Impact and Importance of the 2008 Guidance in Diabetes Care

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Disclosures

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Company	Role	Product	Significance
Merck, Sharpe & Dohme	Co-Investigator	Sitagliptin	Significant
AstraZeneca	Co-Investigator	Exenatide	Significant
Boehringer Ingelheim	Principal Investigator	Empagliflozin	Significant
GlaxoSmithKline	Co-Investigator	Albiglutide	Significant
Sanofi	Principal Investigator	Sotagliflozin	Significant
Intarcia Therapeutics	Principal Investigator	ITCA-650	Significant
Janssen	Co-Investigator	Canagliflozin	Nominal

Scientific Advisor/Consulting Fees:

Company	Product	Significance
Merck, Sharpe & Dohme	MK-3102, MK-8835	Nominal
AstraZeneca	Exenatide	Nominal
Boehringer Ingelheim	Empagliflozin	Significant
Sanofi/Regeneron	Alirocumab	Nominal
Daiichi Sankyo	DS-8500	Significant
NovoNordisk	Semaglutide	Significant

Impact and Importance of the 2008 Guidance in Diabetes Care

- ***The good, the bad, the ugly, and the future***

The Good

- **Completed CVOTs**
  - **Provide reassurance** that newer drugs for T2DM do not increase risk MACE
  - Have **established CV benefits** of several drugs
    - *In patients at high CV risk*
    - *As a complement to existing CV risk reduction strategies*

CV = cardiovascular
CVOT = cardiovascular outcomes trial
MACE = major adverse cardiovascular events

The Good

- **Completed CVOTs**
  - **Highlighted HF** as an important complication in T2DM
  - Suggest **heterogeneity** of CV, other effects of drugs both between and within classes
  - Identified **unexpected other benefits** of treatments
    - *Heart failure*
    - *Renoprotection*

CV = cardiovascular
CVOT = cardiovascular outcomes trial
HF = heart failure

The Good

- **Completed CVOTs**
  - **Provide important data re: other safety outcomes**
    - Addressed or identified issues of clinical interest

      Thyroid malignancy, pancreatic safety, amputations, fractures, HHF
    - Frequency with which complications occur
    - Some safety data potentially not otherwise available

CV = cardiovascular
CVOT = cardiovascular outcomes trial
HHF = hospitalization for heart failure

The Good

- **Benefits of enhanced safety expectations**
  - **Taspoglutide** (~600 pt years) development discontinued due to emergence of rare allergic reactions, including anaphylaxis.
  - **Aleglitazar** (>14,000 patient years) development discontinued due to lack of CV efficacy and increases in fractures, kidney problems, GI bleeds, and heart failure.
  - **Fasiglifam** (~2000 patient years) clinical development program was terminated due to drug-associated liver injury (10-fold increase in elevated LFTs)

Rosenstock J et al. Diabetes Care 2013; 36: 498–504.
Lincoff AM et al. JAMA 2014; 311: 1515-1525.

The Good

- Evidence generated by CVOTs meeting specifications of FDA guidance has contributed to a remarkable evolution and refinement of diabetes care guidelines for the highest risk patients

Diabetes Care Guidelines Circa 2006-2008

Emphasis upon intensive glycemic control to reduce risk complications

ADA Guidelines

Table 8—*Summary of glycemic recommendations for adults with diabetes*

A1C	<7.0%*
Preprandial capillary plasma glucose	70–130 mg/dl (3.9–7.2 mmol/l)
Peak postprandial capillary plasma glucose†	<180 mg/dl (<10.0 mmol/l)

Key concepts in setting glycemic goals:

- A1C is the primary target for glycemic control
- Goals should be individualized based on:
  - duration of diabetes
  - pregnancy status
  - age
  - comorbid conditions
  - hypoglycemia unawareness
  - individual patient considerations
- More stringent glycemic goals (i.e., a normal A1C, <6%) may further reduce complications at the cost of increased risk of hypoglycemia
- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals

*Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay. †Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

2006 ACE/AACE targets for glycemic control

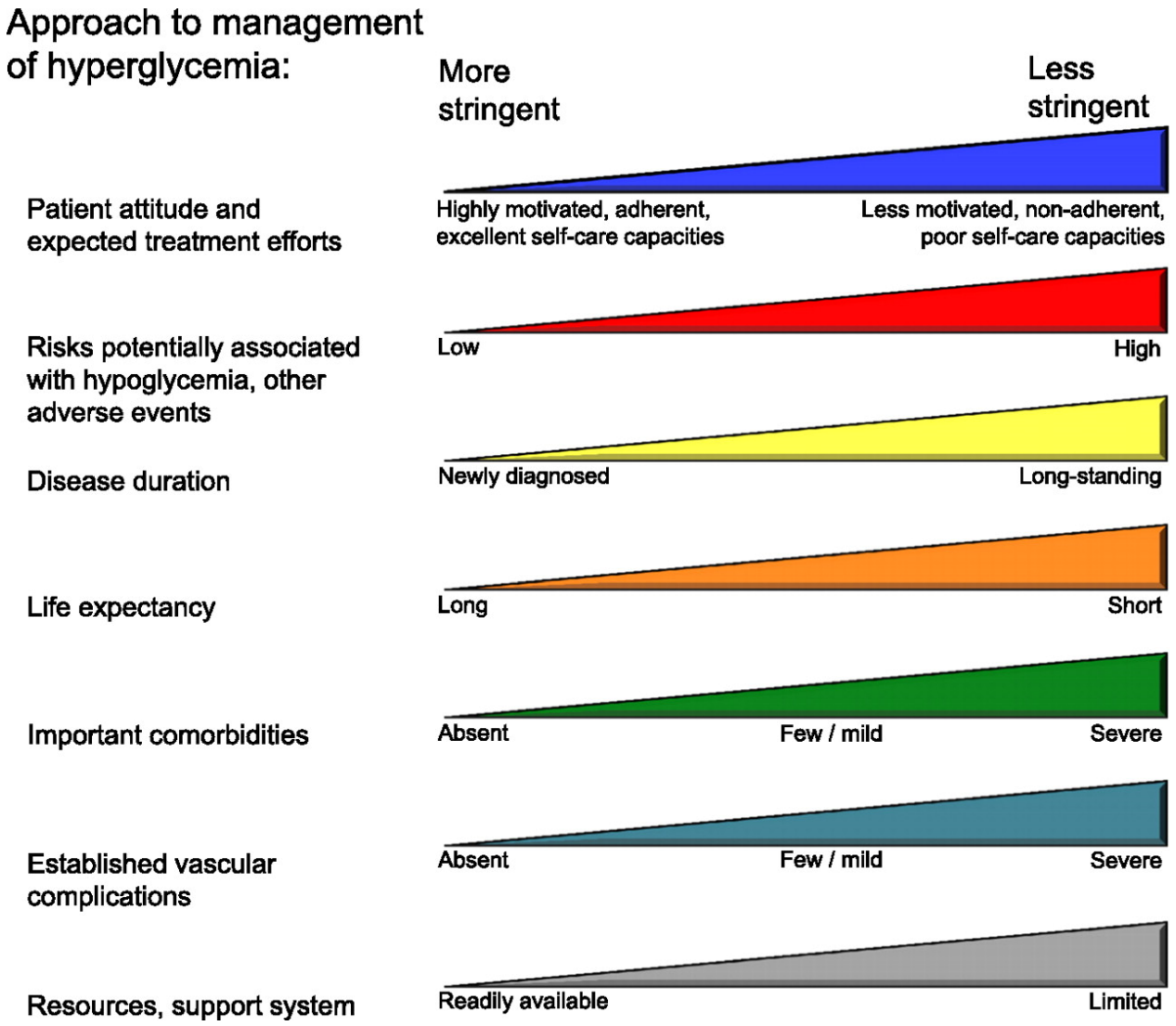
- A1C ≤6.5%
- Fasting/preprandial plasma glucose <110 mg/dL
- 2-hour postprandial plasma glucose <140 mg/dL

