OBJECTIVE

To critically appraise an RCT and develop a brief synopsis of the study results using a similar format to the one outlined.

Presenter Disclosure

- Presenter's Name: James McCormack
- I have no current or past relationships with commercial entities
- Speaking Fees for current learning activity:
  - I have received a speaker's fee from CPPD for this learning activity

Commercial Support Disclosure

- This Learning Activity has received no financial or in-kind support from any commercial or other organization

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Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

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ABSTRACT

BACKGROUND

Epidemiologic studies have shown a relationship between glycated hemoglobin levels and cardiovascular events in patients with type 2 diabetes. We investigated whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors.

METHODS

In this randomized study, 10,251 patients (mean age, 62.2 years) with a median glycated hemoglobin level of 8.1% were assigned to receive intensive therapy (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a level from 7.0 to 7.9%). Of these patients, 38% were women, and 35% had had a previous cardiovascular event. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The finding of

therapy after a mean of 3.5 years of follow-up.

therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; P=0.04). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group (P<0.001).

CONCLUSIONS

As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously

Let's recap

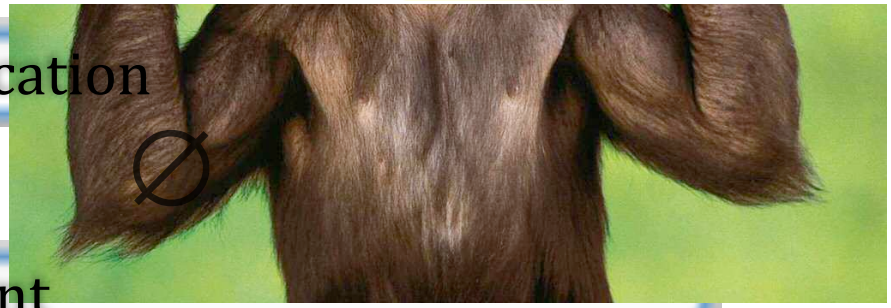
- Look at the Abstract
- Read the title
- Look at what was studied
- Look at the outcomes
- Read the conclusions

random

All 10,251 patients were randomly assigned

blind

premature death, blindness, kidney failure



allocation

∅

intent

Analyses of primary and secondary outcomes were performed with the use of time-to-event methods according to the intention-to-treat principle, and occurrences of these outcomes in the

follow

of patients within the previous 12 months; 50 patients (0.5%, including 26 patients in the intensive-therapy group and 24 in the standard-therapy group) were lost to follow-up, and 162 patients

