

HYPERTENSION

Canada



Published by the
Canadian
Hypertension
Society

June 2007
Bulletin No. 91

Out-of-office Blood-pressure Measurement in Pregnancy

By Glenna Ramsay, Peter von Dadelszen and Laura Magee

Hypertensive disorders of pregnancy (HDP) are a leading cause of maternal and perinatal mortality and morbidity. The burden of complications associated with the HDP occurs in women with pre-eclampsia. The definition of hypertension in pregnancy is office diastolic blood pressure (dBp) ≥ 90 mmHg according to the same measurement techniques used outside pregnancy. A dBp of 90 mmHg identifies a level above which perinatal morbidity is increased in non-proteinuric hypertension.

Classification of the Hypertensive Disorders of Pregnancy

Hypertension is classified as pre-existing or gestational. Pre-existing hypertension pre-dates pregnancy or appears before 20 weeks' gestation, and gestational hypertension appears at or after 20 weeks. Women with pre-existing or gestational hypertension may develop pre-eclampsia.

Women with pre-existing hypertension have a 10% to 20% risk of developing pre-eclampsia, defined by resistant hypertension, new/worsening proteinuria, or one or more end-organ complications of pre-eclampsia (such as eclampsia or elevated liver enzymes). Women with certain co-morbidities (*e.g.*, renal disease or pre-gestational diabetes mellitus) are also at increased risk. Women with gestational hypertension with onset before 34 weeks (as opposed to after 34 weeks) are more likely to evolve into a pre-eclampsia picture, with rates of about 35%.

Pre-eclampsia is a hypertensive disorder most commonly defined by new-onset proteinuria and, potentially, other end-organ dysfunction. A "restrictive" definition often used by the research community defines it as gestational hypertension with proteinuria. An "inclusive" definition defines pre-eclampsia as gestational hypertension with proteinuria or typical end-organ dysfunction. Both the Canadian and Australasian guidelines use this "inclusive" definition.

Using population-based data, approximately 1% of pregnancies are complicated by pre-existing hypertension, 5% to 6% by gestational hypertension without proteinuria, and between 1% and 2% by pre-eclampsia. It can be expected that these numbers will increase given the trend towards an older and more obese obstetric population.

continued on page 2

Table of contents

- | | |
|---|--|
| 5 | Unmasking "Masked Hypertension" |
| 7 | Implications From Results of the DREAM Study |



Canadian Hypertension Society

Executive

Venkat Gopalakrishnan
president

Marcel Lebel
past president

Rhian Touyz
president-elect

James van Huysse
secretary treasurer

Past Presidents

George Fodor
Jacques de Champlain

Otto Kuchel
John K. McKenzie

Frans H.H. Leenen
Pavel Hamet

Martin Myers
R. Brian Haynes
Alexander Logan
S. George Carruthers

Ernesto L. Schiffrin
Richard Ogilvie

Simon W. Rabkin

Pierre Larochelle

Robert Lee

Ellen Burgess

Ross Feldman

Michel Bouvier

Norm Campbell

Donald D. Smyth

John Floras

Johanne Tremblay

Tim Reudelhuber

Richard Lewanczuk

Published by the

Canadian
Hypertension
Society



Editorial Board

Luc Poirier, *Quebec City,*
Chairman

Carl Abbott, *Halifax*

Luc Lanthier, *Sherbrooke*

Venkat Gopalakrishnan, *Saskatoon*
(ex-officio)

Richard Ogilvie, *Toronto (ex-officio)*

Alain Vanasse, *Sherbrooke*

Sudesh Vasdev, *St. John's*

Albert Yeung, *Edmonton*

Editorial Office

Richard Ogilvie,
editor

John Floras

Paula Harvey

Alexander Logan

BP Measurement in Pregnancy

Continued from page 1

Out-of-office BP Monitoring in Pregnancy

Out-of-office BP measurement in pregnancy refers to serial measurements either by 24-hour ambulatory BP monitoring (ABPM), in an obstetrical day unit, or by home BP monitoring.

