Treatment of Type 1 Diabetes

Goals of T1D Management

- Utilize intensive therapy aimed at near-normal BG and A1C levels
- Prevent diabetic ketoacidosis and severe hypoglycemia
- Achieve the highest quality of life compatible with the daily demands of diabetes management
- In children, achieve normal growth and physical development and psychological maturation
- Establish realistic goals adapted to each individual's circumstances

T1D, type 1 diabetes.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Routine Care Recommendations for Patients With T1D

	Children/Adolescents (0-19 years)	Adults (≥20 years)
Height	Every 3 months	N/A
Weight	Every 3 months	
Nutritionist	Diagnosis, then annually	
Retinal examination	Begin 5 years after diagnosis Every 1-2 years thereafter	Begin 5 years after diagnosis or earlier with visual symptoms or if date of T1D onset is unknown Every 1-2 years thereafter
A1C	Every 3 months	
Lipid profile	Annually, once glycemia is stable	Annually or as needed based on treatment
Blood pressure	Every physical examination	
Creatinine clearance, eGFR	At diagnosis, then annually	
ACR	Begin 5 years after diagnosis, then annually	At diagnosis, then annually

ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; T1D, type 1 diabetes.

Chiang JL, et al. *Diabetes Care*. 2014;37:2034-2054.

AACE Glucose Goals for Nonpregnant Adults with Diabetes

Parameter	Treatment Goal
A1C, %	Individualize on the basis of age, comorbidities, and duration of disease: • In general, ≤6.5 for most* • Closer to normal for healthy • Less stringent for "less healthy"
FPG, mg/dL	<110
2-Hour PPG, mg/dL	<140

* Considerations include

- Residual life expectancy
- Duration of diabetes
- Presence or absence of microvascular and macrovascular complications
- CVD risk factors
- Comorbid conditions
- Risk for severe hypoglycemia
- Patient's psychological, social, and economic status

CVD, cardiovascular disease; FPG, fasting plasma glucose; PPG, postprandial glucose.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

ADA A1C Goals: Patients with Type 1 Diabetes

Age Group	A1C Goal*
Youth (<18 years)	<7.5%
Adults	<7.0%
Older adults	
Healthy†	<7.5%
Complex/intermediate health	<8.0%
Very complex/poor health	<8.5%

*Individualize goal based on patient's circumstances:

- <6.5% may be appropriate for select patients if achievable without significant hypoglycemia
- <8.5% may be appropriate for patients with history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced complications, or extensive comorbidities

†No comorbidities, long life expectancy.

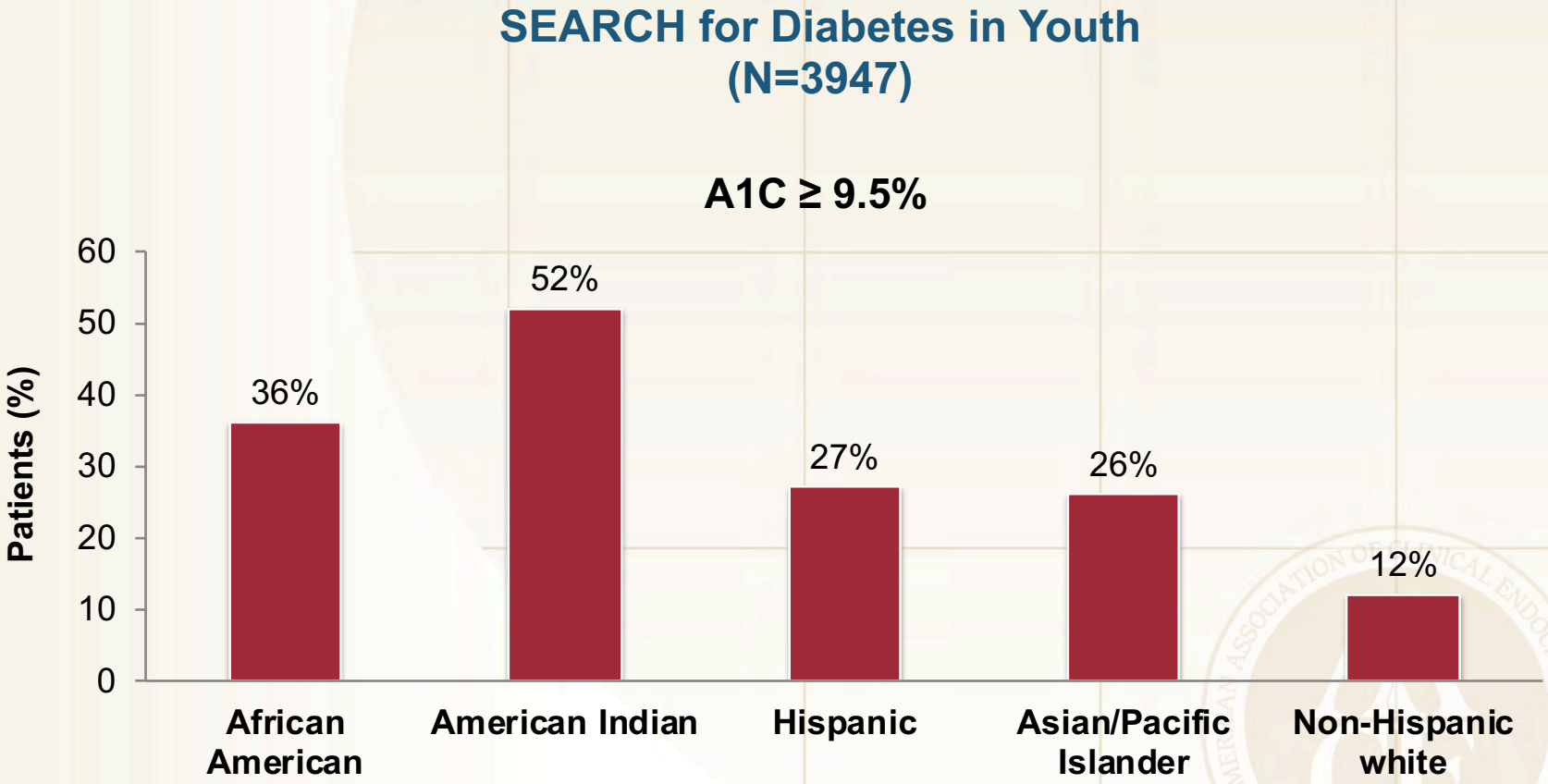
T1D, type 1 diabetes.

Chiang JL, et al. *Diabetes Care*. 2014;37:2034-2054.

Treatment of Type 1 Diabetes

RATIONALE FOR GLYCEMIC CONTROL

Poor Glycemic Control Among Youth With T1D

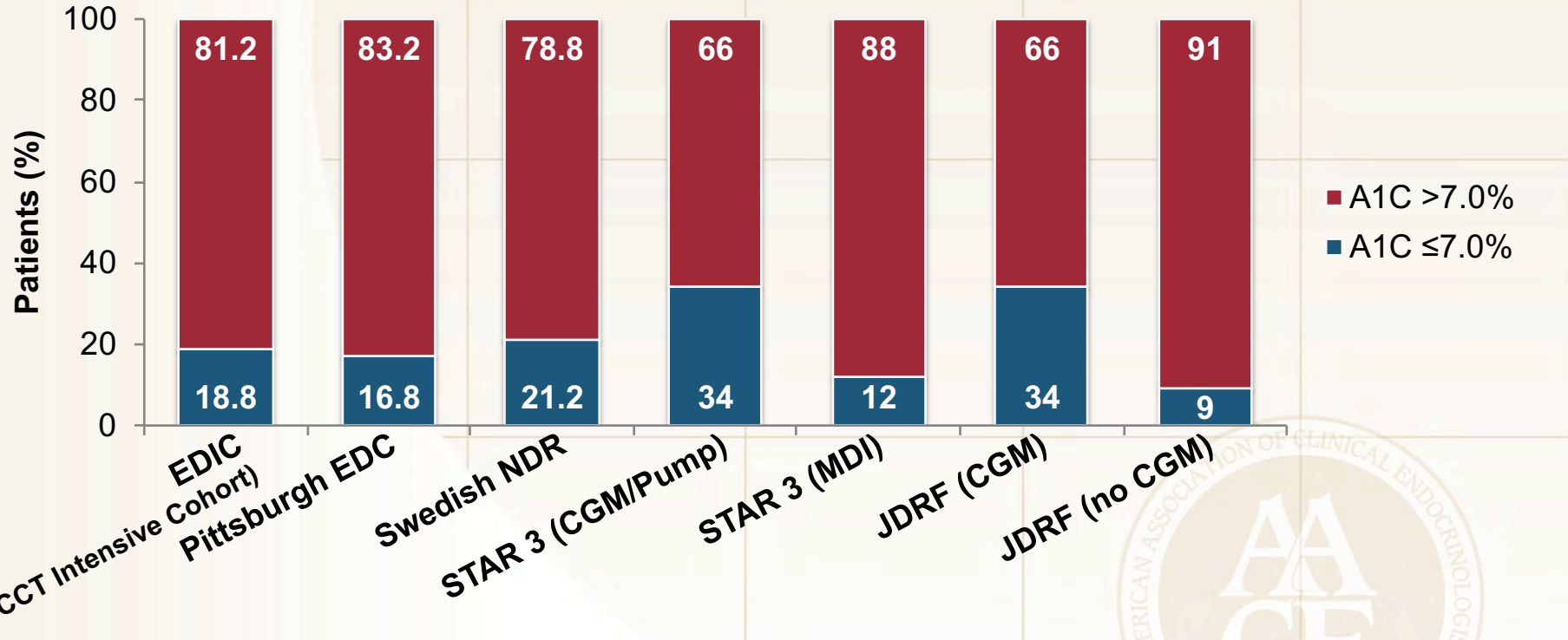


Cross-sectional analysis.

T1D, type 1 diabetes.

Petitti DB, et al. *J Pediatr*. 2009;155:668-72.e1-3.

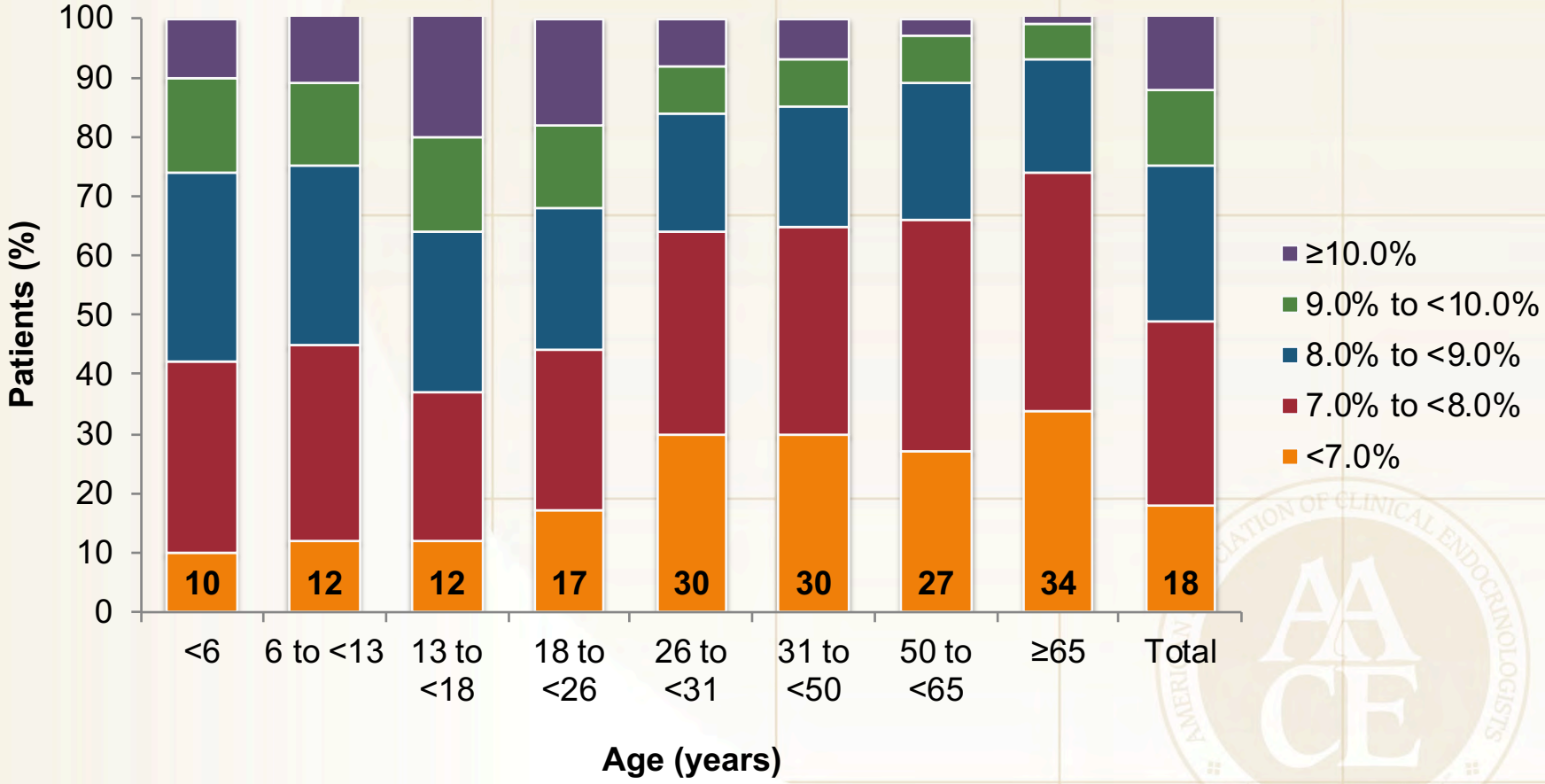
Suboptimal Glycemic Control in Adults With T1D



CGM, continuous glucose monitoring; EDIC, Epidemiology of Diabetes Interventions and Complications ; JDRF, Juvenile Diabetes Research Foundation; Pittsburgh EDC, Pittsburgh Epidemiology of Diabetes Complications; Swedish NDR, Swedish National Diabetes Register; STAR 3, Sensor Augmented Pump Therapy for A1C Reduction; T1D, type 1 diabetes.

Nathan DM, et al. *Arch Intern Med*. 2009;169:1307-1316. Eeg-Olofsson K, et al. *Diabetes Care*. 2007;30:496-502. Bergenstal RM, et al. *N Engl J Med*. 2010;363:311-320. JDRF CGM Study Group. *N Engl J Med*. 2008;359:1446-1476.

Rates of Glycemic Control in T1D by Age Group



T1D, type 1 diabetes.

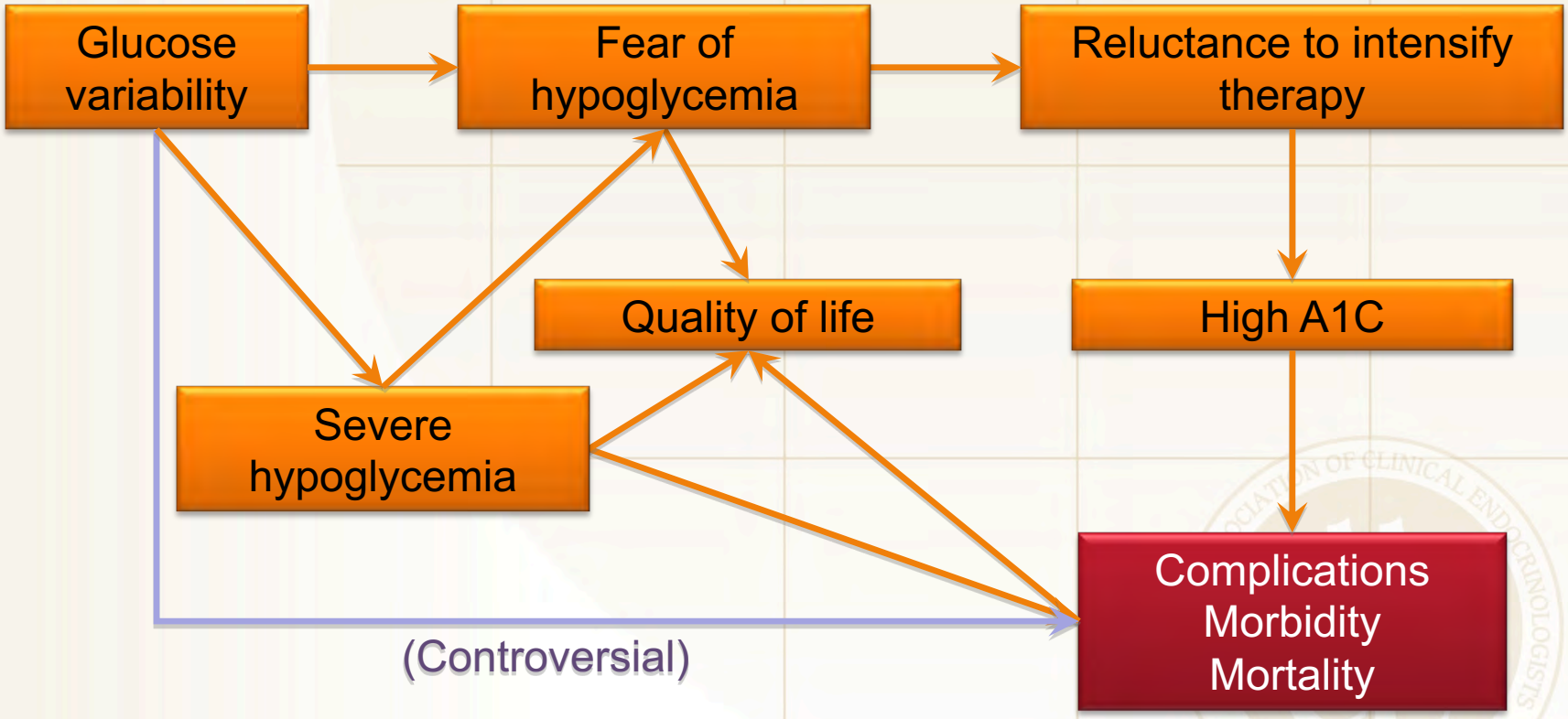
Beck RW, et al. *J Clin Endocrinol Metab*. 2012;97:4383-4389.

Predictors of Poor Glycemic Control

- Younger age
- Longer diabetes duration
- Weight <85th percentile
- Not living in a 2-parent household
- Type of diabetes care provider
- Nonwhite race/ethnicity
- Female gender
- Lower parental education
- Poor early glycemic control (2nd year after diagnosis predictive of poor glycemic control later)

Petitti DB, et al. *J Pediatr.* 2009;155:668-672.e1-3; Chemtob CM, et al. *J Diabetes.* 2011;3:153-157.

Glucose Variability and Health Outcomes: Direct and Indirect Pathways

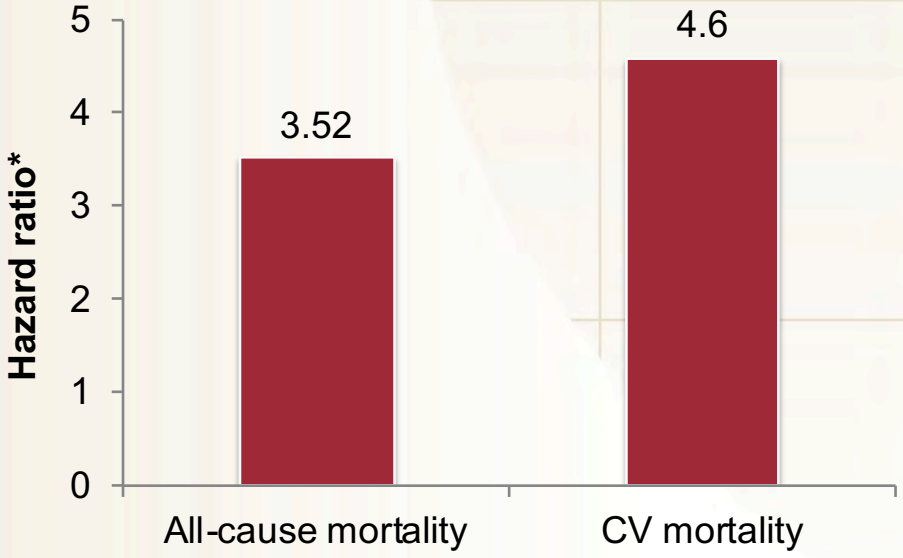


Irvine AA, et al. *Health Psychol*. 1992;11:135-138; Thompson CJ, et al. *Diabetes Care.* 1996;19:876-879; Reach G. *Diabetes Technol Ther*. 2008;10:69-80.

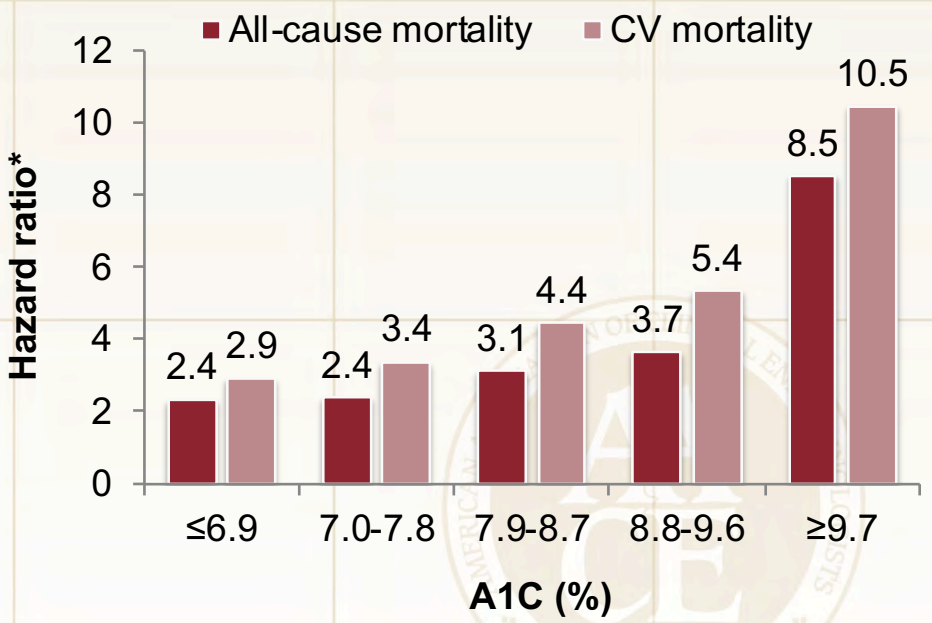
Mortality in Patients With T1D

Swedish National Diabetes Register (n=33,915 with T1D; n=169,249 without diabetes)

Mortality Risk vs Patients Without Diabetes



Mortality Risk by A1C Level



*Adjusted for age, diabetes duration, sex, birthplace, education, CVD status, and cancer status.

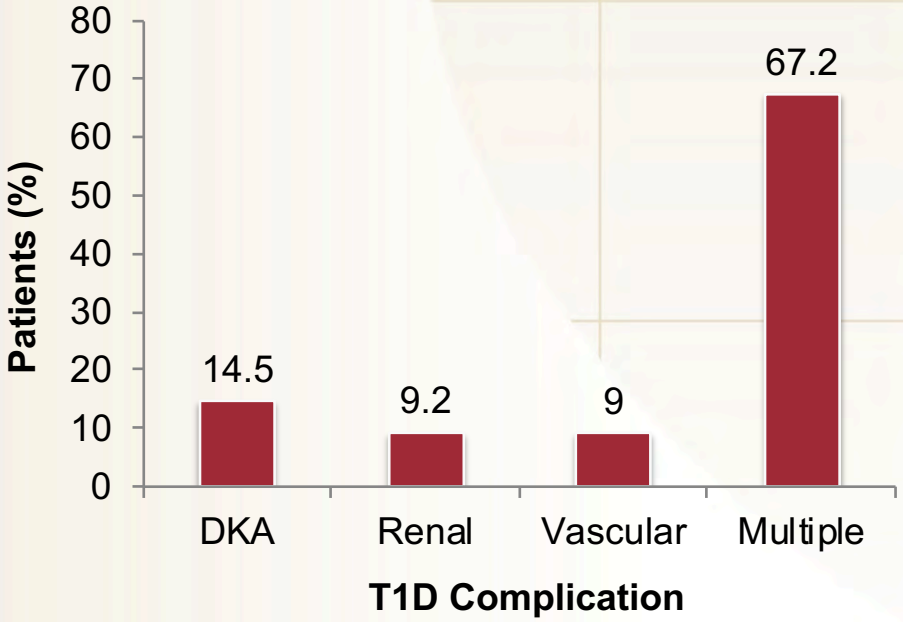
T1D, type 1 diabetes.

Lind M, et al. *N Engl J Med*. 2014;371:1972-1982.

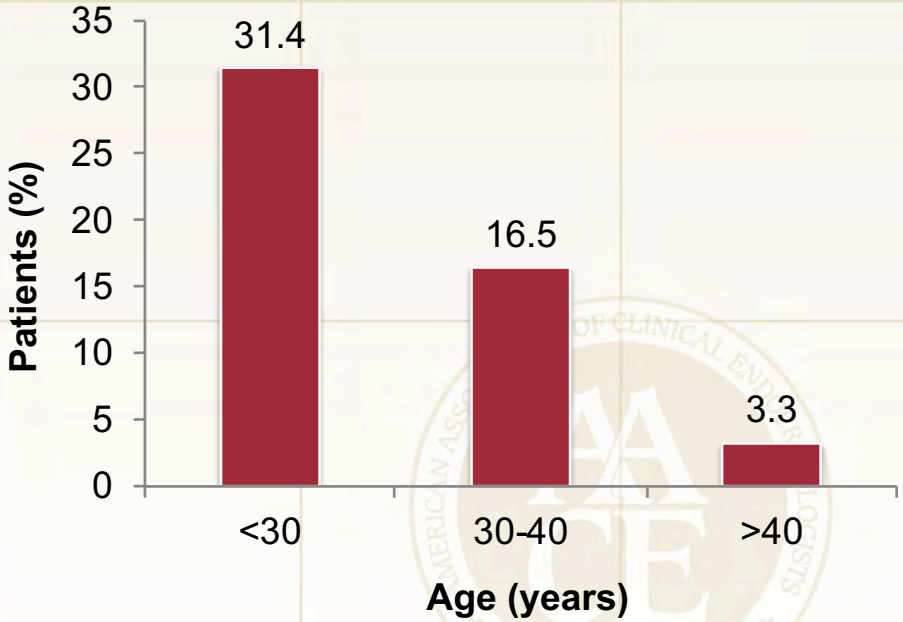
T1D-Related Mortality

Swedish National Diabetes Register (n=33,915)

Cause of Diabetes-Related Death, All Patients



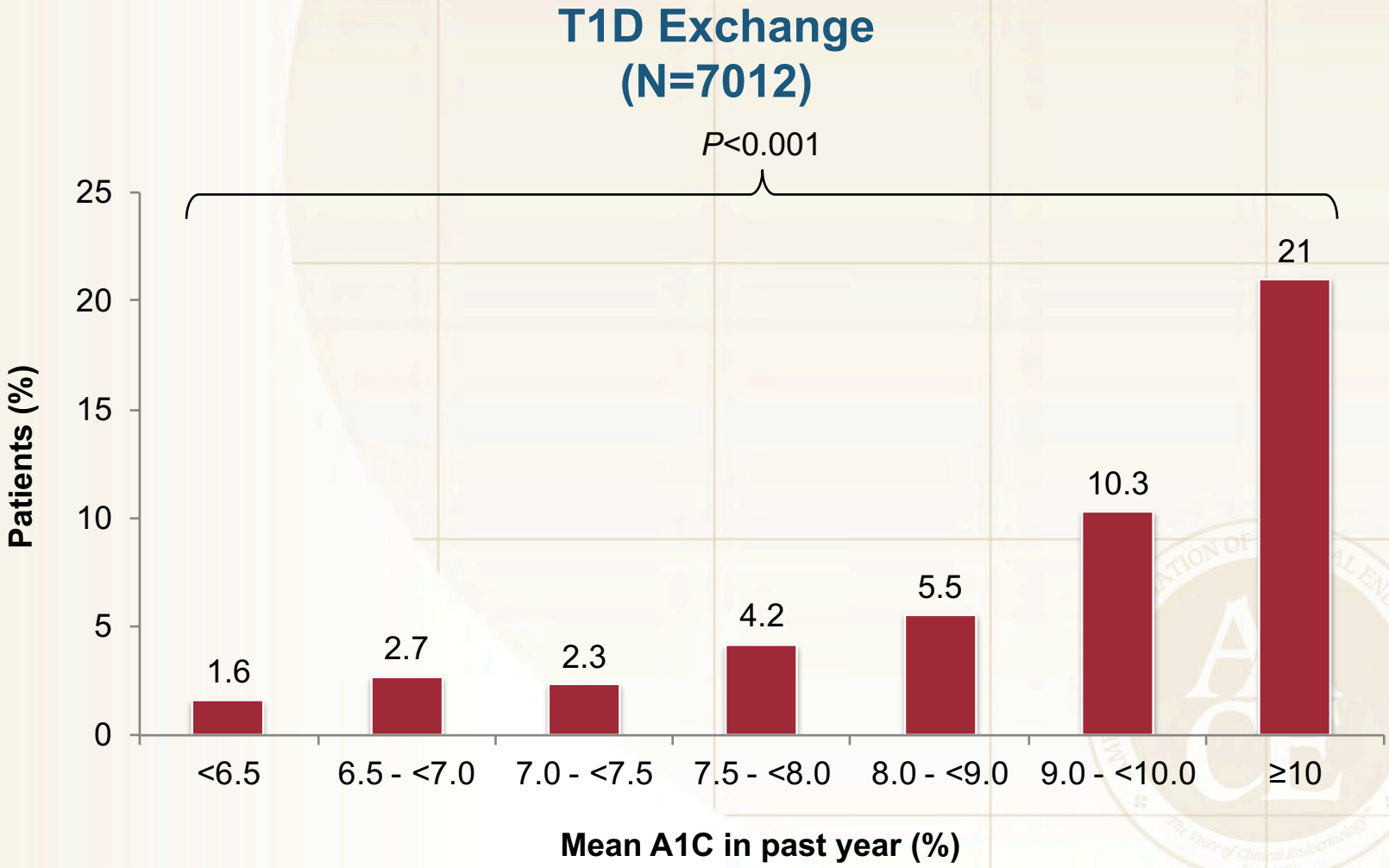
DKA Mortality



DKA, diabetic ketoacidosis; T1D, type 1 diabetes.

Lind M, et al. *N Engl J Med*. 2014;371:1972-1982.

Rates of DKA Over 12 Month Period in Adults with T1D



DKA, diabetic ketoacidosis; T1D, type 1 diabetes.

Weinstock RS, et al. *J Clin Endocrinol Metab*. 2013;98:3411-3419.

DCCT and EDIC Findings

- Intensive treatment reduced the risks of retinopathy, nephropathy, and neuropathy by 35% to 90% compared with conventional treatment
- Absolute risks of retinopathy and nephropathy were proportional to the A1C
- Intensive treatment was most effective when begun early, before complications were detectable
- Risk reductions achieved at a median A1C 7.3% for intensive treatment (vs 9.1% for conventional)
- Benefits of 6.5 years of intensive treatment extended well beyond the period of most intensive implementation ("metabolic memory")

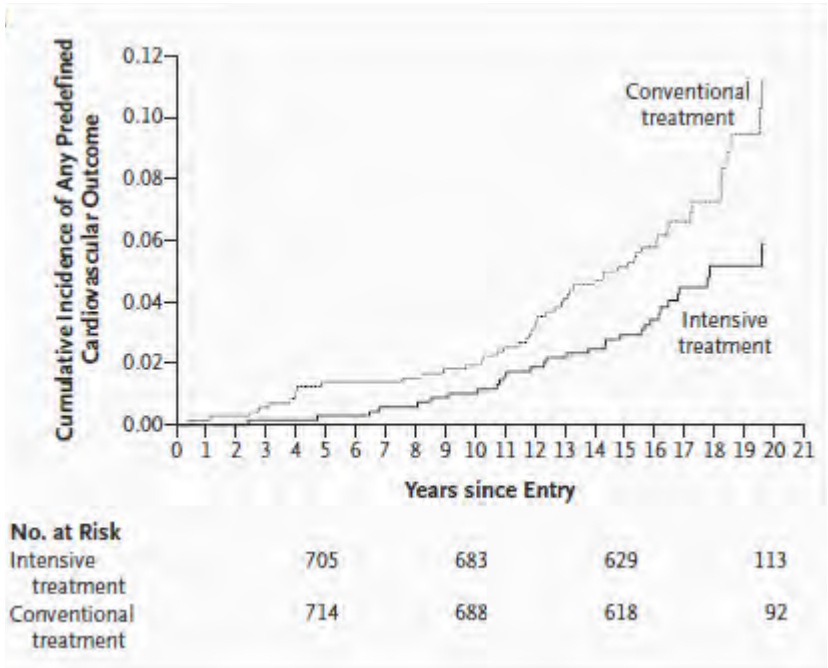
Intensive treatment should be started as soon as is safely possible after the onset of T1D and maintained thereafter

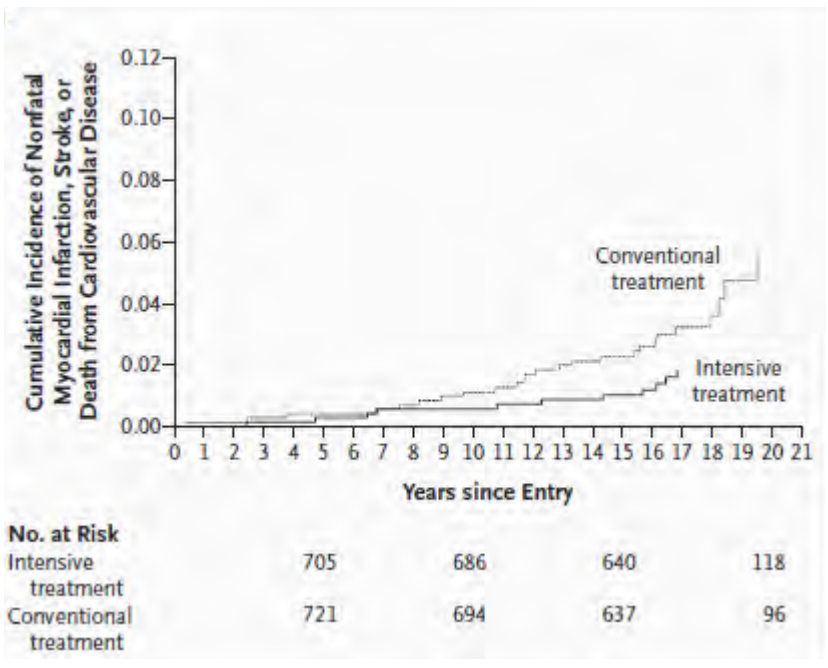
DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; T1D, type 1 diabetes.

DCCT/EDIC Research Group. *JAMA*. 2002;15;287:2563-2569.

Long-Term Benefits of Early Intensive Glycemic Control

DCCT-EDIC (N=1441)





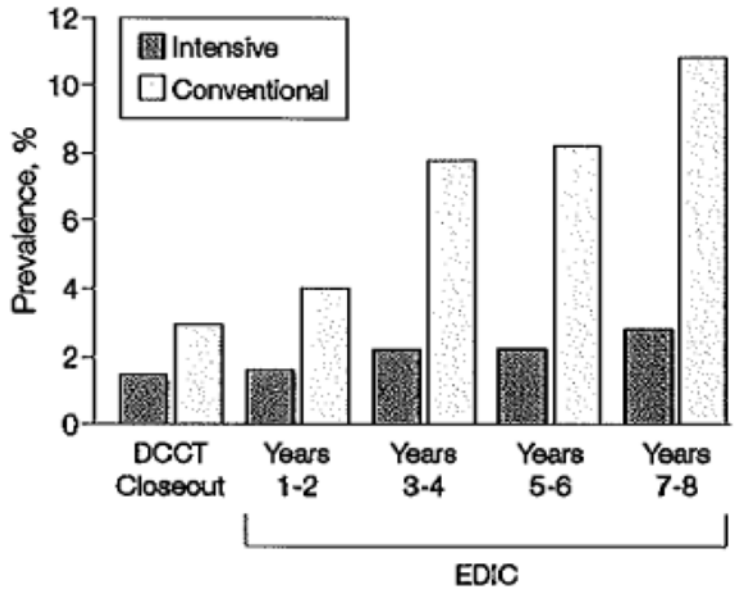
Intensive glycemic control over a mean of 6.5 years reduced CVD complications by 57% after a mean of 17 years of follow-up

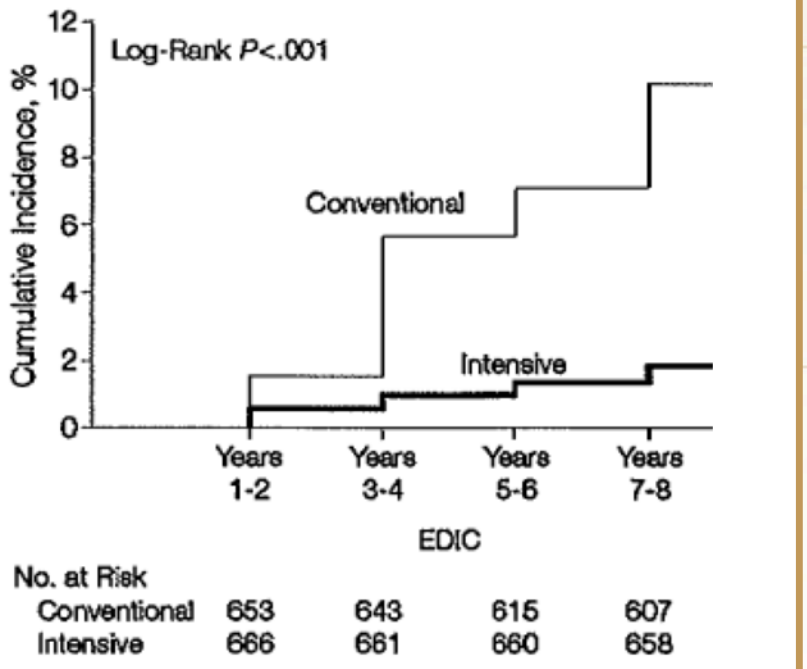
DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications .

