Primary Care Practitioners
Symposium on Diabetes

AT THE CDA MEETING IN TORONTO Metro Toronto Convention Centre
- - Saturday Oct 29 - - 9AM to noon - - Room 35 - -

SYMPOSIUM CHAIRS

Dr. J. Robin Conway MD,
Smiths Falls, ON www.diabetesclinic.ca

Medical Director, Diabetes Clinic Research; Director, Canadian Centre for Research on Diabetes

Dr. Thomas Ransom, MD, FRCP,
Halifax, NS

Staff Endocrinologist with the Division of Endocrinology & Metabolism at the Queen Elizabeth II Health Sciences Centre in Halifax

There will be 4 talks of about 40 min each (30 min with 10 minutes for questions)

9:00-9:40	**Update on Pharmacotherapy**	Dr. Amir Hanna
9:40-10:20	**When basal insulin alone is not enough** (Intensification of Insulin)	Dr. Alice Cheng
10:20-10:40	*Break, exhibits*	
10:40-11:20	**Vascular Protection Beyond Glycemic Control:** Diabetes is not all Sweetness	Dr. Ron Goldenberg
11:20-12:00	**What the family Dr. needs to know about pregnancy in Diabetes**	Dr. Denice Feig

This program is accredited by the Canadian Society of Endocrinology & Metabolism
There will be handouts on each talk as a take home package on treatment of diabetes.
It is anticipated that these sessions will be recorded so that they can be presented on the CDA web site.

Printing of this handout was supported by an unrestricted educational grant from Novo Nordisk Canada.

Update on Pharmacotherapy 2011

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Director Diabetes Clinics, St. Michael's Hospital, Toronto, ON

Past-chair, Clinical & Scientific Section, Canadian

Diabetes Association
Past Editor-In-Chief, "Diabetes Dialogue", Canadian Diabetes Association

Member Executive Committee, DCCP program, St. Michael's hospital

Member steering committee, Clinical Practice guidelines for the prevention & management of diabetes in Canada: 2006-2008 & 2010-2013

Objectives: **To review the effect of glucose control on vascular complications and to explore the efficacy & safety of available antihyperglycemic agents.**

The benefits of intensive glycemic control on microvascular complications of diabetes such as retinopathy, nephropathy and neuropathy are well established. The benefits of intensive glycemic control on macrovascular complications of diabetes such as heart attack & stroke are not as clear although long term outcome studies such as EDIC have demonstrated that there is a value to glycemic control in reducing macrovascular disease as well as microvascular disease. In order to reduce risk we want to achieve fasting glucose values less than 7, post prandial values less than 10 mmol/L and A1c less than 7%.

Every person with Type 2 Diabetes needs lifestyle interventions and most will need medications. We aim to achieve glycemic control within 6 months. The foundation of diabetes pharmacotherapy is Metformin which has a long history of safe effective control of glycemia. Dose range is up to 2000 mg a day, usually 2 tablets in the morning and 2 at supper. If A1c <7% cannot be maintained on life style and Metformin alone then we have to consider other medications.

Other second line agents are Sulphonylures, Meglitinides, Thiazolidenediones, Acarbose. New agents likely to come on the market are SGLT-2 inhibitors (flozins), Dopamine agonists and bile acid sequestrants.

New medications which have come on the market since the 2008 CDA-CPG are the Incretin Agents. Incretins are small polypeptide hormones secreted by cells in the gut in response to oral ingestion of food. These hormones, Glucagon Like Peptide-1 (GLP-1) and Glucose Insulinotrophic Peptide (GIP) have effects to increase insulin production in a glucose dependant manner, decrease glucagon secretion thereby decreasing hepatic glucose production, slow gastric emptying and increase satiety. GIP is less effective in persons with diabetes so we rely on increasing GLP-1 levels to improve glycemic control. GLP-1 is rapidly inactivated by the enzyme Dipeptyl Peptidase-4 (DPP-4) so in order to increase GLP-1 levels we can suppress the activity of DPP-4 with an oral DPP-4 inhibitor or gliptin. Examples of the DPP-4 inhibitors are sitagliptin (Januvia 100 mg), saxagliptin (Onglyza 5 mg) or linagliptin (Trajenta 5 mg); these are all given once daily, supress DPP-4 activity by at least 90% for 24 hours. Side effects are minimal and they decrease A1c by about 0.7%. Saxagliptin & sitagliptin are primarily excreted by the kidney whereas linagliptin is primarily excreted in bile so no dosage adjustment is needed in moderate renal failure. The GLP-1 agonists liraglutide (Victoza) and exenatide (Byetta) are injectable synthetic GLP-1 analogues that are not inactivated by DPP-4. They lower A1c by about 0.8-1.5% and are associated with increased satiety and slowed gastric emptying so there is frequently weight loss and side effects of nausea.

Since no single class of oral hypoglycemic monotherapy targets all pathophysiologic factors, combination therapy is usually required and since over time beta cell function deteriorates, adjustment of therapy is needed. In choosing a second agent to Metformin we need to consider baseline glycemia & efficacy, hypoglycemia risk, cost, safety, weight gain, CV benefit/risk and renal function.

Update on Pharmacotherapy in T2DM CDA/CSEM Annual Scientific meeting 2011

AMIR HANNA, MB, BCH, FRCPC, FACP
UNIVERSITY OF TORONTO & ST. MICHAEL'S HOSPITAL

Disclosure

- Received research support, speaking honoraria and consultation fees from all Canadian pharmaceutical companies with interest in diabetes
- Does not own stocks in any pharmaceutical companies, and not employed by any

Objectives

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- **To explore the efficacy and safety of available antihyperglycemic agents**

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Does Intensive glucose control reduce vascular complications

- **In newly diagnosed patients with T2DM**
- **In patients with established diabetes and CV risk factors or events**

UKPDS Initial & F/U results: Legacy Effect of Earlier Glucose Control

	Randomized Trial Results* (RRR) 1998	P	Post-trial Follow-up Results** (RRR) 2008	P
Any diabetes-related endpoint	12%	0.029	9%	0.04
Microvascular disease	25%	0.0099	24%	0.001
Myocardial infarction	16%	0.052	15%	0.014
All-cause mortality	6%	0.44	13%	0.007

** Intensive (Insulin/SU) vs. Conventional*
***After median 8.5 yrs. post-trial follow-up; no glycemic differences after 1 year of follow-up*

Holman R et al. N Engl J Med 2008; 359

Glucose control and diabetes complications in patients with established diabetes & CV events or risk factors

	ACCORD	ADVANCE	VADT
n	10,251	11,140	1,791
Mean age (years)	62	66	60
Duration of diabetes (years)	10	8	11.5
History of CVD (%)	35	32	40
BMI (kg/m²)	32	28	31
Median baseline A1C (%)	8.1	7.2	9.4
A1C goals (%) (I vs. S)	<6.0 vs. 7.0 - 7.9	≤6.5 vs. local guidelines	<6.0 (action if >6.5) vs. 8 - 9
Median follow-up (years)	3.5 (terminated early)	5	5.6
Achieved A1C (%) (I vs. S)	6.4 vs. 7.5	6.5 vs. 7.3	6.9 vs. 8.4

1. The action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group. *N Engl J Med* 2008;358:2545-59.
2. The ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560-72.

Does Intensive Glycemic Control Reduce Microvascular Complications in Type 2 Diabetes?

Relative Risk Reduction

	UKPDS (n=3,867)	ACCORD (10,215)	ADVANCE (n=11,140)
A1C (%)	7.0 vs. 7.9	6.4 vs. 7.5	6.5 vs. 7.3
Follow-up Duration (yrs.)	10	3.5	5
Combined Microvascular	25%*	NS	14%*
Nephropathy	34%	NS	21%*
Microalbuminuria	33%*	+/-	9%*
Retinopathy	21%*	+/-	5%

** Statistically significant*

UKPDS Group. Lancet 1998; 352:837-852
ACCORD. Lancet 2010; 376: 419-430
ADVANCE Collaborative Group. N Engl J Med 2008; 358:2560-2572

Does Intensive Glycemic Control Reduce Macrovascular Complications in Type 2 Diabetes?

Relative Risk Change

	UKPDS[1] (n=3,867)	ADVANCE[2] (n=11,140)	ACCORD[3] (n=10,251)	VADT[4] (n=1,791)
A1C (%)	7.0 vs. 7.9	6.5 vs. 7.3	6.4 vs. 7.5	6.9 vs. 8.4
Follow-up Duration (yrs.)	10	5	3.5	6
Cardiovascular composite	N/A	-6%	-10%	-13%
Total mortality	-6%	-7%	+22%*	+7%
CV mortality	N/A	-12%	+35%*	+26%
Non-fatal MI	-21%	-2%	-24%*	-15%

** Statistically significant*

1. UKPDS Group. *Lancet* 1998; 352:837-852.
2. ADVANCE Collaborative Group. *N Engl J Med* 2008; 358:2560-2572.
3. ACCORD Study Group. *N Engl J Med* 2008; 358:2545-2559.
4. VADT. Presented at American Diabetes Association 68th Scientific Sessions; June 8, 2008.

Glycemic Control: Overall Conclusions

- Start aggressive glucose control right after diagnosis
- Attain the target A1C: ≤ 7% or ≤6.5% or as close to normal as possible
- Choice of medications to avoid hypoglycemia and weight gain

Glycemic Control: Overall conclusions

- The benefits of intensive glycemic control on microvascualr complications are well established. (UKPDS & ADVANCE)

Glycemic Control: Overall conclusions

- The lack of significant reduction in CV events with intensive glycemic control in ACCORD, ADVANCE & VADT and the increased mortality in ACCORD should not lead clinicians to abandon the A1C target of <7%, discounting the benefit of such target on microvascular complications

Glycemic Control: Overall conclusions

ACCORD, ADVANCE, VADT:

- Subgroup analysis suggested that intensive glycemic control in patients with shorter duration of diabetes and less CV risk profile was associated with decreased CV outcomes.

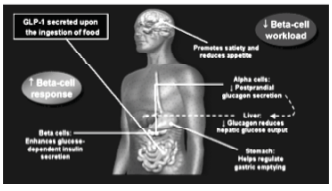
Objectives

- To review the effect of glucose control on vascular complications
- To explore the efficacy and safety of available antihyperglycemic agents

Antihyperglycemic Agents: new additions since 2008 CDA guidelines

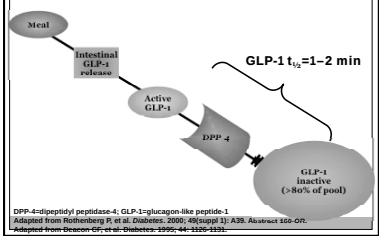
- GLP-1 receptor agonists (GLP-1RA)
- DPP-4 inhibitors (DPP-4 I)
- Newer Agents, not yet approved

GLP-1 Effects in Humans: Understanding Glucoregulatory Role of Incretins



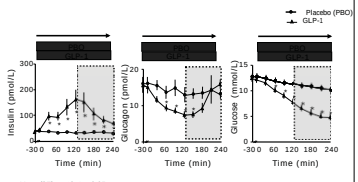
Adapted from Flint A, et al. J Clin Invest. 1998;101:515-520; Larsson H, et al. Acta Physiol Scand. 1997;160:413-422; Nauck MA, et al. Diabetologia. 1996;39:1546-1553; Drucker DJ. Diabetes. 1998;47:159-169.

GLP-1 secretion and inactivation



DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1
Adapted from Rothenberg P, et al. Diabetes. 2000; 49(suppl 1): A39, Abstract 160-OP.
Adapted from Deacon CF, et al. Diabetes. 1995; 44: 1126-1131.

Incretin effect is glucose dependent



Mean (SE); n=10; *p<0.05

Nauck et al. Diabetologia 1993;36:741

Classification of Incretin Agents

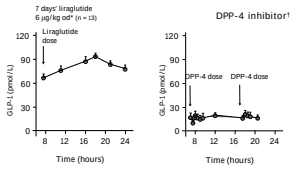
- **GLP-1 RA**
  - Exenatide
  - Liraglutide
- **DPP-4 I**
  - Linagliptin
  - Saxagliptin
  - Sitagliptin

Actions of incretin-based therapies for type 2 diabetes: GLP-1 receptor agonists and DPP-4 inhibitors

Action	GLP-1 receptor agonists	DPP-4 inhibitors
↑ Insulin production	+++	++
↑ First-phase insulin response	+++	++
↓ Glucagon ↓ Glucose output	+++	+
↓ Gastric emptying	Delayed	No effect
↓ Weight loss	Observed	Neutral
↓ Food intake	Decreased	No effect

Defronzo RA, et al. *Curr Med Res Opin.* 2008;24(10):2943–2952.
Drucker DJ and Nauck MA. *Lancet.* 2006;368:1696–1705.
Nicolucci A, et al. *Acta Biomed* 2008;79:186–91.

