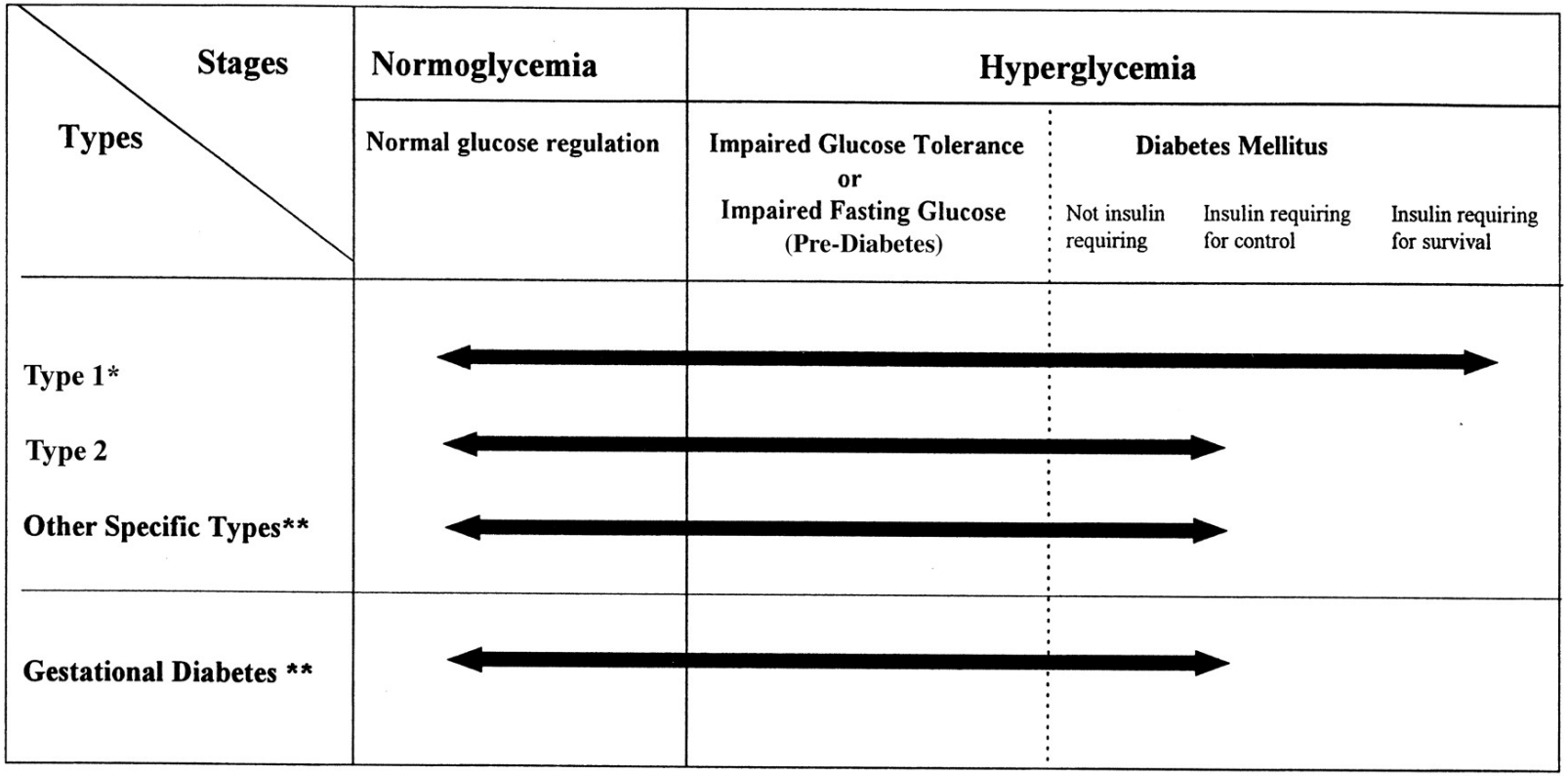
Diabetes: An old friend revisited

Dr. YC Woo

This is how we classify DM since 1998



Etiologic classification of diabetes mellitus.

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
   A. Immune mediated
   B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types
   A. Genetic defects of β-cell function
      1. MODY 3 (Chromosome 12, HNF-1α)
      2. MODY 1 (Chromosome 20, HNF-4α)
      3. MODY 2 (Chromosome 7, glucokinase)
      4. Other very rare forms of MODY (e.g., MODY 4: Chromosome 13, insulin promoter factor-1; MODY 6: Chromosome 2, *NeuroD1*; MODY 7: Chromosome 9, carboxyl ester lipase)
      5. Transient neonatal diabetes (most commonly ZAC/HYAMI imprinting defect on 6q24)
      6. Permanent neonatal diabetes (most commonly KCNJ11 gene encoding Kir6.2 subunit of β-cell K_{ATP} channel)
      7. Mitochondrial DNA
      8. Others
   B. Genetic defects in insulin action
      1. Type A insulin resistance
      2. Leprechaunism
      3. Rabson-Mendenhall syndrome
      4. Lipoatrophic diabetes
      5. Others
   C. Diseases of the exocrine pancreas
      1. Pancreatitis
      2. Trauma/pancreatectomy
      3. Neoplasia
      4. Cystic fibrosis
      5. Hemochromatosis
      6. Fibrocalculous pancreatopathy
      7. Others
   D. Endocrinopathies
      1. Acromegaly
      2. Cushing's syndrome
      3. Glucagonoma
      4. Pheochromocytoma
      5. Hyperthyroidism
      6. Somatostatinoma
      7. Aldosteronoma
      8. Others
   E. Drug or chemical induced
      1. Vacor
      2. Pentamidine
      3. Nicotinic acid
      4. Glucocorticoids
      5. Thyroid hormone
      6. Diazoxide
      7. β-Adrenergic agonists
      8. Thiazides
      9. Dilantin
      10. γ-Interferon
      11. Others
   F. Infections
      1. Congenital rubella
      2. Cytomegalovirus
      3. Others
   G. Uncommon forms of immune-mediated diabetes
      1. Stiff-man syndrome
      2. Anti-insulin receptor antibodies
      3. Others
   H. Other genetic syndromes sometimes associated with diabetes
      1. Down syndrome
      2. Klinefelter syndrome
      3. Turner syndrome
      4. Wolfram syndrome
      5. Friedreich ataxia
      6. Huntington chorea
      7. Laurence-Moon-Biedl syndrome
      8. Myotonic dystrophy
      9. Porphyria
      10. Prader-Willi syndrome
      11. Others

IV. Gestational diabetes mellitus

Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

American Diabetes Association Dia Care 2014;37:S81-S90

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American Diabetes Association.

How it works

- T1 or T2?
  - Autoantibodies against pancreatic islet β-cell antigens
  - Age at diagnosis (younger for type 1 diabetes).
- LADA, a third subgroup
  - Presence of glutamic acid decarboxylase antibodies (GADA)
  - Phenotypically indistinguishable from type 2 diabetes at diagnosis, but becomes increasingly similar to T1
- MODY and neonatal diabetes
  - Rare monogenic forms of diabetes
  - Dx by gene sequencing

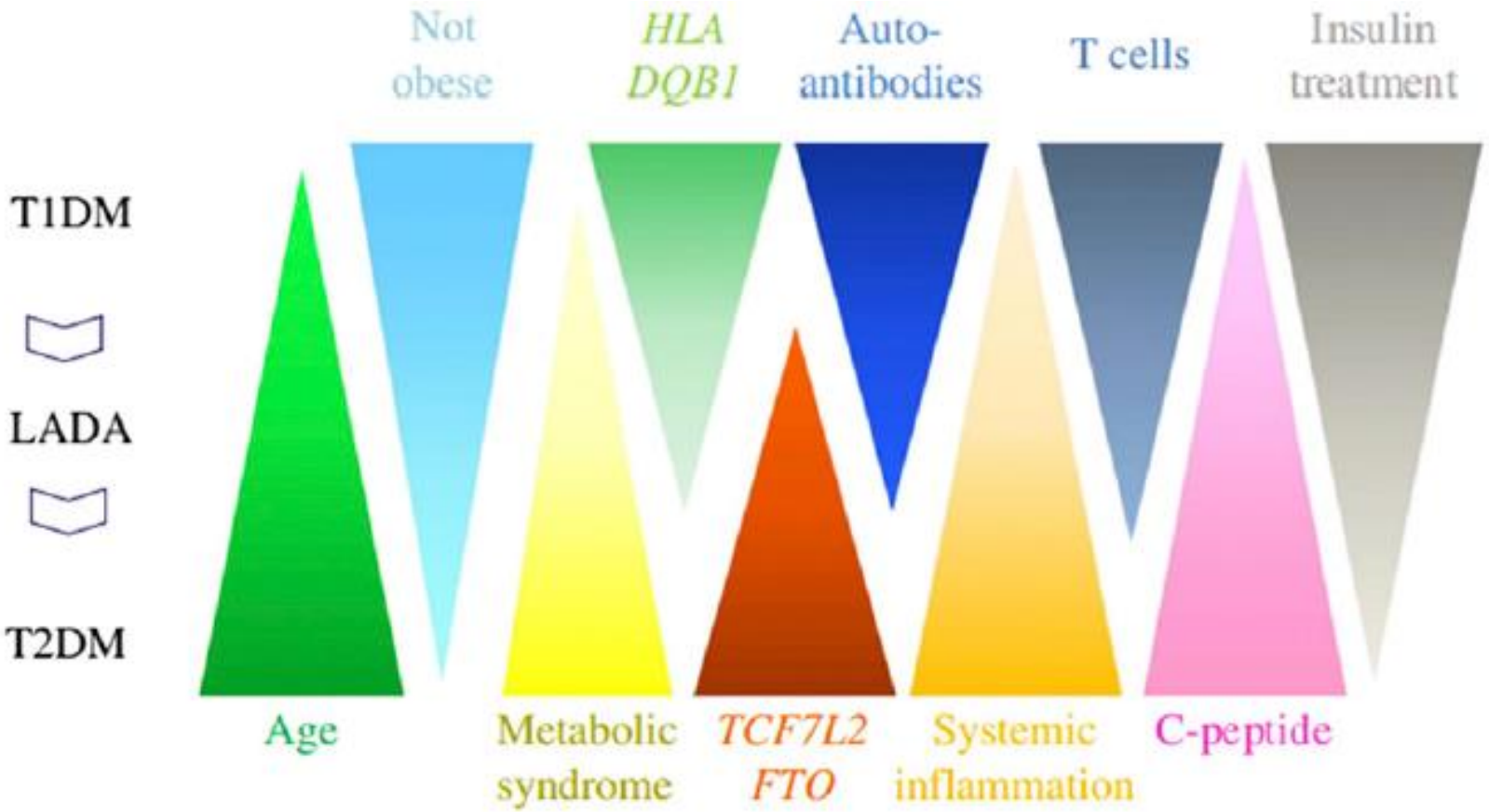
Is it that simple?

- Overlap
  - T1 with IR
  - T2 with insulin deficiency
- LADA
  - ? A form of T2DM with fast destruction of b-cells
  - ? a late manifestation of T1DM
  - ? a distinct entity with its own genetic footprint
- IR vs. T2DM
  - Role of b-cells function

Implications

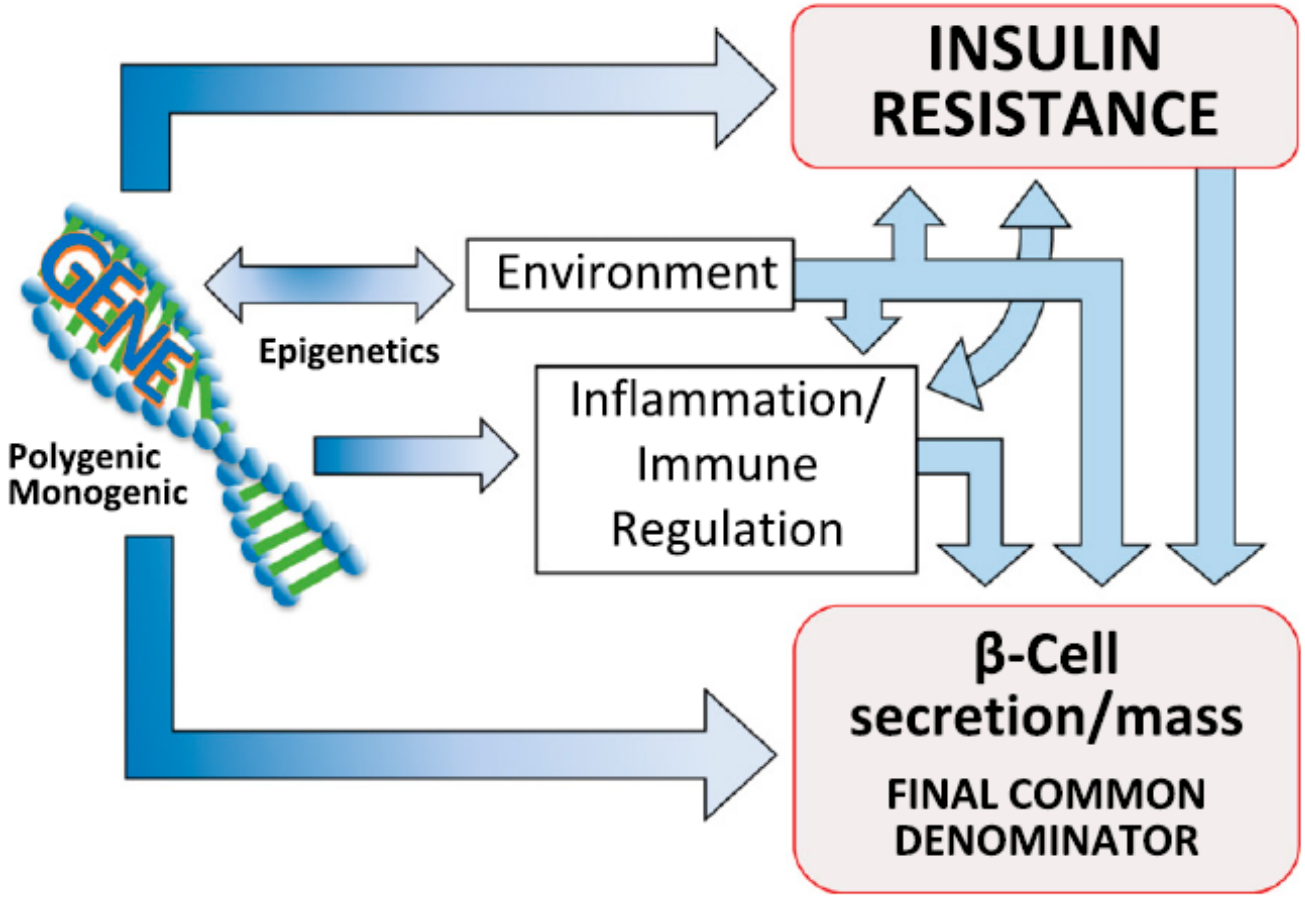
- Patient education
  - Insulin deficient vs insulin resistant
- Choice of Rx
  - Role of insulin
  - Role of other agents including SGLT2-I, TZD, DPP4-I, GLP1-a
- Rx reimbursement
  - Consumables of self monitoring
  - Insulin analogues
  - Other anti-diabetic agents

