Decoding what to do when your patient has Diabetes and Cardiovascular Disease

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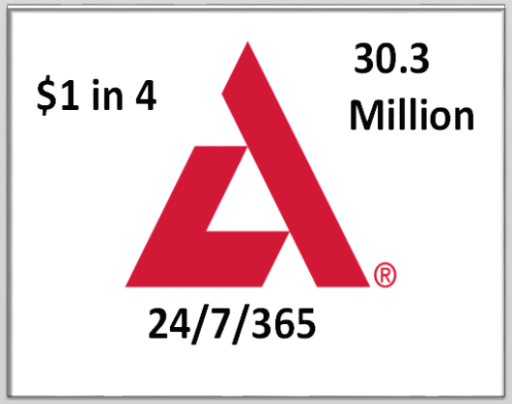


Center for Women's Health Research

Disclosures

- Consultation: Medtronic
- Honoraria: Sanofi
- Research Support: CU Foundation CWHR Fellowship (Lilly)

Case Study

- 41-year-old South Asian female
  - Initial visit after moving to town
- Past Medical History
  - T2DM, hypertension, dyslipidemia
  - Non-smoker
- Medications:
  - Metformin 1g bid
  - Lisinopril 20 mg qd
  - Hydrochlorothiazide 25 mg qd
  - Atorvastatin 10 mg

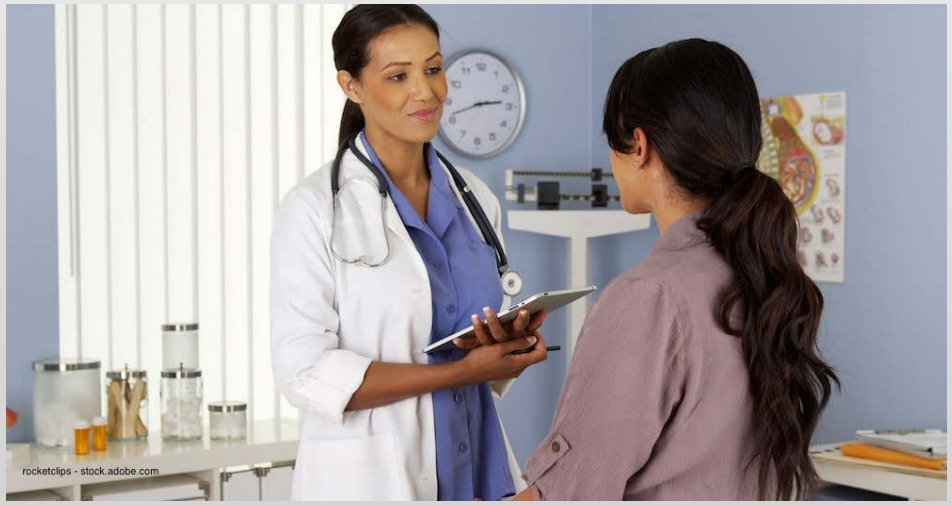
- Physical Exam:
  - 200 lbs, 5’10”, BMI 28.6
  - BP 156/78, Pulse 80, Resp 20
- Lab results:
  - A1C: 8.0%
  - FPG: 180 mg/dL
  - Lipids: Total cholesterol 160 mg/dL, LDL 125 mg/dL, HDL 35 mg/dL, TG 175 mg/dL
  - Urine albumin/creatinine ratio 13

Question: Where do we start?

Comprehensive cardiovascular risk reduction

- Type 2 Diabetes
- Hypertension
- Dyslipidemia

- Glucose control ? Target?
- BP control ? Target?
- Cholesterol control ?Target?



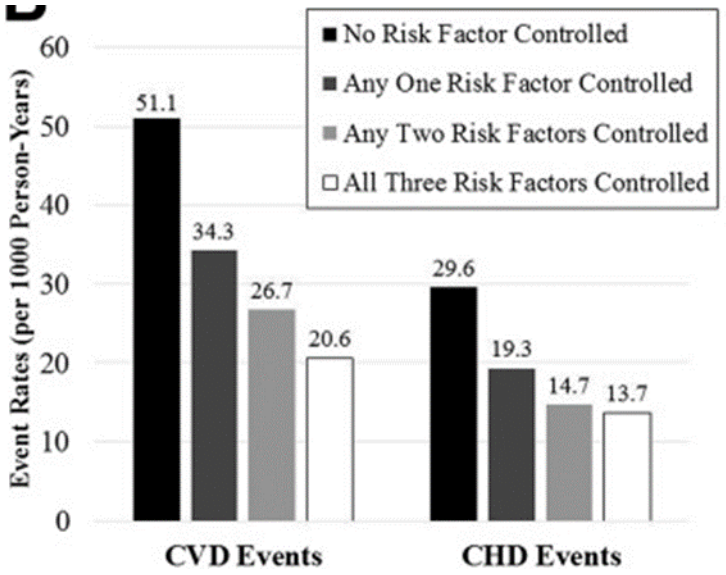
I got this….

But the devil is in the details

DIABETES & RISK OF MI & STROKE

Lancet 2010; 2215 (102 prospective studies, 700K people, 8.5M p-years f/u)

Cardiovascular (CV) Risk Factor Targets in Diabetes:



Wong, et al. Diabetes Care 2016 May; 39(5) 668-676.

Percent at target levels for any one, two, or all three factors among the 2018 persons with diabetes:

Any 1 of 3	Any 2 of 3	3 of 3
41.1%	26.5%	7.2%

Percent CVD risk reduction for being at target level among :

