

Microvascular Complications in Diabetes:

Perspectives on Glycemic Control to Prevent Microvascular Complications

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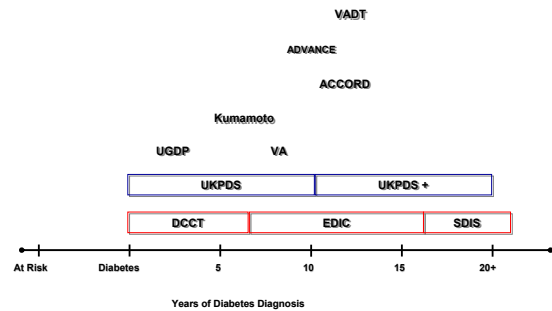
Discussion Outline: Glycemia and Microvascular Complications

- Clinical Trials - A Brief History
 - Intensive glucose control and microvascular disease risk
 - A brief reminder of the Serial Position Effect
- Early vs. Late Intervention – A Clinical Perspective
 - EARLY = DCCT, UKPDS, Kumamoto
 - LATE = ACCORD, ADVANCE, VADT and SDIS
 - Updates from ACCORD
- A Rational Clinical Approach
 - Balancing Risk – Benefit with intensive glycemic control

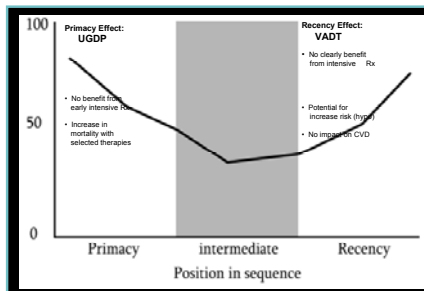
Glycemic Control for Microvascular Complications: Is Late Too Late?

Type 1 Diabetes	N	Duration of Diabetes	Baseline A1C	Follow Up (yrs)	Publication
Stockholm (SDIS)	102	~18	9.4%	7	1993
Type 2 Diabetes					
Kumamoto	110	2-10	9.4	8	1995
UKPDS	5102	<1	~9%	10	1998/2008
ADVANCE	11140	8	7.5	5	2008

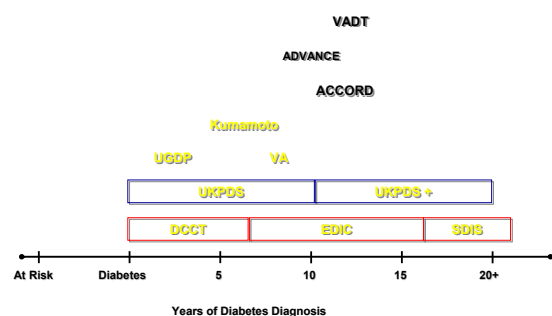
Glycemic Control for Microvascular Complications: Is Late Too Late?



The Serial Position Effect Microvascular Complications Risk in Diabetes



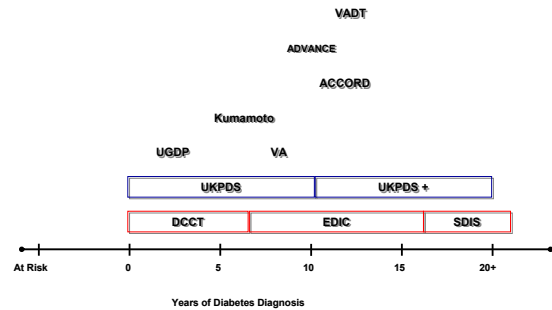
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The Impact of Early Intervention

Glycemic Control for Microvascular Complications: Is Late Too Late?

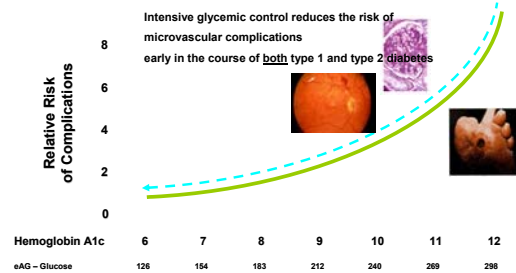


Early Intensive Diabetes Therapy: Reduction in Microvascular Complications

	DCCT	Kumamoto	UKPDS
HbA1c	9 → 7.1%	9+ → 7.2%	8 → 7%
Retinopathy	53%	53%	17-29%
Nephropathy	54%	70%	24-33%
Neuropathy	60%	Improved	-
CV disease	NS	-	16%

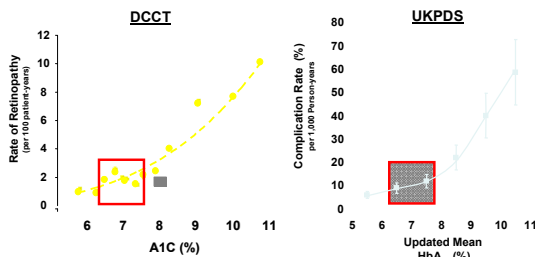
DCCT Research Group. *N Engl J Med*. 1993;329:977-986.
 Chouko Y, et al. *Diabetes Res Clin Pract*. 1995;28:103-117.
 UKPDS 33. *Lancet* 1998; 352: 857-853.

