Impact of treating hyperlipidemia or hypertension to reduce the risk of death from coronary artery disease

Evidence

Études

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Abstract

Objective: To compare the prevalence of modifiable risk factors for cardiovascular disease among hypertensive and nonhypertensive adults and to estimate the effect of treating hyperlipidemia or hypertension to reduce the risk of death from coronary artery disease.

Methods: The authors evaluated a sample of 7814 subjects aged 35–74 years free of clinical cardiovascular disease from the Canadian Heart Health Surveys to estimate the prevalence of cardiovascular risk factors. They identified hyperlipidemic subjects (ratio of total cholesterol to high-density lipoprotein cholesterol [total-C/HDL-C] 6.0 mmol/L or more for men and 5.0 mmol/L or more for women) and hypertensive subjects (systolic or diastolic blood pressure 160/90 mm Hg or greater, or receiving pharmacologic or nonpharmacologic treatment). A life expectancy model was used to estimate the rate of death from coronary artery disease following specific treatments.

Results: An elevated total-C/HDL-C ratio was significantly more common among hypertensive than nonhypertensive men aged 35–64 (rate ratio [RR] 1.56 for age 35–54, 1.28 for age 55–64) and among hypertensive than nonhypertensive women of all ages (RR 2.73 for age 35–54, 1.58 for age 55–64, 1.31 for age 65–74). Obesity and a sedentary lifestyle were also more common among hypertensive than among nonhypertensive subjects. According to the model, more deaths from coronary artery disease could be prevented among subjects with treated but uncontrolled hypertension by modifying lipids rather than by further reducing blood pressure for men aged 35–54 (reduction of 50 v. 29 deaths per 100 000) and 55–64 (reduction of 171 v. 104 deaths per 100 000) and for women aged 35–54 (reduction of 44 v. 39 deaths per 100 000). Starting antihypertensive therapy in subjects aged 35–74 with untreated hypertension would achieve a greater net reduction in deaths from coronary artery disease than would lipid lowering. Nonetheless, the benefits of lipid therapy were substantial: lipid intervention among hypertensive subjects aged 35–74 represented 36% of the total benefits of treating hyperlipidemia in the total hyperlipidemic population.

Interpretation: The clustering of hyperlipidemia and the potential benefits of treatment among hypertensive adults demonstrate the need for screening and treating other cardiovascular risk factors beyond simply controlling blood pressure.

In Canada coronary artery disease (CAD) is still the leading cause of death and illness despite the decline in the age-adjusted death rate.[1] Hypertension is highly prevalent and is an important risk factor for CAD.[2] A review of hypertension trials showed that the treatment of hypertension leads to a reduction in coronary event rates.[3,4] However, among people with mild hypertension, the risk of CAD is influenced by a variety of risk factors other than blood pressure, including increased age, male sex, personal history of cardiovascular disease, dyslipidemia, diabetes mellitus, smoking, obesity and sedentary lifestyle.[2,5,6] Various epidemiologic studies have demonstrated that these risk factors are more prevalent among hypertensive subjects than among normotensive subjects.[7–12]

The aim of our study was to compare the prevalence of modifiable cardiovascular risk factors among hypertensive and nonhypertensive Canadian adults. We then estimated the potential effect of treating hyperlipidemia or hypertension to reduce the risk of death from CAD for primary prevention, using a validated cardiovascular life expectancy model.

Methods

The Canadian Heart Health Surveys are population-based, cross-sectional surveys from the 10 provinces completed between 1986 and 1992. In each province the sampling design consisted of stratified, 2-stage, replicated probability samples to provide 2200 responses from women and men aged 18–74 years in the community. A total of 29 855 people were selected, of whom 23 251 participated in the surveys. The survey methods have been described in detail previously.[13] Information on sociodemographic characteristics, hypertension and diabetes status, lifestyle, and knowledge and awareness of cardiovascular risk factors were obtained during interviews at home with a trained nurse.[13] About 2 weeks later the participants were invited to attend a clinic for fasting blood samples and anthropometric measures. Blood pressure was measured twice during the home interview and twice at the clinic visit by means of standardized methods developed for the Hypertension Detection and Follow-up Program.[14] The mean of the 4 measurements was used in this report.

