Type 2 Diabetes: An Update on Oral and Injectable Medications

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Family Medicine Grand Rounds

March 2021

UCLA Health

Financial Disclosures

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- Abbott Diabetes
- Novo Nordisk

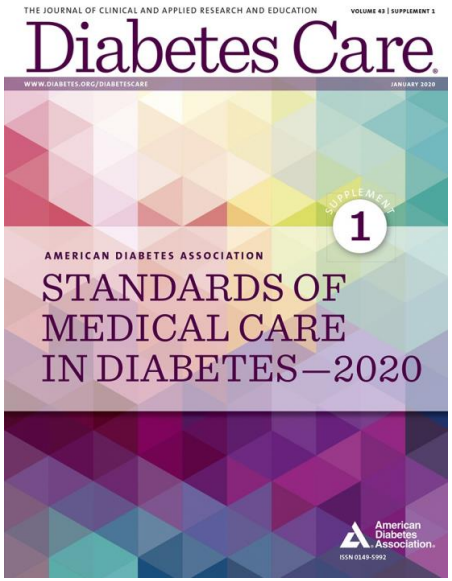
Outline

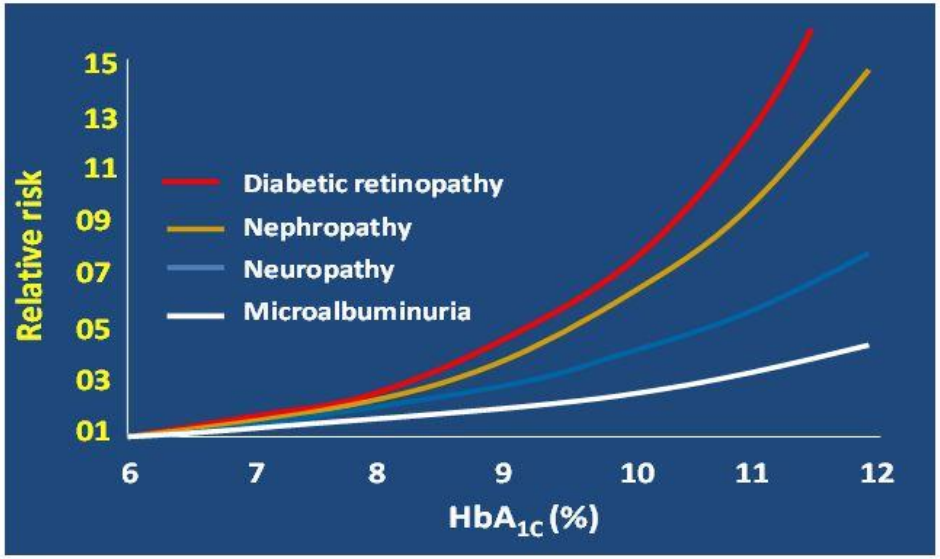
- Glycemic Targets
- Diabetes Education: Nutrition, Exercise
- Type 2 DM Management
  - Guidelines
  - Medications
    - Shared decision-making / factors
    - Risks & benefits of specific medication classes
      - Cardiovascular outcomes
      - Renal outcomes
- Glucose Monitoring

Approach to Glycemic Control in Type 2 Diabetes Mellitus

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C.





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American Diabetes Association. Diabetes Care. 2020
Qaseem A et al. Annals Int Medicine. 2018

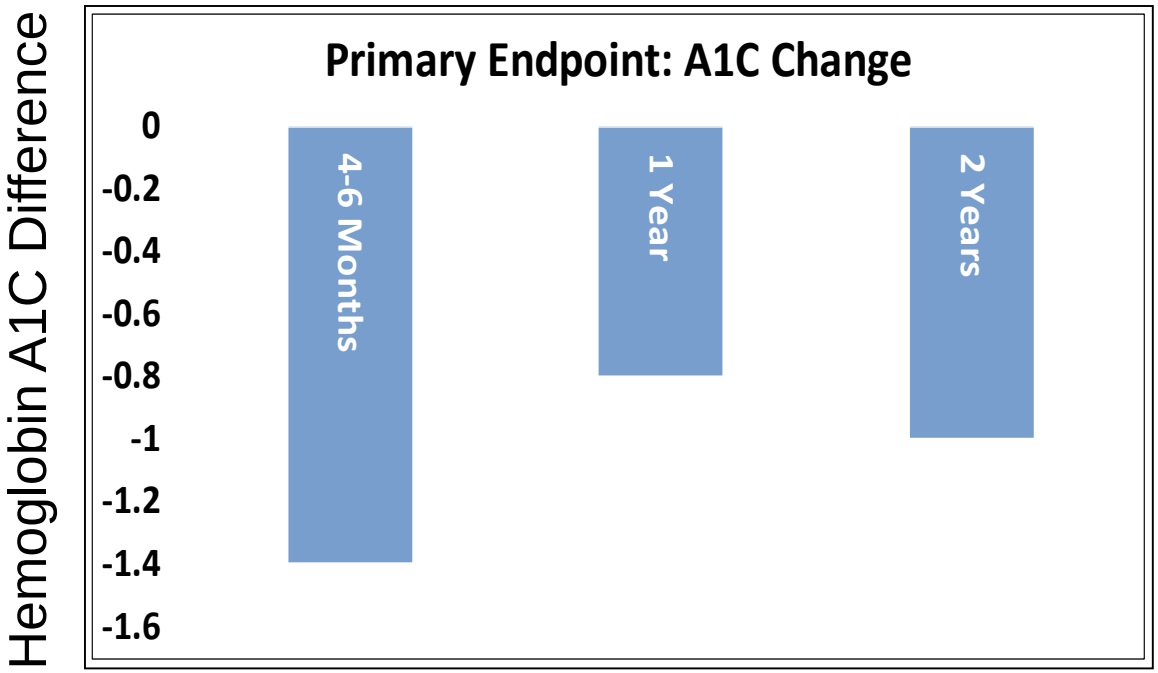
Guidelines for Glycemic Control: What's Best for the Patient?

- A1C < 7% for most patients
- A1C goals may be adjusted based on risk (i.e. older adult, CAD, Stroke, Dementia)
  - Individualize de-intensification based on hypoglycemia risk and other potential harmful effects
    - Examples…
    - < 7.5 to 8% → CAD, Stroke or > 70 years
    - < 8 to 8.5% → Dementia or other significant co-morbidities
- A1C levels > 8.5% increase polyuria, polydipsia, renal dysfunction.

American Diabetes Association. Diabetes Care. 2019
Draznin et al. Annals Int Medicine. 2018

Diabetes Education Outcomes – Clinical Benefits

Group-based <u>diabetes education</u>: 11 studies, 1532 patients



<u>Secondary Endpoints</u>

Weight Loss: -1.6 Kg

@ 12-14 months

Blood Pressure (SBP):

-5 mmHg @ 4-6 mos

Reduce DM Meds: NNT = 5

THE COCHRANE COLLABORATION®

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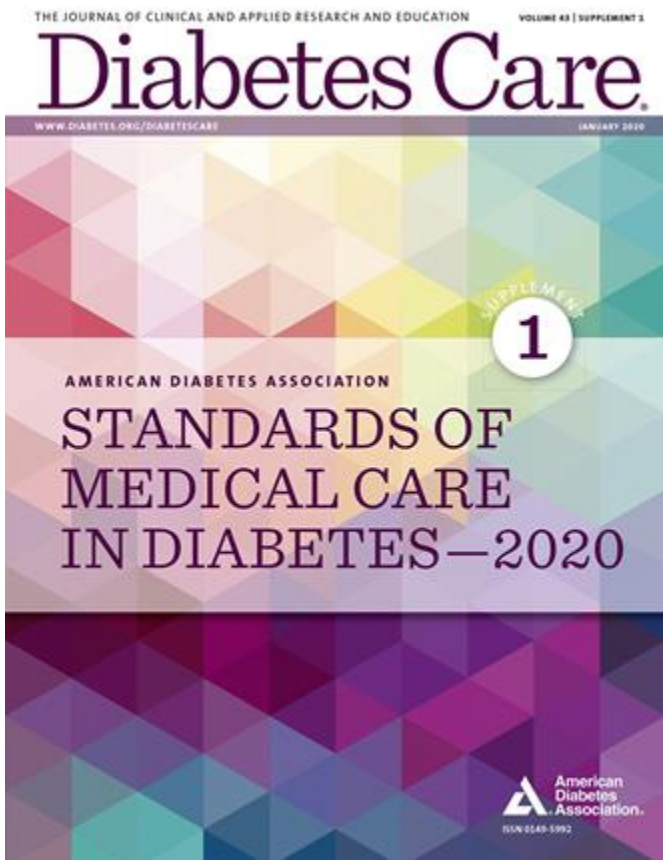
Deakin T, et al. Cochrane. 2009.

Type 2 Diabetes Management Guidelines

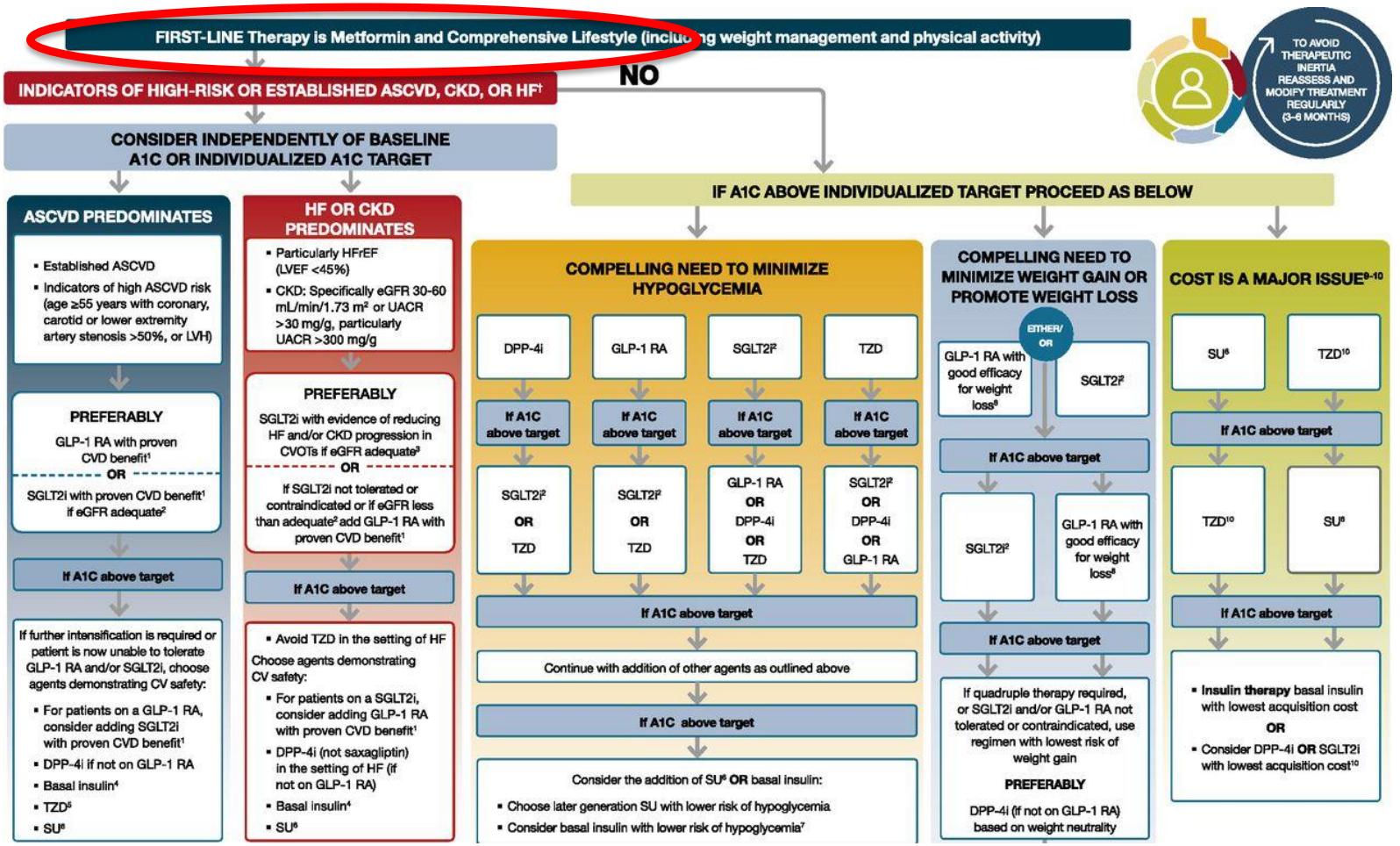


Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies,[1,2] David A. D'Alessio,[3] Judith Fradkin,[4] Walter N. Kernan,[5] Chantal Mathieu,[6] Geltrude Mingrone,[7,8] Peter Rossing,[9,10] Apostolos Tsapas,[11] Deborah J. Wexler,[12,13] and John B. Buse[14]

