Type 2 diabetes
& Cardiovascular disease
update

Barcelona, March 15th 2018

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Disclosures

Consultant:
AstraZeneca, Boehringer Ingelheim, Lilly, Novartis, Novo Nordisk and Sanofi.

Research Support:
AstraZeneca, Novartis.

Speaker's Bureau:
AstraZeneca, Boehringer Ingelheim, Lilly, Novartis, Novo Nordisk and Sanofi.

Agenda

- Diabetes and CV disease
- Intervention trials and CV benefits
- Cardiovascular outcome trials (CVOTs)
- Beneficial/Neutral/Harmful
- Recommendations update
- Take home messages

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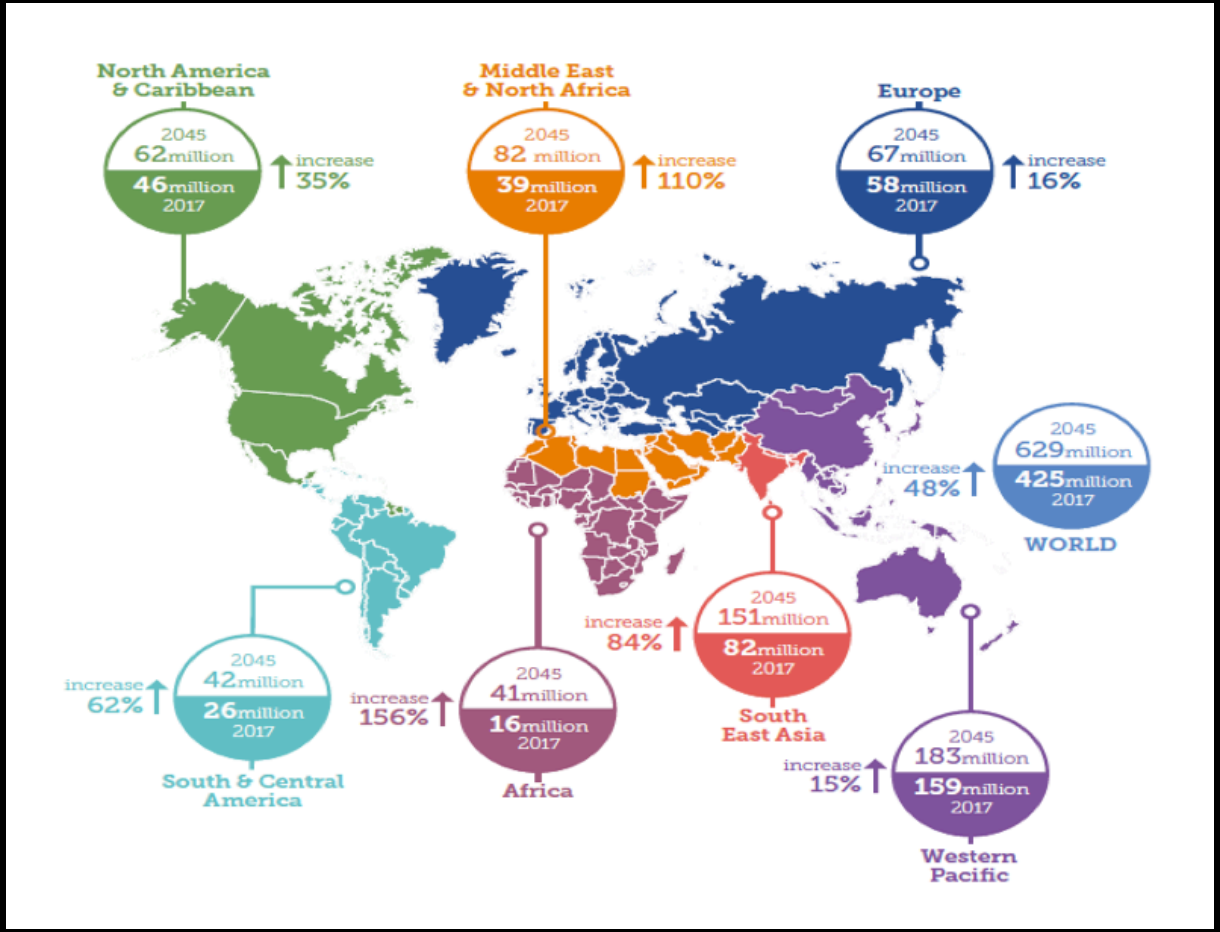
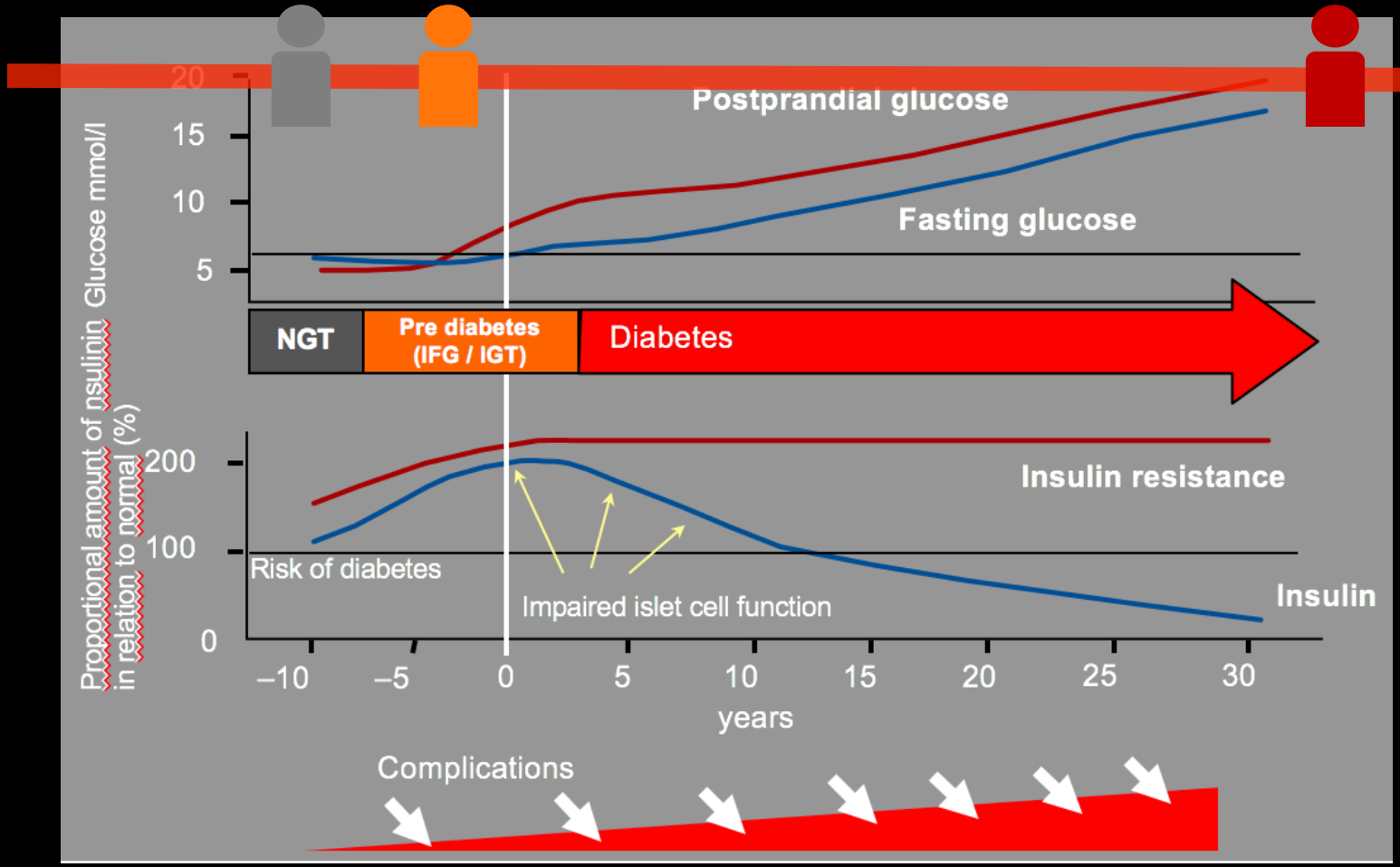


IDF Atlas 2017

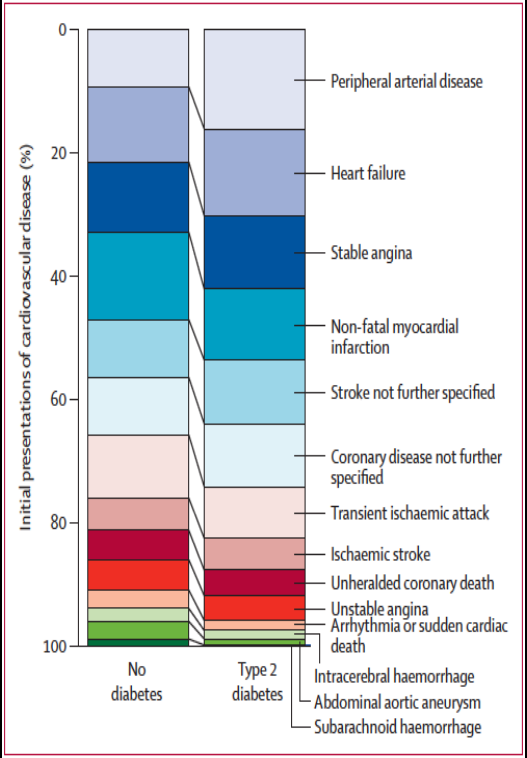
Type 2 diabetes & Cardiovascular disease



Adapted from International Diabetes Center. Type 2 Diabetes BASICS. Minneapolis, Minn: International Diabetes Center; 2000.

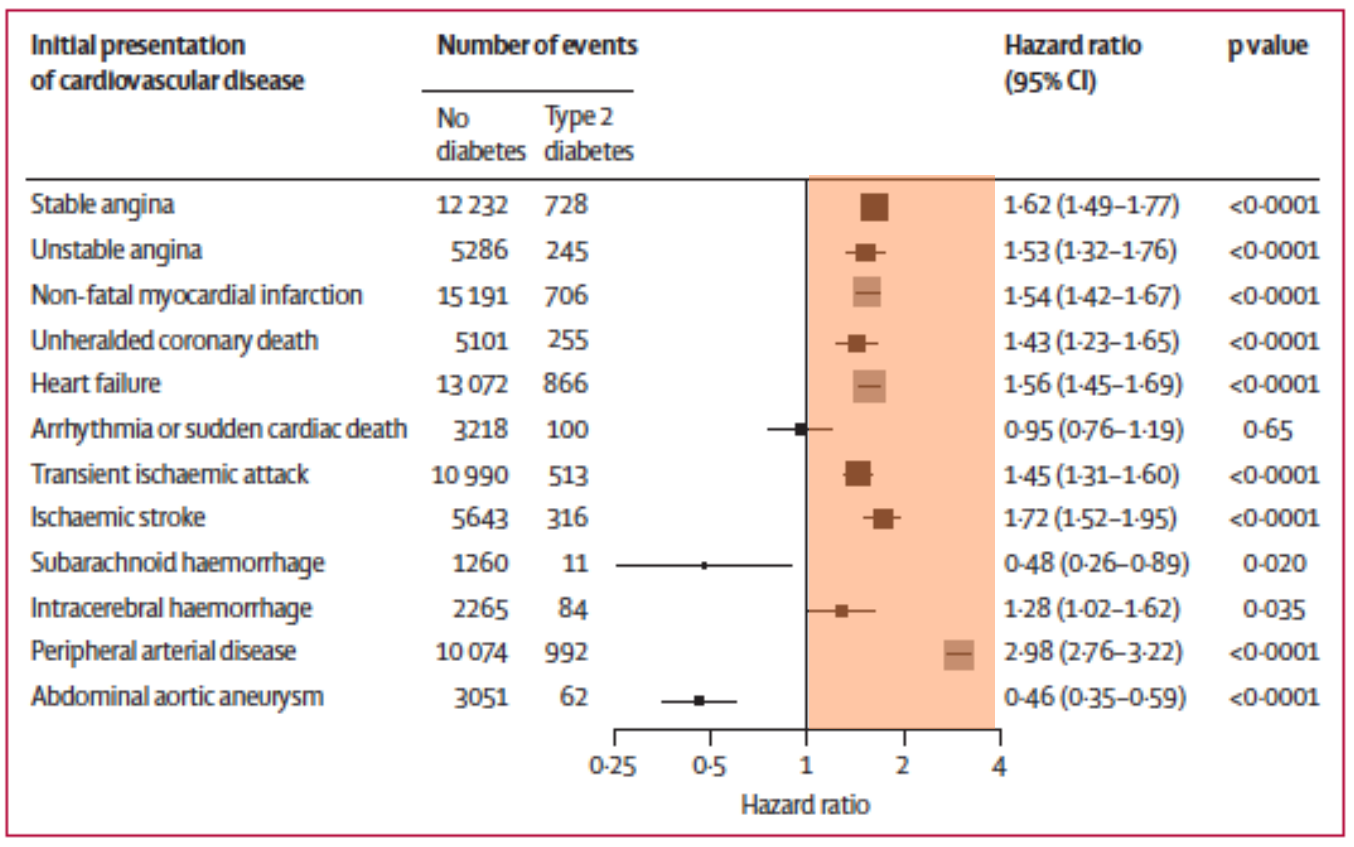
CVD difference between T2DM and non T2DM

