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* [8⊗] 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) [% t] 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 [8⊗] vs NPH / N	Detemir LEVEMIR [8⊗] 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 **8**=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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INSULIN Comparison Chart

1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19; CDN Guidelines Sept 2008; ADA Oct2008

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Type of Insulin [generally 100 unit/mL] avail. OTC ("clear" = solution appears clear)	Form 100u/ml	Source, Given	Onset (variable)	Peak (variable)	Duration (hrs)	~$/ 15ml
Bolus / Prandial						
Rapid acting {give just before or within 20min of starting meal}	{clear}	Recombinant DNA tech analog -SC,IV,IM	10-15 min	60-90 min	3.5 – 6h	52V 67c 81P
Insulin lispro **Humalog** %t B	v, c, p 8 t		◆↓ variability between sites, flexible, less need for snacks ◆less early night hypoglycemia than reg. ◆better control of postprandial glucose (PPG) ◆1 unit is equal to ~ 10-15g of carbohydrate VARIABLE!			54V 70c
Insulin aspart **NovoRapid** %t B	v, c					
Insulin glulisine **Apidra** 8⊗ *New*	v,p	(Aspart & glulisine SC only)	10-30 min	60min	≤5h	48V 62P
Short-acting / Regular Insulin	{clear}	Recombinant DNA tech. Human -SC,IV,IM	0.5 – 1h	2 – 3h	~ 6.5hr 5 – 10h	40V 51c
Humulin R B	v, c		Note: For **very large doses, a special 500 U/ml** Humulin R is avail. via Special Access Program			41V 52c
Novolin ge Toronto B	v, c					
Hypurin II R (rarely used!)	v⊗	Pork-SC,IV,IM				160V
Basal						
Intermediate-acting or NPH B	v, c, p 8 t	Recombinnt DNA tech. Human -SC	2 – 4h	4 – 10h	12 – 18h (range 12-24)	40V 50c
Humulin N	v, c		◆**Human analog insulins** generally shorter acting than Beef/Pork insulins. ◆**Beef** insulin no longer in Canada; available from the UK through Health Canada-Special Access Program at 613-941-2108.			41V 52c
Novolin ge NPH						
Hypurin NPH (rarely used!)	v⊗	Pork -SC				160V
Premixed *Humulin* 20/80 - Not available *(regular/intermediate)* *30/70*	c 8 t					40V
Novolin GE (10/90; 20/80) Plan D/C July 2007	v, c		Premix: May give 1, 2 or 3 times a day, but avoid giving at bedtime! May be useful if non-intensive regimen for T2DM patient with consistent lifestyle (bedridden/institutional/elderly). Premixed analogues: Similar control to premixed human insulin, & tighter BG control but ↑ hypoglycaemia than LAIA. Lack clinical outcome data. Ann Int Med 2008 #78 Administer: Humalog/NovMix just before meal; other premixes ~30min before meals.			51c
30/70	c					
40/60; 50/50	v, c					41V
Humalog Mix25 8&; Mix50 8⊗ lispro & lispro protamine	c					52c
NovoMix30 aspart 30%, aspart protamine 70% 8⊗	c,p	Recombinant DNA tech. Human -SC	0.5 – 1h	2-12h Dual Peak	14 – 18h (range 12-24)	52c 64c
	c					61c
Discontinued (DC'd) 2003: *Novolin ge Ultralente*, *Novolin ge Lente*; DC'd 2004: *Iletin II Lente* Pork; DC'd 2006: *Humulin L* , *Humulin U*						
Long-acting (LAIA) C	{clear}	Analog -SC	1h initial ~3.5 50% effect	6 - 8 h	16 - 24h if dose ≥0.4U/kg, duration longer with ↑ dose	135P
Insulin detemir neutral PH **Levemir** 8⊗ ◆ give daily or twice daily~20% of pts; {room temp: good 42days after open}	c		If switching from daily NPH, use ≤ same total daily dose; If switching from BID NPH to daily LAIA, use ~80% of total NPH daily dose; Start ≤10units if not previously on NPH			
Insulin glargine Lantus %& ?Type 1 ◆ **acidic PH→ some inj site pain; a bit more absorption variability than detemir** ◆ forms microprecipitates in sc tissue⇨slow release ◆ given once daily at HS (or in the morning); split dose if >50units ◆ prefilled disposable SoloStar pen max 80u/inj/Autopen max 42u/inj C	{clear} v, c, p 8⊗ vial: stable 28days	Analog -SC	>2 - 4h	No Peak	20 - 24h	105V 105c

Comments

See also *Insulin Management: Evidence, Tips & Pearls*

DOSING: (see Insulin Management chart)

Note re bolus admin: regular given 20-30min ac; rapid acting: give just before or within 20 min starting meal

Cost: Vial $; Cartridge $$↑30%; Humalog $$$; NovoRapid $$$; Hypurin/Detemir/Glargine $$$$ {vials good for ~28 days at room temp after opening}

MIXING:

- Compatabilities: Regular with all insulins; NPH with Regular; Lispro & Aspart with NPH if used immediately after mixing; {Glulisine, Glargine or detemir-do NOT mix per CPS}
- always draw up short-acting/R first to prevent contamination with longer acting
- inject mixtures immediately as alterations in formulation's pharmacodynamics occur dependent on concentration & elapsed time {If delayed, be consistent with mix to inj. Time}

{Novolin-Pen 4: for all Novolin products & Levemir; HumaPen Luxura for Humulin & Humalog}

HYPOGLYCEMIA: (see also Insulin Management Chart)

- **Symptoms**: Mild/moderate = sweating, tremor, tachycardia, hunger, lethargy, weakness Severe = confusion, disorientation, altered behavior/speech, seizures, coma
- **Incidence**: higher with intensive vs conventional; (in UKPDS risk of ANY hypoglycemic event/year: glyburide=21%; insulin=28% {1.8% severe}
- **Treat Mild**: 15g glucose tabs; orange juice ¾ cup, 3 sugar cubes, honey/syrup/sugar 1 tablepoonful, 9 jelly beans, 6 LifeSavers® (glucose/dextrose absorbed directly, don't require prior digestion) If **Severe** (e.g. unconscious) = 1mg lucagons IM/SC > $100/dose; or D50W 20-50mL IV
- **Prevention**: regular monitoring/exercise/↓↓ alcohol, balanced meals; adjust regimen

OTHER SIDE EFFECTS:

- **Weight ↑**: more with intensive vs conventional (4.6kg/5yrs DCCT 11,12); diet & exercise encouraged; less with detemir & ?glargine ◆**Lipodystrophy** – rotate sites within anatomical area

SC VARIABILITY:

- onset/peak/duration for SC insulins is **highly variable** between pts & even at different times for same pt; the longer acting the insulin, the greater the variability seen (e.g. +/- 15% with Reg; +/- 30% with NPH) not the case with detemir & glargine

SUPPLEMENT DOSING: rapid or short acting insulin used to correct hyperglycemia; conservative dose. Individual requirements will vary, somewhat according to total daily dose & response. Insulin to carbohydrate ratios used to guide bolus CSII & MDI. {Caution if <3 hrs since previous insulin, or planning exercise}.

Pregnancy: Category B. *Regular or Rapid* preferred. C (Caution): detemir, glargine & glulisine. Tight glucose control critical in the first 42 days of pregnancy organogenesis. Minimize hypoglycemia. Hyperglycemia: ↑ of macrosomia & pre-eclampsia. Neonatal hypoglycemia if maternal BG high before/during delivery. If antenatal steroids used in preterm labour ↑ insulin dose. Postnatal care: insulin dose ↓ after the birth.

INSULIN REGIMEN	SCHEDULE	COMMENT –treat to effect, no maximum dose for insulin
Conventional Regimens	OD insulin: N, D or G at HS (or rarely before breakfast)	Useful with daytime oral hypoglycemics in T2DM. Simple but poor control; <24hr coverage
RAIA = Lispro (ILis) **or Aspart** (IAsp) **R = Human Regular or Toronto N = NPH or N D = Detemir** (IDet)**; G = Glargine** (IGla)	BID insulin: N or D before breakfast & supper	Improved morning control & overnight coverage; no provision for meal coverage
	BID insulin: {also premixed options} { R or RAIA ac breakfast & supper **and** N (or D) ac breakfast & supper }	More common; better meal control (Or *breakfast & bedtime*; less hypoglycemia)
	TID insulin: { R or RAIA ac breakfast & supper **and** N ac breakfast & bedtime }	Most likely to last till next morning; (may substitute D or G for N)
Multidose Intensive Regimens (MDI) (≥40% of total insulin dosed as basal insulin; bolus/prandial dosing adjusted with meal/CHO)	R or RAIA TID ac; N or D ac supper or hs (or G in am or hs)	Good control, flexible regarding meals; demands frequent & consistent testing at start!
	Eg. Lispro/Aspart/Glulisine/R 4-8u tid ac & Glargine/Detemir/NPH 8-16u hs.	Breakfast 25% R & 45% N; Dinner 15% R; Bedtime 15% N. Based on total daily dose.
	R or RAIA TID ac; **&** N or D BID (ac breakfast & supper or bedtime)	Better suited for people with varying schedules; flexibility with regards to meals
Intensive Continuous SC Infusion (CSII)	R or RAIA; basal & boluses prn; rapid analogues preferred most flexible	More flexible, better control; ↑$ $5000+$250/mo; ↑ risk of rapid ketoacidosis, etc. if discontinued.
Insulin + Oral Hypoglycemics esp. if A1c>9% (in Type 2 Diabetes)	Common: N, G (or D) **at bedtime**, with **1-2 oral agents during day** See Approach to ...Diabetes & Insulin Management charts for dosing information, etc.	Less insulin required ~0.1u/kg eg. 5-10u & ↓weight gain than insulin alone (esp. with Metformin!) Tip: If ↑ PM blood sugar may need bid insulin regimen. If ↑ PPG may need short acting insulin with meals, (or premix).

- Shorter acting insulins given before meals help prevent meal related hyperglycemia!
- BID regimens require regular lifestyle (e.g. institutional)
- 50-75% as long acting & 25-50% as short acting

Form: **v**=vial **c**=cartridge (for reloadable pen) **p**=pen (disposable pre-loaded pen) ; **ac**=before meals **CSII**=continuous subcutaneous insulin infusion **d/c**=discontinuation **pt**=patient %=Exception Drug Status (EDS) in SK. 8 =Nonformulary Sk. t covered by NIHB

Tips: **Fix** the **lows first** & highs later**, correct morning blood glucose, assess Somogyi effect** if unexplained highs in the am **& only adjust one insulin** at a time**.** &=prior approval NIHB ⊗=not NIHB =↓dose for renal dysfx

EXUBERA : **Discontinued**! Inhaled (8⊗)adults type 1&2;dry powder given 10min ac, rapid acting, no difference in A1c from regular/NPH regimens; pts may prefer over sc; SE: cough, hypoglycemia,↓pulmonary fx tests short term, anti-insulin antibodies; CI: COPD, smoking if within prev 6 months; long term lung safety ?cancer; $$$$.