ADA/EASD. Diabetes Care 2018
ADA Guidelines. Diabetes Care. 2020

Type 2 Diabetes Management Guidelines: First-Line Therapy is Metformin



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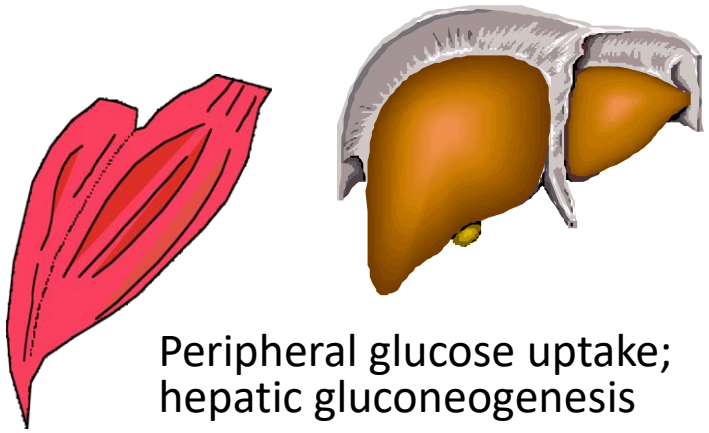
ADA Guidelines. Diabetes Care. 2020

Biguanides (Metformin)

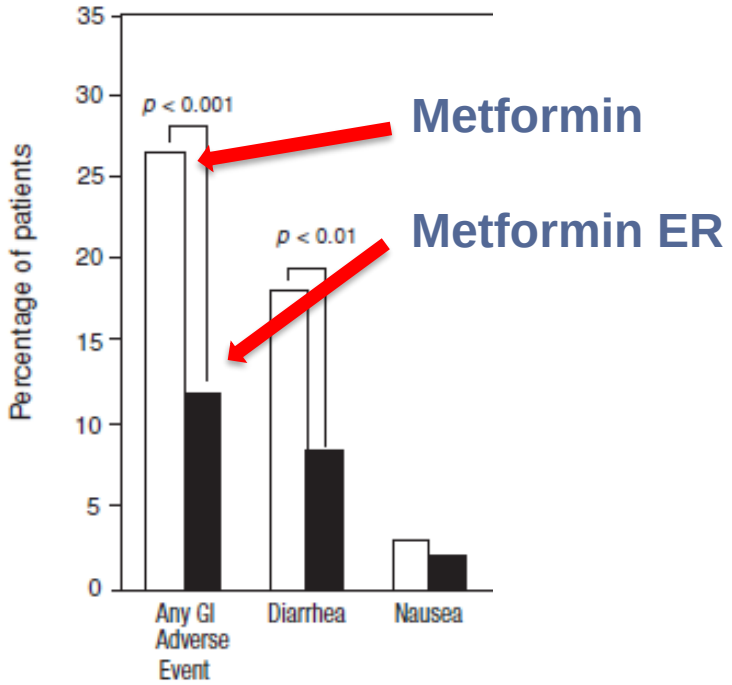
- **A1C Effect:** 1 to 2%
- **Reasons to Consider:**
  - Weight loss (2-3 kg)
  - PO Route
  - No Hypoglycemia
- **Side effects, Limiting Factors:**
  - GI side effects
  - Risk for lactic acidosis (rare)
    - Absolute: GFR < 30 (do not start with GFR < 45)
    - Relative: (1) Liver dysfunction, (2) Heart failure, (3) Age > 80 years, (4) Heavy alcohol intake



Peripheral glucose uptake; hepatic gluconeogenesis

What About the Patient Who Doesn't Tolerate Metformin?

Gastrointestinal side effects? Consider Metformin ER…



But a number of brands have been recalled…

A diabetes drug has been recalled because it contains high levels of cancer-causing agent

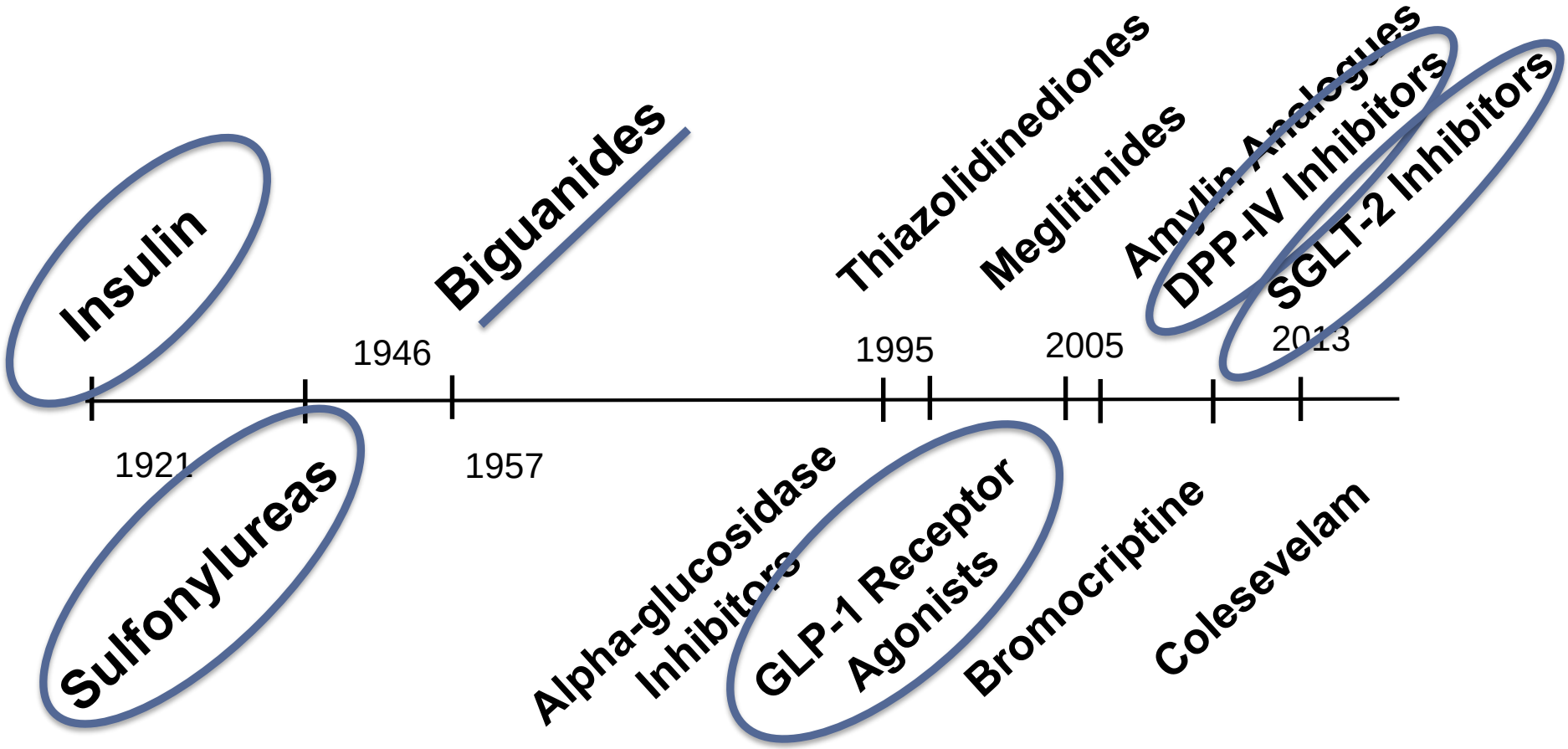
By Scottie Andrew, CNN

Updated 9:45 AM ET, Fri October 9, 2020

An Indian pharmaceutical company is recalling some metformin tablets because they may cont higher-than-normal levels of a carcinogen.

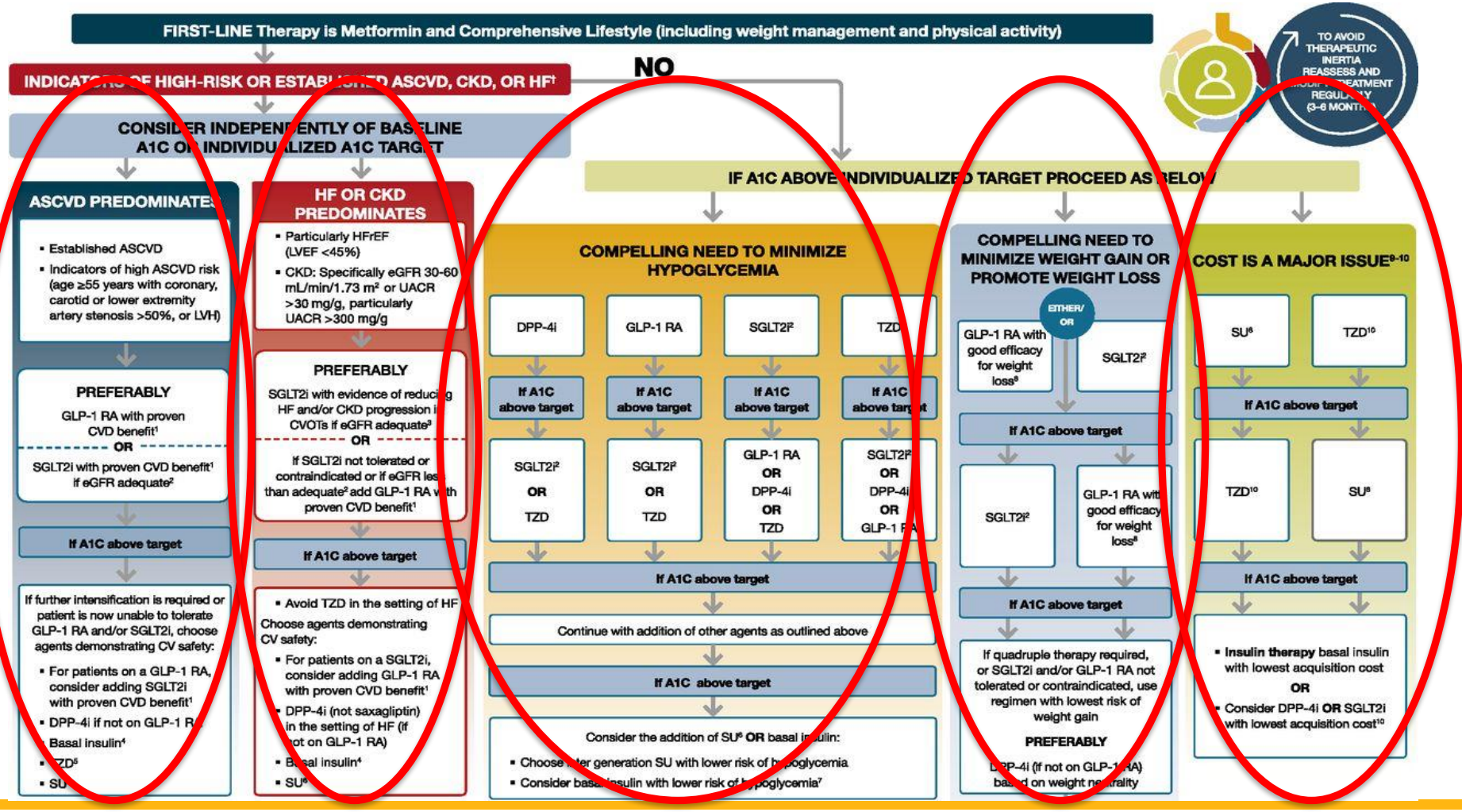
Blonde et al. GI Tolerability of Metformin