Levels of GLP-1 With Incretin Therapy

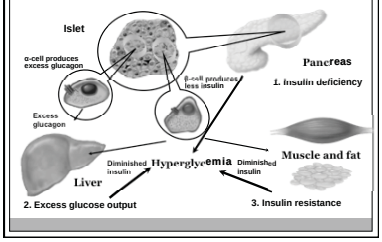


*GLP-1 levels for liraglutide calculated as 1.5% free liraglutide

†28 days vildagliptin 100 mg bid (n = 9)

Adapted from Degn KB, et al. *Diabetes* 2004;53:1187
Mari A, et al. *J Clin Endocrinol Metab* 2005;90:4888

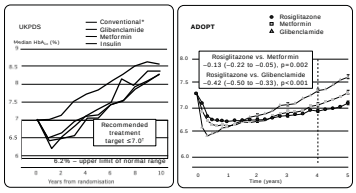
The pathophysiology of T2DM includes three main defects



No Single Class of Oral Antihyperglycemic Monotherapy Targets All Key Pathophysiologic Factors

Pathophysiology	Alpha-Glucosidase inhibitors	Meglitinides	SUs	TZDs	Metformin	DPP-4 I & GLP-1RA
Insulin deficiency		✓	✓			✓
Insulin resistance				✓	✓	
Excess hepatic glucose output				✓	✓	✓

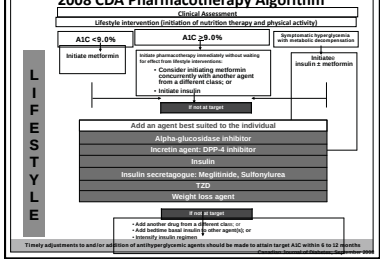
Over time, glycaemic control deteriorates



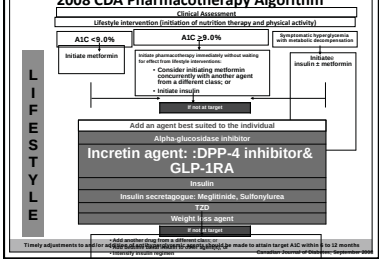
*Diet initially then sulphonylureas, insulin and/or metformin if FPG>15 mmol/l
†CDA clinical practice recommendations. n=5102

UKPDS 34. *Lancet* 1998;352:854–65; Kahn *et al* (ADOPT). *NEJM* 2006;355(23):2427–43

2008 CDA Pharmacotherapy Algorithm



2008 CDA Pharmacotherapy Algorithm



Metformin

- **Recommended as first-line therapy in all clinical practice guidelines.**
- **WHY?**
  - **As effective as SU & TZD in glucose lowering (ADOPT study)**
  - **More durable A1C reduction than SU (ADOPT study)**
  - **Old drug with "known" side-effect profile**
  - **Low cost**
  - **Associated with decreased vascular outcomes in a small group of patients in UKPDS (n=342)**

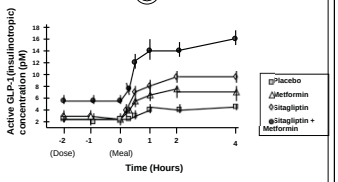
Metformin in UKPDS: Vascular outcomes in overweight patients (n=342)

- **Diabetes Related End-points: significant decrease vs. intensive and conventional policies (P< 0.0023, <0.0034 respectively)**
- **Decreased MI vs. conventional policy (P<0.01)**
- **No difference in microvascular outcomes vs. intensive or conventional**
- **UKPDS: JAMA 1999; 281:2005**

How Does Metformin Work?

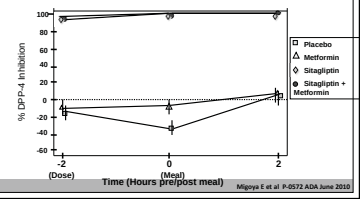
- **Decreased hepatic glucose production by decreasing hepatic insulin resistance**
- **Possible decrease in intestinal glucose absorption**
- **Increased GLP-1 levels (synergy with DPP-4 inhibitors)**
- **decrease in appetite & weight loss**

Co-administration of metformin + sitagliptin increases cumulative post-prandial mean active GLP-1 concentrations greater than sitagliptin or metformin alone



Migoya E et al P-0572 ADA June 2010

Metformin does not inhibit DPP-4 activity



Migoya E et al P-0572 ADA June 2010

Metformin: side-effects & precautions

- **GI side effects**
- **B12 malabsorption**
- **Contraindicated**
  - **CKD: eGFR <30 ml/ min**
  - **CKD: eGFR 30-60: can give ½ maximum dose**
  - **CHF: only in presence of CKD**

When metformin fails to maintain glycemic targets, what is the next step?

- **??????????**

Add an agent best suited to the individual based on the advantages / disadvantages listed below (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 agents: 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 Sulfonylurea	↓ to ↓↓ ↓↓	Yes* Yes	Improved postprandial control Newer sulfonylureas (gliclazide, glimepiride) are associated with less hypoglycemia than glyburide	Requires TID to QID dosing Weight gain
TZD	↓↓	Rare	Durable monotherapy	Requires 6-12 weeks of maximal effect Weight gain Edema, more CHF, more fractures in females
Weight loss agent	↓	None	Weight loss	GI side effects (orlistat) Increased heart rate/BP (sibutramine)

↓= <1.0% decrease in A1C
↓↓= 1.0-2.0% decrease in A1C
↓↓↓= >2.0% decrease in A1C

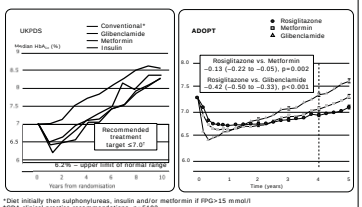
* Less hypoglycemia in the context of missed meals

2008 CDA Guidelines, CJD 2008, Suppl 1

When metformin fails to maintain Glycemic Targets, what should I combine it with?

- **The most commonly used drugs are SUs**
- **Why?**
  - **Old drugs, more familiarity**
  - **Cheap**
  - **Effective: as effective as other options, but the least durable**
  - **Negative Aspects:**
    - **Weight gain**
    - **Hypoglycemia**

Over time, glycaemic control deteriorates



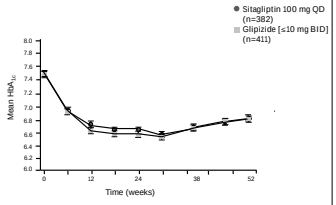
*Diet initially then sulphonylureas, insulin and/or metformin if FPG>15 mmol/l
†CDA clinical practice recommendations, n=5102

UKPDS 34, Lancet (1998;352:854–65); Kahn et al (ADOPT), NEJM 2006;355(23):2427–43

Comparing Incretin agents to SU's

- DPP-4 I Vs. Sulphonylurea
- GLP-1RA Vs. Sulphonylurea

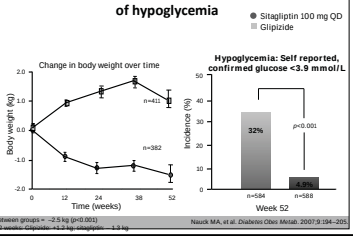
Sitagliptin shows comparable glycemic efficacy to glipizide (SU) when added to metformin (52 weeks)



Achieved primary hypothesis of non-inferiority to glipizide

Nauck MA, et al. *Diabetes Obes Metab.* 2007;9:194–205.

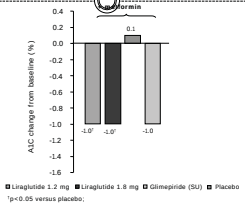
Sitagliptin provided weight reduction (vs. weight gain) and lower incidence of hypoglycemia



Δ between groups = −2.5 kg (p<0.001)
at 52 weeks: Glipizide: +1.2 kg; sitagliptin: −1.3 kg

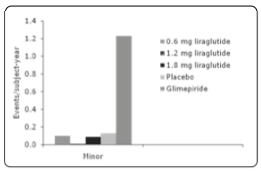
Nauck MA, et al. *Diabetes Obes Metab.* 2007;9:194–205.

A1C Reductions with Liraglutide + Metformin



†p<0.05 versus placebo;

Hypoglycemia: LEAD 2 (add-on to metformin)

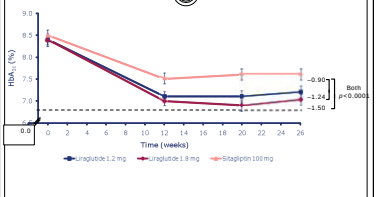


- At all liraglutide dosages, there are significantly fewer minor hypos vs. glimepiride

Comparing GLP-1RA to DPP-4I

- Efficacy

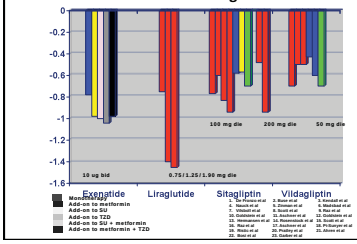
Liraglutide Vs. Sitagliptin added to metformin: mean HbA_{1c} levels



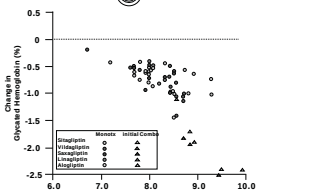
Mean (1.96 SE); data are from the full analysis set LOCF

Pratley *et al. Lancet* 2010;375:1447–56

A1C reduction with incretin Agents

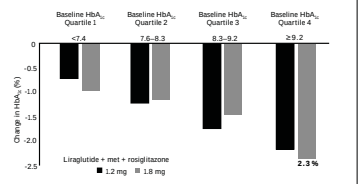


HbA1c Lowering Efficacy of DPP-4 Inhibitors in Relation to Baseline HbA1c Levels



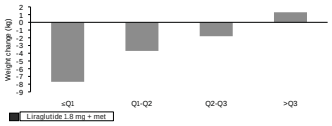
Deacon CF. Diabetes, Obesity and Metabolism 2011; 13: 7–18

Liraglutide reduces HbA_{1c} even further in very poorly controlled patients



Study NN2211-1574 presented as poster 898 by Zinman at EASD 2008

A quarter of patients lose more than 7.5 kg with liraglutide



0–Q1: mean weight change for the 25% of subjects who had the largest weight loss
Q1–Q2: mean weight change for the 25–50% weight loss quartile
Q2–Q3: mean weight change for the 50–75% weight loss quartile
Q3–Q4: mean weight change for the 75–100% weight loss quartile, that is, the 25% who had the smallest weight loss

Slide No 47

Meta -analysis: Effect of non-insulin antidiabetic agents added to metformin

- Meta-analysis: 11,198 patients in 27 RCT's
- Duration 32 weeks
- Drugs studied: SU, Glinides, DPP-4I, TZD's and 2 studies of GLP-1 RA.
- Results: All non-insulin agents were associated with similar HbA1c reductions but differed in their associations with weight gain and risk of hypoglycemia

(Phung, OJ et al. JAMA 2010;303:1410)

Effects of Adding different antihyperglycemic agents to metformin + SU. A network meta-analysis

- Analysis of 18 trials (n=4535), adults ≥18 yr., T2DM, A1C >7% while receiving Metformin >1000 mg/d + SU
- Study duration ≥24 weeks

Options explored:

- Insulin
- Acarbose
- TZD's
- DPP-4 inhibitors
- GLP-1 agonists

Gross, JL et al. JAMA 2011; 154: 672303: 1410

Effects of Adding different antihyperglycemic agents to metformin + SU. A network meta-analysis Results

- A1c ↓ 0.96% when third agent added to metformin + SU
- No clear statistically significant difference in A1C reduction between different classes
- Insulin studies were underpowered or lacked proper titration. Insulin caused twice the absolute number of severe hypoglycemia than noninsulin agents
- GLP-1 associated with weight loss, but GI side effects.
- Insulin, TZDs associated with weight gain

(Gross, JL et al Annals Int Med 2011;154:672)

Considerations in choosing a second agent to add to metformin

- Issues to consider:
  - Baseline glycemia & efficacy
  - Hypoglycemic risk: drug & patient
  - Cost (value)
  - Safety
  - Weight gain
  - CV benefit/ risk
  - Renal Function

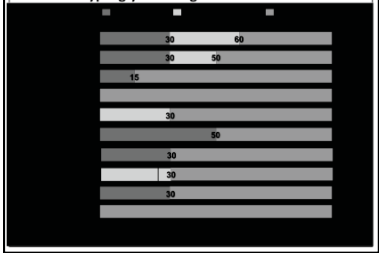
Composite of: No hypoglycemia + No weight gain + Glycemic Control

- GLP-1RA (Wt. loss)
- DPP-4 I
- Acarbose

Antihyperglycemics & kidney disease

- Metformin
- SU's: Glyburide& gliclazide
- Repaglinide
- TZD's
- DPP- inhibitors
- GLP-1 RA
- Acarbose
- Insulin

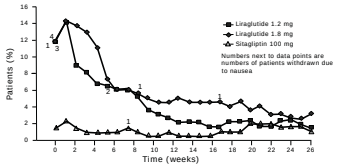
Antihyperglycemic Agents and Renal Disease



Incretin Agents: safety

- DPP-4 I are well tolerated
- GLP-1RA: GI side effects, usually transient
- FDA Database of reported adverse events
- Elashoff, M et al. Gastroenterology 2011; 141:150

Frequency of nausea by week



- Nausea with liraglutide was initially higher, but transient

Data are from the safety analysis set
Pratley et al. *Lancet* 2010;375:1447–56

2.1-fold higher risk for type 2 diabetes vs. general population.[1]

Incidence of pancreatitis (per 1000 patient years)

Nondiabetic	Diabetic
1.9[1]	**5.6**[1]

Incidence of pancreatitis with incretin agents (per 1000 patient years)

	Comparator	Incretin therapy
Exenatide[1]	not available	**5.7**
Liraglutide[2]	0.6	**2.2**
Sitagliptin[1]	not available	**5.6**
Saxagliptin	not available	not available

1. Garg R et al. *Diabetes Care* 2010;33:2359–64; 2. Liraglutide Canadian Product Monograph, Novo Nordisk Canada Inc., 2011.

Pancreatitis risk associated with incretin therapies and type 2 diabetes.

Is there a c-cell cancer risk with GLP-1 receptor agonists?

Dose- and treatment-duration-dependent c-cell tumours reported at clinically relevant doses of liraglutide

No c-cell stimulation, even at >60 times clinical dose of liraglutide

No c-cell stimulation after 2 years of liraglutide exposure
No c-cell cancer after 840,000 patient-years of exenatide exposure

Bjerre Knudsen et al. *Endocrinology* 2010; DOI: 10.1210/en.2009-1272

No evidence to support that GLP-1 agonists increase the risk of c-cell cancer development in humans.

