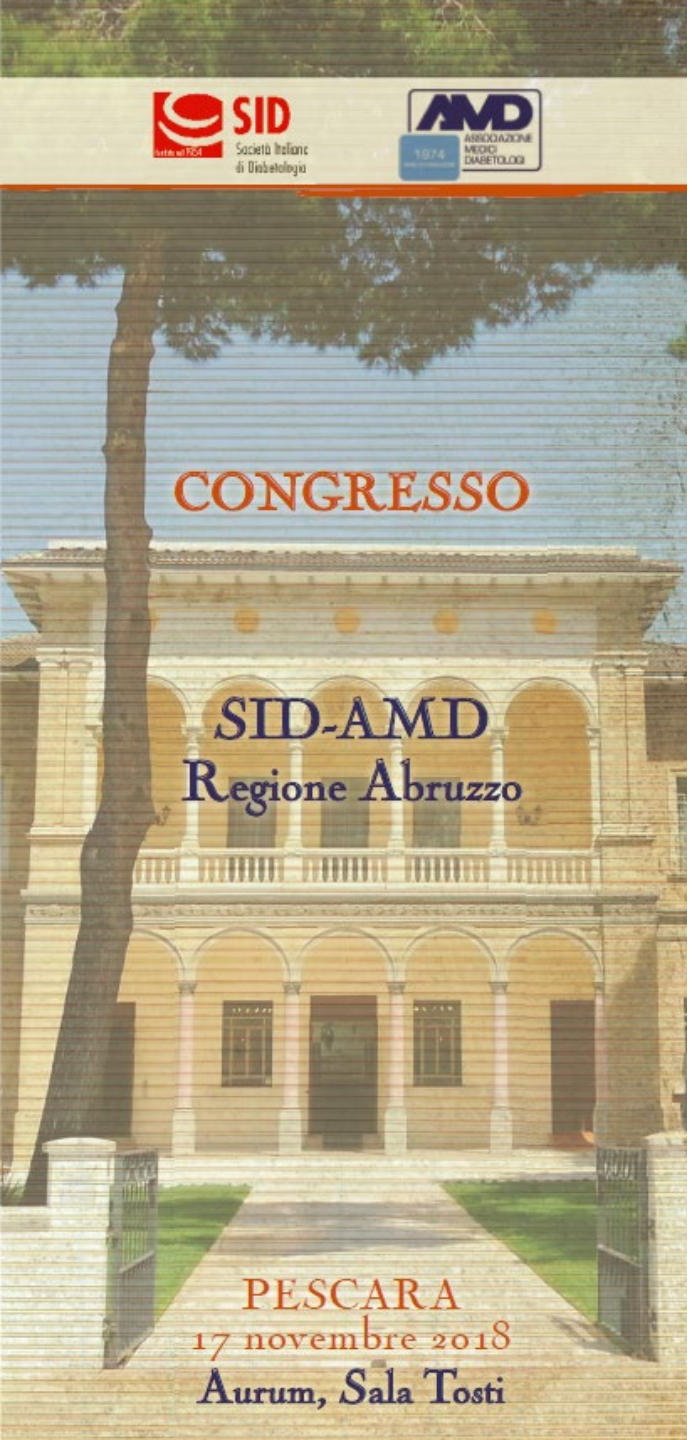


I Nuovi Standard di Cura SID-AMD
Le ragioni delle novità

AGOSTINO CONSOLI

DMSI & CeSI-MeT Università d'Annunzio – CHIETI

ITALY

Ai sensi dell'art. 76 del Regolamento applicativo dell'Accordo Stato-Regioni 02.02.2017, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Abbot, Astra Zeneca, Boheringer Ingelhaim , Eli Lilly, Merck Sharp & Dhome , Menarini Diagnostici, Novo-Nordisk, Sanofi-Aventis, Sigma-Tau, Takeda.
(Speaker)

Astra Zeneca, Boheringer Ingelhaim, Eli Lilly, Janssen Farmaceutici, Merck Sharp & Dhome, Novo-Nordisk, Sanofi-Aventis.
(Advisory Board)

Astra Zeneca , Novo-Nordisk
(Consultant)

Astra Zeneca, Eli Lilly, Novo-Nordisk
(Research Grant)

In fede, *AGOSTINO CONSOLI*

Ringrazio sinceramente la SID per lo straordinario contributo alla mia formazione culturale, scientifica e clinica.

Opinioni e giudizi espressi durante questa presentazione sono di mia esclusiva responsabilità e non possono essere imputati alla SID e/o ad alcuno dei suoi "officers".

Standard of Medical Care in Diabetes – 2017

Pharmacologic Approaches to Glycemic Treatment

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

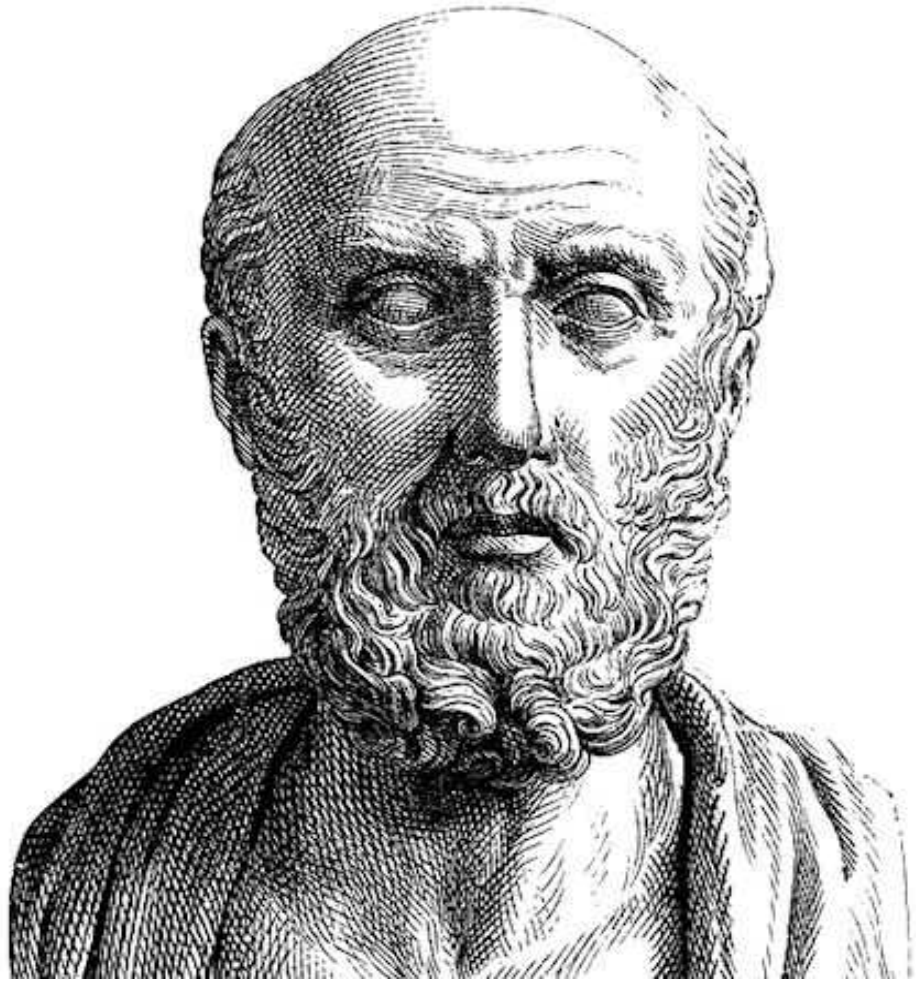
If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

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 [illegible]	or GLP-1-RA	or Insulin[9]	or GLP-1-RA
or Insulin[9]	or Insulin[9]		or Insulin[9]		

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)



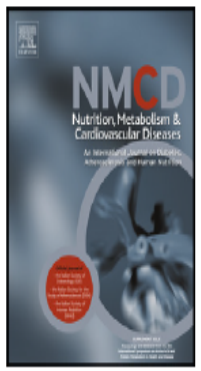
Primum non nocere

Nutrition, Metabolism & Cardiovascular Diseases (2016) **26**, 759–766

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd



Novel antidiabetic drugs and cardiovascular risk: *Primum non nocere*

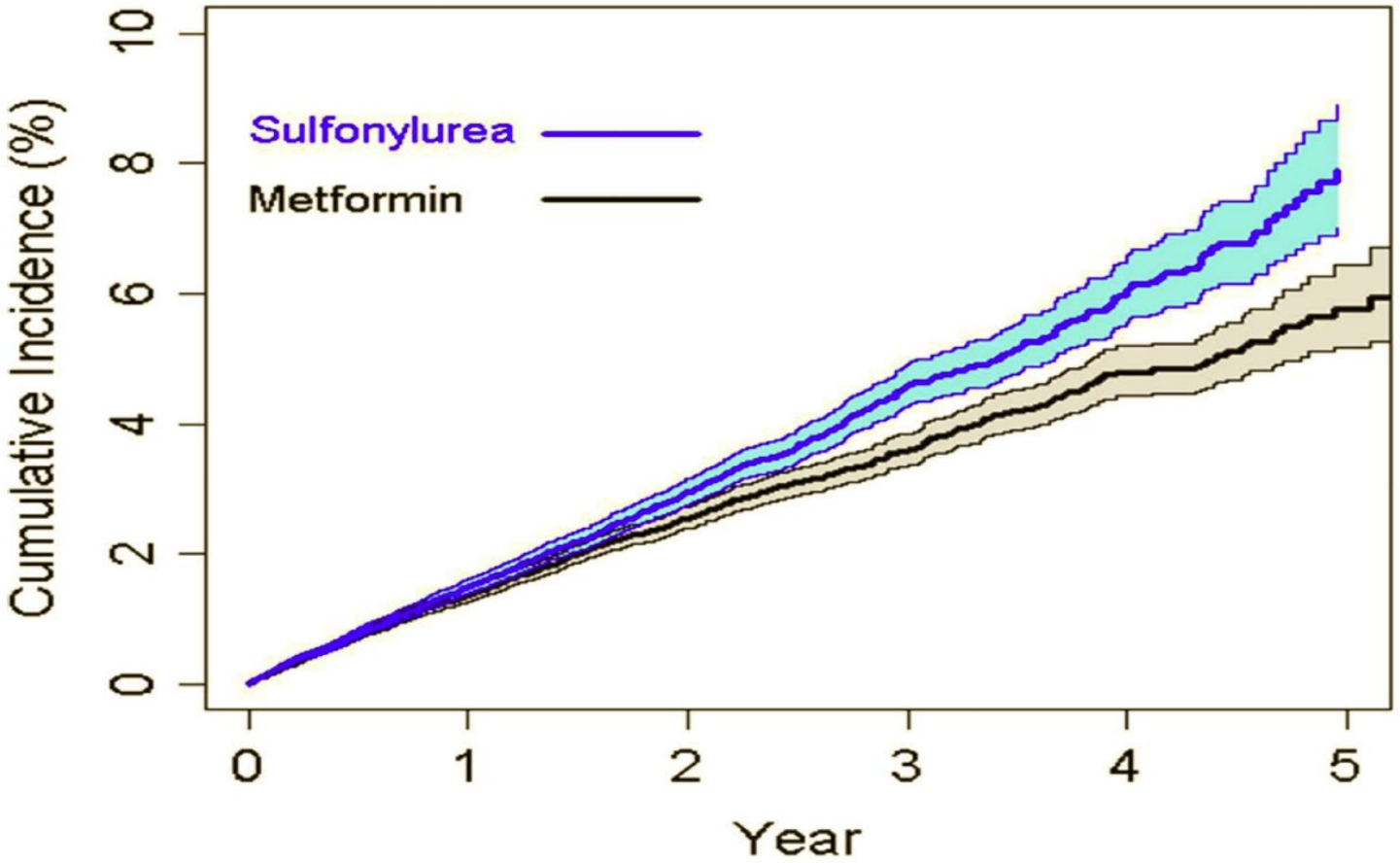
R.C. Bonadonna [a,1], C. Borghi [b,1], A. Consoli [c,*,1], M. Volpe [d,e,1]

Risk of incident cardiovascular diseases during 5–10 years of follow-up according to current use of sulfonylurea

Li et al., Diabetes Care 2014

	Duration of sulfonylurea (years)					Yes vs. no
	No	1–5	6–10	>10	P for trends	RR (95% CI), P
Total CVD						
Person-years	14,399	11,996	4,438	2,924		19,358 vs. 14,399
Number of cases	122	126	51	40		217 vs. 122
(per 10 Incident rate person-years)	847	1,050	1,149	1,368		1,121 vs. 847
Adjusted RR (95% CI)						
Model 1		1.25 (0.97–1.61)	1.37 (0.98–1.90)	1.61 (1.12–2.31)	0.006	1.33 (1.07–1.67), P = 0.01
Model 2		1.25 (0.97–1.62)	1.36 (0.98–1.90)	1.60 (1.11–2.30)	0.007	1.33 (1.06–1.67), P = 0.01
Model 3		1.20 (0.91–1.58)	1.39 (0.98–1.98)	1.64 (1.11–2.40)	0.007	1.31 (1.01–1.68), P = 0.04
Model 4		1.20 (0.91–1.58)	1.40 (0.98–1.99)	1.65 (1.12–2.43)	0.007	1.31 (1.01–1.68), P = 0.04
CHD						
Number of cases	62	72	30	27		129 vs. 62
(per 10 Incident rate person-years)	431	600	676	923		666 vs. 431
Adjusted RR (95% CI)						
Model 1		1.40 (0.99–1.97)	1.55 (1.00–2.40)	2.15 (1.36–3.39)	0.001	1.55 (1.14–2.10), P = 0.005
Model 2		1.37 (0.97–1.94)	1.52 (0.97–2.36)	2.10 (1.32–3.34)	0.002	1.51 (1.11–2.06), P = 0.009
Model 3		1.24 (0.85–1.81)	1.50 (0.94–2.40)	2.08 (1.27–3.39)	0.003	1.41 (1.01–1.99), P = 0.047
Model 4		1.24 (0.85–1.81)	1.51 (0.94–2.42)	2.15 (1.31–3.54)	0.002	1.42 (1.01–2.00), P = 0.04
Stroke						
Number of cases	60	54	21	13		88 vs. 60
(per 10 Incident rate ^{5} person-years)	417	450	473	445		455 vs. 417
Adjusted RR (95% CI)						
Model 1		1.10 (0.76–1.60)	1.17 (0.70–1.93)	1.05 (0.57–1.93)	0.70	1.11 (0.79–1.55), P = 0.54
Model 2		1.13 (0.78–1.66)	1.17 (0.70–1.95)	1.07 (0.58–1.98)	0.68	1.13 (0.81–1.59), P = 0.47
Model 3		1.19 (0.78–1.80)	1.29 (0.75–2.21)	1.21 (0.63–2.30)	0.43	1.21 (0.83–1.77), P = 0.32
Model 4		1.19 (0.79–1.81)	1.29 (0.75–2.20)	1.19 (0.62–2.27)	0.46	1.21 (0.83–1.77), P = 0.32

