

Typically “evidence-based” guideline recommendations are not based on “solid” evidence



Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines
 Pierluigi Tricoci, Joseph M. Allen, Judith M. Kramer, et al.
 JAMA. 2009;301(8):851-841 (doi:10.1001/jama.2009.250)

Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines
 Dong Han Lee, MD, Ole Videmeyer, MD
 Arch Intern Med. 2011;171(1):18-22

Cardiology	LEVEL	Infectious disease
11%	Evidence Level (1 or A) based on RCTs	14%
48%	Evidence Level (3 or C) based on opinion	55%

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 the decision-making process and the (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 the implementation of the therapeutic intervention; and the number of descriptions of specific or comparative costs of treatment.

DESIGN Retrospective, observational review.

MAIN OUTCOME MEASURES The presence or absence of specific mentions of the importance of incorporating patients' values and preferences in the decision-making process and the (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 the implementation of the therapeutic intervention; and the number of descriptions of specific or comparative costs of treatment.

RESULTS Three of 5 CPGs mentioned that patients' 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 quantitative mentions of the importance of incorporating patients' values and preferences in decision-making terms and 19% met our criteria for applicability to decision making for individual patients. Two of the 5 CPGs did not enumerate the number of descriptions of specific or comparative costs of treatment.

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.

1.97 PAGES, 90,000 Words
 99% (0.1%) words - relevant to patients' values and preferences
 79 drugs available in Canada
 Only for ~ 5 could one use the information presented in the guidelines to estimate a potential benefit.

TYPE 2 DIABETES GUIDELINES - 2013 CATEGORIES FOR THE RECOMMENDATIONS

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

TREATMENT TARGETS

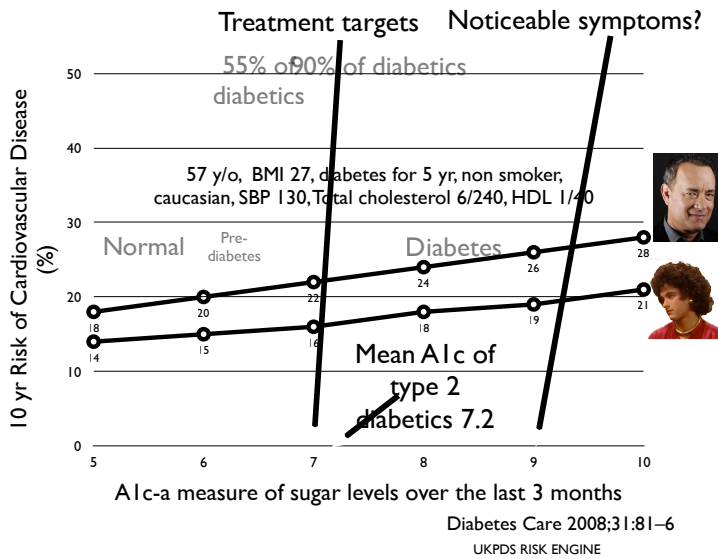
Level A = recommendation based on evidence from multiple randomized trials or meta-analyses

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	
FRS ≥20%		
Moderate	<2 mmol/L*	Class IIa, level A
FRS 10% to 19%	or	
LDL-C >3.5 mmol/L	≥50% ↓ LDL-C	
FRS <10% and women	apoB <0.92 mmol/L in men	
FRS <10% and women	apoB <1.00 mmol/L in women	
FRS <10% and women	apoB <1.00 mmol/L in women	
moderate risk		
Low	≥50% ↓ LDL-C	Class III, level A
FRS <10%		

