Challenging Medical Dogmas with Data: Diabetes, Lipids, Blood pressure and Cardiovascular Risk

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Methods for Informing & Improving Individualized Estimates for Net Treatment Benefit

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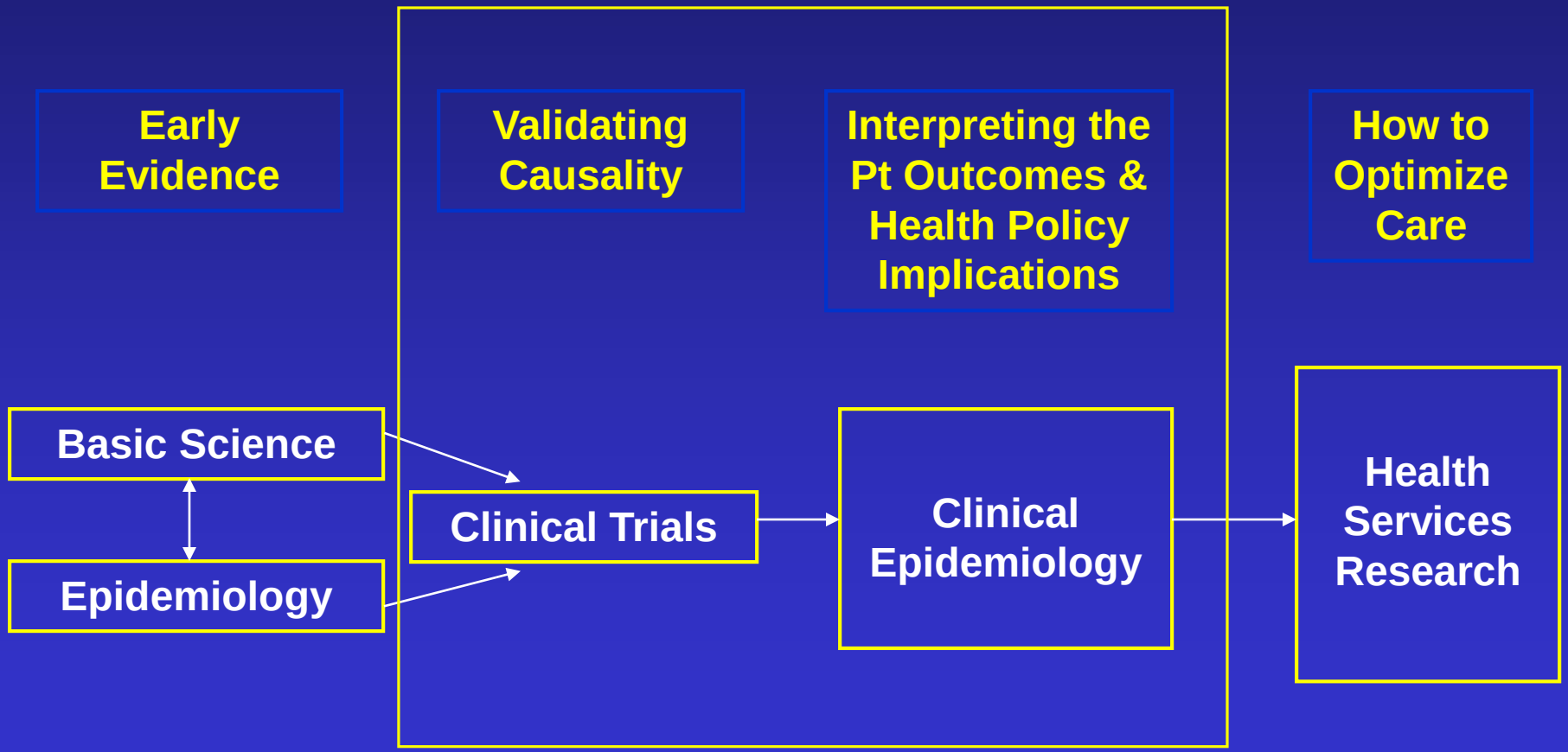
Disclosures

- No financial conflicts, but
- I’m in a bit of a snit abt the recent European Lipid Guidelines
- Frank, there will be NNTs presented

Research Directed at Improving Health Care



Steps to More Personalized Patient Decision-making

1. Judicious assessment of heterogeneity in the relative treatment effect (rHTE)
2. Assess heterogeneity in individualized absolute risk reduction (iARR) for target conditions
3. Assess population continuum of net benefit, with emphasis on those in a highly preference-sensitive zone

Traditional Treat-to-Target Recommendations

- LDL < 70mg/dl
- CRP < 2
- A1c < 7%
- BP < 130/80
- Exercise 90min/day
- BMI $\leq$ 22

Benefit-based Tailored Treatment

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Factors that determine net treatment benefit:

$Risk_{NoRx}$ → Absolute Risk of bad outcome in absence of treatment (Obs Studies)

RRR_{Rx} → Relative risk reduction in the bad outcome from treatment (RCTs)
(HET in RRR should be examined better, especially by RRR_{Rx})

ARI_{Rx} → Absolite Risk of adverse effects of treatment (RCTs)

Net Benefit from Rx = ($Risk_{NoRx}$ * RRR_{Rx}) - ARI_{Rx}

Steps to More Personalized Patient Decision-making

1. Judicious assessment of heterogeneity in the relative treatment effect (rHTE)

Unexpected rHTE for target outcomes is *extremely* rare

1. Review of ~1200 rHTE examinations, 7% positive rate! (Sun X et al BMJ 2012)
2. Given usual stat power in RCTs, rHTE for categorical variables should usually only be done if prior >25%-50%. (Burke J, et al BMJ 2018)
3. Power for rHTE for continuous variables can have excellent power (Hayward et al BMC Res Methods)

Positive Predictive Values for Subgroup Analyses (Burke BMJ 2017)

Prior probability (%)	20% power			50% power		
	1	5	10	1	5	10
5	17	14	11	35	18	12
10	31	25	20	53	32	22
20	50	43	36	71	52	38
30	63	56	49	81	65	52
40	73	67	60	87	74	62
50	80	75	69	91	81	71

What Do We Get From Traditional Subgroup Analyses?

- Multiple Comparisons = False positives
- Mistaking lack of statistical power for a consistent treatment effect
- Tragic confounding (e.g., "Older pts didn't appear to benefit, therefore, results only apply to middle-aged.")
- Almost no consideration of heterogeneity of ARR at the individual level

