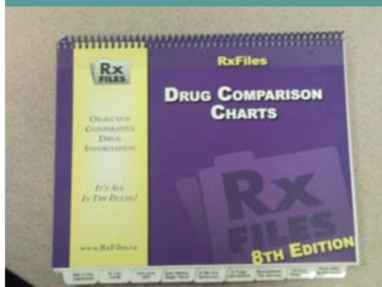
Outcome & Other Considerations of Anti-hyperglycemic Agents

- A comparative look at the various treatment options for lowering BG
- Consideration for both the benefits & harms of drug treatment
- Acknowledgement that lowering BG or A1C does not automatically confer patient benefit (e.g. ACCORD trial ↑ death in intensive glucose lowering arm; rosiglitazone & CV risk)
- Consider evidence from outcome trials
- RxFiles Academic Detailing does not receive any industry funding



Loren Regier, Program Coordinator, RxFiles

www.RxFiles.ca

Last reviewed/updated: November 2011

Saskatoon SK CANADA

Take Home Points for Best Outcomes

- Time-Out!
  - Although this part of the discussion focuses on BG, remember…
    - **Lifestyle interventions**
      - Weight, diet, activity, smoking cessation…
    - **BP lowering, statin**, & ??ASA
      - Especially in high CV risk
  - For intensive lowering of BG
    - **Risk vs benefit** remains uncertain
      - ***It all depends! How intensive & in who?***
        - Lack of macrovascular benefit
        - Some microvascular benefit
        - Possibility of increased mortality in some

          (Boussageon et al. Metaanalysis. BMJ 2011;343:d4169)

Outcomes: benefit with multfactorial intervention– STENO-2

Antihyperglycemics in CDA 08 Guidelines

- Metformin
  - 1st line for most, not just for obese
  - May use: in ↓ renal: 30-60ml/min; adjust dose; HF non-acute
- 2nd line: all other orals (or insulin)
  - Secretagogues: SU's Gliclazide, Glyburide; Glitinides
  - TZD: cautions (HF, fractures, macular edema; ? CV)
  - Sitagliptin, Linagliptin, Saxagliptin
  - Acarbose
  - Weight loss agents: orlistat, sibutramine; surgery
- Advantages / Disadvantages (RxFiles scale)

~ Best				Problem
✓✓✓	✓✓	✓	✖	✖✖

BG - Landmark Outcome Trials - Summary

Diabetes – Blood Glucose (BG) Control: Landmark Outcome Trials – Summary

Loren Regier, Brent Jensen – www.RxFiles.ca – Aug 11

	Trials (Mean follow-up)	Population (Risk, hx, age)	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; mostly retinal • 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.} • BG control ⇨possible microvascular benefit ADVANCE & UKPDS; not ACCORD • 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)[6], but ↑ HF & wt {rosiglitazone: ↑HF, wt, fractures; uncertain CV outcomes (neutral in RECORD, but limitations) [31] • 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] ~2.9yrs; 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=50/2.9yr • ↑wt 3.6kg/yr; ↑HF NNH=31/2.9yr & edema.	
	ACCORD [7] ~3.5yrs; n=10,251; ↑ death maintained @5yr follow-up	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% 7.2% vs 7.6% @~5yrs	• ↑ 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	
	RECORD [31]: n=4447, ~ 5.5yr; T2DM (A1C mean ~ 7.9%⇨7.4-7.9%); open label; metformin or SU + rosiglitazone vs metformin + SU. No difference in CV death, MI; ↑HF & fracture.					
	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)					
	ADDITION-Europe [30] (Aug11): n=3057 new T2DM, age ave ~60; 5.3yrs; multifactorial intensive (A1C, BP, ACEI, cholesterol & lifestyle) ⇨ slight improvement in surrogates (A1C, LDL, BP) but non-significant ↓ in CV events/death; 7.2% vs 8.5%; HR 0.83, 95% CI: 0.65-1.05					
	UGDP [10]: (1971) n=1027; ~8yrs; T2DM. Tolbutamide ↑ CV mortality 2.6x; 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 11.5yr; 40% CAD Hx (Veterans Affairs). Intensive vs standard A1C Achieved: 6.9 vs 8.4%. NS effect: CV event, death 102 vs 95 or microvascular complications; but ↑ serious adverse events 17.6 vs 24.1% mostly hypoglycemia. ↑CVD risk if DBP<70.					