Nathan DM, et al. *N Engl J Med*. 2005;353:2643-2653.

Sustained Effect of Intensive Treatment on Nephropathy in T1D

DCCT-EDIC (N=1349)



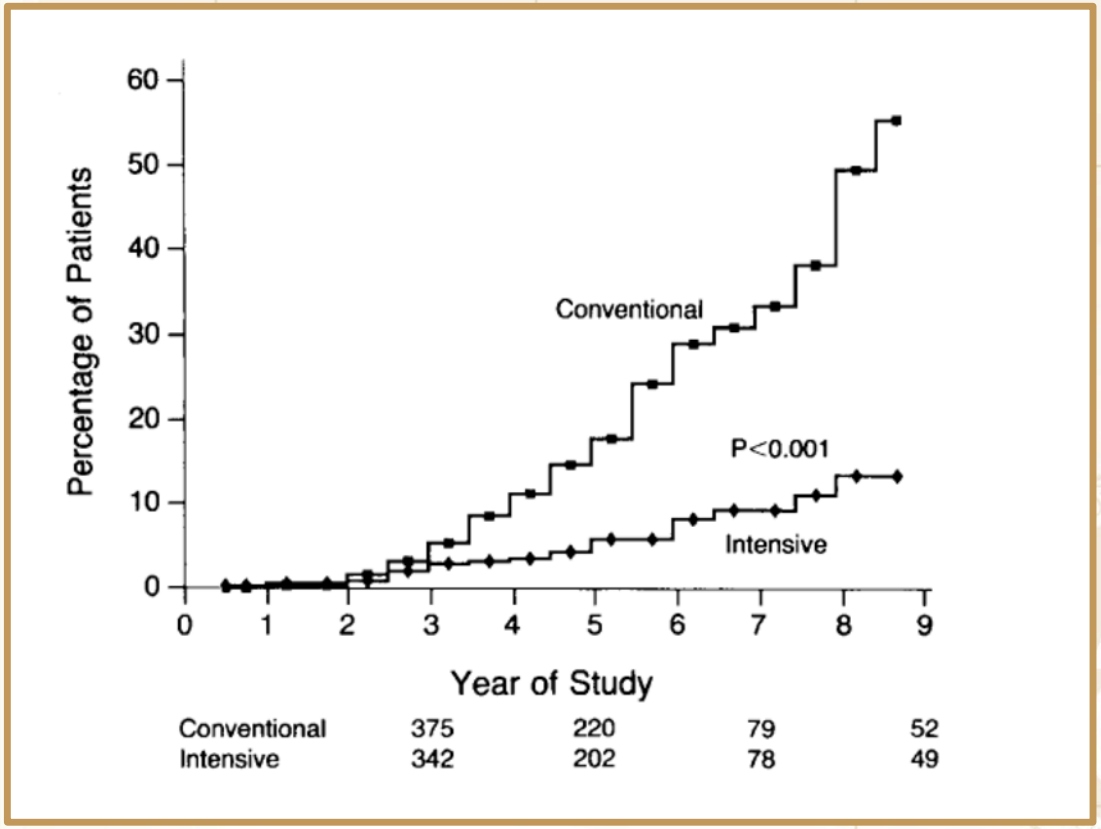


DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; T1D, type 1 diabetes.

DCCT EDIC. *JAMA*. 2003;290:2159-2167.

Effect of Intensive Treatment on Retinopathy in T1D

DCCT
(N=1441)

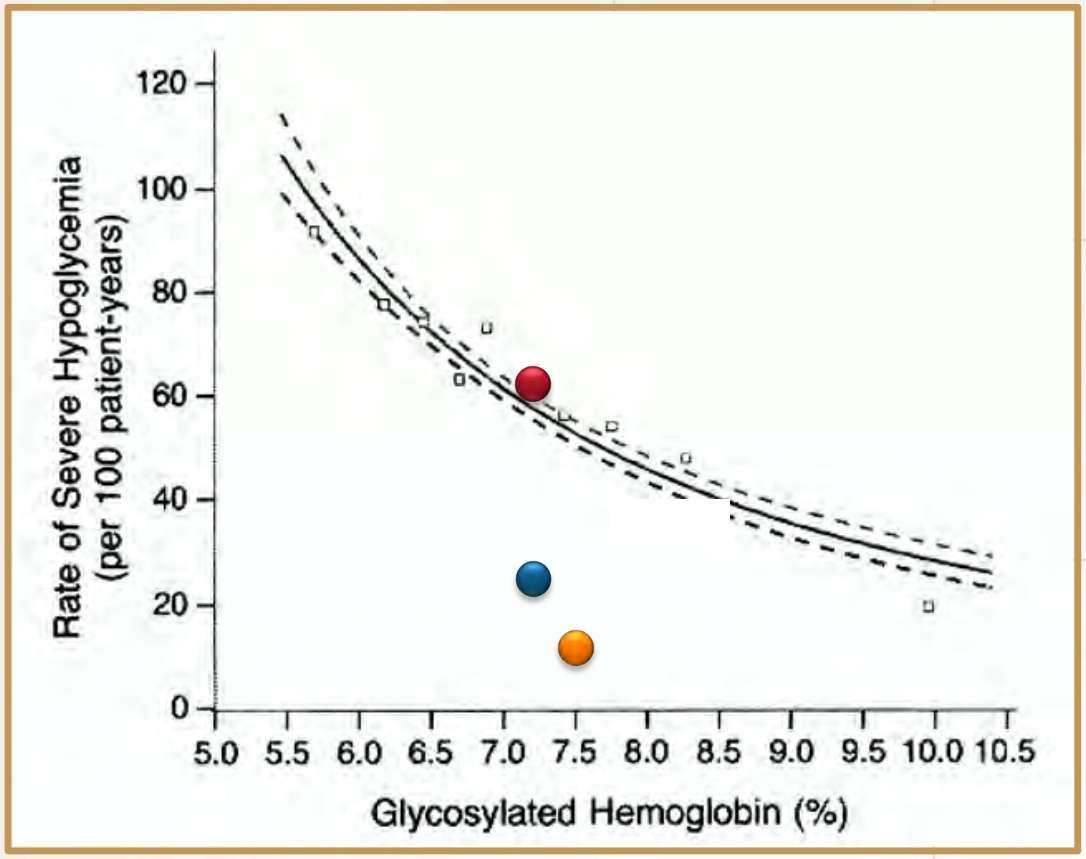


DCCT, Diabetes Control and Complications Trial; T1D, type 1 diabetes..

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

Severe Hypoglycemia and A1C

DCCT, JDRF, and STAR 3 Studies



- DCCT (intensive therapy):
  62 per 100 patient-years;
  A1C: 9.0% → 7.2% (6.5-y F/U)
- JDRF CGM (adults):
  20.0 per 100 patient-years;
  A1C: 7.5% → 7.1% (6.0-mo F/U)
- STAR 3 SAP:
  13.3 per 100 patient-years;
  A1C: 8.3% → 7.5% (1-y F/U)

CGM, continuous glucose monitoring; DCCT, Diabetes Control and Complications Trial; JDRF, Juvenile Diabetes Research Foundation; SAP, sensor augmented pump; STAR 3, Sensor Augmented Pump Therapy for A1C Reduction.

DCCT. *N Engl J Med*. 1993;329:977-986. JDRF CGM Study Group. *N Engl J Med.* 2008;359:1465-1476.
Bergenstal RM, et al. *N Engl J Med*. 2010;363:311-20.

Treatment of Type 1 Diabetes

MANAGEMENT OF HYPERGLYCEMIA

Therapeutic Options for Type 1 Diabetes

- Multiple daily injections of rapid acting insulin with meals combined with a daily basal insulin
- Continuous subcutaneous insulin infusion via an insulin pump
- Adjunctive therapy with pramlintide

T1D, type 1 diabetes.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Advances in the Care of Persons With Type 1 Diabetes

- Development of insulin analogues
- Insulin pump therapy
- Home glucose monitoring
- Advent of continuous glucose monitoring (CGM)

Treatment of Type 1 Diabetes

INSULIN OPTIONS

Physiologic Multiple Injection Regimens: The Basal-Bolus Insulin Concept

Basal insulin ~50% TDD

- Controls glucose production between meals and overnight
- Near-constant levels

Bolus insulin ~50% TDD

- Limits hyperglycemia after meals
- Immediate rise and sharp peak at 1 hour post-meal
- 10% to 20% of total daily insulin requirement at each meal

For ideal insulin replacement therapy, each component should come from a different insulin with a specific profile or via an insulin pump (with 1 insulin)

TDD, total daily dose.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Pharmacokinetics of Insulin

	Agent	Onset (h)	Peak (h)	Duration (h)	Considerations
Basal	NPH	2-4	4-10	10-16	Greater risk of nocturnal hypoglycemia compared to insulin analogs
	Glargine Detemir	~1-4	No pronounced peak*	Up to 24†	Less nocturnal hypoglycemia compared to NPH
	Degludec	~1	No pronounced peak*	>42	Less nocturnal hypoglycemia compared to NPH
Basal-Prandial	Regular U-500	≤0.5	~2-3	12-24	• Inject 30 min before a meal • Indicated for highly insulin resistant individuals • Use caution when measuring dosage to avoid inadvertent overdose
Prandial	Regular	~0.5-1	~2-3	Up to 8	• Must be injected 30-45 min before a meal • Injection with or after a meal could increase risk for hypoglycemia
	Aspart Glulisine Lispro Inhaled insulin	<0.5	~0.5-2.5	~3-5	• Can be administered 0-15 min before a meal • Less risk of postprandial hypoglycemia compared to regular insulin

* Exhibits a peak at higher dosages.

† Dose-dependent; degl.

NPH, Neutral Protamine Hagedorn.

Moghissi E et al. *Endocr Pract*. 2013;19:526-535. Humulin R U-500 (concentrated) insulin prescribing information. Indianapolis: Lilly USA, LLC. Haahr H, Heise T. *Clin Pharmacokinet*. 2014;53:787-800.

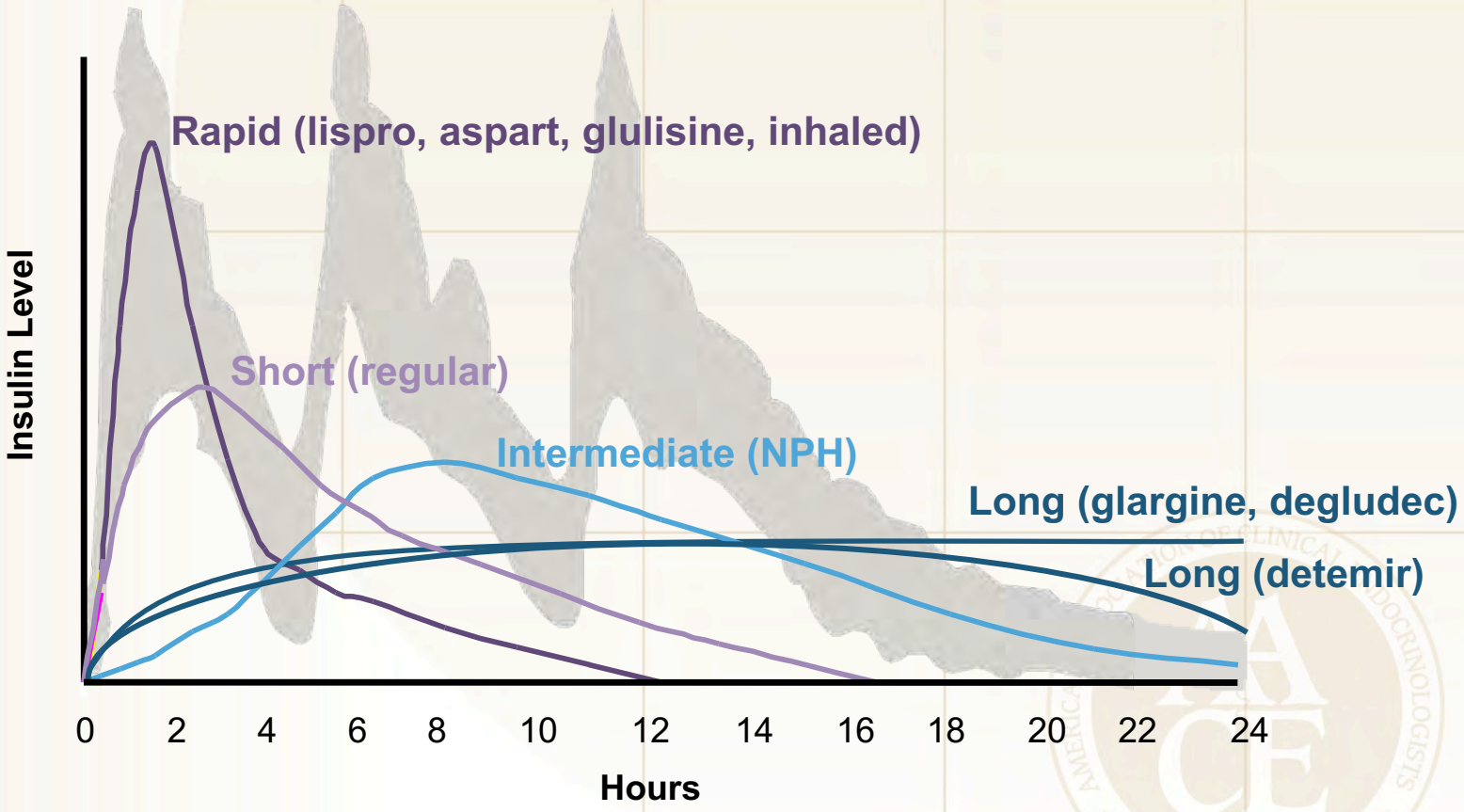
Principles of Insulin Therapy in Type 1 Diabetes

- Starting dose based on weight
  - Range: 0.4-0.5 units/kg per day
- Daily dosing
  - Basal
    - 40% to 50% TDI
    - Given as single injection of basal analog or 2 injections of NPH per day
  - Prandial
    - 50% to 60% of TDI in divided doses given 15 min before each meal
    - Each dose determined by estimating carbohydrate content of meal
- Higher TDI needed for obese patients, those with sedentary lifestyles, and during puberty

TDD, total daily dose.

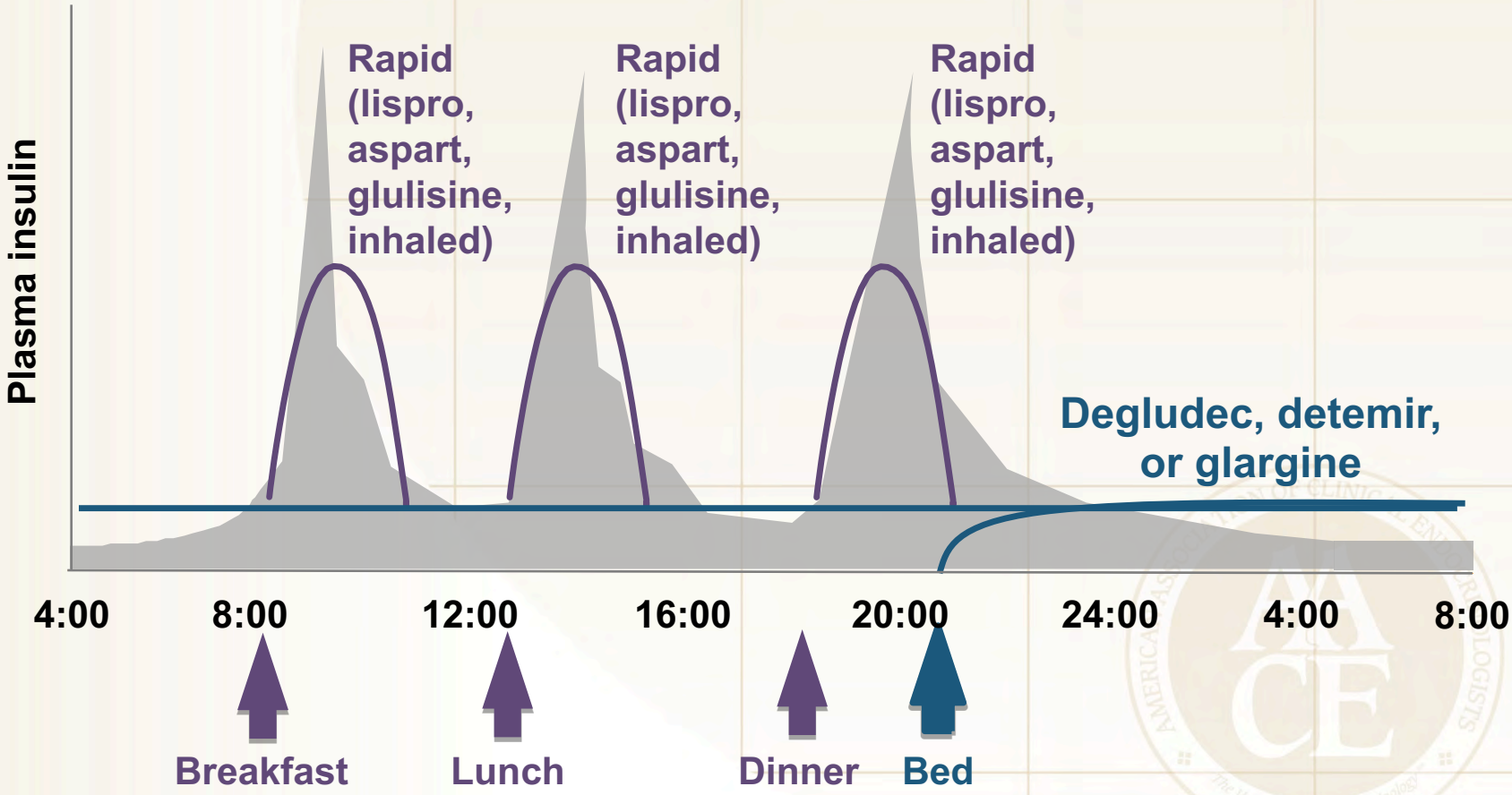
Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Pharmacokinetic Profiles of Insulins



Adapted from Hirsch I. *N Engl J Med*. 2005;352:174-183.

Basal/Bolus Treatment



Treatment of Type 1 Diabetes

PRAMLINTIDE

Insulin Replacement Not Always Sufficient for Glucose Control in T1D

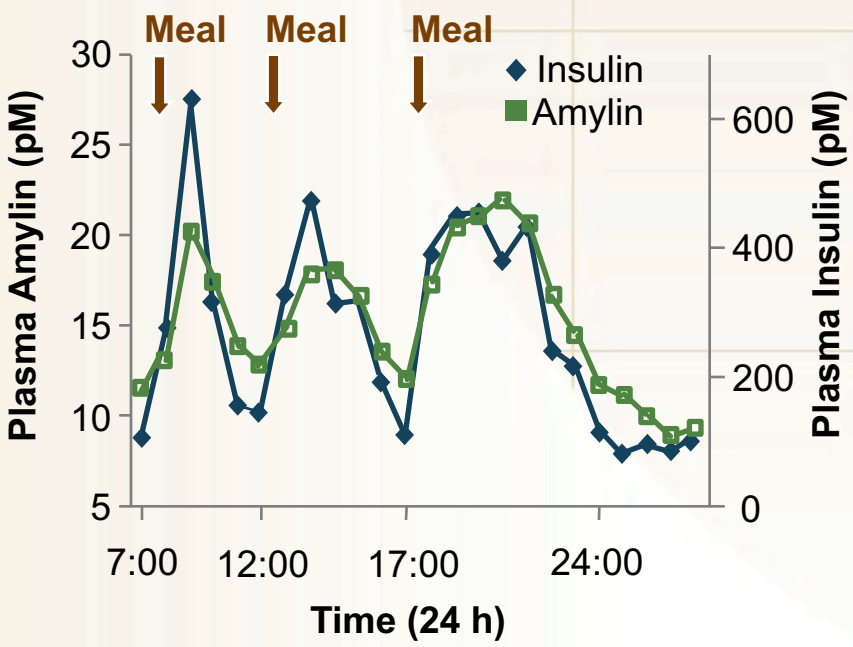
- Normal glucose regulation involves multiple hormones (eg, insulin, glucagon, amylin, incretins) and multiple organ systems (eg, pancreas, liver, stomach, brain)
- Insulin replacement therapy does not fully mimic the actions of insulin secreted by the pancreas in a healthy individual
  - Insulin exposure in the liver is lower with replacement therapy than with natural production, resulting in inadequate suppression of endogenous glucose production
  - Higher doses of insulin are required to achieve sufficient suppression of endogenous glucose production, but these are associated with hypoglycemia and weight gain

T1D, type 1 diabetes.

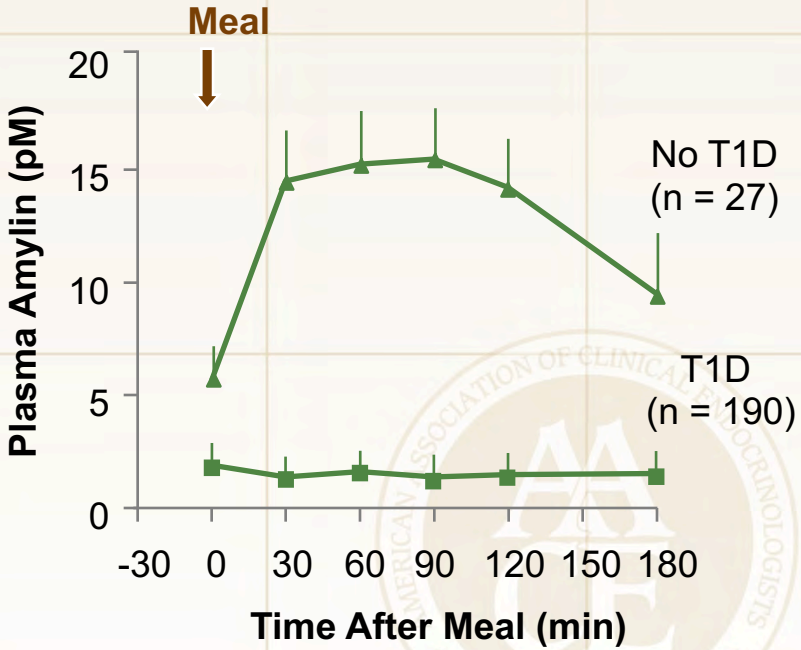
Aronoff SL, et al. *Diabetes Spectrum*. 2004;17:183-190;
Brown L, et al. *Sci Transl Med*. 2010;2:27ps18; Lebovitz HE. *Nat Rev Endocrinol*. 2010;6:326-334.

Amylin Is Deficient in Patients with T1D

Normal Diurnal Insulin and Amylin Secretion in Healthy Adults (N=6)



Amylin Secretion in Individuals With and Without T1D



T1D, type 1 diabetes.

Kruger D, et al. *Diabetes Educ*. 1999;25:389-398.

Pramlintide

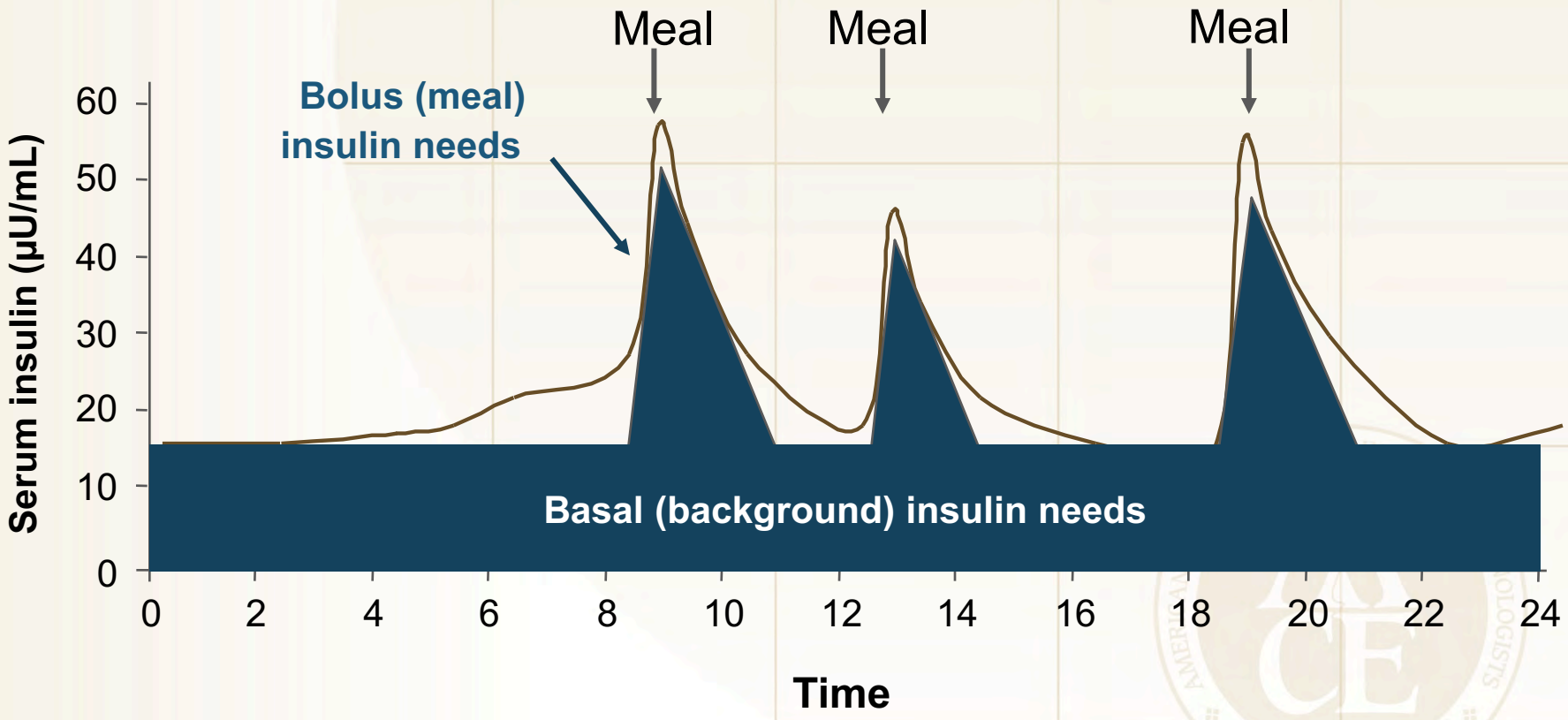
- Human amylin analog with pharmacokinetic and pharmacodynamic properties similar to endogenous hormone
- Mechanism of action
  - Promotes satiety and reduces caloric intake
  - Slows gastric emptying
  - Inhibits inappropriately high postprandial glucagon secretion

Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.

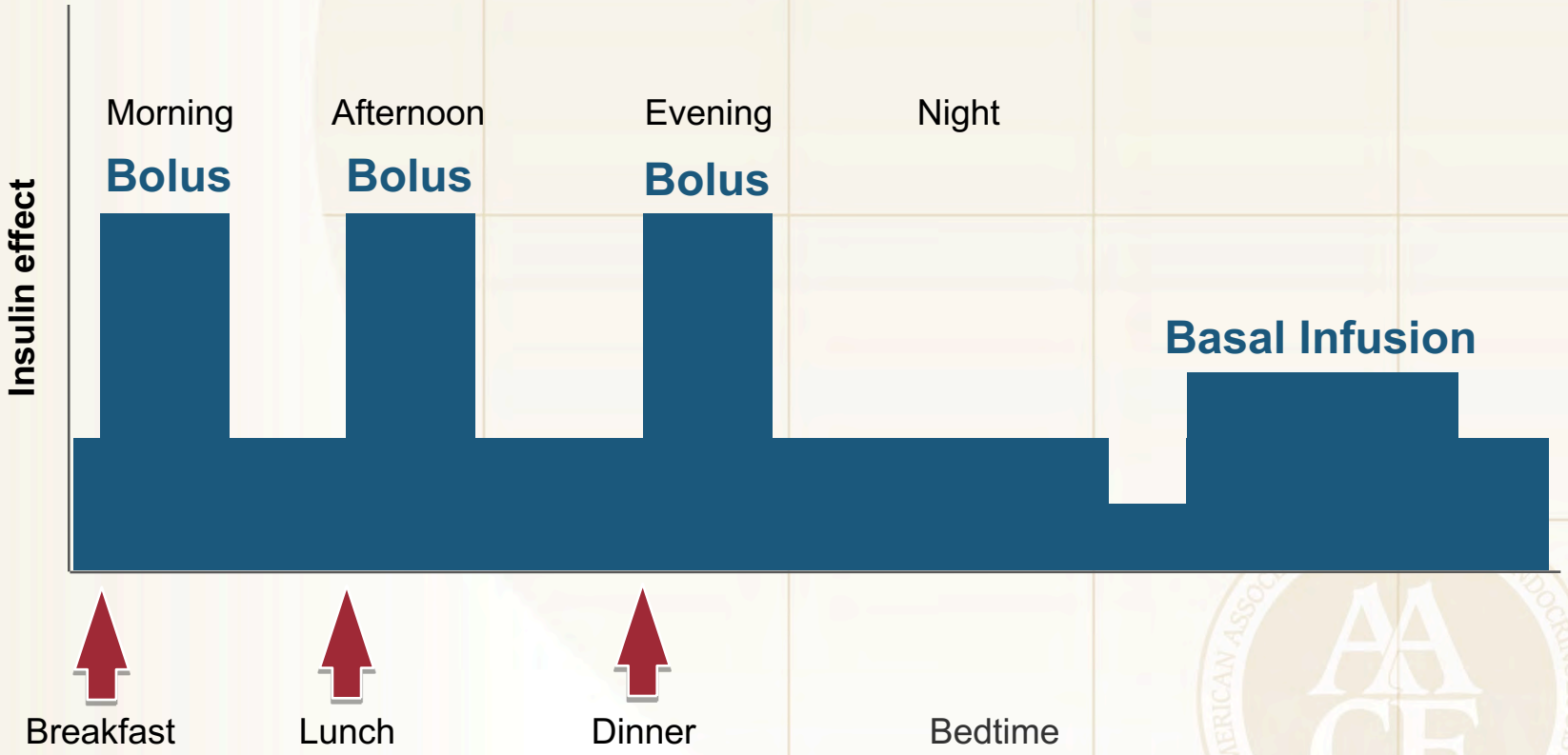
Treatment of Type 1 Diabetes

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

Normal Insulin Secretion



CSII With Rapid-Acting Analog



CSII, continuous subcutaneous insulin infusion.

Features of Modern Insulin Pumps Not Shared by MDI

- Variable basal and prandial infusion rates
  - Meal profiles (eg, normal and advanced bolus), pre-set basal rate changes, temporary basal rates, etc
- On-board calculators for meal insulin boluses
- Alarms/reminders (eg, missed bolus)
- Ability to download pump data to computer
- Integration with CGM for automatic feedback control and threshold suspend automation ("semi-closed loop")

CGM, continuous glucose monitoring; MDI, multiple daily injections.

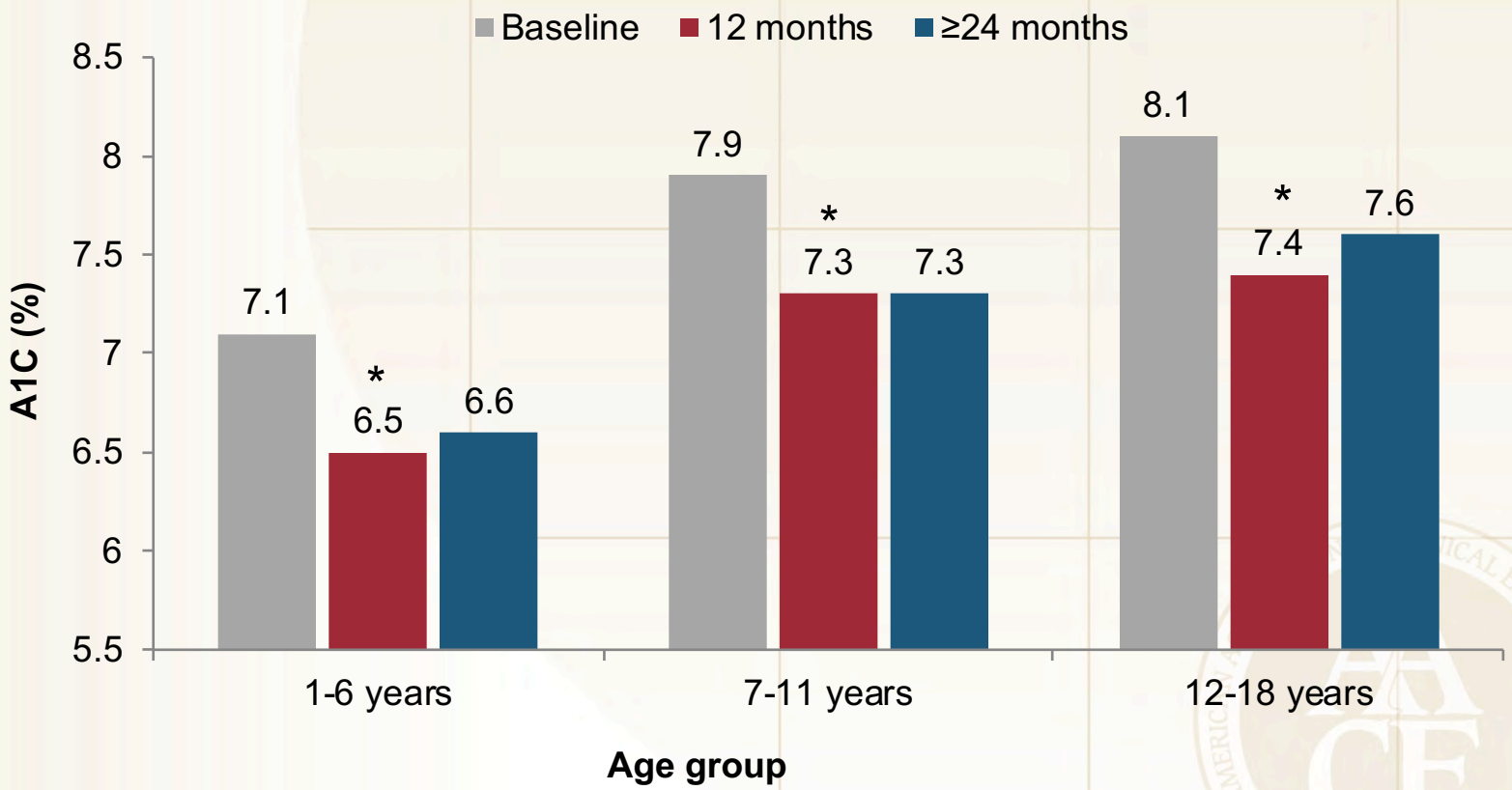
Technological Features of Insulin Pumps*

Insulin delivery	• Small bolus increments: 0.05-0.10 units • Extended boluses for delayed digestion or grazing • Multiple insulin-to-carbohydrate ratios, sensitivity factors, BG targets • Bolus calculators (based on BG level and carbohydrate quantity) • Low basal rates: 0.025-0.05 units/h • Multiple basal rates • Temporary basal rates and suspension mode
Safety features	• Alarms for occlusion and low insulin reservoir • Active insulin to prevent insulin stacking • Keypad lock • Waterproof or watertight
Miscellaneous	• Electronic logbook software (insulin doses, BG levels, carbohydrates) • Integrated food databases with customization • Reminder alarms for BG checks, bolus doses • Wireless communication with remote glucose meter • Integration with continuous glucose monitoring technology

* Will vary by insulin pump make and model.

BG, blood glucose.