Cumulative incidence and 95% confidence intervals of cardiovascular disease or death among sulphonylureas or metformin users (propensity matched cohort)

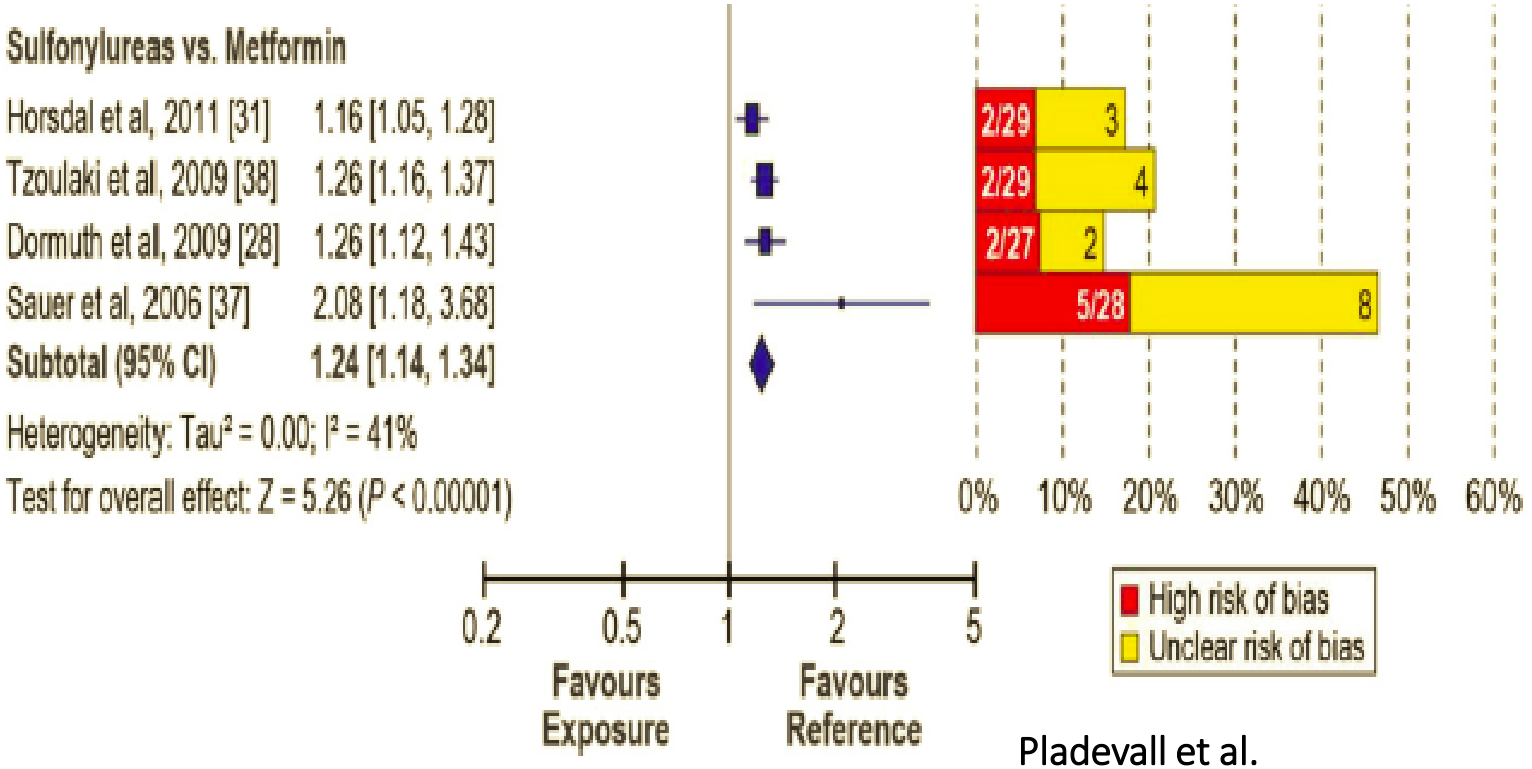


Metformin	80648	33418	16887	7976	3297	718
Sulfonylurea	80648	29502	14118	6185	2301	462

Roumie et al. Ann Intern Med 2012

RESEARCH ARTICLE Open Access

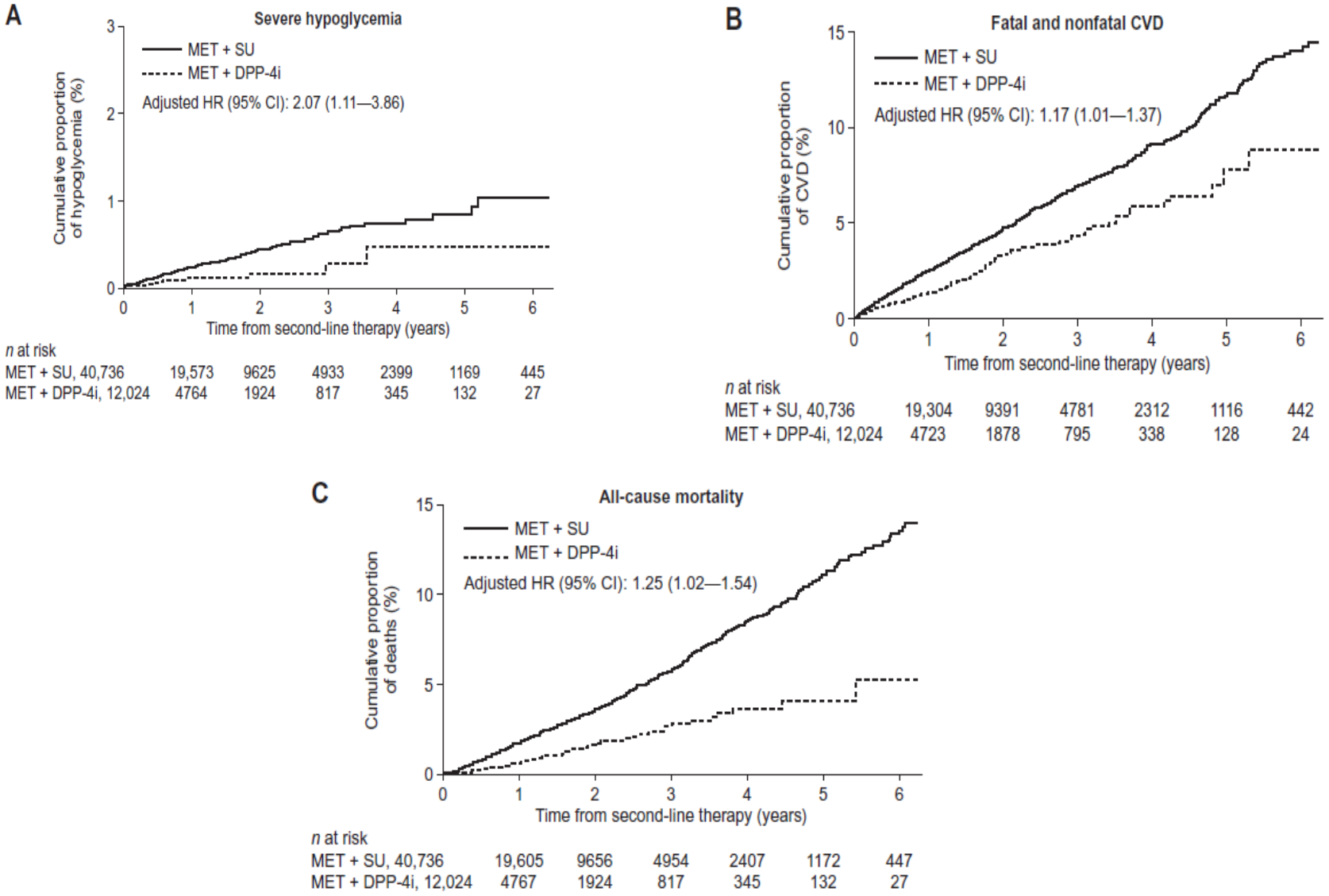
Cardiovascular risk associated with the use of glitazones, metformin and sufonylureas: meta-analysis of published observational studies



Pladevall et al.
BMC Cardiovascular Disorders 2016; 16:14

Sulfoniluree vs DPP-4I

Studio di registro svedese, condotto su oltre 52.000 pazienti,



Eriksson JV et al Diab Res and Clin Pract 2016: 117:39-47

Il farmaco di prima scelta per il trattamento dei soggetti con diabete tipo 2 è la metformina. *I A*

In caso di marcato scompenso glicometabolico o presenza di sintomi specifici del diabete, anche nel paziente non precedentemente trattato con farmaci si può prendere in considerazione sin dall'inizio la terapia con metformina da subito associata a un'altra molecola. *I B*

Qualora la monoterapia con metformina non sia sufficiente ad ottenere o mantenere un buon controllo glicometabolico, è necessario associare un secondo farmaco. Quando la combinazione della metformina con un altro farmaco non è sufficiente a mantenere un soddisfacente controllo della glicemia, si deve aggiungere un terzo farmaco. *I A*

In associazione a metformina, sulla base del profilo complessivo di efficacia, tollerabilità e sicurezza, pioglitazone, inibitori DPP4, agonisti GLP1 o inibitori SGLT2 sono preferibili rispetto a acarbose, sulfoniluree o glinidi. *I B*

La scelta dei farmaci da aggiungere alla metformina deve essere effettuata tenendo conto delle caratteristiche del paziente, comprese le comorbilità, i rischi e i benefici di ciascun farmaco, individualizzando la terapia. *VI B*

Nei pazienti obesi, si devono preferire, ove possibile, i farmaci che non determinano aumento di peso, ovvero, oltre alla metformina, agonisti del GLP-1, inibitori DPP4 e inibitori SGLT2. *I B*

I farmaci che sono in grado di conseguire calo ponderale (agonisti GLP1 e inibitori SGLT2) sono efficaci anche nei soggetti normopeso o sovrappeso. *I A*

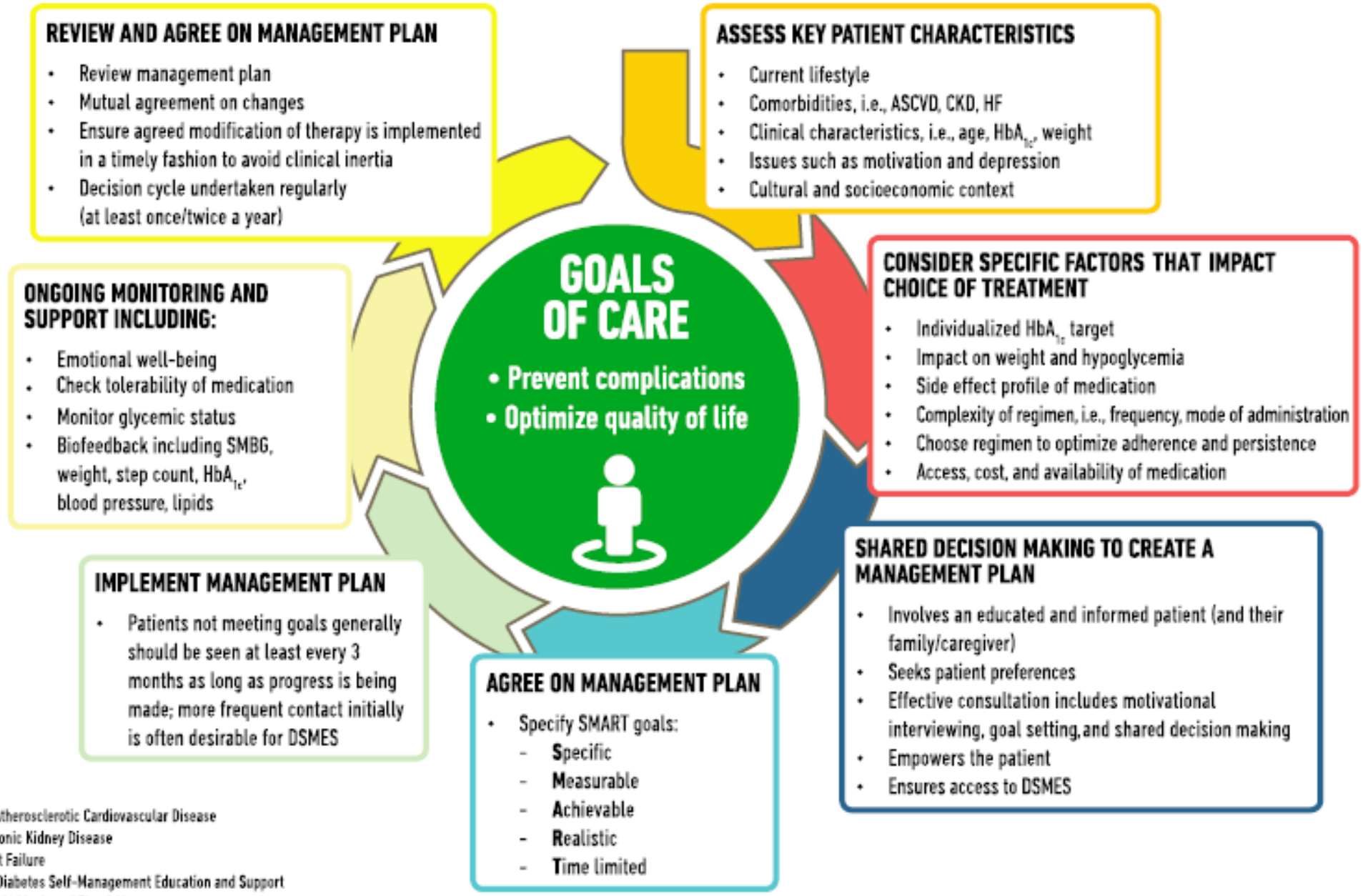
In quei pazienti che, per età avanzata, comorbilità, uso di macchinari o guida protratta di veicoli, sono a rischio di subire conseguenze gravi dall'ipoglicemia, è preferibile utilizzare, entro i limiti del possibile, farmaci che non provocano ipoglicemia. *I B*