“Recommended target”
 <2 mmol/L/80mg/dL

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

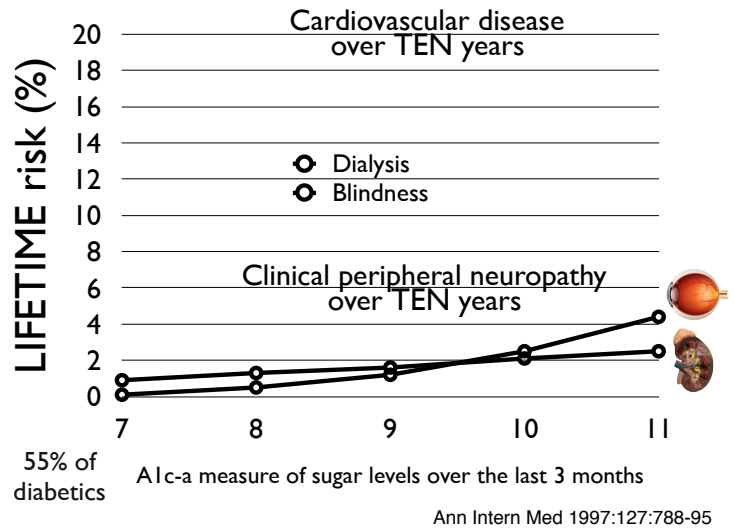
“The Expert Panel was UNABLE TO FIND RCT EVIDENCE to support titrating cholesterol-lowering drug therapy to achieve target LDL-C or non-HDL-C levels, as recommended by ATP III”



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

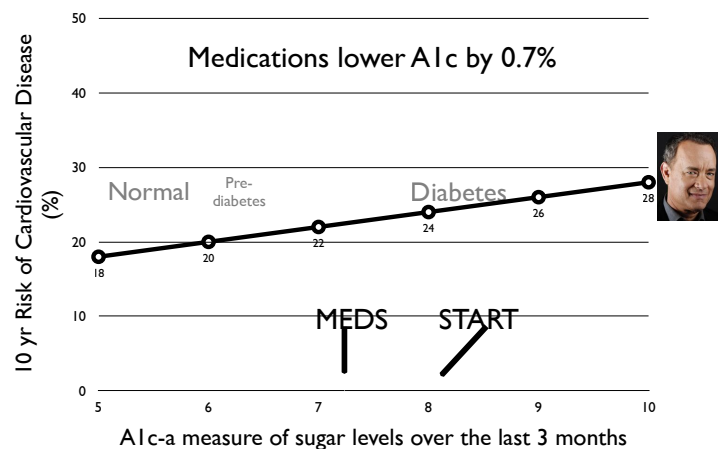


Treatment of type 2 diabetes Glucose lowering meds

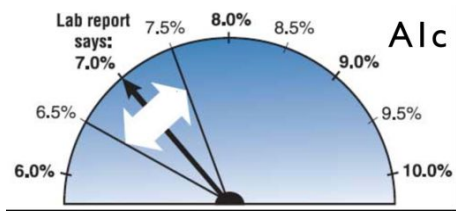
Approved by regulators on the basis of blood glucose lowering ability NOT reduction in symptoms or cardiovascular events

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

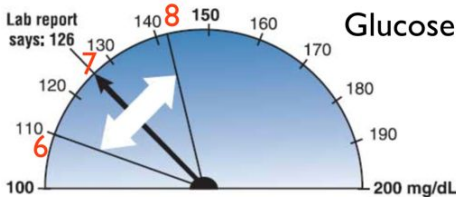
Very few if any head to head comparisons