Diabetes if it was diagnosed within the first 6months of age consider genetic testing, since **Kir6.2 mutations** successfully **switched from insulin to sulfonylureas** (eg. glyburide 0.05-**0.45**-1.5mg/kg/d) Pearson NEJM Aug/06

Insulin Management: Evidence, Tips & Pearls [1,5]

M Jin, L Regier, B Jensen - © www.RxFiles.ca – Feb09

Indications for the Use of Insulin[1]

- Type 1 Diabetes Mellitus (T1DM); gestational diabetes not controlled with diet & activity; Type 2 Diabetes Mellitus (T2DM) not controlled with meal choices, activity & use of oral agents; T2DM with severe infection, major surgery, oral hypoglycemics contraindications, lactating, or requiring corticosteroid; ketoacidosis or hyperosmolar nonketotic syndrome; severe hyperglycemia where rapid glucose reduction/control is desired. {Also: Low rate of drug interactions.}

{Note: Recent Chinese trial: early intensive insulin till normal glycemia achieved x2 weeks induced remission in new T2DM.[2]; n=382; evaluated at 1year; remission in 50% CSII vs 27% oral hypoglycemics. Preliminary!}

Administering Insulin - Subcutaneous (SC) Injection

- Abdomen (not within a 5cm radius of the umbilicus), upper arms, , anterior/lateral thigh, buttocks.
- Alcohol is no longer recommended for topical preparation of the skin; soap & H_2O adequate.
- Give insulin injections at a 90° angle subcutaneously to ensure adequate absorption.
- DO NOT pinch skin {Pinching of the skin prior to injection is only necessary when using a 12 mm pen/syringe needles, if the individual is thin and/or in children. (Most needles 6-10mm)}
- People with a BMI > 27 kg/m^2 may use the 12mm length needle (Becton Dickson recommendation)
- If leaking is occurring at the injection site, check that the client is:
  - Injecting at a 90° angle & using the appropriate needle length
  - Leaving the needle under the skin for 5 seconds after injecting

[**Insulins generally given SC, but rapid & short acting formulations can be given IV]**

Variables That Can Affect Insulin Action

1. Mixing insulin together

Best not to mix rapid acting IAs, & not necessary with most devices.

   a. Regular (short acting) insulin can be mixed with NPH with no effect on insulin action (draw up short acting first to avoid contamination with NPH e.g draw *clear before cloudy*)
   b. Lispro *Humalog* binds rapidly with NPH & must be injected immediately after mixing
   c. Aspart *NovoRapid* may be mixed with NPH & must be injected immediately e-CPS
   d. Glargine *Lantus*: mixing with any other insulin not recommended {but some studies report that mixing with bolus insulin for BID administration in T1DM Pediatric suitable[3,4]}.
   e. Detemir *Levemir*: not to be mixed with any other insulin (potential for crystallization)

2. Insulin dosage and absorption variance factors
   a. Larger doses of insulin may have slightly longer duration of action. For lispro & aspart an increase in dose has no effect on the duration of action.
   b. Daily absorption can vary up to 30% using same site at the same time
   c. Speed/consistency of absorption: Fast to slow: abdomen → arm → thigh → buttock
   d. Absorption ↑ by exercise, heat, massage, injection into muscle
   e. Absorption ↓ by cold, lipohypertrophy, decreased blood flow (avoid areas of scar tissue)
   f. Avoid injecting into SC tissue adjacent to the main muscles being used in exercise
3. Injection site: Systematically rotate injection site by at least 1-2 inches to prevent lipodystrophy. The abdomen is often the preferred site; most consistent & fast rate of absorption
4. Other: improper storage (too hot or too cold); proper re-suspension of suspension insulins important! (Store insulin in a cold place 2 to 8°C, preferably a fridge, but not a freezer. Avoid direct sunlight.)

Canadian Guidelines - Notes Regarding Insulins [5]

- CDA Guidelines 2008 & some specialist reviewers advocate for a more prominent role for the newer insulin analogues, if economic and drug plan coverage issues are not major considerations. Primary advantage valued is less hypoglycemia in some patients. (A1C & weight endpoints lack meaningful differences.) [5,6,7,8]
- Trend in current clinical thinking is to pursue tighter BG control, both basal & postprandial. Newer insulin analogues theoretically may allow for more precise tailoring of regimen if patients willing to be highly aggressive in carbohydrate counting, BG testing & titrating of insulin. Limited evidence together with varying appreciation of economic analysis result in conflicting viewpoints in this area.

References available online at www.RxFiles.ca

Insulin Analogues (IA): Systematic Reviews (Tables 1 & 2)

Insulin Analogue Systematic Reviews (SR): 1) Cochrane SAIA[6]; 2) Cochrane LAIA[7]; 3) COMPUS – IA[8,34]. {Many studies; however none assess long-term complications or mortality & most of low-quality.} Related LINKs[9].

Table 1: IAs: Guide to Advantages/Disadvantages of Insulins [6,7,8,10]

	Insulins	Advantages	Disadvantages
Bolus	**HI** Short Acting Human Regular Humulin R; Novolin ge Toronto	• more long-term & safety experience • low cost (10ml/mo x1yr: $430 vs $550 ILis-$590 IAsp) • pregnancy-extensive safety experience	• injecting 20-30min pre-meal impractical (short acting but not rapid acting)
Bolus	**RAIAs** Rapid Acting **Lispro (ILis)** Humalog **Aspart (IAsp)** NovoRapid -rapid onset may ⇨ better PPG control if pre-meal (significance uncertain)	• inject & eat convenience (may give just before or within 15min of starting meals); valuable when dietary/activity patterns unpredictable, e.g. adolescents • may have less hypoglycemia • ↑ patient satisfaction in T1DM • safe in pregnancy (less extensive experience)	• moderately high cost utility in T2DM (but reasonable cost utility in T1DM)[8] • lack evidence for any clinical outcome or A1C advantage over HI {T1DM studies: A1C difference was < -0.2%} • limited long-term & safety evidence
Basal	**NPH** Intermediate Acting Human NPH Humulin N, Novolin ge NPH	• long-term safety & outcome evidence • low cost (10ml/mo x1yr: $430 vs $830 IGar-$1040 IDet) • may avoid need for lunchtime bolus injection (↑convenience) e.g. in children	• NPH vial must be mixed before withdrawing dose affects absorption • intermediate action & peak at 4-12hrs predispose to hypoglycemia
Basal	**LAIAs** Long Acting **Detemir (IDet)** (daily or BID) Levemir **Glargine (IGlar)** (daily) Lantus	• ↓ hypoglycemia, nocturnal subjective, not blinded (T2DM: Estimated NNT= ≥6 /6-12 mo[7,8]) • slight ↓ in weight (<1kg) vs NPH (in T2DM, only detemir had ↓ weight*) • OD dosing; IDet: some will require BID	• very high cost utility relative to NPH • no difference in severe hypoglycemia • limited long-term & safety evidence • ↑# of injections if not mixed with bolus • ↑caution in pregnancy (IDet may be an option)[5]
-	**Premixed**	• convenience;↓A1C more than HS only T2DM	• cost; limited flexibility with fixed dose

Insulins: Selection Considerations (Evidence & Economic)* Systematic Reviews 8,6,7;34,35

- **A1C differences of Insulin Analogues (IAs) compared to Regular & NPH:**
  - -Rapid Acting IA: range from -0.03% to -0.18% vs R; Long Acting IA: range from -0.12% to 0.28% vs NPH. adult
  - -There are no clinically significant differences in A1C control likely to impact clinical outcomes.[6,7,8]
- **T1DM – Bolus (rapid or short acting):**
  - Adults: Regular HI, Lispro or Aspart may be used. {ILis vs Reg: ↓ severe hypoglycemia (est. NNT=54/yr CI: 32-260)}
    - -Consider a Rapid Acting IA especially if meal flexibility and/or hypoglycemia concerns.
  - Adolescents: Lispro & Aspart offer convenience, flexibility & ↓hypoglycemia & preferred over regular HI.
- **T1DM – Basal (intermediate or long-acting):**
  - NPH preferred in COMPUS SR[8]; Detemir or Glargine are suitable if major hypoglycemia history or concern. {less hypoglycemia with IDet BID vs IGla OD[11]; but ↑ FG (7.7 vs 7.0) & ↑ serious adverse events (8.7% vs 6.9%) not Tx related?}
  - Preadolescent: a twice daily NPH regimen not requiring a lunch time injection may be useful in some.
- **T2DM – Bolus:** Regular HI preferred in COMPUS SR[8]; Lispro or Aspart suitable if hypoglycemia history or concern.
- **T2DM – Basal:** NPH preferred in COMPUS SR[8]; Detemir or Glargine suitable if hypoglycemia history or concern. {IDet vs IGla[12]: similar A1C; but 55% of IDet required BID where wt gain advantage lost & 2x daily dose required; ↑ site rx's with IDet}
- **Pregnancy, Pre-existing T1DM / T2DM or Gestational:**
  - Most safety experience with HI; RAIAs also safe & allow for tight PPG control, but no evidence of superiority.
  - Detemir & Glargine do not have sufficient safety data to recommend in pregnancy or preconception state.

*Evidence for insulin analogues is often limited (small, short-term trials) and benefits modest; anecdotal experience is favorable. The COMPUS systematic & economic reviews rigorously assessed benefits, risks and incremental cost.[8]

Weight change with LAIA: (T1DM: 0.36-0.71kg less than NPH); (T2DM: IDet: 0.96kg less than NPH; IGlar: no difference) [8] {There is question as to the clinical significance of the minor weight changes (<1kg here, or <5% in general).}

Hypoglycemia: Most pronounced ↓ risk for LAIA is on nocturnal hypoglycemia. {LAIA vs NPH: NNT ≥6 (CI range 4-33)}[7]

Cost Approx: Bolus: Regular $2–3/ml; Aspart $3-4/ml; Lispro $3-5/ml. Basal: NPH $2-3/ml; Glargine $6/ml; Detemir $8/ml.

