Review

Diabetes Review:

What's New?

Andrew Farquhar, MB, ChB, BSc, DA

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The epidemic of Type 2 diabetes continues to explode, with an especially worrying trend affecting younger people. The anticipated increase in CV morbidity and mortality will reverse a downward trend in CVD that has been evident in the general population over the past three decades. Projected costs in human and economic terms are staggering.

In spite of an almost bewildering choice of drugs and insulins, the statistics on diabetes remain grim (Table 1).

FPs are the gatekeepers to diabetes care. The primary care physician is responsible for initial diagnosis and ongoing management. Essential components of optimum patient care include:

- keeping a patient registry,
- using flow sheets,
- scheduling regular follow-ups and
- having a working physician-patient partnership.

People with diabetes must be involved and informed. They should be reminded they are the key stakeholders in their diabetes, their diabetes is their responsibility and they must try to become their own best experts. All patients (if possible) should be referred to a Diabetes Education Center where survival skills and critical day-to-day management techniques are taught. Unfortunately only a minority of people receive self-management education. This is

Roger's case

Roger, 53, is a married businessman, smokes 1 pack per day and leads a sedentary lifestyle. He was diagnosed 1 year ago following presentation with erectile dysfunction (ED).

He was told he had "a touch of diabetes. Lose weight, watch your diet, get more exercise."

Family history: Father: Coronary artery disease
Brother: Type 2 diabetes

Assessment (A-H)

- A1C: 9.3
  Fasting blood glucose: 13 mmol
- BP: 140/90
  BMI: 35 (waist circumference, a better risk indicator, is 105 cm)
  Bruits (carotid or femoral) absent
- Cholesterol: LDL-C 3.2, HDL-C 0.9, risk ratio-total cholesterol: HDL-C 4.5, triglycerides 2.5
- Dietary assessment; rule out depression
- ED: ask about ED
  Exercise: ask about physical activity level
- Feet: peripheral pulses palpable, skin intact, sensation to 10 mg monofilament intact
  Fundi: appear normal, referral made for expert assessment
- Glomeruli: creatinine 122, estimated glomerular filtration rate (eGFR) 58, albumin/creatinine ratio (ACR) 8.6
- Heart: ECG (suggested in new Clinical Practice Guidelines if > 40-years-old, to rule out silent MI)

Turn to page 77 for more on Roger.

Table 1

Grim stats

- Shortened life expectancy: 10-15 years
- Increased CVD risk 3-5 times: 15 years earlier, more deadly
- 80% will die from CVD
- Commonest cause ESRD
- Commonest cause severe visual loss
- Commonest cause non traumatic BKA
- Commonest cause ED

ESRD: End stage renal disease
BKA: Below knee amputation

Table 2

Combination therapy for vascular protection: beating the odds

1. A to E:
   - ASA
   - A1C (goal < 7)
     Metformin is first-line drug. If needed to achieve goal second-line agent could be any one of the following:
     - Secretagogue (gliclazide MR once daily preferred because less hypoglycemia, repaglinide before meals three times a day and at bedtime as needed)
     - Dipeptidyl peptidase 4 inhibitor (DPP4I) (sitagliptin once daily)
     - Sensitiser (pioglitazone or rosiglitazone, once daily)
     - α-glucosidase inhibitors (acarbose before meals three times a day)
     - Insulin may be considered at any time (analogue preferred)
   - BP (goal < 130/80):
     ACE or ARB flirst-line, +/- thiazide, calcium channel blocker, renin inhibitor, β-blocker
   - Cholesterol (goals LDL < 2; risk ratio < 4):
     Statin +/- cholesterol absorption inhibitor, niacin, fibrate
   - Diet: high fibre, low fat, fish, nuts, fruit, vegetables
   - Exercise: prioritize. Walk (or equivalent) 30+ mins/day
2. "The longevity cocktail" in Type 2 diabetes—consider it the default (metformin, ASA, ACE/ARB, statin)
3. Do not smoke

especially alarming since most diabetes care is in fact carried out by the patients themselves.

New trials/new evidence

Since most people with diabetes will die prematurely from macrovascular disease (*i.e.*, CVD), a key goal of management to reduce that risk is vascular protection.[1] While strict glucose control (A1C < 7) has a proven benefit in reducing microvascular disease (retinopathy and nephropathy), the role of glucose in macrovascular disease remains unclear. Recent trials suggest that tight glucose control later in the disease provides no CV benefit and may actually increase mortality.[2-4] Tight glucose control earlier in the disease, even if only for a limited period of time, does appear to reduce long-term CV risk.[5,6]

Powerful evidence supports multifactorial intervention using multiple drugs (especially metformin, ASA, ACE inhibitor, statin) and LSM. In a group of high-risk patients (defined by presence of microalbuminuria), long-term outcomes were dramatic, with a 20% ARR in all cause mortality and 29% in CV events.[7] Of note, the average A1C achieved in the intensive treatment group was reduced from 8.4 to a very modest 7.9.