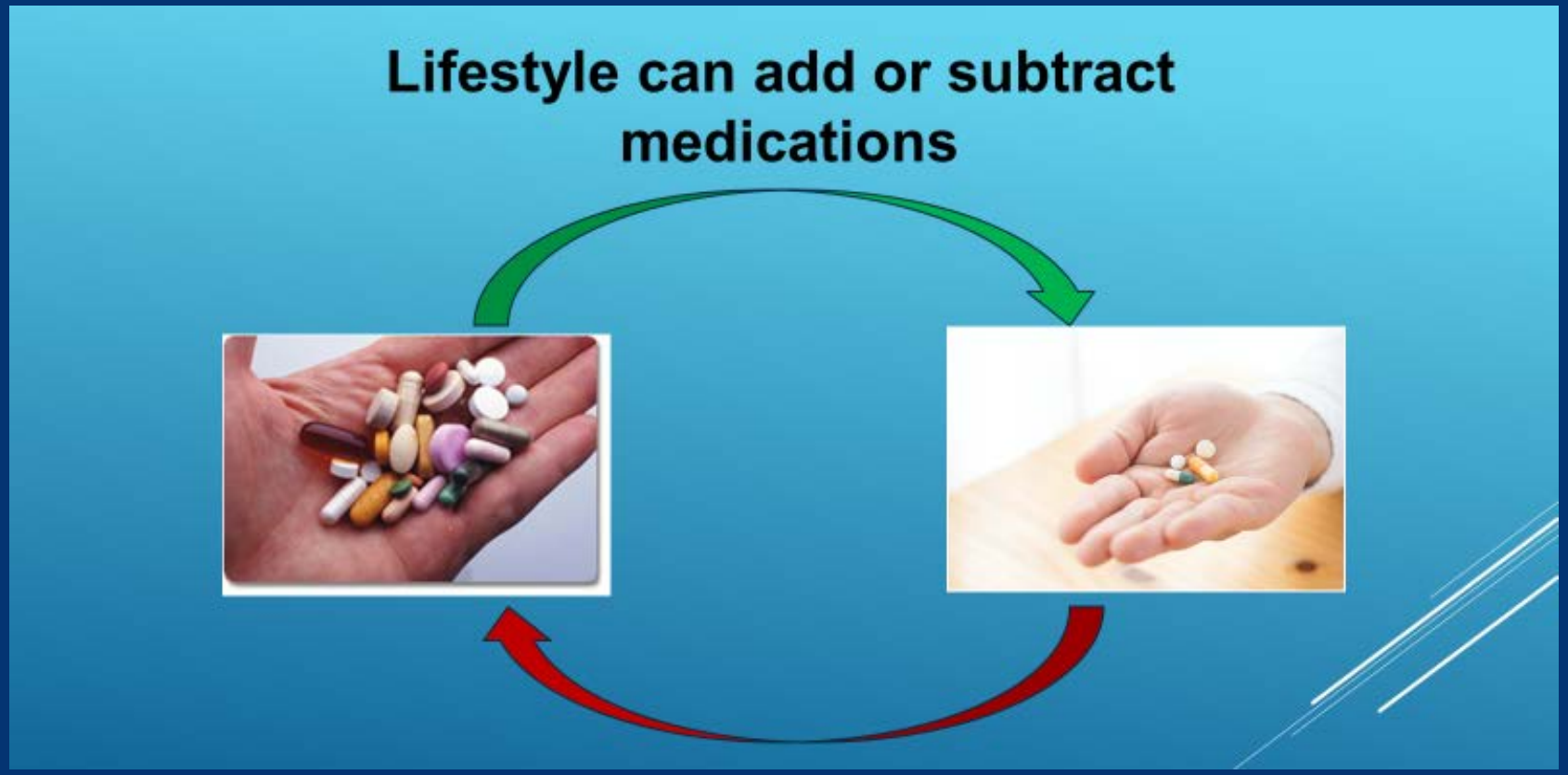
Blood pressure	LDL-C	HBA1c
17%	33%	37%

Percent lower adjusted risk of CVD events with one, two, or three risk factors at target level:

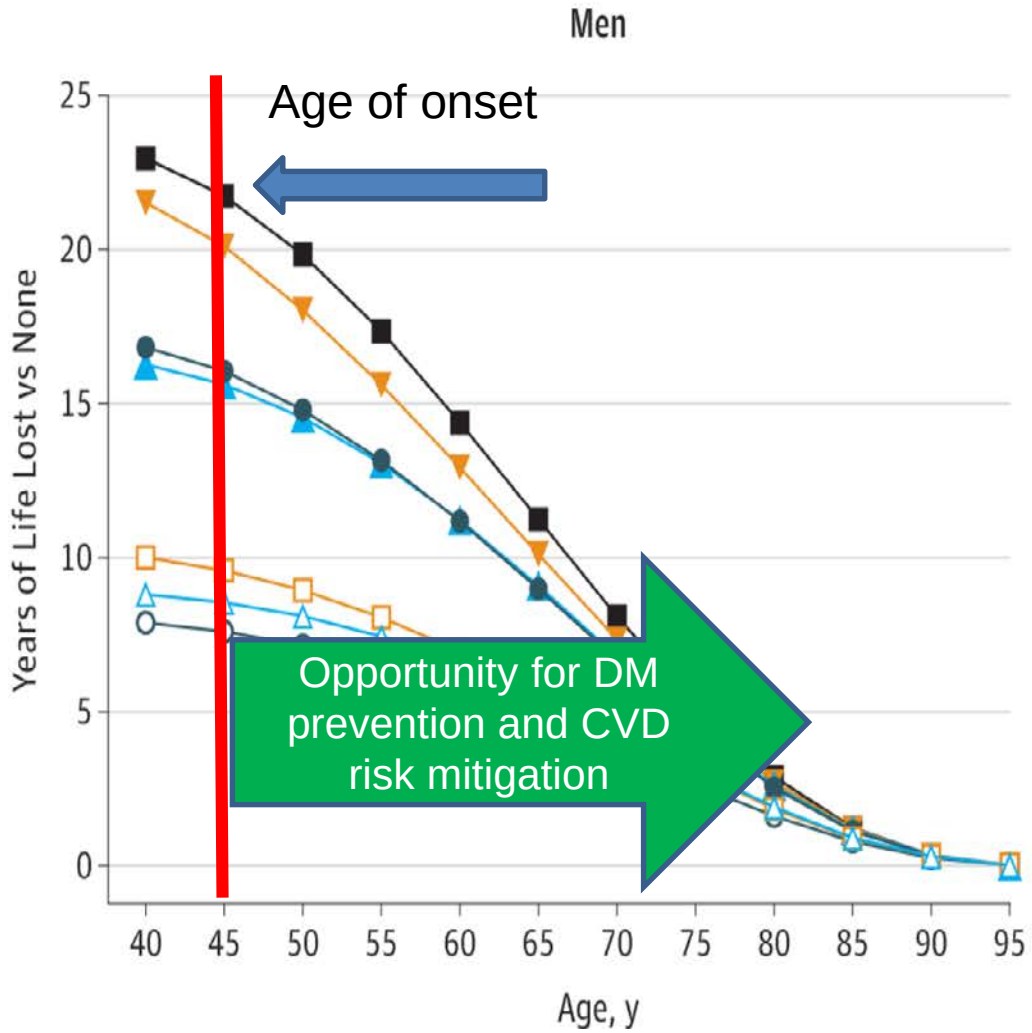
Any 1 of 3	Any 2 of 3	3 of 3
36%	52%	62%

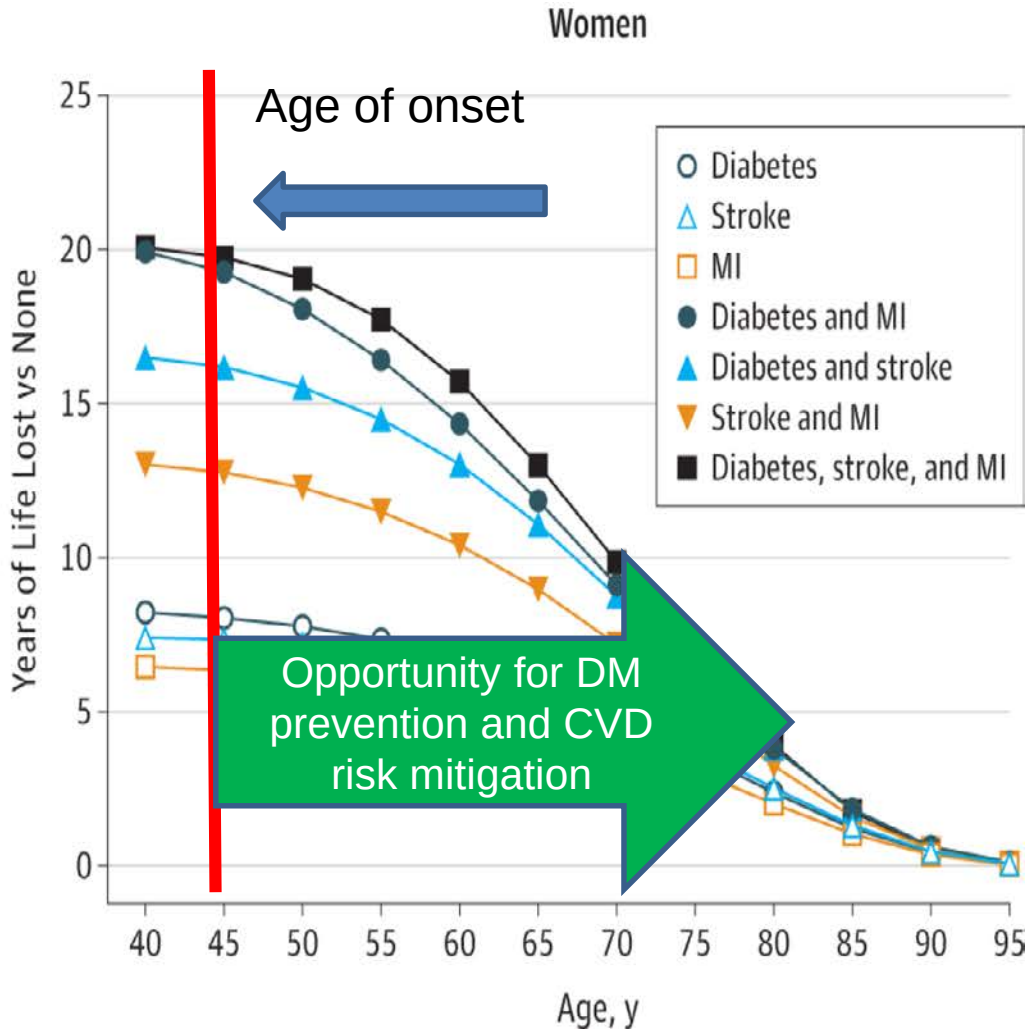
Comprehensive CVD risk factor modification saves lives:

- Every encounter presents an opportunity
- Employ our educational support systems to ensure adherence
- Diabetes means polypharmacy
- **Don’t forget diet and physical activity !!!**



Prevention or delay is the best risk reduction





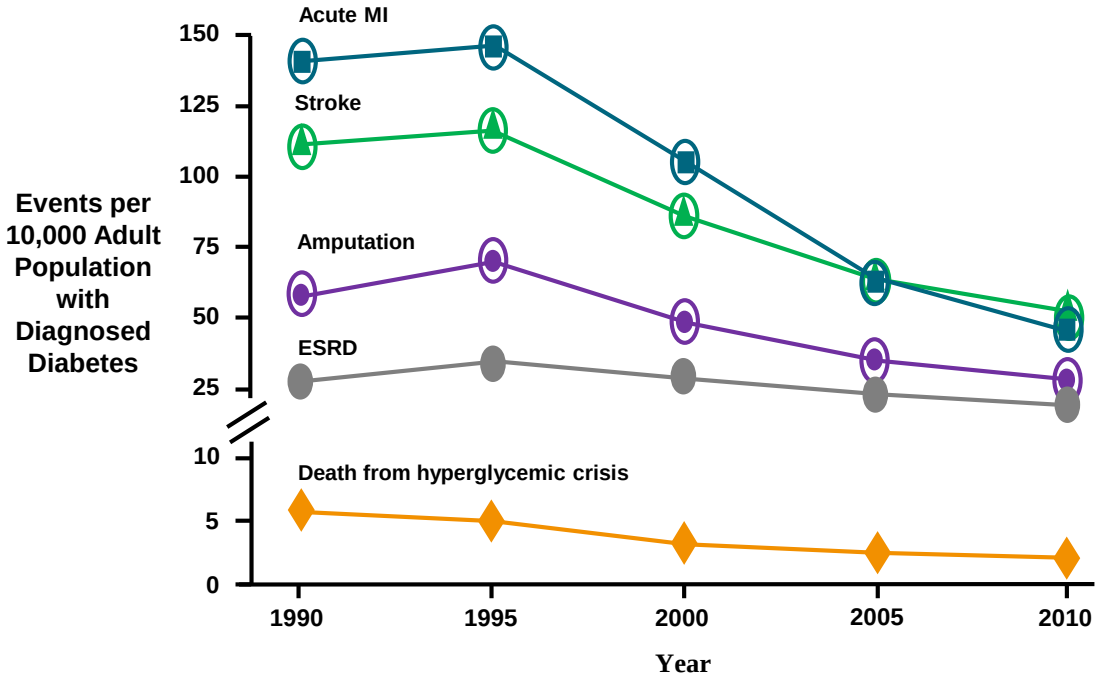
JAMA. 2015;314(1):52-60. doi:10.1001/jama.2015.7008

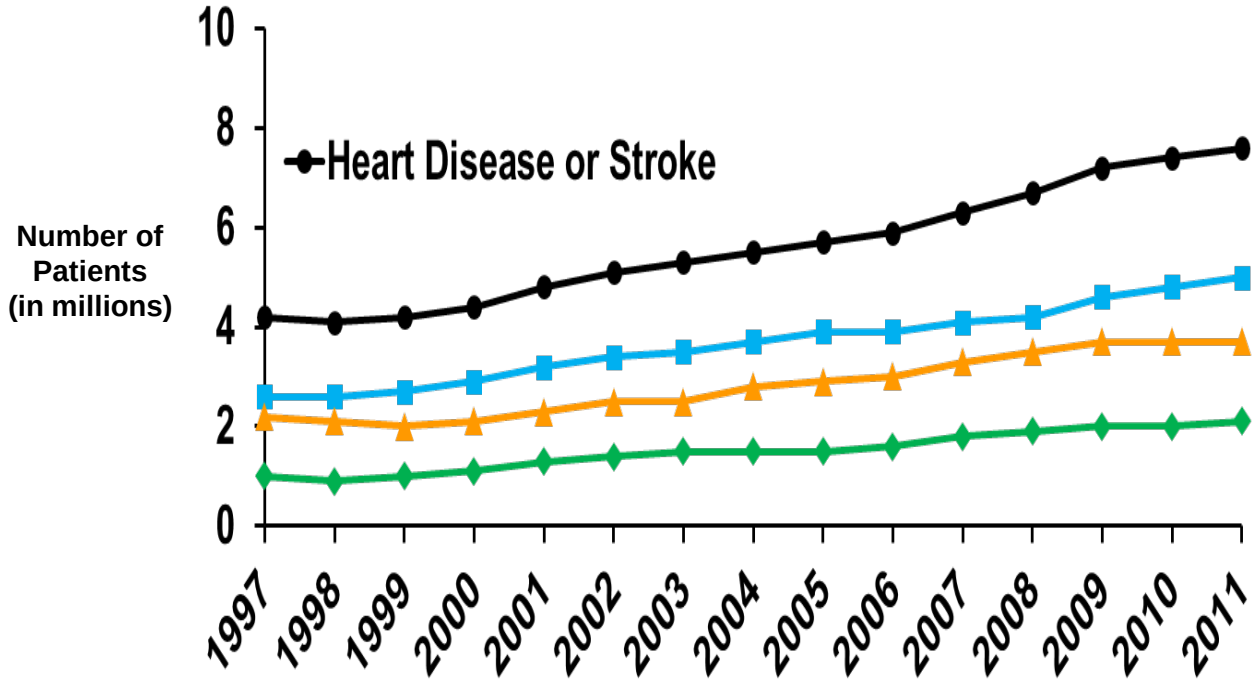
American Heart Association.

American Diabetes Association.
Connected for Life

Good News: Events per individual are lower

Bad news: absolute numbers are up





NHIS Data 1990-2010; Modified from Gregg et al. *NEJM* 2014
https://www.cdc.gov/diabetes/statistics/cvd/fig1.gif

Know Diabetes by Heart™

CV Outcome trials (CVOT) History: FDA objective: SAFETY

Year	Drug	Safety concerns and response
1992	Human proinsulin	Trials and development suspended **CV issues and ↑ risk of acute myocardial infarction**[a]
2005	Muraglitazar	**↑ Risk of death, major CV adverse events, CHF**[b]
2007	Rosiglitazone	**↑ CV risk; withdrawn from market in many countries**[c]
2008	–	FDA issued guidance document for the evaluation of CV risk[d] Studies are required to demonstrate that **new anti-diabetic therapies do not increase CV** risk in comparison with existing therapies

a. Galloway JA, et al. *Diab Care.* 1992;15:666-92.; b. Nissen SE, et al. *JAMA.* 2005;294:2581-2586.;
c. Nissen SE, et al. *N Engl J Med.* 2007;356:2457-71.; d. FDA Guidance For Industry, December 2008.

American Heart Association.

