Complications of Type 2 Diabetes Mellitus Diabetologist perspective

Introductory Note

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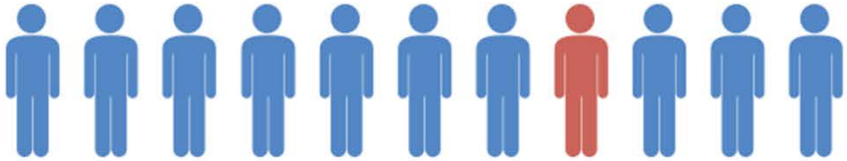
21-1-2018

Burden of Diabetes

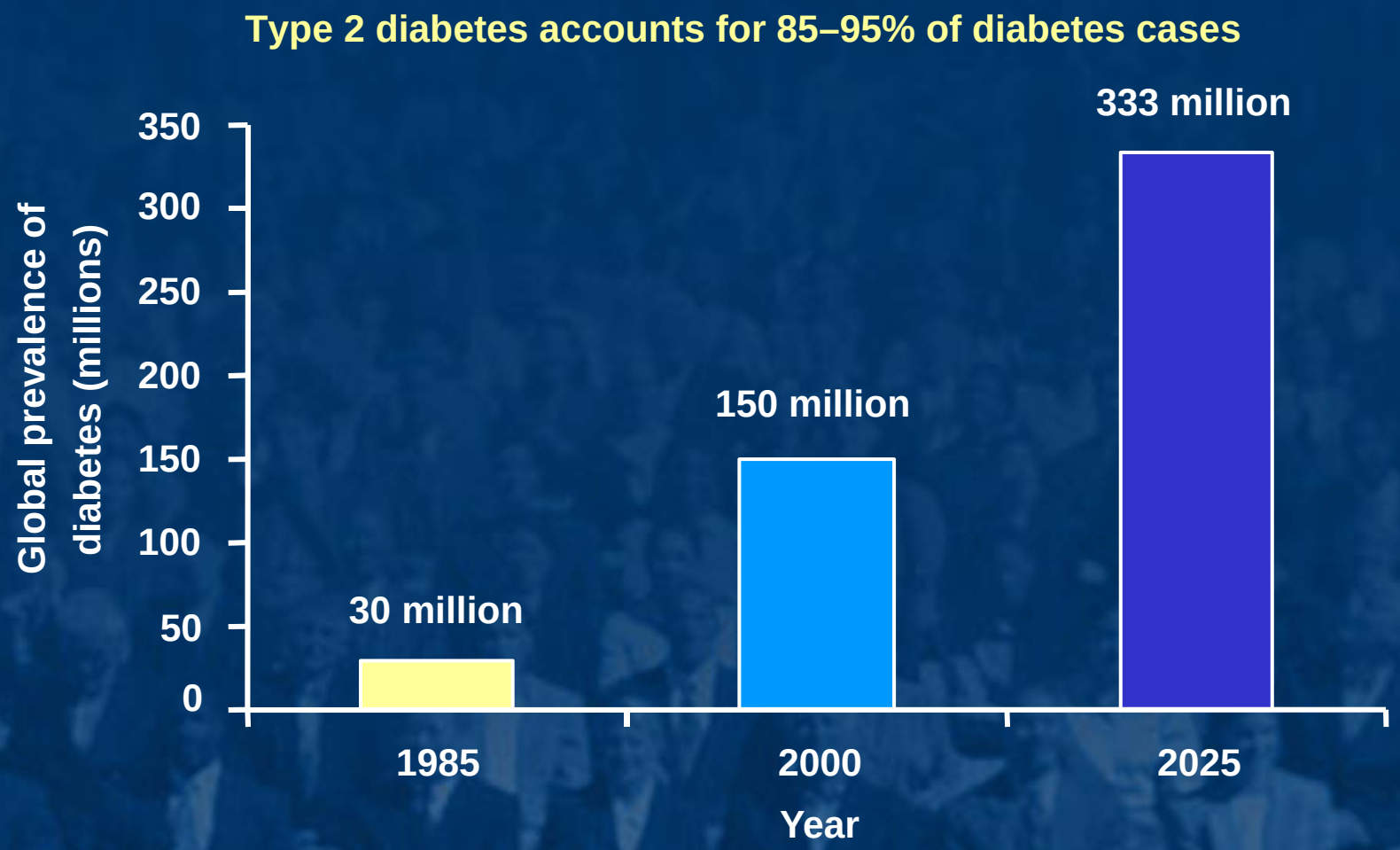
1 in 11 adults has diabetes (425 million)