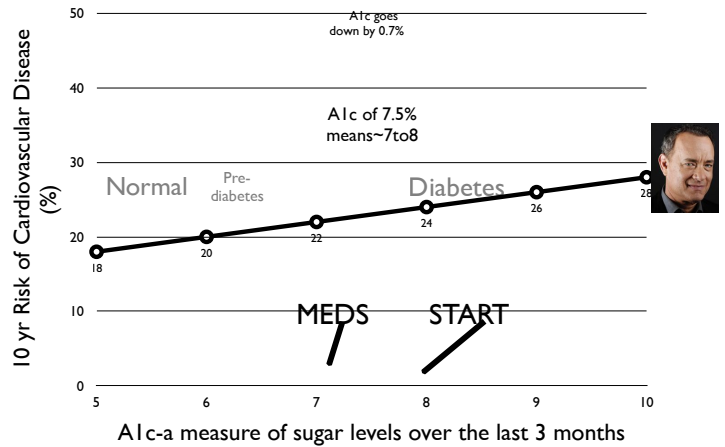
Variability in glucose measurements



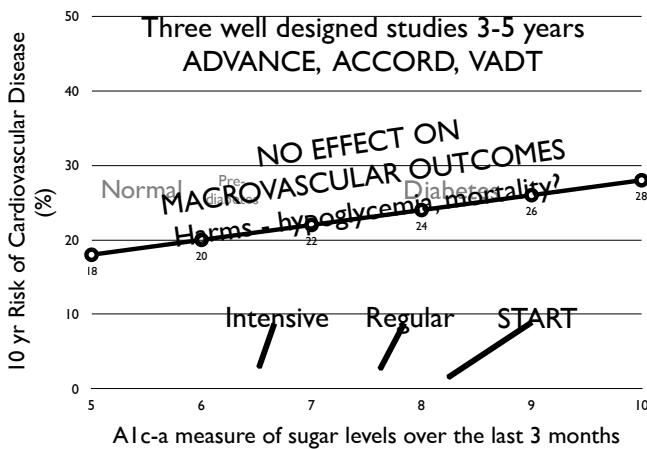
Seasonal variation
0.2-0.5%
Higher in winter
Am J Epi 2004;161:565-74



The A1C Test and Diabetes
National Diabetes Information Clearinghouse



Intensive glucose control



ALL LOWER GLUCOSE	Key RCTs patients/years		MA (# of studies)		
	METFORMIN - Glucophage, Glumetza, generic	700/11	7%	13	
SULFONYLUREAS - Gliclazide (Diamicon, generic), Glimperide (Amaryl), Glyburide (Diabeta, Euglucon, generic)	4,000/10		4-11		3%
INSULIN	12,000/6 4,000/10		None done		
DPP4s - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Trajenta)	5,000/1.5 16,000/2		None done		
GLITAZONES - Pioglitazone (Actos), Rosiglitazone (Avandia)	4,400/4 5,200/3	?	42	? CHF harm	? ? ?
GLPs - Liraglutide (Victoza)	? - not studied		?		? ? ?
MEGLITINIDES - Nateglinide (Starlix), Repaglinide (GlucoNorm)	? - not studied		?		? ? ?
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
SULFONYLUREAS - Gliclazide (Diamicon, generic), Glimperide (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

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”

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-Tohégué, 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

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

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



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, Anneli Sandbak, 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

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 Huffner, 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](http://dx.doi.org/10.1016/S0140-6736(13)62061-9)

BMI and Outcome

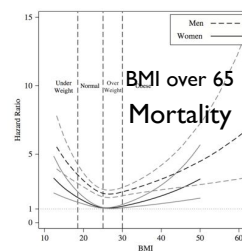
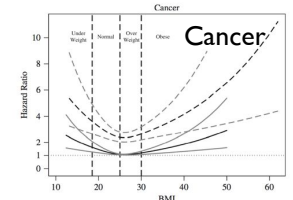
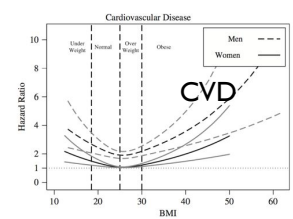


Figure 1. Hazard ratios of all-cause mortality according to body mass index (BMI) in men and women aged 70 to 75 (lines are 95% confidence intervals).

J Am Geriatr Soc 2010; 58:234-241

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

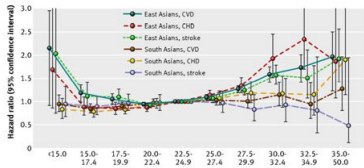
Similar data in
 Lancet 2006;368:666-78
 J of Nutrition, Health & Aging 2013



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

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

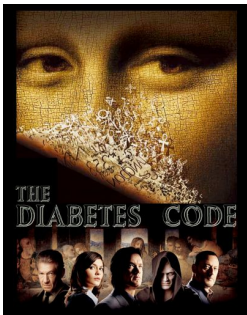
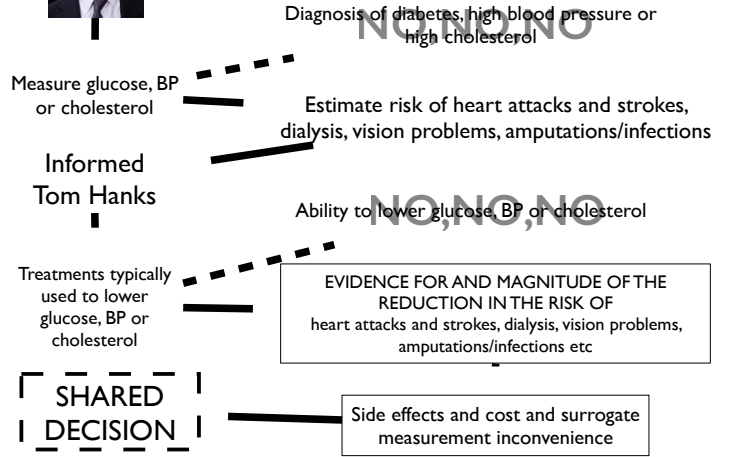