In this article, we will focus on the use of out-of-office BP measurement for prognosis (*i.e.*, prediction of adverse maternal and perinatal outcomes) among women with office hypertension. There is, however, other literature examining the ability of 24-hour ABPM to predict pre-eclampsia among women at increased risk (*e.g.*, previous pre-eclampsia), particularly as part of multivariable models with other clinical and laboratory risk markers.

Accuracy of ABPM Devices in Pregnancy

Automated BP measurement devices will eliminate observer error. These devices work by use of either an auscultatory device or an oscillometer that detects arterial oscillations. Devices that detect oscillations depend on a number of factors, all of which are affected by normal pregnancy and further affected by pre-eclampsia: arterial compliance, systemic vascular resistance, and intravascular volume. Also, the edema of pre-eclampsia can dampen the transmission of pressure waves to the cuff, thereby leading to an underestimate of the true BP. It follows, therefore, that automated BP devices may not be accurate in pregnancy and/or pre-eclampsia. This has been true of the OMRON HEM 705 CP, Welch Allyn "Vital Signs," and Spacelabs 90207 (British Hypertension Society [BHS] grade C/C, AAMI pass) devices, all of which were found to be acceptable for use in pregnancy but not in women with pre-eclampsia, according to standardized criteria. Automated devices may underestimate BP in pre-eclampsia by an average of 5 mmHg systolic and diastolic, but



there is wide variation between patients. To date, two oscillometric devices have received acceptable grading for BP measurement in pre-eclampsia: Microlife 3BTO-A (BHS grade A for sBP and grade B for dBP) and the OMRON MIT (BHS grade B for sBP and grade A for dBP; now withdrawn from the market).

Prevalence of Isolated Office Hypertension

Based on various cut-offs, approximately 30% of women will have isolated office hypertension by 24-hour ABPM, but the prevalence has been up to 70% among hypertensive women, particularly near term and followed in an obstetrical day unit or by home BP assessment.

Validation of Out-of-office BP Measurements in Pregnancy

What constitutes an elevated out-of-office BP measurement should be based on a level that is associated with an excess of adverse outcomes. All relevant studies have used the Spacelabs 90207, which is acceptable for use in pregnancy but not in pre-eclampsia.

24-hour ABPM

Twenty-four-hour ABPM has limited availability. In Canada, patients are generally charged between \$50 and \$75 per study, and are not normally reimbursed by insurance providers. Although 24-hour ABPM is well-tolerated with few complications, 49% of pregnant women have reported some interference with normal activity and 76% have reported some disruption of sleep.

One prospective study has followed women with early-pregnancy isolated office hypertension by serial 24-hour ABPM, and reported on evolution into persistent hypertension. Among 78 such women, 40% developed gestational hypertension (without proteinuria), and 8% developed pre-eclampsia.

Prospective observational studies have enrolled women with gestational or pre-existing hypertension, and examined the

relationship between 24-hour ABPM and adverse pregnancy outcomes. Compared to standard office BP measurement, 24-hour ABPM is better at identifying hypertensive pregnant women at increased risk of adverse pregnancy outcomes such as severe hypertension, preterm delivery, Caesarean section, small for gestational infants, and admission to a neonatal intensive care unit. The BP cut-offs used in

to 140 mmHg by 24-hour ABPM or 140 mmHg in the obstetrical day unit.

Therefore, based on NPV, 24-hour ABPM may be somewhat useful for prediction of adverse outcomes, using the most common criterion of average daytime dBP cut-off of 85 mmHg.

