American Diabetes Association.

66th ADVANCED
POSTGRADUATE COURSE
New York, NY

Panel Discussion on New Diabetes Medications: *Which to Use and When?*

Silvio E. Inzucchi MD
Yale School of Medicine
New Haven, CT

Presenter Disclosure Information

In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

Silvio E. Inzucchi MD

Research Support: NINDS, NIDDK, Boehringer-Ingelheim*, AstraZeneca*, Novo Nordisk*, Sanofi/Lexicon*, Eisai (TIMI Group*) (*clinical trial steering, executive or publications committees)

Employee: ---

Board Member/Advisory Panel: Astra Zeneca, VTV Therapeutics, Zafgen

Stock/Shareholder: ---

Consultant: ---

Other: Boehringer-Ingelheim (lectures)

25 years of outcome trials in diabetes…

1. Intensive glucose control (A1c ~7%) reduces microvascular complications in both T1D and T2D (↓ ~25-60%)[1–3]
2. Impact of intensive glucose control on macrovascular complications in T2D is small (↓ ~15%, mainly MI), and requires long-term efforts before it can be detected[4,5]
3. Some data suggest increased risk of CV mortality when strategies are too intense in high-risk T2D patients[6]
4. Until very recently, no diabetes medication had been conclusively shown to reduce CV events[7–14]

1. UKPDS 33. *Lancet* 1998;352:837; 2. DCCT. *N Engl J Med* 2000;10:381; 3. Zoungas S *et al. N Engl J Med* 2014;371:1392; 4. Turnbull FM *et al. Diabetologia* 2009;52:2288; 5. Holman RR *et al. N Engl J Med* 2008;359:1577; 6. Gerstein HC *et al. N Engl J Med* 2008;358:2545; 7. Scirica BM *et al. N Engl J Med* 2013;369:1317; 8. White WB *et al. N Engl J Med* 2013;369:1327; 9. Pfeffer MA *et al. N Engl J Med* 2015;373:2247; 10. Green JB *et al. N Engl J Med* 2015;373:232 11. Zinman B *et al. N Engl J Med* 2015;373:2117; 12. Marso SP *et al. N Engl J Med* 2016;375:311; 13 Marso SP *et al. N Engl J Med* 2016;375:1834; 14. Neal B *et al. N Engl J Med* 2017; doi: 10.1056/NEJMoa1611925

DM Meds and CV Outcomes Pre-FDA Guidance

Classes	Generic Names	↓ A1c	Impact on CVD
Insulin	Degludec, Glargine, Detemir, NPH, Regular, Lispro, Aspart, Glulisine	No limit	
SU's	Glyburide, Glipizide, Glimepiride	1%–1.5%	
Metformin	Metformin	1%–1.5%	PRE
TZD's	Rosiglitazone, Pioglitazone	1%–1.5%	PRE
			FDA GUIDANCE
DPP-4 i's	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin	0.5%–1%	POST
GLP-1 RA's	Exenatide, Liraglutide, Albiglutide, Dulaglutide, Lixisenatide	1%–1.5%	POST
SGLT2-i's	Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin	0.5%–1%	