Factors associated with different forms



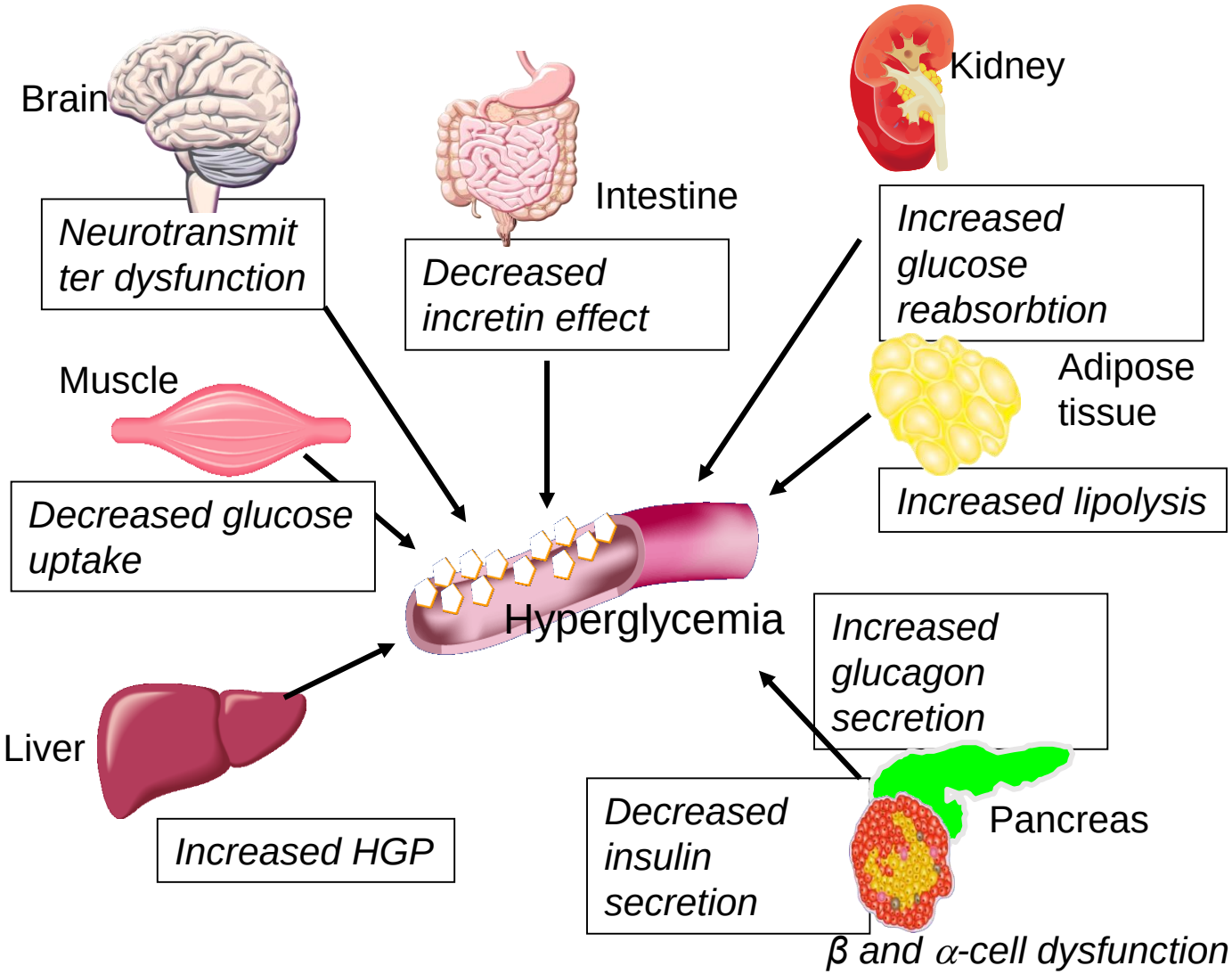
SS Schwartz. Diabetes Care 2016

B-cells are the key



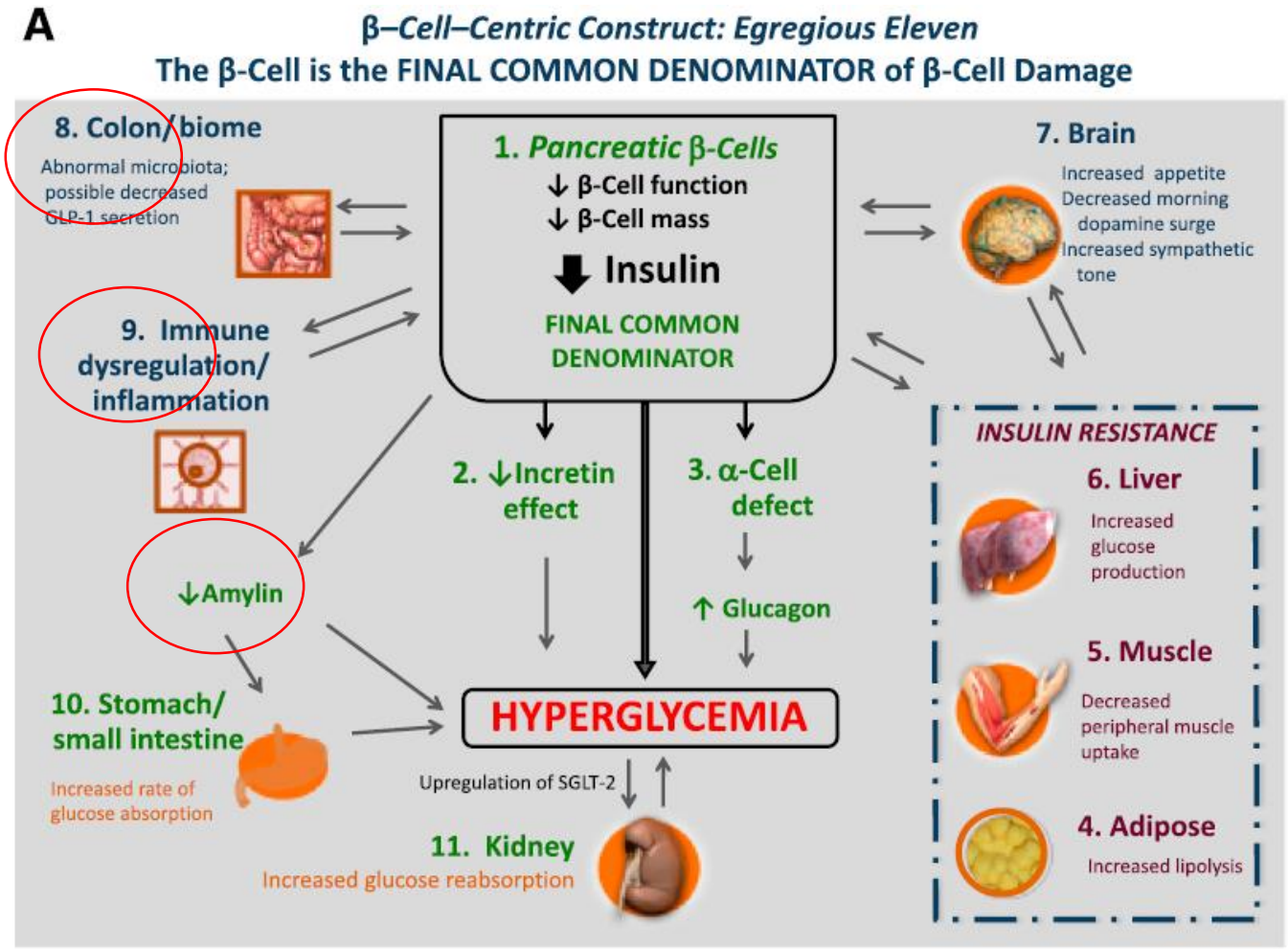
SS Schwartz. Diabetes Care 2016

The multiple pathophysiological abnormalities in type 2 Diabetes: the Ominous Octet



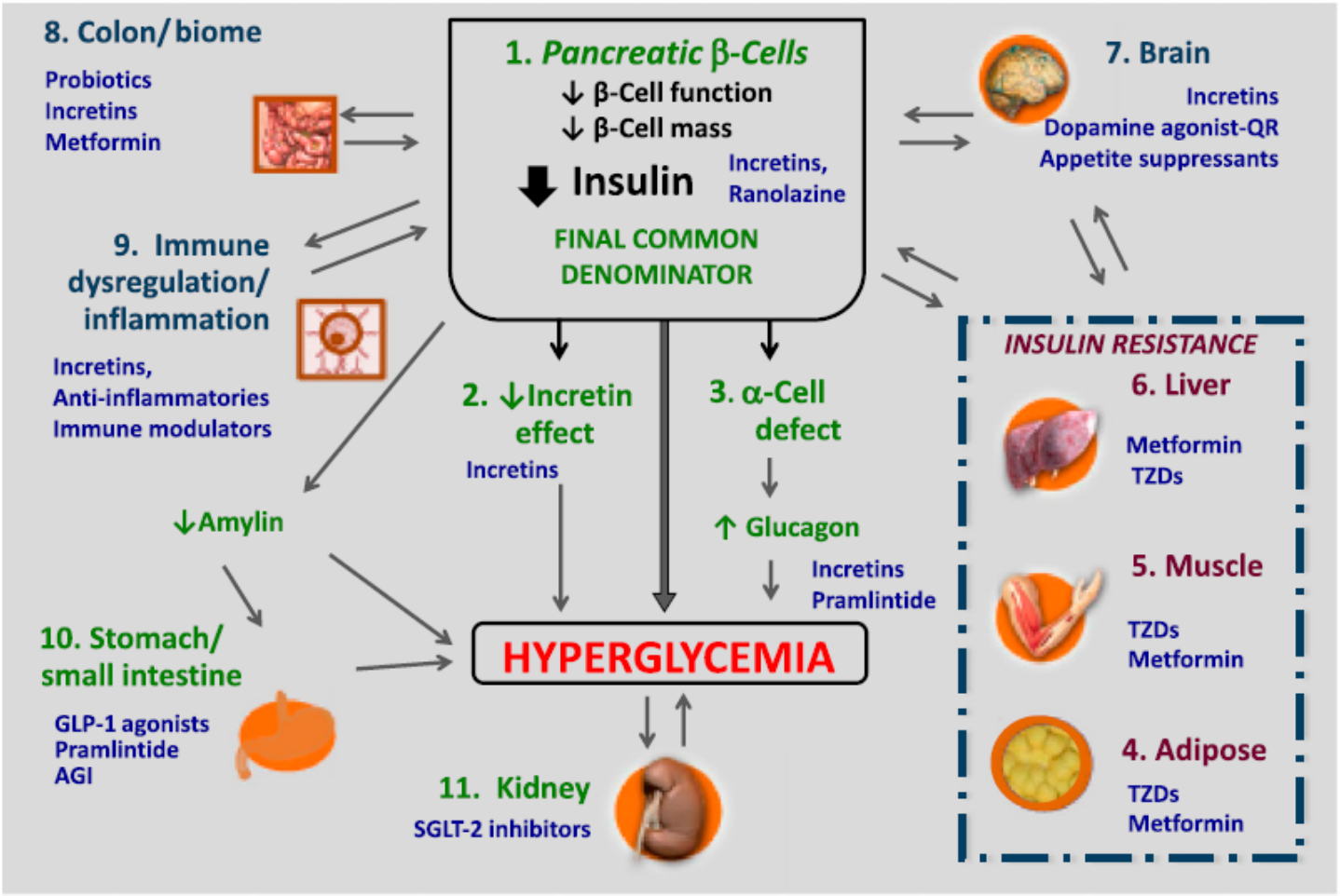
Adapted from R.DeFronzo

B-cell-centric Construct



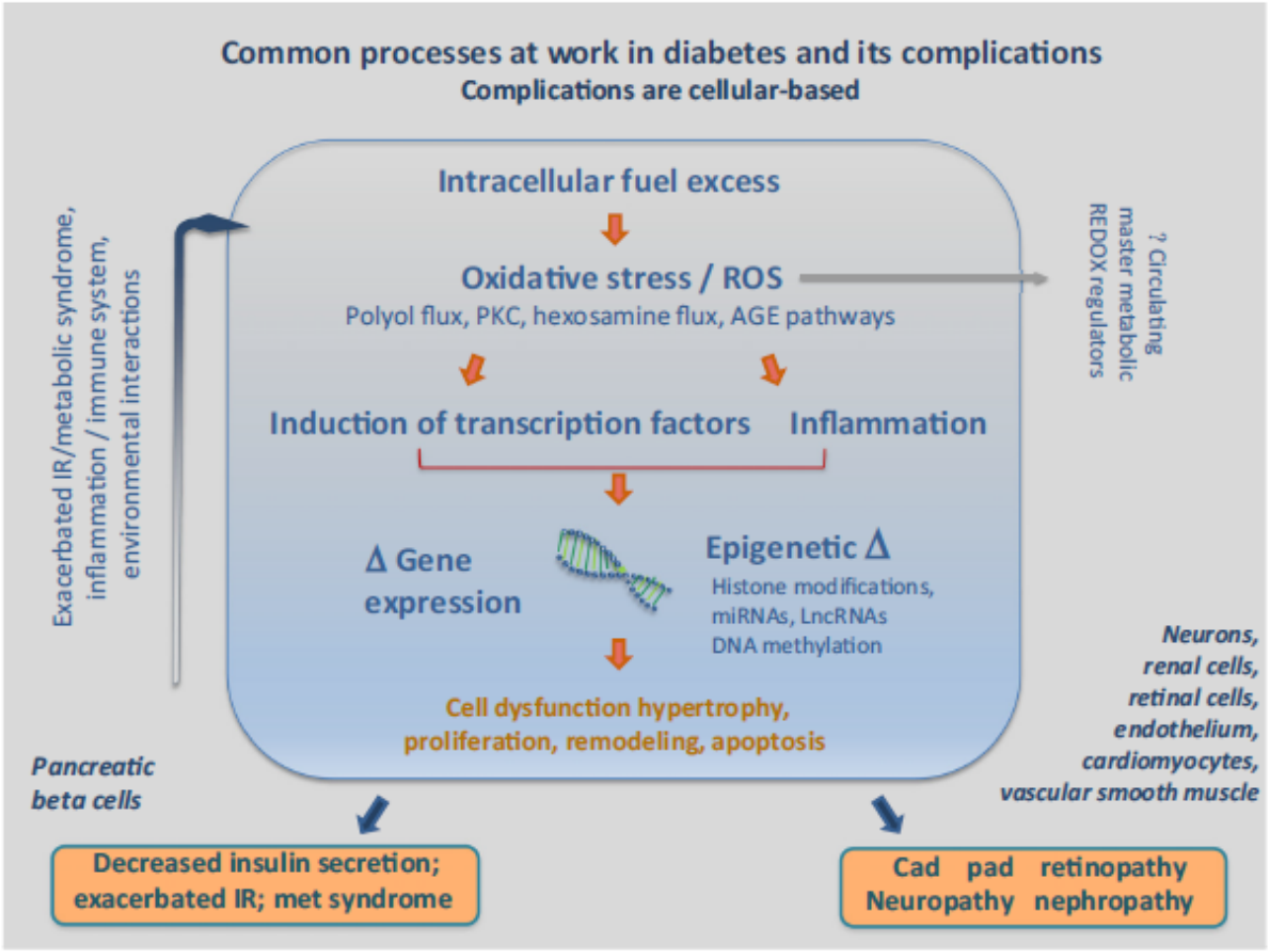
SS Schwartz. Diabetes Care 2016

Anti-diabetic treatment based on the model



SS Schwartz. Diabetes Care 2016

Common processes at Work in all Target (Vulnerable) Cells Implicated in Diabetes



SS Schwartz et al. Trends in Endocrinology & Metabolism 2017

Implications

- The ideal treatment regimens should not be potentially detrimental to the long-term integrity of the b-cells.
- Any benefits associated with sulfonylureas and glinides (including low cost) are not enduring and are far outweighed by their attendant risks (and associated treatment costs)
- When insulin therapy is needed, we suggest it be incorporated as add-on therapy rather than as substitution for noninsulin antidiabetes agents.

