APPROACH TO MANAGEMENT OF TYPE 2 DIABETES

Nonpharmacologic Therapy

- **Lifestyle Modifications** [1] & **Patient Education** are important at all levels!!! [2,3,4]

If individualized goals for glucose are not achieved in 2-4 months,
⇨reassess; advance to next level of therapy

See Health Canada's Food & Fitness Guides

Oral Hypoglycemic Monotherapy

MF target dose in UKPDS (age ≤65): 1700mg am + 850mg @supper (↓mortality)

If obese (BMI ≥30)
- ⇨ start metformin (**MF**) **500mg po OD** or BID (↑dose over 3-4 weeks; usual ≤2,000mg/day; lower doses in elderly-see Table 6)
- ⇨ alternative agents used if metformin contraindicated/not tolerated (e.g. acarbose, sulfonylureas, repaglinide, "glitazones"; see chart)

If non-obese
- ⇨ start sulfonylurea (SU) or metformin (↑dose over 3-4 weeks)
- ⇨ consider acarbose or repaglinide if main target is **PPBG**
- ⇨ alternative agents such as "glitazones" may also be considered (note these agents can take a long time before effect seen (8-16 weeks). There are theoretical advantages to early use, but await studies on morbidity and mortality outcomes

Repeat A1C ; Reassess lifestyle modifications in 2-4 months,
⇨If targets for glucose control not achieved, advance combination therapy
(Combination therapy will be required in most Type 2 patients)

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

- a variety of 2-drug combinations may be considered esp. if A1C ≥9% initially (see Table 7)
- combination of repaglinide and sulfonylureas not usually recommended

Repeat A1C ; Reassess lifestyle modifications in 2-4 months,
⇨If targets for glucose control not achieved, advance to next level of therapy

Add Insulin Therapy +/- Oral Agents

- **Option 1: Bedtime insulin** (e.g. Humulin N/Novolin N) **+ daytime oral hypoglycemics**
  - ⇨**if** on SU + other oral agent, may consider discontinuing / reducing the SU
  - **- add intermediate acting insulin, 5-15units at HS (initial ~0.1units/kg; max 0.25units/kg)**
  - -↑ insulin dose by **2 units every 3-4 days** until fasting glucose of 4 -7
  - -may result in better control, lower insulin dose, less weight gain than insulin alone
  - -if target BG not achieved at 30units/day, or if daytime BG rises, may switch to split-mixed insulin or a more intensive regimen (usual range: 0.25-1unit/kg/d)
- **Option 2: Switch to insulin therapy 1-4x/day**
  - ⇨may discontinue certain oral hypoglycemics (see Table 7)
  - -adjust insulin dose and frequency to achieve target levels
  - **e.g. Split-mixed insulin regimen**
  - -estimate total starting daily dose (0.3-0.6 units/kg)
  - -divide daily dose: 2/3 in morning before breakfast; 1/3 in evening before supper
  - -divide each dose: 2/3 intermediate-acting & 1/3 short-acting insulin (or 30/70 mix)

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

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

GLUCOSE TARGETS Canadian **2003**

	Target for most	Normal range	→consider achieving
A1C q3-6 mon (calibrate meter qyr)	**≤ 7**	**≤ 6**	**if** can be done
FPG (mmol/L)	**4-7**	**4-6**	**safely** without
PPBG (mmol/L) 2hr post	**5-10**	**5-8**	hypoglycemia etc..

Note: role for individualizing targets (ie. less aggressive in frail elderly [31]; more aggressive in younger candidates).

BP [2004] Diabetes→**130/80** if no proteinuria; **125/75** if proteinuria >1g/d. **LIPID** [2003] Diabetes→ LDL<**2.5** Total Chol/HDL<**4**

RENAL	Normal	Microalbuminuria	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

BMI (kg/m²)		WEIGHT (Kg; *lbs*)																	
		45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130
		99	*110*	*121*	*132*	*143*	*154*	*165*	*176*	*187*	*198*	*209*	*220*	*231*	*242*	*253*	*264*	*275*	*286*
HEIGHT (Cm; *inches*)	150 *59*	**20**	**22**	**24½**	26½	29	31	33	35½	38	40	42	44½	46½	49	51	53	55½	58
	155 *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
	190 *75*	12½	14	15	16½	18	**19½**	**21**	**22**	**23½**	25	26	27½	29	30½	32	33	34½	36
	195 *77*	12	13	14½	16	17	18½	**19½**	**21**	**22½**	**23½**	25	26	27½	29	30	31½	33	34