DM Meds and CV Outcomes Pre-FDA Guidance

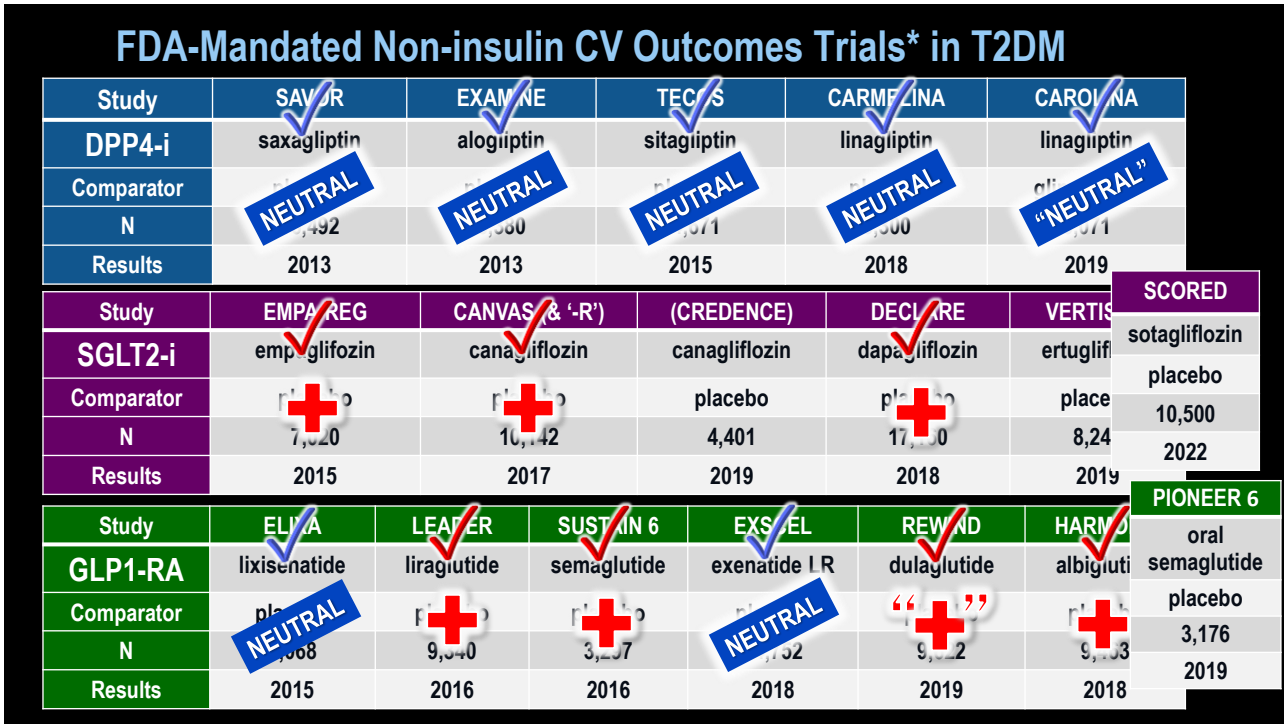
Classes	Generic Names	↓ A1c	Impact on MACE
Insulin	Degludec, Glargine, Detemir, NPH, Regular, Lispro, Aspart, Glulisine	No limit	↔
SU's	Glyburide, Glipizide, Glimepiride	1%–1.5%	↔
Metformin	Metformin	1%–1.5%	↓*
TZD's	Rosiglitazone, Pioglitazone	1%–1.5%	↔ – ↓†
DPP-4 i's	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin	0.5%–1%	?
GLP-1 RA's	Exenatide, Liraglutide, Albiglutide, Dulaglutide, Lixisenatide	1%–1.5%	?
SGLT2-i's	Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin	0.5%–1%	?

FDA-Mandated Non-insulin CV Outcomes Trials* in T2DM

Study	SAVOR	EXAMINE	TECOS	CARMELINA	CAROLINA
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	placebo	glimepiride
N	16,492	5,380	14,671	8,300	6,071
Results	2013	2013	2015	2018	2019

Study	EMPA-REG	CANVAS (& '-R')	(CREDENCE)	DECLARE	VERTIS CV
SGLT2-i	empaglifozin	canagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo	placebo
N	7,020	10,142	4,401	17,160	8,246
Results	2015	2017	2019	2018	2019

Study	ELIXA	LEADER	SUSTAIN 6	EXSCEL	REWIND	HARMONY
GLP1-RA	lixisenatide	liraglutide	semaglutide	exenatide LR	dulaglutide	albiglutide
Comparator	placebo	placebo	placebo	placebo	placebo	placebo
N	6,068	9,340	3,297	14,752	9,622	9,463
Results	2015	2016	2016	2018	2019	2018