Twenty-four-hour ABPM has the ability to detect women with masked hypertension in pregnancy. The prevalence was

Using population-based data, approximately 1% of pregnancies are complicated by pre-existing hypertension, 5% to 6% by gestational hypertension without proteinuria, and between 1% and 2% by pre-eclampsia. It can be expected that these numbers will increase given the trend towards an older and more obese obstetric population.

these prospective observational studies have varied: average 24-hour ambulatory BP of > 135/85 mmHg; average daytime ambulatory BP of > 130/85 mmHg; one or more of either average 24-hour BP of > 125/74 mmHg, average daytime BP of > 128/78 mmHg, or average nighttime BP of > 121/70 mmHg; or 48-hour ambulatory BP “excess” above a gestational-age-specified reference limit. (Two other prospective studies have found significant inverse relationships between 24-hour ambulatory (but not clinic) BP measurements, and both higher 24-hour proteinuria levels in pre-eclampsia and lower birthweight.)

Using reported sensitivities and specificities, and the prevalence of the outcomes among hypertensive pregnant women, the positive and negative predictive values (PPV and NPV) for dBP (≥ 85 mmHg for 24-hour ABPM or ≥ 90 mmHg in the obstetrical day unit) are as follows: for severe hypertension (prevalence 33%; PPV 50%, NPV 80%), preterm delivery (prevalence 20%; PPV 30%, NPV 85-95%), and admission to the neonatal intensive care unit (prevalence 10%; PPV 10% to 15%, NPV 91% to 97%). The predictive value of sBP was similar, using cut-offs of 130 mmHg

15%, similar to that outside of pregnancy, among primiparous women in one prospective study. Of interest was the fact that the frequency of adverse pregnancy outcomes was similar to that in women with persistent gestational hypertension. The role of ABPM in detecting masked hypertension in pregnancy is uncertain.

Serial BP Measurement in Obstetrical Day Units

Many obstetric units now have a “day unit,” where women can be followed serially over daytime working hours by an experienced obstetric nurse. These units allow for serial BP measurement, fetal monitoring, and laboratory investigations.

Three of the prospective cohort studies that examined the predictive value of 24-hour ABPM also performed serial BP assessment in an obstetrical day unit. ABPM was more predictive than were the BP measurements in the obstetrical day unit, using a dBP cut-off of 90 mmHg.

Home (Self) BP Monitoring

Home BP monitoring is widely available, economical, comfortable, and easy to repeat when disease evolution is sus-



pected. Home BP monitoring has become part of antepartum home-care programmes, run from a number of tertiary perinatal units in Canada.

Pregnant women prefer home BP monitoring to 24-hour ABPM. In a prospective study that included healthy pregnant women and those with pre-eclampsia, only 28% of women rated the 24-hour device as very good, compared with 64% who rated the home BP monitor as very good. Home BP values have not been validated against adverse pregnancy outcomes in hypertensive pregnancy.

In summary, 24-hour ABPM is the out-of-office BP measurement technique that best identifies hypertensive pregnant women at increased risk of adverse pregnancy outcomes. However, the negative predictive values for those outcomes are not sufficiently high that women with office hypertension can be followed substantially differently from those with elevated 24-hour ABPM. There is insufficient information to define the role of home BP monitoring in hypertensive pregnancy. To date, no RCT has been performed to assess the impact of any out-of-office BP measurement technique (vs. conventional office values) on maternal or perinatal outcomes.

Antihypertensive Therapy

Unlike the situation outside pregnancy, identifying subjects with persistent (“true”) hypertension will not necessarily identify those who would most likely benefit from antihypertensive therapy, or more intensive antihypertensive therapy.

It is unclear how best to manage non-severe hypertension in pregnancy, in order to do more good than harm. Theoretical concern about harm is based on the fact that the placenta does not autoregulate blood flow. Therefore, lowering BP may decrease placental perfusion, and because of poorer fetal growth, babies may do more poorly.

The relative benefits and risks of antihypertensive therapy in pregnancy have not been established, based on the re-

sults of systematic reviews of randomized controlled trials (46 trials involving 4,282 women). Allowing BP to be somewhat elevated (to non-severe levels below 160/110 mmHg) may decrease the risk of SGA infants, but may also increase the risk of severe maternal hypertension. The reviews do not provide sufficient evidence on which to base clinical decisions because of reporting bias and between-trial heterogeneity in outcome. Canadian obstetricians are divided on this issue.