"Early use of insulin therapy is frequently needed for timely achievement of glycemic goals."

Diabetes Care 2008 Jan; 31(Supplement 1): S12-S54
Endocrine Practice Vol 12 No. 1 January/February 2006

2012 Update to ADA Guidelines

Individualization of glycemic targets…

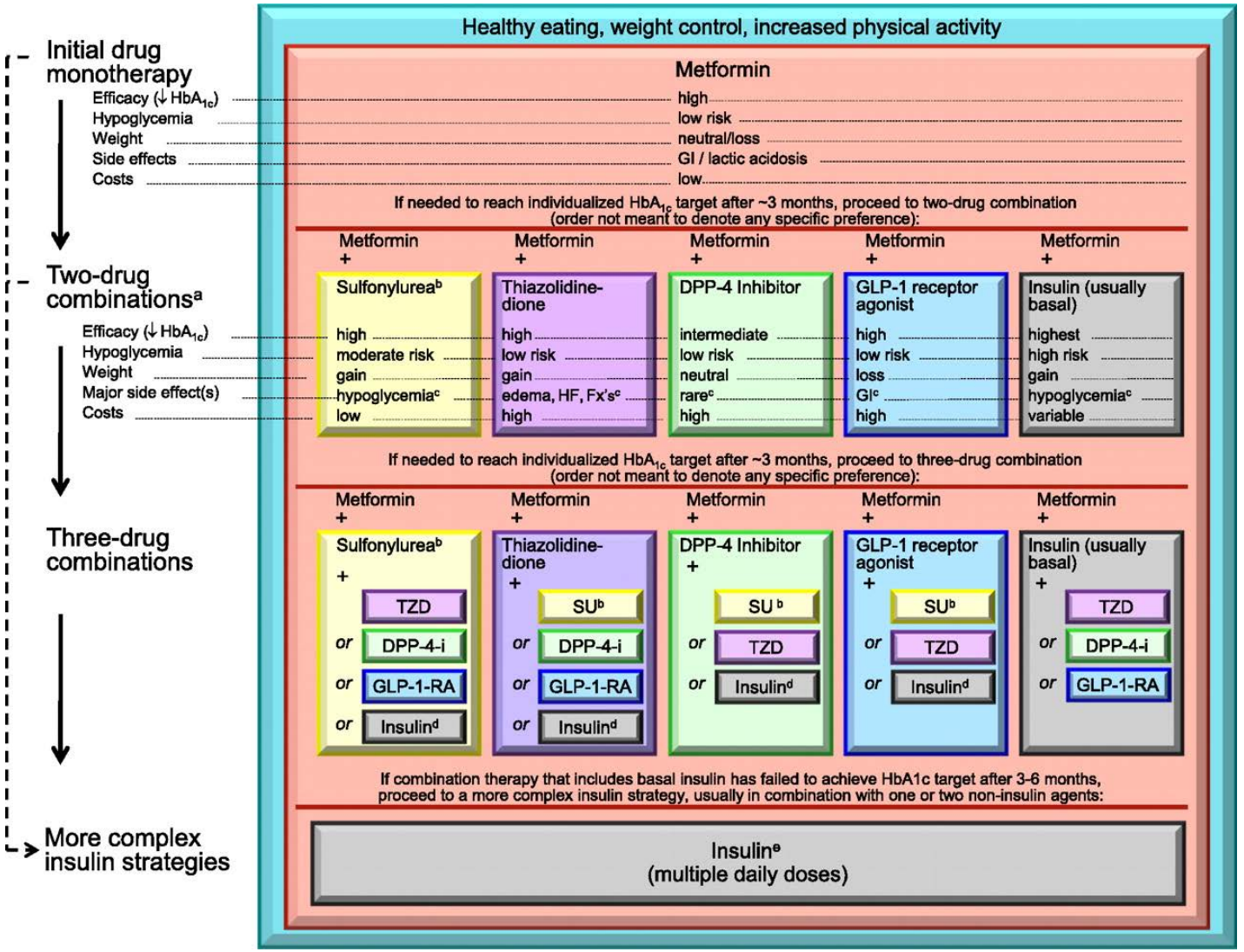


American Diabetes Association.