rHTE

1. Real rHTE does exist (Time to TT/PCI, high competing risk)
2. *Unexpected* rHTE = very very rare or a framing issue

Net Benefit from Rx = ($Risk_{NoRx}$ * RRR_{Rx}) - ARI_{Rx}

3. Heterogeneity in net benefit = universal!

Steps to More Personalized Patient Decision-making

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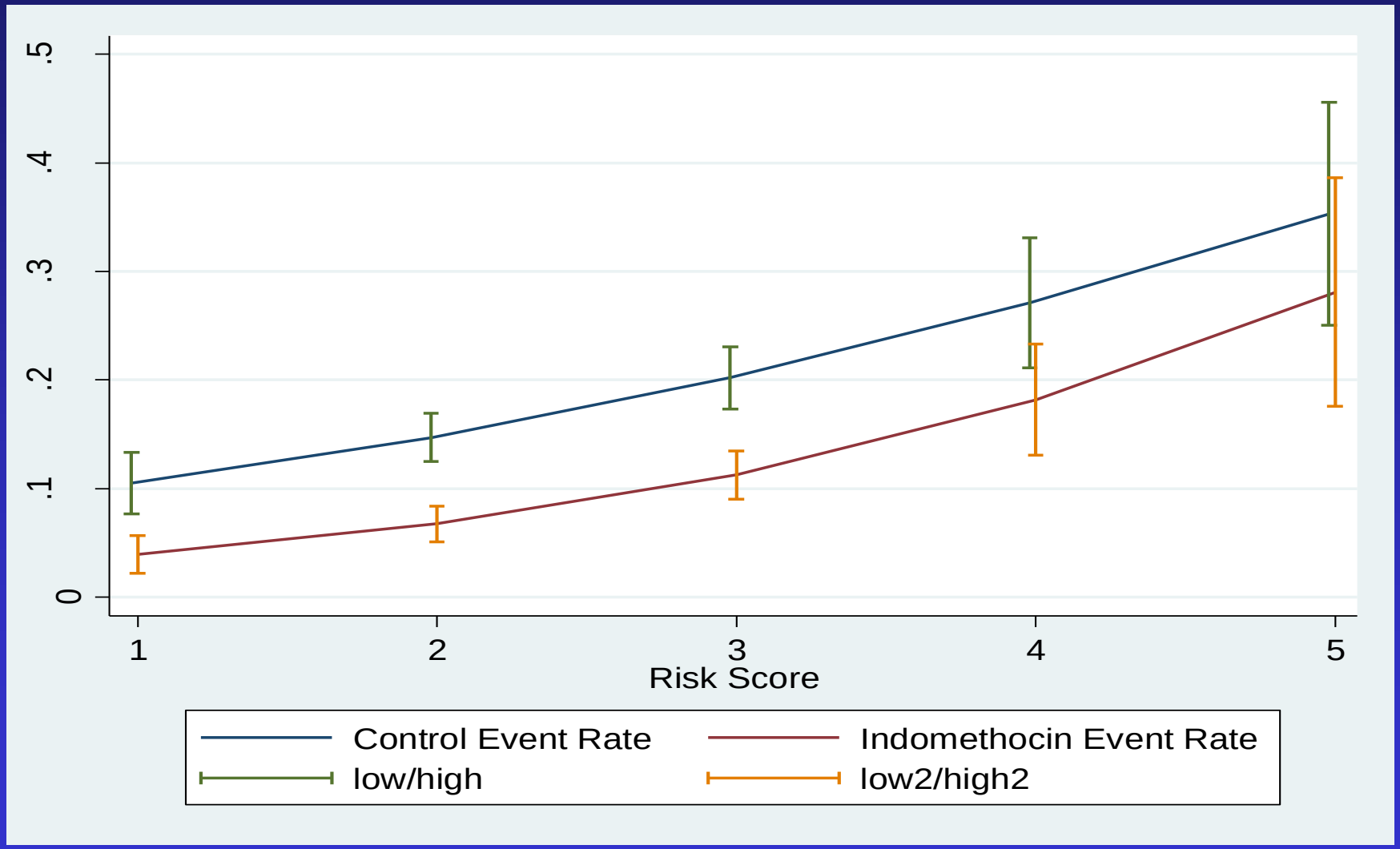
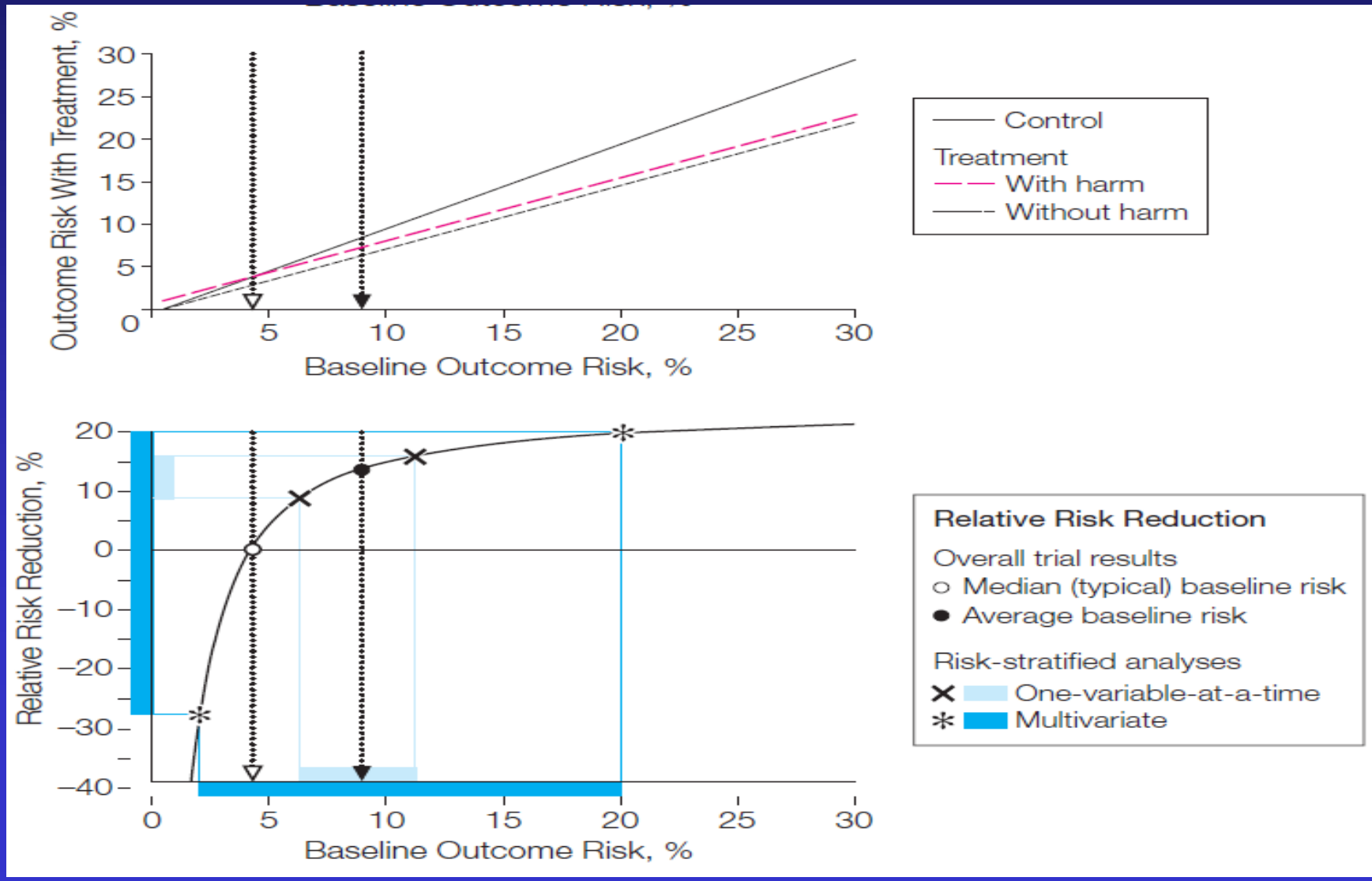
ARR In Post-ERCP Pancreatitis:
Rx = Indomethacin (Elmunzer NEJM 2012)



