Preventing Diabetic Complications

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Classified by the World Health Organization (WHO) as one of the major global epidemics of the 21st century, diabetes mellitus is the fifth leading cause of death in Canada. Ontario data (Figure 1)[1] indicate that life expectancy is reduced by approximately 13 years in people with diabetes. Furthermore, those living with diabetes are twice as likely to require assistance with everyday activities.

Eighty per cent of adverse outcomes are CV and occur 15 years earlier than usual. Having diabetes doubles cardiac risk in men, but the risk is tripled in women.

Four out of five Type 2 diabetics meet the criteria for the Metabolic syndrome with coexisting hypertension, dyslipidemia and abdominal obesity and one in four people with diabetes continue to smoke. This constellation of modifiable risk factors explains some, but not all, of the accelerated atherosclerosis that is the hallmark of the diabetic state. Other, as yet unidentified factors are postulated to play a role.

Some headway has been made in reducing the rates of MI and stroke.

Stroke rates are threefold higher overall in diabetes but tenfold increased under the age of 50.

A similar encouraging downward trend in hospitalization rates for stroke has been seen (Figure 2).

Over the 5 year study period, admission for AMI fell by an encouraging 9% and congestive heart failure (CHF) admissions decreased by 23% among those with diabetes, attributable, at least in part, to increased use of cardioprotective polypharmacy. Even so, the AMI and CHF rates were 7-to-10 fold higher in diabetics.

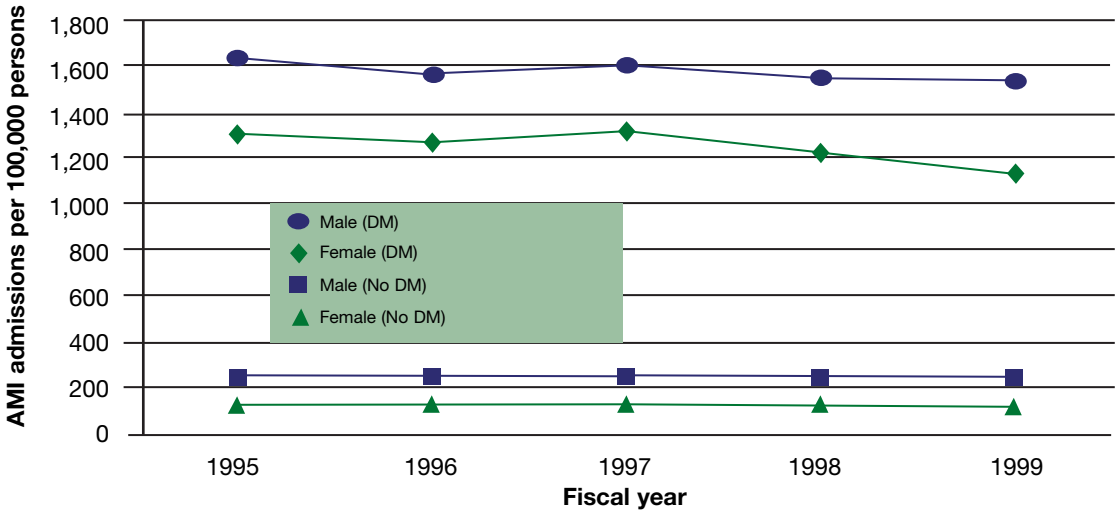

Figure 1. Acute MI (AMI) rates by gender and diabetes mellitus (DM) status in Ontario, 1995-1999.

What strategies have been shown to reduce CV events?

Hypertension control

Based on five epidemiologically-sound studies on controlling hypertension in 4,000 people with Type 2 diabetes, the NNT to prevent a CV event or death ranges from six to 23, a highly cost-effective strategy. Achieving and maintaining the current recommended target of ≤ 130/80 mmHg usually requires incremental dose titration of two or more antihypertensive classes.

There was a decline in stroke hospitalization rates over the study period in persons with and without DM.

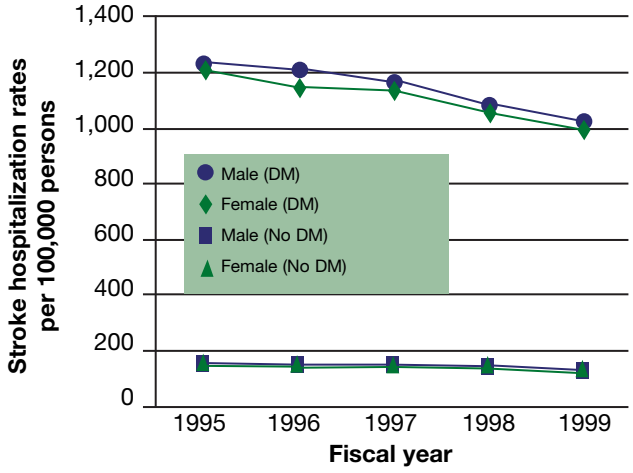

Figure 2. Age-/sex-specific hospitalization rates for stroke per 100,000 Ontarians with/without DM ≥ 20-years-of-age, 1995-1999.

