Leading with Innovation
Serving with Compassion
St. Michael's Hospital
A teaching hospital affiliated with the University of Toronto
Terrence Donnelly Heart Centre

Cardiology

University of Toronto

Special Feature
Visit us at www.cardiologyupdate.ca for PowerPoint teaching slides on this topic

AN EDUCATIONAL PUBLICATION FROM THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Prevention of Cardiovascular Events in Diabetic Patients: The ADVANCE Study

Originally presented by: J Chalmers, MD; G Mancia, MD; S MacMahon, MD; N Poulter, MD

A Presentation at a Satellite Symposium at the European Society of Cardiology Congress 2007

Vienna, Austria September 1-5, 2007

By JUAN CARLOS MONGE, MD, FRCPC, FACC

Arterial hypertension is extremely frequent in patients with diabetes mellitus. After 30 years, at least 50% of patients with type 1 diabetes and 67% of those with type 2 diabetes have hypertension. This is associated with a marked increase in cardiovascular (CV) risk. Various trials have confirmed that blood pressure (BP) reduction is crucial to reduce CV risk; however, although most of these trials have included patients with diabetes, there are limitations associated with their recommendations for this patient group. The BP-lowering arm of the ADVANCE study, reported at the recent European Society of Cardiology Congress, examined the effects of a combination of perindopril and indapamide in lowering BP in >11,000 patients with type 2 diabetes to ascertain if the risk of major macrovascular and microvascular disease would be reduced with this treatment. These results are presented in this issue of *Cardiology Scientific Update*.

Blood pressure, diabetes, and CV prognosis – trial data

Data from the Multiple Risk Factor Intervention Trial (MRFIT) demonstrated that, at any blood pressure (BP) level, diabetic patients have a significantly higher risk of CV mortality.[1] BP reduction results in a decrease in CV events for diabetic and nondiabetic patients in a manner that is, to a certain degree, independent of the antihypertensive drugs used.

In the Systolic Hypertension in the Elderly Program (SHEP), diabetic patients with isolated systolic hypertension had a higher incidence of CV events than nondiabetic patients; however, the antihypertensive treatment, which was based on a thiazide diuretic, resulted in similar relative risk reductions.[2] BP reductions in diabetic patients with other drugs, such as angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), or angiotensin receptor blockers (ARBs) also result in decreased CV events.[3] The conclusion could be inferred that in hypertensive diabetic patients, CV protection depends substantially on BP lowering *per se,* regardless of how it is obtained.

However, challenges to this concept emerged as a result of a number of clinical trials. For example, in the Intervention as a Goal in Hypertension (INSIGHT) trial, based on treatment with a CCB, there was excess residual CV risk in diabetic patients despite similar on-treatment BP levels in diabetic and nondiabetic patients.[4] To address this excess residual risk, several strategies have been proposed such as lipid-lowering therapy, antiplatelet treatment, rigorous blood glucose control, greater BP reduction, lower targets, and the use of drugs with direct organ-protective properties.

There is evidence to support the use of greater BP reduction and lower targets in diabetic patients. A meta-analysis of multiple trials performed by the Blood Pressure Lowering Treatment Trialists' Group compared the rates of events in patients with more aggressively treated hypertension with those who were less aggressively treated. A greater BP reduction – by 6.0 mm Hg systolic and 4.6 mm Hg diastolic – was

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

associated with a significant 36% reduction in stroke and 31% reduction in congestive heart failure. There were also reductions in coronary events and CV events, but they failed to achieve statistical significance.[3]

A retrospective analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT) also demonstrated that diabetic patients who achieved on-treatment BP levels that were <130 mm Hg systolic had an almost 40% reduction in the risk of heart failure compared to those remaining around 140 mm Hg systolic.[5]

In the diabetic subgroup of the Hypertension Optimal Treatment (HOT) trial, patients randomized to a target diastolic BP (DBP) of 80 mm Hg had a 50% reduction in major CV events compared to those randomized to the more traditional target of 90 mm Hg.[6]

Similar benefits have been observed in diabetic patients with relatively normal, or only minimally elevated BPs, such as those enrolled in the MICRO-HOPE substudy that included 3,577 high-risk diabetic patients randomized to an ACEI or placebo. Patients treated with the ACEI had significant reductions in myocardial infarction (MI), stroke, CV death, total mortality, and microvascular disease.[7]

