

Hypertension in diabetes: A call to action

Norman RC Campbell MD¹, Lawrence A Leiter MD², Pierre Larochelle MD³, Sheldon Tobe MD⁴,
Arun Chockalingam PhD⁵, Richard Ward MD⁶, Dorothy Morris MA CCN(C)⁷, Ross Tsuyuki PharmD MSc⁸

NRC Campbell, LA Leiter, P Larochelle, et al. Hypertension in diabetes: A call to action. *Can J Cardiol* 2009;25(5):299-302

The Canadian Hypertension Education Program, Blood Pressure Canada, Canadian Hypertension Society, Heart and Stroke Foundation of Canada, Canadian Diabetes Association, College of Family Physicians of Canada, Canadian Pharmacists Association and the Canadian Council of Cardiovascular Nurses call on Canadian health care professionals to redouble efforts to help patients achieve treatment targets (blood pressure less than 130 mmHg systolic and less than 80 mmHg diastolic) in people with diabetes. Treatment of high blood pressure in people with diabetes results in large reductions in death and disability within a short period of time and needs to be a therapeutic priority. Achieving blood pressure targets requires sustained lifestyle modification, and three or more drugs including a diuretic are often required. Antihypertensive treatment in people with diabetes is one of the few medical treatments estimated to reduce overall health costs. The cost of treatment is less than the cost of complications prevented. Blood pressure needs to be assessed at all visits and home blood pressure assessment is encouraged. Management strategies need to include assessment and management of cardiovascular risks including smoking, unhealthy eating, physical inactivity, abdominal obesity, dyslipidemia as well as dysglycemia. The risks and benefits of acetylsalicylic acid in primary prevention of cardiovascular disease are uncertain in people with hypertension and diabetes. Intensive individualized lifestyle modification is recommended to prevent and treat hypertension, dyslipidemia, dysglycemia and other vascular risks in people with diabetes.

Key Words: Cardiovascular disease; Diabetes; Hypertension; Myocardial infarction prevention; Stroke

Hypertension et diabète : Appel à la mobilisation

Le Programme éducatif canadien sur l'hypertension (PECH), la Société canadienne de l'hypertension artérielle, la Fondation des maladies du cœur du Canada, l'Association canadienne du diabète, le Collège des médecins de famille du Canada, l'Association des pharmaciens du Canada et le Conseil canadien des infirmières et infirmiers en soins cardiovasculaires demandent aux professionnels de la santé canadiens de redoubler d'efforts pour aider leurs patients diabétiques à atteindre leurs objectifs tensionnels (soit tension artérielle [TA] systolique < 130 mm Hg et TA diastolique < 80 mm Hg). Chez les personnes atteintes de diabète, le traitement de l'hypertension artérielle donne lieu à d'importantes réductions de la mortalité et de l'invalidité en peu de temps et doit constituer une priorité thérapeutique. L'atteinte des objectifs de tension artérielle exige des modifications soutenues au style de vie et il faut souvent administrer trois médicaments ou plus, dont un diurétique. Le traitement antihypertenseur chez les personnes atteintes de diabète est l'un des rares traitements médicaux jugés capables de réduire les coûts de santé globaux. Le traitement coûte moins cher que les complications qu'il prévient. La tension artérielle doit être mesurée à chaque visite médicale et il faut encourager la vérification de la tension artérielle à domicile. Les stratégies thérapeutiques doivent inclure une évaluation et une prise en charge des facteurs de risque cardiovasculaires, c.-à-d., tabagisme, alimentation malsaine, sédentarité, obésité abdominale, dyslipidémie et dysglycémie. Les risques et avantages de l'acide acétylsalicylique en prévention primaire de la maladie cardiovasculaire restent à déterminer chez les personnes souffrant d'hypertension et de diabète. On recommande une modification intensive et individualisée du style de vie pour prévenir et traiter l'hypertension, la dyslipidémie, la dysglycémie et autres risques vasculaires chez les personnes souffrant de diabète.

INCREASED BLOOD PRESSURE AND VASCULAR RISK IN PEOPLE WITH DIABETES MELLITUS

Increased blood pressure is the leading risk for death and the second leading risk for disability in the world (1). Over 90% of those living an average lifespan are estimated to develop hypertension (2), which is largely a reflection of sedentary behaviour, poor dietary habits and obesity (3,4). These lifestyles are often associated with other cardiovascular and health risks such as dyslipidemia and diabetes; hence, it is not surprising that many people have additional cardiovascular risks if they have hypertension (5). The majority of people with diabetes have hypertension and 17% of those with hypertension (blood pressure 140/90 mmHg or greater, or on treatment) have been diagnosed with diabetes (6). Most of the burden of disease is associated with type 2 diabetes. Importantly, the definitions of diabetes and hypertension have changed over time and a significant amount of research has used older definitions. The current definition of hypertension and diabetes is provided in Table 1 (7).