{Cost estimate for converting 50% of patients to new insulin analogues ranges from $50-100million/yr Canada.[13] The COMPUS economic analysis modeled the overall impact of these costs & the potential benefits of lower A1C & hypoglycemia over the lifetime of the patient. Compared to regular insulin T2DM, the cost per Quality Adjusted Life Year (QALY) for RAIAs ranged from $22,448 - $130,865. The analysis comparing LAIAs with NPH insulin in T2DM was less favourable; for IGla the cost per QALY was $642,994 & for IDet the value was not calculated as it was less effective than NPH in terms of A1C.[14]}

MONITORING (BG, A1C, Ketones)

Blood Glucose (BG) Targets

- Preprandial: Optimal BG 4-7 mmol/L before meals
- Postprandial (PPG): BG 5-10 mmol/L 2hrs after meals (5-8 mmol/L if A1C target not being met)
  {Limited observational data suggests PPG as a potential risk factor for mortality [15]}
- Prevent extreme lows (<3.5 mmol/L) and high BG levels (>14mmol/L)
- Individualize with each person [16]: e.g. ambitious targets may be counterproductive in elderly (risk of hypoglycemia, etc.); for patient who has coronary artery disease (CAD), low BG can trigger atrial fibrillation therefore ambitious targets may not always be achievable/beneficial.[17]

Self Monitoring Blood Glucose (SMBG)[1,5]

- No gold standard of testing frequency established. {**Systematic/Economic Review** Draft: COMPUS [32]}
  {$/QALY: non-insulin T2DM, ≥1strip/day = $113,643; 1-4 strip/wk=$6,322-46,445}
  - Diet Only: may check occasional postprandial
  - OHA only: routine self monitoring not necessary in T2DM patients not on insulin & without hypoglycemia [18,19,20] {If done, twice in a day at staggered times, e.g. pre- & post-prandial.}
  - OHA & bedtime insulin: testing once daily at variable times is recommended.[5]
  - OHA & insulin MDI: individualize
  - Insulin monotherapy: individualize eg. Tid, pre & post prandial

  ◆AC/PC meals, up to 7x/day or more in patients with intensive regimens
  - Strips: yearly cost (1 test/day= >$165; 3 tests/day= >$500; 7 tests/day=$1100-2400) generics: Life, Sidekick, Truetrack
- Paired meal testing (AC & 2hr PC) helpful to match regimen to BG patterns; may stagger times:
  - Day 1: AC & PC breakfast; Day 2: AC &PC lunch; Day 3: AC & PC supper; Check HS somewhere.
  - This gives a good cross sectional representation of pattern of hyperglycemia, with less testing.
- Test more often: during pregnancy; illness; before driving to detect & treat hypoglycemia; when diet & activity changes; when adjusting insulin/pills; if hypoglycemic unawareness; exercise?; driving?
- Rapid-acting insulin analogues, oral glitinides: e.g. repaglinide (Gluconorm®) – may be particularly important to check 2 hours postprandial to determine if the dose is accurate
- Testing at ~3:00am or overnight expected insulin peak time may be required to rule out nocturnal hypoglycemia

Variables Affecting Accuracy Of Self-Monitoring Blood Glucose (SMBG)

- Sample Size: too little blood on test strip may cause problems for some meters
- Test strips: if expired or exposed to extreme temperature or humidity.
- Clean finger needed (especially sensitive to sugar containing foods or drinks).
- Meter inaccuracy: if old, dirty, or exposed to extreme temperatures. Lab/meter comparison recommended (annually). A fasting lab/meter comparison should be done annually to check meter accuracy; acceptable reading could be within 15-20% higher or lower than the lab value.
- Hematocrit: most test strips make allowance for this (results vary from 4-30% for every 10% change in hematocrit)
  - Anemia can falsely ↑ & polycythemia can falsely ↓ the BG values obtained by meters
- Alternate site testing or misrepresentations of BG results (clients falsify the test results)

Glycated Hemoglobin (A1C): an indicator of overall glycemic control in the preceding 3 months

- A1c may be measured every 3 months in all clients taking insulin & every 6 months in people on nutrition therapy, oral antihyperglycemic agents (OHA) or during tx & lifestyle stability
- Accuracy affected by: anemia falsely ↑ if slow RBC turnover e.g iron deficiency; falsely ↓ if fast RBC turnover e.g. hemolysis; PRBC transfusion; Hemoglobinopathies; ESRD (depending on assay used)
- Target A1c for most: ≤ 7%. A1c targets should consider patient factors & intervention intensity. (Overly intensive regimens may cause harm in T2DM populations ACCORD; see Diabetes Trials chart)
- Blood Glucose & A1c relationship (derived from DCCT in T1DM) [21]
  - Mean BG (mmol/L) = [1.98 x A1C(%)] – 4.29. (E.g., A1c = 10, Mean BG= 19.8-4.29 = 15.5mmol/L)

⇨Estimated Average Glucose (eAG) is another new way to reflect A1c; reported as mmol/L [22]

- eAG (mmol/L) = 1.59 x A1C(%) – 2.59

A1c: 6% = eAG 7mmol/L
7% = eAG 8.5mmol/L
10% = eAG 13.3mmol/L

Urine Ketone Testing (Primarily in T1DM)

- Required during significant hyperglycemia periods to assess risk of potentially life-threatening ketoacidosis e.g., when pre-prandial BG >14$_{mmol/L}$, nausea, vomiting, abdominal pain, illness &/or if dehydration
- May test urine ketones during pregnancy to ensure mother & baby's nutritional needs are met (Blood ketone testing may be preferred over urine ketone testing, since assoc. with earlier detection of ketosis & response to tx.)

HYPOGLYCEMIA

- Clinically hypoglycemia is defined as a state that results in:
  - Biochemical low – e.g BG <3.5 or < 4 mmol/L (common definition in DM trials)
  - Autonomic (adrenergic) OR neuroglycopenic symptoms {better recognition if infrequent occurrence}

  {Symptoms may occur at euglycemic BG levels in chronic hyperglycemia; typically resolves with time.}
- Mild: autonomic symptoms: tremors, palpitations, sweating, excessive hunger; able to self-treat
- Moderate: autonomic & neuroglycopenic symptoms – headache, mood △, irritability, ↓ attentiveness, paresthesias, visual disturbances; may be able to self-treat
- Severe hypoglycemia = distinguished by unresponsiveness, unconsciousness, seizures or coma; unable to self-treat, requires assistance. (Some studies also use thresholds e.g. ≤2.8mmol/L)
- Nocturnal: night sweats, nightmares; patient may not be aware. (Subjectively defined in studies.)
- Causes - Iatrogenic: dose of insulin or sulfonylureas is too high; diabetes therapy too intensive; decreased renal function can result in increased frequency of hypoglycemia in those on insulin or sulfonylureas; increase in the level of activity; insufficient carbohydrates in diet; Drug Causes[23]: insulin, sulfonylureas (chlorpropamide & glyburide); alcohol delayed, beta-blockers, salicylate, chromium, marijuana {Tight glucose control in critically ill hospitalized patients offers no benefit but ↑↑ risk of hypoglycemia. JAMA 2008; 24}
- Other: develop meal & activity plan; a bedtime snack may be helpful in those at risk (if BG <7mmol/L)

Treatment For Mild To Moderate Hypoglycemia

- 15g of carbohydrate (glucose or sucrose tablets) should ↑ BG about 2.1 mmol/L in 20 min
  - {Other 15g examples: ¾ cup juice or regular soft drink, 3 teaspoonfuls table sugar or honey, 6 LifeSavers®. 3 sugar cubes, 9 jelly beans. (glucose/dextrose absorbed directly)}
- Children – 0.3g/kg (10g carbohydrate in child <5yrs or <20kg)
- Wait 15 minutes, retest BG and retreat with another 15g glucose/sucrose if BG < 4.0mmol/L
- After initial glucose treatment, another carbohydrate containing snack should be taken within 1 hour. If meal more than 1 hour away, a snack with 15g carbohydrate & protein source is also recommended.
- If on Acarbose - use glucose tablets, milk or honey; (sucrose will not be absorbed!!!)

Treatment For Severe Hypoglycemia Occurring Outside Hospital Setting*

- If conscious and able to take oral treatment:
  - Treat with 20g glucose in tablet form, then wait 15 minutes (if possible).
  - Retest BG & retreat with another 15g glucose if BG <4.0mmol/L. (Repeat till sustained >4$_{mmol/L}$)
- If unconscious / unable to swallow: (BG <2.8mmol/L associated with unconscious)
  - Administer glucagon (details below). {Kits available > $100; portable for emergencies}
  - Once the individual is conscious & able to take oral food, hospitalization is probably not necessary; however, cause should be determined so that recurrence can be avoided.
  - Glucose gel should NOT be used buccally since minimal absorption through mucosa. Glucose gel is slow to react (< 1mmol/L rise in 20 min) & must be swallowed.

Table 2: Glucagon Treatment Of Acute Hypoglycemia

- Converts stored glycogen in the liver to glucose. Glucagon is only helpful if liver glycogen is available. {Less effective if suffering from starvation, chronic hypoglycemia &/or adrenal insufficiency.}
- Adult: glucagon dose SC/IM 1mg (if IM, administer in the deltoid or anterior thigh)
  - BG may rise from 3 -12 mmol/L within 60 min
- Child: glucagon SC/IM 15-30mcg/kg [MAX 1mg/dose] {<5yrs: 0.25-0.5mg; 5-10yrs: 0.5-1mg; >10 yrs: 1mg}
  - {Also: mini-dosing for impeding hypoglycemia due to refusal to eat (20mcg/yr of age; Max 150mcg)}
- BG response is greater in T2DM than in T1DM. Glucagon side effects: may cause nausea & vomiting
- Following glucagon administration: turn patient on side to avoid aspiration; never leave alone.
- When individual becomes alert, usually 10-15 min after receiving glucagon IM/SC, he/she should be given a fast acting carbohydrate (e.g., glass of juice, or glucose/sucrose tablets) followed by a carb. snack such as crackers & cheese or a sandwich (to prevent recurrent hypoglycemia). Ongoing monitoring is essential!

* If access to hospital/medical care, IV dextrose will act rapidly (Dextrose 10 to 25 g (20 to 50 cc of D50W) should be given over 1 to 3 minutes. Repeat BG in 15-30minutes. (The pediatric dose of glucose for IV treatment is 0.5 to 1 g/kg). Follow with D5W IV.

INITIATING INSULIN

Type 2 DM (adult) on oral medications (see also RxFiles - Approach to Management of T2DM)

- Start low dose for safety, then titrate upward!!!
- 5-10 units of intermediate insulin e.g. NPH or 0.1-0.2 units/kg of total body weight (TBW) at hs; titrate by 2 units every 2-3days. {More cautious with initiation & titration in elderly & non-obese (e.g. start with 5 units)}
- Adding insulin to already established metformin may be very useful to ↓ insulin dose required; also may result in less weight gain & less hypoglycemia
- Secretagogues e.g. sulfonylureas useful with hs basal insulin; should be stopped if mealtime insulin given
- Caution/Avoid: TZD glitazone & insulin combinations; ↑ heart failure, weight gain & edema[25] (not approved).

Type 1 DM

- Adult: 0.1-0.5 units/kg of body weight. (Typical requirement 0.5 units/kg.) If newly diagnosed, but not acutely ill or ketotic – start with lower dose (e.g. 0.3 units/kg or 4 units ac meals and hs).
- Adolescent: start similar to adult; but expect eventual higher requirement e.g. ≤1 unit/kg (tight follow-up required)

SWITCHING INSULINS* {temporary ↑BG monitoring required; ↓ dose to 80% for more conservative approach}

Short-acting human insulin → Rapid Acting IA: may be transferred on a unit for unit basis
NPH OD → glargine OD: may use same total number of units/day
NPH BID → glargine or detemir OD: ↓ total daily dose to 80% of the NPH daily dose
NPH OD → detemir OD: may use up to the same total # of units/day (↑ in dose is likely after switch; some may require BID)
Basal only hs → premixed given BID: use same or less total number of units/day (as ↑'d effect)[16]
*If hypoglycemia history or reason for switching, may be more conservative in initial dose chosen.

