Risk Factor Control in Type 2 Diabetes: Is Lower Really Better?

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Disclosures

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  - AstraZeneca LP
  - Bristol-Myers Squibb
  - Novartis Pharmaceuticals

Agenda

- Current guidelines (and how we got there)
- Controversies in risk factor control
- Greg's study of the association between A1C and CVD
- Isolated vs. simultaneous risk factor control
- Greg's study of simultaneous control
- Greg's study of glycemic burden

Current ADA Guidelines

- Levels specified for CVD risk reduction but less clear for microvascular disease
- HbA1c < 7%
  - < 6.5% for short DM duration, long life expectancy, no CVD
  - < 8% for advanced, complicated diabetes
- Blood Pressure < 140/80 mm Hg (<130 until 2013)
  - Systolic may be higher or lower depending on characteristics
- Low-density lipoprotein cholesterol < 100 mg/dl
  - Reduction of 30-40% if LDL is very high or close to 100
  - < 70 mg/dl for very high risk patients with overt CVD

Lipids in Type 2 Diabetes

- NCEP ATP III recommends LDL < 100 mg/dl with < 70 as an optional goal for those at very high risk
- Statin trials not designed to identify treatment thresholds
- LDL reductions in statin trials generally 30-40%
- Treat all patients with statins (if possible) regardless of LDL
- Other lipid parameters
  - Non-HDL
  - HDL
  - Triglycerides
  - VLDL, Apolipoproteins, etc.

Blood Pressure in Type 2 Diabetes

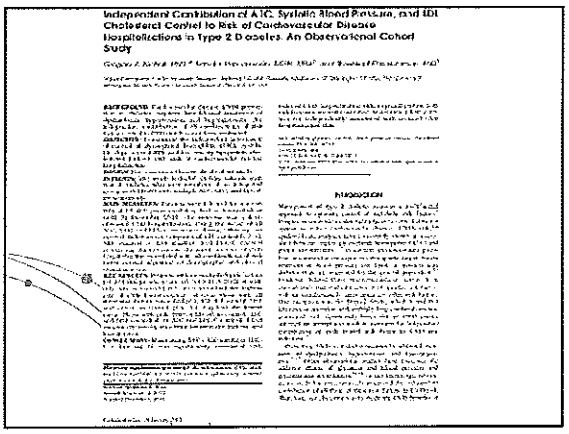
- Elevated CVD risk begins at >115/75 mm Hg
- UKPDS demonstrated large macro and microvascular benefits to "tight" blood pressure control (144/82 vs. 154/87)
- Diabetes = Hypertension, so hypertension in DM is diagnosed at ≥130/80 vs. 140/90 in general population
- ACCORD found no benefit to tight vs. standard BP control (119/64 vs. 133/70)
- ONTARGET and INVEST found no benefit to achieving <130 compared with <140
- ACE inhibitors or ARBs may be enough

Glycemic Control in Type 2 Diabetes

- A1C < 7% based on UKPDS
- Consistent data for microvascular risk reduction
- ACCORD found increased risk of mortality with tight glycemic control
- Subsequent epidemiologic analyses in specific populations suggest higher CVD and mortality risk at both high and low levels of A1C
- ADVANCE found a threshold of about 7% below which additional CVD risk reduction not achieved

1 + 1 + 1 = ???

- Risk factors in clinical trials are almost always evaluated in isolation
- ADVANCE: A1C + SBP = no effect
- UKPDS: A1C + SBP = Sum of independent effects
- Swedish National Diabetes Register:
  - A1C + SBP = 33% risk reduction (effects not isolated)
  - A1C + TC/HDL < Independent effects of A1C and TC/HDL
- Steno-2: Intensive treatment of A1C, SBP and TC = 53% risk reduction (n=160 and effects not isolated)



Independent Contribution of A1C, Systolic Blood Pressure, and HDL Cholesterol Control to Risk of Cardiovascular Disease Hospitalizations in Type 2 Diabetes: An Observational Cohort Study

Objective

- To determine which risk factors alone or in combination were most strongly associated with risk of cardiovascular disease hospitalization