Novel subgroups of adult-onset diabetes

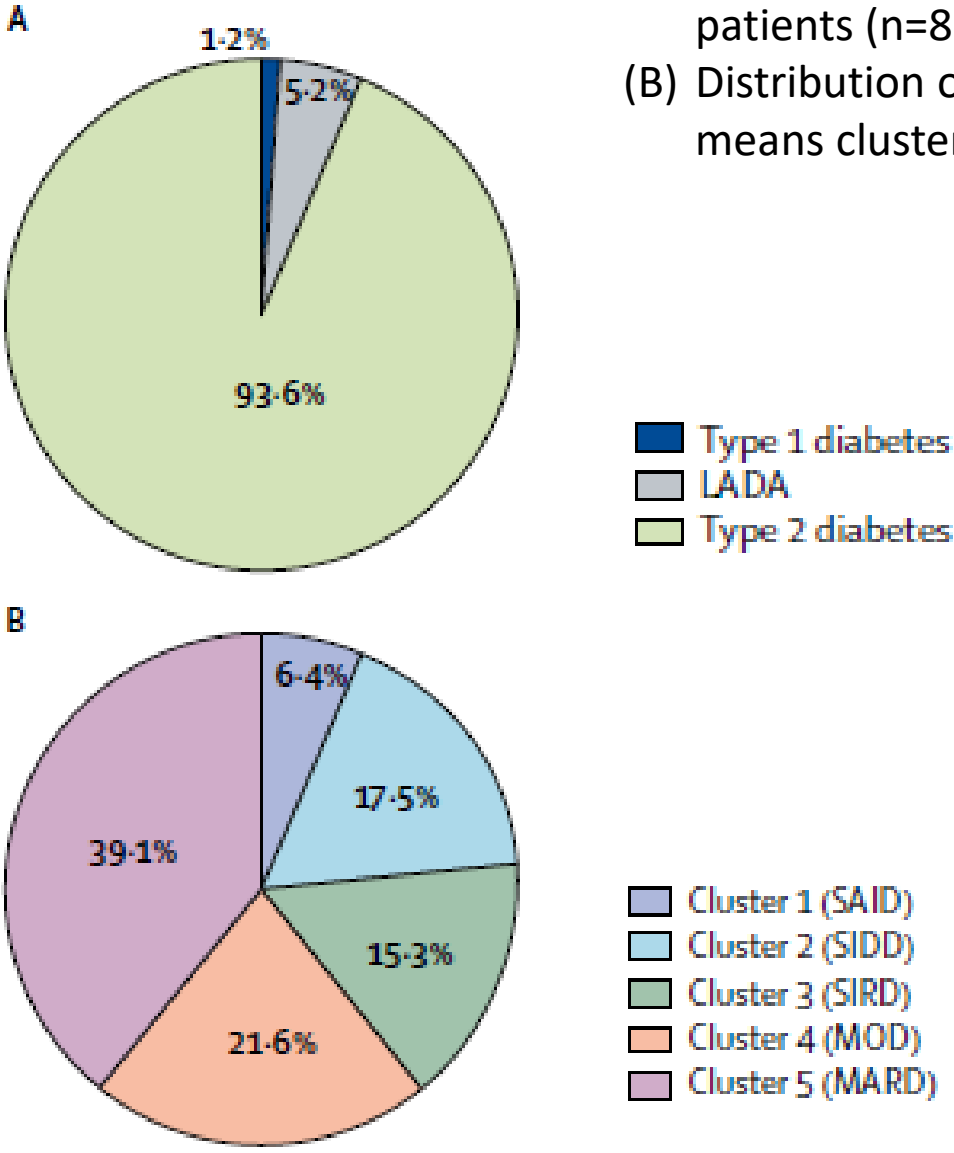
- Based on 6 variables
  - BMI
  - Age at onset of diabetes
  - HbA1c
  - HOMA2-B
  - HOMA2-IR (based on C-peptide concentrations, which performs better than insulin in patients with diabetes)
  - Presence or absence of GADA

E Ahlqvist et al. Lancet Diabetes Endocrinol, 2018

5 Clusters

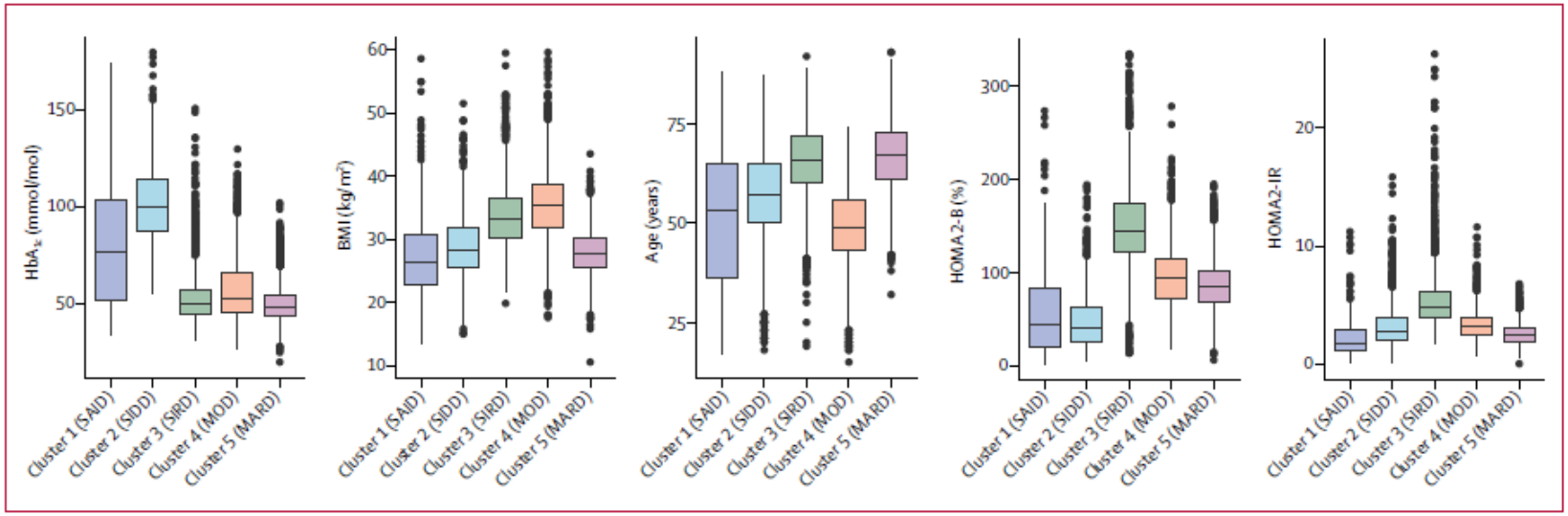
- Cluster 1, severe autoimmune diabetes (SAID).
  - early-onset disease, relatively low BMI, poor metabolic control, insulin deficiency, and presence of GADA
- Cluster 2, severe insulin-deficient diabetes (SIDD)
  - GADA negative but otherwise similar to cluster 1
- Cluster 3, severe insulin resistant diabetes (SIRD)
  - Insulin resistance (high HOMA2-IR index) and high BMI.
- Cluster 4, mild obesity-related diabetes (MOD)
  - Obesity but not insulin resistance
- Cluster 5, mild age-related diabetes (MARD)
  - Older than patients in other clusters, but only modest metabolic derangements

(A) Distribution of All New Diabetics in Scania (ANDIS) patients (n=8980) according to traditional classification.
(B) Distribution of ANDIS patients (n=8980) according to k-means clustering.



E Ahlqvist et al. Lancet Diabetes Endocrinol, 2018

Variation of variables in different subgroups



E Ahlqvist et al. Lancet Diabetes Endocrinol, 2018

Implication in treatment

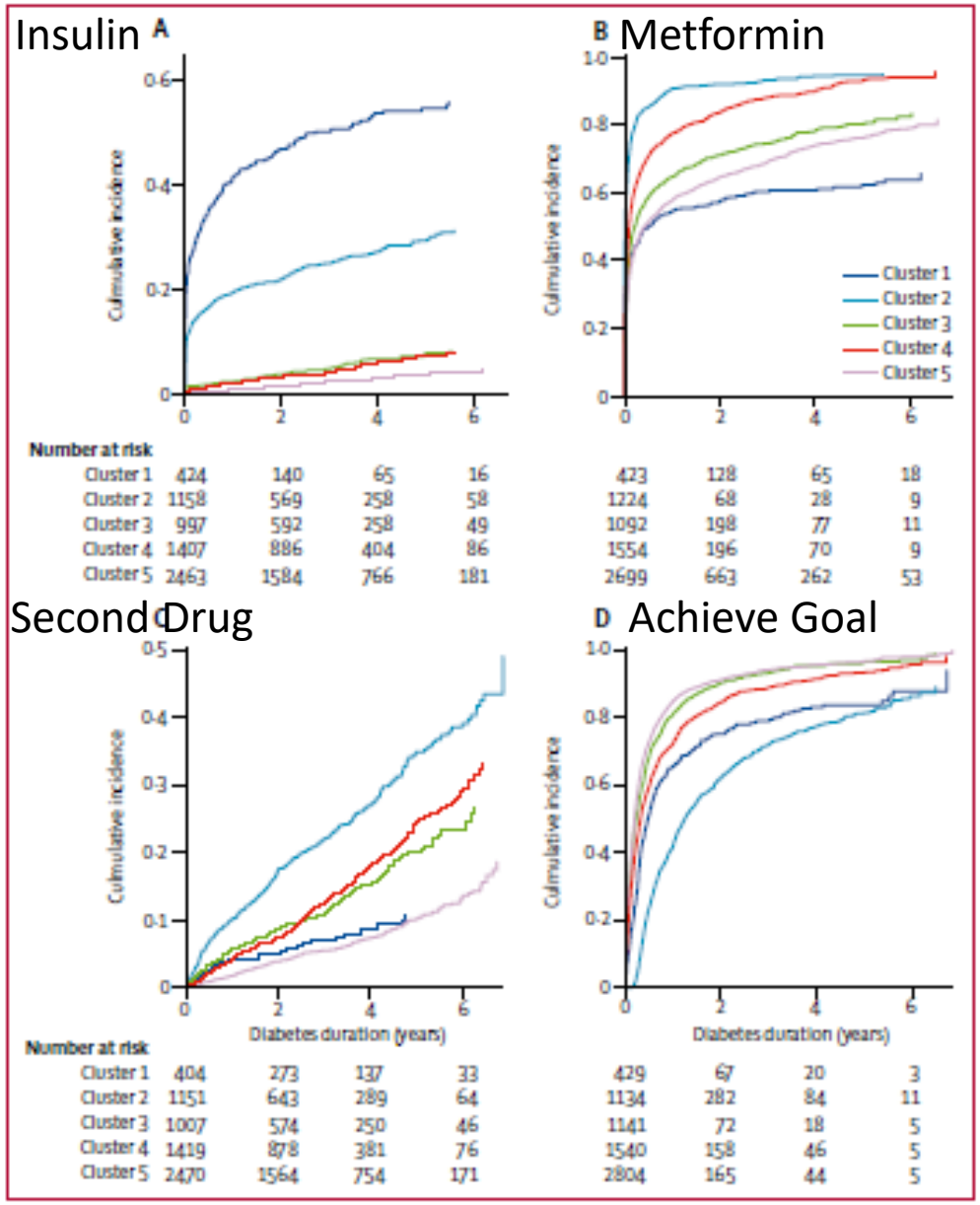
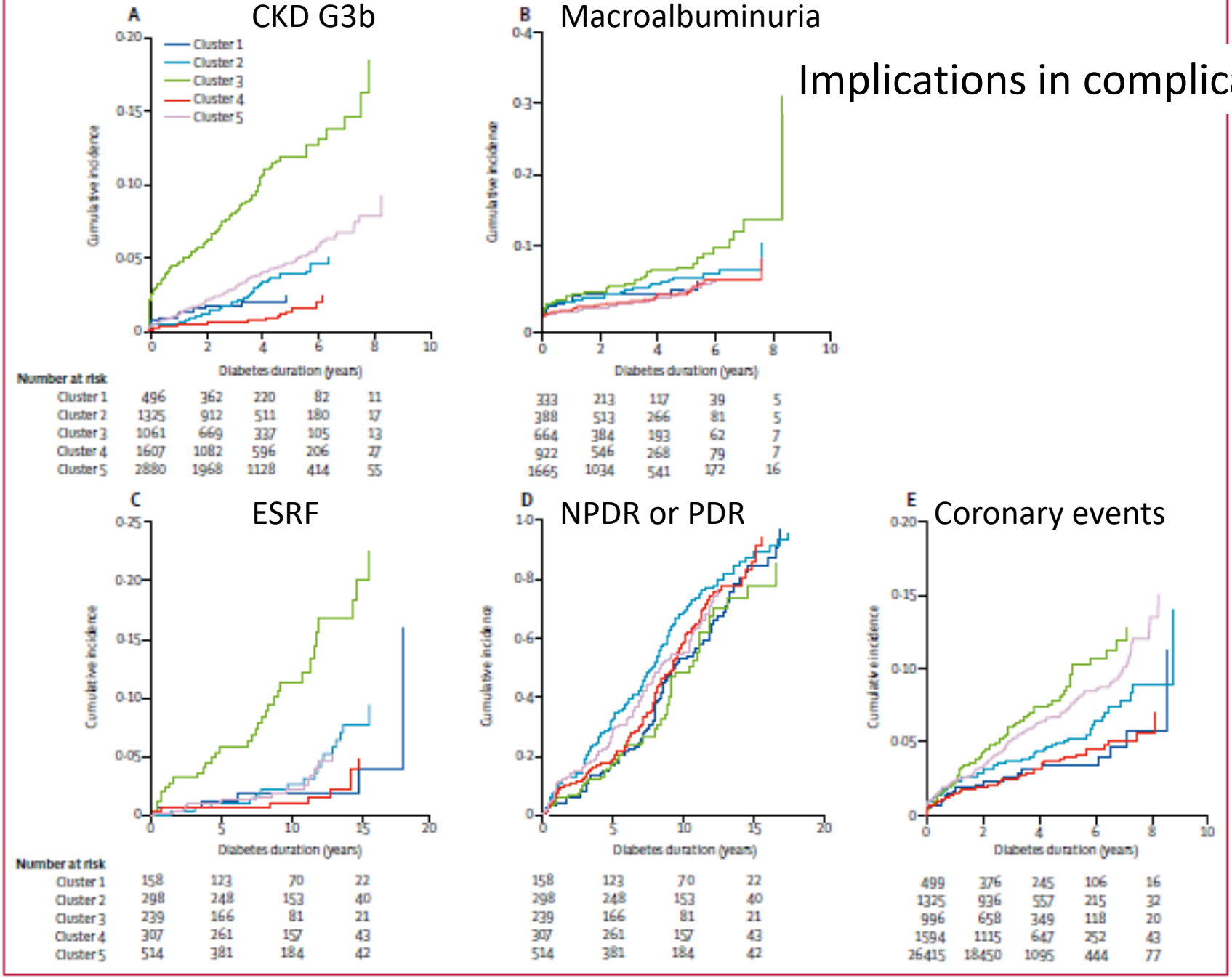


Figure 4: Antidiabetic therapy in All New Diabetics in Scania cohort during follow-up
(A) Time to sustained insulin use. (B) Time to metformin treatment. (C) Time to treatment with oral medication other than metformin. (D) Time to reach treatment goal (HbA_{1c} <6·9% [52 mmol/mol]).

