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Any 1 Care (A1c) about Clinical Outcomes?

Simplifying Diabetes Management

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Presenter: Dr. Michael Allan & Dr Tina Korownyk

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- Patents: N/A
- Other: CFPC – Employee (MA), University of Alberta (TK)

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

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Making sense of diabetes


NEJM Journal Watch

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CLINICAL SPOTLIGHT | GENERAL MEDICINE

PRACTICE CHANGING

January 16, 2020

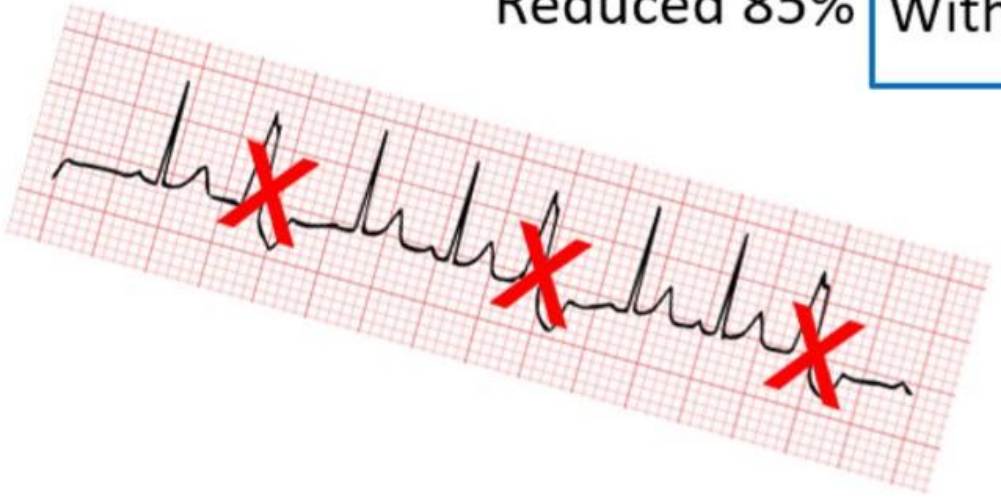
Sulfonylureas for Patients with Type 2 Diabetes: Still an Option

Reasoning: They lower glucose cheaply and probably not increasing cardiovascular disease

Stories matter, … what about evidence?

Extra Beats

Reduced 85%



RCT of 1455 Patients x 10 months

On Placebo	3% Died
On Treatment	8% Died

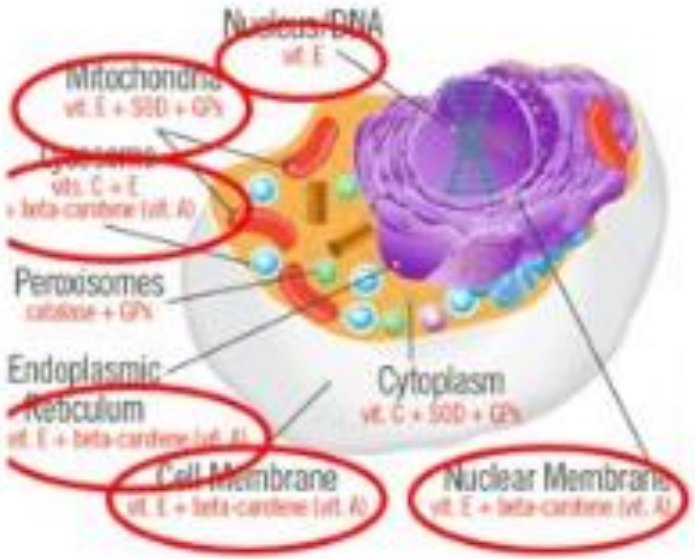
We Killed one in every 21 people going to the CCU for our help.

With the Best Intention & a Great Story

NEJM 1989; 321(6): 406-12

Antioxidant: Story

Oxidative Stress



Antioxidants

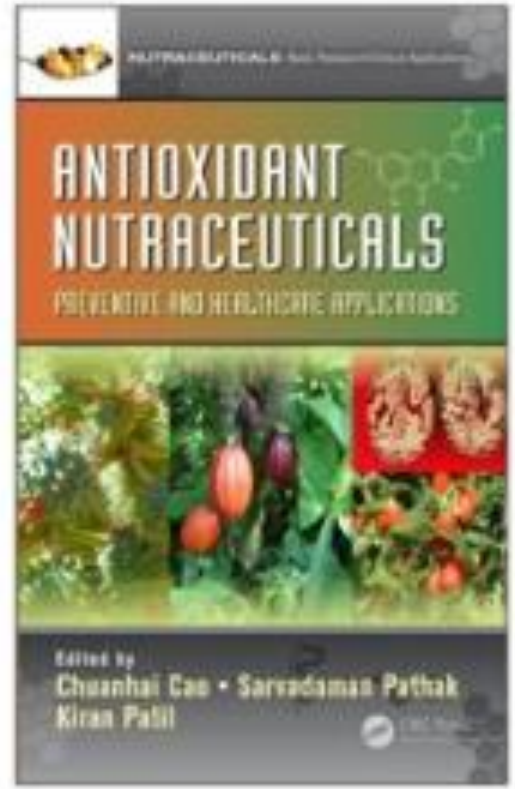
We just need more Vitamin A & E !

78 Randomized Trials
Studied 296,707

We killed 1 in every ~200 people x3.5 yrs

https://pomaapro.ca/wp-content/uploads/tools-for-practice/1478716169_2016updatedtfp10antioxidants.pdf

How much evidence does it take to slay a great theory?