Study Site and Sample

- Kaiser Permanente Northwest
- Individuals with type 2 diabetes diagnosed prior to 2009
- Beginning in 2002, first A1C measured after diagnosis and at least one subsequent A1C measurement
- Excluded patients with previous CVD hospitalization
- n = 26,636

Study Design

- Observed from earliest point patients had A1C, SBP and LDL measurements within 6 months of each other
- Latest of 3 dates was index date
- Dichotomous categories of A1C control (<7%), SBP control (<130mm Hg) and LDL control (<100mg/dL) using mean between baseline and end of follow-up
- Incidence rate of CVD hospitalization independently associated with all combinations of risk factors controlling for age, sex, and diabetes duration
- Cox regression models to estimate hazard ratios adjusted for age, sex, diabetes duration, comorbidities, body mass index, smoking, and pharmacotherapy

Study Outcomes

- **Hospitalization with primary diagnosis of Cardiovascular Disease:**
  - Coronary Artery Disease (ICD-9-CM 410.x - 414.x)
  - Cerebrovascular Disease (430.x, 431.x, 432.x, 434.x, 435.x, 436.x, 437.1)

Sample Characteristics

	No CVD Hospitalization (n=24,693)	Had CVD Hospitalization (n=1,943)	P value
Age	58.6 (12.0)	65.5 (11.1)	<0.001
Men	49.7%	56.4%	<0.001
DM Duration	3.4 (4.2)	5.2 (5.1)	<0.001
BMI	33.7 (7.9)	32.0 (6.7)	<0.001
CVD	28.0%	67.1%	<0.001
Heart Failure	13.4%	25.9%	<0.001

Mean Risk Factor Levels and Proportion in Control

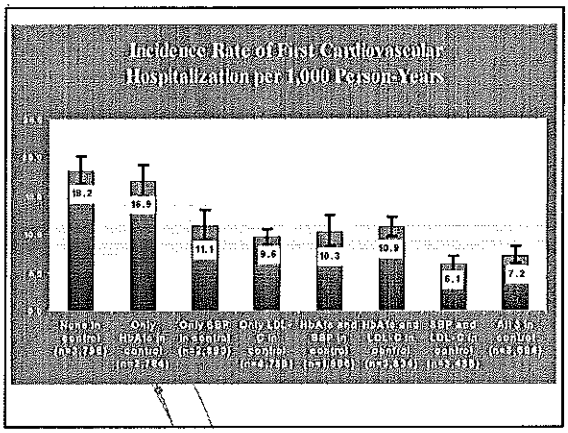
	No CVD Hospitalization	Had CVD Hospitalization	p value
Mean A1C	7.3% (1.2)	7.3% (1.2)	0.581
Mean SBP	132 (11)	137 (13)	<0.001
Mean LDL	97 (26)	102 (29)	<0.001
A1C <7%	45.6%	47.2%	0.174
SBP <130 mm Hg	44.1%	27.9%	<0.001
LDL < 100mg/dl	59.5%	51.9%	<0.001

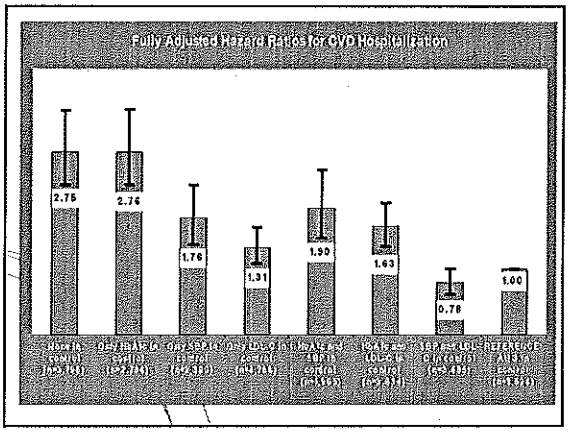
Adjusted Hazard Ratios

	Adjusted Hazard Ratios (95% CI)	p value
A1C (per 1%)	1.01 (0.96-1.07)	0.661
SBP (per 5 mm Hg)	1.16 (1.13-1.18)	<0.001
LDL-C (per 10 mg/dl)	1.14 (1.12-1.16)	<0.001
A1C in Control (<7%)	1.14 (1.02-1.27)	0.024
SBP in Control (<130 mm Hg)	0.63 (0.56-0.71)	<0.001
LDL-C in Control (< 100 mg/dl)	0.52 (0.47-0.57)	<0.001

