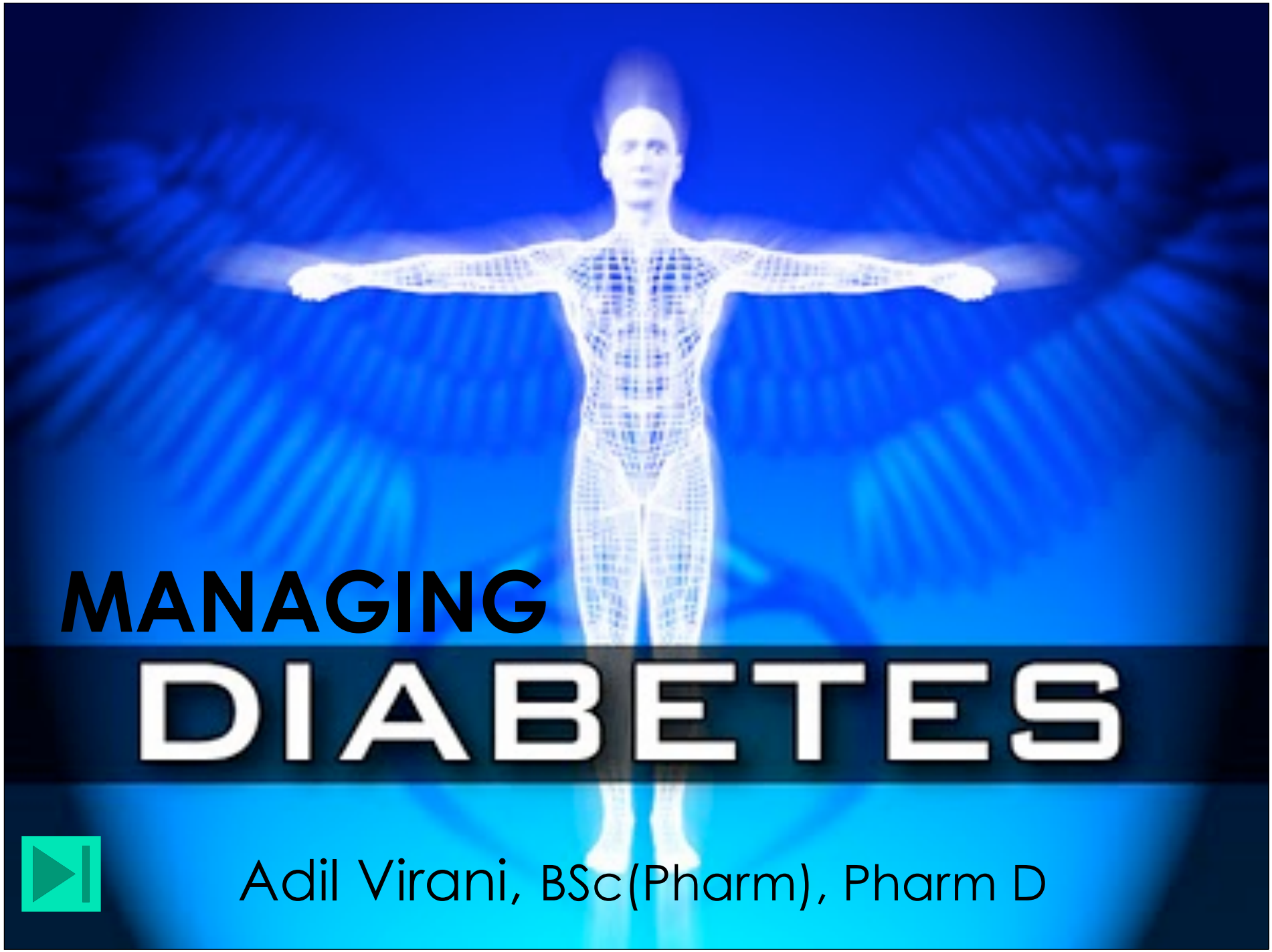


Adil Virani, BSc(Pharm), Pharm D

Objectives

- Compare and contrast treatment options for Type 2 DM on the basis of efficacy and safety
- Select a patient specific pharmacotherapy regimen for someone diagnosed with Type 2 diabetes
- Describe the importance of lifestyle modification in treating diabetes
- List the monitoring parameters you would use in a person taking either insulin or oral hypoglycemics
- Describe the benefits and drawbacks of patient self monitoring of blood glucose (SMBG)

Diabetes: Additional References:

- Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008;32(suppl 1):i-S201. Available from: http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
- CADTH second-line OT draft recommendations: http://www.cadth.ca/media/compus/pdf/C1110-OT-Recs-draft-for-feedback.pdf
- NICE Diabetes guidelines (UK): http://www.nice.org.uk/nicemedia/pdf/CG66FullGuideline0509.pdf

Matt Formin

- Age 60, weight 235lbs (BMI = 33)
- Symptoms: Blurred vision, excess urination, fatigue, pain in knees
- Medical History
  - Hypertension: BP 140/90
  - Osteoarthritis affecting knees (moderate pain)
  - 1 ppd smoker
  - No allergies
- Takes ibuprofen 400 mg 2-3 times a day
- Plasma Glucose = 12.5mmol/L

Discuss how you would approach Simon's treatment with someone sitting beside you…Discuss the goals of therapy and treatment options.

Write a prescription for this person. You must write something but, feel free to write what ever you want.

Goals of Therapy for Simon?

- Control symptoms
- Minimize cardiovascular risks (assess for CVD risk factors and control where possible/applicable)
- Minimize complications from hyperglycemia
- Avoid hypoglycemia
- Establish and maintain glycemic control (HbA1C)
- Education (promote good diet and lifestyle)

Long Term Complications Associated with having Hyperglycemia

- Neuropathy
- Retinopathy (Blindness)
- Renal Dysfunction
- Cardiovascular
  - Dyslipidemia
  - Hypertension
  - Ischemia
- Psychological
- Lower limb amputation
- Sexual
- Risk of hypoglycemia with too aggressive treatment

Effect of intensive BG control with metformin on complications in overweight patients with Type 2 DM (UKPDS 34)

- 4075 patients 15 centres in the UK; Mean age 53 years for UKPDS study
- 753 entered a RCT, median duration 10.7 yrs:
  - conventional (primarily diet alone n=411) vs metformin (n=342)
- A secondary analysis compared the 342 metformin vs. 951 overweight pts given either chlorpropamide (n=265), glibenclamide (n=277)) or insulin (n=409)
- **Primary outcome:** Any DM clinical endpoint, DM death, and all-cause mortality.
- Results: Metformin HbA1c was 7.4% vs 8.0% in the conventional group
- Metformin > chlorpropamide, glibenclamide, or insulin for any diabetes-related endpoint (p=0.0034), all-cause mortality (p=0.021), and stroke (p=0.032)

Lancet. 1998 Sep 12;352(9131):854-65.

