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Landmark Trials of Intensive Diabetes Control and Cardiovascular Complications

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Introduction

- What impact does intensive blood glucose control have on CV complications in patients with diabetes?
- What are the major findings of CV outcome trials conducted the past 10 years?
- Does intensive glucose control improve CV mortality?
- What are important considerations for future studies?

CV, cardiovascular.

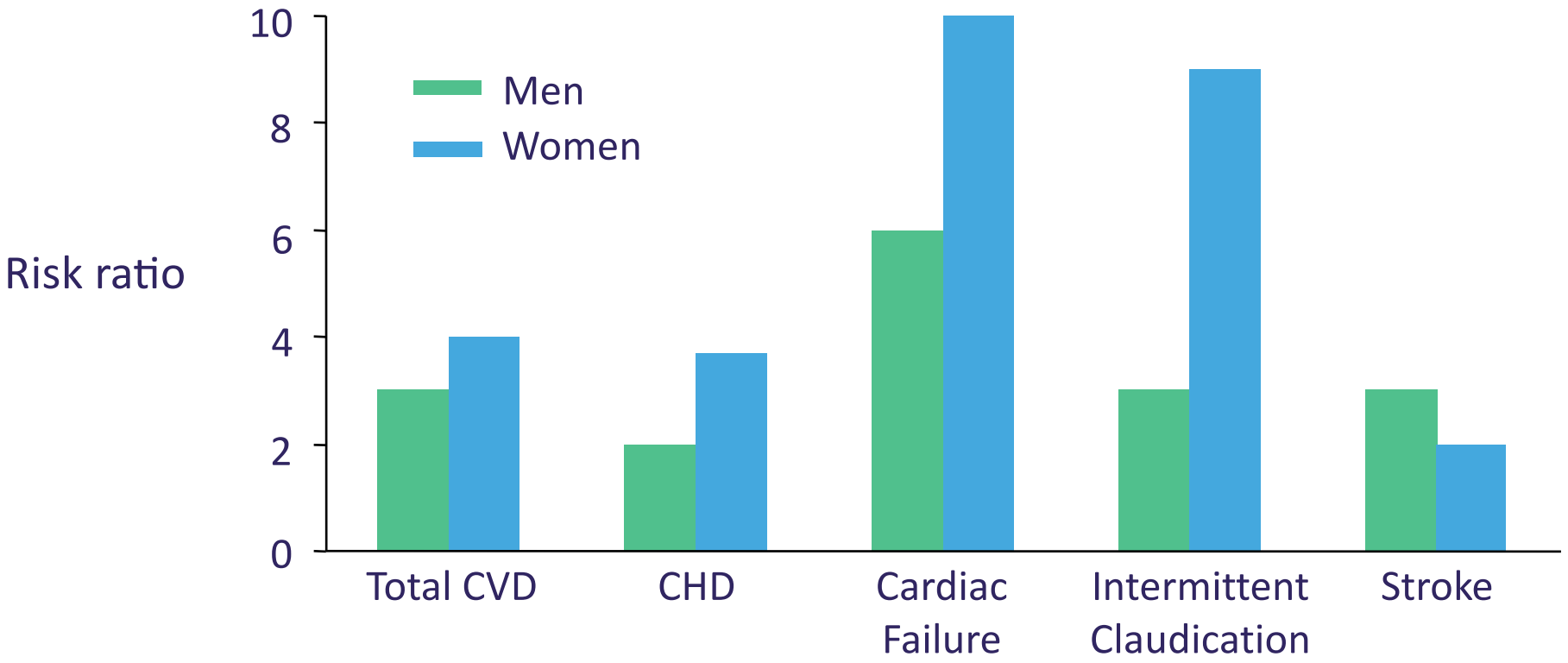
Diabetes and Cardiovascular Disease

- An estimated 30.3 million people (9.4% population) are living with diabetes in the U.S.[1]
- CV complications (micro- and macrovascular) are the leading cause of morbidity and mortality among people with diabetes.
- In 2014, 1.5 million hospital discharges among persons with diabetes were attributed to CVD, including:[1]
  - 400,000 (18.3 per 1,000 persons with diabetes) for ischemic heart disease
  - 251,000 (11.5 per 1,000 persons with diabetes) for stroke
- Control of risk factors (hyperglycemia, blood pressure, and lipids) reduces the risk of CV complications[2]

CV=cardiovascular; CVD=cardiovascular disease; U.S.=United States.

1. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf; 2. American Diabetes Association. *Diabetes Care.* 2018 Jan; 41(Supplement 1): S86-S104.

Diabetes is a Vascular Disease



Wilson PWF, et al. eds. *Hyperglycemia, Diabetes, and Vascular Disease. New York: Oxford University Press*; 1992:21-29.

Key Randomized Controlled Trials Evaluating the Impact of Intensive Diabetes Control On CV Outcomes

STUDY (publication date)	OBJECTIVE
DCCT (1993)	Studied whether intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range decreased the frequency and severity of microvascular and neurologic complications of T1D[1]
UKPDS 33 (1998)	Compared the effects of intensive blood glucose control and conventional treatment on the risk of microvascular and macrovascular complications in patients with T2D[2]
DCCT EDIC (2003)	Evaluated the long-term (up to 30 years) effects of intensive vs conventional diabetes treatment during DCCT on kidney function and CVD[3]
STENO-2 (2008)	Compared the effects of targeted, intensified, multifactorial intervention vs conventional treatment on modifiable CVD risk factors in patients with T2D and microalbuminuria[4]
ADVANCE (2008)	Examined the effects of intensive glucose control on vascular outcomes[5]
ACCORD (2008)	Determined whether intensive therapy to target normal A1C levels reduced CV events in patients with T2D + established CVD or CV risk factors[6]
VADT (2008)	Evaluated the effects of intensive glucose control on CV events in patients with long- standing T2D[7]

CV, cardiovascular; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; T1D, type 1 diabetes; T2D, type 2 diabetes.

1. DCCT. *N Engl J Med.* 1993;329(14):977-986. 2. UKPDS (UKPDS 33). *Lancet.* 1998;352(9131):837-853. 3. [DCCT/EDIC. *JAMA.* 2003;290(16):2159-2167] [DCCT/EDIC. *N Engl J Med.* 2005;353(25):2643-2653] [DCCT/EDIC. *Arch Intern Med.* 2009;169(14):1307-1316]. 4. Gaede, P, et al. *N Engl J Med.* 2003;348(5):383-393. 5. Patel A, et al. *N Engl J Med.* 2008;358(24):2560-2572. 6. Gerstein H, et al. *N Engl J Med.* 2008;358(24):2545-2559. 7. Duckworth W, et al. *N Engl J Med.* 2009;360:129-139.

DCCT: Diabetes Control and Complications Trial Research Group

- ***Objective:*** To examine if intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range could decrease the frequency and severity of microvascular and neurologic complications of T1D[1]
- ***Methods:*** Data were collected from 1983 to 1989; 1441 patients with T1D were randomly assigned to intensive therapy and followed for a mean of 6.5 years; mean baseline A1C ranged between 8.8% and 9.0%, and patients were assessed regularly for retinopathy progression and other complications[1]
- ***Conclusion:*** In patients with T1D, intensive therapy effectively delays onset and slows the progression of onset for diabetic retinopathy, nephropathy, and neuropathy[1]

A1C, glycated hemoglobin; T1D, type 1 diabetes.