TIPS FOR INSULIN DOSE ADJUSTMENT

1. Fix the lows first & the highs later. Once the lows gone, rebound hyperglycemia often eliminated.
2. Adjust insulin by 5-10% per week, or 1 or 2 units at a time to prevent hypoglycemia.
3. Adjust one insulin at a time. Begin with the insulin that will correct the 1st problem BG of the day.
4. Overnight control is difficult & requires the right basal dose. {Goal: keep BG between 4-8mmol/L from bedtime to morning without causing a low & usually without requiring a bedtime snack.}
5. To assess for Somogyi (nocturnal hypoglycemia with rebound hyperglycemia in the morning) or overnight control, check BG at 0300 or 0400 not just once but a for a few nights, especially if experiencing unexplained morning highs. {Dawn phenomena also causes early AM rise but due to hormonal surge.}
6. Nightmares, restless sleep, headache on waking, wet pillow or sheets may be signs of sleeping through a low BG reaction. {One specialist uses BG from both 2AM & 5AM to assess.}
7. Postprandial targets are helpful when assessing the meal insulin. Assessing PPG control provides information to determine which insulin needs adjusting (the meal insulin or the basal insulin). The goal is to achieve PPG levels of 5-10mmol/L without lows between meals.
8. Sliding Scale Insulin: practice generally discouraged. Consider basal/bolus & supplemental regimen. {Supplemental insulin useful in addition to daily regimen (e.g. 1 unit bolus insulin for every 3mmol/L greater than 7 mmol/L; but will vary!)}

Activity/Exercise Principles: Patient education important for success!!!

1. In general, insulin therapy does not require adjustment for periods of activity < 30 minutes.
2. If activity > 30 minutes, & the activity is spontaneous & not preplanned, supplemental CHO before and during the activity can be used to balance the effects of ambient (previously injected) insulin.
3. Self Monitoring of Blood Glucose (SMBG) is recommended post event period q1-2h to assess response to activity and food consumption and to avoid post activity hypoglycemia.
4. On days of planned activity, reduction of pre-activity dose of insulin will help prevent hypoglycemia induced by exercise. If exercise will be after breakfast, lower the dose of regular insulin that would be taken before breakfast. If rapid acting insulin is used (aspart or lispro), decrease insulin dose only if exercise takes places within 2-3 hours after injection. (See Table 3.)
5. BG readings before, after, and possibly during exercise should be used to determine the appropriate change in insulin dose or food intake the next time the activity is done.
6. Prolonged activity can have a delayed BG lowering effect; ↓ in basal insulin may be required.

{If T1DM & BG acutely high >14-16mmol/L, exercise will speed up ketosis process & should be delayed till BG lowered.}

Table 3: Exercise Intensity & % Of Insulin Dose Reduction[26] VO2 max = max rate of O_2 consumption

Intensity (% VO2 max)	30 min of exercise		60 min of exercise
Mild exercise (25%)	25	(patient variable)	50
Moderate exercise (50%)	50		75
Strenuous activity (75%)	75		No insulin

TRAVEL THROUGH TIME ZONES

- General comment: goal is to switch to new time zone as soon as possible after arrival at new destination. {North-South travel may involve little if any time change so no insulin adjustment required.}
- In North America (3 hours max) → no adjustment
- Travel EAST (lose hours, shorter day): usually need less intermediate or long-acting insulin & less sleep

Canada →Europe *Lose 5-7 hrs; shorter day*	• Decrease bedtime dose of intermediate-acting insulin (NPH) by 1/3 or ½ on the travel day (usually on the plane crossing the Atlantic)
Europe →Canada *Gain 5-7 hrs; longer day*	• When arrive home, have an extra meal & extra dose of bolus insulin • The dose will need to last 5-6 hours, until return to usual routine

SICK DAY GUIDELINES for Patients on Insulin

- Check BG before meals &/or q4h around the clock (more often if necessary); drink extra sugar-free fluids
- Acute illness has variable effect on insulin requirement; management patient & regimen dependent
- T1DM: additional doses of bolus insulin for elevated BG or urine ketones (if BG not low); may ↓ insulin dose to avoid low BG if unable to ingest required amounts of carbohydrate & BG is not high.
- T2DM: ↓ or hold mealtime insulin if not eating; ↑ or additional doses of bolus insulin if high BG
- If on oral hypoglycemics, may need to temporarily decrease dose
- If the individual cannot eat as usual, they should replace solid food with glucose containing fluids. They should try to take ≥10 grams of carbohydrate every hour (see *clear fluids* below).

PRE-PROCEDURE CONSIDERATIONS e.g. outpatient with diet restrictions pre-gastroscopy [27]

- Management depends on: T1DM vs T2DM; duration of fasting; time/duration of procedure; insulin regimen
- E.g. Days Before Test: no change or ↓ basal insulin dose(s) by ~20%; ↓ bolus insulin dose(s) by ~50%. BG in range of 5-12mmol/L are OK for 1-2 days. On Day of Test: ↓ morning basal insulin by ~30% (up to 50% if very long procedure) & do not take bolus until test is done & ready to eat. Test BG before giving next insulin.
- Clear fluids containing sugar: (e.g. fruit/sports drink, pop, popsicle, regular Jell-O®); test BG more frequently (e.g. q4h); if BG <4mmol/L or symptoms, take 15-20g carbohydrate & retest in 15min

PREGNANCY & PRE-EXISTING DIABETES – Targets & Comments [5]

Pre-pregnancy: A1c (%)	≤7.0
Once pregnant:	
FBG & preprandial (mmol/L)	3.8-5.2
1-hour PPG (mmol/L)	5.5-7.7
2-hour PPG (mmol/L)	5.0-6.6
A1c (%) of somewhat limited value in pregnancy	≤6.0 if possible
In some ♀, especially T1DM or obese, higher targets may be necessary to avoid excessive hypoglycaemia!	

1. Stop OHAs, ACEI/ARB & statin prior to conception*,**
2. Use intensive insulin therapy - MDI or CSII
3. SMBG: pre & postprandial at least 4 x per day

{Hyperglycemia Effects: T1: developmental defects; T3: macrosomia, delivery & neonatal complications}

Postpartum: ◆ Insulin may not be required on the day of delivery & up to 24-48 hours postpartum
◆5-7 days post-delivery, insulin requirements have usually returned to pre-pregnancy levels. Encourage breastfeeding!

Pregnancy Category B-*Likely safe*: Human regular, NPH; Aspart, Lispro. Category C-*Caution*: Detemir, Glargine theoretical early risk
*There is evidence that glyburide & metformin e.g. in PCOS may be safe & not contraindicated in all cases. **Give 5mg/d folic acid![28]

GESTATIONAL DIABETES (GDM) [5]

- **Targets**: same as "Pre-existing" in table above. Avoid FBG < 3.3 mmol/L & 1 hr PPG < 5.0 mmol/L.
- Intervention: Diet & light exercise (small plate; walk after meals). If targets not achieved within 2 wks with nutrition alone, insulin should be initiated. {Glyburide or metformin[MtG] are 2nd line "off-label" options.} Regimen & dose depends on the pattern of hyperglycemia. Follow up: screen OGT for DM @ 6weeks-6months post-partum.
- Example of MDI regimen in GDM (dosing will depend on patient!)
  - High FBG: NPH qhs 0.1 unit/kg body weight (or start 5-8 units NPH qhs); Avoid LAIAs (Glargine, Detemir)
  - High PPG: Regular or RAIA of 1.5 units/10g CHO at breakfast due to insulin resistance, & 1 unit/10g CHO at lunch & dinner (or start 5 units bolus insulin for each meal with high PPG)

APPROACH TO MANAGEMENT OF TYPE 2 DIABETES (T2DM) in Adults

Nonpharmacologic Therapy: {nutrition & activity ⇨ weight loss of ≥5% or ≥4kg can ↓ hyperglycemia}

◆**Lifestyle Modifications** [1] portion plate,pedometer & **Patient Education** are important at all levels! [2,3,4]

If individualized goals for glucose are not achieved in 2-3 months, ⇨reassess; advance to next level of therapy

See Health Canada's Food & Fitness Guides &/or CDA Guidelines.{Consider low-glycemic,Mediterranean diet.[Shai 08]}

Oral Hypoglycemic Monotherapy {Note: if A1C ≥ 9%, consider MF + 2nd agent concurrently.}

◆**For most, especially if obese or overweight**

FYI: MF target dose in UKPDS-34 (obese, age ≤65): 1700mg am + 850mg @ supper (↓ mortality [NNT=14/10yr])

⇨ start **metformin (MF) 250-500mg po OD**
(Titrate dose up slowly to improve GI tolerance!; **over 3-4 weeks or longer if GI side effects**; usual dose ≤ 2,000mg/day; lower doses in elderly &/or ↓renal fx (see Table 6)

⇨ alternative agents used if metformin contraindicated/not tolerated
eg. secretagogues (e.g. sulfonylureas, repaglinide), TZDs [not rosiglitazone-ADA'08], insulin, acarbose; see chart
{In rare "young, thin T2DM", sulfonylurea (SU) [low-moderate dose] or metformin suitable for initial tx}

⇨ If TZDs considered, these agents can take a long time before full effect seen (6+ weeks). There are theoretical advantages to early use but also concerns about ↑ weight, HF, fractures (♀) & possibly cardiovascular (CV) risk. {CV & MI risk concerns mostly with rosiglitazone.}

Repeat A1C ; Reassess lifestyle modifications in 2-4 months {Attain target A1C in 6-12 months.}

⇨*If targets for glucose control not achieved, consider advancing to combination therapy*

Oral Combination Therapy (2 agents often needed: after 3yrs 50%; after 9yrs 75%)

◆a variety of 2-drug combinations e.g. (MF + SU [lower half of dose range]) may be considered (see Table 7); repaglinide +sulfonylurea not usually recommended; consider risks & benefits of other combos.
{2rd line/agent options: basal insulin [NPH, detemir or glargine]; a TZD [e.g. pioglitazone]; new agents? (Consider early insulin!)

