Glucose Goals and Complications Management for Type 2 Diabetes

Type 2 Diabetes Glucose Goals and Complications Management

INDIVIDUALIZED GOALS

AACE Comprehensive Diabetes Care: Glucose Goals

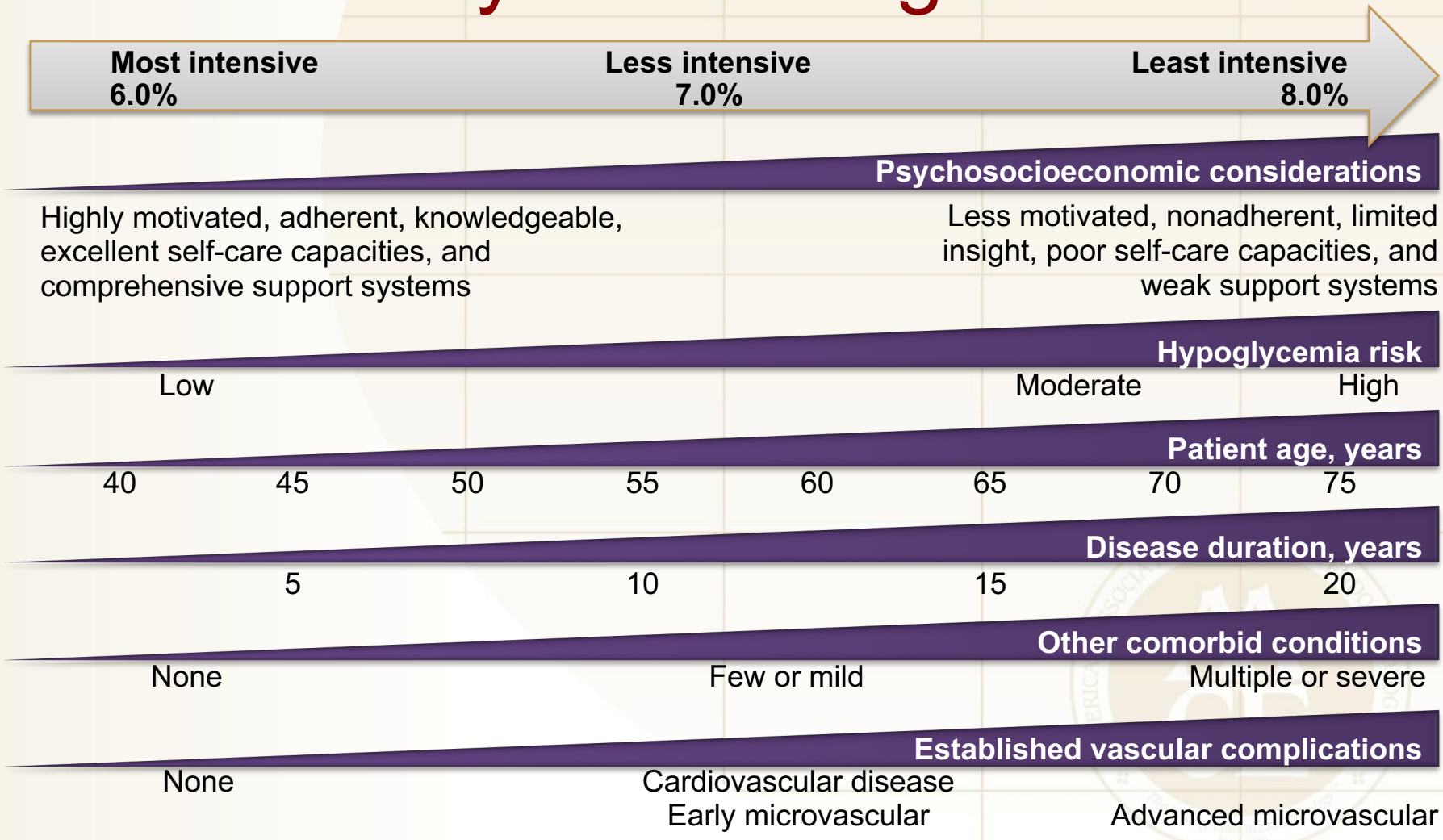
Parameter	Treatment Goal for Nonpregnant Adults
A1C (%)	Individualize targets: • ≤6.5 if it can be achieved without substantial hypoglycemia or other unacceptable consequences • >6.5% to 8% for those at risk*
FPG (mg/dL)	<110
2- hour PPG (mg/dL)	<140

*As long as patient remains free of polydipsia, polyuria, polyphagia, or other symptoms of hyperglycemia. Factors indicating a higher A1C target include

- Risk for hypoglycemia
- History of severe hypoglycemia
- Limited life expectancy
- Long-standing T2D in which the A1C goal has been difficult to attain despite intensive efforts

Handelsman Y, et al. *Endocr Pract*. 2015;21(suppl 1):1-87. Garber AJ, et al. *Endocr Pract*. 2018;24:91-120.

Algorithm for Individualizing Glycemic Targets



Ismail-Beigi F, Moghissi E, et al. *Ann Intern Med*. 2011;154:554-559.

ADA-Recommended Glucose Goals

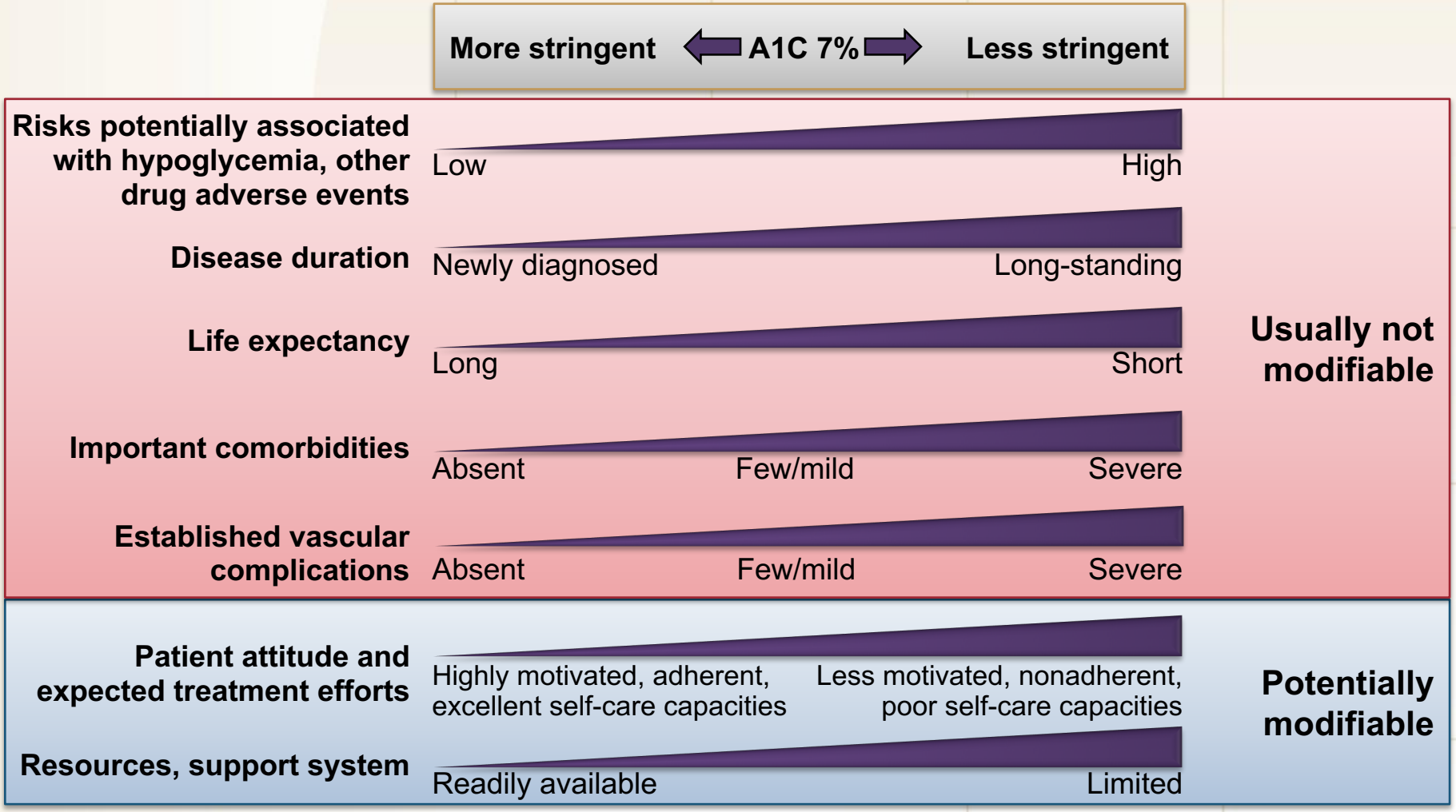
Parameter	Treatment Goal for Nonpregnant Adults
A1C (%)	Individualize • <7.0% for most nonpregnant adults • <6.5 if it can be achieved without significant hypoglycemia or other adverse effects of treatment* • <8% for those at risk†
Preprandial glucose (mg/dL)	80-130
Peak postprandial glucose (mg/dL)	<180

*Appropriate patients
- Short duration of diabetes
- T2D treated only with lifestyle or metformin
- Long life expectancy
- No significant cardiovascular disease

†At risk patients
- History of severe hypoglycemia
- Limited life expectancy
- Advanced micro- or macrovascular complications
- Extensive comorbid conditions
- Long-standing T2D in which A1C goal has been difficult to attain despite intensive efforts

ADA. *Diabetes Care*. 2018;41:S55-S64.

ADA-Recommended Approach to Management of Hyperglycemia



ADA. *Diabetes Care*. 2018;41:S55-S64.

Risk Factors for Hypoglycemia

Well- Known Risks

- Use of insulin secretagogues or insulin therapy in any of the following settings:
  - Missed or irregular meals
  - Advanced age
  - Longer duration of diabetes
  - Impaired awareness of hypoglycemia
  - Exercise
  - Taking greater than the prescribed medication dose
  - Excessive alcohol intake
  - Preexisting impairment, or sudden worsening, of renal or hepatic function

Less Well-Known Risks

- Female sex
- African-American race
- Lower education level

Amiel SA, et al. *Diabet Med*. 2008;25:245-254.
ADA. *Diabetes Care.* 2005;28:1245-1249.

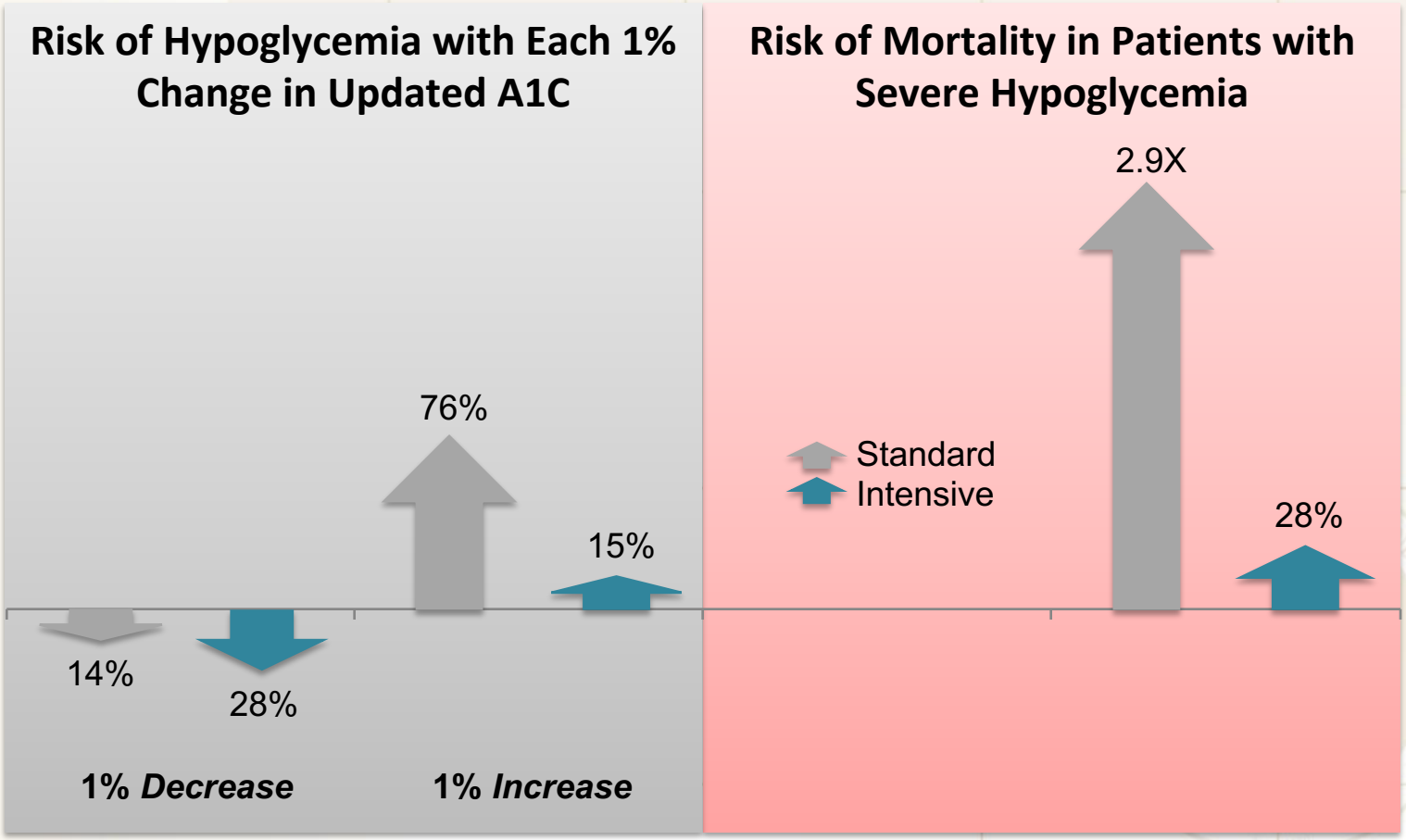
Potential Consequences of Hypoglycemia

- Neurogenic symptoms
  - Tremor, palpitations, anxiety, sweating, hunger (weight gain), paresthesias
- Neuroglycopenia morbidity
  - Cognitive impairment, psychomotor abnormalities, abnormal behavior, seizure, coma, mortality (brain death)
- Rebound hyperglycemia, brittle diabetes
- Barrier to glycemic control and adherence to treatment secondary to fear of hypoglycemia
- Greater risk of dementia
- Prolonged QT interval with increased risk of dysrhythmias, sudden death
- Harm to property or to others (eg, if driving)