Looking Ahead

- SGLT-2 Inhibitors: dapagliflozin, others
  - Increased renal glucose excretion
- Dopamine Agonists: Quick Release Bromocriptin
  - Central decrease in SNS activity, reducing HGP and lipolysis
- Colesevelam HCL: Bile acid sequestrant
  - Reduced A1C 0.5 %, when added to Metformin, SU or insulin

Conclusions

- Many antihyperglycemic agents are now available for patients with T2DM, and more will be introduced
- Each agent has pros and cons
- Metformin (when tolerated) remains the drug of choice as an initial agent if life-style intervention fails to attain glycemic targets
- Initial combination therapy is recommended at diagnosis if A1C is >9% (CDA 2008 Guidelines), expected A1C reduction >2%

Conclusions

- In monotherapy failure, adding a second agent should be individualized
- Factors to consider include:
  - Baseline glycemia & efficacy
  - Hypoglycemic risk: drug & patient
  - Cost (value)
  - Safety
  - Weight gain
  - CV benefit/ risk
  - Renal Function

When Basal Insulin is Not Enough …

Alice Y.Y. Cheng
MD, FRCPC

Dr. Cheng is a member of the Division of Endocrinology and Metabolism at Credit Valley Hospital in Mississauga and St. Michael's Hospital in Toronto and is an Assistant Professor in the Department of Medicine at the University of Toronto. She completed medical school, internal medicine and Endocrinology training at the University of Toronto and has completed the Master Teacher Program offered through the Department of Medicine. She has served on the Expert Committee for the 2003 Canadian Diabetes Association clinical practice guidelines and the Steering and Expert Committees

for the 2008 revision, along with the Dissemination & Implementation committee. She is serving as Chair for the 2013 CDA clinical practice guidelines. In addition to guideline development, Dr. Cheng has co-written several textbook chapters on dyslipidemia, diabetes and other endocrine topics and is actively involved in continuing medical education.

When should insulin be considered in type 2 diabetes?

As outlined in the Canadian Diabetes Association 2008 clinical practice guidelines, insulin use is appropriate in the following scenarios in type 2 diabetes:

- At any point that glycemic control is inadequate (A1C >7%)
- As initial therapy if presenting A1C >9% in newly diagnosed diabetes
- Metabolic decompensation (hyperglycemic symptoms, diabetic ketoacidosis)
- End-organ failure (renal failure, heart failure, liver failure)
- Pregnant or planning pregnancy
- Temporarily for acute illness, stress or medical procedure/surgery

What are the insulins available?

1) Basal
2) Bolus
3) Premixed

Within each category, the insulins are further divided into "human" or "analogue". The human insulins are the traditional ones that have been available for decades. The analogue insulins are modified versions with improved time-action profiles (see Table 1).

What are the insulin regimens for type 2 diabetes and their pros and cons?

There are **three** primary insulin regimens for type 2 diabetes:

- Basal insulin once daily
- Basal + Bolus insulin
- Premixed insulin twice daily

Basal insulin once daily: In this regimen, patients take one injection of basal insulin per day, usually in combination with metformin +/- sulfonylurea. The basal insulin is often given at bedtime and the result is improved fasting glucose levels. In the case of the basal analogue insulins, their longer action profile allows for the dose to be given at any time of day. The main advantage of this regimen is the convenience and ease of one injection. This is a good starting point for insulin therapy and has been shown to result in less weight gain and less hypoglycemia as the initial regimen compared to the others. However, this regimen can not maintain control indefinitely because of progressive failure of the beta cells and ability to provide postprandial control.

Basal + Bolus insulin: In this regimen, patients take bolus insulin with each meal and basal insulin (usually) at bedtime. Metformin is continued but the sulfonylurea is discontinued once bolus insulin is introduced. There is an option of only giving bolus insulin at the largest meal and continuing the bedtime basal. Over time though, postprandial control of the other meals will gradually deteriorate and bolus insulin will need to be added at the other meals too. The advantages of this regimen are the flexibility (timing and size of meals) and better mealtime control. The disadvantage is the higher number of injections.

Premixed insulin twice daily: In this regimen, patients take an injection of premixed insulin before breakfast and before supper. The advantage of this regimen is the convenience of 2 injections but the primary disadvantage is the lack of flexibility since the insulin is premixed. Therefore, this regimen is ideal for the patient who leads a consistent and predictable lifestyle with regular meals (timing and quantity) and regular activity. This is important to assess because skipped or delayed meals can result in hypoglycemia because of the intermediate-acting component of the premixed insulin that would have already been injected earlier in the day. Also, there is a need for a bedtime snack to avoid the nocturnal hypoglycemia that may result from the intermediate-acting portion of the premixed insulin injected at supper time.

What should be done with the oral antihyperglycemic medications?

- Metformin: Should be continued unless there is a contraindication to its use
- Secretagogues: If on basal insulin alone, options include continuing full dose, reducing the dose or stopping. The insulin dosage requirements would increase if the dose is reduced or stopped. Once bolus insulin or premixed insulin is used, the secretagogue should be discontinued.
- Thiazolidinediones (TZDs): Should be discontinued once insulin is added
- DPP-4 inhibitors: Not indicated for combination use with insulin in Canada. However, there are data showing improved postprandial glycemic control
- GLP-1 receptor agonists: Not indicated for combination use with insulin in Canada. However, there are data suggesting that combining GLP-1 receptor agonist and insulin results in lower A1C and weight loss.

How to dose the insulin

There are **three** important principles to remember when dosing insulin:

1. Whatever starting dose you select will be wrong
2. Titration is the key to success
3. There is no maximum dose of insulin

The following is a discussion of the dosing and titration for each of the three insulin regimens.

1. Basal insulin once daily

Start at a dose of 10 units at bedtime. Most patients will require 40-50 units before achieving the target fasting blood glucose levels. Therefore, the patient should self-titrate by increasing the dose by 1 unit every night until the fasting glucose level is achieved.

2. Basal + Bolus insulin

If the patient has already been on basal insulin and now bolus insulin is to be added to the basal regimen to achieve better mealtime control, one could add bolus insulin at a dose of 10% of the basal dose. For example, if the patient is taking 50 units of basal insulin at bedtime but now his/her postprandial glucose levels are high, add 5 units of bolus insulin with meals. As per one of the basic principles of insulin dosing, the starting bolus dose selected will likely be wrong. However, titration until target postprandial glucose levels are achieved will ensure that the appropriate dose is found.

If the patient is naïve to insulin, then one method of calculating the starting doses is:

- Total daily insulin = 0.5 units/kg
- 40% of total daily insulin = basal dose
- 60% of total daily insulin = total bolus doses (divided into the 3 meals)

Some people choose to divide the total daily insulin into 50% basal and 50% bolus. Either of these methods work because the most important step is the titration – not the starting dose! The basal dose can then be titrated based on the fasting glucose level as discussed in the "Basal insulin once daily" section above. The bolus doses should also be titrated by the patient based on either the blood sugar level prior to the next meal or the level 2 hours after the meal.

3. Premixed insulin twice daily

The easiest way to initiate this regimen is to start at a dose between 5-10 units before breakfast and supper – then titrate (6). The more complicated way would be to calculate the total daily insulin (as above) and then divide the dose into 2/3 at breakfast and 1/3 at supper or half at breakfast and half at supper. Again, the key is titration.

Is there an easy way to remember all of this?

The Ontario College of Family Physicians developed an Insulin Educational Tool that serves the dual purpose of education and function (see Figure 1).

Summary

Insulin is a proven and effective, yet underutilized tool, to achieve glycemic control. Hopefully, this simple approach to insulin initiation, plus the Insulin Educational Tool from the OCFP can begin to make insulin use easier and practical. Remember the Rule of 3's:

- 3 categories of insulin (bolus, basal, premixed)
- 3 principles of dosing insulin
  -Whatever starting dose you select will be wrong
  -Titration is the key to success
  -There is no maximum dose of insulin

Table 1. Currently available insulins in Canada

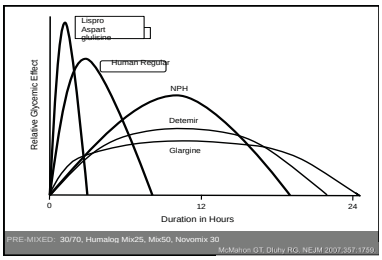
Category of insulin	Human insulin	Analogue insulin
BOLUS	Humulin Regular Novolin Toronto	Apidra (glulisine) Humalog (lispro) Novorapid (aspart)
BASAL	Humulin N Novolin NPH	Lantus (glargine) Levemir (detemir)
PREMIXED	Humulin 30/70 Novolin 30/70 Novolin 40/60 Novolin 50/50	Humulog Mix25 Humalog Mix50 Novomix 30

The Rules of 3's

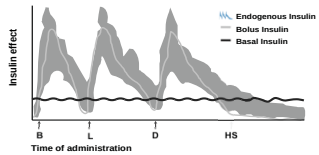
Types of insulins

BOLUS	BASAL
• Regular or Toronto	• NPH
• Apidra (glulisine)	• Lantus (glargine)
• Humalog (lispro)	• Levemir (detemir)
• Novorapid (aspart)	

PRE-MIXED
- **30/70**
- **Humalog Mix25, Mix50** (insulin lispro/lispro protamine)
- **Novomix 30** (biphasic insulin aspart)



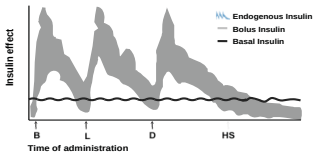
Normal Insulin Secretion: The Basal-Bolus Insulin Concept



B = breakfast; L = lunch; D = dinner; HS = bedtime.
1. Leahy JL, In: Leahy JL, Cefalu WT (eds). *Insulin Therapy*. Marcel Dekker Inc., New York, 2002.
2. Bolli GB, et al. Diabetologia 1999; 42:1151-67.

3 Regimen Options

Basal insulin



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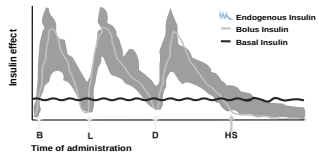
1. Leahy JL, In: Leahy JL, Cefalu WT (eds). *Insulin Therapy*. Marcel Dekker Inc., New York, 2002.
2. Bolli GB, et al. Diabetologia 1999; 42:1151-67.

Basal-Bolus Insulin



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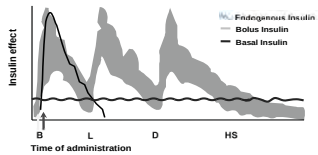
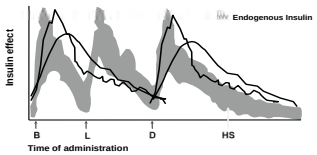
2. Bolli GB, et al. Diabetologia 1999; 42:1151-67.

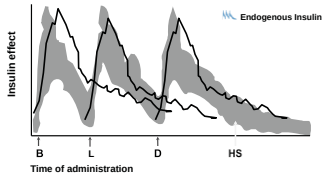
Basal Plus Bolus (main meal)



BID Premixed



TID Premixed



When is basal insulin alone not enough?

Fastings at target
BUT
A1C still >7%

What are the pros and cons?

Basal Bolus

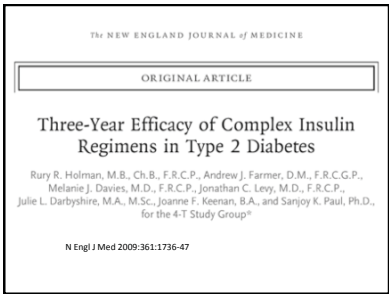
PROS
- Flexibility in timing
- Flexibility in quantity
- Physiologic
- Do not need a pancreas

CONS
- 2-4 injections
- 2-4 SMBG
- Hypoglycemia

Premixed BID or TID

PROS
- 2-3 injections
- 1 insulin

CONS
- No flexibility in dosing
- No flexibility in timing


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes

Rury R. Holman, M.B., Ch.B., F.R.C.P., Andrew J. Farmer, D.M., F.R.C.G.P., Melanie J. Davies, M.D., F.R.C.P., Jonathan C. Levy, M.D., F.R.C.P., Julie L. Darbyshire, M.A., M.Sc., Joanne F. Keenan, B.A., and Sanjoy K. Paul, Ph.D., for the 4-T Study Group*

N Engl J Med 2009;361:1736-47

Therefore …

- Diabetes is PROGRESSIVE
- The regimen must change over time
- All roads lead to Basal Bolus concept

- If you're not going to titrate – don't start

How to dose?

"Whatever you pick will be WRONG … and that's okay!"

Basal Plus Bolus (MDI)

- 0.5 u/kg = TDI
- 50% bolus, 50% basal (or 60:40)

- Add 10% of basal dose as bolus insulin with each meal

- Add 5-10 units at each meal

Premixed

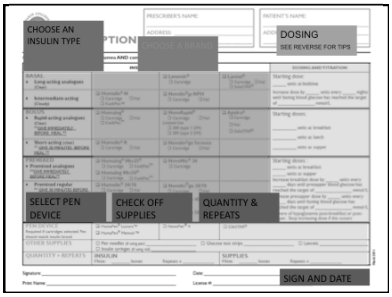
- 0.5 units / kg = TDI
- 1/2 in the AM + 1/2 in the PM

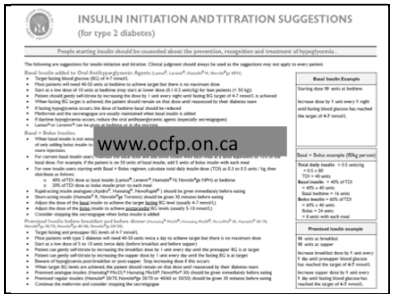
- 5-10 units BID

What about the orals?

- METFORMIN
- METFORMIN
- METFORMIN

- Secretagogues only if basal alone
- TZD – stop
- DPP-4 – benefit but cost (off-label)
- GLP-1 receptor agonist – benefit (dose & weight) but cost (off-label)





How to titrate?