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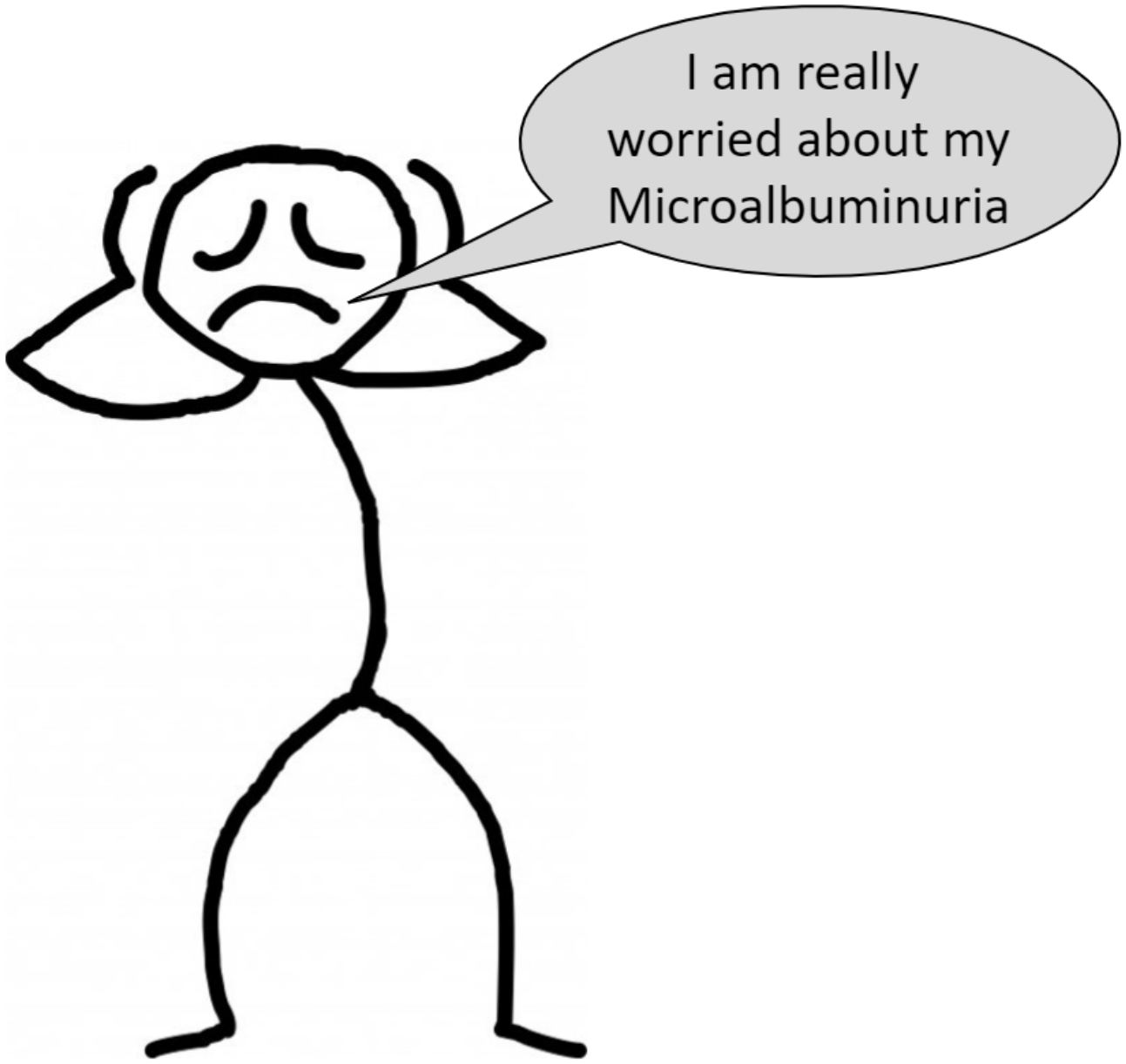
What do Patients Feel or Worry about?

- They might say they are worried about their cholesterol, sugar or maybe A1c”
- For the most part, we had to teach them to fear these.



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We have to start distinguishing,....

What we measure,...

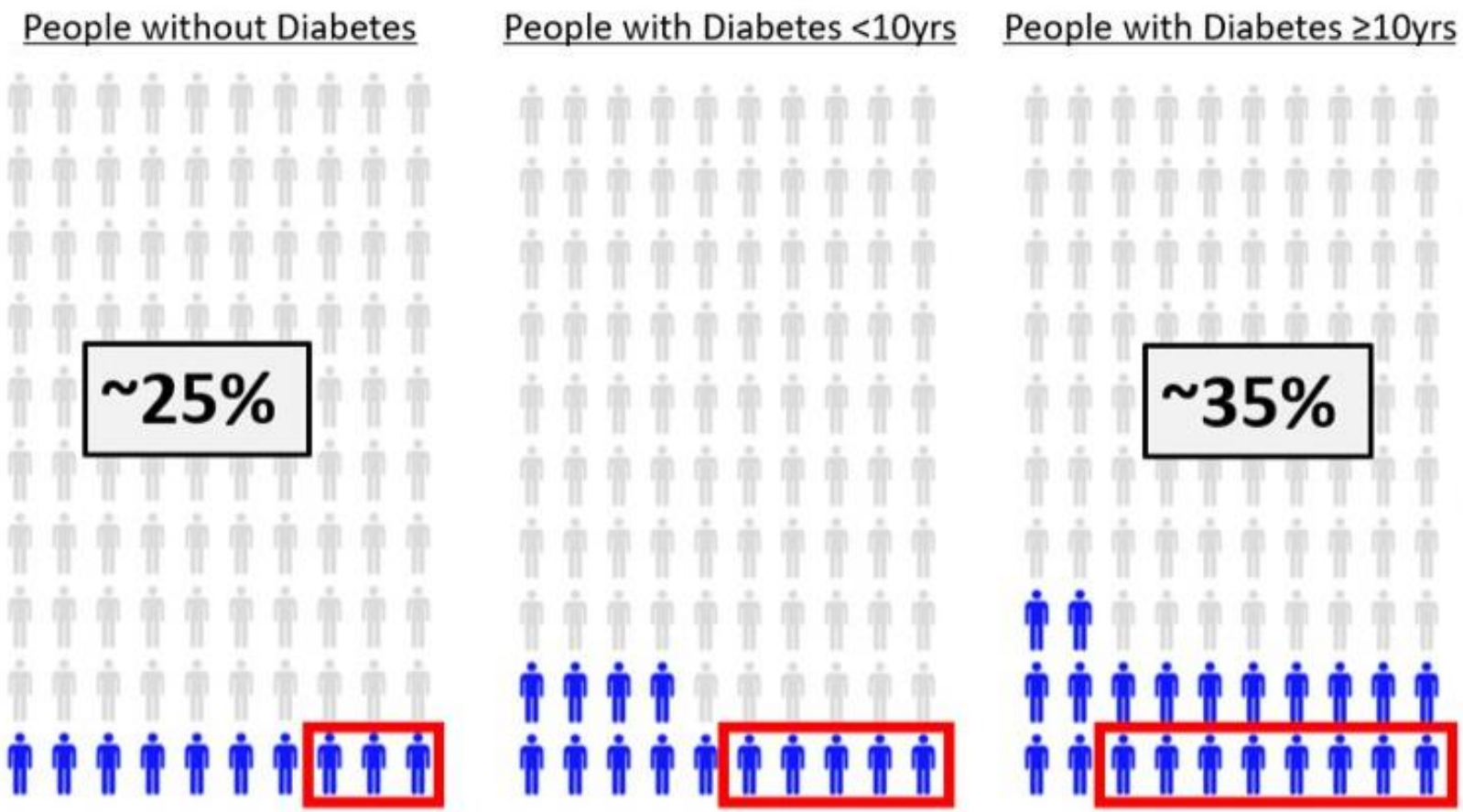
- Sugar
- Microalbuminuria
- Lipids
- Blood pressure
- Monofilament
- Diabetic Retinopathy

What Matters to Patients

- Survival
- Quality of Life
- Heart Disease & Stroke
- Sensation/Pain
- Vision
- Avoiding Renal Outcomes

What are the bad things that happen?