Improved Glucose Control with CSII

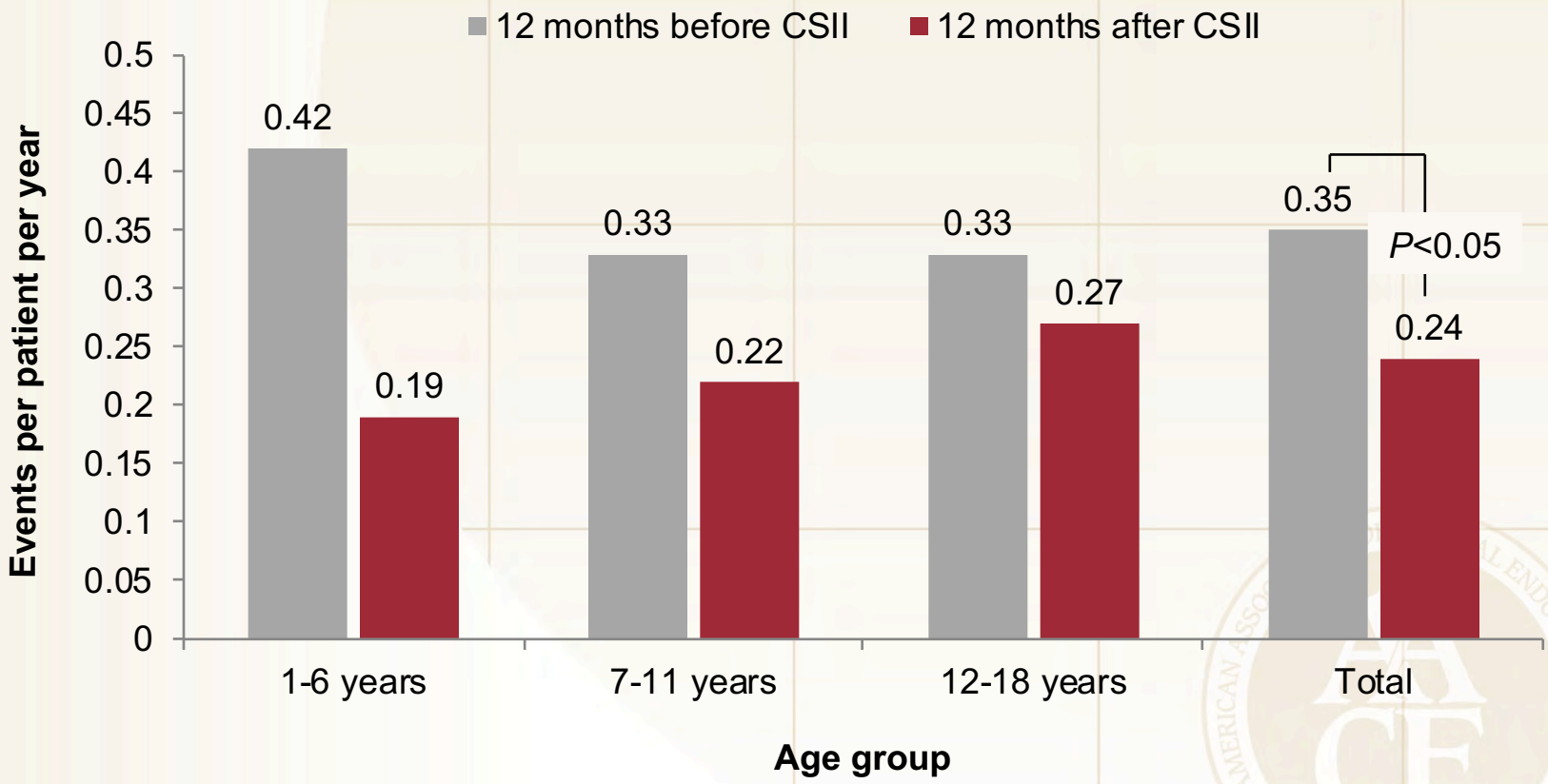


*P<0.02 vs baseline.

CSII, continuous subcutaneous insulin infusion.

Ahern JA, et al. *Pediatr Diabetes.* 2002;3:10-15.

Reduced Risk of Severe Hypoglycemia with CSII



CSII, continuous subcutaneous insulin infusion.

Ahern JA, et al. *Pediatr Diabetes.* 2002;3:10-15.

Efficacy of CSII

- Switching to CSII results in
  - Lower A1C, by ~0.5%-0.6%
  - Mean A1C ~7.5%-7.6%
  - Less hypoglycemia
  - Less glucose variability
  - No excessive weight gain
  - Greater patient satisfaction and quality of life

CSII, continuous subcutaneous insulin infusion.

Tamborlane WV, et al. *Rev Endo Metab Disorders*. 2006;7:205-213.

CSII Improves A1C and Hypoglycemia Compared with MDI

Meta-analysis
(N=22 studies)

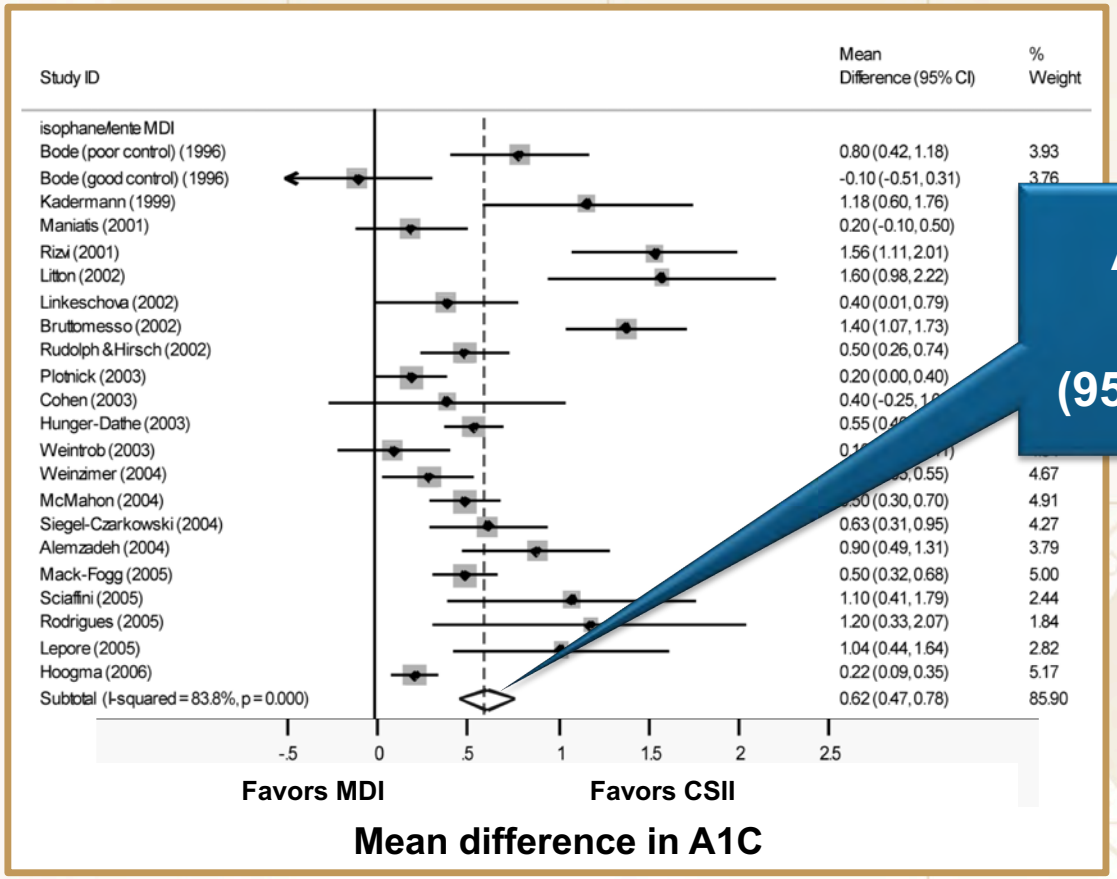
- Rate of severe hypoglycemia T1D was markedly lower during CSII than MDI, with greatest reductions in
  - Patients with most severe hypoglycemia on MDI
  - Patients with longest duration of diabetes
- Greatest improvement in A1C occurred in patients with the highest A1C on MDI

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; T1D, type 1 diabetes.

Pickup JC, Sutton AJ. *Diabet Med*. 2008;25:765-774.

CSII Significantly Reduces A1C Compared with MDI

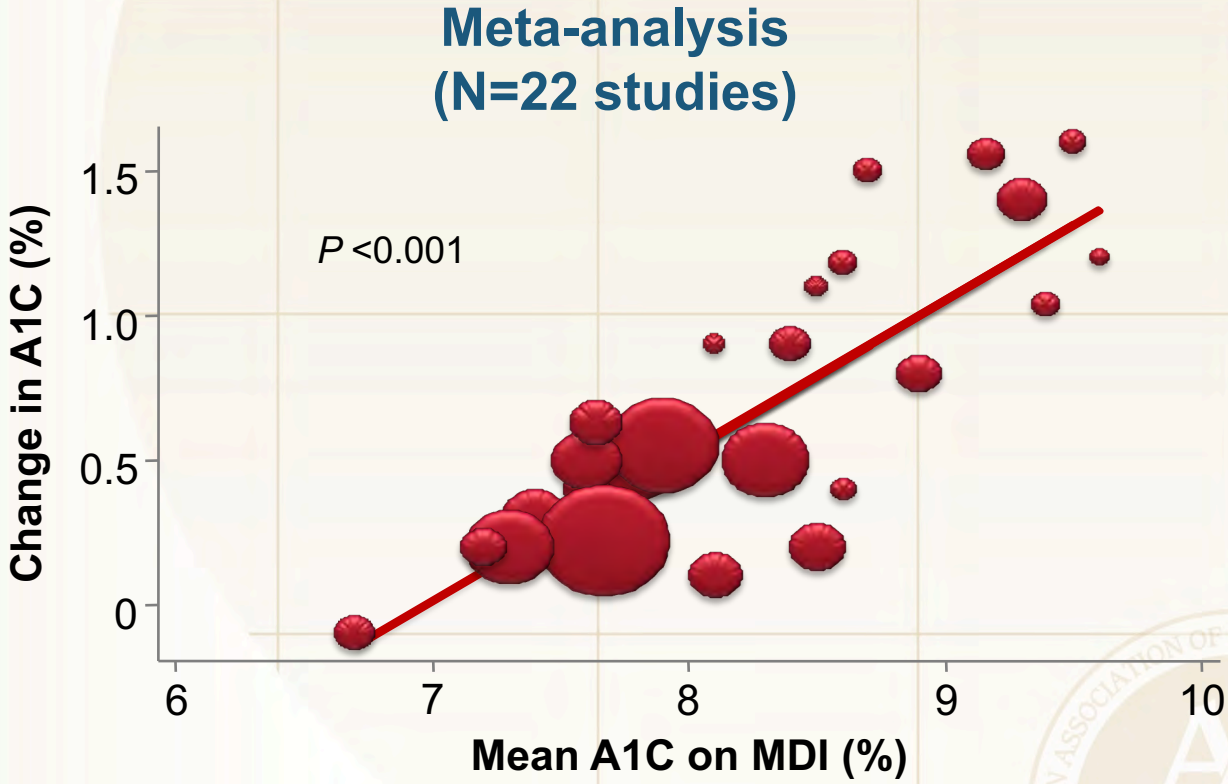
Meta-analysis (N=22 studies)



CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

Pickup JC, Sutton AJ. *Diabet Med*. 2008;25:765-774.

Relationship Between Glycemic Control on MDI and A1C While on CSII

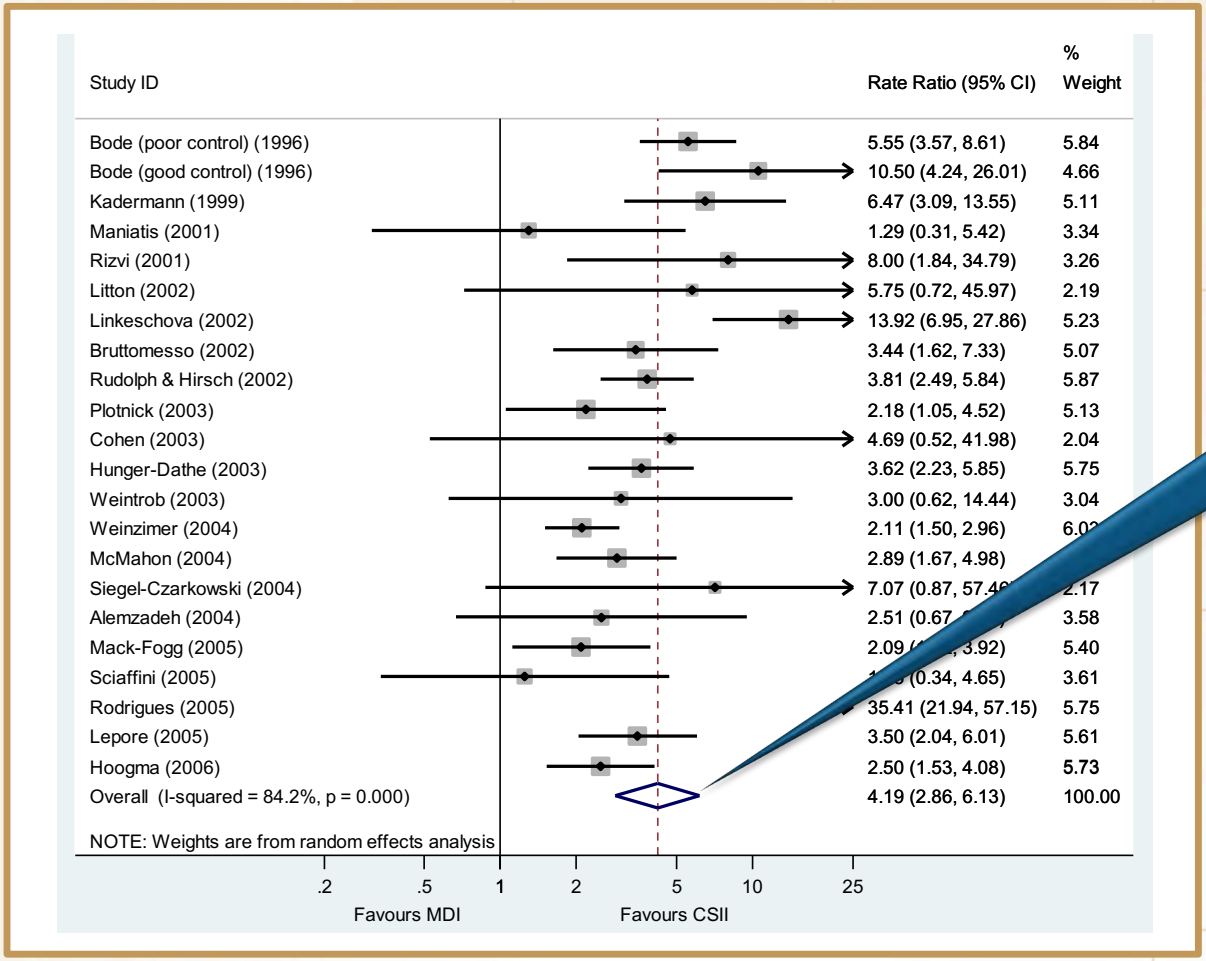


Change in A1C (MDI vs CSII) depends on A1C while on MDI:
CSII is most effective in patients with the worst glycemic control on MDI

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

Pickup JC, Sutton AJ. *Diabet Med*. 2008;25:765-774.

Severe Hypoglycemia with MDI vs CSII



Severe hypoglycemia reduced by ~75% by switching to pump therapy

No difference between randomized, controlled trials and before/after studies

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

Pickup JC, Sutton AJ. *Diabet Med*. 2008;25:765-774.

CSII vs MDI

2010 Meta-Analysis
(N=23 studies; 976 participants with T1D)

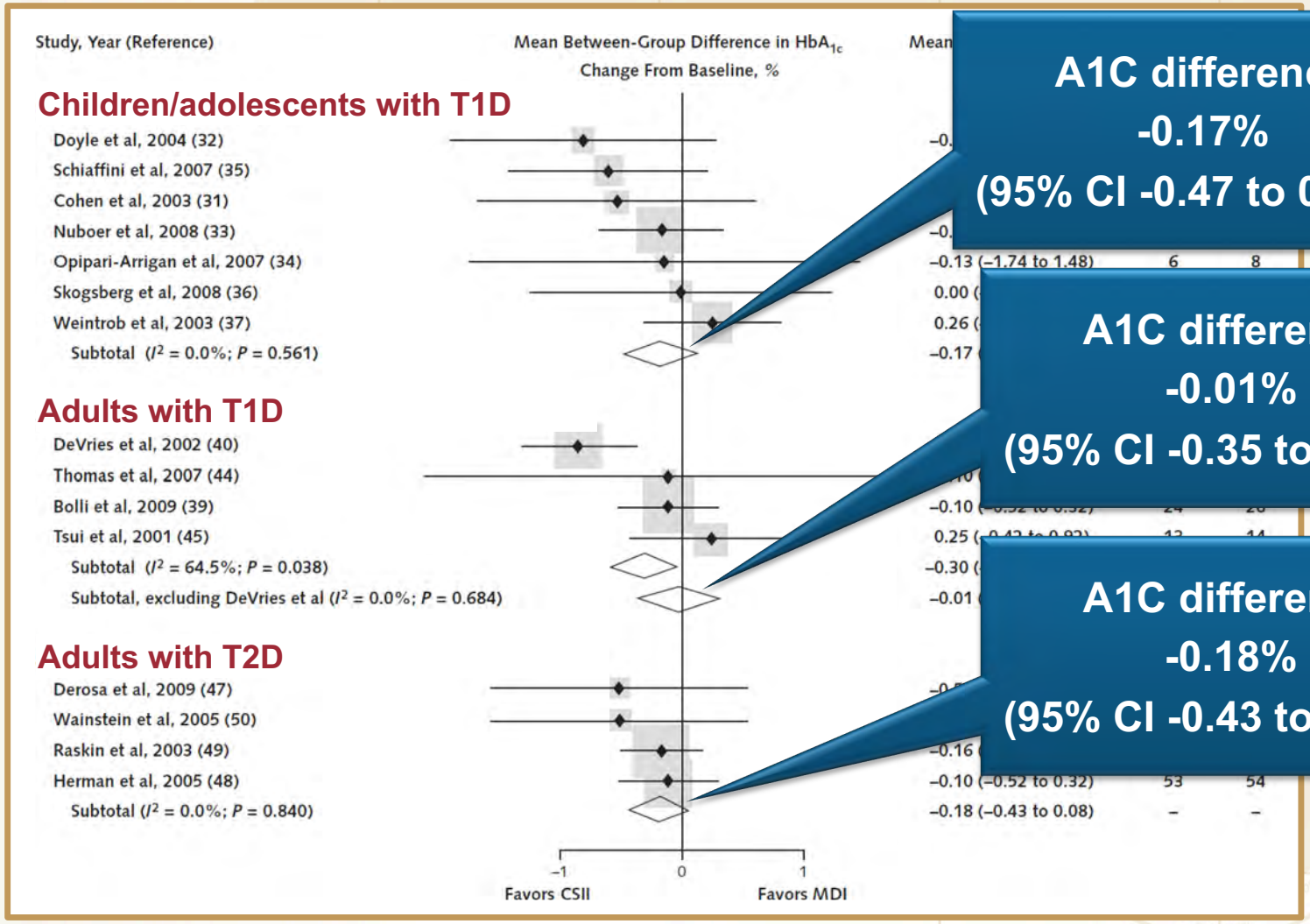
- Statistically significant difference in A1C favoring CSII
  - Weighted mean difference: -0.3% (95% confidence interval -0.1 to -0.4)
- Severe hypoglycemia appeared to be reduced in those using CSII
- Quality of life measures favored CSII

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; T1D, type 1 diabetes.

Misso ML, et al. *Cochrane Database Syst Rev.* 2010:CD005103.

CSII vs MDI

2012 Meta-Analysis



A1C difference
-0.17%
(95% CI -0.47 to 0.14%)

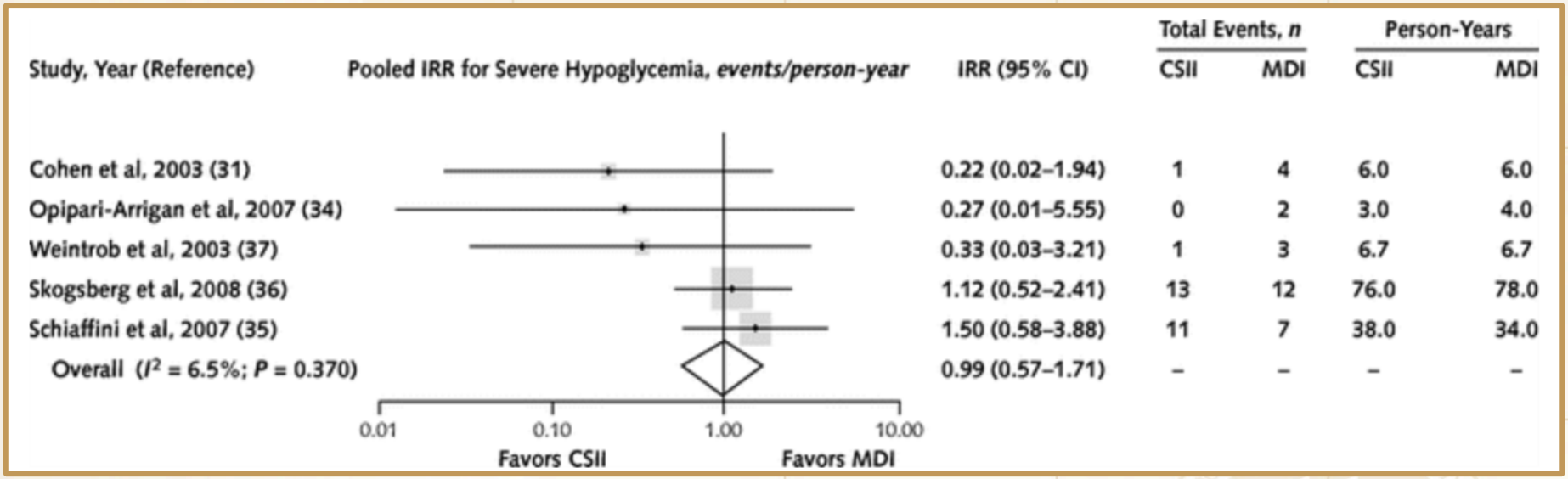
A1C difference
-0.01%
(95% CI -0.35 to 0.34%)

A1C difference
-0.18%
(95% CI -0.43 to 0.08%)

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; T1D, type 1 diabetes.
Yeh HC, et al. *Ann Intern Med*. 2012;157:336-347.

CSII vs MDI

2012 Meta-Analysis



The meta-analysis did not demonstrate any improvements in severe hypoglycemia with CSII compared to MDI in children and adolescents

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

Yeh HC, et al. *Ann Intern Med*. 2012;157:336-347.

2006 Berlin Consensus Conference on Pumps in Pediatrics

Almost all pediatric patients with T1D are candidates for CSII

- CSII strongly recommended for children with
  - Recurrent severe hypoglycemia
  - A1C above target range for age
  - Unacceptable fluctuations in blood glucose
  - Microvascular complications
  - Lifestyle compromised by insulin regimen
- CSII may also be beneficial in
  - Very young children
  - Dawn phenomenon
  - Competitive athletes

T1D, type 1 diabetes.

Phillip M, et al. *Diabetes Care.* 2007;30:1653-1662.

Insulin Pump Use in Children

Advantages

- Improved blood sugar control
- Insulin availability and convenience
- Use of multiple basal rates, temporary basal rates
- Ease of administering multiple boluses
- Reduction of hypoglycemia
- Flexibility and freedom
- Control of post-meal blood sugar/CGM values
- Ease of adjusting insulin doses with exercise and travel

Disadvantages

- Remembering to give insulin boluses with food intake
- Ketonuria or ketoacidosis
- Psychological factors
- Expense
- Weight gain
- Skin infections
- Insulin unavailability and instability
- Infusion site locations and set changes
- Physical/logistical considerations

Maahs DM, et al. *Diabetes Technol Ther*. 2010; 12(S1):S-59-S-65.

Characteristics of Successful CSII Patients

- Access to diabetes team knowledgeable in CSII, with 24/7 HCP access (physician or RN/CDE)
- Insurance
- Adequate intellectual ability to
  - Understand glycemic trending, even without CGM
  - Master carbohydrate counting or similar system for estimation of prandial insulin dosing (frequent SMBG can make up for poor carb estimation)
  - Understand basics of insulin therapy, including how to correct hyperglycemia before and after meals

CSII, continuous subcutaneous insulin infusion.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Characteristics of Successful CSII Physicians

- Time to spend with the patient
- Consistent philosophy of insulin use among all members of diabetes healthcare team
- Electronic infrastructure in the office or clinic to facilitate downloads and utilize the technology most effectively
- Basic understanding of principles of insulin use (MDI or CSII)

CSII, continuous subcutaneous insulin infusion.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

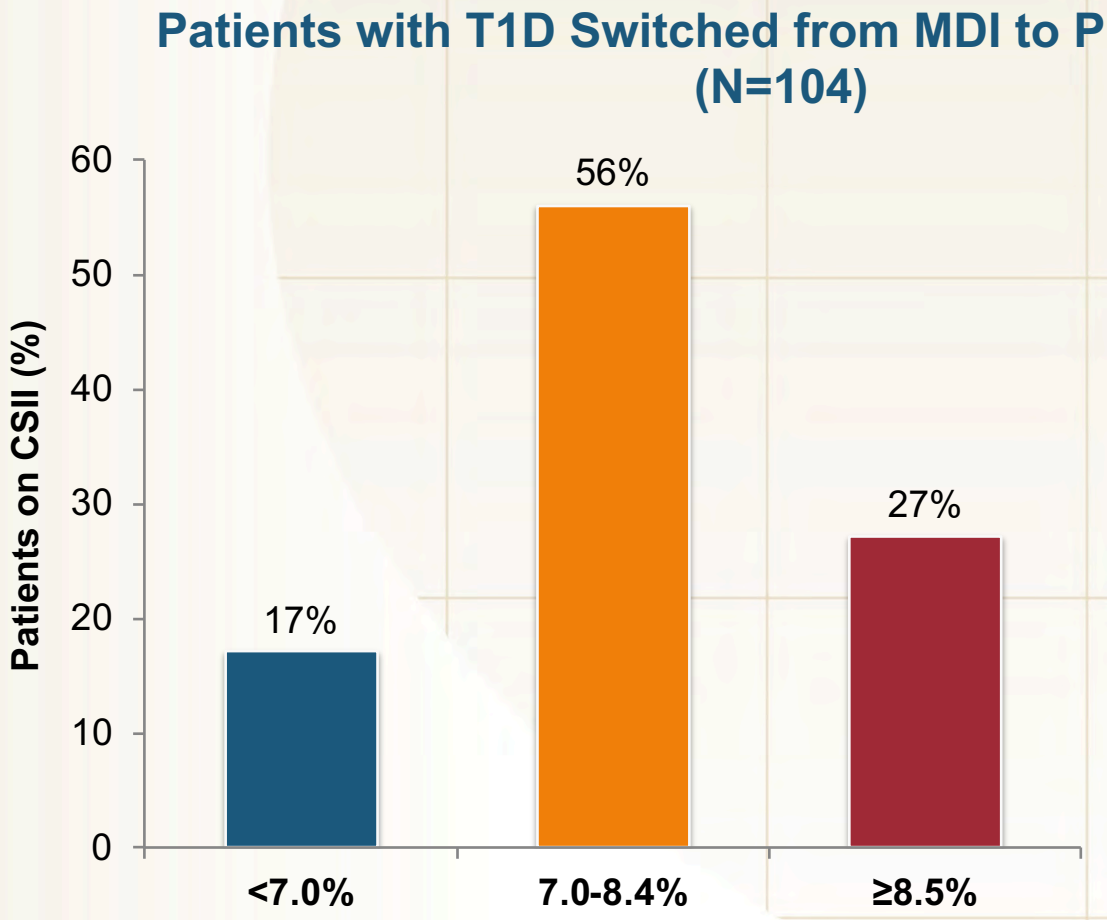
Definitions in the Context of Insulin Pumps

- Pharmacodynamics vs pharmacokinetics
  - Insulin-on-board (IOB)
    - Amount of insulin from the last bolus that has not yet been absorbed based on pharmacodynamic (not pharmacokinetic) data
  - Insulin stacking
    - Correction dose of insulin, used to treat before-meal or between-meal hyperglycemia in a situation when there is still significant IOB
- Insulin sensitivity factor
  - Correction factor based on amount of glucose reduction (mg/dL) expected from 1 unit of insulin for the individual patient

CSII: “Smart Pump” Limitations

- All modern pumps include a “bolus calculator” with goal of preventing insulin stacking, but patient must still
  - Check blood glucose
  - Understand “glycemic trends”
  - Estimate carbohydrate content with reasonable accuracy
  - Account for lag time
  - Assume no variability of food or insulin absorption
  - Use appropriate IOB

Not All Patients Have Good Control on CSII



A1C on CSII significantly correlated with prior A1C on MDI

(r=0.66; P<0.001)

CSII, continuous subcutaneous insulin infusion; T1D, type 1 diabetes.

Nixon R, Pickup JC. *Diabetes Technol Ther*. 2011;13:93-98.

Treatment of Type 1 Diabetes

CONTINUOUS GLUCOSE MONITORING

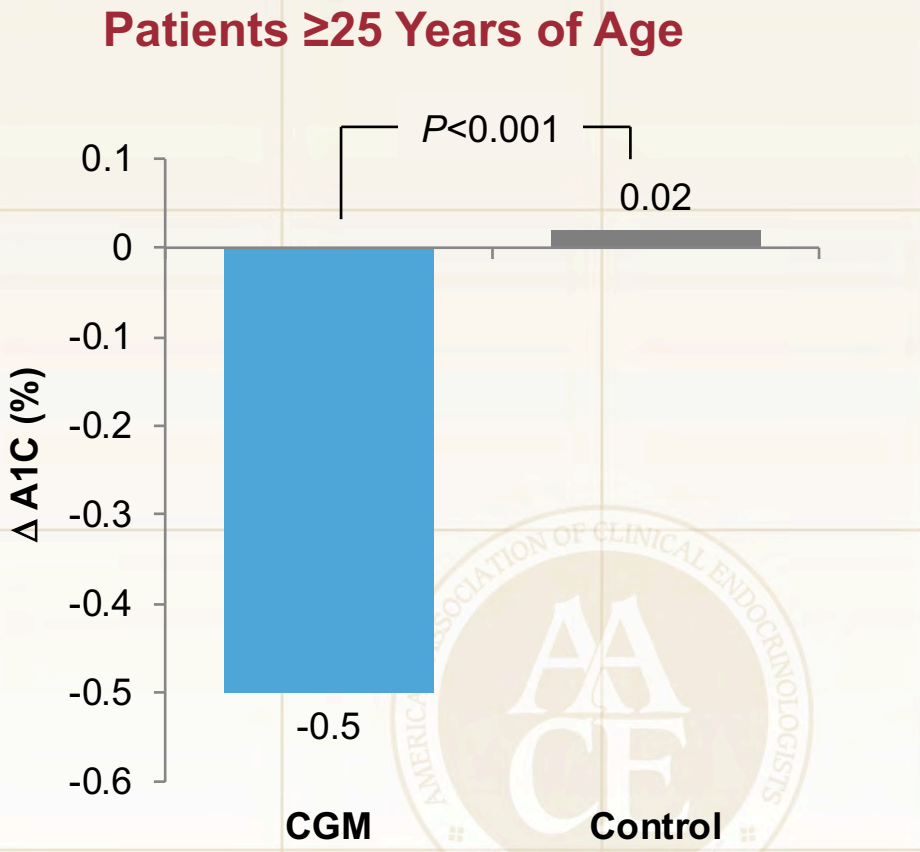
Definitions

- Professional CGM
  - Equipment owned by the provider
  - CGM Data may be blinded or visible to patient
- Personal CGM
  - Device owned by patient
  - Blood glucose data visible, able to be seen continuously

Continuous Glucose Monitoring in Type 1 Diabetes

JDRF Sensor Trial

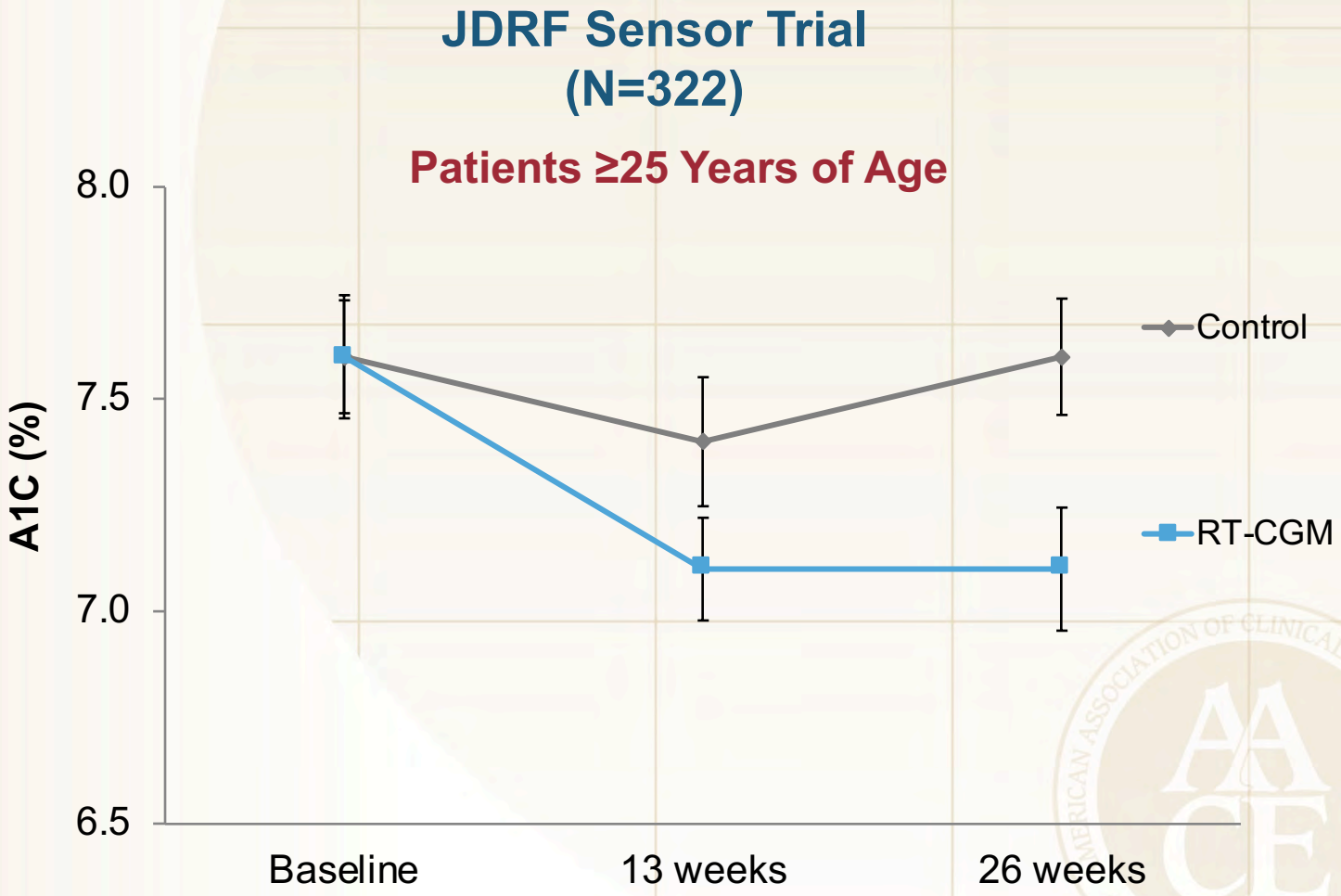
- Patients
  - Baseline A1C >7.0%
  - Age cohorts
    - 8-14 years (n=114)
    - 15-24 years (n=110)
    - ≥25 years (n=98)
- Improvement sustained for 12 months in patients aged ≥25 years
- No significant difference between CGM and control group among patients <25 years of age



JDRF, Juvenile Diabetes Research Foundation.

JDRF CGM Study Group. *New Engl J Med*. 2008;359:1464-1476.