1. DCCT. *N Engl J Med.* 1993;329(14):977-986.

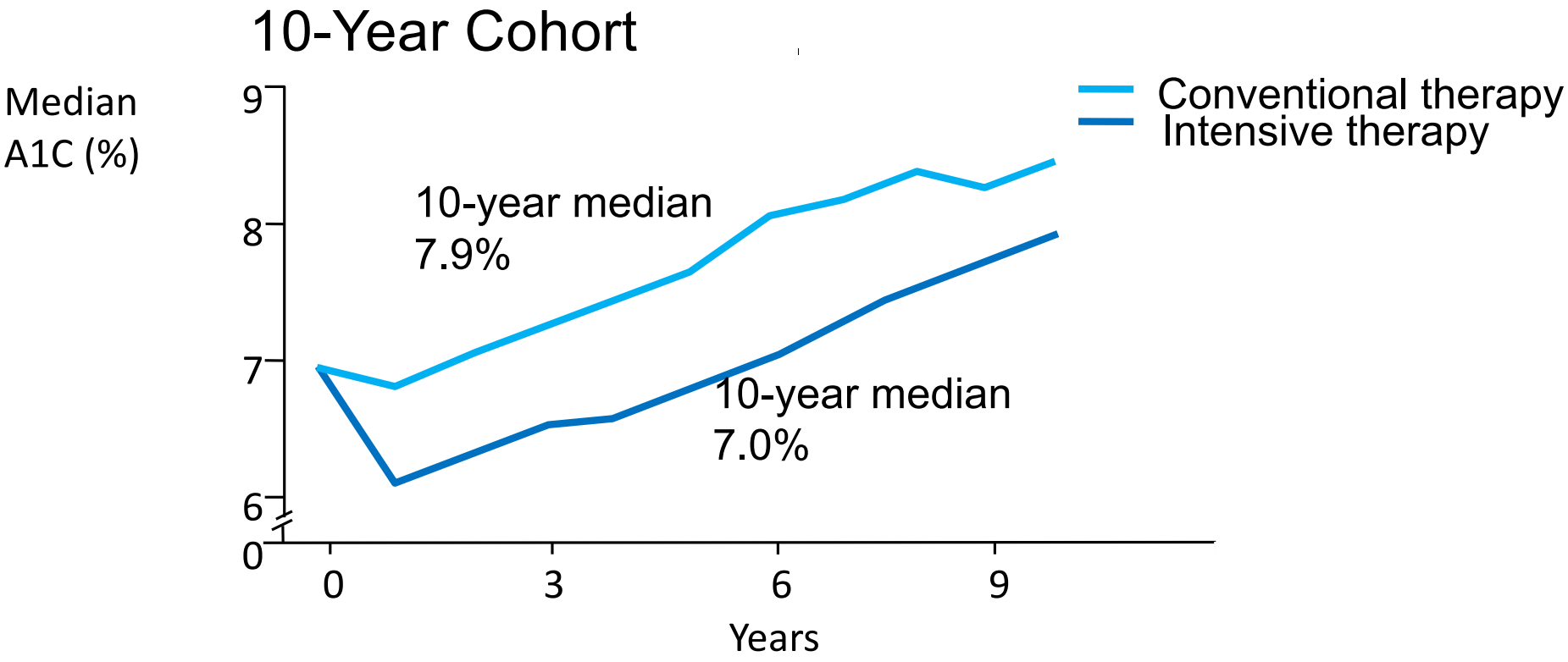
UKPDS:
United Kingdom Prospective Diabetes Study

- ***Objective:*** To compare the effects of intensive blood-glucose control vs conventional treatment on the risk of microvascular and macrovascular complications in patients with newly diagnosed T2D
- ***Methods:*** Data were collected from 1977 to 1991. Randomized controlled trial of 3,867 newly diagnosed patients with T2D (median age 54 years) randomly assigned to intensive treatment with sulfonylureas or insulin vs conventional therapy (primarily diet). Additionally, 753 patients were randomized to receive metformin vs conventional therapy. Mean baseline A1C ranged from 6.1% to 7.1%. The 3 aggregate endpoints were: any diabetes-related endpoint, diabetes-related death, and all-cause mortality
- ***Conclusion:*** Intensive blood glucose control substantially decreased the risk of microvascular complications, but not macrovascular disease, in patients with T2D

A1C, glycated hemoglobin; T1D, type 1 diabetes; T2D, type 2 diabetes.