Cryer PE. *J Clin Invest*. 2007;117:868-870.
Cryer PE. *Diabetes Care*. 2003;26:1902-1912.

Hypoglycemia and Mortality

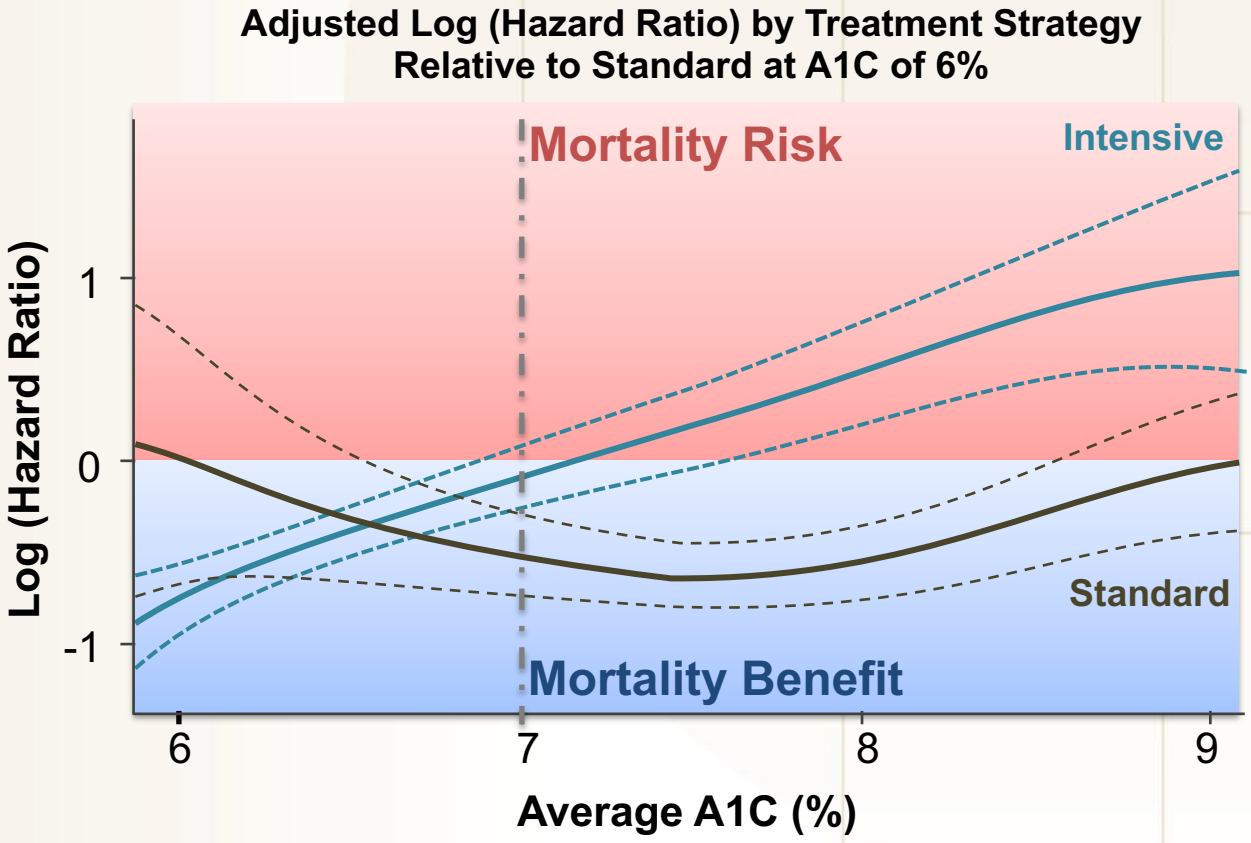
ACCORD Posthoc Analysis



Miller ME, et al. *BMJ*. 2010;340:b5444-b5444.

Glucose Control and Mortality

ACCORD Posthoc Analysis



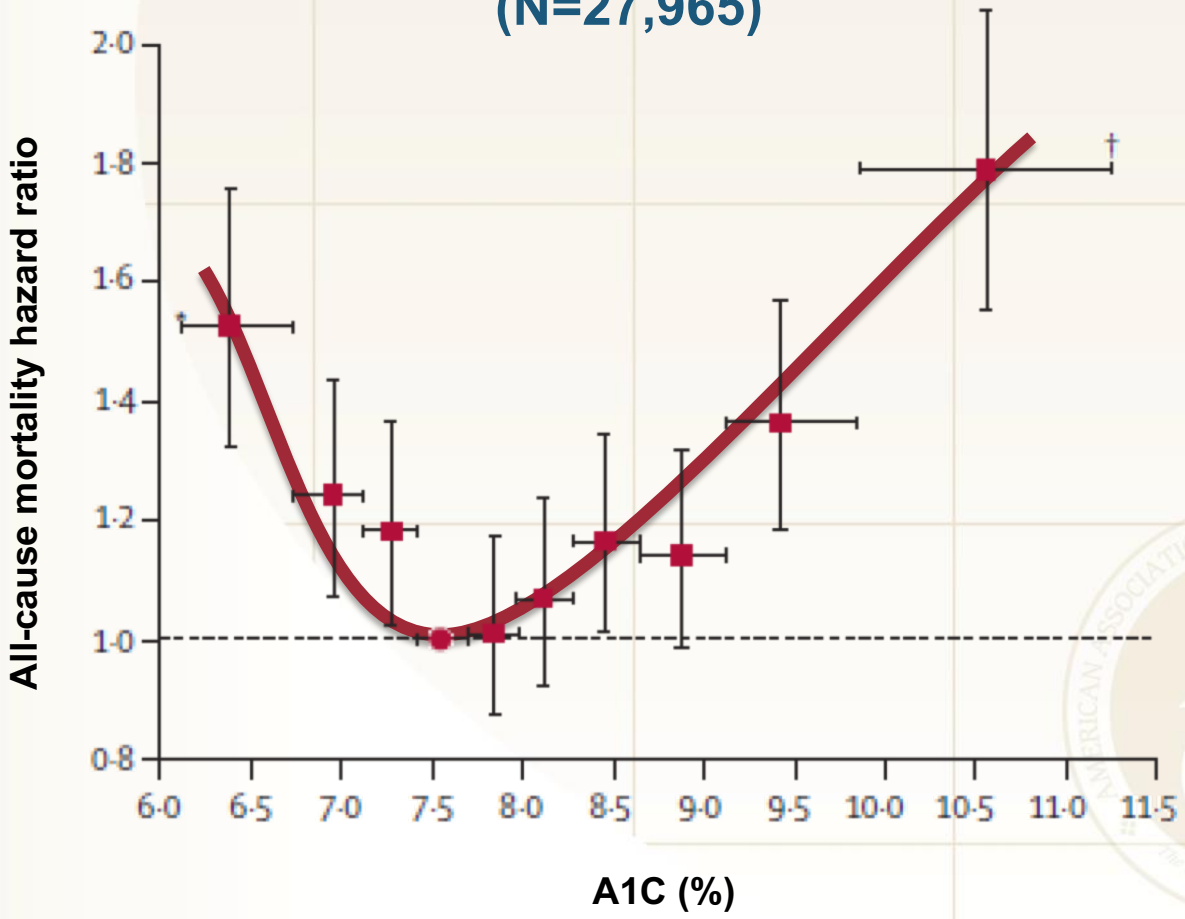
Risk increase with each 1% increase in A1C

	P Value
66%	<0.0001
14%	0.17

Riddle MC, et al. *Diabetes Care*. 2010;33:983-990.

A1C and Mortality in Clinical Practice

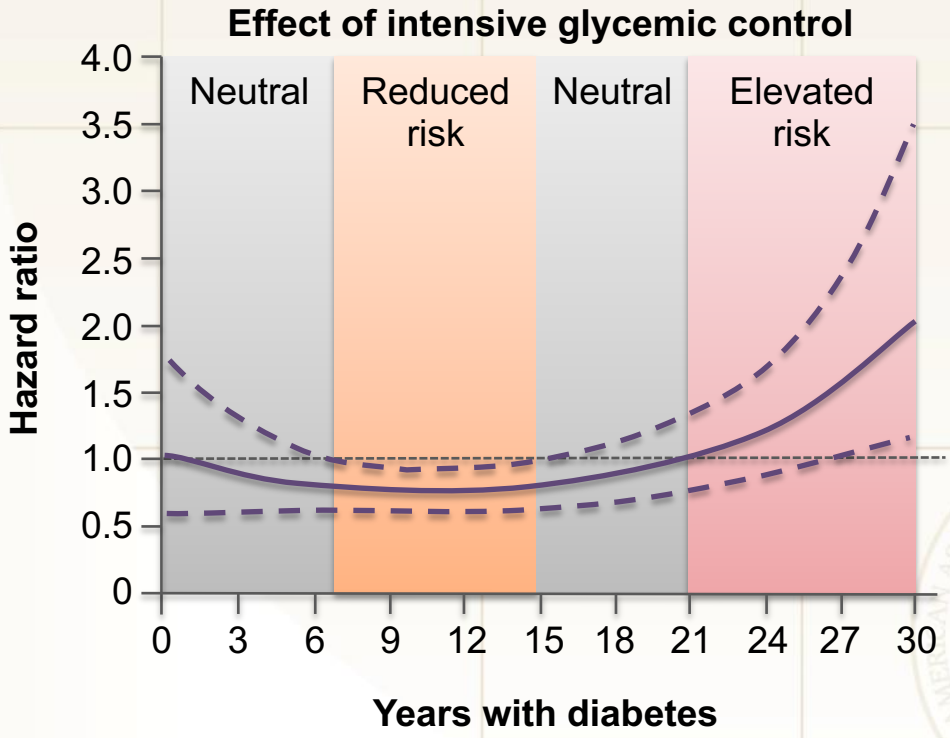
Retrospective Cohort Study
(N=27,965)



Currie CJ, et al. *Lancet.* 2010;375:481-489.

