Jewish General Hospital
Lady Davis Institute for Medical Research

McGill

DIABETES AND CARDIOVASCULAR DISEASE: FOCUS ON DIABETES IN WOMEN

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MUHC Women's Heart Health Symposium

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DISCLOSURES

NATURE OF RELATIONSHIP	NAME OF THE FOR-PROFIT OR NOT-FOR PROFIT ORGANIZATION	DESCRIPTION OF RELATIONSHIP
Any direct financial interest	NONE	
Membership on advisory boards or speakers' bureaus	NONE	
Funded grants or participated in clinical trials	CIHR Diabète Québec	Project grant Research grant
Patent for a product, drug, or device	NONE	

*No commercial support
*No potential biases to mitigate

LEARNING OBJECTIVES

- Explain women-specific risk factors for diabetes
- Review evidence supporting glycemic targets in women throughout the lifespan
- Discuss the use of anti-hyperglycemic agents to attain glycemic control among women

TYPE 2 DIABETES

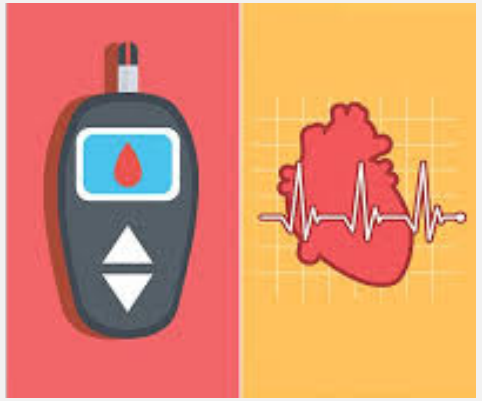
- Prevalence
  - **10.9% of Canadian adults (11.8% male, 10.0% female)**
    - **90-95% type 2 diabetes**
  - Expected increase of 30% by 2030

- Long-term sequelae
  - Microvascular: neuropathy; nephropathy; retinopathy
  - Macrovascular

LeBlanc AG, *et al*. Health Promot Chronic Dis Prev Can. 2019;39(11): 306–309.
Diabetes in Canada: Backgrounder. Ottawa: Diabetes Canada; 2020.

DIABETES AND CARDIOVASCULAR DISEASE (CVD)

- Adults with type 2 diabetes
  - 2.5 times increased risk of incident CVD
  - 2 to 4 times increased risk of cardiovascular mortality
  - 5 to 15 years of life lost



Mozaffarian D, *et al*. Circulation. 2015;131(4):e29-322.
The Emerging Risk Factors Collaboration. N Engl J Med. 2011;364(9):829-841.
Diabetes in Canada: Facts and figures from a public health perspective [Internet]. Ottawa: Public Health Agency of Canada; 2011 p. 126.

WOMEN WITH TYPE 2 DIABETES

- Elevated risk of **incident CVD**

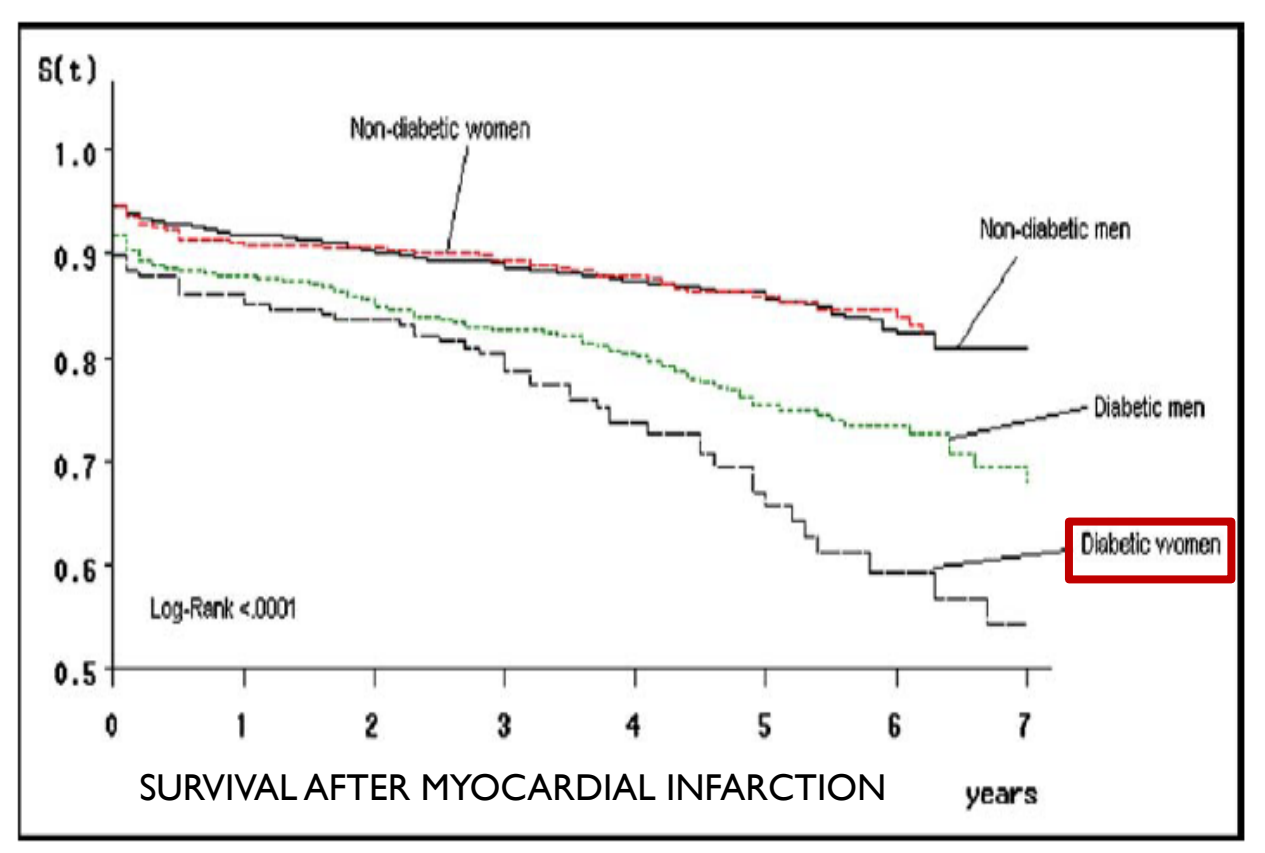
	Relative risk (95% confidence interval)*
Coronary heart disease	1.44 (1.27-1.63)
Stroke	1.27 (1.10-1.46)

*Multiple-adjusted women-to-men relative risk ratio
(age, blood pressure, cigarette smoking, BMI and lipids)

Peters SAE, *et al.* Diabetologia. 2014;57(8):1542-51.
Peters SAE, *et al.* Lancet. 2014;383(9933):1973-80.

