Challenges and Scientific Considerations in Hypertension Management Reflected in the Canadian Hypertension Education Program Recommendations for 2012

Sheldon W Tobe, MD,[1]Luc Poirier, M.Sc.,[2]Guy Tremblay, MD,[2] Patrice Lindsay, PhD,[3]Debra Reid, PhD,[4]Norman RC Campbell, MD,[5] Nadia Khan, MD,[6]Robert R Quinn, MD, PhD[5] on behalf of the Canadian Hypertension Education Program.

[1]Sheldon Tobe, Sheldon.tobe@sunnybrook.ca, is Chair of the Canadian Hypertension Education Program, and Associate Professor in the Division of Nephrology, Sunnybrook Health Sciences Centre, University of Toronto;
[2] Luc Poirier, luc.poirier@crchul.ulaval.ca, is Chair of the Recommendations Task Force for CHEP and is a Senior Pharmacist at the Hypertension Unit and Pharmacy Department Centre Hospitalier Universitaire de Québec (CHUL)niversité Laval, Québec, Canada;
[3]Patrice Lindsay, patty.lindsay@me.com , is the Director, Performance and Standards Canadian Stroke Network Adjunct Faculty, University of Toronto Institute of Health Policy, Management and Evaluation Appointed Member, Health Canada
Canadian Task Force on Preventative Health Care Canadian Stroke Network, Toronto,
[4]Debra Reid, debra.reid@phac-aspc.gc.ca , is Senior Policy Analyst/ Analyste principale des politiques
Office of the Assistant Deputy Minister/ Bureau de la Sous-ministre adjointe
Health Promotion and Chronic Disease Prevention Branch/ Direction générale de la promotion de la santé et de la prévention des maladies chroniques Public Health Agency of Canada/ Agence de la santé publique du Canada Department of National Defense, Ottawa,
[5]Norm Campbell, ncampbel@ucalgary.ca, is Professor of Medicine, Community Health Sciences and Physiology and Pharmacology at the University of Calgary and is a member of the Libin Cardiovascular Institute of Alberta. Dr Campbell is the CIHR Canadian Chair in Hypertension Prevention and Control.
[5] Rob Quinn is Adjunct Assistant Professor, Division of Nephrology, University of Calgary.
[6]Nadia Khan, nakhanubc@gmail.com, Centre for Health Evaluation and Outcomes Sciences, Division of General Internal Medicine, University of British Columbia, Vancouver.

Short Title: The 2012 CHEP Scientific Summary

Word Count 1716

Corresponding Author.
Dr SW Tobe, Division of Nephrology,
Faculty of Medicine
Sunnybrook Health Sciences Centre,
University of Toronto
A240, 2075 Bayview Avenue,
Toronto, Ontario M4N 3M5
T 416-480-6901 F 416-480-6940
Sheldon.tobe@sunnybrook.ca (prefer that email address is not used)

Key Words Hypertension, High Blood Pressure, Clinical Practice Guidelines, Knowledge Translation, Cardiovascular disease prevention

Abstract

This article addresses the scientific considerations that are reflected in t**he 2012 Canadian Hypertension Education Program (CHEP) Recommendations for the Management of Hypertension: Blood Pressure Measurement, Diagnosis, Assessment of Risk and Therapy**
This is a summary of the theme, key new recommendations and supporting science of the 2012 Canadian Hypertension Education Program (CHEP).
For 2012 the major change to the CHEP clinical practice recommendations is the change of the blood pressure target for patients with chronic kidney disease without diabetes to < 140/90 mmHg. The blood pressure target for people with diabetes remains < 130/80 mmHg. There is now strengthened evidence for the use of home blood pressure monitoring to diagnose and confirm white coat hypertension. Aldosterone antagonists (mineralocorticoid receptor antagonists) have been added for the treatment of hypertension in the setting of systolic heart failure. The theme for 2012 is the prevention of hypertension.
The full CHEP recommendations are available online at www.hypertension.ca .

