Diabetic Sugar Meds: The Unsweetened Evidence for Outcomes That Matter Most

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My Premise

T2DM is not a disease but simply a risk factor

The tests used to diagnose/monitor a person with T2DM are at best tricky to use and are very misleading

The majority of T2DM treatments have been shown to have no benefit and cause harm

A1c is a risk factor so you need to be able to estimate risk

For medications that have been shown to have a possible benefit, the benefit is of such a low magnitude and a high cost that the vast majority of people would likely not take them

Type 2 Diabetes

Feeling Fatigued or Irritable? There's a 1 in 4 Chance You Suffer from Diabetes...

10 Things You Should Eat If You Are Suffering From Diabetes

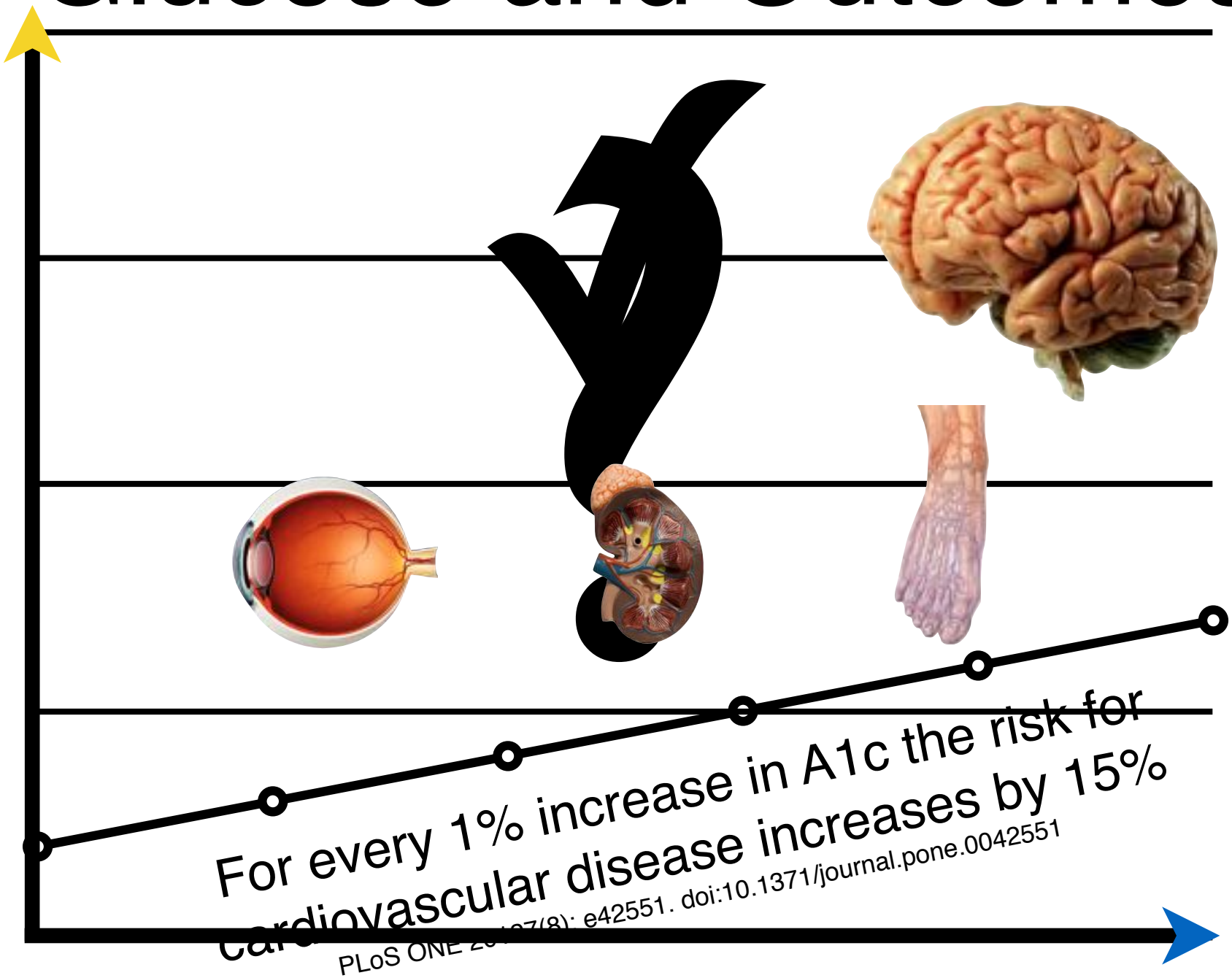
It is NOT a disease

It is a RISK Factor

Suffering from diabetes? Here's some good news for you

Suffering from diabetes? Fight it like your favourite B-town celebs

Glucose and Outcomes



The tests used to diagnose/ monitor a person with T2DM are at best tricky to use

TOMORROW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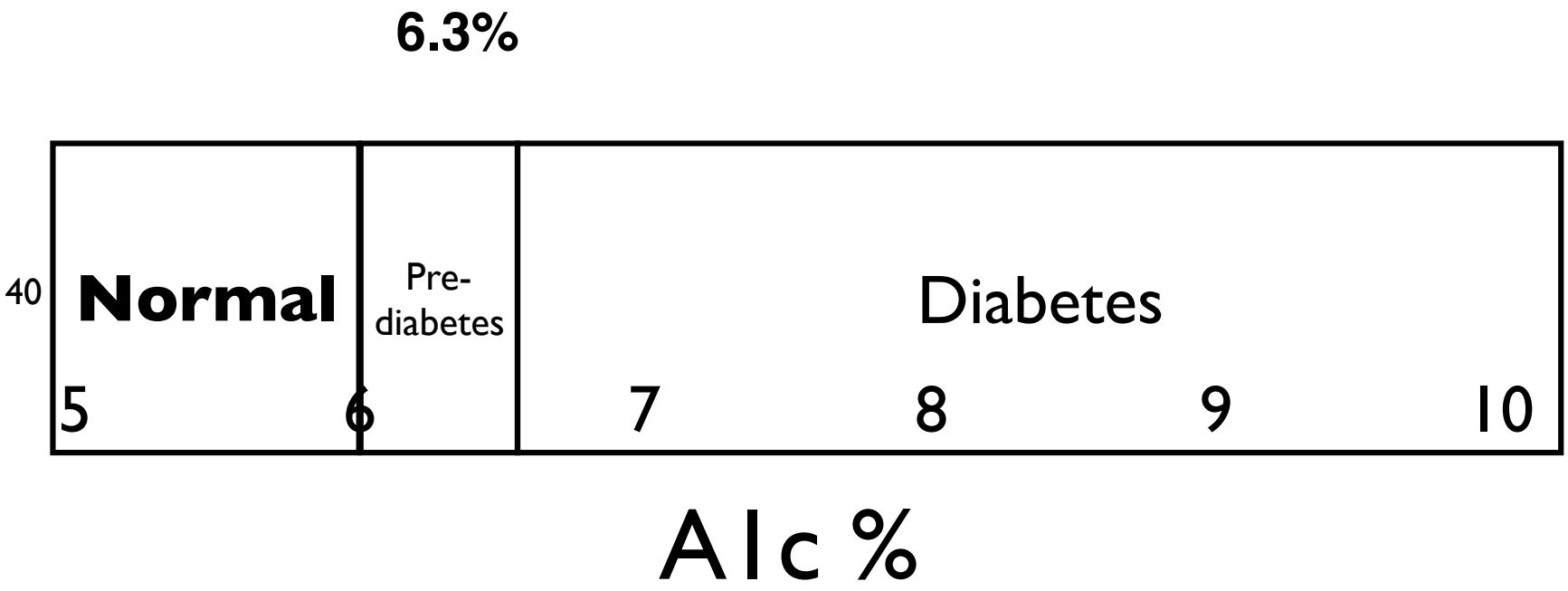
PRACTICAL EVIDENCE
Interpreting Lab Tests:
The Magic of "Normal" Ranges
and Repeat Testing
therapeuticseducation.org
medicationmythbusters.com