All Possible Combinations of Risk Factor Control

	No CVD Hospitalization	Had CVD Hospitalization
None In Control	13.7%	21.0%
Only A1C in Control	10.1%	15.4%
Only SBP in Control	9.2%	6.5%
Only LDL-C in Control	18.0%	18.3%
A1C/SBP in Control	7.6%	5.2%
A1C/LDL-C in Control	14.2%	17.4%
SBP/LDL-C in Control	13.6%	7.1%
All 3 in Control	13.8%	9.2%





Summary and Conclusions

- Higher mean levels of SBP and LDL were significantly associated with increased risk of CVD hospitalization, but A1C was not
- SBP control and LDL control were associated with substantially reduced risk of CVD
- HbA1c control below 7% did not appear to add any risk reduction

So What's Up with A1C?

- High A1C is clearly bad—bad enough to drive previous studies results
- If A1C is not "high", is there marginal benefit to further tightening control?
- Studies in selected populations have suggested a non-linear, U-shaped relationship between A1C and CVD/mortality

The Association of HbA1c with Risk of Cardiovascular Hospitalization and All-Cause Mortality is U-Shaped

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Objective

- Evaluate the relationship between glycemic control and CVD hospitalizations and all-cause mortality among general patients with type 2 diabetes in a real-world clinical setting

Study Site and Sample

- Kaiser Permanente Northwest
- Individuals with type 2 diabetes diagnosed prior to 2009
- Beginning in 2002, first A1C measured after diagnosis and at least one subsequent A1C measurement
- Excluded patients with previous CVD hospitalization
- n = 26,673

Study Design

- Observational longitudinal cohort analysis
- Observed from date of first A1C measure through 2011
- Mean of all A1C measures between first measure, event, or censoring, categorized into 0.5% increments
- Incidence rates of study outcomes adjusted for age, sex, duration of diabetes by A1C categories
- Cox regression analyses examining association of A1C categories with outcomes adjusted for other risk factors, comorbidities, pharmacotherapy, and mean number of A1C tests per year

Study Outcomes

- Hospitalization with primary diagnosis of Cardiovascular Disease:
  - Coronary Artery Disease (ICD-9-CM 410.x - 414.x)
  - Cerebrovascular Disease (430.x, 431.x, 432.x, 434.x, 435.x, 436.x, 437.1)
- All-cause Mortality

Total Sample and Proportion with Outcomes by A1C Category

	CVD Hospitalization		All-Cause Mortality	
Mean A1C	Total in Category	Events (%)	Total in Category	Events (%)
< 6.0%	2,348	219 (9.3%)	2,302	495 (21.5%)
6.0 - 6.4%	4,253	332 (7.8%)	4,214	718 (17.0%)
6.5 - 6.9%	5,345	444 (8.3%)	5,352	763 (14.3%)
7.0 - 7.4%	4,912	395 (8.0%)	4,960	660 (13.3%)
7.5 - 7.9%	3,550	280 (7.9%)	3,595	388 (10.8%)
8.0 - 8.4%	2,318	170 (7.3%)	2,354	254 (10.8%)
8.5 - 8.9%	1,449	128 (8.8%)	1,440	133 (9.2%)
≥ 9.0%	2,498	208 (8.3%)	2,456	190 (7.7%)
Total	26,673	2,176 (8.2%)	26,673	3,601 (13.5%)

