가톨릭대학교
THE CATHOLIC UNIVERSITY OF KOREA

Type 2 DM-Sulphonylurea :

Vecchio amore ?
Progressive amore ?

2017. 5. 13. 제 30차 대한당뇨병학회 춘계학술대회

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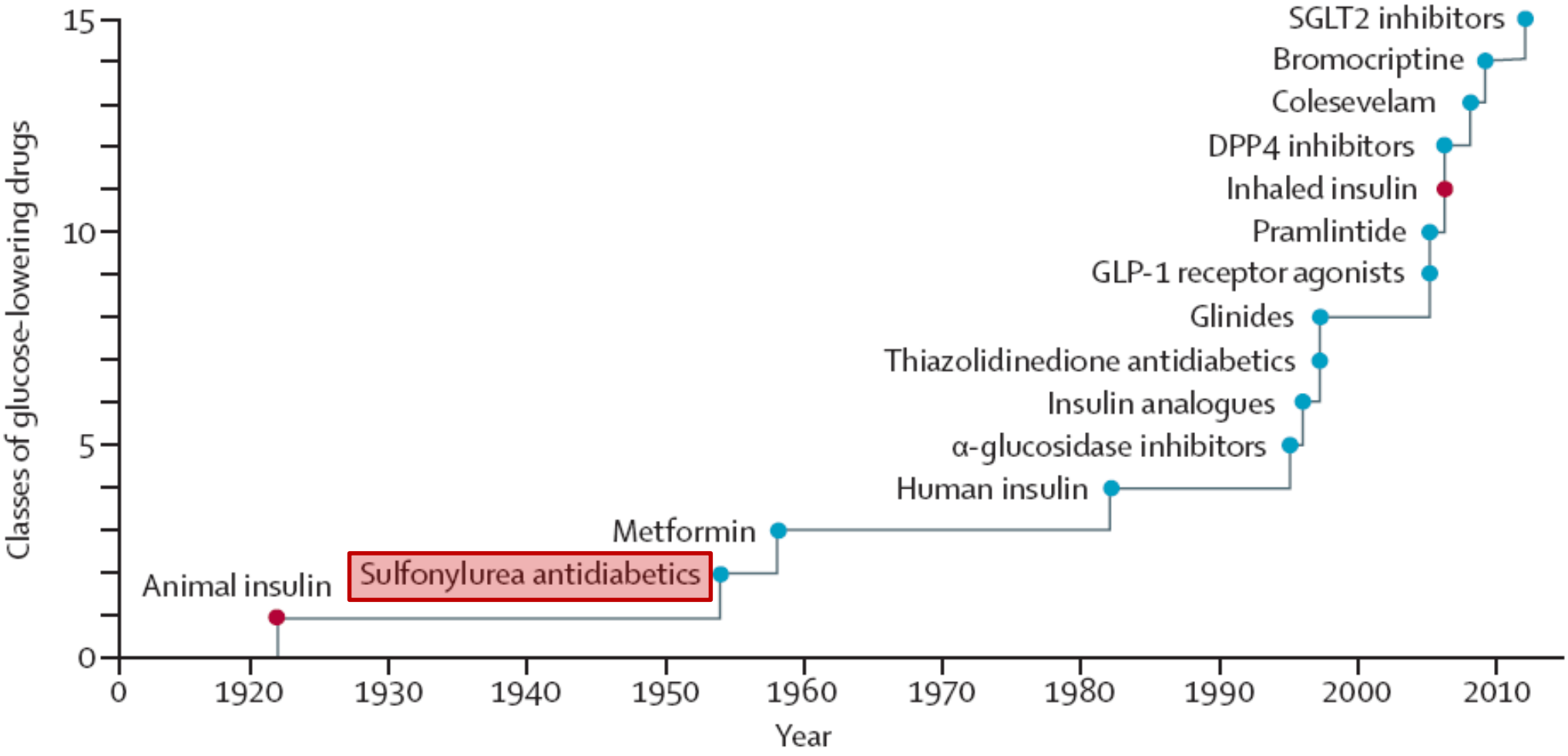
SU-exit: is it inevitable?

Ponte Vecchio

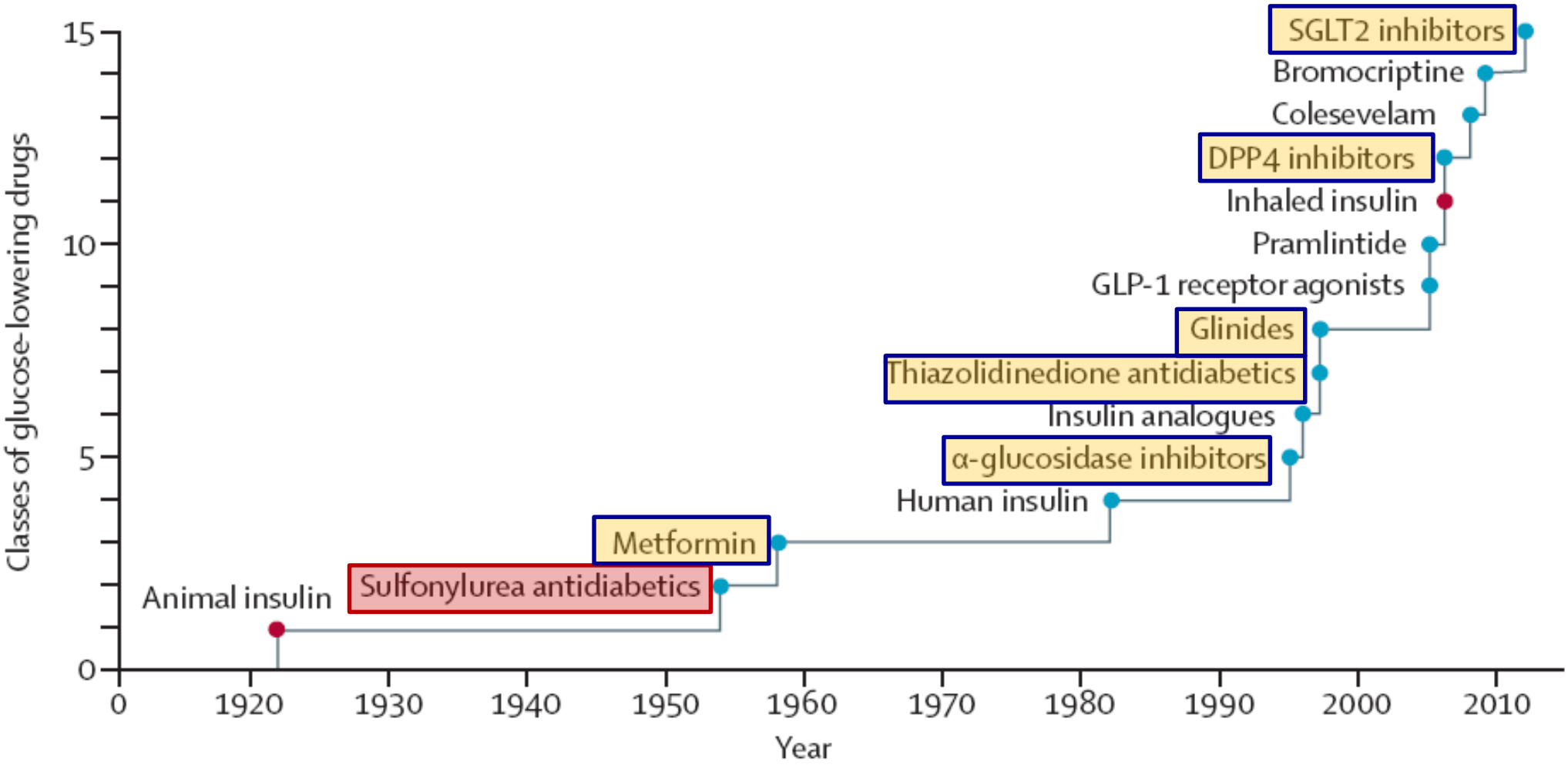
Dante Meets Beatrice at Ponte Santa Trinita, 1883

History of glucose-lowering agent development



Kahn SE et al. *Lancet*, 2014;383(9922):1068-83

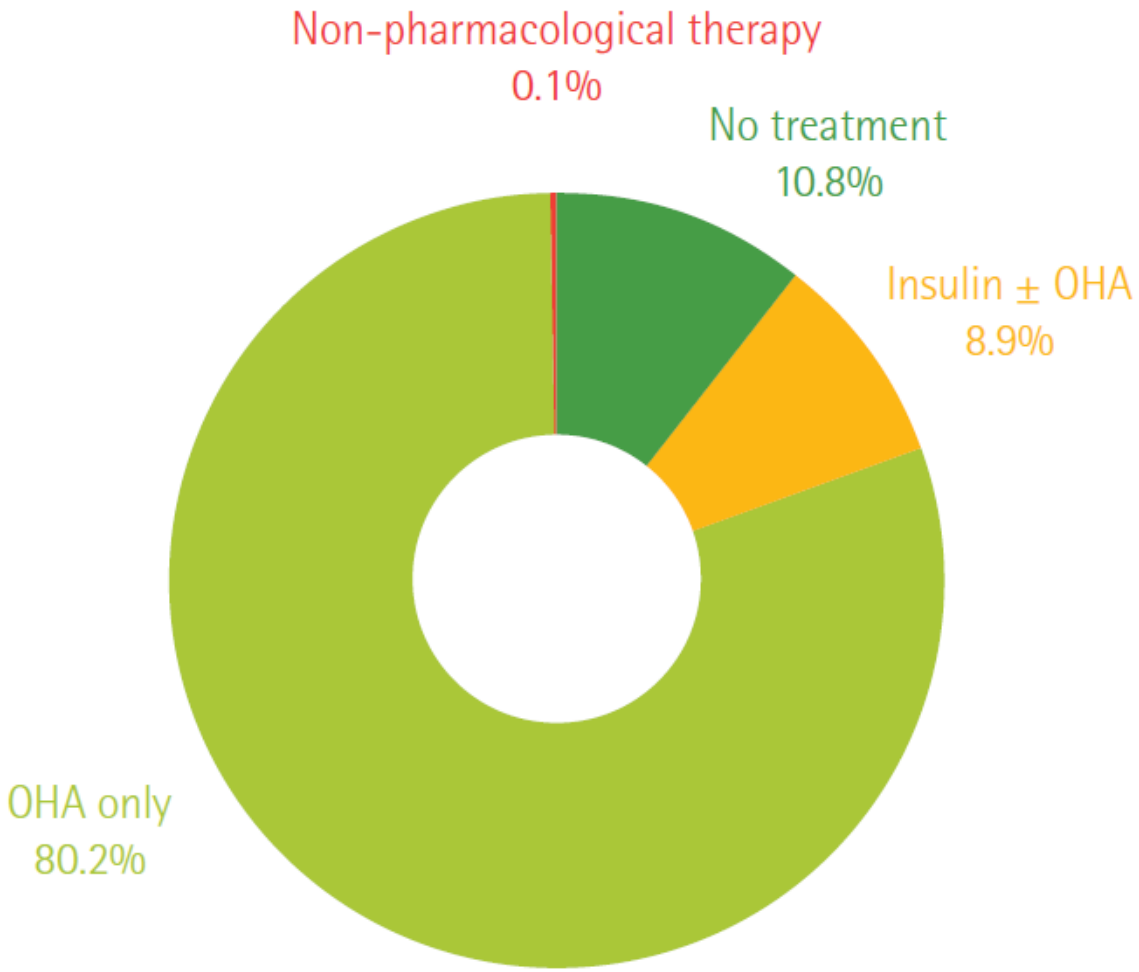
History of glucose-lowering agent development



Kahn SE et al. *Lancet*, 2014;383(9922):1068-83

Treatment of diabetes

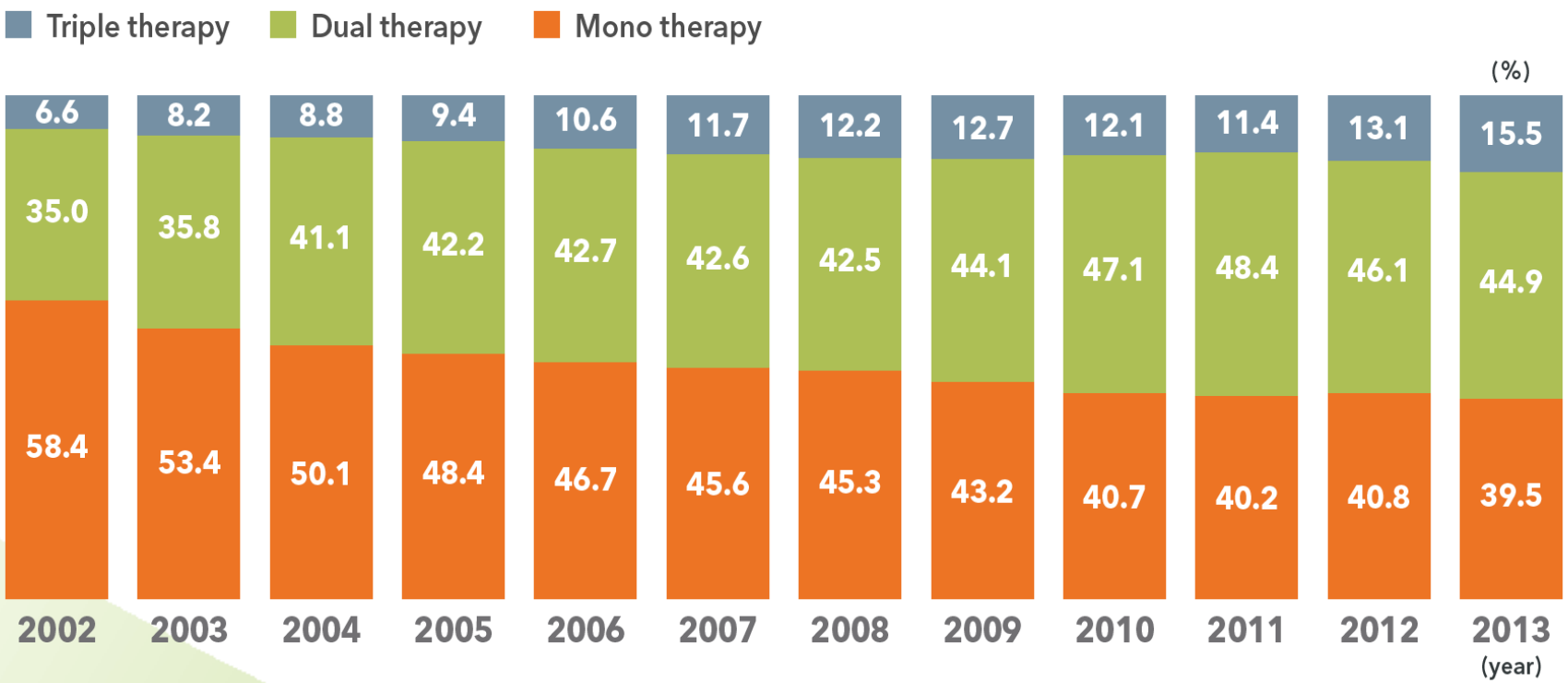
- **Most persons with diabetes (80.2%) are treated with oral hypoglycemic agents, but 10.8% of them have remained untreated.**



*In persons with diagnosed diabetes. OHA, oral hypoglycemic agent(s)

Korean diabetes fact sheet 2016

Percentage of dual or triple therapy steadily increased

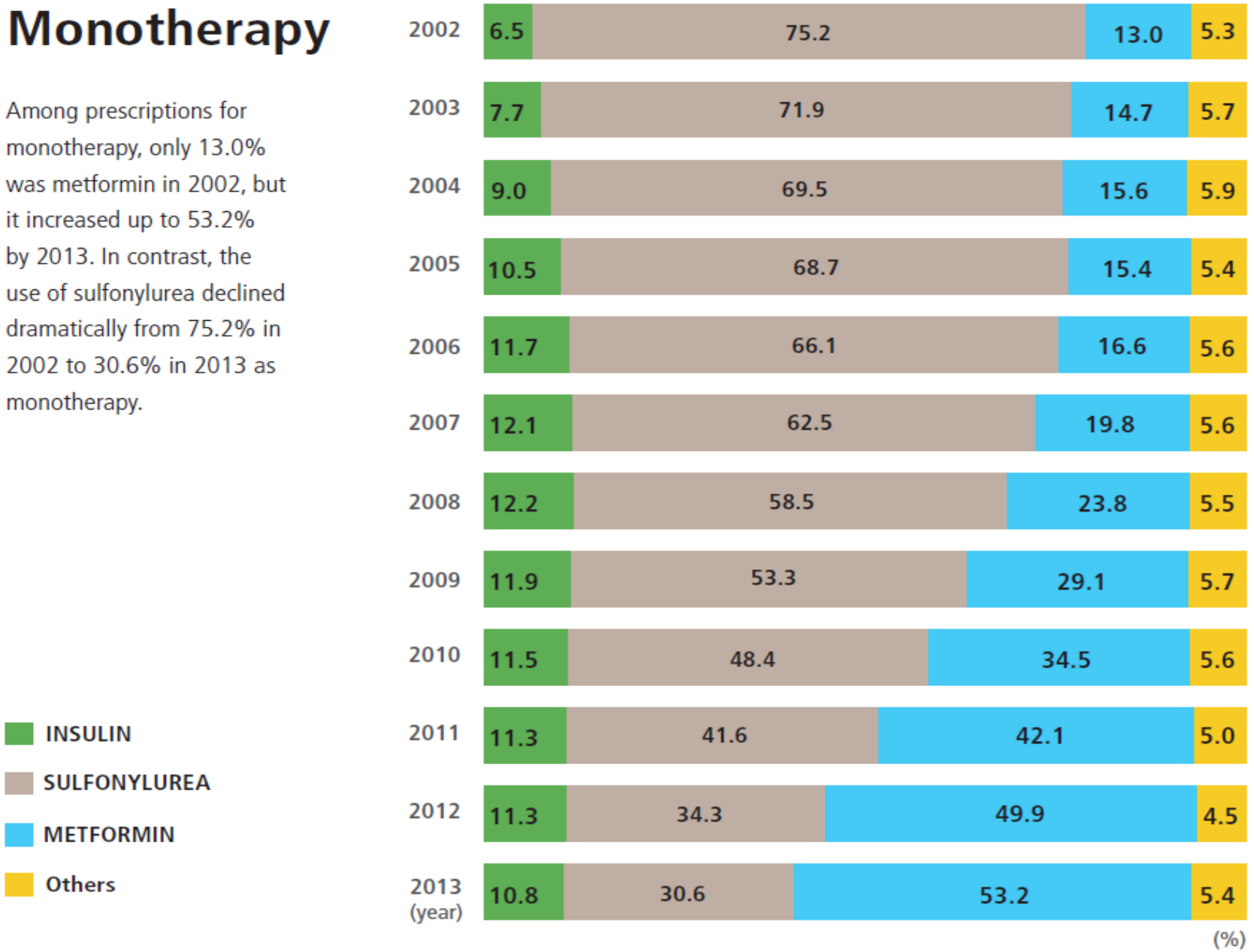


Korean Diabetes Fact Sheet 2015

Monotherapy in Korea

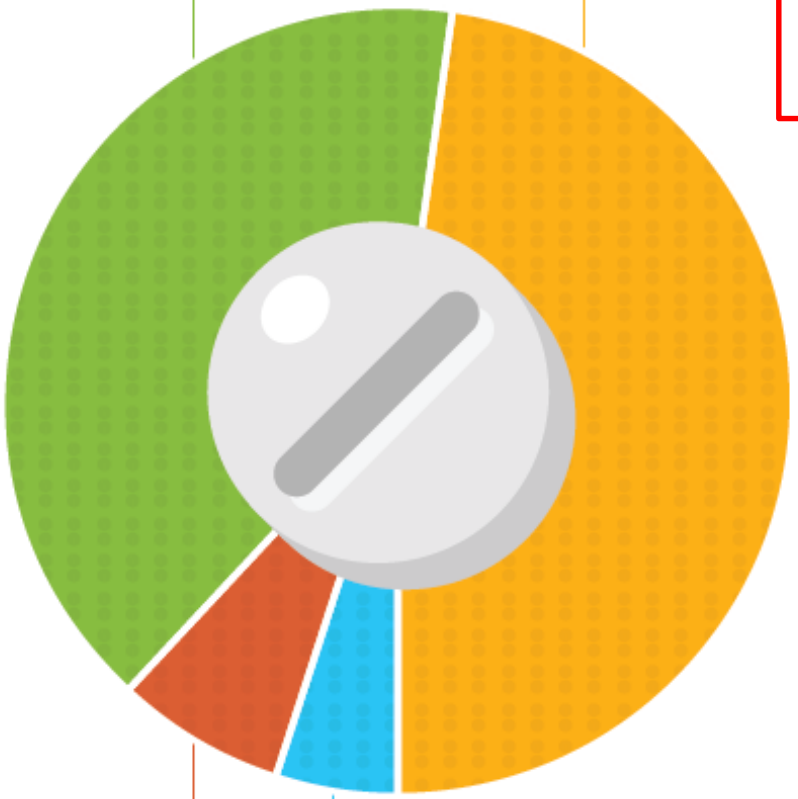
Monotherapy

Among prescriptions for monotherapy, only 13.0% was metformin in 2002, but it increased up to 53.2% by 2013. In contrast, the use of sulfonylurea declined dramatically from 75.2% in 2002 to 30.6% in 2013 as monotherapy.