Precisely Imprecise

What an A1c result really means



Typical A1c change seen with a medication = 0.7% ⬇

Seasonal variation 0.2-0.5%
Higher in the winter

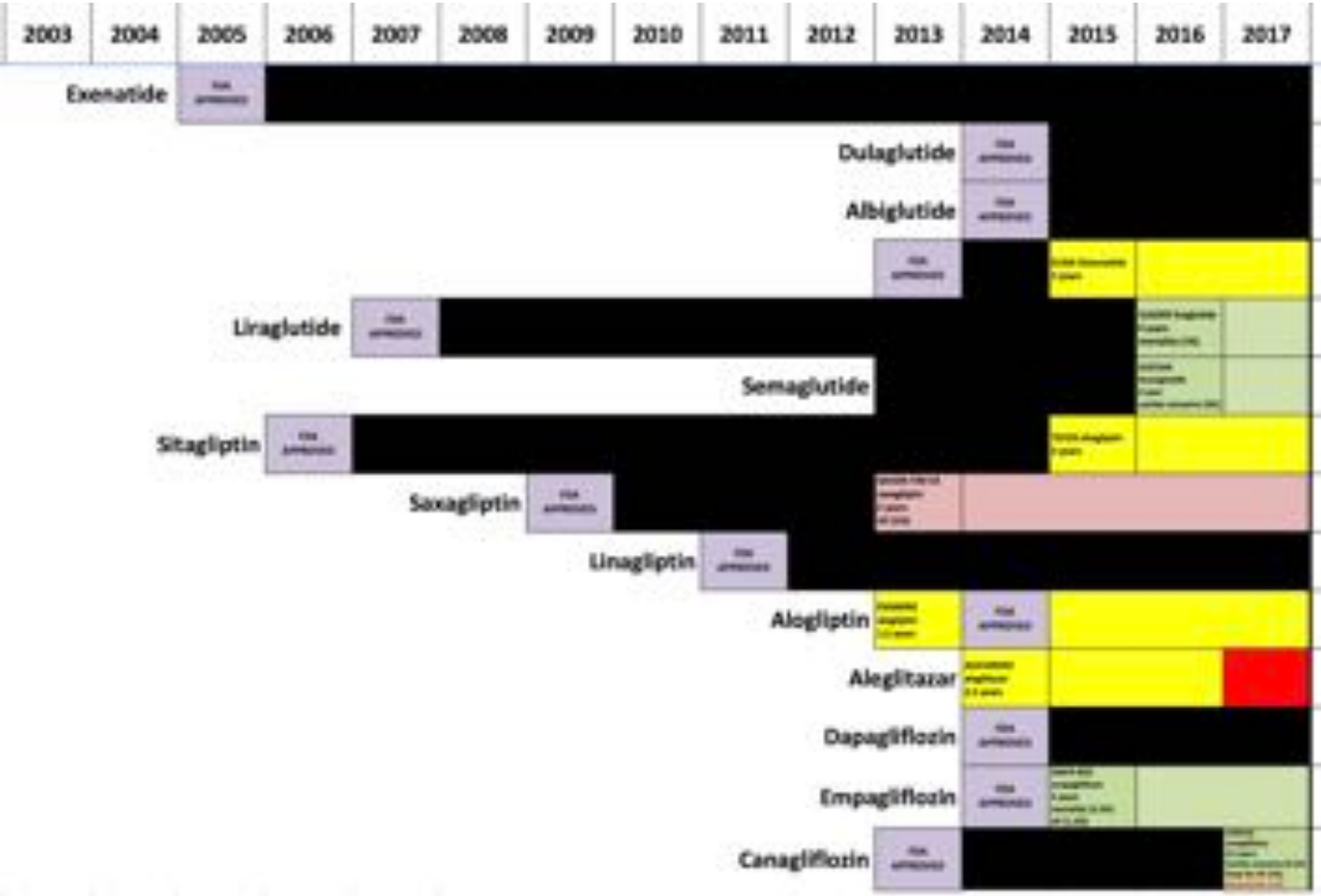
Am J Epi 2004;161:565-74

The majority of T2DM treatments have been shown to have no benefit and they ALL cause some sort of harm

1) At a minimum cost and inconvenience

2) Some adverse events, weight gain, heart failure, hypoglycemia, genital infections, amputations

The History of T2DM Treatments



	YEARS ON MARKET	YEARS ON MARKET NO CVD DATA
Exenatide	13	13
Dulaglutide	4	4
Albiglutide	4	4
Lixisenatide	2	2
Liraglutide	9	6
Semaglutide	3	0
Sitagliptin	12	9
Saxagliptin	9	4
Linagliptin	7	7
Alogliptin	5	0
Aleglitazar	0	NA
Dapagliflozin	4	4
Empagliflozin	4	1
Canagliflozin	5	4

A 100-year History Lesson

(60 if you don't include insulin)

28 medications

26 have received regulatory approval

20 have been evaluated in at least 1 RCT assessing impact on important outcomes

MY DEFINITION OF IMPORTANT OUTCOMES

1) microvascular (end-stage renal disease/dialysis, renal death, blindness, clinical neuropathy)

and/or

2) macrovascular (all cause mortality, CVD mortality, non-fatal MI, stroke, amputation, heart failure or a composite CVD endpoint)

Large RCTs evaluating the impact of medications on Clinically Important Outcomes in T2DM

YEAR	NAME	MEDICATION	RESULT	OUTCOME CHANGED
1970	UGDP	tolbutamide (Orinase)	NEGATIVE	CVD mortality