✝ **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
	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 △Body wt: -4.2kg (-4.8 to -3.6) vs -0.8kg (-1.3 to -0.3) control 7 yr follow-up: effect persists 4.3 vs 7.4cases/100 person-yrs 10yr follow-up: no effect on CV or total mortality
...ctive Options	**DPP** [19] 2.8yr, n=3,234 (Diabetes Prevention Project)	Age >25 (mean 51yrs); BMI≥24 (mean=34); IGT (FBG of 5.3-6.9 mmol/L, 2hBG of 7.8-11 mmol/L) [partly obscured]	Intensive lifestyle* n=1079 Lifestyle+ metformin 850mg po BID n=1073 Lifestyle + placebo [partly obscured]	1°: incident diabetes (2.8yrs): 4.8 cases/100 [partly obscured]
	[obscured]	[obscured]	[obscured]	... NNT=30/4yrs; ↓ 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}
	[partly obscured] ...n=5,269 {Canoe Rosi 2mg+MF500mg bid n=207 3.9yr,NNT=4}	...≥30yrs (~55yrs); IGT +/- IFG or IFG Mean FBG=5.8mmol/l	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	No DM or CV disease (eligibility expanded during trial)	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%}
	NAVIGATOR [27] 5yr	IGT & ↑CV risk/disease	Nateglinide: no ↓ in progression to diabetes or ↓CV event. Valsartan ↓diabetes RR 14% but no CV benefit.	

Summary {Note: "prevention of DM" a non-clinical outcome.}

1) **Intensive Lifestyle Interventions ✓**
   a. Most effective intervention for patients with IGT
   b. How intensive was *intensive lifestyle*?
      i. Individualized counseling/education importan[t] [partly obscured]
      ii. Weight loss: ... [obscured]

[obscured] ...e to ... age <60yr)

... 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; valsartan ↓diabetes RR 14%, not CV
      ii. Glitazones (Rosi- & Pio-glitazone Act Now): effective delay, not prevent after D/C but concern {↑wt, edema, ↑HF, ↑fracture, (& ?CV Rosi)}[15,16]
      iii. Nateglinide: ↑ risk of hypoglycemia without any benefits

*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]

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 NS=non-sig PPBG=post-prandial blood glucose SU=sulfonylurea Tx=treatment wt=weight yr=year

Links: CDA Professional: 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[28] NICE T2DM: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11983 COMPUS: link[29] Ann Int Med: link[30]

Comparisons

Death/Major CV Events	
A1C	
Weight {wt loss vs neutral vs wt gain}	
Hypoglycemia risk	
HF / Edema {non-acute}	
LDL	
GI	
Cost	
Other	
Overall	

http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf

Rx FILES

Metformin Glucophage

Metformin dose in UKPDS-34 : 1700mg am; 850mg pm

Death/Major CV UKPDS-34 in Obese	✓ ✓ ✓
A1C	✓ ✓ ✓
Weight {wt loss vs neutral vs wt gain}	✓ ✓ ✓
Hypoglycemia	✓ ✓ ✓
HF / Edema {non-acute}	✓ ✓
LDL	✓ ✓ ✓
GI	✖ Start low & titrate
Cost	✓ ✓ ✓
Other	✓ acute illness/HF/renal
Overall	✓ ✓ ✓

Outcomes: UKPDS-33,**34**,80. (ADOPT; some use in ADVANCE)

Sulfonylureas: Gliclazide / Glyburide

	Diamicron	Diabeta
Death/Major CV	✓	✓
A1C	✓ ✓ ✓	✓ ✓ ✓
Weight	✓	✓
Hypoglycemia	Note: data from regular formulation; ?MR ✖	✖ ✖ sev 1.4%/yr
HF / Edema	✓ ✓	✓ ✓
LDL	✓	✓
GI	✓ ✓	✓ ✓ 1.8%
Cost – (generic)	✓ ✓	✓ ✓ ✓
Other	ADVANCE (+/- MF)	✖ renal/elderly
Overall	✓	✓

Outcomes - Glic: ADVANCE; Glyb: UKPDS-33,80. (Glyb: ADOPT)

TZDs: Pioglitazone / Rosiglitazone

	Actos /	Avandia
Death/Major CV	✓	✖ ?
A1C	✓ ✓	✓ ✓
Weight	✖ ✖	✖ ✖
Hypoglycemia	✓ ✓ ✓	✓ ✓ ✓
HF / Edema	✖ ✖	✖ ✖
LDL	✓	✖
GI	✓ ✓	✓ ✓
Cost	✖	✖ ✖
Other	✖ ?fractures, macular	✖ ?fractures, macular
Overall	✓?	✖ ?