Our analyses were limited to people aged 35–74 years (n = 11 333). Among those who were interviewed, 89%, 92% and 92% of men aged 35–54, 55–64 and 65–74 respectively and 90%, 90% and 87% of women respectively attended the clinic (total n = 10 165); 85%, 87% and 86% of men and 86%, 85% and 81% of women respectively provided a fasting blood sample (total n = 9610 fasting 8 hours or more). Losses due to failure to attend the clinic or to give a fasting blood sample were similar for all age–sex categories.

We excluded people with known cardiovascular disease (n = 1796), resulting in a sample of 7814 men and women, of whom 2064 were hypertensive. Data included systolic and diastolic blood pressure, blood lipid levels, the presence of self-reported diabetes treated by pharmacologic and nonpharmacologic means, obesity (body mass index 27 or greater), self-reported cigarette smoking and sedentary lifestyle (physical activity less than once per week). Subjects with systolic or diastolic blood pressure of 160/90 mm Hg or greater, or receiving pharmacologic or nonpharmacologic treatment were classified as having hypertension.[15] Subjects were classified as having hyperlipidemia if the ratio of total cholesterol to high-density lipoprotein cholesterol (total-C/HDL-C) was 6.0 mmol/L or more for men or 5.0 mmol/L or more for women. These values were based on analysis showing that the total-C/HDL-C ratio improves the risk-discriminating ability of total cholesterol and low-density lipoprotein cholesterol measures.[16–18]

The Cardiovascular Life Expectancy Model is based in part on data from the Lipid Research Clinics Prevalence Study, conducted from 1972 to 1976.[17] Specifically, survival data for a 15% random sample of men and women aged 30 years or more were used for an average of 12.2 years of follow-up. Specific causes of death were ascertained from death certificates and hospital records, and the vital status of 99% of the participants was established at least once during the follow-up period.[17]

The Cardiovascular Life Expectancy Model estimates the risk of death from CAD, stroke and other causes based on the levels of independent risk factors (e.g., age, blood pressure and blood lipid levels) found in the cohort of the Lipid Research Clinics. The model was validated by comparing its predictions with the observed fatal outcomes in 9 randomized clinical trials.[17] The Cardiovascular Life Expectancy Model has been shown to forecast the benefits of treating hyperlipidemia or hypertension in both primary and secondary prevention hypertension and lipid trials.[17] We used this model to forecast the annual rates of death from CAD among Canadians. The variables used to estimate the risk of death included age, sex, cigarette smoking (yes, no), mean blood pressure levels (1/3 systolic + 2/3 diastolic), diabetes (yes, no) and the natural log of the total-C/HDL-C ratio.

We estimated the benefits of modifying cholesterol or blood pressure by specifying a subject's initial and expected post-treatment lipid levels or blood pressure readings, holding all other risk factors constant, and subtracting the resulting estimates of annual rates of death from CAD. The hypothetical intervention groups consisted of men and women with and without hypertension who were free of clinical cardiovascular disease and whose baseline CAD risk factors (age, total-C/HDL-C ratio, cigarette smoking and diabetes) were reported in the Canadian Heart Health Surveys.

The hypothetical intervention of a lipid-lowering drug was applied to men with a total-C/HDL-C ratio of 6.0 mmol/L or greater and to women with a ratio of 5.0 mmol/L or greater.[16,18] The effect of lipid pharmacotherapy was assumed to be a 17% decrease in the total cholesterol level and a 7% increase in the HDL cholesterol level, similar to the results reported for lovastatin.[19]

The hypothetical intervention on blood pressure was applied to each treated or untreated hypertensive subject whose systolic or diastolic blood pressure was 160/90 mm Hg or greater. The intervention simulations assumed mean blood pressure (1/3 systolic + 2/3 diastolic) reductions of 10 mm Hg (13 mm Hg in systolic and 7 mm Hg in diastolic blood pressure). This reduction approximates the reported results of 3 positive clinical trials of mild hypertension treatment.[20–22]

We contrasted the effect of lowering total-C/HDL-C ratio or elevated blood pressure among hypertensive (treated or untreated) men and women stratified by age. We then calculated the net benefits associated with treatment by subtracting predicted annual rates of death from CAD after intervention from estimated baseline CAD death rates.