Complications Risk in Diabetes The Impact of Intensive Glycemic Control



Adapted from:
 Stratton JR. *Endocrinol Metab Clin North Am*. 1995 Jun;20(2):343-54.
 DCCT Study Group. *N Engl J Med* 1993; 329: 977-986.
 UKPDS 33. *Lancet* 1998; 352: 857-863.

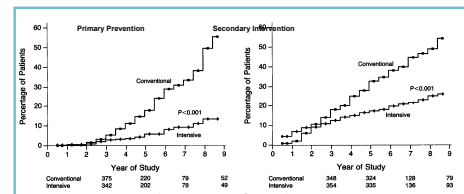
DCCT and UKPDS Glycemic Control and Microvascular Risk



DCCT Study Group. *N Engl J Med* 1993;329:977-986.
 UKPDS 33. *Stratton JM. BMJ*. 2000;321:405-412.

Early Intervention – Is It Truly Early? Benefit in Primary and Secondary Prevention

- Reduction in microvascular disease risk
 - Occurred with both primary and secondary prevention
 - Effect observed in DCCT, UKPDS and Kumamoto

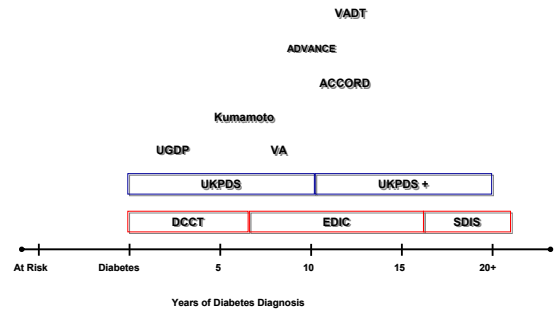


DCCT Research Group. *N Engl J Med*. 1993;329:977-986.

Glycemic Control for Microvascular Complications: Is Late Too Late?

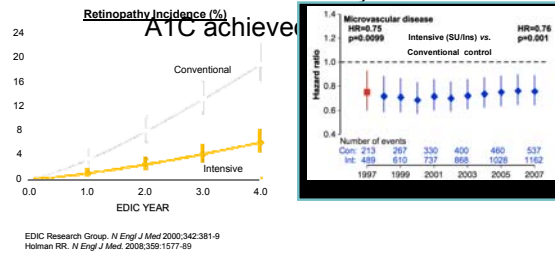
Enduring Impact of Early Intervention EDIC and UKPDS

Glycemic Control for Microvascular Complications: Is Late Too Late?



The Durable Effect of Early Intervention EDIC and UKPDS

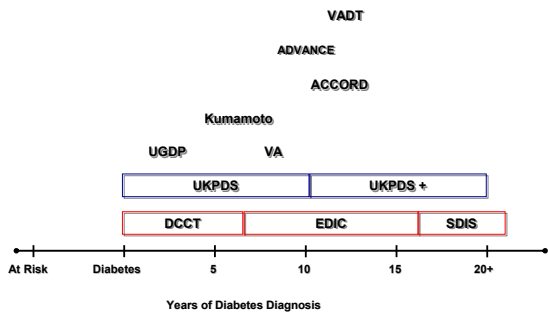
Follow up cohort with similar glycemic control for 4-10+ years



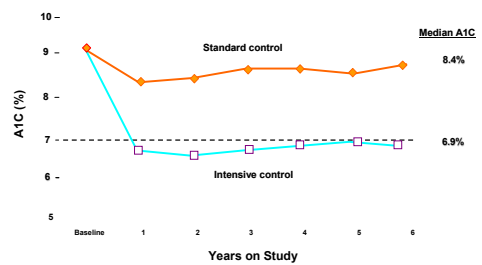
Glycemic Control for Microvascular Complications: Is Late Too Late?

The Impact Late Intervention

Glycemic Control for Microvascular Complications: Is Late Too Late?