E Ahlqvist et al. Lancet Diabetes Endocrinol, 2018

Implications in complications



Drivers of heterogeneity: Differences in diabetes-associated genetic loci

- A variant in the TCF7L2 gene (rs7903146), previously associated with T2DM, was associated with severe insulin deficient, obesity-related diabetes, and age-related diabetes but not severe insulin-resistant diabetes

	EA/NEA	MAF	Cluster 1 (SAID; n=313)	Cluster 2 (SIDD; n=676)	Cluster 3 (SIRD; n=603)	Cluster 4 (MOD; n=727)	Cluster 5 (MARD; n=1646)	p value of difference among clusters 1–5
TCF7L2 (rs7903146)	T/C	0·26	1·17 (0·97–1·40); p=0·077	1·51 (1·33–1·71); p<0·0001	1·00 (0·87–1·15); p=0·86	1·38 (1·21–1·56); p<0·0001	1·41 (1·28–1·55); p<0·0001	<0·0001*

- Altered incretin signalling has been suggested as a potential mechanism by which TCF7L2 variation increases T2DM risk

Greater biologic precision regarding the underlying disease allows for optimization of the clinical impact of the available therapies in diabetes

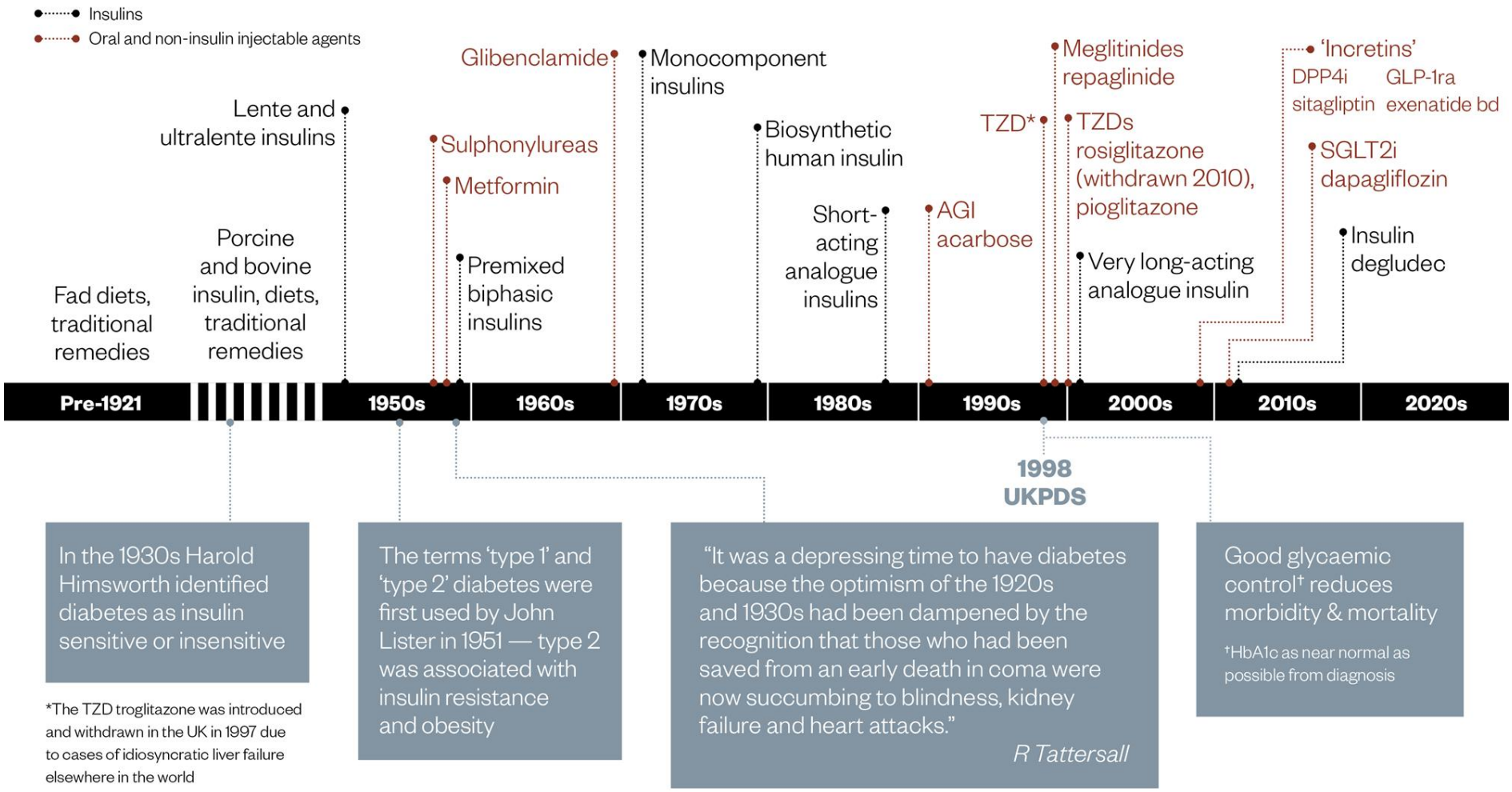
Where are we in 2018?

- Old classifications
  - Simple and user friendly
  - Have limitations
- Beta cell centric model
  - More like a pathophysiological model, make sense for pros
  - Difficult for lay ppl to understand
- The novel subgroups
  - Need further validation

Treating diabetes

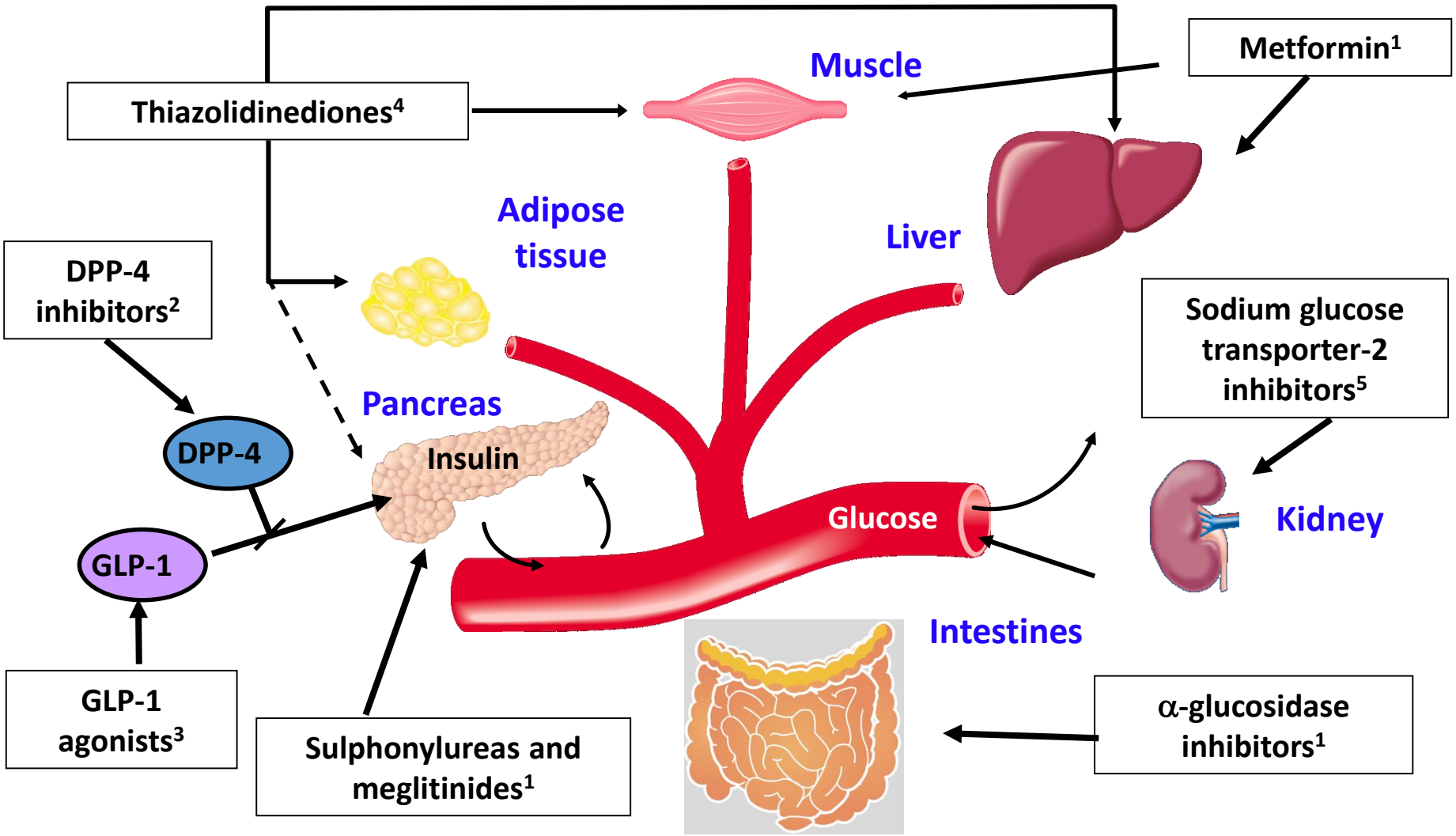
- Those were the days…
  - Metformin
  - Daonil
  - Insulin

The evolution…



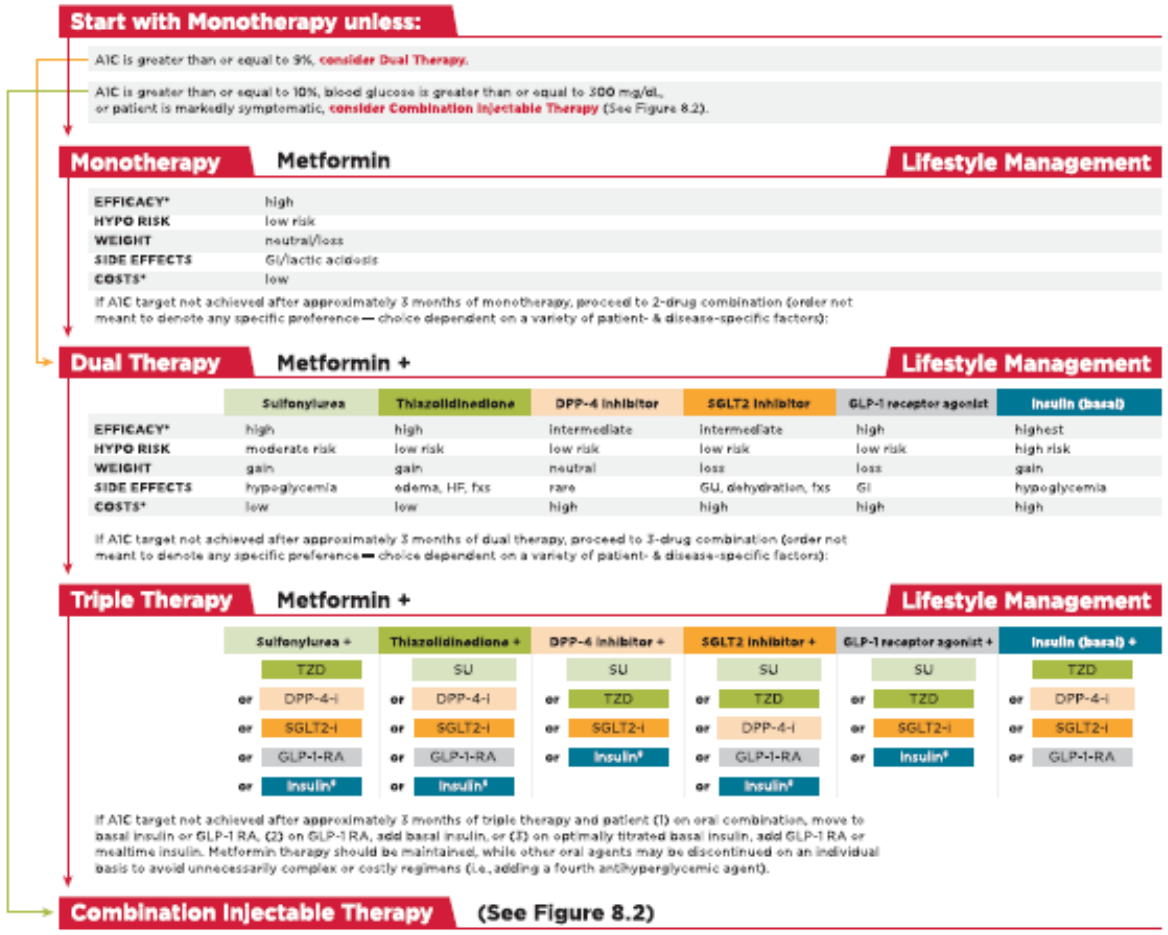
AV Bailey et al. The Pharmaceutical J. 2017