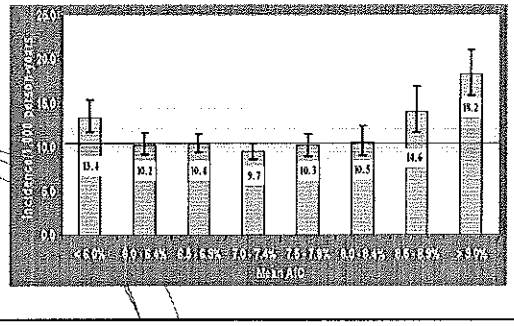
Patient Characteristics by A1C Category

	Mean A1C During Follow-up								
	< 6%	6.0 - 6.4%	6.5 - 6.9%	7.0 - 7.4%	7.5 - 7.9%	8.0 - 8.4%	8.5 - 8.9%	≥ 9.0%	Total
Age (years)	61.8	62.8	61.7	60.2	57.8	55.9	53.9	50.5	59.1
Duration of Diabetes (years)	2.5	2.5	3.1	3.8	4.2	4.4	4.2	4.0	3.5
Body Mass Index (kg/m²)	32	32	33	33	34	35	35	35	33
Macrovascular Complications (%)	40.8	40.2	37.8	36.8	35.9	34.4	29.5	26.8	36.2
Microvascular Complications (%)	48.4	50.8	54.7	57.1	60.0	61.2	62.9	59.0	56.1
Oral Anti-hyperglycemics (%)	25.5	41.1	59.4	63.4	63.2	61.2	57.5	53.6	54.3
Insulin (%)	5.9	6.1	12.8	24.7	36.1	42.8	47.2	40.9	23.4
Length of Follow-up (years)	5.4	5.8	6.2	6.6	6.7	6.5	6.4	5.8	6.2

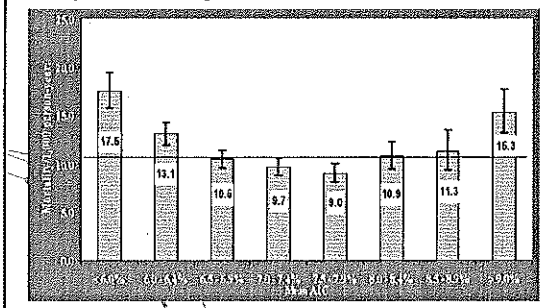
Patient Characteristics by A1C Category

	Mean A1C During Follow-up								
	< 6%	6.0 - 6.4%	6.5 - 6.9%	7.0 - 7.4%	7.5 - 7.9%	8.0 - 8.4%	8.5 - 8.9%	≥ 9.0%	Total
Men (%)	51.4	49.1	46.7	50.3	50.5	53.3	53.3	52.7	50.2
African-American (%)	2.3	2.1	3.1	2.8	2.8	4.3	5.0	5.0	3.2
Smoker (%)	12.9	11.3	11.5	12.2	14.5	15.0	14.6	18.7	13.2
GFR (ml/min/1.73m²)	76	77	78	78	81	83	86	94	80
Systolic Blood Pressure (mm Hg)	128	130	130	130	132	132	133	132	131
LDL Cholesterol (mg/dL)	94	91	88	88	89	91	94	101	91
HDL Cholesterol (mg/dL)	49	47	46	46	45	44	44	45	46
Triglycerides (mg/dL)	154	169	176	185	193	203	209	231	186
Anti-hypertensive Agents (%)	68.4	75.2	76.2	75.7	74.4	73	67.8	58.3	72.6
Statin (%)	45.4	55.3	59.7	58.8	58.7	56.9	51.4	42.4	55.1

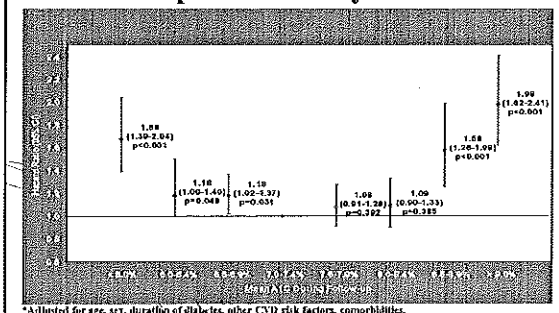
Incidence of First CVD Hospitalization per 1,000 Person-years Adjusted for Age, Sex, and Diabetes Duration



Incidence of All-Cause Mortality per 1,000 Person-years Adjusted for Age, Sex, and Diabetes Duration