The 10-year risk of death from CAD for each subject was calculated as described above and transformed into an annual risk by dividing by 10. We estimated the overall number of Canadians experiencing a fatal CAD event in the population by multiplying subject-specific risks by population weights based on the 1986 census reports.[23] Average annual rates per 100 000 were obtained for nonhypertensive, treated hypertensive and untreated hypertensive men and women by age group (35–54, 55–64 and 65–74 years). We calculated annual rates per 100 000 by dividing the overall number of CAD-related deaths estimated to occur in each group by the total number of Canadians in each group and then multiplying by 100 000.

All reported measurements have been weighted to account for the sampling design and for complete (as opposed to item) nonresponse at the interview and clinic stages of the survey. The estimates represent population estimates. We compared the characteristics of hypertensive and nonhypertensive men and women using a t-test adjusting for population weights. The relative frequency of modifiable cardiovascular risk factors among hypertensive compared with nonhypertensive subjects is reported as a rate ratio (RR) (and 95% confidence interval).[24]

Results

The prevalence of hypertension among subjects free of cardiovascular disease ranged from 23% among Canadian men aged 35–54 to 32% among men aged 65–74. Among Canadian women, the prevalence ranged from 10% among those aged 35–54 to 36% among those aged 65–74. Overall, 53% of all hypertensive adults had uncontrolled

Table 1: Characteristics of 7814 hypertensive* and nonhypertensive Canadian men and women free of cardiovascular disease[13] stratified by age

	Men		Women	
Characteristic	Hypertensive	Nonhypertensive	Hypertensive	Nonhypertensive
Age 35–54 yr				
No. of patients	454	1580	290	1834
Mean age (and SD), yr	44 (5)†	43 (6)	47 (5)†	43 (6)
Mean blood pressure (and SD), mm Hg				
Systolic	135 (13)†	121 (9)	138 (16)†	114 (12)
Diastolic	92 (6)†	78 (6)	88 (8)†	74 (7)
Mean total-C/HDL-C ratio (and SD)	5.1 (1.4)†	4.8 (1.4)	4.5 (1.4)†	3.7 (1.2)
Mean body mass index (and SD)	28.0 (4.4)†	26.0 (3.5)	29.1 (6.2)†	24.4 (4.8)
Risk factors, % of subjects				
High total-C/HDL-C ratio‡	24.4†	17.2	28.6†	12.8
Obese§	52.5†	35.1	61.2†	23.3
Sedentary lifestyle¶	54.2†	40.1	44.2†	35.5
Diabetes mellitus**	9.1†	2.7	9.0†	2.8
Smoker††	24.3†	31.5	30.9	29.7
Age 55–64 yr				
No. of patients	210	437	243	462
Mean age (and SD), yr	60 (3)	60 (3)	60 (3)	60 (3)
Mean blood pressure (and SD), mm Hg				
Systolic	151 (14)†	128 (12)	148 (16)†	125 (13)
Diastolic	91 (8)†	79 (7)	88 (8)†	77 (7)
Mean total-C/HDL-C ratio (and SD)	4.9 (1.6)†	4.6 (1.4)	4.4 (1.4)†	4.0 (1.2)
Mean body mass index (and SD)	28.2 (3.4)†	26.5 (4.1)	28.9 (6.0)†	26.5 (4.9)
Risk factors, % of subjects				
High total-C/HDL-C ratio	22.5	18.6	26.3†	18.5
Obese	60.4†	45.9	65.1†	39.9
Sedentary lifestyle	46.7†	37.1	32.3	39.7
Diabetes	12.7†	5.6	6.4	4.1
Smoker	19.8	25.3	13.3†	19.2
Age 65–74 yr				
No. of patients	390	754	477	683
Mean age (and SD), yr	70 (3)†	69 (3)	70 (3)†	69 (3)
Mean blood pressure (and SD), mm Hg				
Systolic	156 (18)†	133 (12)	157 (19)†	133 (12)
Diastolic	88 (9)†	76 (7)	84 (11)†	76 (7)
Mean total-C/HDL-C ratio (and SD)	4.8 (1.4)	4.8 (1.3)	4.5 (1.2)†	4.2 (1.4)
Mean body mass index (and SD)	27.4 (4.2)†	25.7 (3.7)	27.9 (5.2)†	25.3 (4.5)
Risk factors, % of subjects				
High total-C/HDL-C ratio	15.9	18.3	33.3†	27.6
Obese	56.3†	31.6	50.9†	34.5
Sedentary lifestyle	38.3	40.5	39.6†	29.8
Diabetes	10.2	11.7	16.6†	4.5
Smoker	14.6	17.8	10.7†	17.7