Silvio E. Inzucchi et al. Dia Care 2012;35:1364-1379

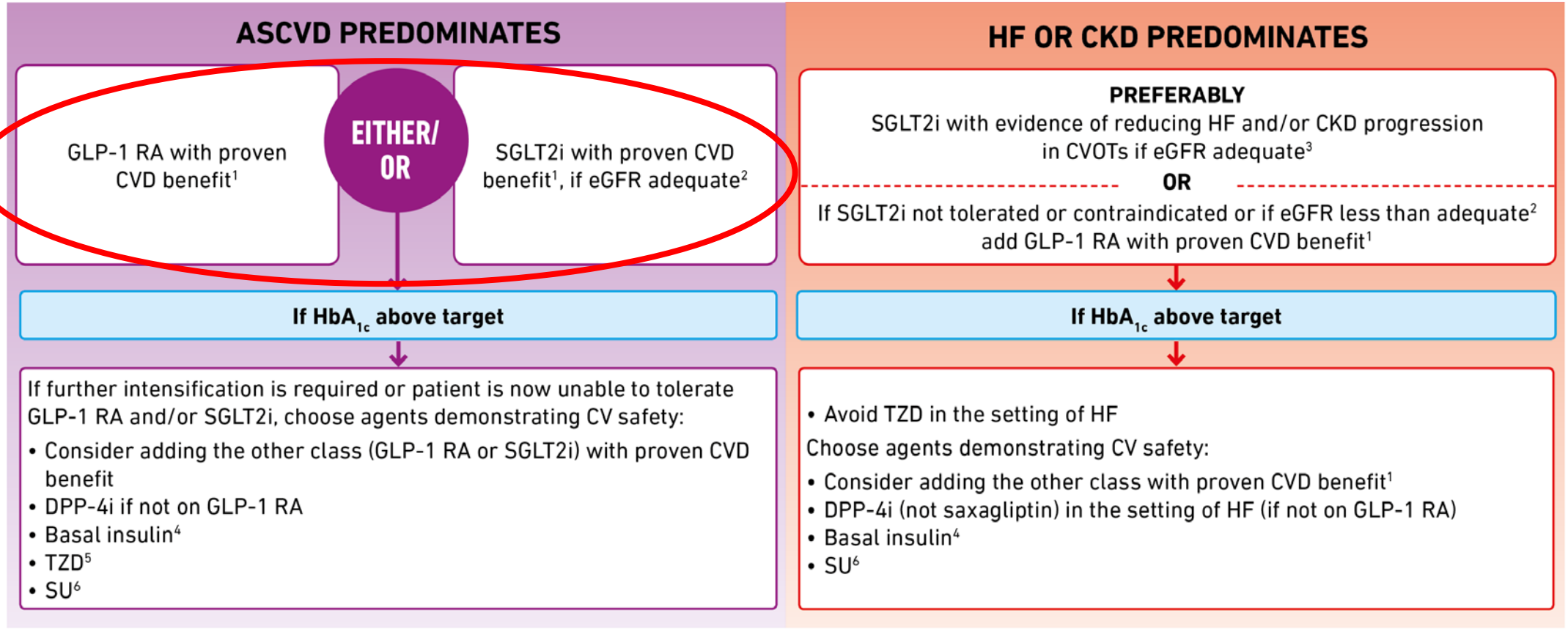
2012 Update to ADA Guidelines

…but drug choices largely guided by type and risk of class side effects



Silvio E. Inzucchi et al. Dia Care 2012;35:1364-1379

Current Guidelines Incorporate Evidence from CVOTs



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence of liraglutide > semaglutide > exenatide. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i 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 and reduction in CKD progression in CVOTs
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 hypoglycaemia

The Bad

- **Guidance requirements increase costs of drug development**
  - Large CVOTs as traditionally conducted can cost >$500 million
- **Costs conveyed to patients, increase total care expenditures**
- **May serve as a disincentive to diabetes drug development**

Impact on Diabetes Drug Development

- **However** 15 CVOTs of agents in 3 new classes and one of insulin therapy completed; numerous ongoing

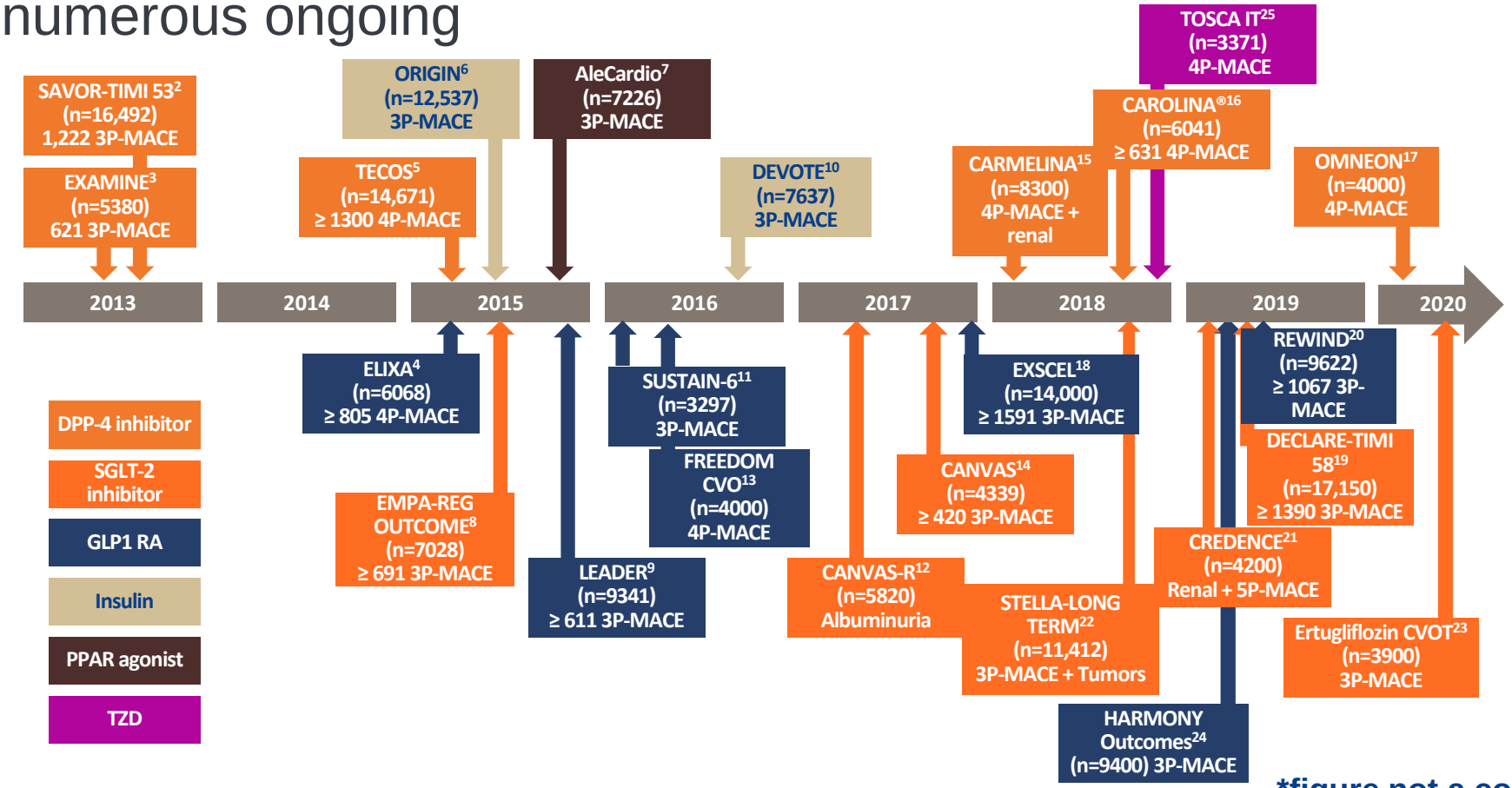


*figure not a comprehensive list

- Johansen OE. 2015
- Scirica BM et al. 2013
- White WB et al. 2013
- Pfeffer MA et al. 2015
- Green JB et al. 2015
- ORIGIN. 2012
- Lincoff AM et al. 2014
- Zinman B et al. 2015
- Marso SP et al. 2016
- NCT01959529
- NCT01720446
- NCT01989754
- NCT01455896
- NCT01032629
- NCT01897532
- NCT01243424
- NCT01703208
- NCT01144338
- NCT01730534
- NCT01394952
- NCT02065791
- NCT02479399
- NCT01986881
- NCT02465515
- NCT00700856

Impact on Diabetes Drug Development

- **14 new agents for T2DM approved in US since 2008**
  - Not including insulins or combination therapies
- **Market steadily increasing**
- **Potential multiple indications (HF, CKD) may serve as incentive**
- **Vibrant research space**
  - Clinicaltrials.gov search 10/10/2018

