



Why Consider Getting A1C Control at Onset of DM?

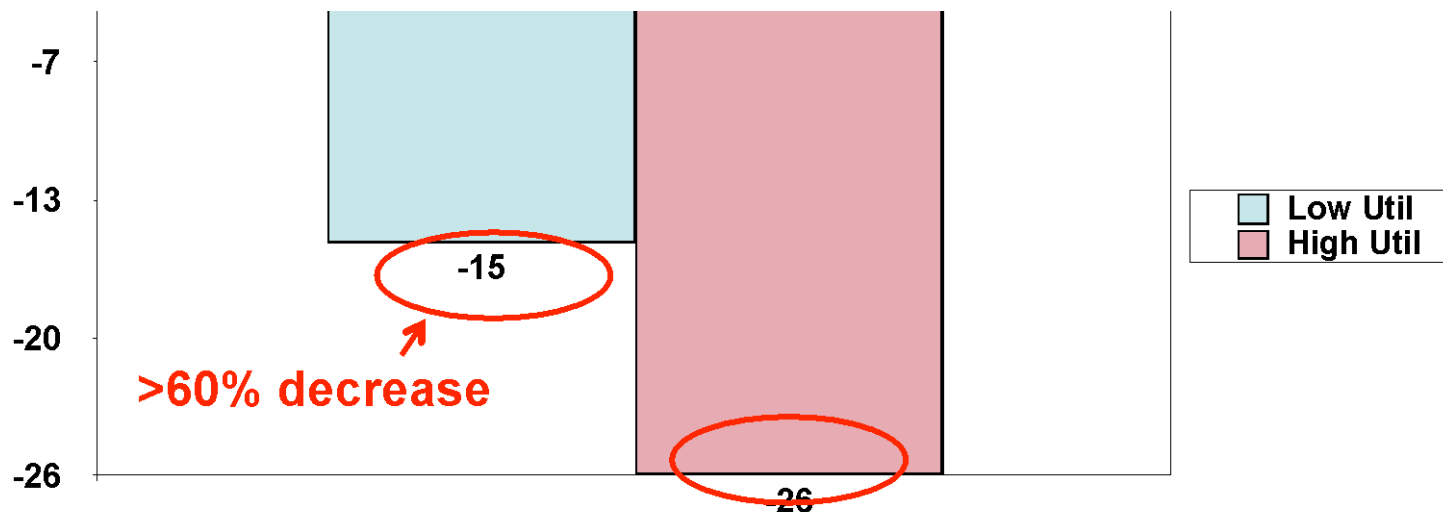
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Diabetes Lead
Care management Institute
Kaiser Permanente

Aspirin, Lisinopril and Lipid Lowering Decreased DM CVD “only” 60-80%

The effect per group was significant

What's CAUSING the other 20-40%?



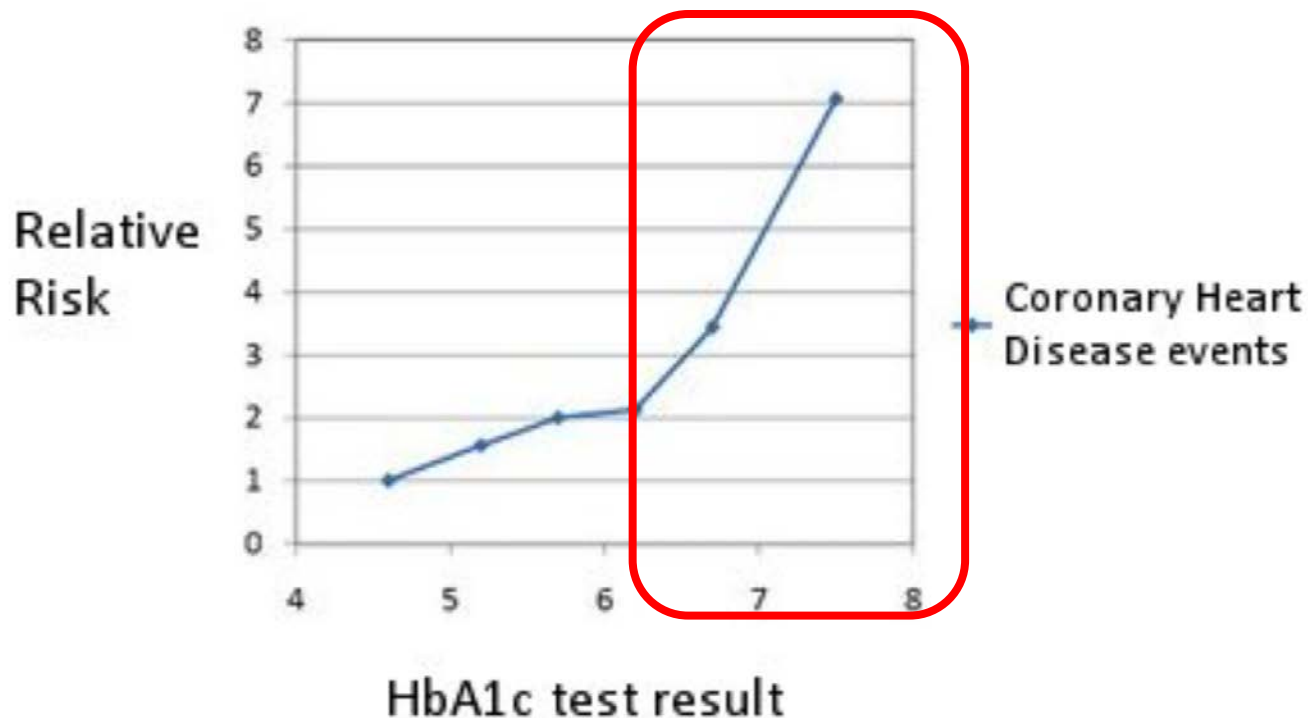
- Even 1 day of 5 utilization was significant
- But taking it 2/3 of the time was much more beneficial

x

Increased A1C is Associated with CVD, But Does it **CAUSE** it?