Repeat A1C ; Reassess lifestyle modifications in 2-4 months,

⇨*If targets for glucose control not achieved, consider next level of therapy* (Note lack good evidence for combos)

Add Insulin Therapy +/- Oral Agents (MF will limit wt gain & insulin dose required)

◆**Option 1: Bedtime basal insulin** (e.g. NPH or N) **+ daytime oral hypoglycemics** [e.g. **metformin**]

⇨**if** on SU + other oral agent, consider discontinuing or reducing the dose of the SU [(or could use a metiglinide)]

-**add intermediate or long-acting insulin, 5-10 units at HS** (or initial dose: ~ 0.1 - 0.2 units/kg)

-↑ insulin: Option 1) by 2 units every 3-4 days until FPG of 4 -7 (or by 1 unit/day till target is reached.)
{or Option 2) Titration is patient specific; however an example of a q-weekly titration regimen could be: if FPG in previous few days: [7.1-8 mmol/L, 2 units]; [8.1-10 mmol/L, 4 units]; [10.1-12 mmol/L, 6 units]; No ↑ or may need ↓ if ≥ 2 episodes of BG <4 [mmol/L] at any time in preceding week, if severe hypoglycemia (i.e. requiring assistance), FPG < 3.1 in preceding week or any nocturnal hypoglycemia.}

-if target BG not achieved at 30units/day, or ↑ in daytime BG, may switch to split-mixed or more intensive regimen (usual range: 0.25-1unit/kg/d). To add bolus insulin to basal insulin, take [current basal insulin dose ÷ 10] = bolus dose at largest meal; reduce basal insulin dose by the same amount; titrate. 2nd & 3rd mealtime injections can be added similarly in succession.

◆**Option 2: Switch to insulin therapy 1-4x/day**

⇨if starting mealtime insulin, discontinue SUs &/or glitinides (see Table 7)

-adjust insulin dose & frequency to achieve targets without hypoglycemia

Some patients may eventually require very high doses of insulin due to insulin resistance (max 400units/day used in UKPDS)

e.g. Split-mixed regimen: total starting daily dose (depends on patient, other drugs, etc.; 0.1-0.5 units/kg; safer to start lower!)
Basal/bolusTID or QID: ≥40% of total dose as basal; other 60% as bolus/prandial divided TID at mealtimes [adjust per diet/exercise]
BID: divide daily dose: 2/3 pre-breakfast; 1/3 in evening pre-supper; divide each dose: 2/3 basal & 1/3 bolus (or 30/70 mix)

(Note: insulin temporarily indicated in any pt with metabolic decompensation, severe fasting hyperglycemia, or severe illness.)

GLUCOSE TARGETS [CDN '08 Adult]	Target for most	Normal	Frail elderly [AGS'03]
A1C q3-6mon (calibrate meter q-yr)	≤ 7 [(≤6.5% in some)]	≤ 6	≤ 8
FPG (mmol/L)	4-7	4-6	
PPG (mmol/L) 2hr post	5-10	5-8 (consider if A1C not met)	
Note: pursue targets if can be done safely without hypoglycemia etc. [ADA'07 30]			

Individualize targets: More aggressive in young adult with recent diagnosis [STENO-2]; less aggressive in **frail elderly** [31]. ACCORD A1C arm halted due to ↑death [NNH= 95 / 3.5yr] in aggressive target group (A1C <6 [Achieved=6.4]) vs standard target group (A1C: 7-7.9 [Achieved=7.5]); in patients with established T2DM at high CV risk [~ 10 yr hx].

Screen: if BP >135/80 [USPSTF'08]; FPG: screen q3yrs if risk factors or ≥40yrs old. Estimate average glucose [eAG]: 8.5mmol/l = an A1C 7%

BP [2008] Diabetes→**130/80** **LIPID** [2006] Diabetes [most]→LDL<**2-2.5** Total Chol/HDL<**4** (Lower risk: younger without risk factors)

RENAL	Normal	Microalbuminuria [Start ACEI or ARB]	Macroalbuminuria
Albuminuria	<30mg/day (<20ug/min)	30-300mg/day (20-200ug/min)	>300mg/day(>200ug/min)
Albumin mg/**C**reatinine mmol **R**atio	Male <2; Female <2.8	Male 2-20; Female 2.8-28	Male >20; Female >28

Self monitoring of BG in T2DM has limited effect on A1C [↓~ 0.25%], yet ↑cost [$160 - $2400 / year] & ↑depression. Consider if: using insulin or secretagogues, in select newly/motivated diabetics, to aid motivation or if at ↑hypoglycemic risk [DiGEM,ESMON,Farmer BMJ07/08.]

BMI (kg/m²)	WEIGHT (kg, lbs)																	
	45 kg	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130
HEIGHT (Cm; inches) cm. / in.	99 lbs	110	121	132	143	154	165	176	187	198	209	220	231	242	253	264	275	286
155 cm / 61	18½	21	23	25	27	29	31	33	35½	37½	39½	41½	43½	46	48	50	52	54
160 / 63	17½	19½	21½	23½	25½	27	29	31	33	35	37	39	41	43	45	47	49	51
165 / 65	16½	18½	20	22	24	26	27½	29½	31	33	35	36½	38½	40½	42	44	46	48
170 / 67	15½	17	19	21	22½	24	26	27½	29½	31	33	34½	36	38	40	41½	43	45
175 / 69	14½	16	18	19½	21	23	24½	26	28	29½	31	32½	34½	36	37½	39	41	42½
180 / 71	14	15½	17	18½	20	21½	23	24½	26	28	29	31	32½	34	35½	37	38½	40
185 / 73	13	14½	16	17½	19	20½	22	23½	25	26	28	29	30½	32	33½	35	36½	38

Underweight = <18.5kg/m²; **Normal** = 18.5-24.9kg/m²; Overweight = 25-29.9kg/m²; **Obese = ≥30kg/m²**

Waist Circumference: ♂ **<94**cm ideal, [>102cm high risk]; ♀ **<80**cm ideal, [>88cm high risk] {better risk predictor than BMI!}

Table 6: Individualization of Drug Therapy: Special Considerations

Patient Factor	Consider ⇨ possibly preferred drugs
Renal failure *	TZDs, repaglinide; insulin; (also tolbutamide or gliclazide [5])
Hepatic disease	**Insulin, repaglinide;** acarbose; (Caution:glyburide,metformin& TZDs)
Hypoglycemia {consider risk of combos below}	**Metformin**, metformin+sitagliptin, TZDs; also: repaglinide; gliclazide or glimepiride [less than long-acting SUs]; acarbose; {basal insulin: glargine or detemir somewhat less than intermediate [e.g. NPH/ N]}
Obese / Overweight	**Metformin** [drug of choice if no Cl's; ↓mortality (UKPDS-34)]; {acarbose; I-Det; new agents?}
Irregular mealtimes	**Repaglinide** (may be preferred over SU)
PPG >10mmol/L & FPG minimally ↑'d	**Repaglinide** (or **Acarbose**); Metformin + sitagliptin; Diet [↑fiber] **Rapid Acting Insulin** (if PPG very high [>10mmol/L]) [e.g. Lispro, Aspart]
IGT/IFG "Prediabetes"	**Lifestyle** (↓wt, diet/exercise)[DPP, FDP]; MF [850mg BID DPP]; orlistat [Xendos], acarbose [Stop-NIDDM]

* **Metformin dosing**: lactic acidosis assoc. with metformin is rare (<1:10,000 treated pts)[6,7,8]

MAX Metformin Dose [9] for CrCl: 60 [ml/min] ≤1700mg/d; >30 [ml/min] ≤850mg/d; ≤30 [ml/min]→contraindicated

Table 7: Combination Therapy/Insulin Therapy in Type 2 Diabetes [10,11]

Drug combination	↓ in A1C	hypo-glyc.	Wt	Comments re Combinations (long-term clinical outcomes not studied!)
SU + MF	↓↓↓	↑↑	↑/↓	◆if SU initially, may add MF or TZD; SU+MF may further ↓A1C by 1.7%; 1 study ↑ mortality[12], but ADVANCE neutral* ◆if MF initial agent, may add SU or repaglinide ◆MF combos generally result in less weight gain than SU combinations; ◆MF+Pioglitazone: positive lipid effects but ↑ edema; MF+rosiglitazone: lower A1C but ↑edema ◆MF+acarbose: ↓wt & PPG but ↑GI SEs
SU + TZD [13]	↓↓	↑↑	↑↑	
MF+ repaglinide [14]	↓↓	↑	↑	
MF+ sitagliptin	↓↓	-	↓	
MF+ TZD [15,16,17]	↓↓↓	-/↑	↑	
MF+ acarbose [18]	↓	-	↓	
Exenatide+MF+SU [70]	↓↓↓	↑↑	↓	
Insulin monotherapy	↓↓↓	↑↑↑	↑↑↑	◆tight BG control but hypoglycemia/weight gain
Insulin + SU (UKPDS 57 [ultralente @ evening])	↓↓↓	↑↑	↑↑	◆evening basal insulin; lower A1C & less hypoglycemia than insulin alone; caution in elderly (hypoglycemia)
Insulin + MF (FINFAT STUDY [19])	↓↓↓	↑	↑	◆overcomes insulin resistance; MF has positive effect on wt & lipids; preferred in obese patient; superior to insulin+SU; insulin sparing ~20-25%
Insulin+ pioglitazone or rosiglitazone	↓↓[20]	↑↑↑	↑↑↑	◆overcomes insulin resistance; but potential harms (e.g. ↑ wt, edema & risk of HF[21]); risk/benefit?.
Insulin+ repaglinide	↓↓	↑↑	↑↑	◆option to ↓ PPG
Insulin + acarbose	↓↓	↑↑↑	↑↑↑	◆↓ PPG [diet high in CHOs]; also ↓ wt & triglycerides
Insulin + 3 orals*	↓↓↓	↑↑↑↑	↑↑↑	◆ACCORD: >50% of pts on 3 orals+insulin; ↑ death *

*ACCORD: baseline A1C=8.3%, wt=93kg & very aggressive intervention (>50% on 3 orals + insulin); ↓A1C to 6.4% but ↑ death [NNH=95 /3.5yr] (& ↑wt. & hypoglycemia). In ADVANCE: baseline A1C=7.5%, wt=78kg; most on SU [gliclazide] + MF; ↓A1C to 6.5% & ↓ microvascular [NNT=67 /5yr] (esp. nephropathy) but also ↑ severe hypoglycemia [NNT=83 /5yr] & ↑ hospitalizations [NNT=42 /5yr].