Outcomes– Pio: ProACTIVE. Rosi: Meta-analysis?, RECORD^{interim}. (ADOPT, DREAM)

Acarbose Glucobay

Death/Major CV Events	✓ ✓
A1C	✓
Weight	✓ ✓ ✓
Hypoglycemia	✓ ✓ ✓
HF / Edema	✓ ✓
LDL	✓
GI	✖ ✖
Cost	✓
Other	✓ ✓ PPG, ?laxative, TID
Overall	✓

Outcomes – (Prevention trial: Stop-NIDDM)

Glitinides: Repaglinide / Nateglinide

	Gluconorm	Starlix
Death/Major CV	?	?
A1C	✓ ✓	✓
Weight	✓	✓ ✓
Hypoglycemia	✓	✓ ✓
HF / Edema	✓ ✓	✓ ✓
LDL	✓	✓
GI	✓ ✓	✓
Cost	✓	✓
Other	✓ ✓ PPG, flexible with meals but TID	✓ ✓ PPG, flexible with meals but TID
Overall	✓	✓

Rx FILES

Incretin Related Agents

	Januvia PO Sitagliptin	**Onglyza** PO Saxagliptin	**Victoza** SC Liraglutide	**Byetta** SC Exenatide
Death/Major CV	?	?	?	? ↑HR
A1C effect	✓	✓	✓ ✓	✓
Weight	✓ ✓	✓	✓ ✓	✓ ✓
Hypoglycemia	✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓
HF / Edema	?	?	?	?
LDL	✓	✓	✓ ✓	✓ ✓
GI	✓ ✓	✓ ✓	✓ nvd	✓ nvd
Cost	✖	✖	✖ ✖	✖ ✖
Other	All {✓✓ (PPG); ✖ (new)}			
	? ↑ Infection e.g. URTI		inj site; ??Pancreatitis; ??ca	
Overall	?	?	?	?

Insulin in T2DM

Range of Intensity: Less (NPH HS + MF) --- More (MDI)

	Less (NPH HS + MF)	More (MDI)
Death/Major CV	✓ ✓?	✓ ✓?/ ✖ ✖?
A1C	✓ ✓	✓ ✓ ✓ ✓
Weight	✓	✖ ✖
Hypoglycemia	✓	✖ ✖ 1.8%/yr
HF / Edema	✓	✓
LDL	✓	✓
GI	✓ ✓ ✓	✓ ✓ ✓
Cost	✓	✖ ✖
Other	✓ Fear/perception	✓ ✓ PPG, fear
Overall	✓ ✓?	✖? - ✓? - ✓ ✓?

Outcomes – UKPDS-33,80; ADVANCE, ACCORD. (T1DM: DCCT/EDIC)

(Also Boussageon et al. Metaanalysis. BMJ 2011;343:d4169)

Metformin

- Unique: decrease all-cause mortality
  - **NNT=14 / 10yrs** [UKPDS-34]
- Start low: 250-500mg … daily or BID
  - Titrate up: 1g BID; (2550/day [UKPDS-34])
- MF + insulin (in T2DM):
  - less wt gain, less insulin required …
- Precautions are not contraindications
  - Renal (lower dose if CrCl $30\text{-}60_{ml/min;}$ avoid if $<30_{ml/min}$)
    - – Caution in acute illness, unstable renal function
  - HF (if non-acute/non-decompensated)
  - Hepatic

– {See RxFiles Q&A: Metformin Precautions}

Secretagogues

- **Sulfonylureas** (glyburide, gliclizide)
  - Outcome benefit: UKPDS, ADVANCE
    - Microvascular: yes; Macrovascular/Death: maybe
      - At the risk of hypoglycemia & hospitalizations
  - 75% effect often at lower half of dosing range
    - Glyburide: 2.5mg daily – 7.5mg BID
    - Gliclazide: MR daily; less hypoglycemia than glyburide
- **Glitinides** (repaglinide, nateglinide)
  - Consider for meal flexibility or PPG control
  - Repaglinide: more A1C reduction than nateglinide

Rx FILES

TZDs

- Effective but Concerns
  - HF, Wt, macular edema, fracture distal, women, other
- **Rosiglitazone** CV controversy
  - ADA unanimously advised against using OCT08
  - Health Canada - restrictions
    - CV: neutral or possible increased MI/CV risk
      - a CDA-2008 option, but other options available
- **Pioglitazone**
  - Outcomes:
      - ProACTIVE - Macrovascular: maybe (with qualifiers e.g. HF)
        - Secondary outcome (primary outcome not significant)
  - Option in renal dysfx, intolerance to MF
  - Uncertainties: e.g. association with bladder ca

Rx FILES

Acarbose

- Some positive CV outcome data
  - (Stop-NIDDM diabetes prevention trial)
    - 2ndary – reduce CV events; NNT=40/3.3yrs
- Good but…
  - Minimal A1C lowering
  - GI side effects…VERY COMMON
    - How much…
  - TID dosing
  - Rare hepatic ADRs

Rx FILES

Sitagliptin Januvia & Saxagliptin Onglyza

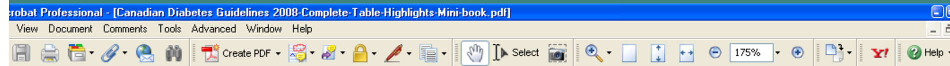
New Kids...

