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CLINICAL PRACTICE UPDATE IN
ENDOCRINOLOGY & DIABETES

Clinical Controversies in Diabetes | Toronto 2011

LMC

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CONTROVERSIES FROM THE ENDOCRINOLOGIST
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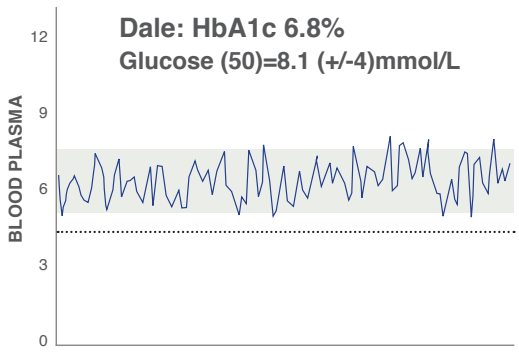
Dr. Stuart Ross started off the event by outlining

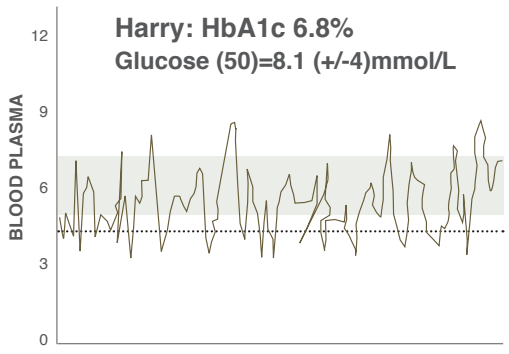
2 typical patients– seemingly achieving identical glycemic control

by traditional measures



- 47 year old
- Type 1 since age 24, pump
- A1c 6.8%
- Mild microalbuminuria, background retinopathy

DALE



- 45 year old
- Type 1 since age 21 - MDI therapy
- A1c 6.8%
- Mild microalbuminuria, background retinopathy

HARRY

- Both patients are well and appear to be achieving our current recommended target A1c of 7%.
- Do they have the same risk for further complications?
- Is there any evidence that glycemic variability can contribute to diabetes-related complications?

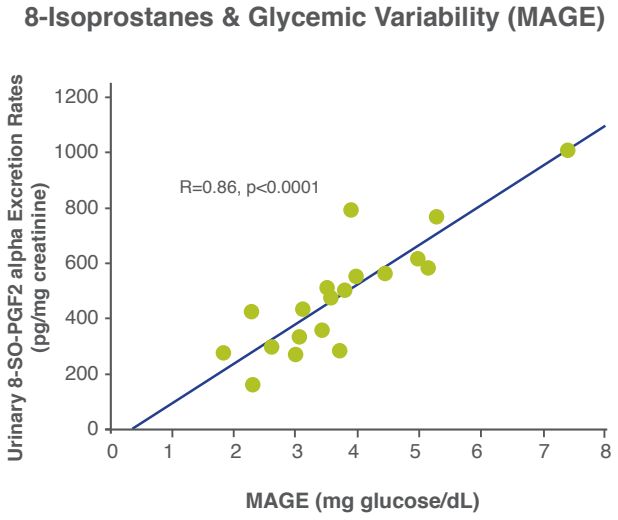
Dr. Ross summarized a growing position –

> “Diabetes complications may not be entirely related to markers of average control, like HbA1c; there is also a likely association with the cumulative variability of blood glucose – the hyperglycemic spikes and the hypoglycemic falls”

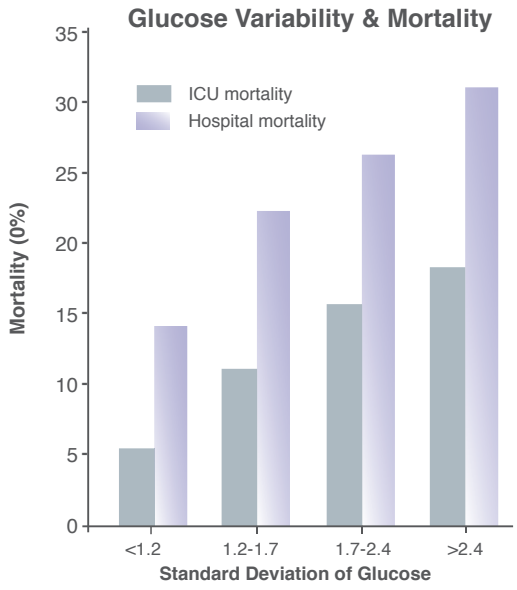
GLYCEMIC VARIABILITY CAN BE MEASURED IN SEVERAL VALID WAYS:

A. Standard deviation in a series of glucose measurements
B. MAGE - measure of glucose variability (available on continuous glucose monitoring devices)
C. Mean of daily differences (MODD)
D. AUC - area above and below the target glucose levels of a glycemia plot over time

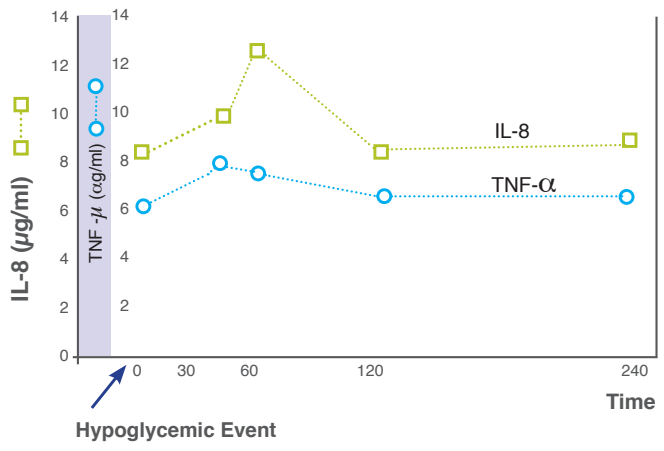
SUGGESTIVE FINDINGS IN ONGOING RESEARCH:



Markers of oxidative stress - Isoprostanes - correlate highly with MAGE, a measure of glycemic variability.



In both hospital and ICU settings, variability of glucose is more predictive of mortality than the average glucose.



Hypoglycemia & Variability

contributes to glycemic variability and possibly to long-term complications through inflammatory mediators which persist for hours after the hypoglycemic event itself.

CHECK YOURSELF

Finally, Dr. Ross reviewed the practical approaches to reducing glycemic variability, especially post-prandially:

A. Adjust Harry's fast-acting insulins to better control post-prandial glucose
B. Improve dietary consistency
C. Modify basal insulin
D. Consider compliance with the prescribed insulin profile

This clinical challenge is being investigated currently by the NIH in the FLAT SUGAR study, using a GLP-1 therapy to minimize post-prandial glycemic swings.

CONTROVERSIES FROM THE CARDIOLOGIST

Milan Gupta MD, FRCPC
- Division of Cardiology
- Brampton Civic Hospital
- McMaster University

CASE STUDY:

- 50 year old man
- Type 2 DM, hypertension, non-smoker
- No CV history, no retinopathy
- Sedentary, asymptomatic
- Atorvastatin 40 mg OD, Metformin 1 gm bid, Perindopril 8 mg OD
- BP 140/80 BMI 28.5
- HbA1c 0.068, LDL-C 1.7 mmol/L, TG 3.0 mmol/L, HDL-C 0.87 mmol/L,
- uACR 12

The case provided the opportunity to review the typical comprehensive CV prevention approach required in most patients with diabetes - lipids, glycemic control, BP management and anti-platelet therapy are all factors to be considered. This patient's triglycerides are elevated, his HDL is low and he has microalbuminuria. His Total/HDL ratio is 5.

CHECK YOURSELF

What additional lipid drug therapy would you recommend?

A. Increase his current statin dose to 80 mg OD
B. Change to rosuvastatin 40 mg OD
C. Add a fenofibrate
D. Add niacin
E. Add ezetimibe
F. Nothing

Dr. Gupta concluded that there is no right answer. More statin effect would drive down LDL-C, which is already < 2. It might improve his Total/HDL ratio and possibly provide some additional minimal TG-lowering.