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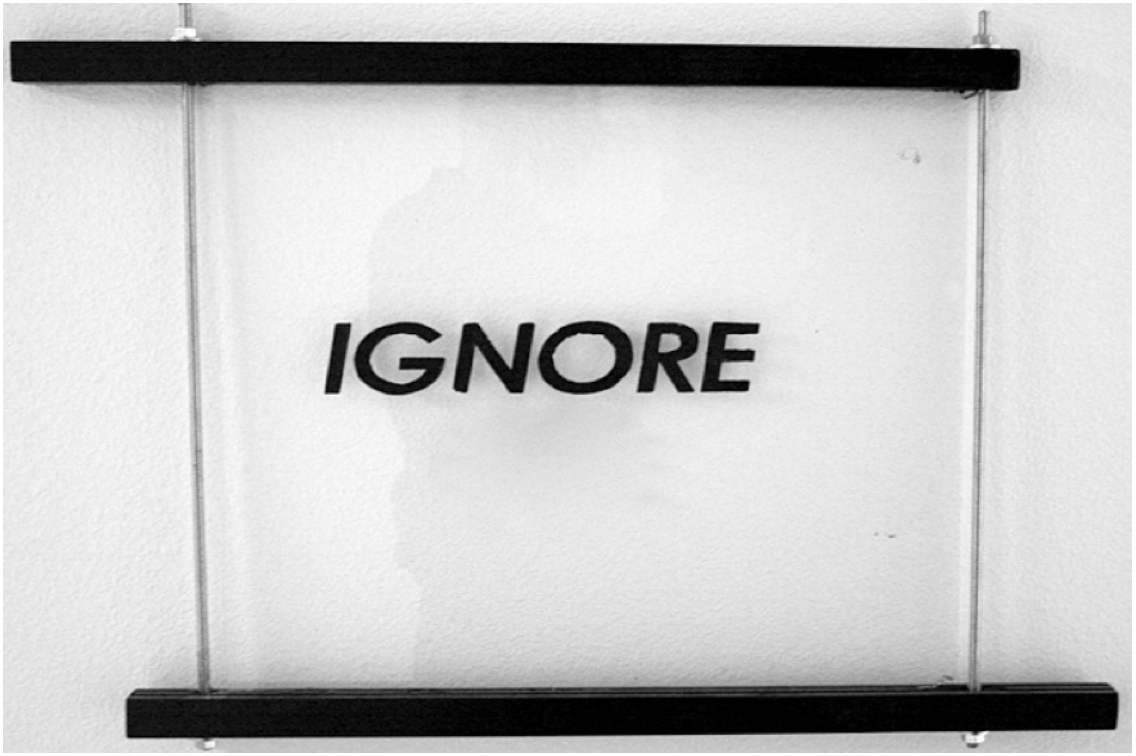
Let's recap

- Random
- Blind
- Allocation
- Intent
- Follow
- Conflicts

MUCH OF THE REST OF THE TEXT

- INTRODUCTION
- MOST OF THE METHODS
- STATISTICAL TESTS
- DISCUSSION



Patient Characteristics

Table 1. Characteristics of the Patients at Baseline.*

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)
Age (yr)	62.2±6.8	62.2±6.8
Female sex (%)	38.7	38.4
Median duration of diabetes (yr)	10	10
Previous cardiovascular event (%)	35.6	34.8
Previous congestive heart failure (%)	4.9	4.8
Race or ethnic group (%)†		
White	64.4	64.5
Black	19.7	18.9
Hispanic	7.0	7.4
Education (%)		
Less than high school	15.7	14.0
High-school graduate	26.1	26.7
Some college	32.7	32.9
College degree or higher	25.5	26.4
Cigarette-smoking status (%)		
Current	14.3	13.7
Former	44.4	44.0
Never	41.3	42.3
Weight (kg)	93.5±18.7	93.6±18.7
Body-mass index	32.2±5.5	32.2±5.5
Waist circumference (cm)	106.8±14.3	106.8±13.8
Blood pressure (mm Hg)		
Systolic	136.2±17.0	136.5±17.2
Diastolic	74.8±10.6	75.0±10.7
Medications (%)		
Insulin	34.1	35.7
Metformin	59.7	60.0
Any sulfonylurea	50.8	49.4
Any thiazolidinedione	19.5	19.2
Any antihypertensive agent	84.9	86.0
Angiotensin-converting–enzyme inhibitor	53.0	53.0
Aspirin	54.8	54.1
Beta-blocker	28.7	29.9
Any thiazide diuretic	26.5	26.4
Statin	61.7	62.4
Glycated hemoglobin (%)		
Mean	8.3±1.1	8.3±1.1
Median	8.1	8.1
Fasting serum glucose (mg/dl)	174.9±56.0	175.7±56.5
Cholesterol (mg/dl)		
Total	183.3±42.1	183.3±41.6
Low-density lipoprotein	104.9±34.0	104.9±33.8
High-density lipoprotein		
Women	47.2±13.0	46.9±12.2
Men	38.4±9.5	38.8±9.8
Median triglyceride (mg/dl)	156	154

No "clinical" differences

N = 5,100

Age 62
Female 38%
Diabetes 10 years
Previous CV event 35%
White 65%
Smoker 14%
BMI 32
BP 136/75
A1C 8.3%
Total Chol 183 or 4.7

