VOLUME 04
ISSUE 03

CLINICAL PRACTICE UPDATE IN
ENDOCRINOLOGY & DIABETES

LMC

PREVENTING CARDIOVASCULAR DISEASE IN THE PATIENT WITH DIABETES

Ronald M. Goldenberg
MD, FRCPC, FACE

Cardiovascular disease is a major complication of diabetes, and approximately 65% of deaths are due to heart disease and stroke.

In fact, CAD deaths and strokes are increased two to four fold amongst diabetes patients and heart failure occurs twice as frequently in men and five times more frequently in women. A major focus, then, in managing diabetes is the prevention of CV complications through implementation of appropriate vascular protective measures. In this issue of Clinical Practice Update, a case-based approach will help illustrate which patients with diabetes are considered to be high risk, the appropriate vascular protective strategies, and how to manage CV risk factors according to the 2008 CDA Clinical Practice Guidelines.

CASE STUDY DESCRIPTION MRS. C

Mrs. C. is a 55-year-old retired school teacher. She was diagnosed with type 2 diabetes one year ago and has been treated with metformin 500mg BID, statin, ECASA, diet and exercise. She has a family history of type 2 diabetes and cardiovascular disease. Other than central obesity, the remainder of her physical exam is unremarkable. Her blood pressure is 128/78. All of her laboratory investigations are relatively unremarkable, with a fasting glucose of 6.5 mmol/l, A1C of 6.4%, and lipids at target levels.

Is Mrs. C. at High Risk for Cardiovascular Disease?

According to the 2008 CDA Guidelines, the following individuals with diabetes should be considered at high risk for cardiovascular events (see

- Men aged > 45 years and women aged > 50 years.
- Men < 45 years and women < 50 years with > one of the following:
  - Macrovascular disease (e.g., MI, peripheral arterial disease or cerebrovascular disease)
  - Microvascular disease (nephropathy and retinopathy
  - Multiple additional risk factors
  - Extreme level of a single risk factor (e.g., LDL C>5.0mmol/l, SBP > 180mmHg)
  - Duration of diabetes > 15 years with age > than 30 years

Therefore, based on age alone, Mrs. C. is considered to be a high risk for cardiovascular events.

VASCULAR PROTECTION IN PEOPLE WITH DIABETES

The CDA Guidelines suggest priorities for the prevention of cardiorenal disease in patients with diabetes. Using this clinical strategy, all patients with diabetes should be initiated with appropriate vascular protective measures as the first priority. The second priority would be to treat elevated blood pressure in patients whose BP remains greater than 130/80 despite vascular protective measures. The third priority would be to initiate renal protection in all patients with proteinuria, despite vascular protective measures and BP less than 130/80mmHg.

The following vascular protective measures should be recommended for all people with diabetes:

- Lifestyle modification
- Optimize BP control (<130/80 mmHg)
- Optimize glycemic control (A1C ≤ 7.0% for most patients)

For all people with diabetes considered at high risk of a cardiovascular event, the following should be instituted:

- ACE inhibitor or ARB therapy (even with out hypertension)
- Anti-platelet therapy (as recommended)
- Lipid lowering medication (LDL-C ≤ 2.0 mmol/L & TC/HDL-C < 4; primarily statins)

LIFESTYLE MODIFICATION

It is recommended that individuals with diabetes achieve a healthy body weight through regular physical activity (150 minutes of moderate to vigorous aerobic exercise weekly and resistance exercise three times per week.) Appropriate dietary changes are recommended to improve glycemic control, encourage weight loss, and include heart health food choices. Smoking cessation is recommended for all smokers, including nicotine replacement, bupropion or varenicline.

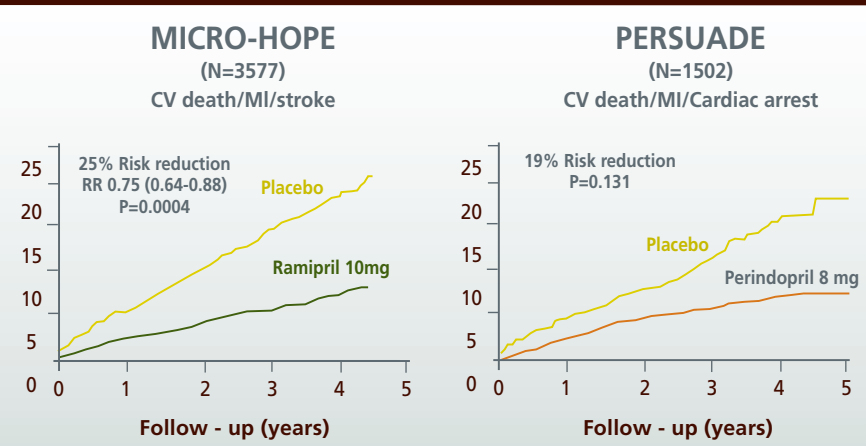
SHOULD MRS. C. BE TREATED WITH A RAAS INHIBITOR?