Average: ~75 y.o. & ~40% male, what happens over 5 years



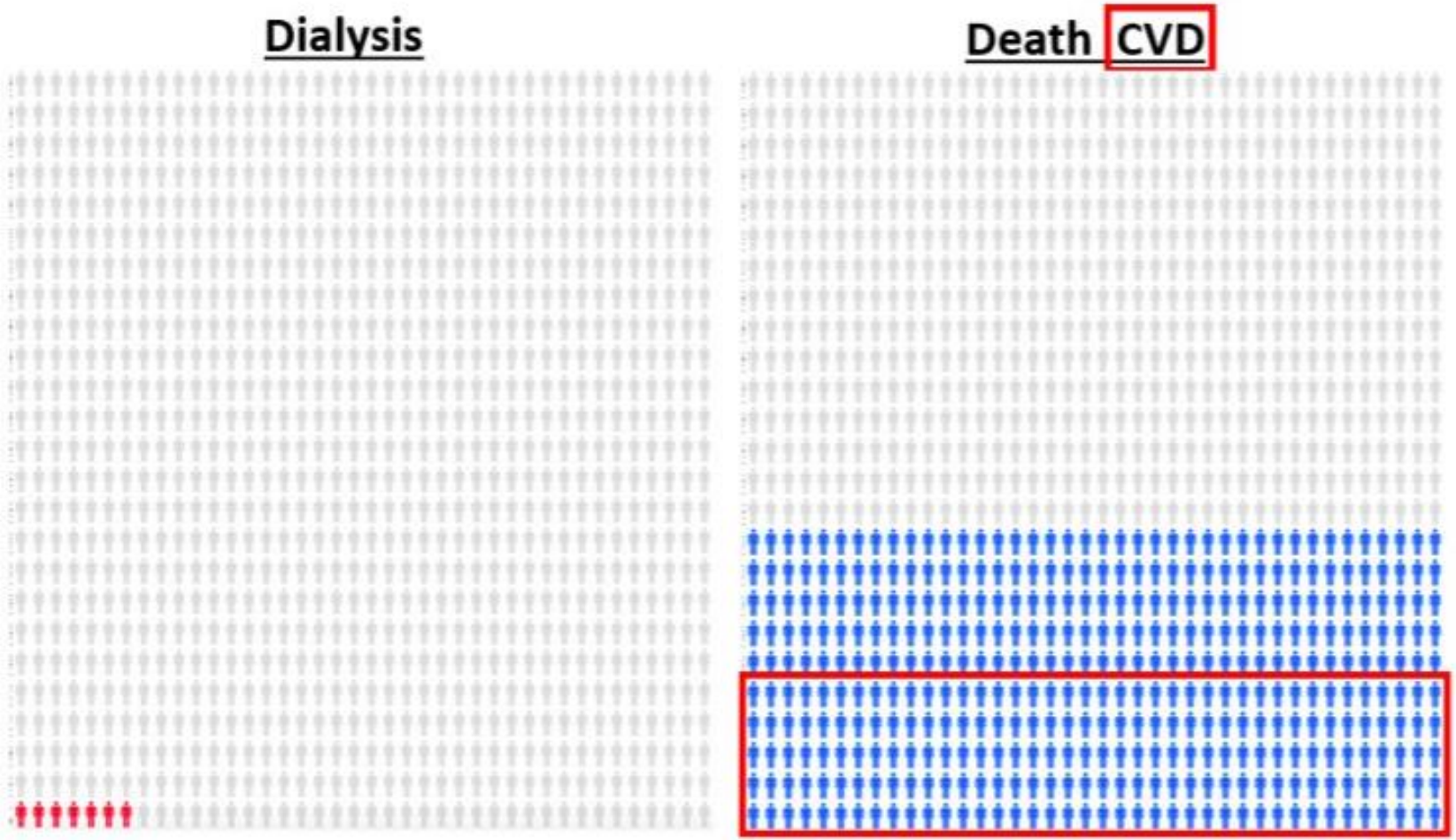
- The worst to happen is debatable
  - Death vs very low Quality of Life
- Death is bad and the final outcome

Diabetes Care, 2020.
Tang o, et al

What about the other bad things that happen?

1000 People with Diabetes x 10 yrs,

- **50% with micro or macroalbuminuria,**
- **At 7 yrs, how many need dialysis & how many die**



Diabetes Care 2003;26:2353-8

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What about the other bad things that happen? (2)

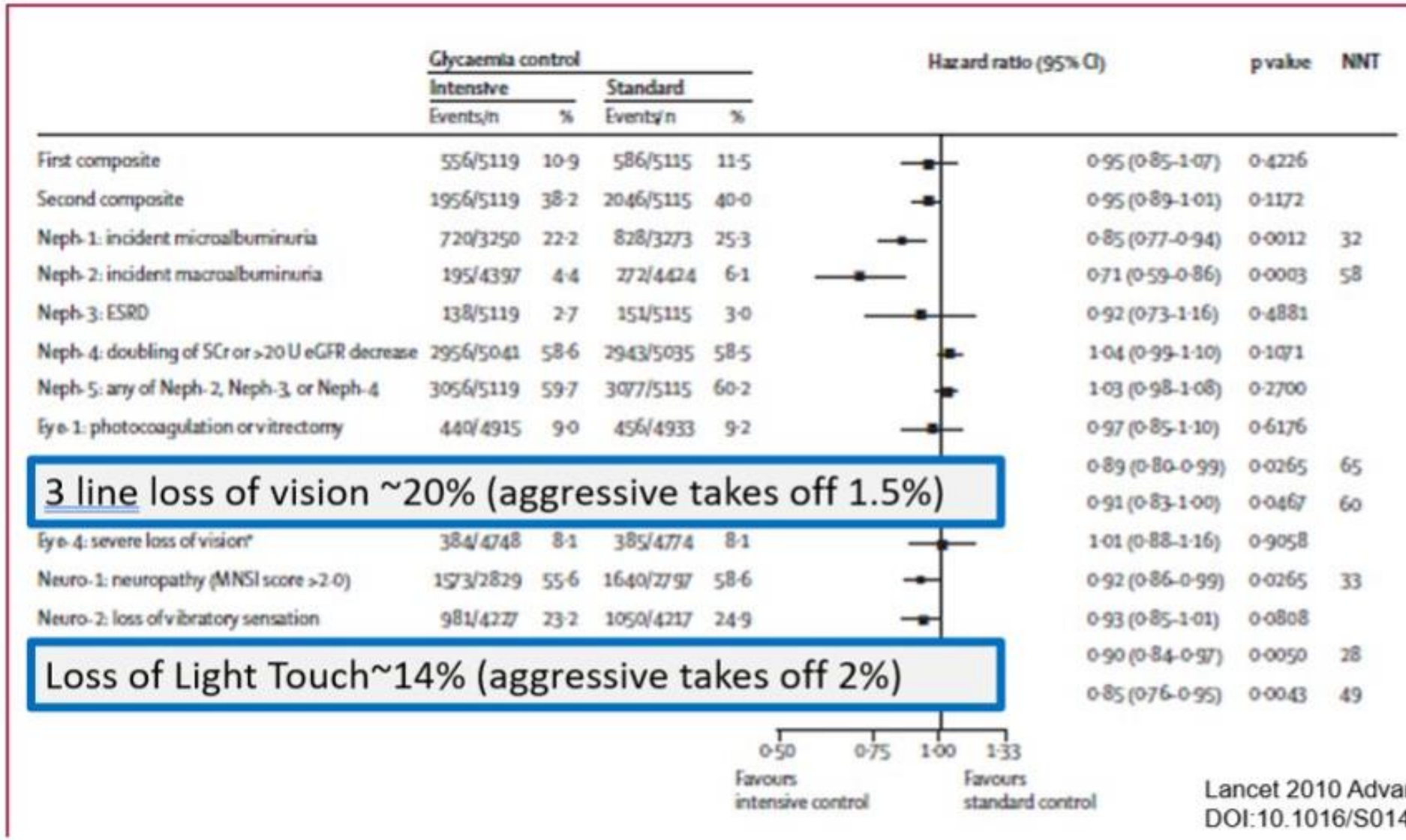
	Death	MI	Stroke	Renal failure (dialysis + Cr>250)
Early Diabetes (UKPDS 10 Year)	18%	14%	5%	0.6%
Later (66) Diabetes (Advance 10 Year)	20%	6.5%	8.7%	0.7%

What about Amputation varies more with baseline risk (& definition):

- All (≥ toes) can be ~12% x10 yrs in very high risk (with 44% hard CVD)

N Engl J Med 2019;380:2295-306.