Primary sites of action of anti-diabetic agents



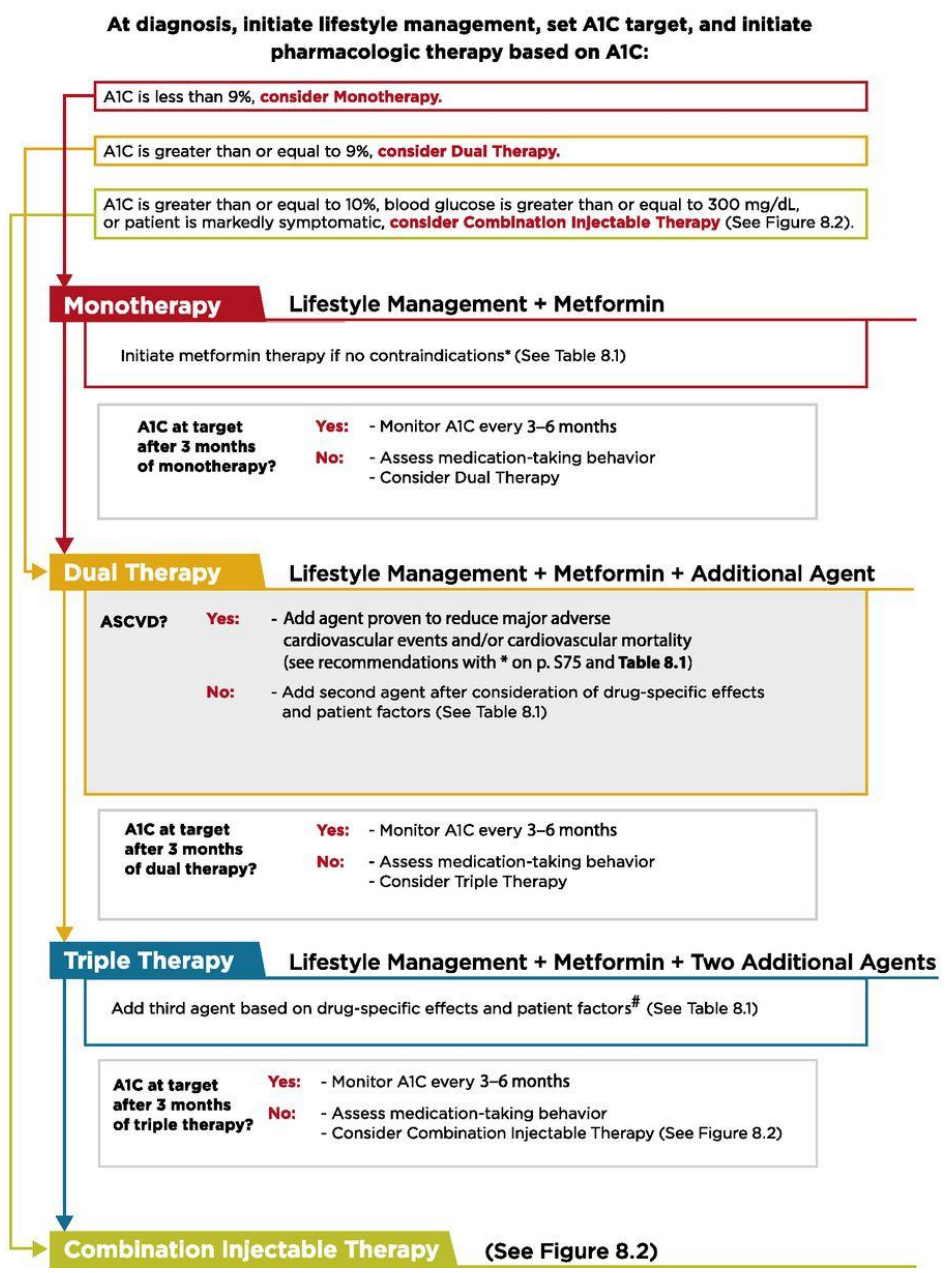
[1]Adapted from Krentz A and Bailey C. *Drugs* 2005;65:358–411; [2]Ahren B. *Expert Opin Emerg Drugs* 2008;3:593–607; [3]Todd JF, *et al. Diabet Med* 2007;24:223–32; [4]Nattrass M, *et al. Baillieres Best Pract Res Clin Endocrinol Metab* 1999;13:309–29; [5]Jabbour S and Goldstein B. *Int J Clin Pract* 2008;62:1279–84.

It's been like this for quite some time



ADA 2017

Antihyperglycemic Therapy in Adults with Type 2 Diabetes



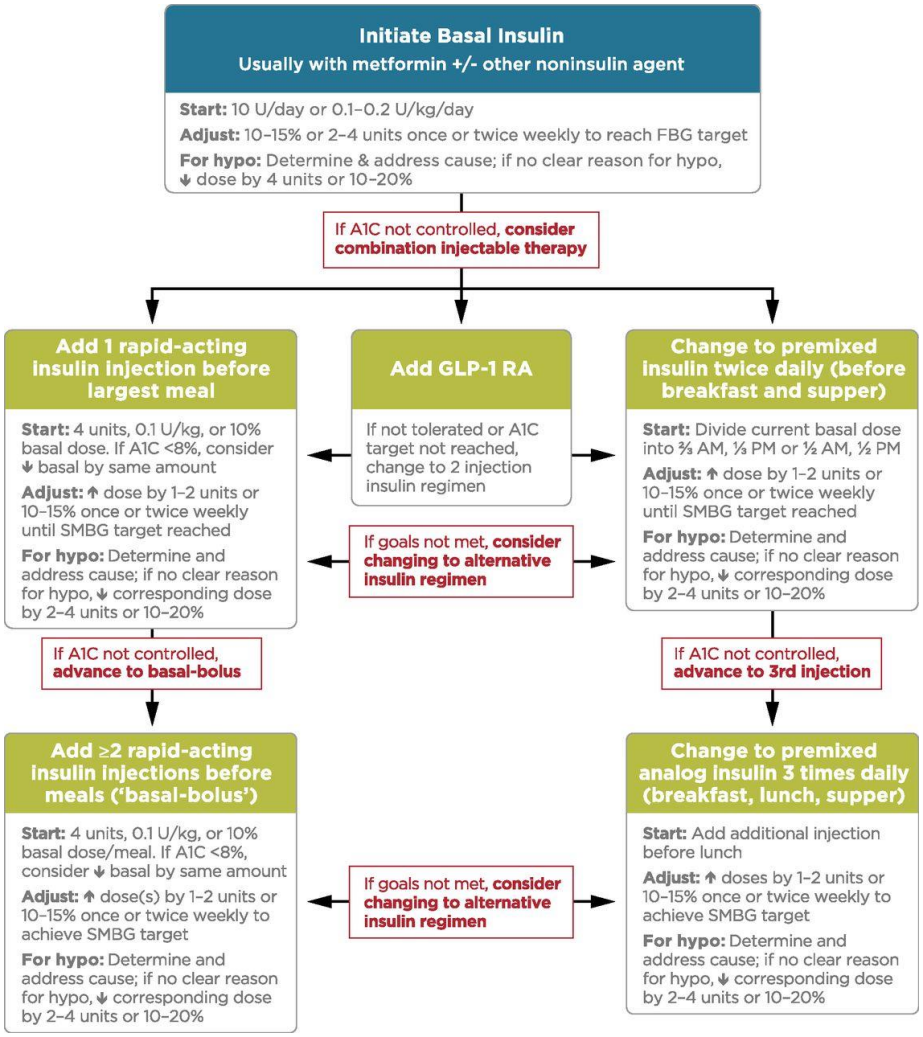
Version 2018

American Diabetes Association Dia Care 2018;41:S73-S85

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Combination injectable therapy for type 2 diabetes.



American Diabetes Association Dia Care 2018;41:S73-S85

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Table 8.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

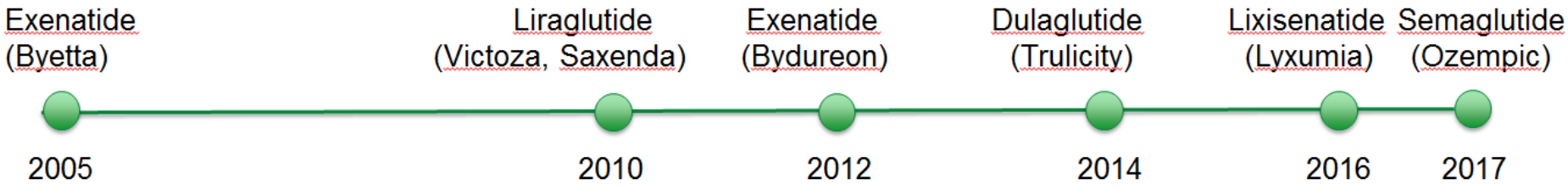
	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required; can be used in renal impairment	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure (**pioglitazone, rosiglitazone**) ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — **Human Insulin**	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — **Analogs**	Highest	Yes	Gain	Neutral	Neutral	High	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs

*See ref. 31 for description of efficacy. †FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes.

Current anti diabetic agents

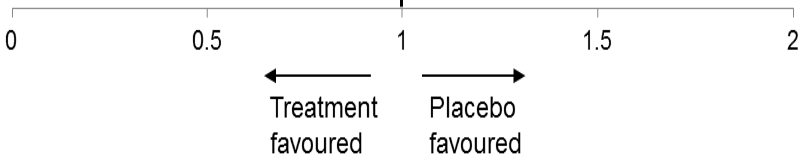
	AGIs	Metformin	SU	Glinides	TZDs	DPP4i	GLP1Ra	SGLT2i	Insulin
Effect on FG	000	+++	+++	+	+++	+	+++	++	++++
Effect on PG	+++	+	++	+++	+	+++	+++	++	++++
Weight	0	0 / ↓	++	+	+++	0	↓	↓	++++
Hypo monotherapy	0	0	+++	++	0	0	0	0	++++
CV study	-	+	+	-	+	+	+	+	+
CHD benefit	-	+	-	_	+	-	+	+	-
Renal benefit	-	-	-	-	-	-	+	+	-
GI S/E	+	+	-	-	-	+	+	-	-
Other S/E		Lactic acidosis B12 def			Oedema CHF Fracture ? Ca Bladder		? pancreatitis	UT/GU infection DKA	
Cost	++	+	+	++	++	+++	++++	+++	Variable
Experience	+++	++++	++++	++	+++	+++	++	++	++++

Approved GLP-1 agonists



3-Point MACE Meta-analysis

	Study drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	P value
ELIXA (1) ¶ lixisenatide vs. placebo	406/3034 (13.4)	399/3034 (13.2)	1.02	0.89, 1.17	<0.01 (NI) 0.81 (S)
LEADER® (2) liraglutide vs. placebo	608/4668 (13.0)	694/4672 (14.9)	0.87	0.78, 0.97	<0.001 (NI) 0.01 (S)
SUSTAIN-6 (3) semaglutide vs. placebo	108/1648 (6.6)	146/1649 (8.9)	0.74	0.58, 0.95	<0.001 (NI) 0.02 (S)
EXSCEL exenatide vs. placebo	839/7356 (11.4)	905/7396 (12.2)	0.91	0.83, 1.00	<0.001 (NI) 0.061 (S)
Overall *	1555/13672 (11.3)	1745/13717 (12.7)	0.88	0.81, 0.95	0.002



Test for heterogeneity
I^2 = 22%
Q test p-value = 0.28

NI = non-inferiority
S = superiority

[1] Pfeffer MA et al. N Engl J Med 2015; 373: 2247–2257
[2] Marso SP et al. N Engl J Med 2016; 375: 311–322
[3] Marso SP et al. N Engl J Med 2016; 375: 1834–1844

¶ Use of MACE-4 primary composite endpoint

* Excludes data from ELIXA

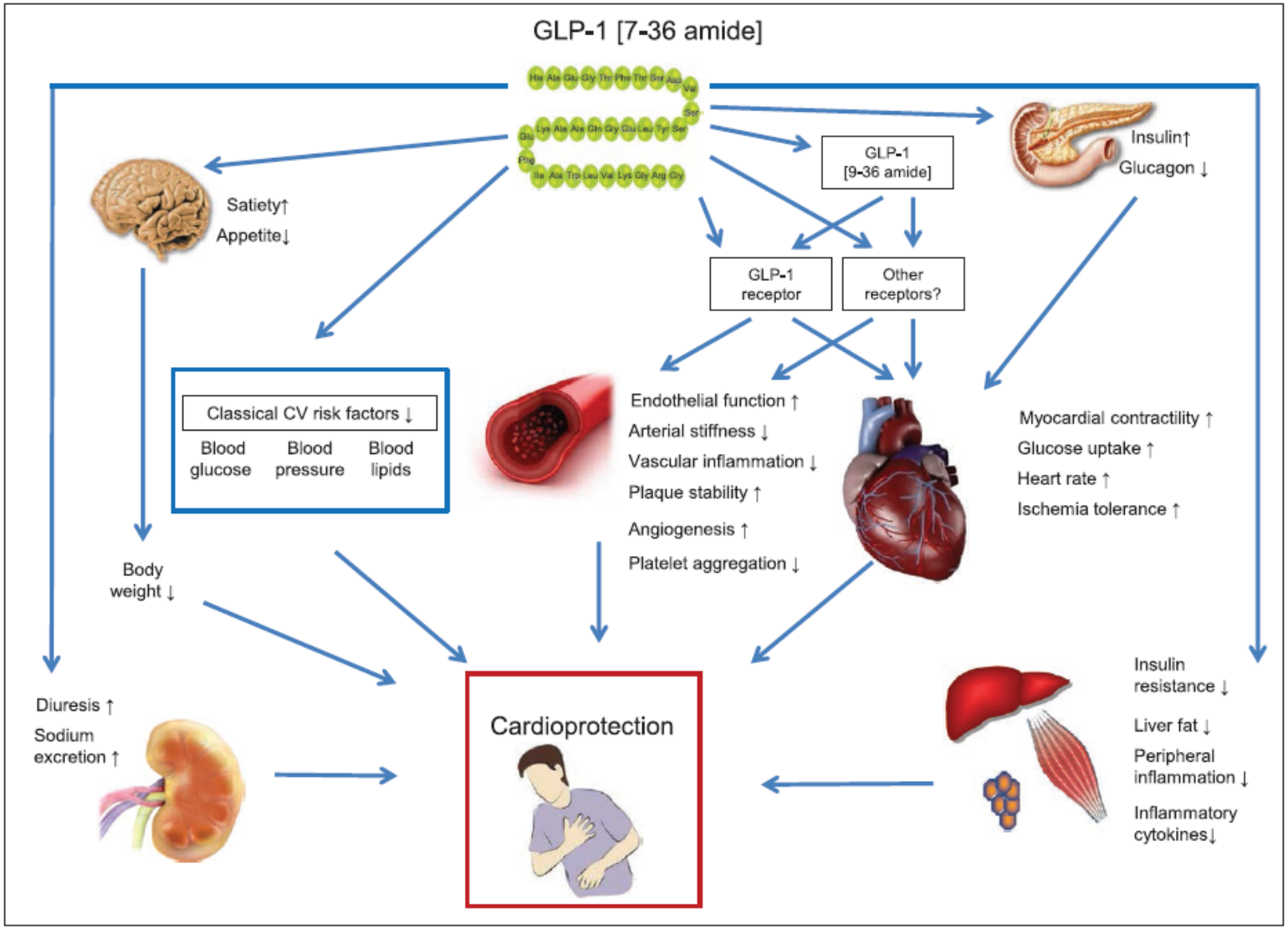
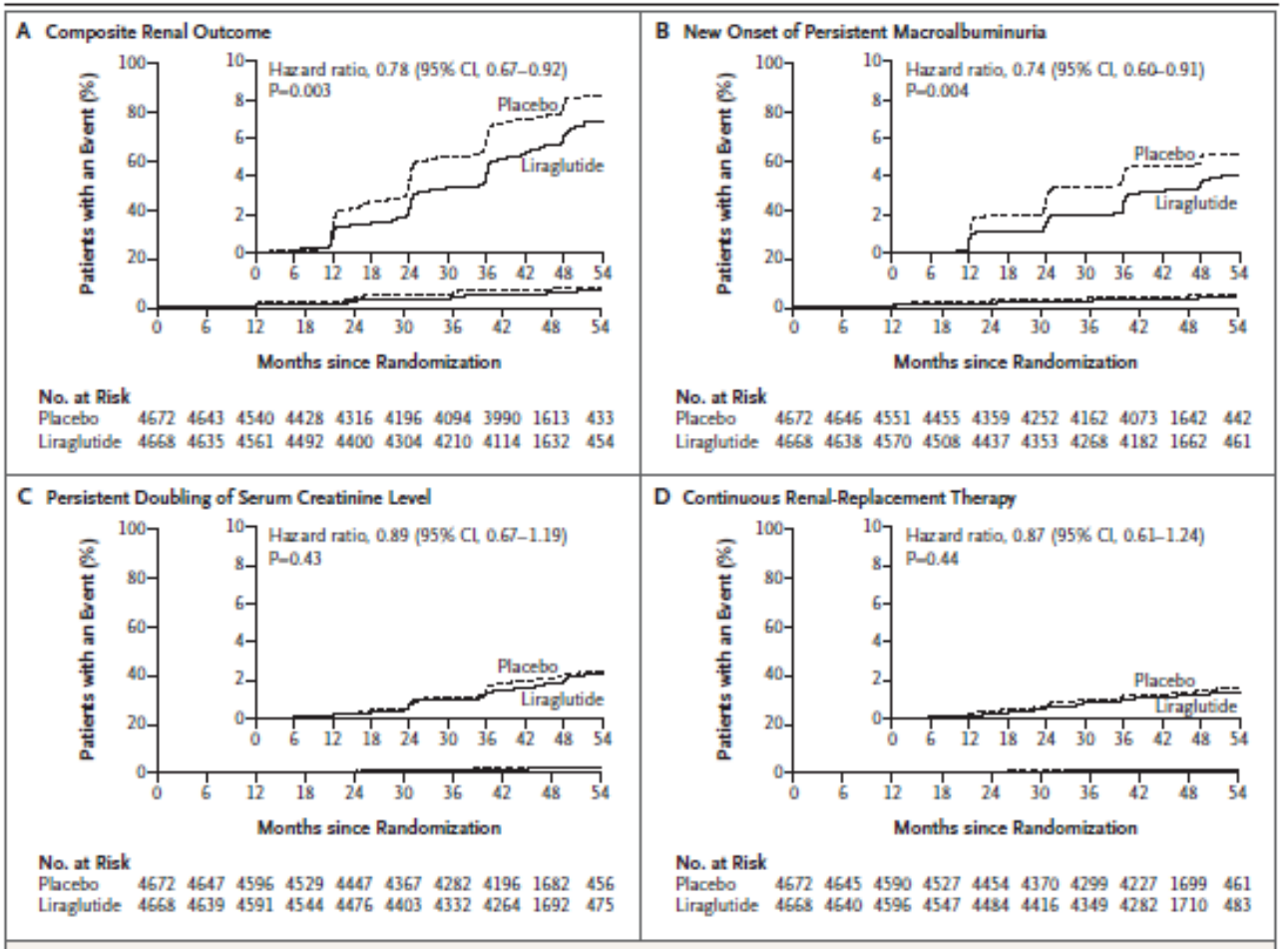


