Type 2 Diabetes (T2DM)
Update & Focus on Insulin Management Issues

October 2008

Recent Guidelines:
- Canadian: Sept 2008[1] http://www.diabetes.ca/for-professionals/resources/2008-cpg/
- American (ADA): Jan 2008 [2] http://care.diabetesjournals.org/content/vol31/Supplement_1/; Oct 2008 Update 28, http://care.diabetesjournals.org/misc/MedicalManagementofHyperglycemia.pdf
- NICE (UK): May 2008 [3] http://www.nice.org.uk/nicemedia/pdf/CG66diabetesfullguideline.pdf ; CKS (NHS): http://www.cks.library.nhs.uk/diabetes_type_2

Systematic Reviews:
- COMPUS: Insulin Analogues[4] http://cadth.ca/index.php/en/compus/current-topics/-dm1 **Also CMAJ Feb09** [29,30,31]
- Long-acting vs NPH in T2DM Cochrane Apr 2007[5] http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005613/frame.html
- Long-acting vs Intermediate in T1DM Cochrane Jul 2008[6] http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006297/frame.html
- Rapid Acting vs Regular in DM Cochrane Apr 2006[7] http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003287/frame.html

Review Articles:
- Tibaldi: Insulin in T2DM Am J Med [8]
- Hirsch: Insulin Analogues NEJM [9]
- Drugs for T2DM; Medical Letter – Treatment Guidelines Jul 2008[10]

Screening tools:
http://www.diabetes.ca/

Patient Resources:
http://www.diabetes.ca/section_about/index.asp

Highlights:
1) Individualize glycemic control targets considering patient and intervention factors.
2) Use metformin first-line as monotherapy and maintain in combination therapies, including with insulin, unless contraindicated.
3) Discuss insulin early on to gain patient buy-in for when it may be needed.
4) To make starting insulin safer & easier, use a low dose of a basal insulin at bedtime (e.g. NPH/N 5-10 units).
5) Newer long-acting insulin analogues may be considered over NPH/N if hypoglycemia, (especially nocturnal) is a problem.

RxFiles Diabetes Charts:
1) Approach T2DM/Hypoglycemics [11]
2) Insulin Comparison [12]
3) Insulin Management [13]
4) Landmark Diabetes Trials [14]
5) Insulin Devices / Pens [12 b]

see **www.RxFiles.ca**

T2DM: Treatment of Hyperglycemia

- **Individualize Targets**: Intensive treatment of hyperglycemia predominantly results in reduced microvascular complications.[15, 16] Two large RCTs have found that more-intensive lowering of plasma glucose (PG) does not reduce CV events, and may be associated with increased risk of major hypoglycemia & all-cause death in some patients (ACCORD[17], ADVANCE[18]). Thus, targets for glucose control need to be individualized taking into account both patient and intervention factors (e.g. weight, CV risk, age, # of drugs required, hypoglycemia).[1] {See Landmark Trials chart, pg 28 [14]}.

Table 1: Recommended glycemic control targets [1] Adult

A1C %	FPG mmol/L	2hr-PPG mmol/L
≤ 7*	4-7	5-10 (or 5-8**)
{Individualize targets! Allow 6-12 months to reach target A1C.}		

FPG=fasting plasma glucose (or preprandial plasma glucose)
PPG=postprandial plasma glucose PG= plasma glucose
*a target of ≤6.5% may be considered in some T2DM patients to lower risk of nephropathy, but this must be balanced against the risk of hypoglycemia & ↑ mortality in high CV risk patients
** consider a PPG target of 5 - 8 if A1C targets not being met