Other clinical outcomes that are not so good.



	Glycaemia control: Intensive Events/n	Intensive %	Standard Events/n	Standard %	Hazard ratio (95% CI)	p value	NNT
First composite	556/5119	10·9	586/5115	11·5	0·95 (0·85–1·07)	0·4226	
Second composite	1956/5119	38·2	2046/5115	40·0	0·95 (0·89–1·01)	0·1172	
Neph-1: incident microalbuminuria	720/3250	22·2	828/3273	25·3	0·85 (0·77–0·94)	0·0012	32
Neph-2: incident macroalbuminuria	195/4397	4·4	272/4424	6·1	0·71 (0·59–0·86)	0·0003	58
Neph-3: ESRD	138/5119	2·7	151/5115	3·0	0·92 (0·73–1·16)	0·4881	
Neph-4: doubling of SCr or >20 U eGFR decrease	2956/5041	58·6	2943/5035	58·5	1·04 (0·99–1·10)	0·1071	
Neph-5: any of Neph-2, Neph-3, or Neph-4	3056/5119	59·7	3077/5115	60·2	1·03 (0·98–1·08)	0·2700	
Eye-1: photocoagulation or vitrectomy	440/4915	9·0	456/4933	9·2	0·97 (0·85–1·10)	0·6176	
3 line loss of vision ~20% (aggressive takes off 1.5%)					0·89 (0·80–0·99)	0·0265	65
					0·91 (0·83–1·00)	0·0467	60
Eye-4: severe loss of vision*	384/4748	8·1	385/4774	8·1	1·01 (0·88–1·16)	0·9058	
Neuro-1: neuropathy (MNSI score >2·0)	1573/2829	55·6	1640/2797	58·6	0·92 (0·86–0·99)	0·0265	33
Neuro-2: loss of vibratory sensation	981/4227	23·2	1050/4217	24·9	0·93 (0·85–1·01)	0·0808	
Loss of Light Touch~14% (aggressive takes off 2%)					0·90 (0·84–0·97)	0·0050	28
					0·85 (0·76–0·95)	0·0043	49

0·50 0·75 1·00 1·33

Favours intensive control

Favours standard control

Lancet 2010 Advance 10 year data:
DOI:10.1016/S0140-6736(10)61028-8

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Bottom-Line: What are the Patient Oriented Outcomes of Diabetes and Can we Influence them?

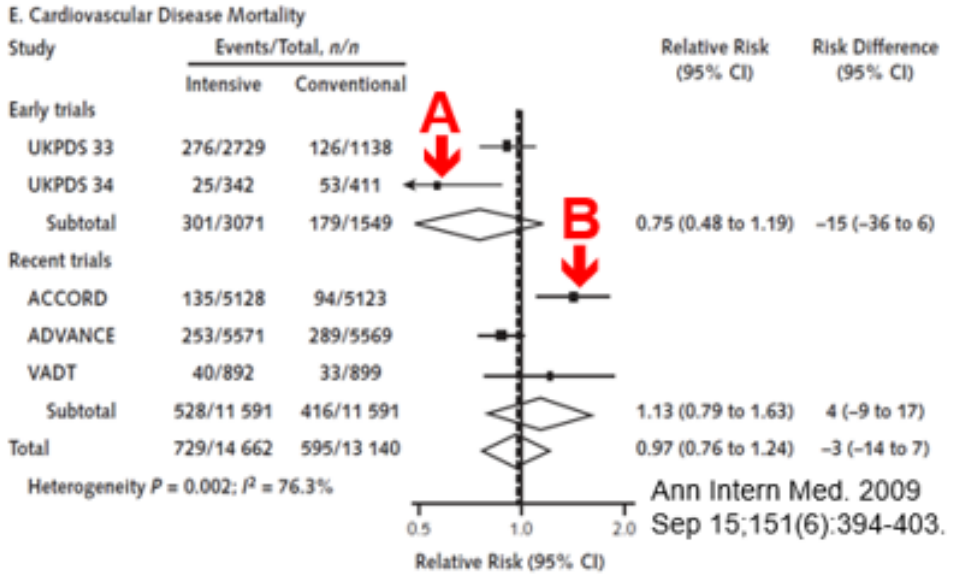
Outcomes

- Macrovascular Complications
  - Heart Disease
  - Stroke
- Microvascular
  - Vision
  - Sensory
  - Renal disease

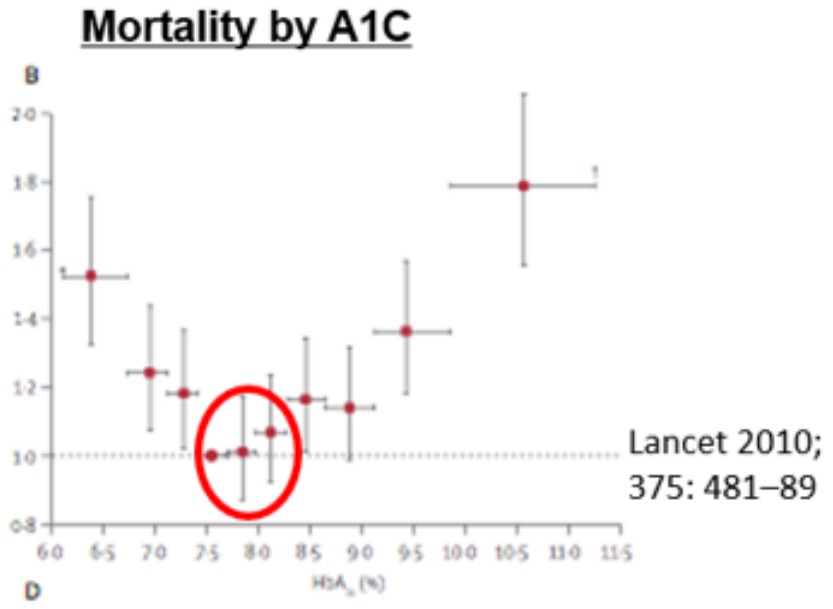
Can we influence them

- Yes:
  - Requires comprehensive approach.
  - Has to balance Quality of Life
  - More to follow

Can we do it with aggressive A1c management?



Ann Intern Med. 2009 Sep 15;151(6):394-403.



Lancet 2010; 375: 481–89

Long-term Care Admission 80 yo, 67% female Requiring assistance (from insulin to no meds) (J Am Geriatr Soc 60:1215–21)	A1C Range	Absolute Risk of Long-term care
	<7%	62%
	7.0-7.9%	58%
	8.0-8.9%	51%
	≥9.0%	56%

