THE TYPE 2 DIABETES STORY

An evidence-based discussion about TYPE 2 DIABETES I would like to have with Tom Hanks

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A handout for all the evidence used in this talk can be found at

therapeuticseducation.org/handouts

Five Takeaways from the Diabetes Drugs Investigation

Diabetes drugs improve lab tests, but not much more, particularly in pre-diabetics.

Physicians and drug makers have reported diabetes drugs as the "primary suspect" in thousands of deaths and hospitalizations.

Diabetes drug makers paid physicians on influential panels millions of dollars.

Risk of a risk now equals disease.

The clinical threshold for diagnosing diabetes has crept lower and lower over the past decade

http://www.medpagetoday.com/PublicHealthPolicy/FDAGeneral/49196

Adding "value" to clinical practice guidelines

James P. McCormack PharmD Peter Loewen PharmD

Can Fam Physician 2007;53:1326-27

ABSTRACT

OBJECTIVE To determine the degree to which current Canadian clinical practice guidelines (CPGs) for common chronic conditions (ie, diabetes, dyslipidemias, hypertension, and osteoporosis) discuss the importance of patients' values and preferences in therapeutic decision making, and provide quantitative information that would allow for comprehensive shared informed decision making.

DESIGN [illegible]

MAIN OUTCOME MEASURES Th[illegible] the importance of incorporating patients' values and preferences into therapeutic decision making; the number and type (relative or absolute) of quantitative descriptions of benefit or harm; the number of interventions for which a means of quantitatively determining the probability that an individual patient will experience an end point without and with implementation of the therapeutic intervention; and the number of descriptions of specific or comparative costs of treatment.

RESULTS Three of 5 CPGs mentioned that [illegible] values or preferences should influence treatment decisions. None of the CPGs recommended that benefits and harms of therapies be discussed with patients. Of the 63 [illegible] mentions of therapeutic effects of interventions, 81% were presented using relative terms and 19% met our criteria for applicability to decision making for individual patients. Two of the 5 CPGs did not enumerate any harms. Three of the 5 CPGs made no mention of cost.

CONCLUSION Five prominent Canadian CPGs paid little attention to the issue of patients' values and preferences in therapeutic decision making, even though these issues are fundamental tenets of evidence-based practice. These 5 CPGs provided limited quantitative information on benefits and harms and therefore could not be used by clinicians to truly involve patients in informed decision making.

5 Canadian Guidelines for blood pressure, cholesterol, glucose, and bone density

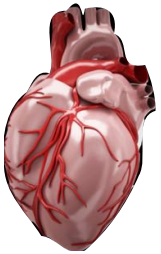
197 PAGES - 90,000 Words

99 (0.1%) words - relevant to patients' values and preferences

Does something really work

(my belief system)

RCT



RCT + RCT + RCT + RCT = Meta-Analysis

TYPE 2 DIABETES GUIDELINES - 2013
CATEGORIES FOR THE RECOMMENDATIONS

Highest level EVIDENCE Lowest Level

	A RCT OR COHORT	B RCT or COHORT not meeting A criteria	C Non-RCT or COHORT?	D OTHER/ CONSENSUS
Glucose Targets	4	2		3
Glucose Monitoring		2	2	6
Medications	3	1		9
	A RCT	B COHORT	C Poor Studies	E OPINION
Glucose Targets		2	1	
Glucose Monitoring		1	1	5
Medications	2	1		2
TOTAL	9	9	4	25

20%? RCT

RCT's USED

UKPDS 33, 34, follow up		ACCORD RETINO	ADVANCE	JAPAN INSULIN		INSULIN MA
6	4?	1	1	1	1?	4

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

Reappraisal of Metformin Efficacy in the Treatment of Type 2 Diabetes: A Meta-Analysis of Randomised Controlled Trials

13 studies - 9,500 metformin/3,500 conventional or placebo - 5 years

	RR	CI
Mortality	0.99	0.75-1.31
CVD mortality	1.05	0.67-1.64
MIs	0.90	0.74-1.09
Strokes	0.76	0.51-1.14
Heart failure	1.03	0.67-1.59
PVD	0.90	0.46-1.78
Amputation	1.04	0.44-2.44
Microvascular	0.83	0.59-1.17

PLoS Medicine 2012;9:e1001204

TREATMENT TARGETS

2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations

TARGETS OF THERAPY

Risk level	Primary target: LDL-C	Class, level
High	<2 mmol/L	Class I, level A
CAD, PVD, atherosclerosis	or	
Most patients with diabetes	≥50% ↓ LDL-C	
FRS ≥20%	apoB <0.80 g/L	
RRS ≥20%		
Moderate	<2 mmol/L*	Class IIa, level A
FRS 10% to 19%	or	
LDL-C >3.5 mmol/L	≥50% ↓ LDL-C	
Other [illegible]	[illegible]	
hs-CRP >2 mg/L in men >50 years and women >60 years of age		
Family history and hs-CRP modulate risk		
Low	≥50% ↓ LDL-C	Class IIa, level A
FRS <10%		