Diabetes factsheet 2015

Dual therapy in Korea



METFORMIN + DPP-4 INHIBITOR

32.5%

SULFONYLUREA + METFORMIN

41.7%

INSULIN + METFORMIN

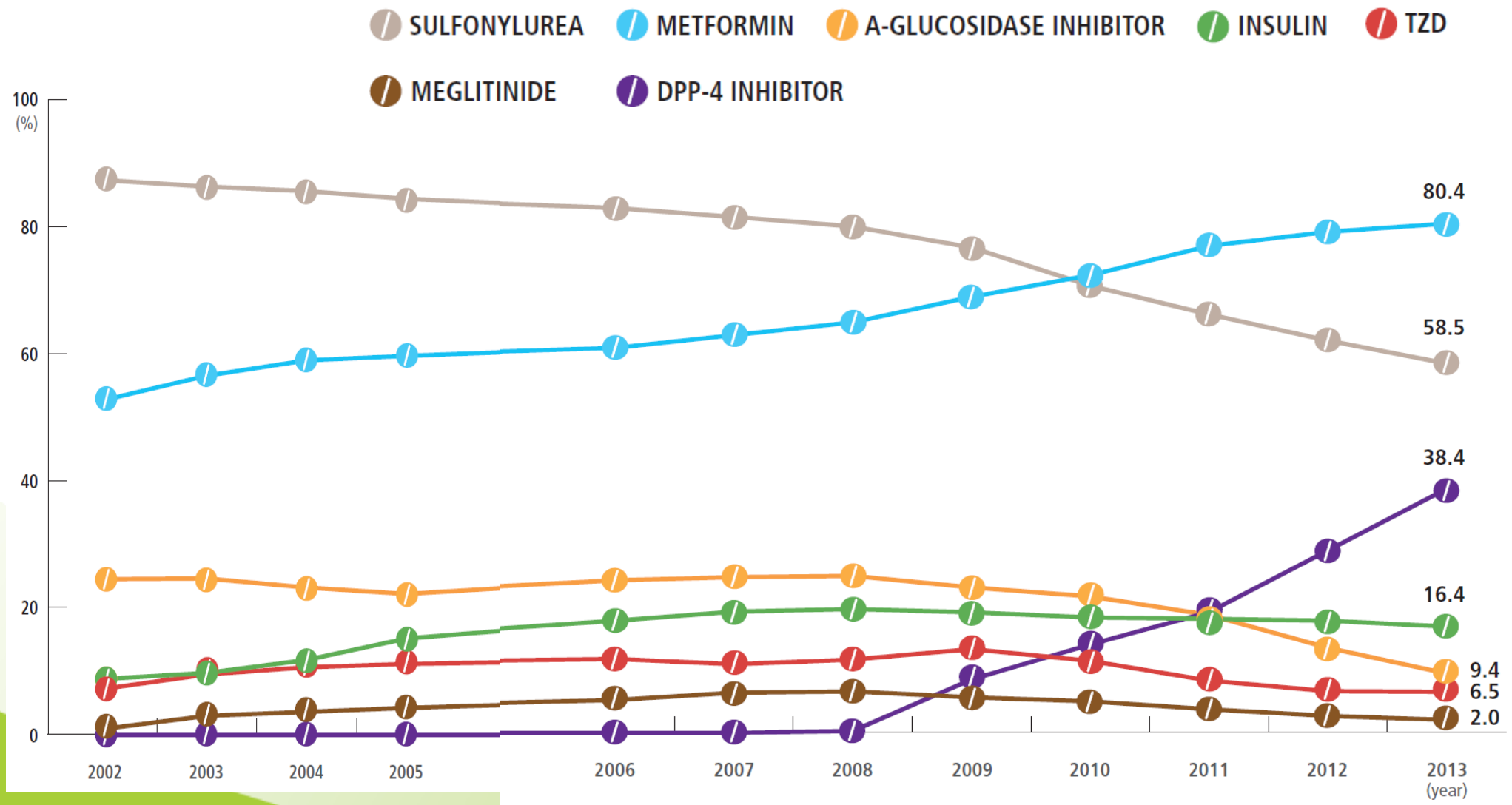
4.4%

SULFONYLUREA + DPP-4 INHIBITOR

4.8%

Diabetes factsheet 2015

Treatment of Diabetes in Korea



Diabetes factsheet 2015

Main Medication changes in Korean Type 2 DM

Before 2000 : **SU** or **SU** + **MET** or **SU** + **MET** + **AGI**

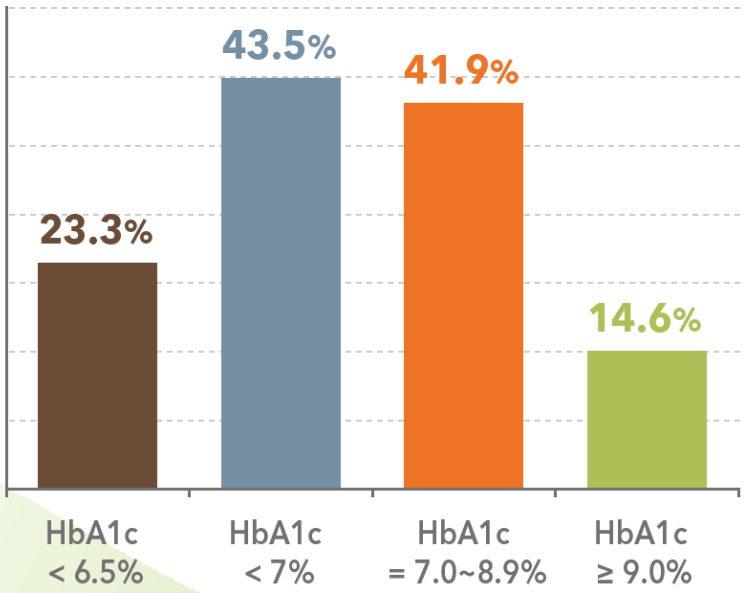
2000 ~ : **SU** + **MET** + **TZD**

2008 ~ : **SU** + **MET** + **DPP 4 inh**

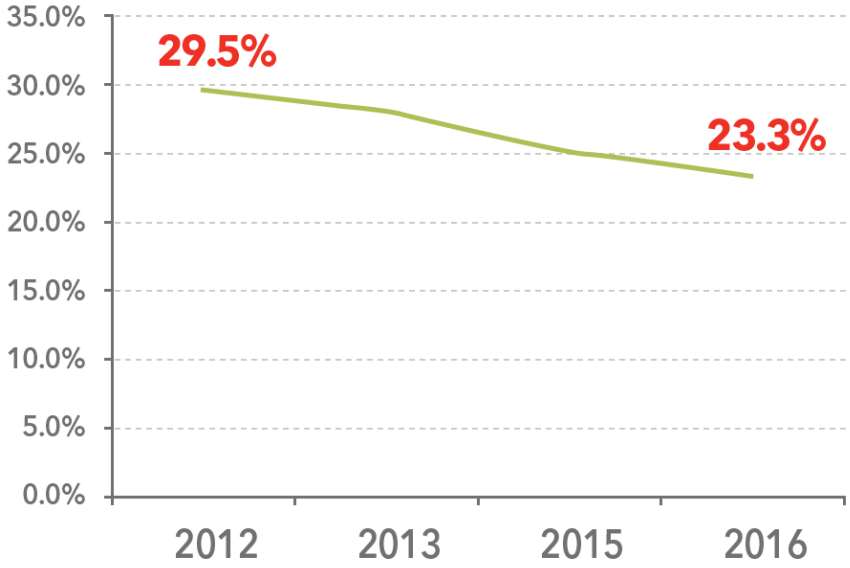
2014 ~ : **MET** + **DPP 4 inh** or **SGLT2 inh**

The control rate of glycemia among Korean T2DM patients

Glycemic control rate of Diabetes



Glycemic control < 6.5%



Korean Diabetes Fact Sheet 2016

Harrison's Principles of Internal medicine 19th edition

	Mechanism of Action	Examples[a]	HbA_{1c} Reduction (%) [b]	Agent-Specific Advantages	Agent-Specific Disadvantages	Contraindications
Biguanides[c*]	↓ Hepatic glucose production	Metformin	**1-2**	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis	Serum creatinine >1.5mg/dL (men) >1.4 mg/dL (women) (see text), CHF, radio-graphic contrast studies, hospitalized patients, acidosis
α-Glucosidase inhibitors[c]**	↓ GI glucose absorption	Acarbose, miglitol, voglibose	**0.5-0.8**	Reduce postprandial glycemia	GI flatulence, liver function tests	Renal/liver disease
DPP-IV inhibitors[c*]**	Prolong endogenous GLP-1 action	Alogliptin, Anagliptin, Gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin	**0.5-0.8**	Well tolerated, do not cause hypoglycemia		Reduced dose with renal disease; one associated with increase heart failure risk; possible association with ACE inhibitor induced angioedema
Insulin secre-tagogues: Sulfonylureas[c*]	↑ Insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide	**1-2**	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver disease
insulin secre-tagogues: Nonsulfonylureas[c*]**	↑ Insulin secretion	Nateglinide, repaglinide, mitiglinide	**0.5-1.0**	Short onset of action, lower postprandial glucose	Hypoglycemia	Renal/liver disease
SGLT-2 inhibitors***	↑ Urinary glucose excretion	Canagliflozin, Forxiga, empagliflozin	**0.5-1.0**	Insulin secretion and action independent	Urinary and vaginal infections, dehydration, exacerbate tendency to hyperkalemia	Limited clinical experience; moderate renal insufficiency
Thiazolidinediones[c*]**	↓ Insulin resistance, ↑ glucose utilization	Rosiglitazone, pioglitazone	**0.5-1.4**	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, liver disease

1. Harrison's Principles of Internal Medicine - 19th ed

Table 418-5. AGENTS USED FOR TREATMENT OF TYPE 1 OR TYPE 2 DIABETES

Trends in Drug Utilization, Glycemic control and rate of Hypoglycemia

OBJECTIVE

To examine temporal trends in utilization of glucose-lowering medications, glycemic control, and rate of severe hypoglycemia among patients with type 2 diabetes (T2DM).

RESEARCH DESIGN AND METHODS

Using claims data from 1.66 million privately insured and Medicare Advantage patients with T2DM from 2006 to 2013, we estimated the annual *1*) age- and sex-standardized proportion of patients who filled each class of agents; *2*) age-, sex-, race-, and region-standardized proportion with hemoglobin A_{1c} (HbA_{1c}) <6%, 6 to <7%, 7 to <8%, 8 to <9%, ≥9%; and *3*) age- and sex-standardized rate of severe hypoglycemia among those using medications. Proportions were calculated overall and stratified by age-group (18–44, 45–64, 65–74, and ≥75 years) and number of chronic comorbidities (zero, one, and two or more).

RESULTS

From 2006 to 2013, use increased for metformin (from 47.6 to 53.5%), DPP-4 inhibitors (0.5 to 14.9%), and insulin (17.1 to 23.0%) but declined for sulfonylureas (38.8 to 30.8%) and thiazolidinediones (28.5 to 5.6%; all $P < 0.001$). The proportion of patients with HbA_{1c} <7% declined (from 56.4 to 54.2%; $P < 0.001$) and with HbA_{1c} ≥9% increased (9.9 to 12.2%; $P < 0.001$). Glycemic control varied by age and was poor among 23.3% of the youngest and 6.3% of the oldest patients in 2013. The overall rate of severe hypoglycemia remained the same (1.3 per 100 person-years; $P = 0.72$), declined modestly among the oldest patients (from 2.9 to 2.3; $P < 0.001$), and remained high among those with two or more comorbidities (3.2 to 3.5; $P = 0.36$).

CONCLUSIONS

During the recent 8-year period, the use of glucose-lowering drugs has changed dramatically among patients with T2DM. Overall glycemic control has not improved and remains poor among nearly a quarter of the youngest patients. The overall rate of severe hypoglycemia remains largely unchanged.

CONCLUSIONS

During the recent 8-year period, the use of glucose-lowering drugs has changed dramatically among patients with T2DM. **Overall glycemic control has not improved and remains poor among nearly a quarter of the youngest patients.**

The overall rate of severe hypoglycemia remains largely unchanged.

Lipska KJ et al. *Diabetes Care*.2016 Sep 22. DOI 10.2337dc16-0985

Trends in Drug Utilization, Glycemic control and rate of Hypoglycemia

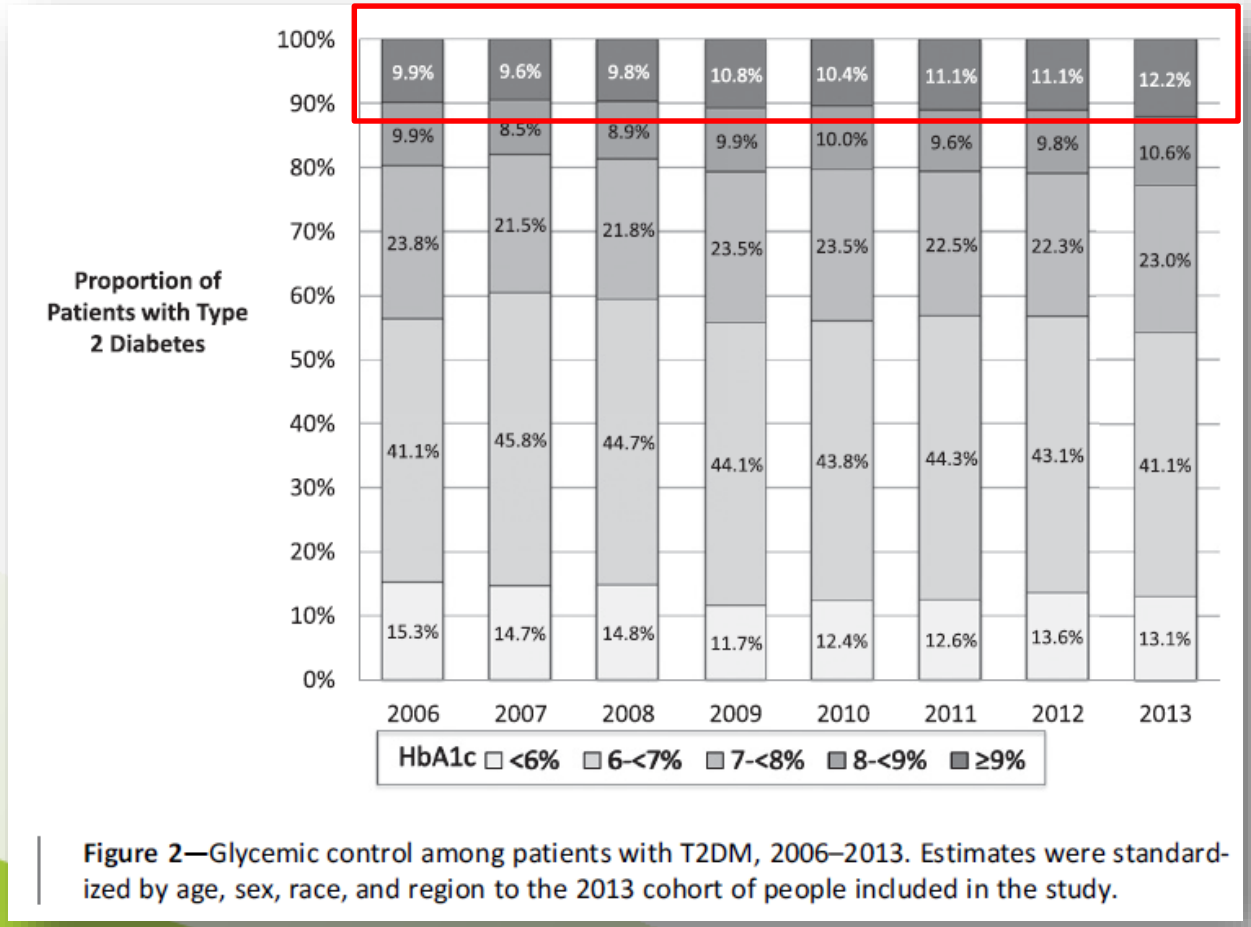


Figure 2—Glycemic control among patients with T2DM, 2006–2013. Estimates were standardized by age, sex, race, and region to the 2013 cohort of people included in the study.

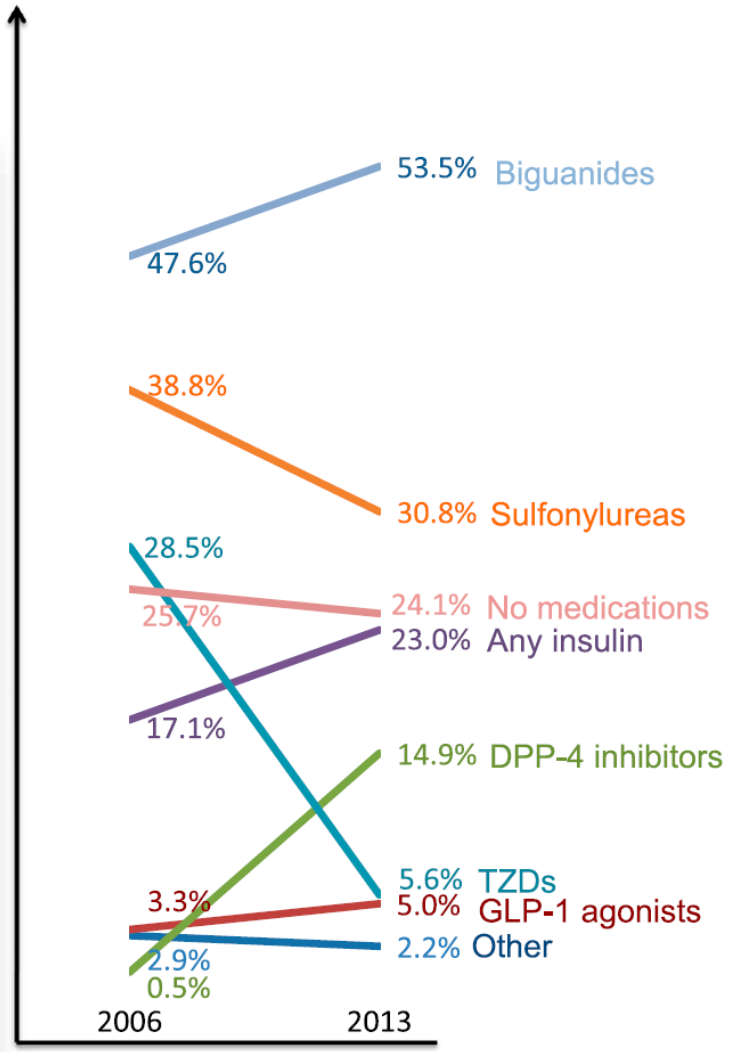
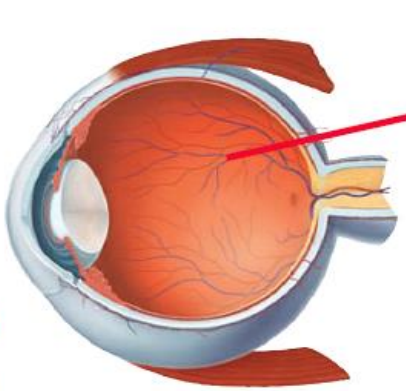


Figure 1—Age- and sex-standardized proportion of patients with T2DM who filled each class of glucose-lowering agents, 2006 and 2013 (see Supplementary Table 1 for annual data). Since patients may fill more than one class in each year, percentages do not add up to 100%. Other medications were comprised of meglitinides, α-glucosidase inhibitors, SGLT-2 inhibitors, and amylin analogs. Patients with no fills for glucose-lowering medications were included in the "No medications" group.

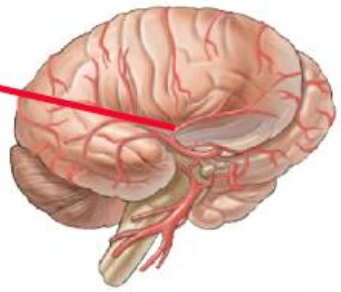
Lipska KJ et al. *Diabetes Care*.2016 Sep 22. DOI 10.2337dc16-0985

Diabetes and Morbidity



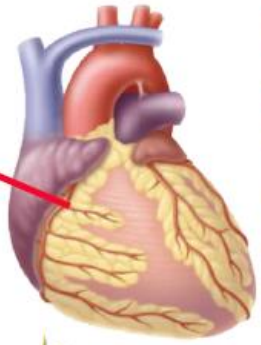
Diabetic retinopathy

Leading cause of blindness in working-age adults[1]



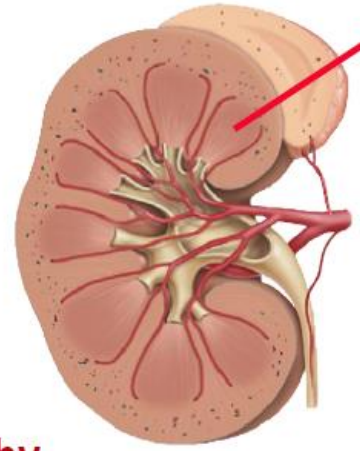
Stroke

3 fold increase in stroke[3]



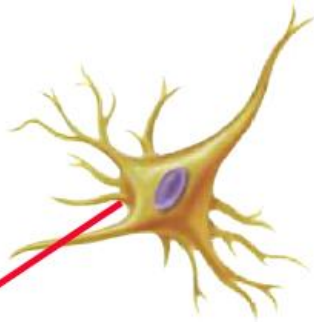
Cardiovascular disease

1 to 5 fold risk increase[4]



Diabetic nephropathy

Leading cause of end-stage renal disease[2]

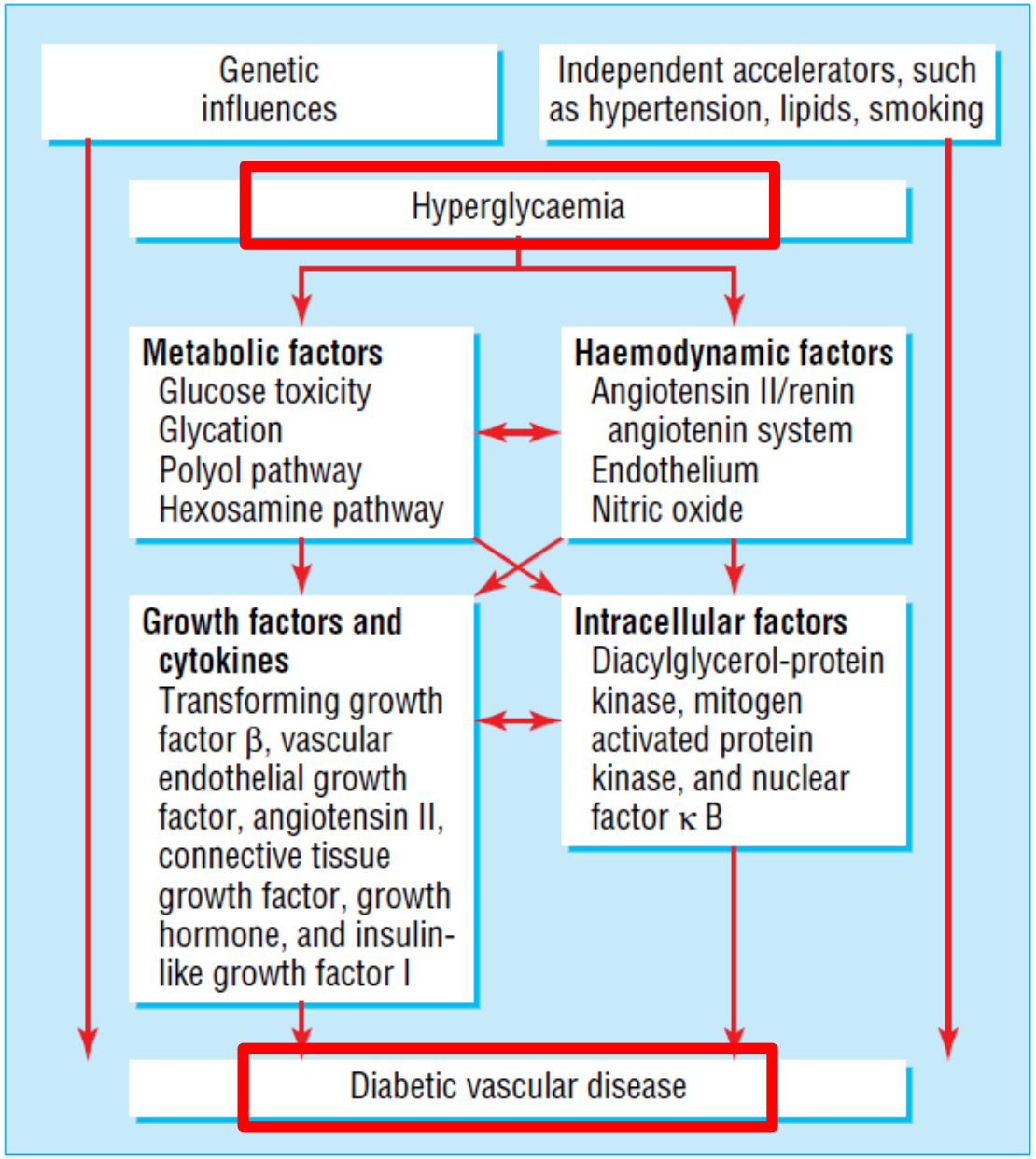


Diabetic neuropathy

Leading cause of non-traumatic lower extremity amputations[5]

1.Fong DS et al. Diabetes Care. 2003;26:S99-S102; 2.Molitch ME et al. Diabetes Care. 2003;261:S94-8;
3,4.2015-Harrisons Principles of Internal Medicine-19th Edition. 5.Mayfield JA et al. Diabetes Care 2003;26:S78–9.