Cohort follow up (5.5 years) 34.198 T2DM 1.887.062 general population



Shah, AD. Lancet Diabetes Endocrinol. 2015; 3: 105–13

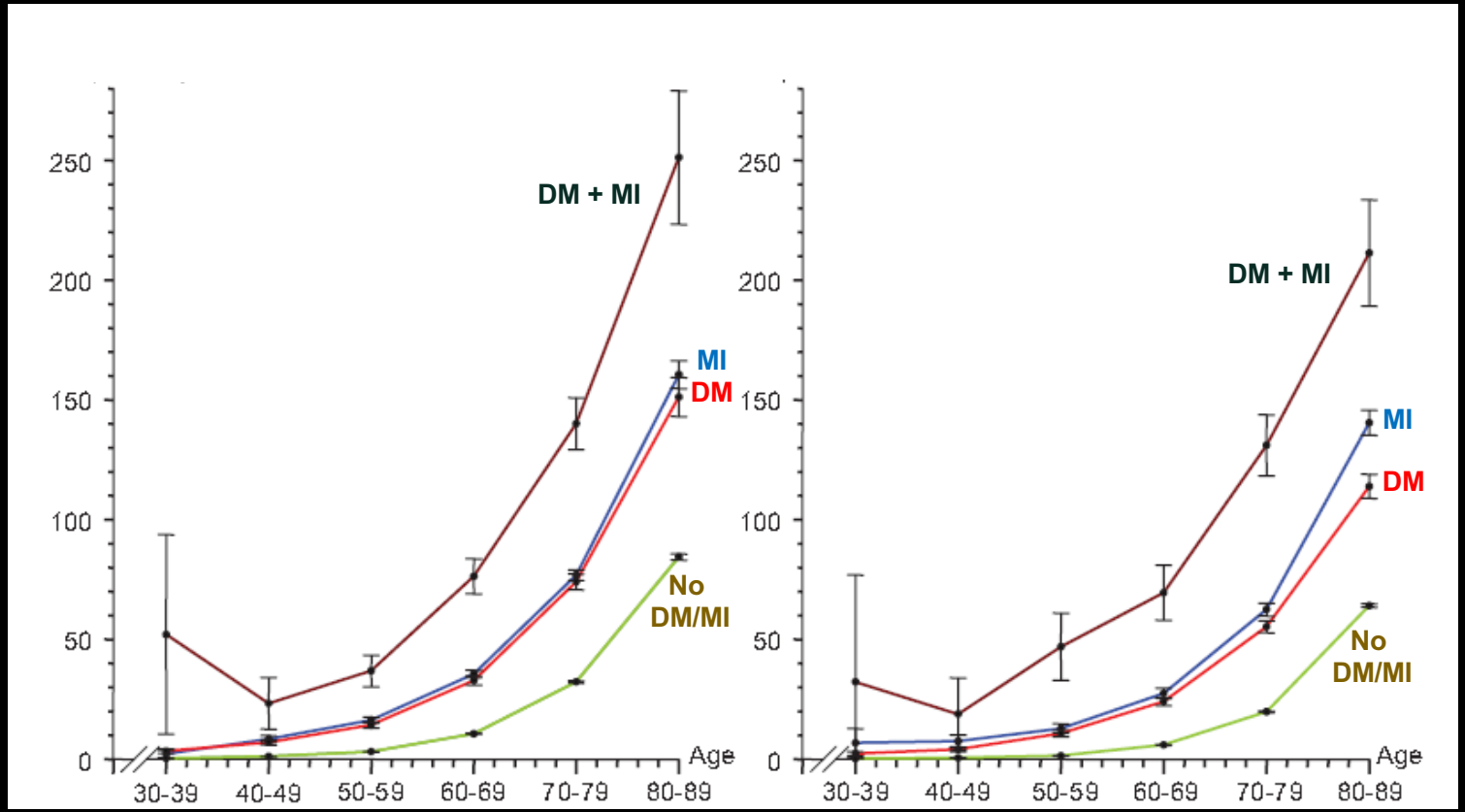
CVD difference between T2DM and non T2DM



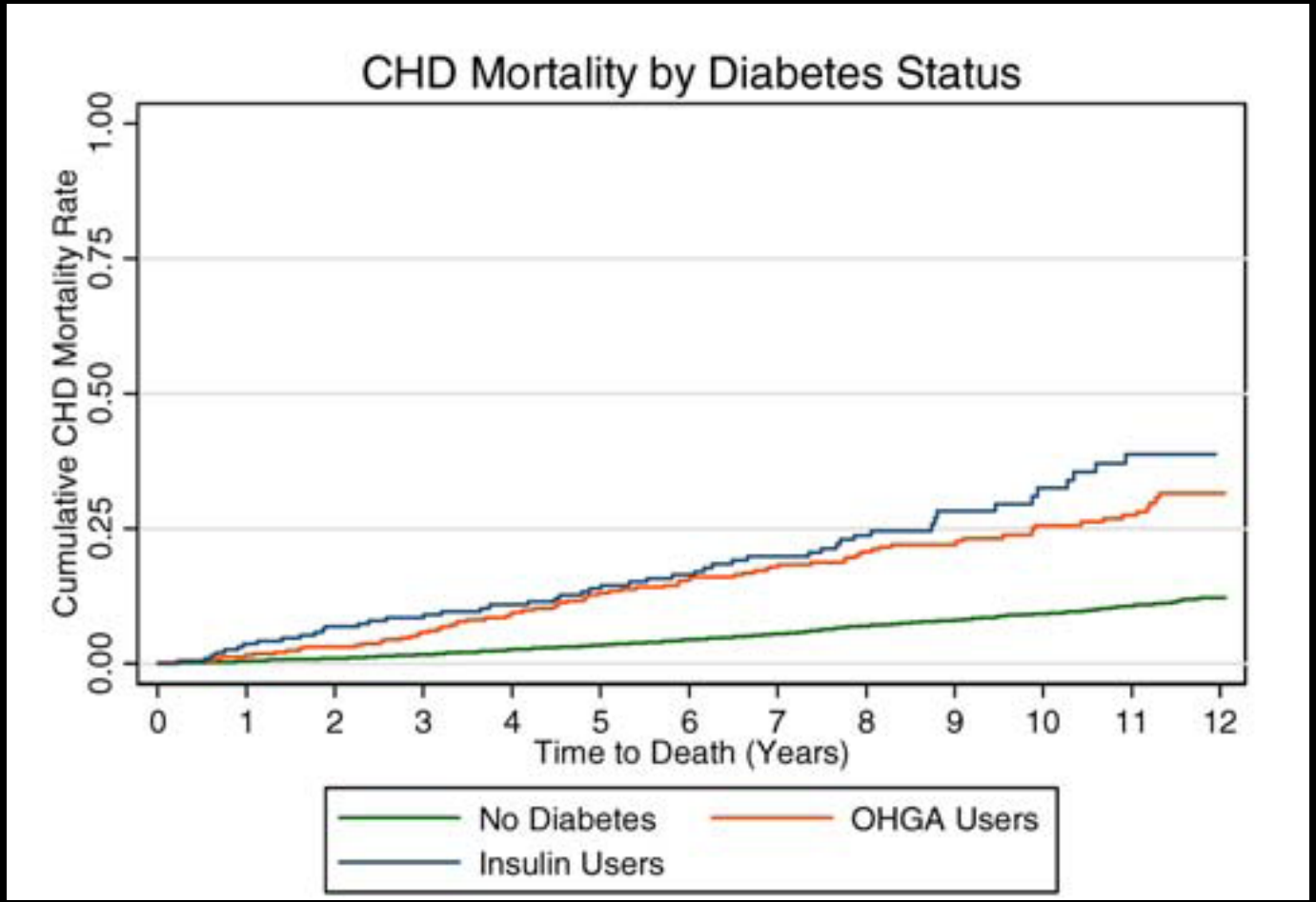
Initial presentation of cardiovascular disease	Number of events: No diabetes	Number of events: Type 2 diabetes	Hazard ratio (95% CI)	p value
Stable angina	12 232	728	1·62 (1·49–1·77)	<0·0001
Unstable angina	5286	245	1·53 (1·32–1·76)	<0·0001
Non-fatal myocardial infarction	15 191	706	1·54 (1·42–1·67)	<0·0001
Unheralded coronary death	5101	255	1·43 (1·23–1·65)	<0·0001
Heart failure	13 072	866	1·56 (1·45–1·69)	<0·0001
Arrhythmia or sudden cardiac death	3218	100	0·95 (0·76–1·19)	0·65
Transient ischaemic attack	10 990	513	1·45 (1·31–1·60)	<0·0001
Ischaemic stroke	5643	316	1·72 (1·52–1·95)	<0·0001
Subarachnoid haemorrhage	1260	11	0·48 (0·26–0·89)	0·020
Intracerebral haemorrhage	2265	84	1·28 (1·02–1·62)	0·035
Peripheral arterial disease	10 074	992	2·98 (2·76–3·22)	<0·0001
Abdominal aortic aneurysm	3051	62	0·46 (0·35–0·59)	<0·0001

Shah, AD. Lancet Diabetes Endocrinol. 2015; 3: 105–13

Diabetes as a CV mortality risk factor



Schramm et al, Circulation, 2008



Kronmal i wsp., PLoS Med., 2006; 3 (10): e400

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↓HbA1c

↓HbA1c

T1DM **DCCT**

T2DM **UKPDS**

Mixed results on tight and rapid HbA1c control

Study	HbA1c (%)		Impact of intensive therapy vs standard therapy on outcome		
	Standard therapy	Intensive therapy	Microvascular	CVD	Mortality
ACCORD	7.5	6.4	?	↔	↑
ADVANCE	7.3	6.5	↓	↔	↔
VADT	8.4	6.9	↔	↔	↔
UKPDS	7.9	7.0	↓	↔	↔
UKPDS – follow-up	~7.9	~7.9	↓	↓*	↓

* Reduction in myocardial infarction

ACCORD Study Group. *N Engl J Med* 2008;358:2545-2559;
ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560-2572;
Duckworth W, *et al. N Engl J Med* 2009;360:129-139;
UKPDS. *Lancet* 1998;352:837-853;
Holman RR, *et al. N Engl J Med* 2008;359:1577-1589.