WOMEN WITH TYPE 2 DIABETES

- **Worse outcomes** following cardiovascular event



Meisinger C, *et al.* Am J Cardiol. 2010;106(12):1680-4.

OUTLINE:
FOCUS ON DIABETES IN WOMEN

- Risk
- Diagnosis
- Management
  - Glycemic targets
  - Anti-hyperglycemic agents
- Conclusions

RISK FACTORS FOR TYPE 2 DIABETES

Age ≥40 years
Male
Family history of type 2 diabetes
Ethnicity
Overweight, Abdominal obesity
Physical inactivity, diet
Hypertension, vascular risk factors
Pre-diabetes
Gestational diabetes or macrosomic infant
End-organ damage (micro- or macrovascular)

Diabetes Canada 2018 Clinical Practice Guidelines, Chapter 4.
https://health.canada.ca/apps/canrisk-standalone/pdf/canrisk-en.pdf

WOMEN-SPECIFIC RISK FACTORS FOR DIABETES

Age ≥40 years
Male
Family history of type 2 diabetes
Ethnicity
Overweight, Abdominal obesity
Physical inactivity, diet
Hypertension, vascular risk factors
Pre-diabetes
Gestational diabetes or macrosomic infant
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Diabetes Canada 2018 Clinical Practice Guidelines, Chapter 4.
https://health.canada.ca/apps/canrisk-standalone/pdf/canrisk-en.pdf

GESTATIONAL DIABETES MELLITUS (GDM)

- **~5% of pregnant women** in Canada
  - **Doubling** in incidence from 1996 to 2010
- Contributing factors
  - Universal screening, Diagnostic criteria
  - Advancing maternal age
  - Increased obesity among women during the reproductive years
- Diagnosis and intervention

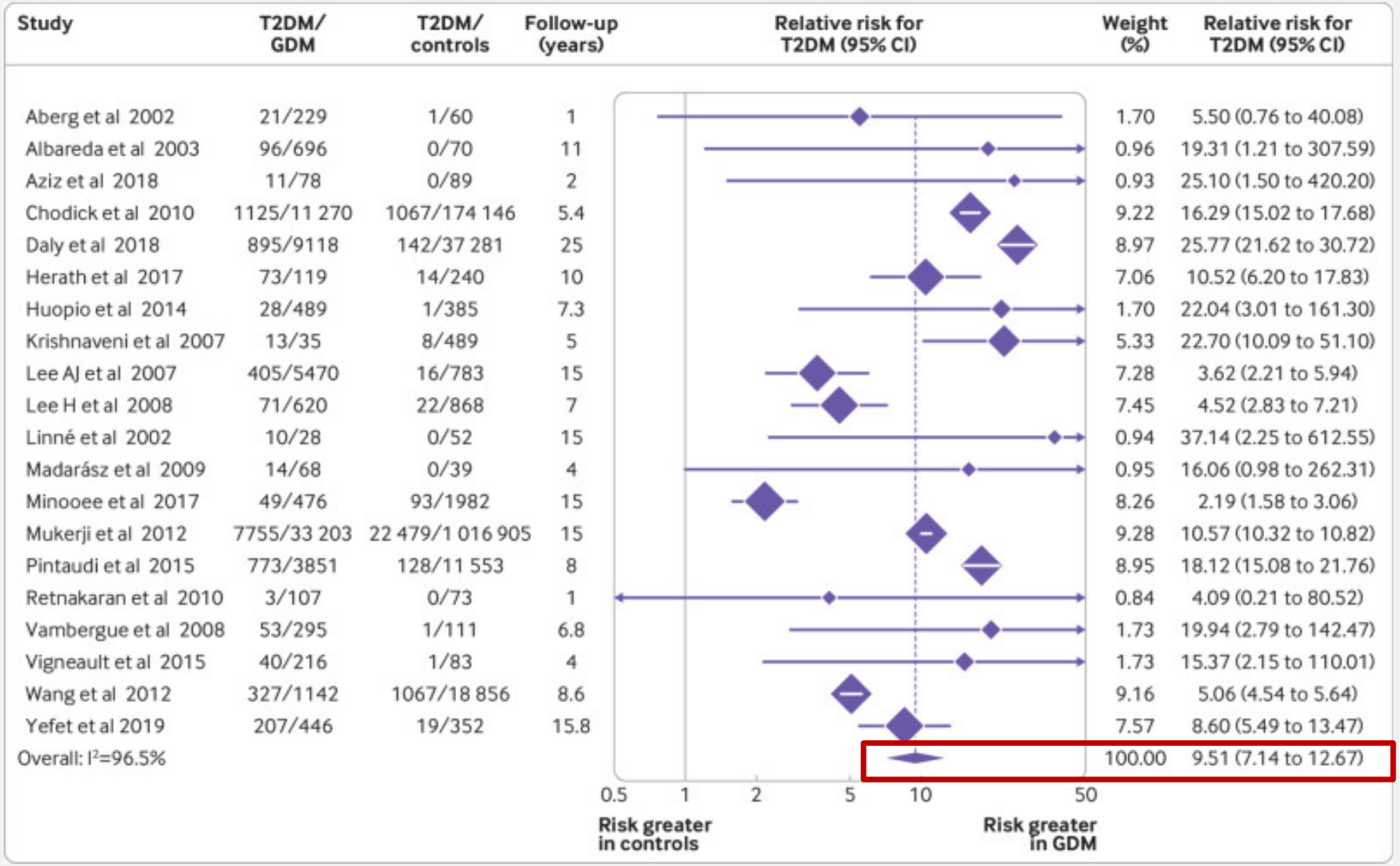
Feig DS, *et al*. Diabetes Care. 2014;37(6):1590-6.
Ferrara A. Diabetes Care. 2007;30 Suppl 2:S141-6.
Behboudi-Gandevani S, *et al*. Diabetol Metab Syndr. 2019;11:11.