820 Studies found for: **Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Interventional Studies | Diabetes | Investigational drug**

Also searched for **Experimental**, **Agent**, **Medications** and more. See Search Details

Applied Filters: ☑ **Recruiting** ☑ **Not yet recruiting** ☑ **Active not recruiting** ☑ **Enrolling by invitation** ☑ **Interventional**

https://www.centerwatch.com/drug-information/fda-approved-drugs/medical-conditions/D#

Impact on Diabetes Drug Development

Therapeutic Area	Preclinical/ Research Project	Phase I	Phase II	Phase III	Filed/ Approved	Total Projects	Total Products
Blood	293	78	104	59	3	**537**	**394**
Cancer	4,621	1,757	1,920	329	24	**8,651**	**5,789**
Cancer, Blood & blood forming malignanci	487	433	434	67	5	**1,426**	**671**
Cancer, miscellaneous cancer	1,826	100	85	21	2	**2,034**	**1,679**
Cancer, Solid tumors, Bladder	29	13	28	11	2	**83**	**27**
Cancer, Solid tumors, Breast	212	80	108	27	-	**427**	**169**
Cancer, Solid tumors, Colorectal	98	46	73	19	1	**237**	**81**
Cancer, Solid tumors, Lung	73	13	21	1	-	**108**	**50**
Cancer, Solid tumors, Melanoma	102	57	87	9	-	**255**	**154**
Cancer, Solid tumors, Prostate	146	39	86	10	-	**281**	**217**
Cancer, Solid tumors, Other	1,648	976	998	164	14	**3,800**	**2,741**
Cardiovascular	642	141	227	77	10	**1,097**	**771**
Diabetes	482	97	125	42	3	**749**	**432**
Gastro-intestinal	305	85	140	54	5	**589**	**413**
Hepatic & biliary	165	47	75	10	1	**298**	**182**

Analysis Group report; The Biopharmaceutical Pipeline: Innovating Therapies in Clinical Development. Data from July, 2017. Available at: http://phrma-docs.phrma.org/files/dmfile/Biopharmaceutical-Pipeline-Full-Report.pdf.

Impact on Diabetes Drug Development

- **Additional Disincentives**
  - **Saturation of classes with demonstrated safe and/or beneficial agents**
    Fewer "me too" drugs
  - **Unclear path forward for drugs found safe but without CV benefit**
    - **These agents remain clinically relevant**
      Increased need for complex regimens over time
      Safety of all agents used is important
    - **Current guidelines outline role in care**
      Antihyperglycemic therapy in lower risk patients
      As a component of antihyperglycemic care for higher risk patient

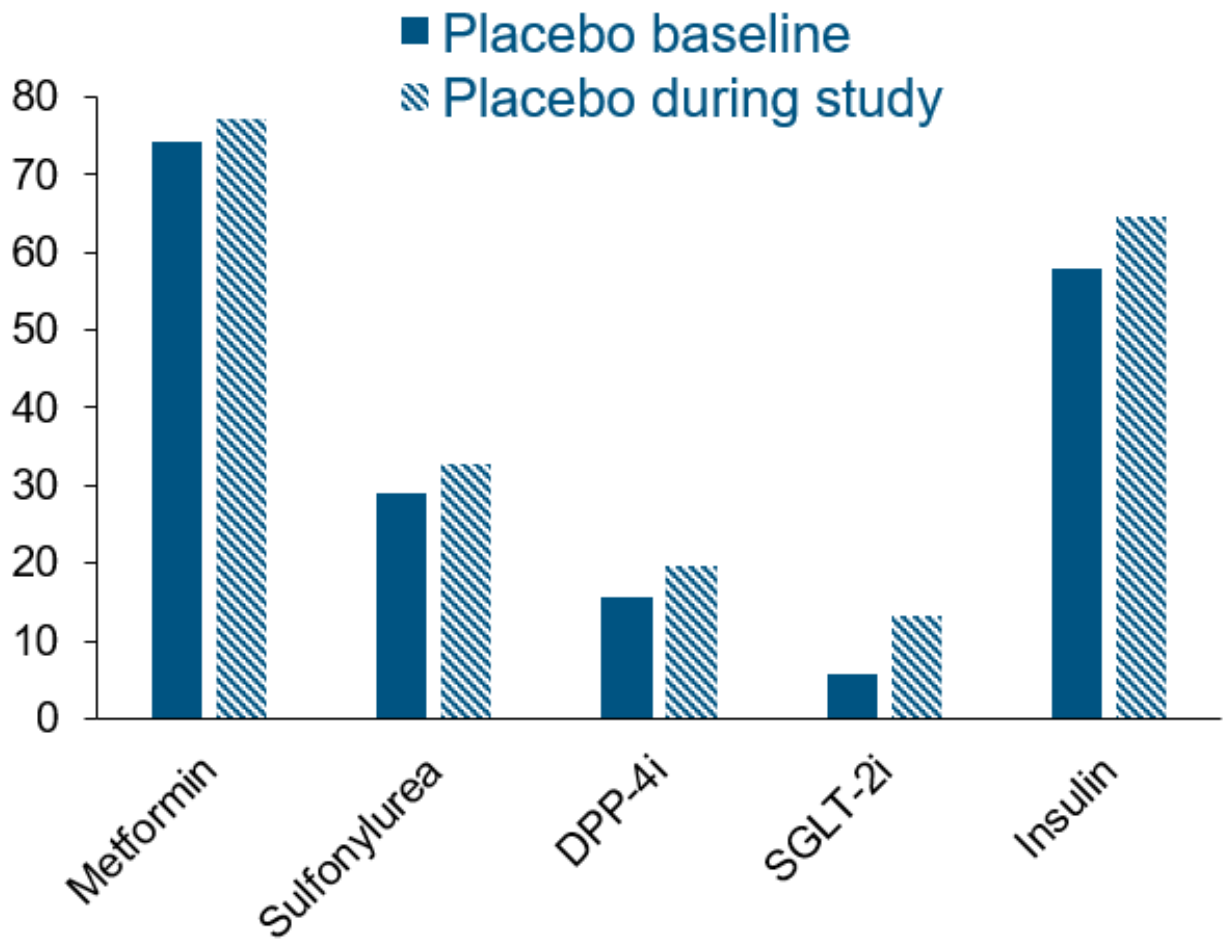
Impact on Diabetes Drug Development

Key Disincentive

Underutilization of beneficial agents in clinical care

Harmony Outcomes Example

- Contemporary trial
  (July 2015-March 2018)
- 100% patients had ASCVD
- Limited baseline and within-trial use of SGLT2i therapy