Macrovascular Benefits of Glycemic Control Depend on Duration of Diabetes

Veterans Affairs Diabetes Trial



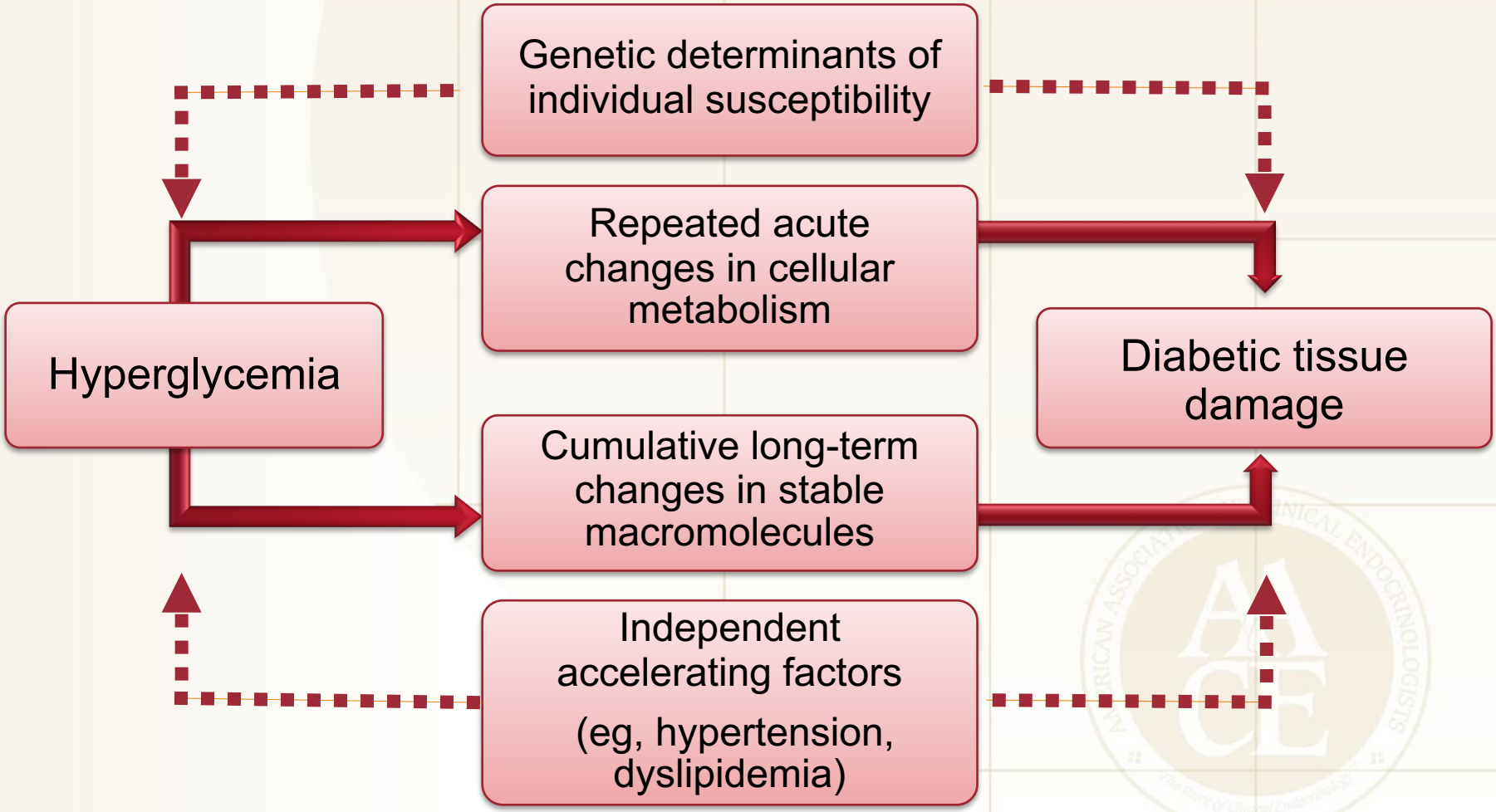
VADT, Veterans Affairs Diabetes Trial.

Duckworth WC, et al. *J Diabetes Complications*. 2011;25:355-361.

Type 2 Diabetes Glucose Goals and Complications Management

MICROVASCULAR COMPLICATIONS

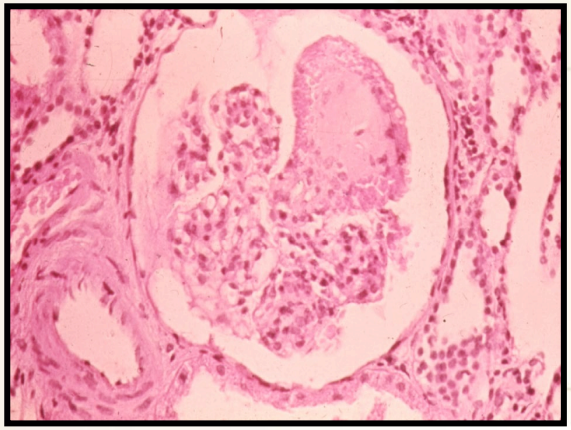
Hyperglycemia-Induced Tissue Damage: General Features



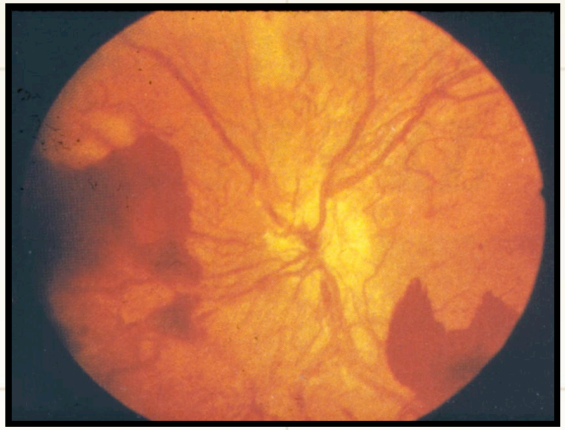
Brownlee M. *Diabetes.* 2005;54:1615-1625.

Microvascular Complications of Diabetes

Nephropathy

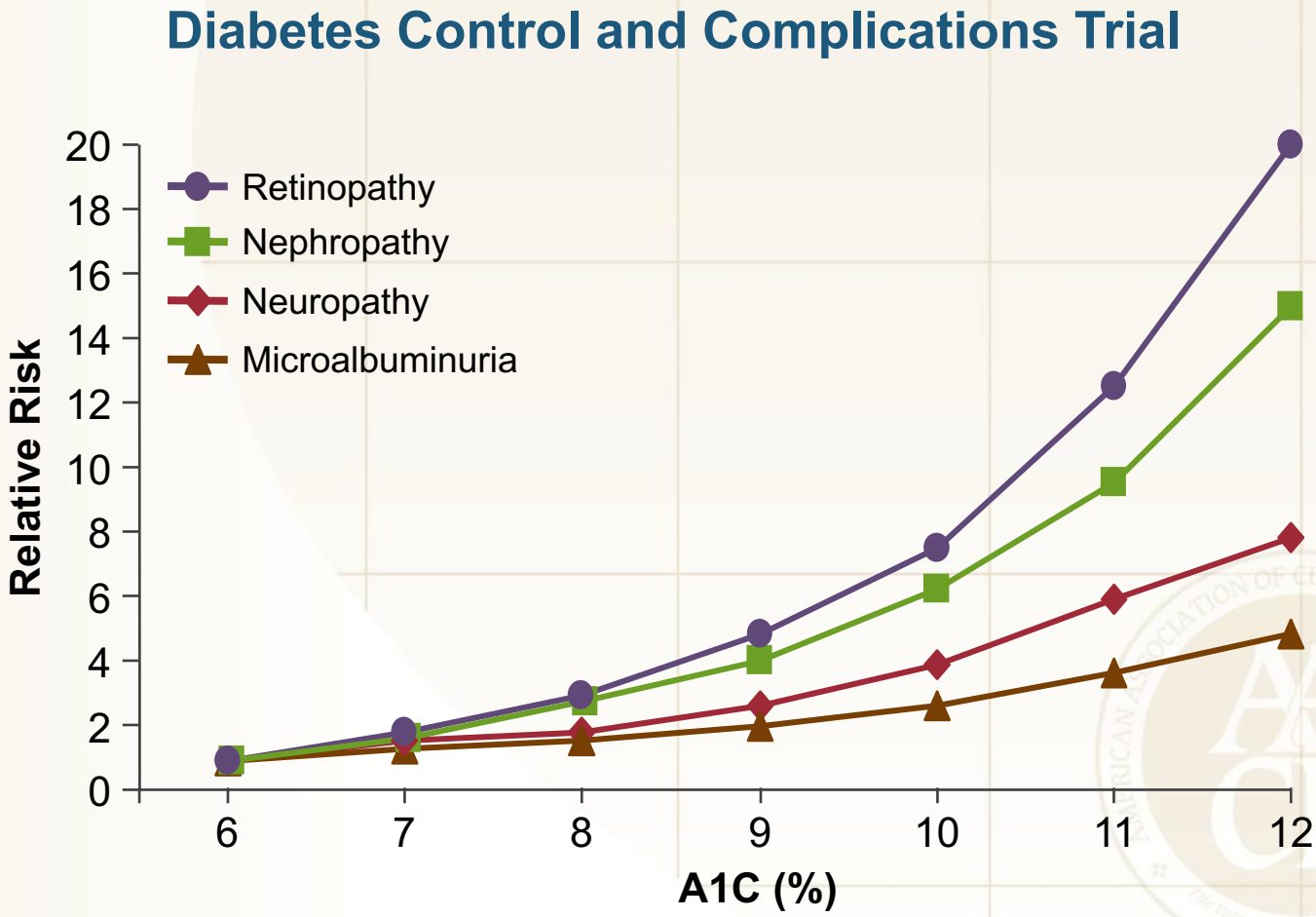


Retinopathy



Neuropathy

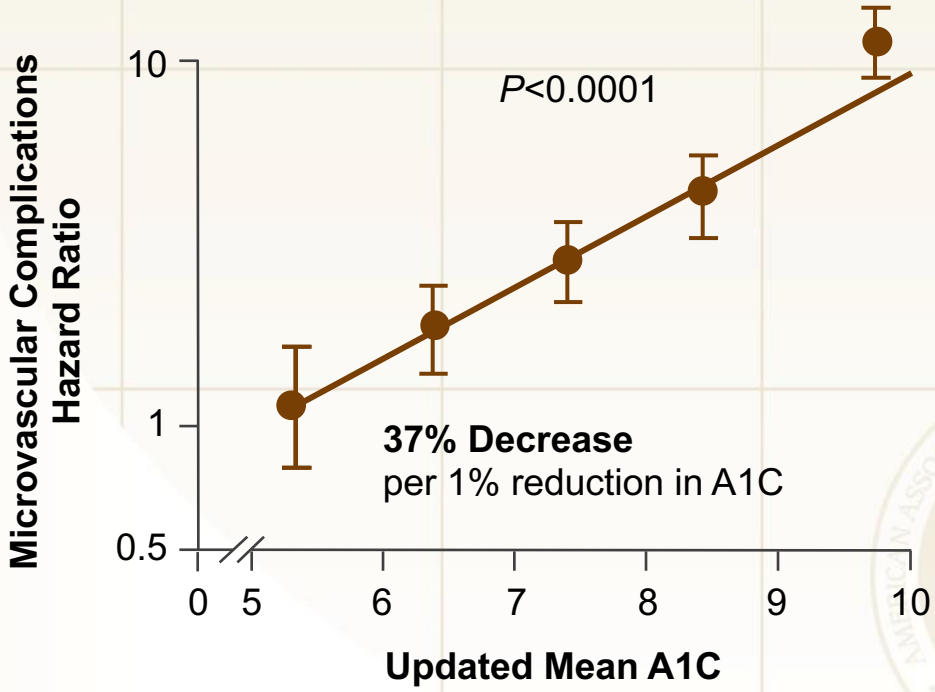
Microvascular Complications Increase With Increasing A1C



Skyler JS. *Endocrinol Metab Clin North Am*. 1996;25:243-254.

Reducing A1C Reduces Microvascular Risk

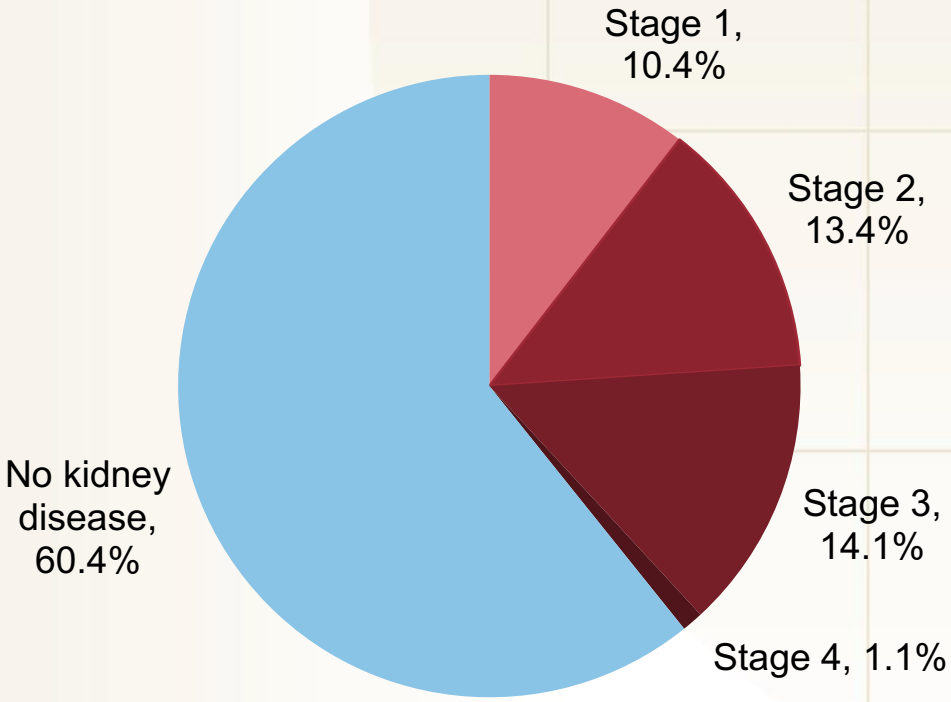
United Kingdom Prospective Diabetes Study



Stratton IM, et al. *BMJ*. 2000;321:405-412.