EPIC Study, 2004

Relative risk of coronary heart disease
episodes in relation to HbA1c levels.



HIDING IN PLAIN SIGHT



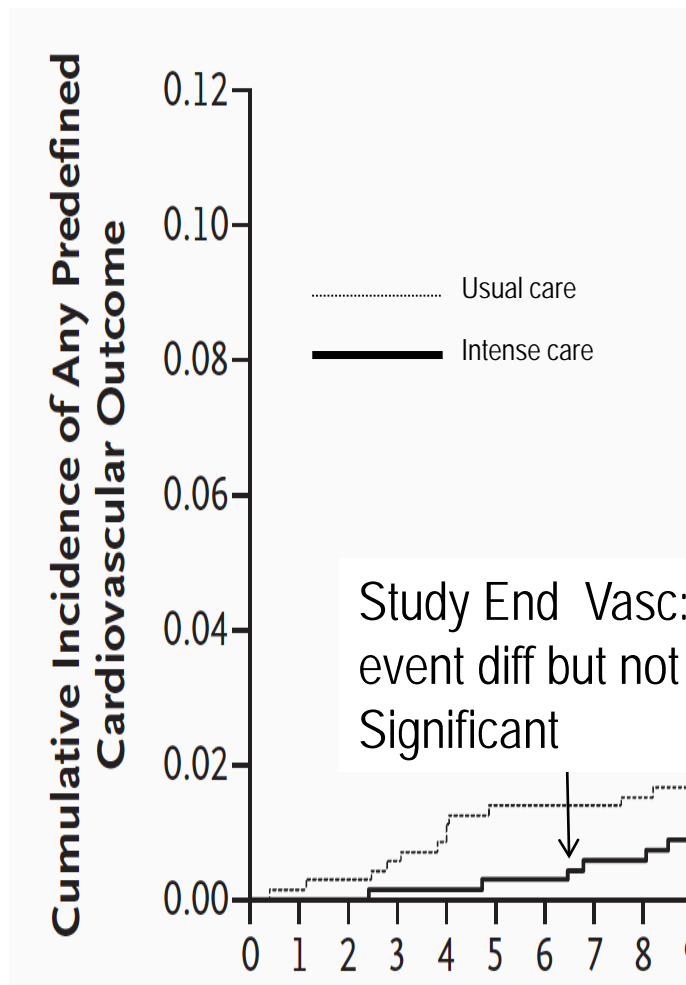




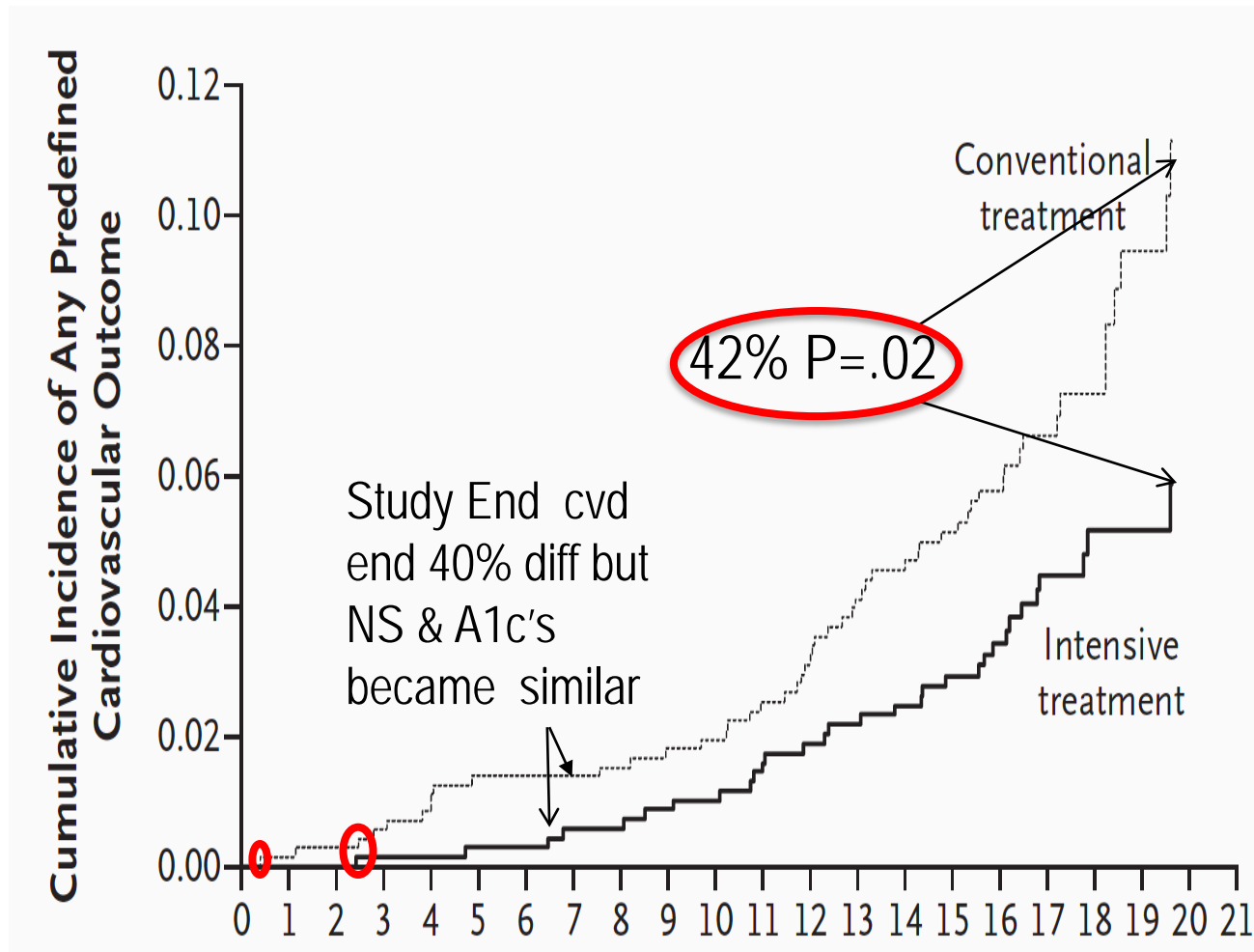
Why we DIDN'T think elevated A1C CAUSED CVD