In a small study, the Appropriate Blood Pressure Control in Diabetes (ABCD) study, patients with moderate BP reduction (on-treatment level of 137/81 mm Hg) were compared with patients treated with more intensive BP-lowering to a level of 128/75 mm Hg. The latter had a significant reduction in the risk of stroke compared with the less intensively-treated patients.[8]

Limitations of these studies in regards to diabetic patients

Evidence from the above studies led to the inclusion of recommendations for more aggressive BP lowering in diabetic patients in the major guidelines, as well as the initiation of treatment at high normal BP levels (≥130/85 mm Hg in the recent European guidelines or ≥130/80 mm Hg in the Canadian guidelines), and the use of drugs that target the renin-angiotensin system.[9,10]

However, there are some limitations for these recommendations in the guidelines – as they pertain to diabetic patients – that need to be acknowledged. These include the fact that few specific studies have been conducted; the studies have often been small in size; the data are largely based on subgroup analysis of studies on general hypertensive populations; the studies make extensive use of retrospective analysis; the CV endpoints were often secondary outcomes of studies with primary renal endpoints; and evidence is particularly limited about the benefits of treating individuals in the normotensive range (defined as a BP of <140/90 mm Hg).

Another important aspect that should be considered is the complexity of treating hypertension in diabetic patients. Most studies have demonstrated the need to use multiple drugs, since monotherapy is almost always insufficient to control BP to recommended targets in this patient population.[11-13] Some guidelines, however, are somewhat circumspect about recommending combination therapy, given the potential need for a large number of pills, the issue of cost, and the possibility of increased side effects, among other reasons. Moreover, an analysis of studies that included hypertensive diabetic patients revealed that most could not lower SBP below 140 mm Hg (an average on-treatment value) in these patients and not a single study reached the recommended target of 130 mm Hg.[14]

There is a significant need, therefore, for more effective, simpler, and safer treatments to achieve greater BP reductions and better long-term BP control in diabetic patients that could lead to reduced morbidity and mortality. This is even more important in the clinical setting, in which the levels of BP control observed in clinical trials are rarely achieved and the difficulties outlined above are often magnified. For example, the ForLife study, conducted in Italy, assessed BP control in >12,000 patients followed by general practitioners, including 2,491 with diabetes. Only 14.9% of the diabetic patients achieved BP levels of <140/90 mm Hg and only a minute number (3.0%) had their BP lowered to the guideline-recommended level of <130/80 mm Hg.[13]

The ADVANCE study

It is currently estimated that there are 247 million people with diabetes in the world and this number is projected to reach 380 million in the year 2025, an increase of 55% in the next 2 decades alone. It is recognized that most people with diabetes will die from the vascular complications of the disease, rather than from its metabolic complications.

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that tighter BP control reduced the risk of any clinical endpoint, fatal or nonfatal, related to diabetes. It also demonstrated a continuous relationship between BP levels and risk of macrovascular and microvascular events.[16] However, all subjects included in UKPDS started in the hypertensive range and were still in that range at study conclusion. The less tightly-controlled group finished with a SBP of 154 mm Hg, while the more tightly-controlled group had a level of 145 mm Hg.

Rationale

This is the landscape in which the "**A**ction in **D**iabetes and **V**ascular Disease: Preter**a**x and Diamicro**n** MR **C**ontrolled **E**valuation" (ADVANCE) study was conceived.[17] (The fixed combination of perindopril and indapamide is known by the trade name COVERSYL Plus in Canada.) In 2000, ADVANCE was designed to address these unresolved questions: Does BP-lowering therapy in diabetics produce

additional benefits when SBP is lowered to <145 mm Hg, going beyond UKPDS and into the normotensive range; would BP lowering result in similar benefits in hypertensive and nonhypertensive patients; and would it add to the benefits of other CV preventive therapies, including ACEIs?

Design

ADVANCE is a factorial, randomized trial of BP-lowering and intensive glucose control in 11,140 patients with type 2 diabetes. The BP-lowering arm was recently reported, while the intensive glucose-control arm is ongoing.[18] The factorial design included a double-blind, placebo-controlled comparison of BP-lowering with a fixed combination of perindopril and indapamide and an open comparison (PROBE design [prospective, randomized, open-label therapy with blind endpoint analysis]) of a glicazide MR-based regimen for intensive glucose control.