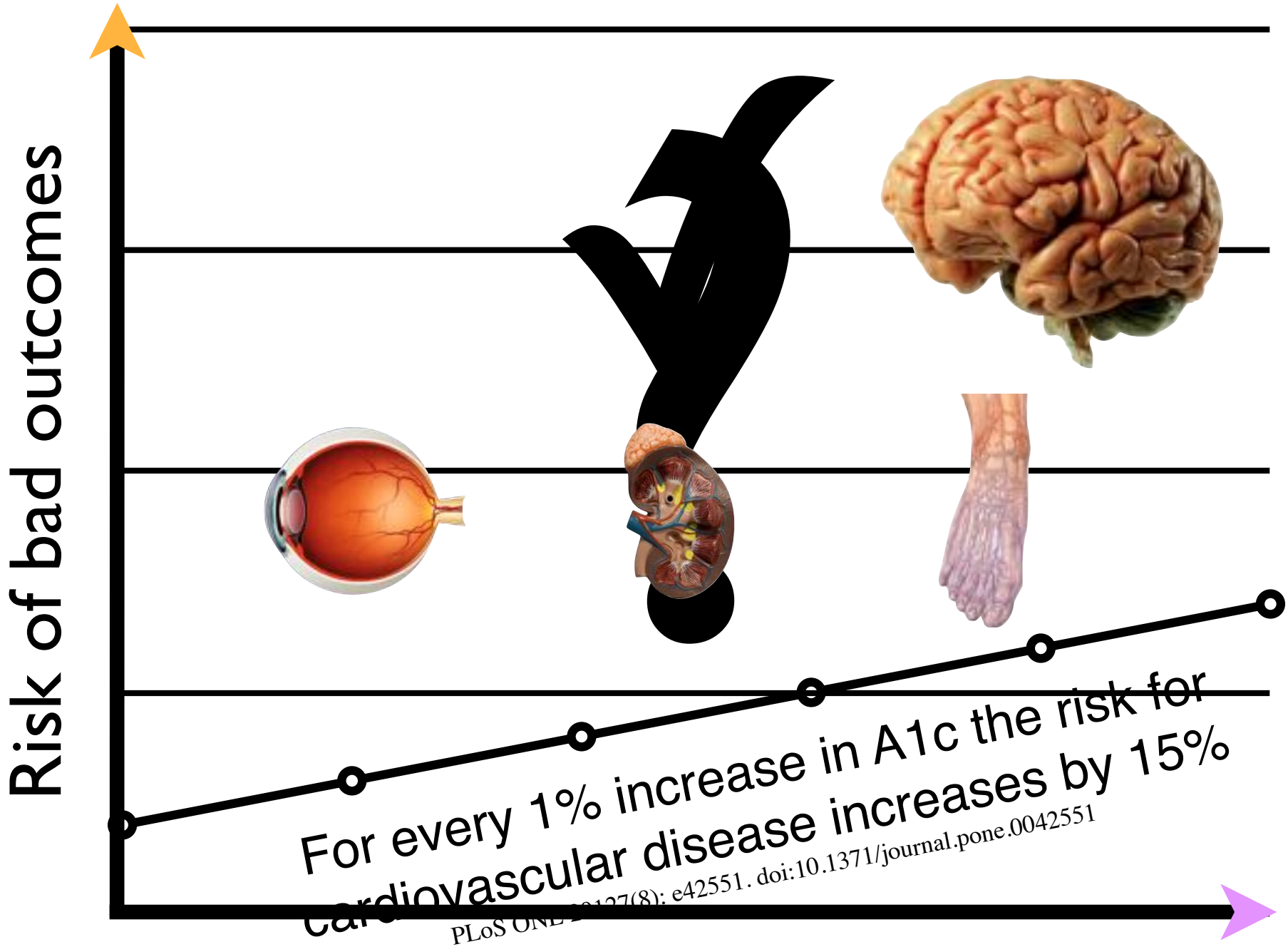
"Recommended target" <2 mmo/L/80mg/dL

Level A = recommendation based on evidence from multiple randomized trials or meta-analyses

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

"The Expert Panel was UNABLE TO FIND RCT EVIDENCE to support titrating cholesterol-lowering drug therapy to achieve target LDL–C or non-HDL-C levels, as recommended by ATP III"

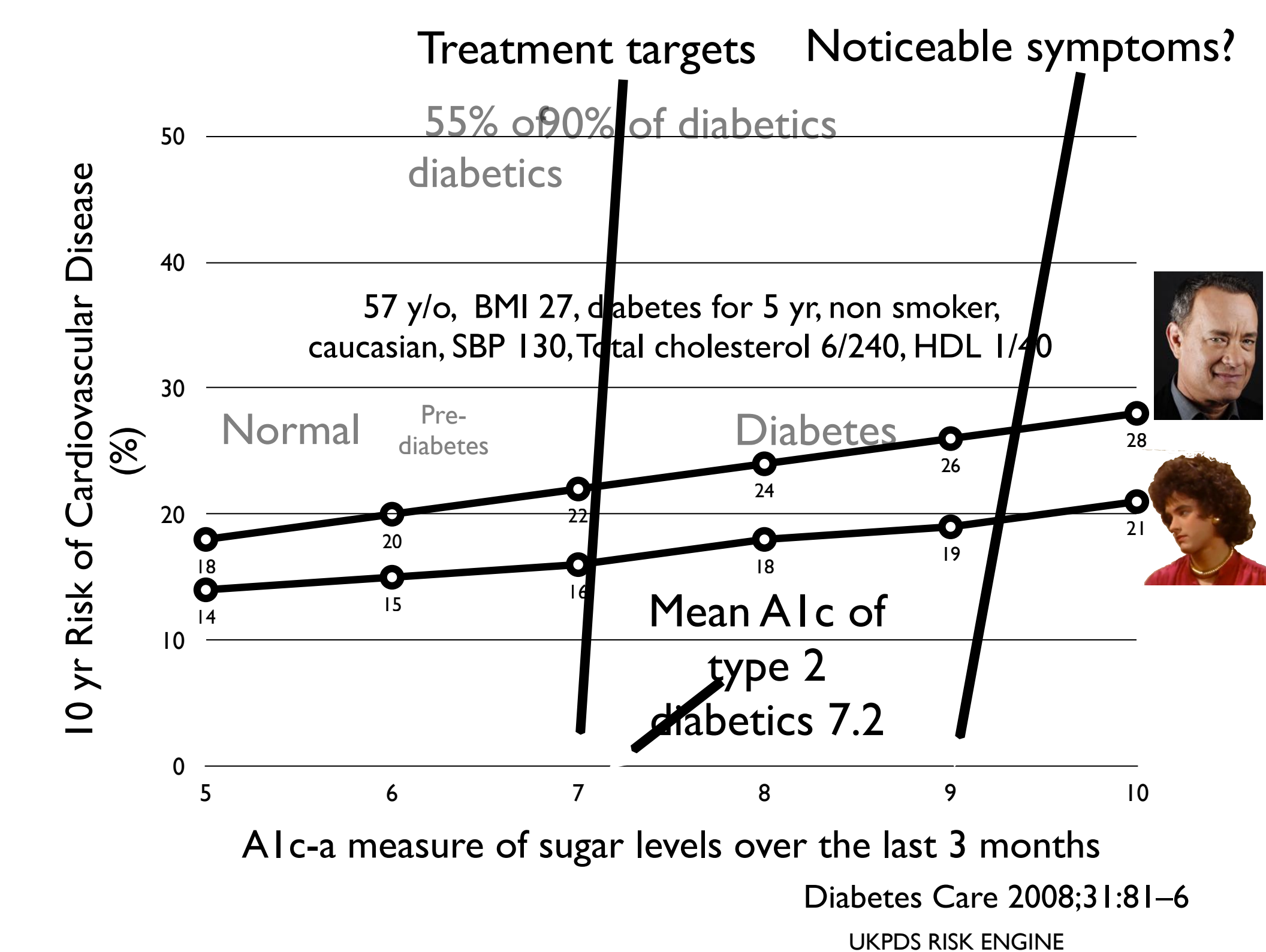
Glucose and Outcomes



An A1c of 6.5%

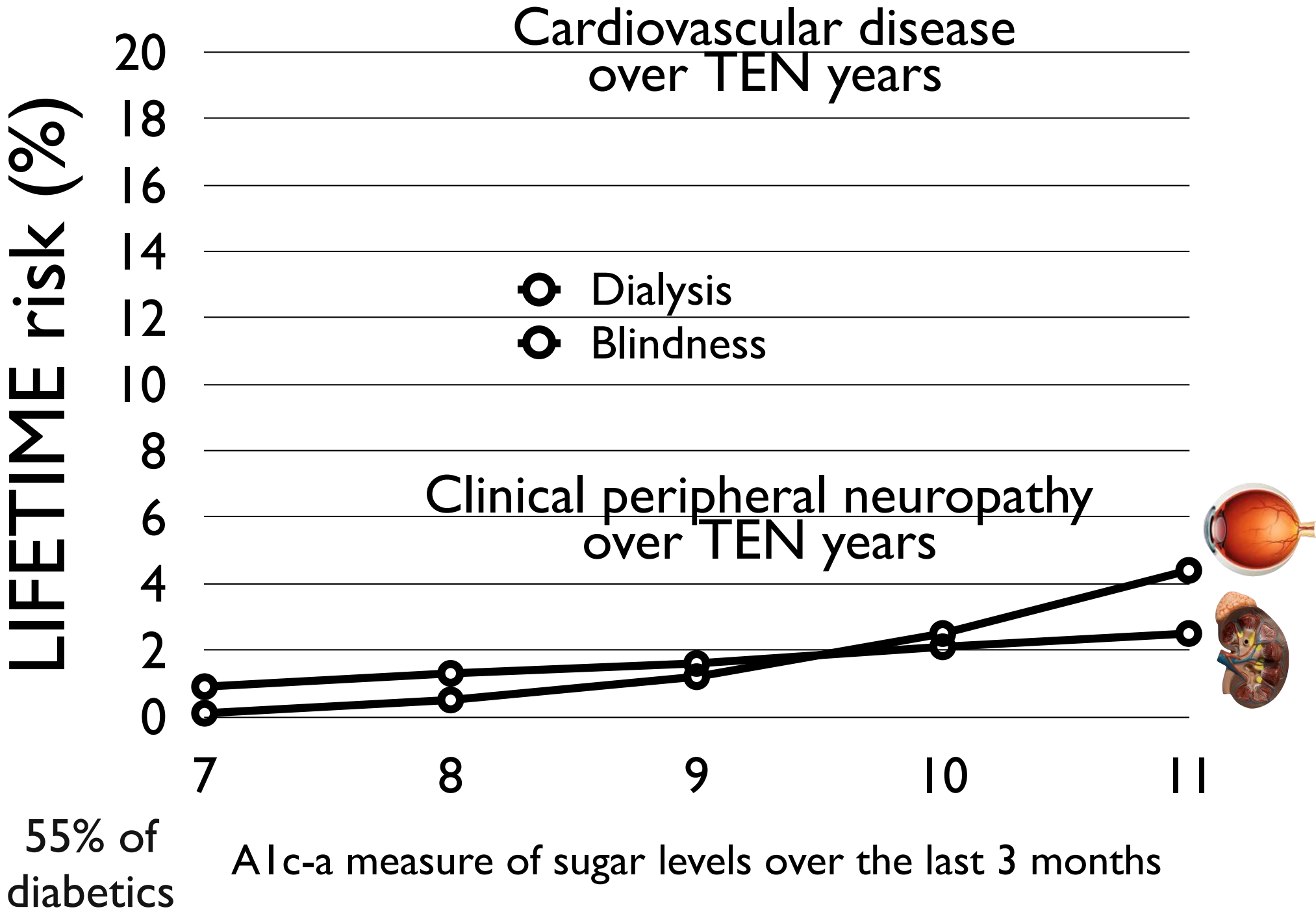
"The diagnostic A1c cut point of 6.5% is associated with an inflection point for retinopathy prevalence, as are the diagnostic thresholds for fasting plasma glucose and 2-h plasma glucose"