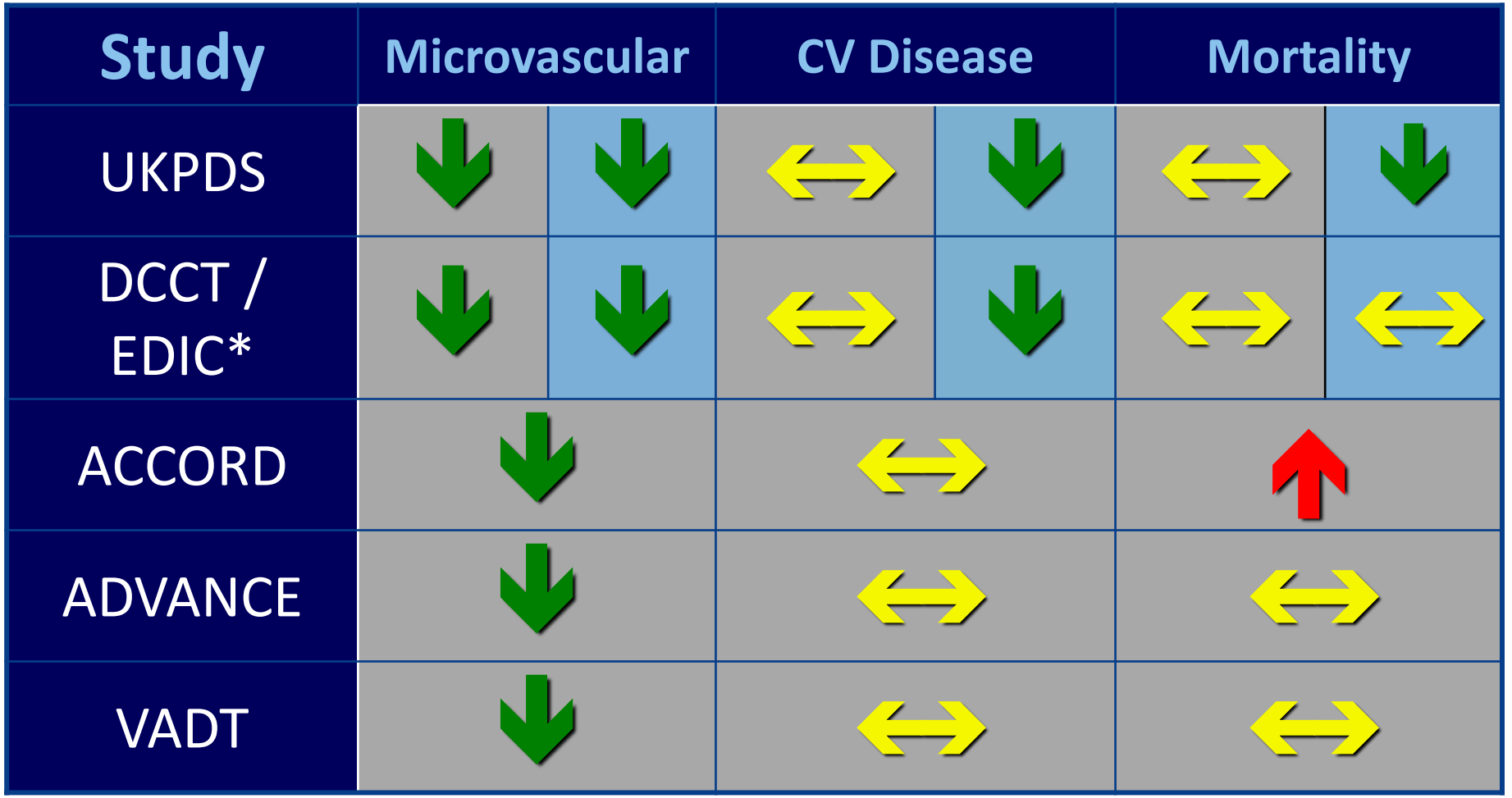
Hernandez A, et al. Lancet; online first October 2, 2018

The Ugly

- Devaluation of glycemic control in diabetes management
- A recent tweet:

> Does HgbA1c matter anymore...isn't it ancillary?

Benefits of Glycemic Control: A Reminder



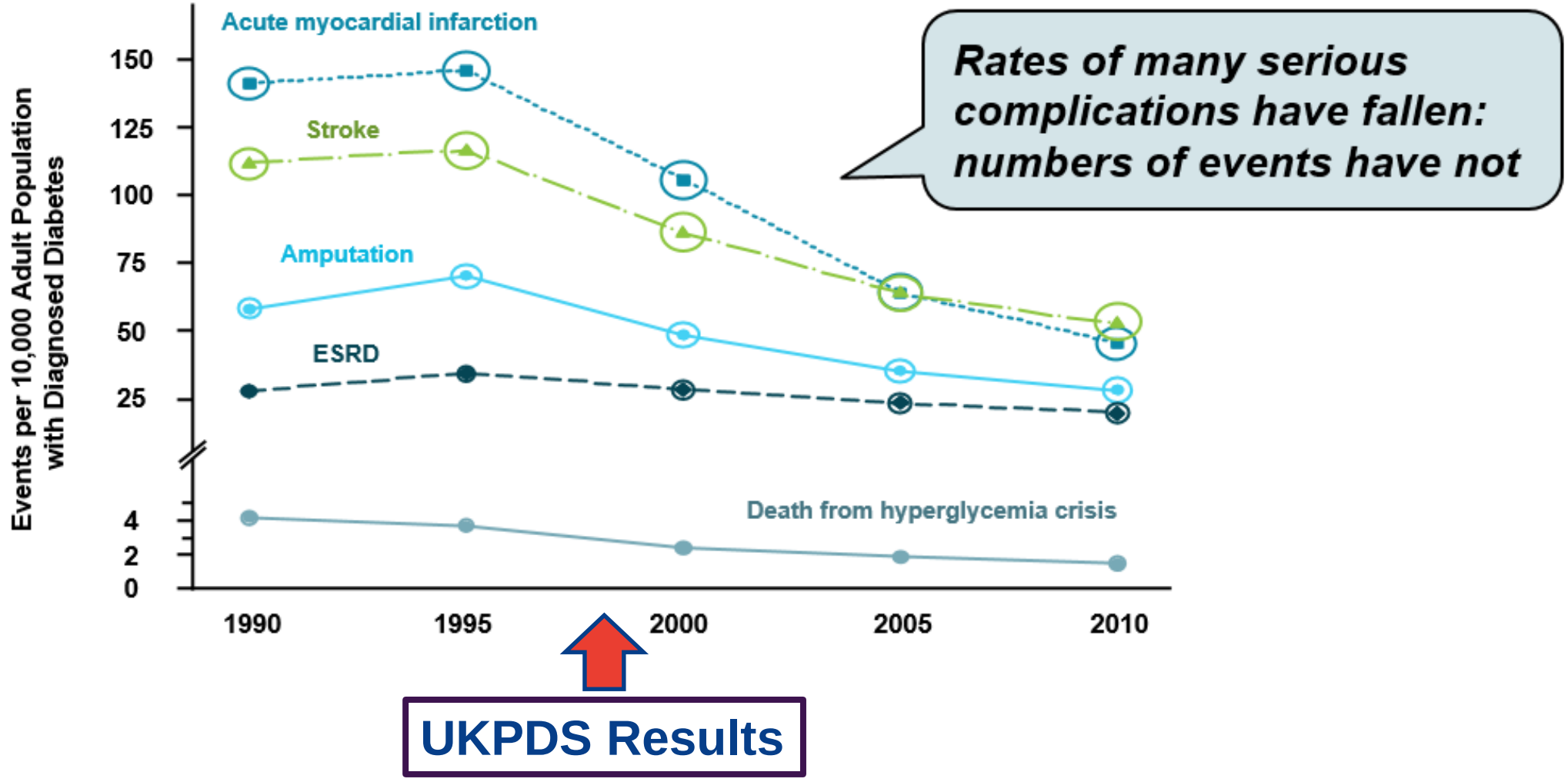
Kendall DM, Bergenstal RM. © International Diabetes Center 2009
UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