Increased blood pressure represents a major health risk to people with diabetes. Sixty per cent to 80% of people with diabetes die of cardiovascular complications and up to 75% of specific cardiovascular complications have been attributed to high blood pressure (Table 2) (8). Hypertension is also a major factor contributing to kidney failure and eye disease in people with diabetes (9,10). Unfortunately, even in a recent survey, two-thirds of Canadians with hypertension and diabetes had uncontrolled blood pressure (6).

REDUCING VASCULAR RISK DUE TO INCREASED BLOOD PRESSURE: LIFESTYLE CHANGE AND IMPROVED SELF-EFFICACY

Hypertension and type 2 diabetes can be prevented. Blood pressure and hyperglycemia can be reduced and other cardiovascular risks can be improved by lifestyle interventions including a healthy diet, regular physical activity, low-risk alcohol consumption, reductions in dietary sodium and in some, stress reduction (Table 3). Brief health care professional interventions can increase the probability of a person making

¹Departments of Medicine, Community Health Sciences, University of Calgary, Libin Cardiovascular Institute of Alberta, Calgary, Alberta; ²Departments of Medicine & Nutritional Sciences, University of Toronto, Toronto, Ontario; ³Institut de Recherches Cliniques de Montreal, University of Montreal, Montreal, Quebec; ⁴Division of Nephrology, University of Toronto, Toronto, Ontario; ⁵Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia; ⁶Faculty of Medicine, University of Calgary, Calgary, Alberta; ⁷Canadian Council of Cardiovascular Nurses, Vancouver Island Health Authority, Victoria, British Columbia; ⁸EPICORE Centre, Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta

Correspondence: Dr Norman RC Campbell, Libin Cardiovascular Institute of Alberta, Health Sciences Centre, 3330 Hospital Drive Northwest, University of Calgary, Calgary, Alberta T2N 4N1. Telephone 403-210-7961, fax 403-283-6151, e-mail hyperten@ucalgary.ca

Received for publication February 25, 2009. Accepted March 19, 2009

TABLE 1
The definition of diabetes and of hypertension in the presence of diabetes

	Definition
Diabetes	Fasting plasma glucose of 7 mmol/L, or Casual plasma glucose of 11.1 mmol/L or higher with symptoms of diabetes, or 2 h plasma glucose of 11.1 mmol/L or higher
Hypertension in people with diabetes	Systolic blood pressure ≥ 130 mmHg or Diastolic blood pressure ≥ 80 mmHg

Data from reference 7

TABLE 2
Proportion of diabetic complications attributable to high blood pressure*

Complication	Proportion attributable to hypertension, %
Stroke	75
Coronary artery disease	35
End-stage renal disease	50
Eye disease [†]	35
Leg amputation	35

*Hypertension defined as $\geq 160/95$ mmHg and $\geq 140/90$ mmHg in different studies; [†]Defined as retinopathy. Data from reference 48

lifestyle changes and more comprehensive interdisciplinary care approaches are more effective (11,12). Self-management and self-efficacy are encouraged through the use of home measurement of blood pressure (13). Home blood pressure readings better predict cardiovascular outcomes than office readings, can detect white coat hypertension and masked hypertension, may improve adherence to medications or lifestyle change, and result in improved blood pressures. However, a weakness of home measurement of blood pressure is the lack of studies in diabetic populations and hence, the absence of validated target blood pressures for people with diabetes. Home blood pressure targets likely should be less than the office target of less than 130/80 mmHg.