VADT: Effect of Intensive Glucose Lowering on Microvascular Complications in T2DM



VADT: Effect of Intensive Glucose Lowering on Microvascular Complications in T2DM

Complication	Microvascular Event	Impact in VADT
DIABETIC RETINOPATHY	<ul style="list-style-type: none"> Proliferative retinopathy Macular edema 2 step progression 	NS NS P=0.07
DIABETIC NEPHROPATHY	<ul style="list-style-type: none"> Doubling of serum creatinine ESRD Micro to macroalbuminuria Normal to micro/macroalbuminuria 	NS NS NS P=0.02
DIABETIC NEUROPATHY	<ul style="list-style-type: none"> Peripheral neuropathy Autonomic neuropathy 	NS P=0.07

From normal to microalbuminuria	41/97 (41.6)	48/97 (49.5)	0.12
From microalbuminuria to macroalbuminuria	26/79 (32.9)	32/77 (41.6)	0.08
From normal to microalbuminuria or macroalbuminuria	58/97 (59.5)	79/97 (81.6)	0.12
From normal to microalbuminuria or macroalbuminuria or ESRD	72/97 (73.2)	107/97 (110.3)	0.12
Any increase in albuminuria	90/97 (91.8)	107/97 (110.3)	0.05
New neuropathy	232/498 (46.6)	262/498 (52.6)	0.04
ESRD	20/498 (4.0)	22/498 (4.4)	0.94
ESRD or death	20/498 (4.0)	22/498 (4.4)	0.94
Death	20/498 (4.0)	22/498 (4.4)	0.94
Death or ESRD	20/498 (4.0)	22/498 (4.4)	0.94

Duckworth W et al. N Engl J Med 2009;360:1304

VADT Correction on Microalbuminuria

“On further examination of the data on albuminuria from the {VADT} we found that the data set that we used to evaluate the progression of disease was constructed improperly.”

- As a result, the rates of progression to microalbuminuria and macroalbuminuria were reported [incorrectly]...

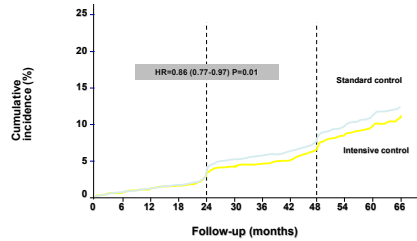
“Both progression from normal to microalbuminuria or macroalbuminuria (P = 0.03) and progression from either normal or microalbuminuria to macroalbuminuria (P = 0.04) favor intensive treatment.”

- Any progression of albuminuria is now statistically significant (P<0.01)

“We appreciate the opportunity to update our results”

ADVANCE Treatment Effect on Microvascular Outcomes

New or worsening nephropathy / retinopathy



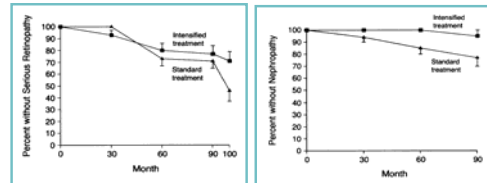
ADVANCE Collaborative Group. N Engl J Med 2008;358:2560-72, 2008

Stockholm Diabetes Intervention Study How Late is too Late in T1DM?

SDIS Study Design

- Intensive insulin therapy – A1C 9.4 → 7.2
- Mean duration of diabetes at study entry = ~18 years
- Significant (but modest) reduction in rates of microvascular disease

When do “advanced” complications become too advanced?

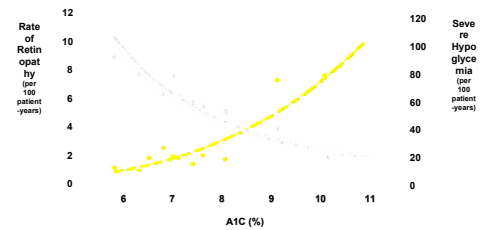


Richter P. N Engl J Med 1993;329:364-369

Intensive Glycemic Control in Diabetes Is It Safe? What are the Risks?

- Severe hypoglycemia risk
 - Increased ~3 fold with intensive therapy
 - ? predictor of adverse outcome/mortality (VADT, ACCORD)
- Increase in health care resource use
 - Increase near-term cost of care (clinic, education, meds, technology)
 - Increased number and type of medications used
- Weight gain
 - Increase in body weight (~5-20 lbs)
 - Unknown long term impact on CV risk, risk factors
- Increased mortality risk?