Prevalence of CKD in Diagnosed Diabetes

Diabetic Kidney Disease Is the Leading Cause of Kidney Failure in the United States



NKF Stage	Description	GFR
1	Kidney damage* with normal or ↑ GFR	≥90
2	Kidney damage* with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure or ESRD	<15 or dialysis

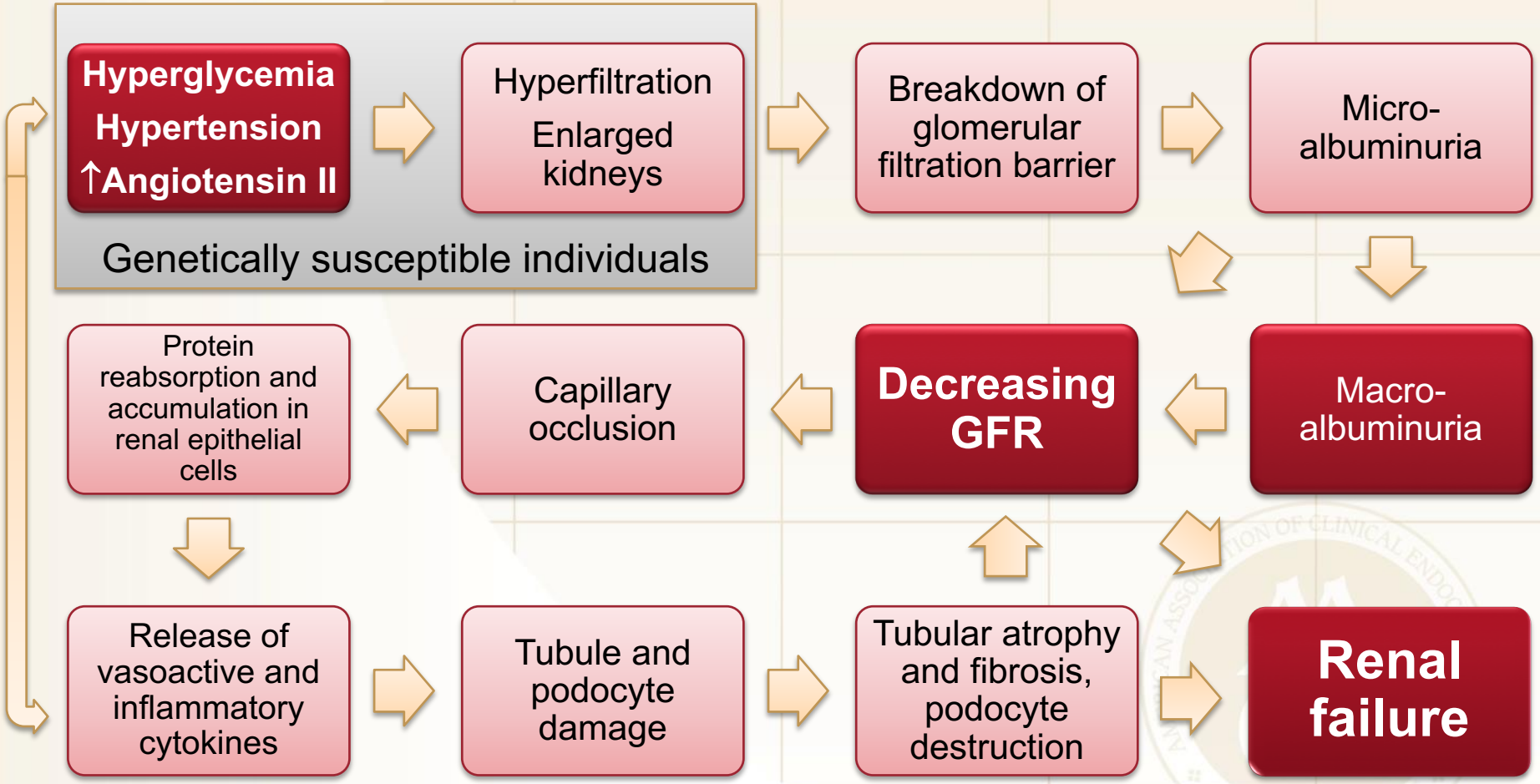
*Pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

ESRD, end-stage renal disease; GFR, glomerular filtration rate (mL/min/1.73 m^2); NKF, National Kidney Foundation.

CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.

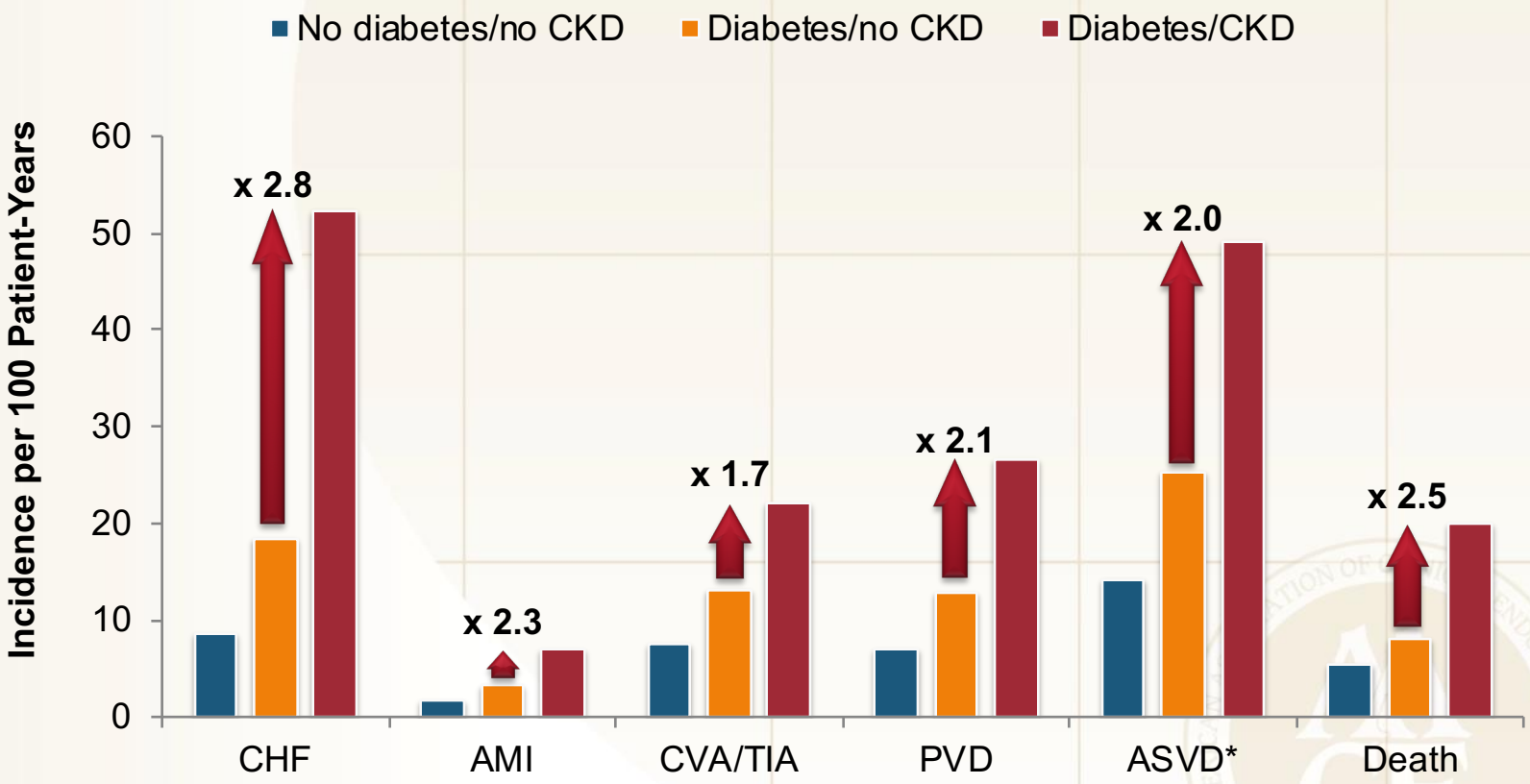
Plantinga LC, et al. *Clin J Am Soc Nephrol*. 2010;5:673-682.

Development of Diabetic Nephropathy



Radbill B, et al. *Mayo Clin Proc*. 2008;83:1373-1381.
Remuzzi G, Bertani T. *N Engl J Med*. 1998;339:1448-1456.

CV Risk Increases With Comorbid Diabetes and CKD

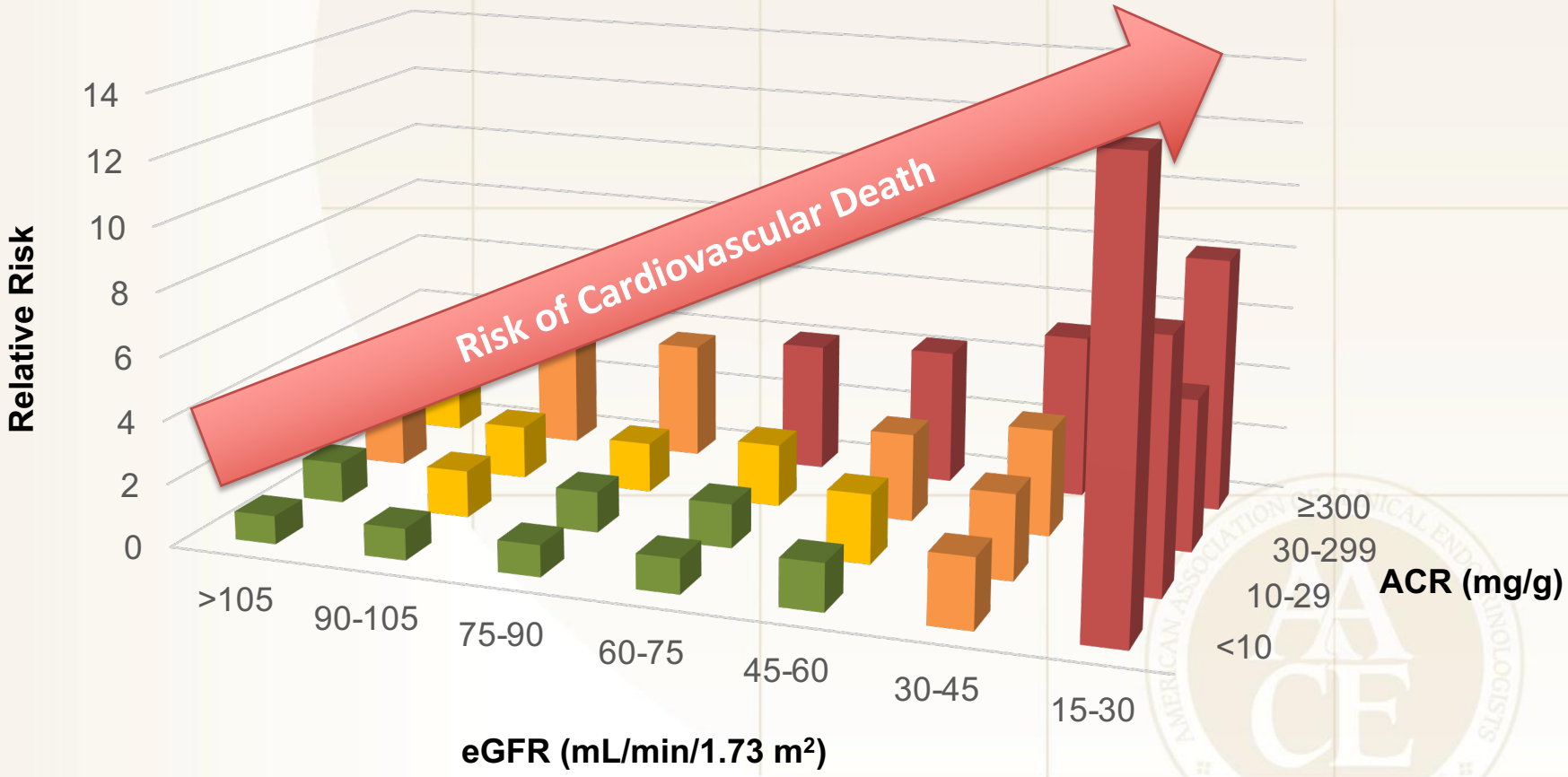


AMI, acute myocardial infarction; ASVD, atherosclerotic vascular disease; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PVD, peripheral vascular disease.