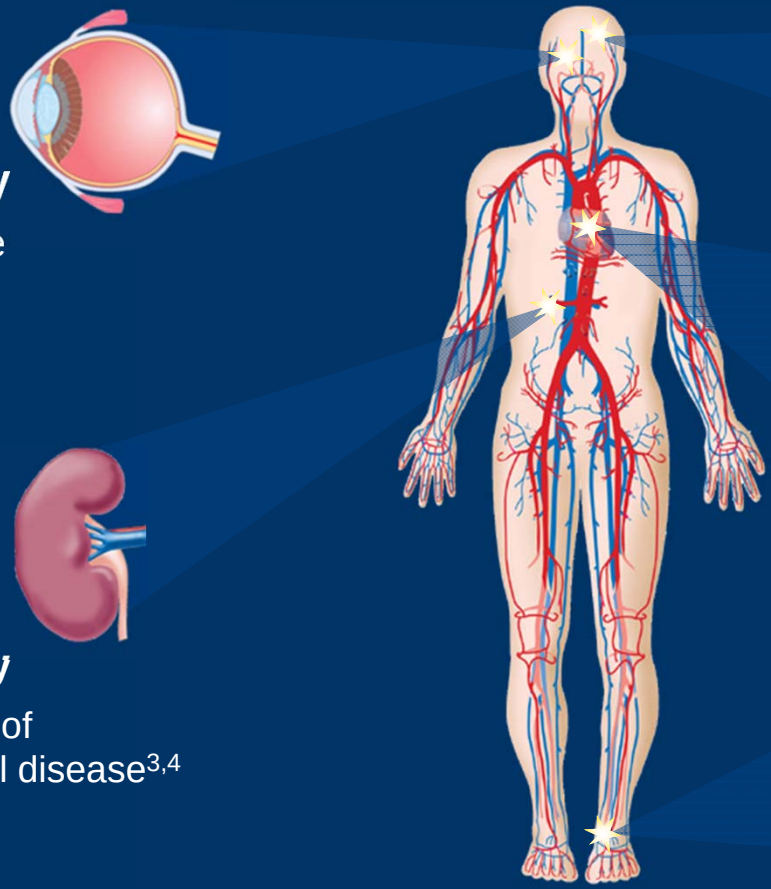
158.8 million people with diabetes live in the Western Pacific region - the highest number of all IDF regions

IDF Diabetes Atlas Eighth Edition 2017

Type 2 diabetes: a global call to action



Type 2 diabetes is associated with serious complications



Diabetic Retinopathy

Leading cause of blindness in adults[1,2]

Diabetic Nephropathy

Leading cause of end-stage renal disease[3,4]

Stroke

2- to 4-fold increase in cardiovascular mortality and stroke[5]

Cardiovascular Disease

8/10 individuals with diabetes die from CV events[6]