Recommendations About Out-of-office BP Measurement in Existing Guidelines

The relevant national and international guidelines are at least five years old. The Australasian pregnancy-specific guidelines (2000) recommend that automated devices and ABPM should not yet be used in routine clinical practice until more detailed information becomes available about their accuracy and effectiveness. The American guidelines (2000) do not make recommendations about ambulatory monitoring.

The Canadian pregnancy-specific hypertension guidelines (1997) do not make specific recommendations about the use of ambulatory or home BP monitoring, although they acknowledge that home BP measurement is practiced in some Canadian centres. Revisions to these guidelines (underway) continue to define hypertension according to office BP measurement. The option to use ABPM to detect isolated office hypertension is given, with a few provisos.

The first is that normal home BP be < 135/85 mmHg based on normal mean awake 24-hour ambulatory BP measurements outside pregnancy. This threshold may be too high, but revision awaits future data. Second, an ABPM device used in pregnancy should have been validated for use in pre-eclampsia. Third, if home BP monitoring is used, then women must be instructed about technique, and calibration should be

performed for each device. Finally, isolated office hypertension does not rule out subsequent development of persistent (gestational) hypertension, or subsequent pregnancy complications. However, confirmation that the office hypertension is isolated may minimize use of antihypertensive medication in pregnancy. Not only may this be of benefit to the fetus, but most women would prefer to avoid drug therapy in pregnancy, if possible.

Conclusions

If out-of-office BP monitoring is used, a pragmatic approach may be to ensure accuracy of a given device for BP measurement in a given woman, according to established criteria. When out-of-office dBp is < 85 mmHg, women are less likely to be at risk for pregnancy complications than are persistently hypertensive pregnant women, but the degree of clinical overlap mandates that all such women be followed closely.

Additional Reading:

1. Helewa ME, Burrows RF, Smith J, et al. Report of the Canadian Hypertension Society Consensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. *CMAJ* 1997; 157:715-25.
2. Brown MA, Hague WM, Higgins J, et al. The detection, investigation and management of hypertension in pregnancy: executive summary. *Aust N Z J Obstet Gynaecol* 2000; 40:133-8.
3. Hermida RC, Ayala DE. Prognostic value of office and ambulatory blood pressure measurements in pregnancy. *Hypertension* 2002; 40:298-303.
4. Villar J, Say L, Shennan A, et al. Methodological and technical issues related to the diagnosis, screening, prevention, and treatment of pre-eclampsia and eclampsia. *Int J Gynaecol Obstet* 2004; 85(Suppl 1):S28-S41.
5. Gupta M, Shennan AH, Halligan A, et al. Accuracy of oscillometric blood pressure monitoring in pregnancy and pre-eclampsia. *Br J Obstet Gynaecol* 1997; 104:350-5.
6. Caetano M, Ornstein M, von Dadelszen P, et al. A survey of Canadian practitioners regarding the management of the hypertensive disorders of pregnancy. *Hypertens Preg* 2003; 23:61-74.

Glenna Ramsay, Medicine, University of Alberta; Peter von Dadelszen, Department of Medicine, University of British Columbia; and Laura Magee, Child and Family Research Institute, University of British Columbia.



Unmasking “Masked Hypertension”

By Donald W. McKay

Technological innovation in blood pressure (BP) measurement enables patients to measure their BP at home or, with the help of ambulatory devices, measure it wherever they roam. Use of these technologies inevitably led people to compare BP readings taken in a non-clinical setting with those observed in the clinic. “White coat” and “masked hypertension” (MH) were derived from these comparisons.

The oft-mentioned “white coat” effect is found when out-of-office BP measurements show values lower than a clinic BP measurement. “Masked hypertension,” in contrast, is defined by a normal clinic BP in the face of either home or ambulatory monitoring showing values in the hypertensive range.