Dyslipidemia

The typical lipid profile in Type 2 diabetes is the highly atherogenic triad of elevated LDL-C and triglyceride with low HDL-C levels. The evidence favouring LDL-C reduction is solid and "statins" have a sound record as a safe and cost-effective way of getting LDL-C to target.[2] The latest guidelines recommend a target LDL-C of < 2.0 mmol/L, but there is a small subset of people with diabetes, those who are young and lean, have recent onset diabetes and who do not have other risk factors, for whom the LDL-C target remains < 2.5 mmol/L. To achieve an LDL-C < 2 mmol/L, high dose statins and/or the addition of a cholesterol absorption inhibitor (ezetimide) is usually required.

A meta-analysis of statin use in diabetic dyslipidemia found a 21% relative risk reduction in both primary and secondary prevention.

By lowering triglycerides and raising HDL-C levels, fibrates would seem to be a logical therapeutic intervention yet their impact on reducing CV outcomes has been repeatedly disappointing. In the recently published Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study,[3] no reduction in primary outcomes, including fatal MI, were found in > 9,000 Type 2 diabetics and the NNT to reduce total CV events was 70.

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The "holy grail" of raising HDL-C levels safely and effectively has been limited by the side-effects experienced with nicotinic acid, as well as the set-back from the withdrawal of torcetrapib from clinical trials because of adverse outcomes.

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ASA and CV protection

Table 1 summarizes the current evidence. The Women's Health Initiative (WHI) study[4] found no benefit from low-dose ASA on heart disease in women < 65-years-of-age; however, there was no subgroup analysis in women with diabetes. In the 2007 American College of Physicians guide, it is suggested that physicians should consider 75 mg to 325 mg of ASA q.d. for all patients who:

- have Type 2 diabetes,
- are > 40-years-of-age,
- have one or more additional risk factors, as well as,
- no specific contraindications.[5]

Table 1
ASA and CV protection

	Primary prevention	Seconday prevention
Men	✓	✓
Women < 65 years	Heart: 0 Stroke: ✓	✓
Women ≥ 65 years	Heart: ✓ Stroke: ✓	✓ ✓

Smoking cessation

Cigarette smoking doubled the mortality rate in the Heart Outcomes Prevention Evaluation (HOPE) trial.[6]

The CV benefits of smoking cessation are well recognized but no study has specifically evaluated the benefits in people with diabetes. In Ontario, in the 1990s, one in four people with diabetes continued to smoke though one in three had quit, comparable to the non-diabetic population.

Glycemic control

In contrast to the evidence linking blood glucose control with microvascular complications, the role of glycemic control in atherogenesis remains controversial though recent evidence favours an association. In the United Kingdom Prospective Diabetes Study (UKPDS), a 20 year study of Type 2 diabetes, no statistically significant reduction in CV events was found in those who maintained a glycosylated hemoglobin (HgbA1C) of 7% compared with 9%,[7] but further analysis has shown that there was a 14% reduction in CV events with each 1% decline in HgbA1C.

Significant morbidity in diabetes results from damage to the microvasculature involving the retina, kidney and peripheral nervous system. Currently, diabetes is the chief cause of new onset visual loss in adults and the second most common cause for end stage renal failure and amputation.

Amputation

Neuropathy is the underlying cause of 70% of amputations and in the majority of people who have had diabetes for ≥ 20 years (Figure 3).

Evidence suggests that at least 50% of amputations can be prevented and though the decline in amputation rate is encouraging, it is postulated that the need for amputation would be halved if the following strategies were routinely employed:

- Earlier detection of the at-risk foot (*i.e.*, deformity, impaired sensation and/or reduced pedal pulses)
- Protection of the vulnerable foot by a combination of patient education, appropriate shoes or orthotics and aggressive management of any break in the skin or infection

Diabetic nephropathy

Diabetic nephropathy accounts for > 50% of chronic renal disease in Canada.

In Ontario, people with diabetes are 12 times more likely to require dialysis than those without. Aggressive control of hypertension, glycemia and lipids have been shown to slow