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

Table 6: Individualization of Drug Therapy: Special Considerations

Patient Factor	Consider ⇨ possibly preferred drugs
Renal failure *	**"Glitazones"**, **repaglinide**; also tolbutamide or gliclazide [5], insulin
Hepatic disease	**Insulin, repaglinide,** acarbose (Caution:glyburide,metformin& glitazones)
Hypoglycemia	**Metformin**, "**Glitazones"**, **Acarbose**; also repaglinide, nateglinide, gliclazide & glimepiride; insulin glargine
Obese	**Metformin**; Acarbose; also "Glitazones"
Irregular mealtimes	**Repaglinide** (may be preferred over SU)
PPBG >10mmol/l & FPG minimally ↑'d	**Repaglinide** or **Acarbose** **Insulin lispro** *HUMALOG* (**if PPBG very high**)

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

Maximum 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 (long-term outcomes not well studied!)
SU + MF	↓↓↓	↑↑	↑	•if SU initial agent, may add MF or a TZD; (SU+MF may ↓A1C by additional 1.7%; one study found ↑mortality with combination[12]) •if MF initial agent, may add SU or repaglinide •**MF combos generally result in less weight gain than SU combinations**; •MF+pioglitazone had positive lipid effects; •MF+acarbose: ↓ weight / PPBG but ↑GI SEs; •for hypoglyc. on acarbose: must treat with glucose as sucrose not absorbed
SU + TZD [13]	↓↓	↑↑	↑↑	
SU + acarbose	↓	↑↑	↑	
MF+ repaglinide[14]	↓↓	↑	↑	
MF+ TZD[15,16]	↓↓	↑	↑	
MF+ acarbose[17]	↓	-	↓	
TZD + acarbose	↓	↑	↑	
Insulin monotherapy	↓↓↓	↑↑↑	↑↑↑	•tight BG control but **hypoglycemia/weight gain**
Insulin + SU	↓↓↓	↑↑	↑↑	•may improve glycemic control over insulin alone; caution in elderly due to **hypoglycemia**
Insulin + MF (FINFAT STUDY [18])	↓↓↓	↑	↑	•**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*	↓↓[19]	↑↑↑	↑↑↑	•**overcomes insulin resistance**; effective but more study needed (e.g. ↑ **risk of edema/HF**[20])
Insulin+ repaglinide	↓↓	↑↑	↑↑	•option to ↓ PPBG
Insulin + acarbose	↓↓	↑↑↑	↑↑↑	•recommended to ↓ PPBG when diet high in CHOs; may also ↓ weight & triglycerides
•some **3-drug regimens** useful for glycemic control but not well studied (e.g. Insulin+SU+MF)				

A1C = glycosylated hemoglobin **BG**= blood glucose **CHO**= carbohydrate **FPG**= fasting plasma glucose
HF= heart failure **MF**= metformin **PPBG** = postprandial blood glucose **SE**= side effects
SU= sulfonylurea **TZD**= pioglitazone & rosiglitazone **Wt**= weight *official labeling: "not indicated"

Oral HYPOGLYCEMIC AGENTS (OHA) - Comparison Chart [21,22,23,24,25,26,27,28,29,30,31,32,33,34]