Lancet 1998;352:837-53

UKPDS 34 – United Kingdom Prospective Diabetes Study Group

	Deaths related to diabetes (%)	All cause mortality (%)	MI (%)	Stroke (%)
Metformin	8.2*	14.6**	11.4*	3.5#
Conventional	13.4	21.7	17.8	5.6
Intensive (e.g., SU/insulin)	10.8	20.0	14.6	6.3
RRR	39	33	36	38
ARR (metformin vs diet)	5.2	7.1	6.4	2.1#
NNT	19	14	16	48

UKPDS 34 – 10 Year Follow up

N Engl J Med 2008;359:1577-89

	Any diabetes related end-point %	Deaths related to diabetes %	All cause mortality %	MI %	Stroke %
Conventional / Baseline	52-53	17-19	30-33	20-21	7
Metformin	8↓	5↓	7↓	6↓	NS
Sulfonylurea / insulin	4↓	3↓	3↓	3↓	NS

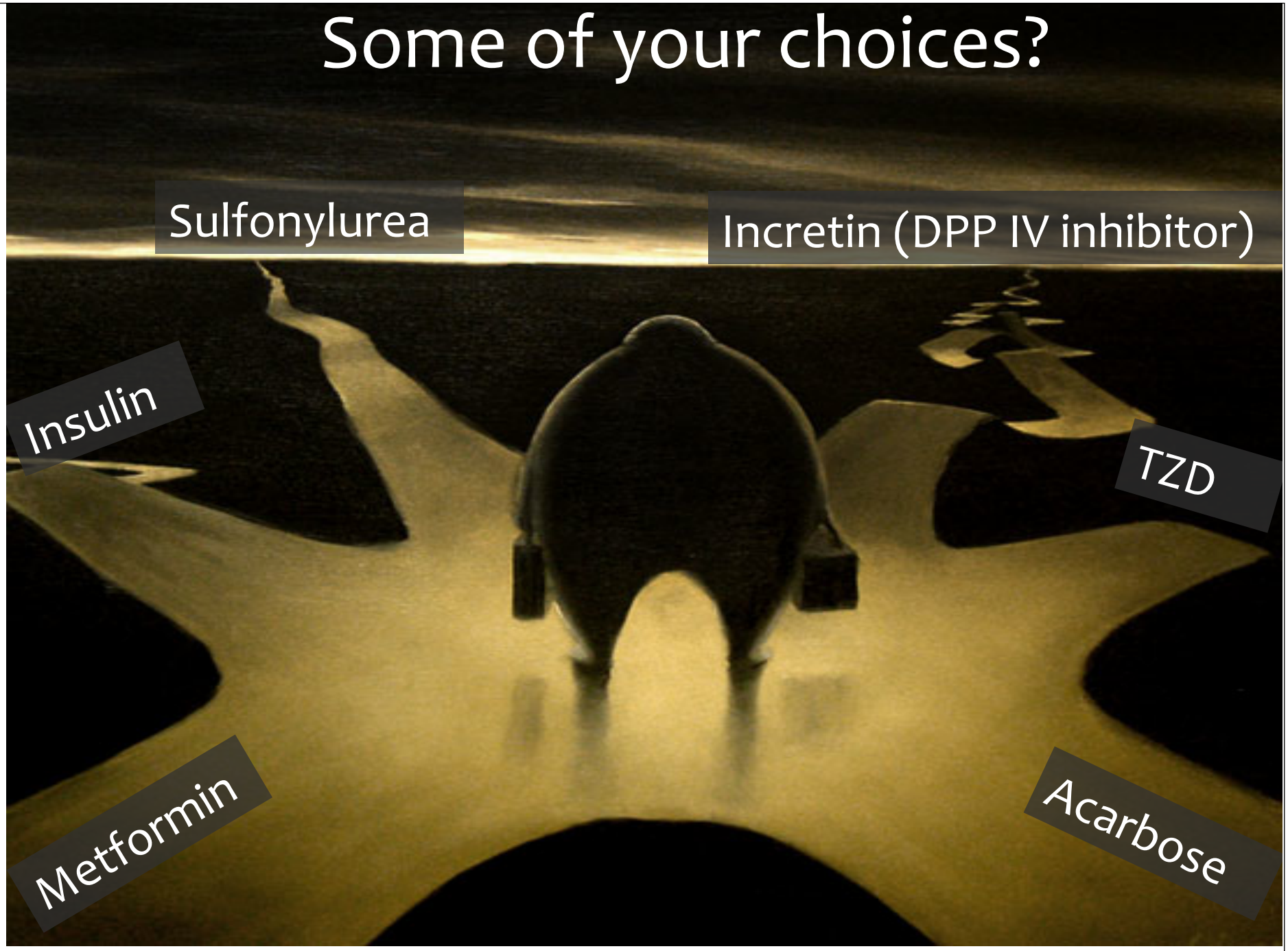
↓ - refers to ARR

Rosy Glitazown

- Age 51, weight 190 lbs (BMI = 30)
- Symptoms: Fatigue, dyspnea
- Medical History
  - BP 130/85
  - Asthma
  - HbA1C =9; LDL = 3.1 mmol/L; TC/HDL = 5
- No allergies
- Metformin 1 gm bid
- Ventolin PRN and Qvar 100 ug BID
- SMBG 2 times daily; Most recent Plasma Glucose = 12.5mmol/L

Treatment options for Rosy

How frequently should Rosy monitor his BG?


Some of your choices?
Sulfonylurea
Incretin (DPP IV inhibitor)
Insulin
TZD
Metformin
Acarbose

Type 2 DM Treatment Options

- Drugs that sensitize the body to insulin and/or decrease hepatic glucose production
  - Biguanides, Thiazolidinediones (TZD), Incretins*
- Drugs that stimulate the pancreas to release more insulin (secretagogues)
  - Sulfonylureas, meglitinides (eg, nateglinide, repaglinide)
- Drugs that slow the absorption of starches
  - α-glucosidase inhibitors (eg, acarbose)
- *Incretins delay gastric emptying, decrease glucagon secretion, increase satiety, increase insulin secretion
  - GLP-1 (exenatide – sc administration)
  - DPP4 Inhibitors (sitagliptin, saxagliptin, vagagliptin*)
- Insulin

Comparative Efficacy, Safety and Cost of Oral Hypoglycemic Agents

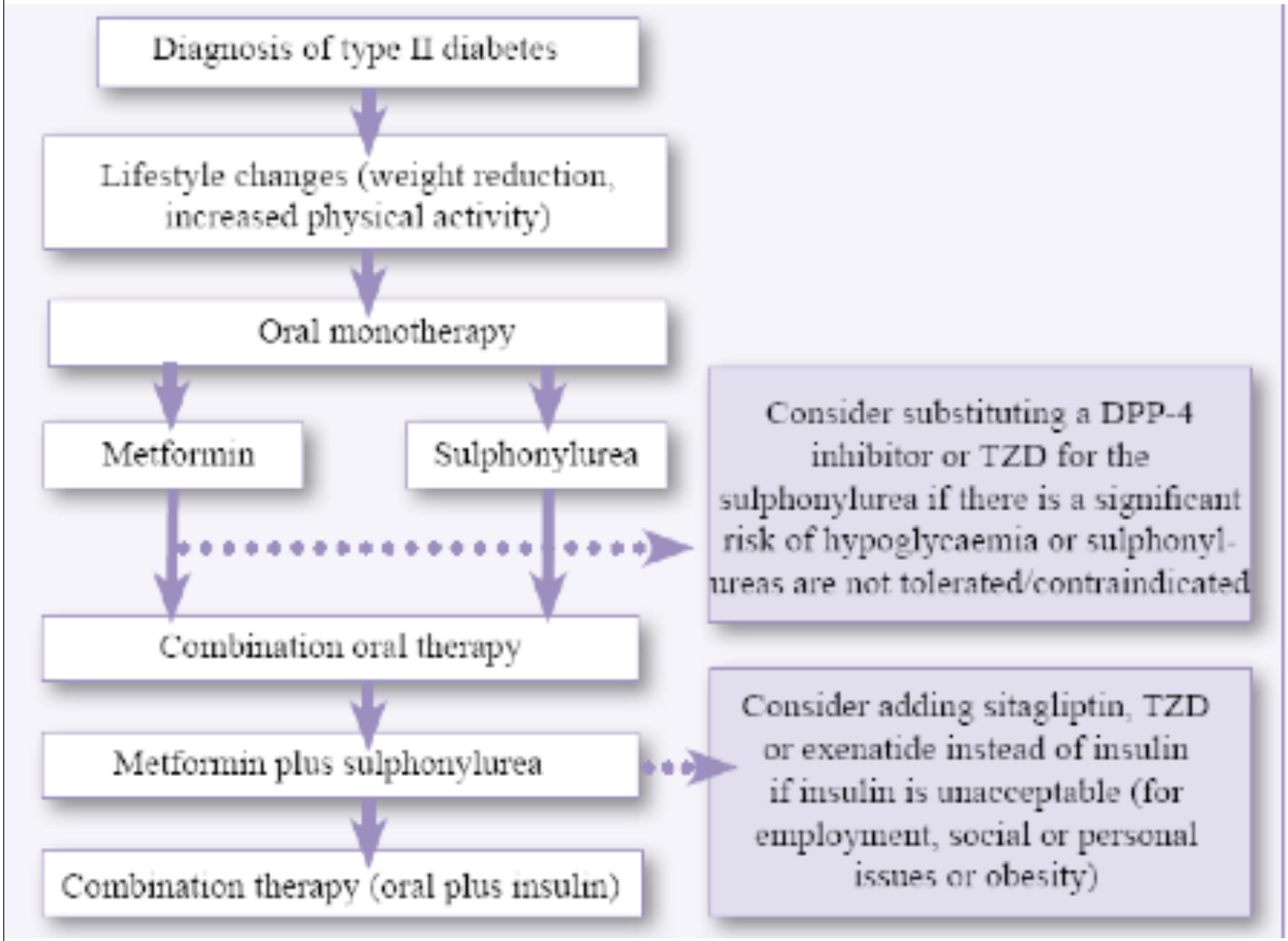
Drug		Death, major CV events	A1c	Weight	Hypo-glycemia	Heart failure and edema	LDL	GI	Cost	Overall
Biguanides (metformin)										
Sulfonylureas										
Glitazones	pioglitazone									
	rosiglitazone									
α-glucosidase inhibitors										
Meglitinides	repaglinide									
	nateglinide									
DPP 4 inhibitors										