How to approach titration?

1. Where are the lows / highs?
2. Why are there lows / highs?
3. Do I adjust / switch or add?
   a) Titrate to avoid hypoglycemia first
   b) Titrate to reduce hyperglycemia

How much to titrate by?

2 units OR 10%

"Not an exact science … trial and error!"

Basal insulin affects …

Basal-bolus will affect …

If on premixed …

Reflects the bolus portion of the premixed injection at breakfast / dinner

If on premixed…

Reflects the intermediate portion of the premixed injected the night before / breakfast

Patrick

- 54 year old man with type 2 diabetes diagnosed 6 years ago
- Saw the diabetes team 6 months ago and says that he is trying his best with lifestyle but finds it challenging because he is on the road so much as part of his job in sales
- Metformin 1g BID, gliclazide MR 120 mg OD, pioglitazone 30 mg OD, acarbose 50 mg TID, simvastatin 40 mg qhs, ramipril/HCTZ 10/25 mg OD, amlodipine 5 mg OD

- Labs: A1c 8.2%; TC 4.23, TG 1.99, HDL 1.00, LDL 2.0 mmol/L; Cr 125 umol/L; ACR 2.3
- Basal insulin was added and titrated
- Pioglitazone and acarbose were discontinued

Patrick (3 years later)

He has generally been feeling well but says that his sugars are no longer as well controlled as they have been in the past. He continues to try his best with respect to food and activity levels but continues to find it challenging because he is on the road so much.

For his diabetes management, you had started him on long-acting bedtime basal insulin 3 years ago and he responded well to the treatment with A1c maintained below 7% for the last 3 years, although it has risen slightly above 7% at the last visit 4 months ago.

- Meds: Metformin 1g BID, gliclazide MR 120 mg OD, "basal" 55 units qhs, simvastatin 40 mg qhs, ramipril/HCTZ 10/25 mg od, amlodipine 10 mg od, ECASA 81 mg od
- On exam: Obese (wt 104kg, ht 175 cm, WC 108 cm), BP 120/80 mmHg, HR 72 regular. Acanthosis nigricans noted. Eyes – no abnormality. Rest normal.
- Labs: A1c 8.1%; Cr 130 umol/L

	Breakfast		Lunch		Dinner		Bedtime	Insulin Dose
	Before	After	Before	After	Before	After		
Monday	5.9		10.0		7.5			55
Tuesday	6.1	12.3			7.1		7.8	55
Wednesday	5.5		8.7					55
Thursday	5.8	10.1			7.6		6.1	55
Friday	5.2		8.1				6.4	55
Saturday	6.4	11.5			6.9			55
Sunday	7.1		9.1		6.4		5.9	55

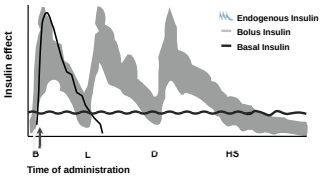
Where are the lows and highs?
Why are there lows and highs?
Adjust / switch / add?

	Breakfast		Lunch		Dinner		Bedtime	Insulin Dose
	Before	After	Before	After	Before	After		
Monday	5.9		10.0		7.5			55
Tuesday	6.1	12.3			7.1		7.8	55
Wed								
Thursday	5.8	10.1			7.6		6.1	55
Friday	5.2		8.1				6.4	55
Saturday	6.4	11.5			6.9			55
Sunday	7.1		9.1		6.4		5.9	55

Add bolus insulin at breakfast

Where are the lows and highs?
Why are there lows and highs?
Adjust / switch / add?

Basal Plus Bolus (main meal)

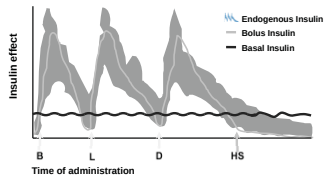


Starting dose?

Will it work?

What will he ultimately need?

Basal-Bolus Insulin



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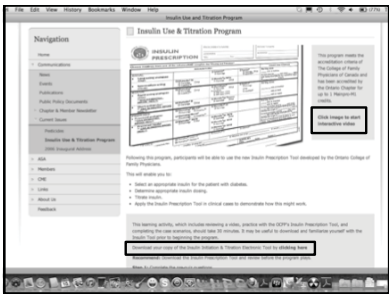
1. Leahy JL. In: Leahy JL, Cefalu WT (eds). *Insulin Therapy*. Marcel Dekker Inc., New York, 2002.
2. Bolli GB, et al. Diabetologia 1999; 42:1151-67.

Summary

- 3 types of insulin
- 3 types of regimens
- Pick a starting dose – it will be wrong – just be sure to titrate
- Change over time as A1c > 7%

Summary

- Approach to titration
  - Where are the lows and highs?
  - Why are the lows and highs?
  - Adjust / switch / add?
    - Titrate to avoid hypoglycemia first
    - Titrate to treat hyperglycemia



INSULIN INITIATION AND TITRATION SUGGESTIONS

(for type 2 diabetes)

People starting insulin should be counseled about the prevention, recognition and treatment of hypoglycemia .

The following are suggestions for insulin initiation and titration. Clinical judgment should always be used as the suggestions may not apply to every patient.

Basal Insulin added to Oral Antihyperglycemic Agents (Lantus®, Levemir®, Humulin® N, Novolin®ge NPH)

- Target fasting blood glucose (BG) of 4-7 mmol/L
- Most patients will need 40-50 units at bedtime to achieve target but there is no maximum dose
- Start at a low dose of 10 units at bedtime (may start at lower dose (0.1-0.2 units/kg) for lean patients (< 50 kg))
- Patient should gently self-titrate by increasing the dose by 1 unit every night until fasting BG target of 4-7 mmol/L is achieved
- When fasting BG target is achieved, the patient should remain on that dose until reassessed by their diabetes team
- If fasting hypoglycemia occurs, the dose of bedtime basal should be reduced
- Metformin and the secretagogue are usually maintained when basal insulin is added
- If daytime hypoglycemia occurs, reduce the oral antihyperglycemic agents (especially secretagogues)
- Lantus® or Levemir® can be given at bedtime or in the morning

Basal + Bolus Insulins

- When basal insulin is not enough to achieve glycemic control, bolus insulin should be added before meals. There is the option of only adding bolus insulin to the meal with the highest postprandial BG as a starting point for the patient who is not ready for more injections.
- For current basal insulin users, maintain the basal dose and add bolus insulin with each meal at a dose equivalent to 10% of the basal dose. For example, if the patient is on 50 units of basal insulin, add 5 units of bolus insulin with each meal
- For new insulin users starting with Basal + Bolus regimen, calculate total daily insulin dose (TDI) as 0.3 to 0.5 units / kg, then distribute as follows:
    - 40% of TDI dose as basal insulin (Lantus®, Levemir®, Humulin® N, Novolin®ge NPH) at bedtime
    - 20% of TDI dose as bolus insulin prior to each meal
- Rapid-acting insulin analogues (Apidra®, Humalog®, NovoRapid®) should be given immediately before eating
- Short-acting insulin (Humulin® R, Novolin®ge Toronto) should be given 30 minutes before eating
- Adjust the dose of the basal insulin to achieve the target fasting BG level (usually 4-7 mmol/L)
- Adjust the dose of the bolus insulin to achieve postprandial BG levels (usually 5-10 mmol/L)
- Consider stopping the secretagogue when bolus insulin is added

Premixed Insulin before breakfast and before dinner (Humalog® Mix25®, Humalog Mix50®, NovoMix® 30, Humulin® 30/70, Novolin®ge 30/70, Novolin®ge 40/60, Novolin®ge 50/50)

- Target fasting and presupper BG levels of 4-7 mmol/L
- Most patients with type 2 diabetes will need 40-50 units twice a day to achieve target but there is no maximum dose
- Start at a low dose of 5 to 10 units twice daily (before breakfast and before supper)
- Patient can gently self-titrate by increasing the breakfast dose by 1 unit every day until the presupper BG is at target
- Patient can gently self-titrate by increasing the supper dose by 1 unit every day until the fasting BG is at target
- Beware of hypoglycemia post-breakfast or post-supper. Stop increasing dose if this occurs
- When target BG levels are achieved, the patient should remain on that dose until reassessed by their diabetes team
- Premixed analogue insulins (Humalog® Mix25,® Humalog Mix50®, NovoMix® 30) should be given immediately before eating
- Premixed regular insulins (Humulin® 30/70, Novolin®ge 30/70 or 40/60 or 50/50) should be given 30 minutes before eating
- Continue the meformin and consider stopping the secretagogue

Basal Insulin Example

Starting dose **10** units at bedtime

Increase dose by **1** unit every **1** night until fasting blood glucose has reached the target of **4-7** mmol/L

Basal + Bolus example (80kg person)

Total daily insulin = 0.5 units/kg
= 0.5 x 80
TDI = 40 units
Basal insulin = 40% of TDI
= 40% x 40 units
Basal bedtime = 16 units
Bolus insulin = 60% of TDI
= 60% x 40 units
Bolus = 24 units
= 8 units with each meal

Premixed insulin example

10 units ac breakfast
10 units ac supper

Increase breakfast dose by **1** unit every **1** day until presupper blood glucose has reached the target of **4-7** mmol/L

Increase supper dose by **1** unit every **1** day until fasting blood glucose has reached the target of **4-7** mmol/L

INSULIN INITIATION AND TITRATION SUGGESTIONS

(for type 2 diabetes)

People starting insulin should be counseled about the prevention, recognition and treatment of hypoglycemia .

The following are suggestions for insulin initiation and titration. Clinical judgment should always be used as the suggestions may not apply to every patient.

Basal Insulin added to Oral Antihyperglycemic Agents (Lantus®, Levemir®, Humulin® N, Novolin®ge NPH)

- Target fasting blood glucose (BG) of 4-7 mmol/L
- Most patients will need 40-50 units at bedtime to achieve target but there is no maximum dose
- Start at a low dose of 10 units at bedtime (may start at lower dose (0.1-0.2 units/kg) for lean patients (< 50 kg))
- Patient should gently self-titrate by increasing the dose by 1 unit every night until fasting BG target of 4-7 mmol/L is achieved
- When fasting BG target is achieved, the patient should remain on that dose until reassessed by their diabetes team
- If fasting hypoglycemia occurs, the dose of bedtime basal should be reduced
- Metformin and the secretagogue are usually maintained when basal insulin is added
- If daytime hypoglycemia occurs, reduce the oral antihyperglycemic agents (especially secretagogues)
- Lantus® or Levemir® can be given at bedtime or in the morning

Basal + Bolus Insulins

- When basal insulin is not enough to achieve glycemic control, bolus insulin should be added before meals. There is the option of only adding bolus insulin to the meal with the highest postprandial BG as a starting point for the patient who is not ready for more injections.
- For current basal insulin users, maintain the basal dose and add bolus insulin with each meal at a dose equivalent to 10% of the basal dose. For example, if the patient is on 50 units of basal insulin, add 5 units of bolus insulin with each meal
- For new insulin users starting with Basal + Bolus regimen, calculate total daily insulin dose (TDI) as 0.3 to 0.5 units / kg, then distribute as follows:
    - 40% of TDI dose as basal insulin (Lantus®, Levemir®, Humulin® N, Novolin®ge NPH) at bedtime
    - 20% of TDI dose as bolus insulin prior to each meal
- Rapid-acting insulin analogues (Apidra®, Humalog®, NovoRapid®) should be given immediately before eating
- Short-acting insulin (Humulin® R, Novolin®ge Toronto) should be given 30 minutes before eating
- Adjust the dose of the basal insulin to achieve the target fasting BG level (usually 4-7 mmol/L)
- Adjust the dose of the bolus insulin to achieve postprandial BG levels (usually 5-10 mmol/L)
- Consider stopping the secretagogue when bolus insulin is added

Premixed Insulin before breakfast and before dinner (Humalog® Mix25®, Humalog Mix50®, NovoMix® 30, Humulin® 30/70, Novolin®ge 30/70, Novolin®ge 40/60, Novolin®ge 50/50)

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Increase supper dose by **1** unit every **1** day until fasting blood glucose has reached the target of **4-7** mmol/L

Vascular Protection Beyond Glycemic Control:
Diabetes is not all sweetness

Dr. Ronald Goldenberg
MD, FRCPC, FACE

Consultant Endocrinologist, North York General Hospital & LMC Endocrinology Centers, Thornhill, Ontario

Dr. Ronald Goldenberg is a consultant endocrinologist affiliated with North York General Hospital in Toronto, Ontario and LMC Endocrinology Centre in Thornhill. He completed his residency in Internal Medicine in 1987 at the University of Toronto, and his fellowship in Endocrinology & Metabolism in 1989 at the University of Toronto. His major areas of interest include clinical care of diabetes, obesity, dyslipidemia and thyroid disorders

Learning Objectives:

1) **Determine which patients with diabetes are considered to be high risk according to the 2008 CDA-CPG**
2) **Know the appropriate vascular protective strategies to apply to the patient with diabetes in order to reduce the risk of diabetes complications**
3) **Manage cardiovascular risk factors according to the 2008 CDA Clinical Practice Guidelines, 2009 CCS Dyslipidemia Guidelines and 2011 CHEP Guidelines**

Cardiovascular disease (CVD) is the primary complication of diabetes. Most patients with diabetes are at high-risk for CVD. A practical tool for recognizing high-risk patients will be reviewed in this session. The first priority in the prevention of diabetes complications should be the reduction of CVD risk by vascular protection through a comprehensive multifactorial approach. For high-risk patients, this includes ACE inhibitor or ARB therapy (independent of BP), lipid-lowering therapy, and antiplatelet therapy (as recommended). All patients with diabetes should be treated with lifestyle modification and should achieve optimal BP (BP < 130/80) and optimal glycemia (A1C ≤ 7.0%). Using a case-based approach, the evidence for all vascular protection recommendations beyond glycemic control will be discussed. Implementing multifactorial risk-factor control in patients with diabetes saves lives and prevents major morbidity.