Prepared by: Loren Regier, Sharon Downey, Brent Jensen–*www.RxFiles.ca*

Sept 05

Generic/TRADE/ (Strength) Pregnancy	KINETICS	EFFECTS ON: FPG	PPBG	A1C	LDL	HDL	TGs	Wt	DRUG INTERACTION	COMMENTS	INITIAL & (Max.) DOSE	USUAL DOSE RANGE	$ /100 day
SULFONYLUREAS (SU) Insulin Secretagogue – stimulate insulin release from β cell; ↑ peripheral glucose utilization (↑ #/sensitivity of insulin receptors?); reduce hepatic gluconeogenesis													
Chlorpropamide C DIABINESE, generic (100, 250mg scored tabs)	P = 6-8h D =24-**72h**	chlorpropamide **not** recommended due to ↑BP & ↑ retinopathy (UKPDS-33)							**Numerous:** • ↑ Hypoglycemic effect with: **EtOH**, NSAIDs,salicylates, sulfonamides, MAOIs, cimetidine. • β-Blockers may mask hypoglycemia • Disulfiram rx. with EtOH, mostly with chlorpropamide • rifampin ↓ effect	Does not correct impaired 1st phase insulin response; many (~75%) require 2nd agent for adequate control (e.g. + metformin or TZD); ~1st choice option for **lean** patient	100mg od (500mg od)	100mg po od 250mg po od	16 **13**
Gliclazide,generic✘▼ DIAMICRON 80ς mg tab; DIAMICRON MR 30ς mg tab C	P = 4-6h D=10-**24h**	↓	↓	↓ 1-1.5	-	-	-	↑↑		**Hypoglycemia**: most with chlorpropamide & glyburide (see note below); **least**: tolbutamide, glimepiride[35,36] & gliclazide [37] Caution in elderly (hypoglycemia risk) & obese (wt gain). **Require consistent food intake** to avoid problems with hypoglycemia (↑risk: elderly, debilitated, malnourished)	40mg (160mg bid) 30mg (120mg od)	80mg po bid 60mg MR po od	**72** 89
Glyburide C DIABETA,generic (2.5, 5mg scored tabs)	O=15-60min P= 2-4h D =12-**24h**	Total Wt gain with glyburide >4kg vs **>6kg insulin** (UKPDS-33)								**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, agents achieve ~75% of effect at **1/2** their max dose.	1.25-2.5mg od (10mg bid $33)	5mg po od 5mg po bid 7.5mg po bid	15 **20** 26
Tolbutamide,generic C ORINASE (500mg scored tab)	P= 3h D=6-**12h**	**Glimepiride** AMARYL ✘ ⊗(1,2,4mg scored tab) 1mg od ($90); 2mg od ($90); 4mg od ($90) /100days C									250mg od (1000mg tid)	500mg po bid 500mg po tid	27 **37**
BIGUANIDES – increase insulin sensitivity and cellular glucose uptake & utilization; reduce hepatic glucose production; ↓ morbidity & mortality in obese patients (UKPDS-34)													
Metformin [38] (MF) GLUCOPHAGE,generic (500ς, 850mg tab) B	P = 3h D = 8-12h	↓	↓	↓ 1-1.5	↓	↑	↓	-/↓	• **EtOH** and cimetidine ↑ effect • contrast media (long-term ↓ B_{12} & folate absorption) {**Caution if CrCl ≤ 60ml/min**}	**Does not by itself cause hypoglycemia** Possible **wt loss** vs wt gain; **⇨ DOC for OBESE !** **SE**: To avoid **GI** SEs, **start low & titrate up q2-4wk** Anemia 6-8:100 (due to B12 malabsorption) Avoid if **severe renal dysfx/CHF** or hepatic disease (lactic acidosis 1:10,000)[7]. +SU, TZD, Ins., CMBA **Elderly**: dose reduction required.[39] May **prevent** NIDDM [40 DPP]	**250-500mg od** (850mg tid)	500mg po bid 850mg bid [DPP] 1g po bid 1700mg po am, 850mg po pm: **UKPDS**	22 **42** **35** 59
Metformin/Rosiglitazone AVANDAMET ☎ ⊗ tabs (500mg/1,2,4mg BID =$150, $260, $350 /100day tab; 1gm/2,4mg =$280, $380)									**+'ve effect on lipids & weight**		TID dosing option for larger doses to ↓ GI intolerance (dyspepsia, nausea & diarrhea)		
α GLUCOSIDASE INHIBITORS –inhibit α-glucosidases in brush border of small intestine; prevent hydrolysis & delay carbohydrate digestion (Tx hypoglycemia with glucose/Insta-gluc, honey or milk)													
Acarbose B PRANDASE (50,100mg scored tabs)	**Meal-time dosing**; may take several weeks for max. effect	acarbose minimally absorbed; monitor 2hr PPBG							• ↓ digoxin effect • Cholestyramine & cathartics ↑ effect • amylase & pancreatic enzymes ↓ effect •↓ Fe^{++}? (**sucrose** not absorbed)	**Does not by itself cause hypoglycemia** ↑ Liver enzymes = 3% with acarbose; monitor. (Caution as may accumulate in chronic renal failure.) **SE: GI intolerance**: **flatulence** [>41%], **diarrhea** [>28%], Maximal effect takes weeks; **↑ dose q4-8wks** **ROLE**: useful in pts with **↑ PPBG**; + SU, MF; (+Ins.?)	**25mg od** (100mg tid) STOP-NIDDM 41	50mg po tid 100mg po tid	94 **127**
Miglitol (**not yet available in Can.**) ✘ ⊗ GLYSET (25,50,100mg tab) B		↓	↓↓	↓ .5-.8	-	-	-/↓	-/↓			25mg od (100mg tid)	25mg po tid 50mg po tid	N/a **N/a**
		miglitol well absorbed											
THIAZOLIDINEDIONES (TZDs) or GLITAZONES –Insulin Sensitizers: ↓ hepatic output of glucose & ↑ peripheral insulin uptake; ~ 4+ weeks before effect (adjust dose at ~3 months)													
Pioglitazone ☎ ✆ ACTOS (15, 30, 45 mg tab) C	**Delayed action**… Onset ~3wks	↓	↓	↓	-	↑	↓	-/↑	• Cholestyramine ↓ absorption ~70% • Hepatic CYP 2C8 • rosigl. not CYP 3A4 • ↓ effect of oral contraceptives? • rosigl. ↑ by gemfibrozil & ↓ by rifampin	More effective in obese or hyperinsulinemia patients **Does not by itself cause hypoglycemia**; resumption of ovulation in anovulatory premenopausal women **SE: Edema 4.8%** (**HF** [42,43],HTN);**Wt gain**; 1% mild anemia (due to hemodilution?);monitor **liver fx** (**ALT**) when indicated;pioglitazone may have more +ve lipid effect [44,45] **ROLE**: + MF,SU; (possibly alone or + Ins. but ↑HF risk)	15mg od (45mg/day)	15mg po od 30mg po od 45mg po od	249 **338** 491
Rosiglitazone ☎ ✆ AVANDIA (2, 4, 8mg tab) C	**Max effect in 8-16 wks**	↓	↓	↓ 1-1.5	46,47 -/↑	48,49 ↑	-/↓	-/↑			4mg od (4mg bid) bid dose ~more effective (50)	4mg po od 4mg po bid 8mg po od	246 465 **340**
CARBAMOYL BENZOIC ACID DERIVATIVES (CMBAs) – short-acting insulin secretagogue; bind to β cell to stimulate insulin release at different site than SUs; (adjust dose at ~7days)													
Nateglinide ☎ ▼ STARLIX (60, 120, 180mg tab) C	O = <**20min** P=60-120min D = ~**4h**	↓	↓↓	↓.5	-	-	-	-/↑	• CYP inhibitors ↑ effect: azole-antifungals, erythromycin, gemfibrozil •CYP inducers ↓ effect: barbs, carbamaz & rifampin	Restores 1st phase insulin release - (↓ PPBG) Rapid, short duration ⇒ ↓ 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	60mg tid ac (180mg po tid)	60mg po tid 120mg po tid 180mg po tid	} **200**
Repaglinide ☎ ▼ 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	} **110** 220