Legacy effect: Early glycaemic control is key to long-term reduction in complications

Good legacy effect

Early, strict glycaemic control brings benefits, reducing the long-term risk of microvascular and macrovascular complications (UKPDS[1])

Bad legacy effect

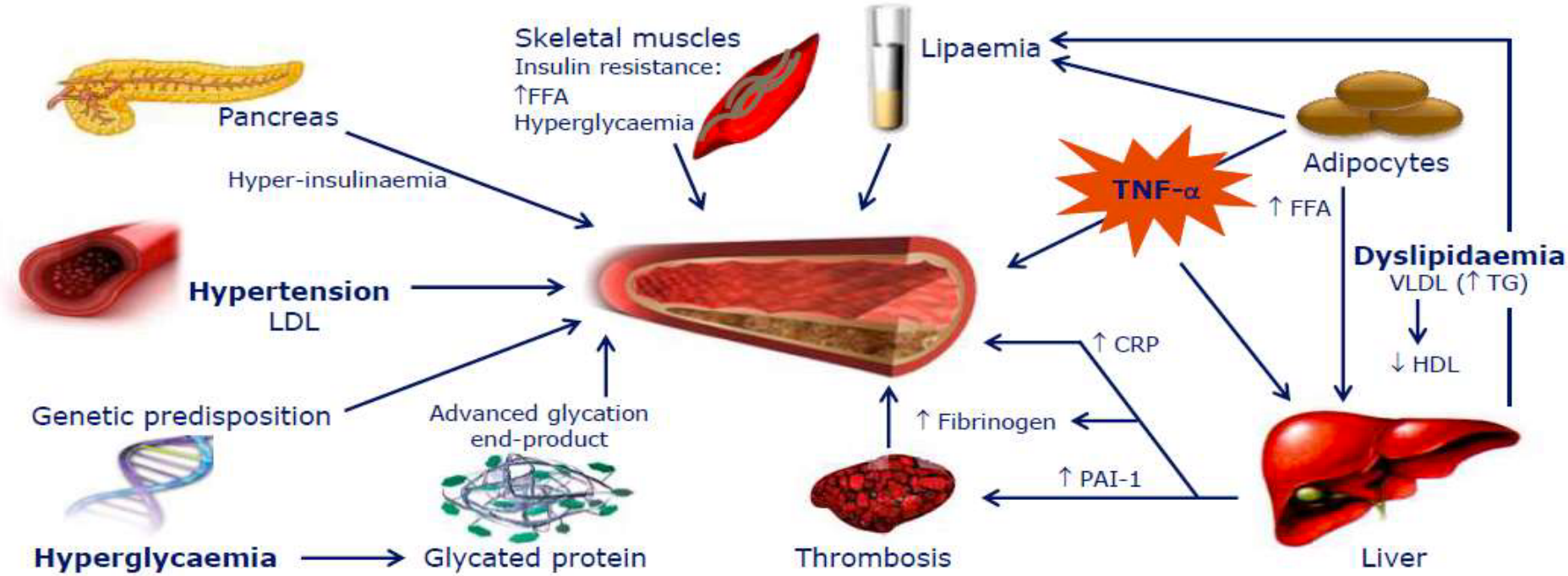
Achieving glycaemic control late in the disease, after a **prolonged period of poor control**, does not improve long-term risk of macrovascular complications[2]

Long-standing, preceding hyperglycaemia accounted for the high rate of complications at baseline in VADT[3]

UKPDS=UK Prospective Diabetes Study; VADT=Veterans Affairs Diabetes Trial.

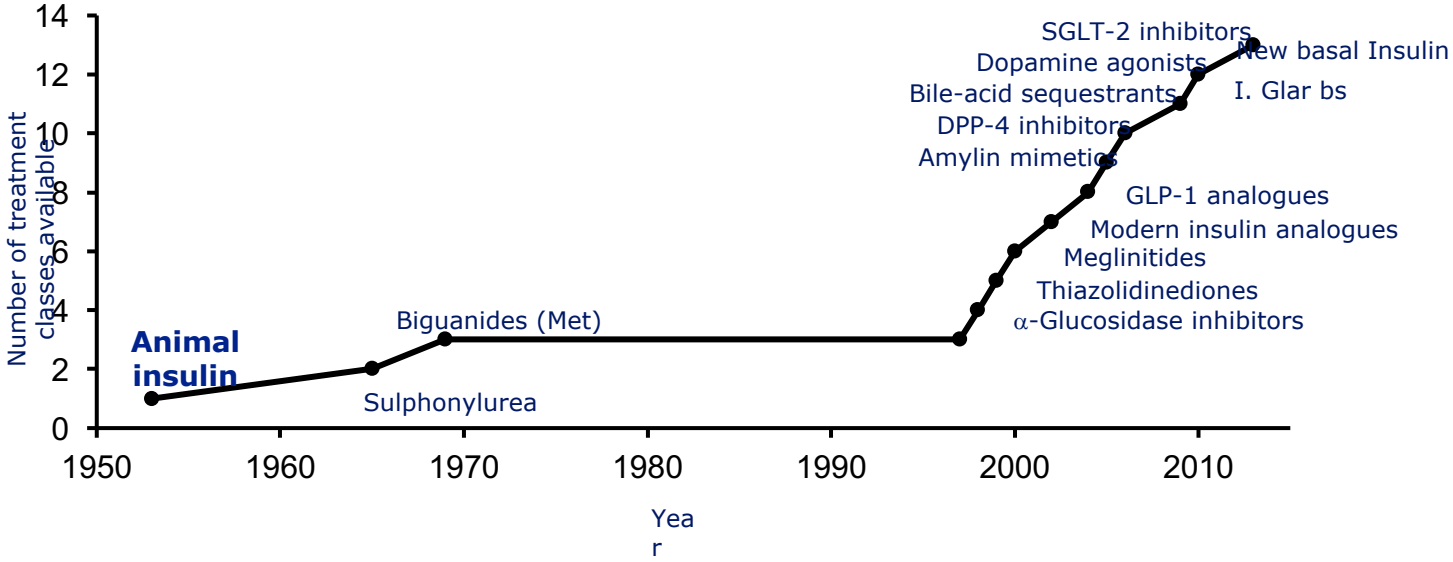
[1]Holman RR, et al. *N Engl J Med*. 2008; 359: 1577–1589.
[2]Duckworth W, et al. *N Engl J Med*. 2009; 360: 129–139;
[3]Del Prato S. *Diabetologia*. 2009; 52: 1219–1226.

Many factors contribute to increased CV risk in T2DM



CRP, C-reactive peptide; CV, cardiovascular; FFA, free fatty acid; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; T2DM, type 2 diabetes mellitus; TG, triglyceride; TNF-α, tumour necrosis factor-α; VLDL, very low-density lipoprotein.
Libby P, Plutzky J. *Circulation* 2002;106:2760–2763.

History of diabetes therapy

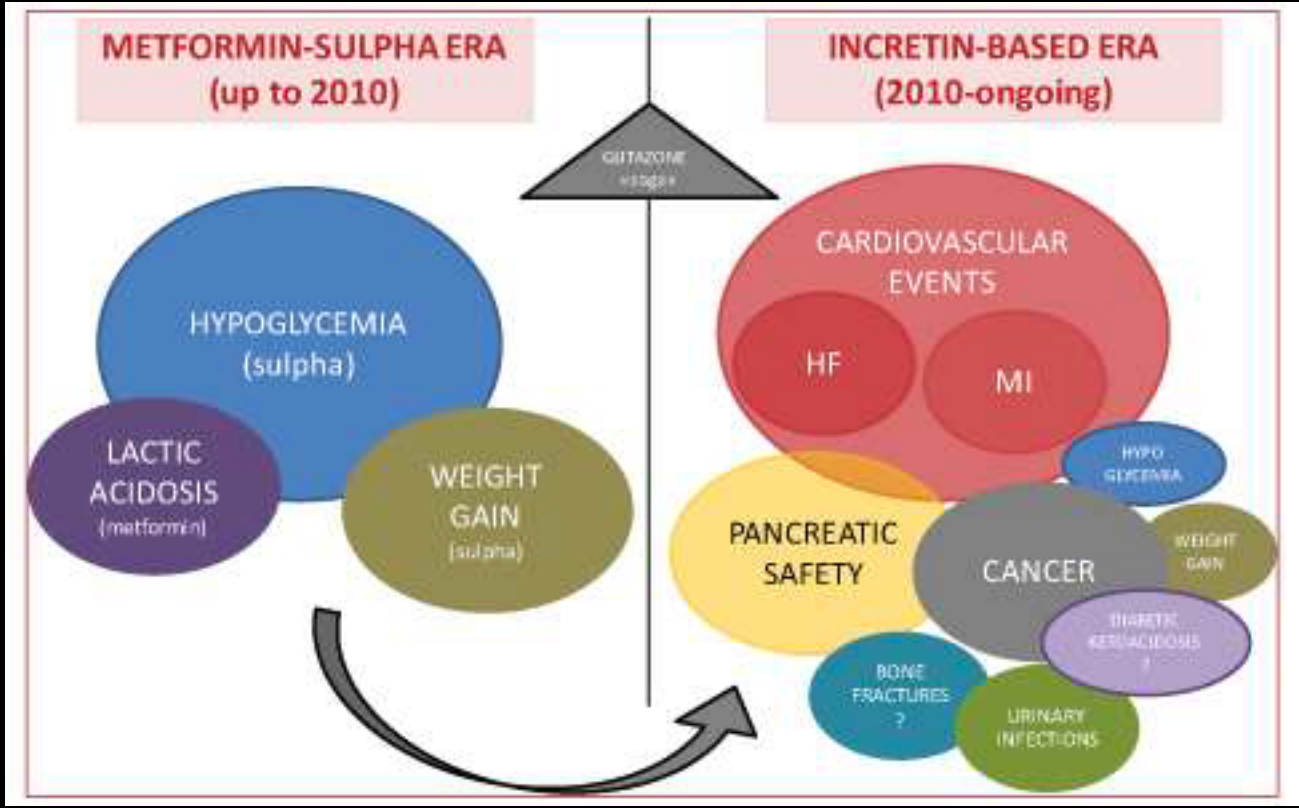


DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose co-transporter-2
White JR, *Diabetes Spectrum* 2014; doi: 10.2337/diaspect.27.2.82.

Characteristics of the ‘ideal’ drug for type 2 diabetes

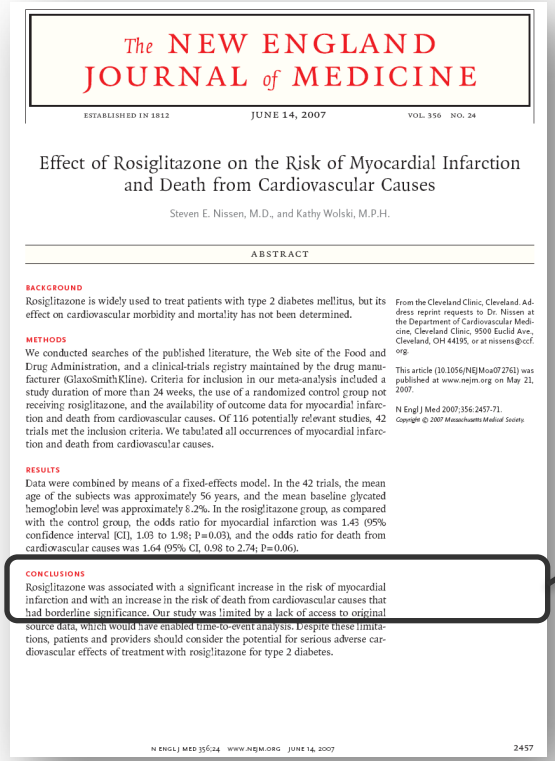
- Safe
- Efficacious
- Durable control
- Well-tolerated
- Low risk of hypoglycaemia
- Weight neutral or weight loss
- Reduction of long term complications

Garber AJ et al. *Endocr Pract* 2013; **19:** 327–36.
Inzucchi SE et al. *Diabetes Care* 2012; **35:** 1364–79.



Type 2 diabetes & Cardiovascular disease

The rosiglitazone issue



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

This article (10.1056/NEJMoa072761) was published at www.nejm.org on May 21, 2007.

N Engl J Med 2007;356:2457-71.

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N ENGL J MED 356;24 WWW.NEJM.ORG JUNE 14, 2007 2457

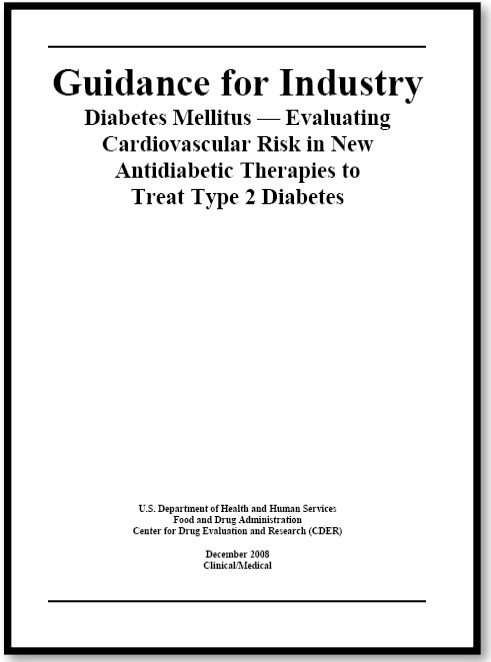
"Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance."