Metabolic pathway



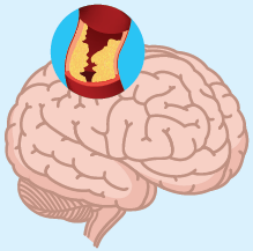
[Metabolic pathways that contribute to vascular complications of diabetes]

Marshall SM et al. *BMJ* 2006;333:475–80

High CV risk in diabetic patients

Cardiovascular events

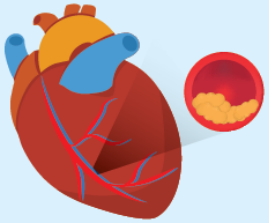
In 2013 (events/10,000 persons)



Ischemic Stroke

295 / 62

Type 2 diabetes — Non-diabetes



Ischemic heart disease

248 / 59

Type 2 diabetes — Non-diabetes

Cerebral hemorrhage

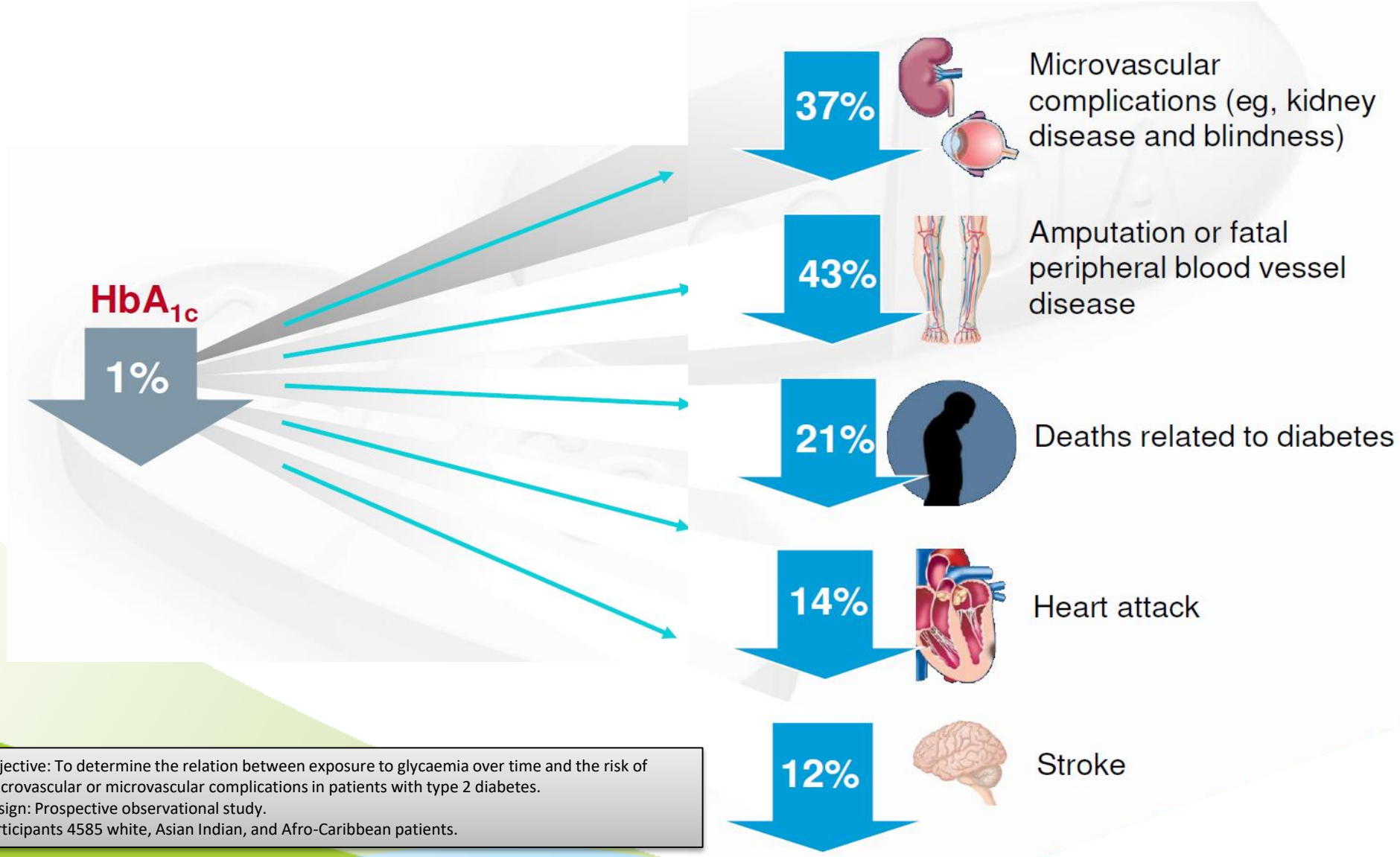
41 / 17

Type 2 diabetes — Non-diabetes

DEFINITION OF CARDIOVASCULAR EVENTS:
ICD-10 code and events-related hospitalization
Ischemic stroke: I63, I64, I693, I694, G45
Ischemic heart disease: I20, I21, I22, I23, I24, I25
Cerebral hemorrhage: I61, I61, I62, I690, I692

Diabetic fact sheet 2015

Glycemic control and Complications

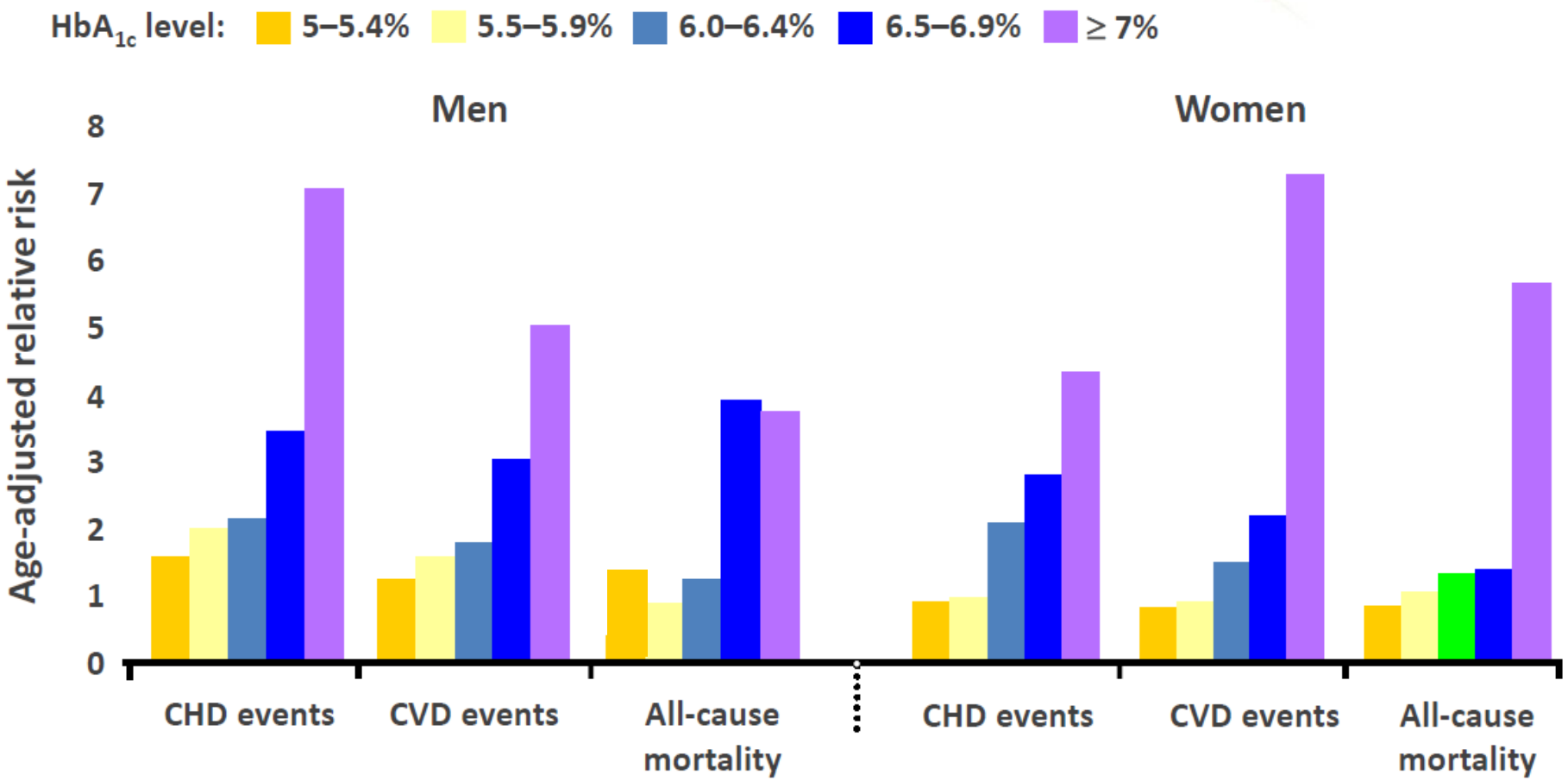


Objective: To determine the relation between exposure to glycaemia over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes.
Design: Prospective observational study.
Participants 4585 white, Asian Indian, and Afro-Caribbean patients.

Stratton IM et al. *BMJ.*2000;321:405-412

Risk of CV events or death associated with HbA1c level

❖ EPIC-Norfolk study



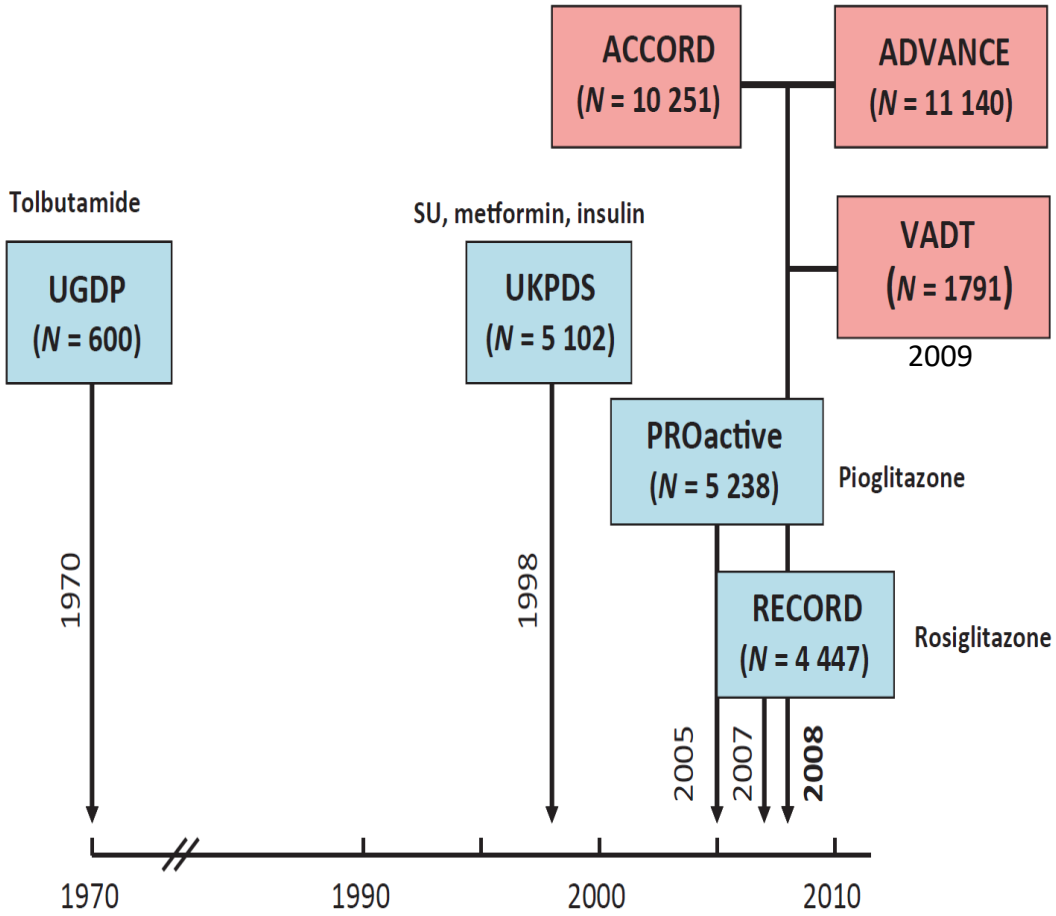
- Objective: To examine the relationship between hemoglobin A1c, cardiovascular disease, and total mortality.
- Design: Prospective population study in Norfolk, United Kingdom.
- Participants: 4662 men and 5570 women who were 45 to 79 years of age and were residents of Norfolk.
- Measurements: Hemoglobin A1c and cardiovascular disease risk factors were assessed from 1995 to 1997, and cardiovascular disease events and mortality were assessed during the follow-up period to 2003.

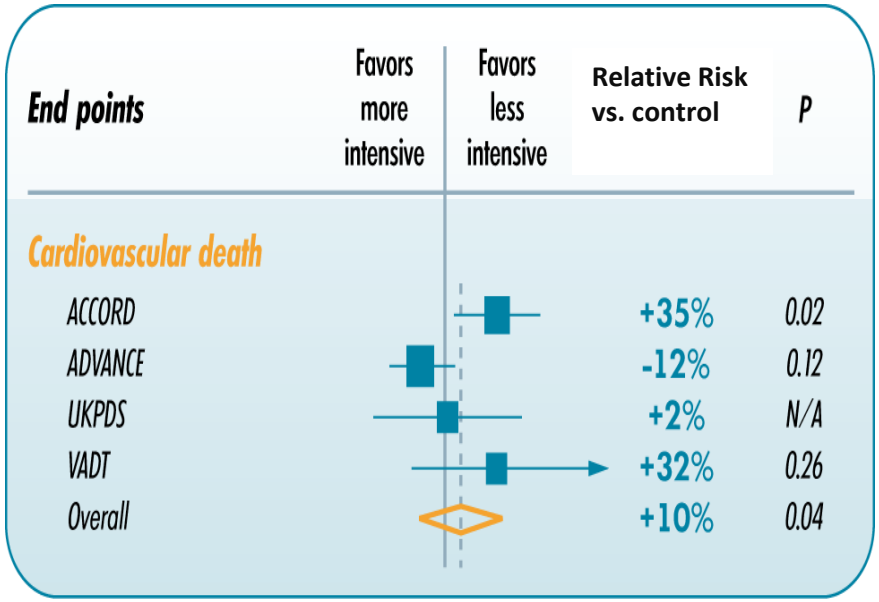
** P < 0.001 for linear trend across hemoglobin A1c categories for all end points. Age-adjusted relative risks were determined by using logistic regression models. (Relative risk of HbA1c < 5.0% = 1)*

Adapted from Khaw et al. *Ann Intern Med* 2004; 141: 413–20

Intensive blood glucose control & vascular risk in T2D

- Evidence and experience





Turnbull FM et al. *Diabetologia* 2009;52:2288-2298

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.

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Safety Alerts for Human Medical Products

2015 Safety Alerts for Human Medical Products

2014 Safety Alerts for Human Medical Products

2013 Safety Alerts for Human Medical Products

2012 Safety Alerts for Human Medical Products

Rosiglitazone-containing Diabetes Medicines: Drug Safety Communication - FDA Eliminates the Risk Evaluation and Mitigation Strategy (REMS)

[Posted 12/16/2015]

AUDIENCE: Family Practice, Endocrinology, Cardiology

ISSUE: FDA is eliminating the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing type 2 diabetes medicines, which are approved as Avandia, Avandamet, Avandaryl, and generics. The REMS is no longer necessary to ensure that the benefits of rosiglitazone medicines outweigh their risks.

In 2013, FDA required removal of the prescribing and dispensing restrictions for rosiglitazone medicines after determining that data did not demonstrate an increased risk of heart attack with rosiglitazone medicines compared to the standard type 2 diabetes medicines metformin and sulfonylurea. FDA also required the drug manufacturers to provide educational training to health care professionals about the current state of knowledge regarding the heart risks of rosiglitazone medicines. Manufacturers have since fulfilled these requirements.

FDA has continued monitoring these medicines and identified no new pertinent safety information. FDA will update the public if any new information becomes available.

BACKGROUND: Type 2 diabetes is a disease that can lead to serious complications such as kidney failure, blindness, and premature death. Rosiglitazone can be used along with diet and exercise to control blood sugar in adults with the disease.

RECOMMENDATION: The REMS is no longer necessary to ensure that the benefits of rosiglitazone medicines outweigh their risks.

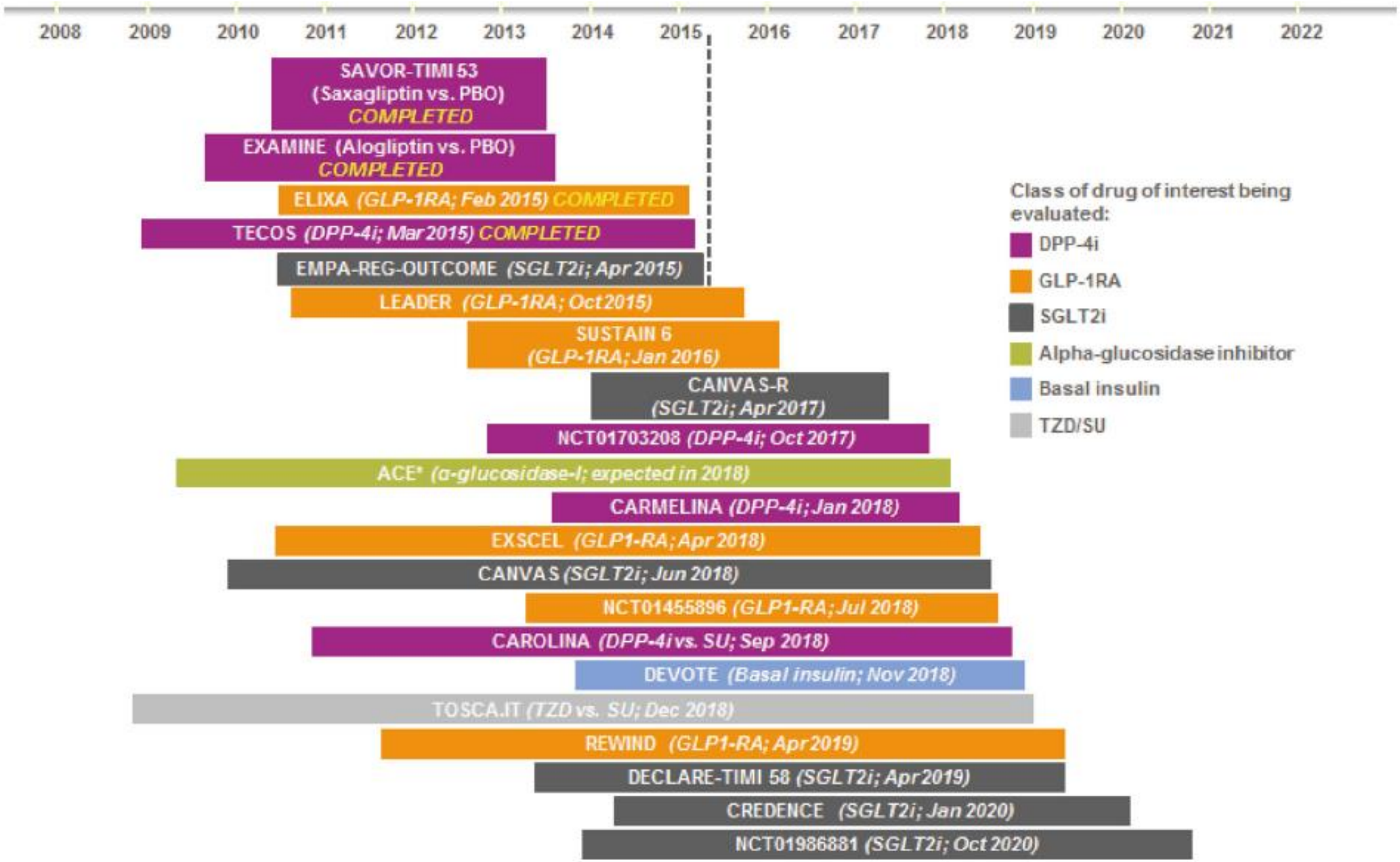


Fig. 2 ▲ CV outcome studies in patients with T2DM: chronology of completion dates. (https://clinicaltrials.gov/ct2/home; last accessed May 29, 2015) (SAVOR-TIMI 53, NCT01107886; EXAMINE, NCT00968708; ELIXA, NCT01147250; TECOS, NCT00790205; EMPA-REG-OUTCOME, NCT01131676; LEADER, NCT01179048; SUSTAIN 6, NCT01720446; CANVAS-R, NCT01989754; ACE, NCT00829660 (*https://www.dtu.ox.ac.uk/ace/; last accessed May 29, 2015); CARMELINA, NCT01897532; EXSCEL,