GDM AND TYPE 2 DIABETES RISK

- **2-12%** of women develop type 2 diabetes **within one year** postpartum
- **30-60%** develop type 2 diabetes **within 10 years** postpartum

Bellamy L, *et al*. The Lancet. 2009;373(9677):1773-9.
Kim C, *et al*. Diabetes Care. 2002;25(10):1862-8.

- Risk of type 2 diabetes (T2DM) after GDM



Vounzoulaki E, *et al*. BMJ. 2020;369:m1361.

POSTPARTUM SCREENING FOR TYPE 2 DIABETES RISK

- **Early identification of persistent dysglycemia**
- Diabetes Canada 2018 Clinical Practice Guidelines
  - Oral glucose tolerance test (75-gram OGTT) between 6 weeks and 6 months
- Poor screening adherence
  - <20% within 6 months

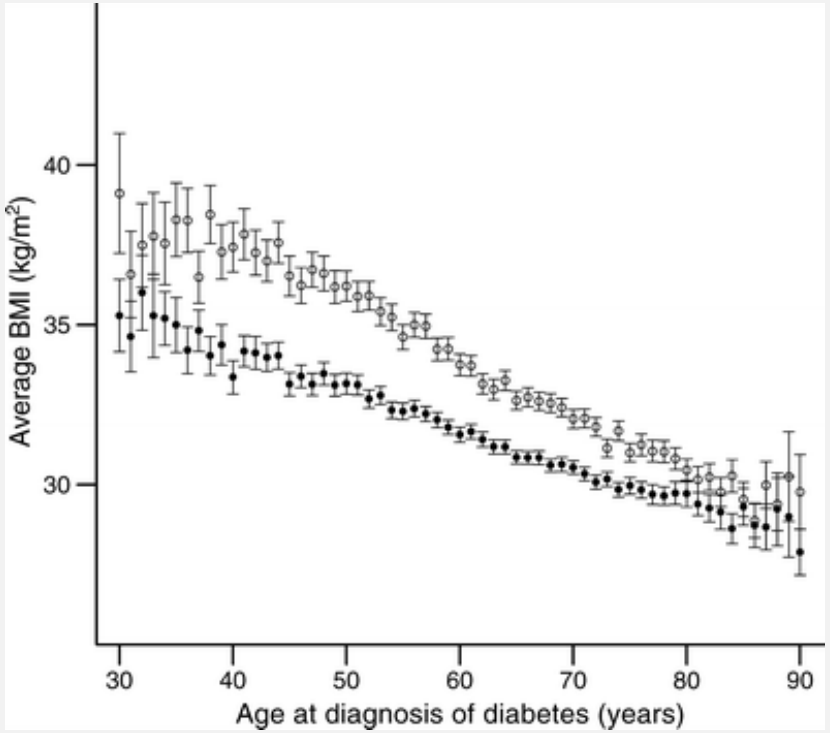
Diabetes Canada 2018 Clinical Practice Guidelines, Chapter 36.
Eggleston EM, *et al*. Obstet Gynecol. 2016;128(1):159-67.
Blatt AJ, *et al*. Obstet Gynecol. 2011;117(1):61-8.
Man B, *et al*. Prev Chronic Dis. 2016;13:E124.

OVERWEIGHT AND ABDOMINAL OBESITY

- Strong risk factor for both women and men
- Body mass index (BMI) = weight/height (kg/m^2)
- Central (abdominal) obesity
  - Waist circumference
  - Waist-to-hip ratio

BMI AND TYPE 2 DIABETES

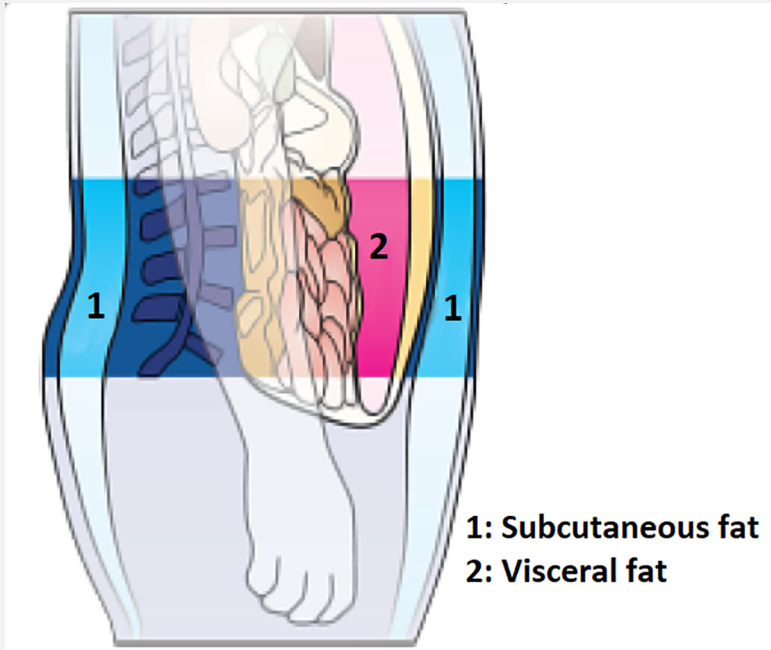
- Women have **higher BMI** at diagnosis of type 2 diabetes



- ○ Women
- • Men

Logue J, *et al*. Diabetologia. 2011;54(12):3003-6.