Nissen SE et al. N Engl J Med 2007;156:2457–2471.

Cardiovascular safety in old and new drugs **type 2 diabetes** management

FDA guidance for industry

- In December 2008, the US FDA issued guidance to industry for evaluating CV safety in diabetes drugs
- Industry should demonstrate that new therapy will not result in an unacceptable increase in CV risk
  - The upper bound of the two-sided 95% CI of the risk ratio should be <1.8


Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

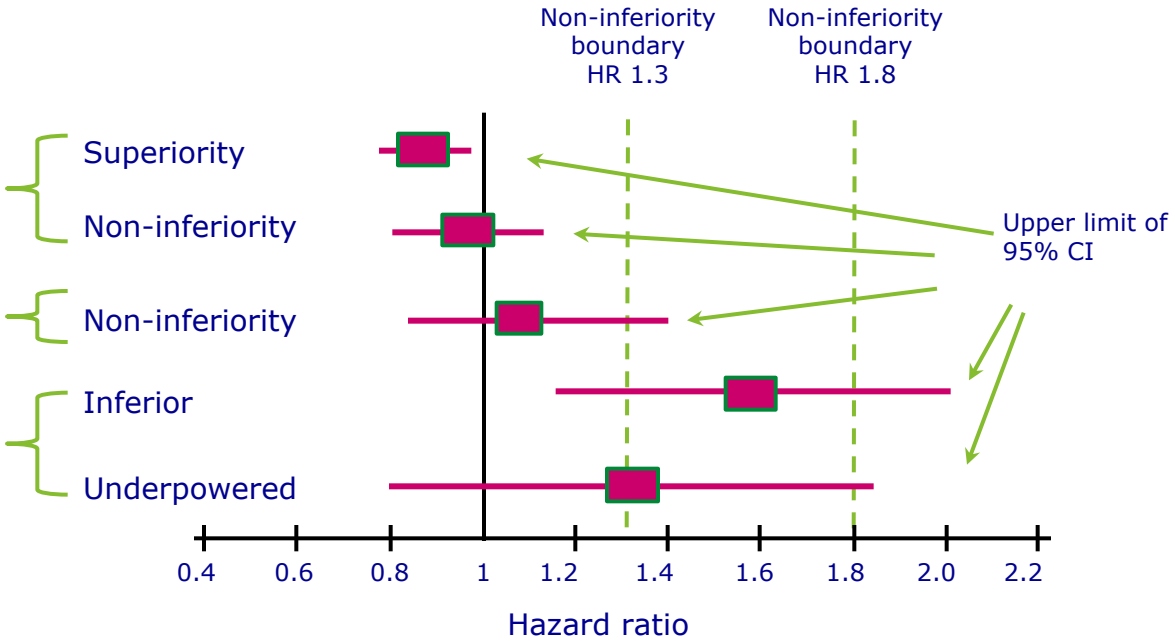
CI, confidence interval; CV, cardiovascular; FDA, Food and Drug Administration.
FDA. Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf.

FDA criteria for requirement of a postmarketing CV outcomes trial

Approvable: no need for postmarketing study

Approvable: need for postmarketing study

Not approvable



Hirshberg B, Raz I. *Diabetes Obes Metab* 2011;34(Suppl. 2):S101–S106.

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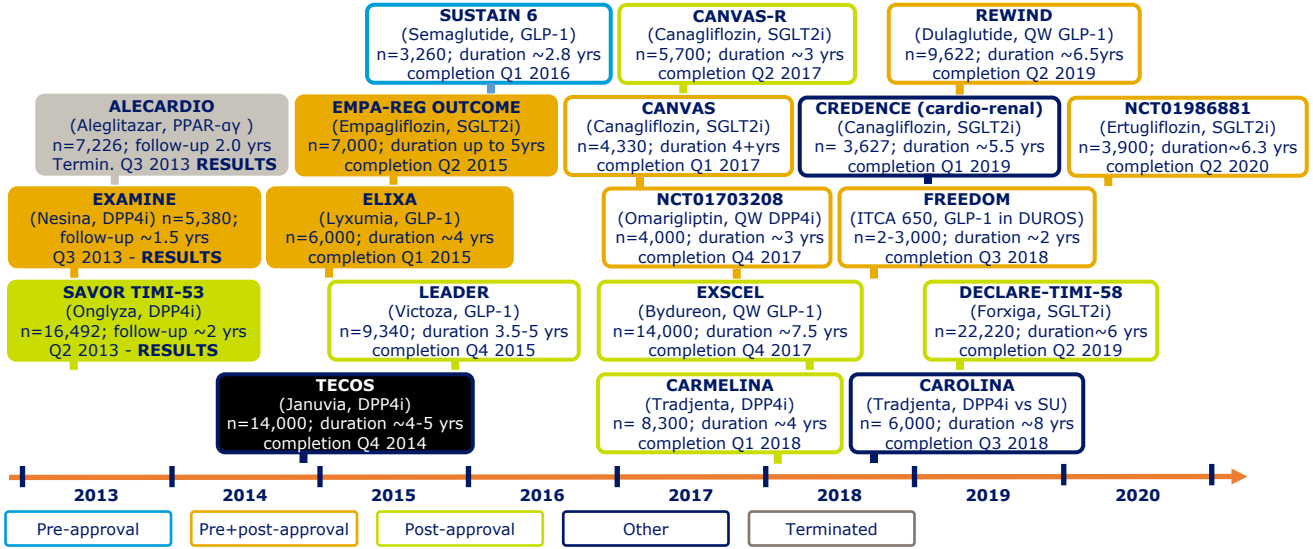
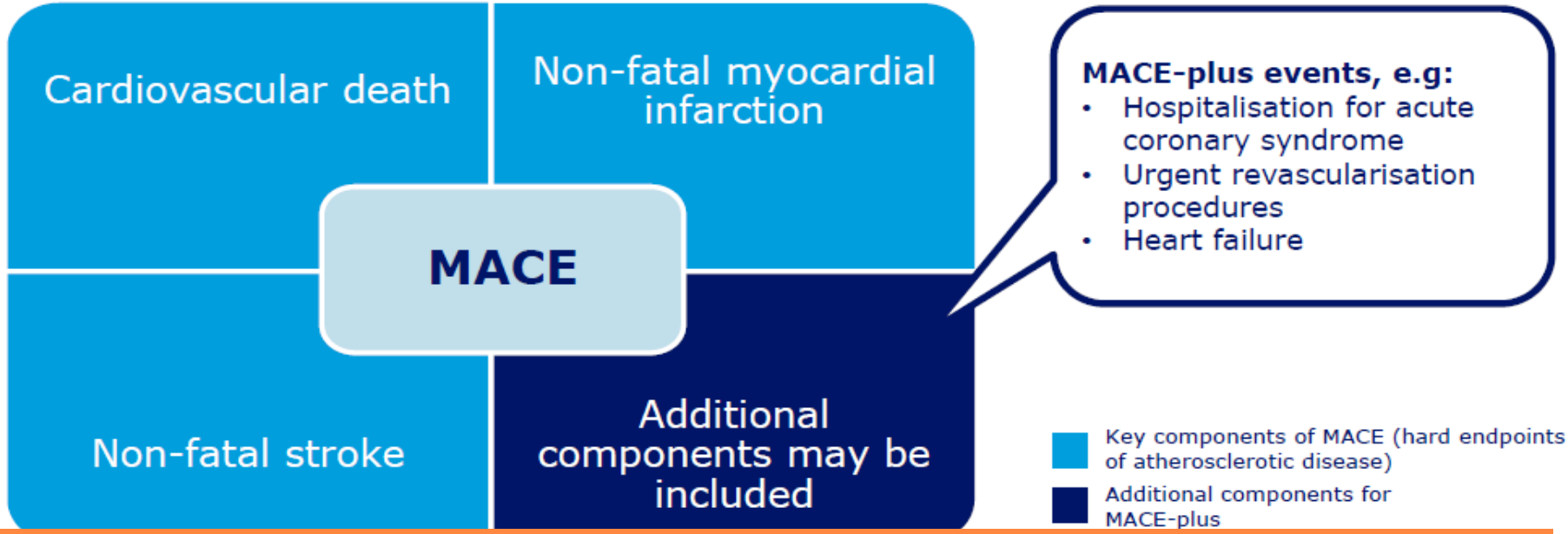
Cardiovascular outcomes trials within diabetes



Source: ClinicalTrials.gov (April 2014). 'Completion date' is the estimated completion date for the primary outcomes measure
CVOT, cardiovascular outcomes trial; DPP4i; dipeptidyl peptidase 4 inhibitor; GLP-1, glucagon-like peptide 1; SU, sulphonylurea
McMurray JJ et al, *Lancet Diabetes Endocrinol* 2014;2:843–51

What are Major Adverse Cardiovascular Events?



3-P MACE: 3 - point major adverse cardiac events (composite of cardiovascular death, nonfatal stroke and nonfatal myocardial infarction)

4-P MACE: Composite of 3-P MACE plus unstable angina, ACS, hospitalization for HF.

	SITAGLIPTINA (JANUVIA., JANUMET., EFFICIB.)	VILDAGLIPTINA (GALVUS., EUCREAS.)	LINAGLIPTINA (TRAJENTA., JENTADUETTO.)	LINAGLIPTINA (TRAJENTA., JENTADUETTO.)	SAXAGLIPTINA (ONGLIZA., KOMBOGLIZE.)	ALOGLIPTINA (VIPIDIA., INCRESYNC.)
Study	TECOS	N/A	CAROLINA (VS GLIMEPIRIDA)	CARMELINA	SAVOR-TIMI	EXAMINE
Patients	14735	N/A	6000	8300	16492	5380
Status	ended	N/A	On going (Set.2018)	On going (Jan 2018)	ended	ended
Duration (years)	3	N/A			2,1	1,5
Primary End point	4P MACE 0.98 (0.88–1.09)	N/A	4P MACE	4P MACE	3P MACE 1.00 (0.89–1.12)	3P MACE 0.96 (0.80–1.16)
Secondary endpoint	N/A	MACE increased	MACE increased Lab changes	MACE 3P RENAL	MACE increased	MACE increased
Results	Neutral in CVR	Metanalysis 17446: Neutral CVR no diferences vs placebo			**Neutral CVR no diferences vs placebo; Inferiority in HF vs placebo**	

3P MACE: major cardiac adverse events ; 3P-MACE (CV mortality, non fatal MI , Non fatal Stroke) 4P-MACE (3P+hospitalization. Inestable angina); 3P RENAL: Kidney death, Renal terminal disease, dism. 50% GF

https://clinicaltrials.gov

	EXENATIDE BID (BYETTA.)	LIXISENATIDE (LYXXUMIA.)	LIRAGLUTIDE (VICTOZA.)	SEMAGLUTIDE	EXENATIDE QW (BYDUREON.)	DULAGLUTIDE (TRULICITY.)	ALBIGLUTIDE (EPERZAN.)
Study	N/A	ELIXA	LEADER	SUSTAIN-6	EXSCEL	REWIND	HARMONY OUTCOMES
Patients	N/A	N=6068	N=9340	N=3299	N~14000	N=9622	N=9400
Status	N/A	Ended (June 2015)	Ended (Nov 2015)	Ended (Jan 2016)	On going (Apr 2018)	On going (Jul 2018)	On going (May 2019)
Duration (years)	N/A	5	3,5-5	2	>7,5	1,5	
Primary End point	N/A	4P-MACE 1.02 (0.89–1.17)	4P MACE	4P MACE	3P MACE 1.00 (0.89–1.12)	3P MACE 0.96 (0.80–1.16)	
Secondary endpoint	N/A	MACE increased	MACE increased	MACE increased	MACE increased	MACE increased	MACE increased
Results	MA showed CVR reduccion compared with other OA	Neutral CVR no diferences vs placebo	Significant reduction of CV events	Significant reduction of CV events	Neutral CVR no diferences vs placebo	On going	On going