ADA/EASD Position Statement

Start with Monotherapy unless:

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 — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

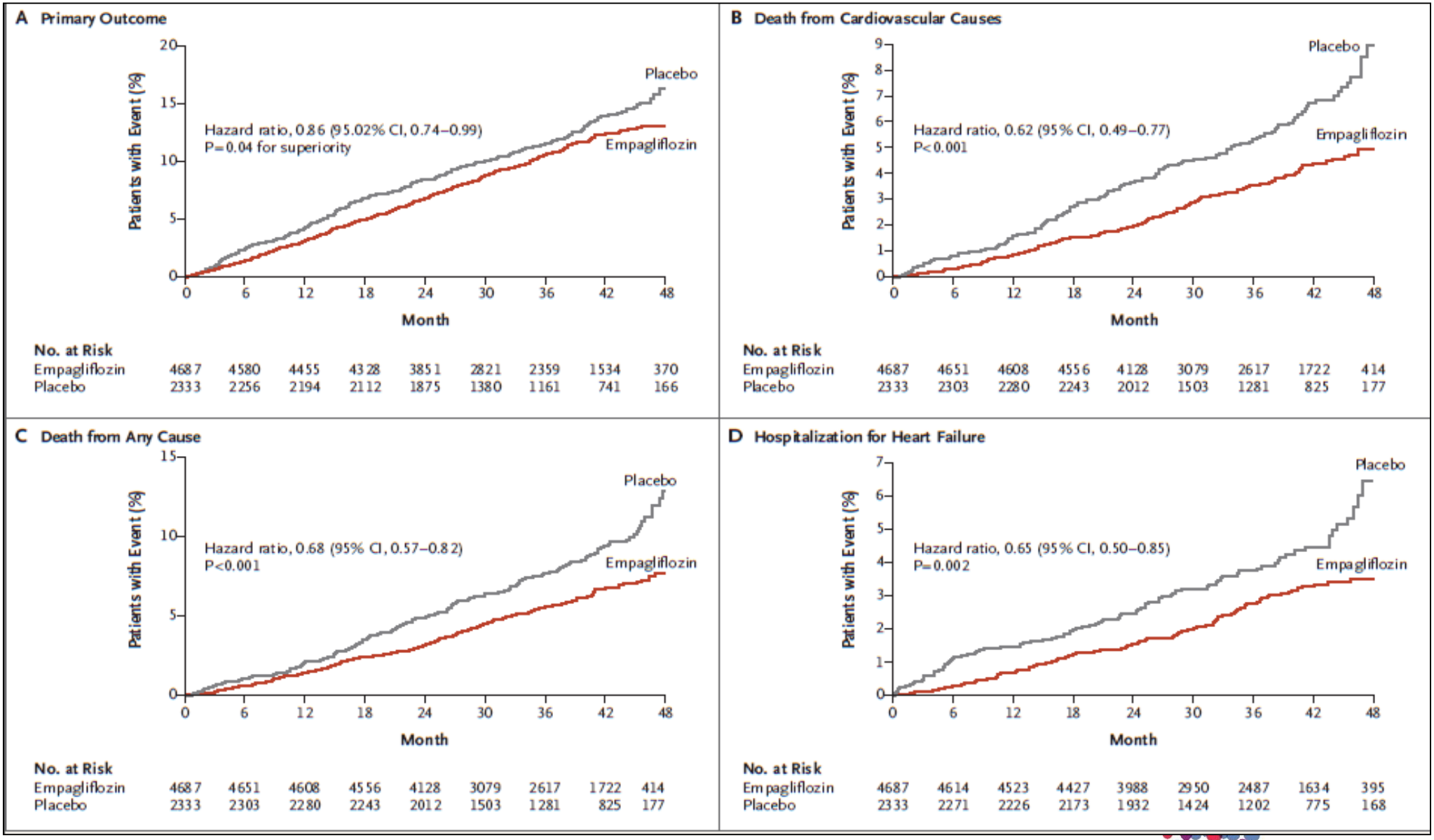
Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

Cardiovascular outcomes

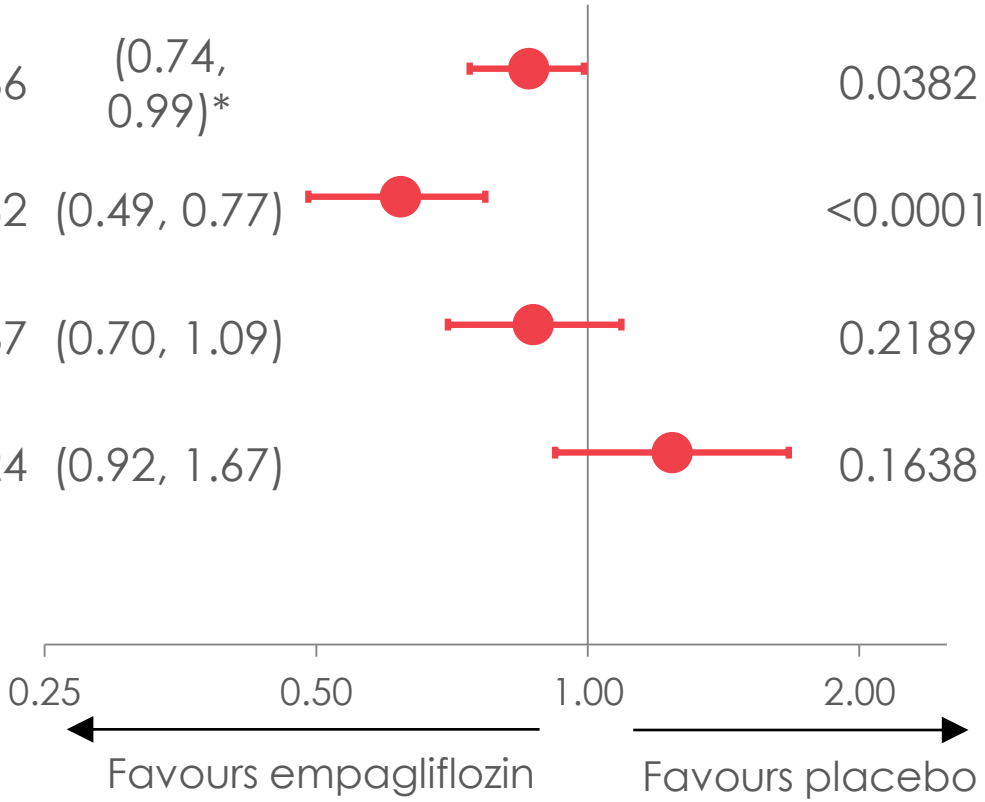
Cardiovascular outcomes



EMPA-REG OUTCOME®

CV death, MI and stroke

	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



Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

EMPA-REG OUTCOME®

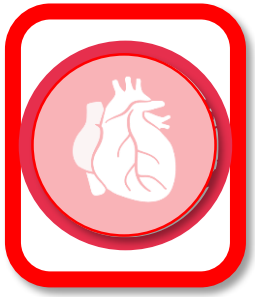
EMPA-REG OUTCOME®: Summary

Empagliflozin in addition to standard of care reduced CV risk and improved overall survival in adults with T2D at high CV risk

14%

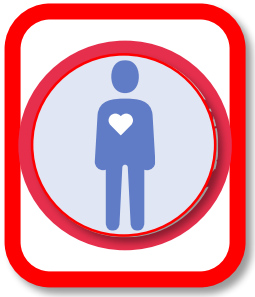
Relative risk reduction in 3P-MACE

38%



Reduction in CV death

32%

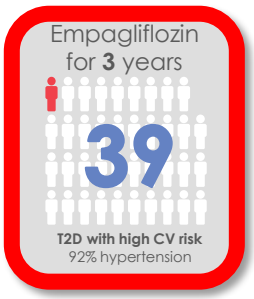


Reduction in all cause mortality

35%

Reduction in hospitalisations for heart failure

39



NNT to save one life in 3 years

The overall safety profile of empagliflozin was consistent with previous clinical trials and current label information

Zinman *et al N Engl J Med* 2015; doi: 10.1056/NEJMoa1504720

EMPA-REG OUTCOME®

Table 1—Cardiovascular outcomes in the EMPA-REG OUTCOME study

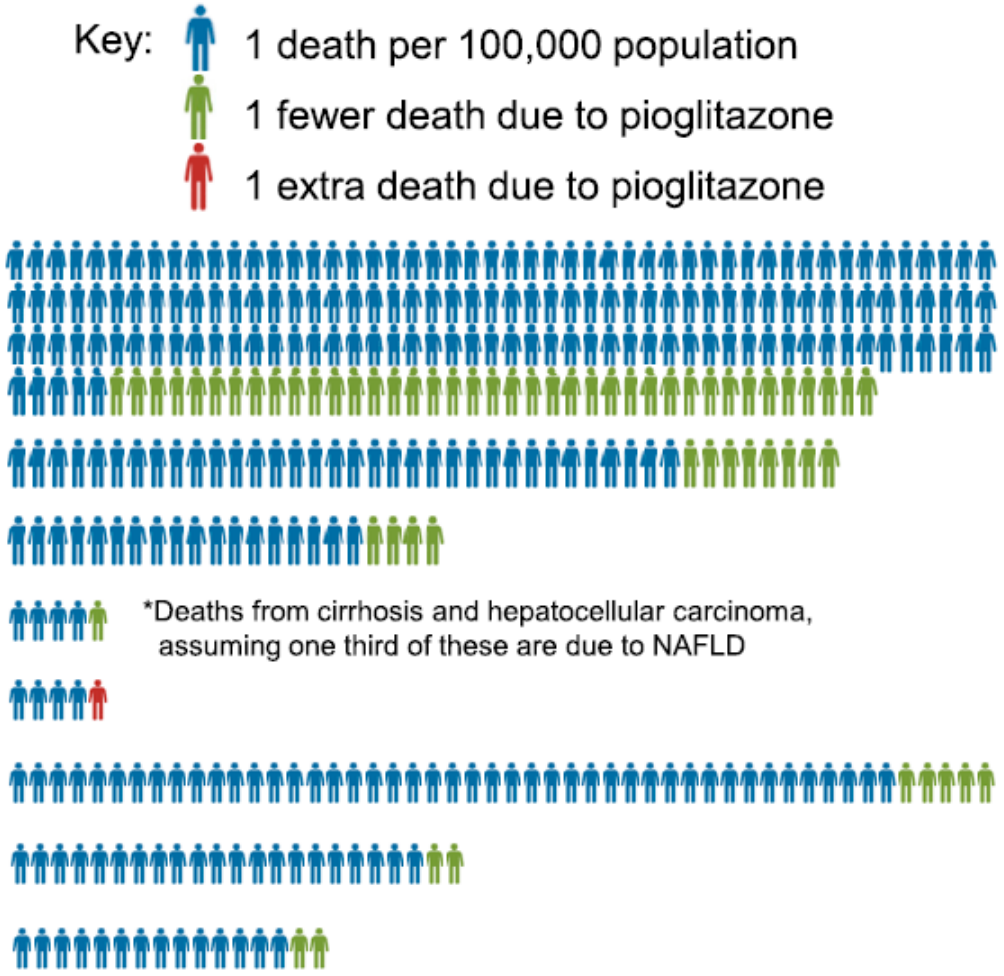
CV outcome	Placebo group (*n* = 2,333)	Pooled empagliflozin group (*n* = 4,687)	Relative risk reduction
CV death, nonfatal MI/stroke	12.1	10.5	−14*
Death from any cause	8.3	5.7	−32*
CV death	5.9	3.7	−38*
Hospitalization for HF	14.5	9.4	−35*
Fatal/nonfatal MI (excludes silent MI)	5.4	4.8	−13**
Nonfatal stroke	3.0	3.5	+24**

Data are %. *Significant. **Nonsignificant.

CV death redection : 1.7 / 1,000

Sunder Mudaliar Diabetes Care 2016;39:1115–11

Cause of death	Deaths per 100,000	Potential effect of pioglitazone	
		Risk	Deaths
Heart Disease	194	-20%	-39
Stroke	42	-20%	-8
Diabetes	22	-20%	-4
NAFLD-related*	5	-20%	-1
Bladder cancer	4	+20%	+1
Lung cancer	50	-10%	-5
Breast cancer	23	-10%	-2
Colon cancer	16	-10%	-2



Cardiometabolic

Total of
52 fewer deaths
per 100,000

Cancer

Net effect:
8 fewer deaths
per 100,000

Hip Fracture (age 65+)

Potentially
20-30 more deaths
per 100,000**

**Assuming pioglitazone increases hip fractures 20% with the typical all-cause mortality within one year (which includes cardiometabolic and cancer causes)

Cell Metabolism 20, October 7, 2014

Age-Specific Trends From 2000–2011 in All-Cause and Cause-Specific Mortality in Type 1 and Type 2 Diabetes: A Cohort Study of More Than One Million People

Diabetes Care 2016;39:1018–1026 | DOI: 10.2337/dc15-2308

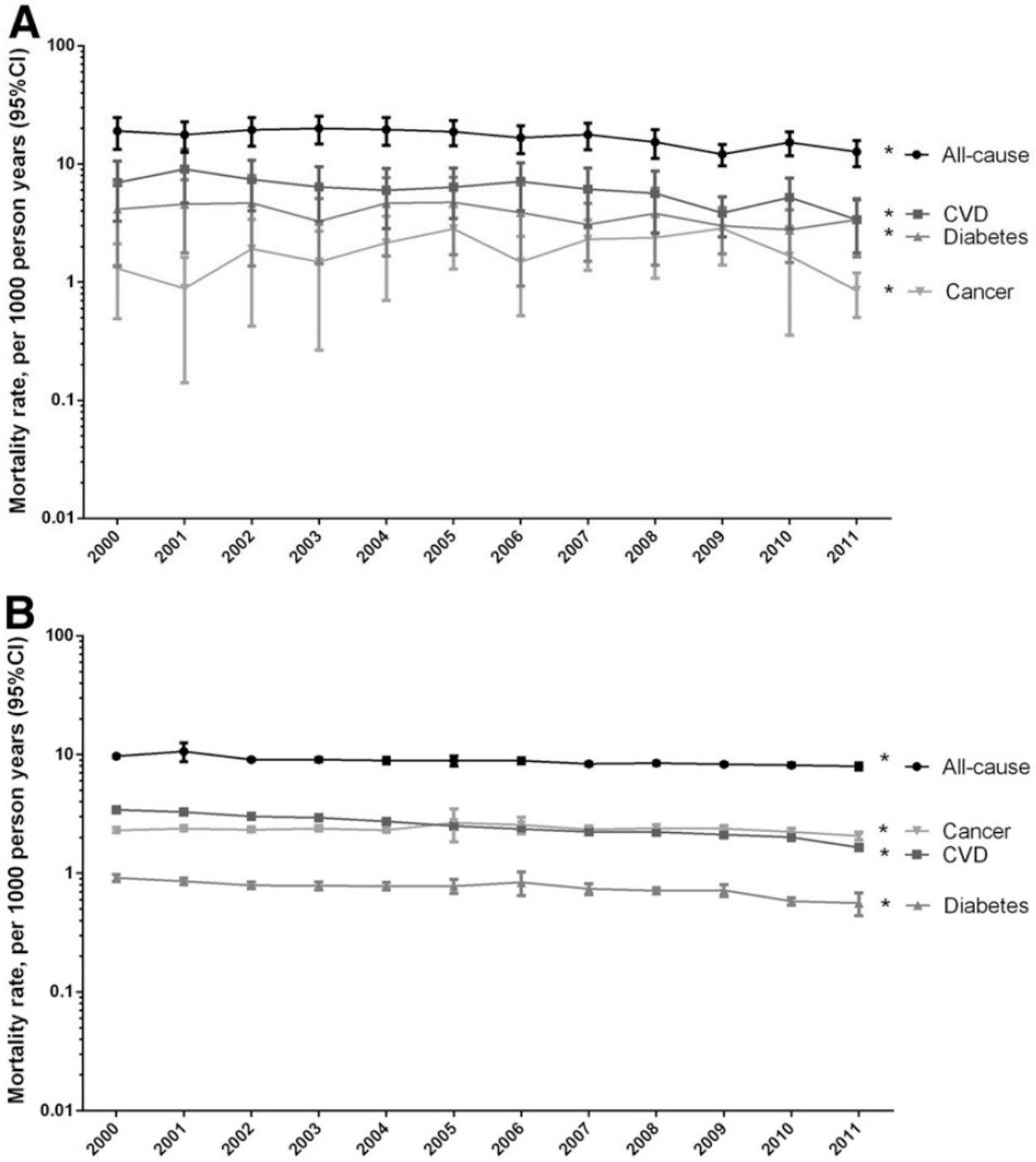


Figure 1—ASMRs in people with type 1 (*A*) and type 2 (*B*) diabetes between 2000 and 2011. Note: rates were standardized to the 2001 Australian population. *$P_{trend} < 0.05$.

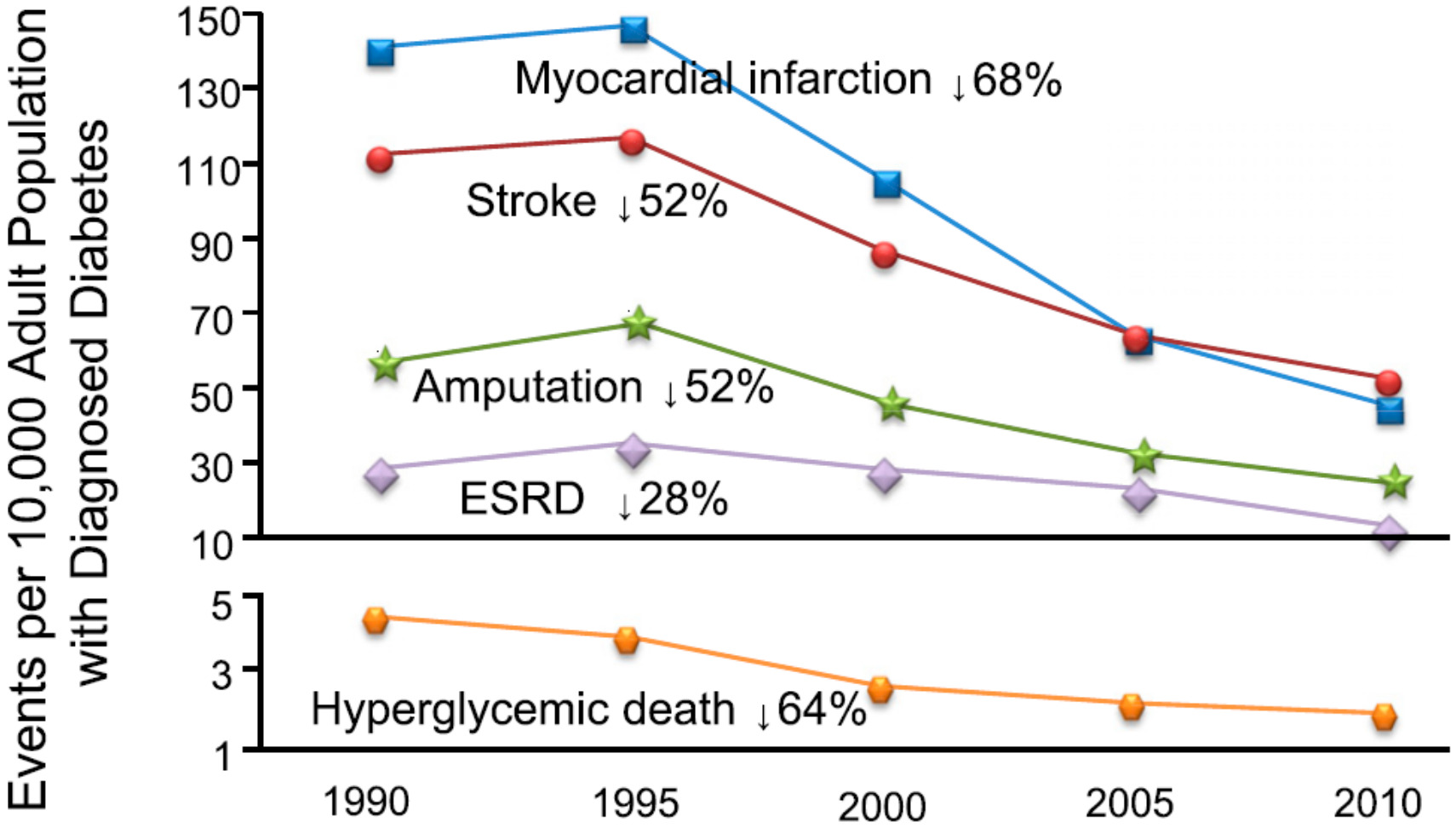


Figure 5—Trends in the occurrence of diabetes-related complications from 1990 to 2010 among adult population with diagnosed diabetes (13). ESRD, end-stage renal disease.

Diabetes Care 2016;39:1657–1663

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 13, 2017 VOL. 376 NO. 15

Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Naveed Sattar, M.D., Ph.D., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.

N Engl J Med 2017;376:1407-18.