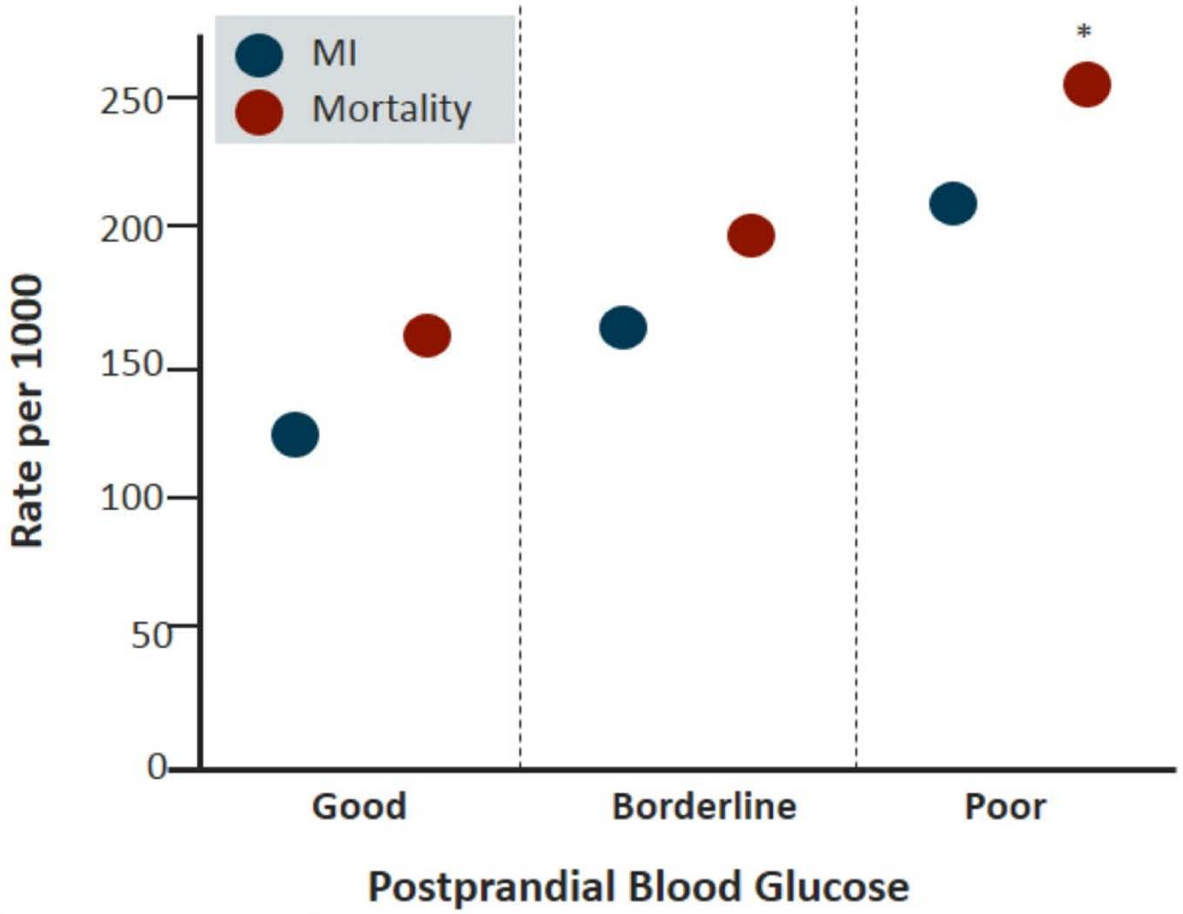
Diabetic Neuropathy

Leading cause of non-traumatic lower extremity amputations[7,8]

[1]UK Prospective Diabetes Study Group. *Diabetes Res* 1990; 13:1–11. [2]Fong DS, *et al. Diabetes Care* 2003; 26 (Suppl. 1):S99–S102. [3]The Hypertension in Diabetes Study Group. *J Hypertens* 1993; 11:309–317. [4]Molitch ME, *et al. Diabetes Care* 2003; 26 (Suppl. 1):S94–S98. [5]Kannel WB, *et al. Am Heart J* 1990; 120:672–676. [6]Gray RP & Yudkin JS. Cardiovascular disease in diabetes mellitus. In *Textbook of Diabetes* 2nd Edition, 1997. Blackwell Sciences. [7]King's Fund. *Counting the cost*. The real impact of non-insulin dependent diabetes. London: British Diabetic Association, 1996. [8]Mayfield JA, *et al. Diabetes Care* 2003; 26 (Suppl. 1):S78–S79.