1971		phenformin (DBI)	NEGATIVE	Mortality
1976		tolbutamide (Orinase)	NEGATIVE	Fatal MI
1982		insulin	NEUTRAL	
1998	UKPDS 33/34	insulin, chlorpropamide, glyburide/glibenclamide,	NEUTRAL	
1998		metformin, insulin, chlorpropamide, glyburide/	NEUTRAL except POSITIVE for	Mortality and MI
2003	STOP-NIDDM	acarbose (Precose)	POSITIVE	MI
2005	PROACTIVE	pioglitazone (Actos)	POSITIVE	MI
2007	RECORD	rosiglitazone (Avandia)	NEGATIVE	Heart failure
2012	ORIGIN	insulin	NEUTRAL	
2013	EXAMINE	alogliptin (Nesina)	NEUTRAL	
2014	SAVOR-TIMI 53	saxagliptin (Onglyza)	NEGATIVE	Heart failure
2014	ALECARDIO	aleglitizar	NEUTRAL	
2015	ELIXA	lixisenatide (Adlyxin)	NEUTRAL	
2015	TECOS	sitagliptin (Januvia)	NEUTRAL	
2015	EMPA-REG	empagliflozin (Jardiance)	POSITIVE	Mortality and heart failure
2016	SUSTAIN 6	semaglutide	POSITIVE	Combo outcome
2016	LEADER	liraglutide (Victoza)	POSITIVE	Mortality
2017	CANVAS	canagliflozin (Invokana)	POSITIVE	Combo outcome and heart failure BUT INCREASED amputations
2017	EXSCEL	exenatide (Byetta)	NEUTRAL	

Studies Overall

16 RCTs have evaluated 20 of the 28 medications

45% of the medications evaluated showed no overall benefit

35% showed some benefit (on at least one, and typically only one, clinically important outcome)

20% showed overall harm (no benefit and harm for at least one clinically important outcome)

590 marketed years

(medications x years on market)