Word count 156

Managing Hypertension by the Numbers

Prevalent cases of hypertension are predicted to reach 7,500,000 in 2012/2013: over 1000 people are newly diagnosed with hypertension daily [1]. Prior to the initiation of CHEP in 1999, self-reported "aware but untreated hypertension" was decreasing by 0.6% per annum; with the advent of CHEP, the rate of untreated hypertension decreased by 3.2% annually over the next decade. [2] In 1992, 13% of hypertensive individuals were treated and controlled, vs 66% in recent surveys. [3,2] Associated with better control of blood pressure (BP), mortality rates for stroke, heart failure and heart attack have fallen faster in the past 10 years than in the previous decade [4]. The prevalence of hypertension and cardiovascular disease (CVD) are expected to increase considerably over the next twenty years, along with associated costs [5]. Projections suggest that hypertension in the US will increase by 9.9%, coronary heart disease by 16.6%, heart failure by 25% and stroke by 25%, with hypertension alone responsible for an extra $130.4 billion in health costs in 2030 compared to 2010[5]. This increase is largely related to aging of the baby-boom generation [6] as well as the sedentary lifestyle and unhealthy eating habits (in particular excess sodium) leading to adolescent overweight [7].

The Theme for 2012's Clinical Practice Recommendations is Prevention

Despite the continuous advancement in CVD reduction, CVD remains a major cause of disability and premature death, and contributes substantially to escalating health care costs in Canada [8]. Modifying exposures to behavioral, environmental and societal risk factors can prevent or delay the onset of chronic disease and resulting disabilities, and is a feasible and practical target for change at both clinical and population levels [9]. High BP is the most common and important modifiable risk factor for a range of chronic diseases including coronary heart disease, stroke, congestive heart failure, chronic kidney disease, peripheral arterial disease and dementia[10].

The majority of Canadians will develop hypertension over their lifetime[11]. Therefore, even modest changes in BP have significant potential to reduce the current chronic disease burden. CHEP has a particular role in primary and secondary prevention associated with suboptimal BP control by providing health care providers with guidance on the promotion of adherence to lifestyle and pharmacologic therapy for their patients and clients.

More emphasis on healthy lifestyle and on preventing or delaying chronic diseases will improve the quality of life of Canadians while reducing the impact these conditions have on individuals, families, communities, the health-care system and society. Expanded use of the CHEP recommendations in the prevention and management of other chronic diseases may help Canada become a world leader in chronic disease prevention and management.

The Government of Canada and the Public Health Agency of Canada (PHAC) are playing an important role in the achievement of high levels of BP awareness, treatment, and control in this country[3]. Prevention of hypertension is reflected in nine specific CHEP 2012 recommendations for lifestyle management as well as screening for hypertension. These recommendations are in continuity with the 2011 CHEP theme, a call to action to Canadians to advocate for policies to keep Canadians healthier though improved prevention and control of hypertension [12]. A

challenge for Canadians in 2012 and beyond is engaging all levels of government to work with the food and beverage processing industry to reduce excessive dietary sodium content by establishing sodium targets for foods and monitoring for excessive sodium content in our food supply.

Clinical Vignette

A 65 year old male is seen in your office for hypertension. He has a past medical history of previous MI with known systolic dysfunction, dyslipidemia and stable chronic kidney disease stage 3 (eGFR 50 ml/min) and is a former smoker. There is no history of diabetes. His current medications include an ACE inhibitor and a beta blocker. On examination he is euvolemic, his blood pressure is 142/76 mmHg. His creatinine is stable at 140 umol/L, his potassium is 4.4 mmol/L and the rest of his labs are unremarkable. He asks whether he is on appropriate medications and if his blood pressure is controlled to target according to recent clinical practice recommendations. He enquires whether you support the home measurement of blood pressure.

The 2012 CHEP recommendations.

BP measurement

New information on BP measurement has expanded the role of home BP monitoring to aid the diagnosis of white coat and masked hypertension. The greater number of BP measurements in these automated measures reduces variability and provides more precise and accurate reflections of true BP by removing the white coat effect[13].