Vascular Protection Beyond Glycemic Control: Diabetes is not all Sweetness

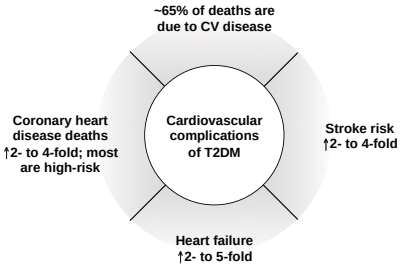
Ronald Goldenberg, MD, FRCPC, FACE
Consultant Endocrinologist
NYGH & LMC Endocrinology Centres

Learning Objectives

At the end of this session, participants will be able to:

1. Determine which patients with diabetes are considered to be high risk according to the 2008 Canadian Diabetes Association Clinical Practice Guidelines
2. Know the appropriate vascular protective strategies to apply to the patient with diabetes in order to reduce the risk of diabetes complications
3. Manage cardiovascular risk factors according to the 2008 CDA Clinical Practice Guidelines, 2009 CCS Dyslipidemia Guidelines and 2011 CHEP Guidelines

Cardiovascular disease and diabetes



T2DM = type 2 diabetes mellitus

Bell DSH. *Diabetes Care*. 2003;26:2433-41.
Centers for Disease Control (CDC). www.cdc.gov.

Mrs. VP: 47-year-old Female

- Russian origin
- Born in Canada
- Family history:
  - mother: diabetes, amputation age 70 years
  - father: MI age 69 years
- Social history:
  - mother (2 children)
  - non-smoker
  - 30 minute walk 3 times /wk
- Medical history:
  - type 2 diabetes diagnosed 5 years ago
  - hypertension for 3 yrs

Mrs. VP: 47-year-old Female

- Medication: metformin 1000 mg bid, ramipril 10 mg od
- Exam
  - weight 75 kg, height 1.6 m, BMI 29 kg/m^2
  - waist circumference 95 cm
  - heart rate 76 bpm, BP 140/86 mmHg
  - no carotid bruit, pedal pulses palpable
  - optic fundi normal
- Laboratory
  - creatinine 95 um/l, urine ACR 1.7 (N < 2.8)
  - fasting blood sugars 5.8-7.2, A1C 6.8%
  - Cholesterol 6.4, HDL-C 1.1, LDL-C 4.4, TG 1.9, TC:HDL-C 5.8
  - ECG: normal

What is Mrs. VP's level of risk for CVD?
High, Moderate, or Low?

Diabetes and High Risk for Cardiovascular Events

The following individuals with diabetes should be considered at high risk for cardiovascular events:

- Men aged ≥ 45 years, women aged ≥ 50 years [Grade B, Level 2]
- Men < 45 years and women < 50 years with ≥ 1 of the following [Grade D, Consensus]:
  - macrovascular disease (*e.g.,* MI, peripheral arterial disease, or cerebrovascular disease)
  - microvascular disease (nephropathy and retinopathy)
  - multiple additional risk factors
  - extreme level of single risk (*e.g.,* LDL-C > 5.0 mmol/L, SBP > 180 mmHg)
  - duration of diabetes > 15 years with age > 30 years

CDA Guidelines 2008.

Mrs. VP: Framingham Risk Score*

Age:	47 Years
Gender:	Female Male
Total cholesterol:	6.4 mmol/L
HDL cholesterol:	1.1 mmol/L
Smoker:	Yes No
Diabetes:	Yes No
Systolic blood pressure:	140 mm Hg
Is the patient being treated for high blood pressure?	Yes No
Your patient's Framingham Risk Score is	24.8%

Mrs. VP is High-Risk

* Available at www.cvdriskcheck.com (iphone & blackberry apps are available)

Reduction of CVD Risk in Prevention of Diabetes Complications

- The first priority in the prevention of diabetes complications should be the reduction of cardiovascular disease risk by vascular protection through a comprehensive multifaceted approach

CDA Guidelines 2008.

Vascular Protection in the Patient with Diabetes

- For patients at high risk of a CV event
  1. ACE inhibitor or ARB therapy (independent of BP)
  2. Lipid-lowering therapy (primarily statins)
  3. Antiplatelet therapy (as recommended)
- For all patients with diabetes:
  1. Lifestyle modification
     - achievement and maintaining healthy body weight
     - healthy diet
     - regular physical activity
     - smoking cessation
  2. Optimize blood pressure control
  3. Optimize glycemic control

CDA Guidelines 2008.

Vascular Protection in the Patient with Diabetes

- For patients at high risk of a CV event
  1. ACE inhibitor or ARB therapy (independent of BP)
  2. Lipid-lowering therapy
  3. Antiplatelet therapy (as recommended)
- For all patients with diabetes:
  1. Lifestyle modification
     - achievement and maintaining healthy body weight
     - healthy diet
     - regular physical activity
     - smoking cessation
  2. Optimize blood pressure control
  3. Optimize glycemic control

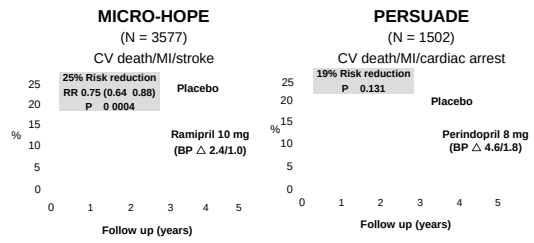
CDA Guidelines 2008.

Renin Angiotensin Modulation

- Individuals with diabetes at high risk for CV events should receive an ACE inhibitor or ARB at doses that have demonstrated vascular protection
  – Grade A Level 1A for people with vascular disease
  – Grade B Level 1A for other high-risk groups

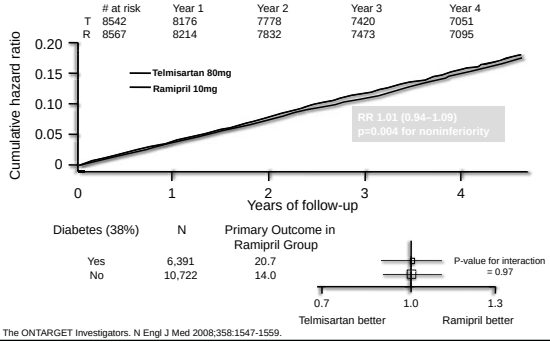
CDA Guidelines 2008.

Vascular Protection in Patients With Diabetes:
MICRO-HOPE, PERSUADE:



HOPE Study Invest ga ors. *Lancet.* 2000;355:253-9.
Daly CA et al. *Eur Heart J.* 2005.

ONTARGET: ACEi vs ARB for the Prevention of CV Events



The ONTARGET Investigators. N Engl J Med 2008;358:1547-1559.

Canadian Cardiovascular Society Guidelines on Dyslipidemia 2009

Risk categories and treatment recommendations

Level of Risk (definition)	Initiate treatment if:	Primary target* LDL-C
High CAD, PVD, atherosclerosis Most with diabetes FRS ≥ 20% RRS ≥ 20%	Consider treatment in all patients	< 2.0 mmol/L or ≥ 50% ↓ LDL-C
Moderate FRS 10% - 19% Family history and hs-CRP modulates risk (RRS)	LDL-C > 3.5 mmol/L TC/HDL-C > 5.0 hs-CRP > 2 mg/L (men > 50y; women > 60y)	< 2.0 mmol/L or ≥ 50% ↓ LDL-C
Low FRS < 10%	LDL-C ≥ 5.0 mmol/L	≥ 50% ↓ LDL-C

* An alternate target for High and Moderate Risk is apoB <0.80 g/L

Genest J et al. Can J Cardiol 2009; 25: 567-579.

Benefits of aggressive LDL-C lowering in diabetes

	Primary event rate (%) Treatment	Control	Aggressive lipid-lowering better	Aggressive lipid-lowering worse	P	LDL-C achieved in aggressive gp.
TNT Diabetes, CHD	13.8	17.9	0.75		0.026	2.0*
ASCOT-LLA Diabetes, HTN	9.2	11.9	0.77		0.036	2.2†
CARDS Diabetes, no CVD	5.8	9.0	0.63		0.001	2.1†
HPS All diabetes	9.4	12.6	0.73		<0.0001	2.3†
Diabetes, no CVD	9.3	13.5	0.67		0.0003	2.2†

0.5 0.7 0.9 1 1.7
Relative risk

*Atorvastatin 10 vs 80 mg/day
†Statin vs placebo

Shepherd J et al. *Diabetes Care* 2006. Sever PS et al. *Diabetes Care* 2005. HPS Collaborative Group. *Lancet* 2003. Colhoun HM et al. *Lancet* 2004.

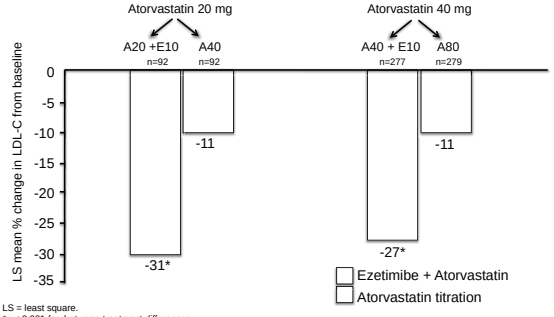
Mrs. VP: 47-year-old Female

- Baseline lipids
  - TC 6.4, HDL-C 1.1, LDL-C 4.4, TG 1.9, TC:HDL-C 5.8
  - Needs > 50% LDL-C reduction
- Started on atorvastatin 40 mg
- 3 months later
  - TC 4.4, HDL-C 1.1, LDL-C 2.6, TG 1.6, TC:HDL-C 4.0

What would you do to reach the primary lipid target?

Is doubling statin dose or changing the statin useful? Would you add ezetimibe?

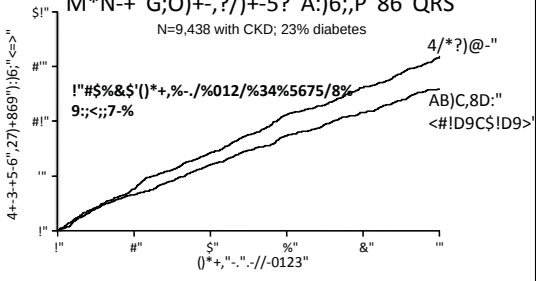
LDL-C Reduction: Incremental Benefit of Adding Ezetimibe vs Uptitrating Statin



LS = least square.
*$p < 0.001$ for between-treatment differences.
Adapted from: Conard S et al. Am J Cardiol 2008 and Leiter L et al. Am J Cardiol 2008.

EFGH4I"J)6)K;,"-." E;*56"L'ÄB)5D8@)'-6'"M*N-+"G;O)+-,?/)+-5?"A:)6;,P"86"QRS'

N=9,438 with CKD; 23% diabetes



Diabetes (23%)	N	Primary Outcome in Placebo Group
Yes	1,054	22.5
No	3.596	10.8

P-value for interaction = 0.45

0.5 1.0 1.5
Eze/Simva better
Placebo better

* Coronary death, MI, non-hemorrhagic stroke, any revascularization

Baigent C et al. Lancet 2011.

Mrs. VP: 47-year-old Female

- Baseline lipids
  - TC 6.4, HDL-C 1.1, LDL-C 4.4, TG 1.9, TC:HDL-C 5.8
  - Needs > 50% LDL-C reduction
- Started on atorvastatin 40 mg
- 3 months later
  - TC 4.4, HDL-C 1.1, LDL-C 2.6, TG 1.6, TC:HDL-C 4.0
- Ezetimibe 10 mg added to atorvastatin 40 mg
- 3 months later
  - TC 3.8, HDL-C 1.2, LDL-C 1.9, TG 1.5, TC:HDL-C 3.2

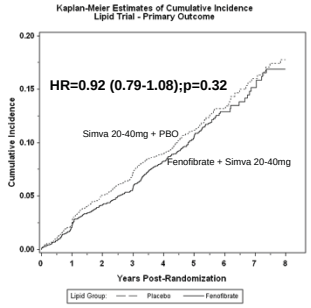
Optional Secondary Targets for High-Risk Patients Only After LDL-C at Target

Test	Target	Intervention
TC/HDL-C	<4.0	Niacin Fibrate
Triglycerides	<1.7 mmol/L	Fibrate Niacin
Non HDL-C	<3.5 mmol/L	Niacin Fibrate
Apo B/A1	<0.8	Niacin Ezetimibe
hsCRP	<2.0 mg/L	Statin Ezetimibe

Clinical advantages of secondary targets, with respect to patient outcomes, remain to be proven

Genest et al. *Can J Cardiol* 2009;25:567-79

ACCORD-Lipid: Effect of Fibrate + Statin vs Statin Alone on CVD Events in High-Risk Type 2 Diabetes



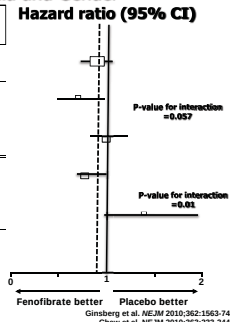
Lipid eligibility criteria for ACCORD Lipids:
LDL 1.6 to 4.7; HDL <1.4 women & blacks; <1.3 others
TG <8.5 if not on drug; <4.5 on drug

The Accord Study Group. N Engl J Med 2010;362:1563-1574.