Diabetes Care 1997;20:1183-97



Diabetes Care 2008;31:81–6

UKPDS RISK ENGINE



Ann Intern Med 1997:127:788-95

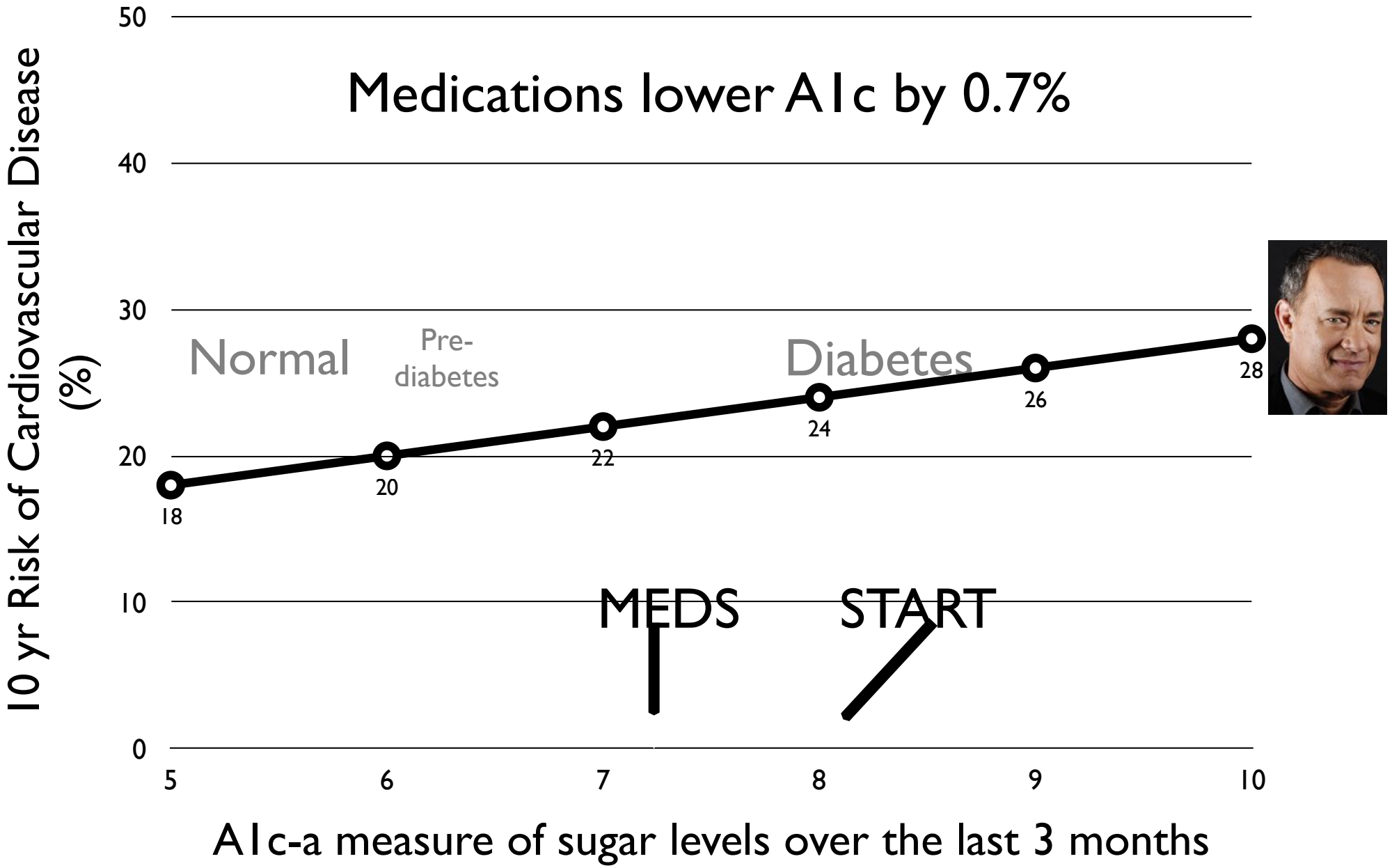
Treatment of type 2 diabetes

Glucose lowering meds

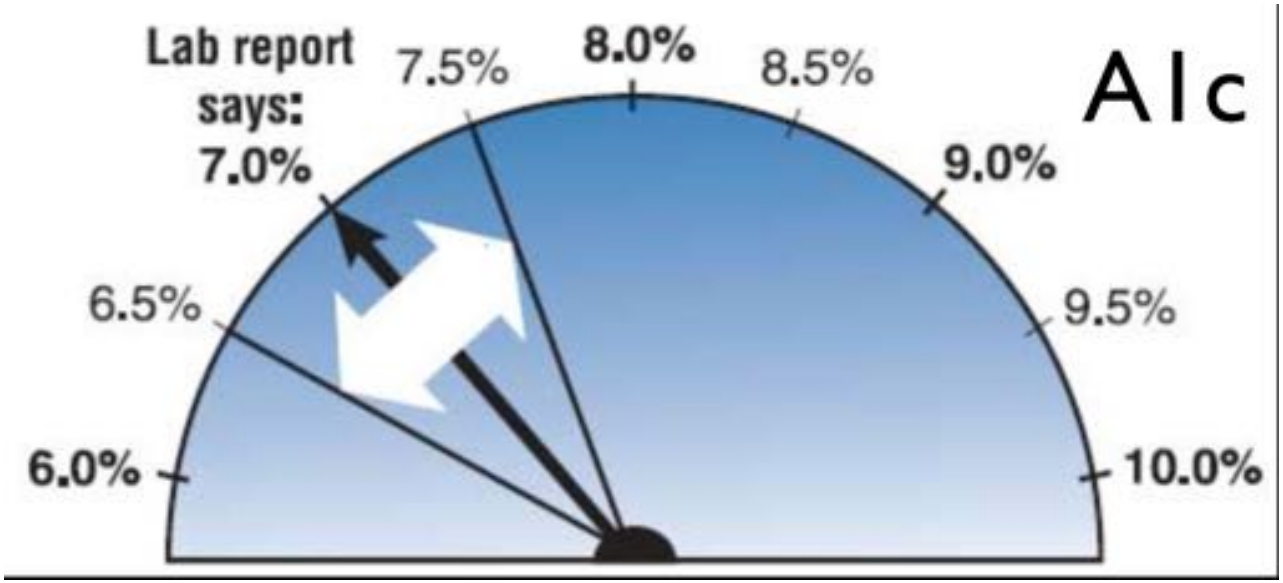
Approved by regulators on the basis of blood glucose lowering ability NOT reduction in symptoms or cardiovascular events