REDUCING VASCULAR RISK DUE TO INCREASED BLOOD PRESSURE: PHARMACOTHERAPY

Pharmacologically reducing blood pressure in people with diabetes is one of the most effective medical interventions available to reduce death and disability. Randomized controlled trials of blood pressure-lowering treatments in people with diabetes have demonstrated major reductions in death, cardiovascular disease, and eye and kidney disease over a short period in time (9,10,14-18). For example, in the Systolic Hypertension in Europe (Syst-Eur) trial of isolated systolic hypertension (systolic blood pressure greater than 160 mmHg, diastolic blood pressure less than 90 mmHg) (19), active treatment reduced total mortality by 55%, cardiovascular mortality by 76% and all cardiovascular events by 67% with a reduction in blood pressure of 9.8/3.8 mmHg. In the United Kingdom Prospective Diabetes Study (UKPDS) (14), more intensive lowering of blood pressure, even by a few mmHg, had a major effect in reducing cardiovascular death and disability in people with diabetes. In a meta-analysis (20) of randomized controlled trials of diabetic people with hypertension, more versus less intensive lowering of blood pressure reduced total mortality by 24% and major cardiovascular events by 25%. In the diabetes subgroup of the Hypertension Optimal Treatment (HOT) trial (21), people with diabetes who were assigned to have a target diastolic blood pressure below 80 mmHg were compared with those assigned to have a target blood pressure below 90 mmHg. Although the achieved blood pressure difference in the two groups at the end of the study was

TABLE 3
Lifestyle therapy to reduce the risk of blood pressure-related cardiovascular complications in hypertension

Healthy diet	High in fresh fruits, vegetables, low-fat dairy products, dietary and soluble fibre, whole grains and protein from plant sources, low in saturated fat, cholesterol and salt in accordance with Canada's Guide to Healthy Eating
Regular physical activity	Accumulation of 30 min to 60 min of moderate intensity dynamic exercise 4 to 7 days per week in addition to daily activities.
Low-risk alcohol consumption	≤ 2 standard drinks/day, and less than 14/week for men and less than 9/week for women. One standard drink is a glass of wine (5 oz/142 mL of 12% alcohol content), one beer (12 oz/341 mL of 5% alcohol) or one shot of spirits (1.5 oz/43 mL of 40% alcohol)
Attaining and maintaining ideal body weight	Body mass index 18.5 kg/m ² to 24.9 kg/m ²
Attaining and maintaining healthy waist circumference	Europid <102 cm for men, <88 cm for women Japanese, South Asian, Chinese <90 cm for men, <80 cm for women
Reduction in sodium intake	Less than 2300 mg/day A smoke-free environment
Stress reduction	In people in whom stress may be contributing to blood pressure elevation, stress management should be considered

With permission from the Canadian Hypertension Education Program

only 4 mmHg, this greater reduction in blood pressure resulted in a 66% reduction in death from heart disease and stroke (21). The use of an angiotensin-converting enzyme (ACE) inhibitor- or angiotensin receptor blocker (ARB)-based therapeutic regime to lower blood pressure has additional advantages in people with chronic kidney disease and micro- or macroalbuminuria (20).

COMBINING THERAPIES TO REDUCE BLOOD PRESSURE

Combinations of lifestyle modification and sometimes four or more drugs are required for blood pressure control (22). An ACE inhibitor or ARB is a potential first-line therapy in all people with hypertension and diabetes (23). Alternative first-line treatments include long-acting calcium channel blockers and low-dose diuretics in people without microalbuminuria (23). Diuretic therapy is markedly underutilized in people with hypertension and diabetes but is generally considered necessary for blood pressure control when multiple antihypertensive drugs are prescribed (24,25). Diuretic therapy reduces major cardiovascular events in hypertensive people with or at risk for diabetes to a similar extent to other first-line drugs such as long-acting calcium channel blockers or ACE inhibitors (26). Often, higher doses of diuretic are required in resistant hypertension (27). Maintaining a normal serum potassium level is important to minimize the effect of diuretics on blood glucose and to maximize cardiovascular event reductions (28,29). Long-acting calcium channel blockers and cardioselective beta-blockers need to be considered if the blood pressure remains above target. A combination tablet of an ACE inhibitor or ARB with a diuretic, and a long-acting calcium channel blocker and a long-acting beta-blocker makes a potent once a day, three-tablet, four-drug blood pressure-lowering combination. The combination of an ACE inhibitor and an ARB has more adverse effects than ACE inhibitor therapy on its own and has no therapeutic advantage (30,31); hence, it is specifically not recommended to be used in the presence of normal urinary albumin levels (trials are ongoing to determine if the combination has a therapeutic role in

the presence of proteinuria). Although multiple drugs are required for control, more extensive lowering of blood pressure in people with diabetes is one of very few cost-saving medical interventions (32). The cost of blood pressure lowering is actually less than the cost of the complications prevented. Further quality of life can improve with more intensive blood pressure lowering (33).