	% of marketed years
No RCTs	61%
With RCTs showing no benefit	18%
With RCTs suggesting harm	12%
With RCTs suggesting benefit	9%

Study Outcome Synopsis

16 studies

MICROVASCULAR OUTCOMES - positive impact = NONE

MACROVASCULAR OUTCOMES

3 - decrease mortality (metformin/empagliflozin/liraglutide)

1 - increase mortality (tolbutamide)

3 - decrease in MIs (1 an increase)

2 - increase in heart failure (2 a decrease)

2 - have shown a decrease in a combination of macrovascular endpoints but not on individual endpoints

1 - increase in amputations

There are others who have found similar things

Original Article

Glycemic Control for Patients With Type 2 Diabetes Mellitus

Our Evolving Faith in the Face of Evidence

August 2016

René Rodríguez-Gutiérrez, MD, MSc; Victor M. Montori, MD, MSc

"no significant impact of tight glycemic control on the risk of dialysis/ transplantation/renal death, blindness, or neuropathy"

"also no significant effect on all-cause mortality, cardiovascular mortality, or stroke; however, there is a consistent 15% relative-risk reduction of nonfatal myocardial infarction"

despite this, over the last 10 years -
"practice guidelines and published statements offer a consistent and confident consensus, with 100% of the guidelines and 77% to 100% of the statements in favor of tight glycemic control to prevent microvascular complications"

Review

Effects of pharmacological treatments on micro- and macrovascular complications of type 2 diabetes: What is the level of evidence?

R. Boussageon [a,*], F. Gueyffier [b,c], C. Cornu [b,c,d]

"In 2013, the level of evidence for the clinical efficacy of antidiabetic drugs is disappointing and does not support the millions of prescriptions being written for them"

Diabetes Metab 2014 Feb 3. pii: S1262-3636

Role of Intensive Glucose Control in Development of Renal Endpoints in Type 2 Diabetes: Systematic Review and Meta-analysis

Steven G. Coca, DO, MS[1,2], Faramarz Ismail-Beigi, MD, PhD[3], Nowreen Haq, MD, MPH[4], Harlan M. Krumholz, MD, SM[1,5,6,7], and Chirag R. Parikh, MD, PhD[1,2]

[1]Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA

7 studies, 28,200 people, 2-15 years

	Baseline	Intensive
Microalbuminuria	24%	21%
Macroalbuminuria	6%	4.5%
Doubling of Scr	4%	NSS
ESRD	1.5%	NSS
Death from renal disease	0.3%	NSS

Arch Intern Med 2012 May 28; 172(10): 761–769.