Most lower A1c by roughly 0.5-0.7% over a period of a few months

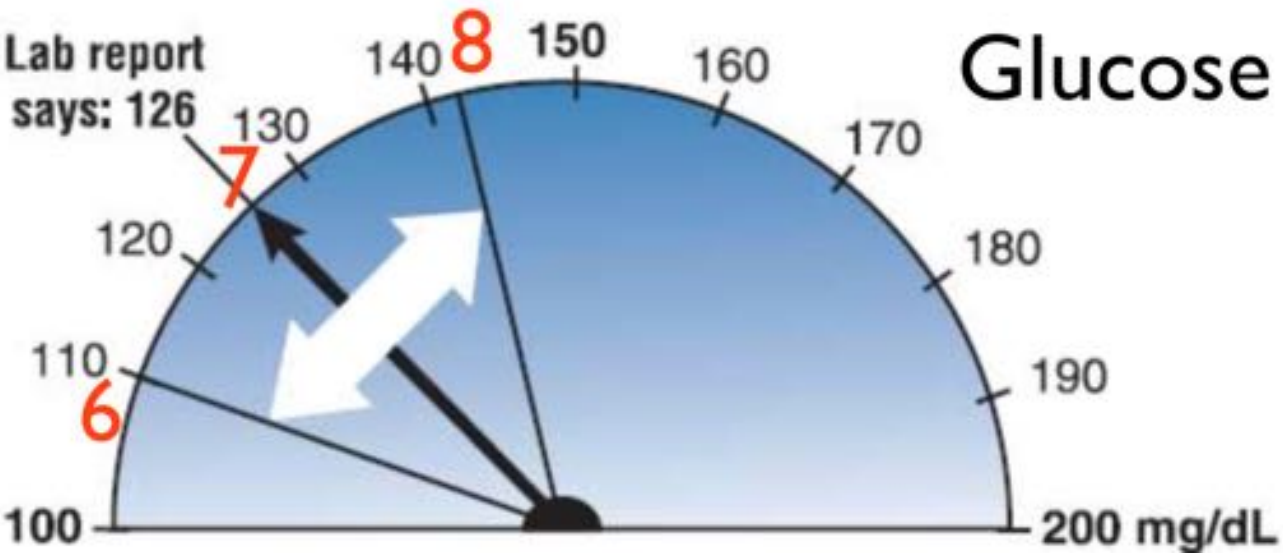
Very few if any head to head comparisons


Medications lower A1c by 0.7%
10 yr Risk of Cardiovascular Disease (%)
50
40
30
20
10
0
Normal
Pre-diabetes
Diabetes
18
20
22
24
26
28
MEDS
START
5
6
7
8
9
10
A1c-a measure of sugar levels over the last 3 months

Variability in glucose measurements



Seasonal variation
0.2-0.5%
Higher in winter
Am J Epi 2004;161:565-74



The A1C Test and Diabetes
National Diabetes Information Clearinghouse

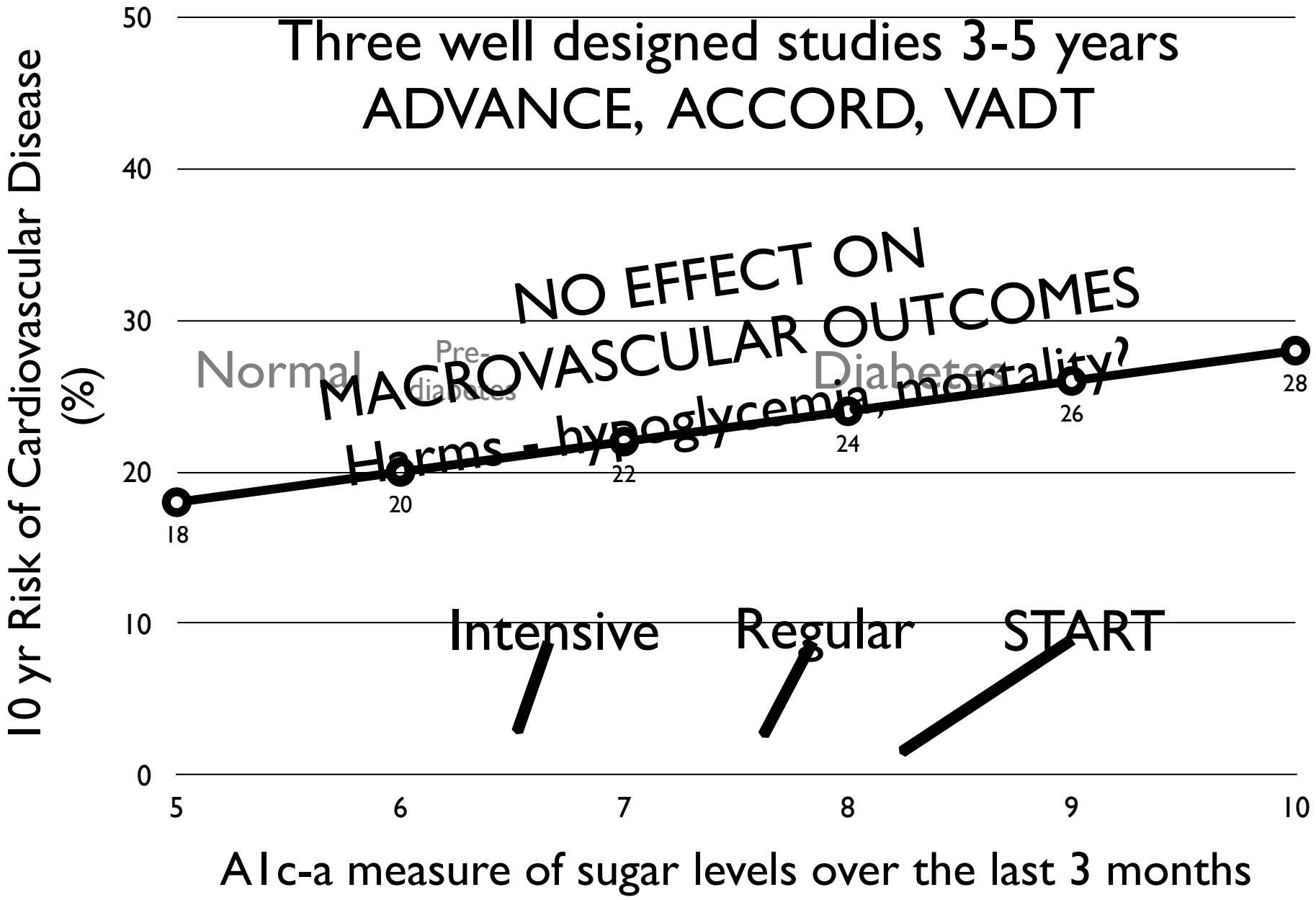
Ten year risk of cardiovascular disease

57 y/o, BMI 27, Diabetes for 5 yr, male, non smoker, caucasian, SBP 130, chol 6/240, HDL 1/40, A1c 8%

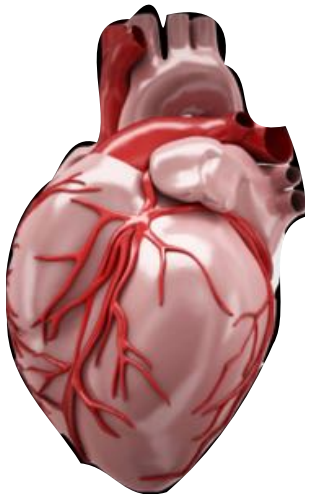
98% No Benefit

	%	TREAT 100 PEOPLE
	76	No event regardless
	20	Event without diabetes
	4	Event caused by diabetes
	2	Potential Benefit from treatment

Intensive glucose control



Intensive glucose control



~~Macrovascular outcomes~~

1% increase in death?