American Diabetes Association.
Connected for Life

NEWS:

The Daily Post

September 2015

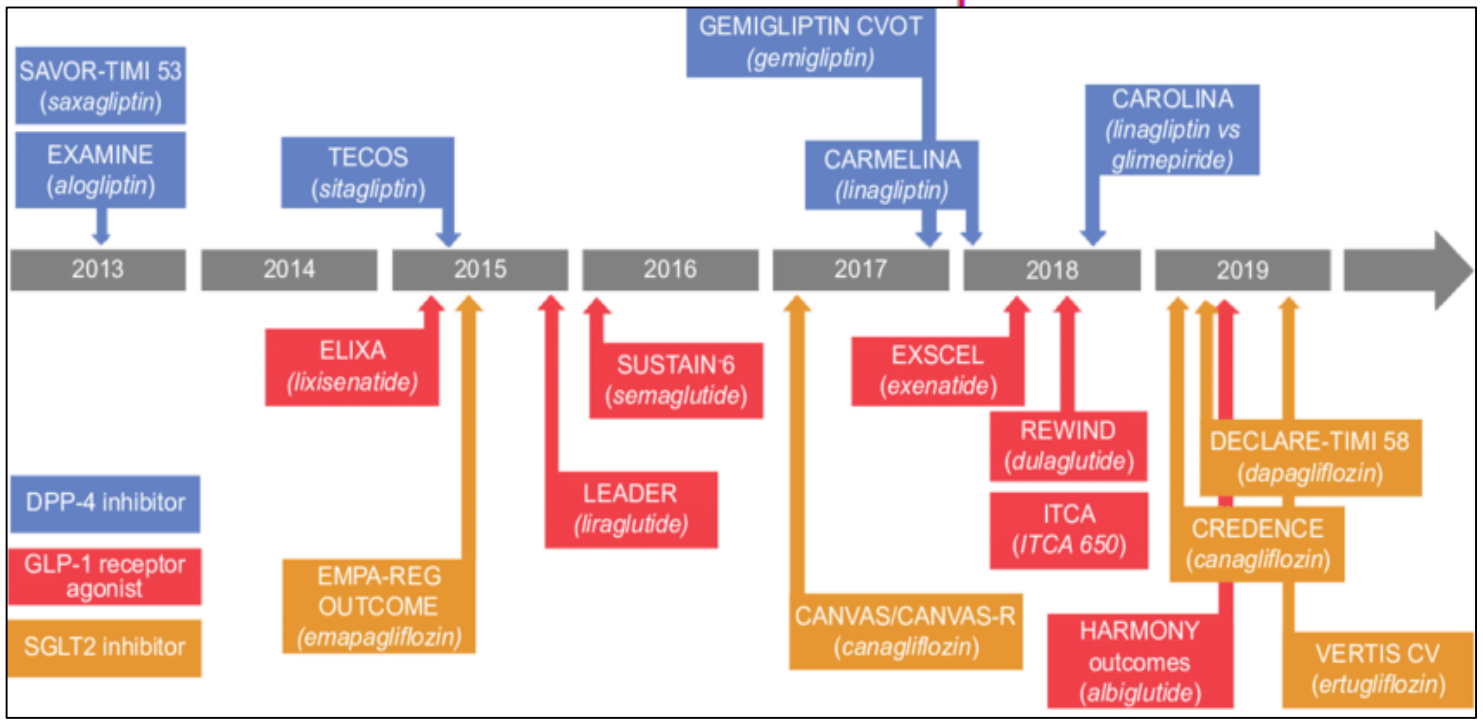
CVD and DM | GLP-1 RA | SGLT2 inhib

Diabetes Medicine prevents MACE

MACE= major adverse cardiac events

GLP-1 agonists and SGLT2 inhibitors decrease CV events:

Trial after trial supports CV benefit



FDA-Mandated CV Outcomes Trials in T2DM

Study	SAVOR[1]	EXAMINE[2]	TECOS[3]	CARMELINA[4]	CAROLINA[5]
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	placebo	glimepiride
N	16,492	5,380	14,671	6,979	6,103
Results	2013	2013	2015	2018	2018

NEUTRAL

FDA objective

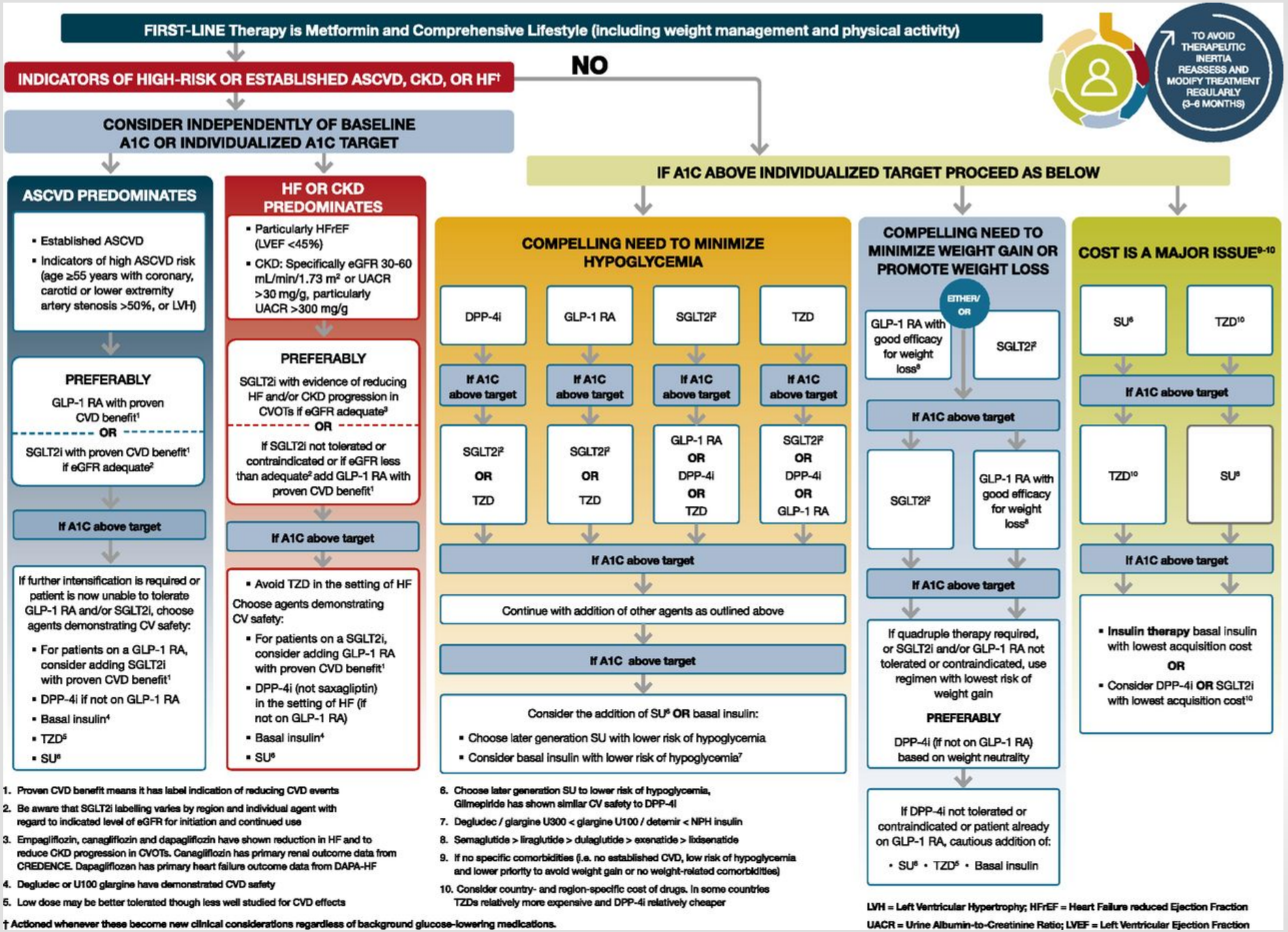
Study	ELIXA[6]	LEADER[7]	SUSTAIN 6[8]	EXSCEL[9]	REWIND[10]	HARMONY[11]
GLP1-RA	lixisenatide	liraglutide	semaglutide	exenatide LR	dulaglutide	albiglutide
Comparator	placebo	placebo	placebo	placebo	placebo	placebo
N	6,068	9346	3297	14,752	9,901	9,463
Results	2015	2015	2016	2017	2018	2018

NEUTRAL

Study	EMPA-REG[12]	CANVAS[13]	(CREDENCE[14])	DECLARE[15]	VERTIS CV[16]
SGLT2-i	empagliflozin	canagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo	placebo
N	7020	4330	4401	17,160	8246
Results	2015	2017	2018	2018	2020

1. NCT01107886 (SAVOR). 2. NCT00968708 (EXAMINE). 3. NCT00790205 (TECOS). 4. NCT01897532 (CARMELINA). 5. NCT01243424 (CAROLINA). 6. NCT01147250 (ELIXA). 7. NCT01179048 (LEADER). 8. NCT01720446 (SUSTAIN 6). 9. NCT01144338 (EXSCEL). 10. NCT01394952 (REWIND). 11. NCT02465515 (HARMONY). 12. NCT01131676 (EMPA-REG). 13. NCT01032629 (CANVAS). 14. NCT02065791 (CREDENCE). 15. NCT01730534 (DECLARE). 16. NCT01986881 (VERTIS CV).