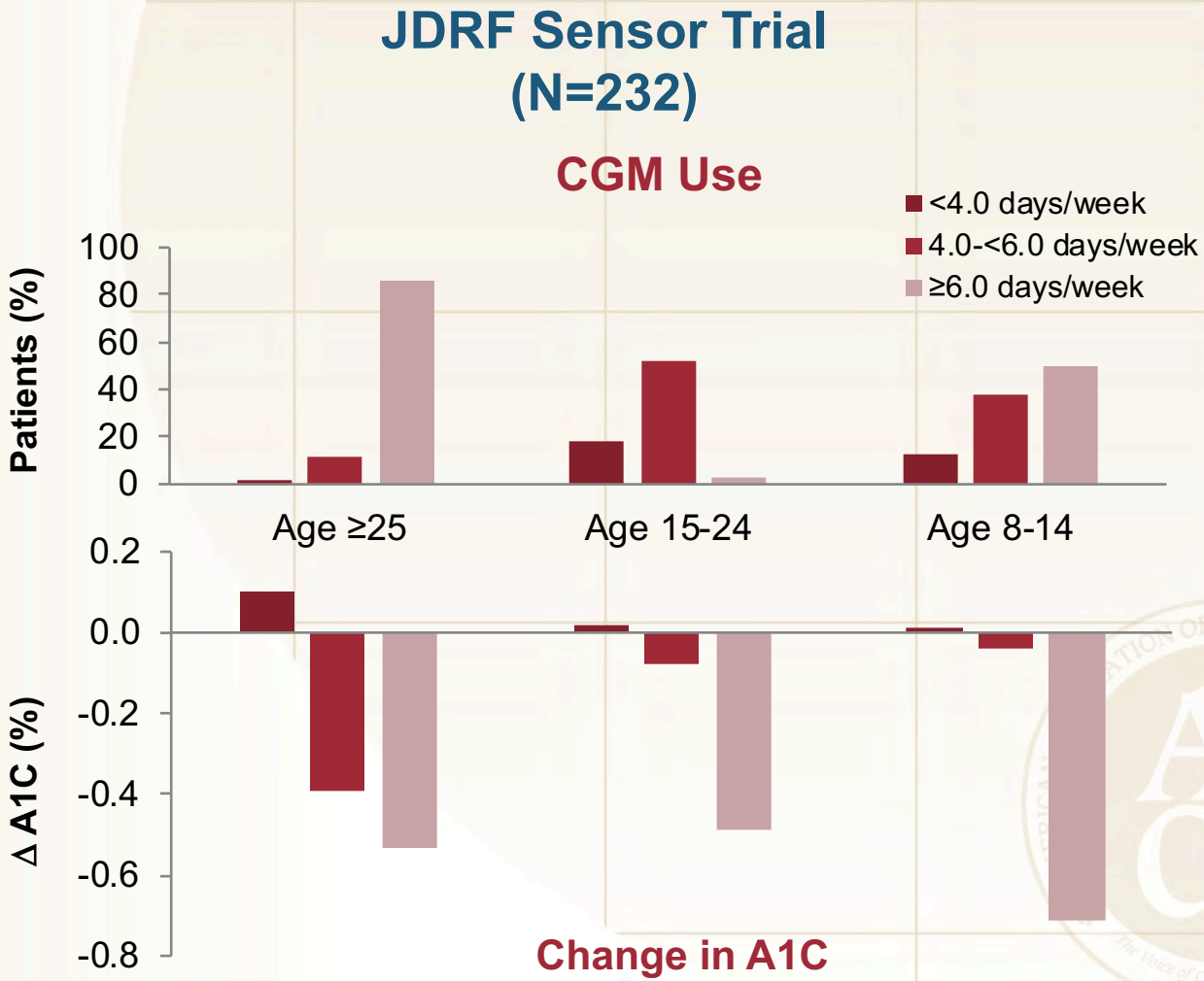
Change in A1C Over Time



CGM, continuous glucose monitoring; JDRF, Juvenile Diabetes Research Foundation.

JDRF CGM Study Group. *New Engl J Med*. 2008;359:1464-1476.

Relationship Between Frequency of CGM Use and Change in A1C



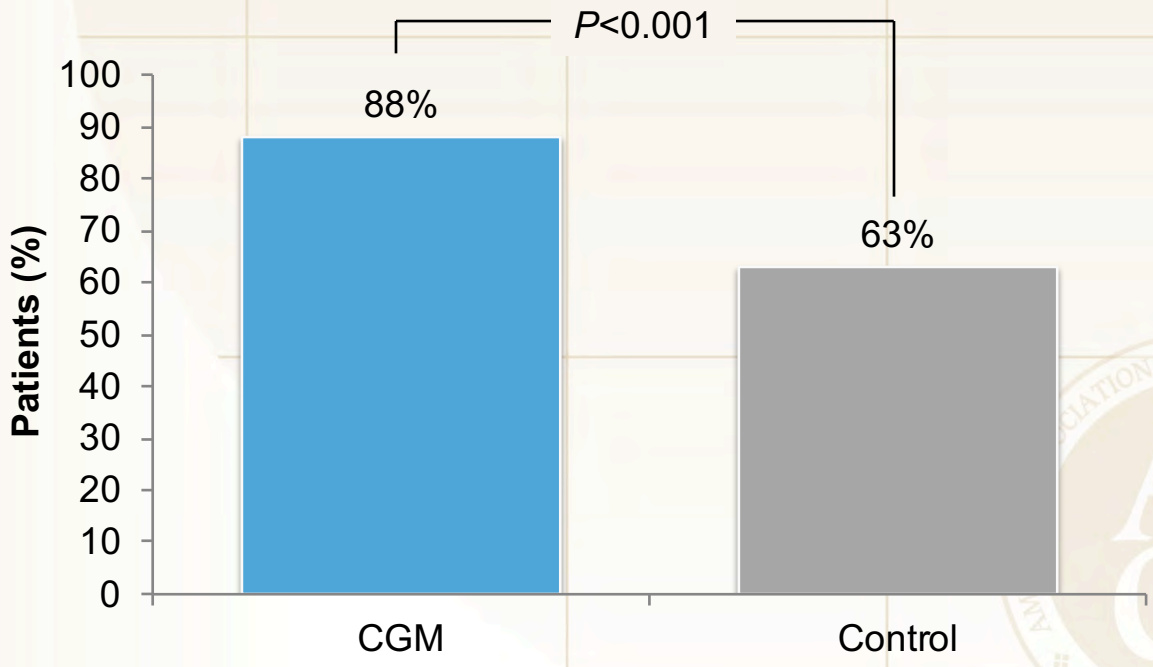
CGM, continuous glucose monitoring.

JDRF CGM Study. *Diabetes Care*. 2009;32:1947-1953.

A1C Goal Attainment

JDRF Sensor Trial (N=232)

Patients Achieving A1C <7%

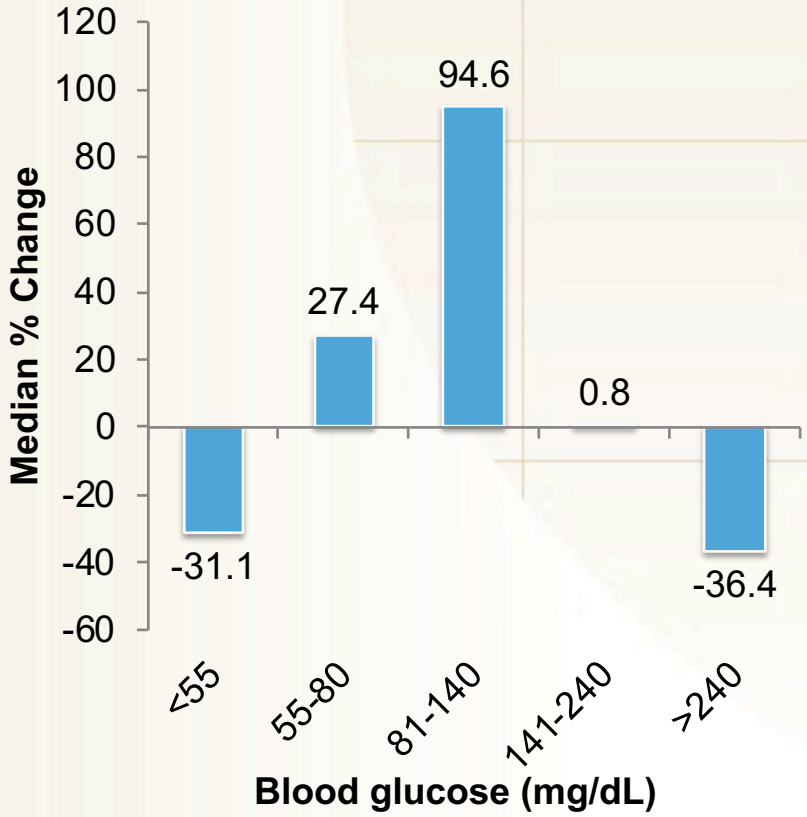


CGM, continuous glucose monitoring.

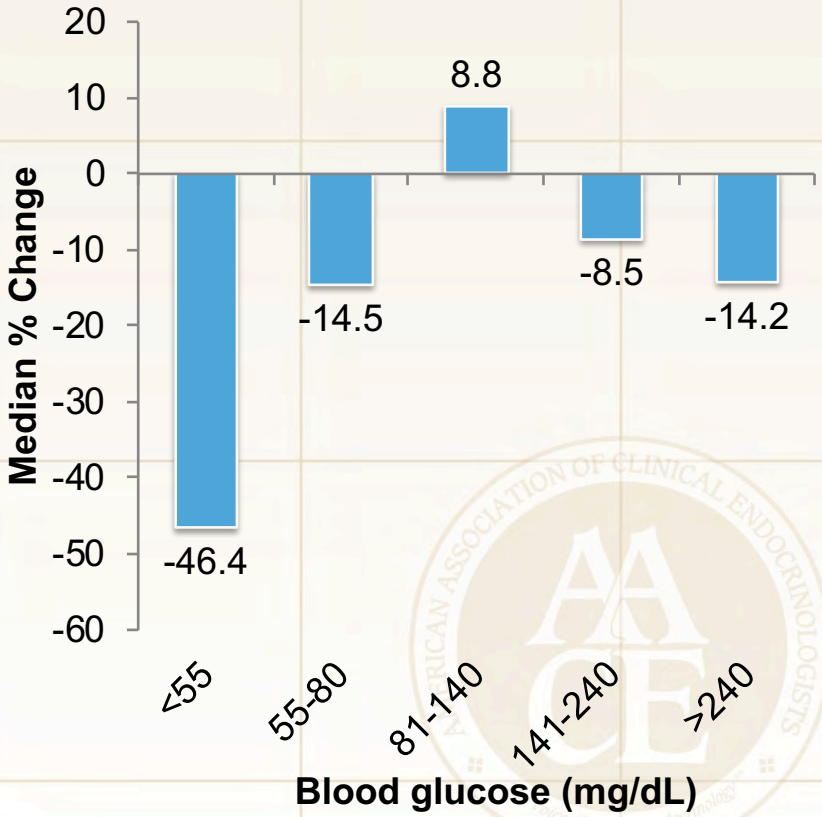
JDRF CGM Study. *Diabetes Care*. 2009;32:1947-1953.

Optimal vs Poor Glucose Control With CGM

Patients With Baseline A1C >9%



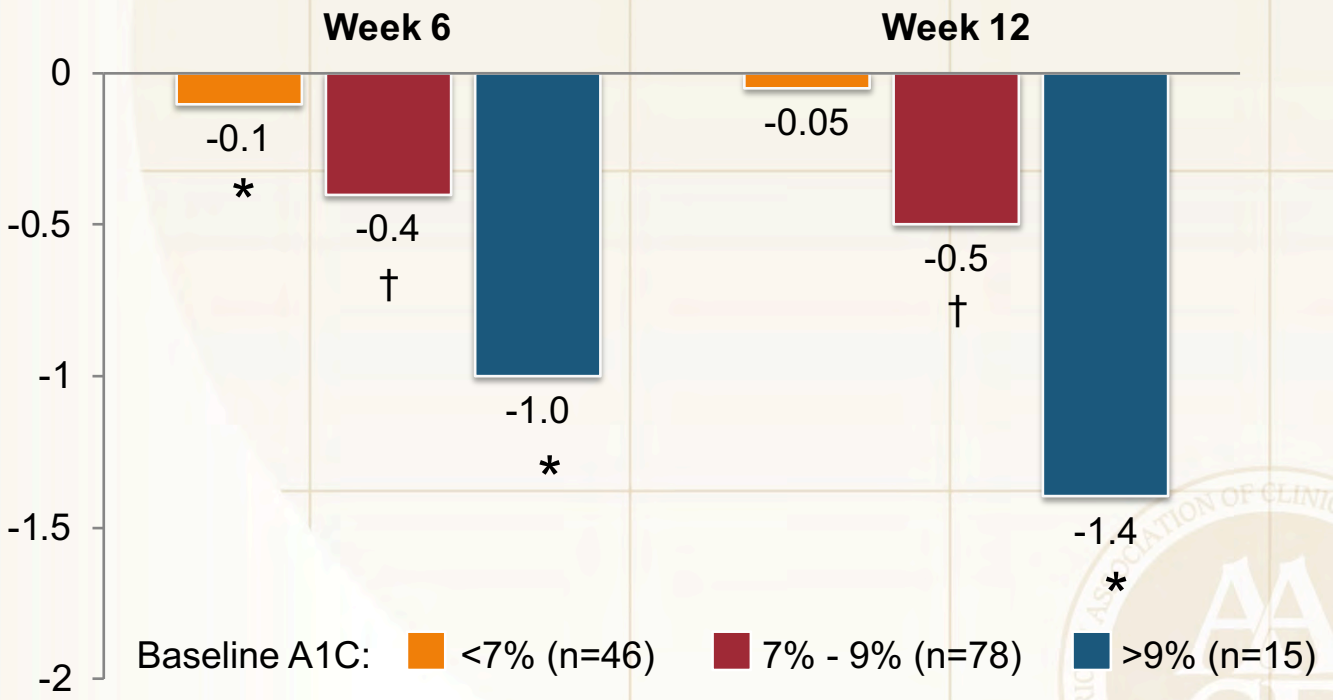
Patients With Baseline A1C ≤7%



CGM, continuous glucose monitoring.

Garg S, Jovanovic L. *Diabetes Care.* 2006;29:2644-2649.

Mean A1C and Change From Baseline with CGM



*P <0.05 vs baseline; †P<0.001 vs baseline.

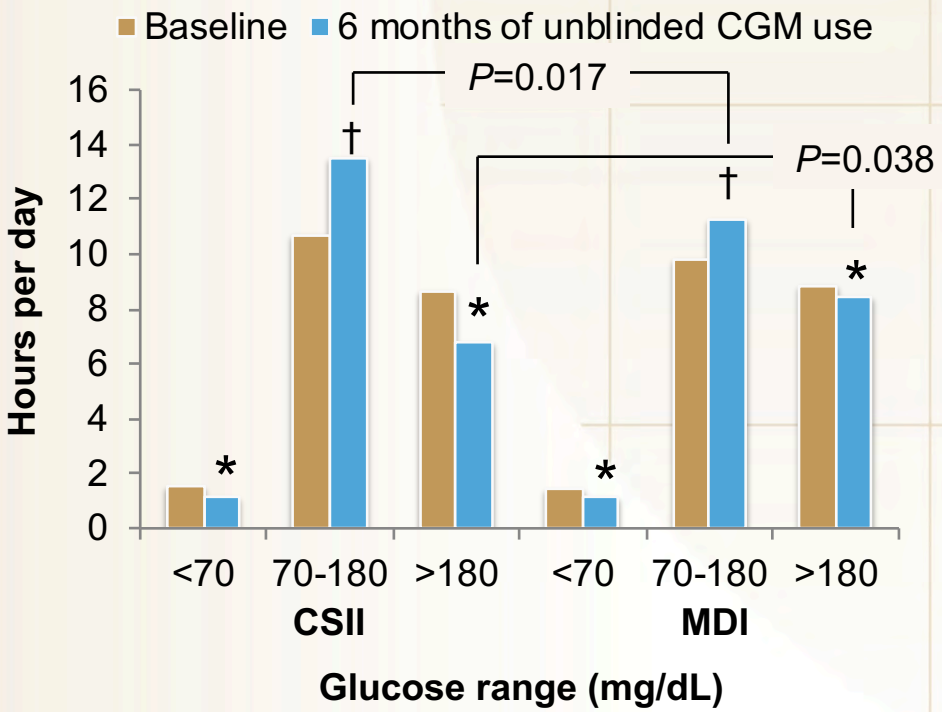
CGM, continuous glucose monitoring.

Bailey TS, et al. *Diabetes Technol Ther*. 2007;9:203-210.

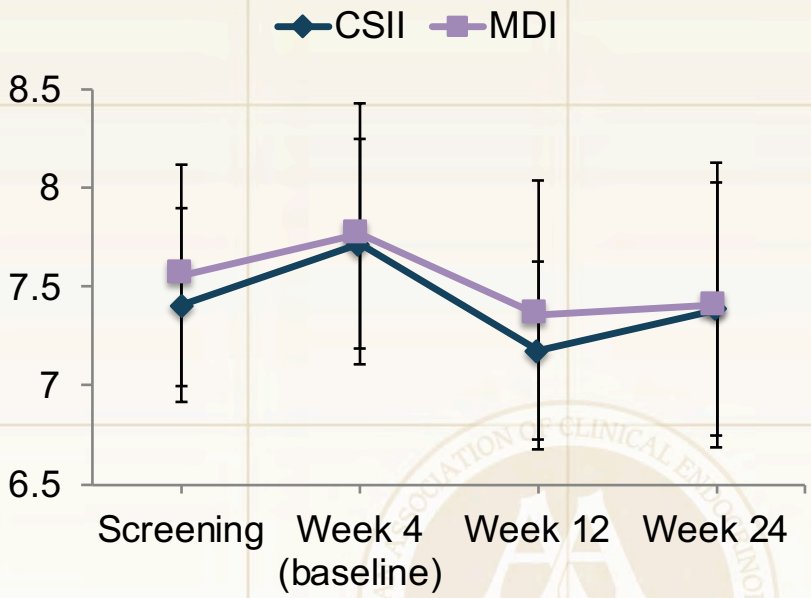
CGM Use with Either CSII or MDI Improves Glycemic Control

Patients with T1D
(N=34, Per Protocol Population)

Time Spent in Different Glucose Ranges



A1C



*P <0.01 vs baseline; †P<0.001 vs baseline.

**Baseline value determined after 4 weeks of blinded CGM use.

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injections; T1D, type 1 diabetes.

Garg S, et at. *Diabetes Care*. 2011;34:574-579.

CGM vs SMBG: Meta-analysis of Randomized Controlled Trials

- CGM associated with significant reduction in A1C, with greatest reductions in patients
  - With highest A1C at baseline
  - Who most frequently used sensors
- CGM reduced hypoglycemia

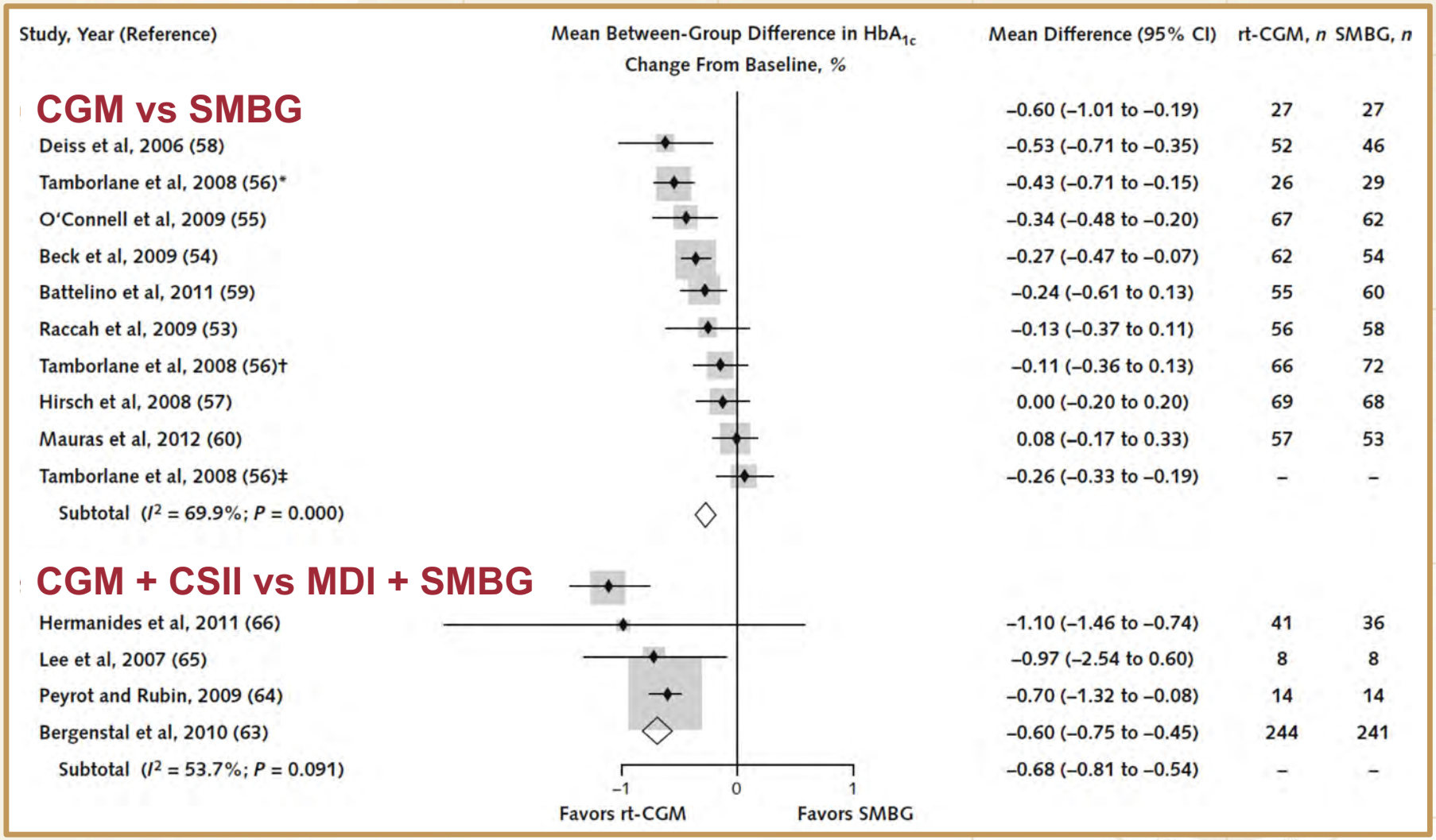
"The most cost effective or appropriate use of continuous glucose monitoring is likely to be when targeted at people with T1D who have continued poor control during intensified insulin therapy and who frequently use continuous glucose monitoring."

CGM, continuous glucose monitoring; T1D, type 1 diabetes.

Pickup JC, et al. *BMJ*. 2011;343:d3805. doi: 10.1136/bmj.d3805.

CGM vs SMBG

2012 Meta-Analysis

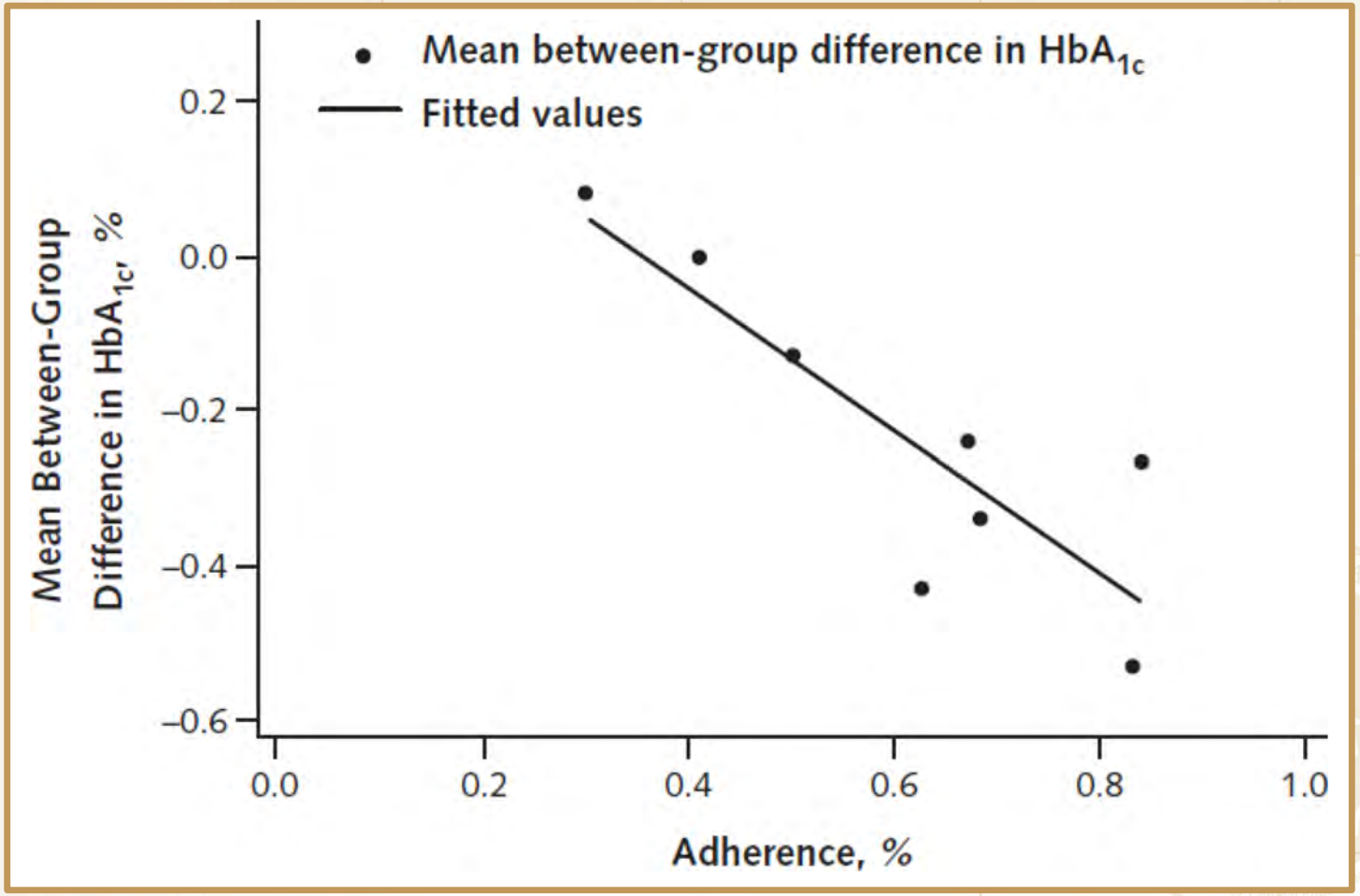


CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injections; SMBG, self-monitoring of blood glucose.

Yeh HC, et al. *Ann Intern Med*. 2012;157:336-347.

CGM Adherence and A1C

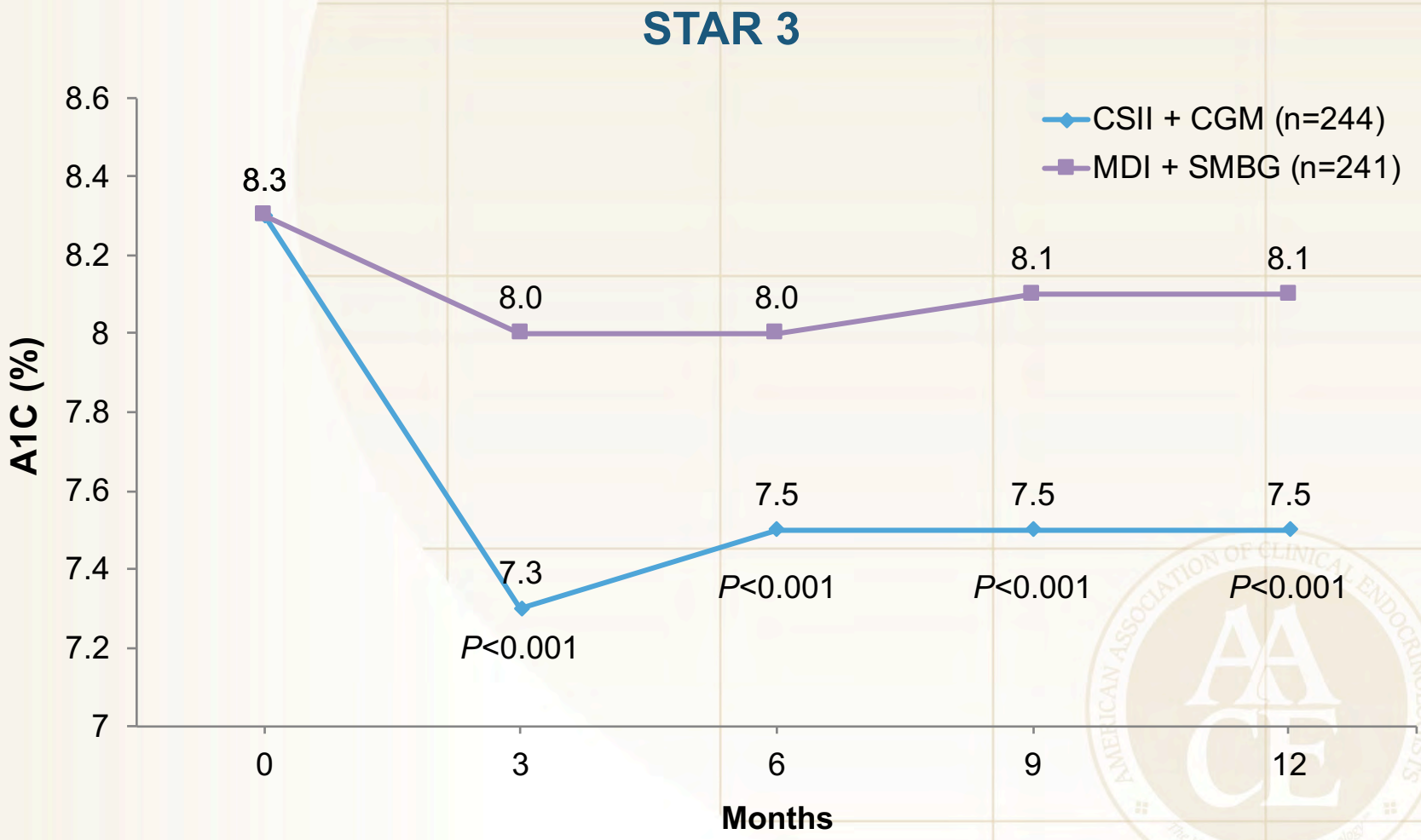
2012 Meta-Analysis



CGM, continuous glucose monitoring.

Yeh HC, et al. *Ann Intern Med*. 2012;157:336-347.

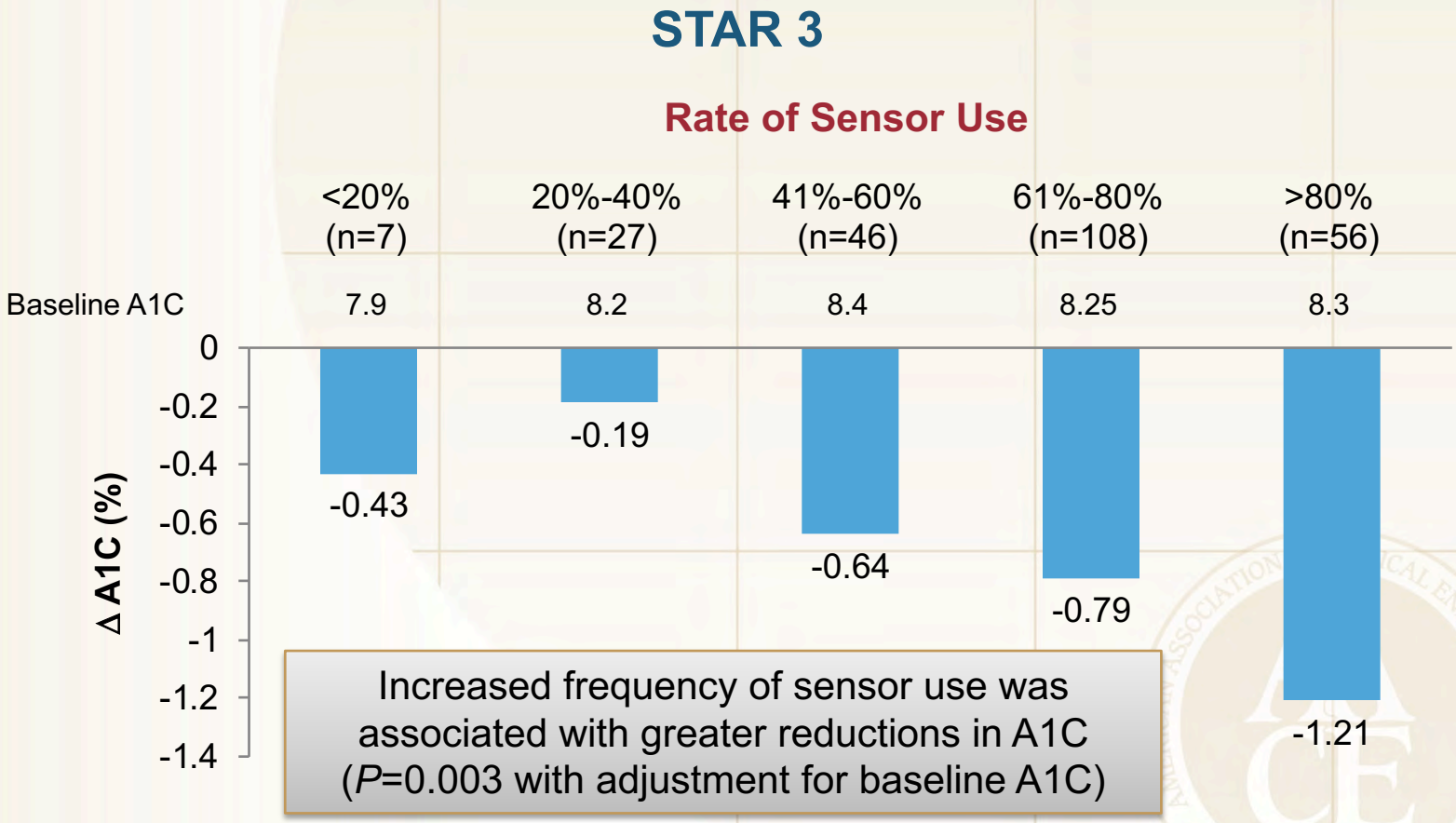
CSII + CGM vs MDI + SMBG



CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injections; SMBG, self-monitoring of blood glucose STAR, Sensor-Augmented Pump Therapy for A1C Reduction.

Bergenstal RM, et al. *N Engl J Med*. 2010;363:311-320.

Effect of 1 Year of CGM Usage on A1C

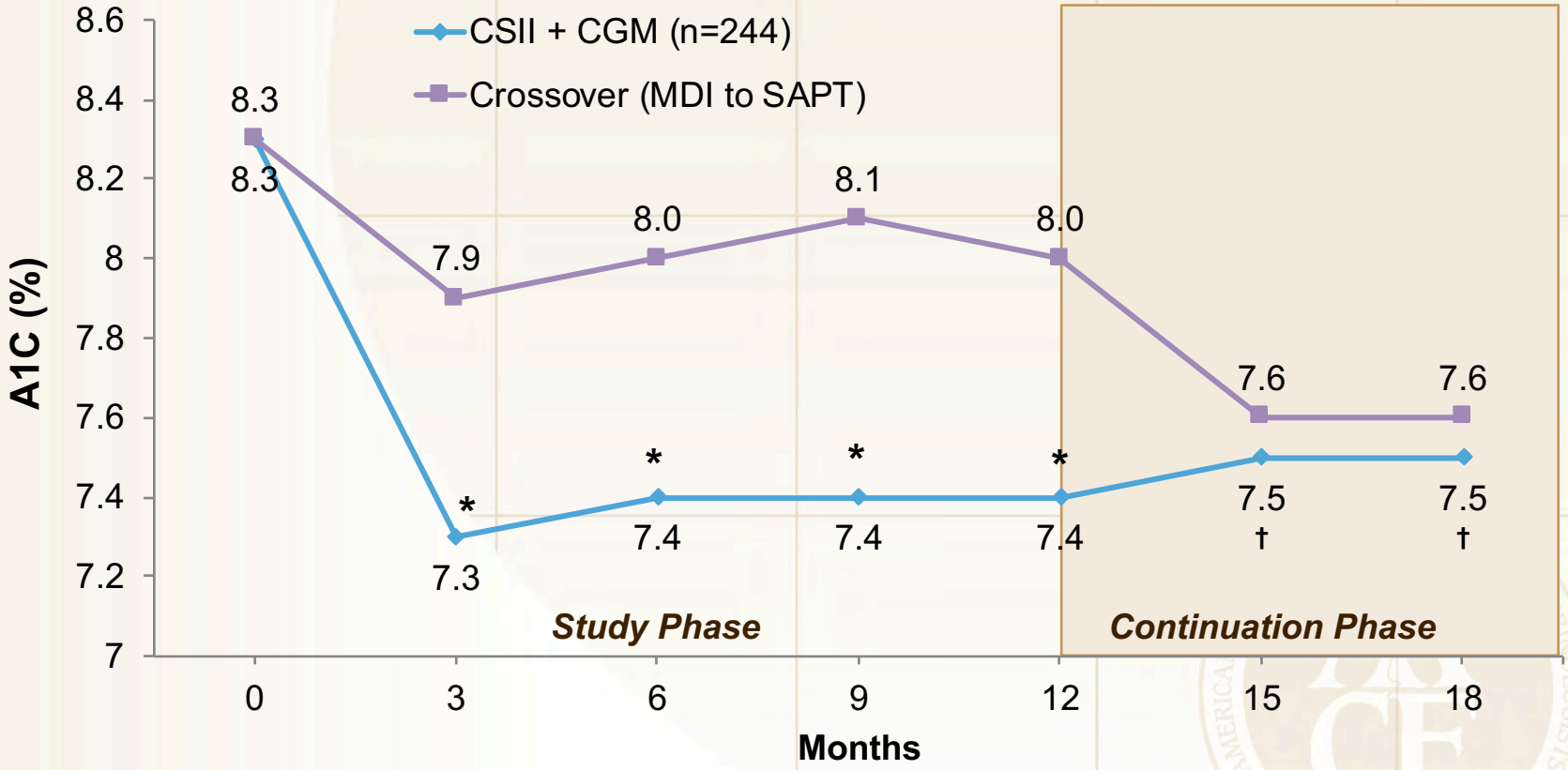


CGM, continuous glucose monitoring; STAR, Sensor-Augmented Pump Therapy for A1C Reduction.

