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# GLYCEMIC CONTROL AMONG PEOPLE AT HIGH CARDIOVASCULAR RISK

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# Disclosure

## Relevant Financial Relationship(s)

- None

## Off Label Usage

- None



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A patient revolution for  
careful and kind care

# Why We Revolt

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# 55 year-old man, 1.5 years after first MI

- Sedentary, accountant, married
- Obesity (BMI 35), DM2, hypertension.
- On antiplatelet, high-dose statin
- For hypertension: beta-blocker + ACEi + diuretic
- For DM2:
  - Metformin (before MI) + sitagliptin (for 1.5 years)
  - HbA1c 7.6%, Creatinine 1.7 mg/dL
  - Last review no microvascular complications



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# What is appropriate for his diabetes at this point?

- a) Add liraglutide to reduce his CV risk, A1c, and weight
- b) Stop metformin (elevated Cr) and add insulin lantus to reduce his A1c and CV risk
- c) Advice to promote activity and healthier diet and review HbA1c in 3-6 months
- d) Start logging blood sugars 1-2 times per day
- e) Lower the statin dose



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# My clinical approach

1. Promote health: diet, activity, **stress**, tobacco
2. Estimate and reduce CVD risk
  - ✓ Statin (even high doses), aspirin
  - ✓ **Glucoretics? GLP-1 agonists?**
  - ✓ Treat hypertension
3. Glycemic control:
  - Involve patients in target (nl-8%) and how  
<http://diabetesdecisionaid.mayoclinic.org>
  - Treat symptomatic hyper; avoid hypoglycemia
5. Failure: intensification vs. adherence



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# Circul

## Cardiovascular Quality

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Rodriguez-Gutierrez and Montori; Circ  
Cardiovasc Qual Outcomes. 2016;9



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# Antidiabetes agents with positive CV Outcome Trials

- Pioglitazone (IRIS)\*
  - Canaglifloxin (CANVAS)\*
  - Empagliflozin (EMPA-REG)
  - Dapagliflozin (DECLARE-TIMI 58)
  - Liraglutide (LEADER)\*
  - Semaglutide (SUSTAIN-6)
- \* Inconsistent results within the class



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## EMPA-REG

- RCT at low risk of bias (blinding)
- 7028 >5y DM2 (A1c 7-10%)+ CV
- Empagliflozin (10 or 25 mg) vs. **Placebo**
- At 2.5y: 14% RRR in CV death, nonfatal MI, nonfatal stroke, from 12 % to 10.5%
- **Certainty:** Consistent with prior trials and CANVAS (cana), but not with DECLARE (dapa), a 17160-patient 4y trial: no effect on MACE/CV death

N Engl J Med 2015;373:2117-28.

## Empagliflozin (HbA1c 0.5%)

Participants with additional:	Placebo	Empagliflozin
Glucose-lowering medications added in concordance with an escalated 'standard of care'	31.5%	19.5%
Insulin	11.5%	5.8%
Dipeptidyl peptidase 4-inhibitor	8.3%	5.6%
Sulfonylurea	7.0%	3.8%
Thiazolidinedione	2.9%	1.2%

**Concerns:** change in protocol, posthoc outcomes, 40% deaths uncertain



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## Liraglutide (HbA1c 0.5%)

RCT at low risk of bias (blinding)

9340 DM2 (A1c 7-10%)+ 80% CV

Liraglutide (1.8 mg daily) vs. placebo

At 3.5y: 13% RRR in CV death, nonfatal MI, nonfatal stroke from 15% to 13%

**Concerns:** Differences between arms in diabetes treatments  
Adverse effects in patients with advanced heart failure?  
Class effect?

Exenatide weekly (EXSCEL, n=14752) Neg

Semaglutide weekly (SUSTAIN-6, n=3297) **Pos**

Lixisenatide daily (ELIXA, n=6068 ACS) Neg



# FDA and metformin

Obtain eGFR before starting metformin + yearly

- >45 Use (careful with contrast studies)
- 30-45 Question use
- <30 Don't use

04/20/2016 - <http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm>



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# Why not do everything to the patient?

For a patient at 30% at 10 years

Statin low dose reduce by 25% to 22.5% (-7.5)

20% Statin high dose reduce by 15% to 19.1% (-3.9)

Aspirin reduces risk by 15%\* to 16% (-3)

Antihypertensive treatment by 20% to 13% (-3)

10% Glycemic control by 15% to 11% (-2)

Liraglutide by 13% to 9.6% (-1.4)

Empagliflozin by 14% to 8.3% (-1.3)

Burden of treatment, cost to patient, and value to patient  
CV risk to take low dose statins >20%

\*ASCEND Trial, NEJM 379;16



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## Therapeutic plan in T2DM

	Primary prevention of CVD	Established CVD without heart failure	Established CVD with systolic heart failure	Established CVD with TIA/stroke
	Lifestyle intervention			
	Metformin	Metformin	SGLT-2 inhibitors Empagliflozin Canagliflozin	Metformin
Hypertension →	SGLT-2 inhibitors Empagliflozin Canagliflozin	SGLT-2 inhibitors Empagliflozin Canagliflozin	Metformin	Thiazolidinediones Pioglitazone
Obesity →	GLP-1RA Liraglutide Semaglutide	GLP-1RA Liraglutide Semaglutide	Long-acting insulin	GLP-1RA Liraglutide Semaglutide
	DPP-4 inhibitors Sitagliptin	DPP-4 inhibitors Sitagliptin	DPP-4 inhibitors Sitagliptin	SGLT-2 inhibitors Empagliflozin Canagliflozin
	Long-acting insulin	Long-acting insulin	<del>GLP-1RA Liraglutide</del>	DPP-4 inhibitors Sitagliptin
	Thiazolidinediones Pioglitazone	Thiazolidinediones Pioglitazone	<del>Thiazolidinediones Pioglitazone</del>	Long-acting insulin
	Sulfonylureas Glipizide	<del>Sulfonylureas Glipizide</del>	<del>Sulfonylureas Glipizide</del>	<del>Sulfonylureas Glipizide</del>

## Burden of treatment?

- Administration
- Side effects (worry)
  - SGLT-2i (class effects)\***
    - Amputations (2:1000py)
    - DKA (1:1000py)
    - Genital infex (10:1000py)
- Cost

\*BMJ 2018; 363

Mayo Clinic Proceedings 2018 93, 1629-1647



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MAYO CLINIC

Decisión sobre medicación para pacientes con diabetes

Herramienta de ayuda para la toma de decisiones

←

ES

EN

BACK

SHOW ALL

QUE TEMA LE GUSTARÍA DISCUTIR PRIMERO?			A1C ↓	RUTINA DIARIA	AZÚCAR BAJA EN SANGRE	BENEFICIOS PARA EL CORAZÓN
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Metformina	1 - 2 %		•	
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Insulina	∞		✖	
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Pioglitazona	1 %		•	
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Incretinas	0.5 - 1%		•	
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Sulfonilureas	1 - 2 %		✖	
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Gliptinas	0.5 - 1%		•	
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Inhibidores SGLT2 (Glifozinas)	0.5 - 1%		•	

What is the situation that requires action?



Which response makes the most intellectual, emotional, and practical sense?





# Questions & Discussion



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