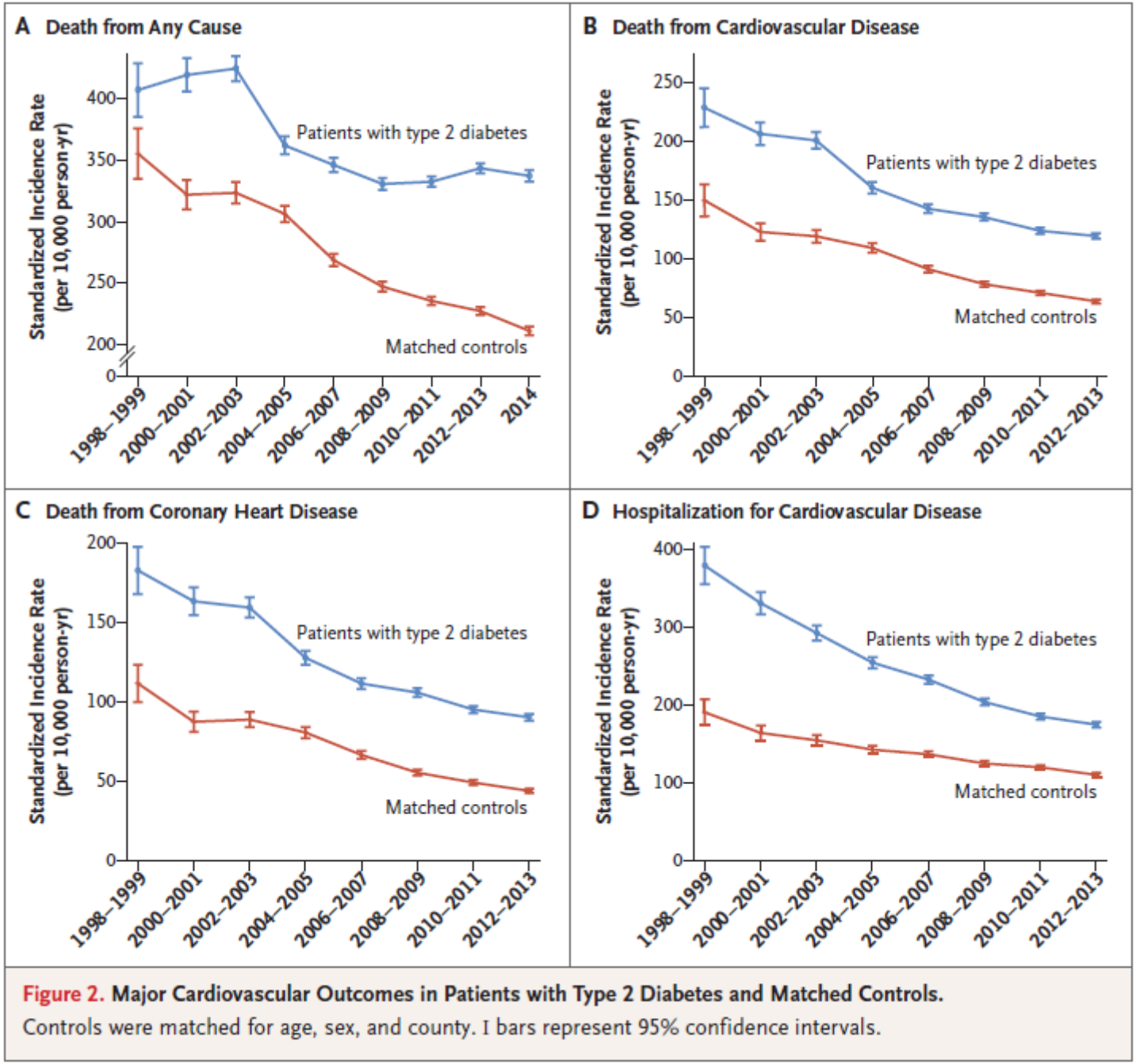
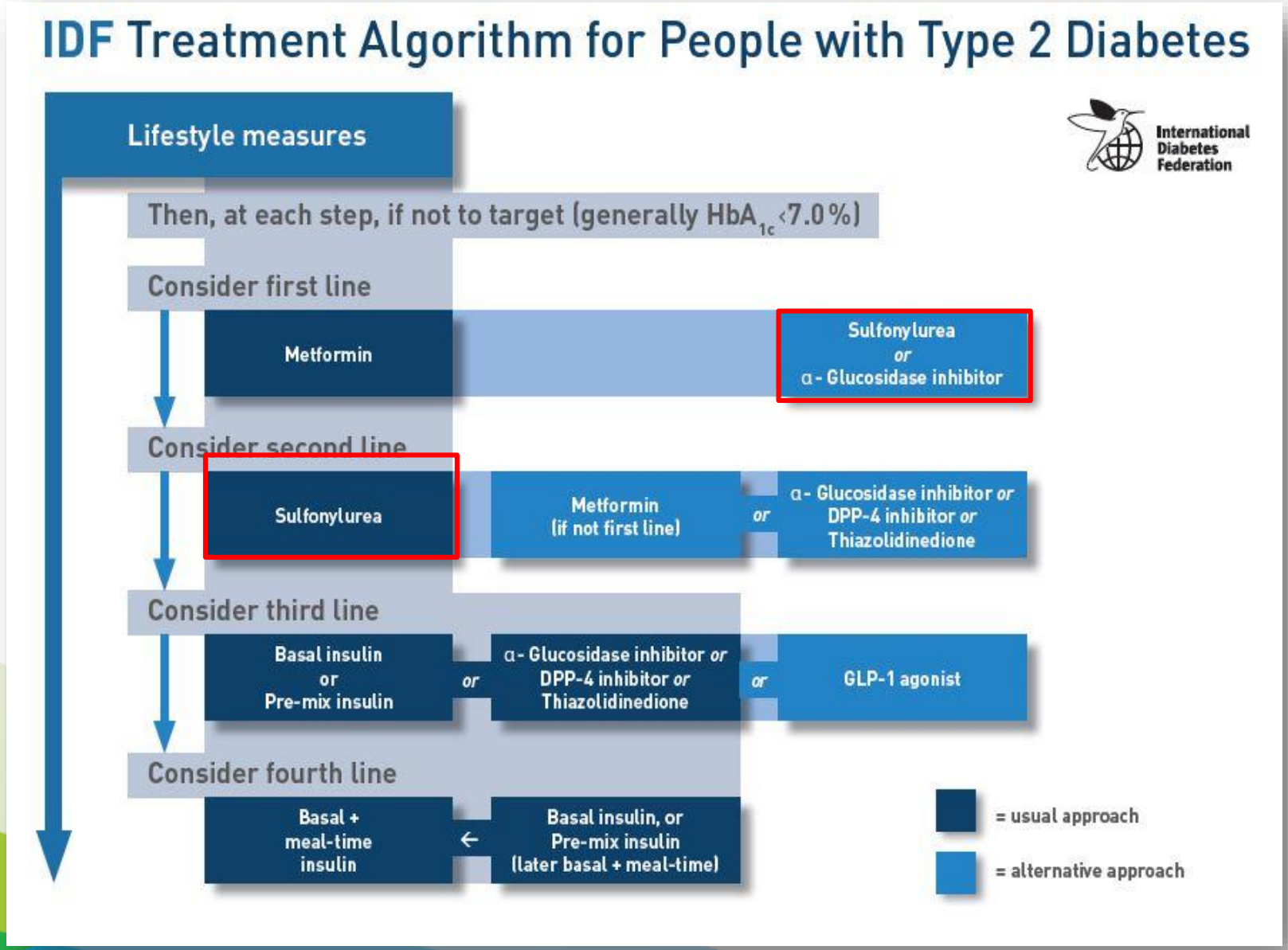


Figure 2. Major Cardiovascular Outcomes in Patients with Type 2 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals.

N Engl J Med 2017;376:1407-18.

Sulfonylurea in the guidelines and its role today

IDF Guideline



International Diabetes Federation, 2012, Global Guideline for Type 2 Diabetes

ADA/EASD Position Statement

Start with Monotherapy unless:

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 — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

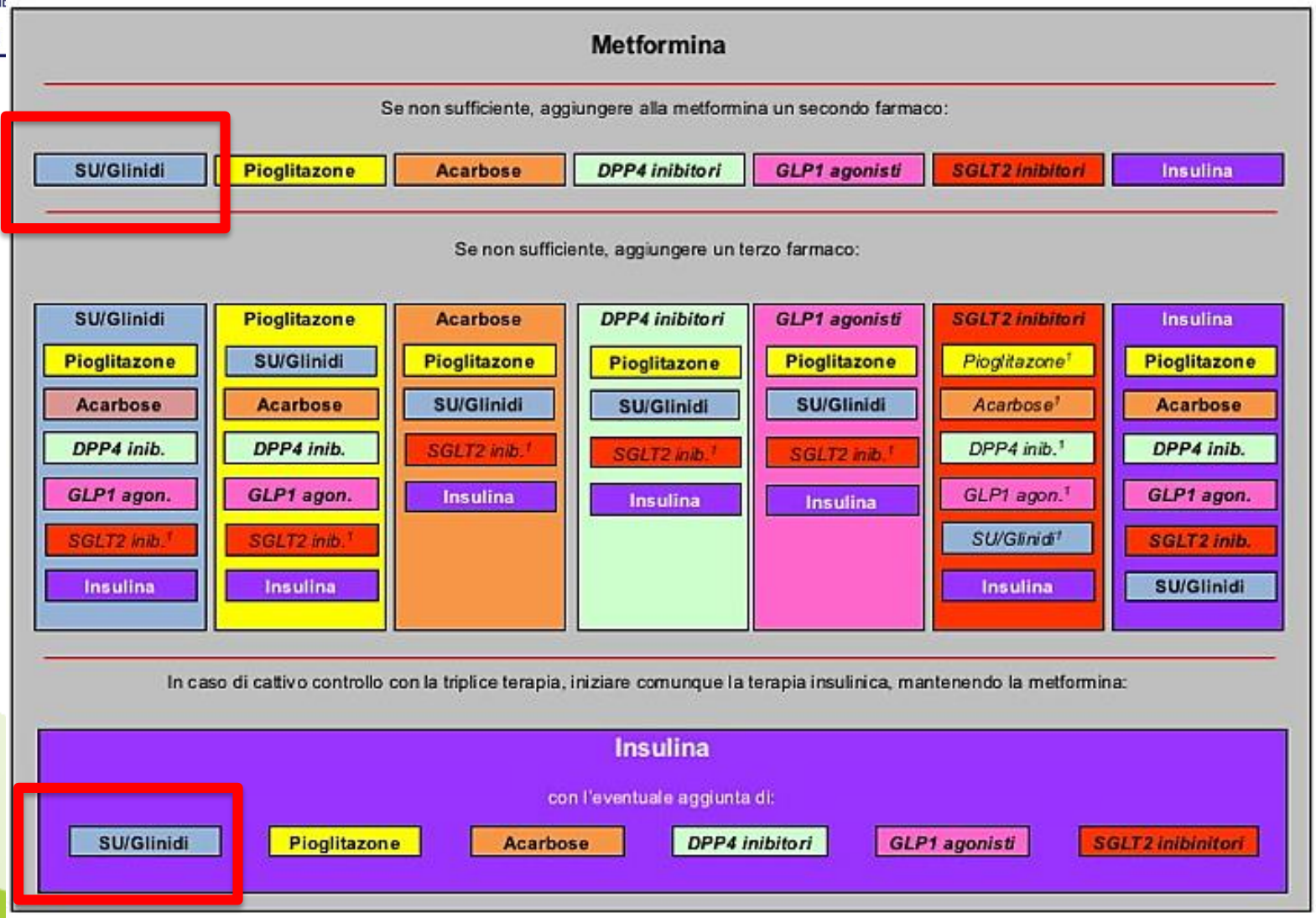
Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

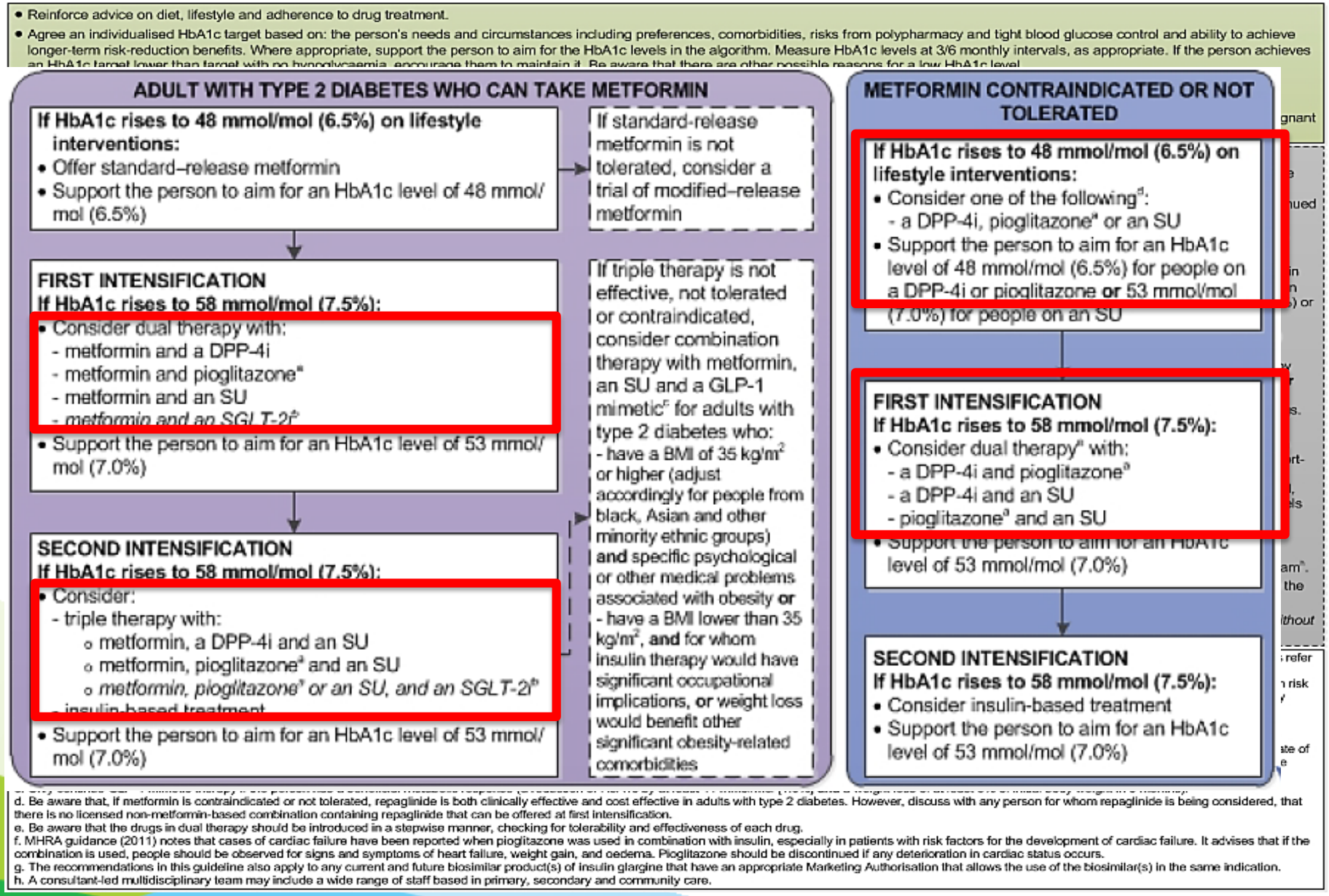
Combination Injectable Therapy (See Figure 8.2)

Italian Diabetes Society



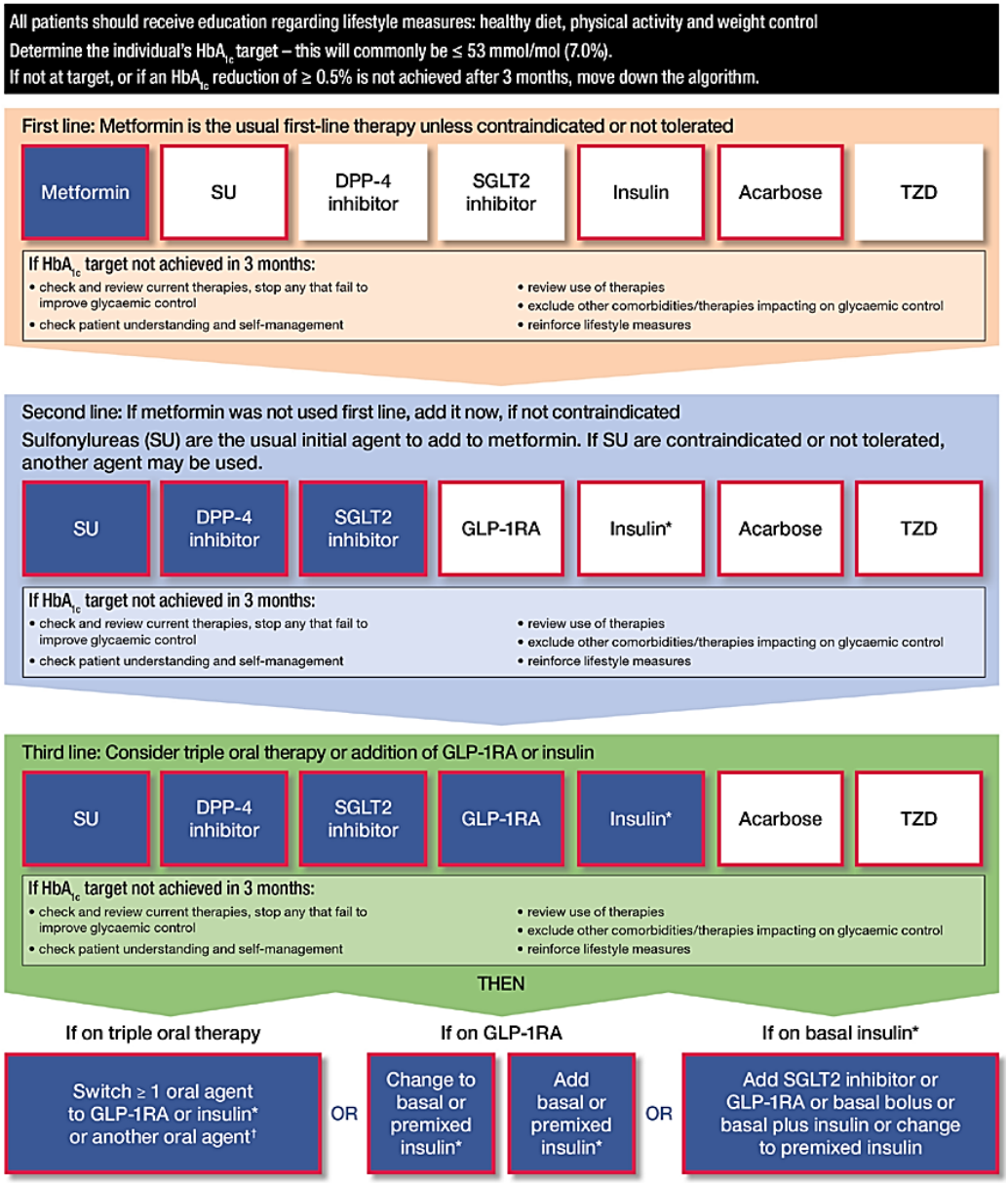
AMD-SID 2016; www.standarditaliani.it

UK NICE - Algorithm for blood glucose-lowering therapy



Type 2 diabetes in adults: management. NICE guideline NG28 (December 2015)

Australian Blood Glucose Treatment Algorithm for Type 2 Diabetes



PBS = Pharmaceutical Benefits Scheme, SU=sulfonylurea, TZD= thiazolidinedione, DPP-4 = dipeptidyl peptidase-4, GLP-1RA= glucagon like peptide 1 receptor agonist, SGLT2 = sodium glucose transporter.
Dark blue boxes indicate usual therapeutic strategy (order is not meant to denote any specific preference) (usual refers to commonly available, evidence based, cost effective therapy). **White boxes** indicate alternate approaches (order is not meant to denote any specific preference). **Red outlines** indicate the classes of glucose lowering agent that include PBS subsidised products.
* Unless metformin is contraindicated, or not tolerated, it is often therapeutically useful to continue it in combination with insulin in people with Type 2 diabetes.
† Switching an oral agent is likely to have the smallest impact on glycaemia.

Gunton JE et al. ADS_POSITION STATEMENT 2016

Suggested Treatment Approach for Specific Patient Profiles

Malaysian Endocrine & Metabolic Society

2nd Gen SU: selected 2nd generation sulphonylurea (gliclazide); DPP-4i: dipeptidyl peptidase-4 inhibitor; SGLT2i: sodium-glucose cotransporter 2 inhibitor; GLP-1 RA: glucagon-like peptide-1 receptor agonist. DPP-4i should be stopped once GLP-1 RA is introduced.

- Patients who are well-controlled on their existing drugs should continue with the treatment regime.
- Bariatric surgery may be considered in patients with BMI ≥32 kg/m2 and their diabetes not controlled by lifestyle changes and pharmacotherapy.