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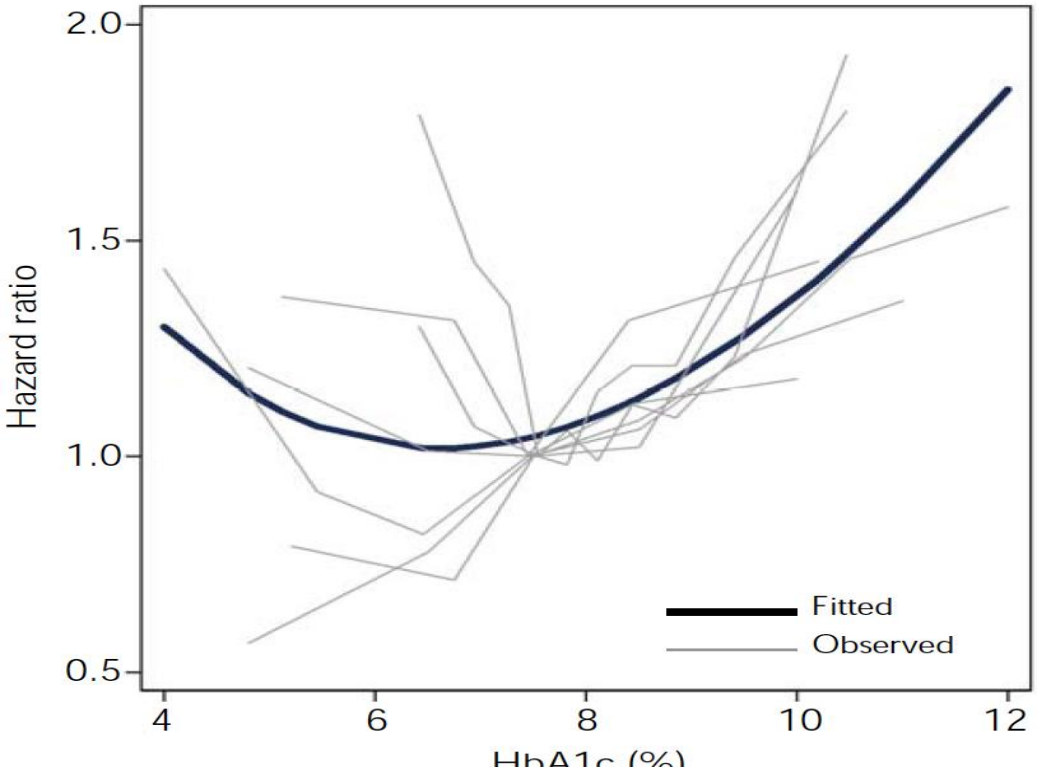
More J-Shaped Curves with A1c

- 6 studies with 7 cohorts examining A1c & survival
  - 147,424 participants followed for 2.4 – 10 years.

- With 7.5% baseline, for every 1% A1c
  - Lower, RR Increases 10%
  - Higher, RR Increases 4%

- **Bottom-Line**: No real change, ~7-7.5 likely best for longevity.



Rev Diabet Stud. 2014 Summer;11(2):138-52.

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Quality of Life for outcomes in Diabetes?

- Quality of Life in Diabetes

Event	QOL Utility
Mild Stroke	0.70
Angina	0.64
Diabetic Neuropathy	0.66

Diabetes Care 2007;30:2478-83

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Quality of Life for outcomes in Diabetes? (2)

- Quality of Life in Diabetes

Event	QOL Utility
Mild Stroke	0.70
Angina	0.64
Diabetic Neuropathy	0.66
Comprehensive Diabetes Care	0.64

ACCORD, looking specifically at intense sugar control found mixed results on QoL for diferent outcomes but overall, no effect. (Diabetes Care 2011;34:807-12.

Diabetes Care 2007;30:2478-83

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Sometimes it can feel discouraging

Managing Diabetes

STENO: Small RCT (160 pts x13 years)

- All DM + microalbuminuria (Danish, white)

	Treatment	Control	NNT
Mortality	30%	50%	5
Mean CVD events	2	3.3	
≥1 CVD events	31%	60%	4
Treating Retinopathy	18%	34%	7
Dialysis	1%	7.5%	16

- Tried again: 3057 patients, early DM (age 60) – better by ≤1% any outcome
  - Less risk and most control group also "aggressively" managed

N Engl J Med 2008;358:580-91. Lancet 2011; 378(9786): 156-167.

Adjunctive Therapies

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Can Lifestyle work in Diabetes?

- RCT 98 Danish DM x5yrs, age 55, 52% male, x1 yr
- Outcome: Intense lifestyle vs standard, similar A1c
  - Reduced DM meds: 74% vs 26%, NNT 3, (Stop NNT 3)
  - Weight: 10% reduced 31% vs 3%, NNT 4 (5% NNT 3)
  - Harms : Mild Hypoglycemia (13% vs 0%),
    - MSK injury (22% vs 0%)
- **Bottom-Line**: Works, 56% vs 15% can actual stop meds plus weight loss. MSK injuries more common.

JAMA. 2017:318(7):637-646.

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Can Diabetes be Cured,… Maybe

- RCT of 298 primary care patients: DM <6yrs, no insulin, 7.6%.
  - Diet ~840 kcal/day for 3 months (+ 2 optional) then slow re-intro.
- Results :
  - 1 yr: lost ≥15kg=0 vs 24% (NNT 5), DM remission 4% vs 46% (NNT 3)
    - If Weight loss >15, then 86%
  - Similar but not quite as good the following year.
  - Qol: 6-10 (out of 100) better.
- **Bottom-Line**: Surprise, weight loss can resolve Diabetes.

Counterweight Plus

Lancet Diabetes Endocrinol. 2019;7(5):344-55. Lancet 2018; 391: 541–51

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What if patients help themselves?

The Best NNTs from the Best Treatments

Smoking: NNT for death in high risk =11

Activity: NNT for any CVD in high risk = 6

Diet (Mediterranean): NNT for CVD in high risk = 12

JAMA. 2017;318(7):637-646. 1) Chest 2007; 131: 446–52 Ann Intern Med. 2005;142:233-9. 2) Circulation 2004;109:1371-8. Cochrane 2011;(7): CD001800. J Am Coll Cardiol 2012;60:1521–8. 3) Lancet 1994; 343: 1454-59. Lancet 2002;360(9344):1455-61. NEJM 2013; 368:1279-1290.

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Is there Better Living through Pharmaceuticals?

Statins (until they're in the water),…

- 18 RCTs (56,934 patients) – age 57 and 60% male.
  - CVD: RR 0.75 (0.70-0.81). 9% vs 12%, NNT 35
  - Mortality: 4.4% vs 5.2%, NNT 132
  - Others find similar

- **Bottom-Line**: Statins reduce CVD from around 12% to 9%, and slight reduces mortality, over around 4 years.

Lancet 2008; 371: 117–25. Cochrane 2013; 1: CD004816.

Primary Prevention: ASA in DM

- 3 RCTs focusing on ASA in Diabetics.
  - 2,500 DM pts, 4.4 yrs: No diff in CVD[1]
  - 1270 DM pts, 6.7 yrs: No Difference in CVD[2]
  - 15480 DM pts, 7.4 yrs: CVD: 8.5% v 9.6% but bleeds up 4.1% v 3.2%

- **Bottom-Line:** Little benefit, if any, seems balanced by the increase in bleeding.

1. JAMA. 2008;300(18):2134-2141. 2. BMJ. 2008 Oct 16;337:a1840. 3. ASCEND study NEJM (epub);

Hypertension

- Regardless of target, Hypertension is the most important risk factor in DM
  - No renal disease: Thiazide, ACE/ARB, Ca+ blocker

Relative risk reductions with different DM interventions[2]

	BP	Lipid	Sugar	ASA
CVD	~ 50%	~25%	~ 15%	Unclear?
Mortality	16%	8%	variable	ns

1) Diabetes Care 2010; 33(1): S11-61 2) Ann Intern Med. 2008;148:846-854. Lancet 2009;373:1765–72. Lancet 2008; 371: 117–25. Ann Intern Med. 2003;138:587-592. Diabetes research and clinical practice 2016;120: 31-39. 3) JAMA Intern Med. 2017;177:920-9.