*ASVD was defined as the first occurrence of AMI, CVA/TIA, or PVD.

Foley RN, et al. *J Am Soc Nephrol*. 2005;16:489-495.

Risk of Cardiovascular Mortality with Decreasing eGFR and Increasing Albuminuria



ACR = albumin-creatinine ratio; eGFR = estimated glomerular filtration rate.

Handelsman Y, et al. *Endocr Pract*. 2015;21(suppl 1):1-87. NKF. *Kidney Int Suppl*. 2013;3:1-150.

KDIGO CKD Classification by Relative Risk

				Albuminuria stages (mg/g)				
				A1		A2	A3	
				Optimal and high normal		High	Very high and nephrotic	
				<10	10-29	30-299	300-1999	≥2000
GFR stages (mL/min per 1.73 m² body surface area)	G1	High and optimal	>105	Very low	Very low	Low	Moderate	Very high
			90-104					
	G2	Mild	75-89	Very low	Very low	Low	Moderate	Very high
			60-74					
	G3a	Mild to moderate	45-59	Low	Low	Moderate	High	Very high
	G3b	Moderate to severe	30-44	Moderate	Moderate	High	High	Very high
	G4	Severe	15-29	High	High	High	High	Very high
	G5	Kidney failure	<15	Very high	Very high	Very high	Very high	Very high

Levey AS, et al. *Kidney Int*. 2011;80:17-28.

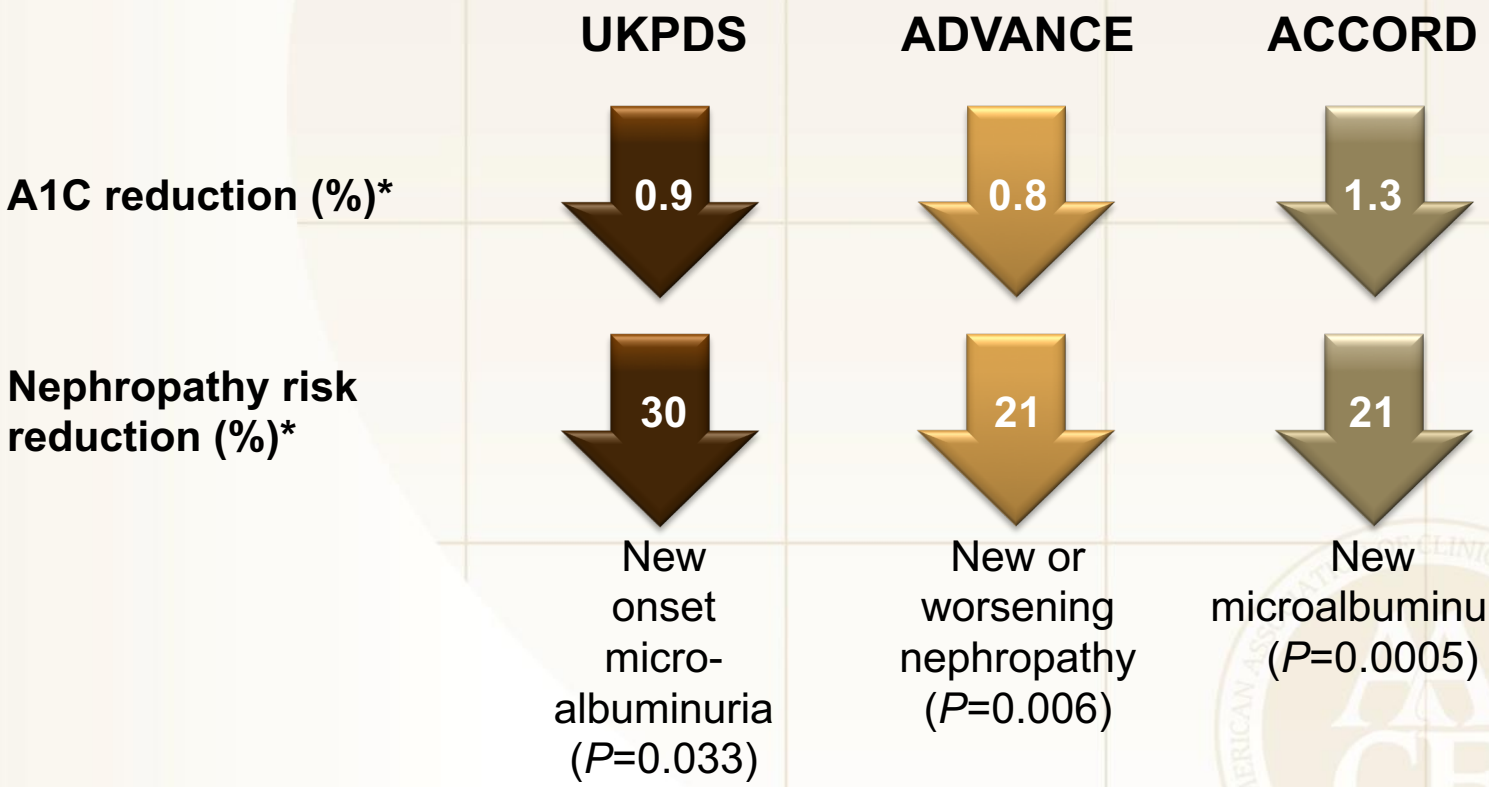
Staging and Monitoring of CKD in Diabetes

GFR categories (mL/min/1.73 m²) Description and range	Previous NKF CKD stage	Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category			Persistent albuminuria categories Description and range		
					A1	A2	A3
					Normal to mildly increased	Moderately increased	Severely increased
					<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	1	G1	Normal or high	≥90	**1 if CKD**	**1**	**2**
	2	G2	Mildly decreased	60-89	**1 if CKD**	**1**	**2**
	3	G3a	Mild to moderately decreased	45-59	**1**	**2**	**3**
		G3b	Moderately to severely decreased	30-44	**2**	**3**	**3**
	4	G4	Severely decreased	15-29	**3**	**3**	**4+**
	5	G5	Kidney failure	<15	**4+**	**4+**	**4+**

CKD = chronic kidney disease; GFR = glomerular filtration rate; NKF = National Kidney Foundation.

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

Reducing A1C Reduces Nephropathy Risk in T2D



*Intensive vs standard glucose control.

UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853.
ADVANCE Collaborative Group. *N Engl J Med*. 2008;358:2560-2572.
Ismail-Beigi F, et al. *Lancet*. 2010;376:419-430.

Management of Diabetic Nephropathy

- Optimal control of blood pressure, glucose, and lipids
- Smoking cessation
- RAAS blockade
  - ACE inhibitor, ARB, or renin inhibitor
  - Do not combine RAAS blocking agents
  - Monitor serum potassium
- Nephrologist referral
  - Atypical presentation
  - Rapid decline in eGFR or albuminuria progression
  - Stage 4 CKD

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAAS = renin angiotensin aldosterone system.

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

DKD Risk Factor Management

Risk Factor	Goal	Management Recommendation
Hyperglycemia	Individualized A1C goals ≤6.5% for most (AACE) ~7.0% (NKF)	Avoid metformin in moderate to severe CKD Consider need for dose reductions and/or risk of hypoglycemia and other renal-related AEs with other antidiabetic agents Do not target A1C <7% in patients at risk of hypoglycemia
Hypertension	BP ~130/80 mmHg	Use ACE inhibitor or ARB in combination with other antihypertensive agents as needed
Proteinuria		Use ACE inhibitor or ARB as directed
Dyslipidemia	LDL-C <100 mg/dL, <70 mg/dL an option for high risk	Statin +/- ezetimibe therapy recommended for all patients except those on dialysis (NKF) Fibrate dose reduction may be required

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.
National Kidney Foundation. *Am J Kidney Dis*. 2007;49(suppl 2):S1-S179.
National Kidney Foundation. *Am J Kidney Dis*. 2012;60:850-886.

Use of Antihyperglycemic Agents in Kidney Disease

Class: Agent(s)	Kidney Disease Recommendation
Amylin analog: pramlintide	Not recommended for CKD stage ≥4
Biguanide: metformin	Contraindicated if SCr >1.5 (men) or 1.4 (women) mg/dL
Bile acid sequestrant: colesevelam	No dosage adjustment
Dopamine-2 agonist: bromocriptine	Use with caution
DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin	Reduce dosage for alogliptin, saxagliptin and sitagliptin if CrCl <50 mg/dL
Glinides: nateglinide, repaglinide	Start at lowest effective dose if GFR <30 mL/min/1.73 m^2
GLP-1 receptor agonists: albiglutide, dulaglutide, exenatide, exenatide XR, liraglutide	Exenatide and liraglutide not recommended with GFR <30 mL/min/
α-Glucosidase inhibitors: acarbose, miglitol	Avoid if GFR <25 (miglitol) or <30 (acarbose) mL/min/1.73 m^2
Insulin: aspart, detemir, glargine, glulisine, inhaled, lispro, NPH, regular	Adjust dose based on patient response
SGLT inhibitors: canagliflozin, dapagliflozin, empagliflozin	Ineffective if GFR <30 mL/min/1.73 m^2
Sulfonylureas: glimepiride, glipizide, glyburide	No dose adjustment for glipizide; start glimepiride conservatively; avoid glyburide and all other SUs
Thiazolidinediones: pioglitazone, rosiglitazone	No dosage adjustment

Garber AJ, et al. *Endocr Pract*. 2017;23:207-238. ADA. *Diabetes Care*. 2017;40:S64-S74. Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87. National Kidney Foundation. *Am J Kidney Dis*. 2012;60:850-886.

Dietary Guidelines for DKD

	CKD Stage		
Macronutrient	1-2	1-4	3-4
Sodium		<2.3	
Total fat, % calories*		<30	
Saturated fat, % calories		<10	
Cholesterol, mg/day		<200	
Carbohydrate, % calories		50-60	
Protein, g/kg/day (% calories)	0.8 (~10)		0.6-0.8 (~8-10)
Phosphorus	1.7		0.8-1.0
Potassium	>4		2.4

*Adjust so total calories from protein, fat, and carbohydrate are 100%.

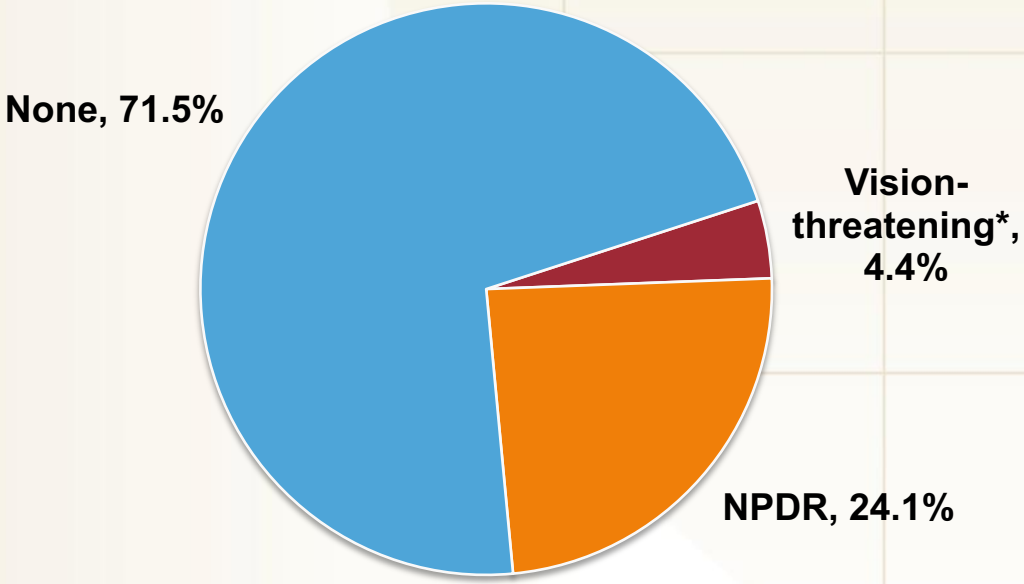
Emphasize such whole-food sources as fresh vegetables, whole grains, nuts, legumes, low-fat or nonfat dairy products, canola oil, olive oil, cold-water fish, and poultry.

Tailor dietary counseling to cultural food preferences.

National Kidney Foundation. *Am J Kidney Dis*. 2007;49(suppl 2):S1-S179.