Best Outcome | Intermediate | Problem | Unknown

GI=gastrointestinal intolerance; LDL = LDL cholesterol level

For References see Evidence Document; Cost information as per Table 2 (see reverse)

Choudhry NK,et al. *Just a spoonful of medicine helps the sugar go down: Improving the management of type 2 diabetes* [Internet]. Boston (MA): Alosa Foundation; 2009.


Diagnosis of type II diabetes
Lifestyle changes (weight reduction, increased physical activity)
Oral monotherapy
Metformin
Sulphonylurea
Consider substituting a DPP-4 inhibitor or TZD for the sulphonylurea if there is a significant risk of hypoglycaemia or sulphonylureas are not tolerated/contraindicated
Combination oral therapy
Metformin plus sulphonylurea
Consider adding sitagliptin, TZD or exenatide instead of insulin if insulin is unacceptable (for employment, social or personal issues or obesity)
Combination therapy (oral plus insulin)

Pharmacologic Management of Type 2 Diabetes

- **Add anti-hyperglycemic agents if:**

  Diet & exercise therapy do not achieve targets after 2-3 month trial

  Or

  newly diagnosed and has an A1C of ≥ 9%

A1C	& BMI	Suggested starting agent
< 9%	BMI ≥ 25	Biguanide alone or in combination
	BMI < 25	Biguanide or sulfonourea alone or in combination
≥ 9%	--	2 agents from different classes or insulin basal and/or preprandial

Biguanide (Metfomin - Glucophage®)

PROS

- Improve insulin uptake & ↓ hepatic glucose production
- HbA1c ↓ ~1mmol/L
- Data demonstrating benefits on clinical outcomes
- No hypoglycemia
- Minor weight loss
- Inexpensive
- Many years of experience
- ↓ LDL and triglycerides
- ↓ C-reactive protein

CONS

- GI upset (e.g., nausea, cramps & diarrhea)
- Caution in renal or hepatic or cardiac dysfunction
- Lactic acidosis (really rare)

FIRST LINE AGENT!

Sulfonylureas
(Glyburide - Diabeta®, Gliclazide - Diamicron®, Glimepiride -Amaryl®)

PROS

- Promote insulin secretion from pancreas (Insulin secretatogue)
- HbA1c ↓ ~1-1.4 mmol/L
- Rapid reduction in BG
- Years of experience
- Inexpensive
- Once or BID dosing

CONS

- Hypoglycemia risk
- Weight gain

MOST COST EFFECTIVE 2nd LINE AGENT!

Meglitinides

(Repaglinide-Gluconorm®, Nateglinide-Starlix®)

PROS

- Increase insulin release from pancreas
- HbA1c ↓ ~1-1.6 mmol/L
- Short acting ↓ risk of hypoglycemia

CONS

- Hypoglycemia
- Taken with meals
- Short acting (frequent dosing, e.g., tid or qid)
- Costly

Thiazolidinediones or "glitazones" rosiglitazone-Avandia®, pioglitazone-Actos®

PROS

- ↓ hepatic glucose production & may ↑ insulin sensitivity (↑ muscle uptake)
- ↓ All cause mortality, nonfatal stroke & MI (NNT=49)
- ↑ HDL's, ↓ triglycerides and FFAs
- No adjustment in renal dysfunction
- ↓ C-reactive protein

CONS

- Edema
- Weight gain
- Worsen heart failure (NNH = 23)
- Weeks to be effective
- Fracture risk
- Costly

Benefit and Risk

Pioglitazone vs. placebo for type 2 diabetes and macrovascular events

Outcomes at mean 34.5 months	Pioglitazone	Placebo	RRR (95% CI)	NNT (95% CI)
Primary Composite endpoint*	20%	22%	9.2% (-0.9 to 18)	Not Significant
Main Secondary Composite Endpoint**	12%	14%	15% (1.9 to 26)	49 (27 to 407)
Any serious adverse event	46%	48%	4.6% (-1.1 to 9.9)	Not Significant
			RRI (95% CI)	NNH (95% CI)
Heart Failure	11%	8%	40% (22 to 60)	23 (16 to 38)

* Death from any cause, non-fatal myocardial infarction, stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg

** Death from any cause, non-fatal myocardial infarction, or stroke.

RRR = relative risk reduction; NNT = number needed to treat; RRI = relative risk increase; NNH = number needed to harm

Dormandy JA, et al. *Lancet.* 2005; 336: 1279-1289.
Isley W. *ACP J Club.* 2006; 142(2): 34.

Glitazone meta-analysis

	Death, MI or stroke (%)	Serious heart failure (%)		MI (%)	Heart failure (%)
Pioglitazone	4.4	2.3	Rosiglitazone	1.5	1.6
Control	5.7	1.8	Control	1.1	0.8
Relative risk	23	28	Relative risk	36	100
Absolute risk	1.3	0.5	Absolute risk	0.4	0.8
NNT/NNH	77	200	NNT/NNH	250	125

JAMA 2007;298:1180-8; JAMA 2007;298:1189-95

Alpha-glucosidase inhibitors
(Acarbose - Glucobay®)

PROS

- Delays absorption of sugars
- Weight loss
- Non-systemic action
- No hypoglycemia

CONS

- Considerable GI upset and flatulence
- Modest HbA1c ↓ ~0.6 mmol/L
- Cost
- TID dosing
- Limited data showing benefits on clinical outcomes
- Used in combination with other agents

DPP-4 Inhibitors (Sitagliptin - Januvia®, Saxagliptin - Onglyza®, vildagliptin - Galvus®*)