UKPDS (UKPDS 33). *Lancet.* 1998;352(9131):837-853.
UKPDS (UKPDS 34). *Lancet*. 1998;352:854-865.

Glycemic Response in the UKPDS



A1C, glycated hemoglobin; UKPDS, United Kingdom Prospective Diabetes Study.
UKPDS (UKPDS 33). *Lancet.* 1998;352(9131):837-853.

EDIC: Epidemiology of Diabetes Interventions and Complications—A Long-Term Evaluation of DCCT with Follow-up at 7-8 years

STUDY	OBJECTIVE	METHODS	CONCLUSION
DCCT EDIC 2003	Investigated the long-term effects of intensive vs conventional treatment for T1D on kidney function during the DCCT[1] Observational study began in 1993, after the completion of DCCT; patients were followed for 7 to 8 years	Observational study following DCCT closeout. Participants were 1349 (of 1375) EDIC volunteers with kidney function evaluation at years 7 or 8. Main outcome measure was development of microalbuminuria, clinical-grade albuminuria, hypertension, or increase in serum creatinine level	The persistent beneficial effects on albumin excretion and the reduced incidence of hypertension 7 to 8 years after the end of the DCCT suggests that previous intensive treatment of diabetes with near-normal glycemia during the DCCT has an extended benefit in delaying progression of diabetic nephropathy[1]

DCCT, Diabetes Control and Complications Trial; T1D, type 1 diabetes.
DCCT/EDIC *JAMA.* 2003;290(16):2159-2167.

EDIC: A Long-Term Evaluation of DCCT Results with Follow-up at 12 Years Post-DCCT Completion

STUDY	OBJECTIVE	METHODS	CONCLUSION
DCCT EDIC 2005	Studied whether the use of intensive vs conventional diabetes treatment during the DCCT affected long-term CVD incidence[1] Observational study began in 1993, after the completion of DCCT; patients were followed for 12 years	93% of original DCCT patients were followed until February 1, 2005; CVD was assessed with standardized measures and classified by an independent committee[1]	Intensive diabetes therapy has long-term, beneficial effects on the risk of CVD in patients with T1D[1]

CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; T1D, type 1 diabetes.

DCCT/EDIC *N Engl J Med.* 2005;353(25):2643-2653.

EDIC: A Long-Term Evaluation of DCCT Results with Follow-up at 30 years Post-DCCT Completion

STUDY	OBJECTIVE	METHODS	CONCLUSION
DCCT EDIC 2009	Described the clinical care, metabolic results, and outcomes of the DCCT/EDIC conventional and intensive treatment groups over a diabetes duration of 30 years; compared these results with the EDC study[1] Observational study began in 1993, after the completion of DCCT; patients were followed for 30 years	An analysis of the cumulative incidence of long-term complications was performed on DCCT T1D cohort (N=1441) and a subset of the EDC cohort (n=161). Outcome measures included the incidence of proliferative retinopathy, nephropathy, and CVD. Results are presented in terms of diabetes duration[1]	The frequency of serious complications in patients with long-term T1D and treated in the DCCT study, especially those treated intensively, are lower than those reported historically After a diabetes duration of 30 years, the DCCT/EDIC intensive treatment cohort had significantly lower cumulative incidence of proliferative retinopathy, nephropathy, and CVD vs the DCCT/EDIC and EDC conventional treatment cohorts[1]

DCCT, Diabetes Control and Complications Trial; EDC, Epidemiology of Diabetes Complications; EDIC, Epidemiology of Diabetes Interventions and Complications; T1D, type 1 diabetes; CVD, cardiovascular disease.