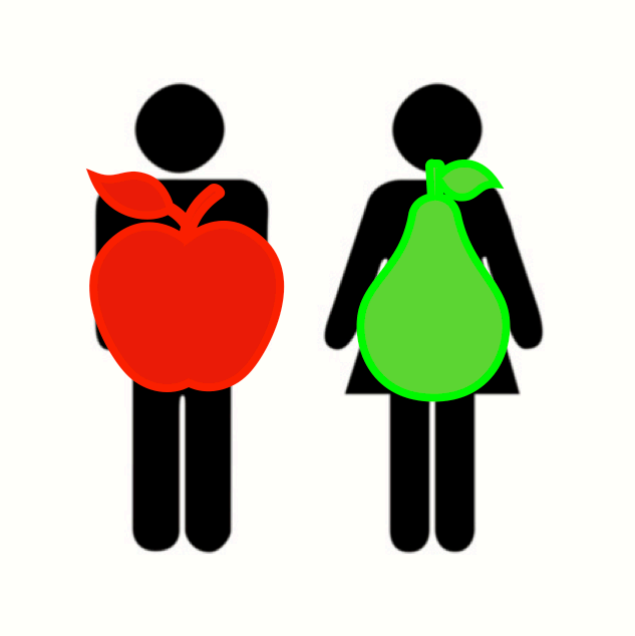
BODY COMPOSITION



doi: https://doi.org/10.1371/journal.pone.0223058.g001

- Women: subcutaneous
- Men: visceral

BODY COMPOSITION



- Android (central)
- Gynoid (peripheral)

BODY COMPOSITION

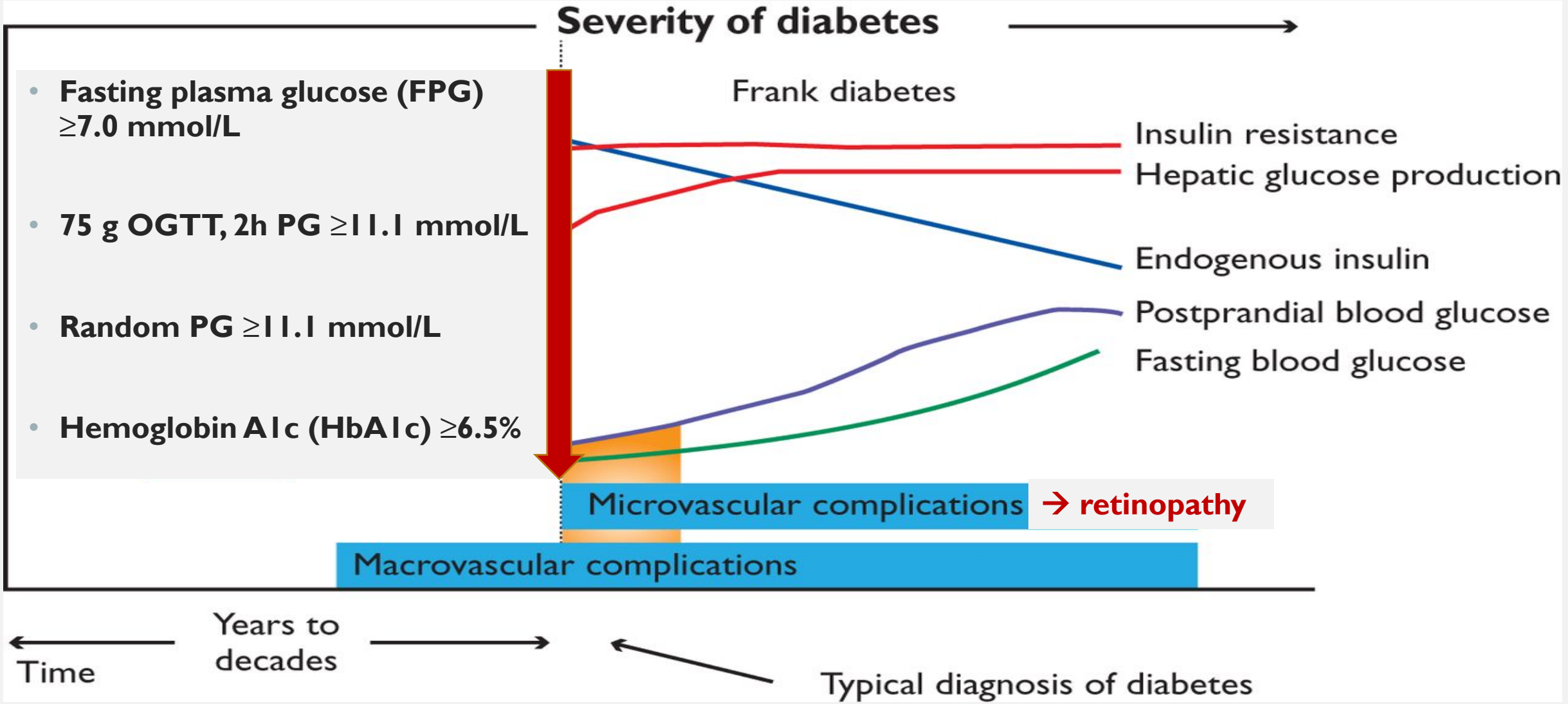
- Central (abdominal) obesity
  - May be better predictor of type 2 diabetes for women
    - vs BMI
    - vs Men

Jafari-Koshki T, *et al*. Diabetes Metab Syndr. 2018;12(4):563-567.
Meisinger C, *et al*. Am J Clin Nutr. 2006;84(3):483-9.
Wannmethee SG, *et al*. Diabetologia. 2010;53(5):890-8.

WOMEN-SPECIFIC RISK FACTORS FOR DIABETES

- Gestational diabetes
- Overweight and obesity
  - Body composition
  - Central (abdominal) obesity

DIAGNOSIS OF TYPE 2 DIABETES IN WOMEN



Authors/Task Force Members, *et al*. Eur Heart J 2013.
Diabetes Canada 2018 Clinical Practice Guidelines, Chapter 3.
Nakagami T, *et al*. Diabetes Res Clin Pract. 2017;124:20-29.