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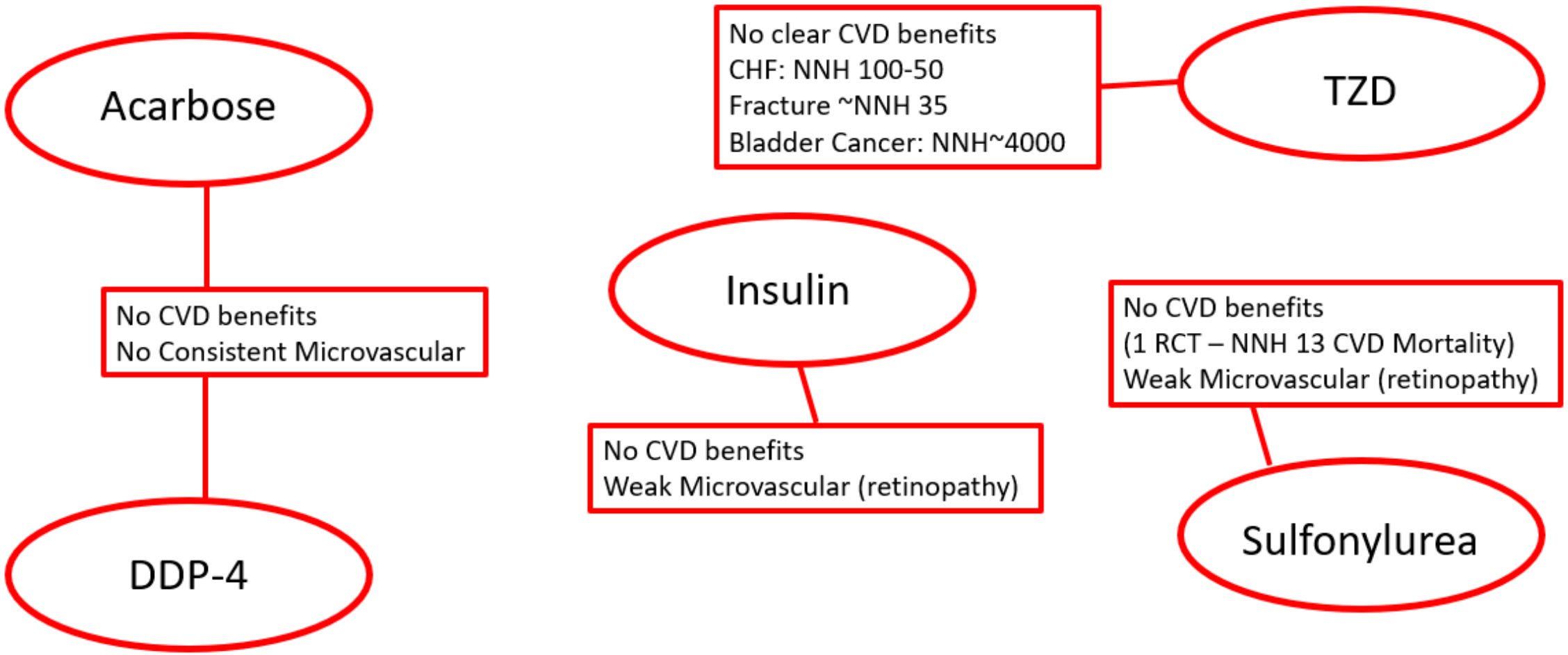
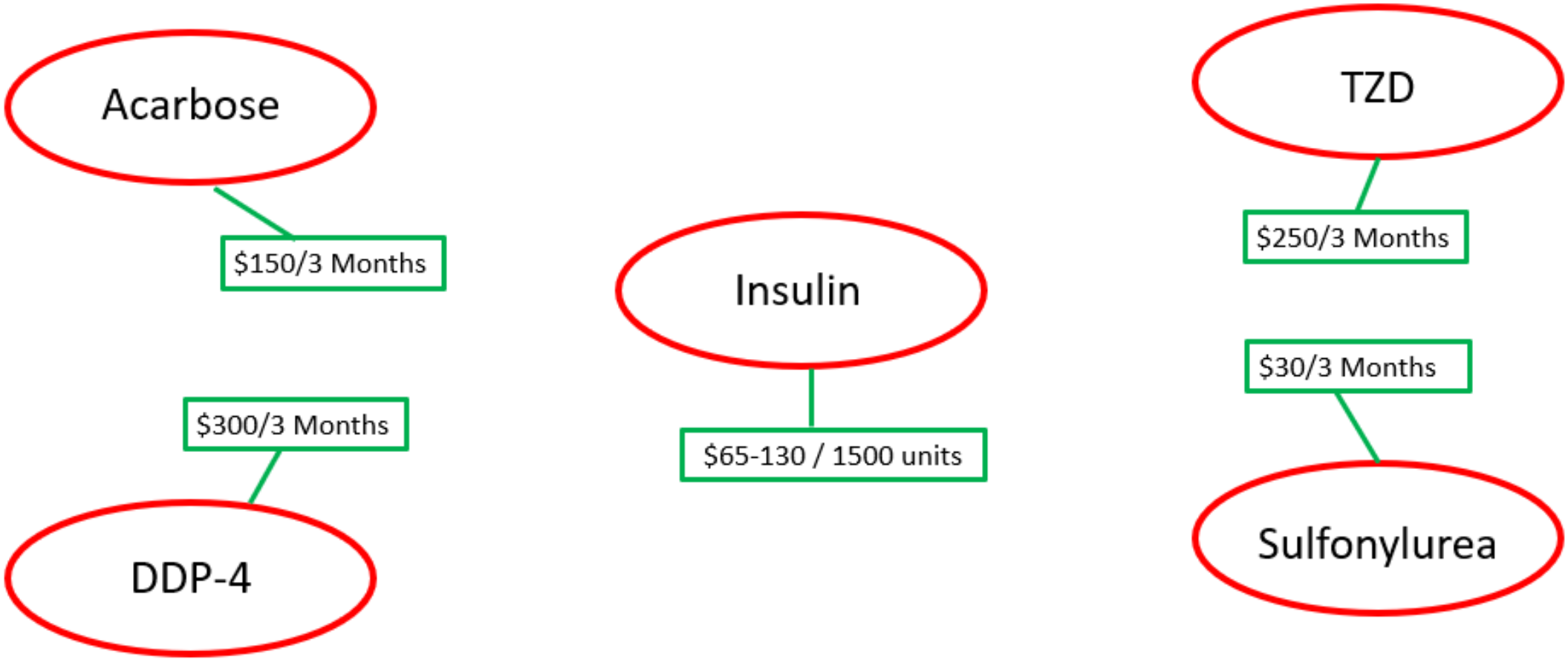
Glucose Drugs