The 11,140 patients were from a wide range of geographic regions, including Caucasian and Asian patients from multiple countries and continents, and were followed for 4-5 years. The hypotheses were that among individuals with type 2 diabetes, the routine addition of a fixed combination of perindopril and indapamide would reduce the risks of major macrovascular disease (including coronary disease, cerebrovascular disease, or death from CV disease), and major microvascular disease (including new or worsening nephropathy or diabetic eye disease). Additionally, it was hypothesized that these results would occur irrespective of initial BP or the background use of other preventive therapies, including ACEIs.

Randomization followed a 6-week, run-in period, during which patients were given open-label perindopril and indapamide. Patients were randomized to the perindopril-indapamide fixed-combination or placebo in the BP-lowering arm, and in the glucose control arm to intensive therapy targeting an A1c level of 6.5% or to standard glucose control according to local guidelines.

The inclusion criteria included type 2 diabetes, age ≥55 years, and additional vascular risk factors that could be age >65 years, a history of major macrovascular disease, a history of major microvascular disease, a diagnosis of diabetes made >10 years prior to entry or one of the major traditional CV risk factors. Importantly, patients could be hypertensive or normotensive.

The randomized study treatments in the BP arm were double-blind perindopril and indapamide versus matching placebo, starting at a dose of 2 mg of perindopril and 0.625 mg of indapamide for the first 3 months, increasing automatically in all patients to 4 mg and 1.25 mg, respectively, thereafter. The fixed-combination of perindopril and indapamide was chosen because it has been shown to be very effective in lowering BP and preventing recurrent strokes and CV events.[19] The combination is well-tolerated and has other potentially desirable properties, such as reducing arterial stiffness in large arteries and enhancing the function of the microcirculation and tissue perfusion in the heart and kidney.[20-25] There was, therefore, a strong rationale to expect clinical benefits in diabetic patients, in whom vascular disease straddles the microvasculature and the macrovasculature.

Any ancillary antihypertensive treatment that the treating physician considered necessary was allowed in ADVANCE, with the exception of thiazide diuretics. Open-label perindopril was made available to the patients if the treating physician considered that an ACEI was indicated. The primary outcomes were a composite macrovascular endpoint that included: nonfatal stroke, nonfatal MI or death from any CV cause, including sudden cardiac death, and a composite microvascular endpoint of new or worsening nephropathy or diabetic eye disease. It was prespecified that the macrovascular and the microvascular endpoints would be analyzed jointly, as well as separately.

Study population

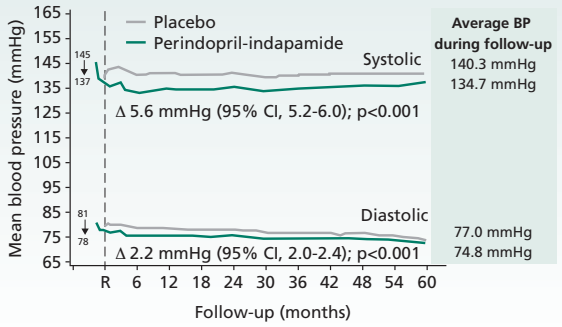
A total of 12,877 patients were registered and 11,140 were randomized after the 6-week run-in period. The study population represented a broad cross-section of diabetic patients from Australia, New Zealand, several countries in the Asia-Pacific region (including large numbers of patients from India, China, Malaysia, and the Philippines, among others), Europe, and Canada. At baseline, the mean age of the patients was 65 years and SBP was 145 mm Hg, which is exactly where UKPDS left off. The DBP was normal at 81 mm Hg and hemoglobin A1c was 7.5%.

ADVANCE Study: morbidity and mortality results

After randomization, there were 5,569 patients assigned to the perindopril-indapamide combination and 5,571 to the control group. Following an average follow-up period of 4.3 years, only 15 patients were lost to follow-up. The SBP in the perindopril-indapamide-treated group was 5.6 mm Hg lower than in the control group. The difference in the DBP was 2.2 mm Hg. The average BP during follow-up was 134.7/74.8 mm Hg for the combination-treated group compared to 140.3/77.0 mm Hg for the control group (Figure 1). There was an excellent use of ancillary drug therapy in the study. For example, in the control group, 83% of the patients received antihypertensive medications, including 60% of the patients who were given open-label perindopril.