Variation In ARR (Kent & Hayward JAMA)



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Benefit of CEA in Symptomatic Patients with 70% to 99% Corotid Stenosis (Rothwell et al. Lancet 1999)*

Risk Score (% of Patients)	5-year CER	Crude Odds Ratio (95% CI)	Estimated 5-year NNT
Total (100%)	17%	0.64 (0.44-0.93)	~14

* European Carotid Surgery Trial

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Risk Score (% of Patients)	5-year CER	Crude Odds Ratio (95% CI)	Estimated 5-year NNT
Total (100%)	17%	0.64 (0.44-0.93)	~14
0 – 3.5 (84%)	12%	1.00 (.65-1.54)	~ ∞
≥ 4.0 (16%)	40%	0.12 (0.44 – 0.93)	~3

* European Carotid Surgery Trial

tPA vs Streptokinose for AMI
(Kent et al AJM 2002)

Predicted Benefit (% of Subjects)	CER	RRR	NNT
All Subjects (100%)	6.7%	14%	100 to 111
Highest Predicted Benefit (25%)	14.2%	16%	~45
Lowest Predicted Benefit (25%)	1.9%	0.3% to (0.4%)	~16,600 to (12,500)

Bad Dogma: Three Case Studies

1. Lipids

2. BP treatment

3. Glycemic Control

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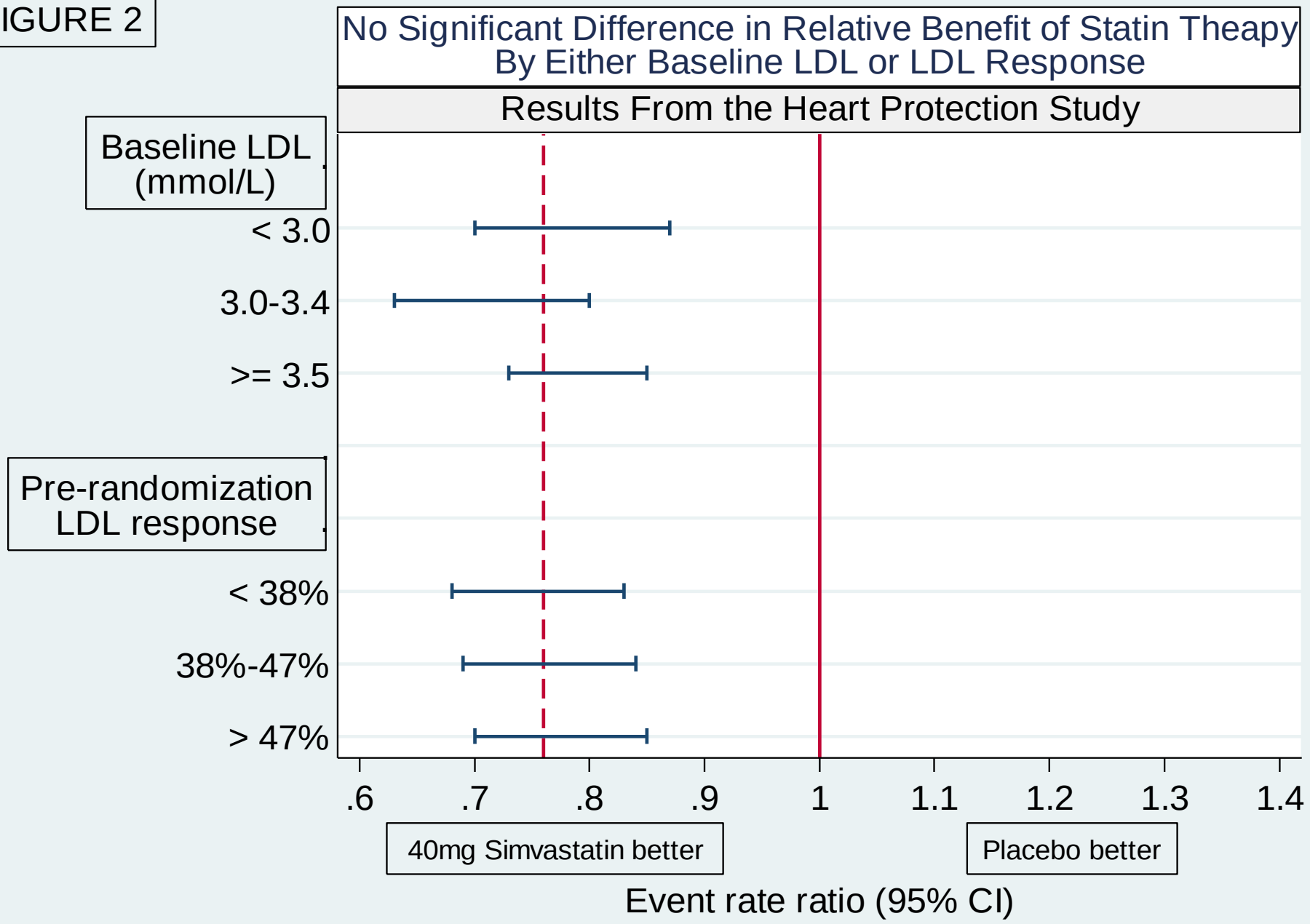
LDL & Statin Benefit