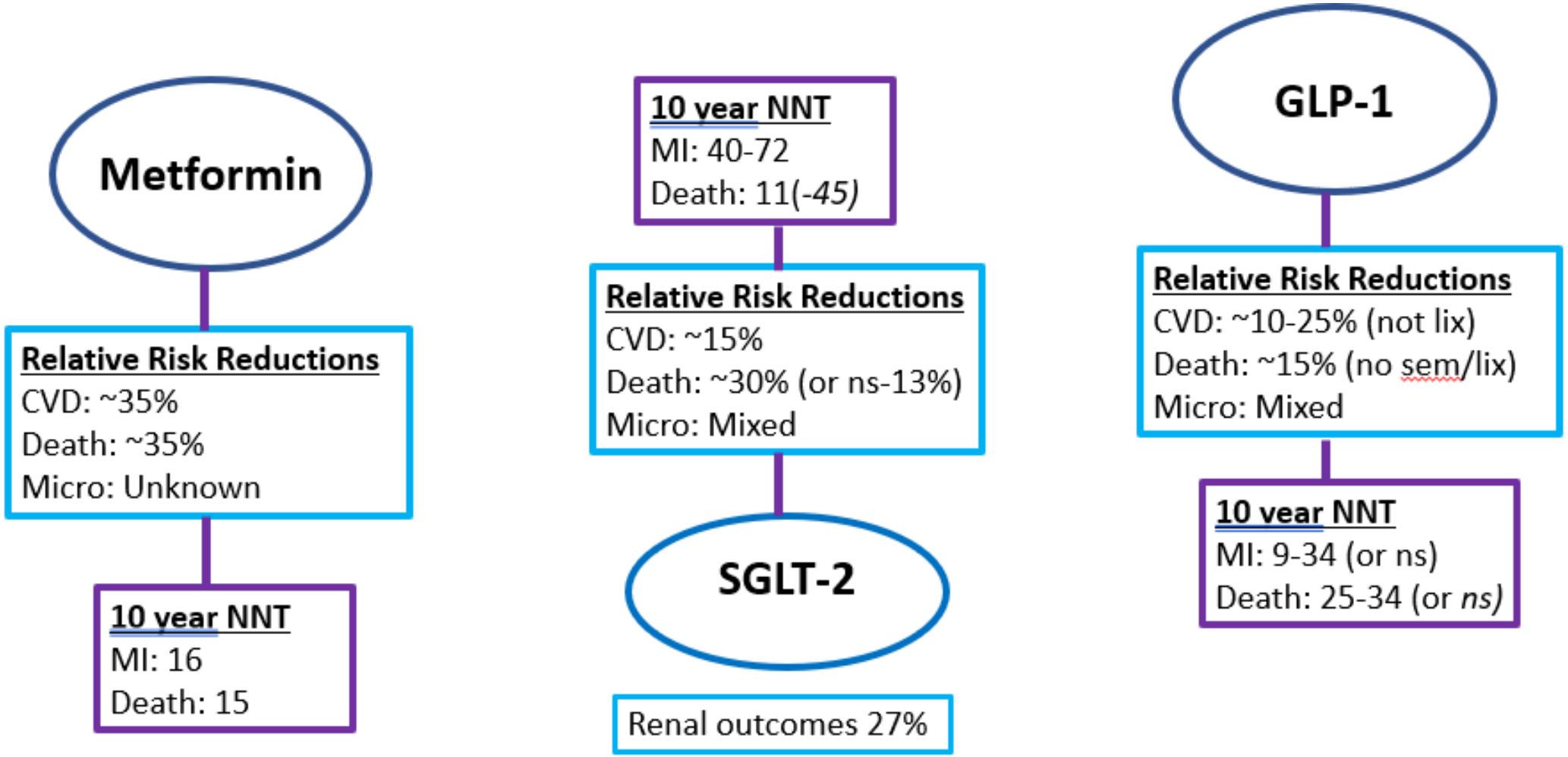
Drugs that change glucose but NOT hard outcomes.



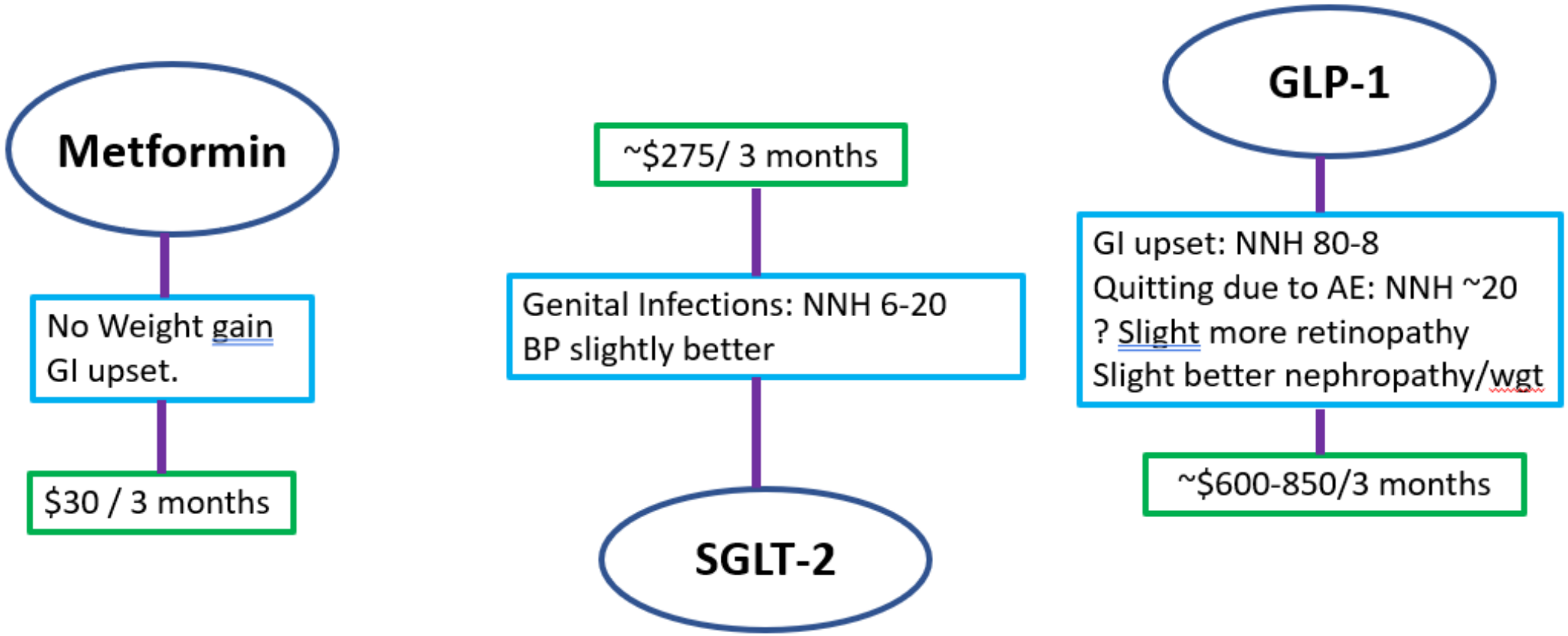
Drugs that change glucose but NOT hard outcomes



Glucose drugs that work: data



Glucose drugs that work: practical



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So, how do we pick,..

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Summary of Glucose Medications

Note: Many Variables here. Example - microvascular hard to prove if looking at Patient Oriented Outcomes.

	CVD	**Death**	**Micro-vascular***	**Positive/negative**	**Drug with Best RCT result**
Metformin	Reduced*	Reduced*	Unclear	+ nil weight	Metformin
Sulfonylurea	No	No	Reduced*	- Possible CVD/death	None
Acarbose	No	No	No	None	None
Insulin	No	No	Reduced*	- SQ, wgt gain	None
TZD	No	No	Unclear	- Fracture/bladder Ca	None
DPP-4	No	No	No*	None	None
SGLT2	Reduced	Reduced	Mixed[1]	+ oral, - genital infections	Empagliflozin
GLP-1	Reduced	Reduced	Mixed[2]	+ Weight loss, - SQ	Liraglutide

Footnotes: *Probably; 1) Worse amputation in one; 2) Worse retinopathy

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Summary of Glucose Medications, continued

Note: Many Variables here. Example - microvascular hard to prove if looking at Patient Oriented Outcomes.