Microvascular outcomes

~1.5-2.5% reduction in each of:

Three-lined worsened visual acuity (but no difference in blindness)

Protein in the urine (but no difference in dialysis)

Loss of light sensation to touch

ACCORD - Lancet 2010;376:419e30

ALL LOWER GLUCOSE							
	Key RCTs (patients/years)		MA (# of studies)				
METFORMIN - Glucophage, Glumetza, generic	700/11	7%	13				
SULFONLYUREAS - Gliclazide (Diamicron, generic), Glimepiride (Amaryl), Glyburide (Diabeta, Euglucon, generic)	4,000/10	COMBO	4-11		3%		
INSULIN	12,000/6 4,000/10	COMBO	None done				
DPP4s - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Trajenta)	5,000/1.5 16,000/2 1,500/2	vs glimiperide	None done				
GLITAZONES - Pioglitazone (Actos), Rosiglitazone (Avandia)	4,400/4 5,200/3	?	42	?CHF harm	?	?	?
GLPs - Exenatide (Byetta) Liraglutide (Victoza)	? - not studied		?		?	?	?
MEGLITINIDES - Nateglinide (Starlix), Repaglinide (GlucoNorm)	? - not studied		?		?	?	?
SGLT2 - Canagliflozin (Invokana) dapagliflozin (Farxiga)	Ongoing ?CV issue		?		?	?	?
Tight control	10,000/3.5 1,800/5.5 11,000/5	?Mortality harm	3		2%	2%	2%

ALL LOWER GLUCOSE	Adverse effects
METFORMIN - Glucophage, Glumetza, generic	Indigestion, nausea, diarrhea
SULFONLYUREAS - Gliclazide (Diamicron, generic), Glimepiride (Amaryl), Glyburide (Diabeta, Euglucon, generic)	Severe low blood sugar (yearly) NNH 175 Weight gain - average 2 kg Rash, diarrhea
INSULIN	Severe low blood sugar (yearly) NNH 85 Weight gain - average 2 kg
DPP4s - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Trajenta)	Hives, rash
GLITAZONES - Pioglitazone (Actos), Rosiglitazone (Avandia)	Fluid retention/heart failure NNH 25 Fractures (three years) NNH 85 Weight gain - average 2 kg
GLPs - Exenatide (Byetta) Liraglutide (Victoza)	Nausea, vomiting, diarrhea NNH 10-20 Weight loss - average 2 kg
MEGLITINIDES - Nateglinide (Starlix), Repaglinide (GlucoNorm)	Hypoglycemia
SGLT2 - Canagliflozin (Invokana) dapagliflozin (Farxiga)	Genital infections NNH 15

Other "side" effects

Estimated Annual Costs
Medications = $150-600 plus
Physician visits (6/year) = $500

Am J Prev Med 2013;45:253–61

Routine self-monitoring of blood glucose (SMBG)

$0.75 per strip
~10 strips/week
CADTH

$400 a year

"In T2DM patients NOT TAKING INSULIN routine SMBG DOES NOT improve glucose control in a clinically meaningful way and may overall REDUCE quality of life"

Can Fam Phys 2011;57

Quality of Life

Diabetes Care 2007;30:2478–83

Screening for Diabetes

Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial

Rebecca K Simmons, Justin B Echouffo-Tcheugui, Stephen J Sharp, Lincoln A Sargeant, Kate M Williams, A Toby Prevost, Ann Louise Kinmonth, Nicholas J Wareham, Simon J Griffin

~15,000 people screened (age 58) - 466 diagnosed as T2DM

"screening for type 2 diabetes in patients at increased risk was not associated with a reduction in all-cause, cardiovascular, or diabetes-related mortality"

Lancet 2012;380:1741-8

Early Treatment

Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial

Simon J Griffin, Knut Borch-Johnsen, Melanie J Davies, Kamlesh Khunti, Guy E H M Rutten, Annelli Sandbæk, Stephen J Sharp, Rebecca K Simmons, Maureen van den Donk, Nicholas J Wareham, Torsten Lauritzen

~3,000 T2DM - mean age 60 - Denmark, Netherlands, UK

"An intervention (STENO-2 - lifestyle, metformin, BP, statins) to promote early intensive management of patients with type 2 diabetes was associated with a small, non-significant reduction in the incidence of cardiovascular events and death."

Lancet 2011;378,156–67

The reality of Type 2 diabetes prevention

"the absence of any persuasive evidence for the effectiveness of community programs calls into question whether the use of public funds or national prevention initiatives should be supported at this time."

Diabetes Care 2014,37:943-9

ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

5145 overweight type 2 diabetics

intensive lifestyle intervention (calories and activity)

followed for 10 year - study stopped early - NO REDUCTION in cardiovascular disease

N Engl J Med 2013;369:145-54.
DOI: 10.1056/NEJMoa1212914

Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis

Thomas Yates, Steven M Haffner, Phillip J Schulte, Laine Thomas, Kim M Huffman, Connie W Bales, Robert M Califf, Rury R Holman, John J V McMurray, M Angelyn Bethel, Jaakko Tuomilehto, Melanie J Davies, William E Kraus

"every 2000 step per day increment in ambulatory activity at baseline (roughly equivalent to 20 min a day of moderately-paced walking activity) was associated with a 10% lower risk of a cardiovascular event"

"each 2000 step increase or decrease in daily ambulatory activity from baseline to 12 months was associated with an additional
8% lower or higher cardiovascular event rate"

www.thelancet.com Published online December 20, 2013
http://dx.doi.org/10.1016/S0140-6736(13)62061-9

Weight cycling

"the relationship with weight gain, weight fluctuation was NOT associated with incidence of diabetes in either sex"

Diabetes 1995;44:261-6

"weight cycling was strongly associated with BMI, but it was NOT independently predictive of developing type 2 diabetes"

Obes Res 2004;12:267-74

"after adjustment for overall weight status, weight cycling was NO LONGER associated with higher rates of diabetes"