T2DM as a Risk Factor for CVD

Chronically Elevated Glycemia, the Key Pathophysiologic Feature of T2DM, Is Itself Associated With Elevated CVD Risk

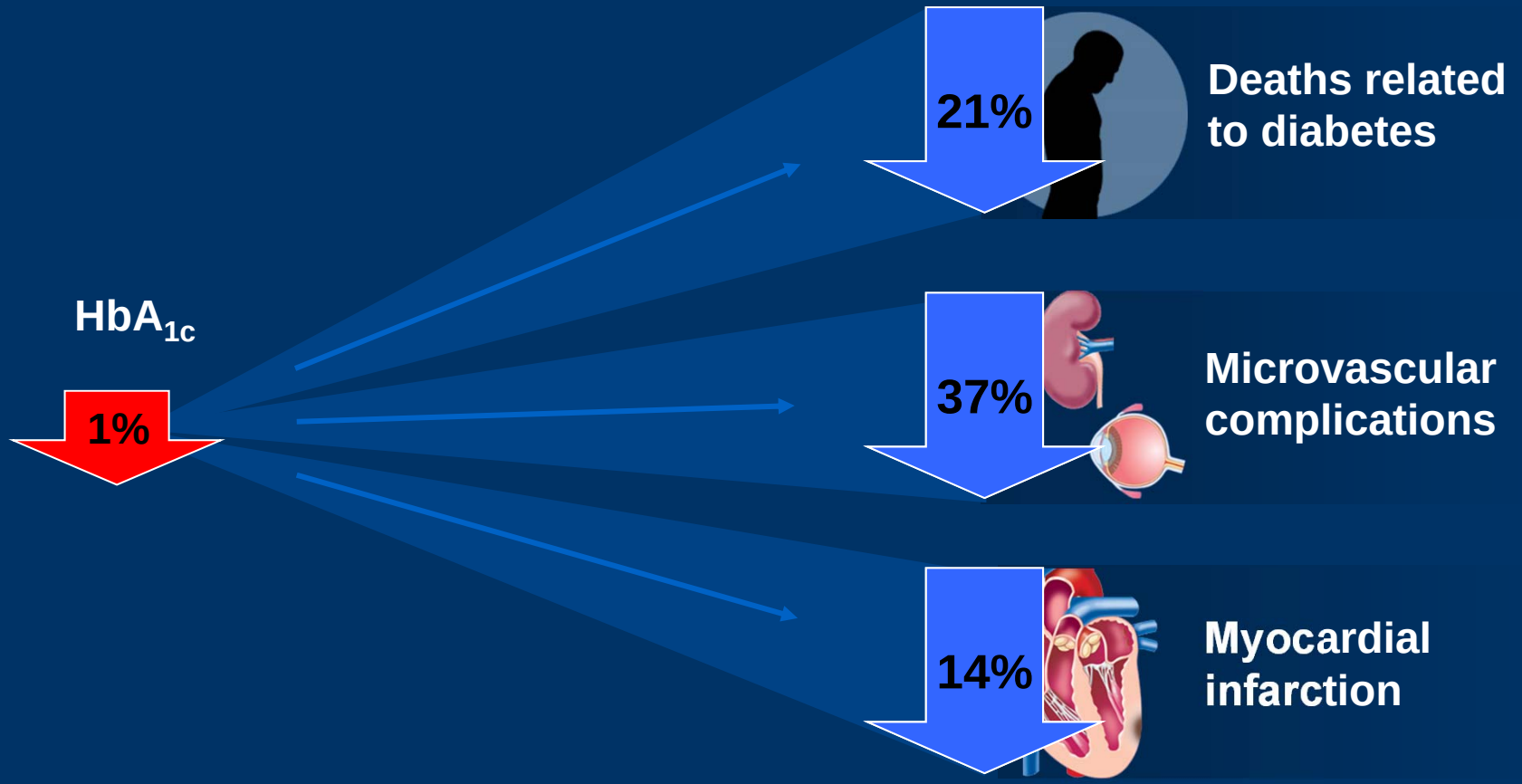


Poor glycemic control was associated with worsening CV outcomes in the long-term follow-up to the Diabetes Prevention Study

*$P < .05$ vs good control

Pistrosch F, et al. *Diabetes Care*. 2011;34(suppl 2):S128-S131.