Glycemic Control

- **Initial approval DM drugs based upon HbA1c lowering**
  - Accepted surrogate for risk microvascular complications
- **UKPDS suggests early glycemic control may affect long term CV risk**
  - Unclear when it becomes less or unimportant to CV risk
    - *Only true of older drugs?*
- **Glycemic contribution to CVOT findings**
  - All trials have had between-group differences in glycemic control
  - Estimated contribution to results varies
- **Competing risks**
  - Will glycemia become more important as people live longer with diabetes?

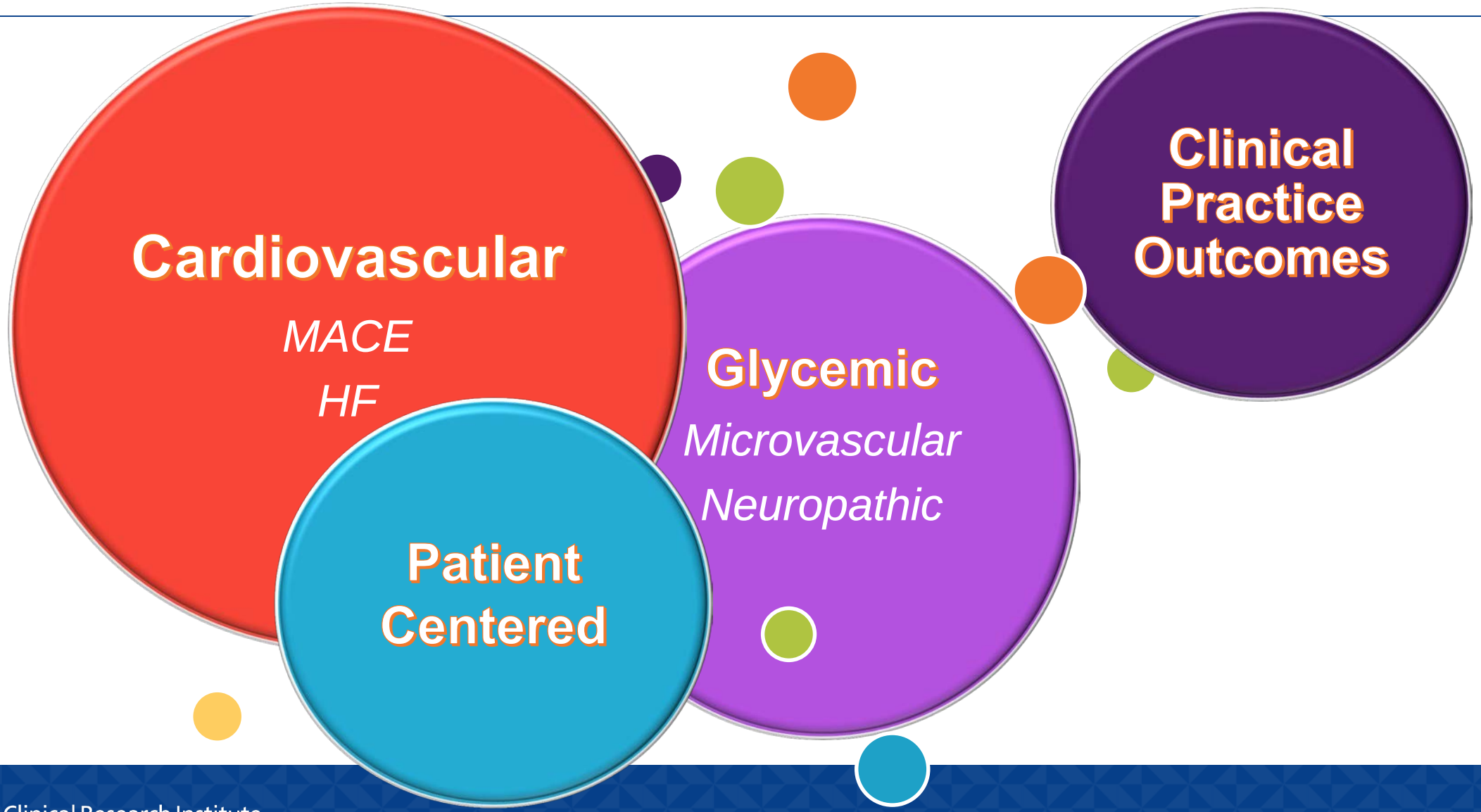
Suissa S, Diabetes Care Volume 41 (pp 219-223), February 2018