Medications to Treat Type 2 Diabetes Mellitus



Adapted from Nathan D. *N Engl J Med* 2007;356:437-440

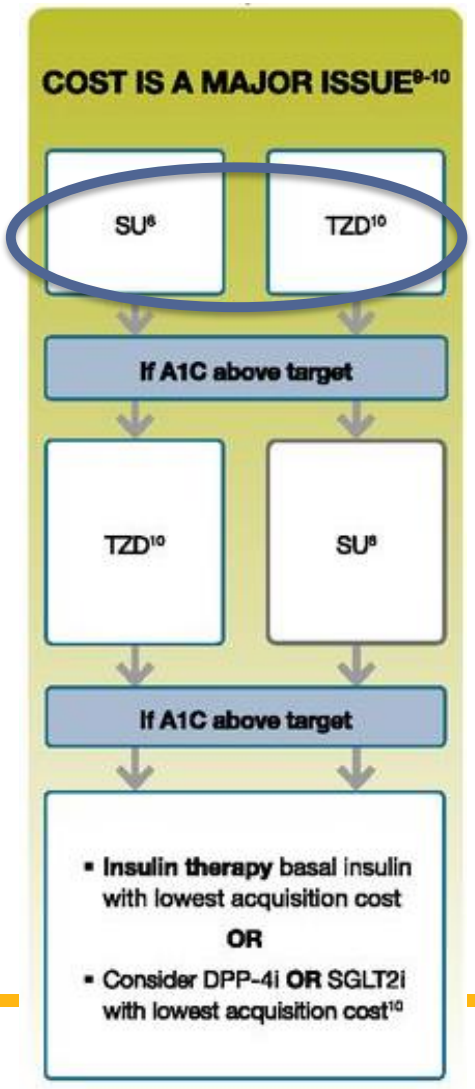
Type 2 Diabetes Management Guidelines: Shared Decision Making Based on Many Factors



ADA Guidelines. Diabetes Care. 2020

Type 2 Diabetes Mellitus: Second-Line Medication Choice…

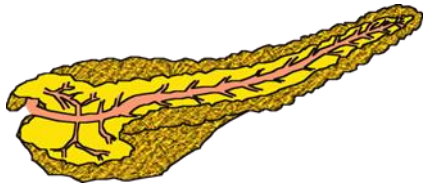
- The choice for second-line therapy is not always straight forward. Consider based on multiple factors…
  - Change in A1C (efficacy)
  - Cost
  - Hypoglycemia risk
  - Side effects
  - Weight Change
  - Cardiovascular disease



ADA/EASD Guidelines. Diabetes Care. 2020

Sulfonylureas and Meglitinides

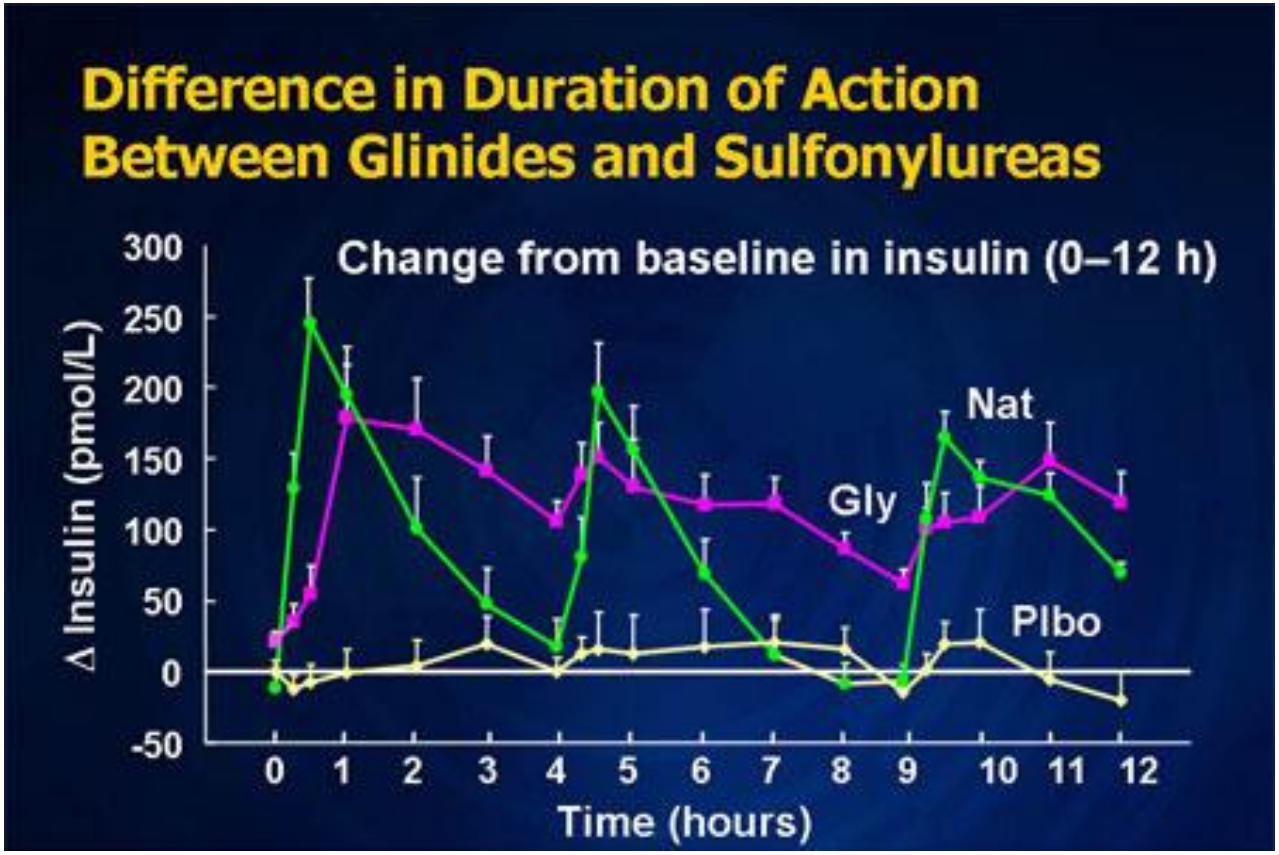
- **Examples**
  - **Sulfonylureas: Glipizide, Glimepiride, Gyburide**
  - **Meglitinides: Repaglinide, Nateglinide**
- **A1C Effect:** 1 to 2%
- **Reasons to Consider:**
  - Established, well-studied generic pill
  - Glinides → lower risk of hypoglycemia
- **Side effects, Limiting Factors:**
  - Hypoglycemia (erratic PO intake, elderly, renal dysfunction)
  - Weight gain (2 kg)



Insulin secretion

Meglitinides & Sulfonylureas: Kinetics

Skipping meals and increasing risk of low sugars?



Case of Hyperglycemia – What Might You Choose?

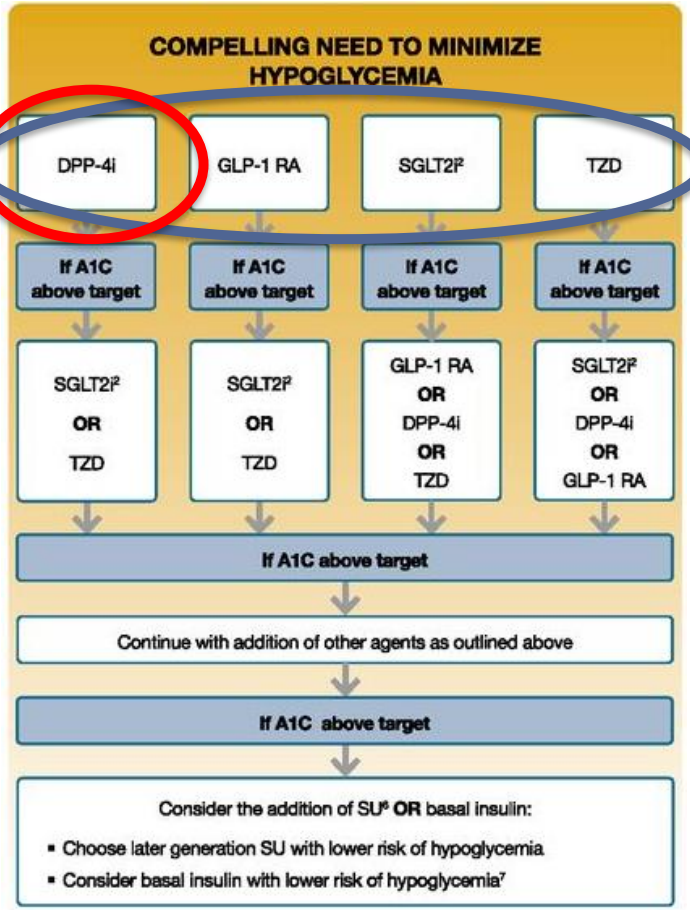
- An 87 year old female presents to your clinic for follow-up for T2DM.
  - She has a history of diabetes for about 6 years duration. She also has hypertension, hyperlipidemia, chronic kidney disease, and dementia.
- Her current diabetes regimen includes metformin 1000 mg BID.
  - She tolerates dosing; no changes for the last 6 years.
- Hemoglobin A1C is 9.1% & GFR 42

Do you add to the regime? If so, what might you recommend?

Sulfonylurea increases hypoglycemia risk, Meglitinide less so….

Type 2 Diabetes Mellitus: Second-Line Medication Choice…

- The choice for second-line therapy is not straight forward and based on multiple factors…
  - Change in A1C (efficacy)
  - Cost
  - Hypoglycemia risk
  - Side effects
  - Weight Change
  - Cardiovascular disease



ADA Guidelines. Diabetes Care. 2020

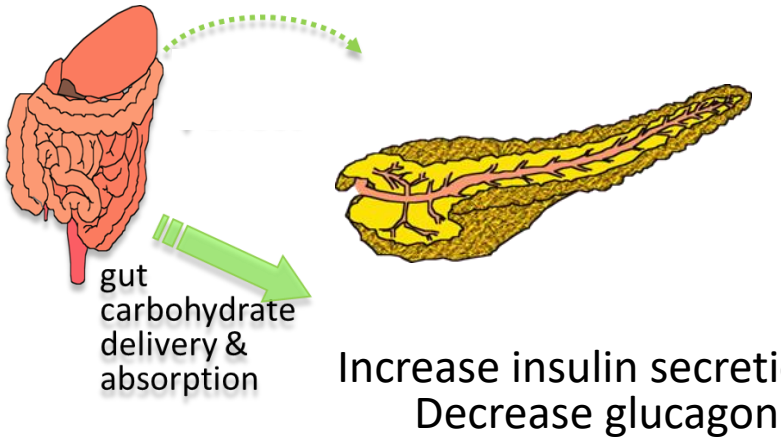
Second-Line Therapy Considerations: Minimize Hypoglycemia

Consider one of the following medication classes:

- Thiazolidinediones
- SGLT-2 Inhibitors
- GLP-1 Receptor Agonists
- **DPP-4 Inhibitors**