The first study demonstrating the vascular protective benefit of ACE inhibitors in diabetes was the diabetes subgroup of HOPE. In this study, 3,577 high risk diabetes patients were randomized to ramipril 10mg vs placebo. There was a 25% risk reduction in CV death, myocardial infarction and stroke. Subsequently, the EUROPA study, showed similar benefits with perindopril 8mg but the smaller sample size (1502 subjects) impaired the ability to reach statistical significance. The ONTARGET study of 25,620 high- risk patients found that telmisartan 80mg was noninferior to ramipril 10mg in the prevention of CV death, MI, stroke or heart failure.

Telmisartan was better tolerated than ramipril in the ONTARGET study, with less cough and angioedema. Furthermore, combination therapy with ACE inhibitor and ARB in ONTARGET was not as well tolerated as ACE inhibitor alone, with more episodes of hypotension, syncope, diarrhea, renal impairment and discontinuation of study medication.

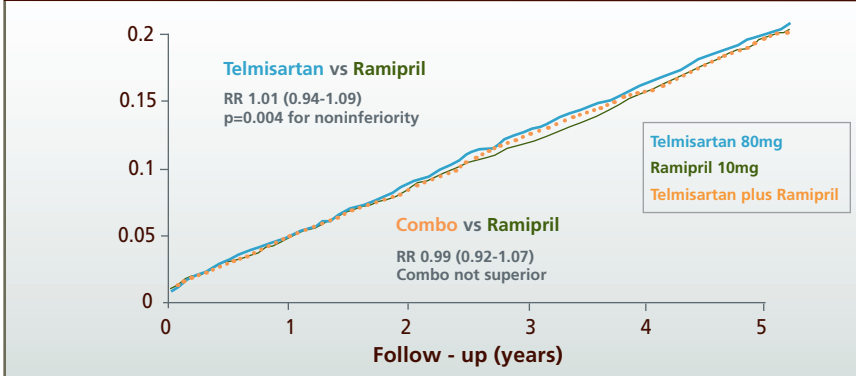
The CDA Guidelines recommend that individuals with diabetes at high-risk for CV events should receive an ACE inhibitor or ARB at doses that have demonstrated vascular protection, regardless of the presence of hypertension. Therefore, ramipril 10mg or telmisartan 80mg would be the recommended RAAS blockers for preventing cardiovascular events in high risk individuals.

ACE Inhibitors for Vascular Protection in DM: MICRO-HOPE, PERSUADE
Primary Outcome



HOPE Study Investigators. Lancer. 2000:355:253-9. Daly CA et al. El Heart J. 2005;28: 1369-78.

ONTARGET: Time to Primary Outcome
N=25,620 with vascular disease or high-risk diabetes (38%)



ONTARGET Investigators. N. Engl J Med. 2008;358:1547-59

HYPERTENSION IN DIABETES

Most patients with diabetes will develop hypertension. Every 10mmHg rise in systolic BP is associated with a 13% increased risk of microvascular disease and a 12% increased risk of myocardial infarction. Cardiovascular disease risk is also increased 2

to 7 fold in individuals with hypertension. Therefore, aggressive treatment of hypertension is warranted to reduce cardiovascular and microvascular complications of diabetes. The UKPDS demonstrated that tight blood pressure control reduces any diabetes-related complication, diabetes-related deaths, stroke and microvascular events. The HOT trial showed that targeting a diastolic BP ≤80, leads to a 51% reduction in major cardiovascular events.

Lifestyle therapies can have a dramatic impact on blood pressure: reducing foods with added sodium, weight loss, aerobic exercise a DASH diet have all been shown to reduce blood pressure significantly.

The target BP for individuals with diabetes is <130/80. For those with nephropathy, an ACE inhibitor or ARB remains a first line choice, due to their added renal protective benefits. For those without nephropathy, while ACE inhibitors or ARBs remain first line choices, there is the option of also considering thiazide-like diuretics or dihydropyridine calcium channel blockers as a first line agent. Most individuals with diabetes will need three or more drugs to achieve adequate blood pressure, one of which should be an ACE inhibitor or ARB. Combinations of an ACE inhibitor with an ARB are specifically not recommended in the absence of proteinuria.

SHOULD MRS. C. BE TREATED WITH ASA?

A recent metaanalysis of randomized trials of antiplatelet therapy for primary prevention of major cardiovascular events in diabetes did not show a significant reduction in these end points. As a result, the decision to prescribe antiplatelet therapy for primary prevention of cardiovascular events should be based on individual clinical judgment. However, quite often it will be determined that the potential benefit will outweigh the risks of this therapy. Low dose ASA therapy may be considered in people with stable cardiovascular disease and clopidrogel may be considered in people unable to tolerate ASA.