La glibenclamide, che si associa ad un rischio di ipoglicemia maggiore anche rispetto alle altre sulfoniluree, non deve essere mai usata. *I A*

Qualora non si possa evitare l'uso di una sulfanilurea, la gliclazide è da preferire rispetto alle altre molecole per un profilo di sicurezza più favorevole, sia per l'incidenza di ipoglicemie che sul piano cardiovascolare. *III B*

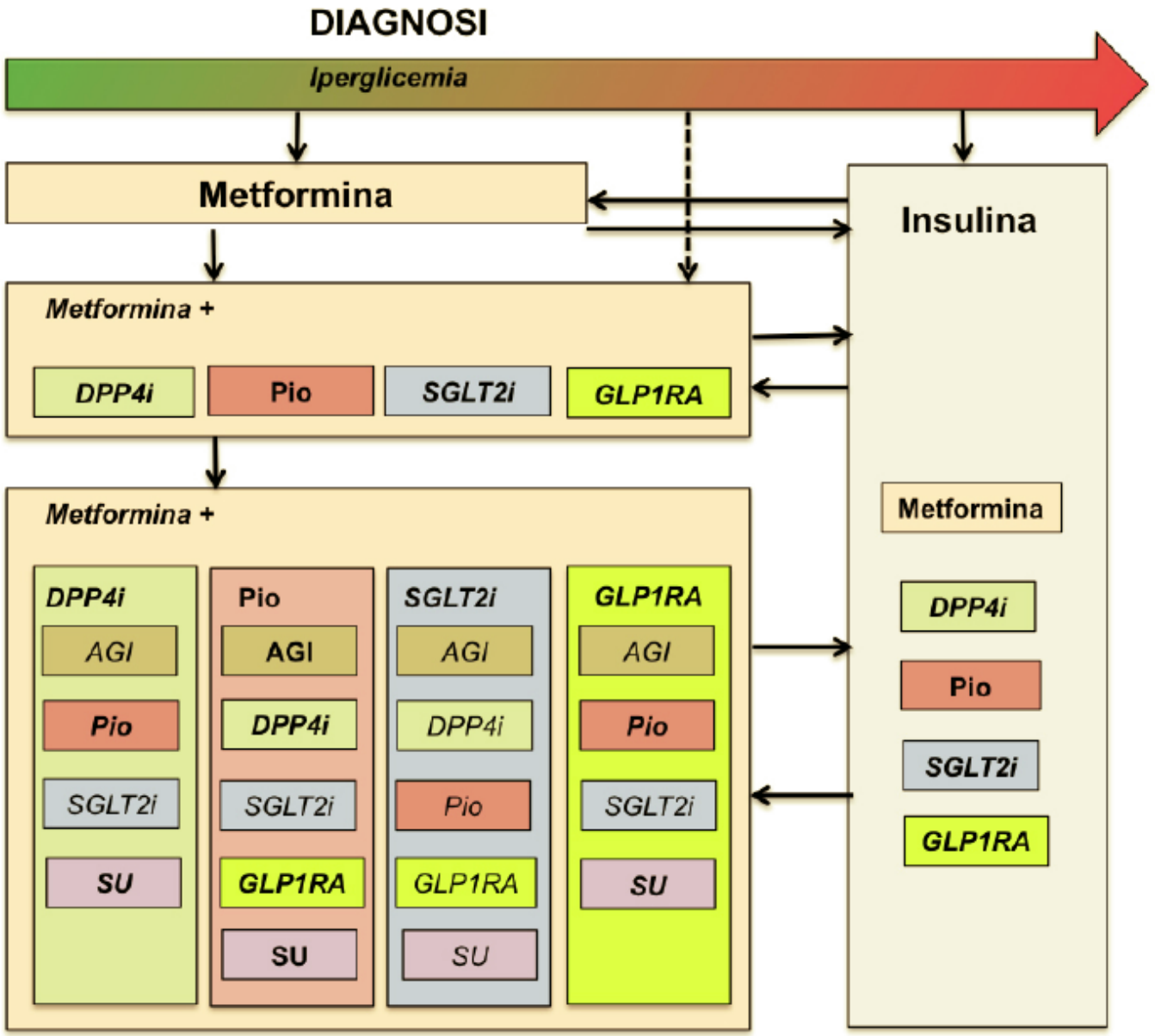
Nei pazienti con pregressi eventi cardiovascolari maggiori SGLT-2 inibitori, GLP-1 agonisti a lunga durata d'azione e pioglitazone devono essere considerati farmaci di prima scelta, salvo controindicazioni. *II A*

DECISION CYCLE FOR PATIENT-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES

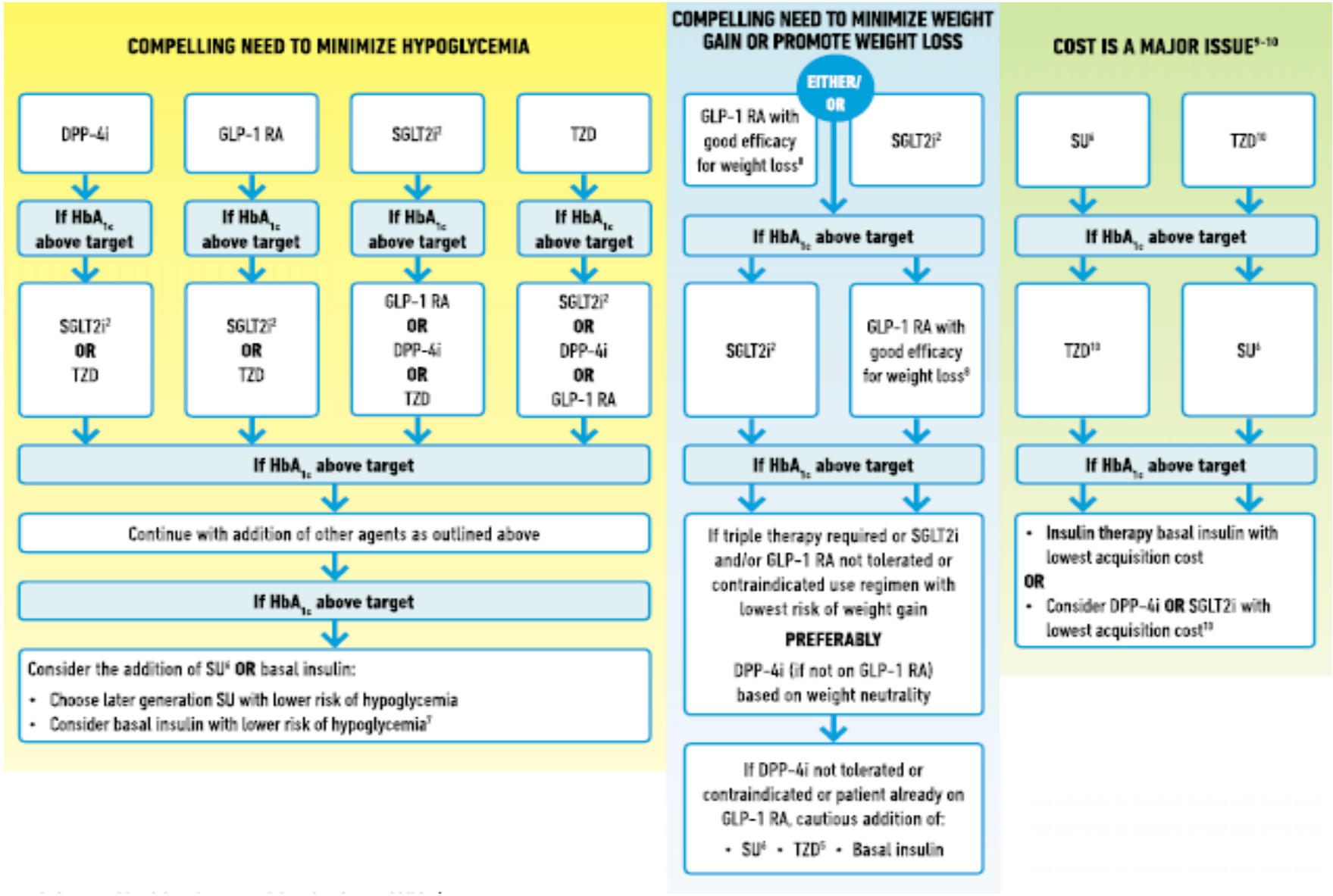


ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

L'algoritmo della terapia farmacologica del diabete di tipo 2.
STANDARD DI CURA SID - AMD 2018



GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



POSITION STATEMENT

SID Società Italiana di Diabetologia

Farmaci ipoglicemizzanti, malattie cardiovascolari e renali

Box 1 *- Al momento attuale i farmaci ipoglicemizzanti che posseggono documentati benefici cardiovascolari sono metformina (prevenzione primaria), empagliflozin, liraglutide e pioglitazone (prevenzione secondaria).*

Box 2 *- L'associazione di empagliflozin e liraglutide potrebbe essere un'eccellente opzione terapeutica per i pazienti con pregressa malattia cardiovascolare, ma sono necessarie ulteriori evidenze al riguardo.*

Box 3 *- In pazienti con pregressa malattia cardiovascolare la terapia ipoglicemizzante dovrebbe includere empagliflozin oppure liraglutide anche in persone in buon controllo glicemico con la terapia in corso.*

Box 4 *- Sembra prudente non considerare necessariamente estendibile ad un'intera classe quanto osservato con una singola molecola ma sembra ragionevole considerare possibile un effetto classe a meno che non ci siano evidenze che lo neghino. Nel caso specifico, l'effetto classe degli agonisti del recettore di GLP-1 è negato dalla valutazione complessiva dei risultati degli studi ELIXA e LEADER, senza che questo escluda che benefici cardiovascolari potrebbero essere osservati negli studi in corso con exenatide (EXSCEL), dulaglutide (REWIND) e semaglutide (SUSTAIN 6). L'effetto classe degli inibitori di SGLT-2 non può essere stabilito con certezza fino a che non saranno disponibili i risultati degli studi in corso con canagliflozin (CANVAS) e dapagliflozin (DECLARE).*

Il farmaco di prima scelta per il trattamento dei soggetti con diabete tipo 2 è la metformina. *I A*

In caso di marcato scompenso glicometabolico o presenza di sintomi specifici del diabete, anche nel paziente non precedentemente trattato con farmaci si può prendere in considerazione sin dall'inizio la terapia con metformina da subito associata a un'altra molecola. *I B*

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La scelta dei farmaci da aggiungere alla metformina deve essere effettuata tenendo conto delle caratteristiche del paziente, comprese le comorbilità, i rischi e i benefici di ciascun farmaco, individualizzando la terapia. *VI B*

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I farmaci che sono in grado di conseguire calo ponderale (agonisti GLP1 e inibitori SGLT2) sono efficaci anche nei soggetti normopeso o sovrappeso. *I A*

In quei pazienti che, per età avanzata, comorbilità, uso di macchinari o guida protratta di veicoli, sono a rischio di subire conseguenze gravi dall'ipoglicemia, è preferibile utilizzare, entro i limiti del possibile, farmaci che non provocano ipoglicemia. *I B*

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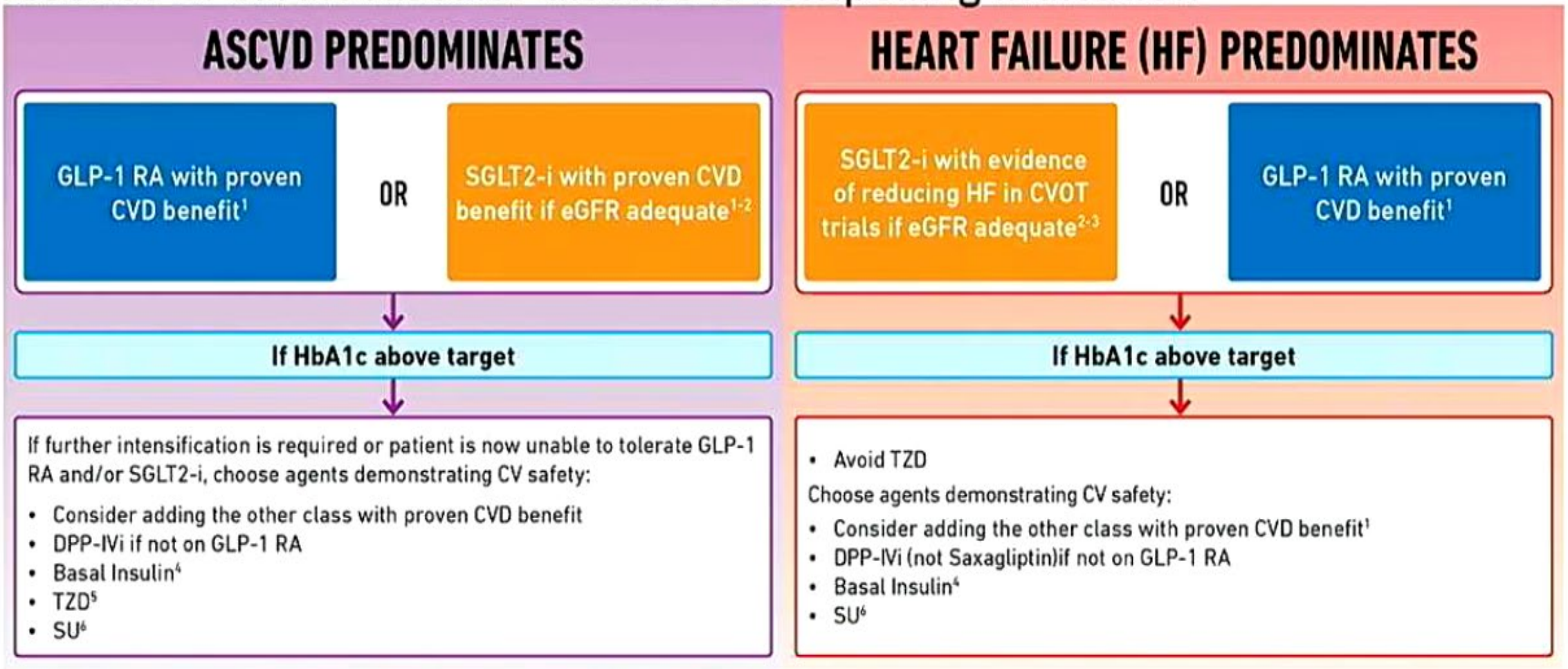
Step 1: Assess cardiovascular disease