Controversy and emerging data for the use of office automated devices like the BpTRU[14] have led to the formation of a blood pressure measurement working group to report in the fall of 2012.

BP target in Chronic Kidney Disease (CKD) without Diabetes is now < 140/90 mmHg

The target BP for CKD without diabetes has been <130/80 mmHg [15-17]. In recent years there has been a retrenchment from this lower target. In 2008, the NICE chronic kidney disease guidelines maintained the target of <130/80 mmHg but only when the urine protein was 1g/day or greater, otherwise targeting < 140/90 mmHg [18]. This recommendation was based on a meta-analysis showing a relative risk of 4.5 for doubling of serum creatinine or end stage renal disease (ESRD) in individuals with $\geq$ 1 g/day proteinuria who achieved a systolic BP of 110-119 vs. 130-139 mmHg [19] and a sub-analysis of the Modification of Diet in Renal Disease (MDRD) study showing a greater decline in GFR in patients with over 3g/day of proteinuria [20]. It was on the strength of the MDRD study that BP targets for non-diabetic chronic kidney disease with proteinuria were set at < 120/75 mmHg in 1999 [18;21]. In 2006 however, the African American Study of Kidney Disease (AASK) and the Blood Pressure Control for Renoprotection in Patients with Chronic Renal Disease (REIN-2) studies [22] showed no renal benefit for the lower BP target of < 120/75 mmHg. Blood pressure targets for all patients with chronic kidney disease were kept at < 130/80 mmHg, largely on the strength of the MDRD[23].
A new AASK trial analysis including an additional cohort phase, found that patients with proteinuria (but not those without) benefited from the lower targeted BP, supporting the NICE guidelines approach of a differential blood pressure target of < 130/80 mmHg for proteinuria (> 1 gm/day) and < 140/90 mmHg for those with less proteinuria [24]. The AASK trial included 1094 African American individuals with hypertensive CKD and assessed the effect on GFR of

reducing BP to a usual BP goal (achieved BP 141/85 mmHg) or a low BP goal (achieved BP 128/78mmHg). In the cohort phase, the blood pressure target was < 130/80 mmHg and follow-up ranged from 8.8 to 12.2 years. On critical appraisal of this study it was noted that a secondary outcome from the original study was used as the primary outcome (change in creatinine) and no benefit was found for the primary outcome of the original study, the change of GFR over time, even in participants with proteinuria [25]. This post-hoc subgroup analysis of a secondary endpoint would therefore be considered only as hypothesis generating. A critical appraisal of the MDRD study for patients with proteinuria, noted that the finding of slower loss of GFR in patients with proteinuria ≥3 grams/day was a post-hoc subgroup analysis in only 32 patients[20]. The lack of strong evidence for a benefit of more intensive blood pressure lowering for patients with non-diabetic chronic kidney disease with or without proteinuria, led to the change of blood pressure target to < 140/90 mmHg. An intensive review of the blood pressure target in patients with hypertension and diabetes including those with chronic kidney disease confirmed the blood pressure target of < 130/80 mmHg (see Rabi D, CMAJ in Press).

Another AASK sub-study shed interesting light on the impact of adherence to recommended therapy. While no differences were found in GFR outcomes between randomly assigned BP goals, there was a substantial slowing of loss of GFR for patients observed to achieve lower BPs within each group [26]. Further, patients in the low BP group who failed to achieve target-BP had significantly worse outcomes than those in the usual-BP group with the same blood pressure, suggesting that a confounding of comorbidities may have been involved[26].

In summary, randomized controlled trials do not provide sufficient evidence to recommend a lower BP target in individuals with non-diabetic chronic kidney disease, even with proteinuria.