New drugs

Dipeptidyl peptidase 4 (DPP4) inhibitors are agents which inhibit the enzymatic breakdown of neuropeptide hormones secreted in the gut in response to ingested food. These hormones, called incretins, stimulate insulin and inhibit glucagon secretion, as well as delay gastric emptying. Native incretins (glucagon-like peptide [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]) are rapidly inactivated by the enzyme DPP4. Inhibitors of this enzyme allow for a more prolonged incretin effect. Sitagliptin,

the DPP4 inhibitor available in Canada, is likely best used early in the natural history of diabetes. Specific advantages of this drug are the lack of hypoglycemia and the lack of weight gain. It may also prolong β-cell survival.

New guidelines

CVD is the number one killer and clearly merits priority hence the most significant changes in the 2008 Canadian Diabetes Association (CDA) guidelines emphasize screening for and managing macrovascular disease (in contrast to the 2003 Clinical Practice Guidelines where emphasis was on microvascular disease). Vascular protection remains paramount.[1]

For glycemic control, metformin remains unequivocally the first-line oral agent. A second drug should be added within two to three months if the A1C remains above goal. A notable change in the guidelines relates to second-line agents—all are now given equal merit. Because of a reduced risk of hypoglycemia, the sulfonylurea of choice is gliclazide MR. Another contender for second-line choice is the DPP4 inhibitor, sitagliptin, with significant benefits of no hypoglycemia and no weight gain. Because of weight gain, fluid retention, congestive heart failure (CHF), osteoporosis and in the case of rosiglitazone, uncertainty regarding its CV safety, glitazones are no longer a "preferred" second-line drug. Two weeks after the CDA guidelines were published, a statement from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) indicated that rosiglitazone, on account of CV safety concerns, was "no longer recommended."

Insulin (usually added to oral agents) is recommended at any point in the management algorithm, with a strong endorsement that it be used sooner rather than later.

Roger's case cont'd...

Risk factors

- > 45-years-old
- Positive family history
- Microvascular disease: nephropathy, neuropathy and early retinopathy
- Smoking + diabetes = disaster
- ED: now considered an indicator of more generalized vascular damage, including likely coronary artery disease
- Increased A1C, BP, LDL, GFR, ACR

Priorities

- Vascular protection is paramount. Inform and involve the patient and review his "ABC goals." Explain the rationale for "multifactorial intervention" and why polypharmacy is essential. Lifestyle modification in terms of diet and physical activity is critical. Encourage the patient to prioritize time for at least 30 mins daily physical activity
- The physician must practice both the Art and Science of medicine. He must convince with conviction
- An early referral should be made to the Diabetes Education Centre

Medications

- The default: metformin, ASA, ACE, statin. May combine metformin with either analogue basal insulin, or DPP4I or gliclazide MR or TZD
- Low dose ASA
- ACE or ARB (do NOT combine): titrate to maximum dose because of increased ACR (monitor eGFR and potassium)
- Statin: titrate to get LDL-C < 2, RR < 4; consider use of most efficacious statin, rosuvastatin (also increases HDL-C)

New approaches to diabetes management

It is clear from several studies that, despite effective medications, many people with diabetes fail to achieve treatment goals.[8] CV risk remains very high,[9] likely in part because of a persisting glucocentric approach to the management of diabetes where an emphasis on glucose

Take-home message

- Why do diabetics die 10-15 years earlier than their peers?
  Accelerated atherosclerosis.
- Why do 80% die from preventable CVD?
  Inadequately treated risk factors.
- Why do high-risk patients not attain lipid targets, BP targets, glucose targets?
  Patient: unaware/unconvinced of benefit, poor adherence, side-effects, cost.
  Physician: unaware/unconvinced of benefit, failure to titrate meds, "clinical inertia."
- Which target is the most important?
  Lipids.
- Which is the easiest?
  Lipids.
- Which is the most difficult?
  Glucose.

control appears to be at the expense of lipids and BP.[10] There seems to be a widespread perception that glucose is the priority for vascular protection. However, the evidence is compelling that lipids are the most important modifiable risk factor for CVD[11] and yet often are inadequately treated through failure to intensify therapy.[10] For macrovascular protection, the evidence, efficacy, ease of use, safety and cost all clearly favour the use of a statin as the number one priority. It is critical however to address all risk factors. This necessitates polypharmacy, which is challenging for both patient and physician. If a physician is not convinced of benefit, then it is very unlikely his patients will be. A physician must convince with conviction. The message must be loud and clear to both physicians and patients that comprehensive vascular protection in diabetes is critical and involves aggressive management of risk factors other than glucose.

Dr. Farquhar is a Family Practitioner; and Medical Advisor to the Central Okanagan Diabetes Program, Kelowna, British Columbia.

For most people with Type 2 diabetes, the "longevity cocktail" should be the default—metformin, ASA, ACE inhibitor, statin. It would be difficult to identify those individuals who would not benefit from such a cocktail.

Conclusion

Most people with Type 2 diabetes are at high risk for a CV event. At diagnosis, the clock is already ticking. Practicing evidence-based "diabetic medicine," FPs have a unique opportunity to save lives. Dx

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Useful web pages:
http://diabetes.ca/
http://www.medscape.com/diabetes-endocrinology
http://www.theheart.org/
http://www.medpagetoday.com/