Effects of Risk Reduction Strategies: Changing Rates of Complications Over Time

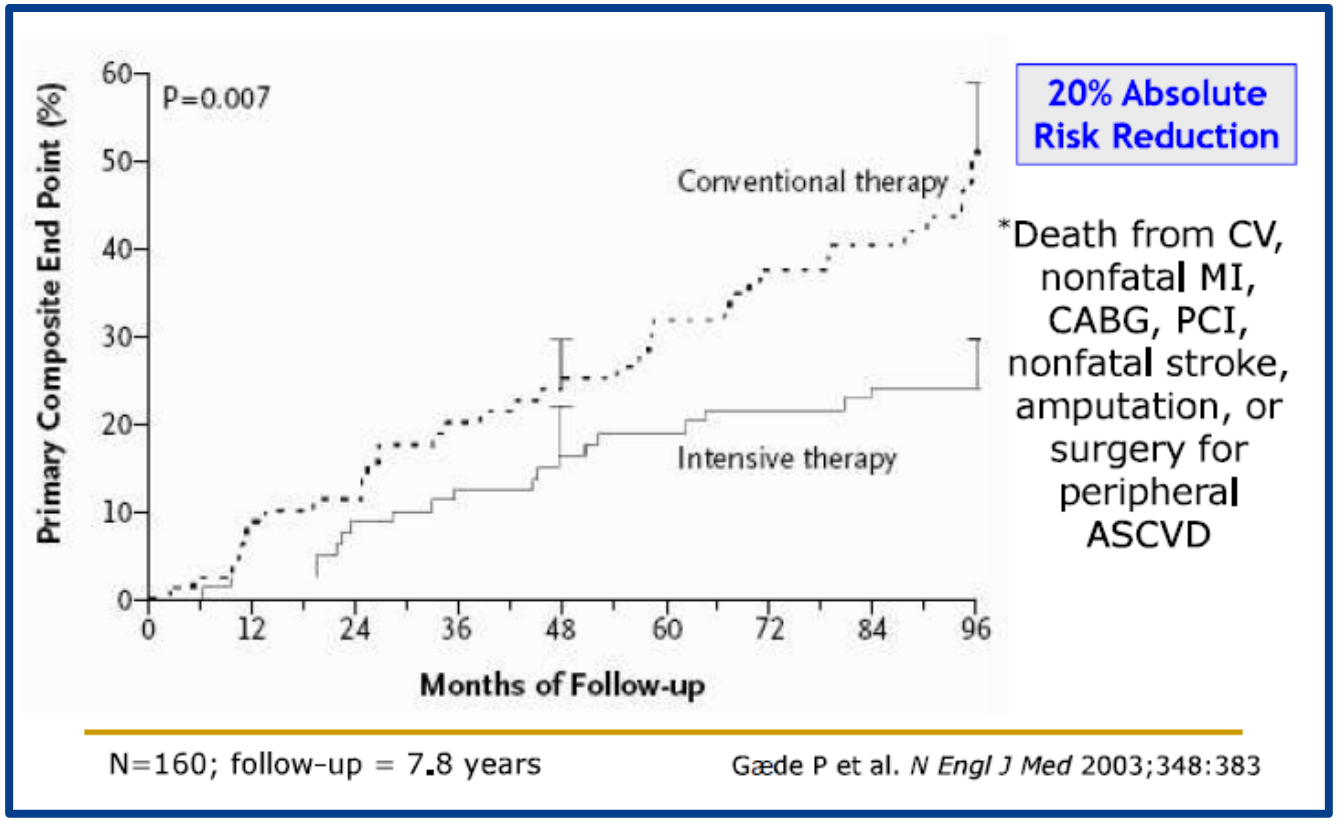


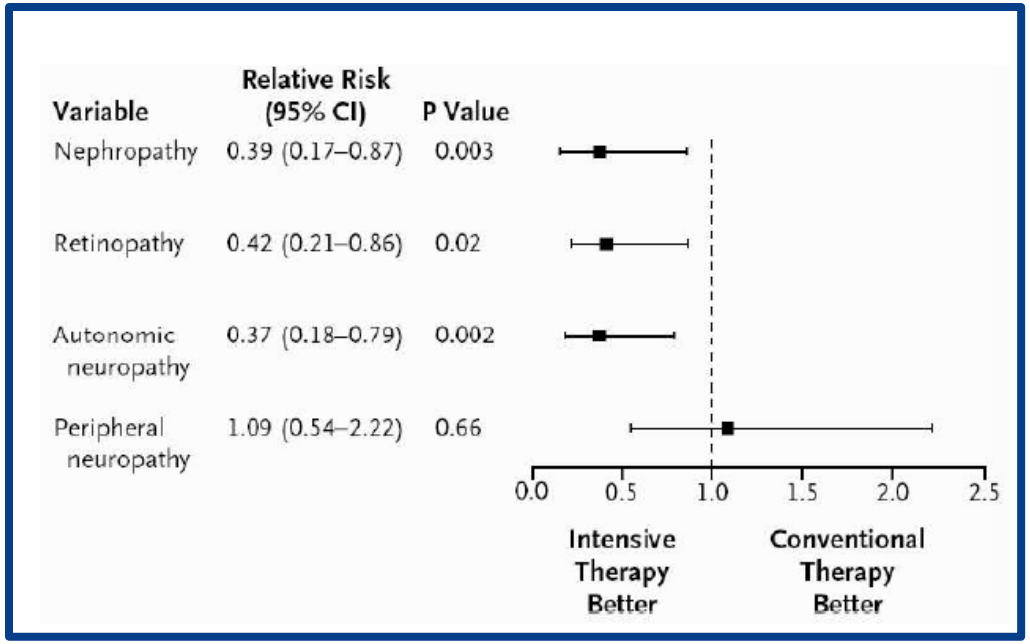
Gregg EW, Li Y, et al. NEJM 370(16) pp 1514-1523. April, 2014

Multiple Overlapping Outcomes of Interest



Steno-2: Efficacy of Multiple Risk Factor Intervention in T2DM with Microalbuminuria





More intensive management of HbA1c, BP, lipids reduced risk of micro and macrovascular complications – using older drugs

The Future

- **Adequately powered, randomized CV outcomes trials of individual antihyperglycemic agents should continue**
  - *Information allows patients and providers to understand effects of available drugs, and make informed decisions regarding care*
- **Work still needed**
  - *Implementation*
  - *More efficient but still robust trials methodology*

Implementation Issues

- **Barriers to Implementation in Clinical Practice**
  - Unawareness
  - Confusion in application
  - Unanswered clinical questions
  - Assessment of actual risk vs. benefit
  - Cost and access issues
  - Time needed to learn, discuss, execute new care plans
  - **Not currently an expectation of care** for the high risk patient
- **Not a justification!**

Implementation Issues

- **Address Barriers**
  - **Need relevant care expectations and quality measures**
  - **Guidelines should**
    - Be readily understandable and applicable
    - Consider audience

      only 15% of all diabetes care is provided by endocrinologists
    - Avoid unnecessary complexity, cost if not evidence-based

2018 ADA Guidelines

In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and **subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality** (currently empagliflozin and liraglutide), after considering drug-specific and patient factors.