Net Rx Benefit = $(Risk_{NoRx} * RRR_{Rx}) - (Harm_{Rx})$

1. $Risk_{NoRx}$ (small impact)
2. RRR_{Rx} (Maybe small impact)
3. $Harm_{Rx}$ (No known impact)

FIGURE 2


No Significant Difference in Relative Benefit of Statin Theapy
By Either Baseline LDL or LDL Response
Results From the Heart Protection Study
Baseline LDL (mmol/L)
< 3.0
3.0-3.4
>= 3.5
Pre-randomization LDL response
< 38%
38%-47%
> 47%
.6
.7
.8
.9
1
1.1
1.2
1.3
1.4
40mg Simvastatin better
Placebo better
Event rate ratio (95% CI)

Why not consider LDL level for early LDL treatment

	40 yrs	50 yrs	60 yrs	70 yrs
Patient A: LDL = 170, Female, HDL= 60, SBP=120, non-smoker, no family history	< 1%	1%	2%	5%
Patient B: LDL = 100, Male, HDL= 30, SBP=135, smoker, + family history	7%	11%	22%	39%

Why not consider LDL level for early LDL treatment

	40 yrs	50 yrs	60 yrs	70 yrs
Patient A: LDL = 170, Female, HDL= 60, SBP=120, non-smoker, no family history	< 1%	1%	2%	5%
Patient B: LDL = 100, Male, HDL= 30, SBP=135, smoker, + family history	7%	11%	22%	39%

Benefit-based Tailored Therapy (BTT) vs. Treat-to-Target (TTT) Statin Strategy

(Hayward et al Annals of IM 2010)*

	Total QALYs Gained in U.S. population in 5yrs	QALYs Gained per 1,000 persons treated
BTT (Compared to TTT)	**+520,000**	**+10**

* While treating slightly fewer people

Bad Dogma: Three Case Studies

1. Lipids

2. BP treatment

3. Glycemic Control

SBP & Statin Benefit

Net Rx Benefit = $(Risk_{NoRx} * RRR_{Rx}) - (Harm_{Rx})$

1. $Risk_{NoRx}$ (small impact)
2. RRR_{Rx} (No impact!)
3. $Harm_{Rx}$ (Unclear)

Why not consider SBP level for early BP treatment

	40 yrs	50 yrs	60 yrs	70 yrs
Patient A: LDL = 120, Female, HDL= 60, SBP=145, non-smoker, no family history	< 1%	1%	2%	5%
Patient B: LDL = 160, Male, HDL= 30, SBP=130, smoker, + family history	7%	11%	22%	39%

Benefit-based Tailored Therapy (BTT) vs. Treat-to-Target (TTT) BP Rx Strategy

(Sussman Circulation 2016)*

	Total QALYs Gained in U.S. population in 5yrs	QALYs Gained per 1,000 persons treated
BTT (Compared to TTT)	**+1.4M**	**+159**

* While using 6% less BP meds

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Basu S, Yudkin J, Sussman J, Millett C, Hayward RA.
Circulation 2016

"`Smarter' BP & Statin guidelines could prevent up to 500,000 more QALYs each year in India & China compared to current WHO guidelines."

4 Common Phenomenon that make TTT strategies terrible

1. Risk reduction is log linear

2. RRR_{Rx} → 1st Rx > 2^{nd} >> 3^{rd} >>> 4^{th}

3. $Harm_{Rx}$ → 1st Rx < 2^{nd} < 3^{rd} < 4^{th}

4. RFs often unreliable

No More Dumb Treat to Target RCTs: Get "SMART"

- N =100,000
- Randomize 800,000 to 1 BP med (200,000 no BP med), and measure BP response
- Of the 800,000 on 1 BP med, 1 month later randomize 600,000 to a 2nd BP med, and measure BP response
- Repeat until you have 200,000 subjects randomized to 1, 2, 3 or 4 BP meds