= ↓ dose for renal dysfx ς =scored tab $ Cost =total cost & markup in Sask; ☎ = Exception Drug Status in SK ✘ = Non-formulary in SK ✆ =prior approval for NIHB ⊗=not covered by NIHB ▼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 **PPBG**= postprandial blood glucose **SE**= side effects **Wt**= weight ς = scored tablet

Drug induced ↑ glucose: antipsychotics, corticosteroids, cyclosporine, diuretics (thiazides [e.g. >25mg HCT]), estrogens, interferon [alpha], nicotinic acid [↑ dose] , phenytoin, sympathomimetics (decongestants), tacrolimus & thyroid meds. Beta-blockers minimal risk of altering glucose control but may alter/mask hypoglycemic response. **Pregnancy:** Encourage diet, moderate exercise; Avoid oral hypoglycemics; Add **insulin** as needed if FBG >5.5 & 2hr PPBG >7.[51]

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 progression of Type 2 diabetic disease, combo therapy with oral agents &/or addition of insulin to the regimen may eventually be required. **PPBG may better reflect risk of cardiovascular disease & all-cause mortality than FBG[52]; FBG & A1C are greater predictors of microvascular complications.**

•Consider: [53] **ASA** ~81mg/d, control of **lipids, diet/exercise,** orlistat [54], **↓ hypertension** [ACE Inhibitor/ARB/thiazide] **& DC smoking!**

New: not in → Exenatide **BYETTA** ✘ ⊗ an incretin mimetic 5-10mcg SC bid ac, ↑ insulin secretion, may ↓wt & ↑nausea. Pramlintide **SYMLIN** ✘ ⊗ an amylinomimetic, 15-60-120mcg SC tid ac may ↓wt & ↑ nausea.