- There was no SIGNIFICANT evidence that DELAYING decline in a1c to <7 **for 5-10 yrs.** had any harm in DM:
 - **Early Onset:** RCT Type 1 [DCCT] & Type 2DM [UKPDS] did not show SIGNIFICANT drop in CVD during the study
 - **Late efforts** showed more harm than benefit [ADVANCE, VA study and ACCORD]
 - Waiting too long to attain good A1C control may be dangerous
- However early control producing a late benefit remained a possibility, [Legacy effect]
 - DCCT & UKPDS looked at the incidence of CVD 10 yrs. after good A1C control during study
 - that reverted to no difference in control within 1 yr of study end
 - what did they find?

Type 1: DCCT CVD: Intense vs Usual Care Effect at Study End*

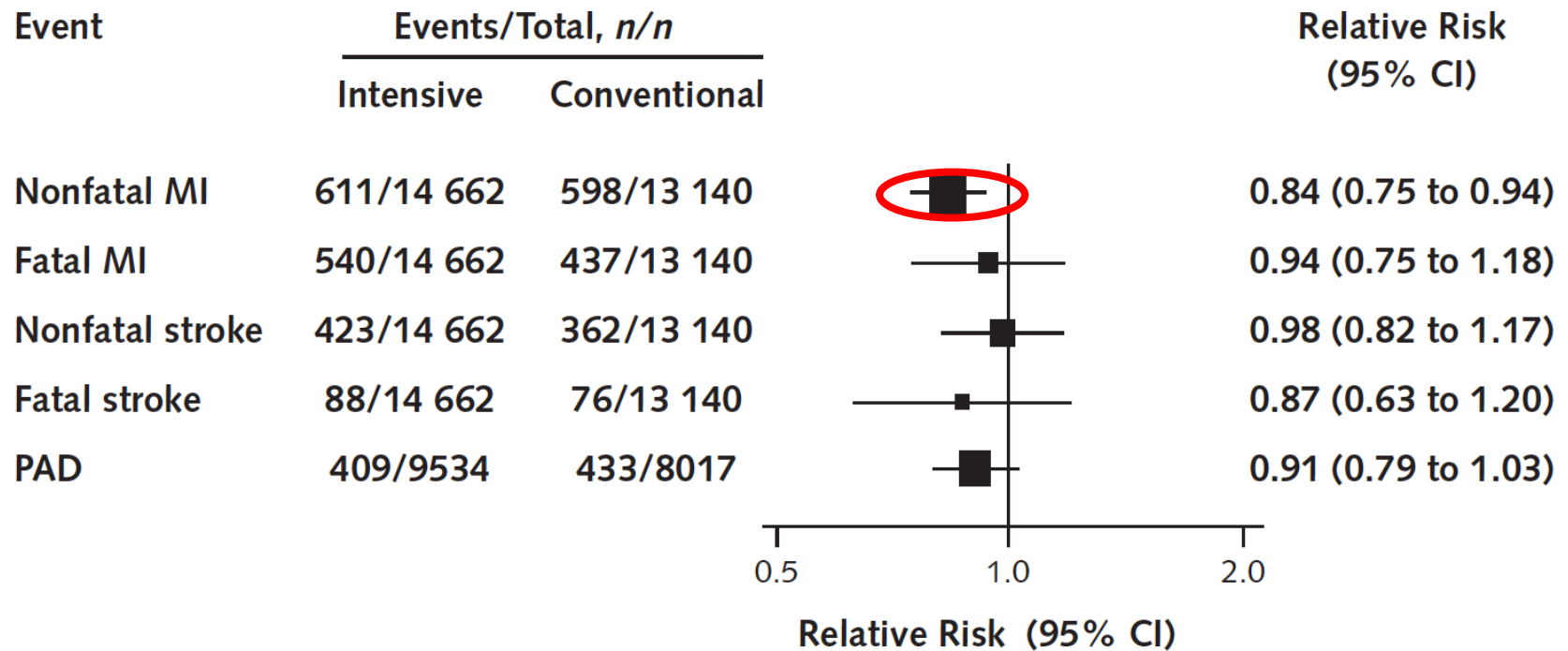


DCCT intense control at study end and 11 yrs. later*



>10 yr Type 2 DM: Meta analysis of RCT's* glycemic control & Non-Fatal Heart Attacks