3P MACE: major cardiac adverse events ; 3P-MACE (CV mortality, non fatal MI , Non fatal Stroke) 4P-MACE (3P+hospitalization. Inestable angina); 3P RENAL: Kidney death, Renal terminal disease, dism. 50% GF

https://clinicaltrials.gov

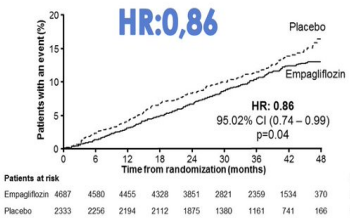
	EMPAGLIFLOZINA (JARDIANCE, SYNJARDY)	CANAGLIFLOZINA	CANAGLIFLOZINA	CANAGLIFLOZINA	DAPAGLIFLOZIN	ERTUGLIFLOZINA
Study	EMPA-REG OUTCOME	CANVAS	CANVAS-R	CREDENCE	DECLARE-TIMI 58	CVOT
Patients	N=7034	N=4339	N=5700	N=3627	N=17150	N=3900
Status	Ended	On going (Apri 2017)	On going (2017)	On going (2019)	On going (2019)	On going (2021)
Duration (years)	3	6-7	3	4	4-5	5-7
Primary End point	3P-MACE 0.86 (0.74–0.99)	3P-MACE	Albuminuria progression		3P-MACE	4P-MACE
Secondary endpoint	4P-MACE	Albuminuria progesion Basal insulin secretion	Changes in eGFR Albuminuria regresion	4P-MACE +HF	4P-MACE+HF+ revascularitz acio	4P-MACE
Results	Significative reduction of CV	Significative reduction of CV	Improvement in Primary end point	On going	On going	On going

EMPA-REG OUTCOME®

39

por 3 años

↓14% MACE[3]



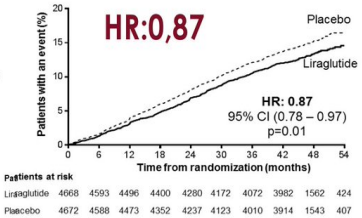
LEADER®

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

66

por 3 años

↓13% MACE[3]



Semaglutide sc once-weekly

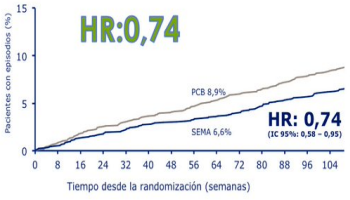
SUSTAIN 6

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

45

Por 2 años

↓26% MACE[3]

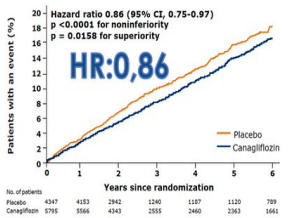


CANVAS Program

44

Por 5 años

↓14% MACE[3]



Safety between GLP-1ra and SGLT2 inh (review)

Aim

Review published data on overall **safety** (hypoglycemia and diabetic ketoacidosis) as well as on **potential adverse effects** on the **CV**, **genitourinary** and **gastrointestinal systems**, on the **pancreas** itself, and on **amputations**.

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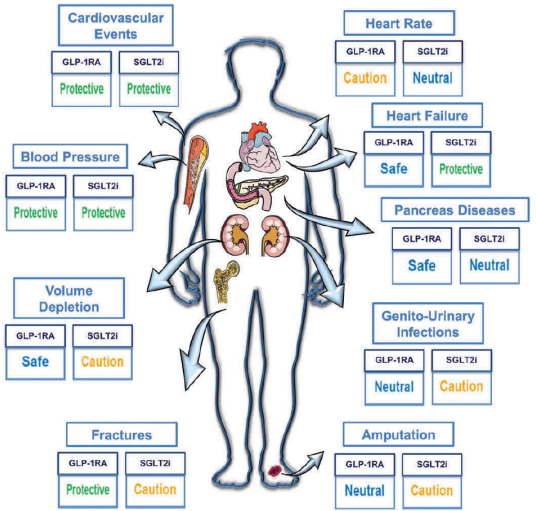
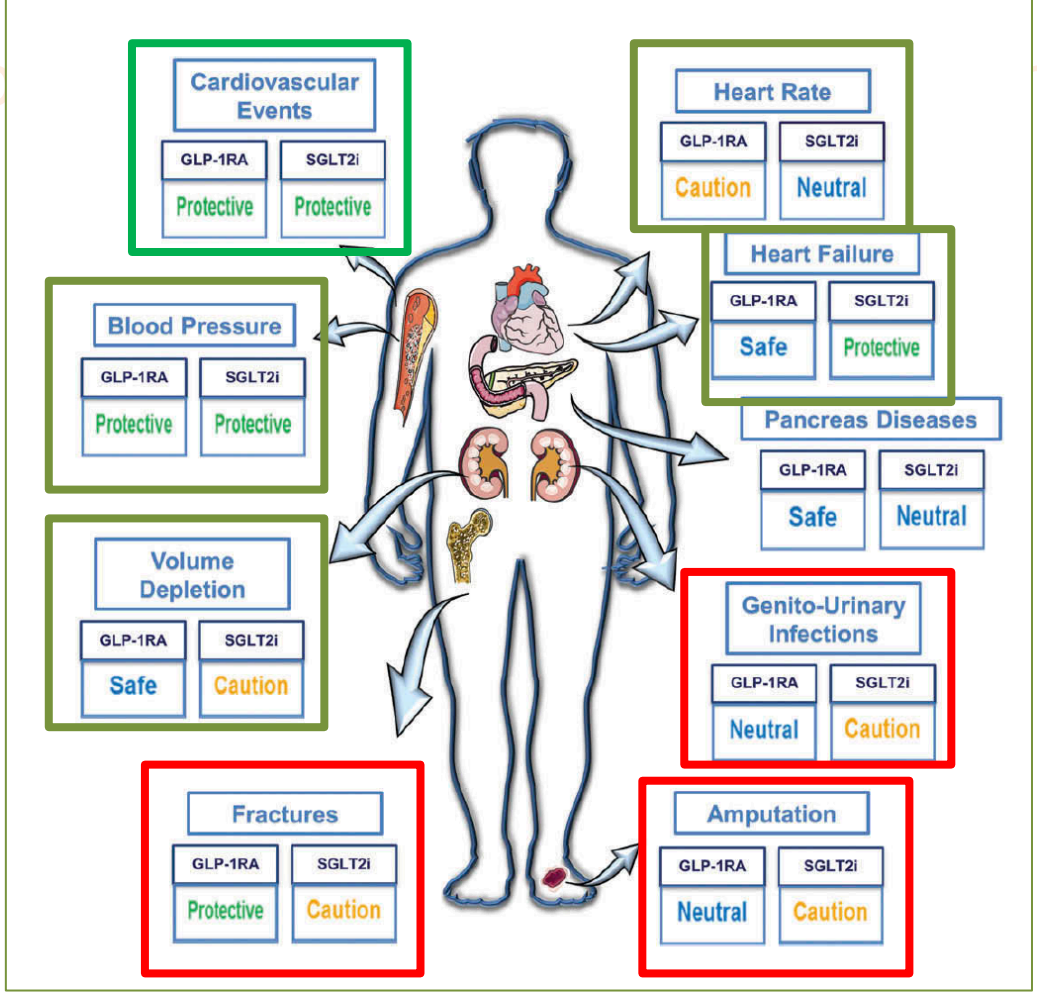


EXPERT OPINION ON DRUG SAFETY, 2018 VOL. 17, NO. 3, 293–302



EXPERT OPINION ON DRUG SAFETY, 2018 VOL. 17, NO. 3, 293–302

Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus

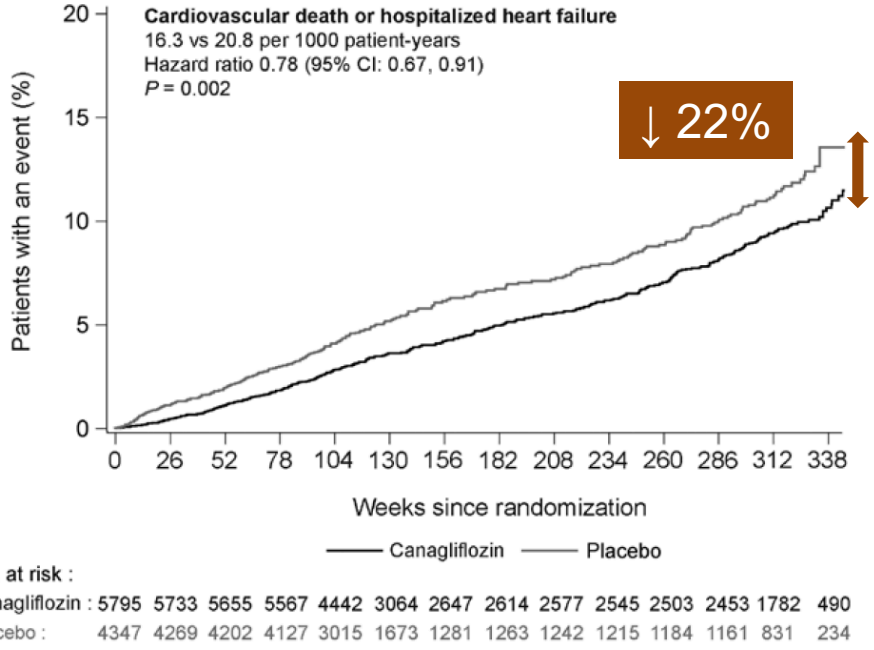
Aim

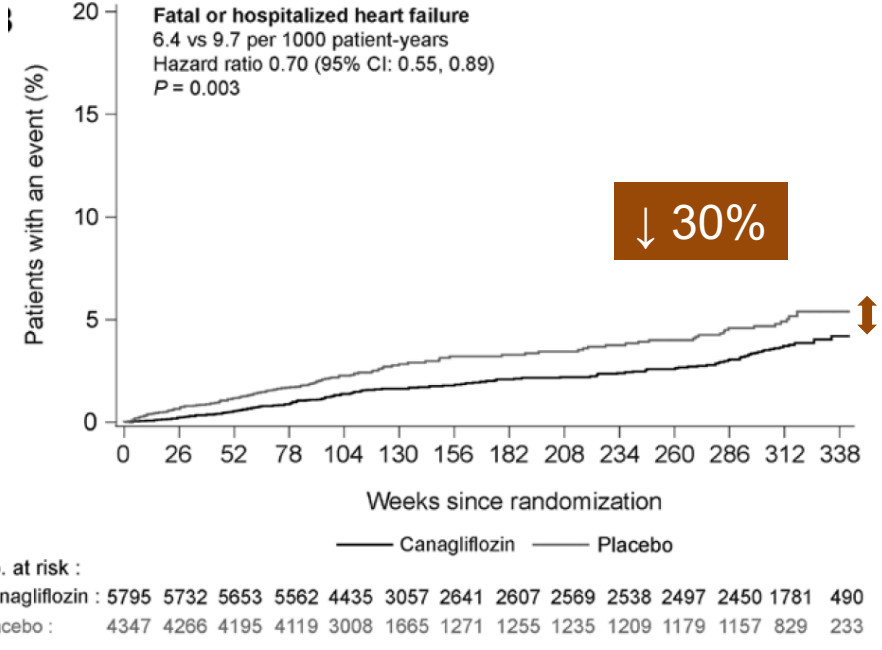
To assess the effects of canagliflozin on a range of efficacy and safety outcomes among CANVAS Program participants with and without a history of heart failure at baseline.