A1C = glycosylated hemoglobin **BG**= blood glucose **CHO**= carbohydrate **FPG**= fasting plasma glucose
HF= heart failure **MF**= metformin **PPG** = postprandial blood glucose **SE**= side effects www.RxFiles.ca
SU= sulfonylurea **TZD**= pioglitazone & rosiglitazone **Wt**= weight

Oral HYPOGLYCEMIC AGENTS (OHA) - Comparison Chart [22,23,24,25,26,27,28,29,30,31,32,33,34,35]

Prepared by: Loren Regier, Brent Jensen, © *www.RxFiles.ca* Oct **08**

Generic/TRADE/ (Strength) Pregnancy	KINETICS	EFFECTS ON FPG	PPG	A1C↓%	LDL	HDL	TGs	Wt	DRUG INTERACTION	COMMENTS	INITIAL & (Max.) DOSE	USUAL DOSE RANGE	$ /100 day
BIGUANIDES – reduces hepatic glucose production; increase insulin sensitivity & cellular glucose uptake & utilization; ↓ morbidity & mortality [NNT=14/10yr] in obese patients (UKPDS-34)													
Metformin [36] (MF) B GLUCOPHAGE, GLYCON generic (500[c], 850mg tab)	P = 3h D = 8-12h	↓	↓	↓ 1-1.5	↓	↑	↓	-/↓	• **EtOH** and cimetidine ↑ effect • contrast media (long-term ↓ B_{12} & folate absorption) {**Caution/↓ dose CrCl ≤60**ml/min}	Does **not** by itself cause **hypoglycemia.** Possible **wt loss**; **⇨ DOC for OBESE ! First line agent** (Used in PCOS[37]) **SE: To avoid GI SEs, start low & titrate up q2-4wk** **Avoid**: ↓ renal fx (**<30** ml/min), acute/decompensated HF, liver dx[severe]; 48hr post [iodinated contrast]. {(Lactic acidosis <1:10,000)[7], watch Na bicarb}. Long-term ↓B12 absorption [7%]; anemia [may occur] **Elderly**: dose reduction required.[38] May **prevent** NIDDM [39 DPP]	**250-500mg od** (Max: 850mg tid; but usual max 1g bid) 1700mg po am, 850mg po pm: **UKPDS**	500mg po bid 850mg bid [DPP] 1g po bid [Adopt]	22 **43** **35** 61
Metformin GLUMETZA 8 ⊗ 0.5&1g ER tab, Max 2g/day [$240] (OD with evening meal). **Metformin/Rosiglitazone AVANDAMET** % ⊗ tabs: (500mg/1,2,4mg BID =$155, $270, $360 /100day tab; 1gm/2,4mg =$290, $390). {**Not in Canada: Metformin/Pioglitazone ACTOplus met** 8 ⊗ tabs 500/15mg, 850/15mg BID}. MF/Rosi ↓A1c by ~2%; ↑edema & hypoglycemia vs MF alone.					**+'ve effect on lipids & wt!**			↓2.9kg Adopt 4yr		TID dosing option for larger doses to ↓ GI intolerance (dyspepsia, nausea & diarrhea)		
SULFONYLUREAS (SU) Insulin Secretagogue – stimulates β cell insulin release; ↑peripheral glucose [utilization] (↑ #/sensitivity of insulin receptors?); ↓hepatic [gluconeogenesis]; may stop if on insulin													
Chlorpropamide ⊗ C DIABINESE, g; (100[c], 250[c] mg tabs)	P = 6-8h D = 24-**72h**	chlorpropamide **not recommended** due to ↑BP & ↑ retinopathy (UKPDS-33)						↑↑	**Numerous:** • ↑ Hypoglycemia with: cimetidine, **EtOH**, fluconazole MAOIs, NSAIDS, salicylates & sulfonamides. • β-Blockers may mask hypoglycemia • Disulfiram rx. with EtOH, mostly with chlorpropamide • rifampin ↓ effect	Many (~75%) require 2nd agent for adequate control (e.g. + metformin or TZD) **Hypoglycemia**: most with chlorpropamide & glyburide (see note below); **least**: tolbutamide, glimepiride[40,41] & gliclazide [42] Caution in elderly (hypoglycemia risk) & obese (wt gain). **Require consistent food intake** to avoid problems with hypoglycemia (↑risk: elderly, debilitated, malnourished) **SE: Wt gain,** headache, dizziness, **sulfa** skin reactions (rash/photosensitivity ~1%),GI side effects [1-3%];concerns with cardiac toxicity & hyperinsulinemia & hyponatremia Reduce dose if hypoglycemia or renal/hepatic dysfx **Dose titration q1-2 weeks**. Failure rates ~5-10%/year. In general, SUs achieve ~75% of effect at **1/2** their max dose.	100mg od (500mg od)	100mg po od 250mg po od	16 **13**
Gliclazide,generic **DIAMICRON** 80[c]mg tab; **DIAMICRON MR**,g 30 mg tab C	P = 4-6h D=10-**24h**	Total Wt gain with glyburide >4kg vs **>6kg insulin** (UKPDS-33) [10yr]		↓ 1-1.5	-	-	-	↑1.6kg Adopt4yr			40mg (160mg bid) 30mg MR (120mg od [Advance])	80mg po bid 60mg MR po od 120mg MR po od	**74** 41g,96 75g,180
Glyburide **DIABETA**,generic (2.5, 5mg scored tabs) B/C	O=<60min P= 2-4h D=12-**24h** ↓placenta[transfer]	**Glimepiride AMARYL**g 8 ⊗(1,2,4mg ς tabs) 1mg od ($65); 2mg od ($65); 4mg od ($65) /100days **Glimepiride/rosiglitazone AVANDARYL** 8 ⊗ (1,2,4/4mg tabs) od with a meal ($310) **Glimepiride/pioglitazone DUETACT** 8 ⊗ in USA C									1.25-2.5mg od (10mg bid $31)	5mg po od-bid 7.5mg bid [Adopt] Peds: 0.05-0.45[mg/kg/d]	15-20 26 ←Kir6.2[mutation]
Tolbutamide,generic C **ORINASE** (500mg scored tab)	P= 3h D=6-**12h**										250mg od (1000mg tid)	500mg po bid 500mg po tid	27 **37**
THIAZOLIDINEDIONES (TZDs) or GLITAZONES –Insulin Sensitizers: ↓ hepatic output of glucose & ↑ peripheral glucose uptake; ~ 4-6+ weeks before effect (adjust dose at ~2 months)													
Pioglitazone % & **ACTOS**,generic (15, 30, 45 mg tab) C	**Delayed action…** Onset ~3wks	↓	↓	↓ <1 or 1-1.5	-	↑	↓	-/↑ ↑3.6kg Proactive3yr	• Cholestyramine ↓ absorption ~70% • Hepatic CYP [2C8] • rosigl. not CYP [3A4] • ?? may ↓ oral contraceptives [pioglitazone] • ↑ by gemfibrozil & ↓ by rifampin	More effective in obese or hyperinsulinemia pts. **Doesn't by itself cause hypoglycemia**; ovulation resumption in anovulatory ♀ [premenopausal PCOS]. **CI**: any HF; triple tx[?MF+SU+ TZDs. **SE: Edema 4.8% (HF 2x** [43,44];HTN);**↑Wt**; anemia [~1% mild (due to hemodilution?);↑fractures [esp ♀,2x];monitor **liver fx (ALT)** when indicated; pioglitazone may have more +ve lipid effect[45,46] **ROLE**: +MF, or SU [if MF CI]; (↑↑ HF with insulin); Rosi: ↑MI risk?[60]	15mg od (45mg/day)	15mg po od 30mg od [Periscope] 45mg od [Proactive]	200g,270 260g,**360** 380g,530
Rosiglitazone % & **AVANDIA**; [1st approved 2000] (2, 4, 8mg tab) =Rosi C	**Max effect in 8-16 wks**	↓	↓	or 1-1.5	47,48 -/↑	49,50 ↑	-/↓	-/↑ ↑4.8kg Adopt 4yr			4mg od {4mg max if with SU} (4mg bid) bid dose ~more effective (51)	4mg po od 4mg po bid [Adopt] 8mg po od [Dream]	250 480 **350**
?? May ↑MI, CV risk [Nissen, DREAM?, FDA];?↑ Macular edema; advise against using rosi ADA'08													
MEGLITINIDES (GTN) – short-acting insulin secretagogue; bind to β cell to stimulate insulin release at different site than SUs; (adjust dose at ~7days); discontinue if on insulin recommended													
Nateglinide % t **STARLIX** (60, 120, 180mg tab) C	O = **<20min** P=60-120min D = ~**4h**	↓	↓↓	↓ 0.5	-	-	-	-/↑	•CYP [3A4] inhib[↑ effect]: azole-antifungal, clarithro /erythromycin, gemfibrozil •CYP [3A4] inducers ↓ effect: barbs, carbamaz & rifampin	Restores 1st phase insulin release - (↓ PPG) Rapid, short duration ⇒ May ↓ risk of hypoglycemia vs SUs ∴option in elderly; **{Flexibility with food intake: skip dose if skip meal; take extra dose if add meal}** If stop other hypoglycemics begin next day & watch for hypoglycemia. **ROLE**: alone or + MF, TZD, or insulin Agents lack outcome data on morbidity &mortality.	60mg tid ac (180mg po tid)	60mg po tid 120mg po tid 180mg po tid	197 197 210
Repaglinide % t **GLUCONORM** (0.5, 1, 2mg tab) C	O=15-60min P=60-90min D = ~**4-6h**			↓ 1-1.5							0.5mg tid ac {if no prev tx or A1C <8%} (4mg qid)	0.5mg po tid 1-2mg po tid 4mg po tid	} **115** 230
α GLUCOSIDASE Inhibitors –inhibit α-glucosidases in brush border of small intestine; prevent hydrolysis & delay carbohydrate digestion {Tx hypoglycemia with glucose tablets [Dex4], honey or milk; (sucrose not absorbed)}													
Acarbose **GLUCOBAY** (prev Prandase) (50,100mg scored tabs) B	Meal-time dosing; ~8 wks for max. effect	acarbose minimally absorbed; monitor 2hr PPG							• ↓ digoxin effect • Cholestyramine & cathartics ↑ effect •Enzymes[amylase/pancreatic] ↓ effect; •↓ Fe^{++}?	**SE: GI intolerance**: **flatulence** [>41%]**, diarrhea** [>28%]; Little hypoglycemia. Acarbose: ↑ LFTs [3%] & hepatic failure. Accumulation in renal failure. Avoid in chronic GI disease. ↑ dose q4-8wks. ROLE minimal: if ↑PPG; + SU, MF; (+Insulin?)	**25mg od** (100mg tid) [STOP-NIDDM 52]	50mg po tid 100mg po tid	95 **130**
Miglitol 8⊗ (not in Can.)		↓	↓↓	↓ .5-.8	-	-	-/↓	-/↓			25mg od (100mg tid)	25-50mg po tid	n/a
		miglitol **GLYSET** (25,50,100mg tab) well absorbed											
Sitagliptin New [2007] **JANUVIA** [8 ⊗] 100mg tab (free base) U	Onset ≤4wks; ~18 wks for max effect	**Dipeptidyl peptidase-4 inhibitor [DPP-4]**							•minimal experience •digoxin: small ↑ in dig levels (AUC 11%; Cmax 18%)	↑ insulin secretion via ↑incretin; ↓glucagon. ROLE: combo with MF SE:throat [sore] (↑ infections [URTI, UTI][Cochrane08], headache, nausea, diarrhea; arthralgias; SJS [rare (FDA caution)], less hypoglycemia [but ↑ with SU]; edema?	100mg po OD [25mg & 50mg avail. in USA] 100mg/day	100mg po OD New: no outcome data & unknown safety! (Not a tier 1 or 2 choice by ADA'08) [72]	$300

= ↓ dose for renal dysfx ς =scored tab **$** Cost =total cost & markup in Sask; % = Exception Drug Status in SK **8** = Non-formulary in SK & =prior approval for NIHB ⊗=not covered by NIHB **t** covered by NIHB; '+' denotes combination options

A1C = glycosolated Hemoglobin (reflects glycemic control over prior 8-10 weeks) **BP**= blood pressure **DOC**= drug of choice **dysfx**= dysfunction **EtOH**= alcohol **FPG**= fasting plasma glucose **GI=** gastrointestinal **HDL**= high density lipoprotein **HF**= heart failure **Ins.**= Insulin **KINETICS**: **O**= onset **P**= peak **D**= duration; **LDL**= low density lipoprotein **PPG**= postprandial blood glucose **SE**= side effects **Wt**= weight ς = scored tablet

Drug induced ↑ glucose: antipsychotics [clozapine, olanzapine], corticosteroids, cyclosporine, diuretics [thiazides e.g. >25mg HCT], estrogens, interferon [alpha], nicotinic acid [↑ dose], phenytoin, sympathomimetics [decongestants], siro & tacro-limus, temsirolimus & thyroid meds. Beta-blockers minimal risk of altering glucose control but may alter/mask hypoglycemic response. **Pregnancy:** Encourage diet, moderate exercise; **Insulin** preferred; generally avoid oral hypoglycemics[53] (See Insulin Management Chart)

Hypoglycemia risk -UKPDS: risk of **≥1 MAJOR** hypoglycemic events/yr (ITT): chlorpropamide=1%, glyburide=1.4%, **insulin 1.8%**; risk of **ANY** hypoglycemic event/yr chlorprop.= 16%, glyburide=21%, insulin 28%.