Let's recap

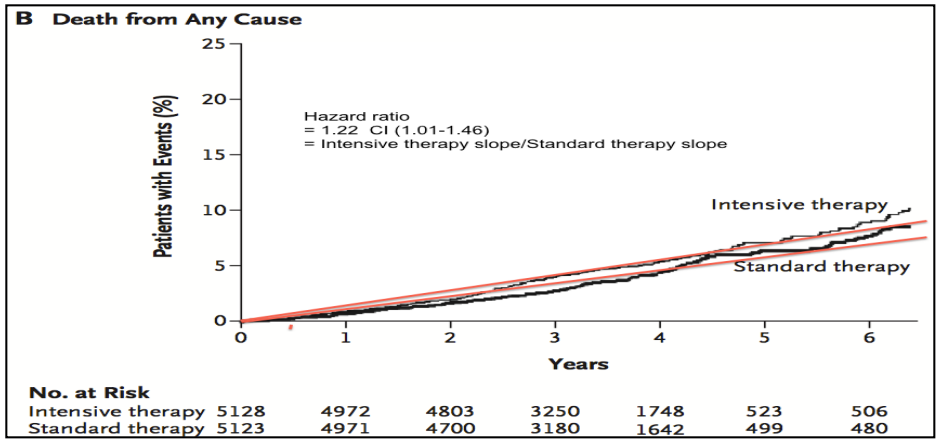
- Differences between groups
- Baseline characteristics

Similar but different relatives

Relative risk/risk ratio (RR) - ratio of two probabilities (%) at one point in time - treatment/control

- eg 8% vs 10% - RR = 8/10 = 0.8
- most useful in low probability events

Hazards ratio (HR) - ratio of two hazard rates (slopes) over a time period



Odds ratio (OR) - ratio of two odds (25/1) - typically used in case-control studies - typically the incidence is not known

OR is a reasonable estimate of the **RR** if a disease is "rare" <~15% but treating an **OR** as if it were an accurate estimate of the **RR** will typically overestimate both the likely benefits and harms of treatment

Main Patient Outcomes

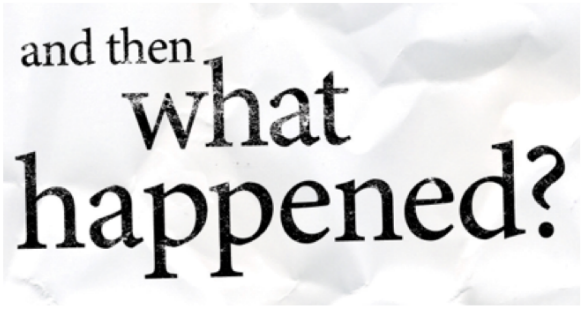


Table 4. Primary and Secondary Outcomes.*

Outcome	A1c = 6.4%		A1c = 7.5%		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per yr*	*no. of patients (%)*	*% per yr*		
Primary outcome	352 (6.9)	2.11	371 (7.2)	2.29	0.90 (0.78–1.04)	0.16
Secondary outcome						
Death						
Any cause	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Cardiovascular causes	135 (2.6)	0.79	94 (1.8)	0.56	1.35 (1.04–1.76)	0.02
Nonfatal myocardial infarction	186 (3.6)	1.11	235 (4.6)	1.45	0.76 (0.62–0.92)	0.004
Nonfatal stroke	67 (1.3)	0.39	61 (1.2)	0.37	1.06 (0.75–1.50)	0.74
Fatal or nonfatal congestive heart failure	152 (3.0)	0.90	124 (2.4)	0.75	1.18 (0.93–1.49)	0.17
Causes of death						
Any	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Unexpected or presumed cardiovascular disease†	86 (1.7)		67 (1.3)			
Fatal myocardial infarction†	19 (0.4)		13 (0.3)			
Fatal congestive heart failure†	23 (0.4)		16 (0.3)			
Fatal procedure†						
For cardiovascular disease	10 (0.2)		3 (0.1)			
For noncardiovascular disease	1 (<0.1)		3 (0.1)			
Fatal arrhythmia†	4 (0.1)		10 (0.2)			
Fatal stroke†	9 (0.2)		11 (0.2)			
Other cardiovascular disease†	8 (0.2)		10 (0.2)			
Cancer	65 (1.3)		63 (1.2)			
Condition other than cancer or cardiovascular disease‡	50 (1.0)		35 (0.7)			
Undetermined	7 (0.1)		11 (0.2)			