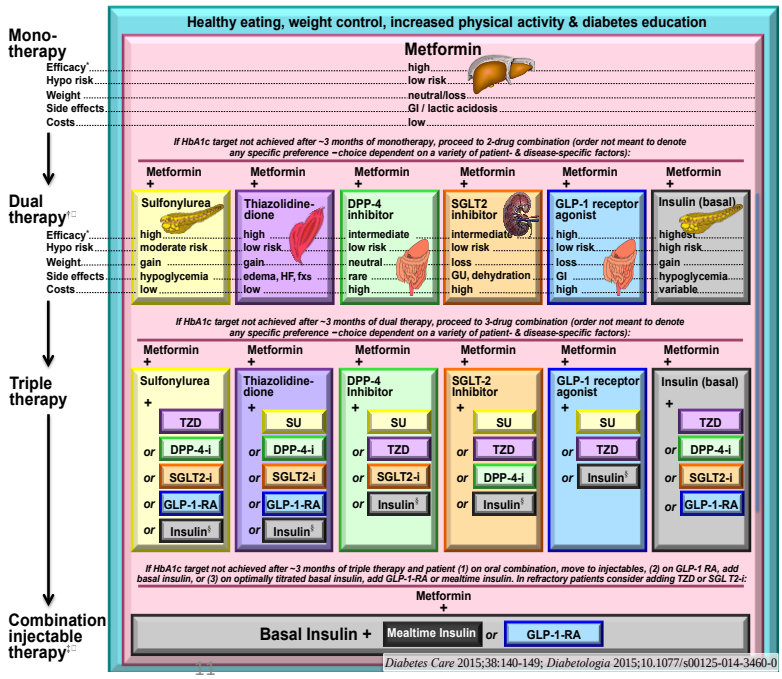


CVOT	EMPA-REG	CANVAS	DECLARE
SGLT2-i	Empagliflozin (0% 1°P)	Canagliflozin (34% 1°P)	Dapagliflozin (59% 1°P)
3-P MACE	**14% RRR (HR=0.86; 0.74-0.99)**	**14% RRR (HR=0.86; 0.75-0.97)**	NS (HR=0.93; 0.84-1.03)
CV Death	**38% RRR (HR=0.62; 0.49-0.77)**	NS (HR=0.87; 0.72-1.06)	NS (HR=0.98; 0.82-1.17)
CV Death *or* HHF	**34% RRR (HR=0.66; 0.55-0.79)**	**22% RRR (HR=0.78; 0.67-0.91)**	**17% RRR (HR=0.83; 0.73-0.95)**
All-cause death	**32% RRR HR=0.68 (0.57-0.82)**		NS (HR=0.93; 0.82-1.04)
Non-fatal MI	NS (HR=0.87; 0.70-1.09)	NS (HR=0.85; 0.69-1.05)	NS (HR=0.89; 0.77-1.01)
Non-fatal Stroke	NS (HR=1.24; 0.92-1.67)	NS (HR=0.90; 0.71-1.15)	NS (HR=1.01; 0.84-1.21)
HHF	**35% RRR (HR=0.65; 0.50-0.85)**	**33% RRR (HR=0.67; 0.52-0.87)**	**27% RRR (HR=0.73; 0.61-0.88)**
CKD Progression	**39% RRR (HR = 0.61; 0.53-0.70)**	**40% RRR (HR=0.60; 0.47-0.77)**	**24% RRR (HR=0.76; 0.67-0.87)**