- **Multifactorial intervention key:** Lifestyle changes, **antihypertensives, statins, ASA** and hypoglycemics are important for reducing cardiovascular endpoints. STENO-2 [19]
- **Metformin (MF):** MF is recommended as the initial agent in most patients[1,28] due to its effectiveness in:
  - reducing all cause mortality (in obese) UKPDS-34 [20]
  - lowering PG without weight gain and with a relatively mild side effect profile. FINFAT [20,21]
- **Stepping up from Metformin; Orals or Insulin:**
  - Other hypoglycemics or insulin may be needed for marked hyperglycemia or achieving targets.
  - The optimal 2nd agent will depend on the pattern of hyperglycemia, plus patient and safety factors {e.g. HF, renal failure, pre- vs post-prandial, hypoglycemia, SE, cost}.
  - **Consider early initiation of insulin** especially if A1C ≥9%, metabolic decompensation or poor PG control. {See Approach to Type 2 DM chart, pg 24.[11]}
  - Avoid using insulin as a "threat". It will eventually be needed in many T2DM patients.
- **Current Uncertainties**:
  - Benefits vs risks of tighter PG or A1C control. [22,23]
  - TZDs especially rosiglitazone: potential adverse CV outcomes.[24]
  - Role of sitagliptin JANUVIA ✗⊗ new incretin; good PPG control & weight neutral, but lack outcome & safety data.[1,28]

{See related Trial Summaries and Q&As at RxFiles.ca}

Approach to Initiation of Insulin in T2DM
{adapted from Knowledge Support Service, CEP, Toronto.[25]}

What is the best initial regimen to use in T2DM?
- Consider bedtime insulin (NPH/N, glargine or detemir) as it is effective, convenient, and relatively easy to accept and initiate compared to multiple daily doses. [26]
- A common starting dose is 5-10 units at hs. Increase dose gradually (e.g. 2 units q 2-3 days) till @ target. {See Insulin Management Chart: Initiating Insulin, pg 27-b [13]}
- Daytime oral hypoglycemics, especially metformin, should often be continued to optimize management (minimizes insulin dose and weight gain).

Should I use NPH/N, glargine or detemir?
- There are no clinically important differences on A1C.[4,5,27]
- Glargine and detemir cause somewhat less hypoglycemia but are more costly than NPH. (See Table 3).[4,5]
- Differences in weight gain are summarized in Table 3. They are small (<1kg) and of uncertain significance.
- The COMPUS clinical & economic review [4,29,30,31] concluded NPH was a preferred initial agent whereas Canadian Guidelines[1] note "long acting analogues may be considered instead of NPH to reduce the risk of nocturnal and symptomatic hypoglycemia."

What about more intensive insulin in T2DM?
- A more intensive insulin regimen will sometimes be necessary. Such regimens achieve better glycemic control at the expense of weight gain, hypoglycemia and regimen complexity. It is easier to use such regimens after patients are comfortable with insulin and the associated monitoring. A short acting (regular) or rapid acting insulin (lispro or aspart) ☎▼ given around meals will allow tighter glucose control. Premixed insulin BID may be useful in some patients. {See Insulin Charts, pg 26-a & 26-b for more information.[12,13]}

Table 2: Starting Insulin; tips for patient buy-in [25]
- Discuss insulin early to change negative insulin perceptions
- Provide information pertaining to insulin benefits
- Consider suggesting a "trial" for 1 month
- Discuss the relative ease of using the newer insulin devices (e.g. insulin pens; smaller needle) compared to syringe/vial
- Link patient to community support such as a Certified Diabetes Educator (CDE) for education on injections & monitoring
- Ensure patient has time to get comfortable with loading and working a pen (or syringe)
- Refer patient for nutrition & physical activity counseling

Table 3: Systematic Review of Insulin Trials: Basal Insulin + Oral Agents in Adults with T2DM [4,5]

	Glargine LANTUS ✗⊗ vs NPH / N	Detemir LEVEMIR ✗⊗ vs NPH / N
A1C% (No clinically important differences.)	Not significant (-0.05% CI: -0.13-0.04) {9 trials; n=3397}	Slight ↑ by detemir (0.13% CI: 0.03-0.22) {3 trials; n=1159}
Hypoglycemia, Nocturnal	Less with glargine: Risk ratio: 0.56 (CI: 0.47-0.68) {7 trials; n=2866; Estimated NNT=7 CI: 6-9; over 4wk-1yr; baseline risk 33%} {No significant difference in Severe (Risk ratio: 0.66 CI: 0.29-1.48)}	Less with detemir: Risk ratio: 0.53 (CI:0.31-0.91) {2 trials; n=808; Estimated NNT=6 CI: 4-33; over 20-24wks; baseline risk 33%} {No significant difference in Severe (Risk ratio: 0.75 CI: 0.03-20.01)}
Weight Change	Not significant; (glargine ↑ wt by 0.18kg CI: -0.11 to 0.47, 7 trials)	Detemir ↓ wt by 0.96kg (CI: -1.69 to -0.23, 3 trials)
Cost 15ml/month	Glargine: $105; NPH/N: $50 {5x3ml cartridges}	Detemir: $135; NPH/N: $50 {5x3ml cartridges}
Other	Once daily dosing	Some patients will require twice daily dosing*