Dr. Gupta referred to the 2009 lipid management guidelines, endorsed by the Canadian Cardiovascular Society (CCS). The current primary target in Canada is LDL-C. The 2006 Canadian lipid management guidelines had a primary target of LDL-C and one secondary target, Total/HDL ratio. The 2003 guidelines had three targets, the third being triglycerides. This pattern of decreasing targets over this past decade represents our understanding from a growing evidence base, that only LDL-C change is associated with improved outcomes. Once LDL-C is at target, Dr. Gupta pointed out, no additional lipid-lowering therapy has been able to change CV outcome.

The current developing consensus then is that in patients with ideal LDL-C, further measures should be taken only for high-risk patients. Young, healthy, low-risk patients starting on combination therapy for secondary lipid targets is not ideal, as there is no evidence of benefit.

Fenofibrate

was studied in ACCORD, which Dr. Gupta reviewed, where patients were treated with a statin to a reasonable LDL, followed by addition of fibrate or placebo. No benefit on CV endpoints or mortality was found.

Ezetimibe

has been studied in various populations, the most recent, and only positive trial, is SHARP. The definitive outcome trial of ezetimibe is the ongoing "IMPROVE-IT", in which 25,000 simvastatin-treated, post-ACS patients are randomized to ezetimibe or placebo.

Niacin

certainly has positive effects in diabetic dyslipidemia, especially. AIM-HIGH was the NIH-funded endpoint trial based on the HATS trial, which had shown a 90% reduction in events. Although the study may have been under-powered and poorly designed, it was stopped prematurely for futility. The only ongoing niacin study is Heart Protection Study (HPS2 THRIVE) comparing niacin, combined with an anti-flushing compound vs placebo.

Residual Risk (When LDL-C at target)
OPTIONAL Secondary Targets in High Risk Patients

Test	Cut-point	Intervention
TC/HDL-C	>4.0	• Niacin • Fibrate
Non HDL-C	>3.5 mmol/L	• Niacin • Fibrate
Apo B/AI	>0.8	• Niacin • Ezetimibe
Triglycerides	>1.7 mmol/L	• Fibrate • Niacin
hsCRP	>2.0 mg/L	• Statin • Ezetimibe

Two new **HDL-raising therapies** (CETP inhibitors) are being evaluated - Dalcetrapib (DAL-OUTCOMES trial) and Anacetrapib (REVEAL trial), together studying > 45,000 patients.

CHECK YOURSELF

What anti-platelet strategy would you recommend to reduce CV risk?

A. Nothing
B. ASA 81 mg od
C. ASA 325 mg od
D. Clopidogrel 75 mg od
E. Ticagrelor 90 mg bid
F. ASA 81 mg od plus clopidogrel 75 mg od

The answer is nothing. Dr. Gupta reviewed this year's CCS anti-platelet guidelines - in a patient with diabetes and no vascular disease, aspirin should not be used, although the guidelines allow some exceptions. In our patient, the presence of microalbuminuria would support aspirin use based on the continuing American Heart Association statement.

Two recent trials have added to a growing body of evidence that has consistently shown no provable CV outcome benefit, although trends have consistently been positive. JPAD, a peripheral arterial disease trial, showed a non-significant trend to benefit and POPADAD, a study of patients with diabetes and PAD, found no benefit at all in either coronary death or stroke death.

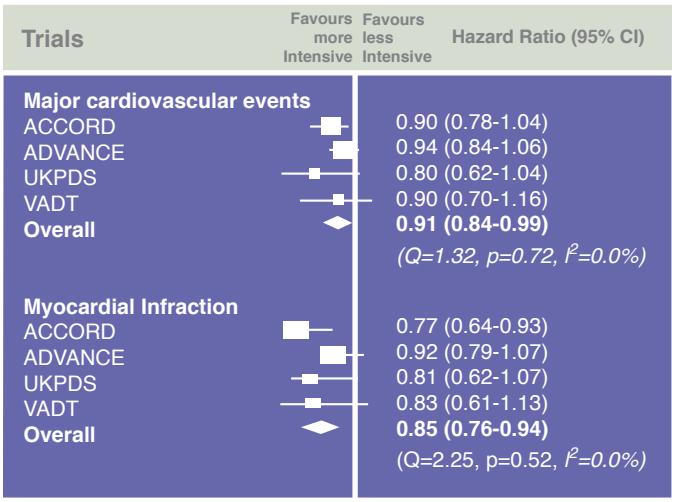
CHECK YOURSELF

If the patient's A1c had been 7.6%, despite maximal dose metformin, Dr. Gupta led a debate on the optimal next add-on therapy.