Note: SD = standard deviation, total-C = total cholesterol, HDL-C = high-density lipoprotein cholesterol.
*Systolic or diastolic blood pressure 160/90 mm Hg or greater, or receiving pharmacologic or nonpharmacologic treatment.
†$p < 0.05$, for comparison with nonhypertensive subjects.
‡6.0 mmol/L or more for men, and 5.0 mmol/L or more for women.
§Body mass index 27 or greater.
¶Physical activity less than once per week.
**Receiving pharmacologic or nonpharmacologic treatment.
††Occasional or regular.

hypertension or were unaware of their hypertension, although 85% had had their blood pressure measured in the previous year.

The characteristics of hypertensive and nonhypertensive men and women free of cardiovascular disease are presented in Table 1. The mean total-C/HDL-C ratio was significantly higher among the hypertensive men aged 35–64 and among the women of all age groups than among the nonhypertensive subjects. The mean body mass index was also significantly greater among the hypertensive subjects than among the nonhypertensive subjects across all age groups for both sexes.

The RRs of modifiable cardiovascular risk factors among the hypertensive and nonhypertensive men and women are given in Table 2. Hypertension tended to occur in association with other modifiable risk factors. For instance, an elevated total-C/HDL-C ratio was more common among the hypertensive than among the nonhypertensive men aged 35–64 (RR 1.28–1.56) and was more common among the hypertensive than among the nonhypertensive women of all ages (RR 1.31–2.73). For both men and women, obesity was significantly more common among the hypertensive than among the nonhypertensive subjects in all age groups (RR 1.80–5.21). A sedentary lifestyle was more common among the hypertensive than among the nonhypertensive men aged 35–64 (RR 1.49–1.77); it was also more common among the hypertensive than among the nonhypertensive women aged 35–54 and 65–74 (RR 1.44–1.55).

The estimated annual risk of death from CAD per 100 000 following treatment for hyperlipidemia or hypertension in men is presented in Table 3. A total of 12% of men aged 35–54 had a blood pressure of 160/90 mm Hg or greater, of whom 54% were receiving treatment. The corresponding values for men aged 55–64 were 23% and 80%, and for men aged 65–74, 18% and 85%.

Table 2: Rate ratios of cardiovascular risk factors among hypertensive and nonhypertensive men and women stratified by age

	Rate ratio (and 95% confidence interval)	
Risk factor	Men	Women
Age 35–54 yr		
High total-C/HDL-C ratio	1.56 (1.54–1.57)	2.73 (2.70–2.75)
Obese	2.04 (2.03–2.06)	5.21 (5.17–5.25)
Sedentary lifestyle	1.77 (1.76–1.78)	1.44 (1.42–1.45)
Diabetes	3.56 (3.51–3.60)	3.38 (3.33–3.43)
Smoker	0.70 (0.69–0.70)	1.06 (1.05–1.07)
Age 55–64 yr		
High total-C/HDL-C ratio	1.28 (1.26–1.29)	1.58 (1.56–1.59)
Obese	1.80 (1.78–1.81)	2.81 (2.79–2.83)
Sedentary lifestyle	1.49 (1.47–1.50)	0.73 (0.72–0.73)
Diabetes	2.45 (2.41–2.49)	1.59 (1.56–1.62)
Smoker	0.73 (0.72–0.74)	0.64 (0.64–0.65)
Age 65–74 yr		
High total-C/HDL-C ratio	0.84 (0.83–0.86)	1.31 (1.30–1.32)
Obese	2.78 (2.75–2.82)	1.97 (1.95–1.99)
Sedentary lifestyle	0.91 (0.90–0.92)	1.55 (1.53–1.57)
Diabetes	0.86 (0.84–0.88)	4.21 (4.13–4.29)
Smoker	0.79 (0.78–0.80)	0.56 (0.55–0.57)

Among men aged 35–54, hypertension treatment is estimated to reduce the number of deaths from CAD per 100 000 by 29 among previously treated men and by 73 among previously untreated men. Lipid treatment is estimated to reduce the number of CAD-related deaths per 100 000 among nonhypertensive, treated hypertensive and untreated hypertensive subjects by 21, 50 and 32 respectively. Among men aged 55–64, the predicted net benefits of hypertension treatment among previously treated and previously untreated subjects were 104 and 235 fewer deaths from CAD respectively, compared with net reductions of 171 and 49 deaths from CAD with lipid therapy.