There was a significant 14% reduction in the secondary endpoint of all-cause mortality with the perindopril-indapamide combination. The benefits were seen beginning at 12 months and continued to accrue throughout the follow-up period (Figure 2). The reduction in all-cause mortality

Figure 1: Blood pressure reduction



primarily reflected a reduction in CV deaths, which were reduced by a significant 18% (Figure 3). The combined primary outcome of macrovascular and microvascular events was reduced by 9% (Figure 4). The separate analysis of these primary outcomes demonstrated nearly identical beneficial trends for the prevention of both of these types of events with the perindopril-indapamide combination. Total coronary events were reduced by a significant 14%. The reduction of 6% in cerebrovascular events did not reach statistical significance. There was also a highly significant 21% reduction in renal events, including new or worsening nephropathy and new-onset microalbuminuria. There was a 5% reduction in eye events with the combination that barely failed to reach statistical significance.

In terms of the absolute benefits of routine treatment of similar patients with the combination of perindopril and indapamide, it would be expected to prevent 1 major vascular event among 66 treated patients, 1 death among 79 patients, 1 coronary event among 75 patients, and 1 renal event among 20 patients (primarily new-onset microalbuminuria). These can be considered fairly reasonable benefits in the context of primary or secondary

Figure 2: All-cause mortality

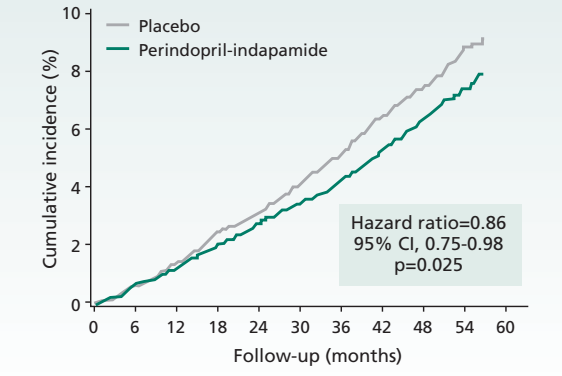
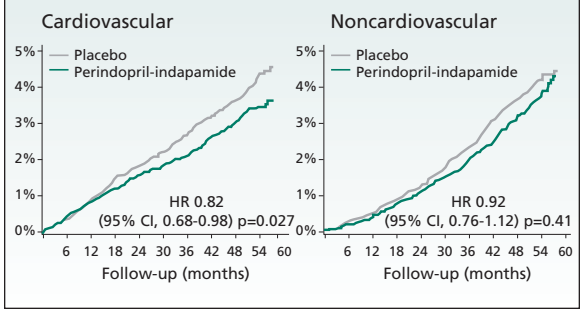


Figure 3: Deaths



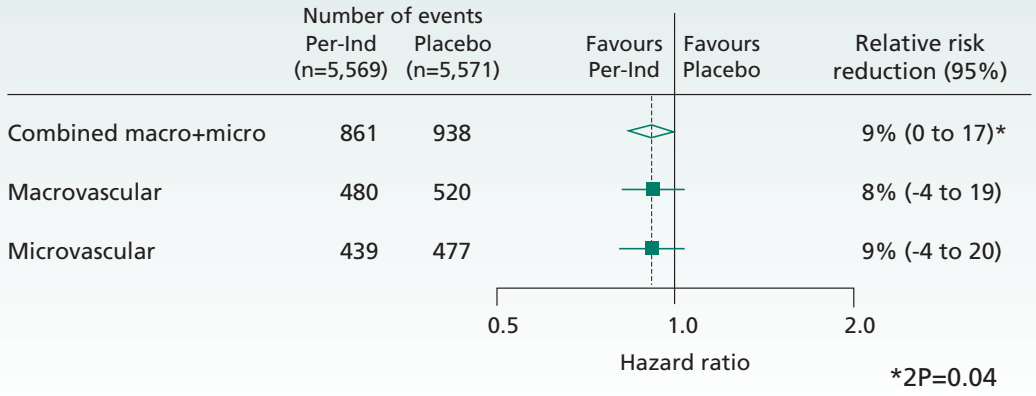
prevention of CV disease. The benefits of treatment were present and largely similar in multiple subgroups that were analyzed (eg, patients aged ±65 years, male or female sex, SBP ± 140 mm Hg, and hemoglobin A1c ± 7.5%. Importantly, the benefits were in addition to those produced by other treatments, including the high use of open-label ACEIs in the control group, and were achieved with remarkable safety and tolerability as reflected by very few withdrawals due to intolerance.