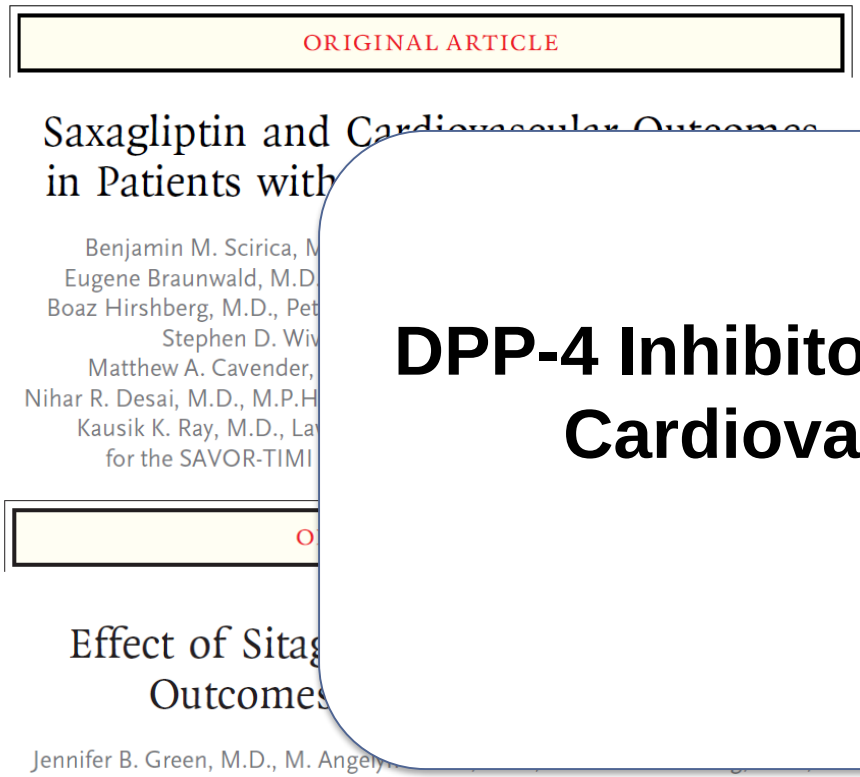
DPP-4 Inhibitors

- **Examples:**
  - **Sitagliptin (Januvia)**
  - **Saxagliptin (Onglyza)**
  - **Linagliptin (Tradjenta)**
  - **Alogliptin (Nesina)**



- **A1C Effect:** 0.5 to 0.9%
- **Reasons to Consider:** (1) PO Route (2) well-tolerated (3) No Hypoglycemia (4) No weight gain
- **Side effects, Limiting Factors:** (1) Cost (2) Modest A1C benefit, (3) CHF in saxa- and alogliptin (4) Low likelihood of pancreatitis (5) Joint pains (6) No positive or negative cardiovascular impact

DPP-4 Inhibitors and Cardiovascular Outcomes Trials


ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with

Benjamin M. Scirica, M
Eugene Braunwald, M.D
Boaz Hirshberg, M.D., Pet
Stephen D. Wiv
Matthew A. Cavender,
Nihar R. Desai, M.D., M.P.H
Kausik K. Ray, M.D., La
for the SAVOR-TIMI

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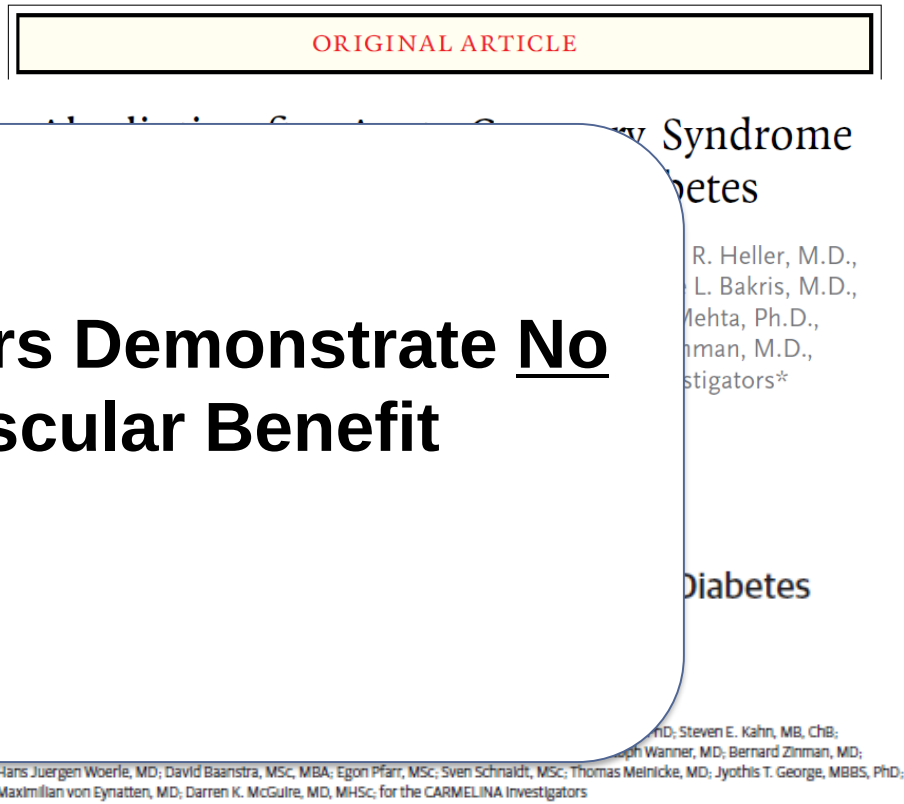
Effect of Sitag
Outcomes

Jennifer B. Green, M.D., M. Angely
John B. Buse, M.D., Ph.D., Samuel S. Engel, M.D., Jyotsna Garg, M.S.,
Robert Josse, M.B., B.S., Keith D. Kaufman, M.D., Joerg Koglin, M.D.,
Scott Korn, M.D., John M. Lachin, Sc.D., Darren K. McGuire, M.D., M.H.Sc.,
Michael J. Pencina, Ph.D., Eberhard Standl, M.D., Ph.D., Peter P. Stein, M.D.,
Shailaja Suryawanshi, Ph.D., Frans Van de Werf, M.D., Ph.D.,
Eric D. Peterson, M.D., M.P.H., and Rury R. Holman, M.B., Ch.B.,
for the TECOS Study Group*


ORIGINAL ARTICLE

Syndrome
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R. Heller, M.D.,
L. Bakris, M.D.,
Mehta, Ph.D.,
hman, M.D.,
stigators*

Diabetes

hD; Steven E. Kahn, MB, ChB;
ph Wanner, MD; Bernard Zinman, MD;
Hans Juergen Woerle, MD; David Baanstra, MSc, MBA; Egon Pfarr, MSc; Sven Schnaidt, MSc; Thomas Meinicke, MD; Jyothis T. George, MBBS, PhD;
Maximilian von Eynatten, MD; Darren K. McGuire, MD, MHSc; for the CARMELINA Investigators

DPP-4 Inhibitors Demonstrate <u>No</u> Cardiovascular Benefit

A second case…
Diabetes & CVD – What do you Choose?

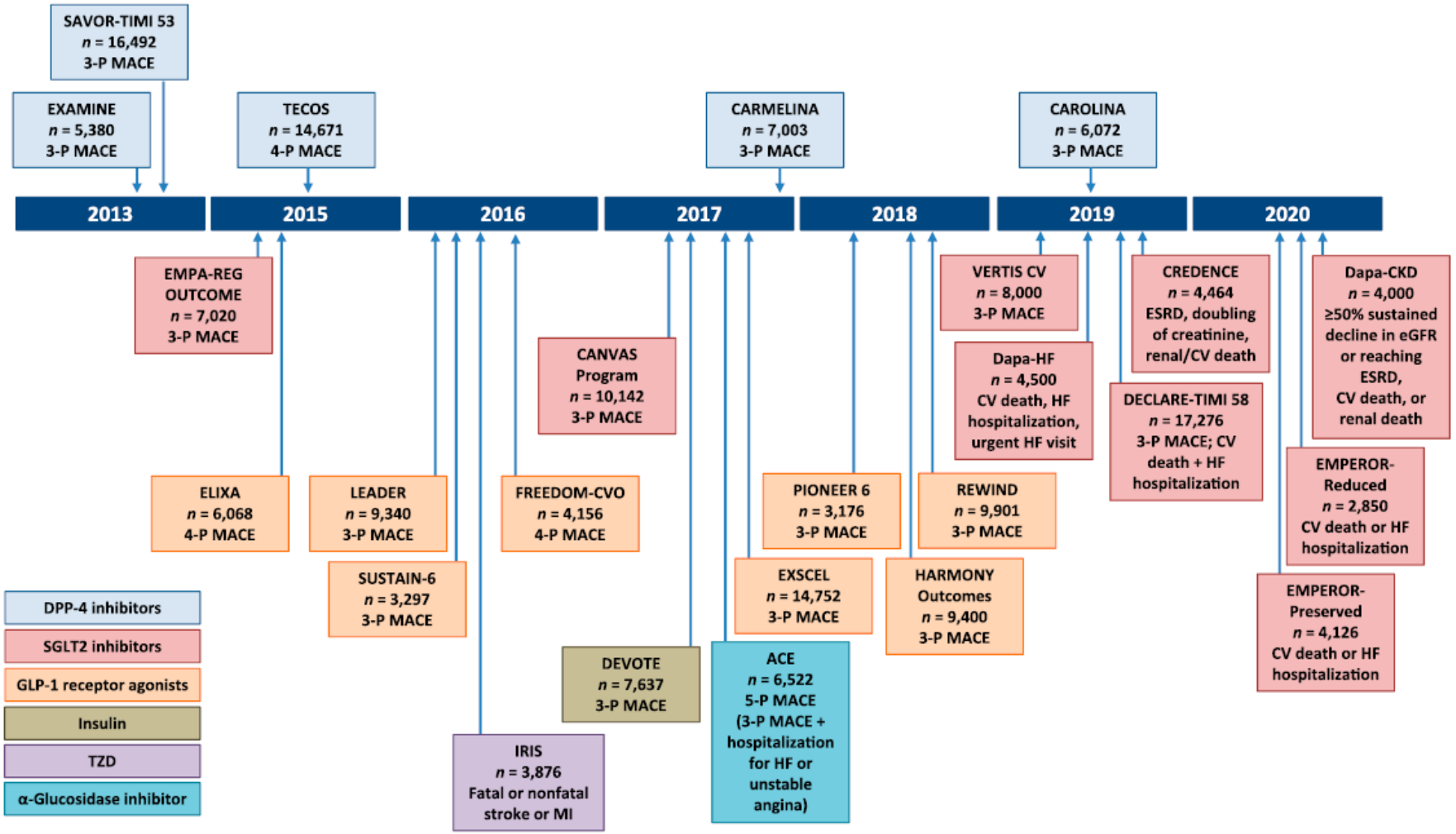
- A 68 year old male presents to clinic for management of type 2 diabetes mellitus of 10 years duration**.** He also has a history of hypertension, hyperlipidemia & coronary artery disease.
- Current regimen includes:
  - Metformin 1000 mg BID & Glipizide 10 mg BID
  - He moderates carbohydrates and exercises 5 days/week.
- Hemoglobin A1C is 8.4%

Do you add to current regimen?

If so, what medication might you choose?

Improving glycemic control has not been shown to improve cardiovascular outcomes in type 2 diabetes mellitus….

Cardiovascular Outcome Trials for Individual Medications – Impacting Choice?