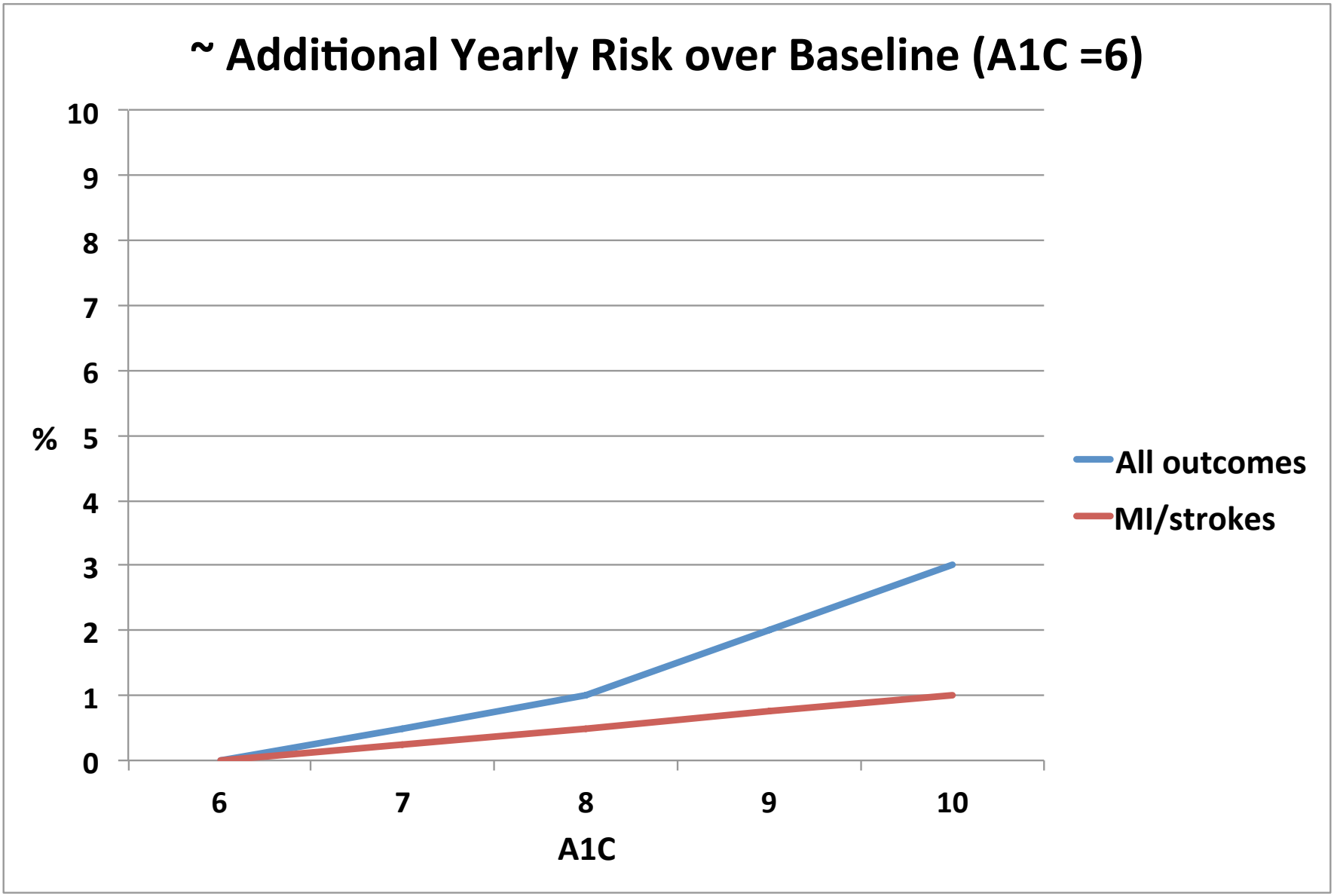
A1c is a risk factor so you need to be able to estimate risk

10 year risk of complications from T2DM

60 y/o male, total chol 5, HDL chol 1, SBP 140, non-smoker

10-year % risk							**~ Additional yearly risk over baseline**	
A1C (%)	**Mortality**	**MI or stroke**	**Severe vision loss**	**RF/ ESRD**	**Pressure sensation loss**	**TOTAL**	**ALL OUTCOMES**	**JUST MI/STROKE**
4	5	10	4	4	6	24	-	-
5	5	11	5	4	7	27	-	-
6	6	13	5	5	8	31	BASE	BASE
7	7	16	6	5	10	37	0.5%/yr	0.25%/yr
8	9	18	7	6	12	43	1%/yr	0.5%/yr
9	10	21	8	7	14	50	2%/yr	0.75%/yr
10	12	25	9	8	17	59	3%/yr	1%

https://sanjaybasu.shinyapps.io/recodesi/ - from the ACCORD study


~ Additional Yearly Risk over Baseline (A1C =6)
10
9
8
7
6
%
5
4
3
2
1
0
6
7
8
9
10
A1C
All outcomes
MI/strokes

The Gliflozins

EMPA-REG - non-inferiority (safety) was the primary outcome

A1c 8.1%, age 63, 71% male, SBP 135, previous CVD 100%, total chol 163 HDL 44 - 3.1 years