Primary outcome = nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes

	Intensive therapy	Standard therapy	Hazard Ratio	Hazard Ratio 95% CI	Relative Risk
Primary outcome (%)	6.9	7.2	0.9	0.78-1.04	0.95
Death (%)	5	4	1.22	1.01-1.46	1.25
Non-fatal MI (%)	3.6	4.6	0.76	0.62-0.92	0.79
Non-fatal stroke (%)	1.3	1.2	1.06	0.75-1.50	1.1
CHF (%)	3	2.4	1.18	0.93-1.49	1.22

Let's recap

- Primary outcomes
- Other outcomes
- Differences
  - Absolute numbers
  - Relative numbers
  - Confidence intervals

Adverse Events

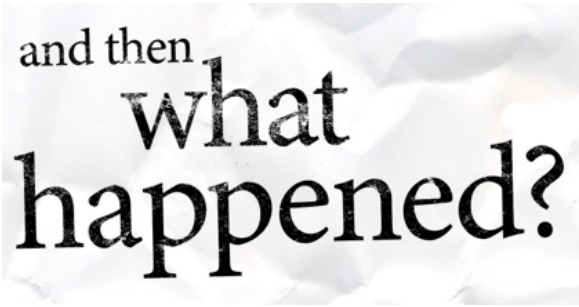


Table 3. Adverse Events, Clinical Measures, Tobacco Use, and Use of Nonglycemic Medication after Randomization.*

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)	P Value†
Adverse events			
Hypoglycemia — no. (%)			
Requiring medical assistance	538 (10.5)	179 (3.5)	<0.001
Requiring any assistance	830 (16.2)	261 (5.1)	<0.001
Fatal or nonfatal heart failure — no. (%)	152 (3.0)	124 (2.4)	0.10
Motor vehicle accident in which patient was driver — no./total no. (%)	9/5033 (0.2)	14/5036 (0.3)	0.40
Any nonhypoglycemic serious adverse event — no. (%)	113 (2.2)	82 (1.6)	0.03
Fluid retention — no./total no. (%)‡	3541/5053 (70.1)	3378/5054 (66.8)	<0.001
Clinical measures			
Weight gain >10 kg since baseline — no./total no. (%)	1399/5036 (27.8)	713/5042 (14.1)	<0.001
Alanine aminotransferase >3 times ULN — no./total no. (%)§	51/5065 (1.0)	77/5061 (1.5)	0.02
Low-density lipoprotein cholesterol — mg/dl¶	90.8±3		
Blood pressure — mm Hg¶			
Systolic	126.4±1		
Diastolic	66.9±1		

	Intensive therapy	Standard therapy	Hazard Ratio	Hazard Ratio 95% CI
Primary outcome (%)	6.9	7.2	0.9	0.78-1.04
Death (%)	5	4	1.22	1.01-1.46
Non-fatal MI (%)	3.6	4.6	0.76	0.62-0.92
Non-fatal stroke (%)	1.3	1.2	1.06	0.75-1.50
CHF (%)	3	2.4	1.18	0.93-1.49
Hypoglycemia (%)	10.5	3.5		
Serious adverse event	2.2	1.6		
Weight gain >10kg	27.8	14.1		

Let's recap

- Adverse outcomes
- Any other outcomes
- Differences
  - Absolute numbers
  - Relative numbers
  - Confidence intervals