Bergenstal RM, et al. *N Engl J Med*. 2010;363:311-320.

CGM Over 18 Months

STAR 3 Continuation Study



* *P*<0.001 for between-groups comparison.

† *P*<0.001 for within-group comparison using crossover group's 12-month A1C value as comparator.

CGM, continuous glucose monitoring; STAR, Sensor-Augmented Pump Therapy for A1C Reduction.

Bergenstal RM, et al. *Diabetes Care*. 2011;34:2403-2405.

Pediatric Diabetes Consensus Conference: Use of CGM

- Frequent, nearly daily use of CGM
  - Can lower A1C levels in children and adolescents who are not well-controlled, irrespective of the treatment regimen
  - Can reduce exposure to hypoglycemia and maintain target A1C levels in well-controlled patients
- Intermittent use of CGM
  - May be of use to detect postmeal hyperglycemia, nocturnal hypoglycemia, and the dawn phenomenon
- Development of smaller, more accurate, and easier-to-use devices is needed to enhance CGM utilization in youth with T1D

CGM, continuous glucose monitoring; T1D, type 1 diabetes.

Phillip M, et al. *Pediatr Diabetes*. 2012;13:215-228.

AACE Recommendations for Personal CGM

Evidence-Based Recommendations

- Use in adults and children with T1D
  - Real-time glucose management by patient
  - Retrospective adjustments to diabetes management
- CGM with CSII or MDI: significant improvements in A1C without increased hypoglycemia
- Threshold suspend integrated CGM + CSII: significant improvements in A1C and reduction in hypoglycemia
- Improved reliability and accuracy with newer devices

Areas for Further Research or Development

- Standardized data reporting across all devices
- Benefits in insulin-using patients with T2D
- Benefits in pregnant women with diabetes
- Cost reductions with CGM vs SMBG

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injections; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes T2D, type 2 diabetes.

Personal CGM defined as CGM owned by the patient and used on daily basis.

Fonseca VA, et al. *Endocr Pract*. 2016;22:1008-1021.

AACE Recommendations: CGM in Pregnancy

- Macrosomia is common due to inability to identify hyperglycemic spikes
- SMBG misses both hyper- and hypoglycemic events
- All CGM-in-pregnancy studies are positive
- Based on the frequency of hyperglycemia, AACE recommends that all pregnant women with T1D receive personal CGM

CGM, continuous glucose monitoring; T1D, type 1 diabetes.

Blevins TC, et al. *Endocr Pract.* 2010;16:731-745. Fonseca VA, et al. *Endocr Pract*. 2016;22:1008-1021.

Treatment of Type 1 Diabetes

CLOSED LOOP SYSTEMS: ARTIFICIAL PANCREAS

Effectiveness and Safety of an Artificial Pancreas

- Study comparing 2 systems in patients with T1D
  - Age 5-18 years (N=17)
  - Closed loop "artificial pancreas" linking CSII insulin delivery with CGM (33 nights)
  - Standard CSII (21 nights)
- No significant difference in glycemic outcomes in primary analysis

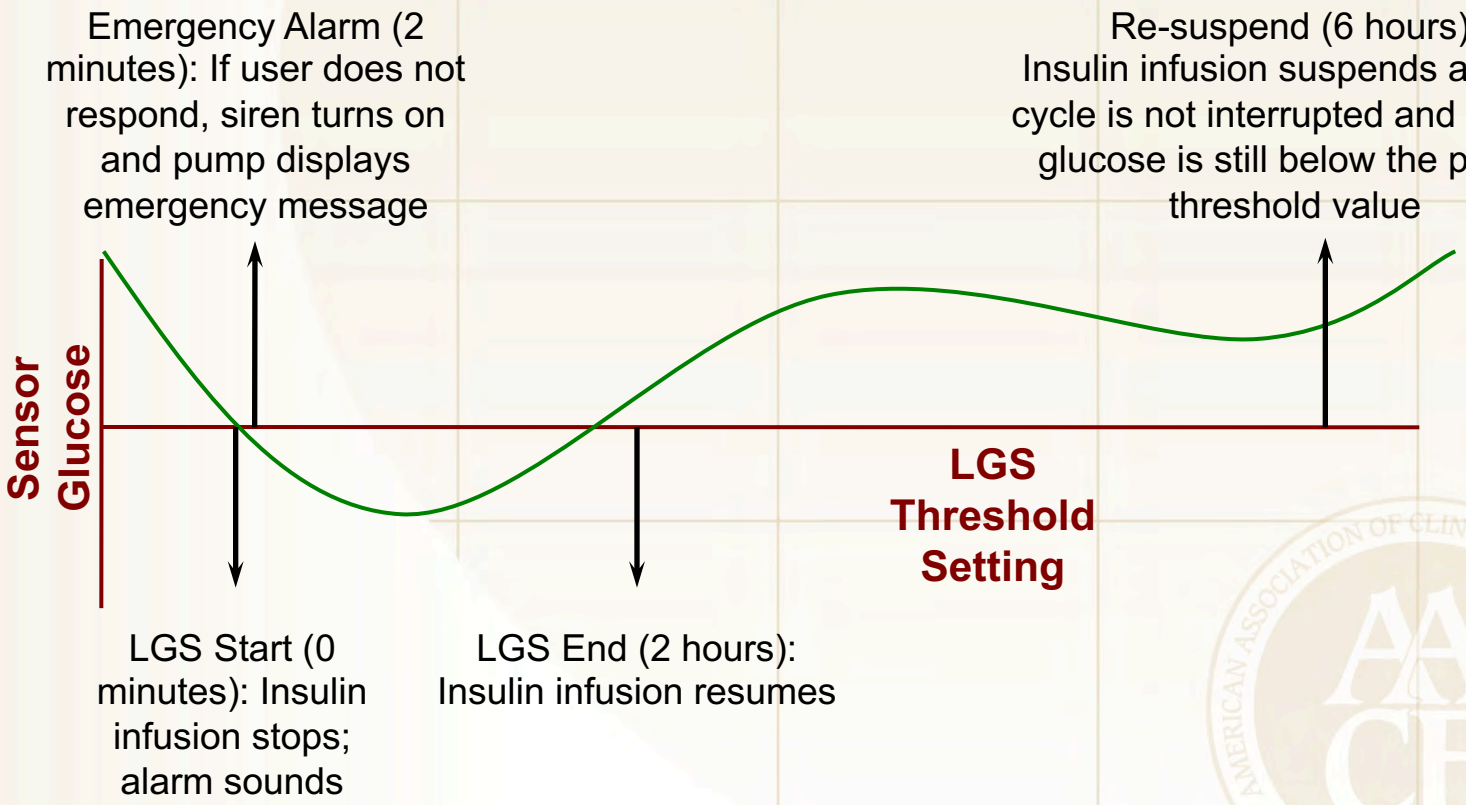
Secondary analysis of pooled data

	Closed loop	CSII	P value
Time in target BG range (%)	60 (51-88)	40 (18-61)	0.0022
Time BG ≤70 mg/dL (%)	2.1 (0.0-10.0)	4.1 (0.0-42.0)	0.0304
BG <54 mg/dL (no. events)	0	9	

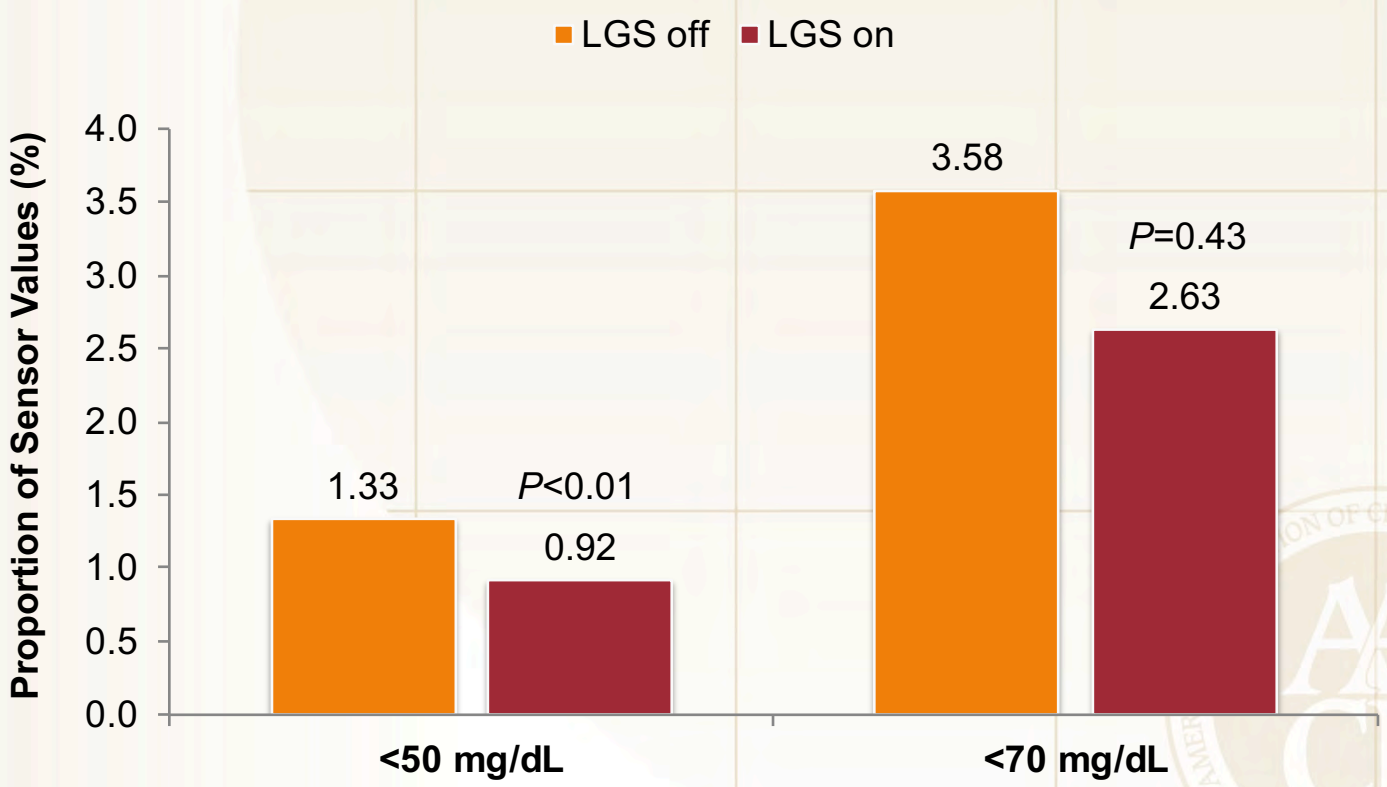
BG, blood glucose; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; T1D, type 1 diabetes.

Hovorka R, et al. *Lancet*. 2010;375):743-751.

Emerging Options: CSII with "Low Glucose Suspend" Feature



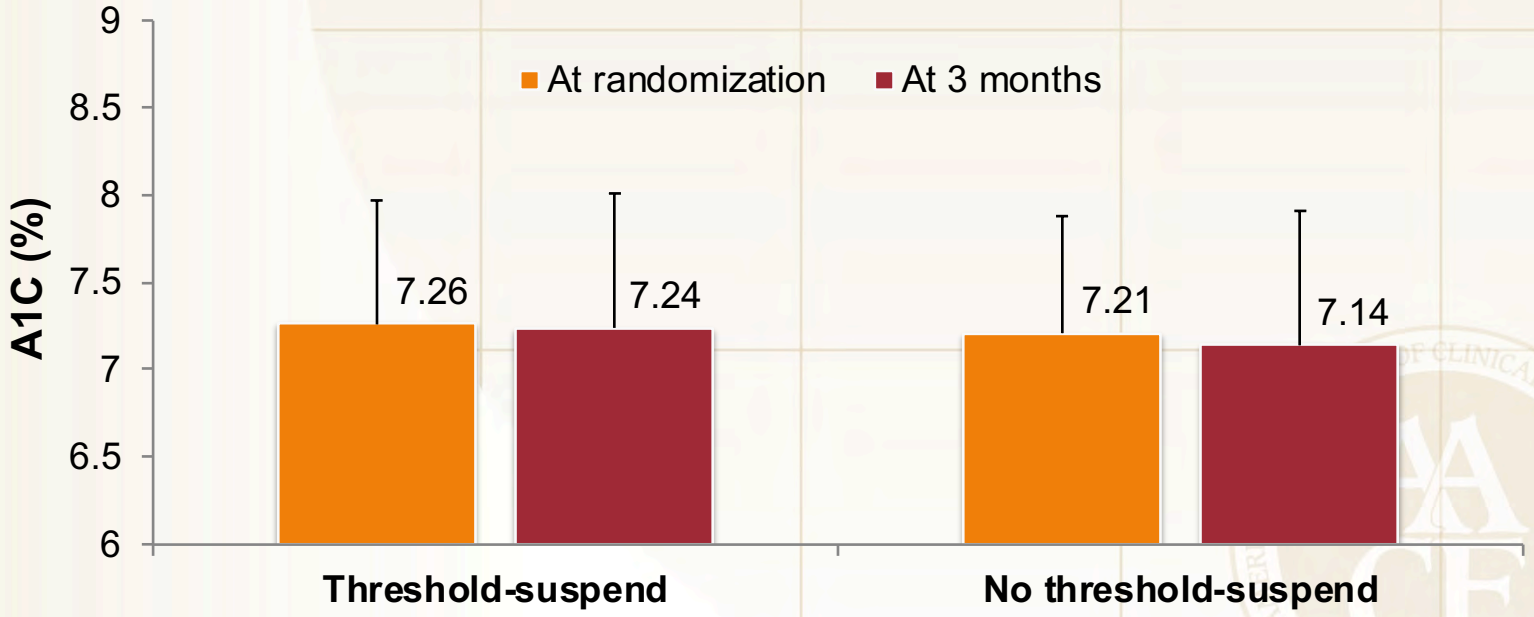
Low Glucose Suspend Feature Reduces Hypoglycemic Exposure



Agrawal P, et al. *J Diabetes Sci Technol*. 2011;5:1137-1141.

Threshold Suspend Reduces Nocturnal Hypoglycemia Without Increasing Hyperglycemia

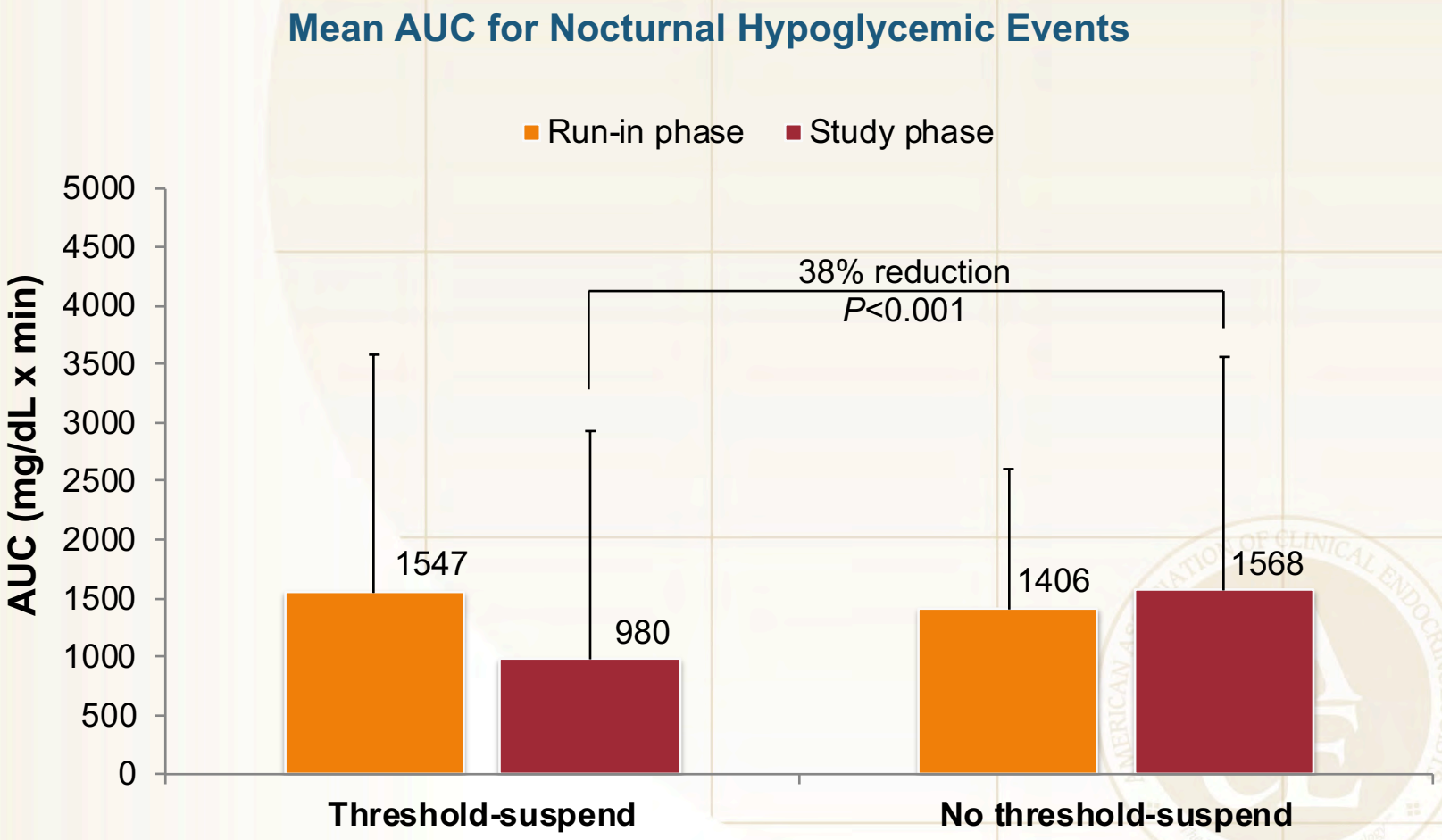
Patients Randomized to Sensor-Augmented Pump with or Without Threshold-Suspend for 3 Months (N=247)



No change in A1C

Bergenstal RM, et al. *N Engl J Med*. 2013;369:324-332.

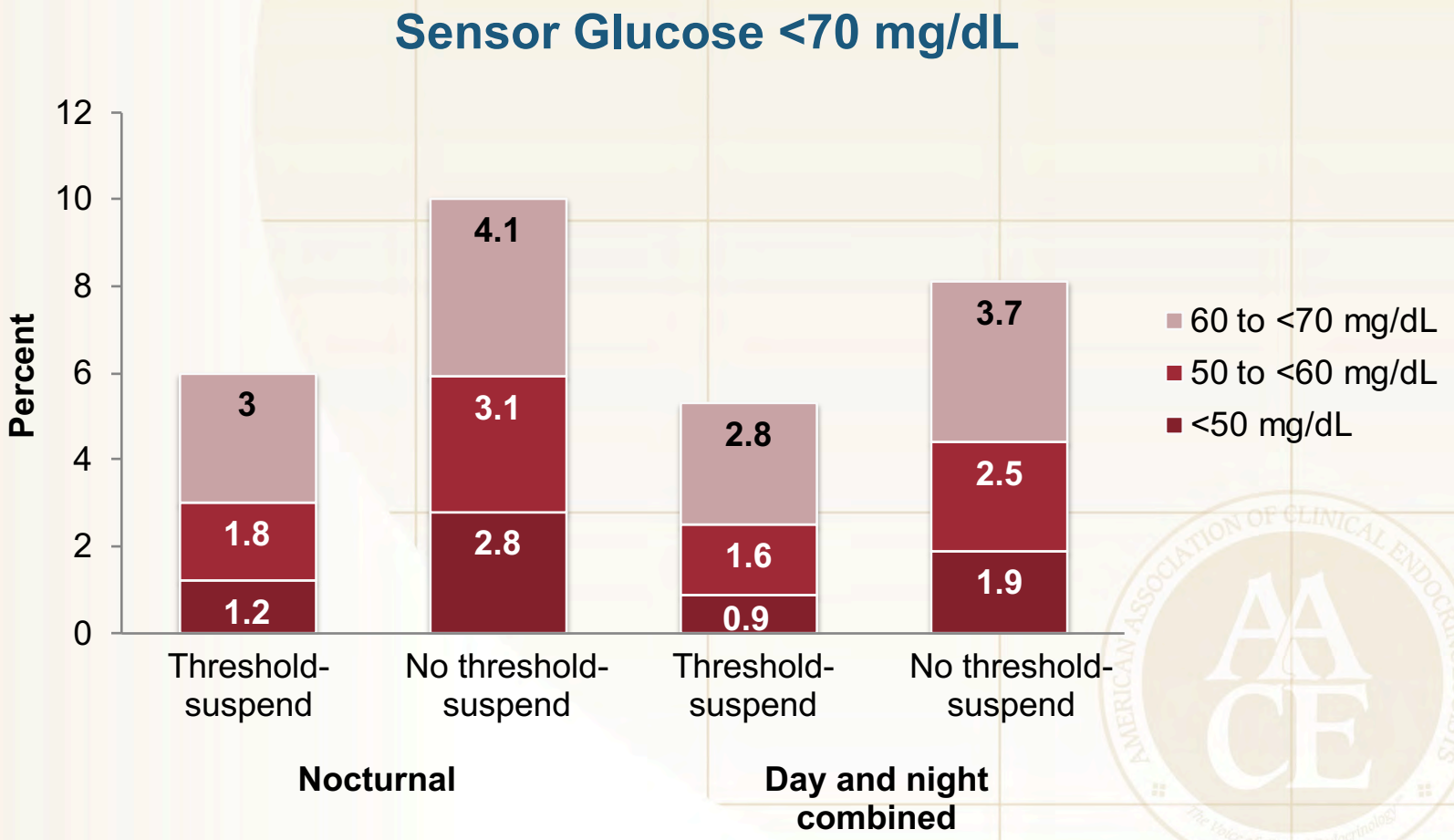
Threshold Suspend Reduces Nocturnal Hypoglycemic Exposure



AUC, area under the curve.

Bergenstal RM, et al. *N Engl J Med*. 2013;369:324-332.

Threshold Suspend Reduces Both Nocturnal and Daytime Hypoglycemia



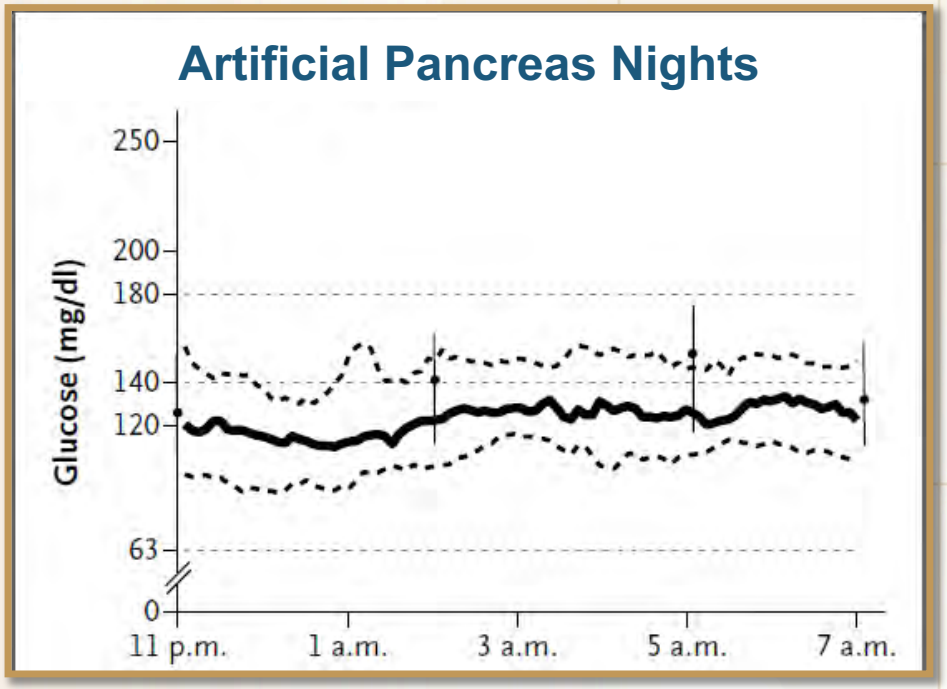
Bergenstal RM, et al. *N Engl J Med*. 2013;369:324-332.

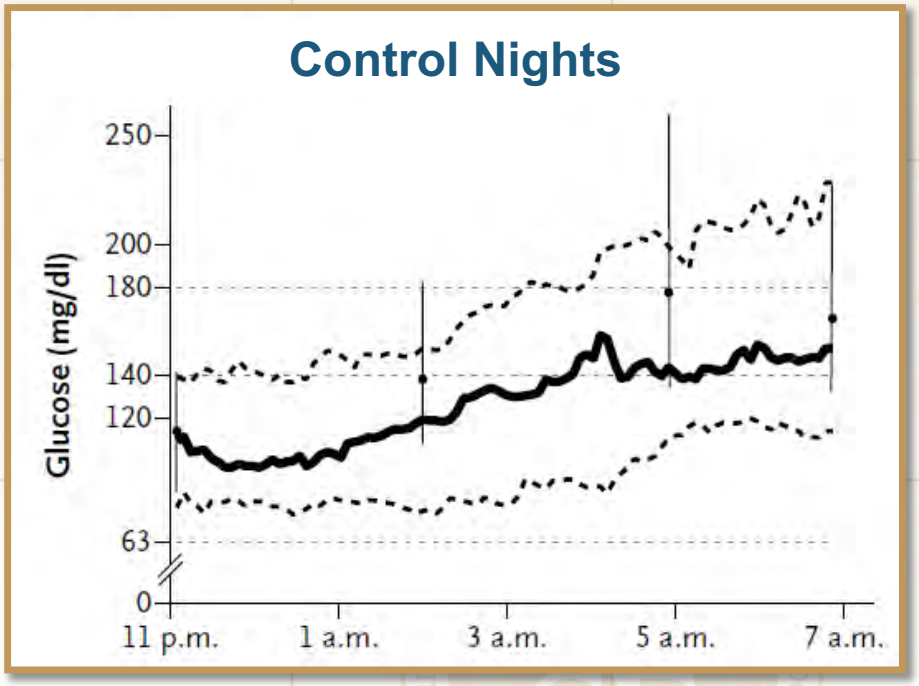
Initial Closed-Loop Studies Result in Less Nocturnal Hypoglycemia at Diabetes Camp

- MD-Logic: a fully automated closed-loop system
- Study participants
  - Children, mean age 14 years (N=54)
  - Randomized to 1 night on closed-loop, then 1 night on sensor augmented pump (or vice versa)
- Results
  - Nocturnal hypoglycemia (glucose <63 mg/dL)
    - Closed-loop system: 7 episodes
    - Control: 22 episodes
  - Less glucose variability with closed-loop system

Philip M, et al. *N Engl J Med.* 2013;368:824-833.

Nocturnal Glycemia With Closed-Loop vs Sensor-Augmented Pump





Philip M, et al. *N Engl J Med.* 2013;368:824-833.

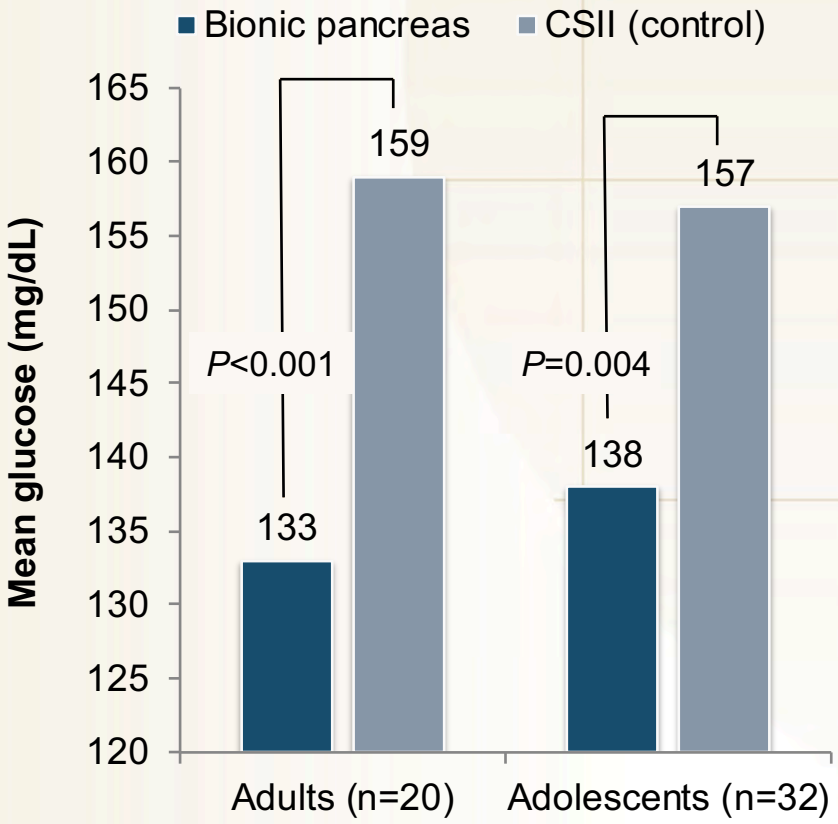
Bionic Pancreas

- Bihormonal secretion
  - Insulin
  - Glucagon
- Integrated continuous glucose monitor
- Fully automated
  - Control algorithm run on smart phone
  - Insulin and glucagon secreted in response to CGM data every 5 minutes
- Insulin bolus priming based on qualitative assessment of meal type and size
- Type
  - Breakfast
  - Lunch
  - Dinner
- Size
  - Typical
  - More than usual
  - Less than usual
  - Small bite

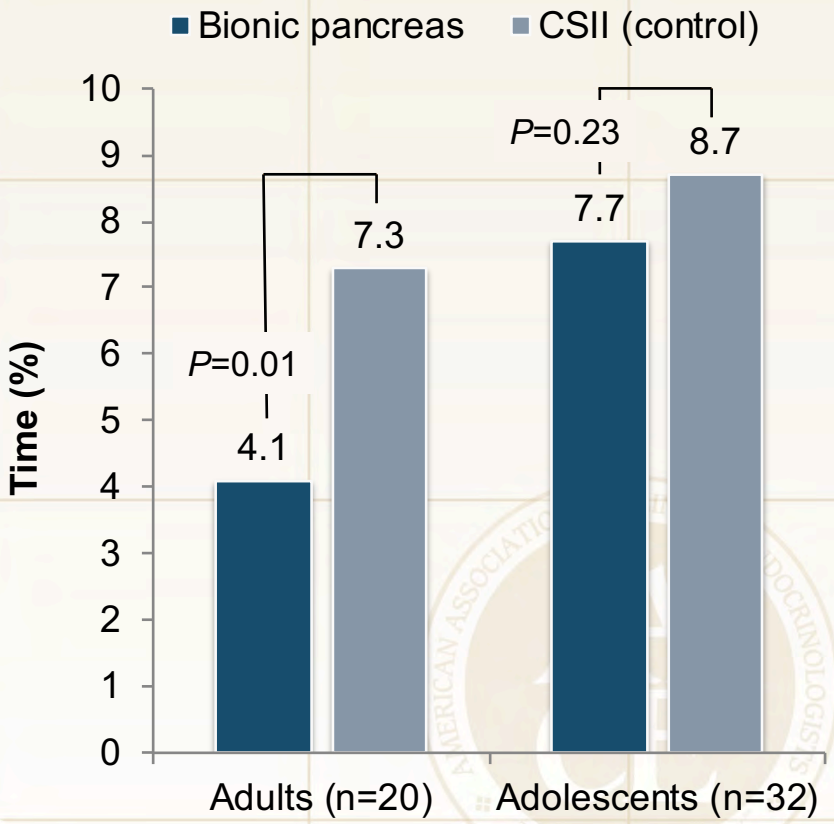
Russell SJ, et al. *N Engl J Med.* 2014;371:313-325.

Effect of Bionic Pancreas on Glycemic Control

Mean Blood Glucose



Time Spent with BG <70 mg/dL

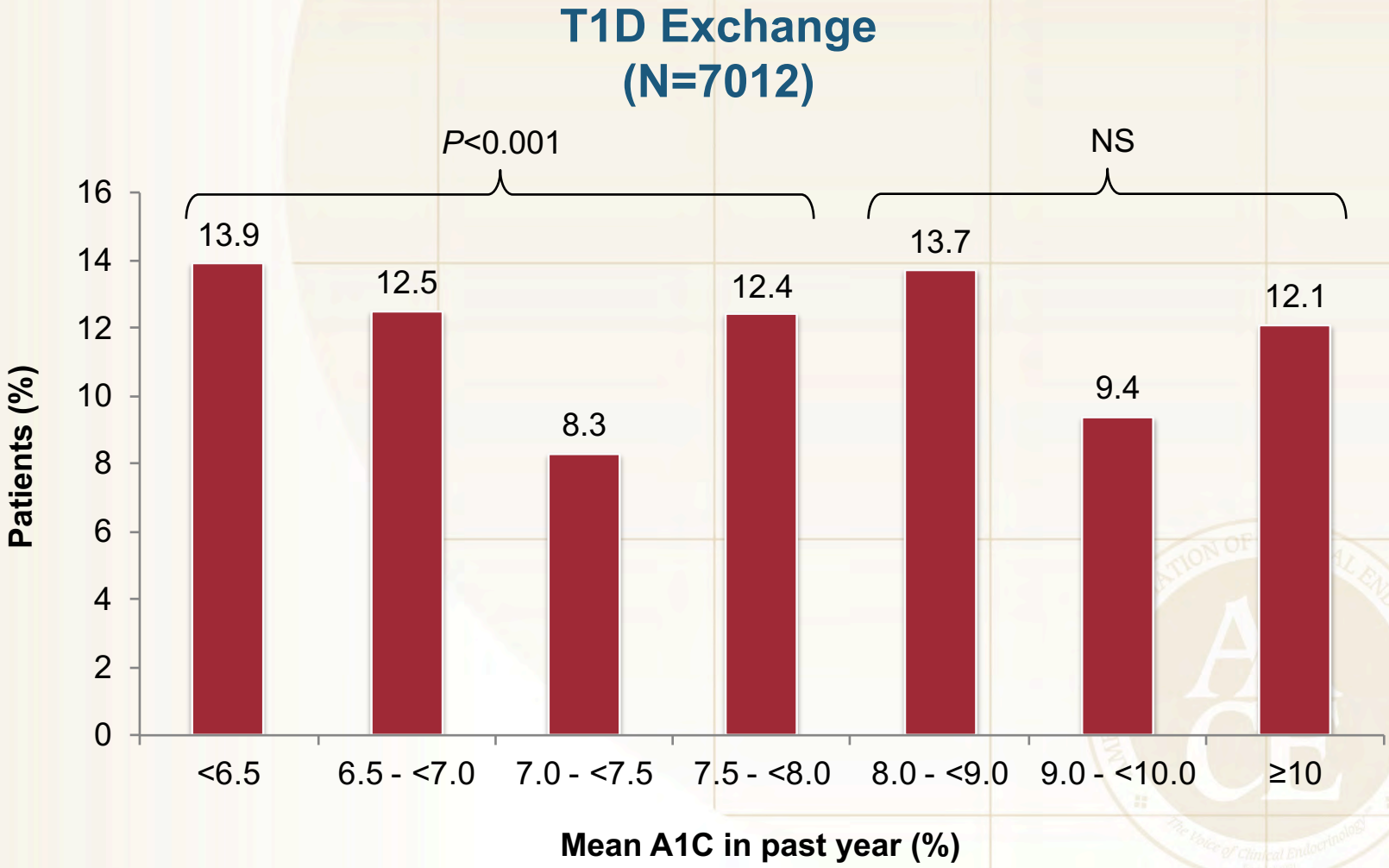


Russell SJ, et al. *N Engl J Med.* 2014;371:313-325.