Diabetic Retinopathy

NHANES 2005-2008
Adults Age ≥40 Years (N=1006)



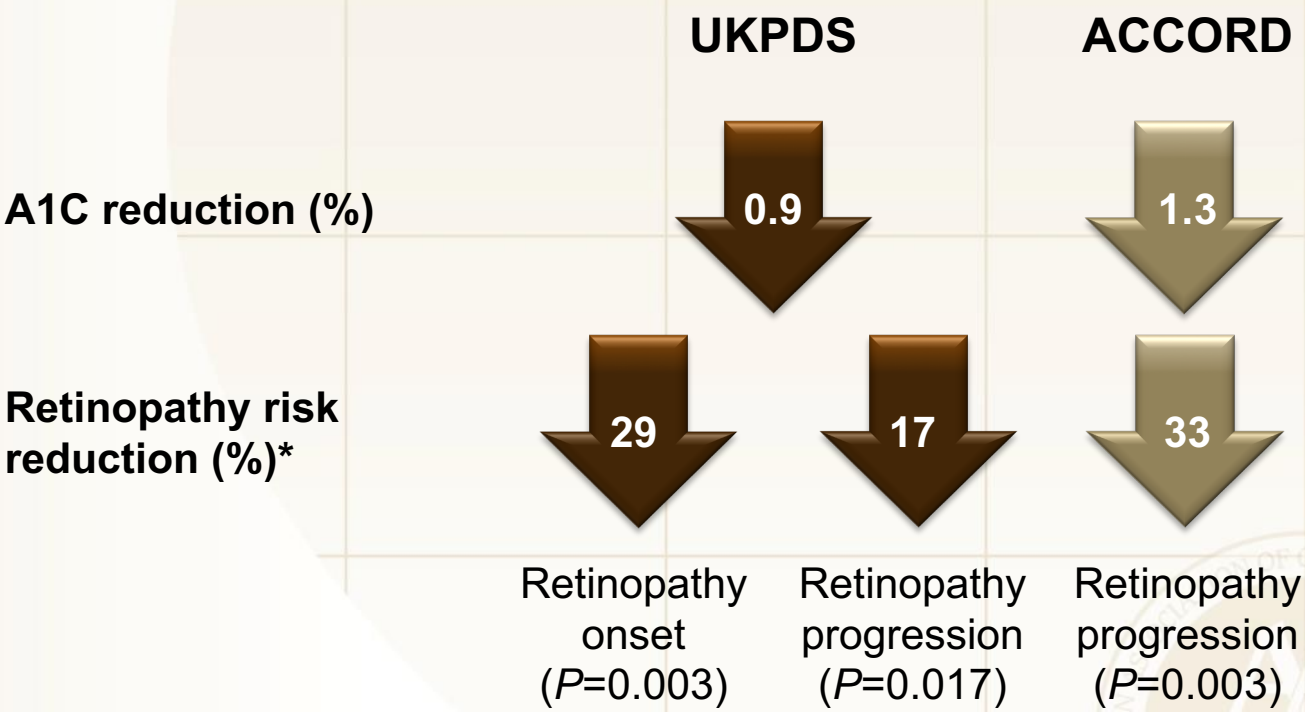
- All T2D patients should have a dilated eye examination by experienced ophthalmologist annually, starting at diagnosis to detect clinically significant retinopathy before vision is threatened
- Lesion types
  - Background or nonproliferative retinopathy
  - Macular edema
  - Preproliferative retinopathy
  - Proliferative retinopathy

*Severe NPDR, PDR, or clinically significant macular edema.

NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T2D, type 2 diabetes.

Zhang X, et al. *JAMA*. 2010;304:649-656.
Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Reducing A1C Reduces Retinopathy Progression in T2D



*Intensive vs standard glucose control.

UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853.
Ismail-Beigi F, et al. *Lancet*. 2010;376:419-430.
Chew EY, et al. *N Engl J Med*. 2010;363:233-244.

Assessment of Diabetic Retinopathy

- Annual dilated eye examination by experienced ophthalmologist or optometrist
- Begin assessment
  - 5 years after diagnosis of T1D
  - At diagnosis of T2D
- More frequent examinations for:
  - Pregnant women with DM during pregnancy and 1 year postpartum
  - Patients with diagnosed retinopathy
  - Patients with macular edema receiving active therapy

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

Diabetic Retinopathy Management

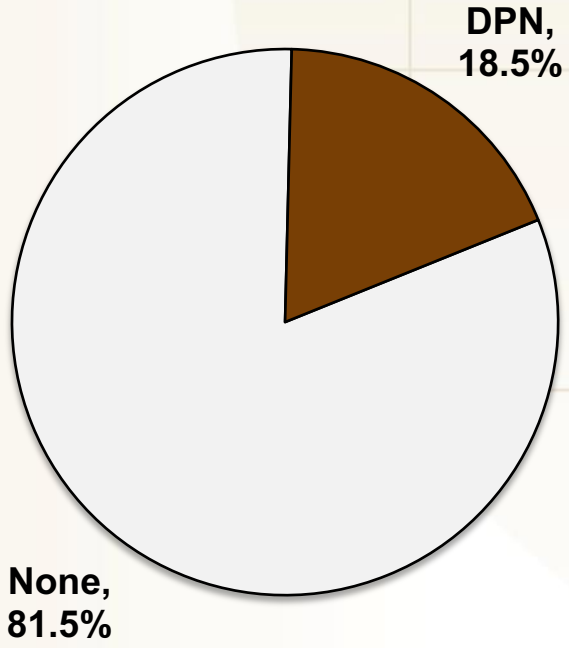
- Goal: detect clinically significant retinopathy before vision is threatened
- Annual dilated eye examination by experienced ophthalmologist, starting at diagnosis for all T2D patients

Lesion Type	Management Recommendation
Background or nonproliferative retinopathy	• Optimal glucose and blood pressure control
Macular edema	• Optimal glucose and blood pressure control • Ranibizumab injection therapy • Focused laser photocoagulation guided by fluorescein angiography
Preproliferative retinopathy	• Optimal glucose and blood pressure control • Panretinal scatter laser photocoagulation
Proliferative retinopathy	• Optimal glucose and blood pressure control • Panretinal scatter laser photocoagulation • Vitrectomy for patients with persistent vitreous hemorrhage or significant vitreous scarring and debris

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

Prevalence of Diabetic Neuropathy

NHANES 1999-2004
Adults With Diabetes, Age ≥40 Years
(N=559)



- Neuropathy is a heterogeneous disorder
- 70% to 100% of T2D patients may have at least mild damage to
  - Proximal nerves
  - Distal nerves
  - Somatic nerves
  - Autonomic nerves
- Neuropathy may be
  - Acute and self-limiting
  - Chronic and indolent

T2D, type 2 diabetes.

Gregg EW, et al. *Diabetes Res Clin Pract*. 2007;77:485-488.
Handelsman Y, et al. *Endocr Pract*. 2011;17(suppl 2):1-53.

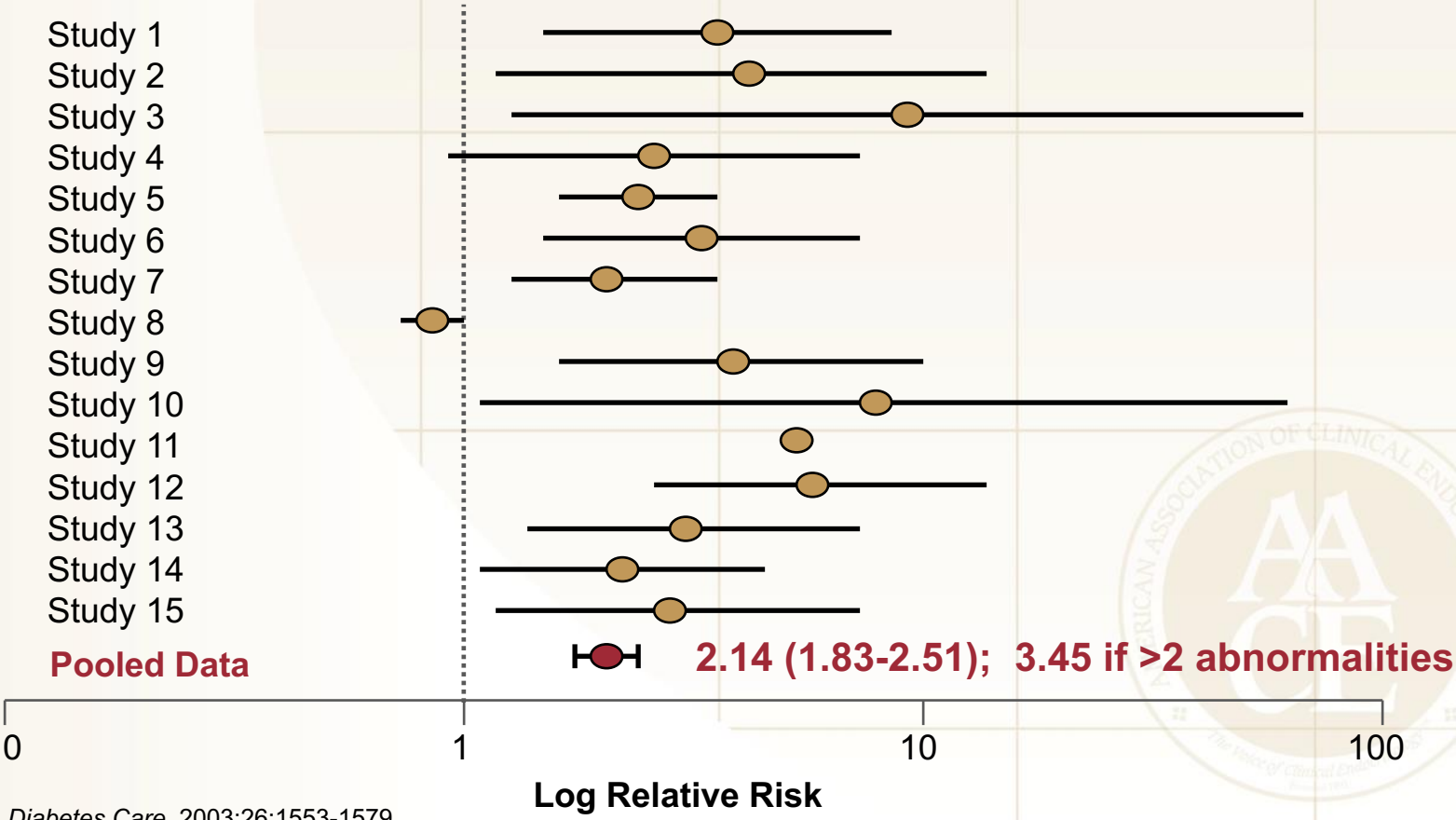
Causes of Death in Diabetic Autonomic Neuropathy

- Sudden unexplained
- Cardiac arrhythmia
- Silent myocardial infarction
  - More likely to die of heart attack
  - Greater incidence of cardiac failure
- Aspiration pneumonia
- Ulcers, amputations, gangrene
- Chronic renal failure

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

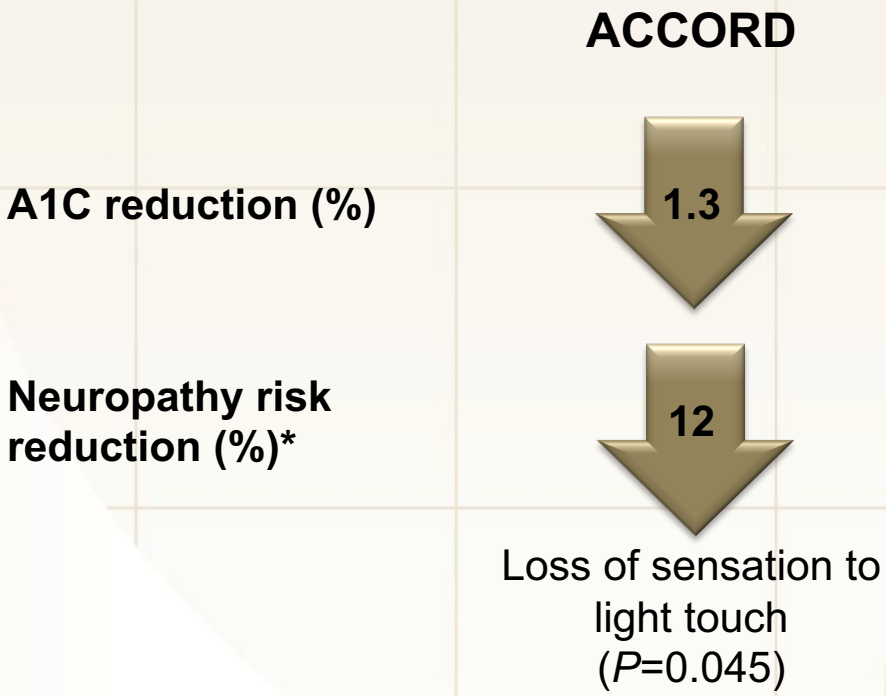
Relative Risk of Mortality from Cardiac Autonomic Neuropathy

Prevalence Rate Ratios and 95% CI from 15 Studies (*P*<0.0001; N=2900)



Vinik AI, et al. *Diabetes Care.* 2003;26:1553-1579.
Maser RE, et al. *Diabetes Care.* 2003;26:1895-1901.