[1] Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001 May 3;344(18):1343-50.
[2] Canada's food guide to healthy eating. Website: **http://www.hc-sc.gc.ca/hppb/nutrition/pube/foodguid/index.html**
[3] Health Canada's Fitness and Healthy Living. Website: **http://www.hc-sc.gc.ca/hppb/fitness**
[4] Impact of Intensive Lifestyle and Metformin Therapy on Cardiovascular Disease Risk Factors in the Diabetes Prevention Program. Diabetes Care. 2005 Apr;28(4):888-894.
[5] Charpentier G, Riveline JP, Varroud-Vial M. Management of drugs affecting blood glucose in diabetic patients with renal failure. Diabetes Metab 2000;26 Suppl 4:73-85
[6] Stang M, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. Diabetes Care 1999;22:925-7.
[7] Lalau JD and JM Race. Lactic acidosis in metformin therapy. Drugs 1999;58 Suppl 1:55-60.
[8] Salpeter SR, Greyber E, Pasternak GA, et al. Risk of Fatal and Nonfatal Lactic Acidosis With Metformin Use in Type 2 Diabetes Mellitus: Systematic Review and Meta-analysis. Arch Intern Med. 2003 Nov 24;163(21):2594-602.
[9] Lalau JD and Race JM. Metformin and lactic acidosis in diabetic humans. Diabetes, Obesity and Metabolism 2000;2:131-137.
[10] Micromedex 2005; Drugs in Pregnancy and Lactation, 7th ed. Briggs GE, Freeman RK, Yaffe SJ, editors. Williams and Wilkins; Baltimore, MD: 2005.; Hansten & Horn-Drug Interactions 2005.
[11] Rosenstock J. Management of type 2 diabetes mellitus in the elderly. Drugs & Aging 2001;18(1)31-44.
[12] Fisman EZ, Tenenbaum A, et al. Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7.7-year follow-up. Clin Cardiol. 2001 Feb;24(2):151-8.
[13] Gale, EAM. Lessons from the glitazones: a story of drug development. Lancet 2001;357:1870-75.
[14] Moses R, Slobodniuk R, Boyages S, Colagiuri S et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 1999 Jan;22(1):119-124
[15] Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. JAMA 2000;283(13):1695-1702.
[16] Einhorn D, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The pioglitazone 027 study group. Clin Ther 2000 2000;1395-1409.
[17] Rosenstock J, Brown A, Fisher J, Jain A et al. Efficacy and safety of acarbose in metformin-treated patients with type 2 diabetes. Diabetes Care 1998;21(12):2050-2055.
[18] Yki-Jarvinen H, Ryysy L, Nikkila K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized controlled trial. Ann Intern Med 1999;130:389-96.
[19] Raskin P, Rendell M, Riddle MC et al. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. Diabetes Care 2001 Jul;24(7):1226-32
[20] Krentz AJ, Bailey CJ, Melander A. Thiazolidinediones for type 2 diabetes: new agents reduce insulin resistance but need long term clinical trials. BMJ 2000;321:252-3.
[21] Chehade AM, Mooradian AD. A rational approach to drug therapy of type 2 diabetes mellitus. Drugs 2000;60(1):95-113.
[22] Drug Information Handbook 10th Edition. Lacy CF et al (editors). American Pharmaceutical Association. Lexi-Comp Inc, Hudson Ohio, 2002-2003 edition.
[23] Boctor, MA. Diabetes Mellitus in Therapeutic Choices (3rd edition). Gray, Jean (editor). Canadian Pharmacists Association. Web-com Ltd, Ottawa, ON, 2000.
[24] Management of Type II Diabetes. Clinical Trends in Pharmacy Practice, 3rd issue, 1997 (p46-52).
[25] Campbell IW. Antidiabetic drugs present and future. Drugs 2000; 60 (5): 1017-28.
[26] Rendell MS and Kirchain WR. Pharmacotherapy of Type 2 Diabetes Mellitus. Ann Pharmacother 2000; 34:878-95.
[27] Yki-Jarvinen, H. Management of Type 2 Diabetes Mellitus and cardiovascular risk- lessons from intervention trials. Drugs 2000; 60(5): 975-83.
[28] Meltzer S, Leiter L, Daneman D. et al 1998 **Clinical practice guidelines** for the management of diabetes in **Canada**. CMAJ **1998**;159 (8 Suppl).
[29] American Diabetes Association: **Clinical Practice Recommendations 2003**, Diabetes Care 2003 26:Supplement 1.
[30] **Treatment Guidelines**: Drugs for Diabetes. **The Medical Letter**: September, **2002**; (1) pp. 1-6.
[31] Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/**American Geriatrics Society** Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc. **2003** May;51(5 Suppl Guidelines):S265-80.
[32] **Canadian 2003 Diabetes Guidelines** http://www.diabetes.ca/cpg2003/download.aspx
[33] Cheng AY, Fantus IG. Oral antihyperglycemic therapy for type 2 diabetes mellitus. **CMAJ**. **2005** Jan 18;172(2):213-26.
[34] Krentz AJ, Bailey CJ. Oral antidiabetic agents : current role in type 2 diabetes mellitus. **Drugs**. **2005**;65(3):385-411.
[35] Dills DG, Schneider J. Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study. Glimepiride/Glyburide Research Group. Horm Metab Res. 1996 Sep;28(9):426-9.
[36] Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. Diabetes Metab Res Rev. 2001 Nov-Dec;17(6):467-73.
[37] Graal MB, Wolffenbuttel HR. The use of sulphonylureas in the elderly. Drugs and Aging 1999;15(6):471-81.
[38] Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med. 2002 Jul 2;137(1):25-33.
[39] Lalau JD and Race JM. Metformin and lactic acidosis in diabetic humans. Diabetes, Obesity and Metabolism 2000;2:131-137.
[40] Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002 Feb 7;346(6):393-403 (Diabetes Prevention Program Research Group. Effects of withdrawal from metformin on the development of diabetes in the diabetes prevention program. Diabetes Care. 2003 Apr;26(4):977-80. The primary analysis of the DPP demonstrated that metformin decreased the risk of diabetes by 31%. The washout study shows that 26% of this effect can be accounted for by a pharmacological effect of metformin that did not persist when the drug was stopped. After the washout the incidence of diabetes was still reduced by 25%.)
[41] Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003 Jul 23;290(4):486-94.
[42] Delea TE, Edelsberg JS, Hagiwara M, Oster G, Phillips LS. Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. Diabetes Care. 2003 Nov;26(11):2983-9.
[43] Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LH, Kahn R; American Heart Association; American Diabetes Association. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation. 2003 Dec 9;108(23):2941-8.
[44] Gegick C, Altheimer M. Comparison of effect of thiazolidinediones on cardiovascular risk factors: observations from a clinical practice. Endocr Pract 2001;7:162-169.
[45] Blickle J. Thiazolidinediones: donnees cliniques et perspectives (French language). Diabetes Metab 2001;27:279-285.
[46] Lebovitz HE, Dole JF, Patwardhan R, et al. Rosiglitazone monothreapy is effective in patients with type 2 diabetes. J Clin Endocrinol Metab 2001;86:280-8.
[47] Chiquette E, Ramirez G, Defronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. Arch Intern Med. 2004 Oct 25;164(19):2097-104.
[48] Yki-Jarvinen Hannele, Drug Therapy: Thiazolidinediones. N Engl J Med 2004;351:1106-18.
[49] Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of **pioglitazone and rosiglitazone** in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005 Jul;28(7):1547-54.
[50] Phillips LS, Grunberger G, Miller E, Patwardhan R, et al.. Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. Diabetes Care. 2001 Feb;24(2):308-15.
[51] Crowther CA, Hiller JE, et al.; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005 Jun 16;352(24):2477-86. Epub 2005 Jun 12. (InfoPOEMs: This randomized controlled trial of treatment of gestational diabetes mellitus (GDM) validates the current practice in the United States to screen for GDM. Treatment leads to a reduction in serious perinatal complications with a number needed to treat of 34. It did not reduce risk of cesarean delivery or admission to neonatal special care nursery. Maternal quality of life may be improved, but data from this study regarding that outcome were limited. This study did not address the important question of whether it is more beneficial to screen all pregnant women or only those with risk factors for GDM. (LOE = 1b))
[52] Hanefeld M, Temelkova-Kurktschiev T. The postprandial state and the risk of atherosclerosis. Diabet Med 1997;14(suppl 3):S6-S11.