Other studies
 Lancet 2009;373:1083-96
 N Engl J Med 2010;363:2211-9
 "Best" BMI ~24

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

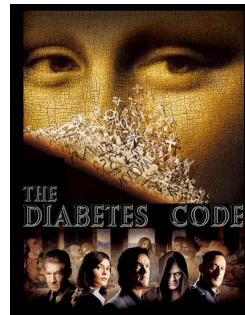


Activity and Nutrition

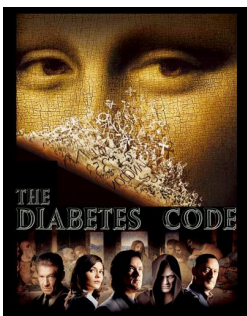


Decoding the type 2 diabetes messages

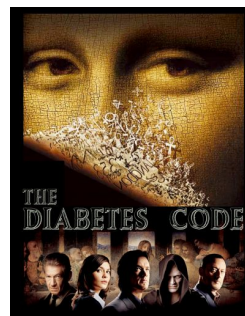
based on the **Best Available Evidence**



- 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

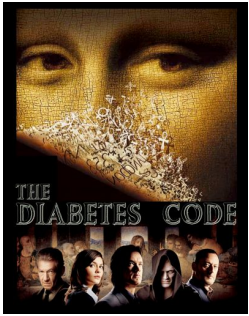


- morbidly obese patients should eat healthier (and less overall)
- Mediterranean diet has little impact on blood pressure, cholesterol, weight but decreases cardiovascular events
- regular physical activity, regardless of whether it leads to weight loss or a change in glucose/cholesterol/blood pressure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

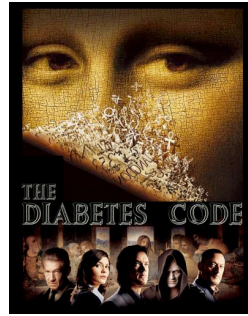


- screening for diabetes had no effect on mortality or cardiovascular disease
- early treatment didn't seem to do much
- the diagnosis thresholds are relatively arbitrary
- glucose numbers are often +/- 5-10%

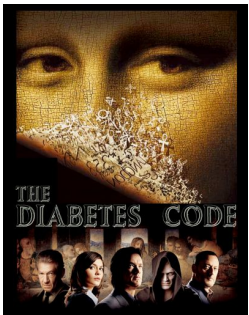




- many drugs lower blood glucose
- lowering glucose often doesn't lead to a clinically important benefit
- metformin has the best evidence for a cardiovascular benefit BUT...
- measuring glucose in people who aren't on insulin doesn't do much except increase worry and cost



- 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 overall risk NOT "Oh no - I have diabetes"
- diabetes for most people is a "surrogate disease"

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

2012

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

"the desires and values of the patient should also be considered, since the achievement of any degree of glucose control requires active participation and commitment"

"Importantly, utilizing the percentage of diabetic patients who are achieving an HbA1c of 7.0% as a quality indicator, as promulgated by various health care organizations, is inconsistent with the emphasis on individualization of treatment goals"

Diabetes Care 2012;35:1364-79

Guidelines and the Law

"As per the Canadian Medical Association Handbook on Clinical Practice Guidelines, guidelines should **NOT** be used as a legal resource in malpractice cases as "their more general nature renders them insensitive to the particular circumstances of the individual cases."



Risk of heart attacks and strokes, dialysis, vision problems, amputations/ infections etc

Treatments

REDUCE RISK
heart attacks and strokes, dialysis, vision problems, amputations/infections etc

Activity and Nutrition



SHARED DECISION

Side effects and cost and surrogate measurement inconvenience