Am J Epidemiol 2010;171: 550-6

BMI and Outcome

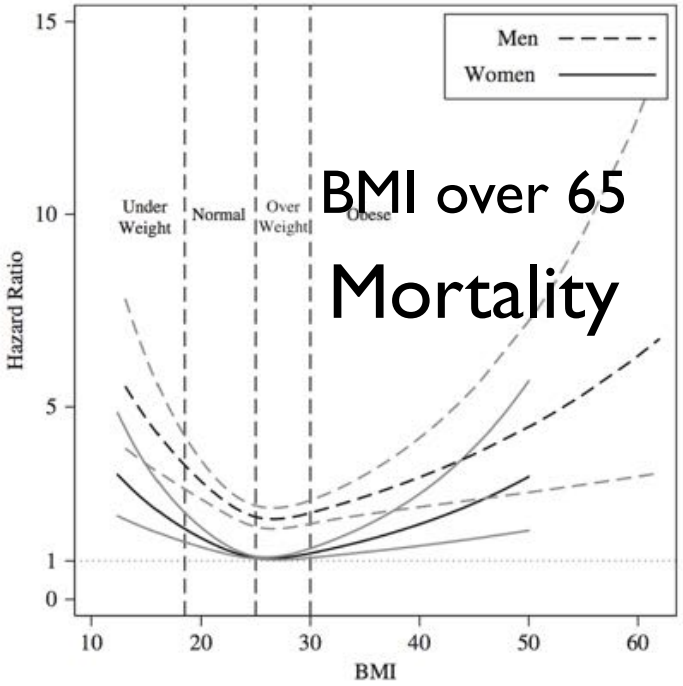
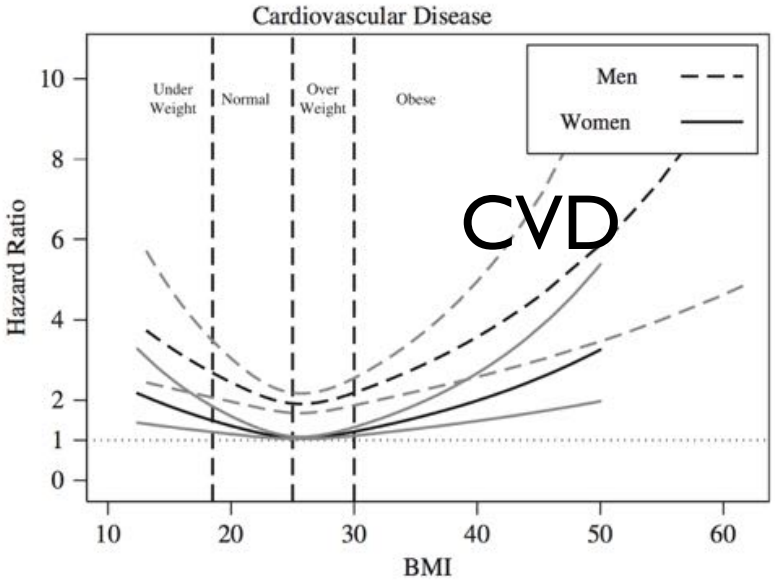


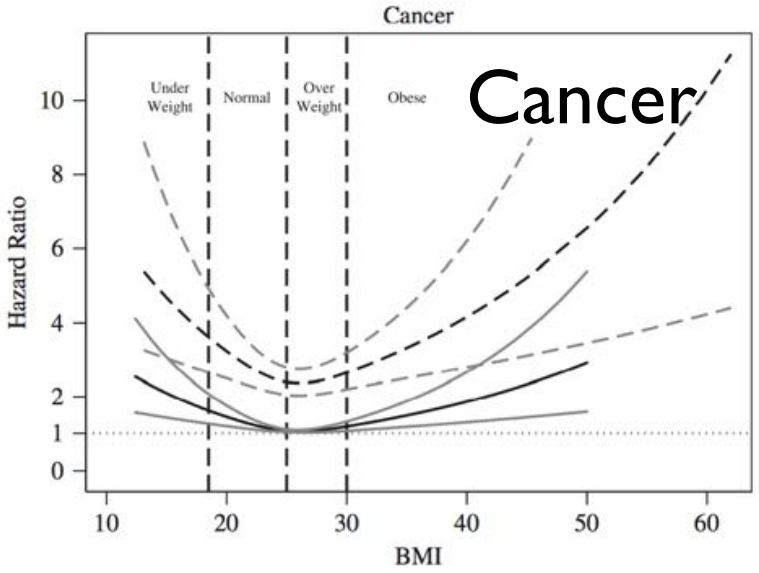
Figure 1. Hazard ratios of all-cause mortality according to body mass index (BMI) in men and women aged 70 to 75 (lines are 95% confidence intervals).

J Am Geriatr Soc 2010; 58:234–241

Similar data for
25-59 years of age
JAMA 2007;298:2028-37

Similar data in
Lancet 2006;368:666–78
J of Nutrition, Health & Aging 2013





Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories

A Systematic Review and Meta-analysis

FOR ALL AGES - Relative to normal weight - BMI of 18.5-25

BMI of 25- <30 - HR 0.94 (0.91-0.96)

BMI of 30 - <35 - HR 0.95 (0.88-1.01)

BMI of >35 - HR 1.29 (1.18-1.41)

JAMA 2013;309:71-82

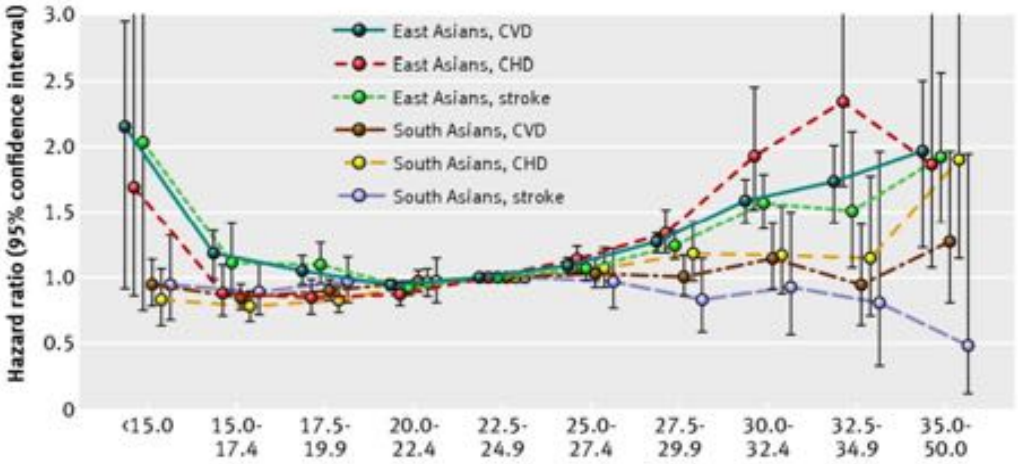
Other studies

Lancet 2009;373:1083–96

N Engl J Med 2010;363:2211-9

"Best" BMI ~24

Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium



BMJ 2013;347:f5446 doi: 10.1136/bmj.f5446

Changes in Diabetes-Related Complications in the United States, 1990–2010

Edward W. Gregg, Ph.D., Yanfeng Li, M.D., Jing Wang, M.D.,
Nilka Rios Burrows, M.P.H., Mohammed K. Ali, M.B., Ch.B., Deborah Rolka, M.S.,
Desmond E. Williams, M.D., Ph.D., and Linda Geiss, M.A.

"Rates of diabetes-related complications have declined substantially in the past two decades" - surveys and registry data

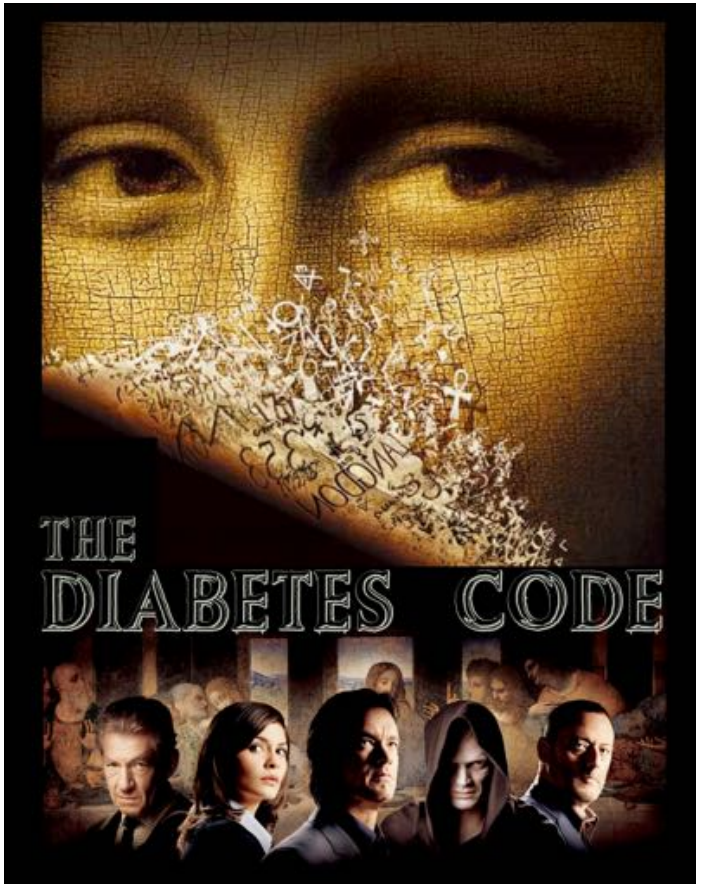
N Engl J Med 2014;370:1514-23.
DOI: 10.1056/NEJMoa1310799