Figure 3. Potential mechanisms mediating a beneficial effect of glucagon-like peptide-1 (GLP-1) receptor agonists on reducing cardiovascular events.

Effects of diabetes mellitus-related parameters (glycemic control, avoidance of [severe] hypoglycemia), cardiovascular risk factors (body weight, blood pressure, lipoproteins/lipids), and interactions with GLP-1 receptors in the cardiovascular system (potentially leading to improved endothelial function/vasodilation, improved cardiac function under conditions of coronary ischemia, and anti-inflammatory/ anti-atherosclerotic effects) have to be considered. CV indicates cardiovascular.

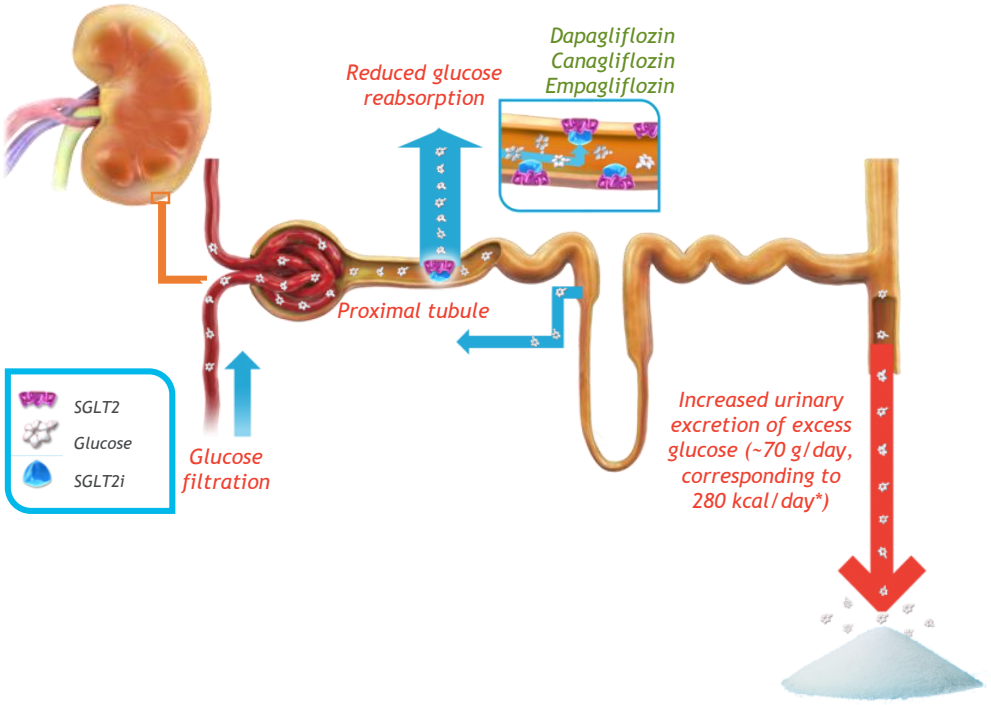
Circulation. 2017;136:849–870.

GLP1-a and renal outcome



NEJM 2017

SGLT2i inhibits SGLT2 and removes excess glucose in the urine independently of insulin



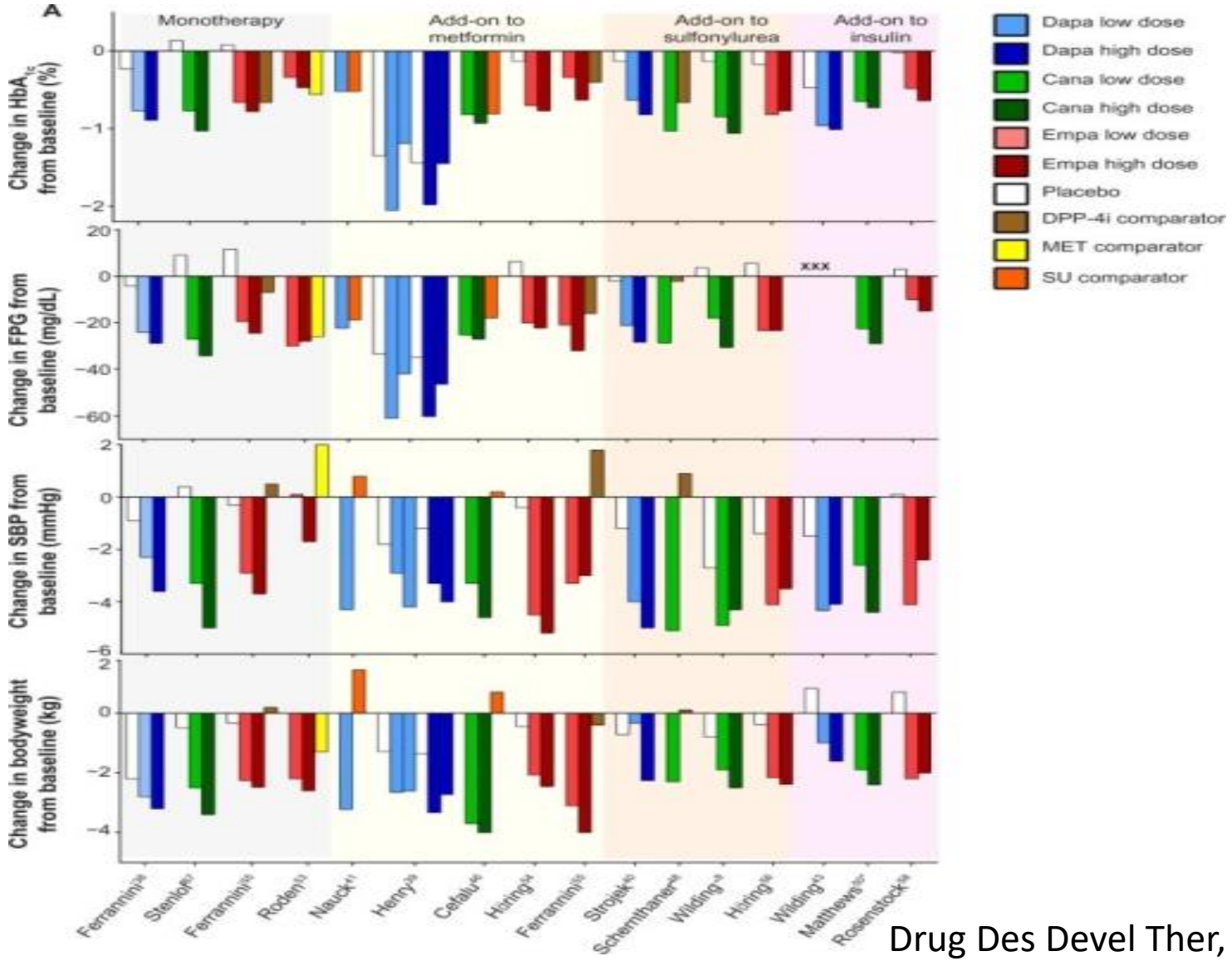
- By inhibiting SGLT2, SGLT2i removes excess glucose and associated calories

*Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with type 2 diabetes.

SGLT2=sodium-glucose co-transporter 2.

Dapagliflozin summary of product characteristics, 2014.

SGLT2-I effects

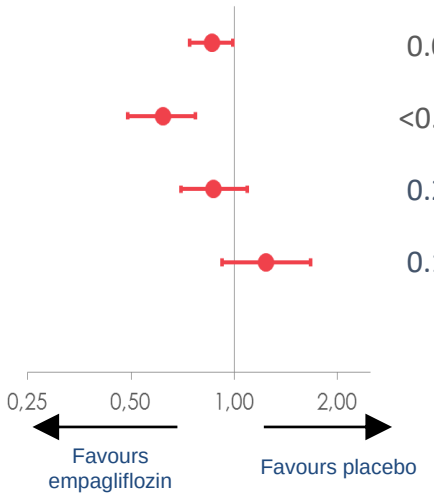


Drug Des Devel Ther, 2014

EMPA-REG: CV death, MI and stroke with empagliflozin vs. placebo

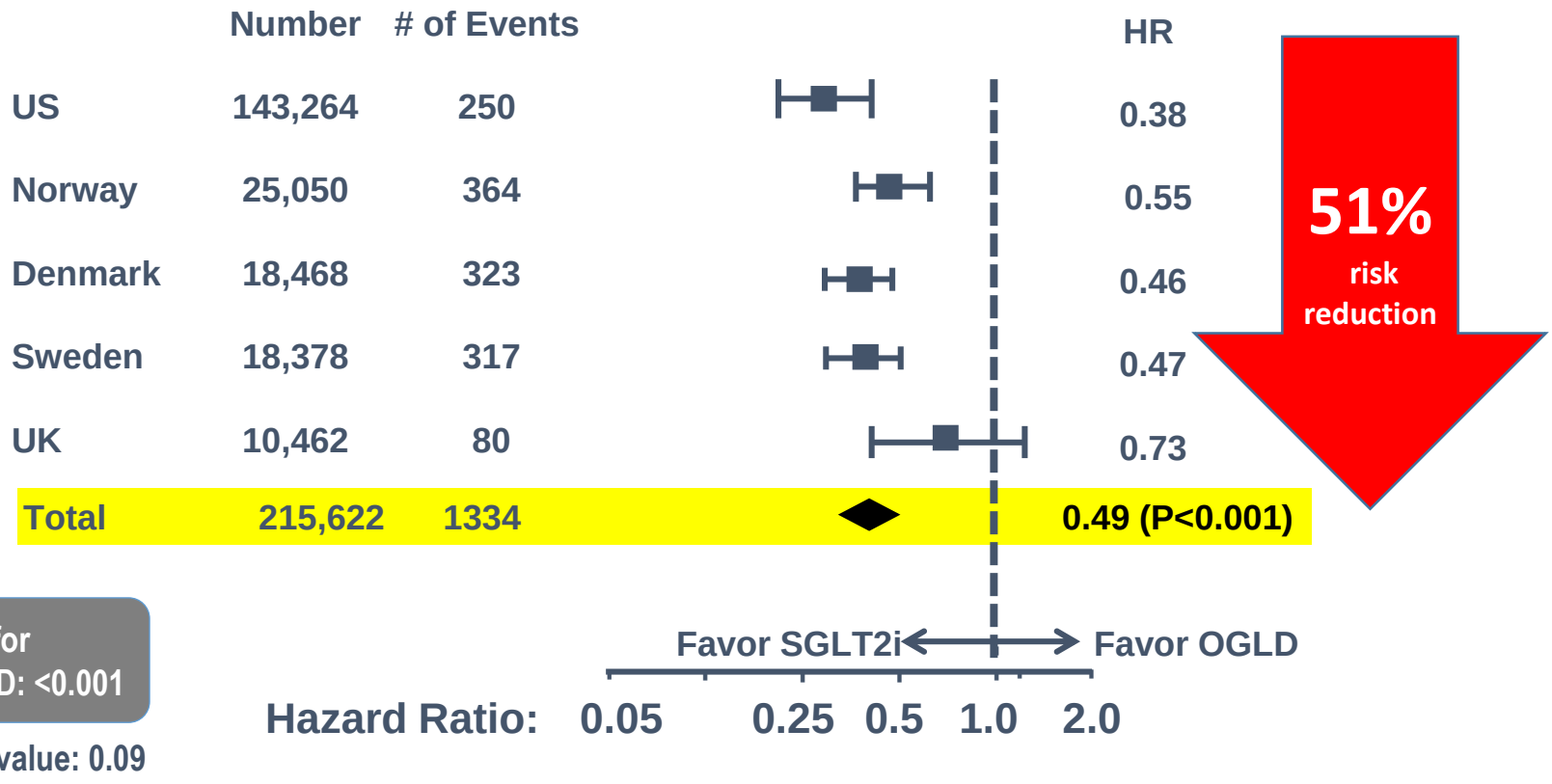
99% with established CVD (MI, stroke, PAD)