Oral agents +/- insulin: with T2DM progression, combo tx with oral agents &/or addition of insulin will eventually be required.

PPG may reflect risk of CV disease & all-cause mortality [observational,54]; FBG & A1C are predictors of microvascular complications.

•Consider: [55] lipids/statin, orlistat [56],↓ hypertension [ACE Inhibitor/ARB/thiazide] & DC smoking! ASA ~81mg/d. Lifestyle: {↑fiber, ↓fat, low glycemic index CHO foods; exercise: aerobic150min/wk, resistance 3x/wk; but start with 5-10 minutes}

New:not in : **Exenatide BYETTA** [8 ⊗] an incretin mimetic; 5-10ug SC bid ac ;↓PPG,↑insulin [secretion],↓A1C 1%; may ↓wt, GI ↓[gastric emptying] & ↑N&V; rare: pancreatitis [acute]. **Pramlintide SYMLIN** [8 ⊗] an amylinomimetic,15-60-120ug SC tid ac; ↓wt & ↑N&V.

Diabetes - Glucose Control: Landmark Outcome Trials – Summary

Loren Regier, Brent Jensen – **www.RxFiles.ca** – **Feb 09**

	Trials Mean follow-up	Population Risk, hx mean age, etc.	Intervention	A1C: baseline⇨final	Results	Summary of RCT Outcome Evidence
Type 1 (T1DM)	**DCCT** [1] ~6.5yrs; n=1,441 {Conducted between 1983-1993.} {note 1° & 2° endpoints, as well as 1° & 2° cohorts.}	T1DM; mean age 27 (13-39)yr; BMI=27 Excluded: if CV disease, ↑ BP,HC, complications. 1° & 2° cohorts (2° if 1-15yr hx, existing mild-mod retinopathy & microalbuminuria; 1°: 1-5yr hx)	Intensive insulin (3+ inj/day or pump) with target A1C of <6.05% (44% achieved once, but only 5% maintained), preprandial BG 3.9-6.7mmol/L, PPBG <10mmol/L, weekly 3A.M. BG >3.6mmol/L vs Standard insulin (1-2 inj/day)	Int. vs Std.: 8.8% ⇨7.4% vs 9.1% {Pre-prandial mean BG Int. vs Std. 8.6 vs 12.8mmol/L} {↑ Wt 4.6kg/5yr}	Endpoint 1° or 2° / △ Rate/100 pt yr NNT/H=100per pt yr / RRR 1°: Retinopathy: 1°↓3.5 NNT=29; 2°↓4.1 NNT=24; 63% 2°: Microalb.: 1°↓1.2 NNT=83; 2°↓2.1 NNT=48; 39% 2°: Macroalb.: 1° ↓0.1 NS; 2° ↓0.8 NNT=125; 54% 2: Neuropathy @5yr: ↓6.7 NNT=15; ↓9.1 NNT=11; 60% Hypogly SEVERE: ↑43 NNH=2.3; ↑Hosp 7.6% vs 4.9%	**Type 1 Diabetes** {ENDIT nicotinamide & DPT-1 low-dose insulin not effective in T1DM prevention} ◆↓ in microvascular complications in initial 6.5yrs (1° endpoint: retinal surrogates) (mostly ↓ retinal △ on fundus photo 3 steps / 25 stage scale, microalbuminuria & neuropathy) ◆a 10% relative reduction in A1C (regardless of what the initial A1c value was) resulted in a 43% relative risk ↓ in progression of retinopathy & a 25% relative risk ↓ in microalbuminuria. (Substantially less at lower A1C levels.) ◆↑severe hypoglycemia including coma/ seizures NNH=9 /100pt-yr & hospitalizations 54 vs 36 ◆possible ↓ in macrovascular complications in long-term follow up(~17yrs); however, limitations such as unmasking could bias results.
	DCCT / EDIC [2] ~17yrs; n=1,394	93% of DCCT in follow-up till Feb05. age 45; BMI=28; 24yr hx	As above, but 94% of standard group changed to intensive insulin.	7.4%⇨7.9% 9.1%⇨7.8%	◆↓ CV events (nonfatal MI, CV death, stroke, angina, revascularization) 5.8% vs 10.3% NNT=23/17yr CI=12-352. (RRR=42% ↓)	
Type 2 (T2DM)	**UKPDS-33** [3] ⌖ ~10yrs; n=3,867	New T2DM; age 54yrs; with FPG 6.1-15 on diet alone	Intensive SU or insulin vs diet. Target FBG <6mmol/L vs <15mmol/L	7%⇨ 7% vs 7.9%	◆↓microvascular endpoints NNT=42/10yr; retinal mostly ◆no effect on CV events⌖ ◆↑ hypoglycemia esp insulin	**Type 2 Diabetes** ◆intensive glucose control may ↑ or ↓ risk depending on type of patient & treatment {e.g. in ACCORD type patients, overly intensive pursuit of A1C target associated with ↑death; no benefit in VADT; whereas in ADVANCE type patients, not quite as intensive tx had some benefit; UKPDS 33,34 reveal variability between extent of BG control & outcomes.} ◆glucose control offers predominantly microvascular benefit ◆metformin in newly diagnosed obese T2DM: reduces macrovascular events & all-cause death without ↑ weight or hypoglycemia UKPDS-34, 80 ◆pioglitazone may ↓CV events (2° outcome & statistical concerns), but ↑ HF & wt ◆macrovascular benefits seen with multifactorial approach to Tx -lifestyle, ↓smoking, diet, exercise, BP, ACEI, statin, ASA, A1C<6.5% STENO-2 -statin therapy { simvastatin 40mg/d HPS; atorvastatin 10mg/d CARDS } -ACEI, BP reduction {e.g. ramipril 10mg/d MICROHOPE}
	UKPDS-34 [4] ⌖ ~10.7yrs; n=1,704	Obese T2DM; age 53yrs Wt=87kg; BMI=31	Metformin 1700mg am, 850mg pm vs conventional (diet mostly)	7%⇨7.4% vs 8%	◆↓diabetes endpoint NNT=10/10yr (RRR=32%) ⌖ ◆↓all-cause death NNT=14/10yr; ↓stroke NNT=48/10yr	
	Kumamoto [5] 6yrs; n=110	Japanese with 2° & without 1° retinopathy; UAE<300mg/24hr	Multiple insulin injection tx (MIT) vs conventional insulin tx (CIT)	9.2-9.4⇨7.1 vs 8.9⇨9.4	◆↓ early microvascular complications (retinopathy [2+ steps on 19 step scale]; nephropathy & neuropathy)	
	PROACTIVE [6] ~3.5yrs; n=5,238	High CV risk; Age 61; BMI=30; A1C≥6.5	Pioglitazone 45mg po daily vs Placebo (>10% higher rate of insulin use)	7.8%⇨7% vs 7.5%	◆1° composite-no effect; 2°↓CV events NNT=50/3.5yr ◆↑wt 3.6kg/yr; ↑HF NNH=30/3.5yr & edema.	
	ACCORD [7] ~3.5yrs; n=10,251	High CV risk; ~10yr hx T2DM; age 62; 93kg; North American	Intensive A1C target <6% {most on 3 oral hypoglycemics + insulin} vs standard A1C target 7-7.9%	8.1%⇨6.4% vs 7.5%	◆↑ all-cause death ↑22% in intensive group at 3.5yr resulted in halting trial (NNH=95/3.5yr); also severe hypoglycemia (NNH=9/3.5yr) & ↑ weight 3.5 vs 0.4kg	
	ADVANCE [8] ~5yrs; n=11,140	Hx of CV disease; 8yr hx T2DM; age 66; 78kg; Austral-Asian/European	Intensive A1C target 6.5% {most on SU (gliclazide) + metformin} vs standard A1C target ~ 7%	7.5%⇨6.5% vs 7.3%	◆↓ microvascular events over 5yrs (NNT=67/5yr), mostly nephropathy indicators; also ↑ severe hypoglycemia (NNH=83/5yr) & minimal wt change	
	STENO-2 [9]: n=160, T2DM & microalbuminuria; multifactorial intensive (A1C <6.5% <20% achieved @13yrs,8.4→7.7%; BP, lipid, ACEI, ASA) vs conventional tx for 7.8yr+ 5.5yr follow-up; ⇨ ↓ death, NNT=5 / 13.3yrs p=0.02, ↓ macro & microvascular events. (Only 1 pt achieved all 5 targets at 13yrs)					
	UGDP [10]: (1971) n=1027; ~8yrs; T2DM. Tolbutamide ↑ CV mortality 2.9x; Phenformin ↑ CV 4x & all cause mortality. Insulin, even with adjustable dosing was no better than diet alone, but no harm. Results criticised e.g. ↑ death in more poorly controlled, etc. 13 yr follow-up.					
	VADT (Dec08) [11]: n=1791, ~5.6yr, Age ~60yr, ♂ mostly, T2DM x 11.5yrs; 40% CAD Hx (Veterans Affairs). Intensive vs standard A1C Achieved: 6.9% vs 8.4%. No significant effect on CV events, deaths 102 vs 95 or microvascular complications; but ↑ serious adverse events 17.6 vs 24.1% mostly hypoglycemia.					