ACCORD Lipid Study

Prespecified Analysis of Primary Outcome in Subgroups by Dyslipidemia and Gender

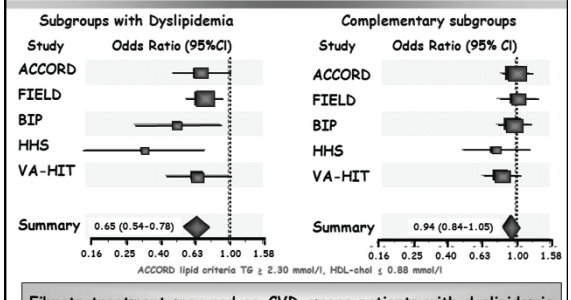
Subgroup	Fenofibrate % of events (no. in group)	Placebo % of events (no. in group)
Overall	10.52 (2765)	11.26 (2753)
TG ≥2.3 mmol/L and HDL-C ≤0.88 mmol/L (17% of patients)	12.37 (485)	17.32 (456)
All others	10.11 (2264)	10.11 (2284)
Males	11.2 (1914)	13.3 (1910)
Females	9.0 (851)	6.6 (843)



Other ACCORD Findings:
- No sign. Interaction in dyslipidemic subgroup by gender
- Combination therapy reduced progression of diabetic retinopathy by 40%
- Combination therapy reduced microalbuminura and macroalbuminuria
- Combination therapy did not increase risk of myopathy /rhabdomyolysis

Ginsberg et al. *NEJM* 2010;362:1563-74
Chew et al. *NEJM* 2010;363:233-244
FDA Advisory Committee Briefing Document. www.fda.gov. Accessed May 18, 2011.

Meta-analysis of fibrate trials in subjects with (n=2428) and without (n=2298) dyslipidemia



Fibrate treatment may reduce CVD among patients with dyslipidemia

Sacks FM et al. NEJM 2010;363:692-694

AIM-HIGH: Effect of ER Niacin + Statin vs Statin Alone on CVD Events in Patients with CVD & Atherogenic Dyslipdiemia

- N=3,414 with CVD & atherogenic dyslipidemia
- Randomized to simvastatin (or simva + ezetimibe) vs simva + ER Niacin
- Trial stopped after 32 months follow-up because of lack of efficacy (primary composite outcome HR=1.05, p=0.56)
- Increase in stroke in simva + ER Niacin arm: 28(1.6%) vs 12(0.7%)
- 9 of 28 strokes in Niacin arm occurred 2 months to 4 yrs after stopping drug

www.nhlbi.nih.gov. Accessed May 27, 2011.

Niacin for prevention of CV events : meta-analysis of 10 trials (N=6545)

Outcome	Odds Ratio (95% CI)	p-value
Major coronary events	0.75 (0.65 to 0.86)	p<0.0001
Stroke	0.74 (0.59 to 0.92)	p=0.007
CV events	0.73 (0.63 to 0.85)	p<0.0001

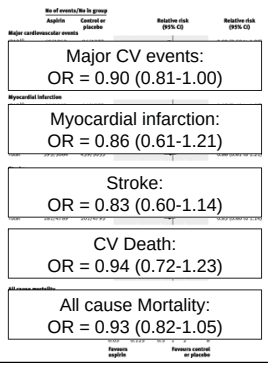
One further ongoing trial (HPS2-THRIVE) will help to establish if niacin has beneficial effects on residual risk in statin-treated patients

Bruckert E et al. Atherosclerosis 2010;210:353-361

Mrs. VP: 47-year-old Female

Should Mrs. VP be treated with ASA?

Aspirin for primary prevention of CV events in people with diabetes: meta-analysis of 6 randomized trials (N=10,117)



Major CV events:
OR = 0.90 (0.81-1.00)

Myocardial infarction:
OR = 0.86 (0.61-1.21)

Stroke:
OR = 0.83 (0.60-1.14)

CV Death:
OR = 0.94 (0.72-1.23)

All cause Mortality:
OR = 0.93 (0.82-1.05)

De Berardis, G. et al. BMJ 2009;339:b4531

Antiplatelet Medication Recommendations

- Low-dose ASA therapy (81-325 mg) may be considered in people with stable cardiovascular disease [Grade D, Consensus]
- Clopidogrel (75 mg) may be considered in people unable to tolerate ASA [Grade D, Consensus]
- The decision to prescribe antiplatelet therapy for primary prevention of CV events, however, should be based on individual clinical judgement [Grade D, Consensus]

CDA Guidelines 2008.
Physicians' Health Study. N Engl J Med 1989; 321:129-35.
Hypertension Optimal Treatment (HOT) trial. Lancet 1998; 351:1755-62.
Primary Prevention Project (PPP) trial. Diabetes Care 2003; 26:264-72.
ETDRS Investigators. JAMA 1992; 268:1292-300.

Vascular Protection in the Patient with Diabetes

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  1. Lifestyle modification
     - achievement and maintaining healthy body weight
     - healthy diet
     - regular physical activity
     - smoking cessation
  2. Optimize blood pressure control
  3. Optimize glycemic control

CDA Guidelines 2008.

Major Clinical Trials of Blood Pressure Lowering in Patients with Diabetes

Trial	N	Mean BP, less intense	Mean BP, more intense	CVD Risk Reduction
ABCD-Norm	480	137/81	128/75	Stroke:68% MI: NS
Syst-Eur	492	162/82	153/78	62-69%
HOT	1,501	148/85	144/81	30-67%
UKPDS	1,148	154/87	144/82	32-44%
ABCD-HTN	470	139/86	133/78	No CVD Reduction
ADVANCE	11,140	140/77	135/75	MACE: NS CV death: 18%
ACCORD	4,733	134/71	119/64	MACE: NS Stroke: 41%

Adapted from Cushman W et al. Am J Cardiol 2007;99:45i-55i. Estacio R et al. Nat Clin Prac Neph 2007;428. Zanchetti A et al. J Hypertens 2003;21:797-804. ADVANCE Collaborative Group. Lancet 2007; 370:829-840. The Accord Study Group. N Engl J Med 2010;362:1575-1585.

Meta-Analysis of Intensive BP Control (SBP ≤ 135) vs Standard Control (SBP ≤140) in Diabetes/Prediabetes

Meta-analysis of 13 trials with 37,736 patients

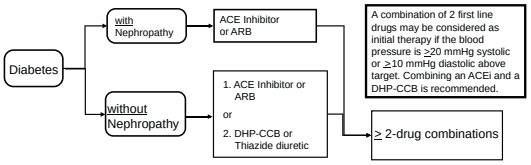
Outcome	Intensive Group (%)	Standard Group (%)	Odds Ratio (95% CI)
All-cause mortality	**6.1**	**6.6**	**0.90 (0.83-0.98)**
CV mortality	**2.9**	**3.1**	**0.93 (0.82-1.06)**
MI	**3.3**	**3.6**	**0.92 (0.80-1.06)**
Heart failure	**2.4**	**2.4**	**0.90 (0.75-1.06)**
Stroke*†	**2.5**	**2.9**	**0.83 (0.73-0.95)**
Nephropathy††	**4.6**	**6.2**	**0.73 (0.64-0.84)**

* Meta-regression analysis showed continued risk reduction for stroke to a SBP of < 120 mmHg, but at levels <130 mmHg there was a 40% increase in SAEs with no benefit for other outcomes.
† More intensive BP control (SBP ≤ 130) associated with 47% RR in stroke.
†† More intensive BP control (SBP ≤ 130) associated with 36% RR in nephropathy.

Bangalore S et al. Circulation 2011;123.

CHEP 2011: Treatment of Hypertension in association with Diabetes Mellitus

Threshold equal or over 130/80 mmHg and TARGET below 130/80 mmHg



Monitor serum potassium and creatinine carefully in patients with CKD prescribed an ACEI or ARB

Combinations of an ACEI with an ARB are specifically not recommended in the absence of proteinuria

More than 3 drugs may be needed to reach target values for diabetic patients

If Creatinine over 150 µmol/L or creatinine clearance below 30 ml/min (0.5 ml/sec), a loop diuretic should be substituted for a thiazide diuretic if control of volume is desired

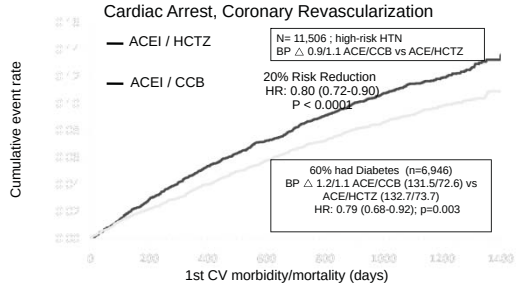
Mrs. NS: 47-year-old Female

- BP 140/86 mmHg on ramipril 10 mg od
- Target BP is < 130/80

What would you do next?

ACCOMPLISH: Kaplan Meier for Time to First Primary Composite Endpoint

CV Death, MI, Stroke, Hospitalized Angina, Cardiac Arrest, Coronary Revascularization



Jamerson K et al. N Engl J Med 2008; 359: 2417-2428.
Weber M et al. JACC 2010;56:77-85.

2011 CHEP Recommendations regarding drug combinations *Diabetes and Hypertension*

For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide or thiazide-like diuretic (Grade A)

Mrs. NS: 47-year-old Female

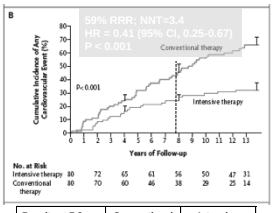
- BP 140/86 mmHg on ramipril 10 mg od
- Target BP is < 130/80

- Added amlodipine 5 mg od
- 6 weeks later: BP 132/80

Why are you giving me so many drugs, doctor? Is it really worth it?

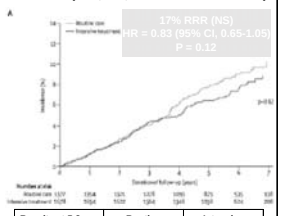
Effects of multifactorial intervention on macrovascular outcomes*: Steno-2 vs ADDITION Trial

Steno-2 (n=160; T2D with MAU)



Results at 7.8yrs	Conventional	Intensive
A1C (%)	9.0	7.9
LDL-C (mmol/L)	3.2	2.2
BP	146/78	132/73

ADDITION (n=3,055; screen-detected T2D)



Results at 5.3yrs	Routine	Intensive
A1C (%)	6.7	6.6
LDL-C (mmol/L)	2.3	2.1
BP	138/81	135/80

Gæde P et al. *N Engl J Med*. 2008;358:580-591.
Griffin S et al. Lancet. 2011.

* CV death, MI, stroke, revascularization, amputation

Mrs. NS: 47-year-old Female

Medications:
- Metformin1000 mg bid
- Atorvastatin 40 mg
- Ezetimibe 10 mg
- ASA 81 mg
- Ramipril 10 mg od
- Amlodipine 5 mg od

- BMI 29 kg/m^2 → 27 kg/m^2
- Waist 95 cm → 93 cm
- BP 140/86 mmHg → 132/80 mmHg
- Biochemistry
  - A1C 6.8%
  - TC 3.8, HDL-C 1.2, LDL-C 1.9, TG 1.5, TC:HDL-C 3.2

Multifactorial risk reduction reduces complications of diabetes and saves lives

Conclusions

- Multifactorial risk-factor control in patients with diabetes saves lives and prevents major morbidity
- Applying lifestyle & pharmacotherapeutic strategies to achieve treatment goals will improve outcomes

What the Family Doctor Needs to Know About Type 2 Diabetes in Pregnancy

Denice Feig
MD (McMaster), MSc (Toronto)
Associate Professor,
Associate SGS Member
Mount Sinai Hospital

Dr Feig is a staff endocrinologist, at the Mount Sinai Hospital, Leadership Sinai Diabetes Centre, specializing in endocrine disorders in pregnancy, and is Head of the Diabetes in Pregnancy Program at Mount Sinai Hospital and University Health Network. She is an Associate Professor at the University of Toronto in the Department of Medicine, and has a Master's degree in Clinical Epidemiology. She holds a cross-appointment with both the Department of Obstetrics and Gynaecology and with the Department of Health Policy, Management and Evaluation. She is currently Chair of the Canadian Diabetes in Pregnancy Study Group (CanDIPS) and she is on the Expert Committee for the Canadian Diabetes Association Clinical Practice Guidelines in the area of diabetes in pregnancy.

Dr. Feig is currently the principal investigator of 2 multi-center randomized trials in women with diabetes in pregnancy and has numerous peer-reviewed publications in the area of diabetes in pregnancy.

In this session you will learn about

a) **Glycemic control and anomalies in women with type 2 diabetes**

b) **Safety of drug use in the first trimester including oral hypoglycemic agents, antihypertensives, antilipidemics.**

c) **Perinatal complications in infants of women with type 2 diabetes**

d) **Safety of drug use during breast feeding**

e) **Prevention of Type 2 diabetes in women with previous GDM**

f) **Importance of breastfeeding for infants of women with diabetes**

What the Family MD Needs to Know About Diabetes in Pregnancy

Dr. Denice Feig
Associate Professor
University of Toronto
Head, Diabetes & Pregnancy Program
Mt Sinai Hospital

Overview

- Pre-pregnancy
  - Type 2
  - GDM
- Postpartum
  - Type 2
  - GDM

Overview

- Pre-pregnancy
  - Type 2
  - GDM
- Postpartum
  - Type 2
  - GDM

Viewpoint

THE LANCET • Vol 340 • July 11, 1992

Type 2 diabetes in pregnancy: a growing concern

Denise S Feig, Andrea E Sermer

Over the past 10 years, good studies have been made documenting the outcomes of women with type 1 (insulin-dependent) diabetes mellitus during pregnancy. However, during the past decade, type 2 diabetes in pregnancy has emerged, and is continuing to become a prominent concern. Recent publications suggest that we are currently underestimating the true prevalence of type 2 diabetes in pregnancy, and that adverse maternal and fetal outcomes are as significant in these women as those who have type 1 diabetes.