DCCT/EDIC *Arch Intern Med.* 2009;169(14):1307-1316.

STENO-2 Study

- ***Objective:*** To compare the effect of a targeted, intensified, multifactorial intervention vs conventional treatment on modifiable CVD risk factors, including hyperglycemia, hypertension, and dyslipidemia in patients with T2D and microalbuminuria[1]
- ***Methods:*** Data were collected from 1993 to 2001; of 160 patients 80 were randomly assigned to receive conventional treatment in accordance with national guidelines and 80 to receive intensive treatment involving a stepwise implementation of behavior modification and pharmacologic therapy. At baseline, mean A1C levels ranged from 8.4% to 8.8%, mean systolic and diastolic BP were 130-168 mmHg and 75-97 mmHg, respectively, total cholesterol was 146-149 mg/dL, and median fasting serum TG was 159 mg/dL for the intensive therapy group and 205 mg/dL for the conventional group. The primary endpoint of this open, parallel trial was a composite of death from CV causes, nonfatal MI, nonfatal stroke, revascularization, and amputation.[1,2]
- ***Conclusion:*** Target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with T2D and microalbuminuria reduced the risk of CV and microvascular events by ~50%.[1]

A1C, glycated hemoglobin; BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; T2D, type 2 diabetes; TG, triglycerides.

1. Gaede P, et al. *N Engl J Med.* 2003;348(5):383-393.
2. Gaede P, et al. *N Engl J Med*. 2008;358(6):580-591.

ADVANCE – Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation

- ***Objective:*** To examine the effects of intensive glucose control on vascular outcomes[1]
- ***Methods:*** Data were collected from 2001 to 2008; patients with T2D (N=11,140) were randomly assigned to receive either standard or intensive glucose control. Baseline mean A1C levels were 7.8% for both the standard and intensive control groups. Primary endpoints were composites of major macrovascular and microvascular events, assessed both jointly and separately[1]
- ***Conclusion:*** Intensive glucose control that targeted A1C levels ≤6.5% yielded a 10% relative reduction in the composite outcome of major macrovascular and microvascular events, primarily driven by a 21% relative reduction in nephropathy[1]

A1C, glycated hemoglobin; T2D, type 2 diabetes.

Patel A, et al. *N Engl J Med.* 2008;358(24):2560-2572.

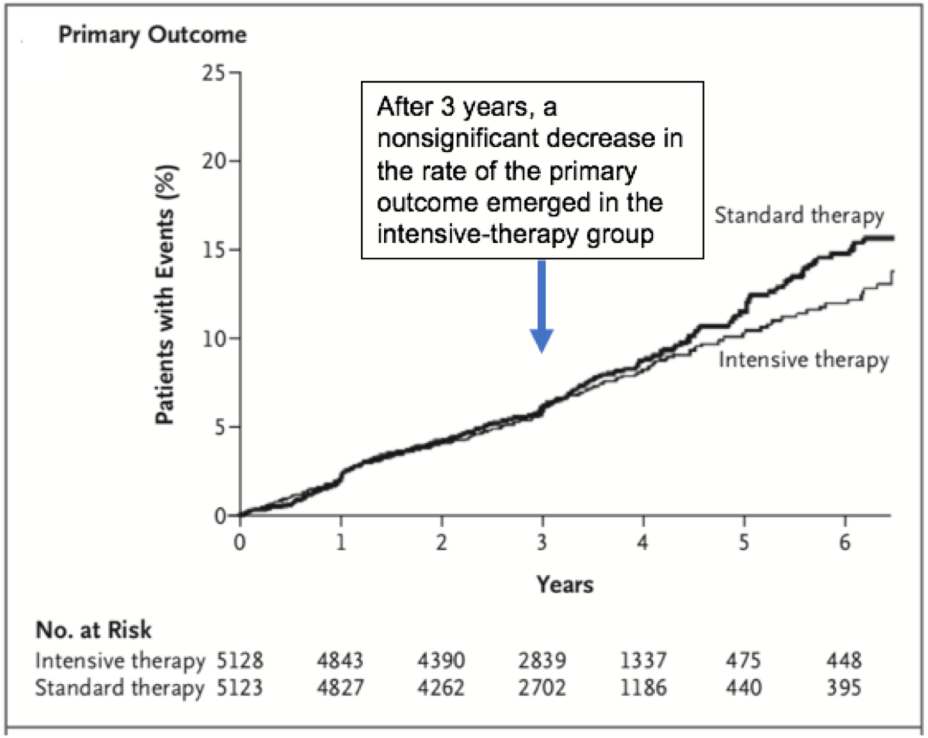
ACCORD: Action To Control Cardiovascular Risk in Diabetes Study Group