Treatment of Type 1 Diabetes

HYPOGLYCEMIA

Rates of Severe Hypoglycemia Over 12 Month Period in Adults with T1D



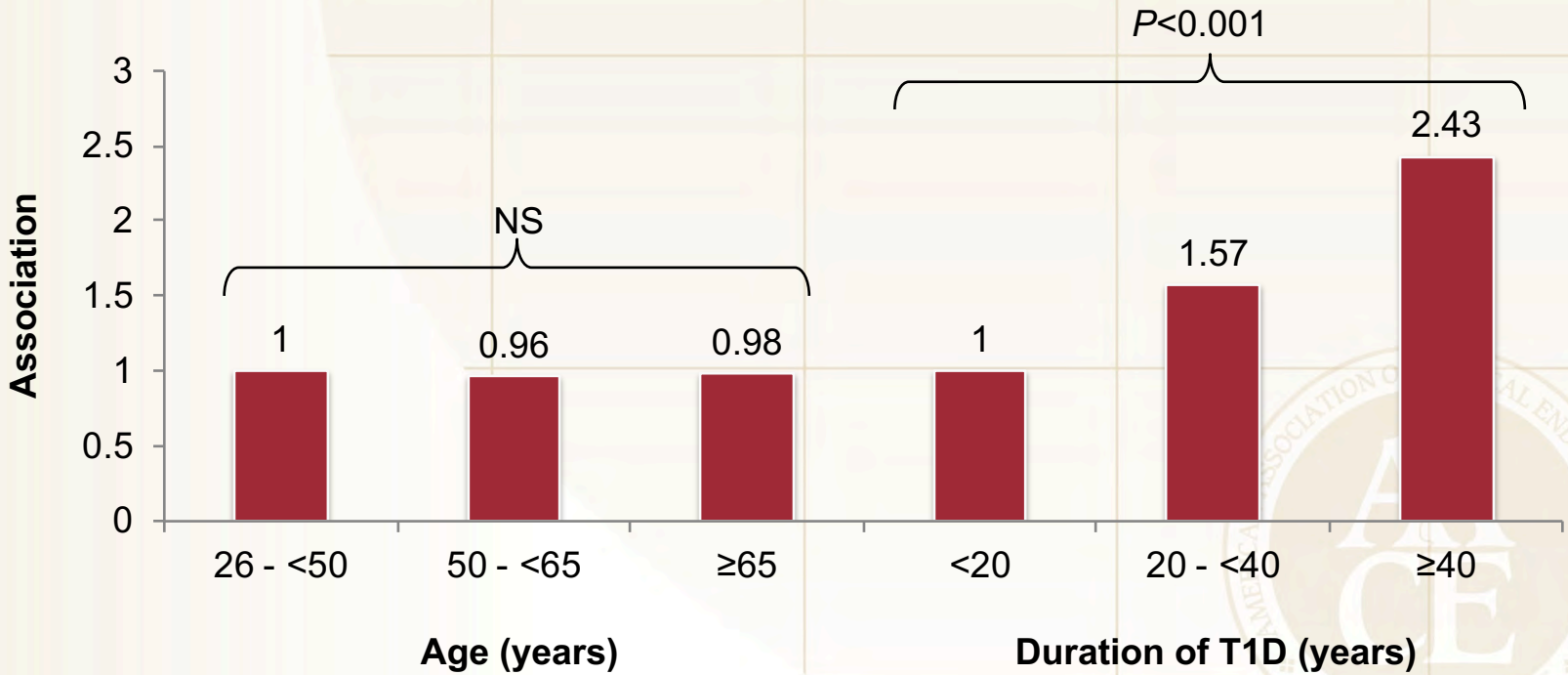
NS, not significant; T1D, type 1 diabetes.

Weinstock RS, et al. *J Clin Endocrinol Metab*. 2013;98:3411-3419.

Incidence of Severe Hypoglycemia Increases with T1D Duration but Not Age

T1D Exchange (N=7012)

Multivariate Regression Model



NS, not significant; T1D, type 1 diabetes.

Weinstock RS, et al. *J Clin Endocrinol Metab*. 2013;98:3411-3419.

Hypoglycemia: Risk Factors

Patient Characteristics

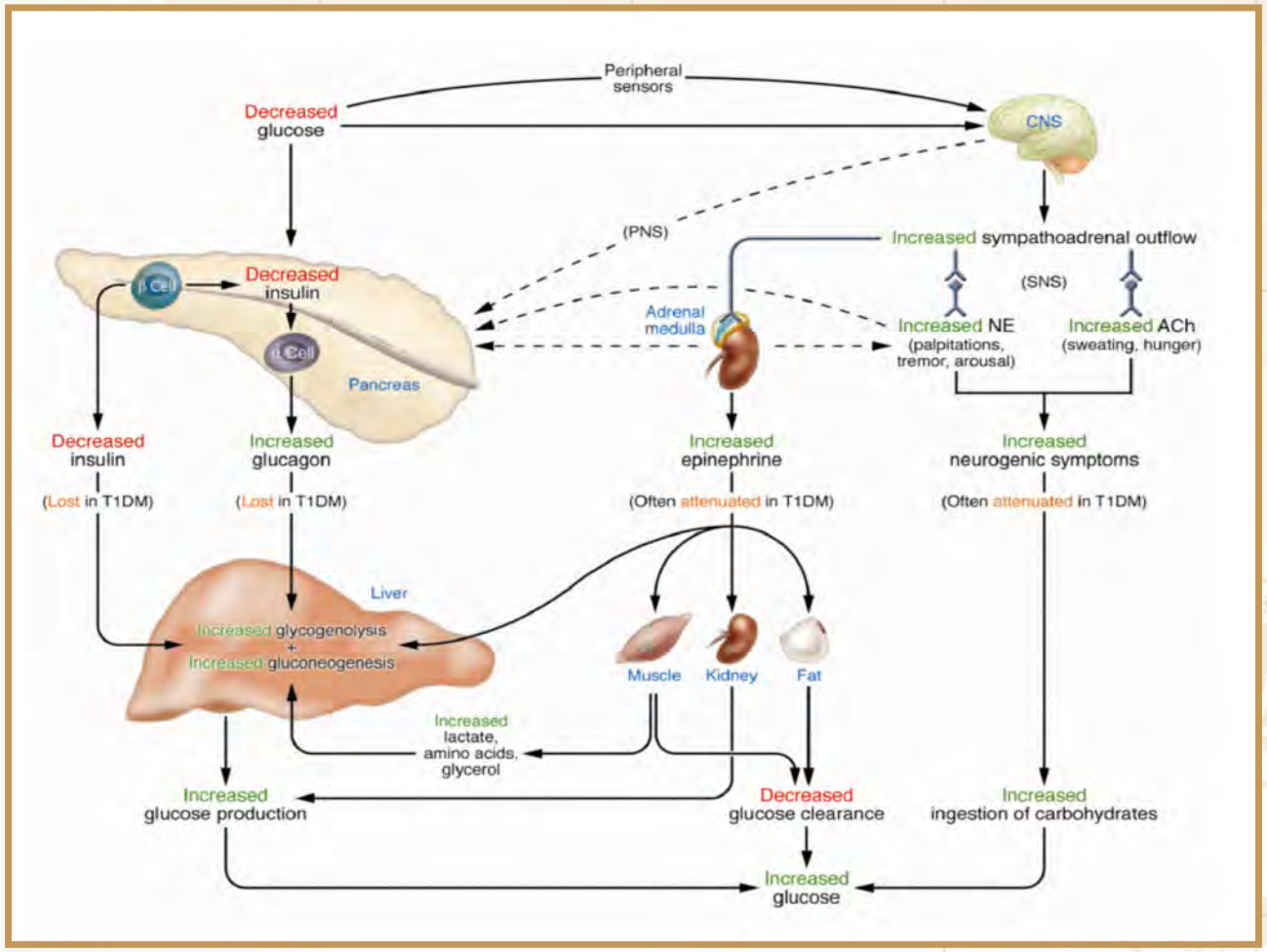
- Older age
- Female gender
- African American ethnicity
- Longer duration of diabetes
- Neuropathy
- Renal impairment
- Previous hypoglycemia

Behavioral and Treatment Factors

- Missed meals
- Elevated A1C

Miller ME, et al. *BMJ*. 2010 Jan 8;340:b5444. doi: 10.1136/bmj.b5444.

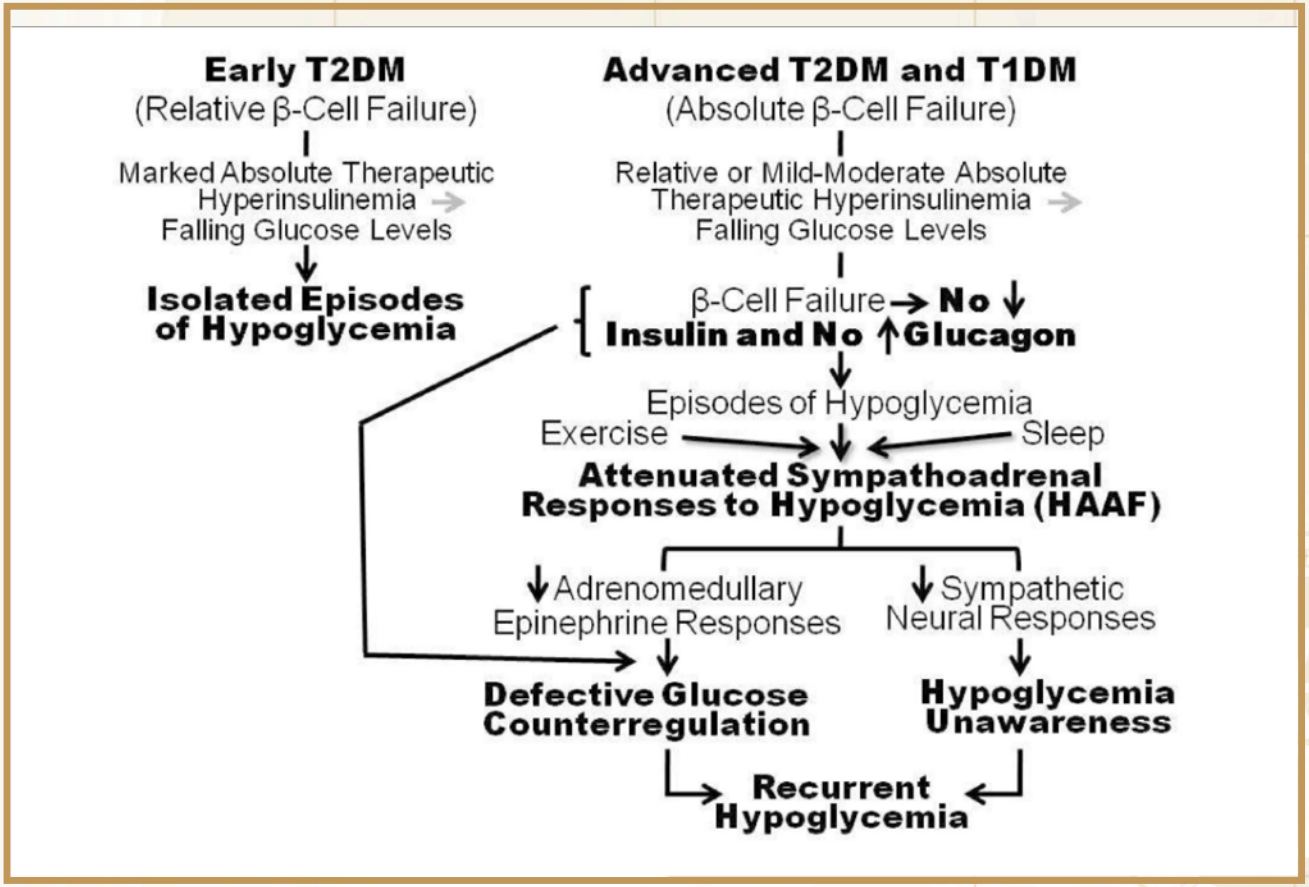
Pathophysiology of Glucose Counterregulation in T1D



T1D, type 1 diabetes.

Cryer PE. *J Clin Invest.* 2006;116:1470-1473.

Defective Glucose Counterregulation and Hypoglycemia Unawareness



T1D, type 1 diabetes.

Cryer PE. *Diabetes*. 2009;58:1951-1952.

Causes of Hypoglycemia in Toddlers and Preschoolers

- Unpredictable food intake and physical activity
- Imprecise administration of low doses of insulin
- Frequent viral infections
- Inability to convey the symptoms of low blood sugar

Litton J, et al. *J Pediatr.* 2002;141:490-495.

Consequences of Hypoglycemia

- Cognitive, psychological changes (eg, confusion, irritability)
- Accidents
- Falls
- Recurrent hypoglycemia and hypoglycemia unawareness
- Refractory diabetes
- Dementia (elderly)
- CV events
  - Cardiac autonomic neuropathy
  - Cardiac ischemia
  - Angina
  - Fatal arrhythmia

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Cognitive Effects of Hypoglycemia in Children With T1D

- Repeated severe hypoglycemia reduces long-term spatial memory in children with type 1 diabetes
- Early exposure to hypoglycemia may be more damaging to cognitive function than later exposure

T1D, type 1 diabetes.

Hershey T, et al. *Diabetes Care*. 2005;28:2372-2377.

Symptoms of Hypoglycemia

Classification	Blood Glucose Level (mg/dL)	Typical Signs and Symptoms
Mild hypoglycemia	~50-70	• Neurogenic: palpitations, tremor, hunger, sweating, anxiety, paresthesia
Moderate hypoglycemia	~50-70	• Neuroglycopenic: behavioral changes, emotional lability, difficulty thinking, confusion
Severe hypoglycemia	<50*	• Severe confusion, unconsciousness, seizure, coma, death • Requires help from another individual
*Severe hypoglycemia symptoms should be treated regardless of blood glucose level.		

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Treatment Challenges in the Elderly With Type 1 Diabetes

- Lack of thirst perception predisposes to hyperosmolar state
- Confusion of polyuria with urinary incontinence or bladder dysfunction
- Increased risk of and from hypoglycemia
  - Altered perception of hypoglycemic symptoms
  - Susceptibility to serious injury from falls or accidents
- Compounding of diabetic complications by effects of aging
- Frequent concurrent illnesses and/or medications
- More frequent and severe foot problems

Cefalu WT, et al, eds. *CADRE Handbook of Diabetes Management*. New York, NY: Medical Information Press; 2004

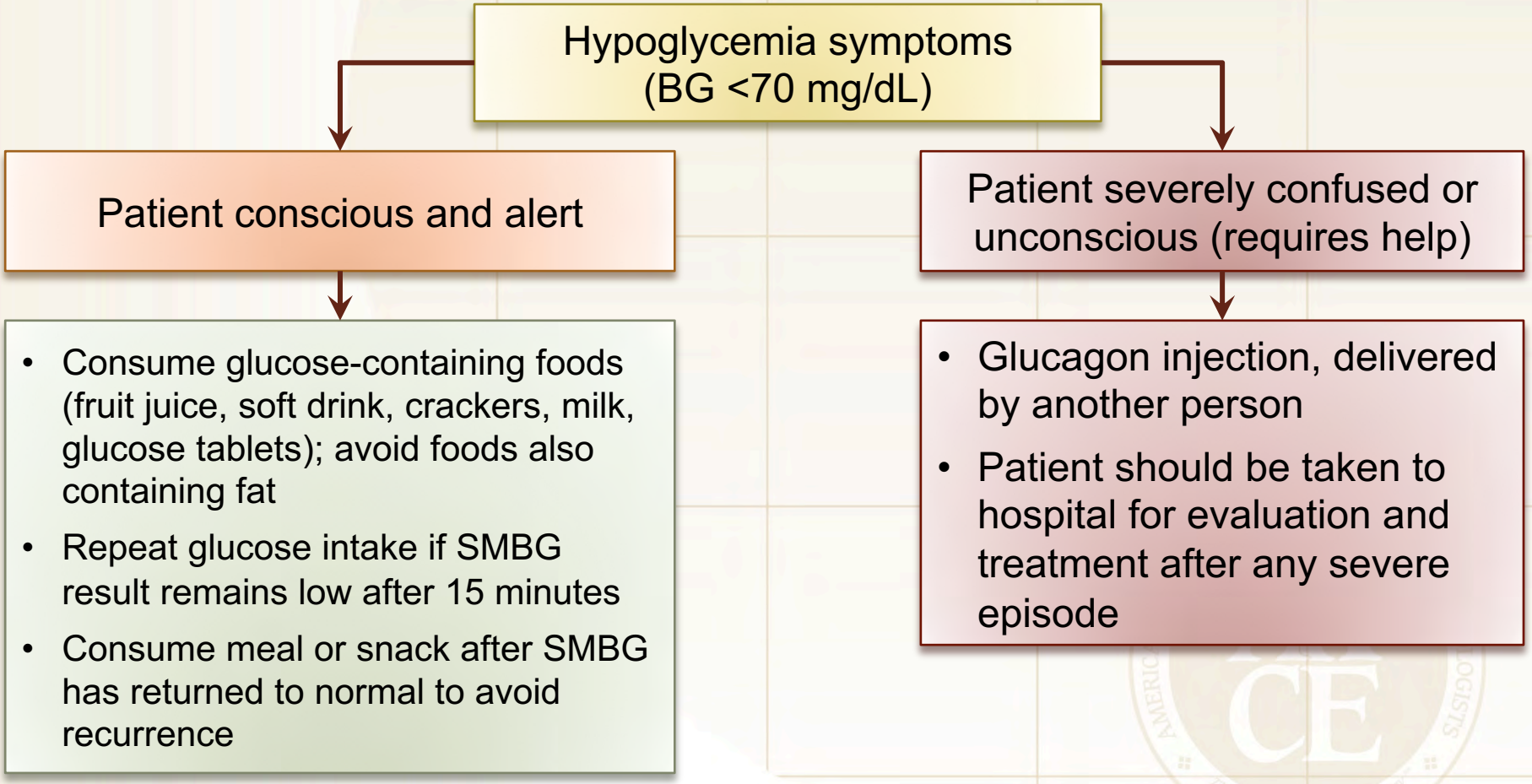
Special Considerations in the Elderly With Type 1 Diabetes

- Intensive therapy/tight control for otherwise healthy elderly patients
- Less strict glycemic goals for elderly patients with severe complications or comorbidities or with cognitive impairment
  - FPG <140 mg/dL
  - PPG <220 mg/dL

FPG, fasting plasma glucose; PPG, postprandial glucose.

Cefalu WT, et al, eds. *CADRE Handbook of Diabetes Management*. New York, NY: Medical Information Press; 2004.

Treatment of Hypoglycemia



BG = blood glucose; SMBG = self-monitoring of blood glucose.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Fear of Hypoglycemia

- Hypoglycemia-associated anxiety, depression, and fear are common among patients with T1D and their caregivers
- Hypoglycemia avoidance behaviors may adversely affect glycemic control

T1D, type 1 diabetes.

Barnard K, et al. *BMC Pediatr*. 2010; 10:50

Treatment of Type 1 Diabetes

MANAGEMENT OF COMORBIDITIES—DYSLIPIDEMIA IN T1D

Factors That May Increase Risk for Ischemic ASCVD in Patients With T1D

Individuals with T1D for >15 years or with ≥2 CV risk factors should be treated as if they had T2D. Given the risks associated with T1D, dyslipidemia in this population must not be overlooked and should be treated aggressively

- Albuminuria
- Late-onset T1D (>30 years of age) without nephropathy, but with:
  - Initiation of intensive control more than 5 years after diagnosis
  - Duration of disease greater than 15 years
- Previous history of MI or poorly controlled A1C
- Insulin resistance or MetS and an hsCRP concentration >3.0 mg/L

ASCVD, atherosclerotic cardiovascular disease; CV, cerebrovascular; hsCRP, highly sensitive C-reactive protein; MetS, metabolic syndrome; MI, myocardial infarction; T1D, type 1 diabetes; T2D, type 2 diabetes.

Jellinger PS, et al. *Endocr Pract*. 2017;23(suppl 2):1-87. Borch-Johnsen K, Kreiner S. *Br Med J (Clin Res Ed)*. 1987;294:1651-1654. Nathan DM, et al. *N Engl J Med*. 2005;353:2643-2653. DCCT/EDIC writing team. *JAMA*. 2003;290:2159-2167. Lehto S, et al. *Arterioscler Thromb Vasc Biol*. 1999;19:1014-1019. Pambianco G, et al. *Diabetes*. 2006;55:1463-1469. Nathan DM, et al. *Arch Intern Med*. 2009;169:1307-1316. Secrest AM, et al. *Diabetes*. 2010;59:3216-3222. de Ferranti SD, et al. *Diabetes Care*. 2014;37:2843-2863. Alexander CM, et al. *Diabetes*. 2003;52:1210-1214. Mackness B, et al. *Atherosclerosis*. 2006;186:396-401.

Cardiovascular Disease Risk Factors

Major	Additional	Nontraditional
• Advancing age • High total serum cholesterol level • High non–HDL-C • High LDL-C • Low HDL-C • Diabetes mellitus • Hypertension • Cigarette smoking • Family history of ASCVD	• Obesity or abdominal obesity • Family history of hyperlipidemia • Small, dense LDL-C • Increased Apo B • Increased LDL particle concentration • Fasting/postprandial hypertriglyceridemia • PCOS • Dyslipidemic triad*	• Increased lipoprotein (a) • Elevated clotting factors • Inflammation markers (hsCRP; Lp-PLA_2) • Elevated homocysteine levels • Apo E4 isoform • Elevated uric acid • Increased triglyceride-rich remnants

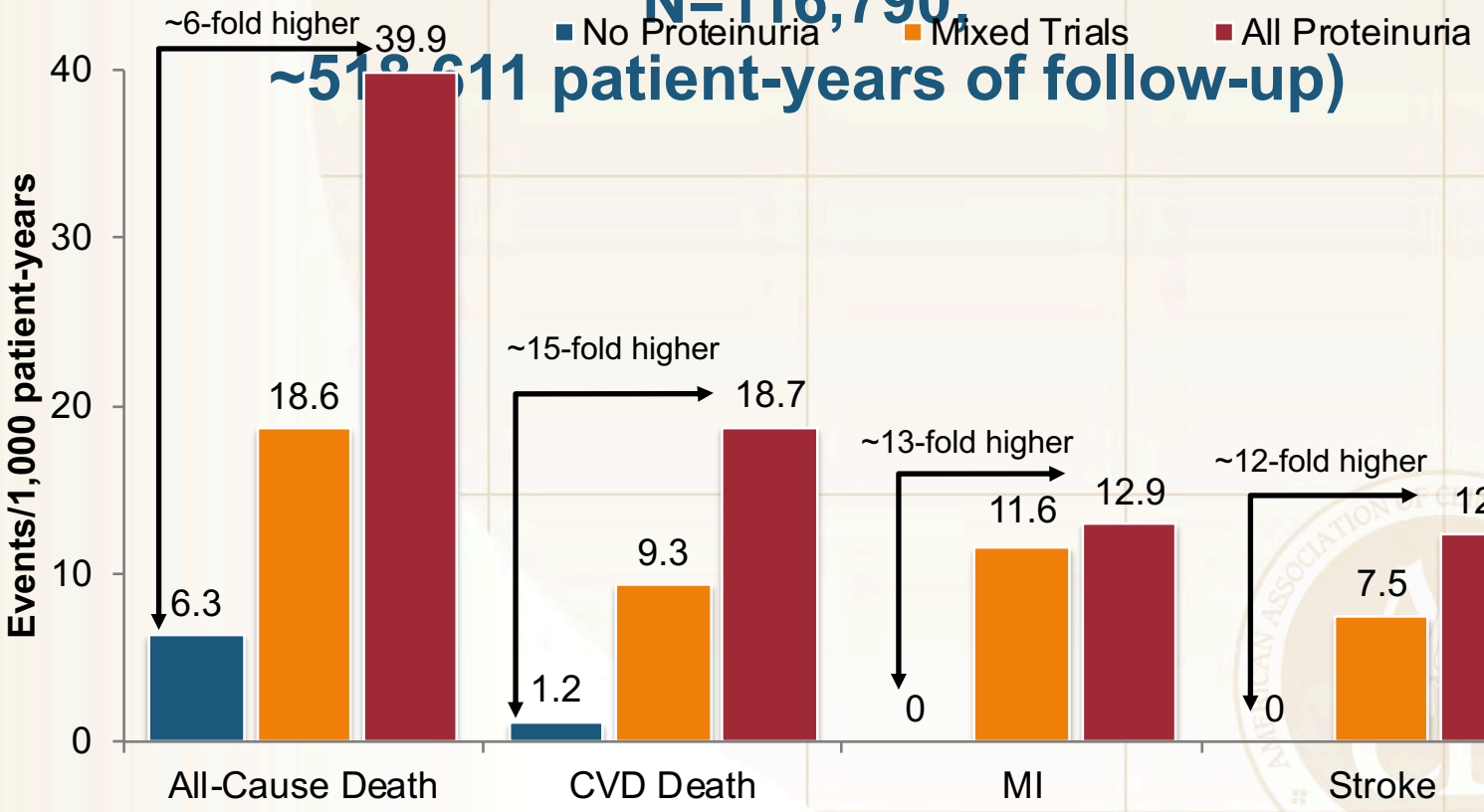
*Hypertriglyceridemia; low HDL-C; and small, dense LDL-C.

Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp-PLA_2, lipoprotein-associated phospholipase A_2; PCOS, polycystic ovary syndrome.

Jellinger PS, et al. *Endocr Pract*. 2017;23(suppl 2):1-87.

Baseline Proteinuria Increases Cardiovascular Risk

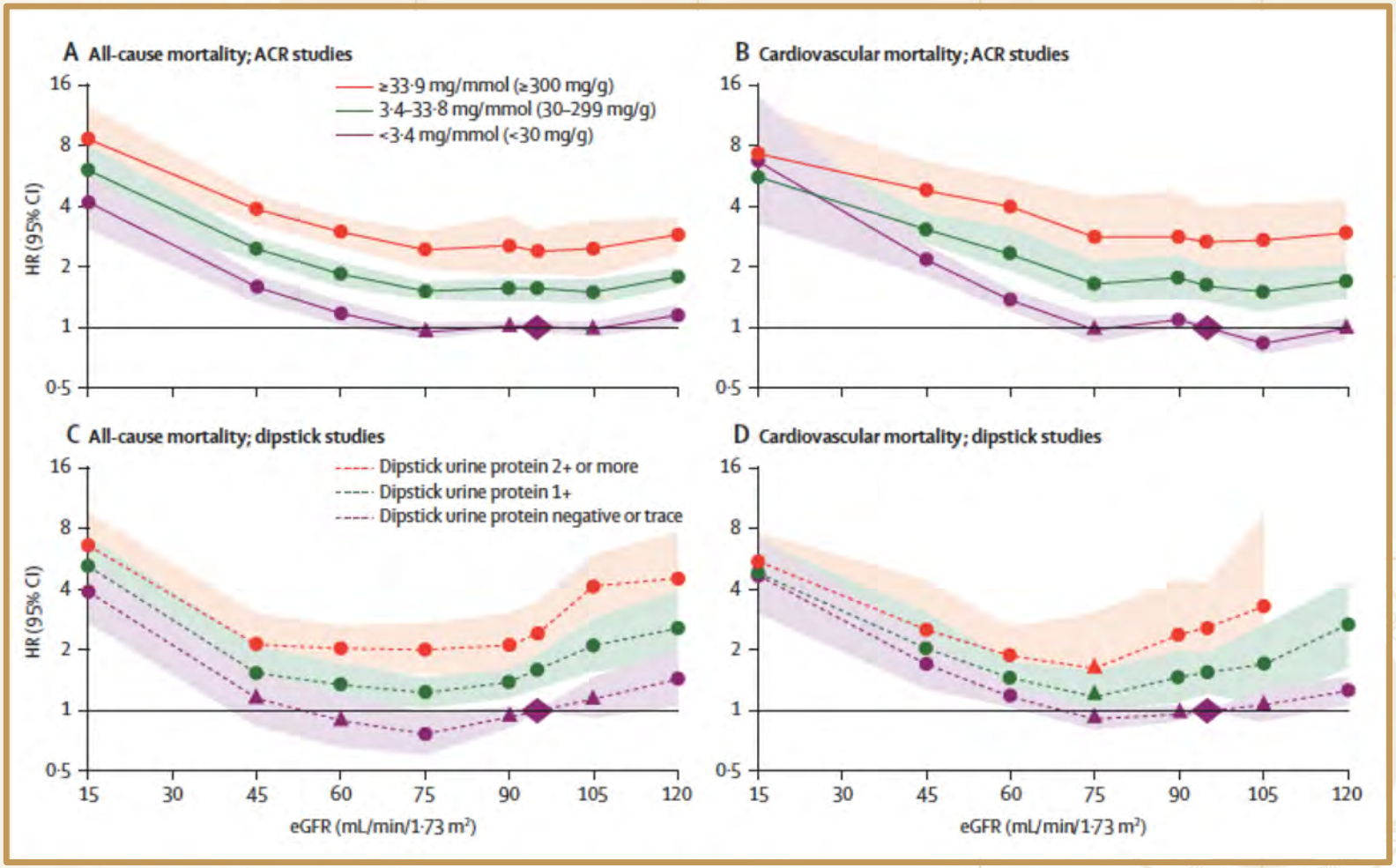
Systematic Review (RCTs: N=29; Patients with DM: N=116,790; ~518,611 patient-years of follow-up)



CVD, cardiovascular disease; MI, myocardial infarction.

Preiss D, et al. *Am Heart J*. 2011;161:210-219.

Risk of All-Cause and CV Mortality According to eGFR and Albuminuria



CV, cerebrovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

Chronic Kidney Disease Prognosis Consortium. *Lancet*. 2010;375:2073-2081 .

AACE ASCVD Risk Categories

Low risk:

- No risk factors

Moderate risk:

- 2 or fewer risk factors and a calculated 10-year risk of less than 10%

High risk:

- An ASCVD equivalent including diabetes or stage 3 or 4 CKD with no other risk factors, or individuals with 2 or more risk factors and a 10-year risk of 10%-20%

Very high risk:

- Established or recent hospitalization for ACS; coronary, carotid or peripheral vascular disease; diabetes or stage 3 or 4 CKD with 1 or more risk factors; a calculated 10-year risk greater than 20%; or HeFH

Extreme risk:

- Progressive ASCVD, including unstable angina that persists after achieving an LDL-C less than 70 mg/dL, or established clinical ASCVD with diabetes, stage 3 or 4 CKD, and/or HeFH, or in those with a history of premature ASCVD (<55 years of age for males or <65 years of age for females)
- This category was added in this CPG based on clinical trial evidence and supported by meta-analyses that further lowering of LDL-C produces better outcomes in individuals with ACS. IMPROVE-IT demonstrated lower rates of cardiovascular events in those with ACS when LDL-C levels were lowered to 53 mg/dL combining ezetimibe with statins.

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CPG, clinical practice guideline; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial.

Jellinger PS, et al. *Endocr Pract*. 2017;23(suppl 2):1-87. Cannon, CP, et al. *N Engl J Med.* 2015;372(25):2387-239.

AACE ASCVD Risk Categories

Risk Category	Risk factors*/10-year risk†	Treatment goals (mg/dL)		
		LDL-C	Non-HDL-C	Apo B
Extreme risk	• Progressive ASCVD including unstable angina in patients after achieving LDL-C <70 mg/dL • Established clinical CVD in patients with diabetes, stage 3 or 4 CKD, or HeHF • History of premature ASCVD (age <55 male, <65 female)	<55	<80	<70
Very high risk	• Established or recent hospitalization for ACS or coronary, carotid, or peripheral vascular disease, or 10-year risk >20% • Diabetes or stage 3 or 4 CKD plus ≥1 additional risk factor(s) • HeHF	<70	<100	<80
High risk	• ≥2 risk factors and 10-year risk 10-20% • Diabetes or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

*High LDL-C, PCOS, cigarette smoking, hypertension, low HDL-C, family history of CAD, stage 3 or 4 CKD, coronary calcification, and age ≥45 years in men and ≥55 years in women.

†Framingham risk score.

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CKD, chronic kidney disease; HDL-C, high density lipoprotein cholesterol; HeHF, heterozygous familial hypercholesterolemia; LDL-C low density lipoprotein cholesterol; NR, not recommended; PCOS, polycystic ovary syndrome.

Jellinger PS, et al. *Endocr Pract*. 2017;23(suppl 2):1-87.

Comprehensive Management of Cardiovascular Risk

- Manage CV risk factors
  - Weight loss
  - Smoking cessation
  - Optimal glucose, blood pressure, and lipid control
- Use low-dose aspirin for secondary prevention of CV events in patients with existing CVD
  - May consider low-dose aspirin for primary prevention of CV events in patients with 10-year CV risk >10%
- Measure coronary artery calcification or use coronary imaging to determine whether glucose, lipid, or blood pressure control efforts should be intensified

CV, cardiovascular; CVD, cardiovascular disease.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Statin Use in Patients with Diabetes

- Majority of patients with T2D have a high cardiovascular risk
- People with T1D are at elevated cardiovascular risk
- LDL-C target: <70 mg/dL—for the majority of patients with diabetes who are determined to have a high risk
- Use a statin regardless of LDL-C level in patients with diabetes who meet the following criteria:
  - >40 years of age
  - ≥1 major ASCVD risk factor
    - Hypertension
    - Family history of CVD
    - Low HDL-C
    - Smoking

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

DYSLIPIDEMIA

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

LIPID PANEL: Assess ASCVD Risk

STATIN THERAPY
If TG > 500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapies to attain goals according to risk levels

RISK LEVELS	HIGH	VERY HIGH	EXTREME
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70	<55
Non-HDL-C (mg/dL)	<130	<100	<80
TG (mg/dL)	<150	<150	<150
Apo B (mg/dL)	<90	<80	<70

RISK LEVELS:
- **HIGH:** DM but no other major risk and/or age <40
- **VERY HIGH:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)*
- **EXTREME:** DM plus established clinical CVD

IF NOT AT DESIRABLE LEVELS: Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

TO LOWER LDL-C:	Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin
TO LOWER Non-HDL-C, TG:	Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
TO LOWER Apo B, LDL-P:	Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin
TO LOWER LDL-C in FH:**	Statin + PCSK9i

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED ** FAMILIAL HYPERCHOLESTEROLEMIA

HYPERTENSION

GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg

ACEi or ARB

For initial blood pressure >150/100 mm Hg:
DUAL THERAPY

ACEi or ARB + Calcium Channel Blocker ✓ / ß-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, ß-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

 DOI 10.4158/EP161682.CS

CVD Risk Factors: AACE Targets

Risk Factor	Recommended Goal		
Blood pressure, mm Hg	Individualize, but generally:		
	Systolic <130	Diastolic <80	
Lipids	**High CV risk**	**Very high CV risk**	**Extreme CV risk**
LDL-C, mg/dL	<100	<70	<55
Non-HDL-C, mg/dL	<130	<100	<80
Triglycerides, mg/dL	<150		
ApoB, mg/dL	<90	<80	<70

Garber AL, et al. *Endocr Pract*. 2017;23:207-238.

Lipid Management in Diabetes

Elevated LDL-C, non-HDL-C, TG, TC/HDL-C ratio, ApoB, LDL particles	LDL-C at goal but non-HDL-C not at goal (TG ≥200 mg/dL and/or low HDL-C)	TG ≥500 mg/dL
• Statin = treatment of choice • Add bile acid sequestrant, niacin, and/or cholesterol absorption inhibitor if target not met on maximum-tolerated dose of statin • Use bile acid sequestrant, niacin, or cholesterol absorption inhibitor instead of statin if contraindicated or not tolerated	• May use fibrate, niacin, or high-dose omega-3 fatty acid to achieve non-HDL-C goal	• Use high-dose omega-3 fatty acid, fibrate, or niacin to reduce TG and risk of pancreatitis

ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HDL-C, high density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TC = total cholesterol.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Dyslipidemia Treatment Options

Class MOA	Efficacy			Main Limitations
	LDL-C	HDL-C	Triglycerides	
HMG CoA reductase inhibitors (statins) Competitively inhibit rate-limiting step of cholesterol synthesis, slowing production in liver	↓ 21-55%	↑ 2-10%	↓ 6-30%	• Risk of myopathy, increased liver transaminases • Contraindicated in liver disease • Liver enzyme monitoring required • Risk of new-onset diabetes
Cholesterol absorption inhibitors Inhibit intestinal absorption of cholesterol	↓ 10-18% (monotherapy) ↓ 34-61% (add-on to statins)	—	—	• Risk of myopathy
PCSK9 inhibitors Inhibit PCSK9 binding to LDL receptors, increasing availability of receptors for LDL clearance	↓ 48-71% (add-on to statins)	—	—	• Injection
Fibric acid derivatives Stimulate lipoprotein lipase activity	↓ VLDL Fenofibrate may ↓ LDL-C 20-25%	↑ 6-18%	↓ 20-35%	• GI symptoms, possible cholelithiasis • Gemfibrozil may ↑ LDL-C • Myopathy risk increased when used with statins

HDL-C, high-density lipoprotein cholesterol; HMG-CoA, hydroxymethylglutaryl-coenzyme A; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL-C, very low density lipoprotein cholesterol.

Jellinger PS, et al. *Endocr Pract*. 2017;23(suppl 2):1-87.