	CVD	Death	Micro-vascular*	Positive/negative	Drug with Best RCT result
Metformin	**Reduced***	**Reduced***	**Unclear**	**+ nil weight**	**Metformin**
Sulfonylurea	No	No	Reduced*	- Possible CVD/death	None
Acarbose	No	No	No	None	None
Insulin	No	No	Reduced*	- SQ, wgt gain	None
TZD	No	No	Unclear	- Fracture/bladder Ca	None
DPP-4	No	No	No*	None	None
SGLT2	**Reduced**	**Reduced**	**Mixed[1]**	**+ oral, - genital infections**	**Empagliflozin**
GLP-1	**Reduced**	**Reduced**	**Mixed[2]**	**+ Weight loss, - SQ**	**Liraglutide**

Footnotes: *Probably; 1) Worse amputation in one; 2) Worse retinopathy

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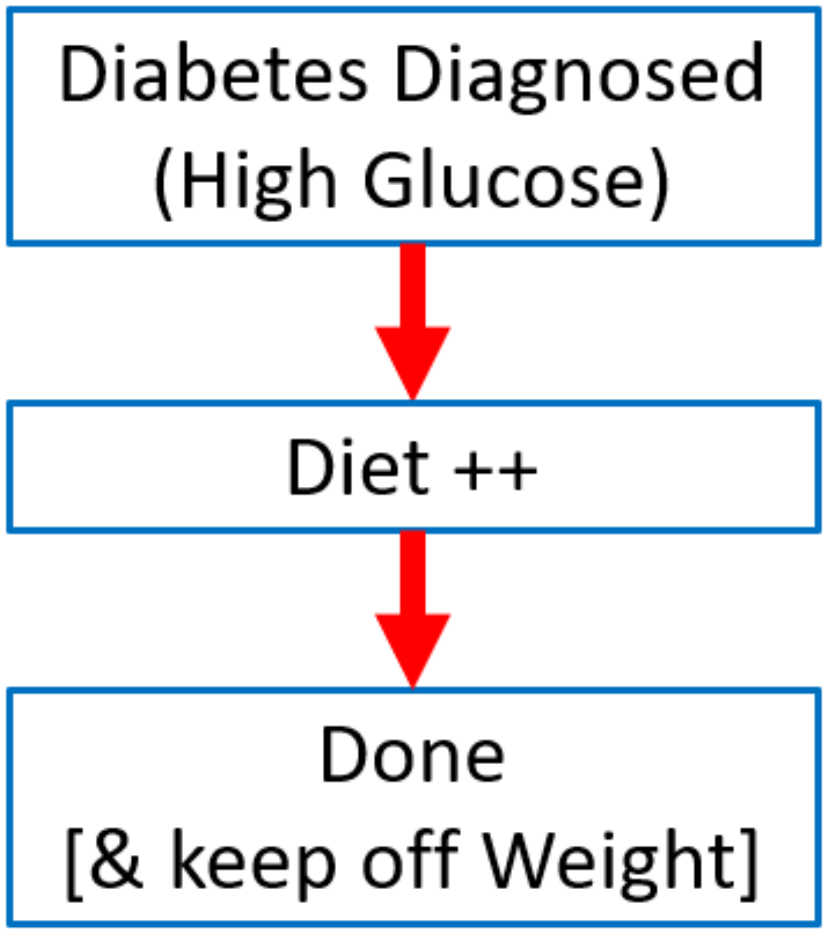
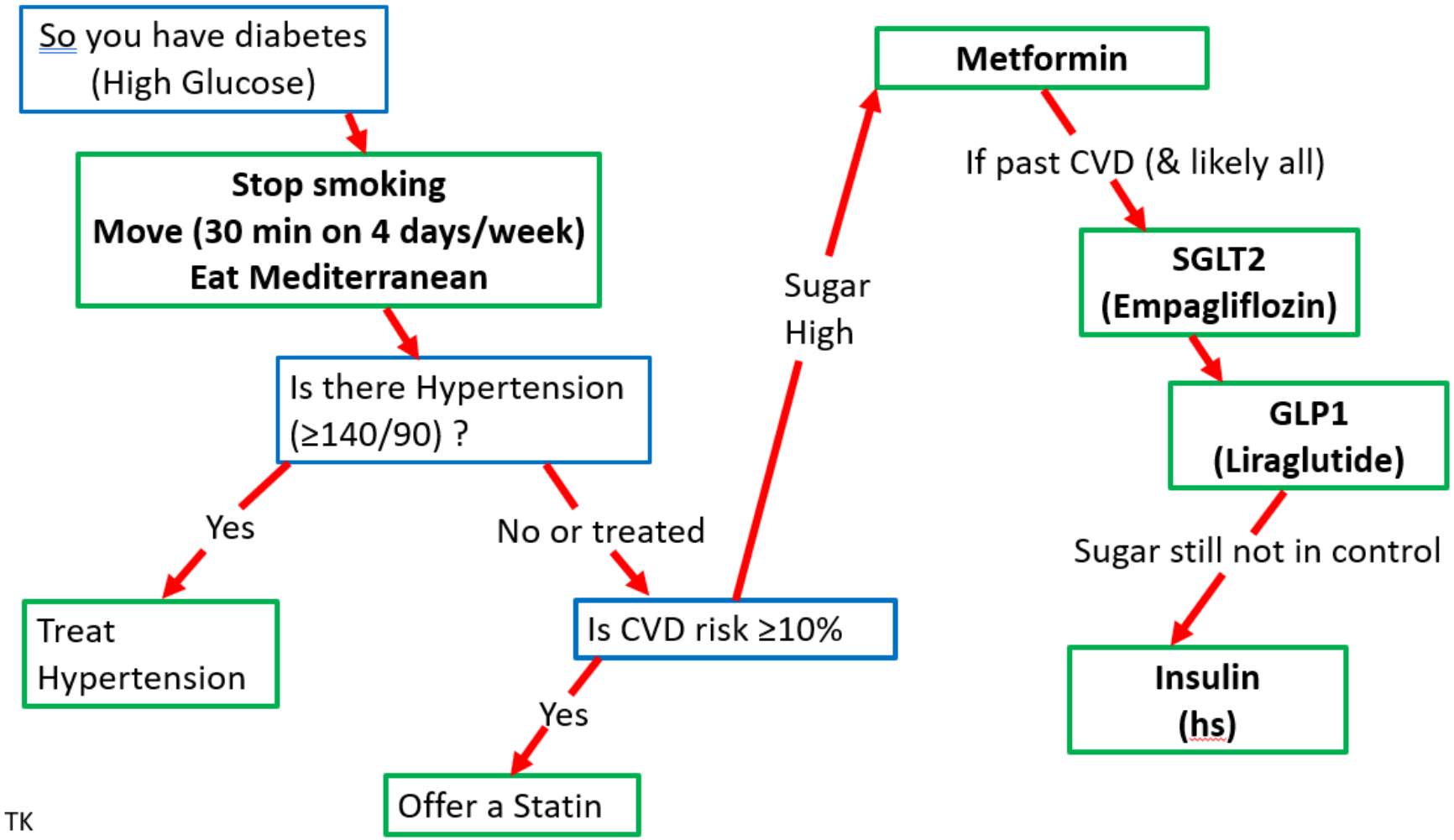
Time for PEER suggested Diabetes Algorithm

Best Diabetes Algorithm



Diabetes Algorithm, continued



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Last Thoughts