Reducing the Risk of Complications Intensive Glycemic Control in Type 1 Diabetes



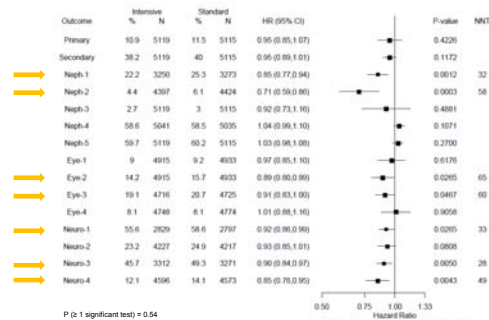
Adapted from: DCCT Study Group. N Engl J Med 2003;349:977-86

A Final Note on ACCORD

Final Results - Microvascular and Eye Study Data

Summary of Microvascular Results

Through End of Study



Conclusions – ACCORD Microvascular

- Intensive treatment of glycemia in the ACCORD cohort did not reduce the risk of *composite measures of advanced microvascular outcomes*
- Intensive therapy *delayed the onset of albuminuria* and some measures of eye complications and neuropathy
- Microvascular benefits of intensive therapy should be weighed against the potential for increased mortality, increased body weight, and the risk for severe hypoglycemia

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes

The ACCORD Study Group and ACCORD Eye Study Group*

ACCORD Eye Study Design

- Baseline and Year 4 comprehensive
- eye exams including:
 - Visual acuity measurements
 - Fundus photography of 7 standard stereoscopic fields
 - Central grading of the fundus photographs using the Early Treatment Diabetic Retinopathy Study (ETDRS) Classification of diabetic retinopathy

Proportion of Participants with Diabetic Retinopathy Progression at 4 years

Glycemia	Blood Pressure		Lipid		N=2856 Total
	Intensive	Standard	Feno+statin	Placebo	
Intensive	9.2% (29/315)	8.1% (25/308)	5.3% (21/400)	7.1% (29/406)	7.5% (104/1429)
Standard	11.4% (38/332)	9.4% (29/308)	7.6% (31/406)	13.4% (51/381)	10.4% (149/1427)
TOTALS	10.4% (67/647)	8.8% (54/616)	6.5% (52/806)	10.2% (80/787)	8.9% (253/2856)

ACCORD Eye Study Conclusions

- **Intensive glycemia** and combination of **fenofibrate and simvastatin** reduced the proportion whose retinopathy progressed by about one-third
 - Effects were consistent across subgroups
- No statistically significant effect of **intensive blood pressure**
 - No subgroup with effect

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

Study	Microvascular
UGDP	↔
UKPDS	↓ ↓
DCCT/EDIC	↓ ↓
SDIS	↓
Kumamoto	↓
ADVANCE	↓
ACCORD	↓
VADT	↔

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 UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854-66. Reprinted with permission.
 DCCT Research Group. N Engl J Med 1995;333:977-86. DCCT Research Group. N Engl J Med 2002;347:977-86.
 National Diabetes Data Institute. Diabetes Control and Complications Trial Group. N Engl J Med 1999;341:977-86.
 Kumamoto Study Group. Diabetes Care 2001;24:1066-71. Kumamoto Study Group. Diabetes Care 2002;25:1769-74.
 ADVANCE Research Group. N Engl J Med 2002;347:407-16. ADVANCE Research Group. N Engl J Med 2005;353:2611-20.
 ACCORD Research Group. N Engl J Med 2008;359:971-82. ACCORD Research Group. N Engl J Med 2009;361:1410-20.
 VADT Research Group. N Engl J Med 2009;361:1375-85. VADT Research Group. N Engl J Med 2010;363:1418-28.

■ Initial Trial
 □ Long Term Follow-up

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

Study	Microvascular	CVD	Mortality
UGDP	↔	↔	↔
UKPDS	↓ ↓	↔ ↓	↔ ↓
DCCT/EDIC	↓ ↓	↔ ↓	↔ ↔
SDIS	↓	↔	↔
Kumamoto	↓	?	↔
ADVANCE	↓	↔	↔
ACCORD	↓	↔	↑
VADT	↔	↔	↔

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 UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854-66. Reprinted with permission.
 DCCT Research Group. N Engl J Med 1995;333:977-86. DCCT Research Group. N Engl J Med 2002;347:977-86.
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 VADT Research Group. N Engl J Med 2009;361:1375-85. VADT Research Group. N Engl J Med 2010;363:1418-28.

■ Initial Trial
 □ Long Term Follow-up

Treatment Considerations Risk – Benefit and Intensive Therapies

"A few observations and much reasoning lead to error. Many observations and a little reasoning lead to truth"

Alexis Carrel



- Intensive glycemic control both early and late in diabetes
 - Significantly reduces the risk of microvascular complications
 - Increases the risk of severe hypoglycemia, weight gain, HCE
- Later intervention may limit the magnitude of these benefits on microvascular risk – and should be weighed against the potential mortality risk of very intensive intervention

Diabetes and Glycemic Control A Rational Approach to Limit Complications

As low as possible
 As early as possible
 For as long as possible
 As safely as possible
 And as rationally as possible

Conclusions