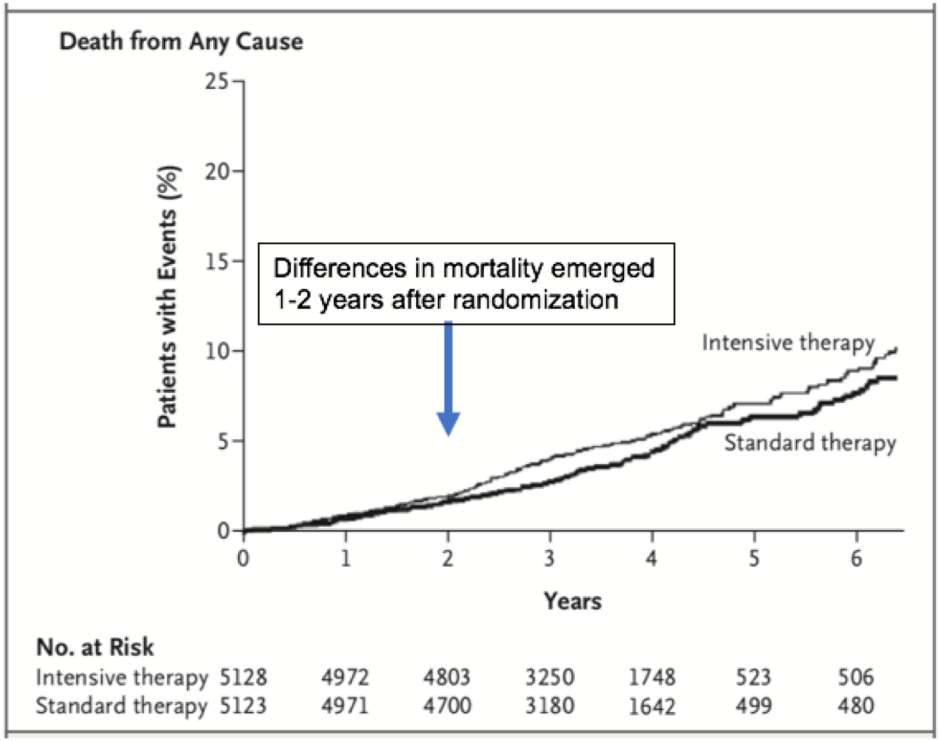
- ***OBJECTIVE:*** To determine if intensive therapy to target normal A1C levels would reduce CV events in patients with T2D + either established CVD or CV risk factors[1]
- ***METHODS:*** 10,251 patients (mean age, 62.2 years) with a median A1C of 8.1% were randomized to receive intensive therapy (A1C target <6.0%) or standard therapy (A1C target 7.0% to 7.9%). The primary outcome was a composite of nonfatal MI, nonfatal stroke, or death from CV causes. The finding of higher mortality in the intensive therapy group led to intensive therapy discontinuation after a mean 3.5 years of follow-up[1]
- ***CONCLUSION:*** Compared with standard therapy, intensive therapy to target normal A1C levels increased mortality and did not significantly reduce major CV events. These findings identified a previously unrecognized harm associated with intensive glucose lowering in high-risk patients with T2D[1]

A1C, glycated hemoglobin; CV, cardiovascular; CVD, cardiovascular disease; T2D, type 2 diabetes; MI, myocardial infarction.
Gerstein H, et al. *N Engl J Med.* 2008;358(24):2545-2559.