CVOT (nonACS)	LEADER	SUSTAIN 6	EXCSEL	HARMONY
GLP-1 RA	Liraglutide (19% 1°P)	Semaglutide (17% 1°P)	Exenatide (27% 1°P)	Albiglutide (0% 1°P)
3-P MACE	13% RRR (HR=0.87; 0.78-0.97)	26% RRR (HR=0.74; 0.58-0.95)	NS HR=0.91 (0.83-1.00)	22% RRR (HR=0.78; 0.68-0.90)
CV Death *or* HHF				NS HR=0.85 (0.70-1.04)
CV Death	22% RRR (HR=0.78; 0.66-0.93)	NS HR=0.98 (0.65-1.48)	NS HR=0.88 (0.76-1.02)	NS HR=0.93 (0.73-1.19)
All-cause death	15% RRR HR=0.85 (0.74-0.97)	NS HR=1.05 (0.74-1.50)	14% RRR HR=0.86 (0.77-0.97)	NS (HR=0.95; 0.79-1.16)
Non-fatal MI	NS HR=0.88 (0.75-1.03)	NS HR=0.74 (0.51-1.08)	NS HR=0.95 (0.84-1.09)	25% RRR* HR=0.75 (0.61-0.90)
Non-fatal Stroke	NS HR=0.89 (0.72-1.11)	39% RRR (HR=0.61; 0.38-0.99)	NS HR=0.86 (0.70–1.07)	NS* HR=0.86 (0.66-1.14)
HHF	NS HR=0.87 (0.73-1.05)	NS HR=1.11 (0.77-1.61)	NS HR=0.94 (0.78-1.13)	NS HR=0.93 (0.82-1.04)
CKD Progression mainly ↓albuminuria	22% RRR (HR=0.78; 0.67-0.92)	36% RRR (HR=0.64; 0.46-0.88)		* *fatal or non-fatal*

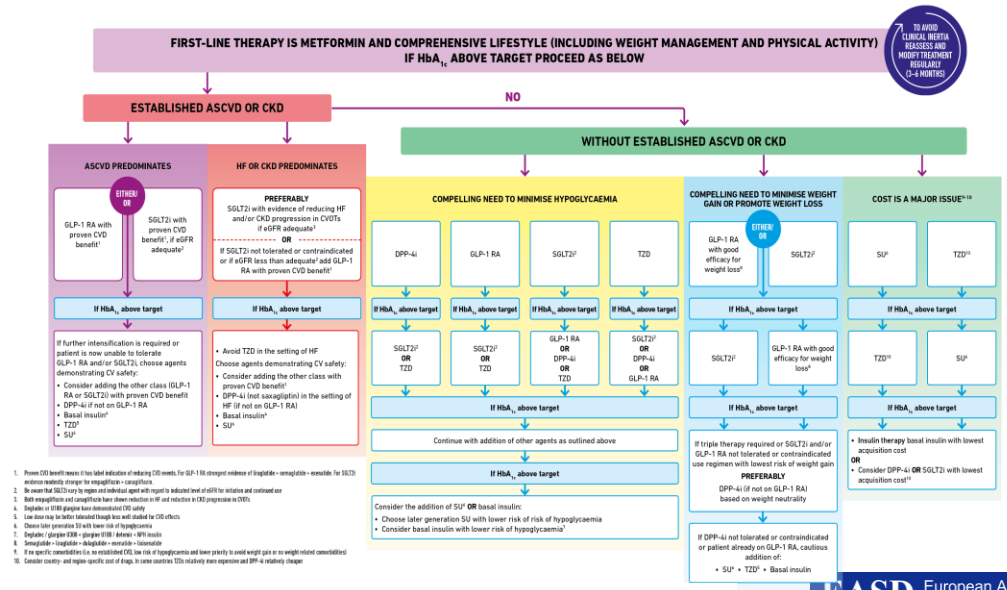
American Diabetes Association.
EASD European Association for the Study of Diabetes

2015 ADA-EASD position statement on management of hyperglycemia in T2DM: *Treatment algorithm*



Inzucchi SE *et al. Diabetes Care* 2015;38:140;
Inzucchi SE *et al. Diabetologia* 2015;58:429

Updated (2018) ADA-EASD Guidelines (Consensus Report):
GLUCOSE-LOWERING MEDICATION IN T2DM: OVERALL APPROACH



American Diabetes Association.