PROS

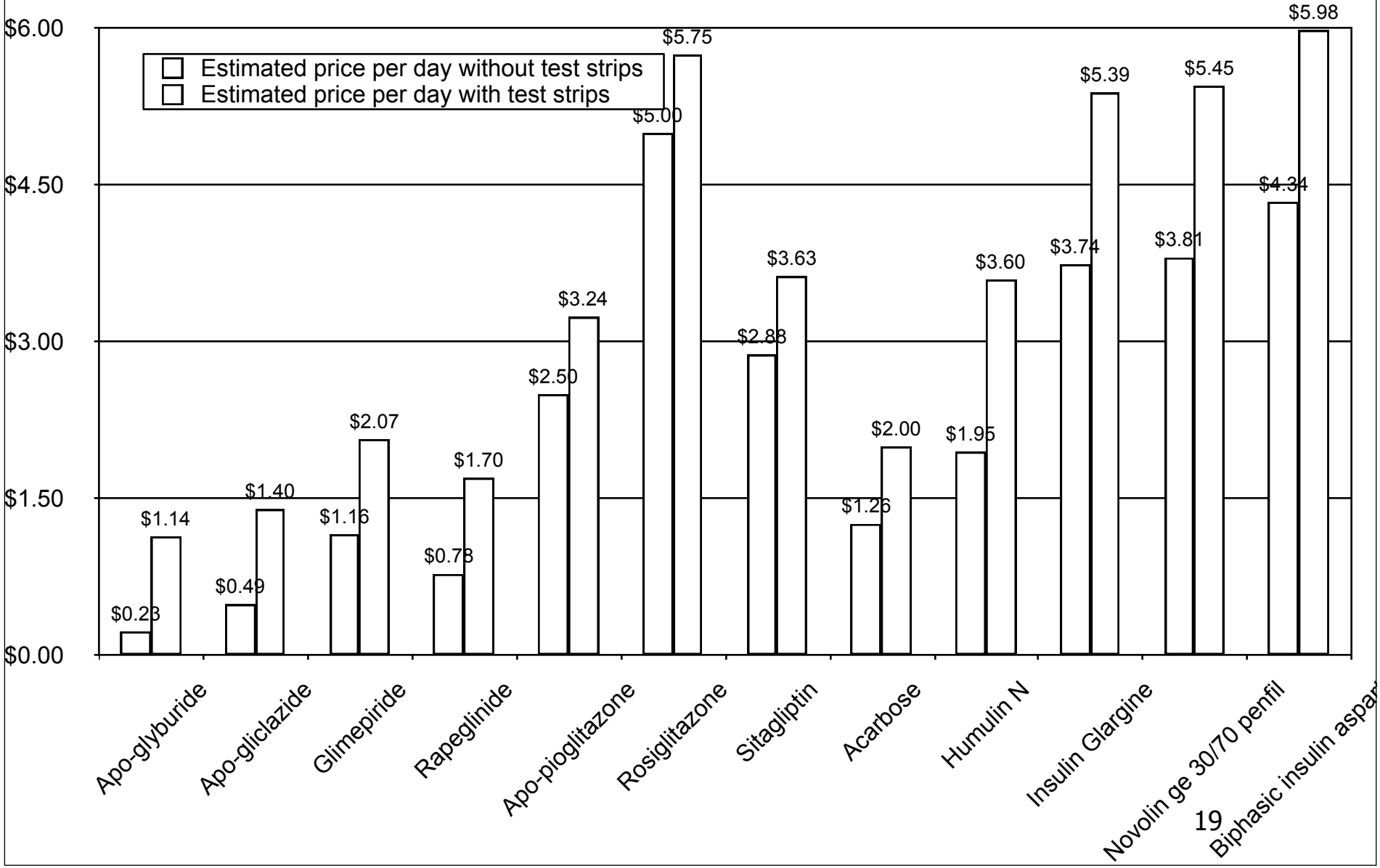
- Enhances incretin effects resulting in ↑ insulin release & ↓ glucagon release
- Modest HbA1c ↓ ~0.7 mmol/L
- No Weight gain
- No hypoglycemia
- Quite costly

CONS

- Unclear if safe in heart failure
- Urticaria, rash
- Avoid in moderate-severe renal failure
- CrCl <50ml/min

*Not currently sold in Canada

Estimated costs/day



Class	Advantages	Disadvantages
Biguanides (metformin)	**Evidence for CVD reduction!** **No hypoglycemia** **No weight gain**	**BID administration** **GI complaints**
Sulfonylureas, (gliburide, glipizide & glimepiride)	**Inexpensive** **Titratability** **?CVD reduction**	**Hypoglycemia** **Wt. gain**
Metaglitinides (repaglinide & nateglinide)	**Repaglinide has a > reduction on A1C (vs nateglinide)**	**TID dosing** **Expense** **May not decrease CVD**
Thiazolidinediones (glitazones)	**?CVD reduction (pioglitazone)**	**Expensive** **Worsen HF (Edema)** **Wt. gain; Fractures**
Alpha-glucosidase inhibitors	**No hypoglycemia** **No wt. gain**	**GI complaints; Expensive** **TID; May not decrease CVD**
Incretins (GLP1 (exenatide) & **DPPIV inhibitors**	**Weight loss (exenatide) or weight neutral** **No hypoglycemia (both)**	**Expensive; limited data** **Injected (exenatide)** **May not decrease CVD**
Insulins (human and analogues)	**Titratability** **Efficacy for A1C reduction** **?CVD reduction**	**Wt. gain** **Hypoglycemia** **Injected**

What's the best 2nd line choice?

- CADTH Systematic Review

- Evidence from 40 RCTs (n = 17,995)
- All important clinical outcomes assessed
- All drug classes resulted in significant A1C reductions
- Outcomes entered into an economic model for analysis
- Multiple sensitivity analyses and meta-regressions were highly consistent with the reference case analysis

http://www.cadth.ca/index.php/en/compus/second-line-therapies-type-2-diabetes/reports

CADTH Results Summary for 2nd line options

Treatment vs. metformin monotherapy	A1C (%) MD (95% CrI)	Weight (kg) MD (95% CrI)	Overall hypoglycemia Mean OR (95% CrI)
Sulfonylureas	**-0.81 (-1.06, -0.53)**	**2.02 (1.11, 2.95)**	**8.81 (4.52, 16.63)**
Meglitinides	**-0.65 (-1.14, -0.20)**	**1.81 (0.37, 3.30)**	**10.04 (3.47, 25.20)**
TZDs	**-0.86 (-1.13, -0.59)**	**2.59 (1.68, 3.51)**	**1.18 (0.54, 2.27)**
DPP-4 Inhibitors	**-0.77 (-1.00, -0.53)**	**0.57 (-0.44, 1.60)**	**1.13 (0.56, 2.21)**
α-glucosidase inhibitors	**-0.72 (-1.14, -0.32)**	**-0.91 (-2.34, 0.53)**	**1.14 (0.01, 6.67)**
GLP-1 analogues	**-0.85 (-1.22, -0.45)**	**-1.77 (-3.40, -0.15)**	**1.37 (0.33, 3.90)**
Basal insulin	**-0.83 (-1.49, -0.21)**	**1.60 (-0.39, 3.66)**	**6.76 (1.48, 21.46)**
Biphasic insulin	**-0.96 (-1.57, -0.38)**	**3.01 (1.00, 5.07)**	**13.77 (3.48, 40.43)**

CrI – credible interval, DPP – dipeptidyl peptidase, GLP - kg- kilogram, MD – mean difference, OR – odds ratio, TZD – thiazolidinedione

The Bottom Line

- The sulfonylureas (e.g., gliclazide, glyburide) are the most cost-effective 2nd line therapy. Hence, it was RECOMMENDED that a "**sulfonylurea be added to metformin for most patients with type 2 diabetes inadequately controlled on metformin monotherapy"**
  - voting: 12 members agree (unanimous); strong recommendation; low-quality evidence

http://www.cadth.ca/index.php/en/compus/second-line-therapies-type-2-diabetes/reports