Annals of Internal Medicine RESEARCH AND REPORTING METHODS

Detecting Heterogeneous Treatment Effects to Guide Personalized Blood Pressure Treatment

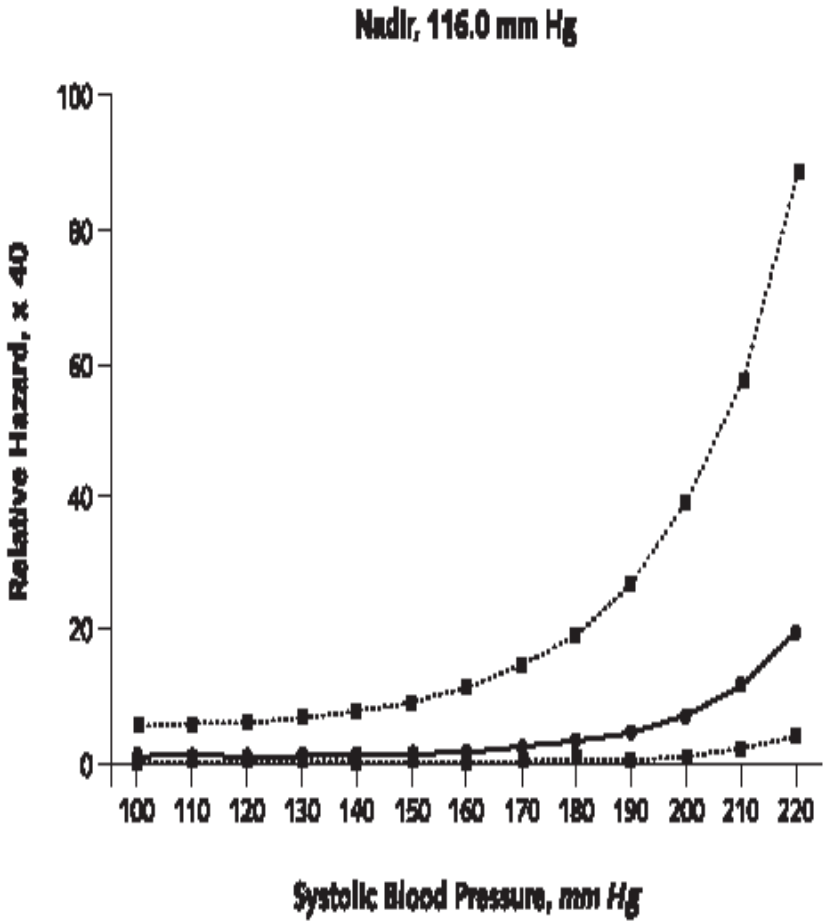
A Modeling Study of Randomized Clinical Trials

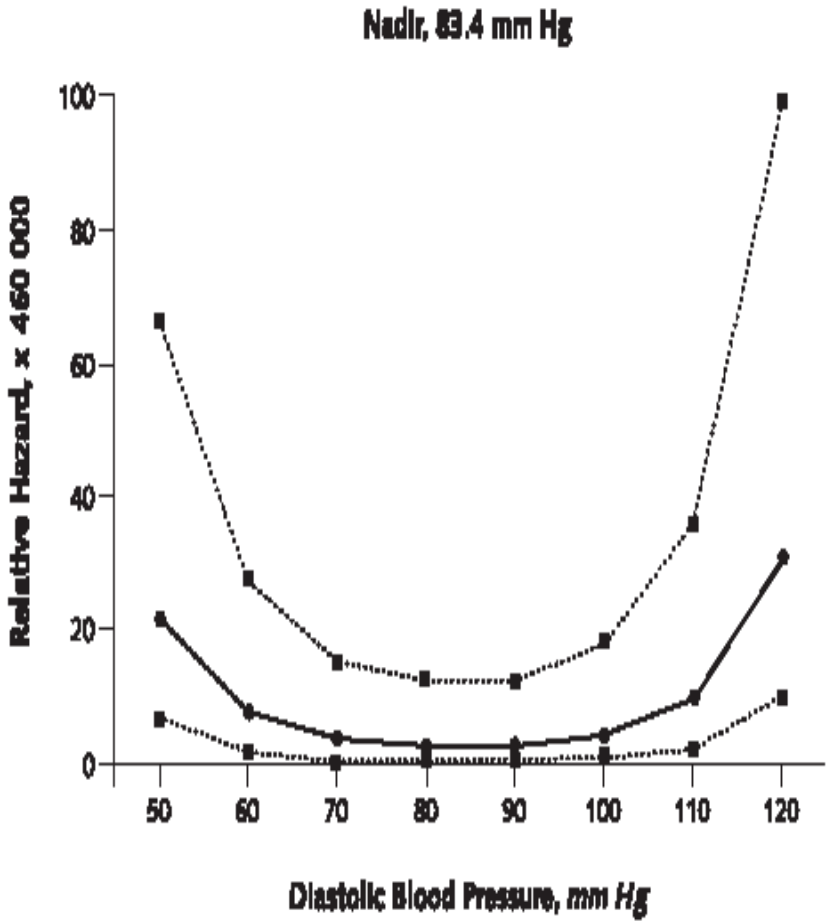
Sanjay Basu, MD, PhD; Jeremy B. Sussman, MD, MS; and Rod A. Hayward, MD