Options:
A. Nothing
B. Glyburide
C. Diamicron MR
D. Sitagliptin
E. Saxagliptin
F. Pioglitazone
G. Liraglutide
H. Insulin

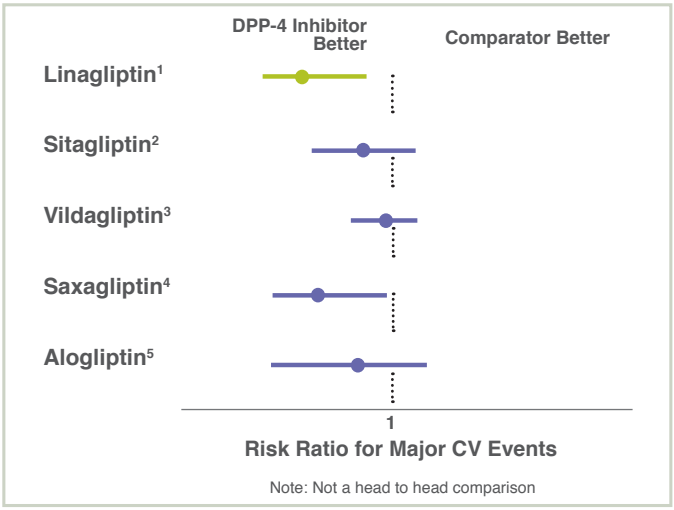
The CONTROL Group meta-analysis shows that further improving glucose control reduces MACE events by 9% and MI itself by 15%. Stroke, heart failure and overall mortality are not affected.

Intensive Glucose Control and CV Outcomes in Type 2DM



Dr. Gupta pointed out that, of the newer Oral Anti-Diabetes (OAD) therapies, incretin therapies may have beneficial effects on the vasculature – shown to improve LV systolic function and endothelial function. A recent series of meta-analyses suggests that DPP4 inhibitors may actually reduce cardiovascular events. Though these trials were not designed with CV event goal, six ongoing CV trials will properly investigate CV outcomes - three DDP4 inhibitors and three with GLP-1 agonists.

DPP-4 Inhibitors & CV Risk



Note: Not a head to head comparison

> "A recent series of meta-analyses suggests that DPP4 inhibitors may actually reduce cardiovascular events."

CONTROVERSIES FROM THE NEPHROLOGIST

Phil McFarlane MD, PHD, FRCPC
- Division of Nephrology
- St. Michael's Hospital
- University of Toronto

CASE STUDY:

- 62 year old woman with type 2 diabetes for six years
- No previous vascular events
- History of hypertension for ten years
- Osteoarthritis of the spine and osteoporosis
- LDL and A1c are at target
- Creatinine is 94 and has been stable over the last year
- Urinary ACR has been elevated on multiple tests fluctuating in the 5 – 15 range
- Physical examination is unremarkable other than BP of 138/78

Medications:

- Metformin 1g bid
- Sitagliptin 100 mg OD
- Atorvastatin 20 mg OD
- Alendronate 70 mg weekly
- Ibuprofen prn

CHECK YOURSELF

How would you characterize her blood pressure?

A. Her blood pressure is at target
B. She has combined systolic and diastolic hypertension
C. She has isolated systolic hypertension
D. She has isolated diastolic hypertension
E. An assessment of her blood pressure cannot be made at this time.

Our current guidelines continue to recommend a BP target < 130/80 for people with diabetes. The patient's blood pressure was approximately 138 so it appears that she has isolated systolic hypertension.