C. All Trials



* Accord, Advance VADT & UKPDS

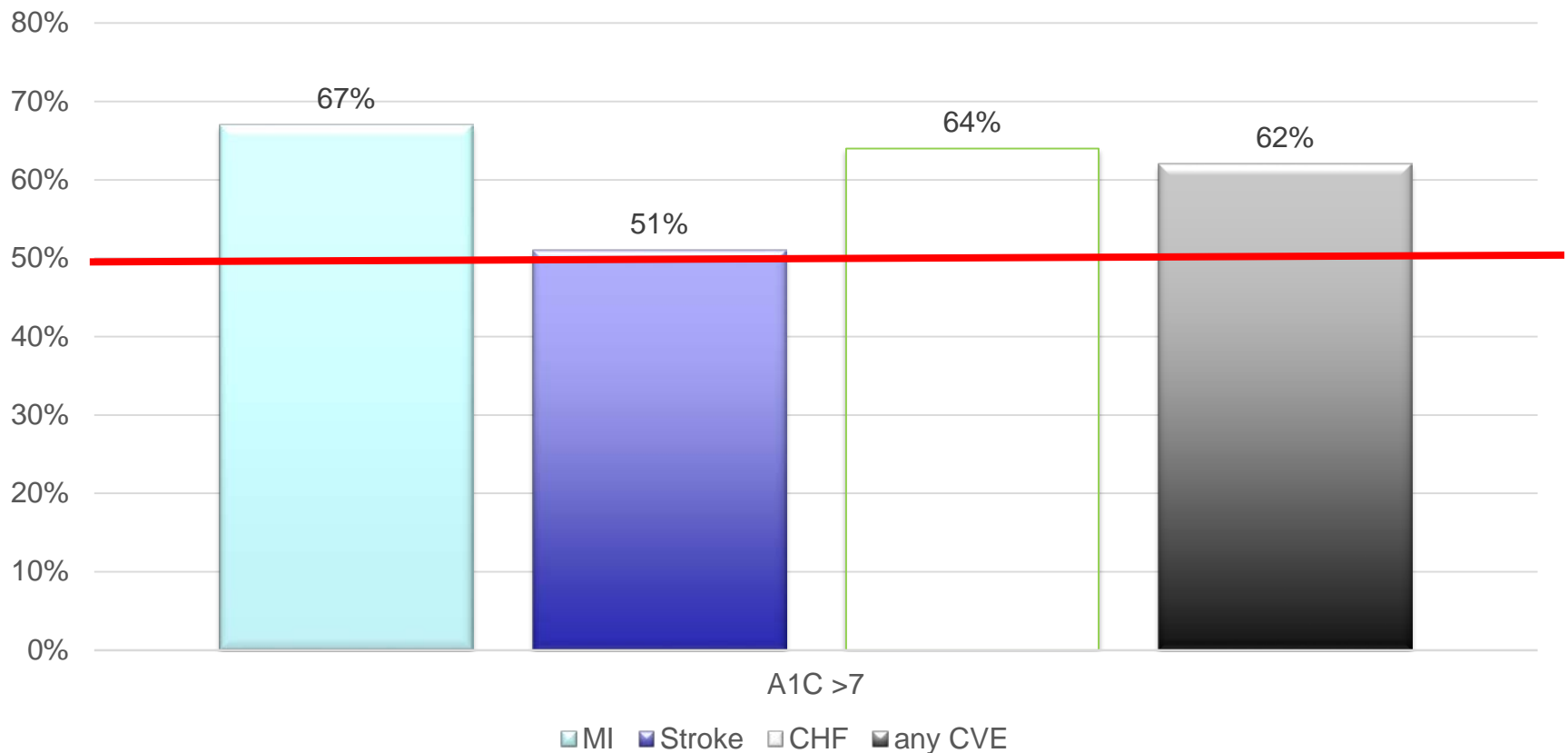
UKPDS Observational Study 5.3

Yrs After New Type 2 DM:

- 105,000 pts were in UKPDS mean age 61
- At onset
 - **8.3% A1C** but In 2 yrs
 - **26%** had an A1C **>7**
 - 5.3 yrs later those >7 were compared with the pts that achieved A1C <7 the first year, regarding CVD complications

At 2 Yr of A1C >7 CVD Events Significantly Increased at 5.3 yrs Follow-up

Relative Risk c/w those with A1C <7 in first year



Paul et al. Cardiovasc Diabetes (2015) 14:100

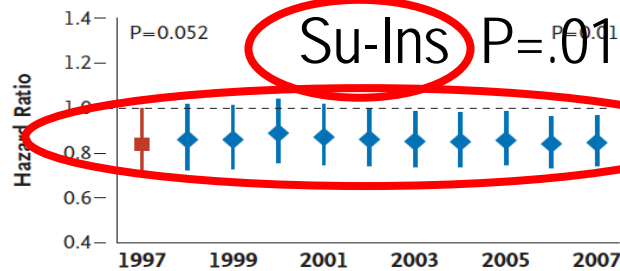
Number Needed to Treat to
treat to Prevent 1 event?

14 for low-risk*

7 for high-risk*

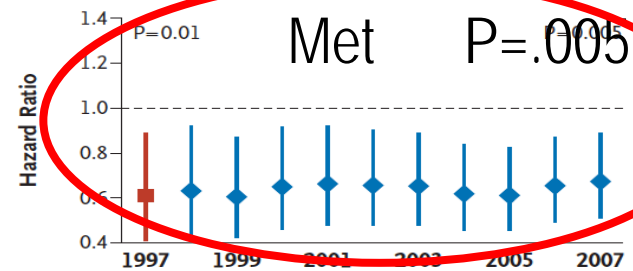
UKPDS 10 yr f/u Post End

C Myocardial Infarction



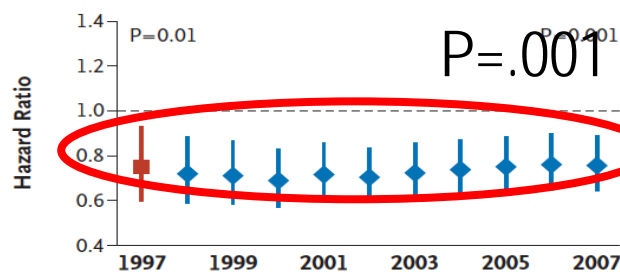
No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	186	212	239	271	296	319
Sulfonylurea-insulin	387	450	513	573	636	678