Circulation. 2018;137:00–00. DOI: 10.1161/CIRCULATIONAHA.118.034222

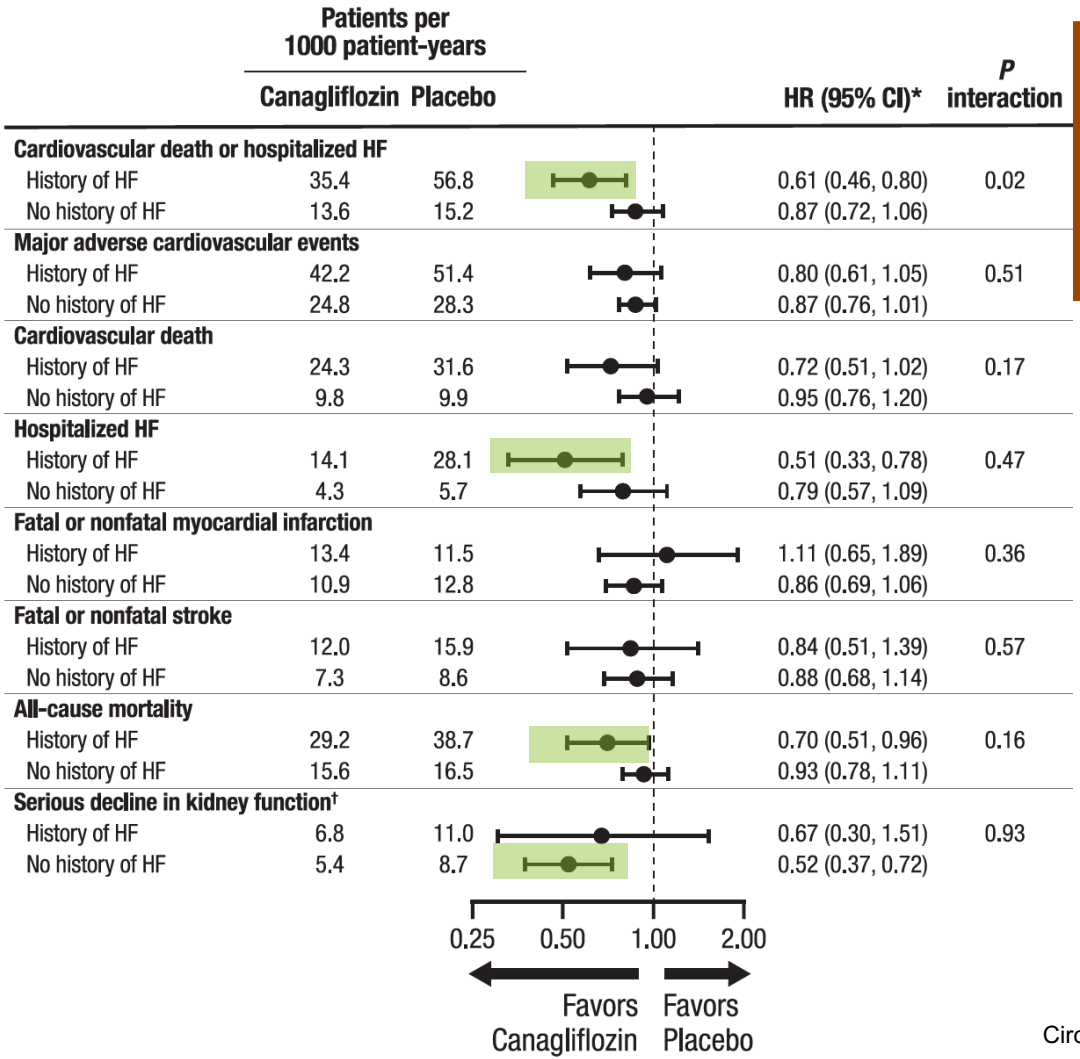
Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus

Effects of canagliflozin on heart failure outcomes





Circulation. 2018;137:00–00. DOI: 10.1161/CIRCULATIONAHA.118.034222



Proportional and absolute effects of canagliflozin compared with placebo on cardiovascular and renal outcomes in patients with and without a history of heart failure at baseline.

Circulation. 2018;137:00–00. DOI: 10.1161/CIRCULATIONAHA.118.034222

Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus

Conclusion

1. In patients with type 2 diabetes mellitus and an elevated risk of cardiovascular disease, canagliflozin reduced the risk of cardiovascular death or hospitalized heart failure across a broad range of different patient subgroups.

2. Benefits may be greater in those with a history of heart failure at baseline.

Circulation. 2018;137:00–00. DOI: 10.1161/CIRCULATIONAHA.118.034222

Glucose-Lowering Therapies and **Heart Failure** in Type 2 Diabetes Mellitus

Improves Overall Cardiovascular and HF Outcomes	Improves Overall Cardiovascular Outcomes but Not HF outcomes	No Effect on Overall Cardiovascular or HF Outcomes	No Effect on Overall Cardiovascular Outcomes But Potential HF Harm

Vijayakumar et al Circulation. 2018;137:1060–1073.

Glucose-Lowering Therapies and **Heart Failure** in Type 2 Diabetes Mellitus

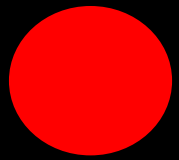
Improves Overall Cardiovascular and HF Outcomes	Improves Overall Cardiovascular Outcomes but Not HF outcomes	No Effect on Overall Cardiovascular or HF Outcomes	No Effect on Overall Cardiovascular Outcomes But Potential HF Harm
Empagliflozin (EMPA-REG OUTCOME[92])	Liraglutide (LEADER[70])	Insulin glargine (ORIGIN[30])	Pioglitazone (PROactive[56])
Canagliflozin (CANVAS/ CANVAS-R[95])	Semaglutide (SUSTAIN-6[73])	Acarbose (ACE[29])	Rosiglitazone (RECORD[58])
		Lixisenatide (ELIXA[69])	Saxagliptin (SAVOR-TIMI 53[83])
		Exenatide (EXSCEL[79])	
		Alogliptin (EXAMINE[82])	
		Sitagliptin (TECOS[85])	

Vijayakumar et al Circulation. 2018;137:1060–1073.

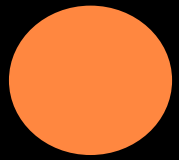
Agenda

- Diabetes and CV disease
- Intervention trials and CV benefits
- Cardiovascular outcome trials (CVOTs)
- Beneficial/Neutral/Harmful
- Recommendations update
- Take home messages

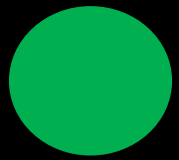
Cardiovascular impact



Harmful



Neutral



Benefit

?

Unknown

Metformin

Improve outcomes

Cardiovascular Outcomes Data

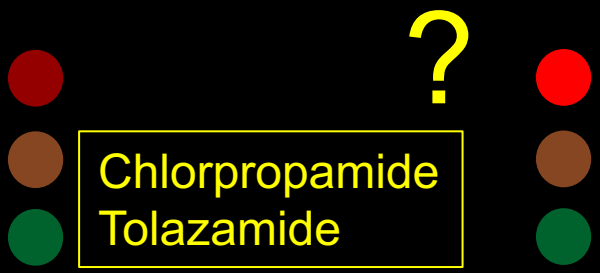
UKPDS trial found with metformin with about 10 years of use MAY reduce the risk of CV mortality , especially in obese patients
NNT = 14 [Evidence level A; high-quality RCT].

Pooled data demonstrate possible reduced CV mortality
NNT =56 ,compared to other DM medications or placebo [Evidence level A; high-quality meta-analysis].

UKPDS 31,32

Sulfonylureas

(first generation)



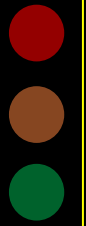
Cardiovascular Outcomes Data

Tolbutamide: use has been associated with increased CV mortality compared to diet alone or diet plus insulin.

UGDP 1973

Sulfonylureas

(Second generation)



Gliclazide
Glipizide
Glimepiride
Glyburide

?

Cardiovascular Outcomes Data

Glimepiride: CAROLINA, CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with T2D is ongoing to evaluate the long-term impact of glimepiride on CV morbidity and mortality.

Meglitinides
(Glinides)

Nateglinide
Repaglinide

?

Cardiovascular Outcomes Data

Nateglinide
No outcome data for in patients with T2D.
NAVIGATOR nateglinide in impaired glucose tolerance patients and at high risk for CV events had a neutral effect on cardiovascular outcomes
[Evidence level A; high-quality RCT]

Alpha-glucosidase inhibitors

Acarbose

Cardiovascular Outcomes Data

Acarbose
The ACE (Acarbose Cardiovascular Evaluation) trial to evaluate if acarbose reduces CV morbidity and mortality in patients with impaired glucose tolerance and established CHD or ACS didn't show benefit or harm in CVD

Thiazolidinediones

Cardiovascular Outcomes Data

Pioglitazone and Rosiglitazone
known associated risk of heart failure (NNH=50) with a meta-analysis treated with either agent for approximately two years
[Evidence level A; high-quality meta-analysis]

Thiazolidinediones

Cardiovascular Outcomes Data

Pioglitazone

The primary endpoint in the PROactive trial **was not improved** with pioglitazone.

A secondary endpoint found use of pioglitazone for about three years in patients with T2D and macrovascular disease (e.g., MI, stroke, PCI) may reduce the risk of all-cause mortality, non-fatal MI, and stroke
(NNT = 50)
[Evidence level A; high quality RCT].

Thiazolidinediones

Cardiovascular Outcomes Data

Pioglitazone

The primary endpoint in the PROactive trial **was not improved** with pioglitazone.

Subgroup analysis found use of pioglitazone for about three years in patients with T2D and a previous stroke may reduce the risk of recurrent fatal or nonfatal stroke
(NNT = 22)
[Evidence level A; high quality RCT].

Thiazolidinediones

Pioglitazone

Rosiglitozone

Cardiovascular Outcomes Data

Pioglitazone

The IRIS trial found use of pioglitazone for about five years in patients with prediabetes and a history of stroke (with mild impairment) or TIA may reduce therrisk of a future stroke or MI
(NNT = 36)[Evidence level A; high-quality RCT].

Thiazolidinediones

Pioglitazone

Rosiglitozone

Cardiovascular Outcomes Data

Pioglitazone

The IRIS trial found use of pioglitazone for about five years in patients with prediabetes and a history of stroke (with mild impairment) or TIA may reduce therrisk of a future stroke or MI
(NNT = 36)[Evidence level A; high-quality RCT].

Kernan et al. N Engl J Med 160217112012002

Thiazolidinediones

Cardiovascular Outcomes Data

Pioglitazone

The IRIS trial found use of pioglitazone for about five years in patients with prediabetes and a history of stroke (with mild impairment) or TIA may reduce therrisk of a future stroke or MI
(NNT = 36)[Evidence level A; high-quality RCT].
The TOSCA.IT Pio vs Glimepiride /gliclazide. No lower CV death or other CV benefits

The Lancet Diabetes & Endocrinology. 2017

Thiazolidinediones

Pioglitazone

Rosiglitozone

Cardiovascular Outcomes Data

Rosiglitazone
The RECORD trial found addingrosiglitazone to metformin or a sulfonylurea for at least five years did not affect overall CV morbidity or mortality
[Evidence level A; high-quality RCT].

Ref RECORD

Dipeptidyl peptidase-4(DPP-4) inhibitors

Dipeptidyl peptidase-4(DPP-4) inhibitors

Alogliptin
Saxagliptin

Cardiovascular Outcomes Data

Alogliptin

The EXAMINE trial found alogliptin use in patients with T2D and a history of a recent ACS, did not increase major adverse CV events, compared to placebo [Evidence level A; high-quality RCT].

Alogliptin is associated with an increased risk of heart failure-related admissions. NNH = 167 [Evidence level A;high-quality RCT].

Ref EXAMINE

Dipeptidyl peptidase-4(DPP-4) inhibitors

Sitagliptin

Vildagliptin
Linagliptin

?

Cardiovascular Outcomes Data

Sitagliptin

The TECOS trial found adding sitagliptin to existing DM therapy did not increase the major adverse CV events, hospitalization for heart failure, or other adverse events compared to placebo
[Evidence level A; high-quality RCT].

Linagliptin

CAROLINA, CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 DM (sept 2018)

Vildagliptin

MA of Phase III RCT pivotal trial.

Glucagon-like peptide-1(GLP-1) receptor agonists

Liraglutide

Exenatide LAR
Lixisenatide

Dulaglutide

?