OUR LETTER TO THE EDITOR

1) the broadening of the definition of diabetes in 1997 naturally leads to a dilution of severity over time and consequently fewer complications

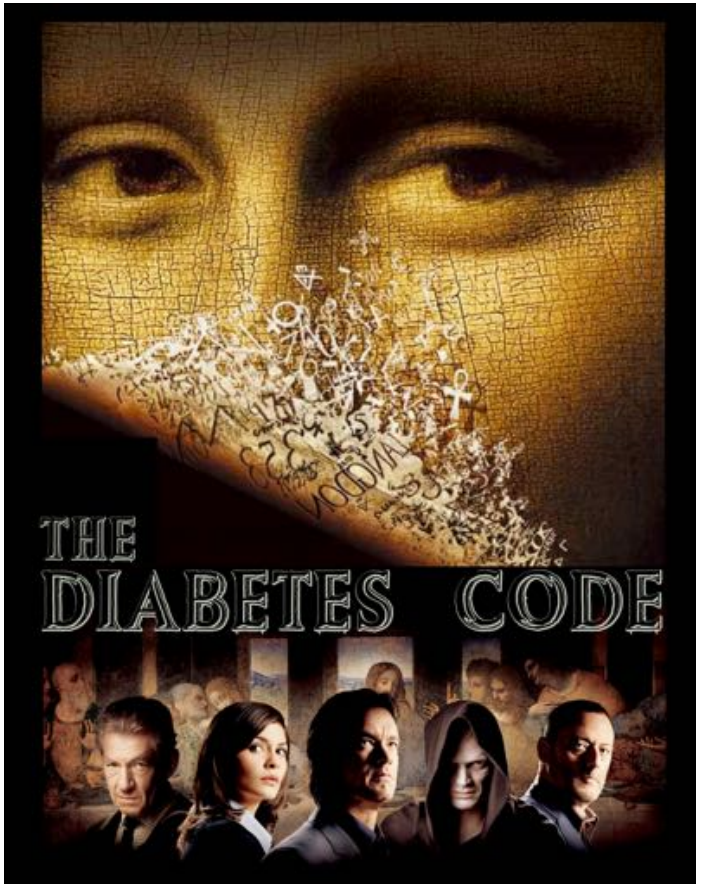
2) the inability to separate Type 1 and Type 2 diabetes obscures their relative contribution to complications and conflates two different diseases

3) many large high-quality intervention trials targeting surrogate markers have shown no benefit and even harm, as have recent meta-analyses of risk factor modification, including glycemic control