D Myocardial Infarction



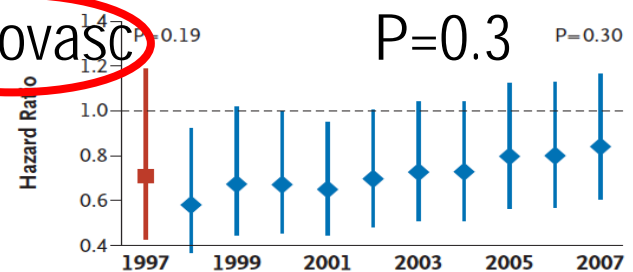
No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	73	83	92	106	118	126
Metformin	39	45	55	64	68	81

E Microvascular Disease



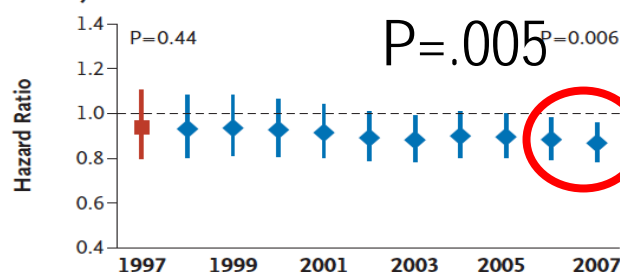
No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	121	155	187	205	212	222
Sulfonylurea-insulin	225	277	338	378	406	429

F Microvascular Disease



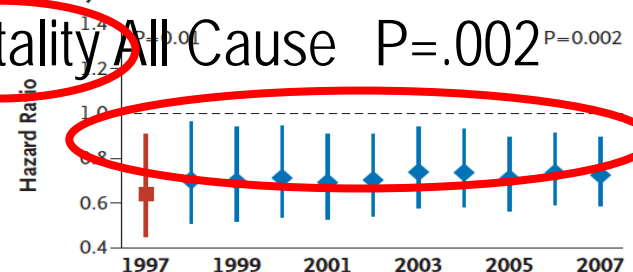
No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	38	58	70	73	74	78
Metformin	24	37	44	52	58	66

G Death from Any Cause



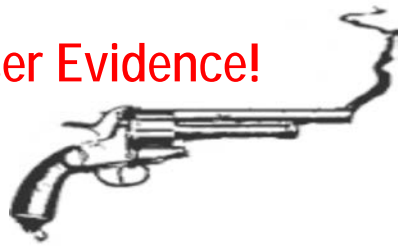
No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	213	267	330	400	460	537
Sulfonylurea-insulin	489	610	737	868	1028	1163

H Death from Any Cause

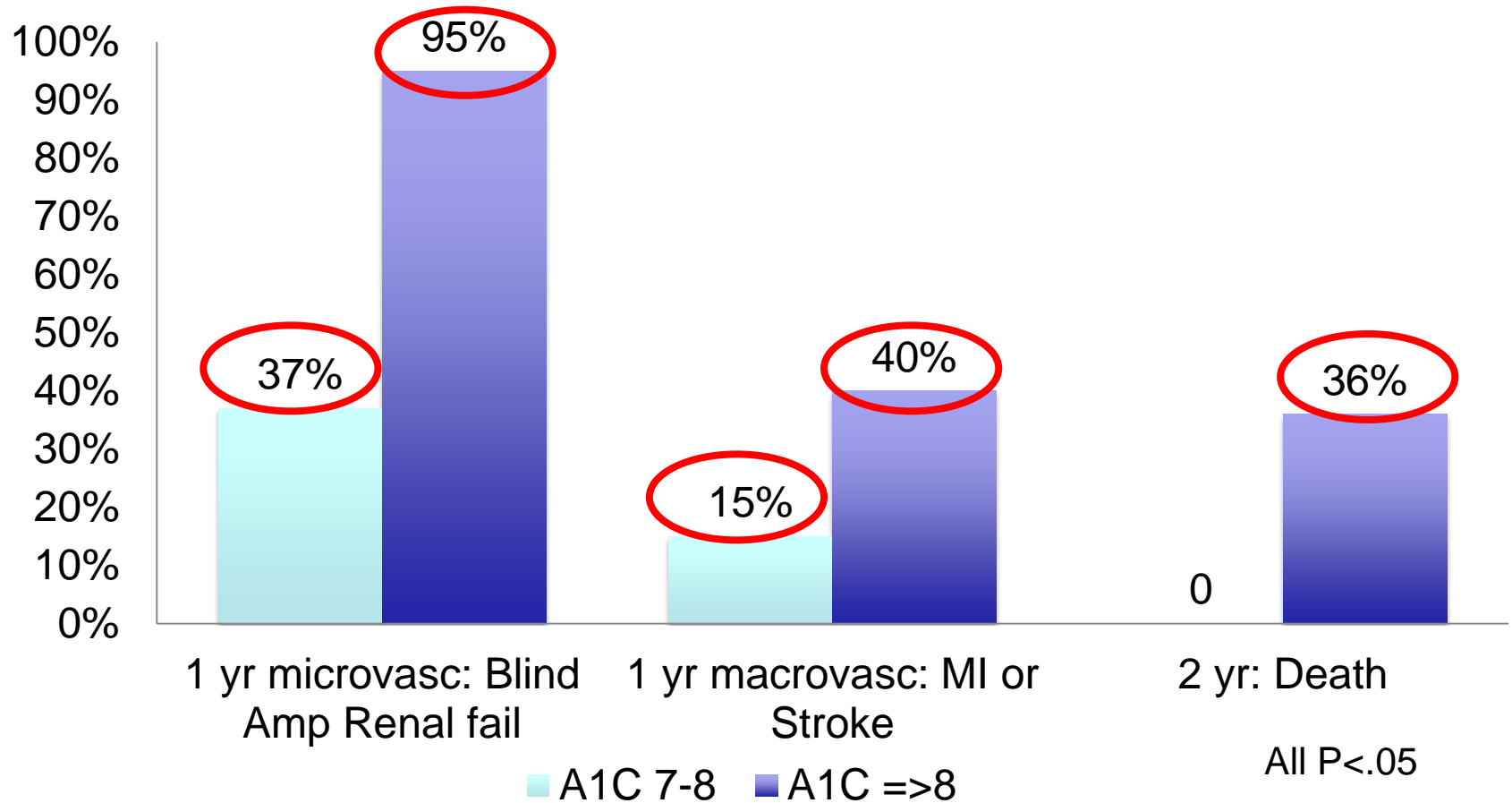


No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	89	113	136	160	183	217
Metformin	50	70	86	110	123	152