REDUCING OVERALL VASCULAR RISK IN PEOPLE WITH DIABETES

Although hypertension is a leading risk in people with diabetes, other health risks are also very important. Dyslipidemia has a large impact in reducing cardiovascular events and a meta-analysis (34) of statin-based lipid lowering therapy in diabetes revealed that every 1 mmol reduction in low-density lipoprotein cholesterol was associated with a 9% reduction in total mortality, 13% reduction in cardiovascular mortality and 21% reduction in major cardiovascular events. Smoking is a risk for the development of diabetes mellitus (35), and a major risk for not only cardiovascular disease and cancer but also nephropathy and retinopathy in the person with diabetes. Interventions for smoking cessation can reduce mortality rates by almost 20% (36). Diabetes is defined by elevated blood glucose levels, and interventions to reduce glucose have resulted in reductions in nephropathy (albuminuria) and reduced development and progression of retinopathy (37-39). The Canadian Diabetes Association recommends reducing blood glucose levels to achieve a glycosylated hemoglobin target of 7.0% or less and consideration of reducing glycosylated hemoglobin to 6.5% or less (7). Current evidence is unclear as to the role of acetylsalicylic acid (ASA) in people with diabetes and hypertension. In the HOT trial (21), hypertensive diabetic people benefited from ASA therapy with reduced cardiovascular events. However, there is a lack of benefit of ASA therapy in the primary prevention of cardiovascular disease in other studies of people with diabetes (40-42). A comprehensive program that included lifestyle and pharmacotherapy for multiple risk factors has been associated with a 40% reduction in total mortality highlighting the importance of integrated programs that assess and address all cardiovascular risks (43). Focusing efforts on improving lifestyle and proven therapies to reduce blood pressure could have a huge impact on the longevity and disability of people with diabetes. Unfortunately, practice surveys demonstrate inadequate use of proven therapies, especially antihypertensive and statin therapies, in people with diabetes (44-46).

REFERENCES

- Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ, Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet* 2002;360:1347-60.
- Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men. *JAMA* 2002;287:1003-10.
- Touyz RM, Campbell N, Logan A, et al. The 2004 Canadian recommendations for the management of hypertension: Part III – Lifestyle modifications to prevent and control hypertension. *Can J Cardiol* 2004;20:55-9.
- Geleijnse JM, Grobbee DE, Kok FJ. Impact of dietary and lifestyle factors on the prevalence of hypertension in Western populations. *J Hum Hypertens* 2005;19:S1-S4.
- Khan N, Chockalingam A, Campbell NR. Lack of control of high blood pressure and treatment recommendations in Canada. *Can J Cardiol* 2002;18:657-61.
- Leenen FH, Dumais J, McInnis NH, et al. Results of the Ontario survey on the prevalence and control of hypertension. *CMAJ* 2008;178:1441-9.
- Canadian Diabetes Association. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2008;32:S1-S201.
- Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: An update. *Hypertension* 2001;37:1053-9.
- Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-9.
- Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60.
- Gillies CL, Abrams KR, Lambert PC, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: Systematic review and meta-analysis. *BMJ* 2007;334:299-307.
- Naik AD, Issac TT, Street RL Jr, Kunik ME. Understanding the quality chasm for hypertension control in diabetes: A structured review of “co-maneuvers” used in clinical trials. *J Am Board Fam Med* 2007;20:469-78.
- The Canadian Hypertension Education Program. The 2008 Canadian Hypertension Education Program recommendations: The scientific summary – an annual update. *Can J Cardiol* 2008;24:447-52.
- UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703-13.
- Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002;61:1086-97.
- Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000;23:B54-B63.

MANAGING HYPERTENSION IN PEOPLE WITH DIABETES: A CANADIAN CARE GAP

The recent Ontario Heart and Stroke Foundation blood pressure survey demonstrated a marked improvement in blood pressure control in hypertensive people with and without diabetes (24). The improved treatment of hypertension in Canada has been associated with a marked reduction in death and hospitalization from cardiovascular disease (47). However, the control of blood pressure in those with diabetes is worse than those without diabetes even using a 140/90 mmHg threshold, and two-thirds of people with diabetes had blood pressures of 130/80 mmHg or greater (24). In diabetic people with uncontrolled blood pressure, 27% were not treated and only 45% of those on multiple drugs were prescribed a diuretic (24). The Ontario survey indicates substantive improvement in blood pressure control is required in people with diabetes, which if implemented, will result in large reductions in death and disability rates, and health care costs.