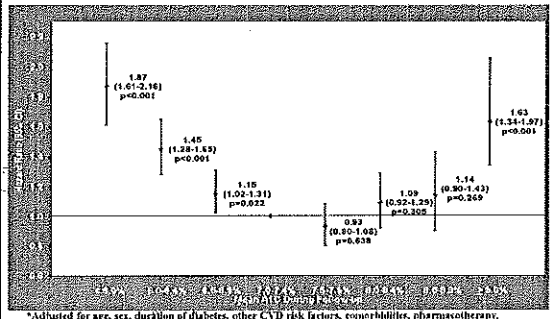


Adjusted* Relative Risk of First CVD Hospitalization by Mean A1C



*Adjusted for age, sex, duration of diabetes, other CVD risk factors, comorbidities, pharmacotherapy, and mean number of A1C tests per year

Adjusted* Relative Risk of All-Cause Mortality by Mean A1C



*Adjusted for age, sex, duration of diabetes, other CVD risk factors, comorbidities, pharmacotherapy, and mean number of A1C tests per year

Summary

- Over a mean of 6.2 years of follow-up, patients with mean A1C <6.0% or ≥8.5% were significantly more likely to experience a CVD hospitalization compared with those with mean A1C 7.0-7.4%
- Patients with mean A1C <7% or ≥9.0% were significantly more likely to die compared with those with mean A1C 7.0-7.4%
- These findings account for demographics, clinical characteristics, CVD risk factors, and pharmacotherapies that could affect risk of CVD hospitalization and mortality

Limitations

- Observational study
- Primary vs. secondary CVD
- Microvascular outcomes were not assessed

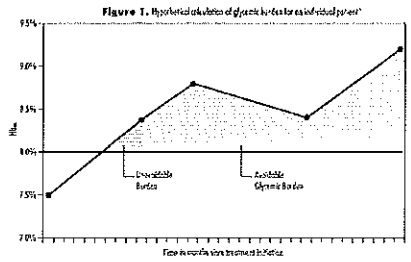
Conclusions

- The results of our study suggest that the association between *treated* mean A1C and risk of CVD hospitalization and mortality is U-shaped
- CVD and mortality risk was minimized at A1C levels between 7% and 8%

Does A1C = Glycemic Exposure?

- A1C is at least partially a function of red blood cell life
- Trials of tight control conducted among patients with 8+ years of diabetes duration with no accounting for glycemic history
- Mean A1C does not account for extreme fluctuations or time spent at sub-optimal levels

Cumulative Glycemic Burden



Brown et al. *Diabetes Care* 2004;27:1533-1540

Difficult Assumptions

- There is a threshold above which glycemic burden begins, and that threshold is the same for everyone
- High A1C over a short period and low A1C over a long period can produce equivalent burden, and therefore equivalent risk
- The relationship between glycemic burden and CVD risk is continuous

Study Design

- Case-control study of 1,228 patients with a CVD hospitalization
- Controls matched on age, sex, duration of diabetes
  - Mean age = 70 years
  - 58% men
  - Duration = 5.3 years
- Calculate and compare glycemic burden from date of diagnosis to date of event

Bivariate Results

	Cases	Controls	P value
% Burden = 0	23.4%	27.0%	<0.001
Total Burden	36.3	31.0	0.060
Months > 7%	24.6	24.2	0.433
Mean Monthly Burden	1.0	0.8	<0.001

And the Winner Is…

	Hazard Ratio	95% CI	P value
Mean A1C	1.22	1.09 - 1.37	<0.001
Glycemic Burden	1.29	1.16 - 1.44	<0.001
A1C Ever > 7%	1.39	1.08 - 1.79	0.011

Remember…

- Measures of hyperglycemia do not distinguish between it's underlying cause
- The precipitating condition (insulin resistance vs. beta cell failure) or the relative mix of these may impact risk
- But we don't know how to measure them

Summary and Conclusions

- Tight control for the newly diagnosed patient (if new to hyperglycemia) may provide substantial benefit especially if maintained
- Good glycemic control is probably good enough for the established diabetes patient
- Blood pressure and LDL control are essential
- Guidelines are not gospel