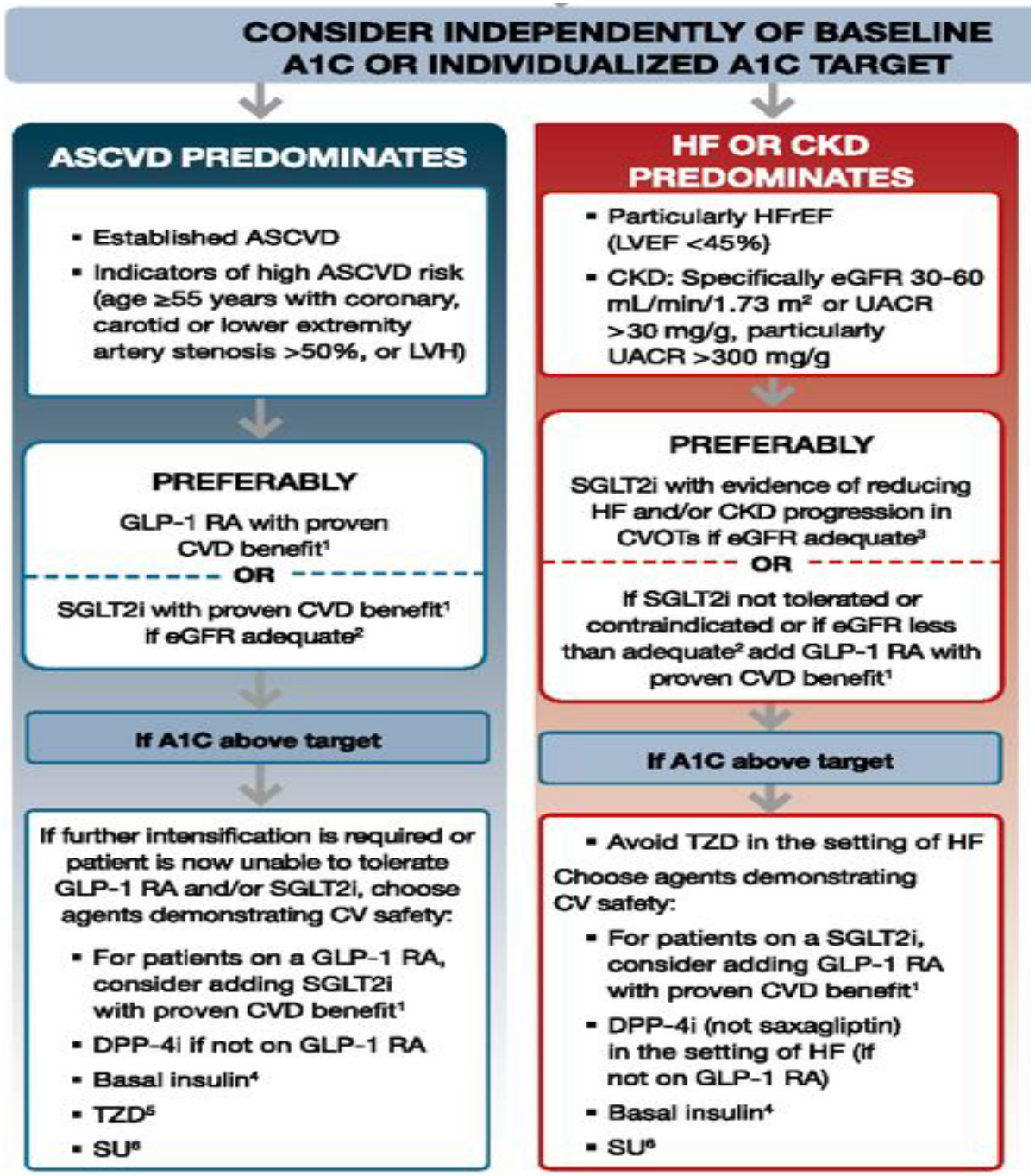
What does this mean for your practice?



Glucose-lowering Medication in Type 2 Diabetes: Overall Approach

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2020. Diabetes Care* 2020;43(Suppl. 1):S98-S110

American Diabetes Association.
Connected for Life



Independent of A1C
That's a change!

Type 2 Diabetes and ASCVD or CHF

Pre-existing and high risk ….regardless of A1c

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2020*. *Diabetes Care* 2020;43(Suppl. 1):S98-S110

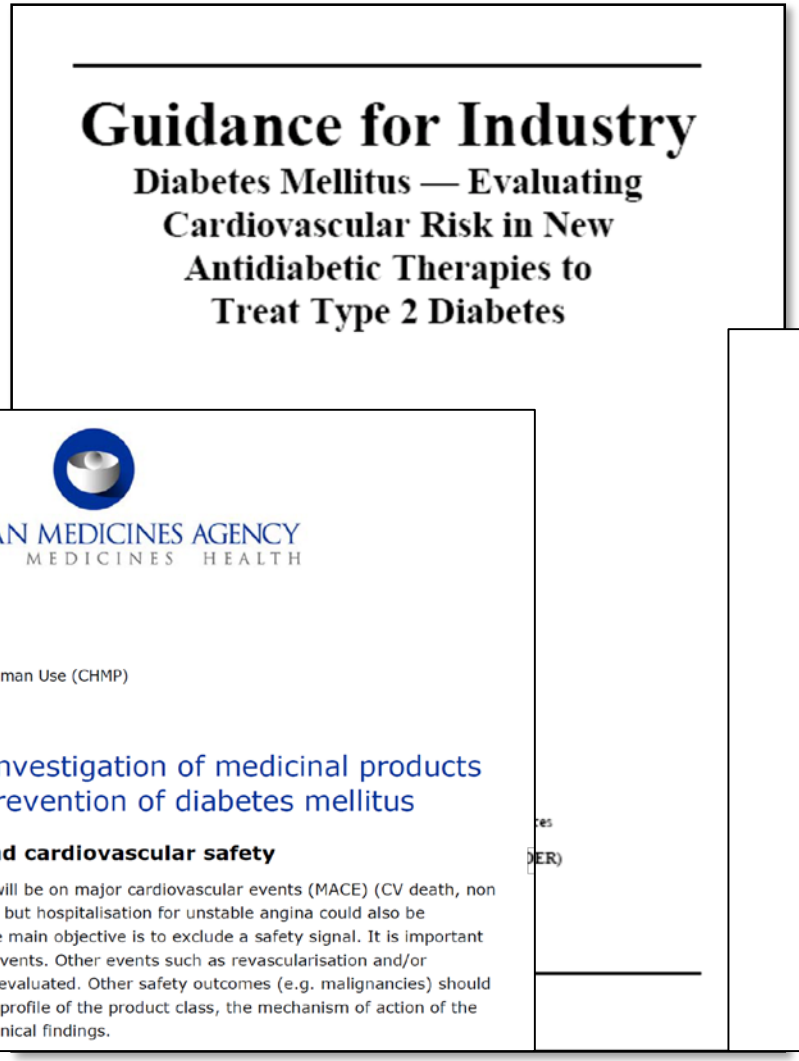
Case Study: 5 years later

- 46-year-old South Asian female
  - Recent hospitalization for ACS and **PCI x1 noted, EF 40%**
- Past Medical History
  - T2DM, hypertension, dyslipidemia
  - Non-smoker
- Medications:
  - Metformin 1g bid
  - Lisinopril 20 mg qd
  - Hydrochlorothiazide 25 mg qd
  - Atorvastatin 40 mg

- Physical Exam:
  - 200 lbs, 5’10”, BMI 28.6
  - BP 122/68, Pulse 80, Resp 20
- Lab results:
  - A1C: 6.8%
  - FPG: 140 mg/dL
  - Lipids: Total cholesterol 120 mg/dL, LDL 66 mg/dL, HDL 40 mg/dL, TG 70mg/dL
  - Urine albumin/creatinine **ratio 35**
  - Cr 1.1

GLP1 RA or SGLT2 inhibitor?