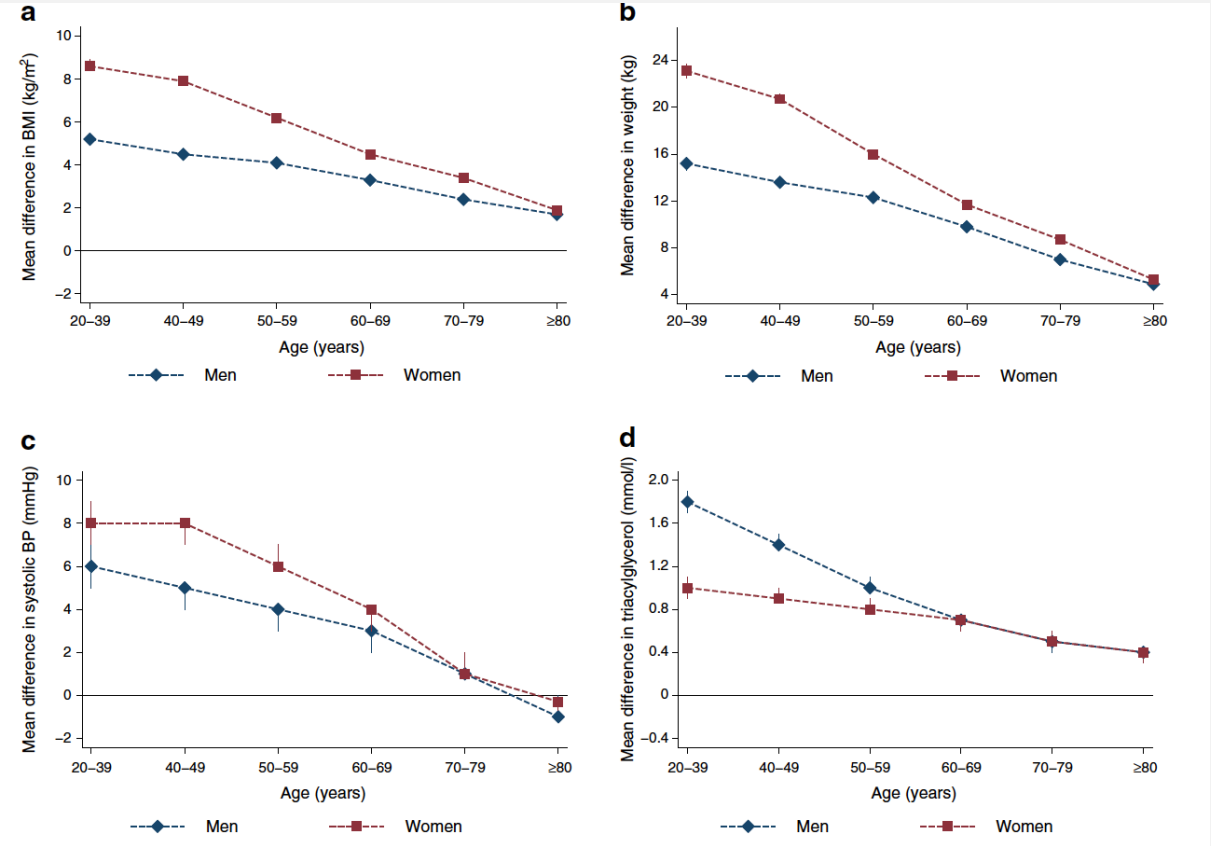
DIAGNOSIS OF TYPE 2 DIABETES IN WOMEN

- Diagnostic criteria: Not sex-specific
- Women: **Impaired glucose tolerance** (postprandial)
  - Beta cell dysfunction
- Men: Elevated fasting glucose
  - Insulin resistance
- Similar HbA1c

Basu R, *et al*. Diabetes. 2006;55(7):2001-14.
Gannon M, *et al*. Mol Metab. 2018;15:82-91.
Mauvais-Jarivs F. Physiol Behav. 2018;187:20-23.
Wright AK, *et al*. Diabetologia. 2020;63(8):1542-1553.

DIAGNOSIS OF TYPE 2 DIABETES IN WOMEN

- Women vs men
  - 3 years older
  - Greater difference vs no diabetes:
    - BMI
    - Body weight
    - Systolic blood pressure



Wright AK, *et al*. Diabetologia. 2020;63(8):1542-1553.

GLYCEMIC TARGETS FOR WOMEN ACROSS THE LIFESPAN

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HbA1c (%)	Comments
≤6.5	If at low risk of hypoglycemia
≤7.0	**MOST ADULTS WITH TYPE 2 DIABETES** • **Fasting or preprandial glucose 4.0 to 7.0 mmol/L** • **2-hour postprandial glucose 5.0 to 10.0 mmol/L**
7.1-8.5	• Recurrent severe hypoglycemia and/or hypoglycemia unawareness • Functionally dependent • Limited life expectancy • Frail elderly and/or with dementia

Diabetes Canada 2018 Clinical Practice Guidelines, Chapter 8.

GLYCEMIC TARGETS FOR WOMEN ACROSS THE LIFESPAN

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7.1-8.5	• Recurrent severe hypoglycemia and/or hypoglycemia unawareness • Functionally dependent • Limited life expectancy • Frail elderly and/or with dementia

Diabetes Canada 2018 Clinical Practice Guidelines, Chapter 8.

RATIONALE FOR GLYCEMIC TARGETS

STUDY	Mean A1c	Microvascular	Macrovascular	% Women	Sex Interaction
ACCORD	6.4% vs 7.5%	↓	↑ mortality Long-term neutral	**38%**	**No interaction**
ADVANCE	6.5% vs 7.3%	↓	↔	**42%**	**No interaction**
VADT	6.9% vs 8.4%	↓	↔ Emergent benefit	**3%**	**Not tested**
UKPDS	Median 7.0% vs 7.9%	↓	↔ Emergent benefit	**~45%**	**Not tested**

ACCORD Study Group. N Engl J Med 2008; 358:2545-2559.
The ADVANCE Collaborative Group. N Engl J Med 2008;358:2560-2572.
Duckworth W, *et al*. N Engl J Med. 2009;360(2):129-39.
UKPDS Group. Lancet 1998;352(9131):837–853.
Holman RR, *et al*. N Engl J Med. 2008;359(15):1577-89.