Dr. McFarlane reviewed the value and meaning of a reported BP measurement. There are many different ways to measure blood pressure - ambulatory BP monitors, home BP monitors, office BP True-type devices and manual office BP measurements. All produce different results – which is most accurate? Dr. McFarlane reframed the question to ask – instead of "most accurate" which is "most predictive" of CV and renal risks for the patient.

24-hour ambulatory monitor can be challenging to access. The least predictive is actually the causal office blood pressure, which correlates very poorly with future CV events. Home BP monitors correlate very well with a daytime component of a 24-hour ambulatory blood pressure monitor and correlate very well with future CV risk. BP True type devices also correlate well with the daytime component of a 24 hour ambulatory blood pressure monitor and more closely reflects the out-of-office BP, since it is done repetitively and unattended without a physician.

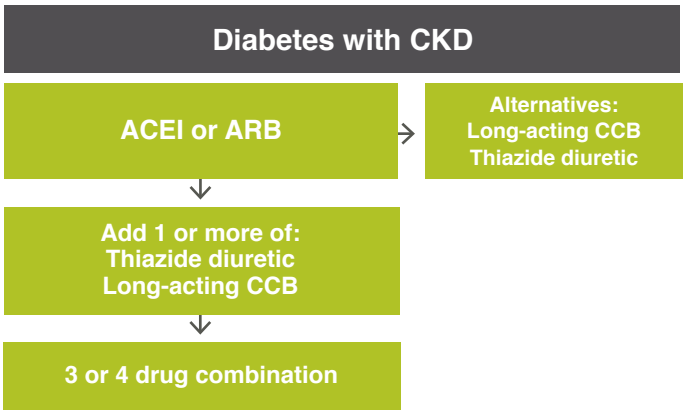
Since the office BP is the one method that does not correlate well, home BP monitoring is recommended. The newer monitors are accurate and models with memory are ideal to avoid depending on the patient's self-report. The patient should have an appropriate cuff size that is not too small, and the patient needs to be trained on how to use it appropriately.

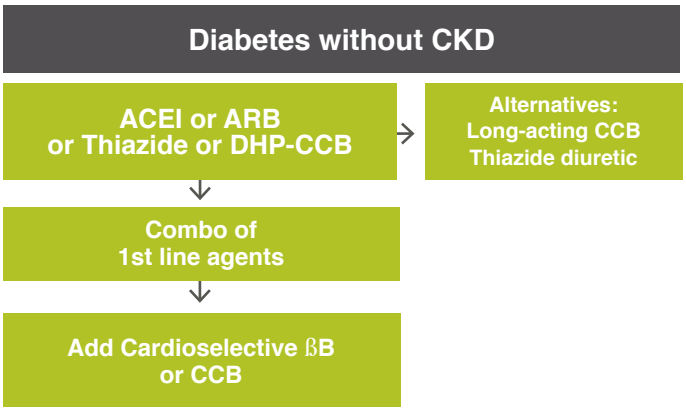
CHECK YOURSELF

If the diagnosis of hypertension is made, what would be the first line antihypertensive medication that you would prescribe?

A. An ARB
B. An ACEi
C. A DRI
D. A CCB
E. A thiazide-type diuretic

The CHEP-CDA joint guidelines on hypertension suggest an ACE-inhibitor or ARB for first-line therapy if the patient has chronic kidney disease (CKD). There are also a few choices of anti-hypertensives for patients who do not have CKD, however ACE and ARB are preferable as they may prevent kidney disease.





CHECK YOURSELF

With regards to the status of her kidneys, she likely has:

A. No renal disease
B. Diabetic nephropathy
C. A renal disease other than diabetic nephropathy
D. I need more information before I can decide.

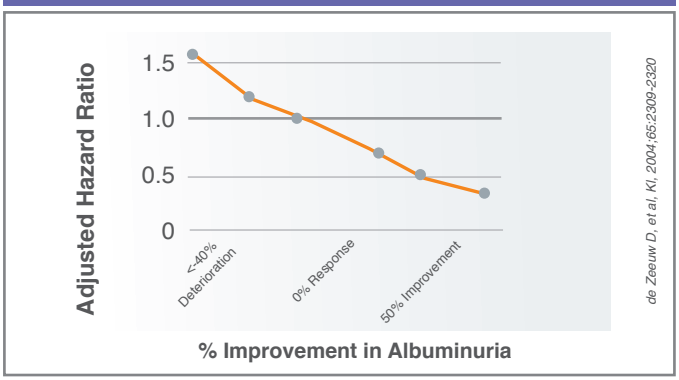
The patient in the example has a creatinine of 98. She is in her 60s and should have a creatinine more in the 60 or 55 range, so 98 is elevated. She also has persistent microalbuminuria, which is one of the earliest signs of diabetic nephropathy.