Furthermore, many patients with gestational diabetes are likely to have type 2 diabetes that has remained undetected

pregnancy if they are taking insulin. This assumption might be valid when referring to populations in which the classic presentation of type 1 diabetes is high—eg, in Sweden and Finland. However, the populations in which the prevalence of type 2 diabetes is higher than that of type 1, many first half the pregnant diabetic women could in fact have type 2 diabetes. In Japan and Kuwait, about 75% of women with gestational diabetes have type 2 diabetes.

Year	Total Deliveries In Ontario	Deliveries in women with PGD (%)
1996	133,516	1,122 (0.8)
1997	131,685	1,191 (0.9)
1998	129,470	1,296 (1.0)
1999	128,[illegible]	[illegible] (1.1)
2000	124,60[illegible]	[illegible]
2001	128,7[illegible]	[illegible]
2002	126,000	1,658 (1.3)
2003	129,743	1,831 (1.4)
2004	130,184	1,982 (1.5)
2005	131,289	1,928 (1.5)

↑ 72%

Feig - Diabetes Care 2006

Case

- 32 yr old woman
- Dx'd with Type 2 diabetes, 3 yrs before
- Told to watch what she ate

Case

- Her glucose control worsened
- She was started by family physician on metformin, glyburide, rosiglitazone
- ramipril for hypertension
- atorvastatin for hypercholesterolemia

She is NOT planning pregnancy

(She is not planning AGAINST pregnancy)

Case

- Presents to the office at 8 weeks gestation
- "Was this pregnancy planned?"
- She answers, "No, it wasn't planned, but if it happened that would be fine"
  - HbA1c - 13%

Case

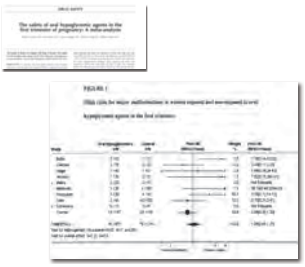
- What would you tell her?
  - ✦ No problem, continue on meds
  - ✦ Stop all meds, refer to endocrinology
  - ✦ Consider a TA and try again
  - ✦ Keep on OHA's, refer to endocrinology
  - ✦ Start on insulin, then stop OHA's

Do oral hypoglycemic agents increase the rate of congenital anomalies?

Let's examine each class of OHA's ...

Glyburide and Metformin

- 10 studies:
  - 471 exposed, 1344 not exposed
- No differences:
  - major malformations
  - neonatal deaths



Drug Ratings in Pregnancy

DPP-IV Inhibitors: Sitagliptin (Januvia)

- ✦ No teratogenicity noted in animal studies
- ✦ No studies in pregnant women
- ✦ Pregnancy Risk 'B'

ACE Inhibitors & Statins

The Risk of Anomalies?

ACE inhibitors in pregnancy

- 1st Trimester
  - Animals: no increase malformations
  - Humans: limited data

Cooper et al - NEJM 2006

- 29,507 infants from Tennessee Medicaid files born 1985-2000
- 3 cohorts:
  - 209 exposed to ACE in 1st trimester
    - RR 2.71 (1.72 - 4.27)
  - 202 exposed other antihypertensives
    - RR 0.66 (0.25-1.75)
  - 29,096 unexposed

Cooper et al - Criticisms

- Attempted to exclude mothers with diabetes....? Successful
  - Could not exclude diet-controlled diabetes or control for obesity

ACE inhibitors in pregnancy

- "ACE Inhibitor Fetopathy"
- 2nd and 3rd Trimester
- Oligohydramnios:
  - fetal limb contractures, craniofacial deformities, pulmonary hypoplasia with RDS
- IUGR, prematurity, neonatal hypotension, anuria, death

ACE in Pregnancy

- For hypertension: use other antihypertensives in women of child-bearing age
  - methyldopa, labetolol
- For those with significant nephropathy: discuss with patient

Statins in Pregnancy

- Cholesterol is essential for fetal development
- Animal data: toxic doses: skeletal malformations
- FDA voluntary reporting: 22 cases of malformations after 1st trimester exposure (CNS, limb defects)
  - No control group

Statins in Pregnancy

- 2 studies:
- Case-control (Taguchi 2008)
  - No difference in congenital anomalies
  - 64 exposed, 64 matched, not exposed
- Population-based registry (Ofori 2007)
  - 153 exposed, 110,000 not exposed

Statins in Pregnancy

- Data encouraging
- Avoid in women of child-bearing age

GLP-1 Agonists: Exenatide

- Some adverse events in animal studies

Thiazolidenediones

- Very little data
- Crosses the placenta
- Not teratogenic in animals but fetal growth retardation in mid-gestation
- Human data (rosiglitazone) - no anomalies
- Pregnancy Risk 'C'

G.J. (continued)

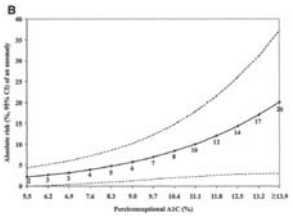
- OHA's D/C'd, Humalog with meals, NPH at bedtime
- 18 wk anatomy scan: small VSD with aortic coarctation, prognosis guarded depending on size of LV
- Patient decided to continue with pregnancy

G.J. (continued)

- spontaneous labor at 32 wks - boy 1550 g
- VSD, aortic arch hypoplasia, small bicuspid abnormal aortic valve
- Repair of VSD and reconstruction of aortic arch at 8 days
- In and out of hospital in 1st year with CHF

WHERE DID WE FAIL HER?

What is the cause of congenital anomalies in pregnant women with Type 2 Diabetes?

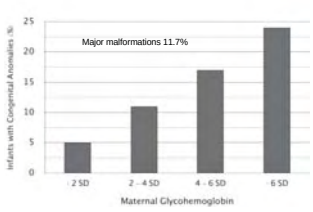


Guerin et Diabetes Care 2007

GHbSD	Corresponding HbA_{1c} (%)*	Absolute risk of a congenital anomaly (%, 95% confidence interval)
0	5.5	2.2 (0.0-4.4)
1	6.2	2.7 (0.2-5.2)
2	6.9	3.2 (0.4-6.1)
3	7.6	3.9 (0.7-7.2)
4	8.3	4.8 (1.0-8.6)
5	9.0	5.8 (1.3-10.2)
6	9.7	7.0 (1.7-12.3)
7	10.4	8.4 (2.0-14.8)
8	11.1	10.1 (2.3-17.8)
9	11.8	12.1 (2.6-21.5)
10	12.5	14.4 (2.8-25.9)
11	13.2	17.0 (2.9-31.1)
≥ 12**	≥ 13.9	20.1 (3.0-37.1)

Guerin et Diabetes Care 2007

Oral Hypoglycemics in Pregnancy



Towner et al, Diabetes Care - 1995

Type 2 Diabetes
Types of Congenital Anomalies

- Major anomalies in 4180 infants
- 2.9% in GDM
- 8.9% Type 2
- Types:
  - Cardiac 37.6%
  - Musculoskeletal 14.7%
  - CNS 9.8%
  - Multiple organ systems 16%

Schaefer-Graf, Am J Obstet Gynecol 2000

Diabetes and Pregnancy

Anomaly	Gestational Age (wks)
Caudal regression	5
Spina bifida, Hydrocephalus, Anencephalus	6
Cardiac anomalies	7 - 8
Renal anomalies	7
Anal/rectal atresia	8

Risk of chromosomal abnormalities NOT increased

Mills et al, Diabetes 1979

- In order to avoid congenital anomalies need to PLAN pregnancies
- Patients remain on birth control until HbA1c<7%
- Then birth control stopped
- Patient proceeds to pregnancy

Prepregnancy Counseling and Birth Control

- Go Hand in Hand

Prepregnancy Counseling

- Retrospective chart review UK
- Women attending general diabetes clinic

Preconception care discussed in only 25% of cases!

Varughese et al 2006

Prepregnancy Counselling

- France
- 138 women Type 1 DM
- 85% received info about preconception care
- 48% unaware of the risk of congenital anomalies

Diabetes Metab 2005

Prepregnancy Counselling

- Possible difficulties in women with Type II DM:
- More cultural variability
  - Language
  - Financial
  - Attitude

- *ANY MEDICAL ENCOUNTER WITH A WOMAN OF CHILD-BEARING AGE WITH DIABETES SHOULD BE CONSIDERED A PRECONCEPTION VISIT!!*

Folic acid

Case

- What would you tell her?
  - No problem, continue on meds
  - Stop all meds, refer to endocrinology
  - Consider a TA and try again
  - Keep on OHA's, refer to endocrinology
  - Stop all meds, start on insulin

Case

- What would you tell her?
  - No problem, continue on meds
  - Stop all meds, refer to endocrinology
  - Consider a TA and try again
  - Keep on OHA's, refer to endocrinology
  - Start on insulin, then stop OHA's

Women with PCOS

- Very high risk of type 2 DM
- Screen them BEFORE pregnancy for type 2 DM
- Screen frequently in pregnancy for GDM

Women with Previous GDM

- Screen for type 2 diabetes with OGTT
- Once pregnant: Screen early and often
- Encourage weight loss prior to pregnancy if obese
  - Increased perinatal complications including congenital anomalies

Change in Body Mass Index Between Pregnancies and the Risk of Gestational Diabetes in a Second Pregnancy

Samantha F. Ehrlich, MPH, Monique M. Hedderson, PhD, Juanran Feng, MS, Erica K. Davenport, Erica P. Gunderson, PhD, and Assiamira Ferrara, MD, PhD

OBJECTIVE: To estimate the association between interpregnancy change in body mass index (BMI) and the risk of gestational diabetes mellitus (GDM) in a second pregnancy.

METHODS: In a retrospective cohort analysis of 22,551 women, logistic regression models provided adjusted estimates of the risk of GDM in women gaining 3.0 or more, 2.0–2.9, and 1.0–1.9 BMI units, or losing 1.0–2.9 and more than 2.0 units between pregnancies (one BMI unit corresponds to 5.9 pounds for the average height [5 feet 4 inches] of the study population). Women with

least 2.0 BMI units. In overweight and obese women, those with GDM in the first pregnancy that did not develop the condition again gained fewer BMI units than those experiencing recurrent GDM (mean change 0.36 [95% CI 0.25–0.47], compared with 2.09 [95% CI 1.56–2.43] BMI units, respectively).

CONCLUSION: Interpregnancy increases in BMI between the first and second pregnancy increases a woman's risk of GDM pregnancy.

(Obstet Gynecol 2011;117:1023–29)
DOI: 10.1097/AOG.0b013e3182160c5d

Ehrlich et al Obstet Gynecol 2011

Change in Body Mass Index Between Pregnancies and the Risk of Gestational Diabetes in a Second Pregnancy

- Women who had GDM in first pregnancy,
  - if they gained weight: risk of GDM increased
  - if they were overweight/obese and lost weight: risk of GDM decreased

Ehrlich et al Obstet Gynecol 2011

Type 2 DM in Pregnancy:

How do their perinatal outcomes compare to those in women with type 1 diabetes?

Maternal and Fetal Outcome in Women with Type 2 *Versus* Type 1 Diabetes Mellitus: A Systematic Review and Metaanalysis

Montserrat Balsells, A. García-Patterson, I. Gich, and R. Corcoy

Servei d'Endocrinologia i Nutrició (M.B.), Hospital Mútua de Terrassa, Terrassa 08221, Spain; Servei d'Endocrinologia i Nutrició (A.G.-P., R.C.) y Servei d'Epidemiologia Clínica (I.G.), Hospital de la Santa Creu i Sant Pau, Barcelona 08025, Spain; and Centro de Investigación Biomédica en Red (CIBER Bioingeneering (R.C.), Biomaterials and Nanotechnology, Instituto de Salud Carlos III, Madrid 28029, Spain

Context: Glycemic disturbance is usually less severe in pregnant women with type 2 than in those with type 1 diabetes mellitus (DM). Nevertheless, a worse perinatal outcome in women with type 2 DM has been reported in some studies.

Objective: Our objective was to review maternal and fetal outcomes in pregnant women with type 2 vs. type 1 DM.

J Clin Endocrinol Metab 94: 4284–4291, 2009

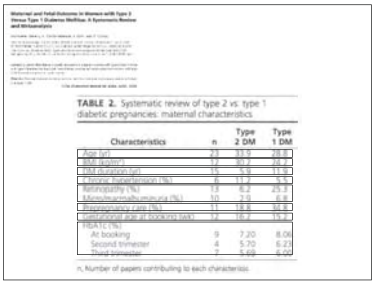
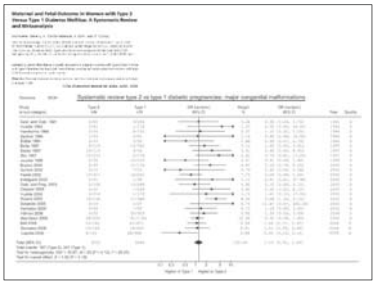
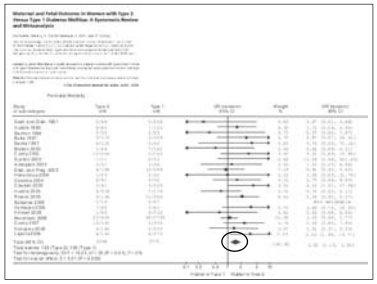


TABLE 2. Systematic review of type 2 vs. type 1 diabetic pregnancies: maternal characteristics

Characteristics	n	Type 2 DM	Type 1 DM
Age (yr)	23	33.9	28.8
BMI (kg/m²)	17	30.2	26.2
DM duration (yr)	15	5.6	11.8
Chronic hypertension (%)	6	17.7	3.5
Retinopathy (%)	13	6.2	25.3
Microalbuminuria/macroalbuminuria (%)	10	7.0	6.8
Preconceptional care (%)	11	18.8	84.8
Gestational age at booking (wk)	12	16.2	11.2
HbA1c (%)			
At booking	9	7.20	8.08
Second trimester	4	5.70	6.23
Third trimester	7	5.68	6.00

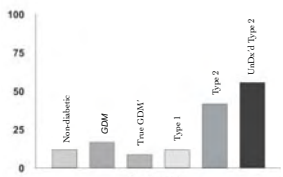
n, Number of papers contributing to each characteristic.