Reducing A1C Reduces Neuropathy Risk in T2D



*Intensive vs standard glucose control.

Ismail-Beigi F, et al. *Lancet*. 2010;376:419-430.

Assessment of Diabetic Neuropathy

- Complete neurologic examination annually
- Begin assessment
  - 5 years after diagnosis of T1D
  - At diagnosis of T2D

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

Diabetic Neuropathy Evaluations and Tests

Foot inspection	Foot structure and deformities Skin temperature and integrity Ulcers Vascular status Pedal pulses Amputations
Neurologic testing	Loss of sensation, using 1 and 10-g monofilament Vibration perception using 128-Hz tuning fork Ankle reflexes Touch, pinprick, and warm and cold sensation
Painful neuropathy	May have no physical signs Diagnosis may require skin biopsy or other surrogate measure
Cardiovascular autonomic neuropathy	Heart rate variability with: • Deep inspiration • Valsalva maneuver • Change in position from prone to standing

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

Diabetic Neuropathy Management

All neuropathies	• Prevent by controlling blood glucose to individual targets • No therapies proven to reverse neuropathy once it is established • May slow progression by maintaining optimal glucose, blood pressure, and lipid control and using other interventions that reduce oxidative stress
Painful neuropathy	• Tricyclic antidepressants, anticonvulsants, serotonin reuptake inhibitors, or norepinephrine reuptake inhibitors
Large-fiber neuropathies	• Strength, gait, and balance training • Orthotics to prevent/treat foot deformities • Tendon lengthening for pes equinus • Surgical reconstruction • Casting
Small-fiber neuropathies	• Foot protection (eg, padded socks) • Supportive shoes with orthotics if needed • Regular foot inspection • Prevention of heat injury • Emollient creams

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

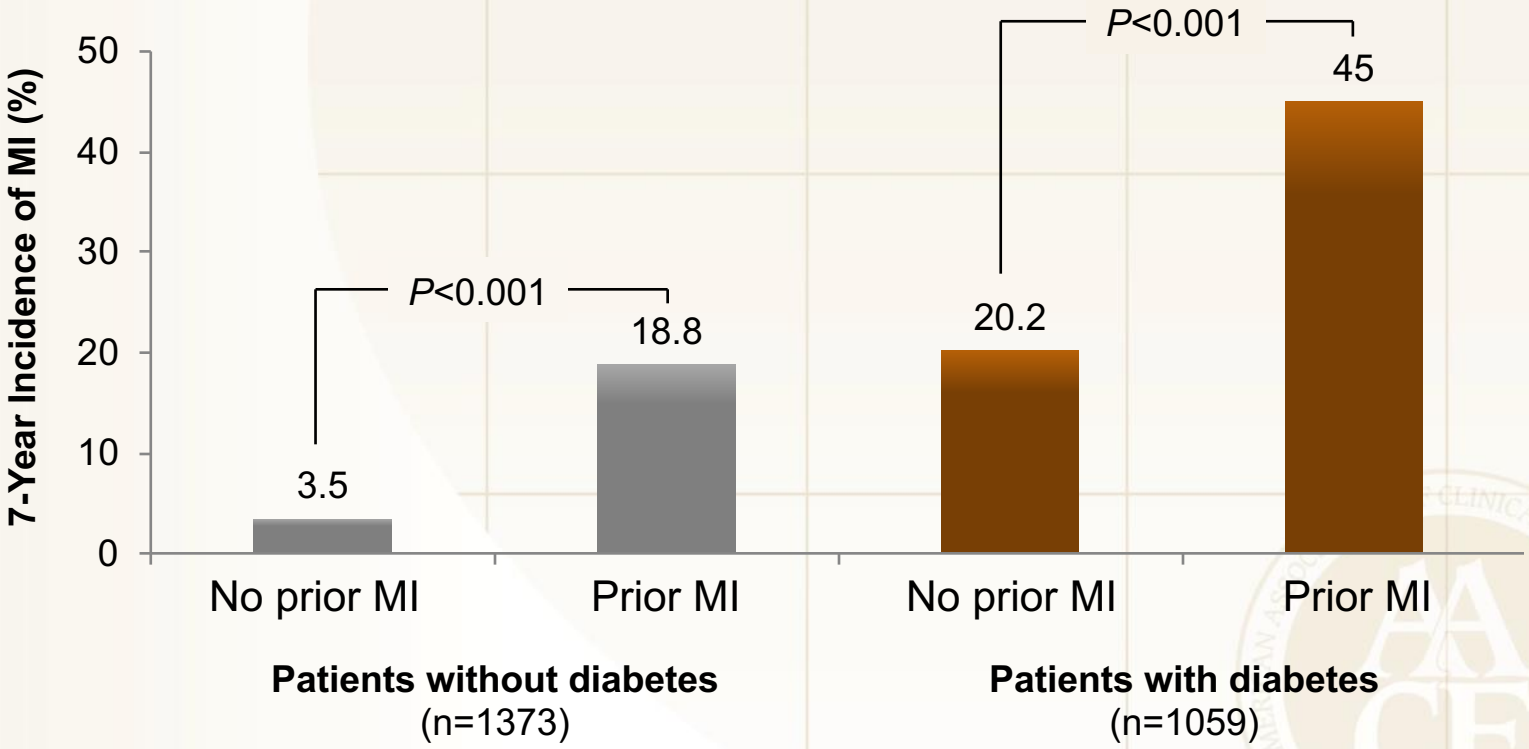
Type 2 Diabetes Glucose Goals and Complications Management

MACROVASCULAR COMPLICATIONS

Macrovascular Complications

- Cardiovascular disease
  - Coronary artery disease
  - Myocardial infarction
- Cerebrovascular disease (stroke)
- Peripheral vascular disease

Diabetes and Cardiovascular Risk

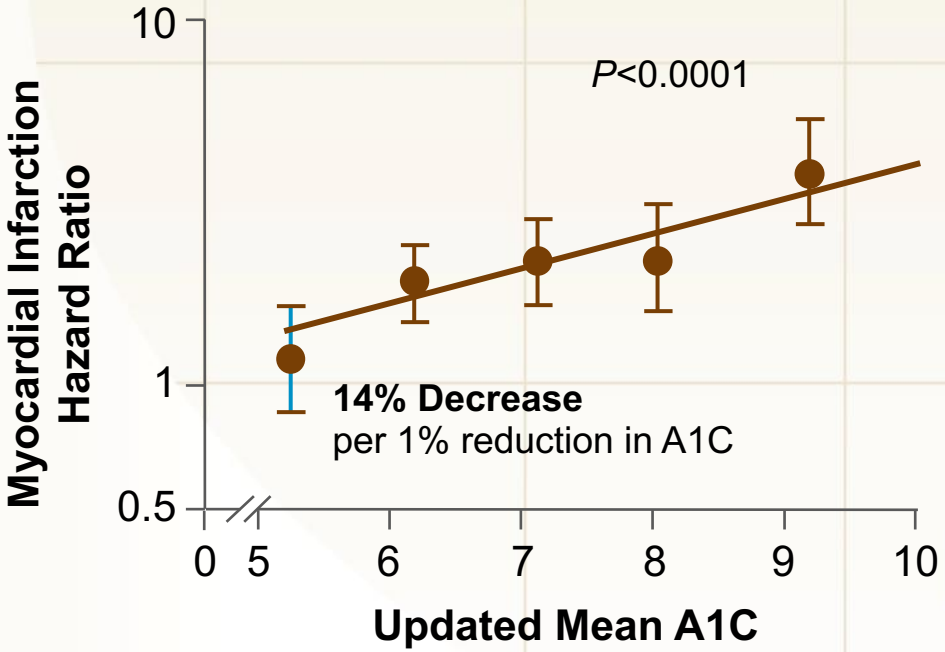


MI, myocardial infarction.

Haffner SM, et al. *N Engl J Med*. 1998;339:229-234.

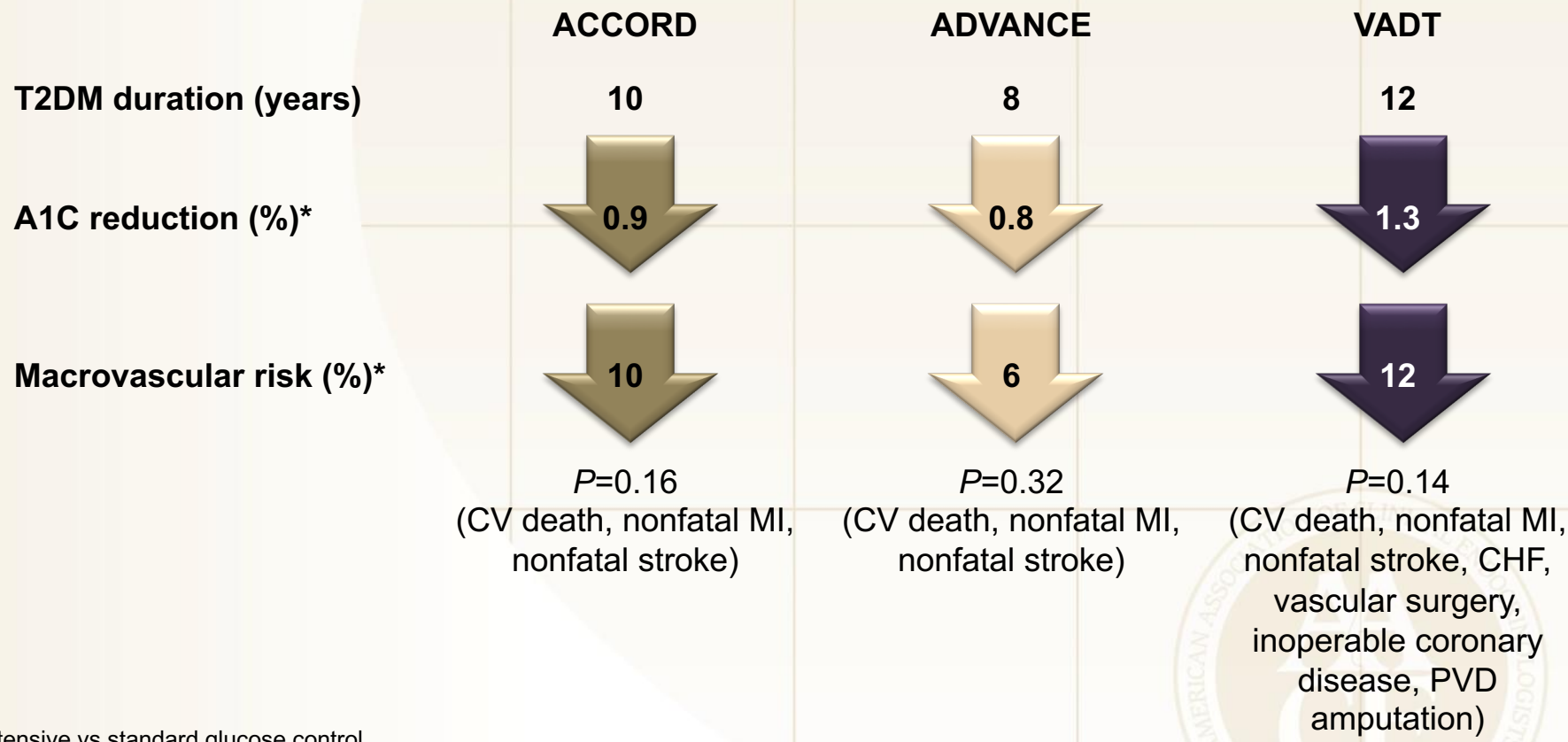
Lower A1C Is Associated With Lower Risk of Myocardial Infarction

United Kingdom Prospective Diabetes Study



Stratton IM et al. *BMJ*. 2000;321:405-412.