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Cefalu WT et al, Diabetes Care, 2018

Type 2 Diabetes Mellitus: Second-Line Medication Choice…

The choice for second-line therapy is not straight forward and based on multiple factors…

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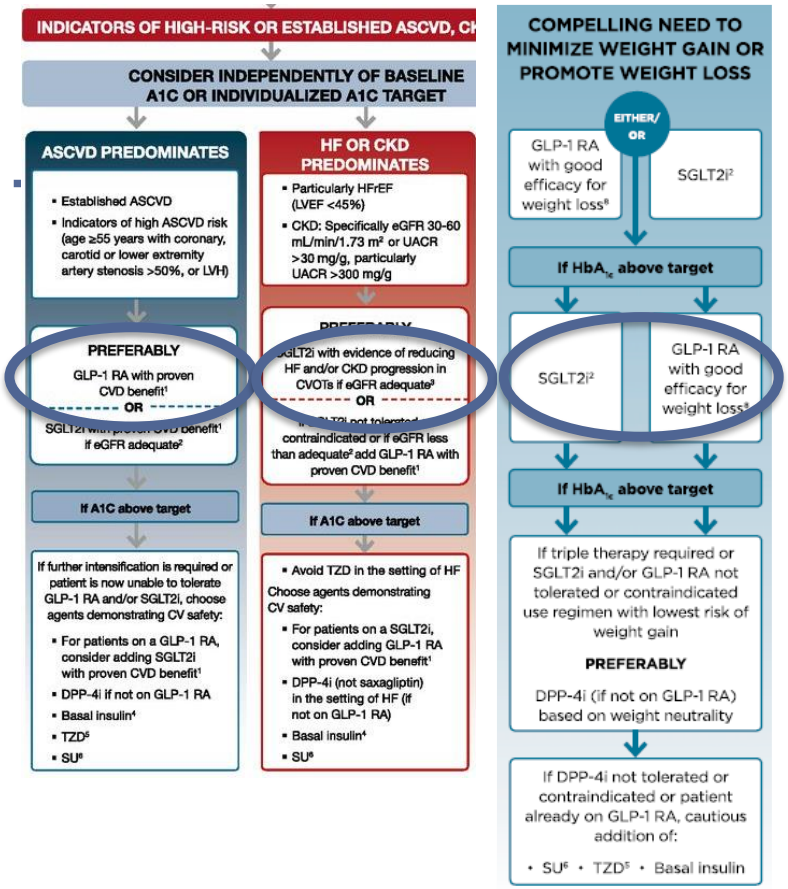
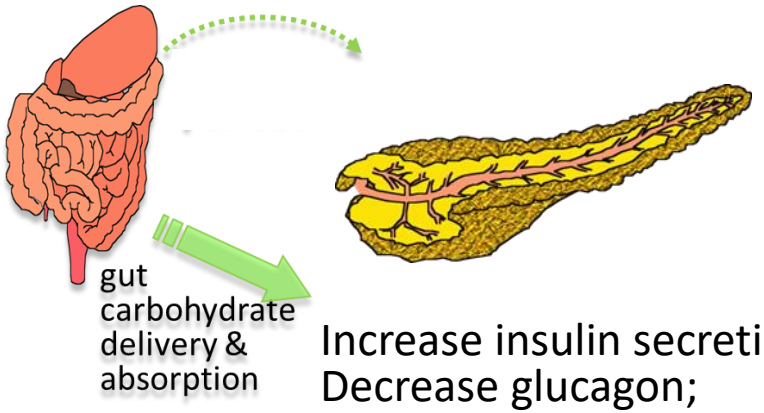


UCLA Health ADA Guidelines. Diabetes Care. 2019

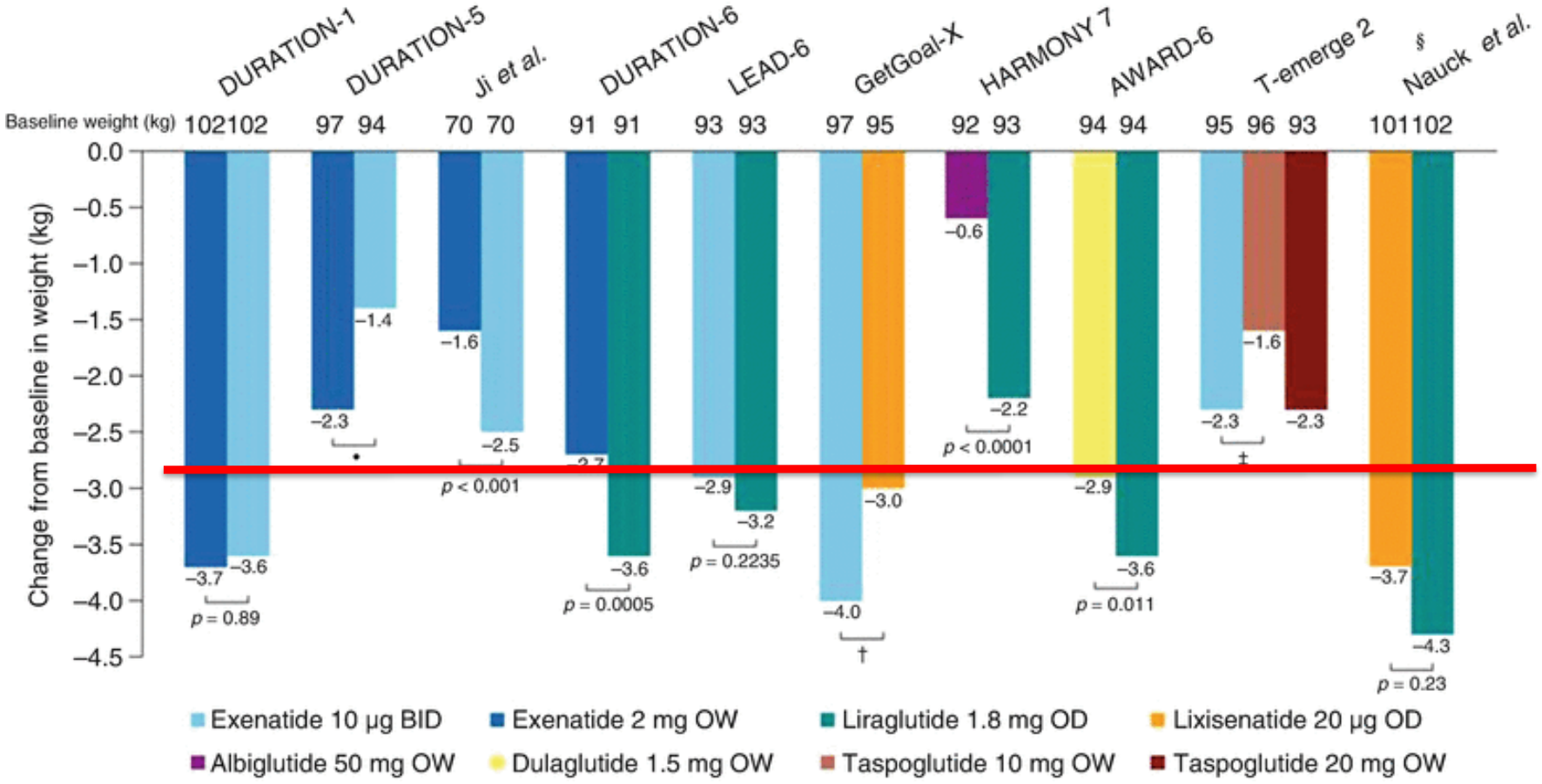
GLP-1 Receptor Agonists

- **Examples:**
  - **Exenatide (**Byetta / Bydureon)
  - **Liraglutide** (Victoza)
  - **Lixisenatide** (Adlyxin)
  - **Dulaglutide** (Trulicity)
  - **Semaglutide** (Ozempic SQ & Rybelsus PO)



- **A1C Effect:** - 0.5 to 1.5%
- **Reasons to Consider:** (1) Weight loss (1 to 4.5 kg) (2) Cardiovascular outcomes (3) Minimal Hypoglycemia
- **Side effects, Limiting Factors:** (1) Cost (2) Gastrointestinal side effects (nausea 39%, diarrhea 21%, vomiting 16%) (3) Thyroid c-cell tumors unlikely

Weight Loss in T2DM & GLP-1 RA



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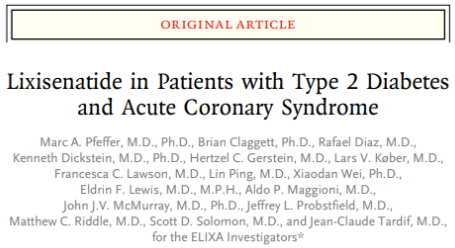
Madsbad S & Holst JJ. Diabetes, Epidemiology, Genetics, Pathogenesis, Diagnosis, Prevention and Treatment. 2018

Summary of GLP-1 RA Cardiovascular Outcomes Trials

Study			Baseline Characteristics					Primary Outcome	
GLP-1 RA: Study name	No. of patients	Median follow-up (years)	% with CV disease*	% of statin use	Baseline age	Baseline HgA1c	Baseline BMI	Primary composite CV outcome HR (95% CI)	P value
Lixisenatide: ELIXA	6068	2.1	100%	93%	60.3	7.7%	30.1	1.02 (0.89 to 1.17)	0.81
Liraglutide: LEADER	9340	3.8	81%	72%	64.3	8.7%	32.5	0.87 (0.78 to 0.97)	0.01
Semaglutide: SUSTAIN-6	3297	2.1	60%	73%	64.6	8.7%	32.8	0.74 (0.58 to 0.95)	0.02
Exenatide QW: EXSCEL	14752	3.2	73.1%	74%	62.0	8.0%	31.8	0.91 (0.83 to 1.00)	0.06
Albiglutide: Harmony	9463	1.6	100%	84%	64.1	8.7%	32.3	0.78 (0.68 to 0.90)	0.0006
Dulaglutide: REWIND	9901	5.4	31.5%	66%	66.2	7.2%	32.3	0.88 (0.79 to 0.99)	0.026
Oral semaglutide: PIONEER 6	3183	1.3	84.7%	85%	66.0	8.2%	32.3	0.79 (0.57 to 1.11)	0.17

Sheahan K et al. Postgraduate Med J. 2020

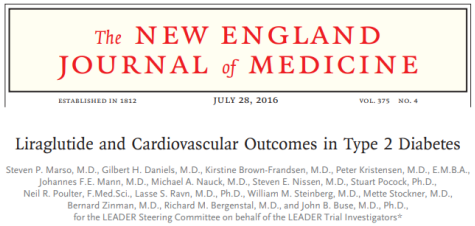
Cardiovascular Endpoints: GLP-1 RA Agonists


ORIGINAL ARTICLE

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

Marc A. Pfeffer, M.D., Ph.D., Brian Claggett, Ph.D., Rafael Diaz, M.D., Kenneth Dickstein, M.D., Ph.D., Hertzel C. Gerstein, M.D., Lars V. Køber, M.D., Francesca C. Lawson, M.D., Lin Ping, M.D., Xiaodan Wei, Ph.D., Eldrin F. Lewis, M.D., M.P.H., Aldo P. Maggioni, M.D., John J.V. McMurray, M.D., Ph.D., Jeffrey L. Probstfield, M.D., Matthew C. Riddle, M.D., Scott D. Solomon, M.D., and Jean-Claude Tardif, M.D., for the ELIXA Investigators*

Lixisenatide

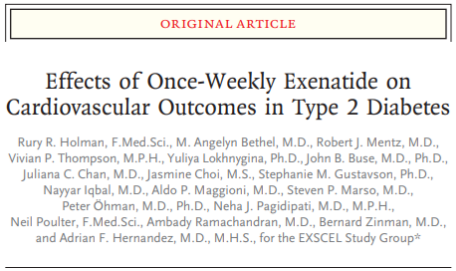

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

Liraglutide


ORIGINAL ARTICLE

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes

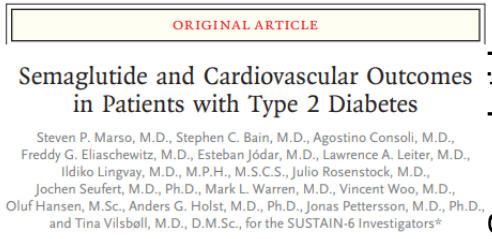
Rury R. Holman, F.Med.Sci., M. Angelyn Bethel, M.D., Robert J. Mentz, M.D., Vivian P. Thompson, M.P.H., Yuliya Lokhnygina, Ph.D., John B. Buse, M.D., Ph.D., Juliana C. Chan, M.D., Jasmine Choi, M.S., Stephanie M. Gustavson, Ph.D., Nayyar Iqbal, M.D., Aldo P. Maggioni, M.D., Steven P. Marso, M.D., Peter Öhman, M.D., Ph.D., Neha J. Pagidipati, M.D., M.P.H., Neil Poulter, F.Med.Sci., Ambady Ramachandran, M.D., Bernard Zinman, M.D., and Adrian F. Hernandez, M.D., M.H.S., for the EXSCEL Study Group*