Mineralocorticoid Receptor Antagonists, Heart Failure and Hypertension

Until now, there has not been sufficient evidence to recommend the aldosterone antagonists in the Canadian hypertension recommendations. The RALES [27], EPHESUS [28] and EMPHASIS-HF [29] studies all demonstrated reductions of death and heart failure hospitalizations in patients with systolic dysfunction receiving mineralocorticoid inhibitors. Over 60% of these study patients had a diagnosis of hypertension and blood pressure was controlled in most patients at study entry. Based on the results of these studies an aldosterone antagonist is recommended for patients with hypertension and recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro B-type natriuretic peptide levels, or NYHA class II to IV symptoms. Because of the risk of hyperkalemia, after starting this therapy appropriate monitoring for hyperkalemia is recommended.

Resolution of clinical vignette. The blood pressure target for this patient with non-diabetic chronic kidney disease is < 140/90 mmHg and given his history of systolic heart failure, an aldosterone antagonist should be considered. He is started on spironolactone , electrolyte testing for potassium is arranged for the following week and he is counseled about the potential for gynaecomastia. Support is given for home blood pressure monitoring and the Measure BP at Home information sheet is given to the patient (see www.hypertension.ca for this patient tool).

Conclusions

For 2012 the major change to the CHEP clinical practice recommendations is the change of the BP target for patients with chronic kidney disease without diabetes to < 140/90 mmHg. There is now strengthened evidence for the use of home BP monitoring to diagnose and confirm white coat hypertension. Aldosterone antagonists (mineralocorticoid receptor antagonists) have been added for the treatment of hypertension in the setting of systolic heart failure. The goal of CHEP is greater awareness, treatment and control of hypertension and the theme for 2012 is the prevention of hypertension.

Acknowledgements

This is an invited clinical practice review based on the Canadian Hypertension Education Program annual clinical practice recommendations consensus conference at the Annual Congress Hypertension Canada October 2, 2011.

Competing Interests:
Sheldon Tobe has received unrestricted grant support from Servier, participated in contract research and with Abbott, AMGEN, AstraZeneca, Boehringer-Ingelheim, , Bristol Myers Squibb, Janssen, Merck, Novartis, Pfizer, Sanofi-Aventis and Takeda
Luc Poirier - Advisory Board : Novartis Canada, Janssen Canada, Participation in research protocols: Takeda, Novartis, Merck
Guy Tremblay – no disclosures to declare
Patrice Lindsay - no disclosures to declare
Norman RC Campbell - Travel support in 2010 from Boehringer-Ingelheim to hypertension meetings
Debra Reid – no disclosures to declare
Nadia Khan – no disclosures to declare
Robert R Quinn – no disclosures to declare

No specific funds were obtained for this review. Funding for the CHEP consensus conference and guidelines comes from Hypertension Canada which receives funds from multiple industry sources as well as the Public Health Agency of Canada.

Contributor Statement

All of the authors listed have contributed substantially to the conception, and design of this article and have helped to revise it and contributed important intellectual content. All of the authors have approved the final version of the manuscript. The first draft of this manuscript was written by Sheldon Tobe who is acting as guarantor and is responsible for the integrity of the work as a whole from inception through to publication. .

Reference List

(1) Robitaille C, Dai S, Waters C, Loukine L, Bancej C, Quach S et al. Diagnosed hypertension in Canada: incidence, prevalence and associated mortality. *CMAJ* 2011.

(2) McAlister FA, Feldman RD, Wyard K, Brant R, Campbell NR. The impact of the Canadian Hypertension Education Programme in its first decade. *Eur Heart J* 2009; 30(12):1434-1439.

(3) Wilkins K, Campbell NR, Joffres MR, McAlister FA, Nichol M, Quach S et al. Blood pressure in Canadian adults. *Health Rep* 2010; 21(1):37-46.

(4) Campbell NR, Brant R, Johansen H, Walker RL, Wielgosz A, Onysko J et al. Increases in antihypertensive prescriptions and reductions in cardiovascular events in Canada. *Hypertension* 2009; 53(2):128-134.

(5) Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD et al. Forecasting the Future of Cardiovascular Disease in the United States: A Policy Statement From the American Heart Association. *Circulation* 2011; 123(8):933-944.