Clinical Practice Guidelines for the Management of Type 2 Diabetes Mellitus. Kuala Lumpur: Joint Publication of the Ministry of Health Malaysia, Academy of Medicine Malaysia, Malaysian Endocrine & Metabolic Society and Diabetes Malaysia; 140 p. 5th Edition, December 2015

National/Regional Diabetes Guidelines in non-Western Countries

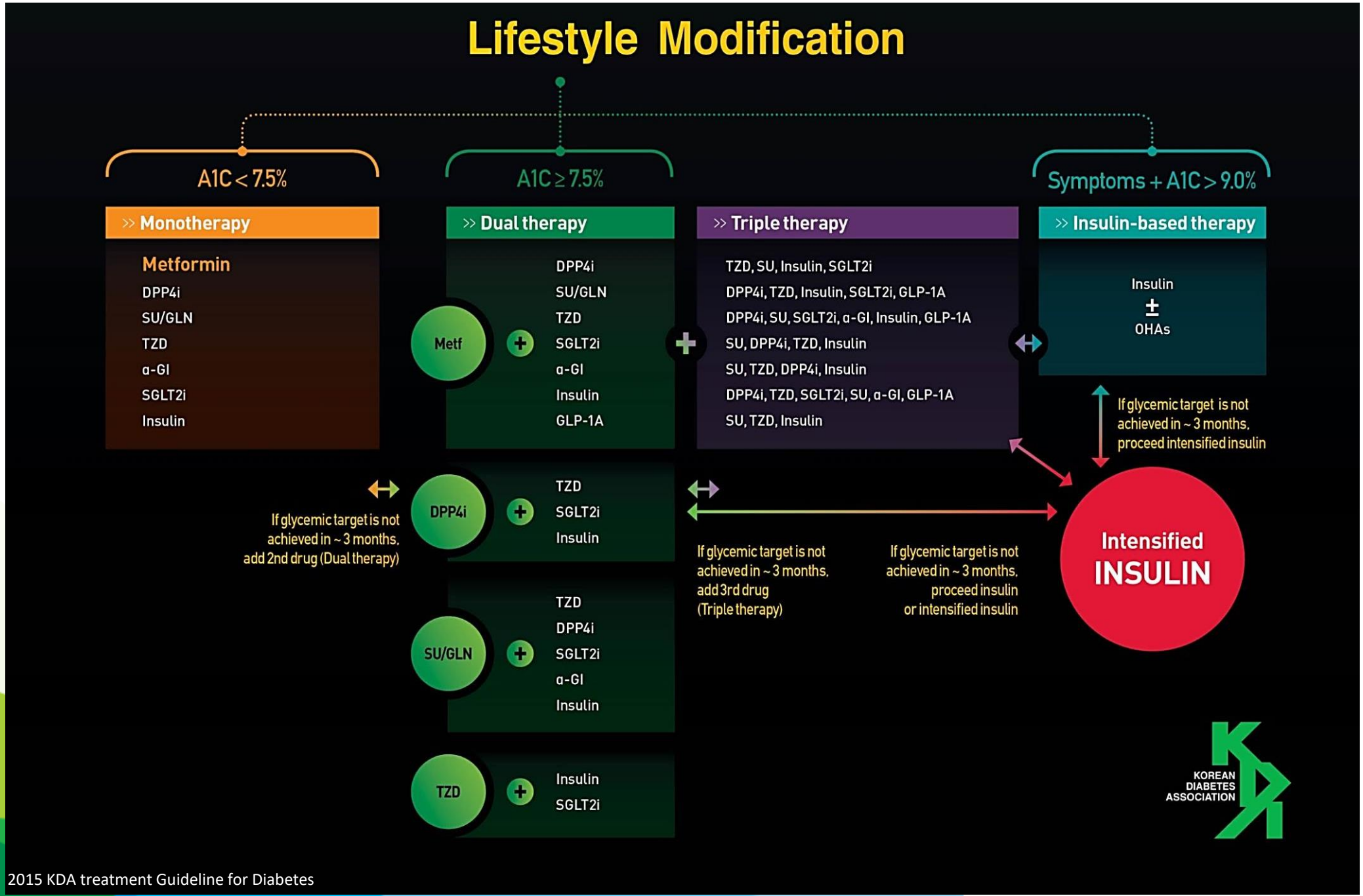
	North Africa and Middle East	East and South Asia	Central and South America	Other
Type 2 diabetes (*n*)	11	9	5	8
33 guidelines	Algeria	Bangladesh	Argentina	Belarus
	Egypt	China	Brazil	Kazakhstan
	Iraq	India	Chile	Israel
	Morocco	South Korea		Ukraine
	Saudi Arabia	Taipei		South Africa
	Syria	Thailand		
	Tunisia			
	United Arab Emirates			

66% recommended addition of a sulfonylurea to metformin as the choice for second-line therapy

*Published online: May 4, 2013

Home P et al. *Diabetes Ther (2013) 4:91–102*

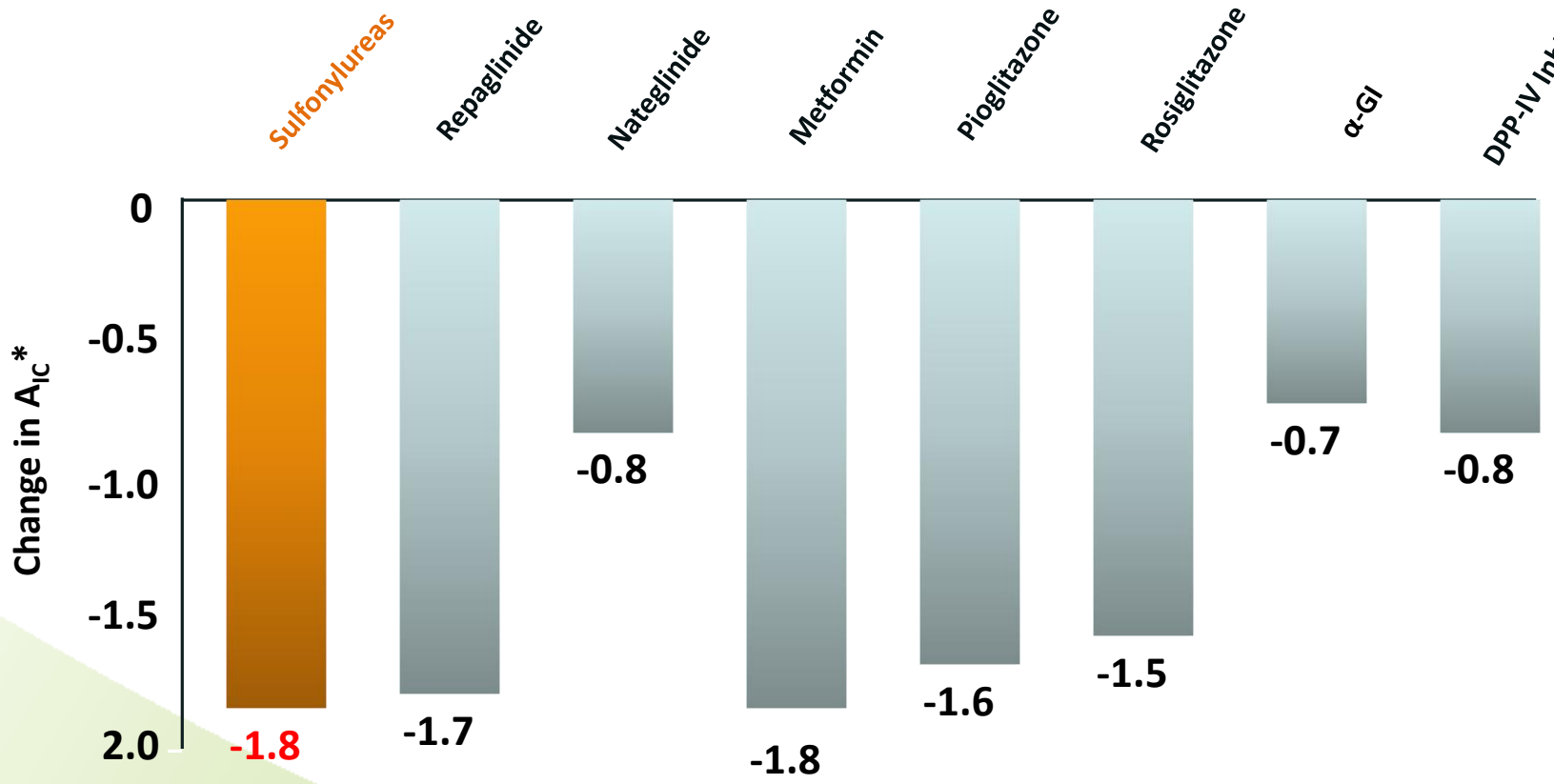
2015 대한당뇨병학회 약물치료 알고리듬



2015 KDA treatment Guideline for Diabetes

SU is effective for lowering HbA_{1C}

❖ Glucose lowering efficacy of OAD



* Difference from placebo; based on package Insert date; combination of different classes of oral agents tend to have an additive effect on HbA1c lowering

Sulfonylurea-efficacy

- **Proven efficacy of SU**

Diabetes Care Volume 37, September 2014 2647

Beyond Metformin: Safety Considerations in the Decision-Making Process for Selecting a Second Medication for Type 2 Diabetes Management

Reflections From a *Diabetes Care* Editors' Expert Forum

William T. Cefalu,[1] John B. Buse,[2] Stefano Del Prato,[3] Philip D. Home,[4] Derek LeRoith,[5] Michael A. Nauck,[6] Itamar Raz,[7] Julio Rosenstock,[8] and Matthew C. Riddle[9]

Diabetes Care 2014;37:2647–2659 | DOI: 10.2337/dc14-1395

The trend toward personalized management of diabetes has focused attention on the differences among available pharmacological agents in terms of mechanisms of action, efficacy, and, most important, safety. Clinicians must select from these features to develop individualized therapy regimens. In June 2013, a nine-member *Diabetes Care* Editors' Expert Forum convened to review safety evidence for six major diabetes drug classes: insulin, sulfonylureas (SUs), thiazolidinediones (TZDs), glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium glucose cotransporter 2 inhibitors. This article, an outgrowth of the forum, summarizes well-delineated and theoretical safety concerns related to these drug classes, as well as the panelists' opinions regarding their best use in patients with type 2 diabetes. All of the options appear to have reasonably wide safety margins when used appropriately. Those about which we know the most—metformin, SUs, insulin, and perhaps now also TZDs—are efficacious in most patients and can be placed into a basic initial algorithm. However, these agents leave some clinical needs unmet. Selecting next steps is a more formidable process involving newer agents that are understood less well and for which there are unresolved questions regarding risk versus benefit in certain populations. Choosing a specific agent is not as important as implementing some form of early intervention and advancing rapidly to some form of combination therapy as needed. When all options are relatively safe given the benefits they confer, therapeutic decision making must rely on a personalized approach, taking into account patients' clinical circumstances, phenotype, pathophysiological defects, preferences, abilities, and costs.

Today, there are more therapy options for managing type 2 diabetes than ever before. Primary care and specialty clinicians and the patients they advise benefit from having a wide range of interventions from which to choose in developing diabetes management plans. However, this abundance also means that therapeutic decision making has become increasingly challenging.

Recommendations published in 2012 by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (1) set forth a flexible

[1]Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA
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[3]Department of Clinical and Experimental Medicine, University of Pisa School of Medicine, Pisa, Italy
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[5]Icahn School of Medicine at Mt. Sinai, New York, NY
[6]Diabeteszentrum Bad Lauterberg, Bad Lauterberg, Germany
[7]Diabetes Unit, Department of Internal Medicine, Hadassah Hebrew University Hospital, Jerusalem, Israel
[8]Dallas Diabetes and Endocrine Center at Medical City and University of Texas Southwestern Medical Center, Dallas, TX
[9]Division of Endocrinology, Diabetes, and Clinical Nutrition, Oregon Health & Science University, Portland, OR

Corresponding author: William T. Cefalu, william.cefalu@pbrc.edu.

This article contains videos online at http://dx.doi.org/10.2337/dc14-1395.

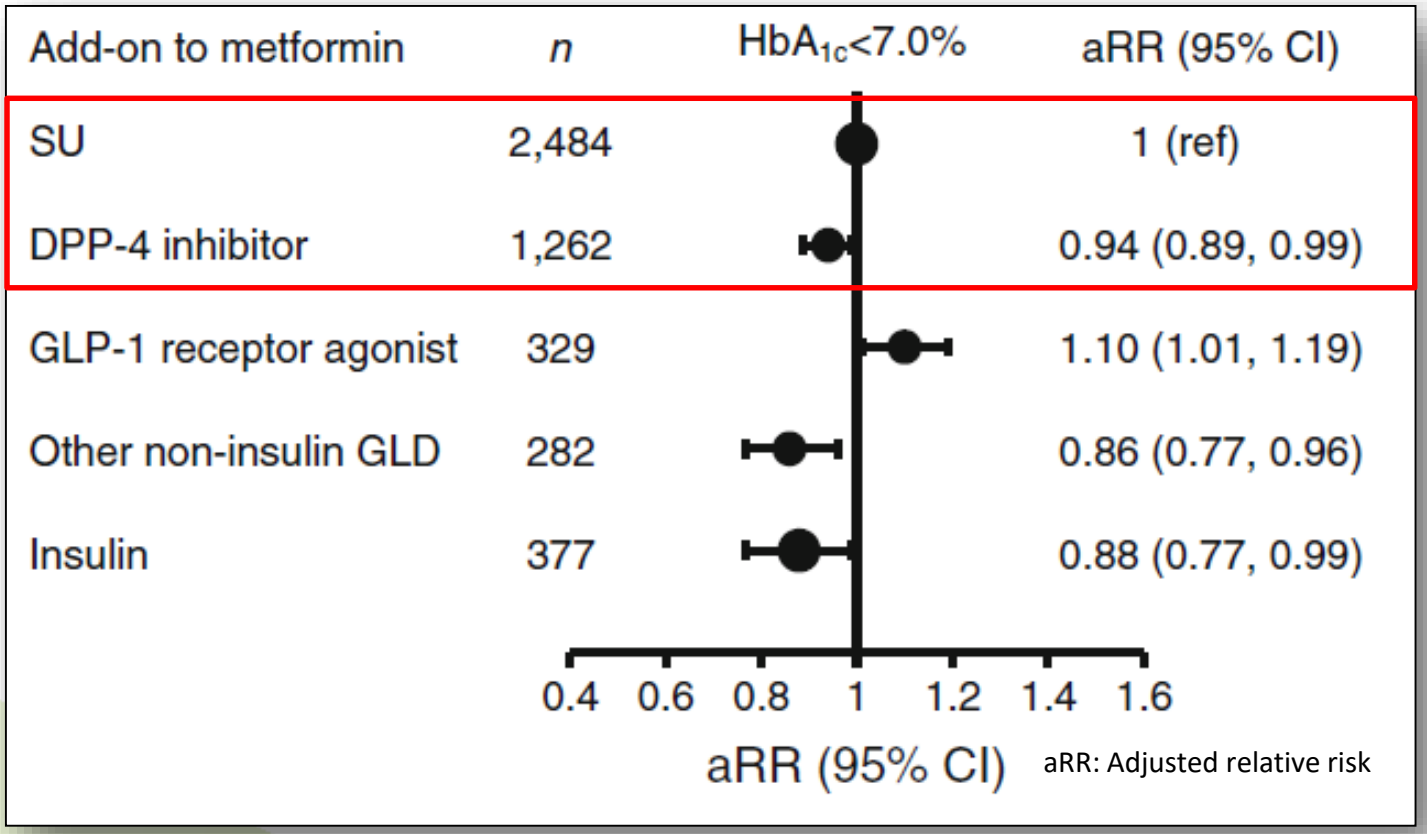
SUs: a Proven and Still Valuable Option

As new drug classes have been introduced, promotional efforts have suggested that SUs are an outmoded class to be replaced by newer agents. However, we do clearly know the efficacy of these agents, just as we are aware of their limitations of hypoglycemia and weight gain. Objectively, one could argue that, given the wealth of clinical experience, new safety concerns are not likely to emerge. Although poor durability of effectiveness has been a major criticism, participants assigned to standard therapy in the ORIGIN trial, treated mainly with metformin and an SU, maintained glycemic control (average A1C 6.5%) for 6 years (9). SUs also offer the advantages of ease of administration, good tolerability, and low cost.

Cefalu WT et al. *Diabetes Care* 2014 37 2647–2659

Sulfonylurea-efficacy

- **As an add-on agent, Sulfonylurea was more effective in achieving HbA1c<7% than DPP-4 inhibitor.**

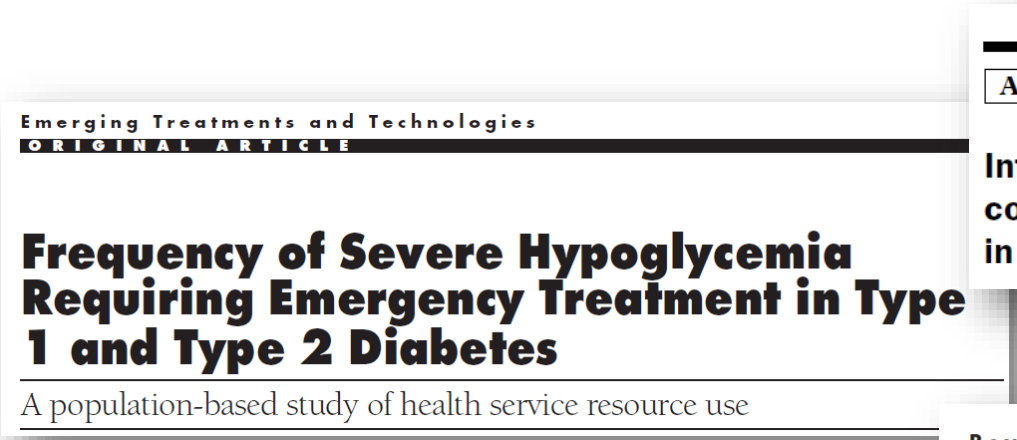


- Aims : To assess glycaemic control in metformin users receiving their first add-on glucose-lowering therapy and to examine the real-life effectiveness of different add-on drugs
- Methods : A population-based cohort study using healthcare databases in northern Denmark during 2000–2012. included 4,734 persons who initiated metformin monotherapy and added another glucose-lowering drug within 3 years. Attainment of recommended HbA1c goals within 6 months of add-on was investigated, using Poisson regression analysis adjusted for age, sex, baseline HbA1c, diabetes duration, complications and Charlson Comorbidity Index.

Thomsen RW et al. *Diabetologia*. 2015 ;58(10):2247-2253

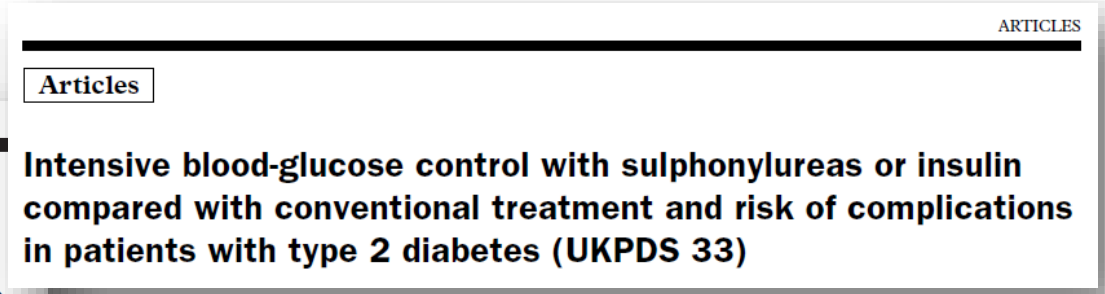
Sulfonylurea-hypoglycemia?

- Old SUs were associated with a high rate of hypoglycemia


Emerging Treatments and Technologies
ORIGINAL ARTICLE

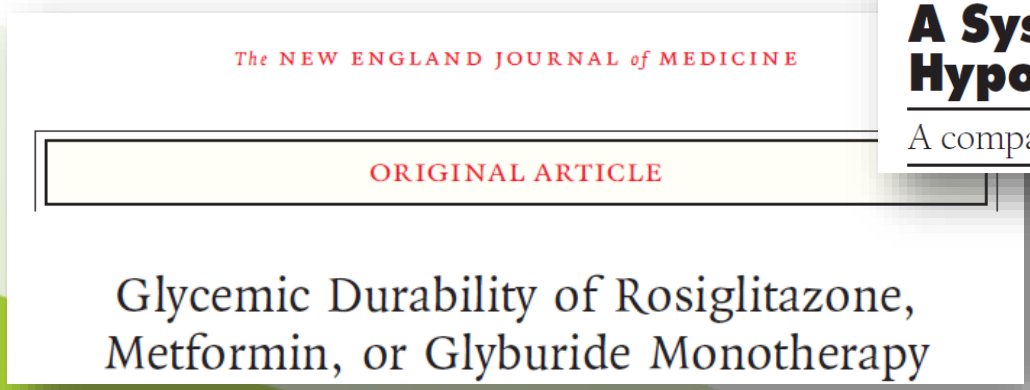
Frequency of Severe Hypoglycemia Requiring Emergency Treatment in Type 1 and Type 2 Diabetes

A population-based study of health service resource use


ARTICLES

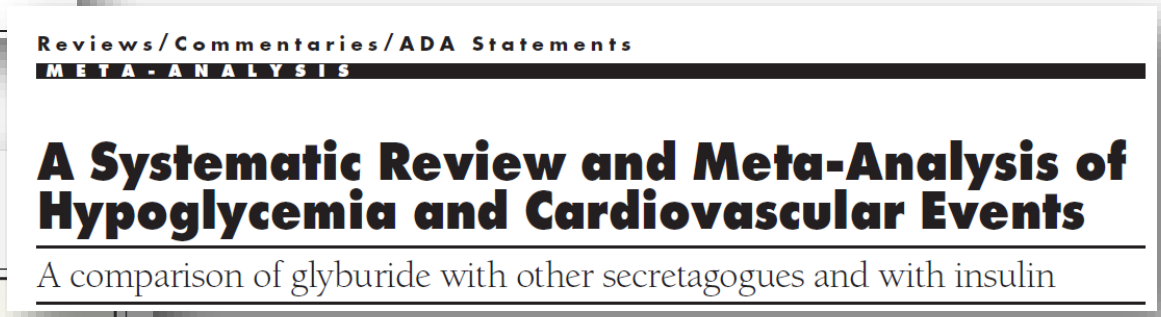
Articles

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy


Reviews/Commentaries/ADA Statements
META-ANALYSIS

A Systematic Review and Meta-Analysis of Hypoglycemia and Cardiovascular Events

A comparison of glyburide with other secretagogues and with insulin

1. Leese GP et al. *Diabetes Care* 2003;26:1176–1180 2. UKPDS Group *Lancet* 1998;352:837-853. 3. Kahn SE et al. *N Engl J Med* 2006;355:2427-2443. 4. Gangji AS et al. *Diabetes Care* 2007;30:389–394.

Hypoglycemia-Which Patients are at Risk?

Risk of Severe Hypoglycemia in Sulfonylurea -Treated Patients from Diabetes Centers in Germany/Austria :How Big is the Problem? Which Patients are at Risk?

ABSTRACT [[Word-count: 250, max 250 allowed]]

Background: We investigated the rate of severe hypoglycemic events and confounding factors in patients with type-2-diabetes treated with sulfonylurea (SU) at specialized diabetes centers, documented in the German/Austrian DPV-Wiss-database.

Methods: Data from 29,485 SU-treated patients were analyzed (median[IQR] age 70.8[62.2-77.8]yrs, diabetes-duration 8.2[4.3-12.8]yrs). The primary objective was to estimate the event-rate of severe hypoglycemia (requiring external help, causing unconsciousness/coma/convulsion and/or emergency.hospitalization). Secondary objectives included exploration of confounding risk-factors through group-comparison and Poisson-regression.