GLYCEMIC TARGETS FOR WOMEN ACROSS THE LIFESPAN

- GDM
  - Strict glucose targets (mmol/L): Fasting <5.3, 1-hour <7.8, 2-hour <6.7
  - Pregnancy outcomes
    - Fetal malformations, intrauterine fetal demise; macrosomia, stillbirth, neonatal hypoglycemia, obstetrical complications
- ?Long-term outcomes
  - Better intrapartum glycemic control → lower risk of type 2 diabetes

Diabetes Canada 2018 Clinical Practice Guidelines, Chapter 36.
Yefet E, *et al*. Cardiovasc Diabetol. 2019;18(1):75.

GLYCEMIC TARGETS FOR WOMEN ACROSS THE LIFESPAN

HbA1c (%)	Comments
≤6.5	Adults with type 2 diabetes • Decreased risk of chronic kidney disease, retinopathy, MACE • If at low risk of hypoglycemia
≤7.0	MOST ADULTS WITH TYPE 2 DIABETES
7.1-8.5	• Recurrent severe hypoglycemia and/or hypoglycemia unawareness • Functionally dependent • **Limited life expectancy** • **Frail elderly and/or with dementia**

Diabetes Canada 2018 Clinical Practice Guidelines, Chapter 8.

MANAGEMENT OF WOMEN WITH TYPE 2 DIABETES

- Lifestyle
  - Diet
  - Physical activity
  - Weight loss / maintenance
- Pharmacotherapy
  - Glycemic control
  - Vascular protection

MANAGEMENT OF WOMEN WITH TYPE 2 DIABETES

- Lifestyle
  - Diet
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  - Vascular protection

ANTI-HYPERGLYCEMIC AGENTS FOR WOMEN WITH TYPE 2 DIABETES

- Prescription and use
- Efficacy and effectiveness of diabetes medications
- Adverse effects

PRESCRIPTION & USE OF ANTI-HYPERGLYCEMIC AGENTS

- Oral anti-hyperglycemic agents
  - **Similar treatment** prescribed as men
    - Number and type of anti-hyperglycemic agents
- Insulin
  - Women **more likely to be prescribed insulin**

Rossi MC, *et al*. Diabetes Care. 2013; 36(10): 3162–3168.
Penno G, *et al*. J Intern Med. 2013;274(2):176-91.
Magee MF, *et al*. Int J Endocrinol. 2015;2015:610239.
McGill JB, *et al*. Diabetes Res Clin Pract. 2013;102(3):167-74.
Kautzky-Willer A, *et al*. Diabetes Obes Metab. 2015;17(6):533-540.

CLINICAL RESPONSE TO ANTI-HYPERGLYCEMIC AGENTS

- Women with type 2 diabetes **less likely to meet target HbA1c**
  - ~20-30% less likely to achieve HbA1c <7.0% than men
- Despite intensive treatment
  - More likely than men to have HbA1c >9.0% even with insulin treatment

Magee MF, *et al*. Int J Endocrinol. 2015;2015:610239.
Penno G, *et al*. J Intern Med. 2013;274(2):176-91.
Rossi MC, *et al*. Diabetes Care. 2013; 36(10): 3162–3168.

EFFICACY & EFFECTIVENESS OF ANTI-HYPERGLYCEMIC AGENTS FOR WOMEN WITH DIABETES

Similar for women and men	Greater for women	Less for women
Metformin* (Li 2020)		
		Sulfonylureas* (Dennis 2018)
Repaglinide* (Marbury 1999)		
DPP4-inhibitors† (Mamza 2016) Sitagliptin† (Tajima 2020)		
Semaglutide*: HbA1c (Petri 2018) Dulaglutide*†: HbA1c and weight loss (Gallwitz 2018; Yoo 2019)	Semaglutide*: more weight loss Liraglutide*†: HbA1c (Chiefari 2016; Berkovic 2017)	
Empagliflozin† Dapagliflozin† Ipragliflozin† (Lee 2019)		
		Insulin* (McGill 2013; Owens 2017)

* **Randomized trial**
† **Observational or Real world data**

Li J, *et al*. Endocr J. 2020;Sep 10:EJ20-0006.
Dennis JM, *et al*. Diabetes Care. 2018; 41(9):1844–1853.
Marbury T, *et al*. Diabetes Res Clin Pract. 1999;43(3):155-66.
Mamza JM, *et al*. Diabetes Technol Ther. 2016;18(2):85-92.
Tajima N, *et al*. J Diabetes Investig. 2020;11(3):640-646.
Petri KCC, *et al.* Diabetes Obes Metab. 2018;20(9):2238-2245.
Gallwitz B, *et al*. Diabetes Obes Metab. 2018; 20(2):409-418.
Yoo JH, *et al*. Diabetes Ther. 2019;10(4):1453–1463.
Chiefari E, *et al*. Diabetes Technol Ther. 2015;17(7):468-74.
Berkovic MC, *et al*. Diabetes Ther. 2017; 8(6):1297–1308.
Lee JY, *et al*. Diabetes Metab J. 2019;43(2).
McGill JB, *et al*. Diabetes Res Clin Pract. 2013;102(3):167-74.
Owens DR, *et al*. Diabetes Obes Metab. 2017;19(11):1546-1554.