Glucagon-like peptide-1(GLP-1) receptor agonists

Liraglutide

Cardiovascular Outcomes Data

Liraglutide

The LEADER trial [Evidence level A; high-qualityRCT] found adding liraglutide to standard care in patients with T2D with CV disease or at high CV risk over almost four years may reduce:

*Death from CV causes, nonfatal MI, or nonfatal stroke, NNT = 53.
*Death from CV causes, NNT = 77.
*Death from any cause, NNT = 71.
*Liraglutide did not reduce the individual rates of MI, nonfatal stroke, or hospitalization for heart failure

Glucagon-like peptide-1(GLP-1) receptor agonists

Exenatide LAR
Lixisenatide

Cardiovascular Outcomes Data

Lixisenatide

The ELIXA trial found adding lixisenatide to conventional therapy in T2D patients with a recent ACS had a neutral effect on CV outcomes.

Exenatide LAR

The EXSCEL (Exenatide Study of Cardiovascular Events Lowering Trial) trial found exenatide added to usual care had a neutral effect on CV outcomes.

Glucagon-like peptide-1(GLP-1) receptor agonists

Dulaglutide ?

Cardiovascular Outcomes Data

Dulaglutide

The REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) trial is ongoing to evaluate if dulaglutide can reduce MACE in patients with T2D.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors

Glucagon-like peptide-1(GLP-1) receptor agonists

Empagliflozin

Cardiovascular Outcomes Data

Empagliflozin

The EMPAG-REG OUTCOME trial found empagliflozin use for about three years, when added to standard glucose-lowering therapy in patients with T2D and underlying CV disease, may reduce :

Hospitalization due to heart failure (NNT = 71).
CV death rates (NNT = 45).
Overall death rates (NNT = 39).
Empagliflozin **did not reduce** the individual rates of MI or stroke.

[Evidence level A; highquality RCT]

Glucagon-like peptide-1(GLP-1) receptor agonists

Canagliflozin

Cardiovascular Outcomes Data

Canagliflozin

CANVAS (CANagliflozin cardioVascular Assessment Study)

Glucagon-like peptide-1(GLP-1) receptor agonists

Dapagliflozin ?

Cardiovascular Outcomes Data

Dapagliflozin

DECLARE-TIMI58 is ongoing to evaluate the impact of adding dapagliflozin to current DM therapy on MI, ischemic stroke, and CV death

What have we learnt from CVOT in type 2 diabetes

Subjects with established CVD (~25%): treatment added to metformin should include drugs with a documented CVD benefit (pioglitazone, liraglutide, SGLT-2 inhibitors). **We know very well what to do with these subjects.**

Subjects apparently at low CVD risk (~75%): treatment added to metformin should primarily include drugs with the best benefits/risks ratio. Benefits include glucose lowering effects on brief, middle and long term, improvement of other CVD risk factors, prevention of chronic complications. Risks include hypoglycemia and adverse effects (e.g., heart failure, fractures, infections, etc.). **We have many options but we have few certainties with these subjects.** In particular, we have very few head-to-head comparisons.

Agenda

- Diabetes and CV disease
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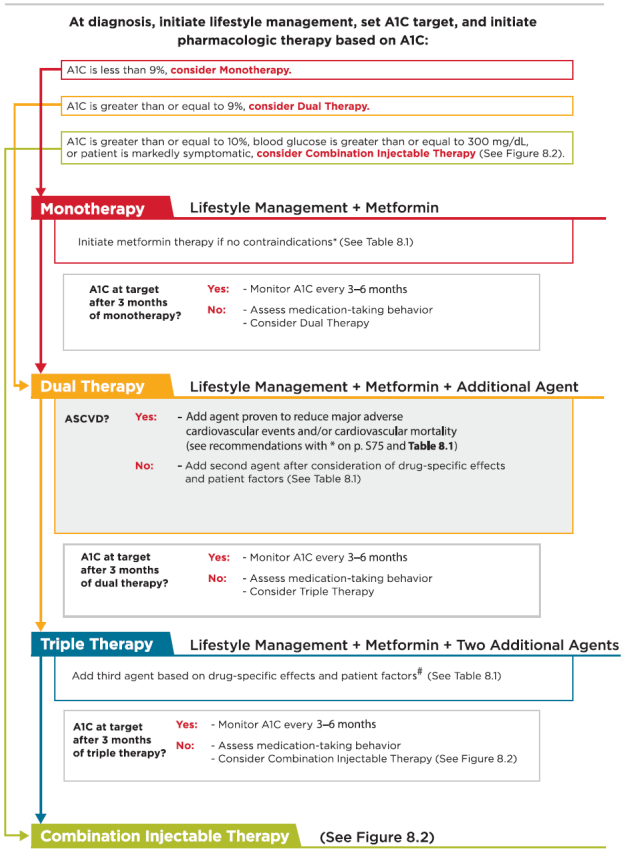
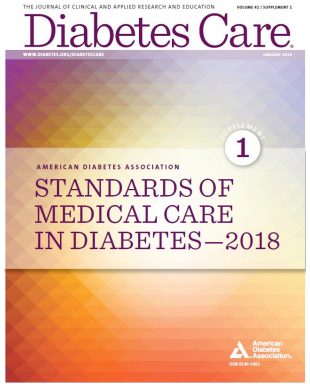
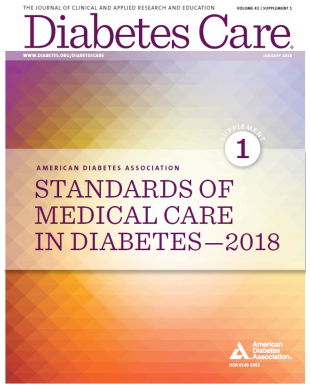
- Beneficial/Neutral/Harmful
- Recommendations update
- Take home messages

Antihyperglycemic Therapy in Adults with T2DM





Antihyperglycemic Therapy in Adults with T2DM



At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

A1C is less than 9%, **consider Monotherapy.**

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

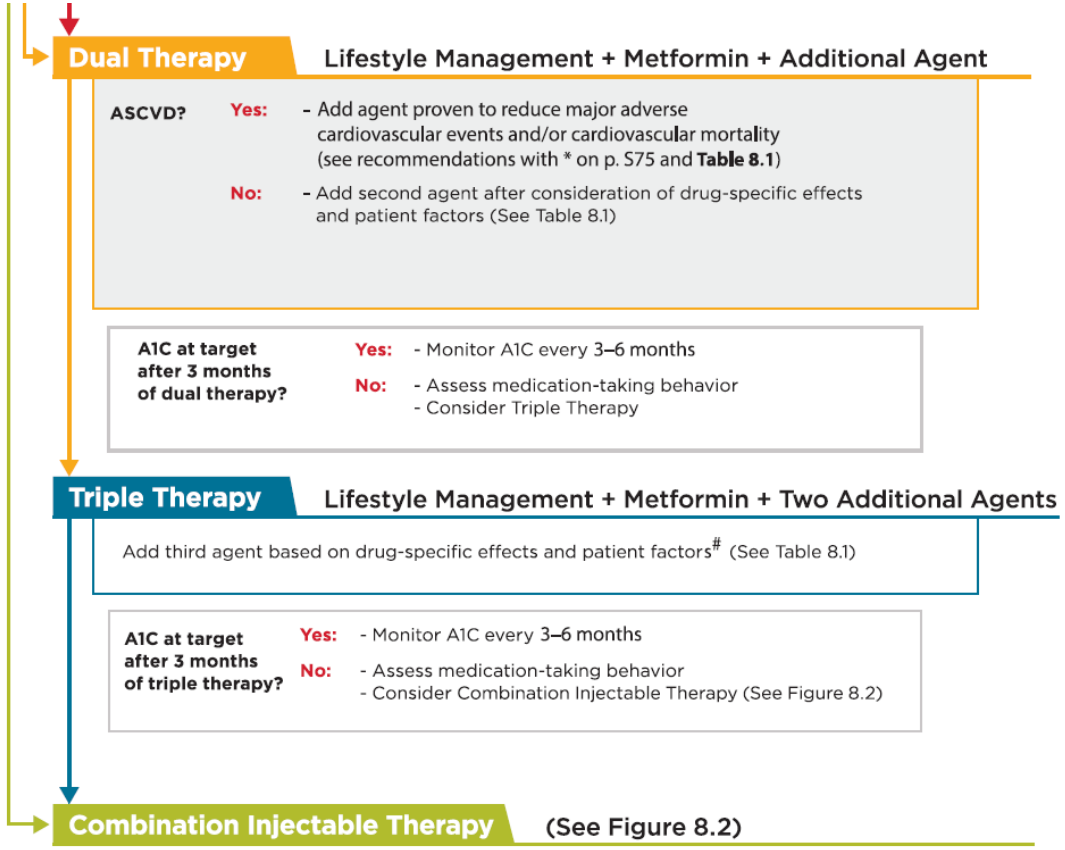
A1C at target after 3 months of monotherapy?

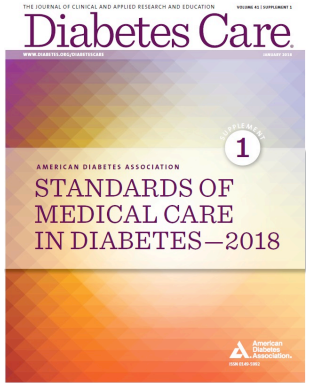
Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

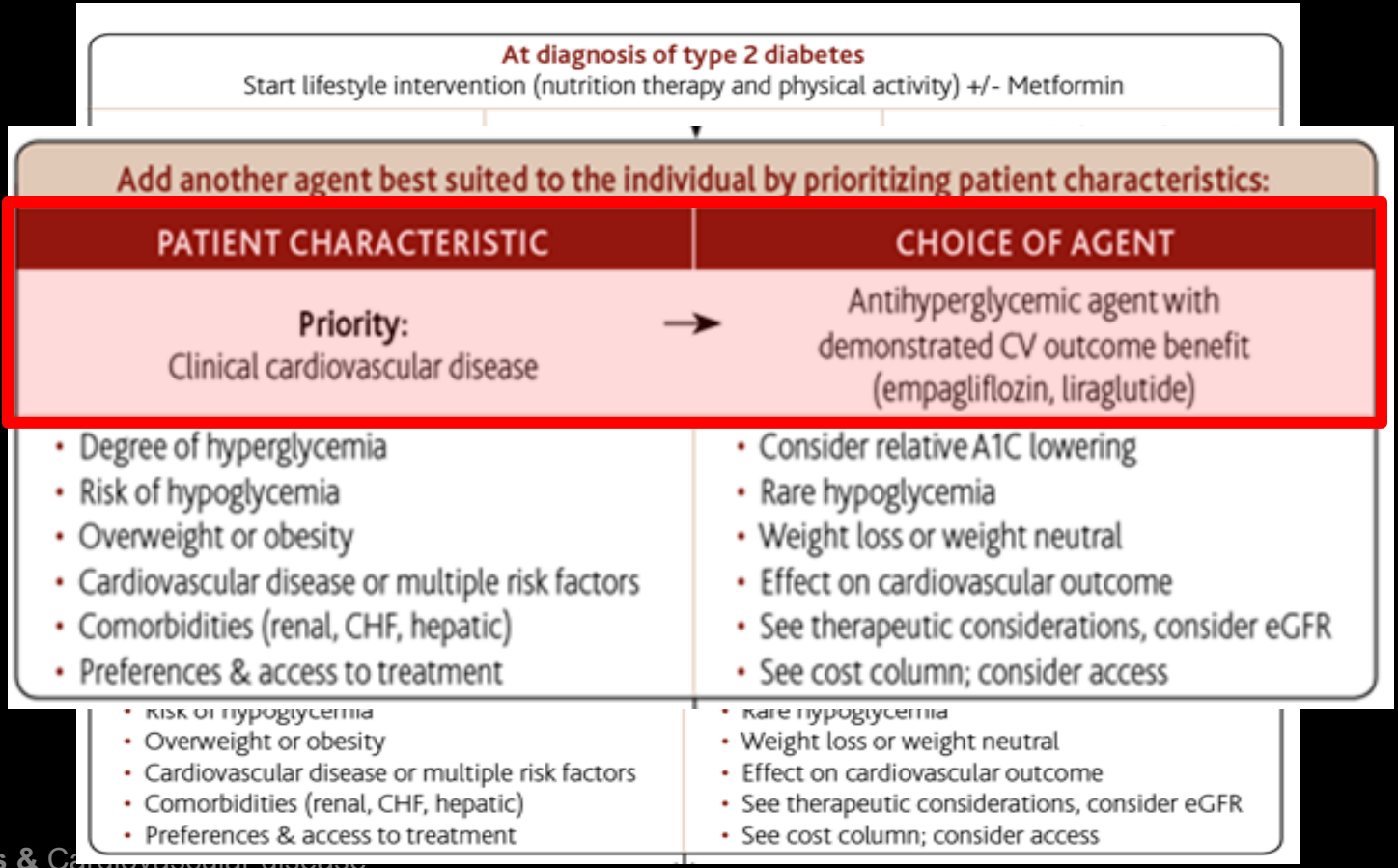
Dual Therapy Lifestyle Management + Metformin + Additional Agent