Exenatide

	Primary outcome	Death, CV causes	Death, All cause
Lixisenatide	No difference (13.4 vs.13.2%)	No difference (7.0 vs. 7.4%)	No difference (5.2 vs. 5.1%)
Liraglutide	**13% reduction** (13.0 vs.14.9%)	**22% reduction** (4.7 vs. 6.0%)	**15% reduction** (8.2 vs. 9.6%)
Exenatide	No difference (11.4 vs.12.2%)	No difference (4.6 vs. 5.2%)	No difference (6.9 vs. 7.9%)

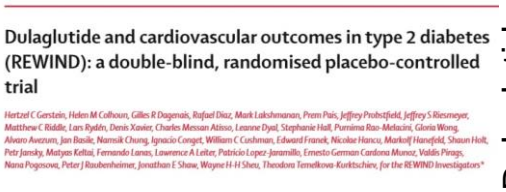
Cardiovascular Endpoints: GLP-1 RA Agonists

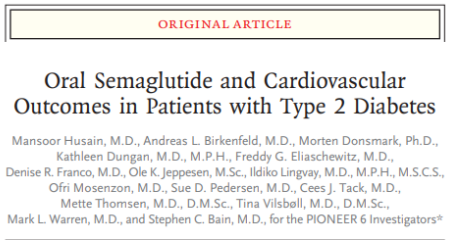
	Primary outcome	Death, CV causes	Death, Any cause
Semaglutide	**26% reduction** (6.6 vs. 8.9%)	No difference (2.7 vs. 2.8%)	No difference (3.8 vs. 3.6%)
Dulaglutide	**12% reduction** (12.0 vs. 13.4%)	No difference (10.8 vs. 12.0%)	No difference
Semaglutide PO	No difference (3.8 vs. 4.8%)	**51% reduction** (0.9 vs. 1.9%)	**49% reduction** (1.4 vs. 2.8%)


ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

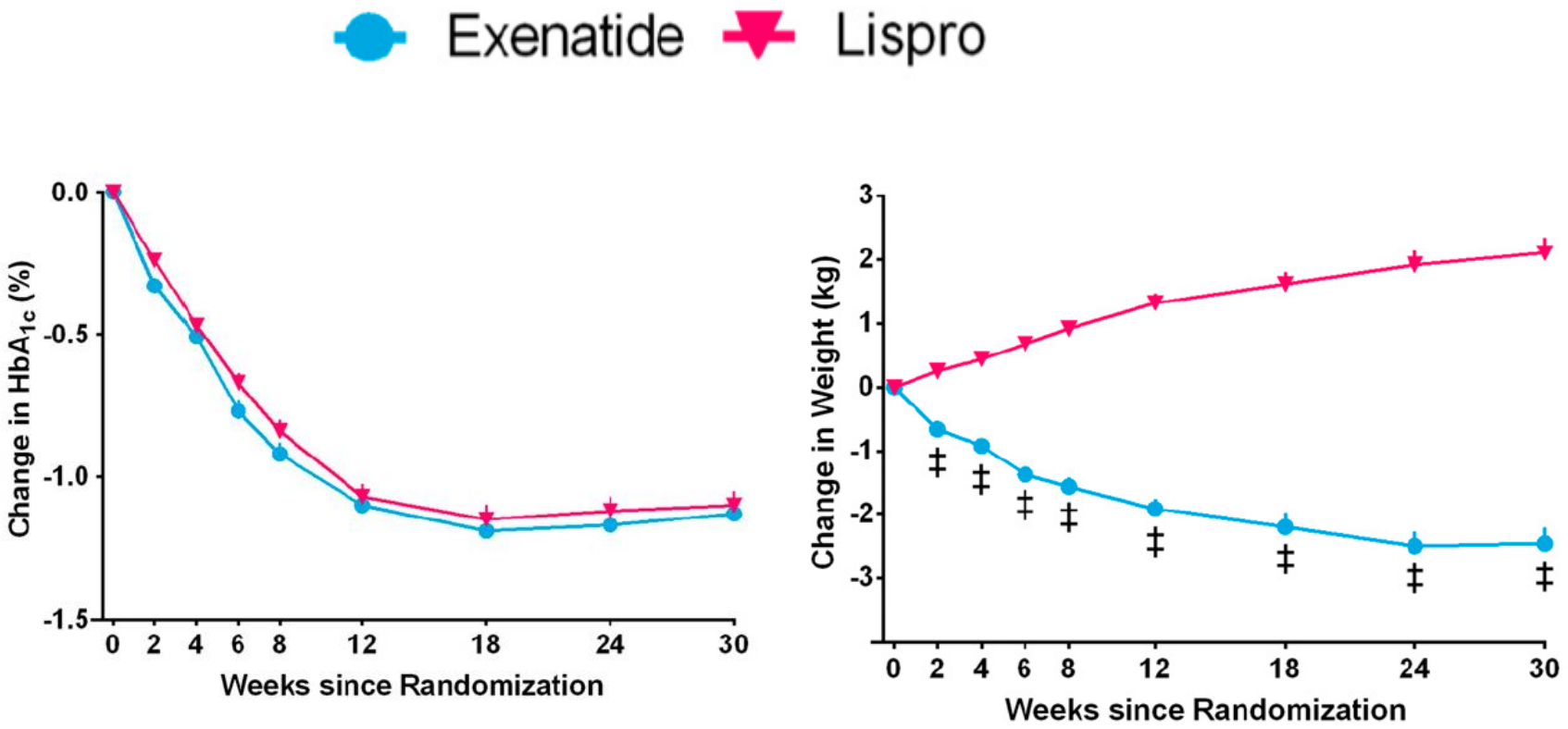

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial


ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Mansoor Husain, M.D., Andreas L. Birkenfeld, M.D., Morten Donsmark, Ph.D., Kathleen Dungan, M.D., M.P.H., Freddy G. Eliaschewitz, M.D., Denise R. Franco, M.D., Ole K. Jeppesen, M.Sc., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Ofri Mosenzon, M.D., Sue D. Pedersen, M.D., Cees J. Tack, M.D., Mette Thomsen, M.D., D.M.Sc., Tina Vilsbøll, M.D., D.M.Sc., Mark L. Warren, M.D., and Stephen C. Bain, M.D., for the PIONEER 6 Investigators*

Consider GLP-1 RA Over Bolus Insulin When Basal Insulin Has Failed

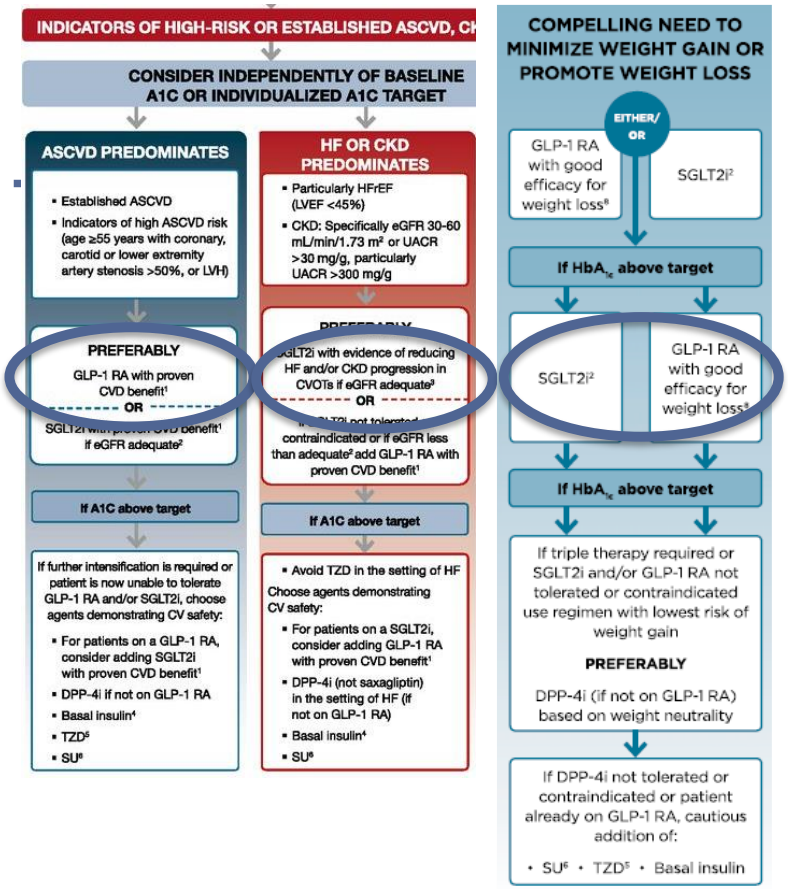


Diamont M, et al. Diabetes Care 2014

Type 2 Diabetes Mellitus: Second-Line Medication Choice…

The choice for second-line therapy is not straight forward and based on multiple factors…

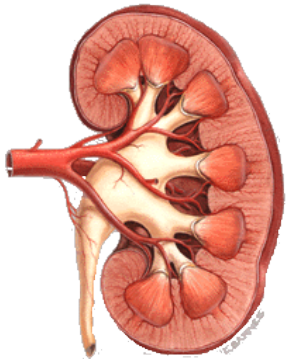
- Change in A1C (efficacy)
- Cost
- Hypoglycemia risk
- Side effects
- Weight Change
- Cardiovascular disease



UCLA Health ADA Guidelines. Diabetes Care. 2019

SGLT-2 Inhibitors

- **Examples:**
  - **Dapagliflozin (Farxiga)**
  - **Canagliflozin (Invokana)**
  - **Empagliflozin (Jardiance)**
  - **Ertugliflozin (Steglatro)**



Reduce Glucose Reabsorption

- **A1C Effect:** - 0.5 to 1%
- **Reasons to Consider:** (1) Weight loss (1 to 2 kg) (2) Cardio-renal outcomes (3) PO route (4) Minimal hypoglycemia
- **Side effects, Limiting Factors:** (1) Euglycemic DKA (<1%) (2) Genitourinary infections (2%) (3) Cost (4) Limitations in GFR levels to start medications (4) LE amputations

Weight Loss and SGLT-2 Inhibitors

Reference, year	Duration (week)	*N*	Treatment arms	Bodyweight change from baseline (kg)
SGLT2 inhibitors				
Bays et al. 2014 [29]	12	376	Placebo Canagliflozin 50 mg Canagliflozin 100 mg Canagliflozin 300 mg	− 1.1 − 1.9 − 2.8 − 2.4
Napolitano et al. 2014 [82]	8	30	Placebo + diet (− 500 cal) Remogliflozin etaborate 250 mg + diet (− 500 cal) Sergliflozin etaborate 1,000 mg + diet (− 500 cal)	− 5.1 − 7.6 − 6.1
Ramirez-Rodriguez et al. 2018 [23]	12	24	Placebo Dapagliflozin 10 mg	− 1.0 − 3.0
SGLT2 inhibitors +GLP1-RA				
Lundkvist et al. 2016 [83]	24	50	Placebo Dapagliflozin 10 mg + Exenatide 2 mg	− 0.4 − 4.5
Lundkvist et al. 2017 [21]	52	50	Dapagliflozin 10 mg + Exenatide 2 mg	− 5.7