Effect of Intensive Glycemic Control on Macrovascular Risk in Older Patients With Longer Duration of Disease



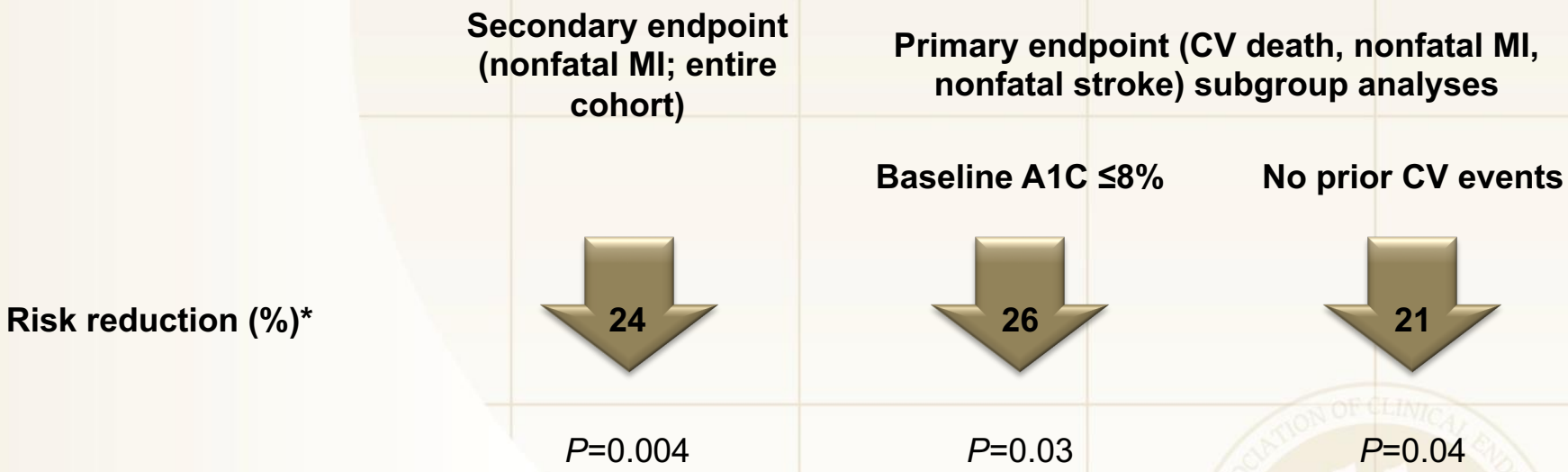
*Intensive vs standard glucose control.

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CHF, congestive heart failure; CV, cardiovascular; MI, myocardial infarction; PVD, peripheral vascular disease; VADT, Veterans Affairs Diabetes Trial.

ACCORD Study Group. *N Engl J Med*. 2008;358:2545-2559. ADVANCE Collaborative Group. *N Engl J Med*. 2008;358:2560-2572. Duckworth W, et al. *N Engl J Med*. 2009;360:129-139.

Intensive Glycemic Control May Have Macrovascular Benefit in Healthier People

Action to Control Cardiovascular Risk in Diabetes



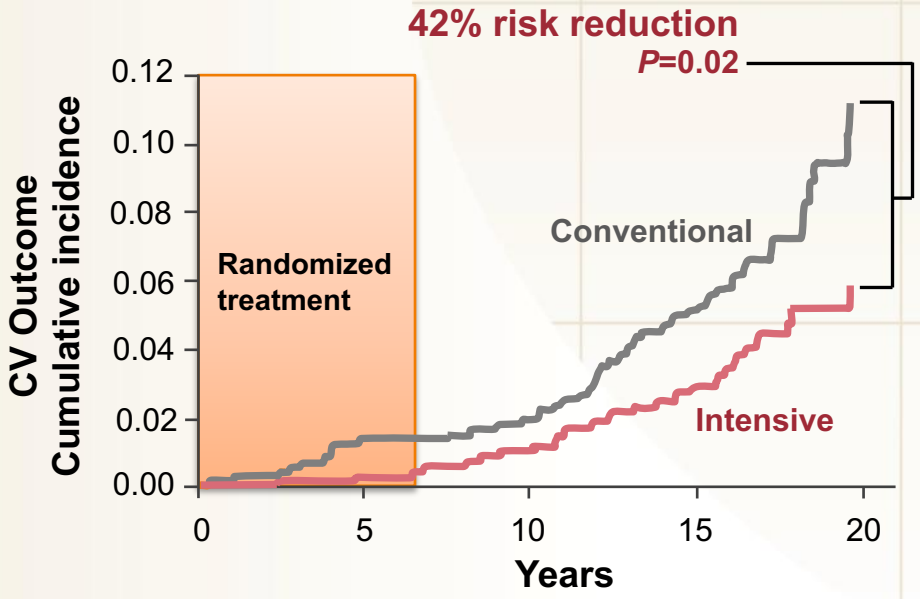
*Intensive vs standard glucose control.

CV, cardiovascular; MI, myocardial infarction.

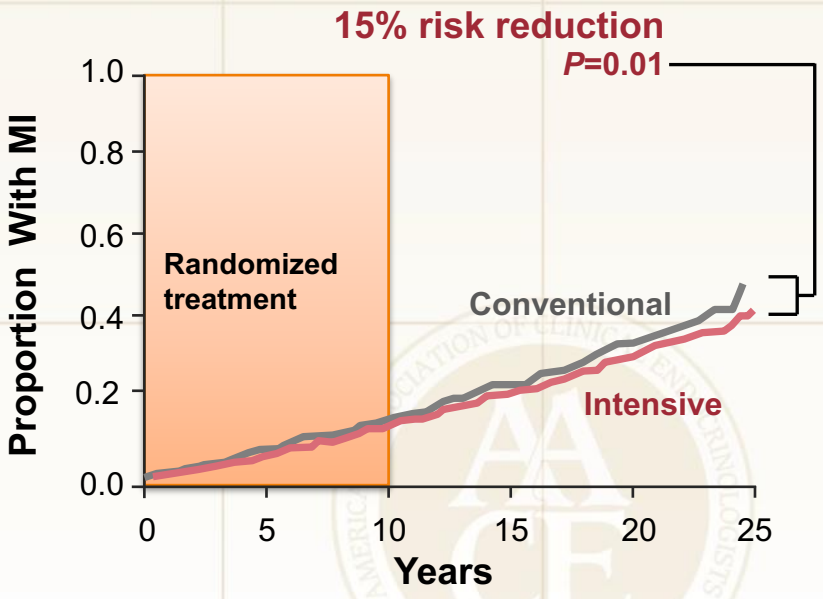
ACCORD Study Group. *N Engl J Med*. 2008;358:2545-2559.

Intensive Glycemic Control Reduces Long-term Macrovascular Risk

DCCT
T1D, 5-6 years duration (N=1441)



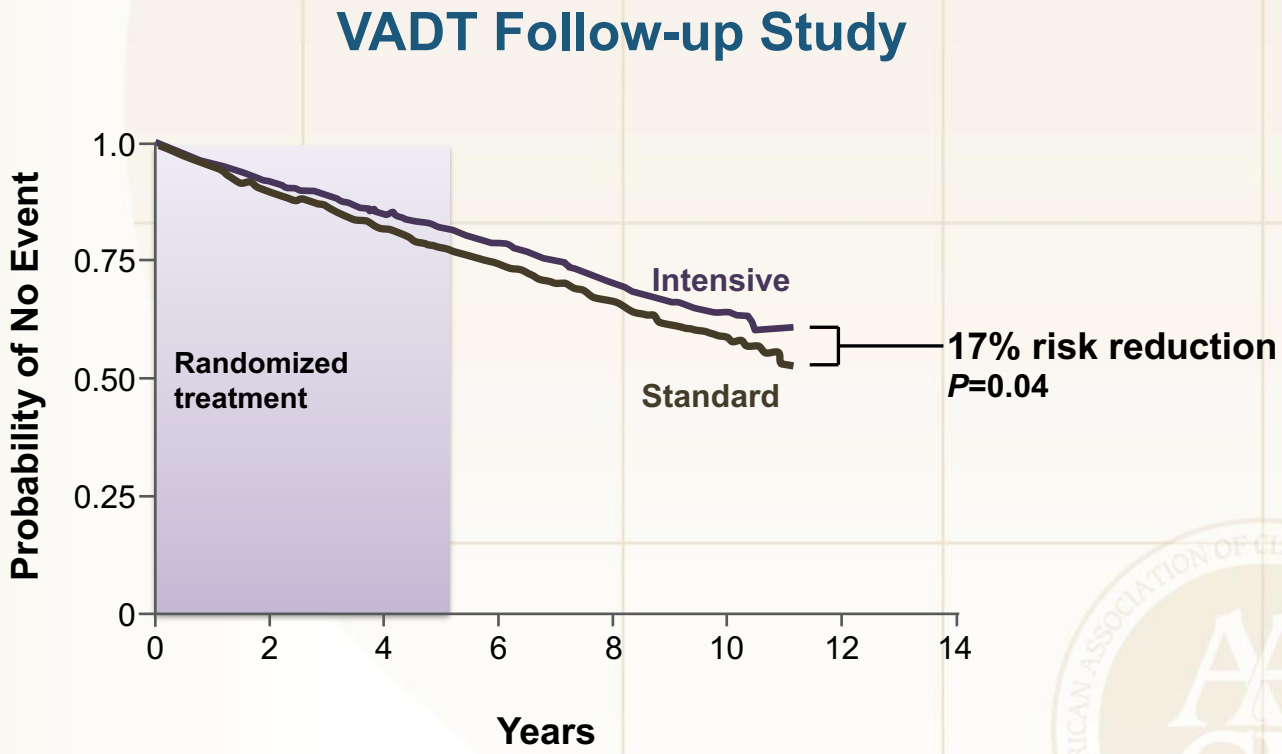
UKPDS
T2D, newly diagnosed (N=4209)



CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction; T1D, type 1 diabetes; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study.

Nathan DM, et al. *N Engl J Med*. 2005;353:2643-2653. Holman RR, et al. *N Engl J Med*. 2008;359:1577-1589.

Long-Term Effect of Intensive Glycemic Control on Macrovascular Risk

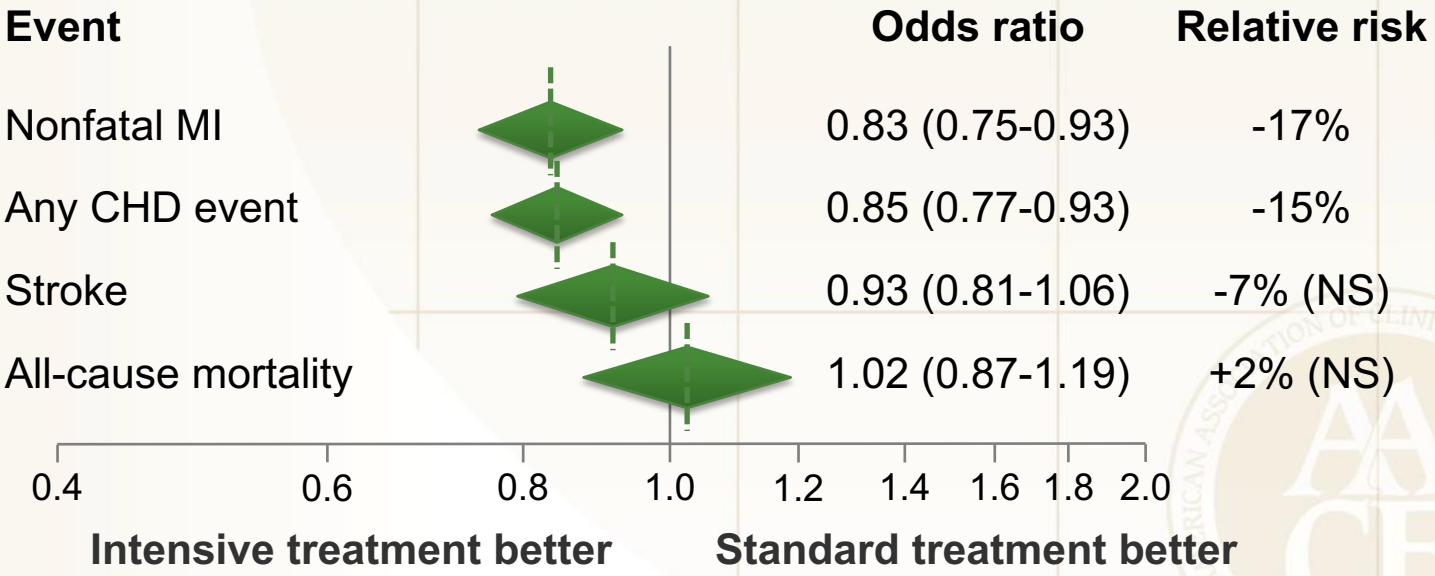


VADT, Veterans Affairs Diabetes Trial.

Hayward RA, et al. *N Engl J Med*. 2015;372:2197-2206.

Effects of Intensive Glucose Control on Macrovascular Risk in T2D

Meta-analysis of 5 Prospective RCTs Assessing Effect of Intensive Glucose Lowering on CV Outcomes (ACCORD, ADVANCE, PROactive, UKPDS, VADT)



ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; NS, not significant; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Ray KK, et al. *Lancet*. 2009;373:1765-1772.

Macrovascular Risk Reduction in Type 2 Diabetes

- Individualized glucose control
- Hypertension control
- Dyslipidemia control
- Smoking cessation
- Aspirin therapy
- Diagnosis and management of:
  - Autonomic cardiac neuropathy
  - Kidney disease

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