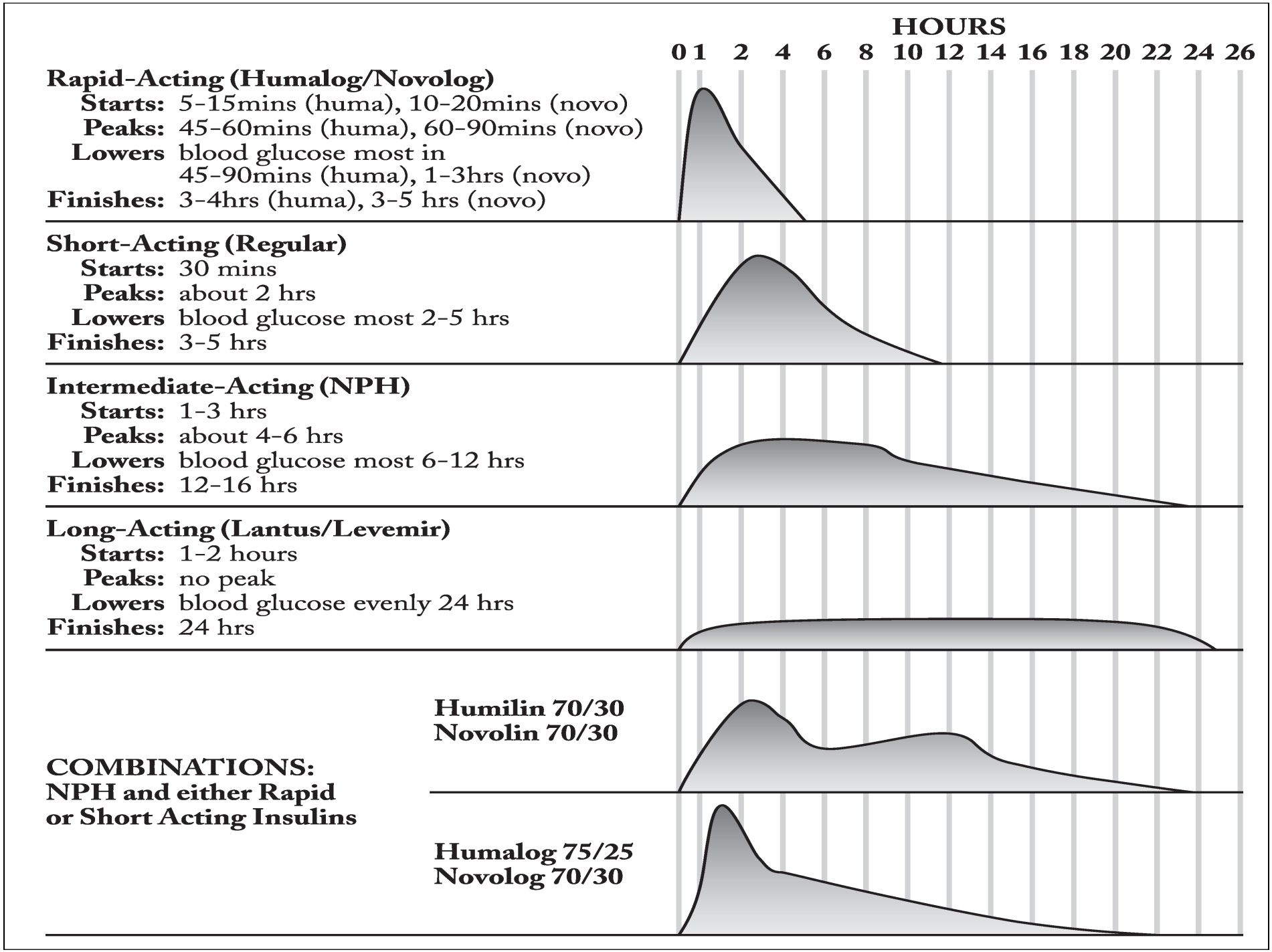
Insulin for Type 2 Diabetes

- If individual treatment goals are not reached by medications, insulin therapy (0.1-0.5 units/kg) can improve glycemic control
- Insulin may be used as initial therapy in type 2 DM if marked hyperglycemia is present (A1C ≥ 9.0%)
- Combining insulin and specific oral antihyperglycemic agents is effective in type 2 diabetes
- Use NPH prior to using long acting insulin analogues for most adults with type 1 or type 2 DM*
- Use human or rapid acting insulin analogues in adults with type 1 or type 2 DM*
- Use Lispro or Aspart preferentially in children and adolescents (less hypoglycemia)*

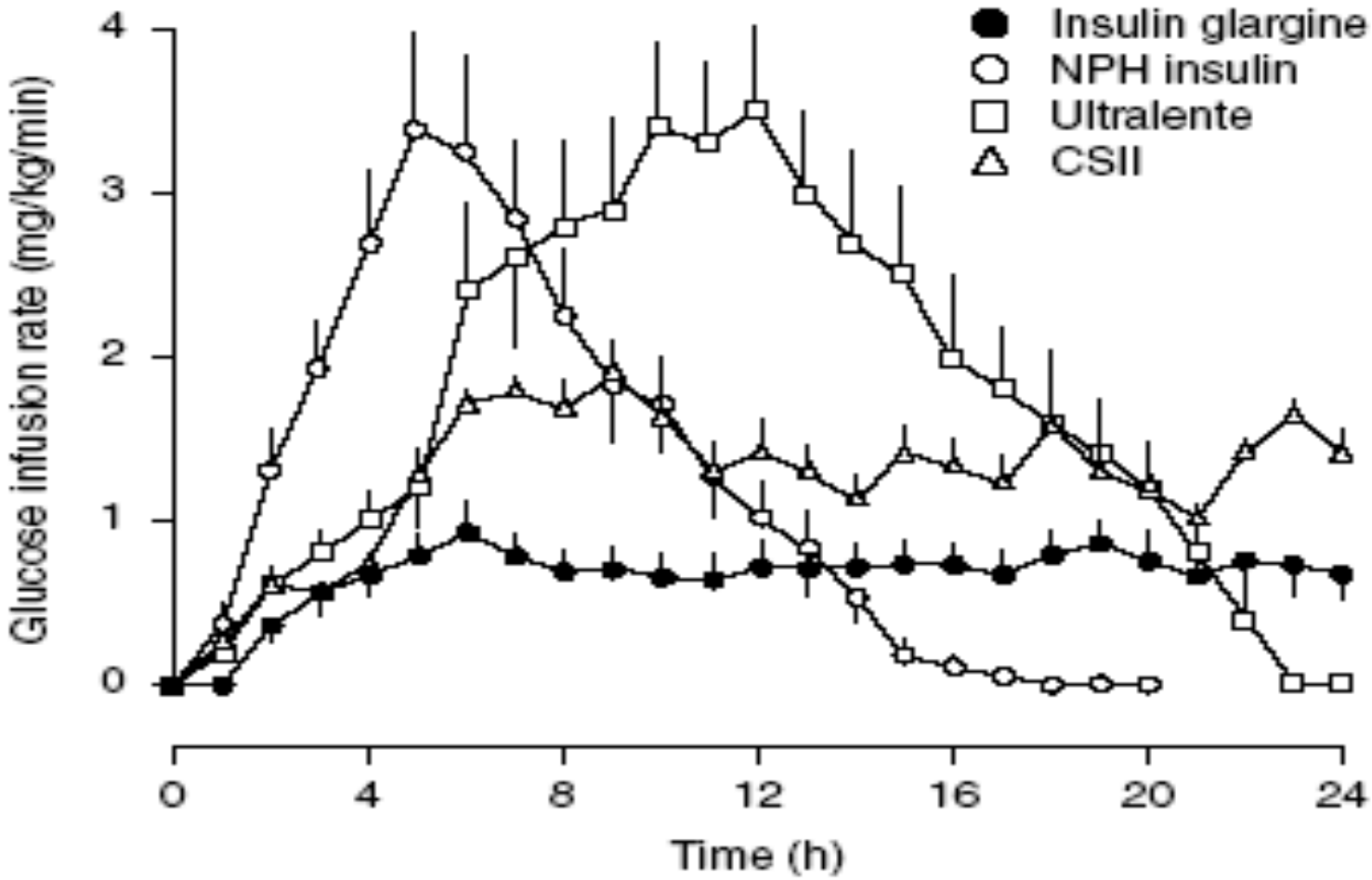
*CADTH. *Optimal Therapy Report - COMPUS* 2008;2(7).