Dr. McFarlane reviewed the typical course of diabetic nephropathy - normal to microalbuminuria, progressing to overt nephropathy that can be picked up easily with a simple urine dip stick; and then eventually with declining renal function and towards end stage renal disease. Through the early phases of diabetic nephropathy, the rate of loss of GFR is relatively slow - ~1-2ml/minute per year; or roughly 1-2% of kidney function per year, as compared to the general population, which loses between .25 - .5 ml/minute per year. In overt nephropathy stage, the process accelerates and yearly GFR loss increases to 5-10 ml/minute, or about 10% of their kidney function a year. The patient has microalbuminuria, a depressed GFR, but is still in the normal range. The etiology is likely diabetic nephropathy.

	DM Nephropathy	Other Renal DX
Level of Proteinuria	Persistent albuminuria	Extreme proteinuria (> 6 g/day)
Progression of Renal Disease	Slow	Rapid
ACR vs eGFR	Low eGFR associated with high ACR	Low eGFR and low ACR
Known Duration of DM	> 5 years	> 5 years

Microscopic hematuria is rare in diabetic nephropathy, affecting only 1 person in 20. Similarly, patients with diabetic nephropathy can have full-blown nephrotic syndrome, with gross proteinuria, anasarca, and low serum albumin, but it is extremely rare. If the disease severity seems to be progressing more rapidly than expected, or if their diabetes duration was too short for the degree of kidney disease, should have a kidney biopsy in order to exclude other renal disease.

Improvement in Proteinuria Predicts ESRD



Dr. McFarlane reviewed the ACCOMPLISH study, in which high-risk and CAD patients, benefitted significantly more from addition of CCB over HCTZ. Although there was a small blood pressure advantage for the CCB, it was not enough to explain these very large differences in important clinical outcomes. Beta-blockade is not on the list because it would have little to add as a 3rd or 4th drug. Vasodilatation is already accomplished by the CCB and the adrenergic stimulus for renin effect is already addressed by the ACEi. The small further benefit of BP-lowering from the reduced heart rate is minimal. Finally, ACEi-ARB combinations are not favoured following the ON-TARGET study which showed a higher rate of adverse effect with combined therapy, and no additional benefit over each medication alone. The ON-TARGET population may not generalize to all of our patients, and adverse effects were likely limited to those vulnerable to volume depletion events, but with other options available, the combination is now typically avoided.

CHECK YOURSELF

Assume that the patient is placed on an ACEi, and titrate to the full treatment dose. If her blood pressure remained above target, which drug would you add next?

A. A CCB
B. A thiazide-type diuretic
C. An ARB
D. A Direct Renin Inhibitor (DRI)
E. I need more information before I can decide.

Dihydropyridine CCBs are preferred as second line therapy over HCTZ. A RAAS blocker, a CCB, and a thiazide diuretic represent synergistic combinations of medications.

CHECK YOURSELF

Her BP is not under acceptable control on an ACEi, CCB, thiazide-type combination. Over the subsequent two years, her degree of albuminuria has slowly increased, so that her urinary ACR now runs in the 30 to 50 range. How does albuminuria change your perception her kidney status?

A. Escalating albuminuria makes me less worried about her kidneys.
B. I already diagnosed her as having kidney disease. Escalating albuminuria does not change my perception of her kidney status.
C. Escalating albuminuria make me a lot more concerned about her kidneys.

The large nephrology trials, such as IDNT and RENAL, found that when patients' albuminuria progressed, despite their assigned therapies, they had a much accelerated risk of progression to ESRD.

Supported by educational grants from members of the pharmaceutical industry.