(6) Odden MC, Coxson PG, Moran A, Lightwood JM, Goldman L, Bibbins-Domingo K. The impact of the aging population on coronary heart disease in the United States. *Am J Med* 2011; 124(9):827-833.

(7) Bibbins-Domingo K, Coxson P, Pletcher MJ, Lightwood J, Goldman L. Adolescent overweight and future adult coronary heart disease. *N Engl J Med* 2007; 357(23):2371-2379.

(8) Arthur HM, Suskin N, Bayley M, Fortin M, Howlett J, Heckman G et al. The Canadian Heart Health Strategy and Action Plan: Cardiac rehabilitation as an exemplar of chronic disease management. *Can J Cardiol* 2010; 26(1):37-41.

(9) Capewell S, Lloyd-Jones DM. Optimal cardiovascular prevention strategies for the 21st century. *JAMA* 2010; 304(18):2057-2058.

(10) Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; 365(9455):217-223.

(11) Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. *JAMA* 2002; 287(8):1003-1010.

(12) Campbell NR, Poirier L, Tremblay G, Lindsay P, Reid D, Tobe SW. Canadian Hypertension Education Program: The Science Supporting New 2011 CHEP Recommendations With an Emphasis on Health Advocacy and Knowledge Translation. *Can J Cardiol* 2011; 27(4):407-414.

(13) Warren RE, Marshall T, Padfield PL, Chrubasik S. Variability of office, 24-hour ambulatory, and self-monitored blood pressure measurements. *Br J Gen Pract* 2010; 60(578):675-680.

(14) Leenen FH, Schiffrin EL. Control rates of hypertension in North America. *Hypertension* 2010; 56(4):571-572.

(15) Rabi DM, Daskalopoulou SS, Padwal RS, Khan NA, Grover SA, Hackam DG et al. The 2011 canadian hypertension education program recommendations for the management of hypertension: blood pressure measurement, diagnosis, assessment of risk, and therapy. *Can J Cardiol* 2011; 27(4):415-433.

(16) Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25(6):1105-1187.

(17) NKF-K/DOQI Clinical Practice Guidelines; Chronic Kidney Disease. *American Journal of Kidney Diseases* 2002; 39(2 Suppl 1):S170-S212.

(18) National Collaborating Centre for Chronic Conditions. *Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care*. Royal College of Physicians, editor. 2011. London, Royal College of Physicians. NICE clinical practice guidelines.
Ref Type: Online Source

(19) Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, De Jong PE et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003; 139(4):244-252.

(20) Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group [see comments]. *New England Journal of Medicine* 1994; 330(13):877-884.

(21) Klahr S. Primary and secondary results of the modification of diet in renal disease study. *Mineral & Electrolyte Metabolism* 1996; 22(1-3):138-142.

(22) Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005; 365(9463):939-946.

(23) Khan NA, McAlister FA, Rabkin SW, Padwal R, Feldman RD, Campbell NR et al. The 2006 Canadian Hypertension Education Program recommendations for the management of hypertension: Part II - Therapy. *Can J Cardiol* 2006; 22(7):583-593.

(24) Appel LJ, Wright JT, Jr., Greene T, Agodoa LY, Astor BC, Bakris GL et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010; 363(10):918-929.

(25) Wright JT, Jr., Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial.[comment]. *JAMA* 2002; 288(19):2421-2431.

(26) Davis EM, Appel LJ, Wang X, Greene T, Astor BC, Rahman M et al. Limitations of analyses based on achieved blood pressure: lessons from the African American study of kidney disease and hypertension trial. *Hypertension* 2011; 57(6):1061-1068.

(27) Pitt B. Effect of aldosterone blockade in patients with systolic left ventricular dysfunction: implications of the RALES and EPHESUS studies. *Mol Cell Endocrinol* 2004; 217(1-2):53-58.

(28) Pitt B, Bakris G, Ruilope LM, DiCarlo L, Mukherjee R. Serum potassium and clinical outcomes in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). *Circulation* 2008; 118(16):1643-1650.

(29) Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364(1):11-21.