Presence of cardiovascular disease is compelling indication

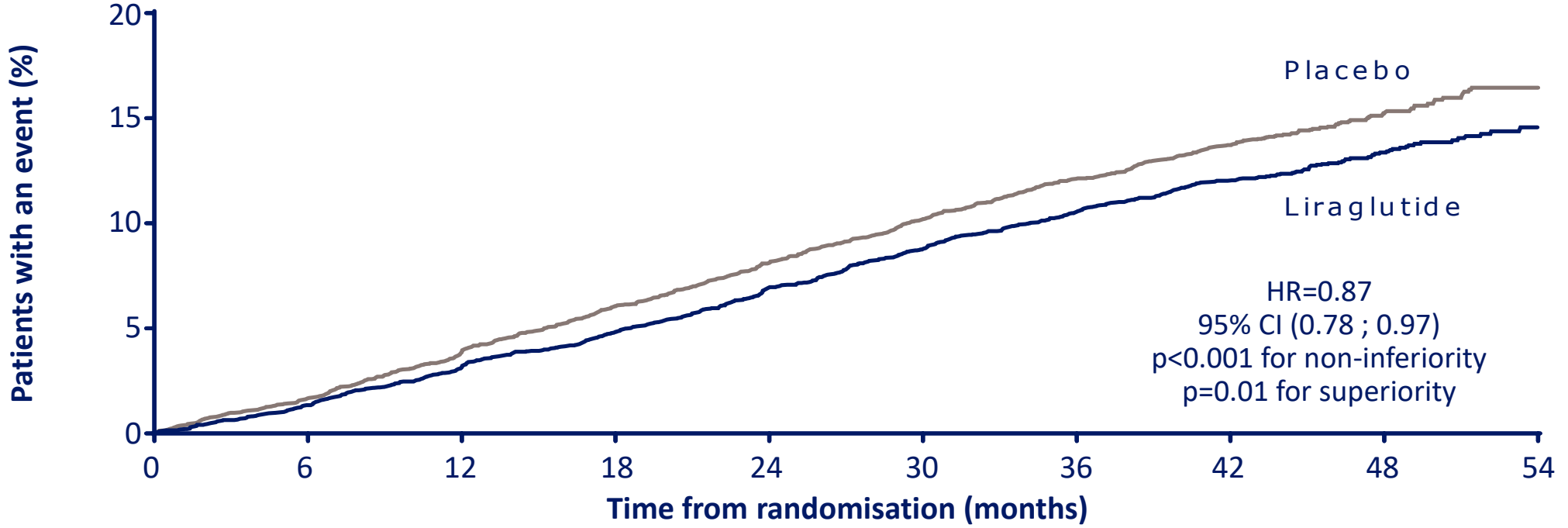


1. SGLT2-i = Empagliflozin preferred, GLP1-RA = Liraglutide preferred. Proven CVD benefit means it has label indication of reducing CVD events please see hierarchy of evidence in manuscript for CVD benefits for agents within the GLP-1 RA and SGLT2-i class, 2. Be aware that SGLT2-i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use, 3. Both Empagliflozin and Canagliflozin have shown reduction in HF in CVOT trials, 4. Degludec or U100 Glargine have demonstrated CVD safety, 5. Low dose may be better tolerated though less well studied for CVD effect, 6.Choose later generation SU with lower risk of risk of hypoglycaemia

LEADER TRIAL

Primary outcome

CV death, non-fatal myocardial infarction, or non-fatal stroke



Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI: confidence interval; CV: cardiovascular; HR: hazard ratio.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Results of Safety CVOTs conducted with available GLP-1 Ras and SGLT2 inhibs.

MACE

TRIAL	HR	98% C.I.
ELIXA *(lixisenatide)*	1,02	0,99 – 1,17
EXSCEL *(exenatide LAR)*	0,91	0,83 – 1,00
LEADER *(liraglutide)*	**0,87**	**0,78 – 0,97**
SUSTAIN-6 *(semaglutide)*	**0,74**	**0,58 – 0,95**

Results of Safety CVOTs conducted with available GLP-1 Ras and SGLT2 inhibs.

CV MORTALITY

TRIAL	HR	98% C.I.
ELIXA	0,98	0,78 – 1,22
EXSCEL	0,88	0,76 – 1,02
LEADER	**0,78**	**0,66 – 0,93**
SUSTAIN-6	0,98	0,65 – 1,48

Results of Safety CVOTs conducted with available GLP-1 Ras and SGLT2 inhibs.

ALL CAUSE MORTALITY

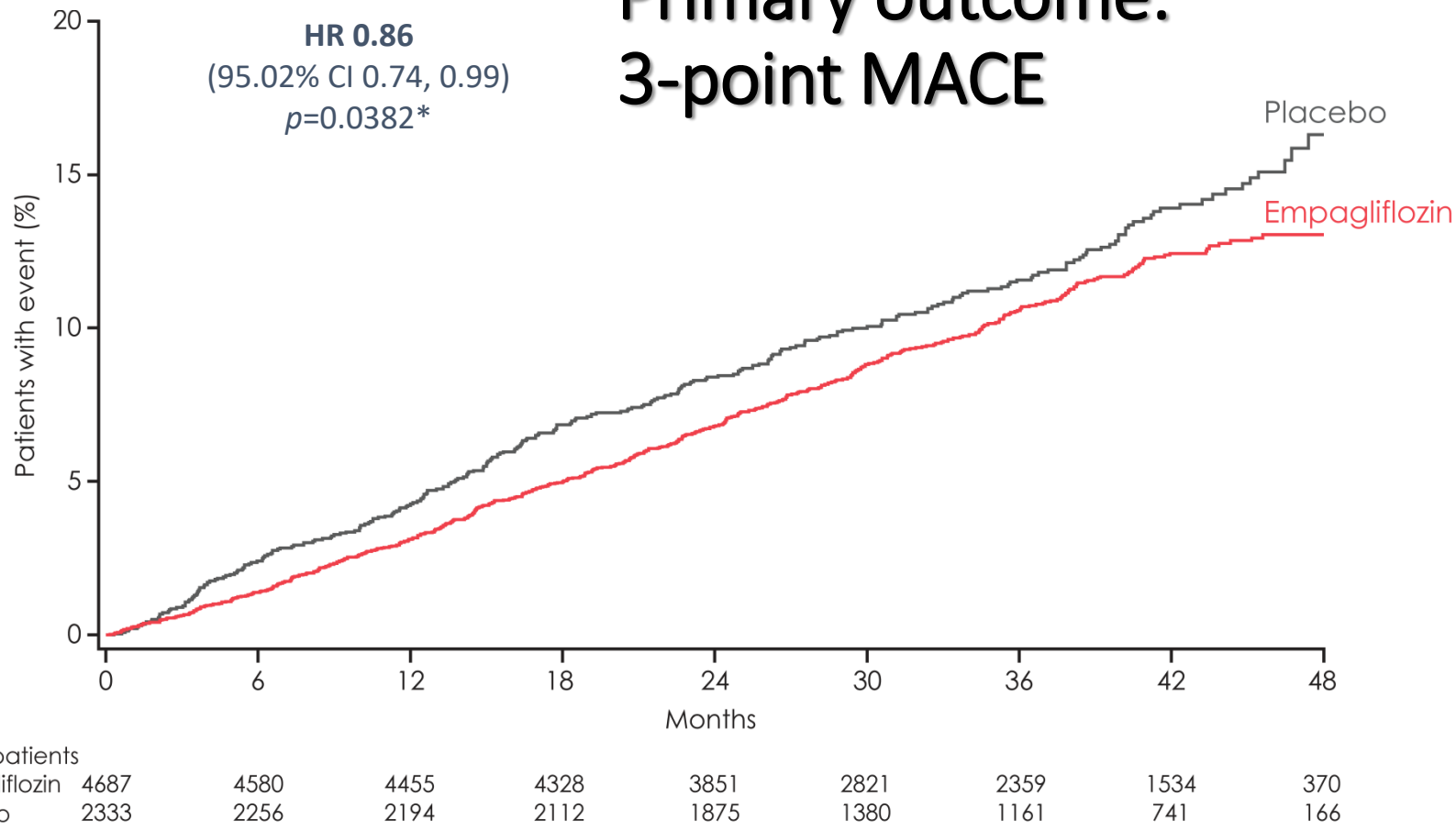
TRIAL	HR	98% C.I.
ELIXA	--	--
EXSCEL	**0,86**	**0,77 – 0,97**
LEADER	**0,85**	**0,74 – 0,97**
SUSTAIN-6	1,05	0,74 – 1,50