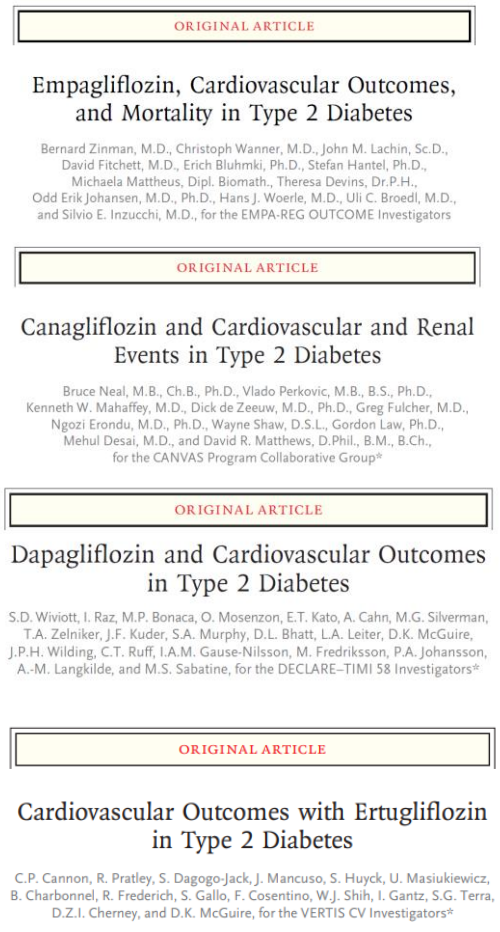
SGLT-2 Inhibitor
1-2 Kg weight loss

SGLT-2 + GLP-1
4 Kg weight loss

Pereira M & Eriksson J. Drugs 2019

Cardiovascular Endpoints: SGLT-2 Inhibitors

	Primary outcome	CHF Hospitalization	Death (Any Cause)
Empagliflozin	14% Reduction (10.5 vs.12.1%)	Reduced by 35% - ***EMPEROR Reduced*** – *25% risk reduction*	Reduced 38%
Canagliflozin	14% Reduction (26.9 vs. 31.5%)	Reduced by 33% - *Evaluated HFrEF*	Reduced 22%
Dapagliflozin	No difference (8.8 vs. 9.4%)	Reduced by 27% - ***DAPA HF*** *- 26% reduction w/ HFrEF*	No difference
Ertugliflozin	No difference (11.9 vs 11.9%)	Reduced by 30% *- HFrEF & HFpEF*	No difference


ORIGINAL ARTICLE

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

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

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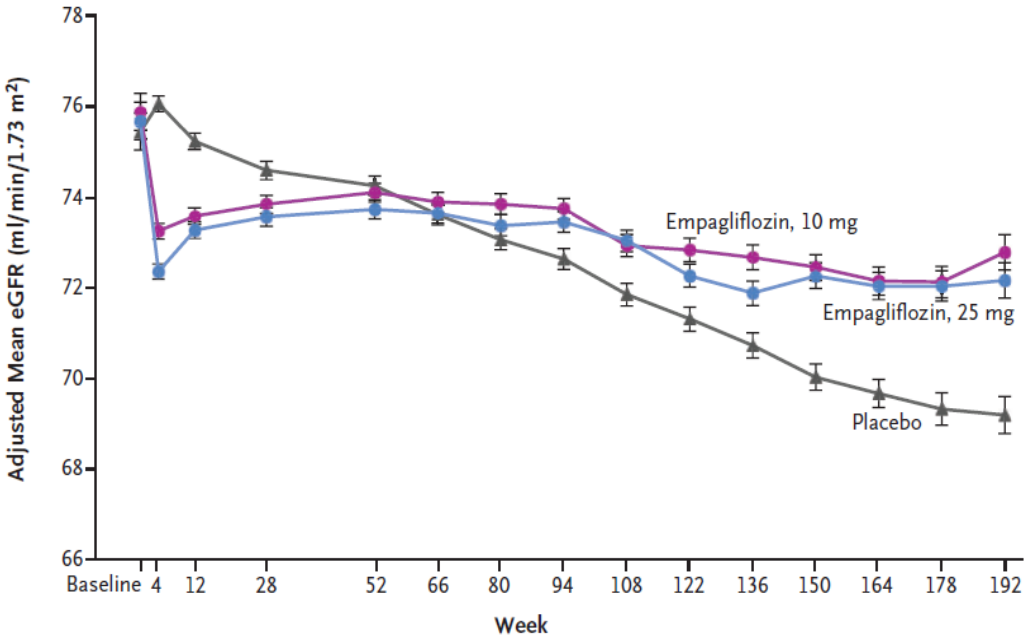
C.P. Cannon, R. Pratley, S. Dagogo-Jack, J. Mancuso, S. Huyck, U. Masiukiewicz, B. Charbonnel, R. Frederich, S. Gallo, F. Cosentino, W.J. Shih, I. Gantz, S.G. Terra, D.Z.I. Cherney, and D.K. McGuire, for the VERTIS CV Investigators*

Renal Endpoints with Empagliflozin

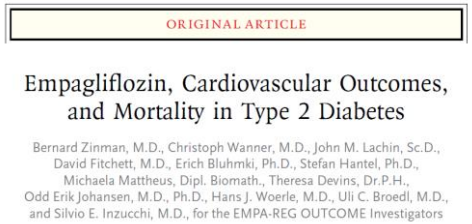
Change in Glomerular Filtration Rate



UCLA Health

Wanner C et al. NEJM 2016

Renal Endpoints: SGLT-2 Inhibitors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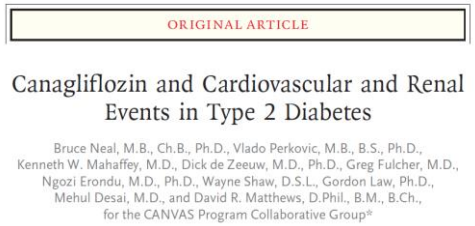
Empagliflozin

EMPA REG

EMPEROR REDUCED

-> *39% reduction* in incident or worsening nephropathy

-> *Empa reduced eGFR rate of decline*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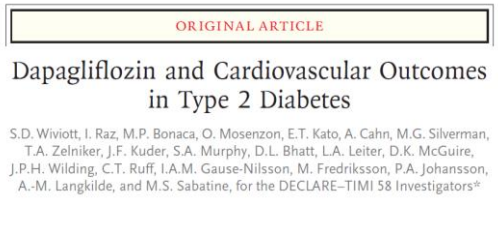
Canagliflozin

CANVAS PROGRAMME

CREDENCE

-> *40% reduction* in composite of >40% reduction in eGFR, requirement for RRT and death from renal causes

-> *30% reduction* in dialysis, transplantation, or sustained GFR of < 15 in those with GFR 30-90 at trial start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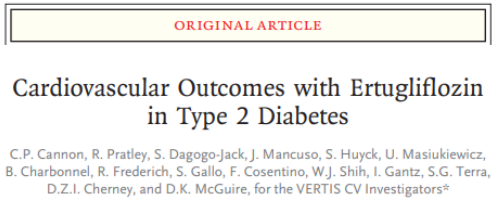
Dapagliflozin

DECLARE TIMI 58

DAPA CKD

-> *24% reduction* in composite of > 40% decrease in eGFR rate to < 60 ml/min, new ESRD or death from renal or CV causes

-> *39% reduction* in composite of sustained decline in eGFR of at least 50%, ESKD, or death from renal or CV causes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Ertugliflozin

VERTIS CV

-> *40% reduction* in composite of sustained decline in eGFR of at least 40%, dialysis/transplant or renal death

Perkovic V et al. NEJM 2019

A Third Case…
Newly Diagnosed Diabetes

- A 58 year old male presents to your clinic with **new-onset hyperglycemia.**

- Experiencing polyuria and weight loss over the last three weeks. On the night prior to his visit, he worked an overnight shift and glucose measured 423 mg/dl. Denies blurred vision, nausea, vomiting or shortness of breath.

- His medical history includes: Hypertension, Obesity, Hyperlipidemia. No CAD.

A Third Case…
Newly Diagnosed Diabetes

Physical exam.

Pulse 74 BP 134/67

BMI 31.1

Otherwise unremarkable

Lab Values

Glucose 379 mg/dl

Hemoglobin A1C 12.3%

Urine ketones - Negative

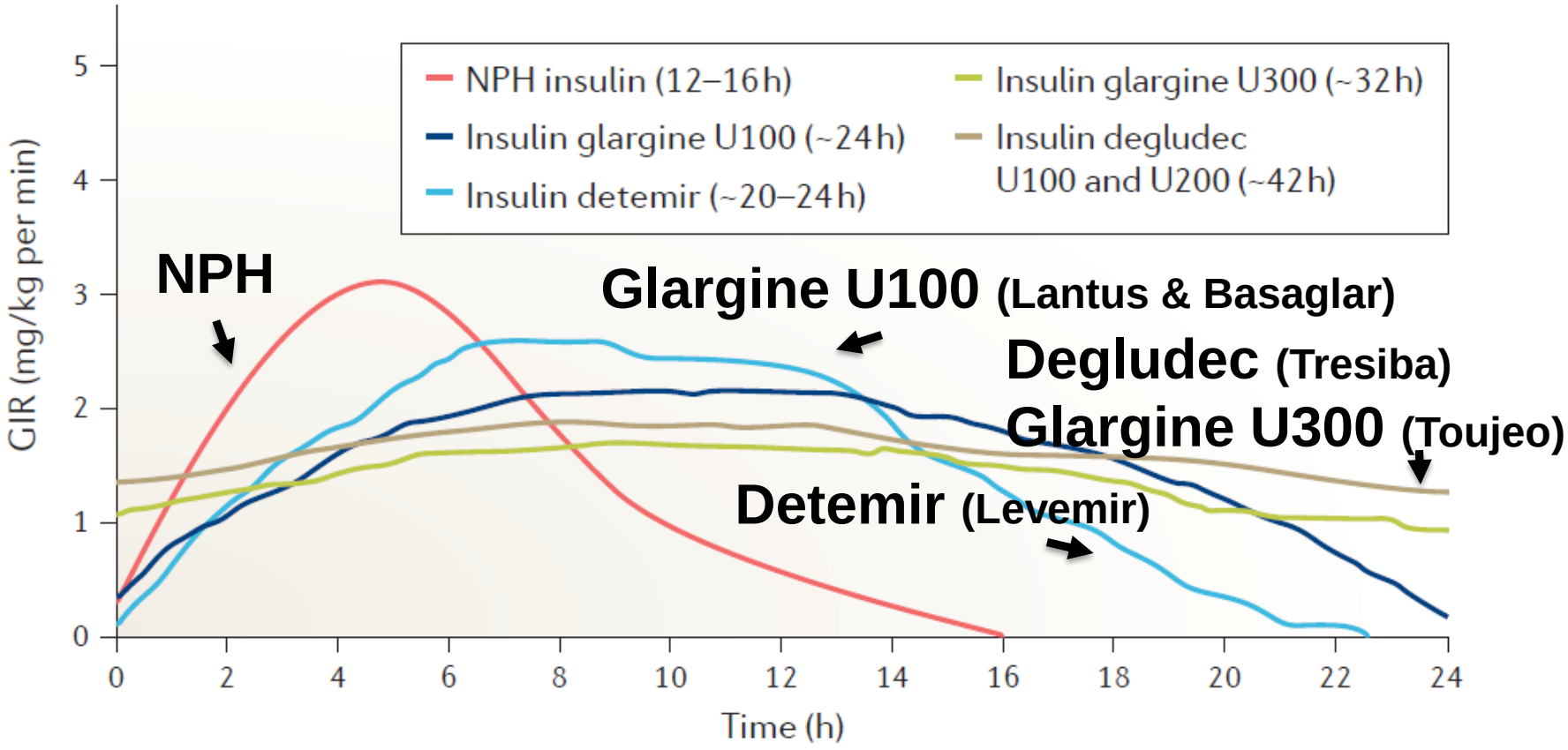
What Do You Recommend?

- **Consider Type 1 Diabetes**
- **Consider Insulin with A1C > 10%**

When To Consider **Insulin** in Type 2 Diabetes Mellitus?