Continued on next slide

Dyslipidemia Treatment Options

Class MOA	Efficacy			Main Limitations
	LDL-C	HDL-C	Triglycerides	
Niacin/nicotinic acid Reduce hepatic synthesis of LDL-C and VLDL-C	↓ 10-25%	↑ 10-35%	↓ 20-30%	• Skin flushing, pruritus, GI symptoms, potential increases in blood glucose and uric acid
Bile acid sequestrants Bind bile acids in the intestine	↓ 15-25%	—	—	• GI symptoms • May ↑ triglycerides
MTP inhibitor Inhibit synthesis of chylomicrons and VLDL	↓ Up to 40%	—	↓ 45%	• Liver enzyme monitoring required • Steatosis of liver and small intestine
Anti-sense ApoB oligonucleotide Degrade mRNA for apoB-100, which is needed for synthesis of LDL	↓ 21%			• Liver enzyme monitoring required • Steatosis of liver and small intestine
Omega-3 fatty acids Reduce hepatic synthesis of VLDL-triglycerides and/or enhancing triglyceride clearance	VLDL-C ↓ 20-42%		↓ 27-45%	• Increase LDL-C levels • Monitor coagulation status • Increased frequency of symptomatic AF

ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MTP, microsomal transfer triglyceride; VLDL-C, very low density lipoprotein cholesterol.

Jellinger PS, et al. *Endocr Pract*. 2017;23(suppl 2):1-87.

Continued from previous slide

Statin Starting Dosages and Dosage Ranges

Agent	Usual recommended starting daily dosage	Dosage range	Administration
Lovastatin	20 mg	10-80 mg	Oral
Pravastatin	40 mg	10-80 mg	Oral
Simvastatin	20-40 mg	5-80 mg*	Oral
Fluvastatin	40 mg	20-80 mg	Oral
Atorvastatin	10-20 mg	10-80 mg	Oral
Rosuvastatin	10 mg	5-40 mg	Oral
Pitavastatin	2 mg	2-4 mg	Oral

*Simvastatin 80 mg not approved for therapy unless individual has been on treatment for more than 1 year without myopathy.

Crestor (rosuvastatin calcium); [PI]; 2016; Jellinger P, et al. *Endocr Practice*. 2017;23:479-497; Lescol (fluvastatin sodium) [PI]; 2012 Lipitor (atorvastatin calcium) [PI]; 2015; Livalo (pitavastatin) [PI]; 2013; ; Mevacor (lovastatin) [PI]; 2014; Pravachol (pravastatin sodium) [PI]; 2016; Zocor (simvastatin) [PI]; 2015.

Statins: Primary Metabolic Effects and Main Considerations

Metabolic Effects

- Primarily ↓ LDL-C 21%-55% by competitively inhibiting rate-limiting step of cholesterol synthesis in the liver, leading to upregulation of hepatic LDL receptors
- Effects on TG and HDL-C are less pronounced (↓ TG 6%-30% and ↑ HDL-C 2%-10%)

Main Considerations

- Liver function test prior to therapy and as clinically indicated thereafter
- Myalgias and muscle weakness in some individuals
- Potential for drug-drug interaction between some statins and CYP450 3A4 inhibitors, cyclosporine, warfarin, and protease inhibitors
- Myopathy/rhabdomyolysis in rare cases; increased risk with coadministration of some drugs (see product labeling)
- Simvastatin dosages should not exceed 40 mg in most individuals; dosages of 80 mg are no longer recommended except in those who have tolerated 80 mg for 12 months or more without muscle toxicity
- Do not exceed 20 mg simvastatin daily with amlodipine or ranolazine
- Plasma elevations of rosuvastatin may be higher among Asian persons than other ethnic groups
- New-onset diabetes is increased in individuals treated with statins; however, it is dose-related, occurs primarily in individuals with MetS, appears to be less common with pravastatin and possibly pitavastatin, and occurs overall to a lesser extent than the associated decrease in ASCVD

ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TG, triglycerides.

Bissonnette S, et al. *Can J Cardiol*. 2006;22:1035-1044; Denke M, et al. *Diab Vasc Dis Res*. 2006;3:93-102; Jellinger P, et al. *Endocr Practice*. 2017;23:479-497; Preiss D, et al. *JAMA*. 2011;305: 2556-2564.

Comparison of Statin Effects on Lipids After 6 Weeks of Treatment

Men and Women With LDL-C ≥160 and ≤250 mg/dL (N=2,431)

Statin	Dosage range, mg daily	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)
Lovastatin	20-80	↓ 21 to ↓ 36	↓ 29 to ↓ 48	↑ 4.6 to ↑ 8.0	↓ 12 to ↓ 13
Pravastatin	10-40	↓15 to ↓ 22	↓ 20 to ↓30	↑ 3.2 to ↑ 5.6	↑ 8 to ↓ 13
Simvastatin	10-80*	↓ 20 to ↓ 33	↓ 28 to ↓ 46	↑ 5.2 to ↑ 6.8	↓ 12 to ↓ 18
Fluvastatin	20-40	↓ 13 to ↓ 19	↓ 17 to ↓ 23	↑ 0.9 to ↓ 3.0	↓ 5 to ↓ 13
Atorvastatin	10-80	↓ 27 to ↓ 39	↓ 37 to ↓ 51	↑ 2.1 to ↑ 5.7	↓ 20 to ↓ 28
Rosuvastatin	10-40	↓ 33 to ↓ 40	↓ 45 to ↓ 55	↑ 7.7 to ↑ 9.6	↓ 20 to ↓ 26

*Not to be used at dosages of 80 mg unless individual has been on treatment for more than 12 months.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

AAP NCEP *Pediatrics.* 1992;89:525-584; Daniels SR, et al. EPIGCVHRRCAFR, 2012; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23:479-497; Jones P, et al. *Am J Cardiol*. 1998;81:582-587; Jones PH, et al. *Am J Cardiol*. 2003; 92:152-160; ; LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357; Pfeffer MA, et al. *J Am Coll Cardiol*. 1999;33:125-130; Plehn JF, et al. *Circulation*. 1999;99:216-223.

PCSK9 Inhibitor Starting Dosages and Dosage Ranges

Agent	Usual recommended starting daily dosage	Dosage range	Administration
Alirocumab	75 mg every 2 weeks	75-150 mg every 2 weeks	SC
Evolocumab	140 mg every 2 weeks or 420 mg once monthly	Not applicable	SC

Metabolic Effects

- ↓LDL-C 48%-71%, ↓ non-HDL-C 49%-58%, ↓TC 36%-42%, ↓Apo B 42%-55% by inhibiting PCSK9 binding with LDLRs, increasing the number of LDLRs available to clear LDL, and lowering LDL-C levels

Main Considerations

- Require subcutaneous self-injection; refrigeration generally needed
- Overall levels of adverse reactions and discontinuation very low
- Adverse reactions with significantly different rates between drug and placebo were: local injection site reactions and influenza
- The most common adverse reactions with similar rates for drug vs. placebo were:
  - Alirocumab: nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia
  - Evolocumab: nasopharyngitis, back pain, and upper respiratory tract infection

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SC, subcutaneous injection; TC, total cholesterol.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23:479-497; Praluent (alirocumab) [PI] 2015; Repatha (evolocumab) [PI]; 2016.

Fibrate Starting Dosages and Dosage Ranges

Agent	Usual recommended starting daily dose	Dosage range	Administration
Fenofibrate	48-145 mg	48-145 mg	Oral
Gemfibrozil	1200 mg	1200 mg	Oral
Fenofibric acid	45-135 mg	45-135 mg	Oral

Metabolic Effects

- Primarily ↓ TG 20%-35%, ↑ HDL-C 6%-18% by stimulating lipoprotein lipase activity
- Fenofibrate may ↓ TC and LDL-C 20%-25%
- Lower VLDL-C and LDL-C; reciprocal rise in LDL-C transforms the profile into a less atherogenic form by shifting fewer LDL particles to larger size
- Fenofibrate ↓ fibrinogen level

HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein, LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

Aguilar-Salinas CA, et al. Metabolism. 2001;50:729-733; Athyros VG, et al. Coron Artery Dis. 1995;6:25-1256; Avellone G, et al. Blood Coagul Fibrinolysis. 1995;6:543-548; Bröijersen A, et al. Arterioscler Thromb Vasc Biol. 1996;16:511-516; Bröijersén A, et al. Thromb Haemost. 1996;76:171-176; Davidson MH, et al. Am J Cardiol. 2007;99:3C-18C; Farnier M, et al. Eur Heart J. 2005;26:897-905; Guyton JR, et al. Arch Intern Med. 2000;160:1177-1184; Hottelart C, et al. Nephron. 2002;92:536-541; Insua A, et al. Endocr Pract. 2002;8:96-101; Jellinger P, Handelsman Y, Rosenblit P, et al. Endocr Practice. 2017;23:479-497; Kockx M, et al. Thromb Haemost. 1997;78:1167-1172; Lopid (gemfibrozil) [PI] 2010; McKenney JM, et al. J Am Coll Cardiol. 2006;47:1584-1587; Syvänne M, et al. Atherosclerosis. 2004;172:267-272; Tricor (fenofibrate) [PI]; 2010; Trilipix (fenofibric acid) [PI]; 2016; Westphal S, et al. Lancet. 2001; 358:39-40.

Fibrates: Main Considerations

- Gemfibrozil may ↑ LDL-C 10%-15%
- GI symptoms, possible cholelithiasis
- May potentiate effects of orally administered anticoagulants
- Gemfibrozil may ↑ fibrinogen level
- Gemfibrozil and fenofibrate can ↑ homocysteine independent of vitamin concentrations
- May cause muscle disorders; myopathy/rhabdomyolysis when used with statin
- Fibrates are associated with increased serum creatinine levels, which may not reflect renal dysfunction
- Fenofibrate dose should be cut by two-thirds and gemofibrozil by one-half when eGFR is 15-60, and fibrates should be avoided when eGFR is <15
- Can improve diabetic retinopathy

eGFR, estimated glomerular filtration rate; GI, gastrointestinal; LDL-C, low-density lipoprotein cholesterol.

Jellinger P, et al. *Endocr Practice*. 2017;23:479-497.

Bile Acid Sequestrant Starting Dosages and Dosage Ranges

Agent	Usual recommended daily dosage	Dosage range	Administration
Cholestyramine	8-16 g	4-24 g	Oral
Colestipol	2 g	2-16 g	Oral
Colesevelam	3.8 g	3.8-4.5 g	Oral

Metabolic Effects

- Primarily ↓ LDL-C 15%-25% by binding bile acids and preventing their reabsorption in the ileum (causing hepatic cholesterol depletion and LDL-receptor upregulation)
- Colesevelam ↓ glucose and hemoglobin A1C (~0.5%); FDA-approved to treat T2D

Main Considerations

- May ↑ serum TG
- Frequent constipation and/or bloating, which can reduce adherence
- Many potential drug interactions (decreased drug absorption), less so with colesevelam (see product labeling)
- May reduce absorption of folic acid and fat-soluble vitamins such as vitamins A, D, and K

FDA, Food and Drug Administration; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; T2D, type 2 diabetes; TG, triglyceride.

Colestid (colestipol hydrochloride) [PI]; 2014; Jellinger P, et al. *Endocr Practice*. 2017;23:479-497; Prevalite (cholestyramine for oral suspension, USP) [PI]; 2015; WelChol (colesevelam hydrochloride) [PI]; 2014; Zieve FJ, et al. Ther. 2007;29:74-839:74-83.

Cholesterol Absorption Inhibitor Starting Dosages and Dosage Ranges

Agent	Usual recommended daily dosage	Dosage range	Administration
Ezetimibe	10 mg	10 mg	Oral
Ezetimibe/ simvastatin	10/20 mg	10/10 to 10/80 mg	Oral

Metabolic Effects

- Primarily ↓ LDL-C 10%-18% by inhibiting intestinal absorption of cholesterol and decreasing delivery to the liver, leading to upregulation of hepatic LDL receptors
- ↓ Apo B 11%-16%
- In combination with statins, additional ↓ LDL-C 25%, total ↓ LDL-C 34%-61%
- In combination with fenofibrate, ↓ LDL-C 20%-22% and ↓ apo B 25%-26% without reducing ↑ HDL-C

Main Considerations

- Myopathy/rhabdomyolysis (rare)
- When coadministered with statins or fenofibrate, risks associated with those drugs remain (e.g., myopathy/ rhabdomyolysis, cholelithiasis)

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Bays HE, et al. *Clin Ther.* 2001;23:1209-1230; Bays HE, et al. *Clin Ther*. 2004;26:1758-1773; Bissonnette S, et al. *Can J Cardiol*. 2006;22:1035-1044; Brohet C, et al. *Curr Med Res Opin*. 2005;21:571-578; Denke M et al. *Diab Vasc Dis Res*. 2006;3:93-102; Dujovne CA, et al. *Am J Cardiol*. 2002;90:109-21097; Farnier M, et al. *Eur Heart J*. 2005;26:897-905; Gagne C, et al. *Am J Cardiol*. 2002;90:1084-1091; Jellinger P, et al. *Endocr Practice*. 2017;23:479-497; Knopp RH, et al. *Int J Clin Pract*. 2013. 57:363-368; McKenney JM, et al. *J Am Coll Cardiol*. 2006;47:1584-1587; Zetia (ezetimibe) [PI] 2013.

Omega-3 Fatty Acid Starting Dosages and Dosage Ranges

Agent	Usual recommended daily dosage	Dosage range	Administration
Omega-3-acid ethyl esters (Lovaza)	4 g	4 g	Oral
Icosapent ethyl (Vascepa)	4 g	4 g	Oral

Metabolic Effects

- ↓ TG 27%-45%, TC 7%-10%, VLDL-C 20%-42%, apo B 4%, and non-HDL-C 8%-14% in individuals with severe hypertriglyceridemia most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles. Other potential mechanisms of action include: increased β-oxidation; inhibition of acyl-CoA; 1,2-diacylglyceral acyltransferase; decreased hepatic lipogenesis; and increased plasma lipoprotein activity
- Icosapent ethyl ↓ LDL-C 5%, whereas, omega-3-acid ethyl esters ↑ LDL-C 45%

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein.

Jellinger P, et al. *Endocr Practice*. 2017;23:479-497; Lovaza (omega-3-acid ethyl esters) [PI]; 2015; Vascepa (icosapent ethyl) [PI]; 2016.

Omega-3 Fatty Acids: Main Considerations

- Assess TG levels prior to initiating and periodically during therapy
- Omega-3-acid ethyl esters can increase LDL-C levels. Monitor LDL-C levels during treatment
- May prolong bleeding time. Monitor coagulation status periodically in patients receiving treatment with omega-3 fatty acids and other drugs affecting coagulation
- Monitor ALT and AST levels periodically during treatment in patients with hepatic impairment. Some patients may experience increases in ALT levels only
- Exercise caution when treating patients with a known hypersensitivity to fish and/or shellfish
- The effect of omega-3 fatty acids on cardiovascular morbidity and mortality and the risk of pancreatitis has not been determined in patients with severe hypertriglyceridemia
- In patients with paroxysmal or persistent atrial fibrillation, therapy with omega-3-acid ethyl esters may be associated with increased frequency of symptomatic AF or flutter, especially within the first 2 to 3 months after initiation
- Most common adverse events include arthralgia (2.3%), eructation (4%), dyspepsia (3%), and taste perversion (4%). May also experience constipation, gastrointestinal disorders, vomiting, rash, or pruritus
- Should be used with caution in nursing mothers and only be used in pregnant women if the benefits of treatment outweigh the potential risk of fetal harm

AF, atrial fibrillation.

Jellinger P, et al. *Endocr Practice*. 2017;23:479-497.

Niacin Starting Dosages and Dosage Ranges

Agent	Usual recommended daily dosage	Dosage range	Administration
Immediate release	250 mg	250-3000 mg	Oral
Extended release	500 mg	500-2000 mg	Oral

Metabolic Effects

- ↓ LDL-C 10%-25%, ↓ TG 20%-30%, ↑ HDL-C 10%-35% by decreasing hepatic synthesis of LDL-C and VLDL-C
- ↓ Lipoprotein (a)
- Transforms LDL-C to less atherogenic form by increasing average particle size and also decreases LDL particle concentration

Main Considerations

- Potential for frequent skin flushing, pruritus, abdominal discomfort, hepatoxicity (rare but may be severe), nausea, peptic ulcer, atrial fibrillation
- Deleterious effect on serum glucose at higher dosages
- Increases uric acid levels; may lead to gout

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; VLDL-C, very low-density lipoprotein cholesterol.

Guyton JR, et al. *Arch Intern Med.* 2000;160:1177-1184; Jellinger P, et al. *Endocr Practice*. 2017;23:479-497; Niaspan (niacin extended-release) [PI] 2015.

MTP Inhibitor Starting Dosage and Dosage Range

Agent	Recommended starting dose	Dosage range	Administration
Lomitapide	5 mg	5-60 mg	Oral

Metabolic Effects

- ↓ Up to LDL-C 40%, TC 36%, apo B 39%, TG 45%, and non-HDL-C 40% (depending on dose) in individuals with HoFH by binding and inhibiting MTP, which inhibits synthesis of chylomicrons and VLDL

Main Considerations

- Can cause increases in transminases (ALT, AST); monitoring of ALT, AST, alkaline phosphatase, and total bilirubin prior to initiation, and of ALT and AST during treatment, is required per FDA REMS
- Causes increases in hepatic fat (steatosis) with or without concomitant elevated transminases, which may be a risk for progressive liver diseases
- Also causes steatosis of the small intestine with resulting abdominal pain and steatorrhea unless a very-low-fat diet is followed; may also cause fat-soluble vitamin deficiency unless vitamin supplements are taken
- Caution should be exercised when used with other drugs with potential hepatoxicity; because of hepatoxicity risk, only available through REMS program

ALT, aspartate amino transferase; AST, amino alanine transferase; FDA, Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MTP, microsomal transfer protein; REMS, Risk Evaluation and Mitigation Strategy; TG, triglycerides; VLDL, very low-density lipoprotein.

Jellinger P, et al. *Endocr Practice*. 2017;23:479-497; Juxtapid (lomitapide) [PI]; 2012.

Anti-sense Apolipoprotein B Oligonucleotide Starting Dosage and Dosage Range

Agent	Usual recommended dosage	Dosage range	Administration
Mipomersen	200 mg once weekly	200 mg once weekly	SC

Metabolic Effects

- ↓ LDL-C 21%, TC 19%, apo B 24%, and non-HDL-C 22% in individuals with HoFH by degrading mRNA for apo B-100, the principal apolipoprotein needed for hepatic synthesis of VLDL (and subsequent intra-plasma production of IDL and LDL)

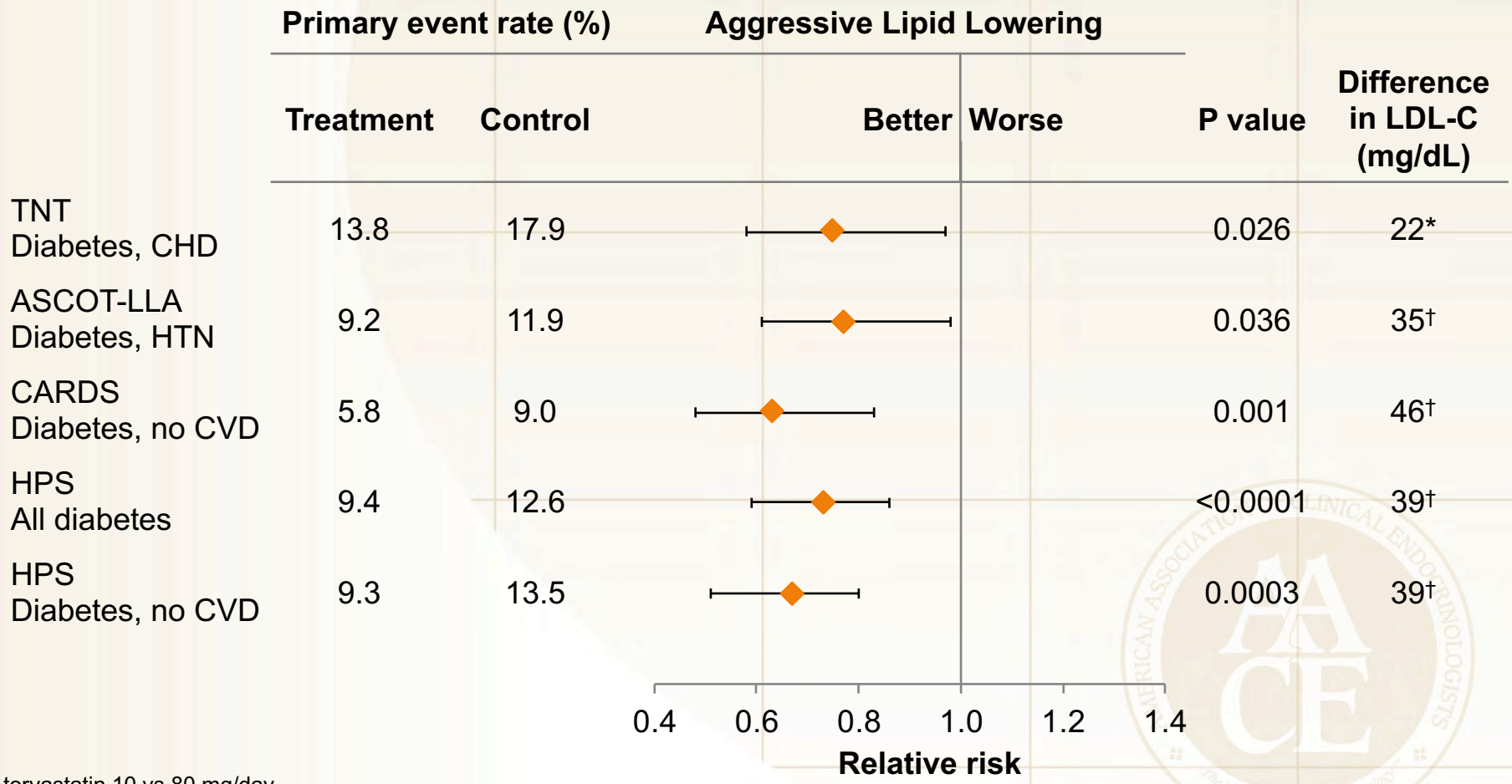
Main Considerations

- Can cause increases in transminases (ALT, AST); monitoring of ALT, AST, alkaline phosphatase, and total bilirubin before initiation, and of ALT and AST during treatment is recommended
- Causes increases in hepatic fat (steatosis) with or without concomitant elevated transminases, which may be a risk for progressive liver diseases
- Caution should be exercised when used with other drugs with potential hepatoxicity; because of hepatoxicity risk, only available through REMS program

ALT, aspartate amino transferase; apo, apolipoprotein; AST, amino alanine transferase; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; mRNA, messenger RNA; SQ, subcutaneous; VLDL, very low-density lipoprotein.

Jellinger P, et al. *Endocr Practice*. 2017;23:479-497; Kynamro (mipomersen sodium) Injection [PI]; 2016.

Benefits of Aggressive LDL-C Lowering in Diabetes



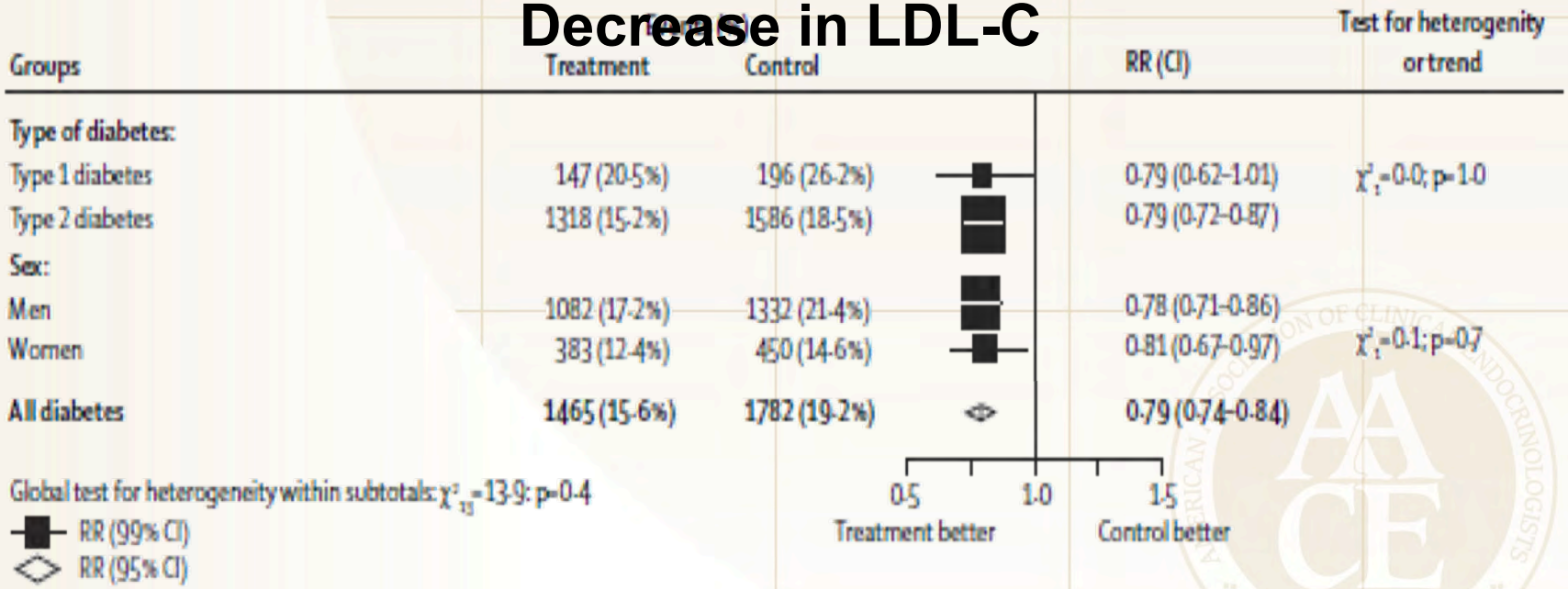
*Atorvastatin 10 vs 80 mg/day.
†Statin vs placebo.

Shepherd J, et al. *Diabetes Care.* 2006;29:1220-1226. Sever PS, et al. *Diabetes Care.* 2005;28:1151-1157. Colhoun HM, et al. *Lancet.* 2004;364:685-696. HPS Collaborative Group. *Lancet.* 2003;361:2005-2016.

Randomized Trials of Statins: A Meta-Analysis of CV Events

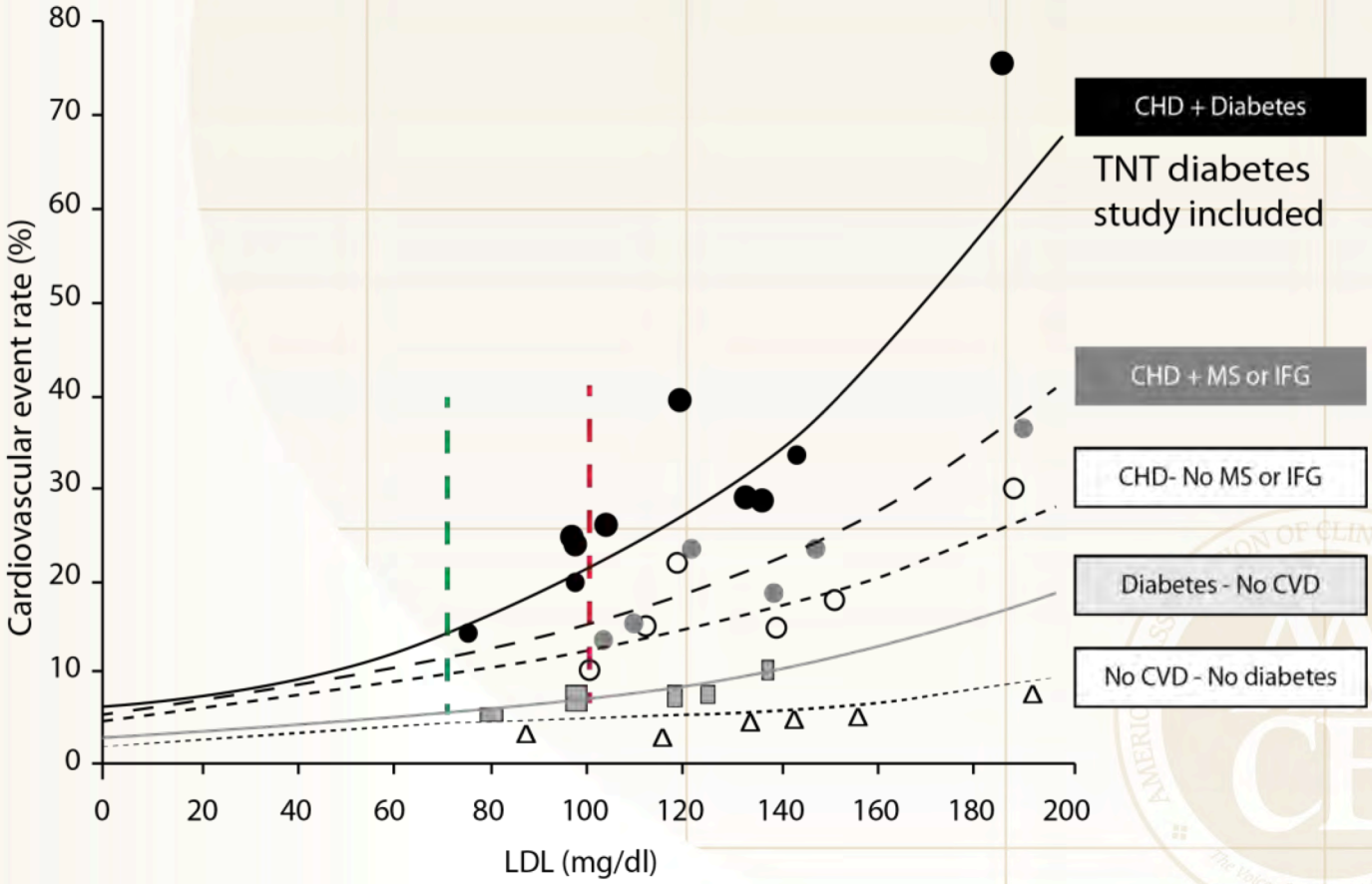
Patients with Diabetes (N=18,686; 14 RCTs)

Risk Reduction in Major Vascular Events per mmol/L Decrease in LDL-C



Cholesterol Treatment Trialists' Collaborators. *Lancet*. 2008;371:117-125.

Treat Patients With the Greatest Absolute Risk the Most Aggressively



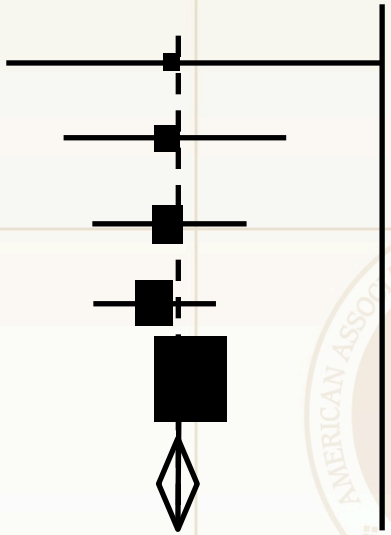
Robinson JG, et al. *Am J Cardiol.* 2006;98:1405-1408.

Statin Benefits Across a Range of Baseline Levels

Cholesterol Treatment Trialists' Collaboration

LDL-C 90-130 mg/dL shows same benefit as LDL-C 50-90 mg/dL

	Events (% per annum)		RR (CI) per 1 mmol/L reduction in LDL-C	
	Statin	Control		
<2 mmol/L (<77 mg/dL)	910 (4.1%)	1,012 (4.6%)	0.78 (0.61-0.99)	
≥2 to <2.5 mmol/L (77-96 mg/dL)	1,528 (3.6%)	1,729 (4.2%)	0.77 (0.67-0.89)	
≥2.5 to <3.0 mmol/L (97-116 mg/dL)	1,866 (3.3%)	2,225 (4.0%)	0.77 (0.70-0.85)	*P*=0.3
≥3.0 to <3.5 mmol/L (117-135 mg/dL)	2,007 (3.2%)	2,454 (4.0%)	0.76 (0.70-0.82)	
≥3.5 mmol/L (>136 mg/dL)	4,508 (3.0%)	5,736 (3.9%)	0.80 (0.76-0.83)	
Total	10,973 (3.2%)	13,350 (4.0%)	0.78 (0.76-0.80)	



1 mmol/L = 38.6 mg/dL

LDL-C, low-density lipoprotein cholesterol.

Baigent C, et al. *Lancet*. 2010;376:1670-1681.

Effect on CHD and Diabetes Primary Prevention

Cholesterol Treatment Trialists' Collaboration

	Events (% per annum)		RR (CI) per 1 mmol/L reduction in LDL-C	
Previous Vascular Disease	Statin	Control		
CHD	8,395 (4.5%)	10,123 (5.6%)	0.79 (0.76-0.82)	
No CHD, vascular	674 (3.1%)	802 (3.7%)	0.81 (0.71-0.92)	*P*=0.3
None	1,904 (1.4%)	2,425 (1.8%)	0.75 (0.69-0.82)	
Diabetes				
Type 1 diabetes	145 (4.5%)	192 (6.0%)	0.77 (0.58-1.01)	
Type 2 diabetes	2,494 (4.2%)	2,920 (5.1%)	0.80 (0.74-0.86)	*P*=0.8
No diabetes	8,272 (3.2%)	10,163 (4.0%)	0.78 (0.75-0.81)	

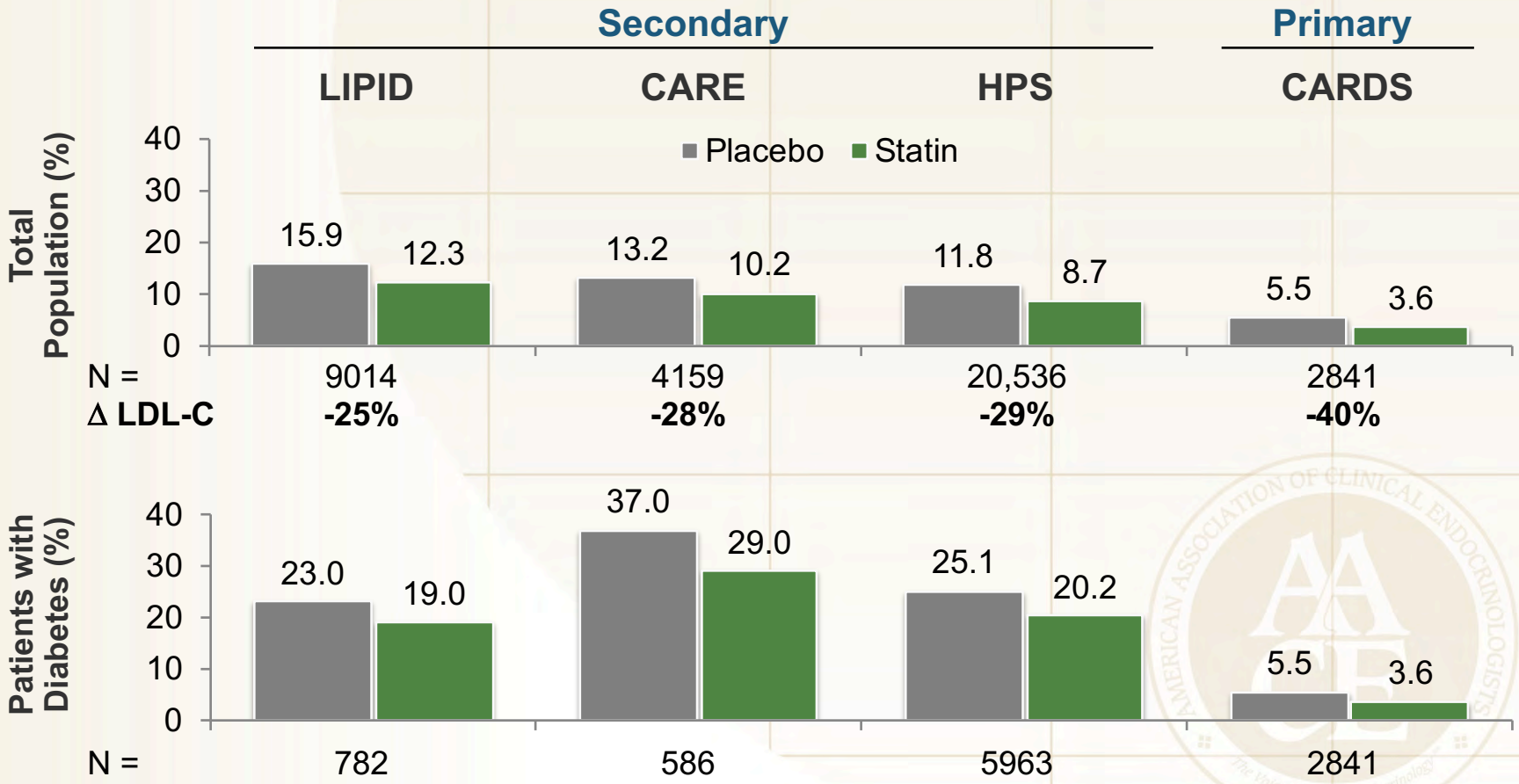
1 mmol/L = 38.6 mg/dL.