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

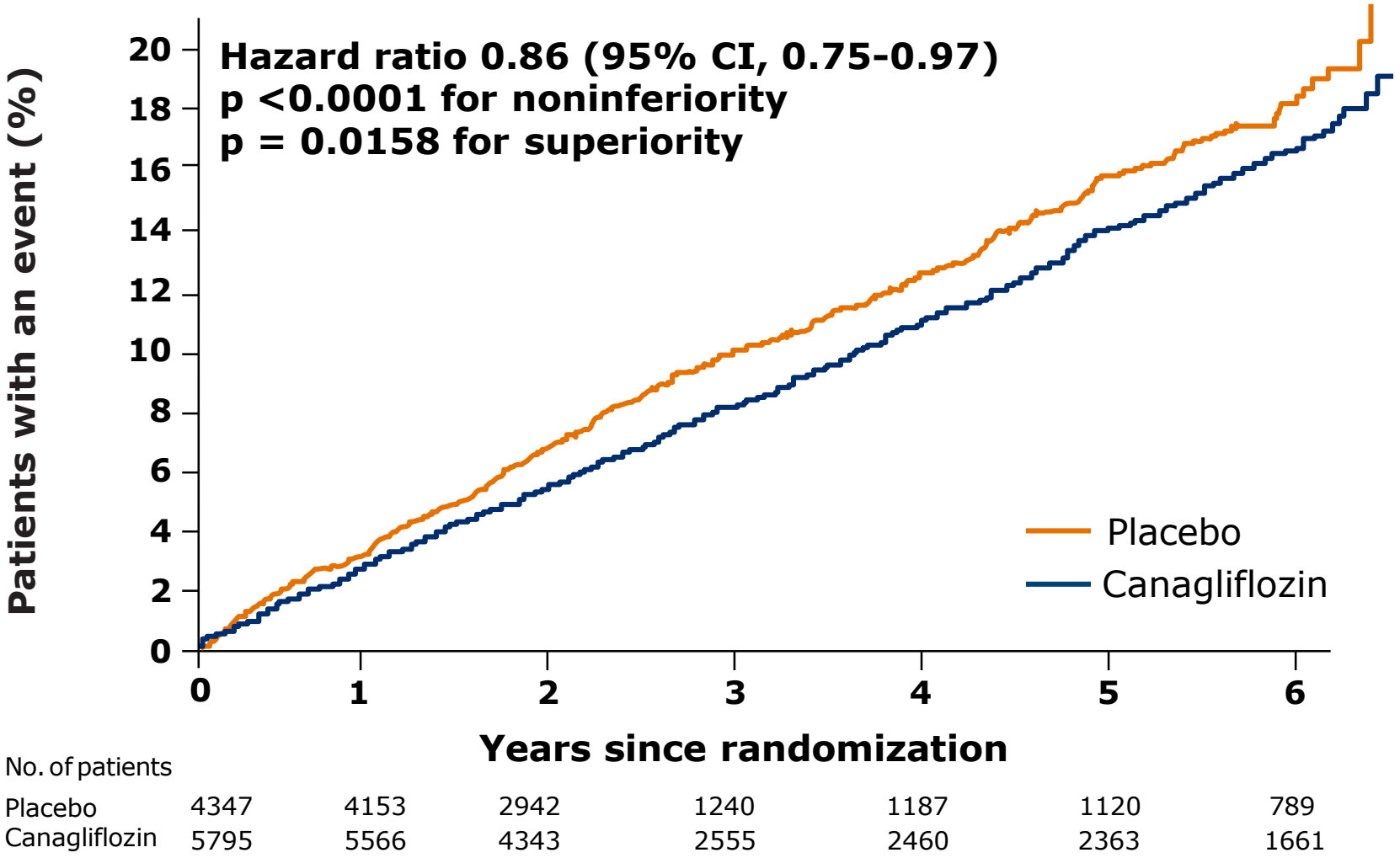
N Engl J Med 2015; 373:2117-2122

Primary outcome: 3-point MACE



CANVAS PROGRAM

Primary MACE Outcome: CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

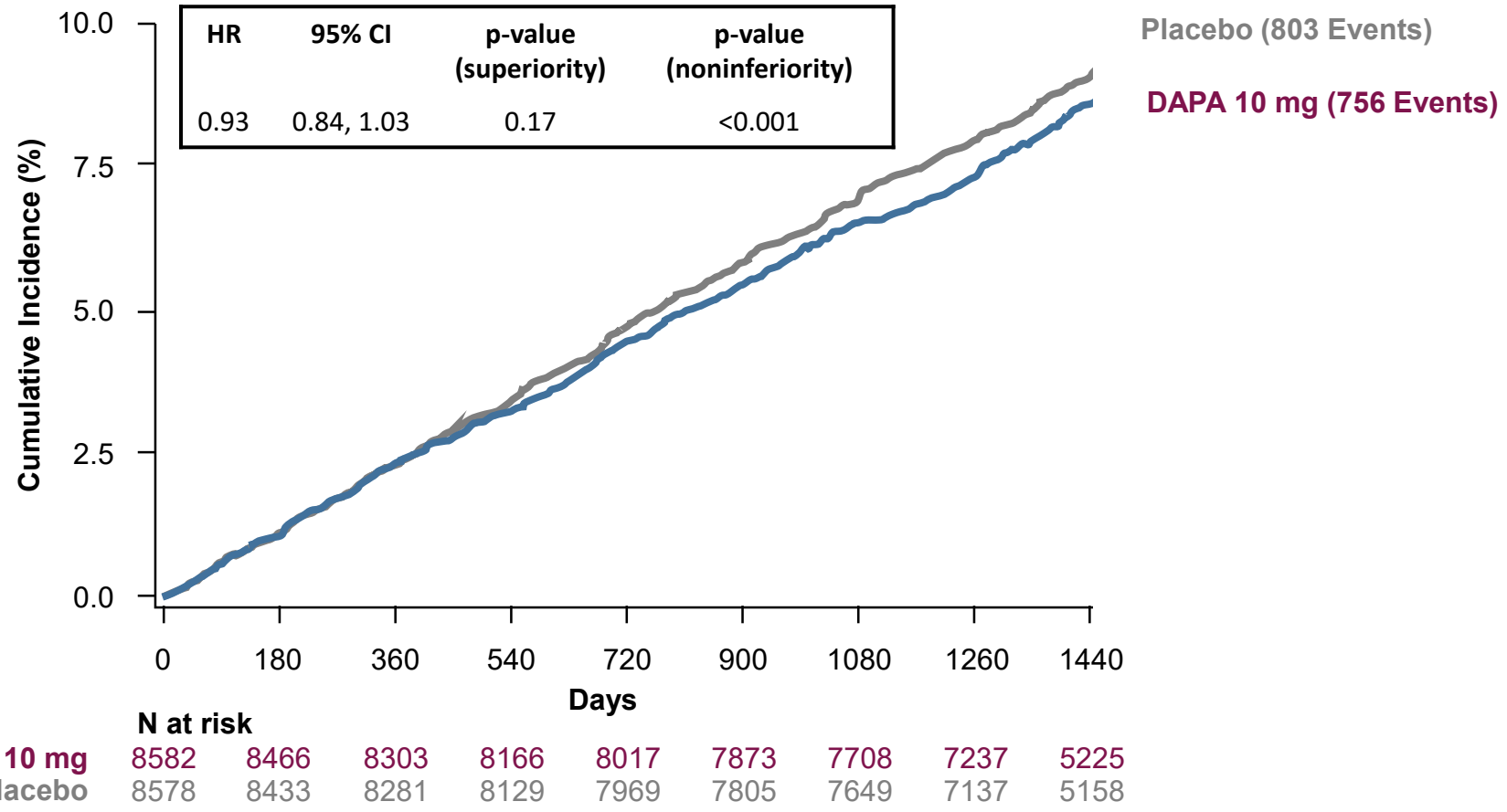


No. of patients							
Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

Neal B. et al., NEJM 2017

DECLARE STUDY

Primary Endpoint: MACE



N at risk is the number of patients at risk at the beginning of the period.

DAPA, dapgliflozin; MACE, major adverse cardiovascular events.

Wiviott SD et al. Online ahead of print. *New Engl J Med*. 2018.

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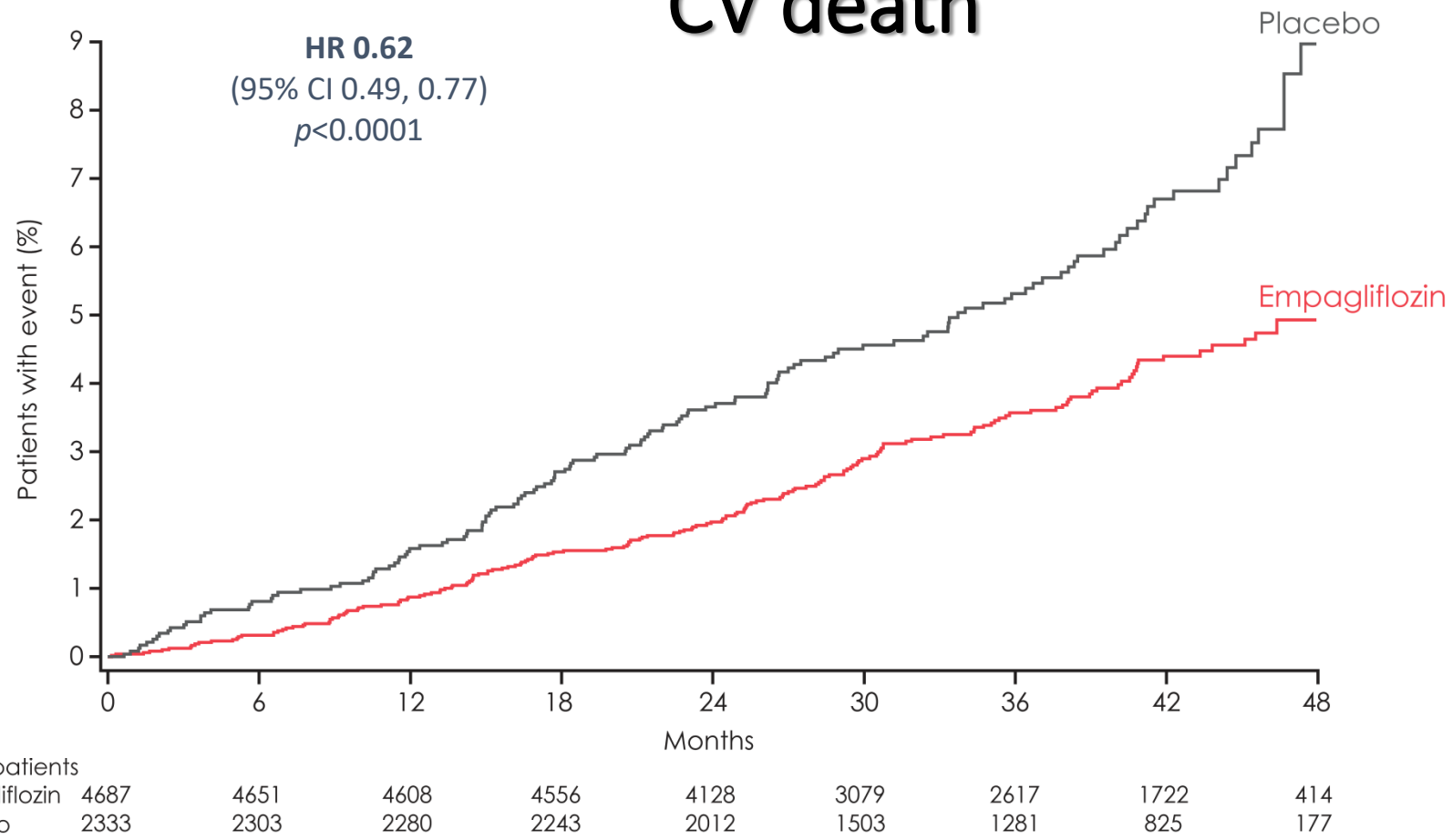
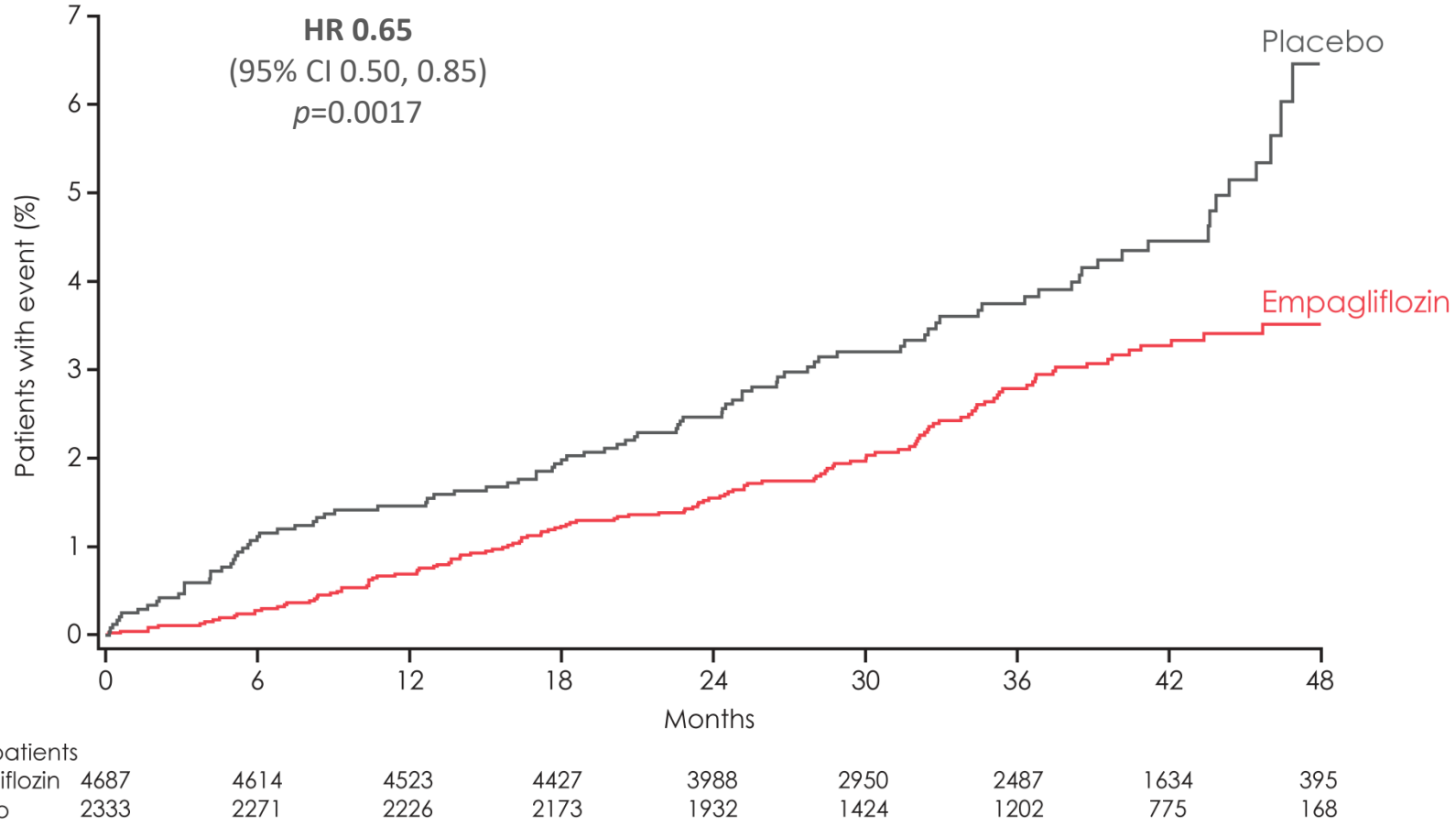
N Engl J Med 2015; 373:2117-2122

CV death



EMPAREG-OUTCOME:

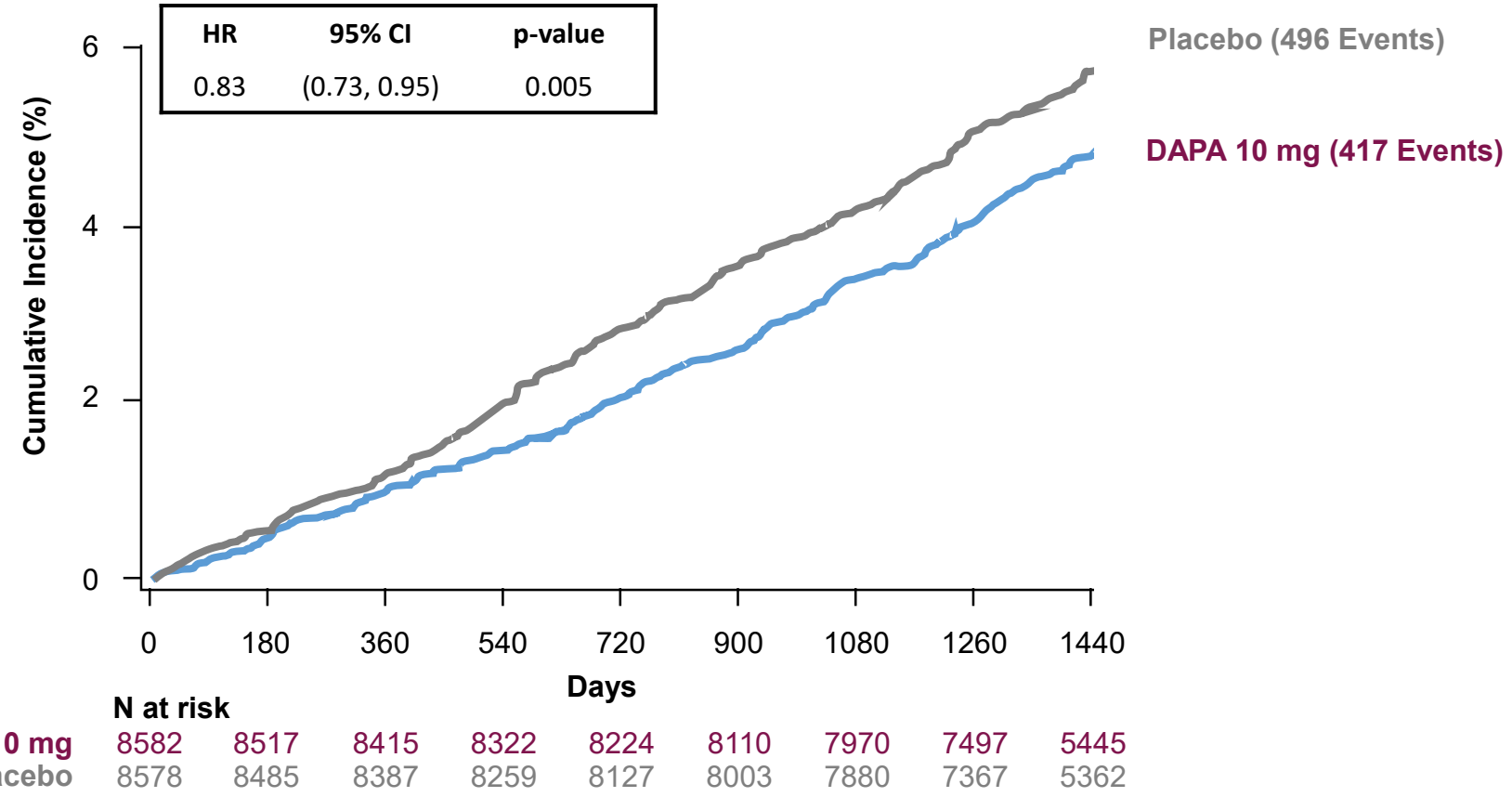
Hospitalisation for Heart Failure



Zinman B. et al, NEJM 2015

DECLARE STUDY

Primary Endpoint: Composite of hHF or CV Death



N at risk is the number of patients at risk at the beginning of the period.