[53] Gaede P, Vedel P, Larsen N, Jensen GV, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes (STENO-2) . N Engl J Med. 2003 Jan 30;348(5):383-93.
[54] Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004 Jan;27(1):155-61. Erratum in: Diabetes Care. 2004 Mar;27(3):856.
[55] Scheen AJ. Renin-angiotensin system inhibition prevents type 2 diabetes mellitus. Part 1. A meta-analysis of randomised clinical trials. Diabetes Metab. 2004 Dec;30(6):487-96.
[56] Padwal R, Majumdar SR, Johnson JA, Varney J, McAlister FA. A systematic review of drug therapy to delay or prevent type 2 diabetes. Diabetes Care. 2005 Mar;28(3):736-44.
[57] Li Z, Maglione M, Tu W, Mojica W,et al. Meta-analysis: pharmacologic treatment of obesity. Ann Intern Med. 2005 Apr 5;142(7):532-46.
(CONCLUSIONS: Sibutramine, orlistat, phentermine, probably diethylpropion, bupropion, probably fluoxetine, and topiramate promote modest weight loss when given along with recommendations for diet. Sibutramine and orlistat are the 2 most-studied drugs.)
(InfoPOEMs: On the basis of flimsy evidence of benefit, The American College of Physicians recommends drug therapy for the treatment of obesity. They also recommend gastric bypass surgery, performed by an experienced surgeon, for patients with marked obesity and other risk factors for premature death. (LOE = 5))