Insulin- tips

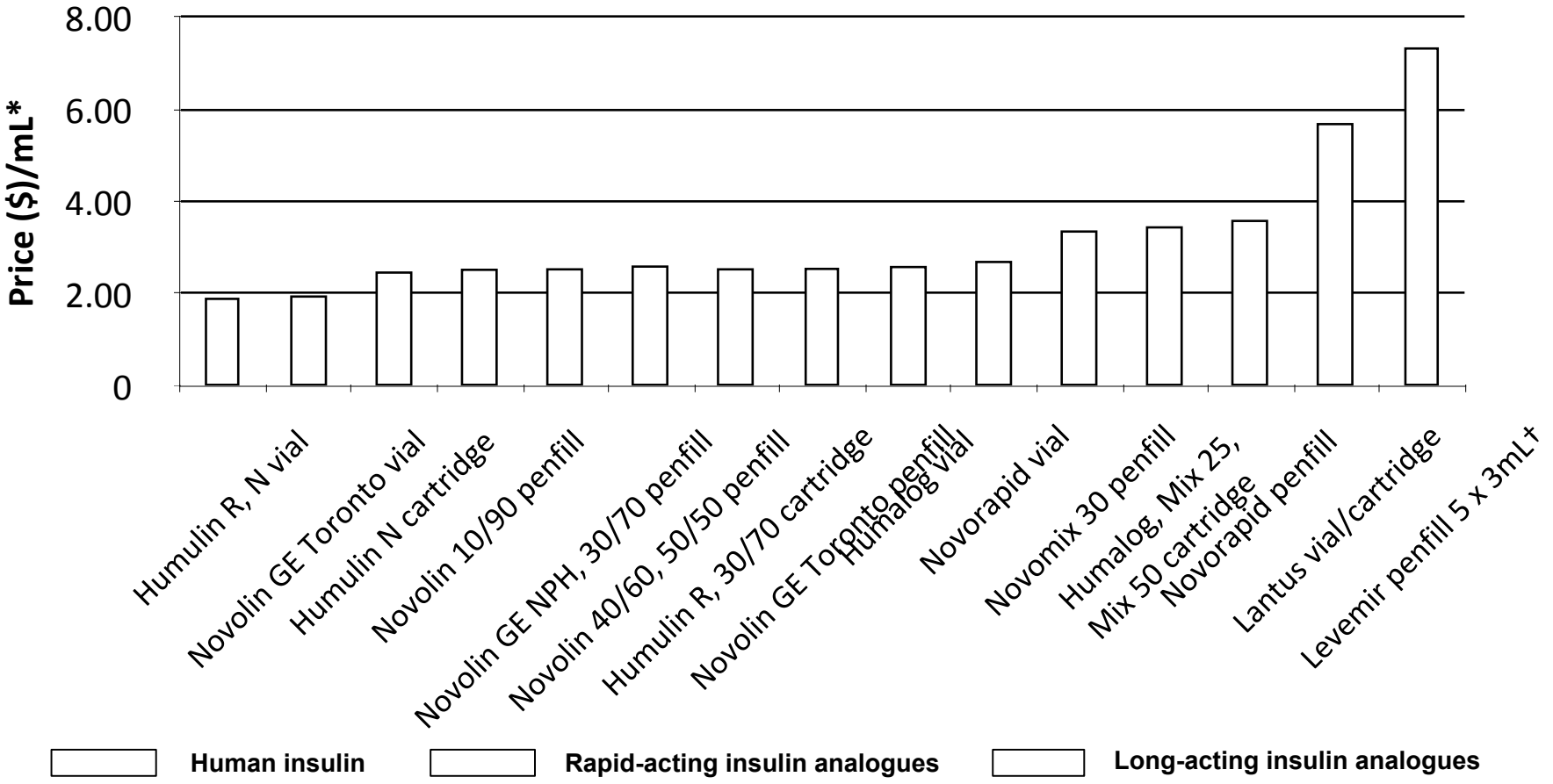
- Most patients started on long acting basal insulin (e.g., NPH then try glargine) ~0.2 units/kg at HS
- Usually adjust by 1-4 units every 2-3 days until target BG
- Reg 30 min pre-meal - ↓ post meal & fasting BG prior to next meal
- NPH at breakfast - ↓ post lunch and fasting supper
- NPH at supper- ↓ fasting bedtime (peak at night)
- NPH at bedtime- ↓ HS glucose and fasting breakfast
- Don't use Reg at HS (hypoglycemia at night)
- Target ONE lab value at a time (i.e. morning fasting)
- Fix the LOWS first then the HIGHs


HOURS
0 1 2 4 6 8 10 12 14 16 18 20 22 24 26
Rapid-Acting (Humalog/Novolog)
Starts: 5-15mins (huma), 10-20mins (novo)
Peaks: 45-60mins (huma), 60-90mins (novo)
Lowers blood glucose most in 45-90mins (huma), 1-3hrs (novo)
Finishes: 3-4hrs (huma), 3-5 hrs (novo)
Short-Acting (Regular)
Starts: 30 mins
Peaks: about 2 hrs
Lowers blood glucose most 2-5 hrs
Finishes: 3-5 hrs
Intermediate-Acting (NPH)
Starts: 1-3 hrs
Peaks: about 4-6 hrs
Lowers blood glucose most 6-12 hrs
Finishes: 12-16 hrs
Long-Acting (Lantus/Levemir)
Starts: 1-2 hours
Peaks: no peak
Lowers blood glucose evenly 24 hrs
Finishes: 24 hrs
COMBINATIONS:
NPH and either Rapid or Short Acting Insulins
Humilin 70/30
Novolin 70/30
Humalog 75/25
Novolog 70/30

Long Acting Insulin's Glucose-Lowering Effects



Insulin price comparison



*_Ontario Drug Benefits Formulary/Comparative Drug Index_ [database on the Internet]; 2008 Dec 3.

† D. Groleau, NovoNordisk Canada, Mississauga, ON: personal communication, 2008 Dec 9.

Targets for Glycemic Control

	A1C (%)	FPG (mmol/L)	2h Postprandial (mmol/L)
Target for most patients (age >12)	≤ 7.0	4.0 – 7.0	5.0 – 10.0
IF SAFE – To reduce nephropathy – Must balance with more hypoglycemia & potential mortality risk	≤ 6.5	4.0 – 6.0	5.0 – 8.0

Aim for target A1C in 6-12 months

* **Treatment goals and strategies must be tailored to the patient, with consideration given to individual risk factors**

Intensive glucose control

Accord - 3.5 years - 6.4% vs 7.5% A1c - 10,251, 62 y/o, diab 10 years, 35% CVD
Advance - 5 years - 6.5% vs 7.3% A1c - 11,140, 66 y/o, diab 8 years, 32%CVD

	Overall mortality (%)		Cardiovascular events (%)		Combined macro and micro* (%)	New or worsening nephro-pathy**(%) (subset of combined)	Hospitaliz-ation (%)	Hypoglycemia requiring medical assistance (%)		Weight gain >10kg (%)	
	ACC	ADV	ACC	ADV	ADVANCE	ADVANCE	ADVANCE	ACC	ADV	ACC	ADV
Intensive	5	8.9	6.9	10	18.1	4.1	45	10.	2.7	29	0.7kg↑
Standard	4	9.6	7.2	10.6	20	5.2	43	3.5	1.5	14	
ARR	1	NSS			1.9	1.1	2	7	1.2	15	NA