- Two similar studies: ACCORD & SPRINT
  w/ SBP Rx goal of 120 mmHg
- SPRINT clear benefit
- ACCORD no clear benefit
- SPRINT = fewer total meds &
  pts w/ higher DBPs

But Could Pushing DBP Too Low Hurt People?

(Ann Intern Med 2006)





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A Modeling Study of Randomized Clinical Trials

Sanjay Basu, MD, PhD; Jeremy B. Sussman, MD, MS; and Rod A. Hayward, MD

1. Generated simulated population that matched baseline and follow-up RCT attributed
2. Assumed 3rd & 4th BP meds lower RRR than 1st two BP meds
3. Assumed J-curve finding correct (harm if DBP < 70mmHg)

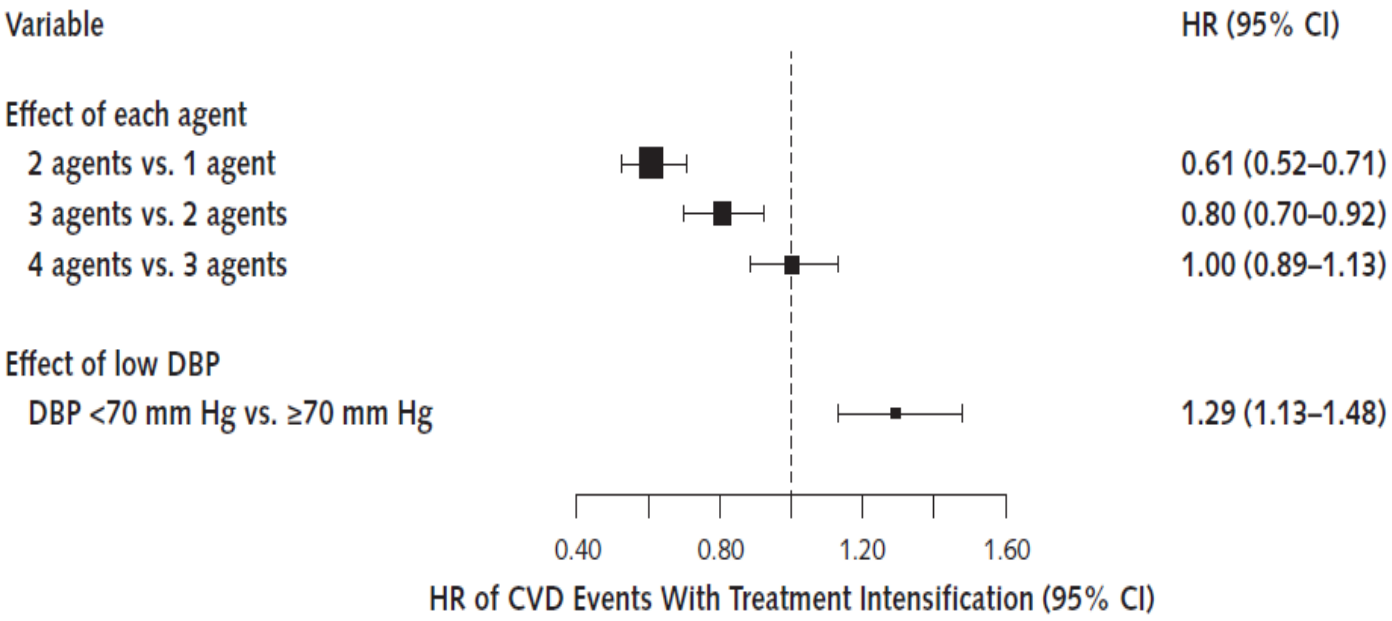
Research Q1: Could HTEs related to J curve and/or # BP meds used explain difference in SPRINT & ACCORD results?

Answer = Yes!

- 3rd BP med ~ half as effective
- 4th BP med = no benefit
- RRI by decreasing DBP < 70

Sequential, multiple assignment, randomized trial (SMART)

Figure 2. HTEs of BP therapy intensification on CVD events potentially hidden from detection in subgroup anal
ACCORD and SPRINT.



Research Q2: Could HTEs related to J curve and/or # BP meds be detected given TTT designs used in SPRINT & ACCORD results?

Answer = No!