2008 FDA Guidance for Industry on Evaluating the Cardiovascular Risk of New Antidiabetic Therapies



Guidance for Industry

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

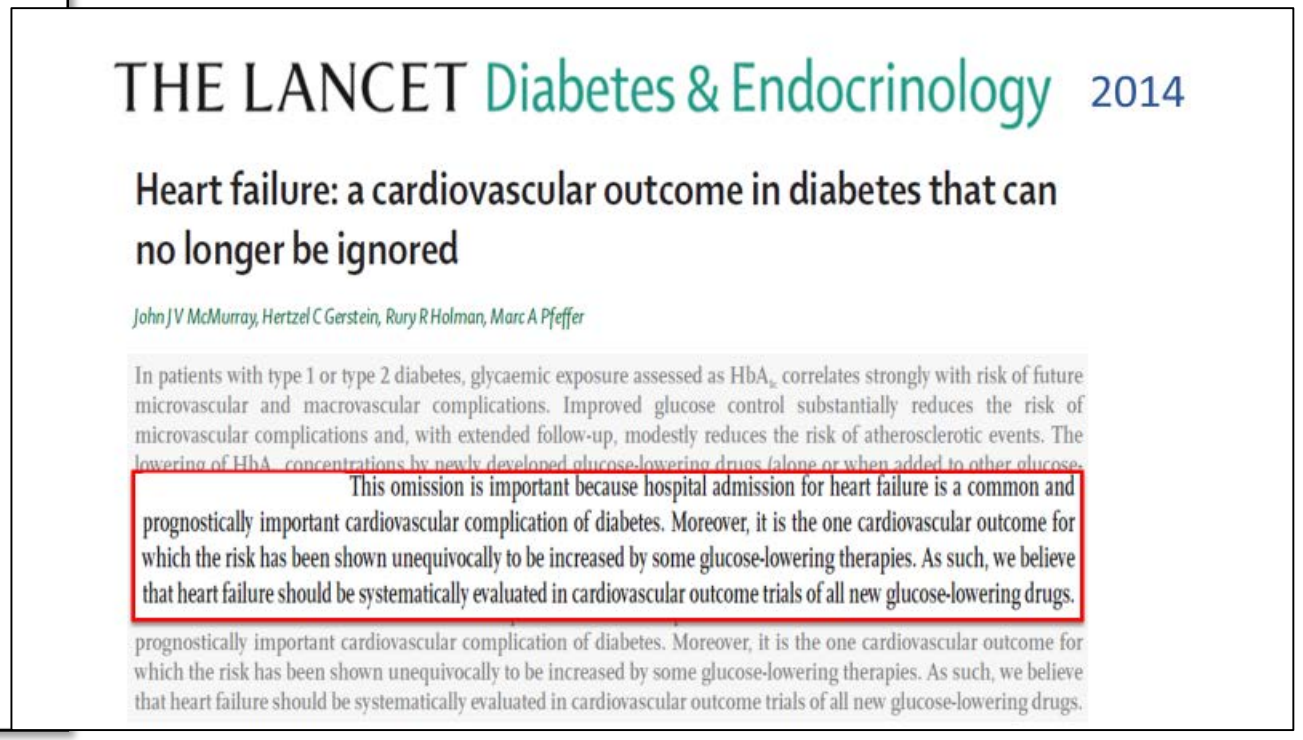
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 May 2012
CPMP/EWP/1080/00 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus

4.4.3 Long-term safety and cardiovascular safety

Concerning CV events, the emphasis will be on major cardiovascular events (MACE) (CV death, non fatal myocardial infarction and stroke) but hospitalisation for unstable angina could also be included in a composite endpoint if the main objective is to exclude a safety signal. It is important to ensure that these are adjudicated events. Other events such as revascularisation and/or worsening of heart failure will also be evaluated. Other safety outcomes (e.g. malignancies) should be chosen based on the known safety profile of the product class, the mechanism of action of the investigational drug and/or the non-clinical findings.



THE LANCET Diabetes & Endocrinology 2014

Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored

John J V McMurray, Hertzel C Gerstein, Rury R Holman, Marc A Pfeffer

In patients with type 1 or type 2 diabetes, glycaemic exposure assessed as HbA_{1c} correlates strongly with risk of future microvascular and macrovascular complications. Improved glucose control substantially reduces the risk of microvascular complications and, with extended follow-up, modestly reduces the risk of atherosclerotic events. The lowering of HbA_{1c} concentrations by newly developed glucose-lowering drugs (alone or when added to other glucose-

This omission is important because hospital admission for heart failure is a common and prognostically important cardiovascular complication of diabetes. Moreover, it is the one cardiovascular outcome for which the risk has been shown unequivocally to be increased by some glucose-lowering therapies. As such, we believe that heart failure should be systematically evaluated in cardiovascular outcome trials of all new glucose-lowering drugs.

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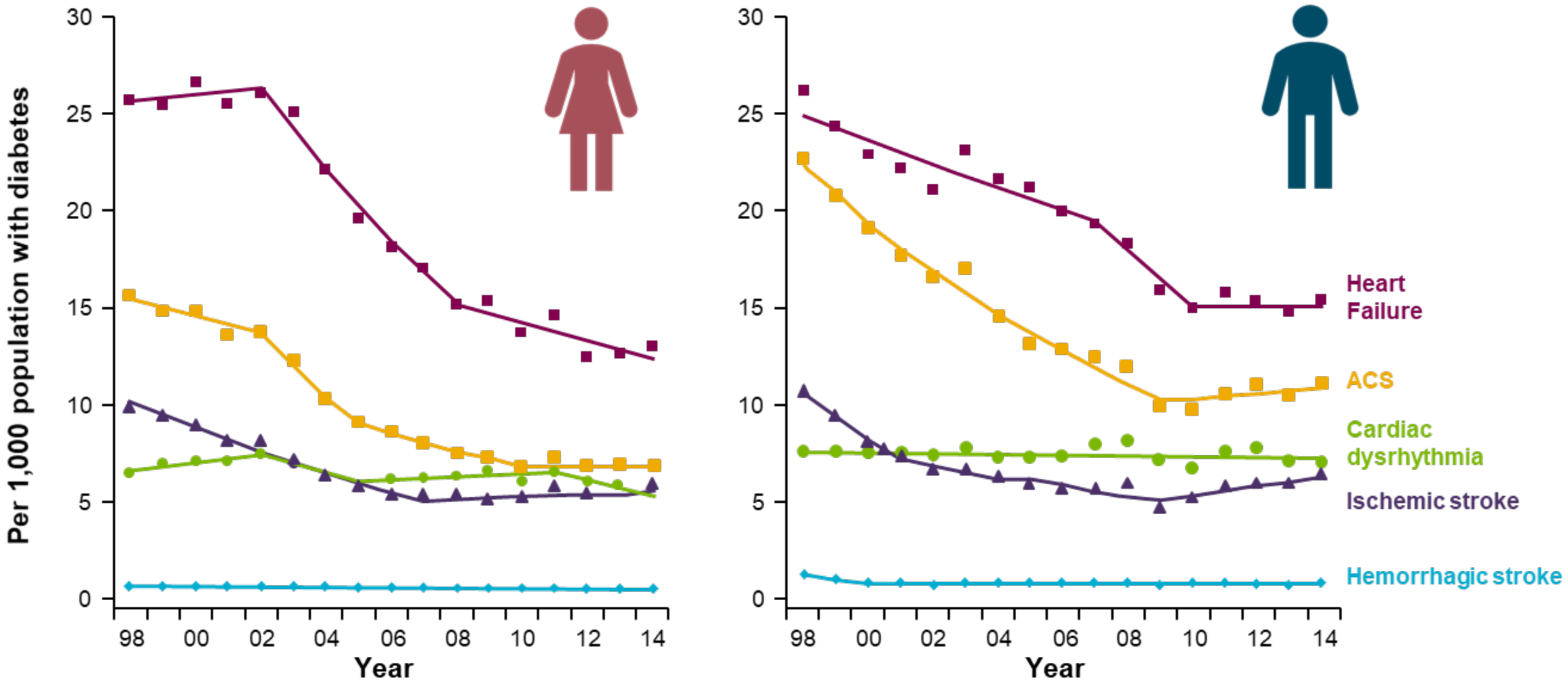
No discussion of heart failure!