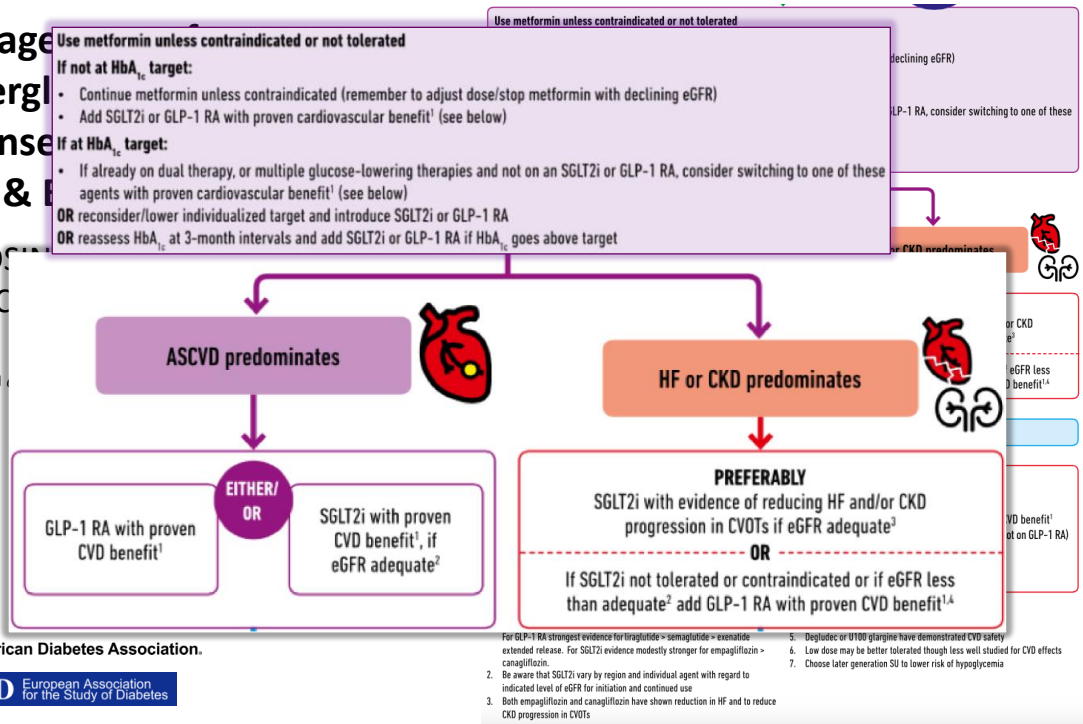
Davies MJ *et al. Diabetes Care* 2018;41:2669-2701