The effect of lipid lowering is lesser among hypertensive men aged 65–74. The predicted reductions in deaths from CAD following hypertension treatment declines from 18% to 11% between 35–54 and 65–74 years of age. The predicted risk reduction with hyperlipidemia treatment declines from 15% to 7% between the 2 age groups. The predicted overall net reduction in deaths from CAD following hypertension therapy exceeds that of lipid lowering among untreated hypertensive men aged 35–74. This is due in part to a lower prevalence of a high total-C/HDL-C ratio in this group. Nonetheless, the benefits of lipid therapy remain substantial. Our model suggests that 31% of the overall potential reduction in CAD mortality from hyperlipidemia treatment in the total hyperlipidemic male population arises from lipid interventions among hypertensive men.

The annual estimated risk of death from CAD per 100 000 following treatment for hyperlipidemia or hypertension among the hypertensive women is presented in Table 4. A total of 7% of women aged 35–54 had a blood pressure of 160/90 mm Hg or greater, of whom 86% were receiving treatment. The corresponding values for women aged 55–64 were 26% and 89%, and for those aged 65–74, 28% and 90%.

The estimated rate of death from CAD was 4 to 5 times higher among the treated and untreated hypertensive women than among the women without hypertension. The predicted net benefits of treating hypertension included a reduction in CAD-related deaths of 39 per 100 000 among the treated hypertensive women and of 44 per 100 000 among the untreated hypertensive women. Lipid therapy would lead to 44 and 9 fewer CAD-related deaths per 100 000 among treated and untreated hypertensive women respectively.

Similar to the case for men, the predicted reduction of the baseline risk of death from CAD following hypertension treatment among hypertensive women decreases from 20% to 12% between 35–54 and 65–74 years of age. The predicted risk reduction with lipid therapy declines from 20% to 8% between the 2 age groups. Initiating antihypertensive therapy among untreated hypertensive women aged

35–74 would achieve a greater net reduction in CAD-related deaths than would lipid treatment. The benefits of lipid lowering also remain substantial. From a population perspective, 55% of the total potential net reduction in CAD mortality from lipid treatment in all hyperlipidemic women can be attributed to lipid intervention among hypertensive women.

Interpretation

It has been shown that, despite antihypertensive treatment, cardiovascular morbidity is still higher among hypertensive people than among normotensive people.[25–28] One potential explanation for this observation is that the excess risk among treated hypertensive people may be due in part to inadequate control of other risk factors apart from hypertension.[6] Among people at high risk, it is therefore essential to document modifiable risk factors, including hyperlipidemia, smoking, obesity and sedentary lifestyle, which are common among hypertensive Canadian adults,[14] and to identify people whose hypertension is not well controlled or who are unaware of their hypertension.[29]

Our results show that a substantial proportion of the Canadian adult population had their blood pressure measured in the year before participation in the Canadian Heart Health Surveys and that the prevalence of hypertension is still high, with a low level of control, mainly among young men. These findings corroborate results of a recent Canadian study.[29] Our results also show that the RRs of risk factors for CAD are higher among hypertensive people than among normotensive people. Accordingly, one would expect that the benefits of managing these risk factors would also be greater among hypertensive adults because they are at increased risk of cardiovascular events.[6] Our findings suggest that treating high lipid levels is as important as further reducing blood pressure among women and men with treated but poorly controlled hypertension. Moreover, careful consideration must be given to both an-

Table 3: Estimated annual risk of death from coronary artery disease per 100 000 following treatment for hyperlipidemia or hypertension among men