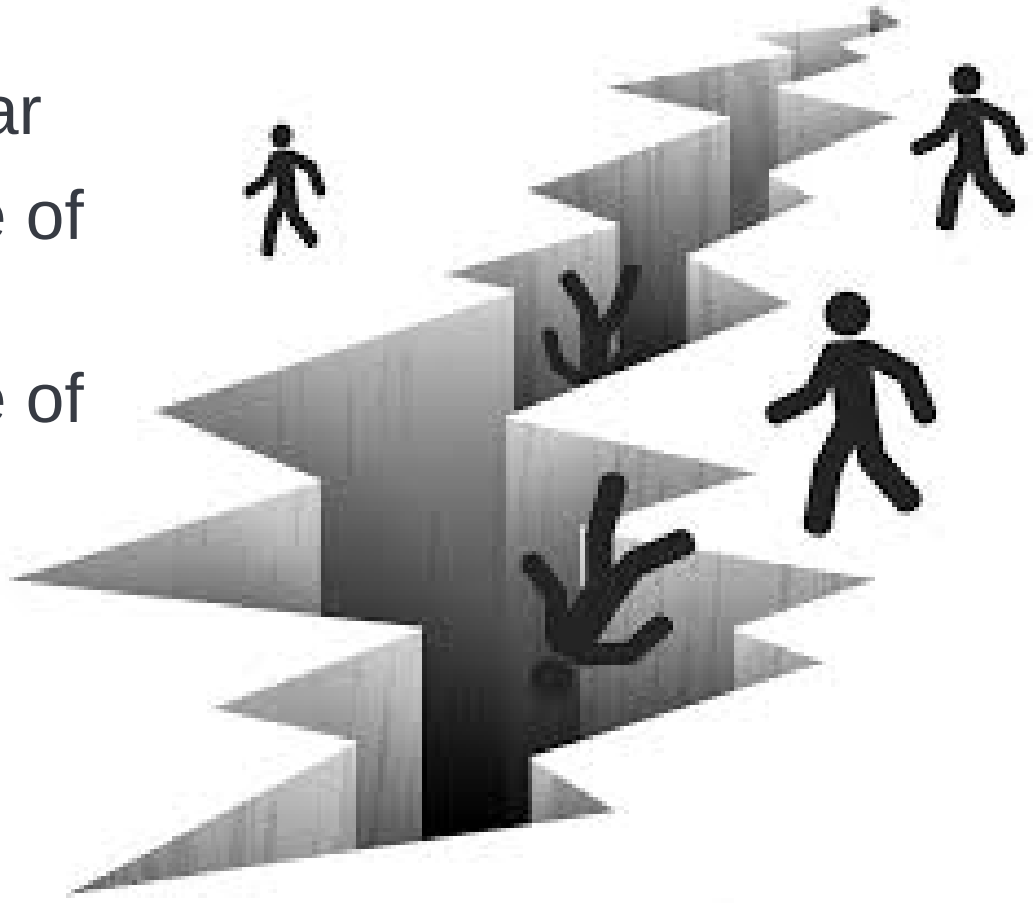
Vigersky et al. J Clin Endocrinol Metab 99: 3112–3121, 2014

ADA Standards of Medical Care in Diabetes. Diabetes Care 2018;41(S1)

Revise Traditional Roles

Diabetologist

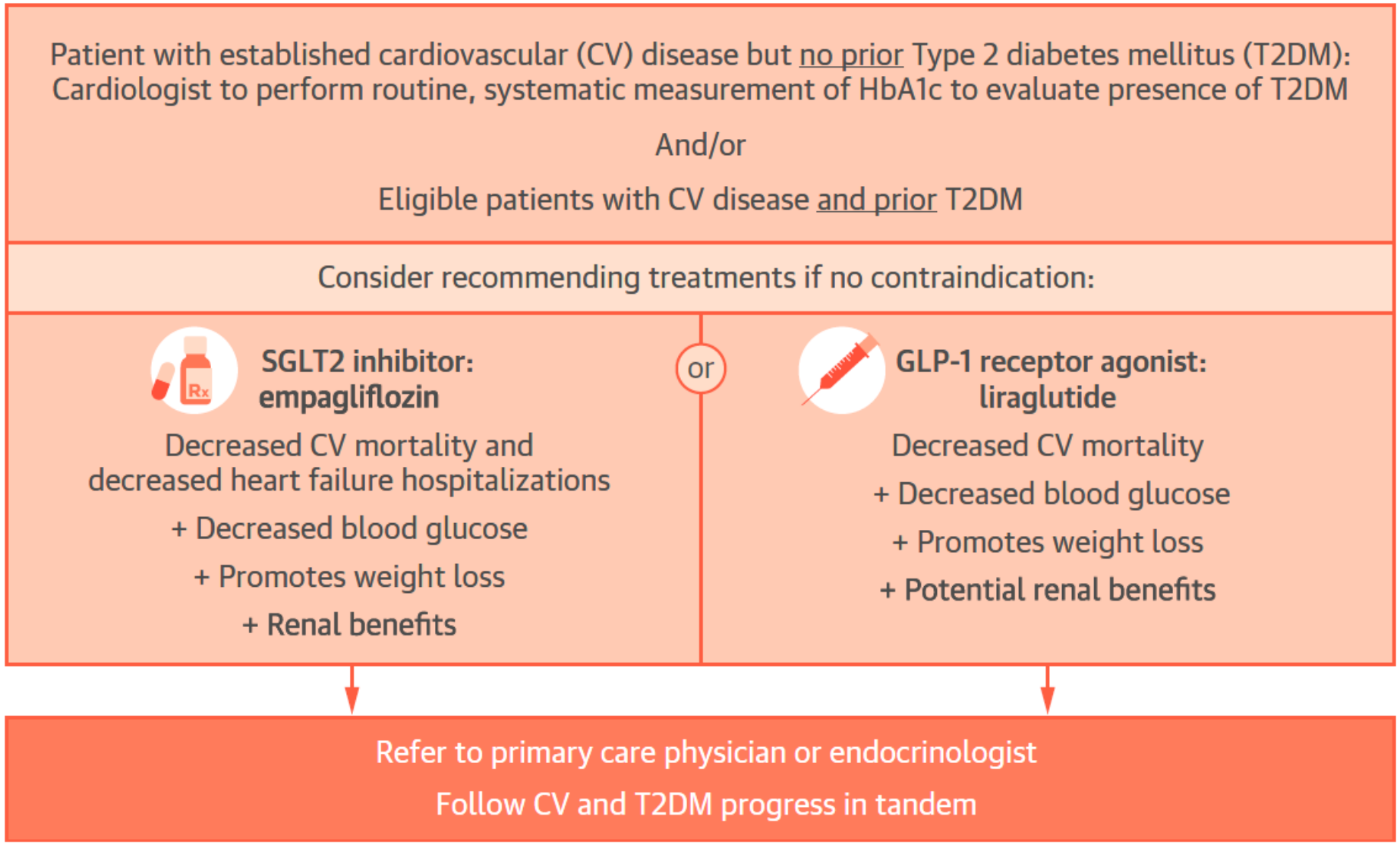
- Focus on blood sugar
- Expert in wide range of diabetes drugs
- Expert in global care of diabetes, microvascular complications
- Often defers to cardiologist for CV protection



Cardiologist

- Focus on hypertension, lipids, diet
- Management of cardiovascular disease
- Defers to diabetologist on diabetes drugs

Novel Paradigm for Care of T2DM and CV Disease



Sattar, N. et al. J Am Coll Cardiol. 2017;69:2646–56.

Address Barriers to Implementation

Start to fill in the missing pieces

- Effects in lower risk, underrepresented populations
- Better define high risk
- Trials with active comparators, drug combinations
- Assess longer term effects
- Best place in therapy

  First line; incorporation into existing regimens

Engagement of other agencies, institutions, societies, and interested groups

Moving the Field Forward

- **Previously used CVOT model should not be the only acceptable path forward**
  - Explore novel approaches to trial design, operations, outcomes
    - Reduce time, costs
    - Maximize ability to identify benefits
  - Pragmatism must be more than a catch phrase
- **Possible new paradigm for DM drug approval**
  - Is HbA1c lowering required if benefit demonstrated in other meaningful outcomes?

Thank you

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