CARDIOVASCULAR OUTCOME TRIALS

Trial Eponym	Total (N)	Median duration (Year)	eCVD	Overall HR (95% CI)	Male, n, (%)	Female, n, (%)	Male, HR (95% CI)	Female, HR (95% CI)	P value for interaction Gender-wise
CVOTs of SGLT-2Is:									
EMPA-REG	7020	3.1	100%	0.86 (0.74, 0.99)	5016 (71.5%)	2004 (28.5%)	0.87 (0.73, 1.02)	0.83 (0.62, 1.11)	0.81
CANVAS	10,142	2.4	65.6%	0.86 (0.75, 0.97)	6509 (64%)	3633 (36%)	0.86 (0.74, 1.00)	0.84 (0.66, 1.06)	0.80
DECLARE-TIMI	17,160	4.2	40.6%	0.93 (0.84, 1.03)	10,738 (63%)	6422 (37%)	0.93 (0.83, 1.05)	0.93 (0.77, 1.12)	0.99
					Subtotal = 22,263 (65%)	Subtotal = 12,059 (35%)			
					Total = 34,322				
CVOTs of GLP-1RAs:									
ELIXA	6068	2.1	100%	1.02 (0.89, 1.17)	4207 (69%)	1861 (31%)	0.91 (0.71, 1.18)	1.06 (0.90, 1.25)	NR
LEADER	9340	3.8	81%	0.87 (0.78, 0.97)	6003 (64%)	3337 (36%)	0.86 (0.75, 0.98)	0.88 (0.72, 1.08)	0.84
SUSTAIN-6	3297	2.1	83%	0.74 (0.58, 0.95)	2002 (61%)	1295 (39%)	0.68 (0.50, 0.92)	0.84 (0.54, 1.31)	0.45
EXSCEL	14,752	3.2	73%	0.91 (0.83, 1.00)	9149 (62%)	5603 (38%)	0.94 (0.84, 1.05)	0.86 (0.73, 1.03)	0.44
HARMONY	9463	1.6	100%	0.78 (0.68.0.90)	6569 (69%)	2894 (31%)	0.82 (0.69, 0.97)	0.67 (0.50, 0.89)	0.23
REWIND	9901	5.4	31%	0.88 (0.79, 0.99)	5312 (54%)	4589 (46%)	0.90 (0.79, 1.04)	0.85 (0.71, 1.02)	0.60
PIONEER-6	3183	1.3	85%	0.79 (0.57, 1.11)	2176 (68%)	1007 (32%)	0.72 (0.50, 1.05)	1.16 (0.54, 2.51)	0.28
					Subtotal = 35,418 (63%)	Subtotal = 20,586 (37%)			
					Total = 56,004				

Singh AK and R Singh. Diabetes Metab Syndr.2020;14(3):181-187.

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Singh AK and R Singh. Diabetes Metab Syndr.2020;14(3):181-187.

EFFICACY & EFFECTIVENESS OF ANTI-HYPERGLYCEMIC AGENTS FOR WOMEN WITH DIABETES

- No sex differences in pharmacodynamics or pharmacokinetics
  - Similar dosing

Arnetz L, *et al*. Diabetes Metab Syndr Obes. 2014;16(7):409-20.
Karim A, *et al*. J Clin Pharmacol. 2007;47(1):37-47.
Deacon CF and Holst JJ. Adv Ther. 2009;26(5):488-99.
Damholt B, *et al*. J Clin Pharmacol. 2006;46(6):635-41.
Kasichayanula S, *et al*. Clin Pharmacokinet. 2014;53(1):17-27.
Devineni D and Polidori D. Clin Pharmacokinet. 2015;54(10):1027-41.

ADVERSE EFFECTS OF ANTI-HYPERGLYCEMIC AGENTS

Medication	General Adverse Effects*	Adverse Effects Among Women
Metformin	Gastrointestinal (GI) side effects Vitamin B12 deficiency	More **GI effects** among women (upon initiation)
Sulfonylureas	Hypoglycemia	2-fold more **hypoglycemia**
DPP-4 inhibitors	Pancreatitis (rare) Joint pain (rare)	Sitagliptin or alogliptin (combination therapy) → 3-fold more **hypoglycemia**
GLP-1 agonists	Nausea, vomiting Gallstone disease (rare)	Semaglutide: more **nausea** Liraglutide: more **gastrointestinal** effects
SGLT2 inhibitors	Genital mycotic infections Urinary tract infections (UTI) Diabetic ketoacidosis (rare) Fractures, lower extremity amputation (canagliflozin) Hypotension	**Genital mycotic infections**: 3-4x increased risk Severe UTI: no sex differences Ketoacidosis: no sex differences Lower extremity amputation: no sex differences
Insulin	Hypoglycemia	**Hypoglycemia** (2- to 3-fold)

ADHERENCE TO ANTI-HYPERGLYCEMIC AGENTS

- Women may be less likely to adhere to (oral) diabetes medications
  - Men vs women (adherence): OR 1.14 (95% CI 1.12, 1.16)
  - Meta-analysis: 3 of 11 studies

Kirkman MS, *et al*. Diabetes Care. 2015;38(4):604–609.
Krass I, *et al*. Diabet Med. 2015;32(6):725-37.

ANTI-HYPERGLYCEMIC AGENTS FOR WOMEN WITH TYPE 2 DIABETES

- Less likely to achieve glycemic targets
  - Similar prescription, efficacy and effectiveness
  - More hypoglycemia – treatment intensity

- Increased risk of adverse effects
  - GI effects
  - Hypoglycemia
  - Genital mycotic infections

CONCLUSIONS

- Women-specific risk factors for type 2 diabetes
  - GDM
  - Aspects of overweight and obesity

CONCLUSIONS

- Diagnosis of type 2 diabetes in women
  - Impaired glucose tolerance

CONCLUSIONS

- Glycemic targets for women with type 2 diabetes
  - Evidence for HbA1c targets for women
  - Individualize targets according to
    - Life stage
    - Risk of diabetes complications
    - Risk of hypoglycemia

CONCLUSIONS

- Anti-hyperglycemic agents to attain glycemic control among women with type 2 diabetes compared with men
  - Similar overall treatment and clinical response for women as men
  - Poorer glycemic control
  - Common adverse events
  - ?Less adherence

BARRIERS TO PRACTICE AND PHYSICIAN CHANGE

- Awareness of excess CVD risk among women with diabetes
- Implementation of knowledge regarding type 2 diabetes among women
  - Screening for type 2 diabetes post-GDM
  - Weight management
- Medical management of women with type 2 diabetes
  - Effectiveness vs potential for adverse effects
  - Choice of medication and monitoring for side effects

QUESTIONS?