ACCORD: CV Outcomes

Kaplan–Meier Curves for the Primary Outcome and Death from Any Cause[1]





CV, cardiovascular.

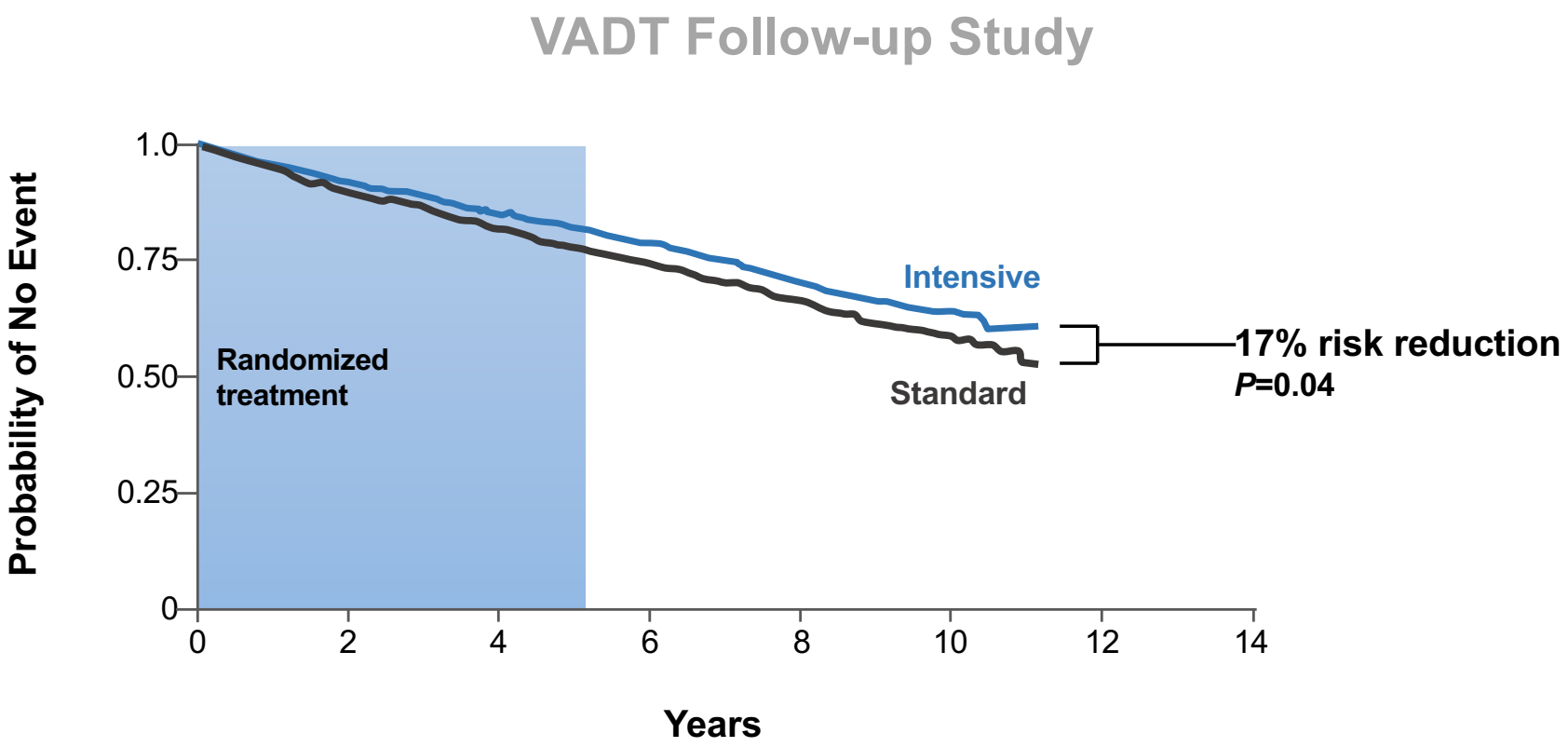
Gerstein H, et al. *N Engl J Med.* 2008;358(24):2545-2559.