CV, cardiovascular; DAPA, dapagliflozin; hHF, hospitalization for heart failure.

Wiviott SD et al. Online ahead of print. *New Engl J Med.* 2018.

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Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

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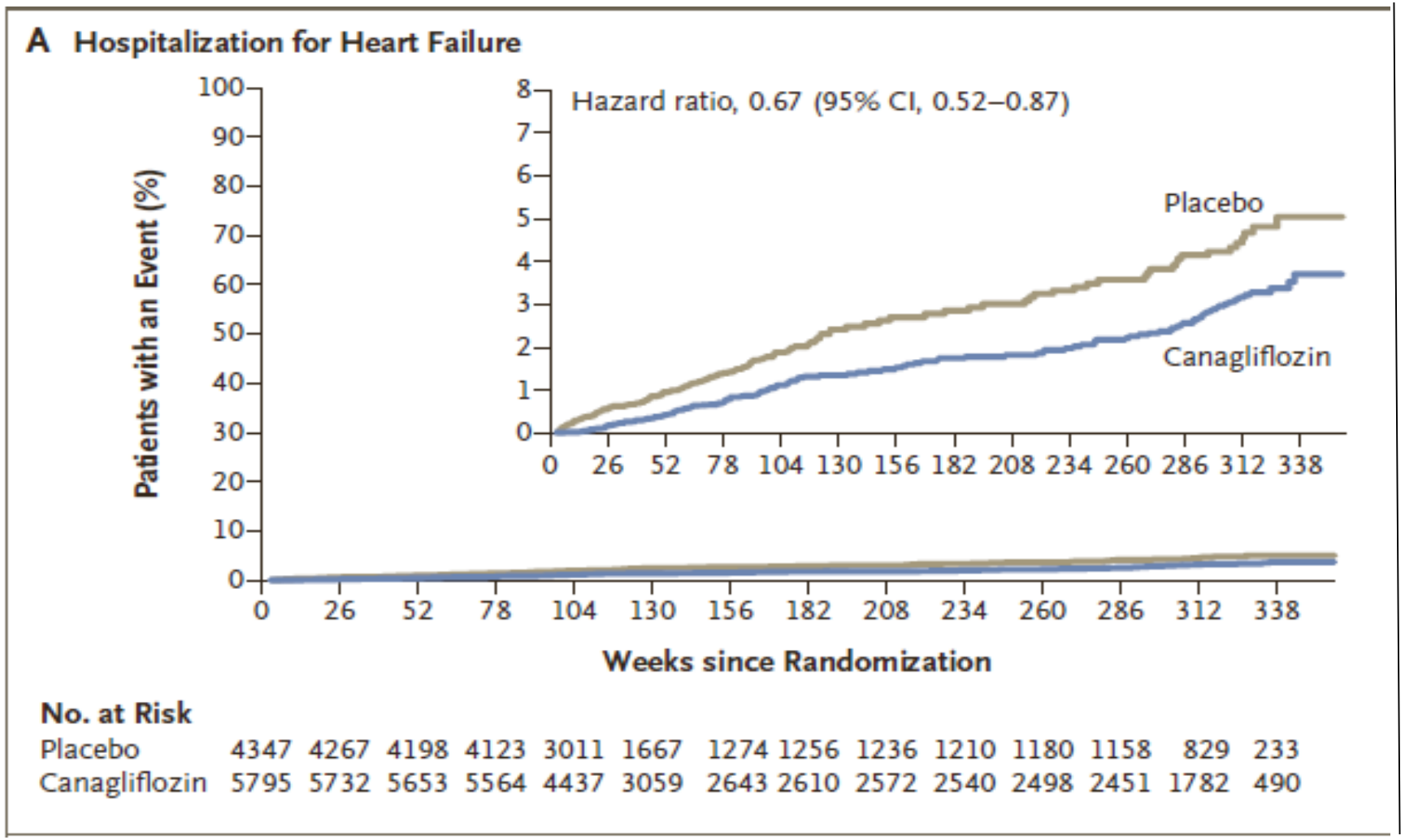
Downloaded from nejm.org on June 12, 2017.



Il farmaco di prima scelta per il trattamento dei soggetti con diabete tipo 2 è la metformina. *I A*

In caso di marcato scompenso glicometabolico o presenza di sintomi specifici del diabete, anche nel paziente non precedentemente trattato con farmaci si può prendere in considerazione sin dall'inizio la terapia con metformina da subito associata a un'altra molecola. *I B*

Qualora la monoterapia con metformina non sia sufficiente ad ottenere o mantenere un buon controllo glicometabolico, è necessario associare un secondo farmaco. Quando la combinazione della metformina con un altro farmaco non è sufficiente a mantenere un soddisfacente controllo della glicemia, si deve aggiungere un terzo farmaco. *I A*

In associazione a metformina, sulla base del profilo complessivo di efficacia, tollerabilità e sicurezza, pioglitazone, inibitori DPP4, agonisti GLP1 o inibitori SGLT2 sono preferibili rispetto a acarbose, sulfoniluree o glinidi. *I B*

La scelta dei farmaci da aggiungere alla metformina deve essere effettuata tenendo conto delle caratteristiche del paziente, comprese le comorbilità, i rischi e i benefici di ciascun farmaco, individualizzando la terapia. *VI B*

Nei pazienti obesi, si devono preferire, ove possibile, i farmaci che non determinano aumento di peso, ovvero, oltre alla metformina, agonisti del GLP-1, inibitori DPP4 e inibitori SGLT2. *I B*

I farmaci che sono in grado di conseguire calo ponderale (agonisti GLP1 e inibitori SGLT2) sono efficaci anche nei soggetti normopeso o sovrappeso. *I A*

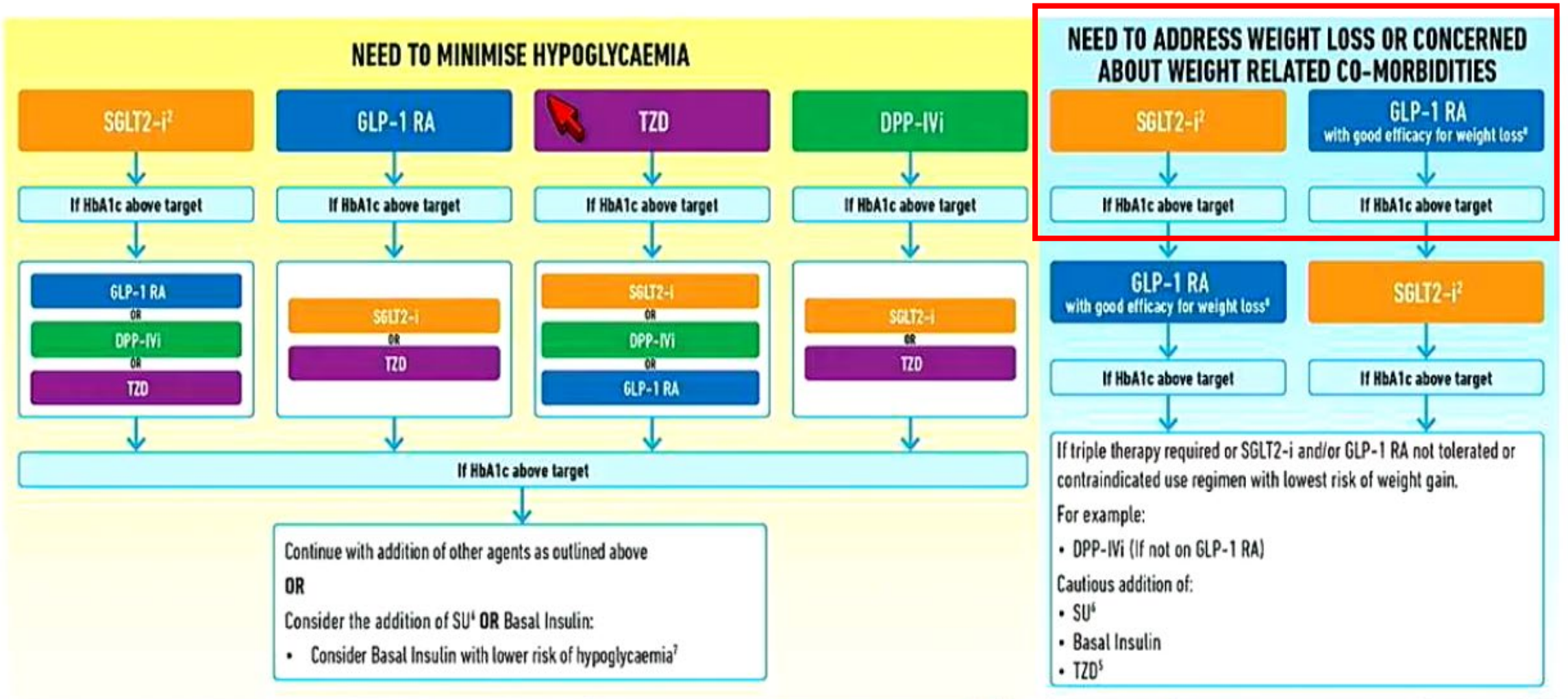
In quei pazienti che, per età avanzata, comorbilità, uso di macchinari o guida protratta di veicoli, sono a rischio di subire conseguenze gravi dall'ipoglicemia, è preferibile utilizzare, entro i limiti del possibile, farmaci che non provocano ipoglicemia. *I B*

La glibenclamide, che si associa ad un rischio di ipoglicemia maggiore anche rispetto alle altre sulfoniluree, non deve essere mai usata. *I A*

Qualora non si possa evitare l'uso di una sulfanilurea, la gliclazide è da preferire rispetto alle altre molecole per un profilo di sicurezza più favorevole, sia per l'incidenza di ipoglicemie che sul piano cardiovascolare. *III B*

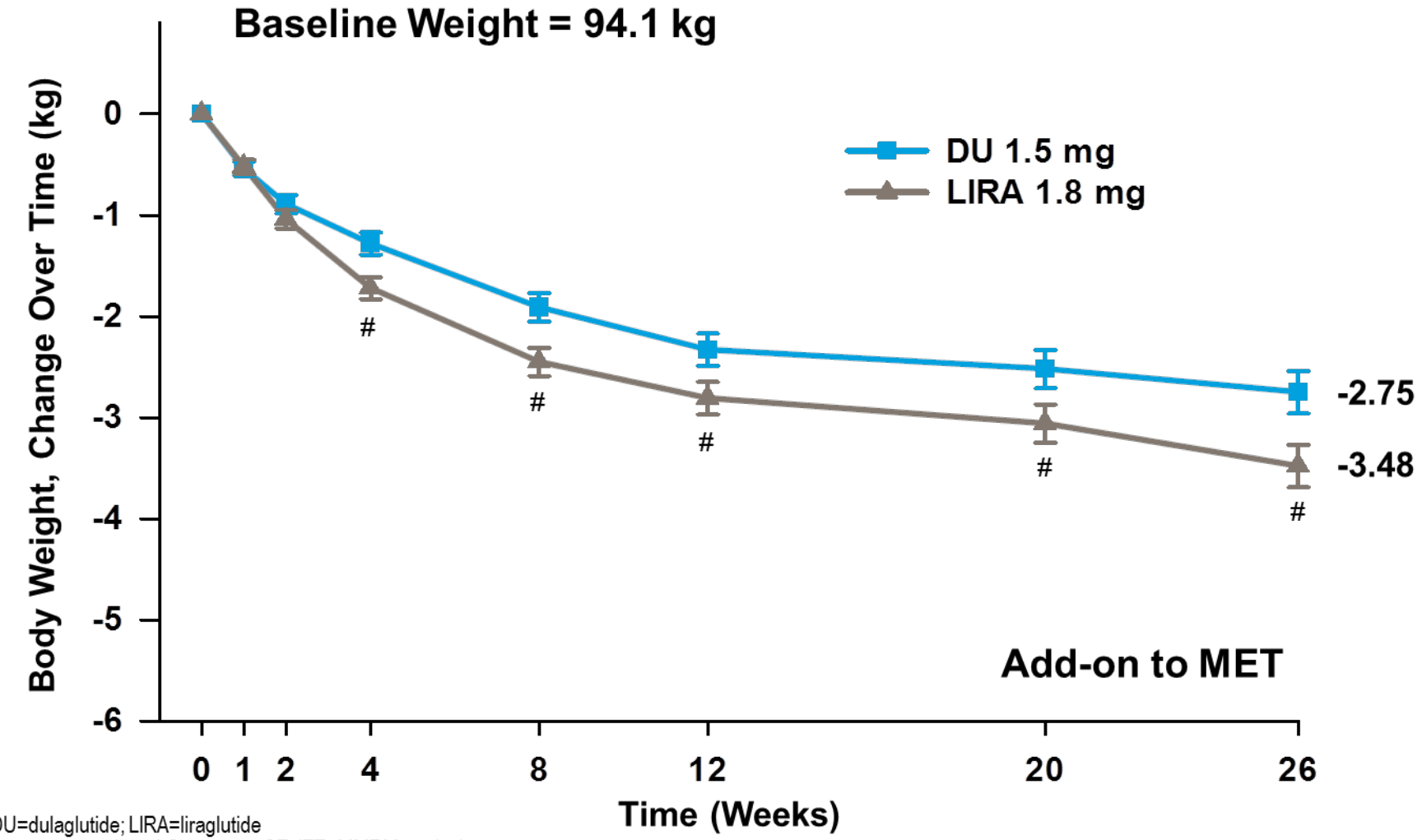
Nei pazienti con pregressi eventi cardiovascolari maggiori SGLT-2 inibitori, GLP-1 agonisti a lunga durata d'azione e pioglitazone devono essere considerati farmaci di prima scelta, salvo controindicazioni. *II A*