*If BID needed, dose required ↑ 2x & wt gain advantage lost vs daily glargine.[27] {See also Insulin Management IAs: Guide to Advantages/Disadvantages, pg 26-b.[13]}

Overview of the RxFiles Diabetes Charts – Oct 2008

{Pages 24-28 of the RxFiles Drug Comparison Charts 7th Edition Book (Oct08)}

Page	Chart Title & Contents	Highlights
24	**Approach to Management of T2DM in Adults** • Approach … • Individual: Special Considerations Table 6 • Combination Therapies Table 7	◆ Start Metformin (MF) low dose (250 or 500mg once daily) & titrate … ◆ Metformin dose adjustment for ↓ renal fx (30-60ml/min) {recent guidelines noted option of using MF lower than official monograph.} ◆ More cautious approach to "targets" and dosing in the elderly ◆ Options for post-prandial glucose control Table 6
25	**Oral Hypoglycemics**	◆ Glyburide: consider use in lower end of dosage range (2.5-7.5mg BID) ◆ Repaglinide *Gluconorm*: short-acting & allows flexibility for meal intake ◆ PPG: limited observational data suggests predictor of CV disease
26-a	**Insulin Comparison Chart**	◆ Comparison of various insulin regimens (daily, BID, TID+/- HS) & cost ◆ Premixed: suitable for some (e.g. less-intensive, institutionalized)
26-b	**Insulin Management: Evidence, Tips & Pearls** • Administering & Mixing Insulin • Variables Affecting Insulin Action • Canadian Guideline Notes • Insulin Analogues: Systematic Reviews ⇨Guide to Advantages & Disadvantages ⇨Selection Considerations	◆ Abdomen provides most consistent & rapid site for absorption ◆ Rapid acting insulins: may be taken just before or within 20 minutes of starting a meal; flexibility advantage useful e.g. in adolescents ◆ Some T2DM detemir patients will require BID; dose & wt implications ◆ Economic considerations for new insulin analogues (various scenarios ranging from cost-effective to estimated cost per QALY of > $642,000)
27-a	• Monitoring • Hypoglycemia: Signs & Treatment	◆ Paired meal testing: reflects pattern of PG control without ↑ testing ◆ Role & dose of glucose tablets and glucagon kits for hypoglycemia
27-b	• Initiating Insulin & Switching Insulins • Tips for Insulin Dose Adjustment • Travel Through Time Zones • Sick Day & Pre-Procedure Considerations • Pregnancy & Pre-existing & Gestational	◆ Options for titrating insulin in both T2DM & T1DM. ◆ Considerations & cautions with sulfonylureas & TZDs with insulin ◆ Switching from NPH BID to glargine or detemir OD: ↓ dose to 80% ◆ Assessing Somogyi effect & Dawn phenomena. ◆ Sliding scale insulin generally discouraged in favor of … ◆ Considerations for patient not eating due to sickness or pre-procedure ◆ Pregnancy: caution especially with glargine; role for po glyburide & MF
28	**Diabetes – Glucose Control:** ⇨Landmark Outcome Trials ⇨T2DM Prevention Trials	◆ Metformin has RCT evidence for ↓ all cause mortality (in obese) ◆ Intensive glycemic control: weighing the benefit with the risk in trials ◆ Weight loss 5-7% & activity 30min/day beneficial in preventing T2DM

☎=EDS Sask ✆=prior NIHB ✗ =not Sask ⊗=not NIHB CV=cardiovascular FPG=fasting plasma glucose HF=heart failure MF=metformin PG=plasma glucose PPG=posprandial plasma glucose wt=weight

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