⌖ **UKPDS 80**: 10 year observational follow-up to UKPDS 33 & 34 (Sep08): glycemic difference lost in follow-up, however risk reduction emerged/sustained for endpoints (MI & Death), especially with MF. {SU/Insulin vs control: ↓Death 30.3⇨26.8 per 1000 patient-yrs; MF vs control: ↓ Death 33.1⇨25.9 per 1000 patient-yrs.} 12

T2DM "Prevention" Trials *Pre-diabetes*		Intervention	Results	Summary {Note: "prevention of DM" a non-clinical outcome.}
Effective Options	**FDPS** [13] 4yr, n=522 (Finnish Diabetes Prevention Study)	Age 40-65 (ave 55yrs); BMI ≥25 (mean 31); IGT (a FBG < 7.8mmol/L; 2hBG >7.8 but <11 mmol/L)	Intensive lifestyle vs control {Lifestyle: detailed, individualized counseling with nutritionist; individualized exercise circuit. Goals: ↓ weight >5%, fat <30% of all energy, fibre >15g/1000kcal, & moderate exercise > 30 minutes/day.}	1°: incident diabetes (4yrs): 11% vs 23% RRR= 58% HR = 0.4 (0.3-0.7) NNT/4yrs = 8 Change in Body weight: -4.2 kg (-4.8 to –3.6) vs -0.8 kg (-1.3 to –0.3) control. 7 yr follow-up: effect persists 4.3 vs 7.4cases/100 person-yrs	1) **Intensive Lifestyle Interventions** 3 a. Most effective intervention for patients with IGT b. How intensive was *intensive lifestyle*? i. Individualized counseling/education important ii. Weight loss: goal of at least 5-7% (& up to 10%) iii. Exercise: moderate activity of 30 minutes/day or 150 minutes/week iv. Diet: healthy, low calorie, low fat (<30% of total kcal & <10% saturated fat), ↑ fibre (>15g/1000kcal). 2) **Pharmacological Options** (+ some lifestyle measures) a. Effective but less so than intensive lifestyle* i. Metformin 250-850mg po BID (Meta-analysis[14]) ◆ 6 trials, n=3119, abd. obesity, IGT, family hx: ↓ time to diabetes onset ≤ 3yrs; NNT=12.5 CI: 9.1-20 {better if age <60yr} ii. Orlistat 120mg po TID ◆ Effective if able to tolerate GI side effects; high cost >$150/mo iii. Acarbose 100mg po TID (CV benefit did not persist) ◆ Effective if able to tolerate GI side effects; high cost >$120/mo b. Not Effective or Harm/Outcome Concerns* i. Ramipril: not effective ii. Glitazones (Rosiglitazone & Pioglitazone): effective but concerns {↑wt, ↑ HF, ↑ fracture, (& ?CV Rosi)}[15,16] *Prevention strategies that utilize drugs risk harming otherwise healthy people; knowledge of long term efficacy, safety & impact on healthcare resources need to be established.[17]} Of note: early intensive insulin Tx (x2 wks) may induce remission in some new T2DM.[18]
	IDDP [21] (India) 2.5yr, n=531	Mean age 46yrs; BMI 26 IGT – in Asian Indians	Lifestyle vs metformin 250mg po BID vs control	1°: incident diabetes (2.5yrs): lifestyle 39.3%, NNT=6; metformin 40.5%, NNT=7; 55% control	
	DPP [19] 2.8yr, n=3,234 (Diabetes Prevention Project) [Troglitazone arm stopped early due to liver toxicity[20]]	Age >25 (mean 51yrs); BMI≥24 (mean=34); IGT (FBG of 5.3-6.9 mmol/L, 2hBG of 7.8-11 mmol/L.) 68% ♀; ~45% ethnic	Intensive lifestyle* n=1079 Lifestyle+ metformin 850mg po BID n=1073 Lifestyle + placebo n=1082, or *{Lifestyle: ↓ weight by 7% (healthy diet & exercise ≥ 150 minutes/week), & 16 individualized lessons, covering diet, exercise & behaviour modification. [Low-cal diet: ↓450kcal/day ave; e.g. 1500kcal/d for 80-95kg ☺]}	1°: incident diabetes (2.8yrs): 4.8 cases/100 person yrs for intensive lifestyle 7.8 cases/100 person yrs for metformin, 11 cases/100 person yrs for placebo, ◆NNT= 7 / 2.8yrs for lifestyle (RRR: 58%; 71% age 60+) ◆NNT= 14 / 2.8yrs for metformin (MF) (RRR: 31%) Weight ↓: 5.6kg Lifestyle, 2.1kg MF, 0.1kg (p<0.001)	
	Stop-NIDDM [22] 3.3yr, n=1,429	Age 40-70 (mean 54yrs); IGT (2hBG ≥ 7.8 & <11.1mmol/L, FBG of 5.6-7.7 mmol/L).	Acarbose 100mg TID vs placebo {also encouraged exercise; met with dietitian}	1°: incident diabetes (3.3yrs): 32.4% vs 41.5%; NNT=11 / 3.3 yrs {↓CV events 2.5%; NNT=40}[23] {GI SE's 83% vs 60%; Stop Tx: 31% vs 19%}	
	XENDOS [24] 4yr, n=3,305	Age 30-60;(mean 43yrs); BMI≥30; no CV disease; 21% had IGT	Orlistat 120mg TID vs placebo (weight loss study) {also ↓calorie diet & physical activity encouraged.} {High drop-out rate.}	2°: incident diabetes: 6.2% vs 9% NNT=36/4yrs; ↓ diabetes in IGT subgroup only 18.8% vs 28.8%; NNT=10 {1°: ↓weight 5.8kg vs 3kg; ↑ GI SE's: 91% vs 65%/1yr}	
	DREAM-Rosi [25] 3yr, n=5,269	Age ≥30yrs (~55yrs); IGT +/- IFG or IFG Mean FBG=5.8mmol/l No DM or CV disease (eligibility expanded during trial)	Rosiglitazone 8mg po daily vs placebo {Trial stopped 5months early due to ↓diabetes; but ↑CV event rate approaching statistical significance.}	1°: incident diabetes or death: 11.6% vs 26%; NNT=7/3yrs (driven by diabetes; no difference in death); CV events: 2.9% vs 2.1% HR=1.37; CI 0.97-1.94	
	DREAM-Rami [26] 3yr, n=5,269		Ramipril 15mg po daily (start 5mg/d x2 months, then ↑10mg/d till 1 yr) vs placebo	1°: incident diabetes or death: 18.1% vs 19.5% NS {Also, no difference in CV event rate 2.6% vs 2.4%}	

2hBG=2hr blood glucose BMI=body mass index CV=cardiovascular FBG=fasting blood glucose HC=hypercholesterolemia HF=heart failure hx=history IGT=impaired glucose tolerance MF=metformin PPBG=post-prandial blood glucose SU=sulfonylurea Tx=treatment wt=weight yr=year

Links: CDA Professionals: http://www.diabetes.ca/for-professionals/resources/2008-cpg/ ADA Prevention/delay of type 2 diabetes. http://care.diabetesjournals.org/cgi/content/full/30/suppl_1/S4#SEC14. AACE Prediabetes link [27] NICE T2DM: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11983 COMPUS: link [28]

EXTRAS Page

Upcoming Trials in Diabetes/CV Risk Prevention:

- **NAVIGATOR** (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research); **TRANSCEND** (Telmisartan Randomized Assessment Study in aCE iNtolerant subjects with cardiovascular Disease); **RAPSODI** (rimonabant in diabetes prevention)

Prediabetes [ADA]:

- Includes: 1) Impaired Fasting Glucose {8hr fasting BG between 5.6-6.9mmol/L) & 2) Impaired glucose tolerance {Postprandial BG of 7.8-11.0mmol/L 2hrs post 75g oral glucose challenge}
- Risk factors: family hx, obesity – especially around waist, age >45, hypertension, gestational diabetes hx, sedentary lifestyle. Screening recommendations vary; USPSTF recommends screening particularly if BP >135/80. Oral Glucose Challenge most recommended, but A1c screen also advocated by some.

Insulin Analogues Systematic Review/Reports, 2008: http://cadth.ca/index.php/en/compus/insulin-analogs

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Q&A: Limitations & Unanswered Questions Regarding A1C Control and Clinical Outcome - Benefits or Risks

There are some important qualifiers on the commonly quoted observation that "with every one percent drop in A1C the risk of developing long-term diabetes complications decreases". (Concept originally based on observational data driven by an eye related microvascular endpoint in the UKPDS). Current evidence call this assumption into question.

- Most recently the ACCORD trial (established, higher risk T2DM) was halted after looking at whether a A1C target of <6% would result in beneficial clinical outcomes compared to 7-7.9%. According to the preliminary results still awaiting publication, it would appear from this RCT that the extra 1.1% drop in A1C seen in the intensive group was actually associated with increased all cause death compared to the standard group. Explanations for this are still pending… (See also; http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf).
- With the current RCT evidence with rosiglitazone, there is some concern that lowering A1C does not necessarily result in CV event reductions? With the limited evidence, it appears to at best be neutral, and at worst be harmful in RCTs/durations studied so far (e.g. up to 4 year RCTs.) Patients studied and hypoglycemic agents used may affect the benefit/risk potential.
- The UKPDS-33, ~ 10 year trial saw reductions predominantly in the microvascular events (predominantly photocoagulation), with stroke and heart related endpoints not significant, but trending favorably and contributing to the composite endpoint benefit. (Exception: metformin had all-cause death reduction in obese T2DM in UKPDS-34)
- In UKPDS 34,[p860] which noted a mortality benefit for metformin in obese T2DM, there is inconsistency in the association of A1C & outcomes (less A1C difference but more benefit [UKPDS34 VS 33])
- In UKPDS 34 Metformin + Sulfonylurea combination led to a lower A1C than Sulf alone (7.7 vs 8.2) but had higher incidence of DM death and all cause death (perhaps due to design issues and a several year delay in moving to combination therapy) .
- The UKPDS epidemiologic evidence for the 1% drop in A1C did not control for obesity/BMI/waist circumference. [UKPDS 35]
- In ADOPT, rosiglitazone decreased A1C more that metformin or glyburide, but glyburide had the lowest rate of CV outcomes.
- In VADT, a 1.5% reduction (6.9% [intensive] vs 8.4% [standard]) in A1C for an average follow-up of 5.6 years resulted in no benefit (microvascular or macrovascular) but increased serious adverse events (predominantly hypoglycaemia).

There is some disconcordence between randomized trial outcome evidence and the frequently reported "1% A1C..." benefit. One thing that has growing certainty is that the risks and benefits of drug regimens that lower A1C is more complex than what was previously commonly accepted. While a high A1C is not good, some methods of lowering A1C in some patient groups, may also be harmful. While we do not want to be lazy in addressing glucose control, the evidence suggests that we not assume a net benefit for all A1C lowering interventions in all Type 2 diabetes patients. {*Let the target serve the patient, and not the patient the target.*}

Multfactorial intervention - blood pressure, lipids, possibly ASA, lifestyle – in addition to glucose control, is essential in reducing macrovascular endpoints!

Additional References

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