MH derives its name from the notion that the true hypertension of the patient is “masked” or hidden from the physician by the normal office BP readings. This is significant, as a number of recent prognostic studies have shown that the risk for these patients aligns with the elevated out-of-office reading and not with the normotensive clinic reading. These findings are consistent with the results of many studies that show better prediction of mortality and morbidity by ambulatory or home BP monitoring (HBPM) than casual office BP measurements. Not surprisingly, MH is associated with target organ damage, including left ventricular hypertrophy and microalbuminuria.

Many studies suggest that prevalence of MH exceeds 8% in a general population and is greater among hypertensive patients. The prevalence figures vary widely from study to study and likely depend on factors such as the age and sex of the people studied, the diag-

nostic thresholds used, and the methodology and care taken in measuring BP both in and out of the office. MH has been identified in young and elderly subjects.

Why an out-of-office BP measure should be greater than an office BP reading is a matter for some conjecture. In treated hypertensive patients, an elevated morning reading could be due to

insufficient duration of action of the antihypertensive medication. A morning surge of BP or even random BP fluctuations are other possible explanations for elevated out-of-office readings. Reasons for a lower clinic reading may include the reduced likelihood of engaging in activities or behaviours while in the office that are known to elevate BP (e.g., physical activity, drinking coffee, smoking).

Many people are unfamiliar with the term “masked hypertension,” and this is understandable. Although the observation of elevated out-of-office readings compared to office readings was discussed in one of the earliest reports on ambulatory BP monitoring (ABPM), the phenomenon went unnamed for many years. Various groups observed it and devised names to describe what they thought they were seeing. As a result, names as diverse as “white coat normotension,” “reverse white coat,” “inverse white

coat,” “home hypertension,” “isolated home hypertension,” “isolated ambulatory hypertension,” “isolated uncontrolled hypertension at home,” “occult office hypertension” and recently, “masked lack of per-treatment BP control” all describe a situation where office BP values are in the normal range, but out-of-office readings fall in the hypertensive range. “Masked hyper-

The oft-mentioned “white coat” effect is found when out-of-office BP measurements show values lower than a clinic BP measurement. “Masked hypertension,” in contrast, is defined by a normal clinic BP in the face of either home or ambulatory monitoring showing values in the hypertensive range.

tension” was offered a few years ago as a unifying term that describes the situation from the viewpoint of the physician, yet avoids naming it after a mechanistic theory that may or may not be true.

MH is found by comparing a series of high-quality readings in the office with a series of high-quality readings at home or with ABPM. Simply knowing how to determine MH is one issue, but knowing who should be tested is a matter of considerable current research and philosophical debate.

Who to Test for Masked Hypertension

Testing for MH at first seems paradoxical: special BP monitoring has to be ordered for people who present to the clinic with BP in the normal range. Given that HBPM or ABPM may be appropriate for many patients who present with elevated BP, one might start to think that some form of out-of-



office monitoring is required for everybody. Indeed, the “if it were a perfect world” argument has been invoked by more than one expert in the field of MH. In their notion of a “perfect world,” everybody would have their BP measured by HBPM or ABPM. That view, however, is not shared by everyone. Pragmatists have searched for key indicators to help physicians identify those patients who should be targeted for out-of-office BP monitoring.

Although there is not complete agreement as to who should be suspected and tested, a “picture” is emerging from the results of several studies conducted so far. Fundamen-

of two different days and comparing the average with the average of triplicate morning and evening readings on each of two different days. Thus, minimally six office readings are compared with 12 home readings. Using fewer readings markedly decreases the sensitivity. More readings can be used in the comparison without much improvement after 15 home readings. Readings taken on the first day of home measurement are not considered in the calculation. If ABPM is available, clinic readings can be compared with either 24-hour or daytime ABPM results.

Although risk associated with BP is graded such that higher values are asso-

Both HBPM and daytime ABPM appear to identify MH in the same people, but only outside of what has been called a “diagnostic grey zone” of 5 mmHg. In other words, in the absence of target organ damage or diabetes, within the band of 135 mmHg to 140 mmHg systolic and 85 mmHg to 90 mmHg diastolic, the two methods often identify different individuals.