Additional articles:

Chanoine JP, Hampl S, Jensen C, et al. Effect of **orlistat** on weight and body composition in obese adolescents. A randomized controlled trial. JAMA 2005;293:2873-83. (InfoPOEMs: Orlistat (Xenical), in combination with diet, exercise, & behavioral modification, improves weight management in obese adolescents. No major safety issues were identified after 1 year, but further follow-up for sustained weight management and safety is important. (LOE = 1b))

Ehrmann DA. **Polycystic ovary** syndrome. N Engl J Med. 2005 Mar 24;352(12):1223-36.

Ioannides-Demos LL, Proietto J, McNeil JJ. Pharmacotherapy for **obesity**. Drugs. 2005;65(10):1391-418.

Kanaya AM, Herrington D, Vittinghoff E, et al. Impaired fasting glucose and cardiovascular outcomes in **postmenopausal women** with coronary artery disease. Ann Intern Med. 2005 May 17;142(10):813-20. (Among postmenopausal women with coronary artery disease, the 2003 definition for impaired fasting glucose was **not** associated with increased risk for new CHD, stroke or TIA, or CHF).

Medical Letter May 23,2005: **Pramlintide** for Diabetes.

Onady G, Stolfi A. Insulin and oral agents for managing **cystic fibrosis**-related diabetes. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004730.

Palomba S, et al. A randomized controlled trial evaluating metformin pre-treatment and co-administration in non-obese insulin-resistant women with **polycystic ovary** syndrome treated with controlled ovarian stimulation plus timed intercourse or intrauterine insemination. Hum Reprod. 2005 Jun 15.

Saenz A, Fernandez-Esteban I, Mataix A, et al. Metformin monotherapy for type 2 diabetes mellitus. **Cochrane** Database Syst Rev. 2005 Jul 20;(3):CD002966. CONCLUSIONS: Metformin may be the first therapeutic option in the diabetes mellitus type 2 with overweight or obesity, as it may prevent some vascular complications, and mortality. Metformin produces beneficial changes in glycaemia control, and moderated in weight, lipids, insulinaemia and diastolic blood pressure. Sulphonylureas, alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, insulin, and diet fail to show more benefit for glycaemia control, body weight, or lipids, than metformin.

Treatment Guidelines: **Drugs for Diabetes**. The **Medical Letter**: August, **2005**; (3) pp. 57-62.

Wahrenberg H, Hertel K, Leijonhufvud BM, Persson LG, Toft E, Arner P. Use of **waist circumference** to predict insulin resistance: retrospective study. BMJ. 2005 Jun 11;330(7504):1363-4. Epub 2005 Apr 15.