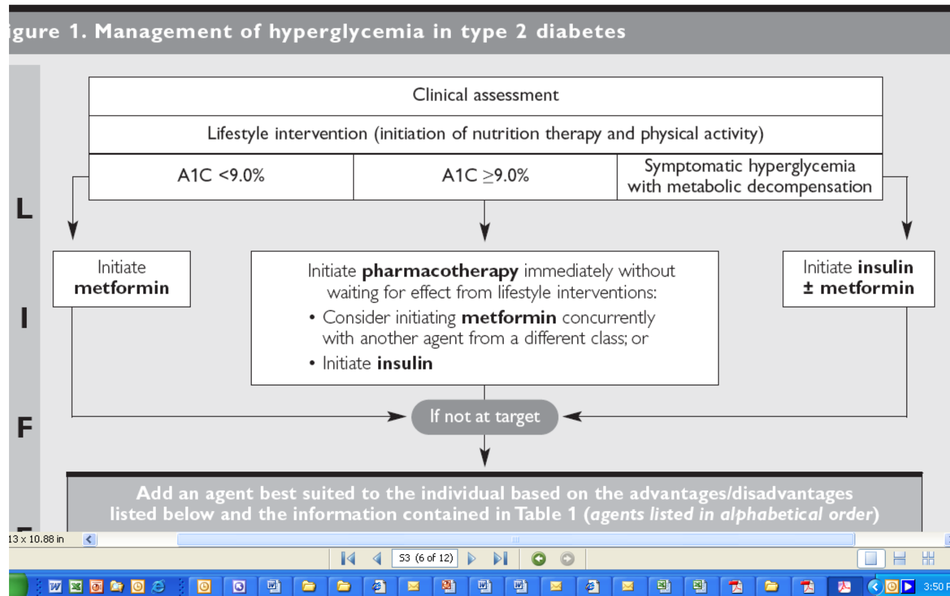
- Advantages
  - Great for PPG Hypoglycemia
  - Weight neutral
  - Well tolerated
- Disadvantages
  - No outcome data
  - Long-term safety??
    - Real world use
    - Infections, skin Rx [SJS]
  - Cost $300/3 month
- Watch for:
  - A1C claims: generally 0.5-0.8% (0.7% [Cochrane])
    - Greater effect:
      - in combo with MF, in newer pts & if higher initial A1C
  - Will safety hold up in post-marketing period?
    - Infection rates (URTI, UTI) / immune system?, SJS, ca
  - Beta cell preservation potential???
  - {See RxFiles Q&A: Sitagliptin}

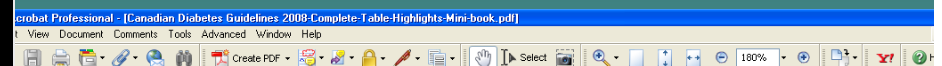
Rx FILES

Clinical Practice Guidelines CDA – 2008

Add an agent best suited to the individual…
advantages/disadvantages…
listed in alphabetical order.







If not at target

Add an agent best suited to the individual based on the advantages/disadvantages listed below and the information contained in Table 1 (*agents listed in alphabetical order*)

Class	*A1C*	*Hypoglycemia*	*Other advantages*	*Other disadvantages*
Alpha-glucosidase inhibitor	↓	Rare	Improved postprandial control Weight neutral	GI side effects
Incretin agent: **DPP-4 inhibitor**	↓to↓↓	Rare	Improved postprandial control Weight neutral	New agent (unknown long-term safety)
Insulin	↓↓↓	Yes	No dose ceiling Many types, flexible regimens	Weight gain
Insulin secretagogue:				
Meglitinide	↓to↓↓	Yes*	Improved postprandial control	Requires TID to QID dosing
Sulfonylurea	↓↓	Yes	Newer sulfonylureas (gliclazide, glimepiride) are associated with less hypoglycemia than glyburide	Weight gain
TZD	↓↓	Rare	Durable monotherapy	Requires 6–12 weeks for maximal effect Weight gain Edema, rare CHF, rare fractures in females
Weight loss agent	↓	None	Weight loss	GI side effects (orlistat) Increased heart rate/BP (sibutramine)