Pooled dose data	Empagliflozin (%)	Placebo (%)
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	10.5	12.1
Hospitalization for heart failure	2.7	4.1
Mortality	5.7	8.3
Genital infections	6.4	1.8
Doesn't increase risk of HF or hypoglycaemia 👍		

Primary outcome = 0.86 RR; 95.02% confidence interval, 0.74 to 0.99
P=0.04 for superiority
Endpoints not looked at - ESRD, blindness, amputation

N Engl J Med 2015;373:2117-28

The Gliflozins - overall

	Empagliflozin EMPA-REG 3.1 y **% = placebo rate**	Canagliflozin CANVAS 3.6 y **% = placebo rate**	Dapagliflozin DECLARE-TIMI 58 (APRIL 2019)
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	0.86 (0.74–0.99) 12.1%	0.86 (0.75–0.97) **9.8%**	?
Mortality	0.68 (0.57-0.82) 8.3%	0.87 (0.74–1.01) **6.5%**	?
Serious adverse events	0.90 (0.84-0.96) 42.3%	0.93 (0.87-1.00) ?	?
Composite renal events increased creatinine or BUN levels, decreased eGFR, renal impairment and renal failure	*0.63 (0.54-0.72) ?	*1.29 (0.78-2.15) ? 0.60 (0.47-0.77) ? CANVAS different renal groupings	*1.64 (1.26-2.13)
Acute renal impairment/ failure events	*0.72 (0.60-0.86) 3.1%?	*0.67 (0.25-1.80) ?	*0.75 (0.33-1.74)
Amputations (primarily toe)	?	1.97 (1.41-2.75) **1.2%**	?
Fractures	No difference	1.26 (1.04–1.52) **4.3%**	?

*from Diabetes Obes Metab 2017;19:1106–15

Effect of Sodium-Glucose Cotransport-2 Inhibitors on Blood Pressure in People With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of 43 Randomized Control Trials With 22 528 Patients

Mohsen Mazidi, PhD; Peyman Rezaie, MSc; Hong-Kai Gao, MD, PhD; Andre Pascal Kengne, MD, PhD