The impact of ADVANCE on the management of diabetic patients

The analysis of the impact of less intensive versus more intensive BP-lowering in diabetic patients conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) suggested the benefits of the latter approach on the endpoints of stroke, coronary heart disease, and heart failure.[3,26] Although not all of the endpoints reached statistical significance, this study suggested that diabetic patients did at least as well, if not better, than nondiabetic hypertensive patients with the more intensive approach to lowering BP. As discussed previously, in the UKPDS, lowering SBP to 144 mm Hg resulted in additional benefits compared to a level of 154 mm Hg in the less intensively-treated diabetic patients. However, BP levels in these studies would not be considered acceptable at this time.

When ADVANCE was designed, there were several important unresolved issues related to BP-lowering in diabetic patients. For instance, it was not known whether lowering SBP to <145 mm Hg would produce additional benefits or whether these benefits would be observed both in hypertensive and nonhypertensive diabetics. The BP levels of the patients studied in ADVANCE, beginning where UKPDS left off, are more commonly seen in the current diabetic population and are, therefore, more relevant to contemporary clinical practice. Importantly, in ADVANCE, the treatment of type 2 diabetics with the fixed perindopril-indapamide combination yielded

Figure 4: Primary outcomes – Major macro- or microvascular event



Per-Ind = perindopril-indapamide

outcome benefits, irrespective of the initial BP or the background use of other preventive therapies, including ACE inhibitors.

The risk reduction in coronary events in the study was almost identical to what would have been expected based on the results of the BPLTTC. The reduction in stroke was somewhat less than expected, but the confidence intervals for this endpoint were rather wide and generally compatible with the previous evidence of the large number of trials included in the BPLTTC analysis. The large 14% reduction in total mortality observed in ADVANCE is greater than would have been expected from BPLTTC, but the confidence intervals also cross the expected data from the Collaboration. The reduction in total mortality was largely driven by an 18% reduction in CV mortality, which is also greater than expected; however, the same caution must be exercised as with the total mortality data.

It is also important to put ADVANCE in context by comparing it to other similar large trials of diabetic patients. While UKPDS included 1,148 patients and MICRO-HOPE included 3,577, ADVANCE is a much larger trial, including >11,000 patients. Additionally, ADVANCE took BP to levels that are lower than in the other 2 studies (UKPDS: 145/82 mm Hg, MICRO-HOPE: 139/77 mm Hg, and ADVANCE: 136/73 mm Hg), providing strong evidence to support more aggressive BP-lowering in diabetic patients. The use of statins was greater in ADVANCE than in MICRO-HOPE, while no statins were used in UKPDS. Glucose control was also much better in ADVANCE as reflected by A1c levels of 6.9%, as compared to 8.3% in UKPDS and 9.5% in MICRO-HOPE.[7,16-18] The event rates for total mortality, CV mortality, and stroke were lower in ADVANCE than in the other 2 studies, reflecting the fact that this was a lower risk population treated with more appropriate contemporary CV preventive therapies (Table 1).

Table 1: ADVANCE in context: Comparative patient profiles: UKPDS, MICRO-HOPE, ADVANCE

	UKPDS	MICRO-HOPE	ADVANCE
BP levels (mm Hg) *Active treatment at end follow-up*	145/82	139/77	136/73
Use of background ACEI	No	No	Yes
Use of statins	No	+	++
A1c end follow-up	8.3%	9.5%	6.9%
Event rate,			
Total and CV mortality	+++	+++	+
Stroke	++	+++	+

Summary

The potential implications of ADVANCE can be estimated by examining the current prevalence of diabetes worldwide, which is estimated to be 246 million. Treating only half of the population with the fixed combination used in ADVANCE would have the potential of averting 311,000 deaths per year, based on a number needed to treat (NNT) of 79 patients for 5 years to prevent 1 death. This exercise assumes, of course, that the NNT can be generalized to the overall diabetic population and is simply meant to illustrate the potentially massive impact of a wide application of the findings of ADVANCE. Currently, the United States (JNC-7) and European (ESH-ESC) guidelines for the treatment of hypertension recommend the use of 2-drug combination therapy as first-line treatment under certain circumstances. For instance, the latter includes patients at high-risk, such as diabetics, as one of the possible situations in which a

low-dose 2-drug combination could be used as first-line treatment.