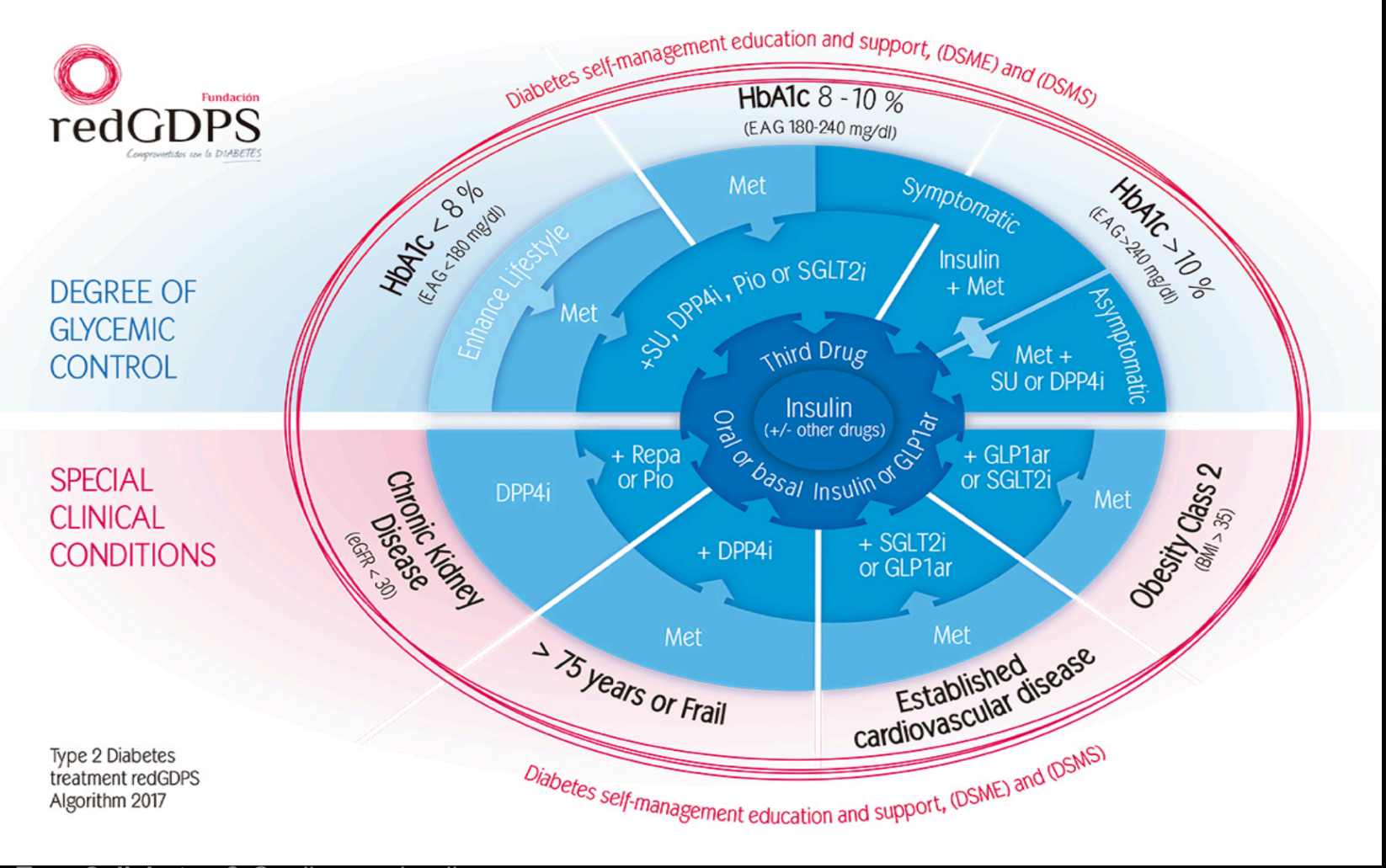
Antihyperglycemic Therapy in Adults with T2DM





Canadian Diabetes 2016



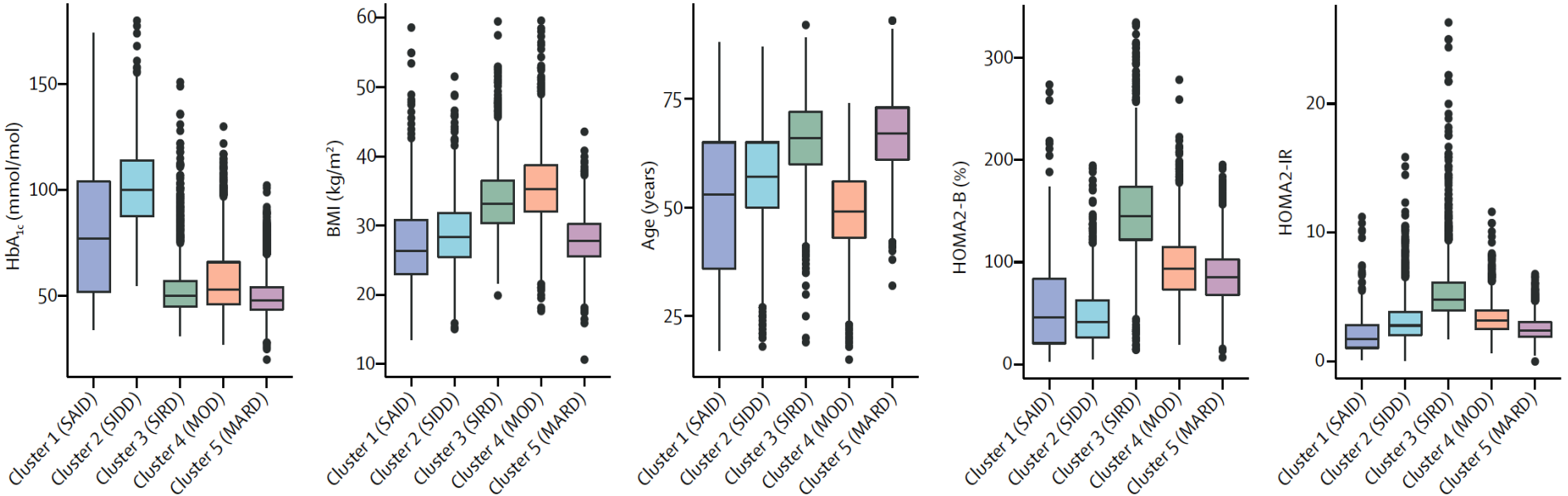

Fundación
redGDPS
Comprometidos con la DIABETES
Diabetes self-management education and support, (DSME) and (DSMS)
HbA1c 8 - 10 %
(EAG 180-240 mg/dl)
HbA1c < 8 %
(EAG<180 mg/dl)
HbA1c > 10 %
(EAG>240 mg/dl)
DEGREE OF GLYCEMIC CONTROL
SPECIAL CLINICAL CONDITIONS
Met
Symptomatic
Enhance Lifestyle
Met
+SU, DPP4i, Pio or SGLT2i
Insulin + Met
Asymptomatic
Met + SU or DPP4i
Third Drug
Insulin
(+/- other drugs)
Oral or basal Insulin or GLP1ar
DPP4i
+ Repa or Pio
+ GLP1ar or SGLT2i
Met
Chronic Kidney Disease
(eGFR < 30)
+ DPP4i
+ SGLT2i or GLP1ar
Obesity Class 2
(BMI > 35)
Met
Met
> 75 years or Frail
Established cardiovascular disease
Diabetes self-management education and support, (DSME) and (DSMS)
Type 2 Diabetes treatment redGDPS Algorithm 2017

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Cluster 1	severe autoimmune diabetes
Cluster 2	severe insulin-deficient diabetes
Cluster 3	severe insulin-resistant diabetes
Cluster 4	mild obesity-related diabetes
Cluster 5	mild age-related diabetes

Lancet Diabetes Endocrinol. Published online March 1, 2018

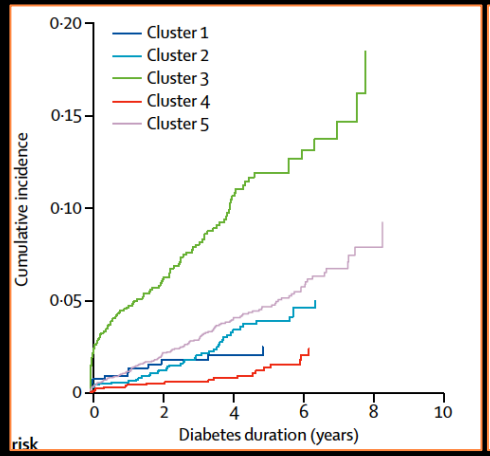
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables



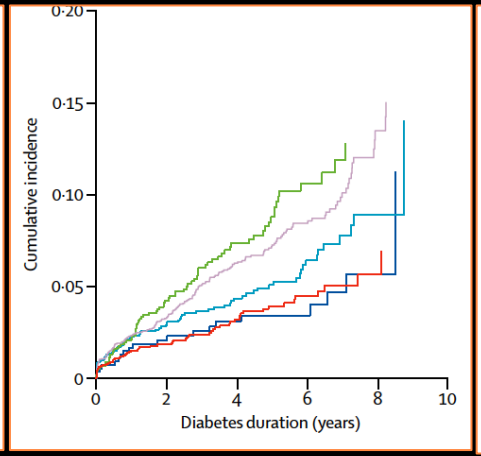
Lancet Diabetes Endocrinol. Published online March 1, 2018

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

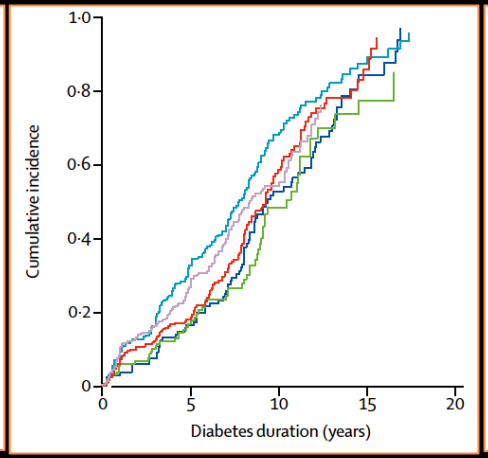
CKD 3a



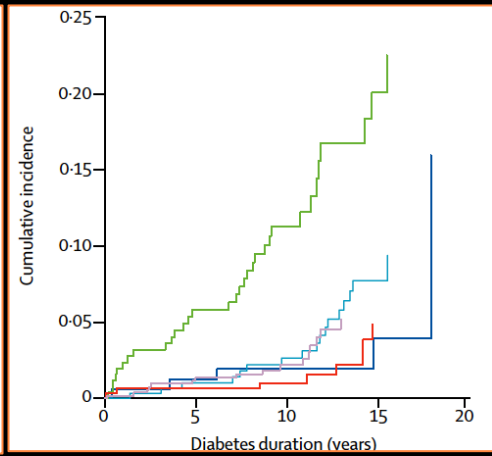
ERD



Mild RD



CHD



Lancet Diabetes Endocrinol. Published online March 1, 2018

Take home messages

- Higher prevalence and CV mortality in Diabetes patients
- Intervention trials (metabolic legacy) /poor CV benefits
- Regulatory CVOTs (non inferiority/Superiority)
- Beneficial/Neutral/Harmful (NNTs)
- Recommendations update (EBM/quality)
- “personalized holostic approach”

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