Although prognostic studies have shown the power of HBPM and ABPM with respect to identifying risk, therapeutic trials based on these technologies are limited. Until such time as results become available from appropriate therapeutic trials, physicians will have to use careful and sound clinical judgement when making therapeutic decisions in their patients with MH.

In the absence of clinical trial results, many clinicians already initiate non-pharmacologic and pharmacologic treatment or modify current drug treatment for individuals with MH and HBPM or ABPM values above the target of daytime $\geq 135/85$ mmHg. Most pay extra attention to individuals with diabetes, coronary disease, stroke, TIA or renal impairment with daytime HBPM or ABPM readings of $\geq 130/80$ mmHg and a higher risk for adverse outcomes.

Although there is not complete agreement as to who should be suspected and tested, a “picture” is emerging from the results of several studies conducted so far. Fundamentally, a person who appears to be at high cardiovascular risk but presents with clinic systolic readings between 130 mmHg and 140 mmHg is a good candidate for MH screening. This priority list for out-of-office testing includes, but is not limited to, overweight patients and those with kidney disease, diabetes mellitus, target organ damage or a strong family history of hypertension.

tally, a person who appears to be at high cardiovascular risk but presents with clinic systolic readings between 130 mmHg and 140 mmHg is a good candidate for MH screening. This priority list for out-of-office testing includes, but is not limited to, overweight patients and those with kidney disease, diabetes mellitus, target organ damage or a strong family history of hypertension.

How to Test for Masked Hypertension

High specificity and sensitivity in finding MH can be achieved by taking a series of three office BP readings on each

ciated with higher risk, specific cut-off values are used to help understand and manage increased risk. The risk associated with HBPM or daytime ABPM readings of $\geq 135/85$ mmHg or 24-hour ABPM of $\geq 130/80$ mmHg is approximately the same as the risk associated with standardized office measurements of $\geq 140/90$ mmHg. Thus, HBPM results of 138/88 mmHg are in the hypertensive range, but the same BP values obtained by standardized technique in the office are not. Lower cut-off values are used for individuals with diabetes, coronary disease, stroke, TIA or renal impairment at daytime HBPM or ABPM readings of $\geq 130/80$ mmHg.

Suggested Reading:

1. Maillon J-M, Clerson P, Bobrie G, et al. Predictive factors for masked hypertension with a population of controlled hypertensives. *J Hypertens* 2006; 24: 2365-70.
2. Stergiou GS, Yiannes NJ, Rarra VC, et al. White-coat hypertension and masked hypertension in children. *Blood Press Monit* 2005; 10: 297-300.
3. McKay DW, Myers MG, Bolli P, et al. Masked hypertension: A common but insidious presentation of hypertension. *Can J Cardiol* 2006; 22: 617-20.
4. Tomiyama M, Horio T, Kamide K, et al. Reverse white-coat effect as an independent risk for left ventricular concentric hypertrophy in patients with treated essential hypertension. *J Hum Hypertens* 2007; 21: 212-19.

Donald W. McKay, Ph.D., Faculty of Medicine, Memorial University of Newfoundland.



Implications From Results of the DREAM Study

By Carl Abbott

Diabetes mellitus (DM) is a major CV risk factor and most DM patients die from coronary artery disease. It is also the leading cause of chronic renal failure and new-onset blindness. The prevalence of type 2 DM has reached epidemic proportions in many areas of the world. In some Middle Eastern countries (such as Saudi Arabia) the prevalence exceeds 20%. In 2007, the number of people worldwide with DM is estimated at 246 million. In 2025, the projected estimate is 380 million.¹ About ninety percent will have type 2 DM. In Canada, the true frequency is unknown but estimates in a 1999 publication² suggested 3.2% in white people and 3.8% in blacks. In Aboriginal people off reserves, the estimate was 5.4% and in those on reserves, 8.5%. A recent study of the incidence and prevalence of DM in Ontario³ between 1995 and 2005 suggests a higher rate (by 69%) of new-onset DM than expected or predicted. Important demographic trends in Canada are increasing the prevalence of DM: an aging population, increasing prevalence of obesity, low levels of physical activity and increasing immigration from high-risk populations.