- No Specific timing – Early or Late in disease course
- Glucose "toxicity" or "severe hyperglycemia"
  - Fasting glucose > 250 mg/dL or random glucose >300 mg/dL
  - Hemoglobin A1C > 10%
  - Ketonuria (Type 1 diabetes mellitus – admission for DKA)
  - Symptoms consistent with hyperglycemia – polyuria, polydipsia, weight loss
- Coexisting medical conditions
  - Pregnancy -> multiple daily insulin injections
  - Glucocorticoids -> Pair kinetics of steroids and insulin

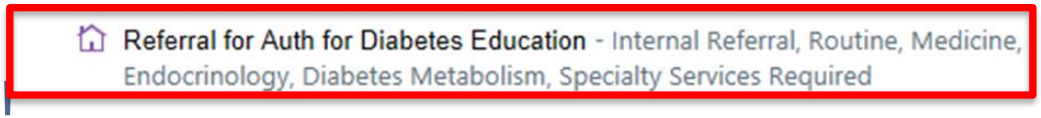
Long-Acting Insulins: Kinetics & Clinical Outcomes…



Mathieu C et al. Nature Reviews. 2017

Starting Basal Insulin Therapy in Type 2 Diabetes Mellitus

- When / How Much to Start?
  - Once daily – HS most common
  - Start with 10 units/day or 0.1 to 0.2 units/kg/day
- Titrate Regimen: Key to Control
  - Increase dose by 2 units (or 10-15%) once to twice weekly
  - Target fasting targets (80-130 mg/dL)
  - Assess for hypoglycemia
- If bolus insulin is required, consider carbohydrate ratio with correction factor -> Consider bolus calculators / pens or insulin pump
- Diabetes Education is key!



American Diabetes Association. Diabetes Care. 2020
Insulin pens: Diabetesnext.com

Insulin Risks: Weight gain & Hypoglycemia

- Weight gain is common
  - Average weight gain (UKPDS study -> approximately 4 kg)
- Hypoglycemia risk is increased with…
  - Advanced age, microvascular complication, erratic food intake
  - Cognitive impairment
  - Lower body mass index (insulin sensitivity)
  - Alcohol use
  - Coexisting chronic illnesses – liver and renal failure
- Review hypoglycemia symptoms and treatment

Treating Hypoglycemia – Rule of 15's

- Check blood glucose if experiencing symptoms
- If blood glucose is low (below 70 mg/dL):
- Treat with 15 grams of fast-acting sugar (simple carbohydrate)
  - ½ cup (4 ounces) of juice
  - 6 ounces of regular soda (NOT Diet)
  - 1 Tablespoon sugar or honey
  - Glucose/dextrose tablets (3 – 4 tablets)
- Re-check blood glucose after 15 minutes

Glucose Monitoring in Type 2 DM: Not Insulin-Requiring

- Benefits of glucose monitoring are mixed and recommendation should be individualized
  - Consider in those titrating medications, high A1C, risk of low sugars

Glucose Monitoring in Type 2 DM: Not Insulin-Requiring

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

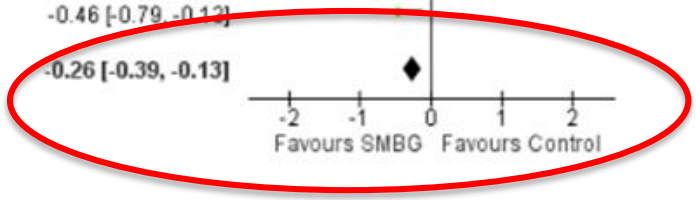
Cochrane Database of Systematic Reviews

Figure 4. Forest plot of comparison: 1 SMBG (self-monitoring of blood glucose) vs control (6 months follow-up), outcome: 1.1 HbA1c [%].

	SMBG			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
Barnett 2008	-1.15	1.14	311	-0.91	1.29	299	22.0%	-0.24 [-0.43, -0.05]	
Davidson 2005	-0.8	1.6	43	-0.6	2.1	45	2.6%	-0.20 [-0.98, 0.58]	
DiGEM trial 2007 (1)	-0.15	0.81	301	-0.08	0.73	152	27.7%	-0.07 [-0.22, 0.08]	
Fontbonne 1989	-0.36	3.14	68	-0.5	1.54	68	2.3%	0.14 [-0.69, 0.97]	
Franciosi 2011	-1.2	0.81	46	-0.7	0.7	16	7.9%	-0.50 [-0.92, -0.08]	
Guerci 2003	-0.9	1.54	345	-0.5	1.54	344	18.3%	-0.40 [-0.63, -0.17]	
Kleefstra 2010	-0.18	0.67	22	0.07	0.75	18	7.0%	-0.25 [-0.70, 0.20]	
Muchmore 1994	-1.54	1.46	12	-0.85	1.87	11	0.9%	-0.69 [-2.07, 0.69]	
SMBG study group 2002	-1	1.08	113	-0.54	1.41	110	11.3%	-0.46 [-0.79, -0.13]	
Total (95% CI)			**1261**			**1063**	**100.0%**	**-0.26 [-0.39, -0.13]**	

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 11.29$, df = 8 (P = 0.19); $I^2 = 29\%$
Test for overall effect: Z = 3.99 (P < 0.0001)

(1) Both intervention groups are combined



Malanda UL, et al. Cochrane Review. 2012

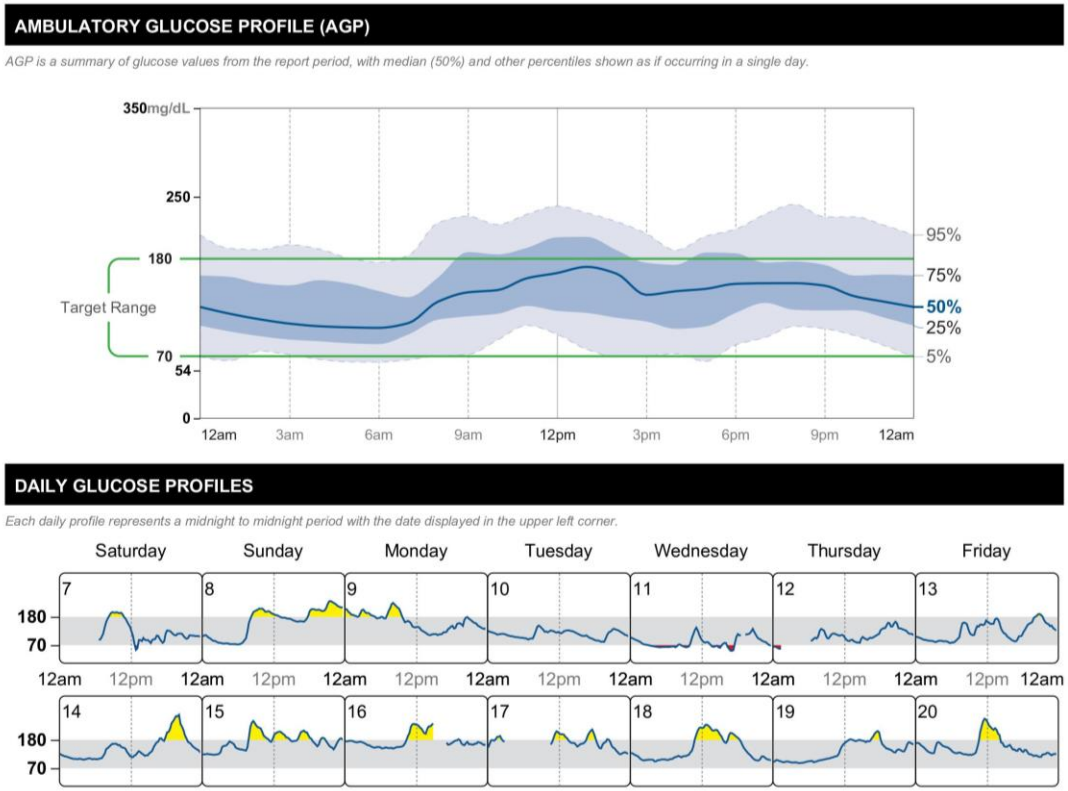
Glucose Monitoring in Type 2 DM: Not Insulin-Requiring

- Benefits of glucose monitoring are mixed and recommendation should be individualized
  - Consider in those titrating medications, high A1C, risk of low sugars
  - No consistent benefit with metformin
- Maximizing monitoring impact…
  - Targeted feedback
    - A1C < 7%: Fasting glucose < 130 & 2 hours post-prandial < 180
    - Immediate feedback for dietary modifications
  - Hypoglycemia monitoring
    - Monitor fasting, pre-lunch or pre-dinner levels.

Continuous Glucose Monitoring (CGM)

- Continuous Glucose monitoring in T1DM and multiple daily insulin injections in T2DM

- Professional or personal use.
- Consider in patients w/:
  - Multiple low sugars
  - At-risk for low sugars
  - Discordant data -- meter and A1C



Continuous Glucose Monitoring: Reports

MRN: _____

DEVICE: FreeStyle Libre

PAGE: 1 / 1

GENERATED: 12/20/2019

AGP Report

December 7, 2019 - December 20, 2019 (14 Days)

LibreView

GLUCOSE STATISTICS AND TARGETS

December 7, 2019 - December 20, 2019	**14 Days**
% Time CGM is Active	**97%**

Ranges And Targets For	Type 1 or Type 2 Diabetes
Glucose Ranges	**Targets** % of Readings (Time/Day)
Target Range70-180mg/dL	Greater than 70%(16h 48min)
Below 70 mg/dL	Less than 4% (57min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h 0min)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial.

Average Glucose	**141** mg/dL
Glucose Management Indicator (GMI)	**6.7 %**
Glucose Variability	**31.6%**

Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

Very High	>250 mg/dL	**1%** (14min)
High	181-250 mg/dL	**18%** (4h 19min)
Target Range	70-180 mg/dL	**78%** (18h 43min)
Low	54-69 mg/dL	**3%** (43min)
Very Low	<54 mg/dL	**0%** (0min)

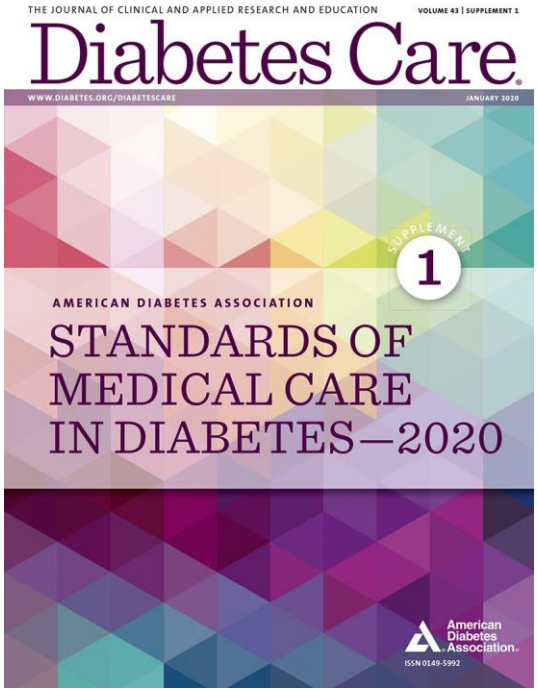
Type 2 Diabetes Management

- Set an A1C target
- Diabetes education is Effective!!
  - Medical nutrition therapy, medication & injectable teaching
  - Epic Order: “Diabetes Education Referral”
- Annual Diabetes Screening is important…
  - Hemoglobin A1C
    - POC A1C testing
  - Diabetes Eye Exam
    - Retinal Camera at 2020 SM Blvd → Epic Order: “Remote Fundus”
  - Urine microalbumin (UMA)
  - Comprehensive foot exam (removed from Health Maintenance)

Diabetes Care 2018
ADA Guidelines. Diabetes Care. 2019

Type 2 Diabetes Management: Take Home Points

- Set an A1C target
- DM education is key!
- Start with Metformin
  - Consider Extended Release → Note recent recall
- Second-line therapy choice is based on multiple factors
  - Cost
  - Side effects
  - Weight gain / weight loss
  - Hypoglycemia risk
  - Cardiovascular (and renal) impact



THANK YOU!!