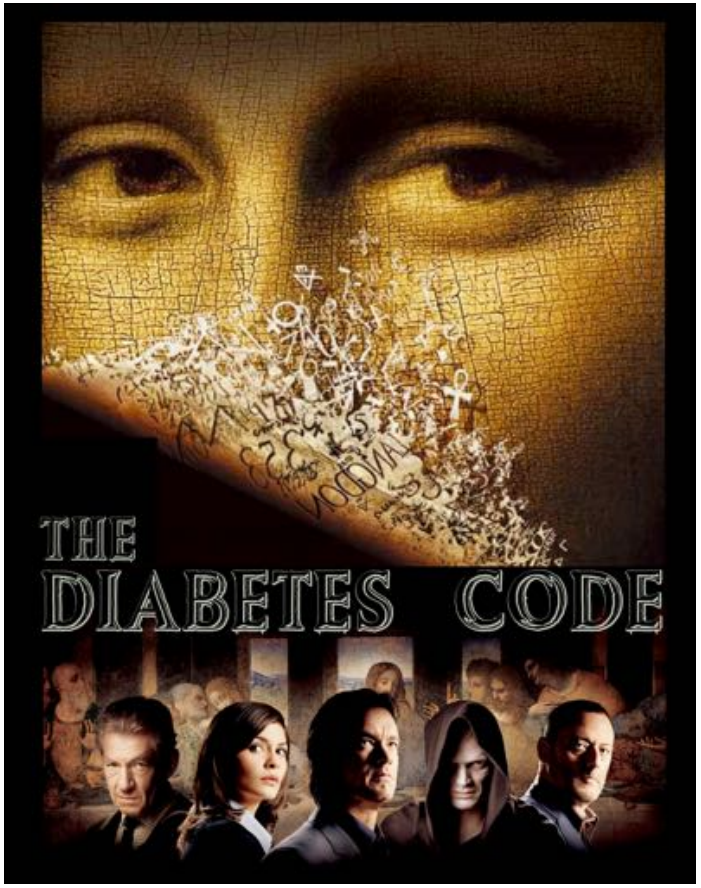


Decoding the type 2 diabetes messages

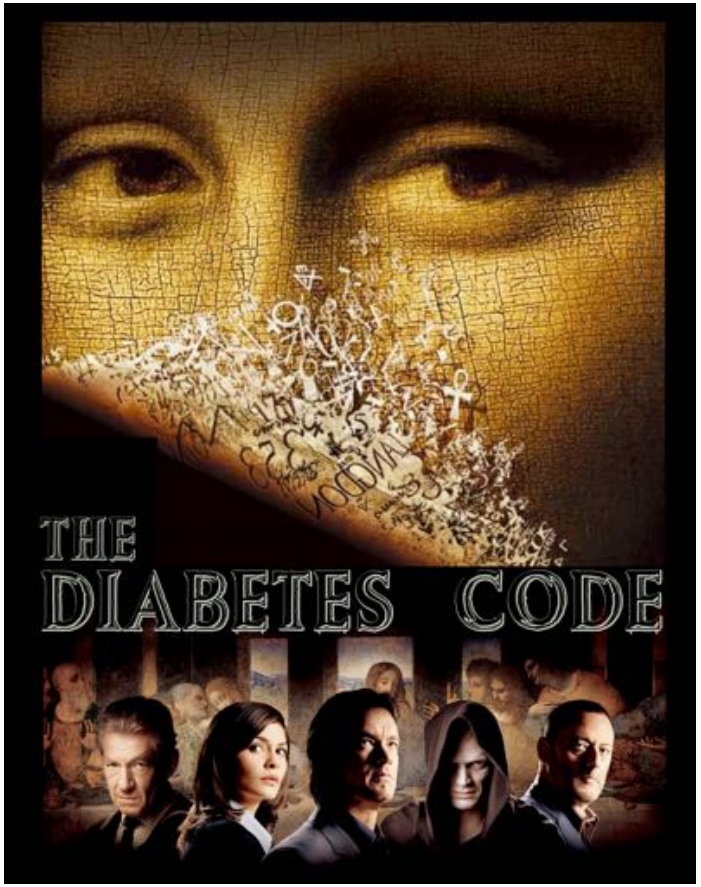
based on the
Best Available Evidence



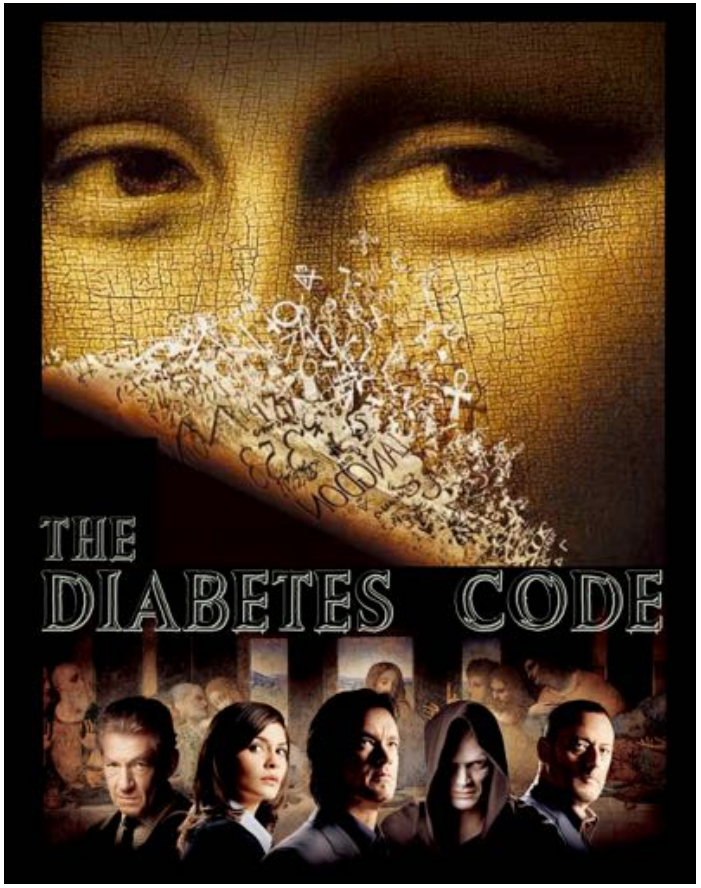
- really big glucose numbers cause symptoms and likely an important increased risk of CVD and other health outcomes - 90%+ don't have "big" numbers
- in a 57 y/o male a "new" diagnosis of "diabetes" (A1c 8%) means
  - ~ a 4% increase in the 10 year risk of developing cardiovascular disease compared to non-diabetic
  - ~0.5% increase in the lifetime risk of dialysis and blindness



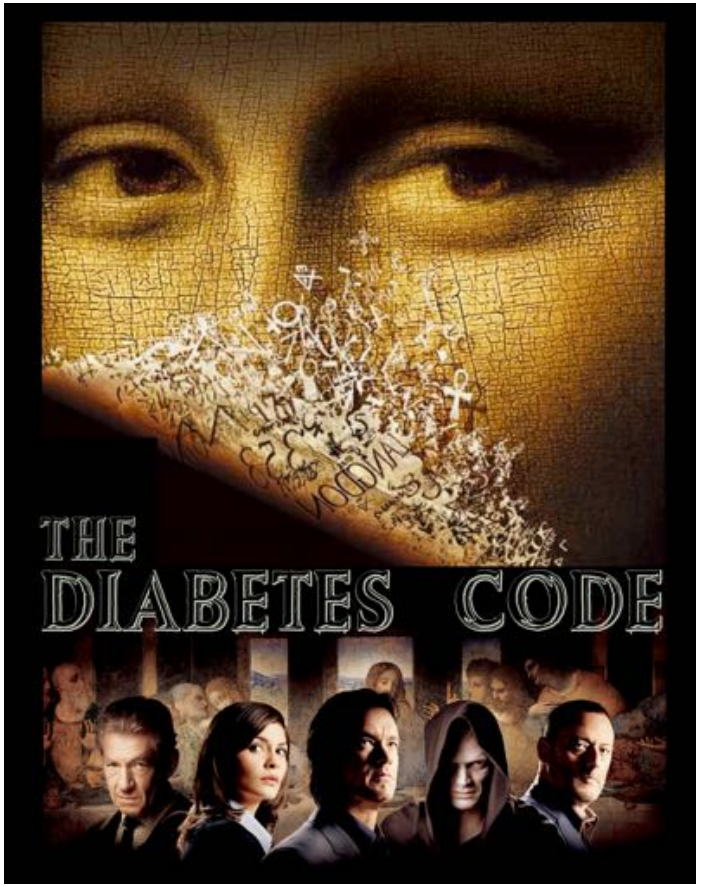
- morbidly obese patients should eat healthier (and less overall)
- Mediterranean diet has little impact on blood pressure, cholesterol, weight but decreases cardiovascular events
- regular physical activity, regardless of whether it leads to weight loss or a change in glucose/cholesterol/blood pressure numbers, has been shown to improve the quality of many aspects of life



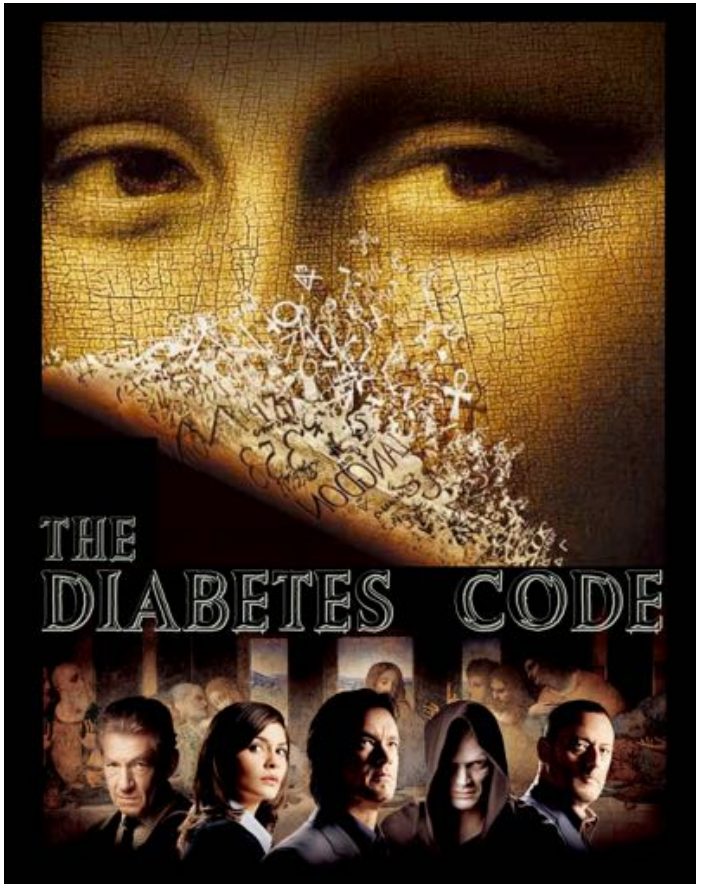
- screening for diabetes had no effect on mortality or cardiovascular disease
- early treatment didn't seem to do much
- the diagnosis thresholds are relatively arbitrary
- glucose numbers are often +/- 5-10%



- many drugs lower blood glucose
- lowering glucose often doesn't lead to a clinically important benefit
- metformin has the best evidence for a cardiovascular benefit BUT…
- measuring glucose in people who aren't on insulin doesn't do much except increase worry and cost



- the best BMI for mortality and cardiovascular disease is basically anywhere between 22-28
- weight cycling doesn't seem to be linked to the development of T2DM



- there is greater benefit from lowering blood pressure (if above 140/90mmHg) or being on a statin than lowering glucose
- think about YOUR RISK NOT

"Oh no - I have diabetes"

- diabetes for most people is a

"surrogate disease"