* MICROVASCULAR DATA NOT YET REPORTED FOR ACCORD

** DEVELOPMENT OF MACROALBUMINURIA ↓ BY 1.2% - NSS IN DOUBLING OF CREATININE OR DIALYSIS

SERIOUS ADVERSE EVENT DATA NOT REPORTED

N ENGL J MED 2008;358:2560-72 AND 2545-59

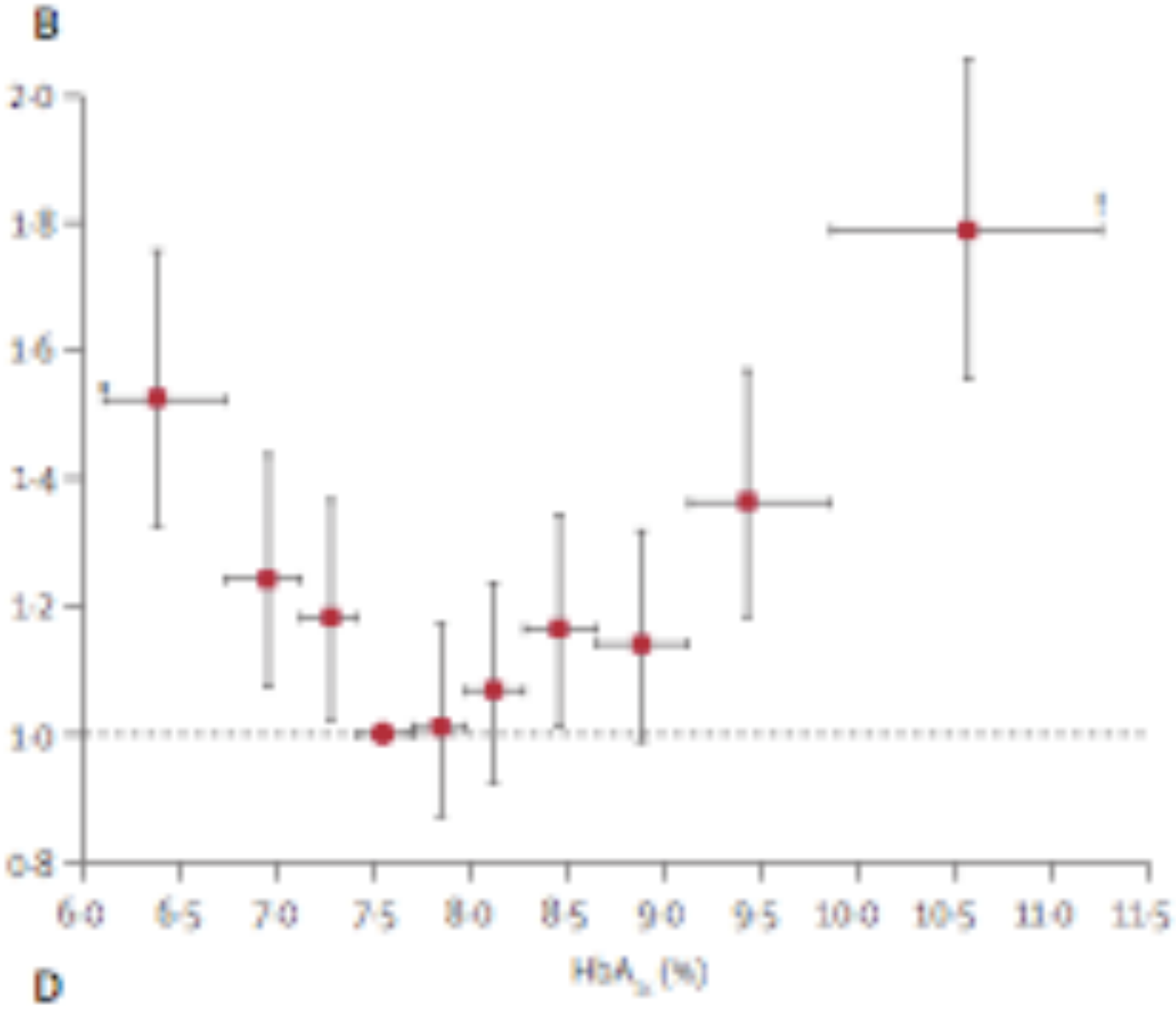
Impact of HbA_1C on absolute risks of cardiovascular events

10 year risk - UKPDS risk engine*

Age	Sex	HbA_1C	CHD (%)	Fatal CHD (%)	Stroke (%)	Fatal Stroke (%)
55	F	6	8.3	4.2	3.3	0.5
		8	10.7	6.2		
		10	13.8	8.8		
	M	6	15.2	7.7	4.6	0.7
		8	19.5	11.1		
		10	24.7	15.7		

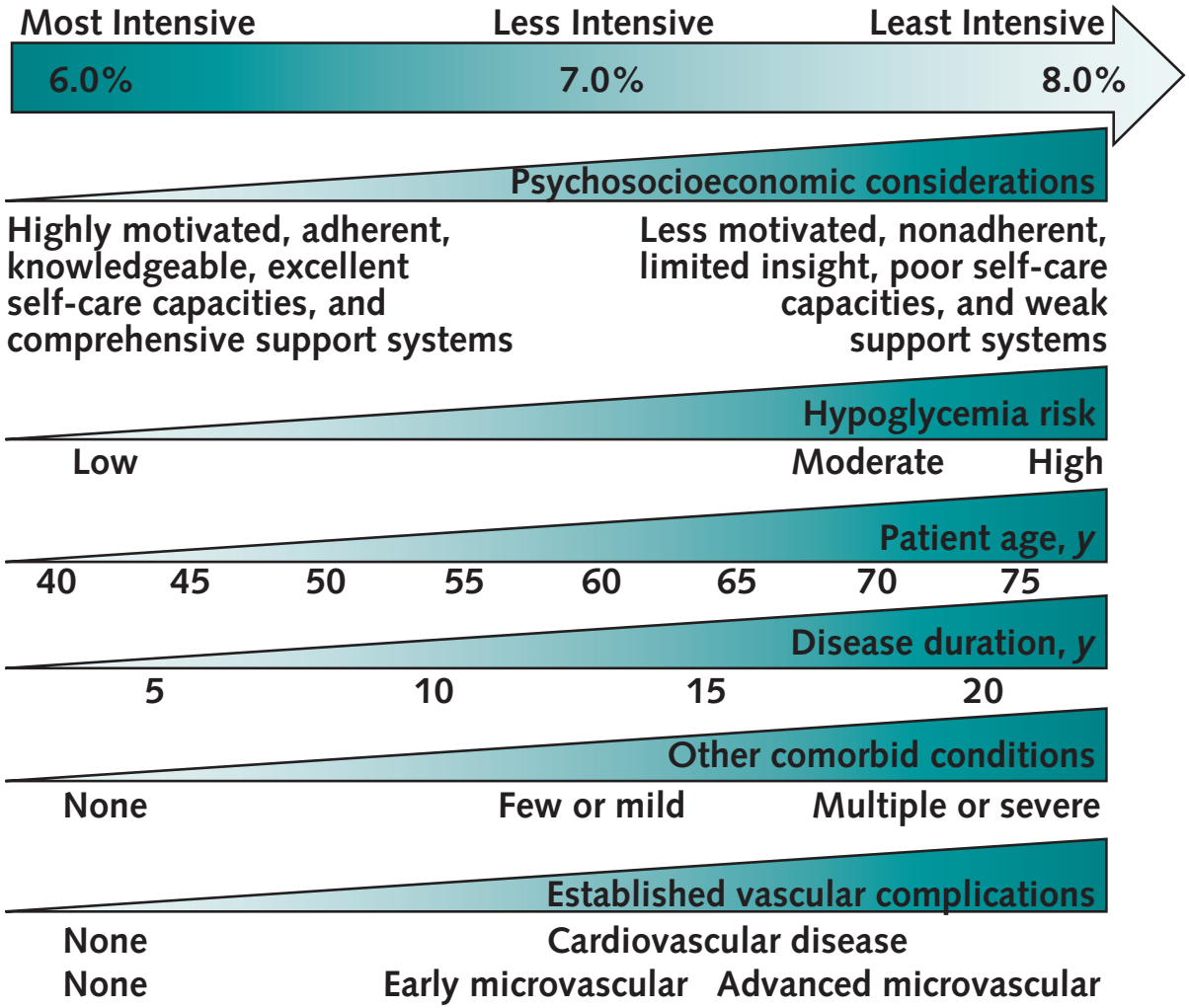
*Non-smoker, TC 5, HDL 1, SBP 140, diabetes 5 years