EASD European Association for the Study of Diabetes

Manage
Hypergl
A Conse
ADA & E

CHOOS
MEDIC

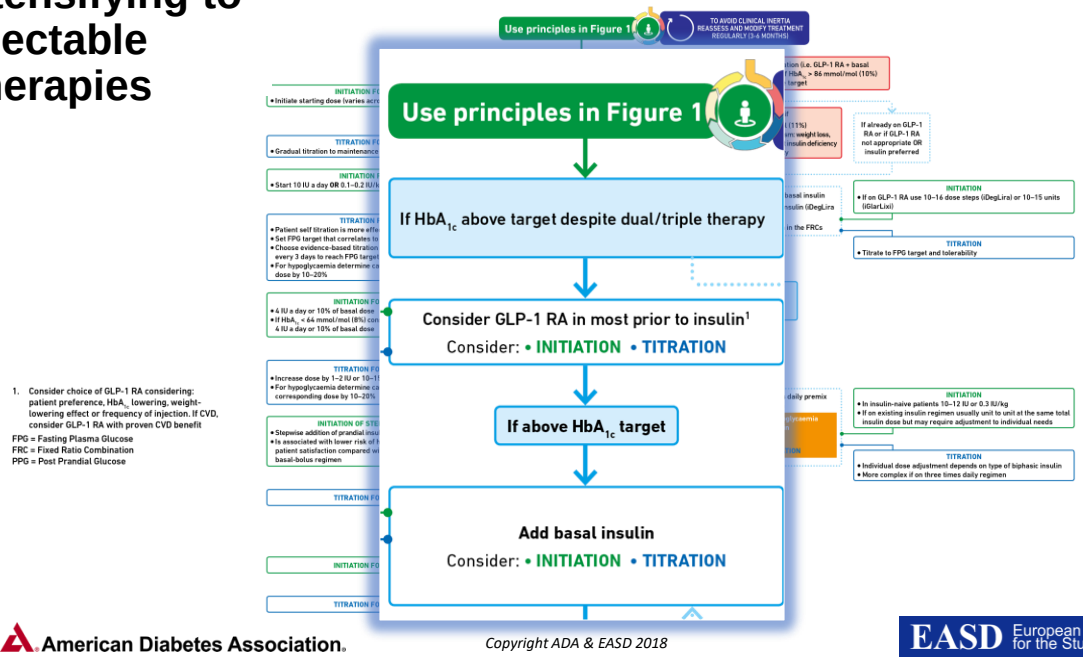
Davies MJ



American Diabetes Association.

EASD European Association for the Study of Diabetes

Intensifying to Injectable Therapies



American Diabetes Association.

Copyright ADA & EASD 2018

EASD European Association for the Study of Diabetes

American Diabetes Association.

SUMMARY

✦ Over the past 3-4 years, FDA-mandated CV outcome trials have confirmed CV *safety* for DPP-4i's and discovered *efficacy* for several SGLT2i's and GLP-1RA's.

✦ These new data are now impacting treatment guidelines.

✦ The *ADA Standards of Medical Care* continue to endorse lifestyle changes and metformin as 'foundation therapy' in T2DM.

✦ However, if additional glucose lowering therapy needed, the 2nd (of 3rd) agent should now be based on *prevalent comorbidities*:

- If ASCVD ➢ GLP-1RA *or* SGLT2i
- If HF or CKD ➢ SGLT2i

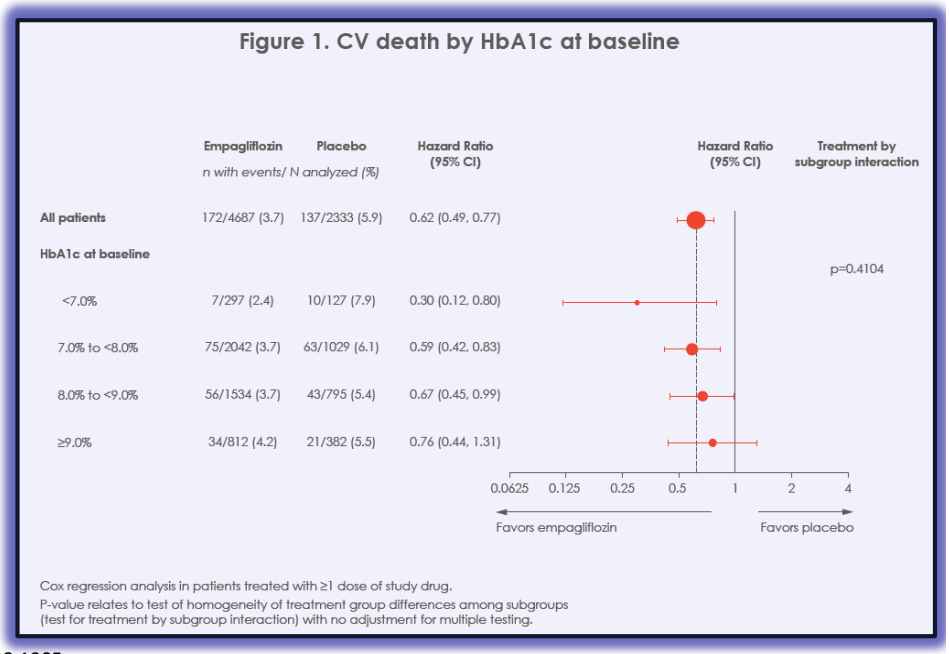
ONGOING QUESTIONS

✦ Does metformin still deserve it's place as the go-to initial therapy for all patients with T2DM?

✦ Should the addition of evidence-based therapies in CVD patients still be based on the need for additional HbA1c reduction?

