit his blood pressure remains elevated at 148/93 mm Hg. Tim is an insurance broker who smokes half a pack a day. He has a family history of CHD, as his father died of it at the age of 59. Tim has impaired fasting glucose, as his FPG is 6.7 mmol/L. Tim's total cholesterol is 5.5 mmol/L and his LDL-C is 3.8 mmol/L.

Q1: In patients with documented CAD, what percentage will have a cholesterol value which would be in the low-risk range?

- A. 10%
- B. 25%
- C. 50%
- D. 75%

Answer: C

Q2: The ASCOT-LLA trial is an important primary prevention lipid lowering trial. Which of the following trials have already provided important preliminary evidence upon which ASCOT-LLA will build?

- A. WOSCOPS
- B. Heart Protection Study
- C. AFCAPS/TexCAPs
- D. All of the above

Answer: D

Q3: Recent clinical trial evidence demonstrates that a 10% decrease in LDL-C corresponds to what percentage in CHD reduction?

- A. 10%
- B. 5%
- C. 1%
- D. 25%

Answer: A

Q4: Based on the NCEP ATP III guidelines, when statin therapy is initiated in moderate-risk patients, what should be the target reduction in LDL-C?

- A. 10%
- B. 20%
- C. 30%
- D. 40%

Answer: C

Discussion

Should Tim be started on statin therapy?

Yes. When Tim's 10-year risk of CAD is calculated, based on the Canadian 2003 guidelines for the management of dyslipidemia, he falls into the high-risk category. This means that his target LDL-C level should be <2.5 mmol/L. Based on the ASCOT-LLA trial, atorvastatin (or other high potency statin) would be an appropriate treatment choice for Tim, as he could potentially derive a relative reduction of 36% in risk of non-fatal MI and fatal coronary heart disease, a 27% reduction in fatal and nonfatal stroke, and a 21% reduction in CV events and procedures if treated over a 3.3-year period. In addition, the CARDS trial, which included patients with hypertension and type 2 diabetes, showed that atorvastatin 10 mg was highly efficacious in reducing the risk of first cardiovascular disease events, including stroke, in patients with diabetes. These results from the CARDS study substantiate using statin therapy in patients with type 2 diabetes without any specific threshold LDL-C level. Tim, due to his insulin resistance, would likely also derive benefit from treatment with atorvastatin. Treating hypertensive patients with statins, who have BP that is either untreated or poorly controlled, yet have normal-to-moderately elevated cholesterol, offers significant reductions in cardiovascular and cerebrovascular events, the benefits of which are additive to appropriate blood pressure control. The results of ASCOT-LLA therefore reinforce the trend to adopt lower lipid-lowering treatment thresholds in patients with hypertension and multiple CV risk factors. ■

disclosure of faculty

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