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



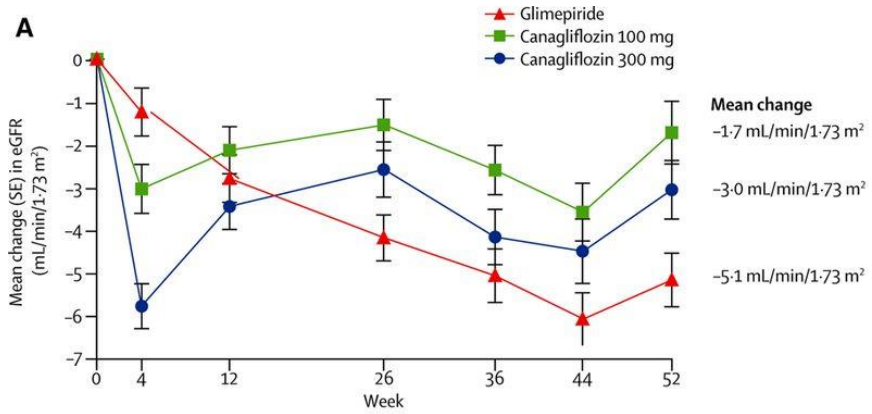
Zinman B, et al. *New Engl J Med* 2015; Sep 17 [Epub ahead of print]

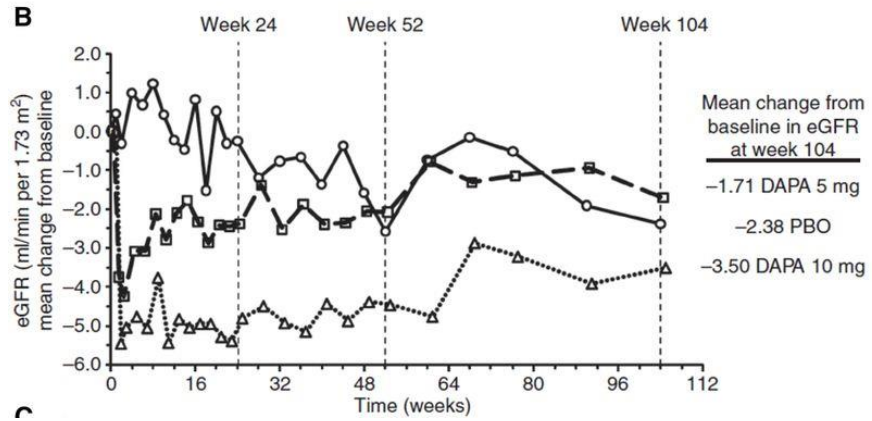
ALL-CAUSE DEATH

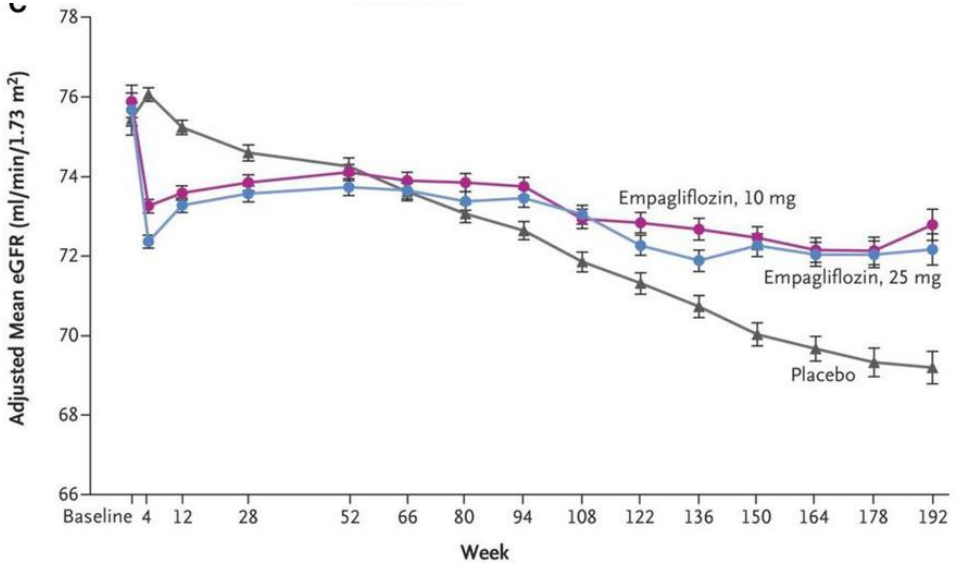


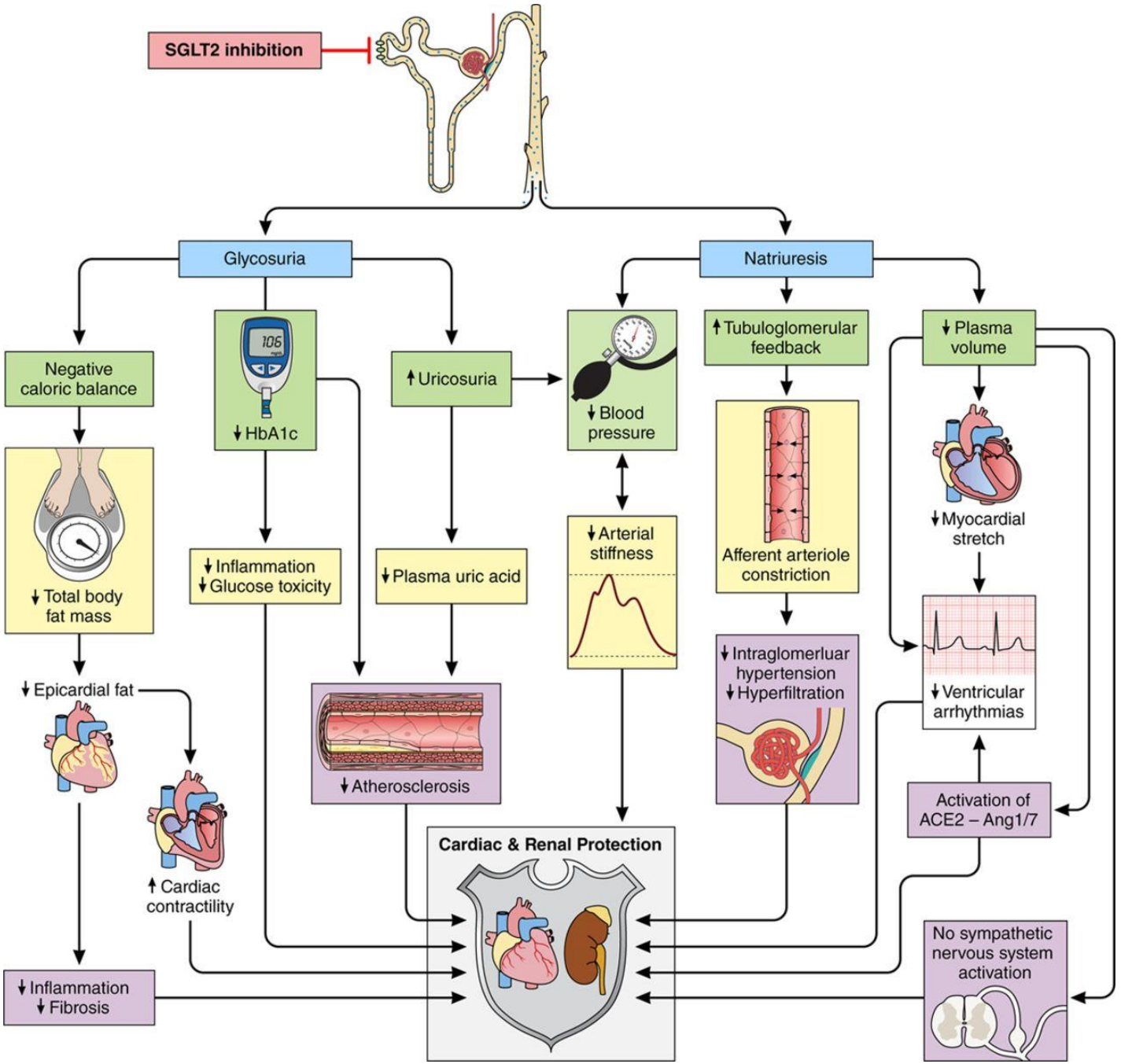
	CVD-REAL NORDIC	EMPA-REG	CANVAS/CANVAS-R
Treatment	Dapagliflozin (n=22,830) vs other glucose lowering drugs (n=68,490)	Empagliflozin (n=4,687) vs placebo (n=2,333)	Canagliflozin (n=5,795) vs placebo (n=4,347)
Age(years)	61	63	63
Mean follow-up (years)	0.9	3.1	3.6
CVD at baseline (%)	25	99	65.6
CV mortality HR (95%CI)	0.53 (0.40 - 0.71)	0.62 (0.49 - 0.77)	0.87 (0.72 - 1.06)
MACE HR (95%CI)	0.78 (0.69 - 0.87)	0.86 (0.74 - 0.99)	0.86 (0.75 - 0.97)
Heart Failure HR (95%CI)	0.70 (0.61 - 0.81)	0.65 (0.50 - 0.85)	0.67 (0.52 - 0.87)

SGLT2-I and renal function



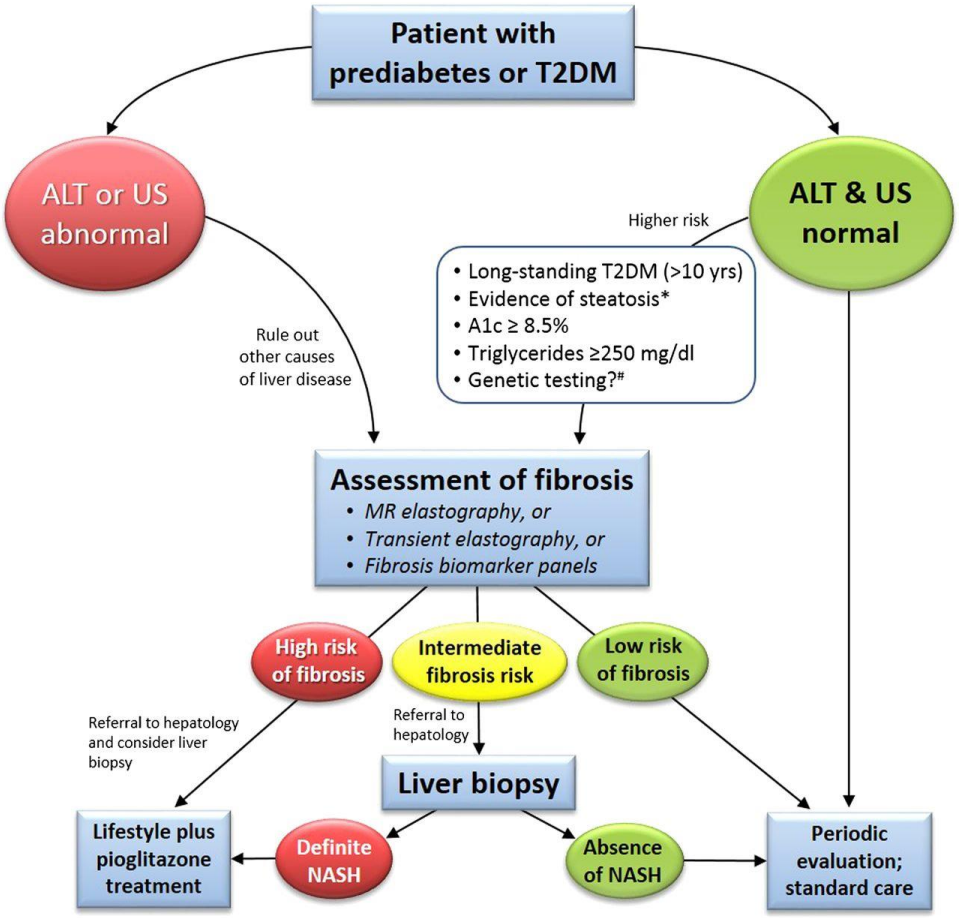






Circulation 2016

What if he has fatty liver?



Treating diabetes in 2018

- Your old friend is nice
  - They did a good job and gave you fond memories
  - But they are the past
- When you make new friends
  - Make sure they are…
  - Powerful (in glycaemic control)
  - Caring (Good for your heart)
  - Protecting (Good for your kidney and other organs)

The evidence behind

- RCT is the gold standard
- PROACTIVE
- ADOPT
- TECOS
- SAVOUR
- CAROLINA
- EMPA-REG
- LEADER

RCT vs Real World Evidence

Variables	RCTs	RWE
Purpose	Efficacy	Effectiveness
Setting	Experimental setting	Real-world setting
Follow up	Designed	In actual practice
Treatment	Fixed pattern	Variable pattern
Study group	Homogenous	Heterogeneous
Attending physician	Investigator	Many practitioners
Comparator	Placebo/selective alternative interventions	Many alternative interventions
Patient monitoring	Continuous, per protocol	Changeable

HS Kim et al. J Korean Med Sci. 2018

Advantages and limitations of real-world evidence compared with RCTs

Pros

- Less time and cost consumption
  - shorten the duration of clinical research
  - No period needed for recruitment/enrollment
- Presentation of the directionality for RCT
- Research that cannot be done with RCT is possible
  - Safe research on high-risk groups
- Detection of less frequent side effects
- Rapid access/easier information and data retrieval
- Prediction model or high-risk group selection
- Set a foundation on AI

Cons

- Need massive amot of data for correct analysis
- Much time needed for data quality management
- Expertise for the analysis of big data
- Lack of privacy/confidentiality/lost data
- Standardized research protocol needs to be established before research
  - High possibility of bias
  - Possible to interpret with bias or incorrectly based on research results

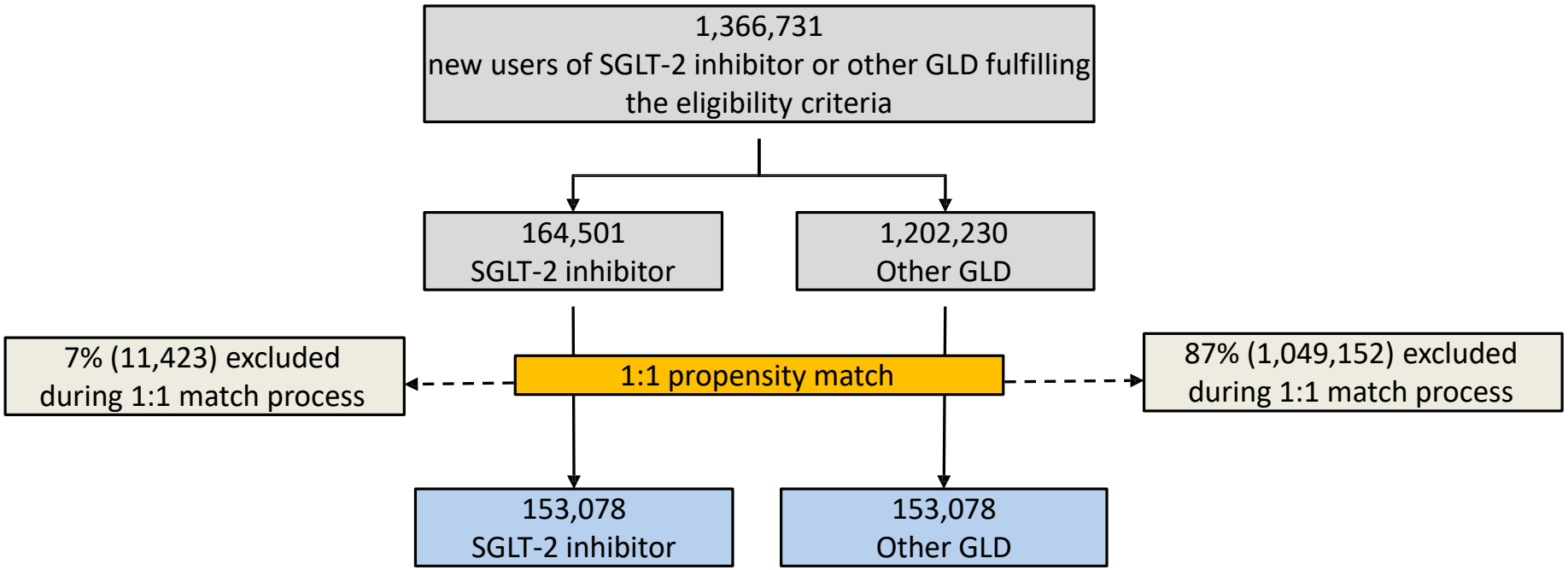
CVD Real methodology

- Inclusion criteria
  - New users of SGLT-2i or new users of other GLDs
  - Established T2D
  - ≥18 years old
  - >1 year historical data prior to index date
- Exclusion criteria
  - Type 1 or gestational diabetes
- Study period
  - 2012-2016 with a mean follow-up time of 225 days
- Outcomes
  - Heart failure events
  - All-cause death
  - Composite of heart failure events or death