Reduction in CV Mortality with Empagliflozin: *Independent of Glycemic Control*

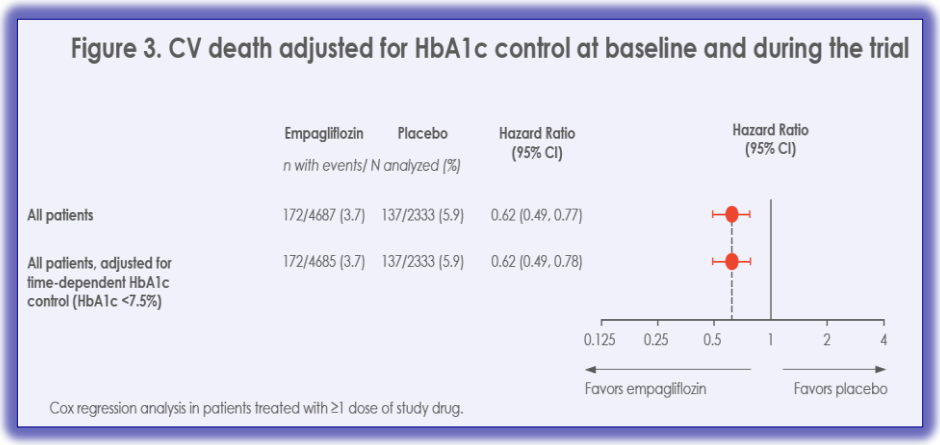
…by baseline A1c



Inzucchi SE *et al.* *Circulation* 2018;138:1905

Reduction in CV Mortality with Empagliflozin: *Independent of Glycemic Control*

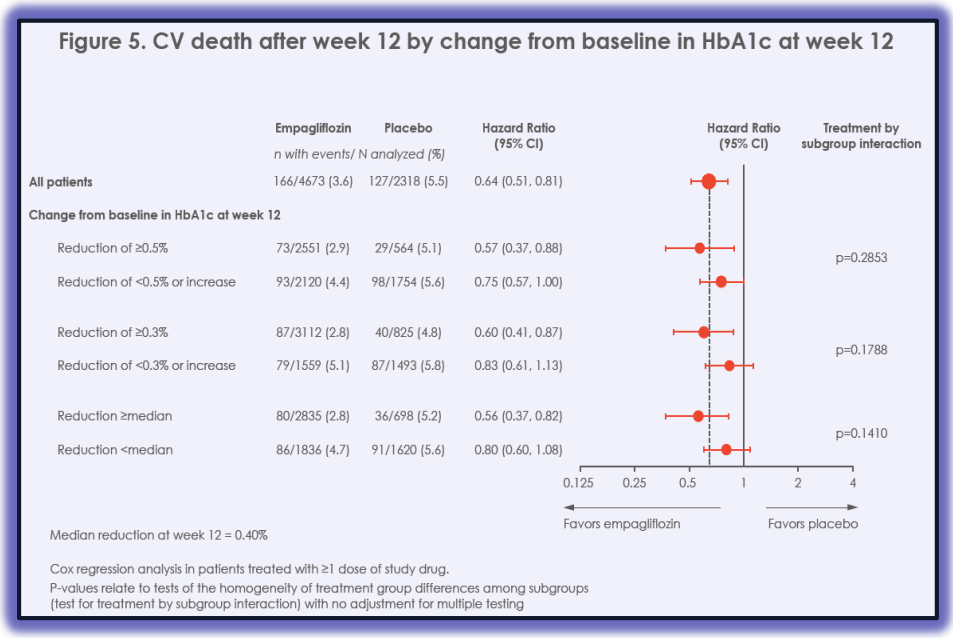
…by on-trial A1c



Inzucchi SE *et al.* *Circulation* 2018;138:1905

Reduction in CV Mortality with Empagliflozin: *Independent of Glycemic Control*

…by A1c @3 mos



Inzucchi SE *et al.* *Circulation* 2018;138:1905

American Diabetes Association.

66th ADVANCED
POSTGRADUATE COURSE
New York, NY

Panel Discussion on New Diabetes Medications: *Which to Use and When?*

Silvio E. Inzucchi MD
Yale School of Medicine
New Haven, CT