Type 2 DM in Pregnancy

Perinatal Mortality (per 1000 births)



Cundy et al - Diabetic Medicine, 1997

Reasons for high perinatal mortality rate

- High BMI
- Greater maternal age
- Increased incidence of essential hypertension
- Low socioeconomic status
- First generation immigrants / language / access

Cundy et al - Diabetic Medicine, 1997

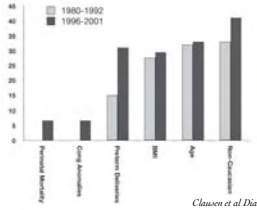
Type 2 DM in Pregnancy

Complication Rates - Literature Review

Study	No.	Perinatal Mortality	Preterm Birth (<37 wks)	RDS	Hypoglycemia	NICU admissions
Sacks 1997	113	7.5%			26.0%	
Cundy 2000						23.0%
Bryden 2000	57		51.0%			
Ostrem 2002		0.1%				
Dorne 2003	182	2.5%				37.0%
Watson 2003	24				51.0%	40.0%
DPG/France 2003	146	4.1%	26.7%			
Holden 2003	16	12.5%				
McElduff 2005	99	5.1%				
Huddle 2005		2.8%				
Roland 2005		3.5%				
Clausen 2003	61	6.7%	31.0%	20.0%		
Macintosh 2006		7.0%				
Hillman 2006		1.1%				
Hughes 2006	214	2.3%	22.9%	13.8%	22.4%	44.3%
Cundy 2007	540	2.9%				
Lapolla 2008	162	3.8%		3.5%	19.5%	
Ortuzzo Gonzalez 2008	147	2.8%	18.8%			13.2%
Average		4.1%	30.0%	17.0%	22.4%	31.8%

Type 2 DM in Pregnancy

Complication rates on the rise, too.



Clausen et al Diabetes Care 2005

Management

- Seen by high risk pregnancy team:
  - endocrinology team: physician,nurse educator, dietician
  - obstetrician, maternal-fetal medicine, neonatologist

Management

- Rx: Insulin
- OHA's are discontinued
- Trial: MiTy

Overview

- Pre-pregnancy
  - Type 2
  - GDM
- Postpartum
  - Type 2
  - GDM

Case

- Patient delivered
- She is breastfeeding and wants to go back on her oral agents
- (A) You put her on glyburide
- (B) You put her on metformin
- (C) You put her on glyburide and metformin but not rosiglitazone
- (D) You keep her on insulin until she stops breastfeeding
- (E) None of the above

Can Women Breastfeed While Taking Oral Antihyperglycemic Agents?

Metformin and Breastfeeding

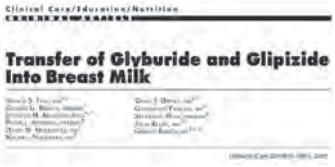
- Hale et al Diabetologia 2002
- Gardiner et al Clin Pharmacol Ther 2003
- Briggs et al Obstet Gynecol 2005

Hale et al, Diabetologia 2002

Metformin and Breastfeeding

- Compared 61 nursing infants vs 50 formula-fed of mothers taking metformin during lactation
- Compared at 3 and 6 months
- No significant difference in weight, height, motor-social development

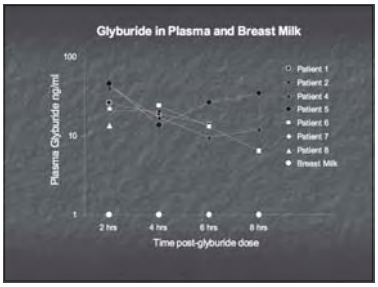
Glueck et al



Glyburide and Breastfeeding

- Single dose study Toronto
  - 5 mg or 10 mg glyburide
- Continuous dose study Long Beach
  - 5 mg glyburide or glipizide

Feig et al, Diabetes Care 2005



Glyburide and Breastfeeding

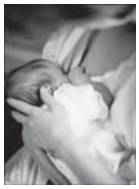
Continuous dosing study Long Beach

- No glyburide or glipizide was detected in milk samples
- 2 exclusively breast-fed infants (glipizide) had normal blood glucose levels
- Max Theoretical Infant Dose as %WAMD
  - <1.5%

Feig et al, Diabetes Care 2005

Thiazolidenediones
DPP IV Inhibitors
GLP-1 Agonists

No Information Regarding Transfer Into Breast Milk or Safety During Lactation in Humans
Not Recommended



Summary

- Metformin, glyburide and glipizide appear compatible with breastfeeding
  - Caution is advised using metformin while nursing premature infants and those with renal impairment

Case

- (A) You put her on glyburide
- (B) You put her on metformin
- (C) You put her on glyburide and metformin but not rosiglitazone
- (D) You keep her on insulin until she stops breastfeeding
- (E) None of the above

Case

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Overview

- Pre-pregnancy
  - Type 2
  - GDM
- Postpartum
  - Type 2
  - GDM

Overview

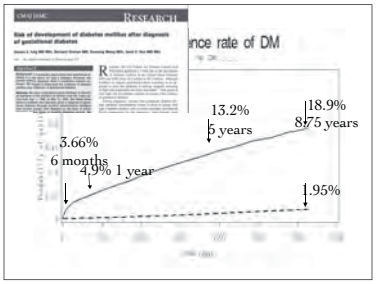
- Pre-pregnancy
  - Type 2
  - GDM
- Postpartum
  - Type 2
  - GDM


CMAJ·JAMC RESEARCH

Risk of development of diabetes mellitus after diagnosis of gestational diabetes

Denice S. Feig MD MSc, Bernard Zinman MD, Xuesong Wang MSc, Janet E. Hux MD MSc

ABSTRACT



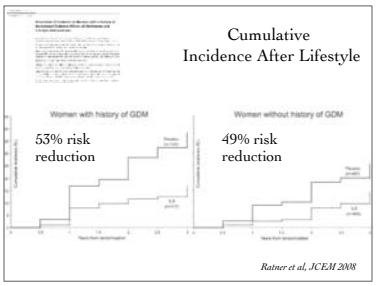

The New England Journal of Medicine

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

Knowler et al, NEJM 2002


Prevention of Diabetes in Women with a History of Gestational Diabetes: Effects of Metformin and Lifestyle Interventions

Ratner et al, JCEM 2008



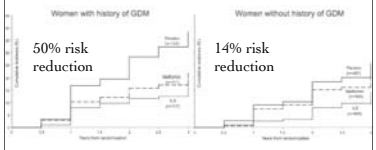
Ratner et al, JCEM 2008

GDM Subset: Study Results

- Number needed to treat to prevent 1 case DM
  - Intensive Life Style
    - No hx GDM: 9
    - Hx GDM: 5-6

Ratner et al, JCEM 2008

Diabetes Prevention Program
Effect of Metformin



Ratner et al, JCEM 2008

Diabetes Prevention Program
Number Needed to Treat ...

- ... to prevent 1 case of DM:

	Metformin	Intensive Lifestyle
History of GDM	5 - 6	5 - 6
No History of GDM	24	9

Breastfeeding

Study Design

- Examined association between lactation and type 2 DM in women from Nurses Health Study (240,000 women)

Steube et al, JAMA 2005

Study Results

- ↑ duration of lactation associated with a ↓ risk of type 2 diabetes
  - 0-3 months HR 0.72
  - >23 months HR 0.47
- For each year of lactation → 15% ↓ in risk

Study Results

- Women with prior GDM had a markedly increased risk of developing DM
- Lactation had no effect on DM risk in the GDM group
  - hazard ratio 0.96 NS

Steube et al JAMA 2005

CARDIA Trial

ORIGINAL ARTICLE

Duration of Lactation and Incidence of the Metabolic Syndrome in Women of Reproductive Age According to Gestational Diabetes Mellitus Status: A 20-Year Prospective Study in CARDIA (Coronary Artery Risk Development in Young Adults)

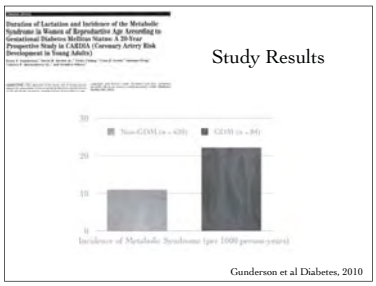
Erica P. Gunderson,[1] David R. Jacobs Jr.,[2] Vicky Chiang,[2] Cora E. Lewis,[3] Jiaoyan Feng,[1] Charles P. Quesenberry Jr.,[1] and Stephen Sidney[4]

OBJECTIVE—The objective of the study was to prospectively assess the association between lactation duration and incidence of the metabolic syndrome among women of reproductive age[5] geographic and lifestyle issues. Lactation may have protected favorable effects on women's cardiometabolic health. Diabetes 59:495–504, 2010

Study Design

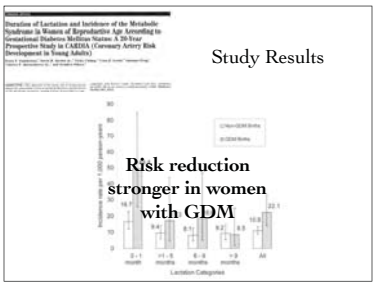
- CARDIA ongoing multicenter, population-based observational cohort study of 1,399 women who were nulliparous and free of metabolic syndrome at baseline 1985-86
- Re-examined at 7, 10, 15 & 20 years

Gunderson et al Diabetes, 2010



Study Results

Gunderson et al Diabetes, 2010



Study Results

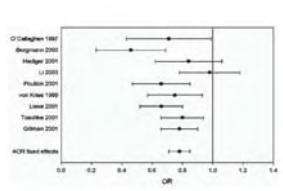
Risk reduction stronger in women with GDM

Why breastfeeding may prevent diabetes:

- Lactation imposes large metabolic burden: ↑ energy requirements by 480 kcal / day
- Evidence for improved insulin sensitivity and glucose tolerance during lactation
- ↑ weight loss: evidence conflicting

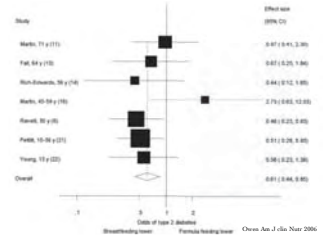
Can breastfeeding reduce the risk of childhood obesity and DM in offspring of Women with Diabetes?

Breastfeeding & Childhood Obesity



Arenz Int J Obesity & Related Metab Disord 200

Breastfeeding & Development of DM



Owen Am J clin Nutr 2006

What about Offspring of Diabetic Mothers?

Breast-Feeding and Risk for Childhood Obesity

Does maternal diabetes or obesity status matter?

Mayer-Davis et al, Diabetes Care, 2006

Study Design

- 15,253 offspring of women in the Nurses Health study who were aged 9-14 yrs in 1996 were included
- 56 pregestational diabetes, 417 GDM

Mayer-Davis et al, Diabetes Care, 2006


Breast-Feeding and Risk for Childhood Obesity

Study Results

- Breastfeeding was associated with reduced overweight in childhood in women with and without diabetes

Mayer-Davis et al, Diabetes Care, 2006


Original Paper

Nutrition & Metabolism

Early-Life Predictors of Higher Body Mass Index in Healthy Children


Early-Life Predictors of Higher Body Mass Index in Healthy Children

Study Results

- 1,178 children at high risk of Type 1 DM
- Found: Shorter duration of breastfeeding associated with childhood obesity
- 69% of this association explained by rapid weight gain in 1st year of life


Early-Life Predictors of Higher Body Mass Index in Healthy Children

↓ Breastfeeding duration → ↑ Infant Weight Gain → ↑ Childhood BMI

Possible Reasons for Advantages of Breastfeeding

- 1) Nutritional content of formula vs breast milk contributes to early adiposity leading to childhood obesity
- 2) Lower plasma insulin in response to breast milk vs formula, which promotes fat storage

Possible Reasons for Advantages of Breastfeeding

- 3) Breastfeeding infants better recognize satiety signals, resulting in enhanced self-regulation of energy intake growing up

Challenges to Breastfeeding in Women with GDM/DM?

Challenges: Obesity

Nested Case-Control Study

- 141 obese mothers matched to 111 normal-weight mothers
- Obese less likely to initiate breastfeeding (48% vs 64%)
  - less likely to maintain full breastfeeding at 1 and 3 months
  - fewer perceived that milk supply sufficient
  - more often uncomfortable breastfeeding in public
- Despite greater breastfeeding difficulties, less likely to seek support for breastfeeding

Mok Pediatrics 2008;122:e1319-e1324

We need to find ways to overcome such barriers to breastfeeding in our highest risk populations

Summary

- Pregnancies in women with type 2 diabetes are high risk pregnancies
- We need to work harder at counselling women with type 2 diabetes regarding the increased risk of congenital anomalies and how to avoid these preventable anomalies ie excellent glycemic control prior to conception, birth control

Summary

- Oral hypoglycemic agents are NOT teratogenic
- Avoid statins and ACE inhibitors in those planning pregnancy
- Test women with PCOS and previous GDM for type 2 before conception and early in pregnancy

Summary

- Metformin, glyburide and glipizide appear compatible with breastfeeding
- Weight loss, metformin and breastfeeding can reduce the risk of diabetes in women with previous GDM
- Breastfeeding can reduce the risk of childhood obesity in infants of women with diabetes and previous GDM

Canadian Diabetes Association

CSEM SCEM
Canadian Society of Endocrinology and Metabolism
La Société canadienne d'endocrinologie et métabolisme

certificate of participation

Awarded to

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This program is accredited by CSEM for 3 hours CME Credit

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