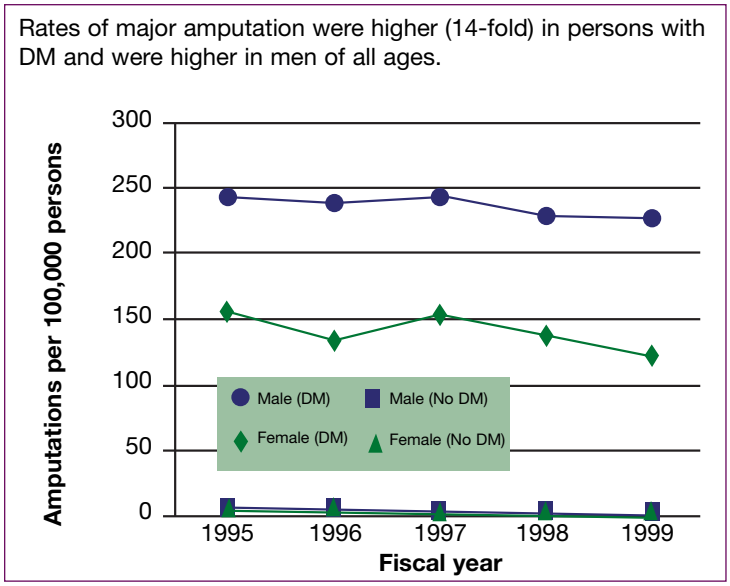

Figure 3. Age-/sex-specific major amputation rates per 100,000 Ontarians with/without DM ≥ 20-years-of-age, 1995-1999.

the rate of progression of renal insufficiency.

The detection of microalbuminuria is the first indication of renal damage and the NNT to prevent the progression of microalbuminuria to early nephropathy (proteinuria and/or increased serum creatinine) is three-to-13 in nine studies using an ACE inhibitor,[8] confirming that this is a highly effective strategy.

Most vision loss from diabetic retinopathy can be prevented by regular retinal screening and timely laser.

Similarly, the NNT to prevent or slow the progression of early nephropathy to end stage renal failure is 10 to 28.[9] Therefore, ACE inhibition is a crucial component in the management of nephropathy over and above its role in hypertension management; some studies have suggested that a combination of an ACE inhibitor and ARB is still more effective.

The current BP target in the presence of nephropathy is < 125/75 mmHg, if tolerated.

Protecting vision

Most vision loss from diabetic retinopathy can be prevented by regular retinal screening and timely laser. Current recommendations call for retinal examination through a dilated pupil at the time of diagnosis in Type 2 diabetes; however, screening rates fall far below those recommended (*e.g.*, only half of all newly-diagnosed Type 2 diabetics underwent an eye examination within one year of diagnosis).[1] More concerning still, the rate of eye examinations fell in Ontario in 1999 following a change in reimbursement by the Ontario Health Insurance Plan for routine eye examination even though people with diabetes were exempt from this restriction.

One in every 25 eye examinations leads to photocoagulation and timely photocoagulation is one of the key strategies in protecting vision.

What are the other situations in which evidence-based outcomes exist?

Flu vaccination

Adults with Type 2 diabetes benefit considerably from flu vaccinations, its effectiveness being equal in first-time and repeated vaccinations.[10]

Pregnancy outcomes

Steady improvement in maternal and fetal outcomes have been achieved in pregnancy in women with Type 1 diabetes through a combination of pre-pregnancy assessment, optimization of glycemic control from preconception through delivery and multidisciplinary management in specialized centres. Unfortunately, the same is not true for women with Type 2 diabetes. With a steadily rising incidence of the latter resulting from increasing obesity, later age at conception and immigration from areas with high rates of Type 2 diabetes, there is a concerning lack of preconception management, resulting in preventable congenital anomaly as well as an increased need for hospitalization and neonatal intensive care unit admission.[11]

The effective management of diabetes and especially Type 2 diabetes, requires a multifaceted approach using proven strategies for CV risk reduction.

Diabetes and the elderly

There is a disturbing lack of evidence concerning the goals and strategies for management of diabetes in the elderly. The 2003 Canadian Diabetes Association guidelines for the management of diabetes state that in the absence of evidence for the contrary, based on expert opinion but without supportive data, the strategies and targets for management in the elderly should be the same as for everyone else.

On the other hand, the American Geriatric Society, in their 2003 guidelines, take a more thoughtful approach, suggesting a target HgbA1C of 7% for the healthy older person and 8% for the frail individual, one with multiple comorbidities, or a reduced life expectation.[12] However, as pointed out by Olsen,[13] these recommendations are not evidence-based and any benefit resulting from improvement in hyperglycemia has not been proven in this age group.

Finally, can we do better?

In a Canadian study looking at 12,000 individuals with Type 2 diabetes, with an average age of 64 years, there was striking evidence of underutilization of medications that have been shown to reduce the CV toll. In primary prevention, ACE inhibition was used in < 50% of patients and < 25% were treated with statins or ASA. Even more concerning in secondary prevention where there is especially strong evidence for risk factor reduction, < 70% were treated with an ACE, < 60% with a statin and < 30% with ASA.

The effective management of diabetes, especially Type 2 diabetes, requires a multifaceted approach using proven strategies for CV risk reduction. Annual eye, foot and microalbumin checks and an individualized and regularly updated regimen to maintain the best achievable glycemic goal will lessen the personal and societal burden caused by diabetes.

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For references, please contact **cme@sta.ca**