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OTHER REPRODUCTIVE & HORMONAL FACTORS

Reproductive factor	Increased risk for type 2 diabetes	Reference
Early age at menarche	RR 1.39 (95% CI 1.25-1.55)	Cheng 2020
Pregnancy	HR 1.04 (95% CI 1.03-1.06)	Peters 2020
Pregnancy loss	HR 1.03 (95% CI 1.00-1.05 for each loss)	Peters 2020
Early age at natural menopause	HR 2.40 (95% CI 1.30-4.30) HR 1.08 (95% CI 1.02-1.14) per standard deviation younger	Muka 2017 Brand 2013

RR: relative risk
HR: hazard ratio
CI: confidence interval

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POLYCYSTIC OVARY SYNDROME

- Insulin resistance
  - 2- to 4-fold increased risk of type 2 diabetes
  - 3-fold increased risk of GDM
- Independent of obesity

- Testosterone
  - Elevated testosterone increases type 2 diabetes risk in women
    - Odds ratio (OR) 1.37 (95% CI 1.22-1.53)
  - Reduces type 2 diabetes risk in men
    - OR 0.86 (95% CI 0.76-0.98)

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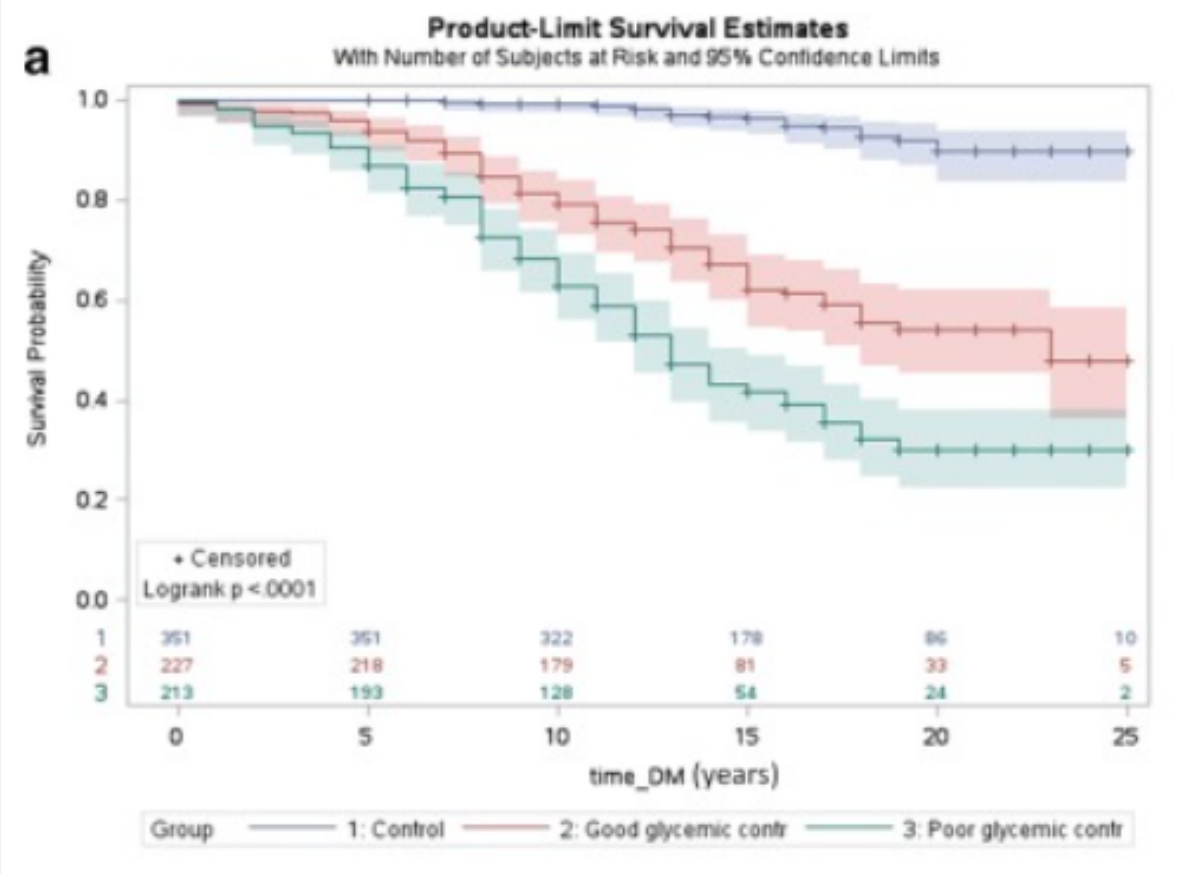
WOMEN-SPECIFIC RISK OF TYPE 2 DIABETES

- Poor intrapartum glycemic control → increased risk of type 2 diabetes



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Medication	Glycemic Efficacy for women	Adverse Effects among women
Metformin		More among women (upon initiation)
Sulfonylureas	Less HbA1c response	2-fold more hypoglycemia
Repaglinide	No sex differences	
DPP-4 inhibitors	No sex differences **Sitagliptin**: no sex differences	**Sitagliptin** or **alogliptin** (combination therapy) → more hypoglycemia
GLP-1 agonists	**Semaglutide**: similar A1c response, more weight loss **Dulaglutide**: similar A1c response and weight loss **Liraglutide**: more effective glycemic response	**Semaglutide**: more nausea **Liraglutide**: more gastrointestinal effects
SGLT2-inhibitors	No sex differences (**empagliflozin**, **dapagliflozin**, **ipragliflozin**)	Genital mycotic infections: increased risk
Insulin	Less A1c response Similar across insulin formulations	Hypoglycemia (any, severe, nocturnal)