An intermediate state of hyperglycemia (also known as prediabetes) exists when fasting glucose is higher than normal (*i.e.*, 6.1 - 6.9) but does not meet the fasting criterion for DM (*i.e.*, 7.0 or greater) and where impaired oral glucose tolerance (IGT) is present. Many with impaired fasting glucose (IFG) will also have IGT but do not meet the criteria for DM. An estimated 8% of adults worldwide have IFG and IGT. Such individuals, who may seem healthy, are at higher CV risk and are at risk of progressing to

DM (at a rate of 5% to 10% per year). The risk of new DM in patients with hypertension is more than two-fold, but management with an ACE inhibitor, ARB or CCB in clinical trials has been shown to reduce the incidence. Diuretic use alone increases the incidence. Prevention of new-onset DM has important public health and economic implications and has led to several studies directed at

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study was designed in part because of the results of the Heart Outcomes Prevention Evaluation (HOPE) and Troglitazone In the Prevention of Diabetes (TRIPOD) studies.^{7,8} Post-hoc analysis of the HOPE study results had shown that, in a population of high-CV-risk patients, the ad-

Diabetes mellitus (DM) is a major CV risk factor and most DM patients die from coronary artery disease. It is also the leading cause of chronic renal failure and new-onset blindness. The prevalence of type 2 DM has reached epidemic proportions in many areas of the world.

Important demographic trends in Canada are increasing the prevalence of DM: an aging population, increasing prevalence of obesity, low levels of physical activity and increasing immigration from high-risk populations.

prevention with lifestyle change and medications. Several examples will be cited below.

In the Diabetes Prevention Program (DPP) study,⁴ intensive lifestyle change (exercise and diet) reduced new DM by 58% in those with IGT compared to 31% in those using metformin 850 mg bid. The Finnish Diabetes Prevention Study (DPS)⁵ with 522 subjects having IGT reported lifestyle modification (modest weight loss, exercise and balanced diet) reduced new DM by 58% after three years. In the STOP-NIDDM Trial,⁶ people with IGT used acarbose 300 mg/day vs. placebo, with new DM seen in 32.8% of those taking acarbose and 41.8% of those taking placebo.

dition of ramipril, to an already complex drug regimen reduced the development of new DM by 34% compared to placebo. In the TRIPOD study, 235 Hispanic women with previous gestational DM were randomized to troglitazone 400 mg/day vs. placebo for several years (prior to withdrawal of the active drug from the market). DM developed in 5.4% receiving active drug and 12.3% receiving placebo.

For the DREAM study, 24,592 healthy subjects at high risk of DM, aged ≥ 30 years, were screened with oral GTT tests in 21 countries. Of 5,269 eligible and randomized candidates, 14% had IFG (≥ 6.1 but < 7.0), 57.5% had IGT and 28.5% had both. Candidates were



Implications of the DREAM Results

Continued from page 7

randomized to either rosiglitazone (up to 8 mg/day) vs. placebo or were given ramipril (up to 15 mg/day) vs. placebo. Treated hypertension was present in about 44% and mean BP was 136/83 mmHg. Details of original and subsequent IGT criteria and results of the DREAM study have been published.^{9,10} In brief, rosiglitazone reduced new DM in this high-DM-risk group by 11.6%, rosiglitazone-placebo by 26%, ramipril by 18.1% and ramipril-placebo by 19.5%. Although ramipril did not significantly reduce new DM or death, it did increase regression to normoglycemia as glucose levels two hours after OGTT were significantly lower at the end than with placebo, thus potentially reducing CV risk. There were the usual adverse effects requiring withdrawal of both study drugs: almost 10% developed a cough with ramipril. Heart failure (0.5%) and weight gain (3%) occurred with rosiglitazone. Significant BP reduction occurred with both but as expected ramipril was better: systolic/diastolic reductions of 8.2/4.3 mmHg from original BP, compared to reductions of 5.4/3.0 mmHg with placebo.