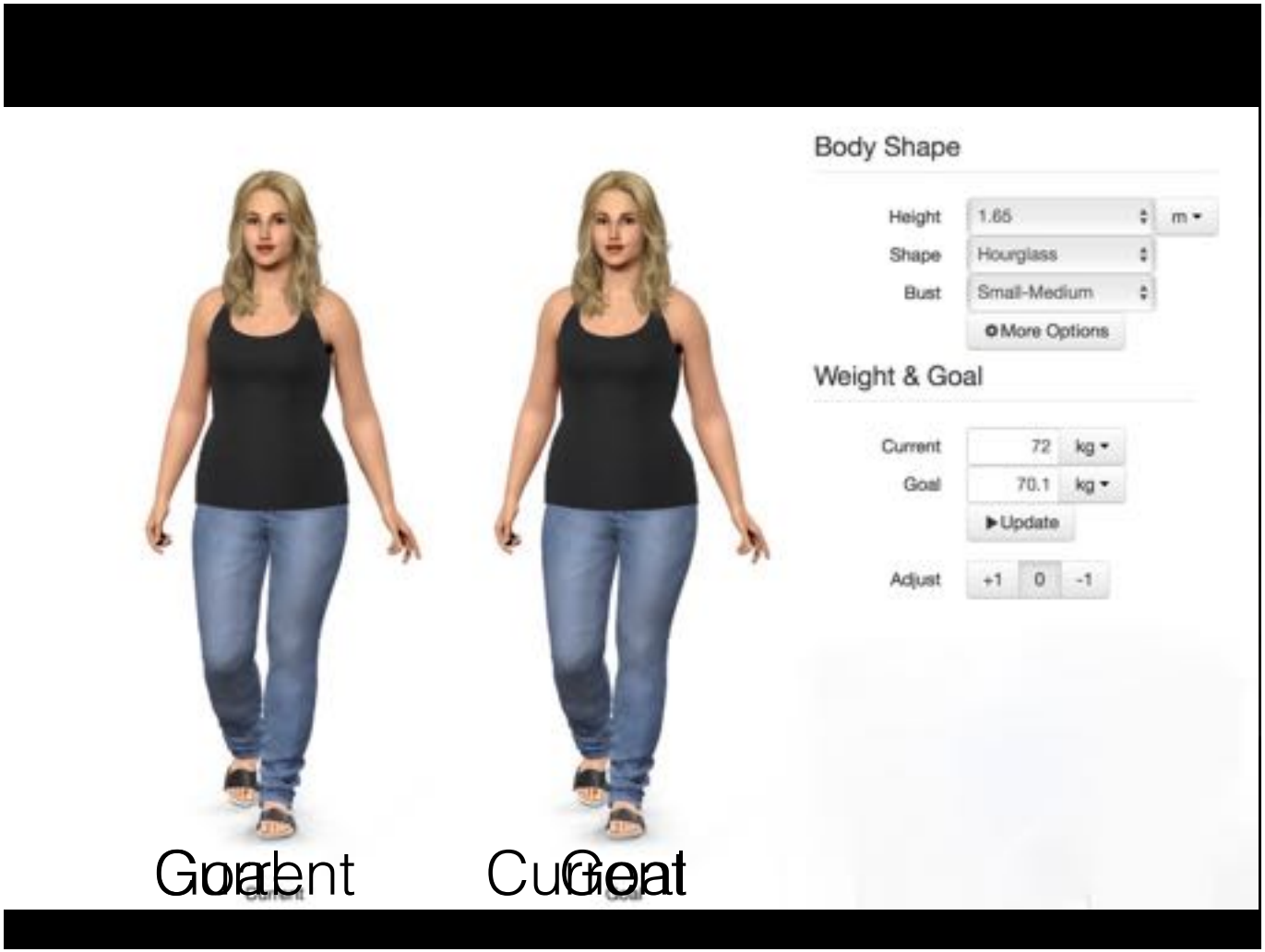
J Am Heart Assoc. 2017;6:e004007. DOI: 10.1161/JAHA.116.004007

Effect on systolic blood pressure

⬇ 2.46 mmHg

Weight

⬇1.88 kg



Those medications that have been shown to have a possible benefit, that benefit is of such a low magnitude and such a high cost that the vast majority of people would likely not take them

Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitor: Comparing Trial Data and Real-World Use

Diabetes Ther 2017;8:365–76

Only ~15% of T2DM patients have a risk similar to that seen in EMPA-REG

You won't feel better, BUT!!	**Secondary (EMPA-REG)**	**Primary ??**
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	4%/yr	2%/yr
~15% relative benefit	0.6%/yr	0.3%/yr
Genital infections	5%	5%
Over 5 years	3%	1.5%
	NNT 33	NNT 67
Cost to prevent one event Yearly Cost = $5 x 365 ~$1,800 Cost for 5 years ~$9,000	$300,000	$600,000

The Potential for the Unknown

Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor

Large claim database = cohort **NEJM June 8, 2017**

Over 18 months
~0.07% with DPP4s
~0.14% with SGLT2

IN CONCLUSION

PLACATE - T2DM is not a disease but simply a risk factor

ORIENTATE - The tests used to diagnose/monitor a person with T2DM are at best tricky to use and are very misleading

ESTIMATE - A1c is a risk factor so you need to be able to estimate risk

EDUCATE - The majority of T2DM treatments have been shown to have no benefit and cause harm

ADVOCATE - For medications that have been show to have a possible benefit, the benefit is of such a low a magnitude and a high cost that the vast majority of people would likely not take them

Three more SGLT2 inhibitors – ipragliflozin, luseogliflozin, and tofogliflozin – have regulatory approval in Japan