ANTIHYPERGLYCEMIC MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



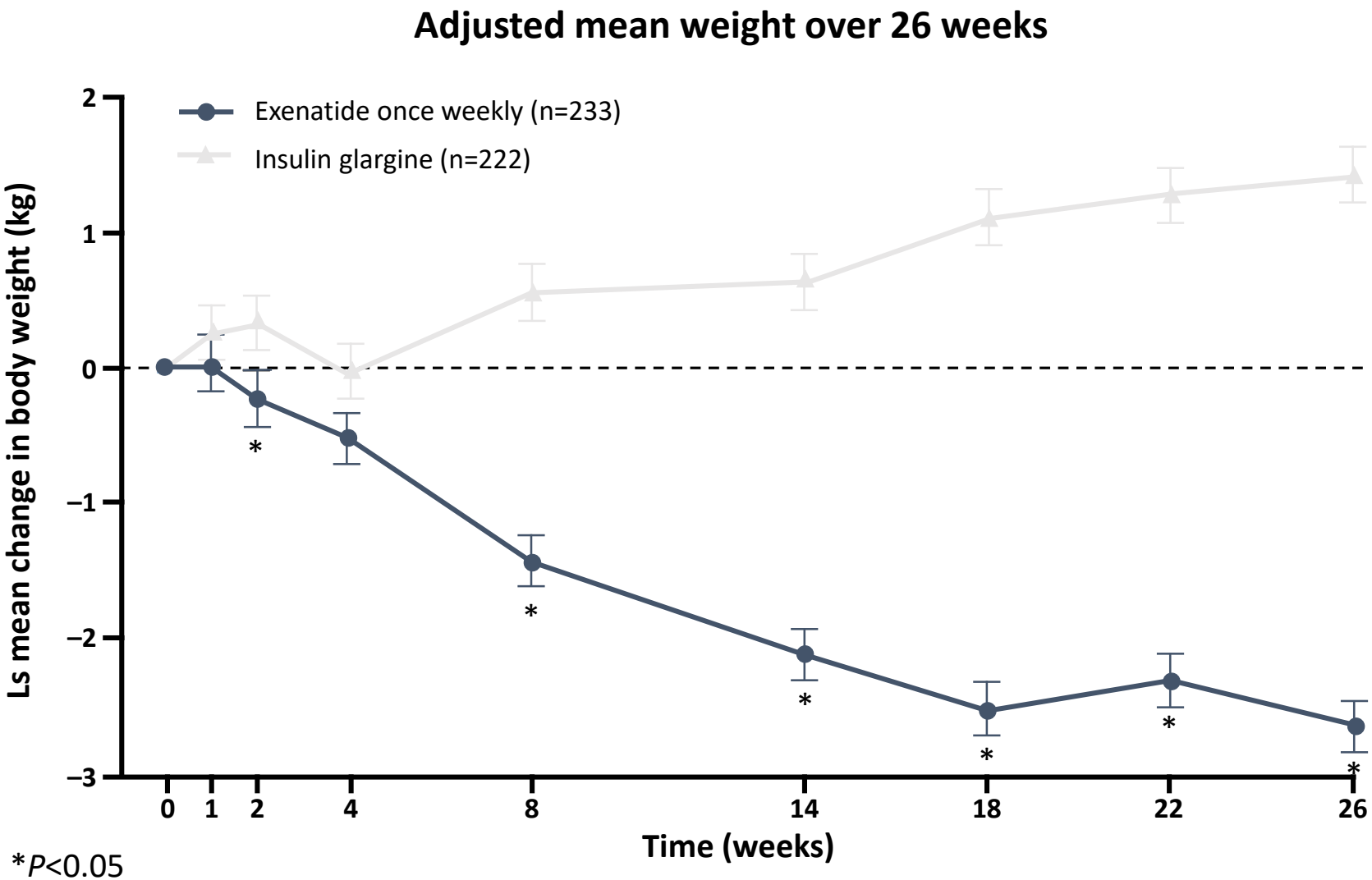
1. SGLT2-i = Empagliflozin preferred, GLP1-RA = Liraglutide preferred. Proven CVD benefit means it has label indication of reducing CVD events please see Section X to see hierarchy of evidence for CVD benefits for agents within the GLP-1 RA and SGLT2-i class
2. Be aware that SGLT2-i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both Empagliflozin and Canagliflozin have shown reduction in HF in CVOT trials
4. Degludec or U100 Glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of risk of hypoglycaemia
7. Degludec / Glargine U300 < Glargine U100 / Detemir < NPH insulin
8. GLP-1 RA with best efficacy for weight loss Semaglutide > Liraglutide > Dulaglutide > Exenatide > Lixisenatide
9. If no specific co-morbidities (i.e. established CVD), low risk of hypoglycaemia and lower priority to avoid weight gain or no weight related co-morbidities: using the algorithm to minimise medication costs
10. Consider country and region specific cost of drugs. In some countries TZD relatively more expensive and DPP-IVi relatively cheaper

Body Weight Change Over Time with Dulaglutide or Liraglutide treatment



DU=dulaglutide; LIRA=liraglutide
Data presented are LS means ± SE, ITT, MMRM analysis
#p<.05 vs dulaglutide
Dungan et al. *Lancet* 2014;384(9951);1349-1357

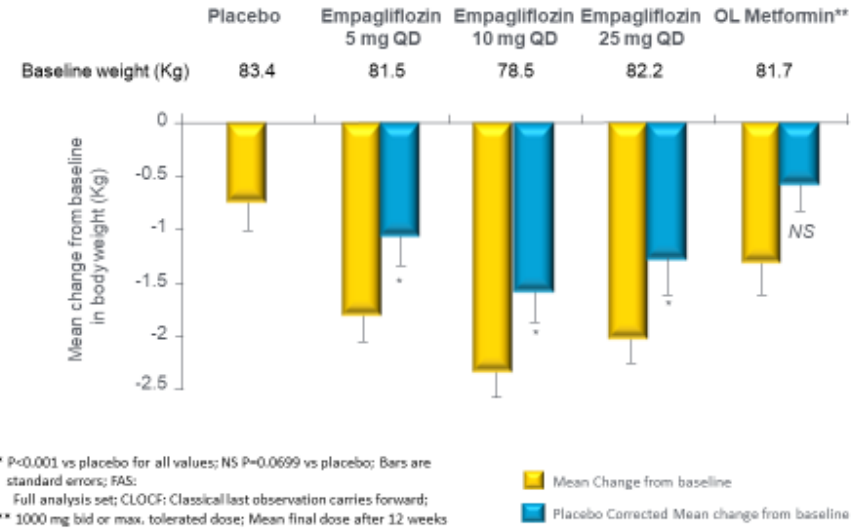
DURATION-3 26-week Data: ExQW was Associated with Weight Loss, as Opposed to Weight Gain with Insulin Glargine



Mean change in body weight at week 26 compared with baseline was –2.6 kg for patients treated with exenatide,
and 1.4 kg for those receiving insulin glargine (difference –4.0 kg; *P*<0.0001)

*$P<0.05$
LS, least squares; T2DM, Type 2 diabetes mellitus
Diamant M, et al. *Lancet* 2010;375:2234–2243

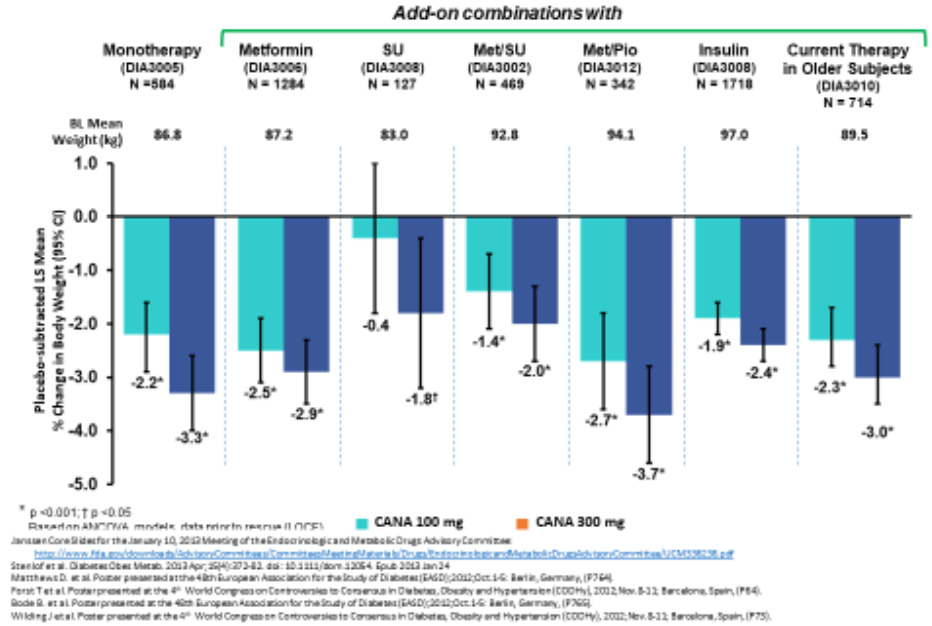
Body weight changes with empagliflozin



* P<0.001 vs placebo for all values; NS P=0.0699 vs placebo; Bars are standard errors; FAS: Full analysis set; CLOCF: Classical last observation carries forward;
** 1000 mg bid or max. tolerated dose; Mean final dose after 12 weeks was ~1700 mg

Ferrannini E, et al. European Association for the Study of Diabetes, 2010 (Poster 877)

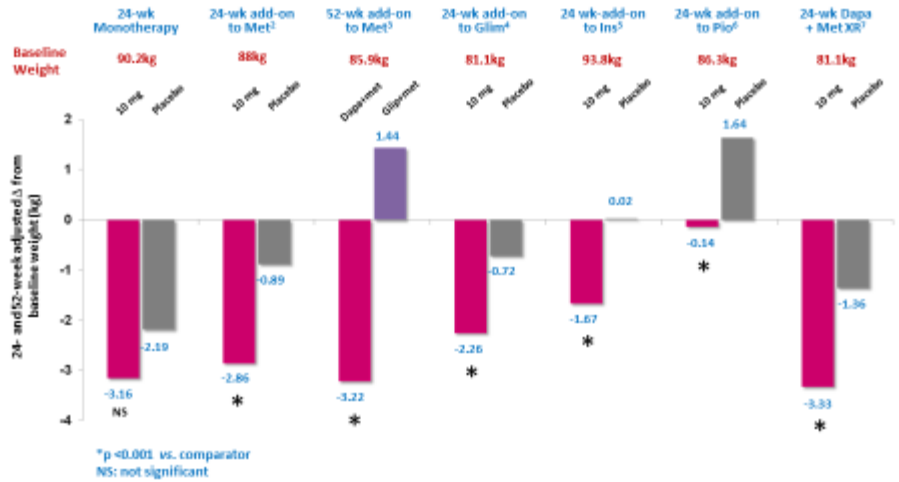
Body weight changes with canagliflozin



* p <0.001; † p <0.05
Based on ANCOVA models, data prior to rescue (LOCF)

Janssen Core Slides for the January 10, 2012 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM298238.pdf
Stenlof et al. Diabetes Obes Metab. 2013 Apr; 15(4):372-82. doi: 10.1111/dom.12054. Epub 2013 Jan 24
Matthews D. et al. Poster presented at the 48th European Association for the Study of Diabetes (EASD);2012;Oct.1-5: Berlin, Germany, (F764).
Forst T et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012; Nov. 8-11; Barcelona, Spain, (F84).
Bode B. et al. Poster presented at the 48th European Association for the Study of Diabetes (EASD);2012;Oct.1-5: Berlin, Germany, (F765).
Wilding J et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012; Nov. 8-11; Barcelona, Spain, (F75).

Body weight changes with dapagliflozin



[2]Ferrannini E, et al. *Diabetes Care* 2010;33:2217–2224; [3]Bailey CJ, et al. *Lancet* 2010;375:2223–2233; [4]Nauck MA, et al. *Diabetes Care* 2011;34:2015-2022;
[5]Strojek K, et al. *Diabetes Obes Metab* 2011;13:928-938 [6]Wilding J, et al. *Diabetes* 2010;59 (Suppl 1):A21–A22 (Abstract 0078-OR); [7]Rosenstock J, et al. 71st *ADA Scientific Sessions*, San Diego, 24–28 June, 2011 (Abstract 0986-P); [7]Henry R, et al. 71st *ADA Scientific Sessions*, San Diego, 24-28 June, 2011 Abstract 307-OR.