Screening for diabetes remains an essential strategy in medical practice but it is suggested about 50% have yet to be identified by this means. There is a large group of individuals who are at high risk for developing DM and who should be targeted for prevention (see Table 1).

The DREAM study results do not appear to justify the use of rosiglitazone or the TZD class drugs for prevention in most people at risk for DM, many of whom are otherwise healthy. Consideration might be given to its careful use in the certain individuals with the meta-

bolic syndrome or occasionally in PCOS where IR is targeted but metformin would be less costly and maybe as effective. Rosiglitazone use carries a significant CV risk in some patients and, based on findings from the A Diabetes Outcome Progression Trial (ADOPT),¹¹ increased fracture risk must be considered in those at risk of falls and those with osteoporosis. Ramipril cannot be recommended for prevention of DM in low-CV-risk populations based on the results of DREAM, but ACE inhibitors remain an important class for use in those with DM and hypertension and in other forms of CV disease. Lifestyle change can prevent DM and has many other health benefits. Often considered less costly than pharmacologic interventions, it should be stressed that the types of intensive lifestyle changes that worked in clinical trials may be more expensive and attainable only with intensive patient support, monitoring and high adherence. Physician discretion will be the deciding factor, but many think lifestyle change should be the cornerstone of intervention.

All the results of the DREAM study and several of its substudies looking at secondary outcomes remain to be published. DREAM-ON will follow the outcomes of participants and epiDREAM will follow many of those ineligible for enrolment. The Study of Atherosclerosis with Ramipril and Rosiglitazone (STARR) results were recently reported at the American College of Cardiology (2007). Using carotid ultrasound in 1,425 randomized participants in DREAM without carotid disease, rosiglitazone showed significant slowing of progression of carotid intima thickening over five years, indicating it can stabilize subclinical vascu-

Table 1

Patients at High Risk for Developing DM

Individuals who:

- are older than 40 years;
- belong to a high-risk ethnic group;
- have a first-degree relative with DM;
- have a history of gestational DM or of having a macrosomic baby;
- exhibit components of the metabolic syndrome* (large abdominal girth, high triglycerides, low HDL cholesterol, IFG (> 5.8) but without DM, elevated BP (defined as \geq 130/85 mmHg) or definite hypertension);
- have polycystic ovary syndrome (PCOS);
- have schizophrenia; or
- show acanthosis nigricans, a marker of insulin resistance (IR).

* The metabolic syndrome has several definitions depending on specific criteria. The definition of high BP (\geq 130/85 mmHg) is similar to the recommended thresholds (> 130/80 mmHg) for initiating treatment in DM. The definition of IFG varies with definition as well.

lar disease. No such change was seen with ramipril. Other substudy results will follow.

References:

1. Report of 19th World Diabetes Congress, Dec. 3-7, 2006, Cape Town, South Africa.
2. Diabetes in Canada. National Statistics and Opportunities for Improved Surveillance, Prevention and Control. Health Canada, 1999.
3. Lipscombe LL, Hux J. *Lancet* 2007; 369:750-6.
4. Knowler WC, et al. *N Engl J Med* 2002; 346:393-403.
5. Tuomilehto J, et al. *N Engl J Med* 2001; 344:1343-50.
6. Chaisson JL, et al. *Lancet* 2002; 359:2072-7.
7. Yusuf S, et al. *JAMA* 2001; 286:1882-5.
8. Buchanan TA, et al. *Diabetes* 2002; 51: 2796-2803.
9. The DREAM Trial Investigators. *Lancet* 2006; 368: 1096-1105.
10. The DREAM Trial Investigators. *N Engl J Med* 2006; 355:1551-62.
11. Kahn SE, et al. *N Engl J Med* 2006; 355:2427-43.

*Carl Abbott, MD, FRCPC, FACP,
Endocrinologist, Dalhousie
University.*

Readers of Hypertension Canada are invited to visit the CHS homepage at www.hypertension.ca and submit suggestions on its improvement.