It must be noted, however, that no large clinical trial evidence exists to support the recommendation of most guidelines to lower BP in diabetics to <130/80 mm Hg. This recommendation is largely based on observational studies. The evidence from ADVANCE is a significant contribution, since the BP level that has been studied and shown to be beneficial in clinical trials is more in line with the guidelines and attests to the validity of their recommendations. As such, and in addition to the potential large benefits of the widespread use of the fixed combination, ADVANCE is a landmark trial that greatly advances our knowledge of the prevention of CV events in type 2 diabetic patients.

Reference List

1. Stamler J, Vaccaro O, Neaton JD et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434-444.
2. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA* 1996;276:1886-1892.
3. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005;165:1410-1419.
4. Mancia G, Brown M, Castaigne A, et al. Outcomes with nifedipine GITS or Coamilozide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). *Hypertension* 2003;41:431-436.
5. Berl T, Hunsicker LG, Lewis JB, et al. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. *J Am Soc Nephrol* 2005;16:2170-2179.
6. Hansson L, Zanchetti A, Carruthers SG, 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. HOT Study Group. *Lancet* 1998;351:1755-1762.
7. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000;355: 253-259.
8. Schrier RW, Estacio RO, Esler A, et al. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002;61:1086-1097.
9. Mancia G, De Backer G, Dominiczak A, et al. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens* 2007;25:1751-1762.
10. Khan NA, Hemmelgarn B, Padwal R, et al. The 2007 Canadian Hypertension Education Program recommendations for the management of hypertension: part 2 - therapy. *Can J Cardiol* 2007;23:539-550.
11. 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;36:646-661.
12. 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;345:861-869.
13. 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;345:851-860.
14. Mancia G, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. *J Hypertens* 2002;20:1461-1464.
15. Mancia G, Ambrosioni E, Rosei EA, et al. Blood pressure control and risk of stroke in untreated and treated hypertensive patients screened from clinical practice: results of the ForLife study. *J Hypertens* 2005;23:1575-1581.
16. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;317:703-713.
17. Study rationale and design of ADVANCE: action in diabetes and vascular disease--preterax and diamicron MR controlled evaluation. *Diabetologia* 2001; 44:1118-1120.
18. 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;370:829-840.
19. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033-1041.
20. Asmar RG, London GM, O'Rourke ME, et al. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/ indapamide combination in hypertensive patient: a comparison with atenolol. *Hypertension* 2001;38:922-926.
21. Lacourciere Y, Beliveau R, Conter HS, et al. Effects of perindopril on elastic and structural properties of large arteries in essential hypertension. *Can J Cardiol* 2004;20:795-799.
22. Manolis AJ, Iraklianou S, Pittaras A, et al. Arterial compliance changes in diabetic normotensive patients after angiotensin-converting enzyme inhibition therapy. *Am J Hypertens* 2005;18:18-22.
23. Ahimastos AA, Aggarwal A, D'Orsa KM, et al. Effect of perindopril on large artery stiffness and aortic root diameter in patients with Marfan syndrome: a randomized controlled trial. *JAMA* 2007;298:1539-1547.
24. Buus NH, Bottcher M, Jorgensen CG, et al. Myocardial perfusion during long-term angiotensin-converting enzyme inhibition or beta-blockade in patients with essential hypertension. *Hypertension* 2004;44:465-470.
25. Mourad JJ, Laville M. Is hypertension a tissue perfusion disorder? Implications for renal and myocardial perfusion. *J Hypertens Suppl* 2006;24:S10-S16.
26. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000;356:1955-1964.

Dr. Monge has stated that he has no disclosures to announce in association with the contents of this issue.

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Servier Canada to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology, St. Michael's Hospital, and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.

Publications Post #40032303

SNELL

202-087