Too much post randomization heterogeniety

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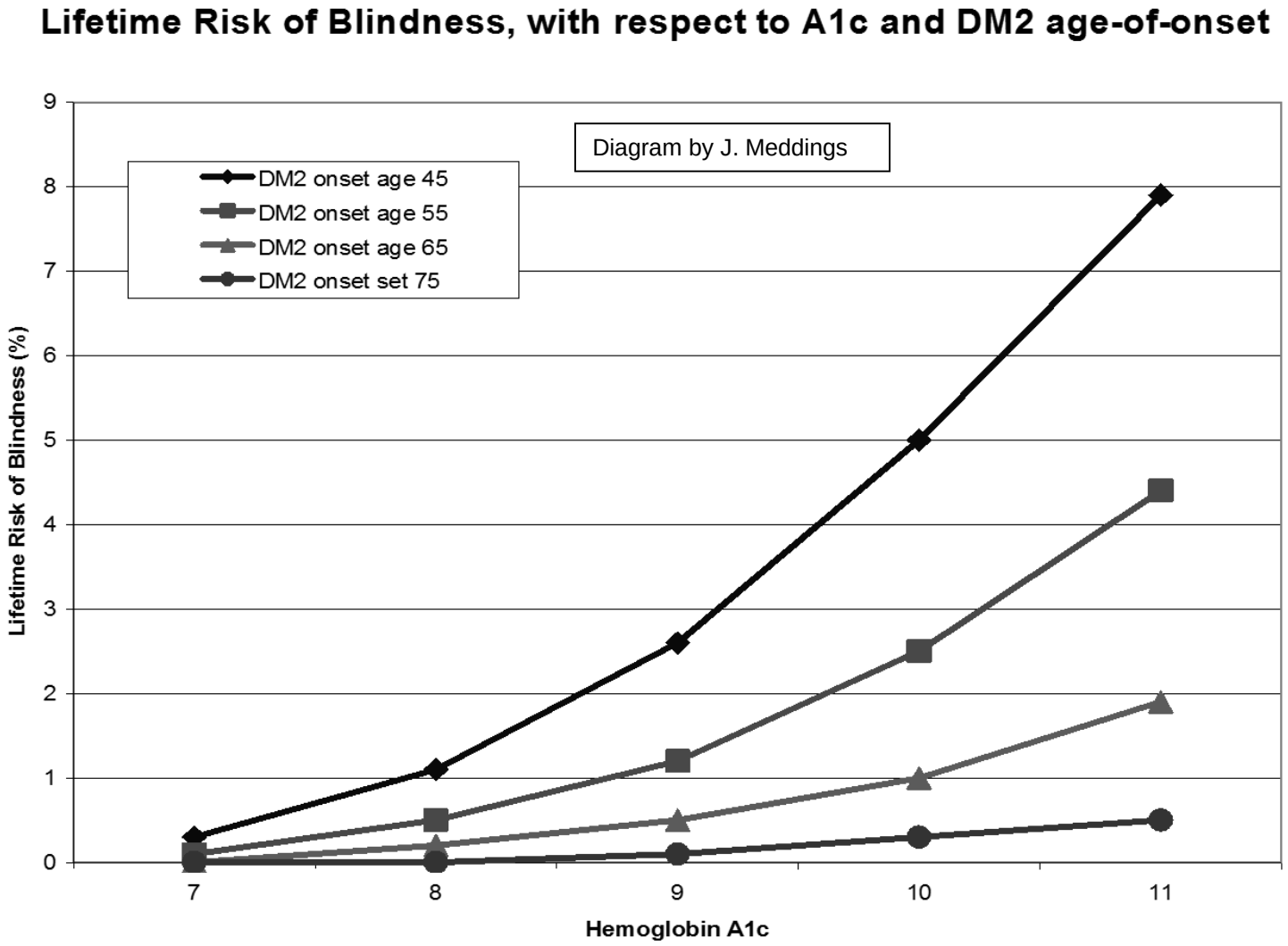
Relationship Between A1c & Microvascular Complications (Vijan Ann Intern Med 1997)



HET in benefit from Glucose Treatment

(Vijan et al. JAMA-IntMed 2014)

Net gains in QALYs,

assuming a 15% reduction in CHD events per 1 point A1c reduction

	Disutility			
	0.001	0.01	0.025	0.05
Age	A1c 8.5 to 7.5%			
45	0.91	0.62	0.14	-0.65
65	0.27	0.11	-0.16	-0.60

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Individualized Therapeutic Reasoning

Remember the 3 elements that form net treatment benefit

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$Risk_{Rx}$ → Risk of adverse effects of treatment (RCTs)

Net Benefit from Rx = ($Risk_{NoRx}$ * RRR_{Rx}) - $Risk_{Rx}$

“Everything should be made as simple as possible – but not one bit simpler”

Albert Einstein