CDA Guidelines therefore suggest that Mrs. C. could be given ASA based on clinical judgment. I would favor treating Mrs. C. with ECASA 81mg daily, as the potential for some long term benefit probably outweighs any risks.

RENAL PROTECTION IN DIABETES

The progression of renal damage in diabetes can be slowed through intensive glycemic control and optimization of BP. Adults with diabetes and persistent albuminuria (ACR > than 2.0mg/mmol in males, >2.8mg/mmol in females) should receive an ACE inhibitor or ARB to delay progression of CKD, even in the absence of hypertension.

Recent studies have shown that telmisartan, an ARB with high lipophilicity and the longest half-life compared with other ARBs, provides benefits on markers of cardiovascular risk, such as microalbuminuria and slowing of early-stage nephropathy. In the INNOVATION study, 514 individuals with type 2 diabetes and microalbuminuria were treated with either placebo, telmisartan 40mg or 80mg. Transition to overt nephropathy was reduced by 55% with telmisartan 40mg and there was a 66% reduction with telmisartan 80mg. The benefit of telmisartan was independent of its antihypertensive effect in this study.

The AMADEO study showed more reduction in proteinuria in type 2 diabetes patients with hypertension and overt nephropathy that were treated with telmisartan compared to losartan. The difference in the anti-proteinuric effect of the two ARBs could not be attributed to their effects on BP as the mean BP between groups was not significantly different.

MULTIFACTORIAL INTERVENTION IN TYPE 2 DIABETES

Is all of the polypharmay in patients such as Mrs. C worthwhile? The STENO-2 study compared an intensified multifactorial intervention to conventional therapy in 160 high-risk patients with type 2 diabetes and microalbuminuria. Intensive treatment targets included BP <130/80mmHg, A1C <6.5%, total cholesterol <4.5mmol/l and triglycerides <1.7mmol/l. After an initial 7.8 years of randomized trial follow-up and a further 5.5years of observational follow-up, there was a significant 46% risk reduction for death from any cause, a 59% reduction in any cardiovascular event and a 43-66% reduction in nephropathy or retinopathy. Therefore, intensive multifactorial intervention is beneficial in preventing mortality and vascular morbidity in individuals with type 2 diabetes.

SUMMARY

Aggressive multifactorial diabetes care can reduce vascular complications and overall mortality. The 2008 CDA Guidelines advocate vascular protection as the first priority of diabetes care. All patients with diabetes should be treated with lifestyle modification and strive for optimal blood pressure and glycemic control. For those individuals considered at high-risk of a cardiovascular event, treatment should include ACE inhibitor or ARB therapy, antiplatelet therapy as recommended and lipid lowering medication.

WHAT IS A PA?

Physician Assistants in Canada – PAST, PRESENT AND FUTURE

The Physician Assistant (PA) profession was born in the 1960's at Duke University in North Carolina. Dr. Eugene Stead recognized the need for "mid-level medical providers" and enrolled four highly trained medics returning from active services in the inaugural PA program. Today in the US, 139 accredited PA programs now exist and over 79,000 PAs are practicing across the country.

Physician Assistants are educated in the medical model, designed to complement physician training. They practice medicine as members of a team with supervising physicians. Within the physician-PA relationship, PAs exercise autonomy in medical decision making and provide a full range of both diagnostic and therapeutic services.

In Canada, "mid-level providers" have been utilized in the Canadian Armed Forces for over 50 years and in 2003, became officially recognized by the Canadian Medical Association (CMA). In 2007, the OMA and the Ministry of Health began a pilot program for PAs to be employed in various settings, including emergency medicine, hospital services, primary care, diabetes management, and long-term care. These initial programs are being carefully evaluated for the quality and quantity of PA care, as well as team and patient access and satisfaction. The outstanding early results have prompted an ongoing project extension.

At LMC Endocrinology Centres, I work as a Diabetes Physician Assistant enriching the health of patients. Medical directives permit me to diagnose and treat patients as determined appropriate by my supervising physician. I follow the standard of practice set forth by the Canadian Diabetes Association and practice in a style reflective of my supervising physician. Upon referral to LMC, new patients have a thorough consultation involving myself and my supervising physician. Follow-up visits are shared between the two of us, allowing for comprehensive medical care and vigilant attention to patients needs. I welcome inter-visit communication via email or telephone, and feel this encourages patient self management.

Cailin Hill
PA-C

The Physician Assistant Initiative in Ontario has been well-received throughout the province. This promising profession enhances the health care team and enables physicians to extend their services to greater populations while maintaining a high quality of health care. With university-level PA programs emerging across Canada, including U of T and McMaster University, this growing profession has a bright Canadian future.

LMC Making Healthy Easier

DIABETES ▪ METABOLISM ▪ ENDOCRINOLOGY

TORONTO • OAKVILLE • ETOBICOKE • THORNHILL • BARRIE • MARKHAM • BRAMPTON • CALGARY

Supported by educational grants from members of the pharmaceutical industry.