A CALL TO ACTION: TARGET BLOOD PRESSURE TO LESS THAN 130/80 mmHg IN PEOPLE WITH DIABETES

The Canadian Hypertension Education Program, Blood Pressure Canada, Canadian Hypertension Society, Heart and Stroke Foundation of Canada, Canadian Diabetes Association, College of Family Physicians of Canada, Canadian Pharmacists Association and Canadian Council of Cardiovascular Nurses call on Canadian health care professionals and people with diabetes to redouble efforts to help patients achieve treatment targets and ensure:

- Blood pressure is maintained at less than 130 mmHg systolic and less than 80 mmHg diastolic. Sustained lifestyle modification and three or more drugs including a diuretic may be required.
- Blood pressure is assessed at all health care professional visits and that home blood pressure assessment is encouraged.
- Assessment and management of cardiovascular risks including smoking, unhealthy eating, physical inactivity, abdominal obesity, dyslipidemia and dyglycemia is required.
- Intensive individualized lifestyle modification is used to prevent and treat hypertension, dyslipidemia, dyglycemia and other vascular risks.
- Self-management education is encouraged including home measurement of blood pressure.

17. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. *Lancet* 2007;370:829-40.
18. Gerstein HC, Yusuf S, Mann JF, et al. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253-9.
19. Tuomilehto J, Rastenyte D, Birkenhager WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 1999;340:677-84.
20. Anderson C, Arima H, Belmans A, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus. *Arch Intern Med* 2005;165:1410-9.
21. Hansson L, Zanchetti A, Carson DS, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755-62.
22. Pool JL. Is it time to move to multidrug combinations? *Am J Hypertens* 2003;16:36S-40S.
23. Khan NA, Hemmelgarn B, Herman RJ, et al. The 2008 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 2 – therapy. *Can J Cardiol* 2008;24:465-75.
24. McInnis NH, Fodor G, Lum-Kwong MM, Leenen FH. Antihypertensive medication use and blood pressure control: A community-based cross-sectional survey (ON-BP). *Am J Hypertens* 2008;21:1210-15.
25. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: A consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000;36:646-61.
26. Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005;165:1401-9.
27. Taler SJ, Textor SC, Augustine JE. Resistant hypertension: Comparing hemodynamic management to specialist care. *Hypertension* 2002;39:982-8.
28. Agarwal R. Hypertension, hypokalemia, and thiazide-induced diabetes: A 3-way connection. *Hypertension* 2008;52:1012-3.
29. Franse LV, Pahor M, Di Bari M, Somes GW, Cushman WC, Applegate WB. Hypokalemia associated with diuretic use and cardiovascular events in the systolic hypertension in the elderly program. *Hypertension* 2000;35:1025-30.
30. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;372:547-53.
31. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547-59.
32. CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. *JAMA* 2002;287:2542-51.
33. Wiklund I, Halling K, Ryden-Bergsten T, Fletcher A. Does lowering the blood pressure improve the mood? Quality-of-life results from the hypertension optimal treatment (HOT) Study. *Blood Pressure* 1997;6:357-64.
34. Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: A meta-analysis. *Lancet* 2008;371:117-25.
35. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: A systematic review and meta-analysis. *JAMA* 2007;298:2654-64.
36. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: A randomized clinical trial. *Ann Intern Med* 2005;142:233-9.
37. Bolen S, Feldman L, Vassy J, et al. Systematic review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med* 2007;147:386-99.
38. Nathan DM, Cleary PA, Backlund J-YC, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643-53.
39. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.
40. Baigent C, Sudlow C, Collins R, Peto R, Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
41. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: A randomized controlled trial. *JAMA* 2008;300:2134-41.
42. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: Factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;337:a1840. (Abst)
43. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580-91.
44. Bolen SD, Samuels TA, Yeh HC, et al. Failure to intensify antihypertensive treatment by primary care providers: A cohort study in adults with diabetes mellitus and hypertension. *J Gen Intern Med* 2008;23:543-50.
45. Naik AD, Kallen MA, Walder A, Street RL Jr. Improving hypertension control in diabetes mellitus: The effects of collaborative and proactive health communication. *Circulation* 2008;117:1361-8.
46. Grant RW, Cagliero E, Murphy-Sheehy P, Singer DE, Nathan DM, Meigs JB. Comparison of hyperglycemia, hypertension, and hypercholesterolemia management in patients with type 2 diabetes. *Am J Med* 2002;112:603-9.
47. Campbell NR, Brant R, Johansen H, et al. Increases in antihypertensive prescriptions and reductions in cardiovascular events in Canada. *Hypertension* 2009;53:128-34.
48. Bild D, Teutsch SM. The control of hypertension in persons with diabetes: A public health approach. *Public Health Rep* 1987;102:522-9.