CHD: coronary heart disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; RR: relative risk.

Baigent C, et al. *Lancet*. 2010;376:1670-1681.

Residual Cardiovascular Risk in Major Statin Trials

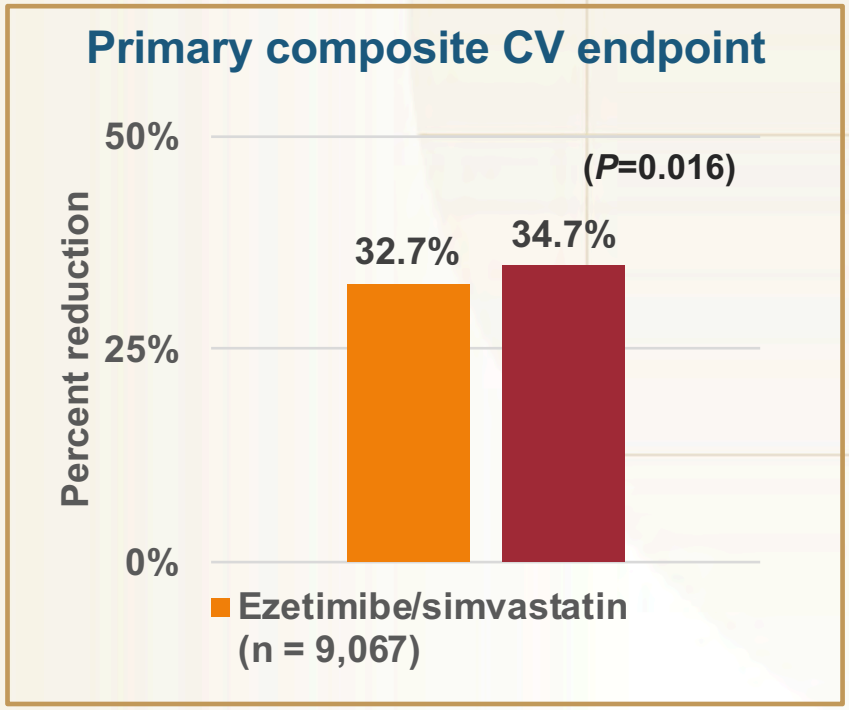
CHD events still occur in patients treated with statins



LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357. Sacks FM, et al. *N Engl J Med*. 1996;335:1001-1009.
HPS Collaborative Group. *Lancet*. 2002;360:7-22. Colhoun HM, et al. *Lancet*. 2004:364:685-696.

IMPROVE-IT: Improved Reduction of Outcomes, Vytorin Efficacy International Trial

Trial design: Patients with recent ACS were randomized 1:1 to either ezetimibe 10 mg + simvastatin 40 mg or simvastatin 40 mg and followed for a median of 6 years



Results

- Primary endpoint (CV death/MI/UA/coronary revasc/stroke/moderate/severe bleeding) for ezetimibe/simvastatin vs. simvastatin: 32.7% vs. 34.7% (HR 0.94, 95% CI 0.89-0.99; *P*=0.016)
- MI: 13.1% vs. 14.8%, *P*=0.002; stroke: 4.2% vs. 4.8%, *P*=0.05; CVD/MI/stroke: 20.4% vs. 22.2%, *P*=0.003
- Median LDL follow-up average: 53.7 vs. 69.5 mg/dL

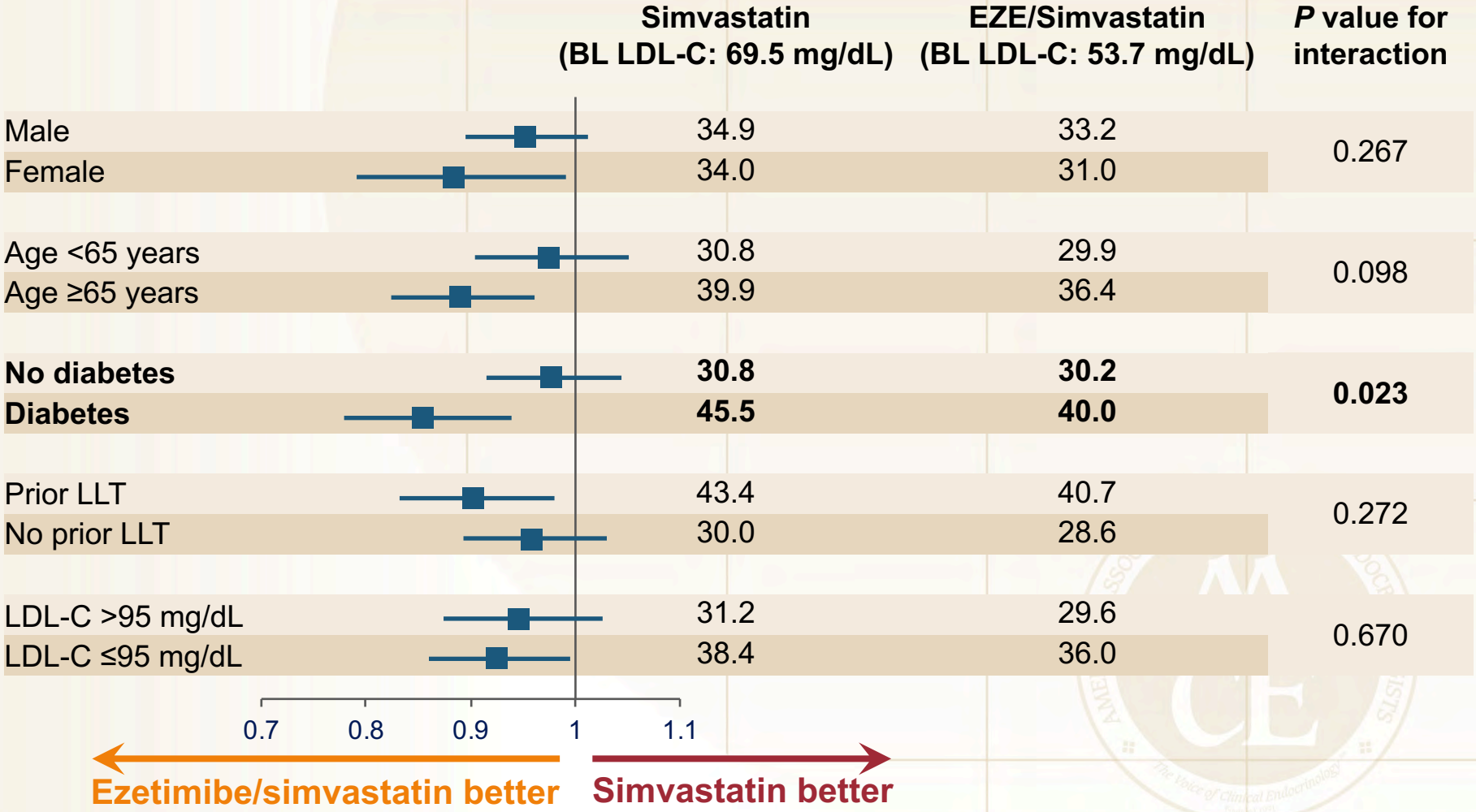
Conclusions

- In patients with high-risk ACS, ezetimibe 10 mg/simvastatin 40 mg was superior to simvastatin 40 mg alone in reducing adverse CV events
- This is the first study powered for clinical outcomes to show a benefit with a non-statin agent
- Reaffirms the "lower is better" hypothesis with LDL-C

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

Cannon CP, et al. *N Engl J Med.* 2015;372:2387-2397.

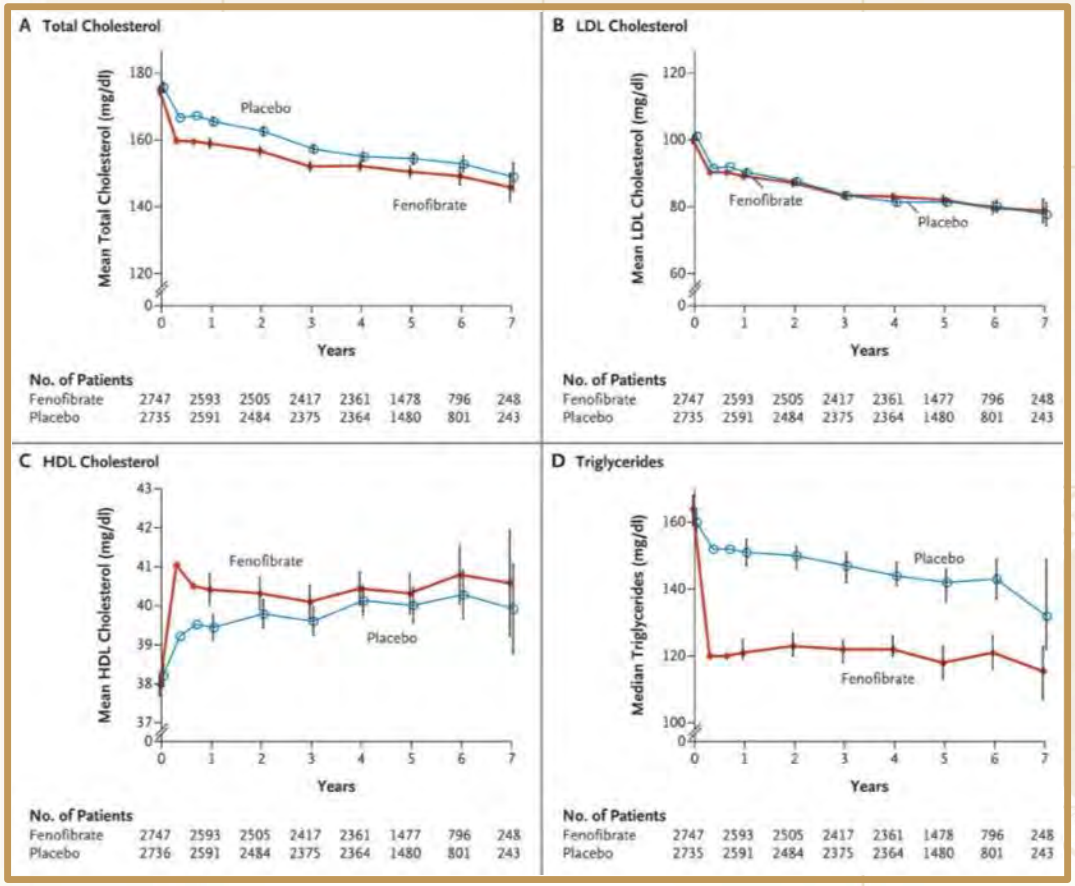
IMPROVE-IT
Major Prespecified Subgroups



EZE, ezetimibe; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.
Cannon CP, et al. *N Engl J Med.* 2015;372:2387-2397.

Lipid Effects of Adding a Fenofibrate to a Statin in Patients With T2D

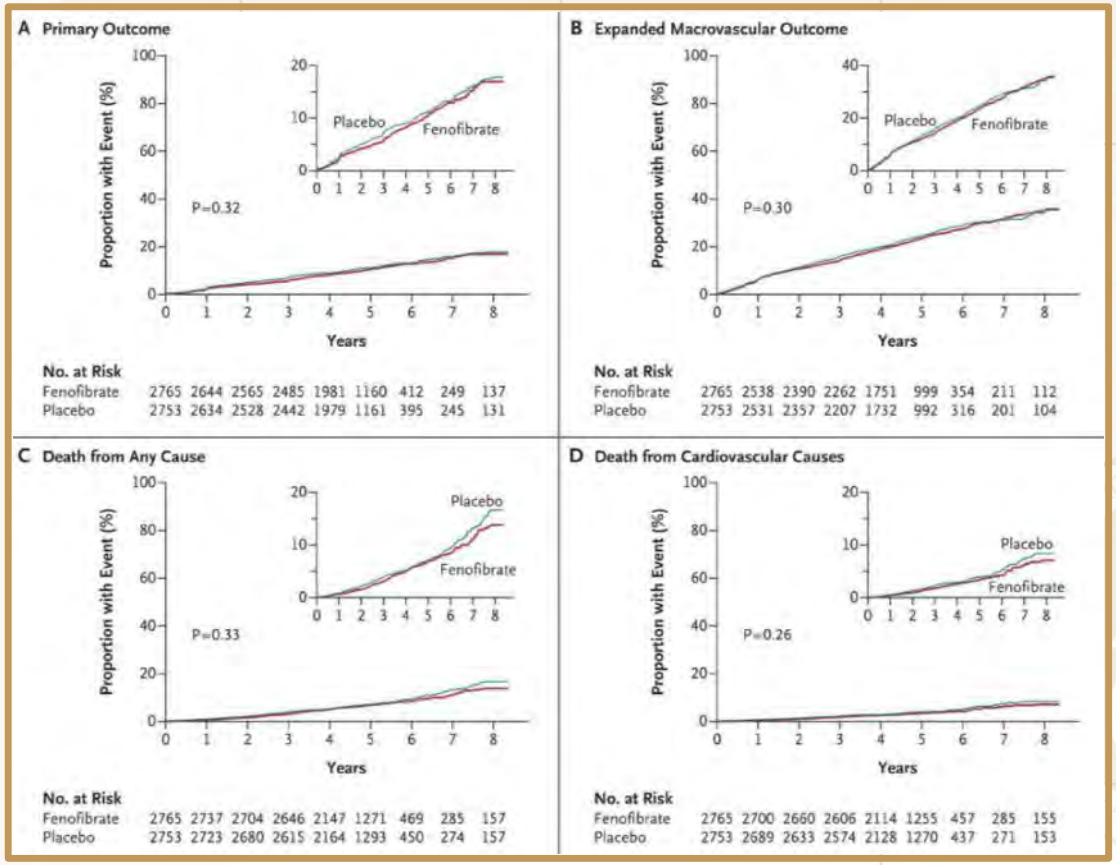
Action to Control Cardiovascular Risk in Diabetes (N=5518)



ACCORD Study Group. *N Engl J Med.* 2010;362:1563-1574.

Effect of Fenofibrate Plus Statin on CV Events in Patients With T2D

Action to Control Cardiovascular Risk in Diabetes (N=5518)

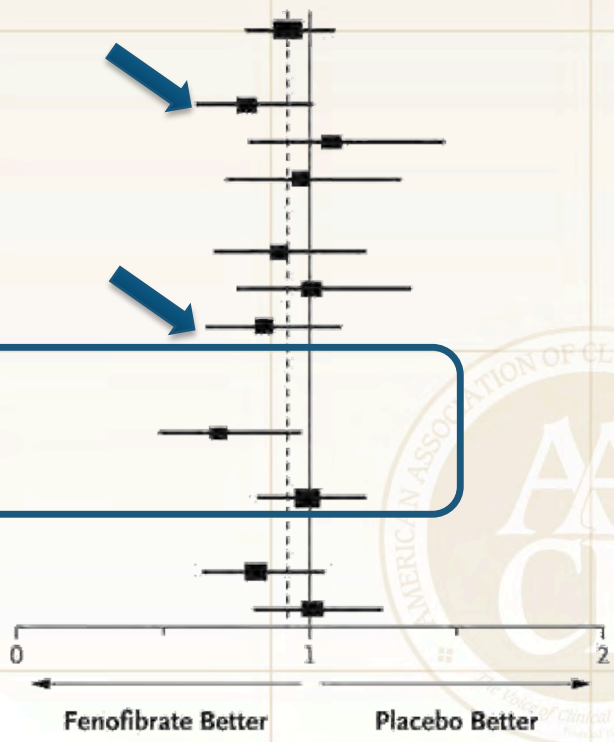


ACCORD Study Group. *N Engl J Med.* 2010;362:1563-1574.

Benefits of Fenofibrate Plus Statin in Patients With T2D

Action to Control Cardiovascular Risk in Diabetes (N=5518)

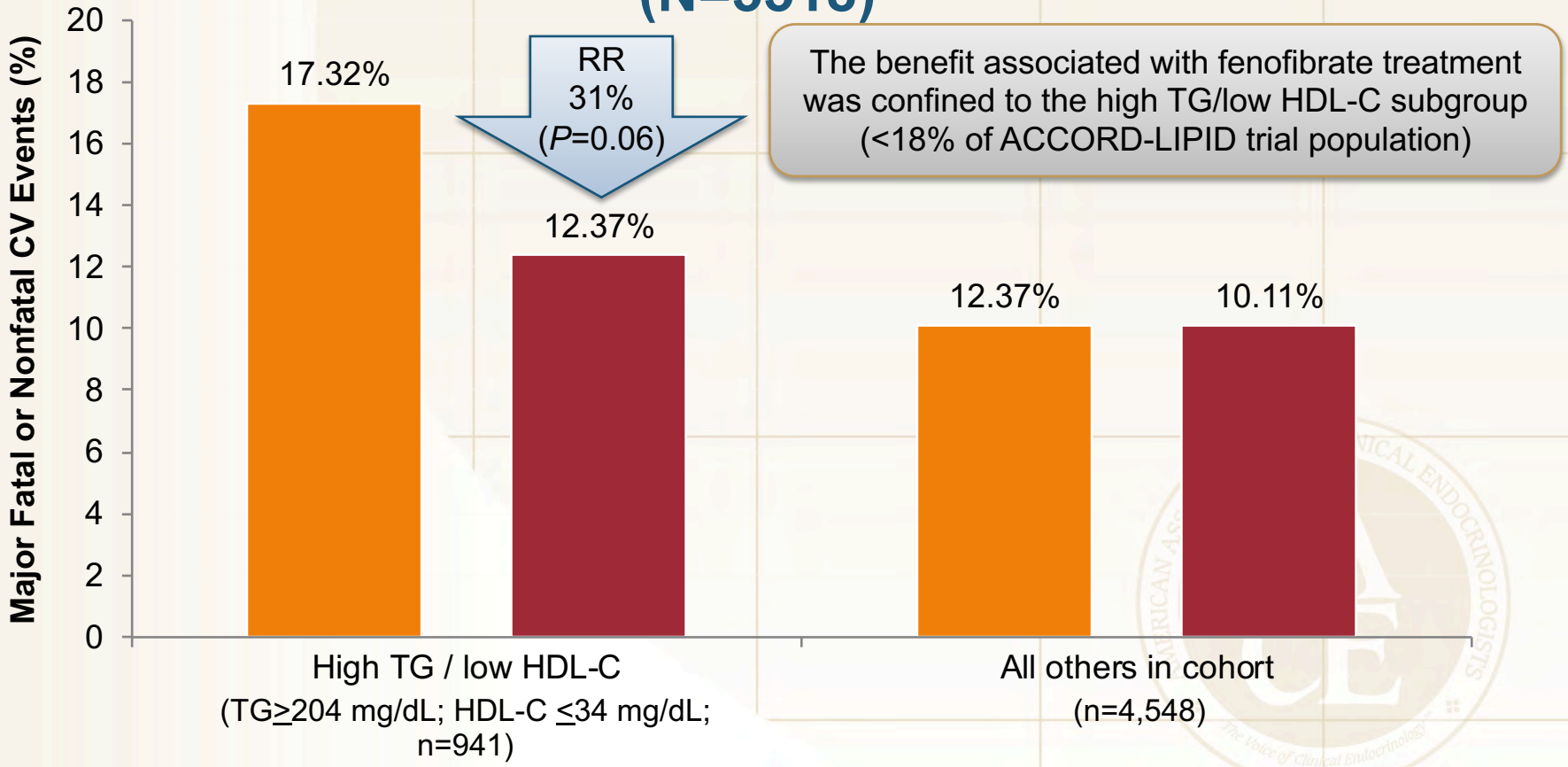
Subgroup	Fenofibrate	Placebo	P Value for Interaction
	% of events (no. in group)		
Overall	10.52 (2765)	11.26 (2753)	
HDL cholesterol			0.24
≤34 mg/dl	12.24 (964)	15.56 (906)	
35–40 mg/dl	10.12 (860)	9.47 (866)	
≥41 mg/dl	9.08 (925)	8.99 (968)	
Triglycerides			0.64
≤128 mg/dl	9.88 (891)	11.29 (939)	
129–203 mg/dl	10.50 (924)	9.86 (913)	
≥204 mg/dl	11.13 (934)	12.84 (888)	
Triglyceride–HDL cholesterol combination			0.06
Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl	12.37 (485)	17.32 (456)	
All others	10.11 (2264)	10.11 (2284)	
Glycated hemoglobin			0.20
≤8.0%	8.69 (1324)	10.56 (1335)	
≥8.1%	12.20 (1435)	11.94 (1415)	



ACCORD Study Group. *N Engl J Med.* 2010;362:1563-1574.

Fenofibrate Benefits Most Likely in Patients with High TG and Low HDL-C

Action to Control Cardiovascular Risk in Diabetes (N=5518)



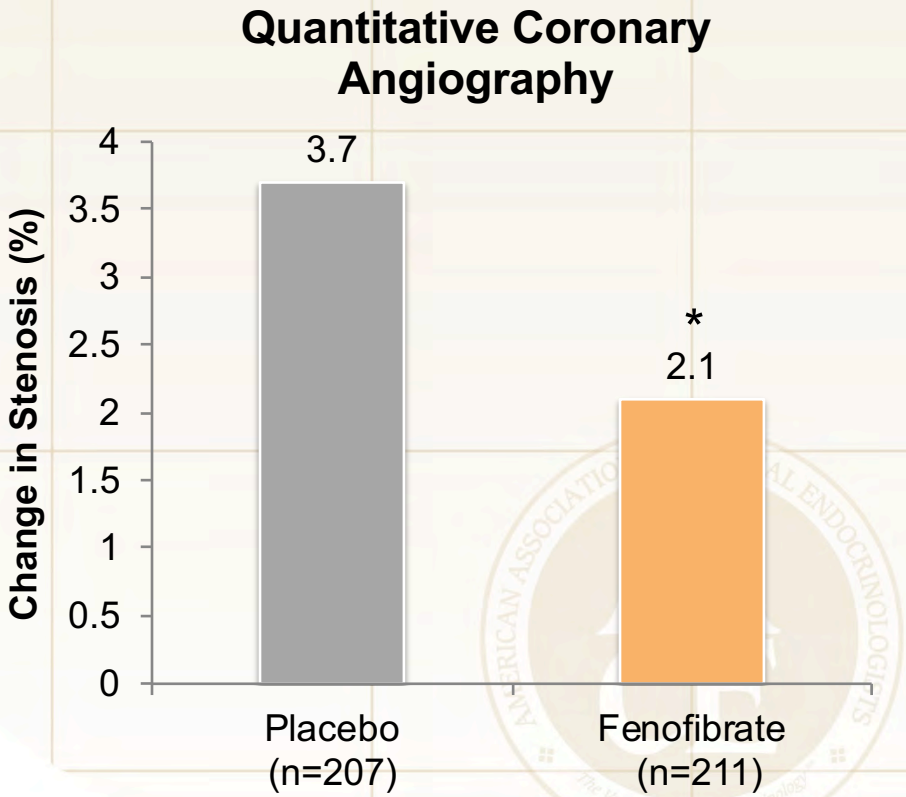
CV, cerebrovascular; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; RR, risk reduction; TG, triglycerides.

Elam M, et al, *Clin Lipidol*. 2011;6:9-20. ACCORD Study Group. NEJM. 2010; 362:1563-1574.

Effect of Fenofibrate on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes

Diabetes Atherosclerosis Intervention Study

	Fenofibrate	Placebo
Triglycerides (mmol/L)		
Baseline	2.59	2.42
Endpoint	-29%	+1%
HDL-C (mmol/L)		
Baseline	1.01	1.05
Endpoint	+7%	+2%



*P=0.02 vs placebo

Diabetes Atherosclerosis Intervention Study. *Lancet*. 2001;357:905-910.

FIELD: Fenofibrate Intervention in Event Lowering in Diabetes

Multinational, randomized controlled trial (N=9,795) of patients with T2D currently taking statin therapy assigned to add-on treatment with fenofibrate or placebo

Outcome	Fenofibrate % (n)	Placebo % (n)	HR	95% CI	*P* value
Coronary events	5% (256)	6% (288)	0.89	0.75-1.05	0.16
CHD mortality	2% (110)	2% (93)	1.19	0.90-1.57	0.22
Nonfatal MI	3% (158)	4% (207)	0.76	0.62-0.94	0.01

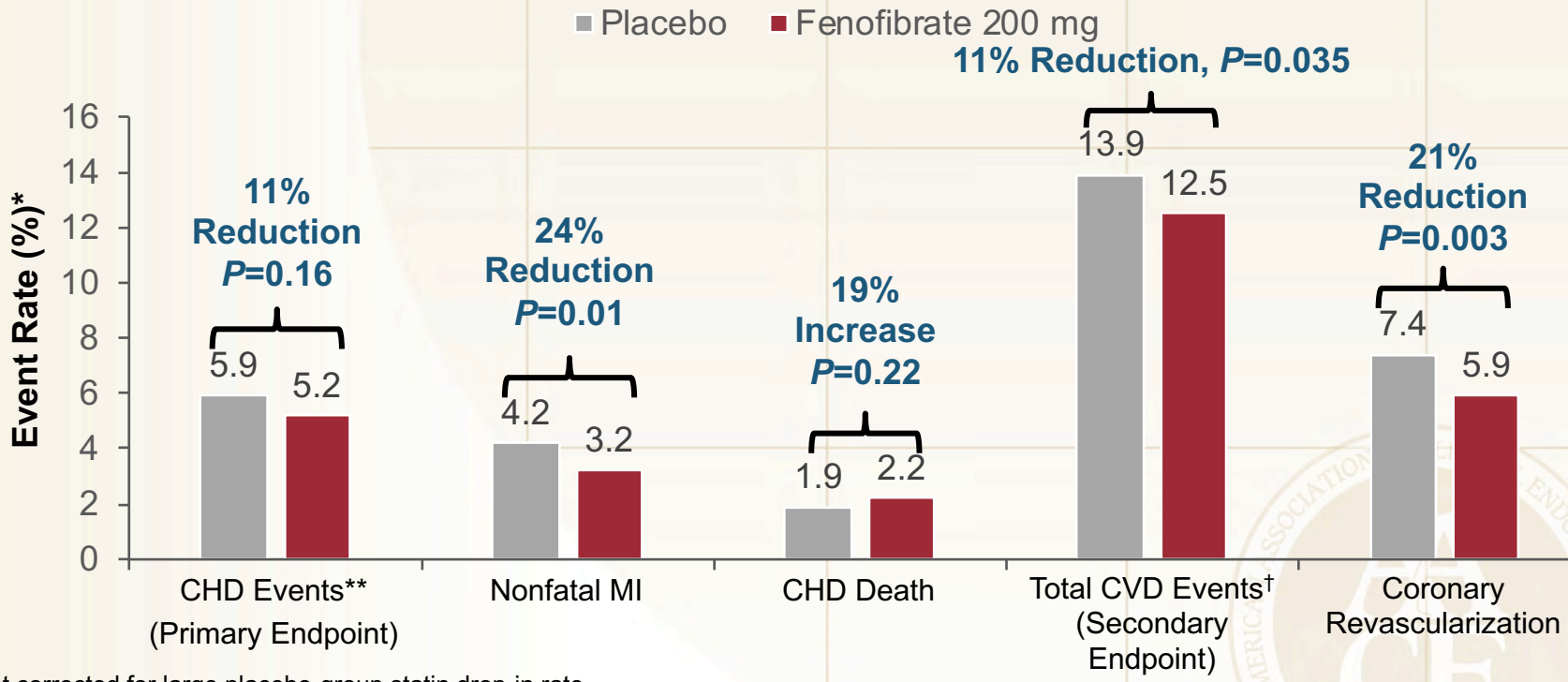
CHD, coronary heart disease; MI, myocardial infarction; T2D, type 2 diabetes.

Keech A, et al. *Lancet.* 2005;366:1849-1861.

Fenofibrate and CV Events

FIELD
(N=9795 Patients With T2D)

Baseline cholesterol (mg/dL): TC 194; TG 154; HDL-C 42; LDL-C 119; Non-HDL-C 152



* Not corrected for large placebo-group statin drop-in rate.

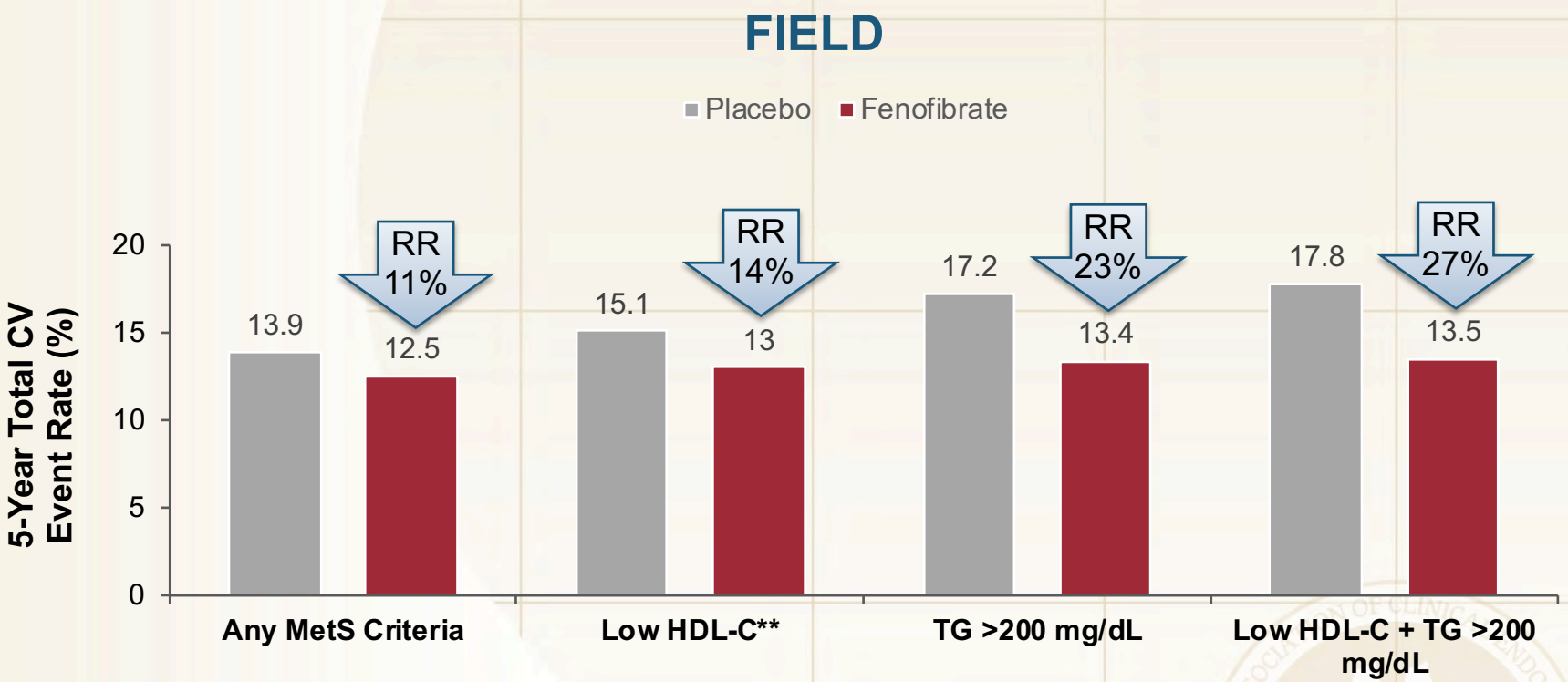
** Nonfatal MI and CHD death.

† CHD events, stroke, CVD death, revascularizations.

CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; T2D, type 2 diabetes; TC, total cholesterol; TG, triglycerides.

Keech A, et al. *Lancet*. 2005;366:1849-1861.

Greatest Benefit of Fenofibrate Seen in Patients With Elevated TG and Low HDL-C



	Any MetS Criteria	Low HDL-C**	TG >200 mg/dL	Low HDL-C + TG >200 mg/dL
Hazard ratio	0.89	0.86	0.77	0.73
95% CI	0.80-0.99	0.75-0.99	0.63-0.94	0.58-0.91
P value	<0.01	<0.01	<0.01	<0.05

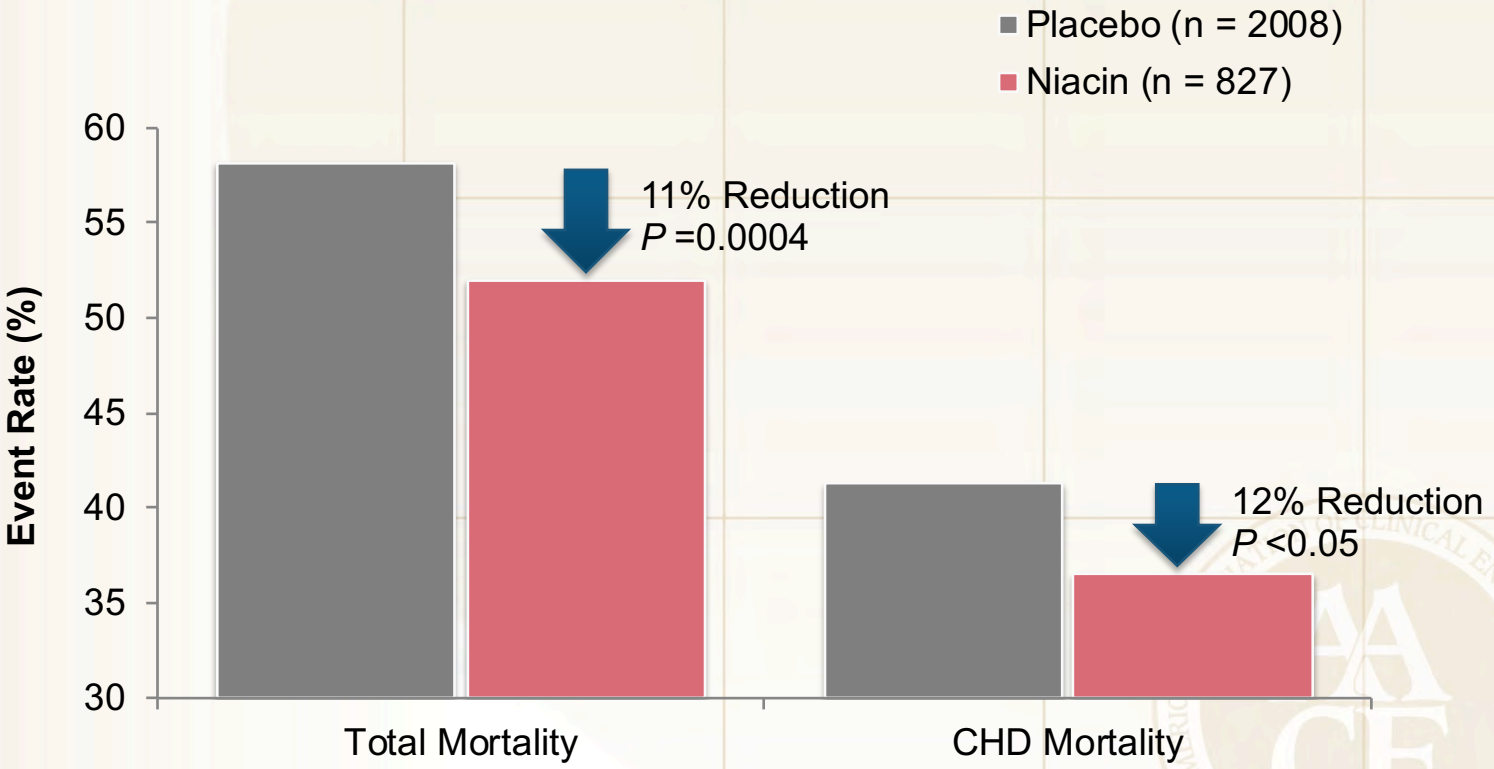
*Not corrected for large placebo group statin drop-in rate

**HDL-C <40 mg/dL (men) and <50 mg/dL (women).

CI, confidence interval; CV, cerebrovascular; FIELD, Secondary Endpoints from the Fenofibrate Intervention and Event Lowering in Diabetes trial; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; RR, risk reduction; TG, triglycerides.

Scott R, et al. *Diabetes Care* 2009;32:493-498

Coronary Drug Project: 15-Year Follow-up



Canner PL, et al. *J Am Coll Cardiol*. 1986;8:1245-1255. Canner PL, et al. *J Am Coll Cardiol*. 2005;95:254-257.

Dyslipidemia Summary

- Patients with diabetes and insulin resistance syndrome have atherogenic dyslipidemia and an increased risk for CVD
- Although statin therapy is effective in lowering LDL-C, residual CVD risk remains after statin therapy
- To reduce residual CVD risk, lipid abnormalities beyond LDL-C (non–HDL-C, triglycerides, HDL-C) should be intensively treated

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Jellinger PS, et al. *Endocr Pract*. 2017;23(suppl 2):1-87.