CV = cardiovascular; MACE = major adverse cardiovascular events.

U.S. National Inpatient Sample (1998 to 2014):

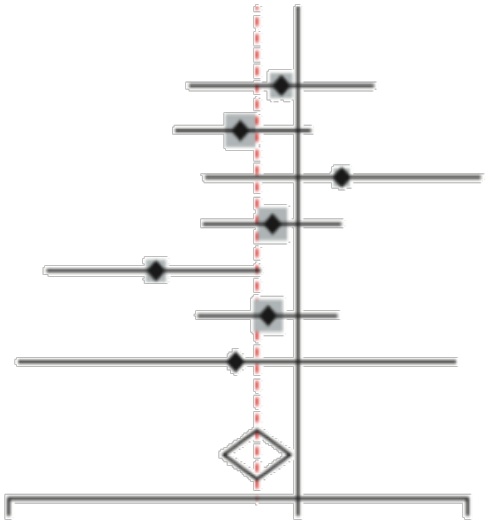
Hospitalization for HF Predominates Among Diabetes-Related Admissions



Burrows NR et al. *Diabetes Care*. 2018;41(2):293-302.

GLP-1 Receptor Agonists and Risk for Heart Failure

Risk reduction in HF hospitalisation by 9%, GLP-1 RA vs. placebo;
NNT 312 (95% CI 165–2810)



Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75–1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73–1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77–1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78–1·13)		0·51
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53–0·94)		<0·0001
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77–1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48–1·44)		0·59
Overall (I^2=0·0%, p=0·595)	**936/27977 (3%)**	**1016/28027 (4%)**	**0·91 (0·83–0·99)**	**312 (165 to 2810)**	**0·028**

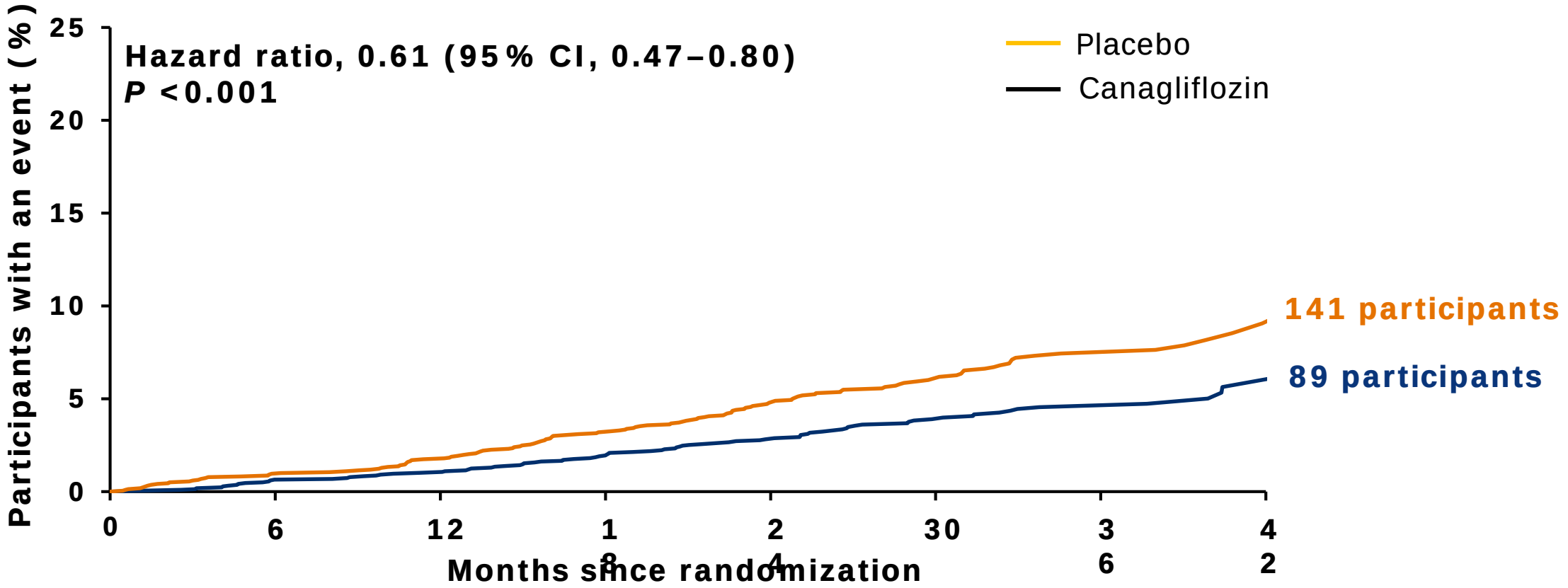
Kristensen S et al. Lancet Diabetes Endocrinol. 2019 pii: S2213-858730249-9.

Hospitalization for Heart Failure: Effects of SGLT2 Inhibitors

EMPA-REG OUTCOME Empagliflozin	CANVAS/CANVAS-R Canagliflozin	DECLARE-TIMI 58 Dapagliflozin
35%	33%	27%
9.4 vs 14.5 events/1000 p-y HR 0.65 (0.50-0.85)	5.5 vs 8.7 events/1000 p-y HR 0.67 (0.52-0.87)	6.2 vs 8.5 events/1000 p-y HR 0.73 (0.61-0.88)

Zinman B, et al. *N Engl J Med*. 2015;373(22):2117-2128
Neal B, et al. *N Engl J Med*. 2017;377(7):644-657
Wiviott SD, *N Engl J Med*. 2019;380(4):347-357

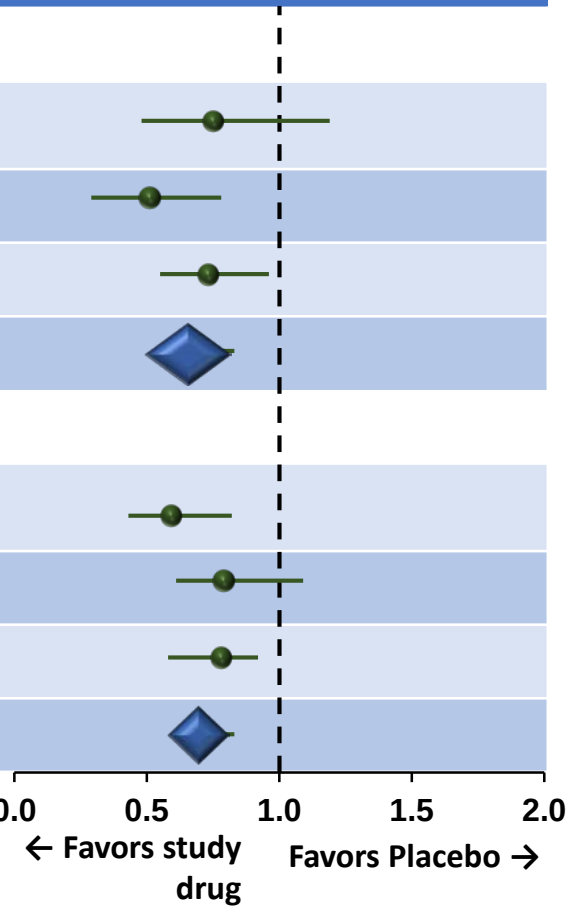
CREDENCE Results: Hospitalization for Heart Failure



No. at risk								
Placebo	2199	2165	2122	2043	1735	1147	638	170
Canagliflozin	2202	2171	2131	2076	1789	1226	668	199

Heart Failure Hospitalization By Prior Heart Failure

	Events per 1000 Patient-Years		Hazard Ratio (95% C.I.)
	SGLT2i	Placebo	
History of HF			Heterogeneity Q=2.14, p=0.34, I^2=6.6%
EMPA-REG Outcomes	40.7	52.4	0.75 (0.48, 1.19)
CANVAS Program	14.1	28.1	0.51 (0.33, 0.78)
DECLARE-TIMI 58	27.7	37.2	0.73 (0.55, 0.96)
Fixed effects model for history of HF (*p*=0.0002)			0.68 (0.55, 0.83)
No history of HF			Heterogeneity Q=1.73, p=0.42, I^2=0.0%
EMPA-REG Outcomes	6.4	10.8	0.59 (0.43, 0.82)
CANVAS Program	4.3	5.7	0.79 (0.57, 1.09)
DECLARE-TIMI 58	4.0	5.6	0.78 (0.58, 0.92)
Fixed effects model for MRF (*p*<0.0001)			0.71 (0.60, 0.83)



Data are not from head-to-head trials and should not be directly compared

Adapted from:
Zelnicker TA, et al. *Lancet*. 2019;393:31-39.