Mortality by A1C



Lancet 2010; 375: 481–89

Figure. **Framework to assist in determining glycemic treatment targets in patients with type 2 diabetes.**

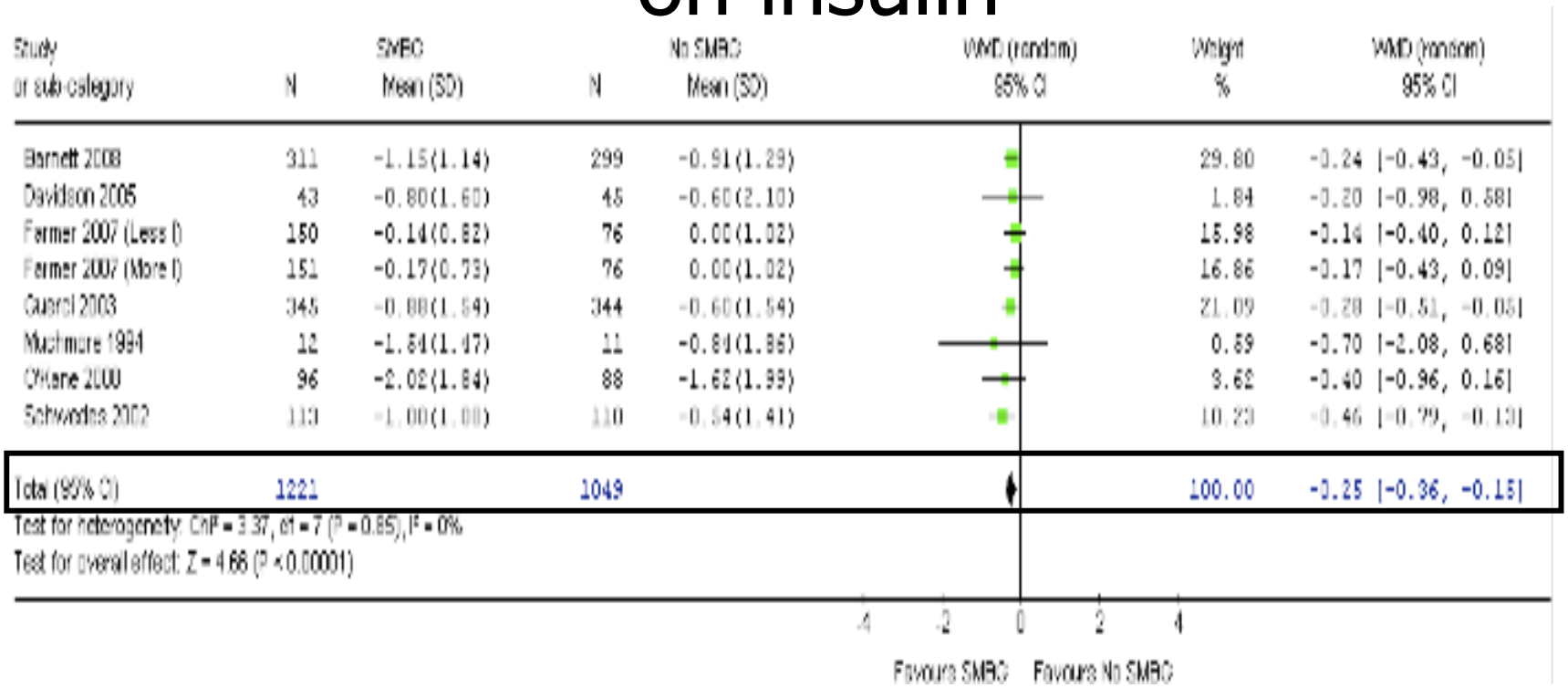


Ismail-Beigi F et al. Ann Int Med, 2012

BG/HbA1c Monitoring

- Hemoglobin A1C q3months
- Self-monitoring of blood glucose
  - Type 1 or type 2 with insulin – 2-3 times daily
  - Type 2 – Only at disease onset and at times of change in medications (or when using insulin secretagogues)
- Ketone testing
  - Type 1 diabetics in periods of acute illness

Systematic Review of SMBG in T2DM not on insulin



SMBG resulted in a slightly lower A1C **{-0.25 (95% CI -0.36 to -0.15)}** vs no monitoring in adults with T2DM not on insulin

SMBG in those not taking insulin is of little clinical value

- Other Systematic Reviews
  - 0.25% decrease in HgA1C[1]
  - O.39% decrease in HgA1C[2]
- RCT: 0.3% decrease in HgA1C[3]
- RCT: no diff in HgA1C[4]
  - More hypoglycemic in self monitoring (NNH=6)
- RCT: no diff in A1C, med use, hypoglycemia,[5]
  - Higher depression scores (by 6%)

1) Diabet Med. 2000;17:755-61; 2) Cochrane. 2005;2:CD005060; 3) Diabetes Metab 2003; 29: 587-94; 4) BMJ 2007;335;132-25; 5) Esmon BMJ 2008; 336:1174-77

CADTH Recommendation for SMBG

- **For most adults with T2 DM not taking insulin, the routine use of blood glucose strips is NOT recommended.**

  Voting: 8 agree, 4 disagree; strong recommendation; moderate quality evidence

- Exceptions:
  - Hypoglycemia concerns (e.g., Those taking secretagogues, history of severe hypoglycemia, inadequate calorie intake, etc)
  - Acute illness
  - Changes in pharmacology or routine
  - Pregnant or planning to be

Hypoglycemia: Symptoms

- Neurogenic (autonomic)
  - Trembling, palpitations, sweating, anxiety, hunger, nausea, tingling
- Neuroglycopenic
  - Difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, dizziness, tiredness

Severity of Hypoglycemia

- Mild
  - Autonomic symptoms present; individual can self-treat
- Moderate
  - Autonomic and neuroglycopenic symptoms; individual can self-treat
- Severe
  - Individual requires assistance of another person; unconsciousness can occur. Plasma glucose typically <2.8 mmol/L

Hypoglycemia - Treatment

Severity	Treatment of hypoglycemia	
Mild to moderate	▪15g of carbohydrate preferably as glucose or sucrose tablets or solution ▪Wait 15 minutes, retest and retreat with 15g if BG<4.0	
Severe	Conscious	▪ 20g of carbohydrate preferably as glucose or sucrose tablets or solution ▪ Wait 15 minutes, retest and retreat with 15g if BG<4.0
	Unconscious	▪ 1mg glucagon SC or IM if ≥ 5 years old ▪ Emergency services should be called

- Once the BG is within target, the person should have the usual snack or meal, or if this is more than 1 hour away, a snack should be taken

Monitoring Complications

Area	Type of screening	Type of diabetes	Recommendation	
Neuropathy	Assess loss of sensation at great toe	Type 1	After 5 years duration in post pubertal, then annually	
		Type 2	At diagnosis, then annually	
Retinopathy	Exam by experienced professional	Type 1	Annually 5 years after onset of diabetes in those ≥ 15 years old	
		Type 2	At time of diagnosis, then every 1-2 years	
Nephropathy	Random urine ACR & random urine dipstick	Type 1	After 5 years duration in post pubertal, then annually	
		Type 2	At diagnosis, then annually	
Dyslipidemia	Fasting lipid profile	Both types	At diagnosis & every 1-3 years. Targets:	
			Moderate risk: LDL-C <3.5 mmol/L TC:HDL-C <5.0	High risk: LDL-C <2.5 mmol/L TC:HDL- C <4.0
Hypertension		Both types	Measured at every visit, target 130/80 mm Hg