VADT: Veterans Affairs Diabetes Trial

- ***OBJECTIVE:*** To evaluate the effects of intensive glucose control on CV events in patients with longstanding T2D[1]
- ***METHODS:*** Data were collected from 2000 to 2008. Median follow-up was 5.6 years. Randomly assigned 1791 military veterans (mean age, 60.4 years) who had a suboptimal response to T2D therapy to receive either intensive or standard glucose control. Mean A1C at baseline was 9.4%[1]
  - The primary outcome was the time from randomization to the first occurrence of a major CV event[1]
- ***CONCLUSION:*** Intensive glucose control in patients with poorly controlled T2D had no significant effect on the rates of major CV events, death, or microvascular complications, with the exception of progression of albuminuria.[1]

A1C, glycated hemoglobin; CV, cardiovascular; T2D, type 2 diabetes.
Duckworth W, et al. *N Engl J Med.* 2009;360:129-139.

Long-Term Effect of Intensive Glycemic Control on Macrovascular Risk



VADT, Veterans Affairs Diabetes Trial.
Hayward RA, et al. *N Engl J Med*. 2015;372:2197-2206.

Intensive Glucose Control and CV Complications: Major RCTs

Study	Microvascular		CVD		Mortality	
UKPDS 33 (7.0% vs 7.9%)	↓	↓	↔	↓	↔	↓
DCCT/EDIC* (7.2% vs 9.1%)	↓	↓	↔	↓	↔	↓
ACCORD (6.4% vs 7.5%)	↓		↔		↑	
ADVANCE (6.3% vs 7.0%)	↓		↔	↔	↔	↔
VADT (6.9% vs 8.4%)	↓		↔	↓	↔	↔

Initial trial

Long-term follow-up

*in T1DM. Courtesy of Silvio Inzucchi MD, Yale University. **Adapted: Kendall DM, Bergenstal RM. International Diabetes Center 2009, 2015**

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CV, cardiovascular; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; RCT, randomized controlled trial; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

UKPDS (UKPDS 34). *Lancet*. 1998;352:854-865; Holman RR. *N Engl J Med* 2008;359:1577-1589; DCCT. *N Engl J Med.* 1993;329(14):977-986; DCCT/EDIC. *N Engl J Med.* 2005;353(25):2643-2653; Gerstein H, et al. *N Engl J Med.* 2008;358(24):2545-2559; Patel A, et al. *N Engl J Med.* 2008;358(24):2560-2572; Duckworth W, et al. *N Engl J Med.* 2009;360:(erratum:361:1024)129-139; DCCT. *JAMA.* 2015;313(1):45-53; Zoungas S. *N Engl J Med* 2014;371:1392-1406; Hayward R, et al. *N Engl J Med.* 2015;372(23):2197-2206.

Summary and Conclusions

- Early studies yielded promising risk reductions in CV outcomes, including microvascular and macrovascular disease, MI and cardiac death, with intensive glucose-lowering therapy in both T1D and T2D
- However, later trials such as ACCORD and VADT found no significant effect of intensive treatment on CV events, with ACCORD demonstrating increased mortality
    - In these trials, mortality was increased in high-risk patients
- DCCT-EDIC demonstrated a powerful, long-term effect of early intensive therapy on CV outcomes in patients with T1D

ACCORD, Action to Control Cardiovascular Risk in Diabetes; CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; MI, myocardial infarction; T1D, type 1 diabetes; T2D, type 2 diabetes..