INTENSIFYING TO INJECTABLE THERAPIES

If HbA1c above target despite dual/triple therapy

Consider GLP-1 RA in most prior to insulin[1]

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred[2]

If HbA1c above target

Add Basal Insulin

For patient on GLP-1 RA and Basal Insulin
Consider fixed ratio combination (FRC) of GLP-1 RA & Insulin

If above HbA1c target
Despite adequately titrated basal insulin

If above HbA1c target
Additional basal insulin or additional prandial insulin

Add Prandial Insulin Usually one dose | CONSIDER SPECIALIST ADVICE ⚠

If HbA1c above target

Stepwise additional injections of prandial insulin

Consider BD or TDS Premix insulin regimen ⚠
Caution higher risk of hypoglycaemia and or weight gain

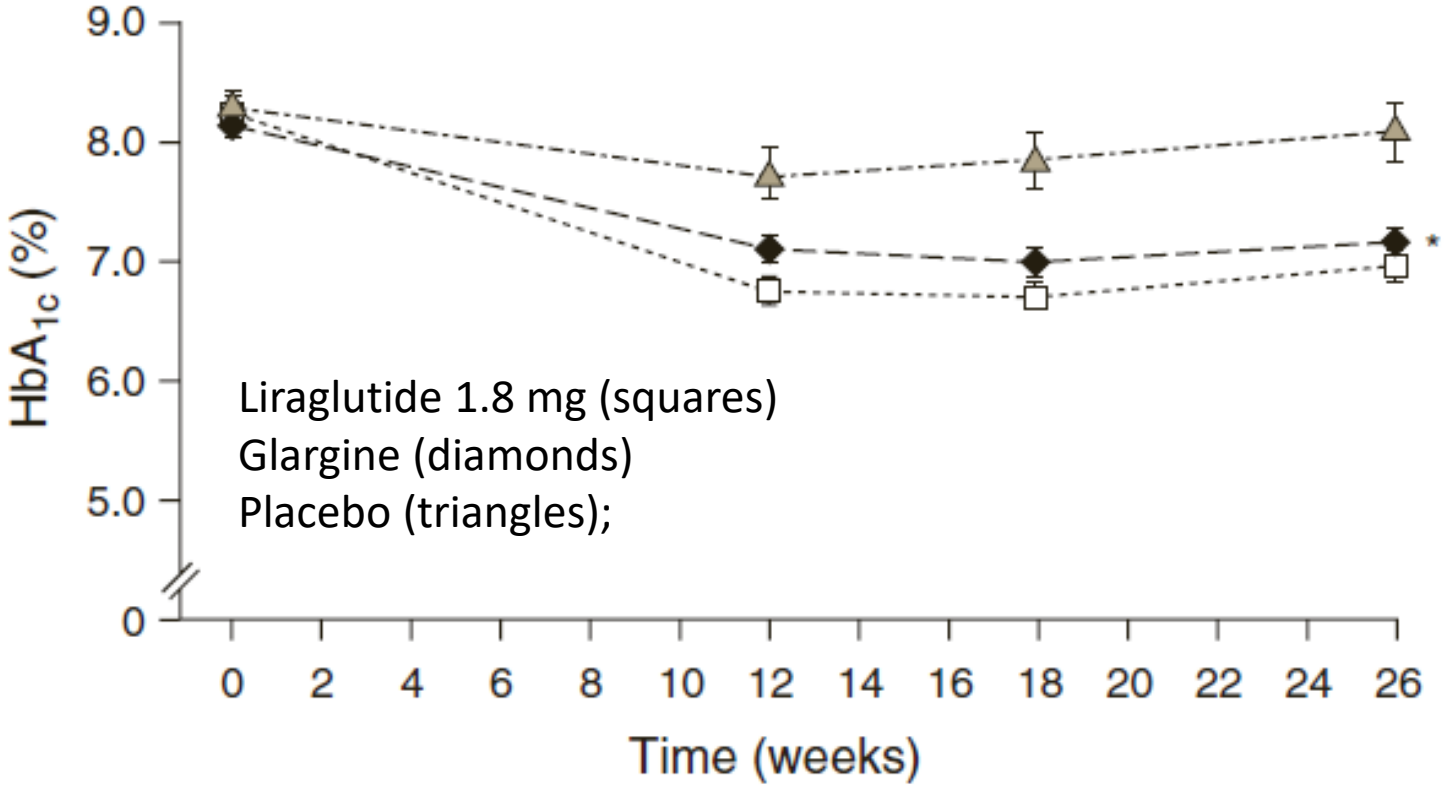
If HbA1c above target

Proceed to FULL basal bolus regimen | IF HbA1c DOES NOT IMPROVE REVIEW NEED FOR BASAL BOLUS REGIMEN ⚠

1.Consider choice of GLP-1 RA considering patient preference HbA1c lowering, weight lowering effect or frequency of injection. If CVD consider GLP-1 RA with proven CVD benefit
2. Consider insulin as preferred to GLP-1RA if symptoms of hyperglycaemia are present, or evidence of ongoing catabolism (polyuria, polydipsia or weight loss)
3. Contraindicated in some countries consider lower dose. This combination has a high risk of fluid retention and weight gain

Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial

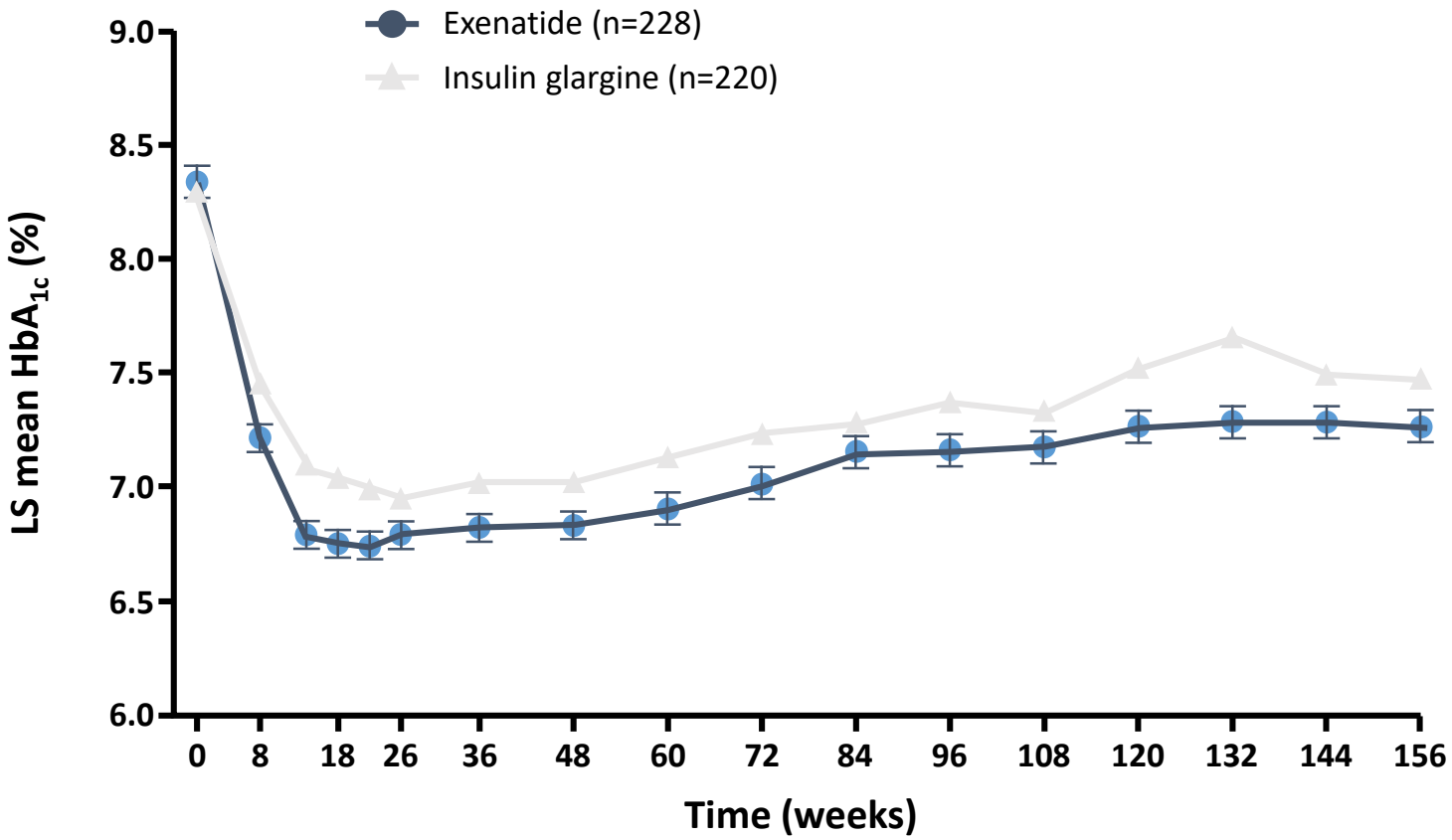
D. Russell-Jones · A. Vaag · O. Schmitz · B. K. Sethi · N. Lalic · S. Antic · M. Zdravkovic · G. M. Ravn · R. Simó · on behalf of the Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group



Liraglutide 1.8 mg (squares)
Glargine (diamonds)
Placebo (triangles);

Diabetologia (2009) 52:2046–2055

DURATION-3 3 Years Data: Significant Reduction in HbA_{1c} Compared with Glargine After 3 Years of Treatment



- At 3 years, LS mean HbA_{1c} change was –1.01% (SE 0.07) in the exenatide group and –0.81% (SE 0.07) in the insulin glargine group (LS mean difference –0.20%, SE 0.10, 95% CI –0.39 to –0.02; *P*=0.03)

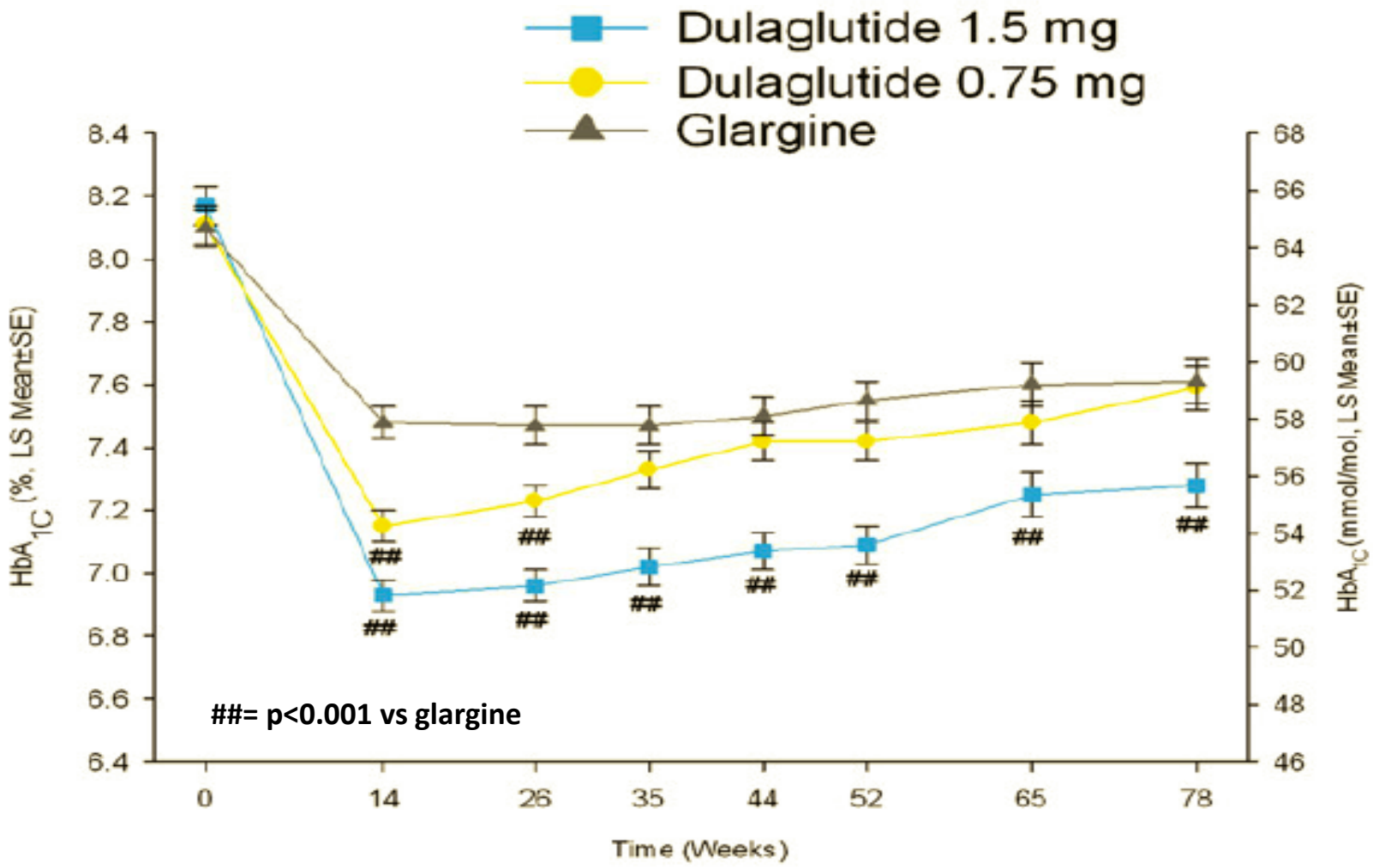
CI, confidence interval; EQW, exenatide once weekly; HbA_{1c}, glycated hemoglobin; LS, least squares; SE, standard error

Diamant M, et al. *Lancet Diabetes Endocrinol* 2014;2:464–473

Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2)

Francesco Giorgino,[1] Marian Benroubi,[2] Jui-Hung Sun,[3] Alan G. Zimmermann,[4] and Valeria Pechtner[5]

Diabetes Care 2015;38:2241–2249 | DOI: 10.2337/dc14-1625



Characteristics of the “ideal” diabetes drug for a “treat to success” strategy

- **EFFICACY**
  - Reduction in HbA1c significant and non inferior to other agents
  - MOA potentially able to impact on disease progression
- **TOLERABILITY**
  - Easy administration
  - No need for titration
  - No minor drug associated ailments (GI symptoms, ankles swelling, headache, itch, etc…)
- **SAFETY**
  - No hypoglycemia risk
  - No weight gain
  - No adverse CV effects
  - No documentable adverse effects on any organ or apparatus
- **SUSTAINABILITY**
  - Affordable cost/benefit ratio

Diabetes Therapy:

E. Gale about expertise

..... People like me, as I am forced to conclude, have nothing to offer other than experience and expertise; and expertise, being unmeasurable, will always be undervalued. It ranks with health and happiness as something never fully appreciated until absent, as when you witness the damage that lack of expertise can inflict upon other people's lives.....

Gale E., Diabetologia 2008