Results: Severe hypoglycemic events were reported in 826(2.8%) of all patients during their most recent year of SU-treatment. Of these, n=531(1.8%) had coma, n=501(1.7%) were hospitalized at least once. The adjusted event-rate of severe hypoglycemia [95%CI] was 3.9[3.7–4.2] events/100 patient-years (coma: 1.9[1.8–2.1]; hospitalization: 1.6[1.5–1.8]). Adjusted event-rates by diabetes-treatment were 6.7 (SU+insulin), 4.9 (SU+insulin+other OAD), 3.1 (SU+other OAD), and 3.8 (SU only). Patients with ≥1 severe event were older ($p<0.001$) and had longer diabetes-duration ($p=0.020$) than patients without severe events. Participation in educational diabetes-programs and indirect measures of insulin-resistance (increased BMI, plasma-triglycerides) were associated with fewer events (all $p<0.001$). Impaired renal function was common (N=3,113 eGFR ≤30mL/min) and associated with an increased rate of severe events (≤30mL/min: 7.7; 30-60mL/min: 4.8; >60mL/min: 3.9).

Conclusions: These real-life data showed a rate of severe hypoglycemia of 3.9/100 patient-years in SU-treated patients from specialized diabetes centers. Higher risk was associated with known risk-factors including lack of diabetes-education, older age, and decreased eGFR, but also with lower BMI and lower triglyceride-levels, suggesting that SU-treatment in those patients should be considered with caution.

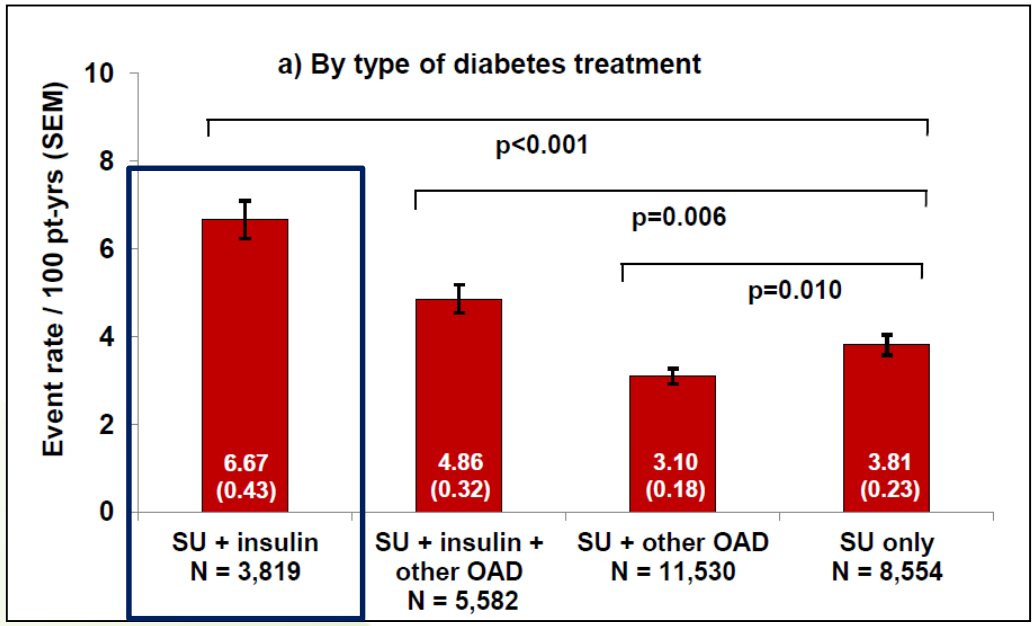
- **Background**: to investigated the rate of severe hypoglycemic events and confounding factors in patients with type-2-diabetes treated with sulfonylurea (SU) at specialized diabetes centers, documented in the German/Austrian DPV-Wiss-database.
- **Methods**: Data from 29,485 SU-treated patients were analyzed
- **Objective** : to estimate the event-rate of severe hypoglycemia.* Secondary objectives included exploration of confounding risk-factors through group-comparison and Poisson-regression.

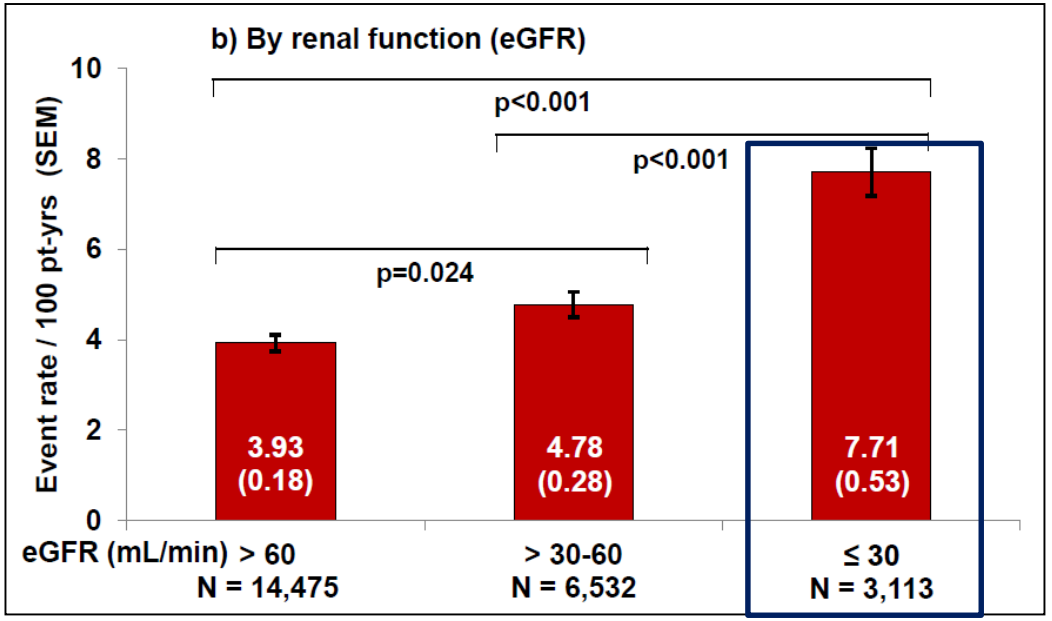
*Severe hypoglycemia:
requiring external help, causing unconsciousness /coma/convulsion and/or emergency.hospitalization

Schloot NC et al. *Diabetes Metab Res Rev*. 2016 Mar ;32(3):316-24 (Epub 2015 Nov 20)

Risk factor for severe hypoglycemia

- The risk of severe hypoglycemia was significantly increased in patients receiving with insulin and in patients with impaired renal function





Schloot NC et al. *Diabetes Metab Res Rev*. 2016 Mar ;32(3):316-24 (Epub 2015 Nov 20)

Risk factor for severe hypoglycemia

❖ **Increased risk of severe hypoglycemia occurs in patients with chronic renal impairment and the elderly.**

Table 1. Patient characteristics

Characteristic	2006	2007	2008	2009	Total	*P* value
N	38	74	128	80	320	
M	13	33	52	35	133	
F	25	41	76	45	187	
Age, yr	70.7±10.0	71.6±10.4	67.6±11.9	70.0±11.9	69.5±10.9	0.316
HbA1c, %	6.9±1.1	6.5±1.3	7.0±1.3	7.3±1.8	7.0±1.5	0.485
Serum creatinine, mg/dL	2.0±2.1	1.9±1.8	2.2±2.3	1.8±1.8	2.0±2.1	0.770
GFR, mL/min/1.73 m^2	59.0±36.1	58.9±35.8	50.4±32.7	54.7±30.6	48.0±33.6	0.034
CKD 3-5 (GFR <60 mL/min/1.73 m^2)	21/38 (55.3)	41/74 (55.4)	81/128 (63.3)	45/80 (56.3)	188/320 (58.8)	<0.01
Duration of diabetes, yr	11.0±10.8	12.7±9.90	11.2±7.6	15.8±10.8	12.7±9.6	0.416
Serum glucose, mg/dL	37.1±14.4	36.8±13.5	34.5±2.3	35.1±15.9	37.9±34.5	<0.007
Serum AST, U/L	22.1±10.1	33.0±24.8	33.5±27.3	36.0±49.4	33.4±33.6	<0.007
Serum ALT, U/L	18.0±8.8	24.5±10.1	27.5±47.8	26.0±30.5	26.7±38.6	<0.035

Values are presented as mean±standard deviation or number (%).

* Most hypoglycemic patients (87.5%, 280/320) were over 60 years old.

- Retrospective analysis of the characteristics, risk factors, and medical costs of 320 severely hypoglycemic patients with diabetes who presented to an ER of Uijeongbu St. Mary's Hospital from January 1, 2006 to December 31, 2009.

Ha WC et al. *Diabetes Metab J* 2012;36 280–2

Hypoglycemia is common with old SUs

- **Glyburide was associated with a higher risk for hypoglycemia than gliclazide MR in older adults.**

Table 2
Ninety-day outcomes in the monotherapy study

	Number of events (%)		Absolute risk difference (%) (95% CI)	NNH (95% CI)	Conditional OR (95% CI)	p value
	Glyburide n=4374	Gliclazide n=4374				
Hospital encounter due to hypoglycemia	69 (1.58%)	8 (0.18%)	1.40% (1.01% to 1.79%)	71 (55 to 99)	8.63 (4.15 to 17.93)	<0.0001
All-cause mortality	100 (2.29%)	84 (1.92%)	0.37% (−0.21% to 0.95%)	(…)	1.21 (0.89 to 1.63)	0.22

Table 4
Ninety-day outcomes in the metformin combination study

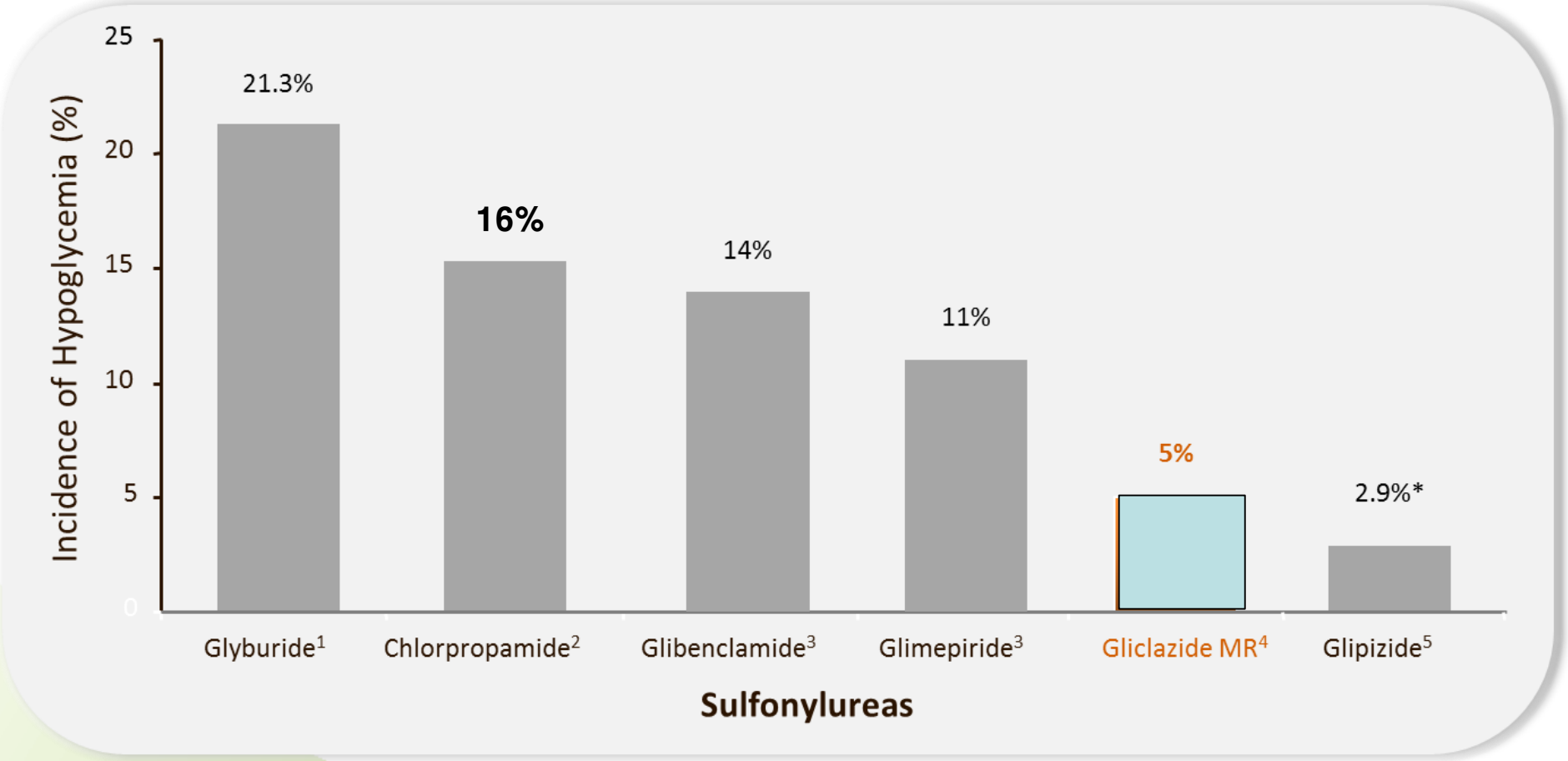
	Number of events (%)		Absolute risk difference (%) (95% CI)	NNH (95% CI)	Conditional OR (95% CI)	p value
	Glyburide n=8038	Gliclazide n=8038				
Hospital encounter due to hypoglycemia	110 (1.37%)	19 (0.24%)	1.13% (0.86% to 1.40%)	77 (71 to 116)	6.06 (3.68 to 9.97)	<0.0001
All-cause mortality	109 (1.36%)	75 (0.93%)	0.43% (0.10% to 0.76%)	233 (131 to 1000)	1.47 (1.09 to 1.97)	0.012

NNH, number needed to harm; *OR*, odds ratio.
Note: Patients prescribed gliclazide MR served as the referent group.

- Objectives: To investigated the risk of a hospital encounter with hypoglycemia following a new prescription for glyburide compared with modified-release gliclazide.
- Methods: In 2 population-based matched retrospective cohort studies in Ontario, Canada, between 2002 and 2011, older adults who were newly prescribed glyburide or gliclazide as monotherapy or in the presence of metformin.
- primary outcome : hospital encounter with hypoglycemia assessed within 90 days.

Clemens K et al. *Can J Diabetes*. 2015; 39 32-40.

Hypoglycemia-Are all SUs same?



*Hypoglycemia: hypoglycemic symptom and fingerstick blood glucose measurement ≤50 mg/dL (2.75 mmol/L)

1. Glucovance [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2004. 2. UKPDS Group. *Lancet* 1998; 352: 837–853. 3. Draeger KE, et al. *Horm Metab Res*. 1996; 28: 419–425.
4. McGavin JK, et al. *Drugs* 2002; 62; 1357–1364. 5. Metaglip [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2002

JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes

MINI REVIEW

Incretin-based drugs for type 2 diabetes: Focus on East Asian perspectives

Yutaka Seino[1,2]*, Hitoshi Kuwata[1,2], Daisuke Yabe[1,2,3,4]*

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J Diabetes Investig 2016; 7: 102–1

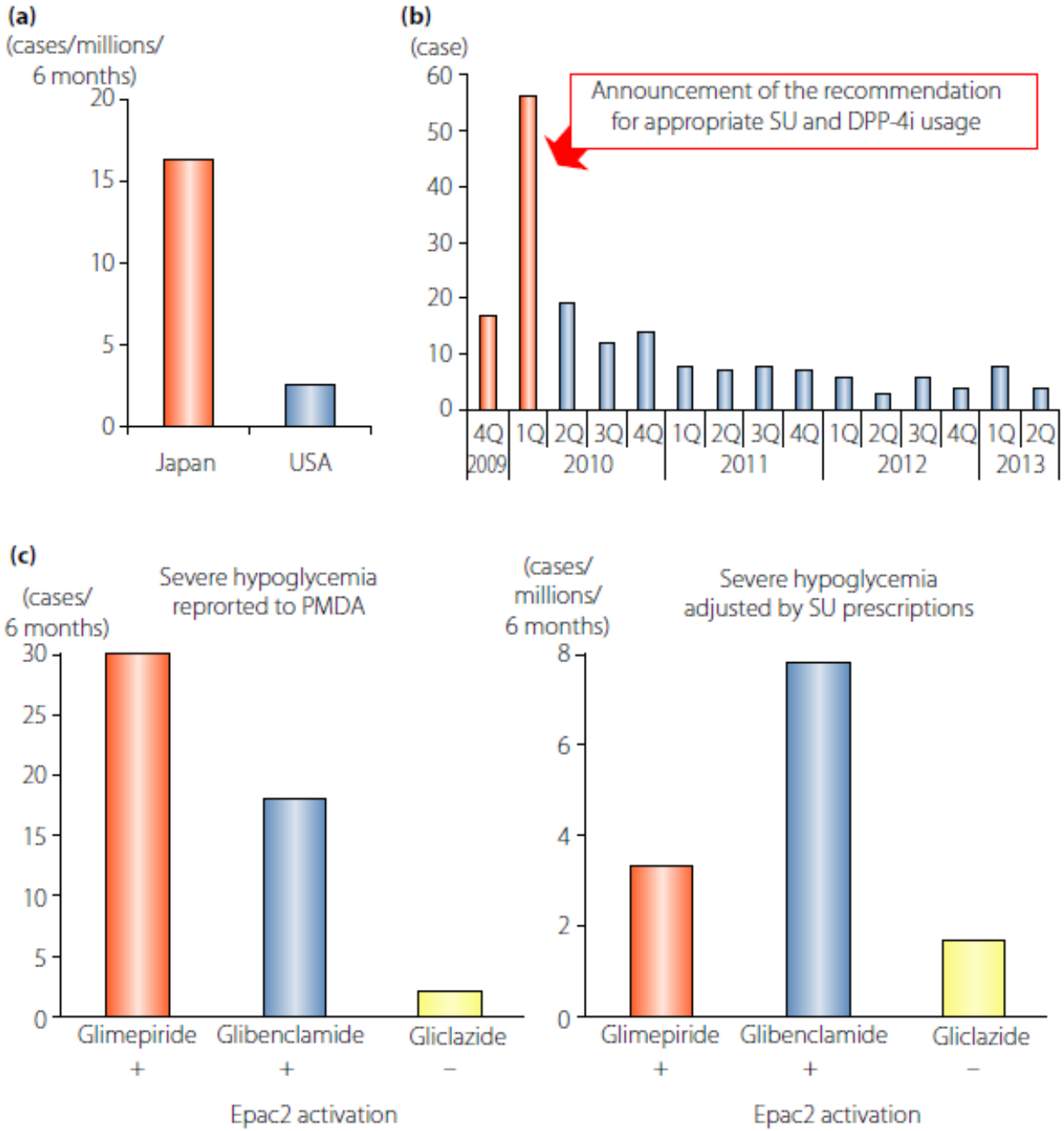

Figure 4 | Severe hypoglycemia in individuals receiving dipeptidyl peptidase-4 inhibitors (DPP-4i) as add-on to sulfonylureas (SUs). (a) Comparison of the incidence rate of severe hypoglycemia in individuals receiving the DPP-4i, sitagliptin, in Japan and the USA. The incidence of hypoglycemic

PLOS | MEDICINE

RESEARCH ARTICLE

The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials

Dimitris Varvaki Rados*, Lana Catani Pinto, Luciana Reck Remonti, Cristiane Bauermann Leitão, Jorge Luiz Gross

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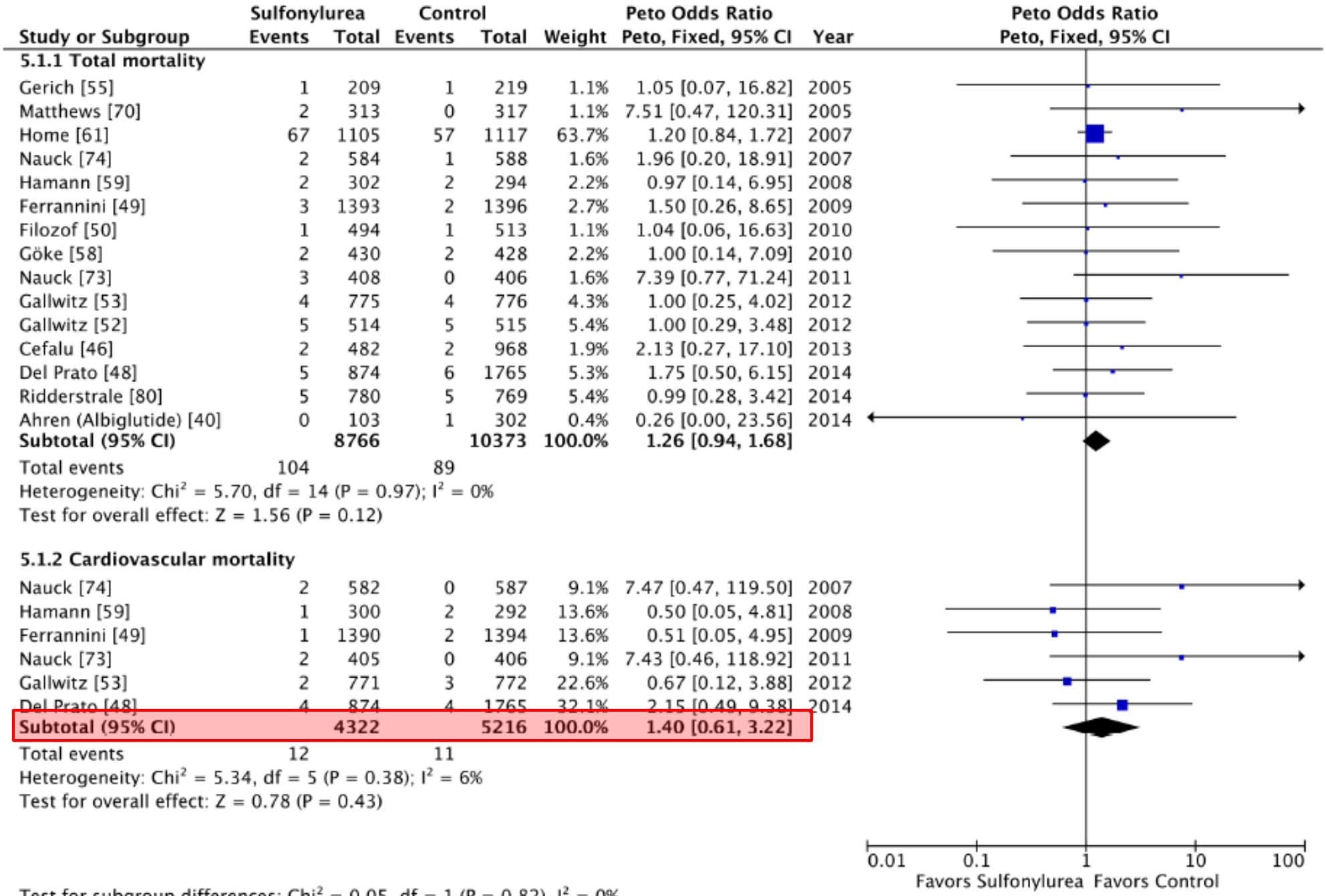

Fig 5. Forest plots for all-cause and cardiovascular mortality of sulfonylureas as an add-on to metformin. For studies with multiple treatment groups, the group being compared is presented in parentheses.

Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies

Laurent Azoulay[1,2,3] *and Samy Suissa*[1,2]

Diabetes Care 2017;40:706–714 | DOI: 10.2337/dc16-1943

Sulfonylurea-CV safety?

American Diabetes Association 75th Scientific Sessions | June 5-9, 2015 | Boston, MA

Sulphonylureas Are Not Associated with Increased Mortality: Meta-analysis and Trial Sequential Analysis of Randomized Clinical Trials

Session New Insights into the Effects of Oral Agents

Sulphonylureas Are Not Associated with Increased Mortality: Meta-analysis and Trial Sequential Analysis of Randomized Clinical Trials

Author(s) DIMITRIS V. RADOS, LANA C. PINTO, LUCIANA R. REMONTI, LUIS H. CANANI, CRISTIANE B. LEITAO, JORGE L. GROSS, *Porto Alegre, Brazil*

The aim of this study was to evaluate the safety of currently used sulphonylureas (SU) in total and cardiovascular mortality, myocardial infarction and stroke, and to analyse if the available sample is powered enough to support the results. We performed a systematic review, meta-analysis and trial sequential analysis (TSA) of randomized clinical trials (PROSPERO registry CRD42014004330). MEDLINE, EMBASE, Cochrane Library, clinicaltrial.gov databases, and manual review of references and recent congresses were researched to identify randomized clinical trials (RCT) with at least 52 weeks of duration evaluating any second or third generation sulphonylureas (glyburide, glibenclamide, gliclazide or glipizide) in the treatment of type 2 diabetes. Peto's OR summarized the data. Sensitive analyses were performed with empirical continuity correction. TSA was conducted for quantifying the statistical reliability of data and included studies with zero events in both arms.Forty-seven RCT were included, totalizing 37650 patients. SU were not associated with total (OR 1.12, 95% C.I. 0.96 to 1.30; I2 = 0%, p = 0.67) or cardiovascular mortality (OR 1.12, 95% C.I. 0.87 to 1.42; I2 = 12%, p = 0.30). SU were also not associated with increased risk of myocardial infarction(OR 0.92, 95% CI 0.76 - 1.12; I2 = 3% p = 0.42) or stroke (OR 1.16, 95% CI 0.81 - 1.66; I2 = 30% p = 0.09). These results were similar across the different comparator classes. Individually, Glipizide was the only sulphonylurea associated with increased risk for total and cardiovascular mortality. Quality of the evidence was considered high for mortality outcomes and moderate for stroke and myocardial infarction. In conclusion, SU are not associated with increased harm. The present analysis has enough power to exclude an absolute risk as small as 0.5%.

Keywords Sulphonylureas, mortality

American Diabetes Association
1701 North Beauregard Street Alexandria, VA 22311

American Diabetes Association.

Rados DV et al. *Diabetes.* 2015 64 Suppl 1 A5

Sulfonylurea-CV safety?

Second and third-generation sulfonylureas may not affect all-cause or cardiovascular mortality but may decrease the risk of non-fatal macrovascular outcomes

Abstract

Background: Guidelines recommend metformin as the first-line oral treatment for type 2 diabetes. We conducted a systematic review to assess whether the use of second- and third-generation sulfonylurea agents is associated with benefits and harms in terms of patient-important outcomes compared with metformin.

Methods: We searched several electronic databases and other sources for randomized clinical trials published to August 2011. We included trials that compared sulfonylurea versus metformin monotherapy among patients 18 years or older with type 2 diabetes and that had an intervention period of at least 24 weeks. We assessed risk of bias and extracted data related to interventions and outcomes. The risk of random errors was assessed by trial sequential analysis.

Results: We included 14 trials (4560 participants). All trials were judged to be at high risk of bias. Data on patient-important outcomes were sparse. Compared with metformin, sulfonylurea did not significantly affect all-cause mortality (relative risk [RR] 0.98, 95% confidence interval [CI] 0.61 to 1.58) or cardiovascular mortality (RR 1.47, 95% CI 0.54 to 4.01). Sulfonylurea significantly decreased the risk of nonfatal macrovascular outcomes (RR 0.67, 95% CI 0.48 to 0.93). However, the definition of this outcome varied among trials, and trial sequential analysis showed that more trials are needed before reliable conclusions can be drawn. No differences between sulfonylurea and metformin were found for change in fasting blood glucose level or glycosylated hemoglobin concentration in the random-effects model. Sulfonylurea resulted in greater weight gain compared with metformin, a finding confirmed in the trial sequential analysis. Significantly more patients in the sulfonylurea arm than in the metformin arm had mild hypoglycemia (RR 2.95, 95% CI 2.13 to 4.07) and severe hypoglycemia (RR 5.64, 95% CI 1.22 to 26.00).

Interpretation: Some evidence suggests that, compared with metformin, second- and third-generation sulfonylureas may not affect all-cause or cardiovascular mortality but may decrease the risk of nonfatal macrovascular outcomes among patients with type 2 diabetes. They may also increase the risk of hypoglycemia. In general, the available data were too few and inconsistent to provide firm evidence concerning patient-important outcomes in relation to the benefits and harms of sulfonylurea versus metformin monotherapy.

The American Diabetes Association and the European Association for the Study of Diabetes consensus algorithm for the treatment of type 2 diabetes recommends beginning metformin treatment at diagnosis or soon after, along with lifestyle interventions.[1] For patients who cannot use metformin, another oral antidiabetic agent might be prescribed, for example a sulfonylurea. The rationale for recommending metformin as the drug of choice for type 2 diabetes seems to be based on its perceived beneficial effect on conventional surrogate outcomes (e.g., weight, tolerability and cost),[1] on the United Kingdom Prospective Diabetes Study (UKPDS) 34 outcomes in a selected subgroup of 342 obese patients[2] and on findings from observational studies.[3–6]

Sulfonylureas are divided into classes. The first-generation agents (carbutamide, tolbutamide, acetohexamide, tolazomide and chlorpropamide) were introduced for diabetes treatment in the 1950s.[1,7–9] The second-generation agents (e.g., glibenclamide, glipizide, glibornuride and gliclazide) and the third-generation agents (glimepiride, gliclazide modified-release and glipizide gastrointestinal therapeutic system) have almost completely replaced the first-generation drugs. The second- and third-generation sulfonylureas are preferred because of their perceived greater potency and perceived better safety profiles.[1,7–9]

The purpose of this systematic review was to determine whether the use of second- and third-generation sulfonylurea

Competing interests: See end of article.

This article has been peer reviewed.

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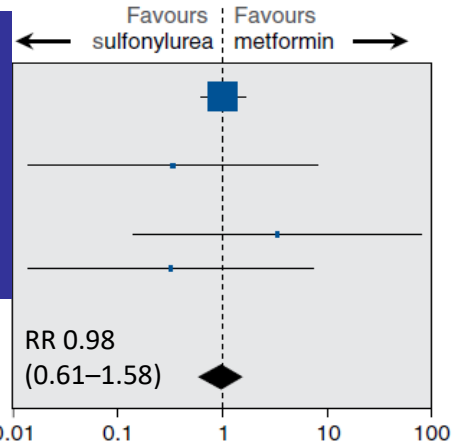
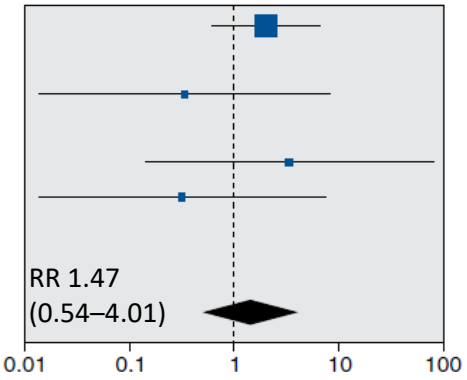
CMAJ Open 2014.DOI:10.9778/cmajo.20130073

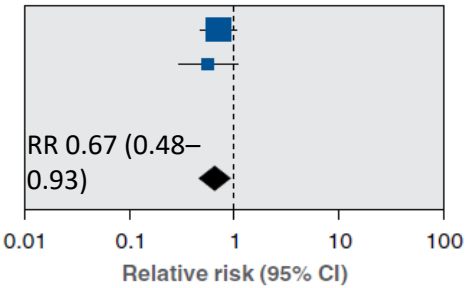
Effect of sulfonylurea versus metformin monotherapy



Cardiovascular mortality



Nonfatal macrovascular outcomes



- Systematic review of 14 RCTs(4560 participants) that compared sulfonylurea versus metformin monotherapy among patients 18 years or older with type 2 diabetes and that had an intervention period of at least 24 weeks.

Hemmingsen B et al. *CMAJ open*. 2014; 2(3):E162-E175.

CV safety-Are all SU same?

Risk of All-Cause Mortality Varies amongst Sulfonylureas: A Network Meta-analysis

Session Diabetes Complications–From Head to Toe

Oral Presentations

Number 335-OR | Monday, June 16, 2014 at 2:45 PM – 3:00 PM | Location: W-2009 (West Building)

It is uncertain if this risk is similar for all sulfonylureas because tissue selectivity and risk of hypoglycemia varies among these drugs.

Sulfonylureas are often used as second-line options for management of type 2 diabetes; however, several studies and recent meta-analyses report an increased risk of adverse cardiovascular events associated with these drugs compared to other antidiabetic drugs. It is uncertain if this risk is similar for all sulfonylureas because tissue selectivity and risk of hypoglycaemia varies amongst these drugs. We conducted a network meta-analysis to compare risk of all-cause mortality amongst the most commonly used second (gliclazide, glipizide, and glyburide) and third (glimepiride) generation sulfonylureas. Based on previous

Where possible, pairwise comparisons were calculated using random effects models and network meta-analyses were performed to compare risk amongst sulfonylureas. We identified 11 studies reporting mortality rates for patients using: gliclazide (839 (4.4%) of 19,177), glimepiride (5,318 (11.4%) of 46,644), glipizide (2,102 (14.6%) of 14,392), and glyburide (5,164 (6.8%) of 75,795). Inconsistency was low for the network meta-analysis and the relative risk of death compared to glyburide was: gliclazide 0.62 (95% CI 0.49-0.79), glimepiride 0.79 (95% CI 0.62-0.99), and glipizide 0.96 (95% CI 0.75-1.20). Our observations from 13,423 (8.6%) deaths in 156,008 type 2 diabetic patients using a second or third generation sulfonylurea suggest that there are important differences in risk amongst sulfonylureas. Although this hypothesis needs to be tested in a randomized clinical trial, clinicians should consider these possible risk differences when selecting a sulfonylurea.

Simpson SH et al. *Diabetes*. 2014 63 Suppl 1 A88-A89

Different tissue selectivity among SUs

- **Molecular structure of SUs and the effect of SUs on these KATP channels in different tissues varies**

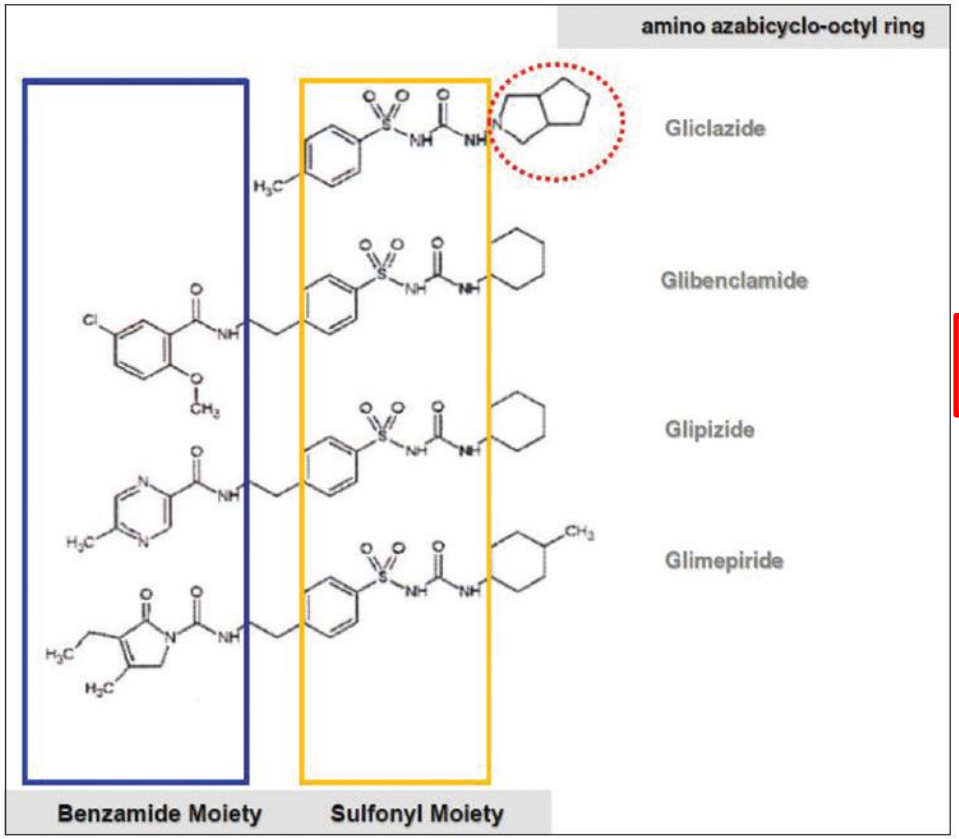


Table 5: SUR type present in different tissues

Tissue	SUR type	Blocked by
Pancreatic beta-cell	SUR_1/Kir6.2	Sulfonylureas
Cardiac and skeletal muscle	SUR_{2A}/Kir6.2	Glibenclamide, glimepiride
Vascular smooth muscle	SUR_{2B}/Kir6.1	Glibenclamide, glimepiride
Nonvascular smooth muscle	SUR_{2B}/Kir6.2	Glibenclamide
Brain	SUR_{1-2B}/Kir6.2	-

SUR: Sulfonylurea receptor

Kalra S et al. *Indian J Endocrinol Metab*. 2015; 19 577-596.

Sulfonylurea-Costs

- If cost of medications needs to be considered when determining what drug to add to metformin, SU would be the preferred class of medication

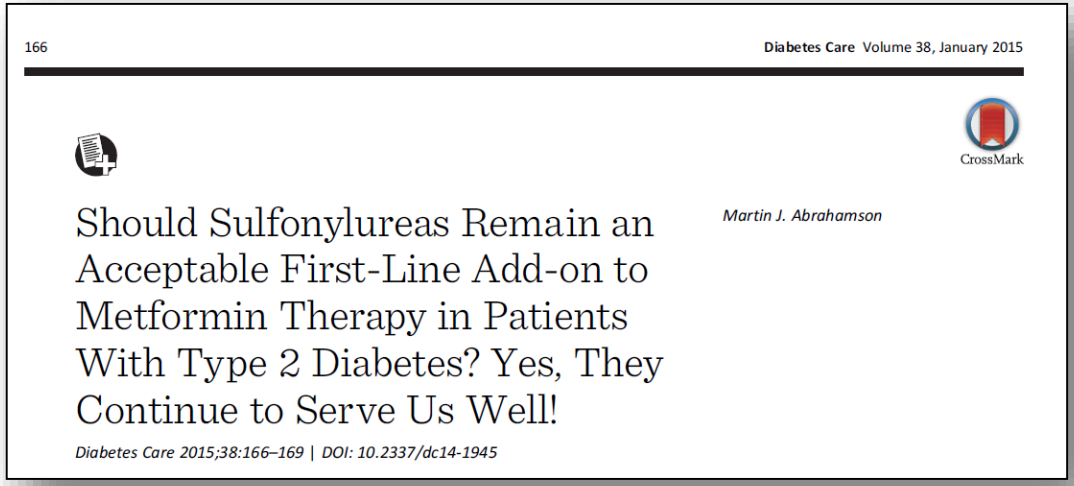
Table 1—Comparison of medications that could be added to metformin

	SU	TZD	DPP-4	GLP-1	SGLT2	AGI	Colesevelam	Cycloset	Insulin
Efficacy	High	High	Moderate	High	High	Moderate	Moderate	Moderate	High
Major side effects	Well tolerated	Edema, CHF, fractures	Pancreatitis (rare)	Nausea, vomiting, pancreatitis (rare)	UTI, vaginal yeast infection, polyuria, orthostasis	Flatulence, diarrhea	Well tolerated	Nausea, vomiting	Well tolerated
Hypoglycemia risk	Moderate	Low	Low	Low	Low	Low	Low	Low	High
Weight	Gain	Gain	Neutral	Loss	Loss	Neutral	Neutral	Neutral	Gain
Cardiovascular safety	Neutral	Neutral	Neutral	Neutral	Unknown	May lower MACE	Neutral	May lower MACE	Neutral
Cost	Low	Low	High	High	High	Moderate	Moderate	Moderate	Variable

AGI, α-glucosidase inhibitors; MACE, major adverse cardiovascular events; UTI, urinary tract infection.

Abrahamson MJ. *Diabetes Care* 2015; 38 :166–169

The Place of Sulfonylureas



166 Diabetes Care Volume 38, January 2015

CrossMark

Should Sulfonylureas Remain an Acceptable First-Line Add-on to Metformin Therapy in Patients With Type 2 Diabetes? Yes, They Continue to Serve Us Well!

Martin J. Abrahamson

Diabetes Care 2015;38:166–169 | DOI: 10.2337/dc14-1945

…the ideal antihyperglycemic agent would be easy to administer, unlikely to cause symptomatic side effects that pose barriers to adherence, inexpensive, reliably efficacious, and safe.

By such standards, it can be argued that the remaining modern SUs do well.

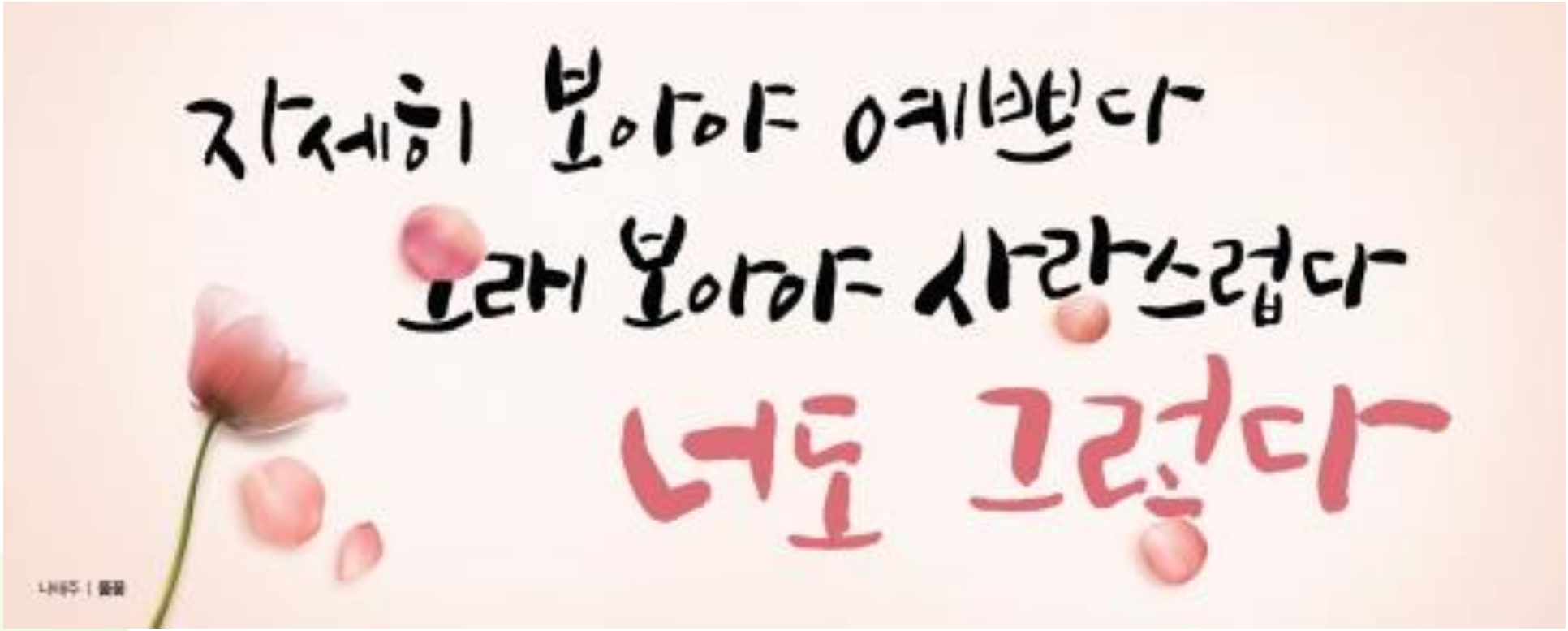
Abrahamson MJ. *Diabetes Care* 2015 38 166–169

Conclusion

Sulfonylureas, An recommended therapy !!!

- ✓ *Efficacy*
- ✓ *Hypoglycemia: different among SUs*
- ✓ *CV safety: could be different*
- ✓ *Cost*

Oldies But Goodies


자세히 보아야 예쁘다
오래 보아야 사랑스럽다
너도 그렇다

Type 2 DM-Sulphonylurea :

Vecchio amore &

Progressive amore

Thank you for your attentions