Group	Population (in 1000s)	Baseline risk per 100 000	Risk per 100 000 after lipid therapy*	Risk per 100 000 after hypertension therapy*
Age 35–54 yr				
Nonhypertensives	2234	166	145 (21)	166 (0)
Treated hypertensives†	184	271	221 (50)	242 (29)
Untreated hypertensives‡	158	284	252 (32)	211 (73)
Age 55–64 yr				
Nonhypertensives	577	548	504 (44)	548 (0)
Treated hypertensives	156	1262	1091 (171)	1158 (104)
Untreated hypertensives	38	981	932 (49)	746 (235)
Age 65–74 yr				
Nonhypertensives	390	1184	1077 (107)	1184 (0)
Treated hypertensives	81	1720	1615 (105)	1556 (164)
Untreated hypertensives	14	2313	2076 (237)	1891 (422)

*Numbers in parentheses represent total number of coronary events prevented after treatment.
†Subjects with systolic or diastolic blood pressure of 160/90 mm Hg or greater receiving pharmacologic or nonpharmacologic treatment.
‡Subjects with systolic or diastolic blood pressure of 160/90 mm Hg or greater not receiving any treatment.

Table 4: Estimated annual risk of death from coronary artery disease per 100 000 following treatment for hyperlipidemia or hypertension among women

Group	Population (in 1000s)	Baseline risk per 100 000	Risk per 100 000 after lipid therapy*	Risk per 100 000 after hypertension therapy*
Age 35–54 yr				
Nonhypertensives	2518	40	38 (2)	40 (0)
Treated hypertensives	168	200	156 (44)	161 (39)
Untreated hypertensives	28	171	162 (9)	127 (44)
Age 55–64 yr				
Nonhypertensives	660	175	166 (9)	175 (0)
Treated hypertensives	232	321	303 (18)	276 (45)
Untreated hypertensives	28	298	253 (45)	228 (70)
Age 65–74 yr				
Nonhypertensives	543	437	413 (24)	437 (0)
Treated hypertensives	195	931	860 (71)	829 (102)
Untreated hypertensives	22	584	567 (17)	439 (145)

*Numbers in parentheses represent total number of coronary events prevented after treatment.

tihypertensive and lipid therapy in adults with untreated hypertension. The predicted reduction of CAD mortality from lipid intervention among hypertensive men and women represents 36% of the total net benefits of treating hyperlipidemia in the total hyperlipidemic population. In addition to controlling blood pressure, it is essential to screen for and treat other modifiable risk factors, particularly hyperlipidemia, among hypertensive adults.

Our estimates have certain limitations. First, we implicitly assumed that intervening on one risk factor would not affect other risk factors. Second, we assumed similar efficacy and tolerability of lipid-lowering drugs consistent across age, sex and hypertensive status.[30] Third, all the benefits associated with a lower total-C/HDL-C ratio were assumed to translate into a lower risk for CAD.[31,32] Fourth, our model also assumed an immediate benefit from risk-factor intervention, whereas in reality there may be a delay in risk reduction.[33–38] Similarly, we assumed that the effect of lowering blood pressure would appear immediately,[4] but it may not actually reach its full benefit in the first year. Finally, all the benefits associated with a lower blood pressure were assumed to translate into lower risk of CAD. However, the benefits of treating hypertension may be overestimated. For instance, the risk reduction associated with blood pressure lowering has been calculated as 50% of the effect predicted by epidemiologic studies in a meta-analysis of clinical trial results.[4]

Although the prevalence of hypertension increases with increasing age, it is important to realize that the burden of hypertension occurs among middle-aged adults, particularly men with poor blood pressure control. To maximize the reduction in coronary risk, hypertension therapy must be combined with other interventions to modify risk factors, such as lowering an elevated total-C/HDL-C ratio.

Our results are consistent with those of other studies forecasting the rate of CAD from a hypothetical cohort according to various combinations of risk factor levels.[2,6] They are also consistent with those of Samuelsson and colleagues,[28] who analysed cardiovascular morbidity in relation to changes in blood pressure and serum cholesterol levels. They found that a combined reduction of both risk factors was necessary to achieve a substantial reduction in morbidity among middle-aged hypertensive men free of cardiovascular disease.

The clustering of modifiable cardiovascular risk factors demonstrates the need for comprehensive screening of risk factors among hypertensive Canadian adults.[14,29] It is thus important to detect hypertension in order to start treatment and to identify a subgroup of the population among whom it may be warranted to search for other modifiable risk factors, such as hyperlipidemia.

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