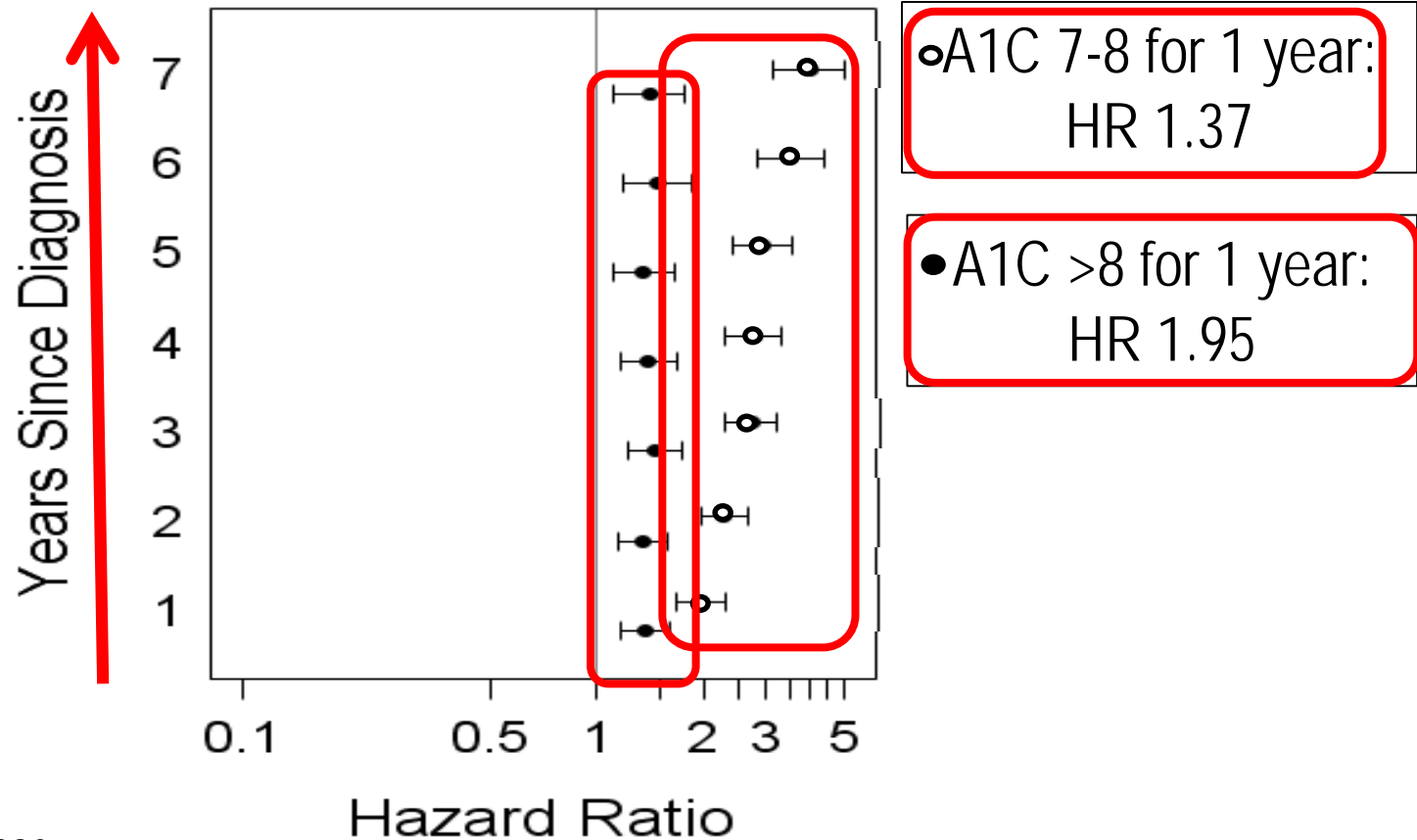
New Kaiser Evidence!



- >8,000 Kaiser new DM pts A1C 7-8 or \Rightarrow 8 yrs for 1 or 2 yrs, then NS diff
- Compared to <7 @ up to 7 yrs later LEGACY effect:

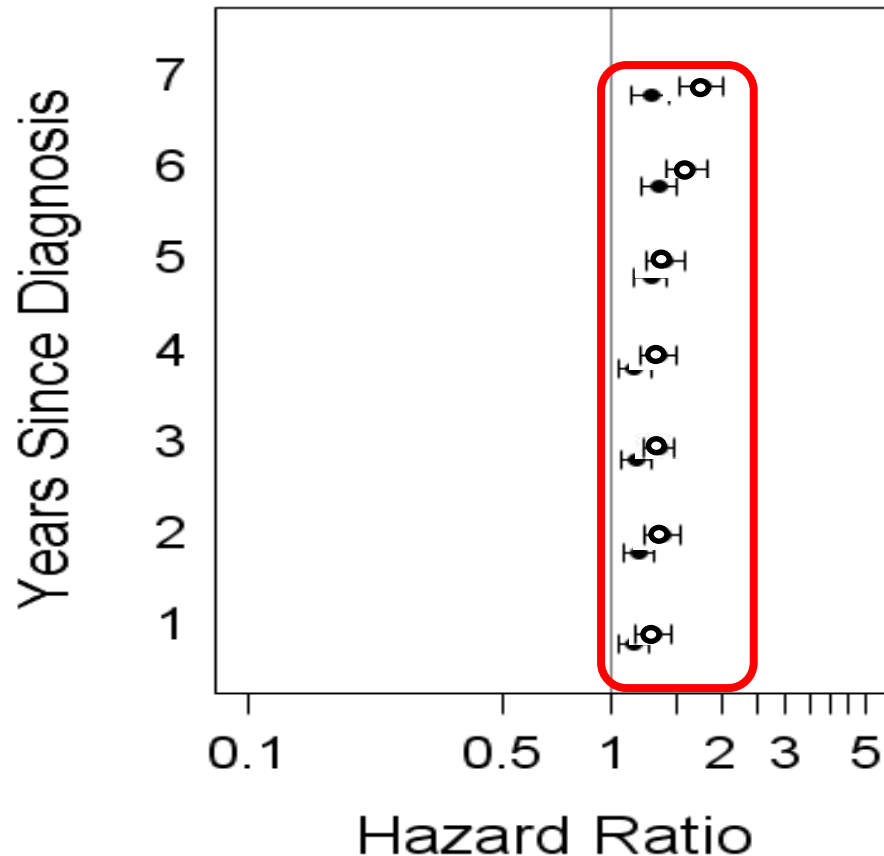


Microvascular Events: Negative Legacy Effect at Year 1



A1C < 7% = Reference
* Adjusted for later A1C

Macrovascular Events: Negative Legacy Effect at Year 1

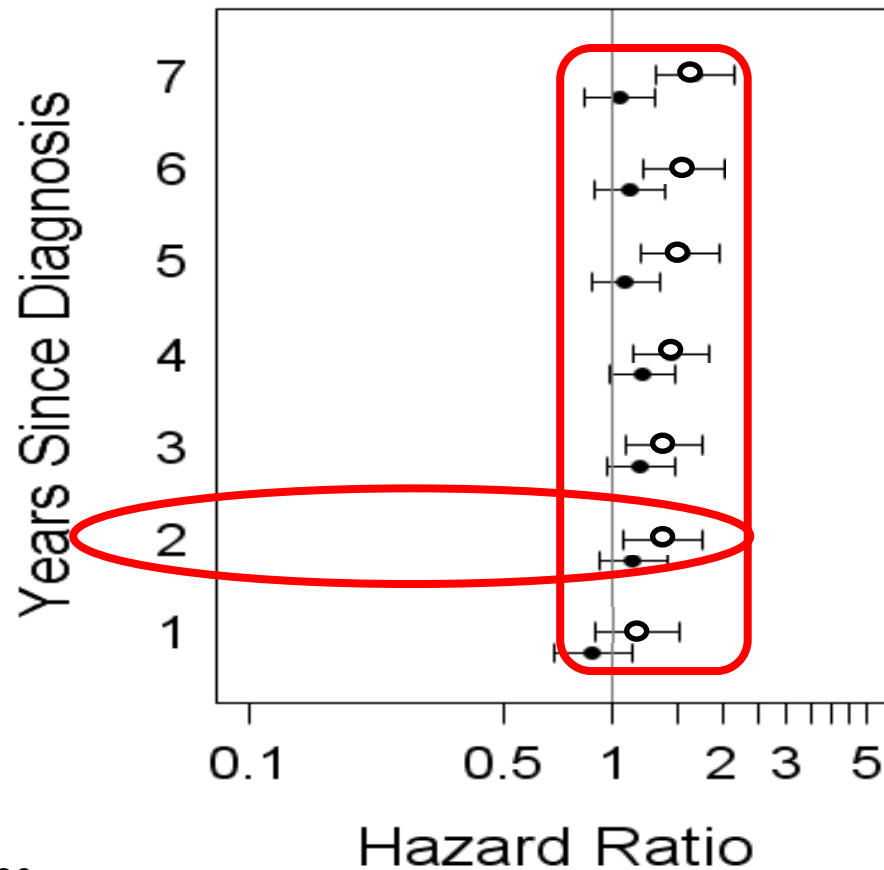


• A1C 7-8 for 1 yr.
HR 1.15

◦ A1C >8 for 1 year:
HR 1.40

A1C < 7% = Reference
* Adjusted for later A1C

Death: Negative Legacy Effect at Year 2 (A1C \geq 8% only)



○ A1C > 8 for 2 years:
HR 1.36

A1C < 7% = Reference
* Adjusted for later A1C

So What Are You Gonna DO?

Metformin EARLY, even pre-diabetes. It's

- **High Quality 10 yr evidence: Prevents complications CVD, & death**
- Its \$10/yr, & **cost savings** even in pre-diabetes
- **Risk/Benefit:** no significant hypoglycemia & slight weight loss. Its easy
- **Pt Preference** to use it vs weight loss and exercise, and additive if those are done

Its safe to treat DM early, not safe later [ACCORD]

Why not try to prevent progression early?