GLP1 RA and SGLT2 inhibitors save lives:

- Endocrinologists and cardiologists should start these agents
- In our health care delivery systems we should optimize PCP education to ensure optimal understanding, appropriate use and comfort with side effects
- Employ our educational support systems to ensure adherence and side effects mitigation /safety
- Improve policies to get these medications on formularies and affordable

Positive Sea Change:

GLP-1 Agonist
SGLT2 inhibitor

It’s a Glucose Medicine

It’s a Heart Medicine

It’s two medicines in One !!

Balancing Risks and Benefits for Personalized Goals

More Stringent Control

- No hypoglycemia
- Less complexity/ polypharmacy
- Lifestyle or metformin only
- Short disease duration
- Long life expectancy
- No CVD

← 7% →

Less Stringent Control

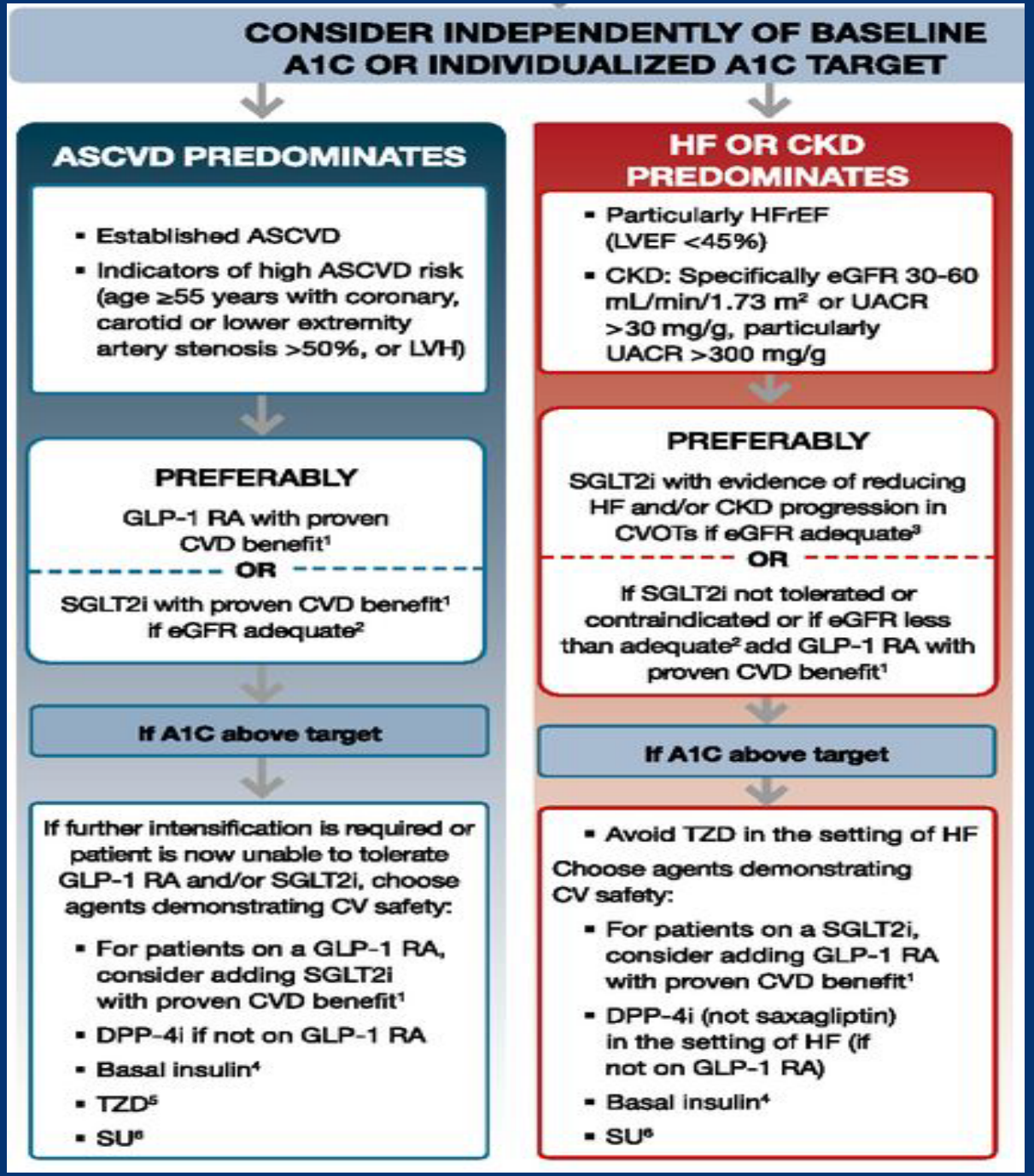
- History of severe hypoglycemia
- High burden of therapy
- Longer disease duration
- Limited life expectancy
- Extensive co-morbidity
- CVD

NOW need to consider "diabetes" medications for CVD beyond glucose

In closing:

Efficacy of anti-hyperglycemic agents for ASCVD, CHF and renal disease changes the indications for these agents

Let's discuss your patients and your challenges



Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2020*. *Diabetes Care* 2020;43(Suppl. 1):S98-S110

Thank you for your time

SGLT2 inhibitors can cause DKA but you need to work at it:

- Endocrinologists and cardiologists should both initiate
- Be aware of high risk settings

This card holder takes diabetes medication that can cause diabetic ketoacidosis without high glucose levels

STOP DKA Protocol

Symptomatic (e.g. lethargy, loss of appetite, nausea, abdominal pain) ➔ **STOP** SGLTi

AND

Test ketones* and glucose every 2-4 hours

(even if blood glucose is not elevated)

AND

Oral ingestion of fluid and carbohydrates

(250–500 mL fluid every 2 hours and up to 30–60 g of carbohydrates every 2-4 hours)

AND

Protocol instructions for supplemental insulin and carbohydrates

(see STOP DKA table)

*Ketosis/DKA may occur without an elevated blood glucose

Goldenberg RM et al. STOP DKA Protocol. *Diabetes Obesity Metab* On-line ahead of print 10 June 2019

Diabetes Self-management Education and Support

5.1 In accordance with the national standards for diabetes self-management education and support, all people with diabetes should participate in diabetes self-management education and receive the support needed to facilitate the knowledge, decision-making, and skills mastery necessary for diabetes selfcare. A

5.2 There are four critical times to evaluate the need for diabetes self-management education to promote skills acquisition in support of regimen implementation, medical nutrition therapy, and well-being: at diagnosis, annually, when complicating factors arise, and when transitions in care occur. E

Diabetes Self-management Education and Support

5.3 Clinical outcomes, health status, and well-being are key goals of diabetes self-management education and support that should be measured as part of routine care. C

5.4 Diabetes self-management education and support should be patient centered, may be given in group or individual settings and/or use technology, and should be communicated with the entire diabetes care team. A

5.5 Because diabetes self-management education and support can improve outcomes and reduce costs B, reimbursement by third-party payers is recommended. C

Diabetes Self-management Education and Support

Four critical time points have been defined when the need for DSMES is to be evaluated by the medical care provider and/or multidisciplinary team, with referrals made as needed:

1. At diagnosis
2. Annually for assessment of education, nutrition, and emotional needs
3. When new complicating factors (health conditions, physical limitations, emotional factors, or basic living needs) arise that influence self-management
4. When transitions in care occur