Statistics

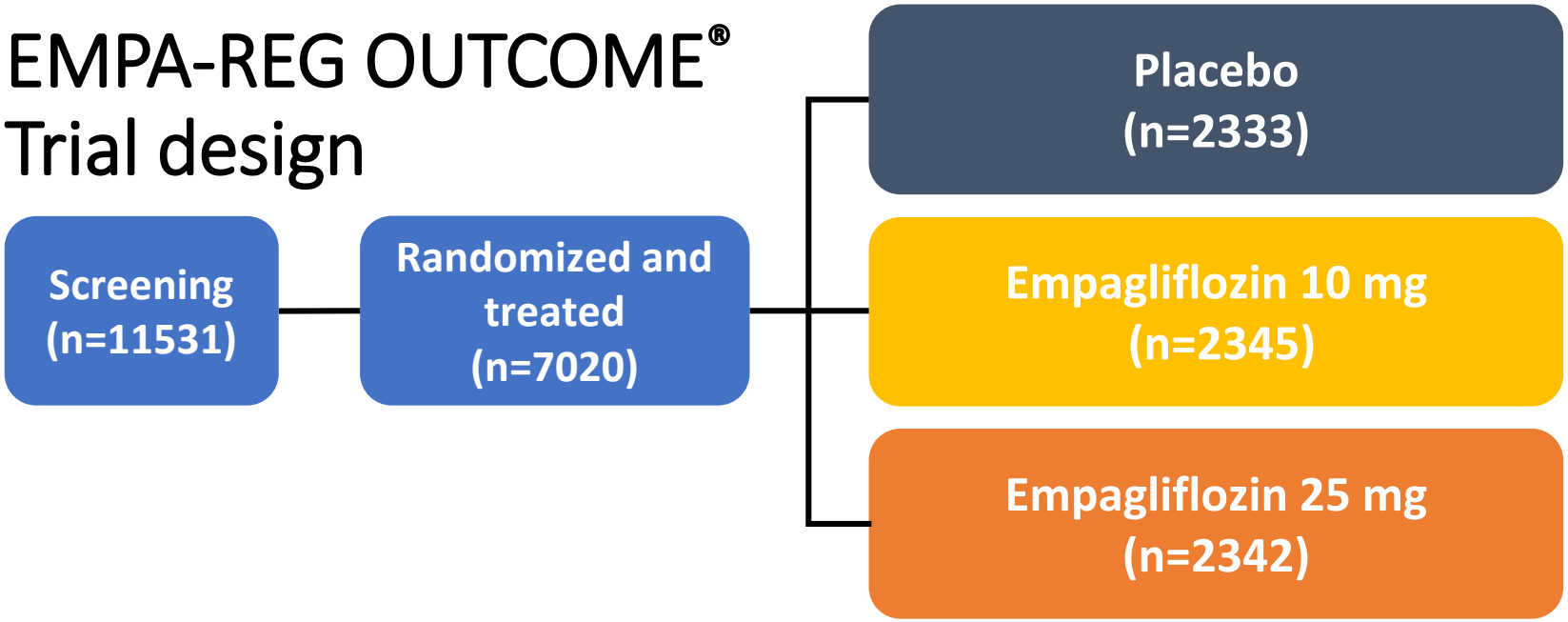
- Non-parsimonious propensity score developed in each country to estimate the likelihood of initiating an SGLT-2i
- Patients matched 1:1 by propensity score
- In the matched cohort:
  - Patients stratified by key-subgroups
  - Event rates for heart failure, all-cause death and composite were calculated
  - Cox proportional hazards models used to estimate the hazard ratios (HRs) and 95% confidence intervals (CI) for all outcomes, adjusted for baseline risk factors and treatments
- Meta-analysis used to pool hazard ratios from each country and obtain summary weighted point estimates

Patient population



Final study population

EMPA-REG OUTCOME® Trial design



- **Study medication was given in addition to standard of care.**
- **The trial was to continue until ≥ 691 patients experienced an adjudicated primary outcome event.**
- **Key inclusion criteria:**
  - Adults with type 2 diabetes and established CVD
  - BMI ≤45 kg/m^2; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m^2 (MDRD)

CV, cardiovascular; BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Zinman B et al. N Engl J Med 2015

Very stringent inclusion and exclusion criteria

Table 1 Key inclusion criteria

Insufficient glycemic control	High risk of cardiovascular events (≥1 of the following)
• ***Drug-naive subjects:*** HbA_{1c} ≥7.0% and ≤9.0% at screening	• History of myocardial infarction >2 months prior to informed consent
	• Evidence of multi-vessel CAD i.e. in ≥ 2 major coronary arteries or the left main coronary artery, documented by any of the following:
• ***Subjects on background therapy:*** HbA_{1c} ≥7.0% and ≤10.0% at screening	– Presence of significant stenosis: ≥50% luminal narrowing during angiography (coronary or multi-slice computed tomography)
	– Previous revascularization (percutaneous transluminal coronary angioplasty ± stent or coronary artery bypass graft >2 months prior to consent
	– The combination of revascularization in one major coronary artery and significant stenosis (≥50% luminal narrowing) in another major coronary artery
	• Evidence of single-vessel CAD, ≥50% luminal narrowing during angiography (coronary or multi-slice computed tomography) not subsequently successfully revascularized, with at least 1 of the following:
	– A positive non-invasive stress test for ischemia
	– Hospital discharge for unstable angina ≤12 months prior to consent
	• Unstable angina >2 months prior to consent with evidence of single- or multi-vessel CAD
	• History of stroke (ischemic or hemorrhagic) >2 months prior to consent
	• Occlusive peripheral artery disease documented by any of the following:
	– Limb angioplasty, stenting, or bypass surgery
	– Limb or foot amputation due to circulatory insufficiency
	– Evidence of significant peripheral artery stenosis (>50% on angiography, or >50% or hemodynamically significant via non-invasive methods) in 1 limb
	– Ankle brachial index <0.9 in ≥1 ankle

CAD, coronary artery disease.

Zinman et al. Cardiovascular Diabetology 2014

Here is the list for exclusion criteria

- Uncontrolled hyperglycemia with glucose >240 mg/dL (>13.3 mmol/L) after an overnight fast during placebo run-in and confirmed by a second measurement (not on the same day)
- Indication of liver disease, defined by serum levels of alanine amininotransferase, aspartate aminotransferase, or alkaline phosphatase above 3 x upper limit of normal (ULN) during screening or run-in phase
- Planned cardiac surgery or angioplasty within 3 months
- Estimated glomerular filtration rate <30 ml/min/1.73m^2 (according to the Modification of Diet in Renal Disease equation) at screening or during run-in phase
- Bariatric surgery within the past two years and other gastrointestinal surgeries that induce chronic malabsorption
- Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells e.g. malaria, babesiosis, hemolytic anemia)
- Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years
- Contraindications to background therapy according to the local label
- Treatment with anti-obesity drugs 3 months prior to informed consent or any other treatment at time of screening leading to unstable body weight (e.g. surgery, aggressive diet regimen, etc.)
- Treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent
- Any uncontrolled endocrine disorder except T2DM
- Pre-menopausal women (last menstruation ≤1 year prior to informed consent) who were nursing, pregnant, or of child-bearing potential and were not practicing an acceptable method of birth control, or did not plan to continue using this method throughout the study, or did not agree to submit to periodic pregnancy testing during the trial
  - Acceptable methods of birth control include tubal ligation, transdermal patch, intrauterine devices/systems, oral, implantable or injectable contraceptives, sexual abstinence, double barrier method, vasectomy of partner
- Alcohol or drug abuse within 3 months of informed consent that would interfere with trial participation or any ongoing condition leading to decreased compliance with study procedures or study drug intake
- Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial or participating in another trial involving an investigational drug and/or follow-up
- Any clinical condition that would jeopardize patient safety while participating in this clinical trial (in Canada, this included current genito-urinal infection or genito-urinal infection within 2 weeks prior to informed consent)
- Acute coronary syndrome, stroke, or transient ischemic attack within 2 months prior to informed consent
- In South Africa: blood pressure >160/100 mmHg at screening

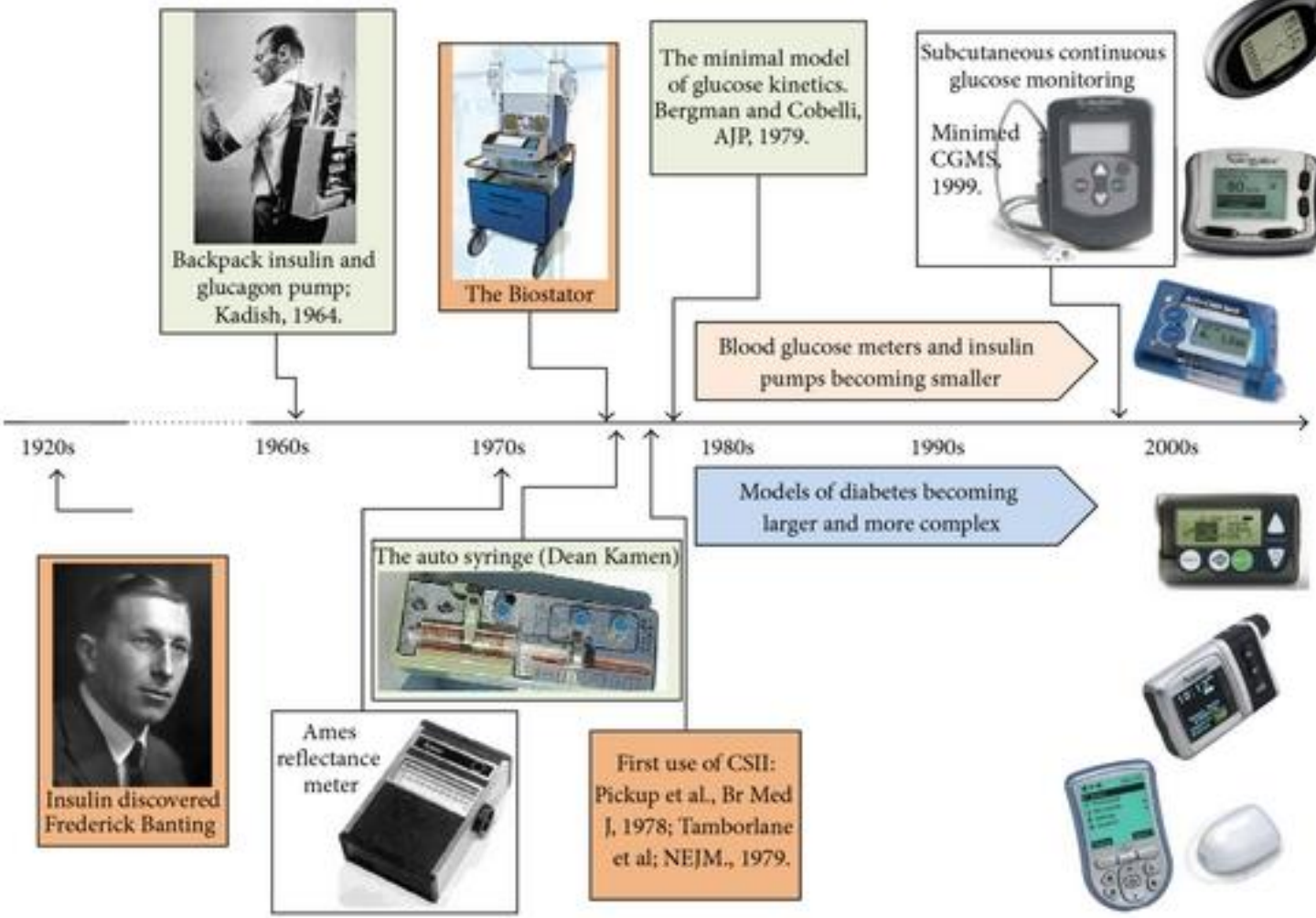
Be alert

- Too much information
- Understanding the strength and limitations of the evidence

Glucose monitoring

- It wasn't that long ago that home blood glucose monitoring wasn't possible for people with diabetes. The first forays into potential home meters began in the late '60s and early '70s, but these machines were very complex beasts that required multistep sequences to obtain a reading that only yielded a very approximate range. In the case of the first "Ames" meter, the user had to match a strip to a color chart, but only after applying a droplet of blood, waiting a precise 50 seconds, then washing off the blood droplet with warm water. There was also a multistep process for preparing the strip before that droplet of blood was applied.

What else do we have?



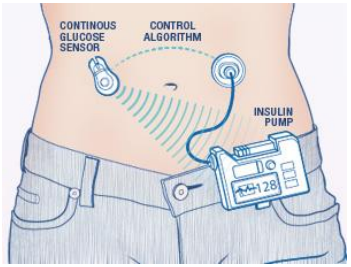
Google Smart Contact Lens

Google and Novartis partner to develop a smart contact lens to monitor diabetic blood sugar via glucose in tears









The Dermal Abyss

- The idea is to incorporate biosensors in the skin
- Reading and picking up biomarkers from the body's interstitial fluid
- The ink turns from green into brown when blood glucose levels increases.
- Pilot trial by the UCSD School of Medicine, enrolling 50 adults aged 18 to 75 years with T1, T2, or other causes DM into the ENGAGE pilot clinical trial
- Scheduled to conclude in June 2019.
- To go beyond wearables in future

What happened to this?

- Originally projected to be on the market by 2020, excitement about the contact lens to measure glucose levels from Novartis and Google has waned. Why?

From the commentators

- Tears have proved not as reliable in measuring glucose
- Prone to be impacted by external variables such as the surrounding environment, temperature and humidity

Old friend revisited

- Your old friend is
  - Not as simple as you think (Novel classification)
  - Getting more and more demanding (glycaemic control and beyond)
  - Puzzling you with different pieces of information (RCT vs big data RWE)
  - Getting more addicted to technology advances (The fancy new glucose monitoring machines)