Summary: Why consider improving A1C within 1 year of onset of A1C over 7

- Why consider improving A1C within 1 year of onset of A1C over 7?
 - In type 1 DM DCCT showed a significant 42-57% increase in CVD 10 yrs later
 - In type 2 DM UKPDS showed elevation resulted in over 50% increased CVD in 5 yrs and in 10 yrs was associated with increased death
 - In addition trying to control glucose late resulted in increased deaths in one large study.
 - In a large population in No California A1C over 8 for 2 yrs was associated with 40% increase in CVD events and if elevated 2 yrs, was associated with increased 36% deaths.
- Given we will want to control it sometime to prevent microvascular disease, why not as soon as we can, when its **easier** and **safer** to do than later?
 - Why not? HASSLE is the biggest blockade to action, so lets remove it!
- Doesn't it also suggest routine screening to pick up A1C before they are elevated above 7 for 1 yr to give us the opportunity to prevent late events

When NOT to Treat elevated A1C's

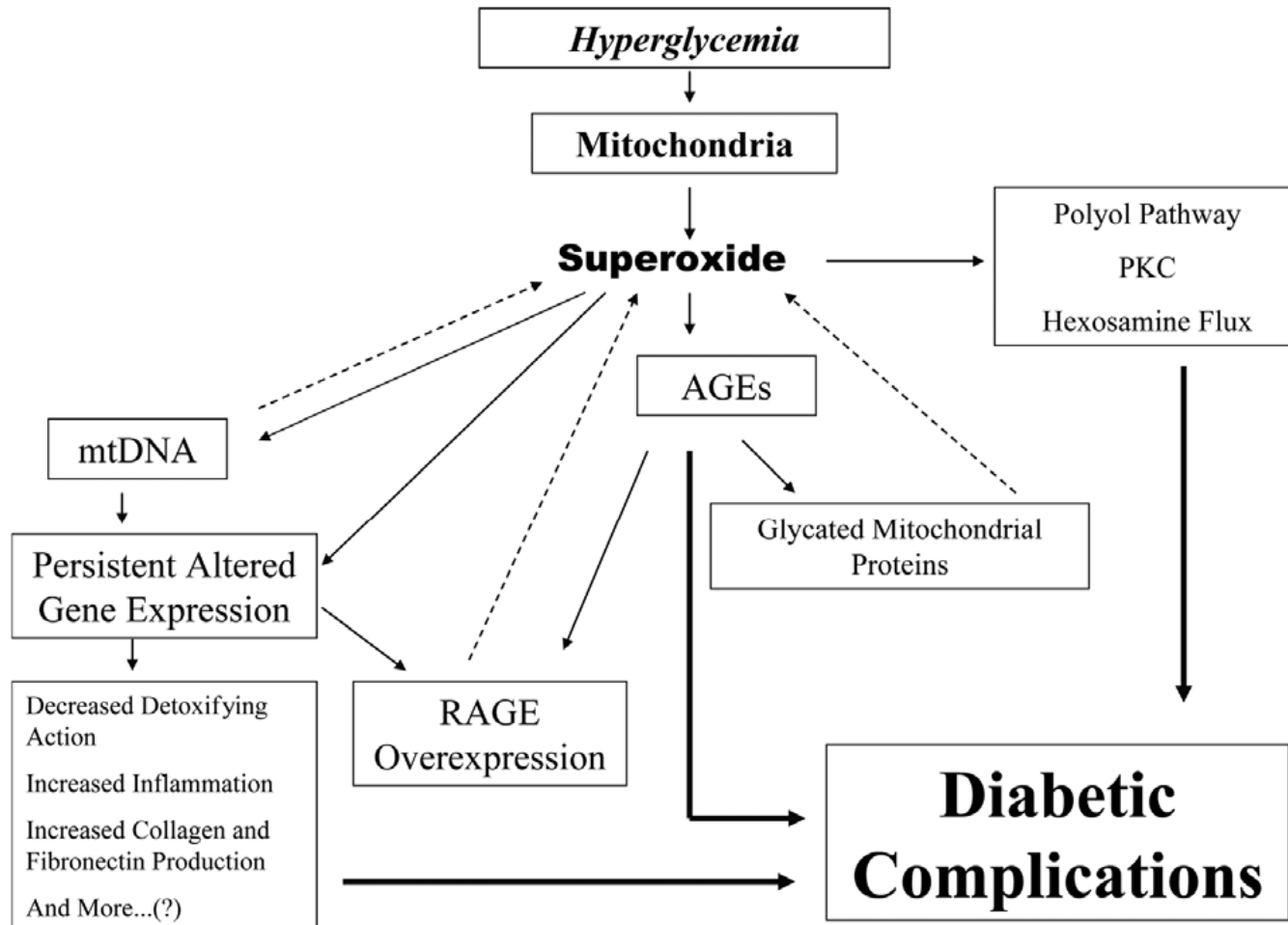
- For metformin: renal disease, and if complications not likely by time of expected death.
- Over 65: consider risk of hypoglycemia, pt preferences and if risk of complications by time of death is low.



Should we implement? GRADE criteria

- Strength of evidence: The evidence is observational good observational
- Risks benefit: risk of hypoglycemia but less so in early type 2 and even type 1, is significant but the benefit is lasso very significant. But it varies by medication, metformin being less likely to produce hypoglycemia and more likely to prevent a CVD event for example.
- Cost benefit: if control is relatively simple cost is not great. The complications are very costly except death.
- Values and preferences: most people do not want to take medication, and insulin especially. However if there is a true relationship to complications and its explained that may vary from individual to individual

Metabolic Memory / Legacy Effect



Ceriello, A. (2009). Diabetes Res Clin Pract



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Legacy effect in type 2 diabetes: Impact of duration and intensity of control on future complications

Neda Laiteerapong, MD, MS; Yue Gao, MPH; Jennifer Liu, MPH; Howard Moffet, MPH; Sandra Ham, MPH; Elbert Huang, MD, MPH, Andrew Karter PhD

Midwest SGIM - September 22, 2016



THE UNIVERSITY OF CHICAGO
DEPARTMENT OF MEDICINE

CHRONIC DISEASE CENTER
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But Our Data is Observational. Are there Two Large RCTS showing the same thing?

- The DCCT 11 yr Follow up
- At the 6.5 yr end of study
 - A1C: 9.1 in conventional care, 7.2% in intense treatment
 - Microvascular disease significant drop
 - Retinopathy Nephropathy Neuropathy
 - Macrovascular combined endpoint*: 0.8% conventional and 0.5% events in intense, trend but not significant
 - No change in death

*MI Stroke CVD Death Angina or vascular procedure

NEJM 1993