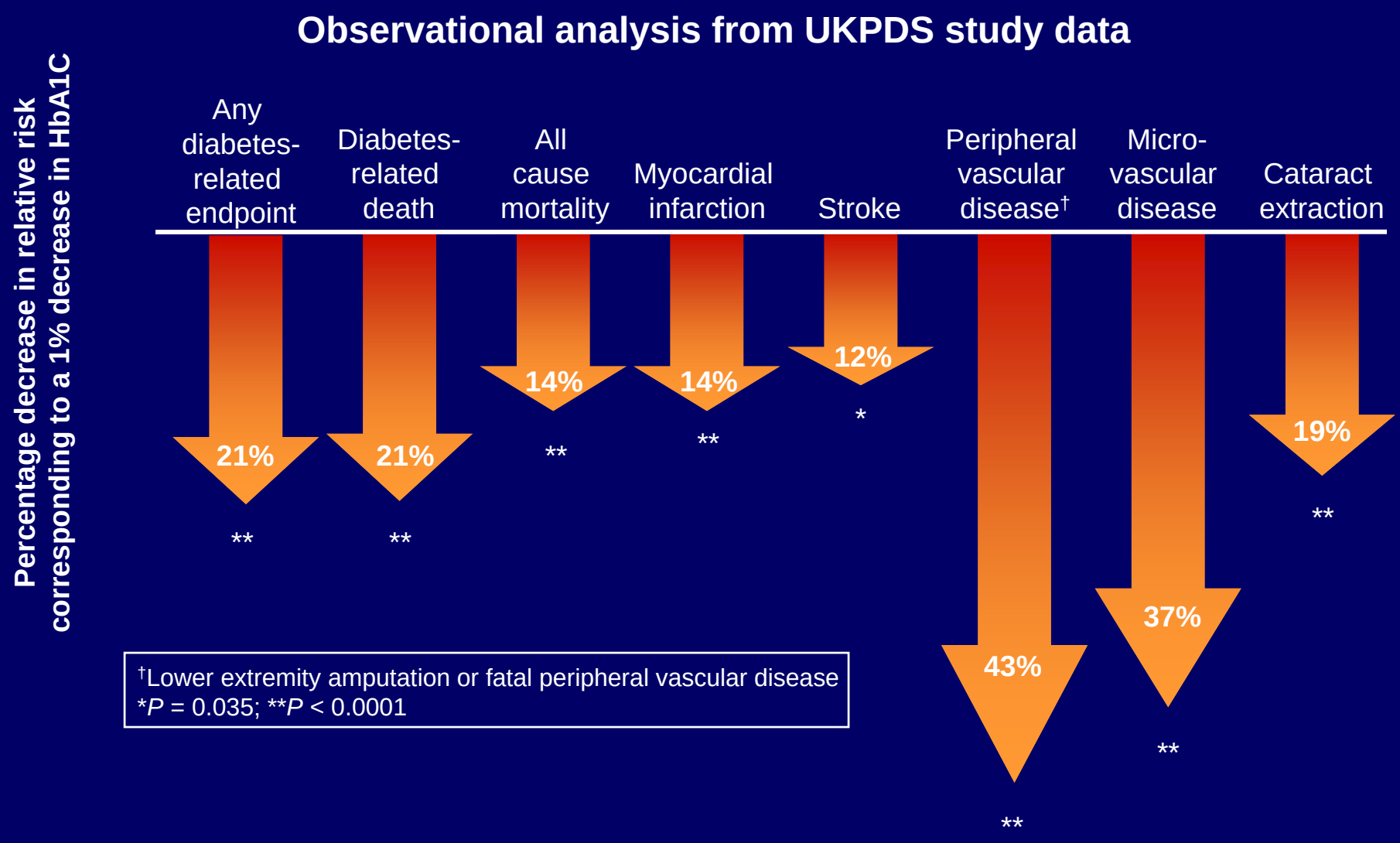
Lowering HbA_{1c} reduces the risk of complications



COMPLICATIONS ARE PREVENTABLE

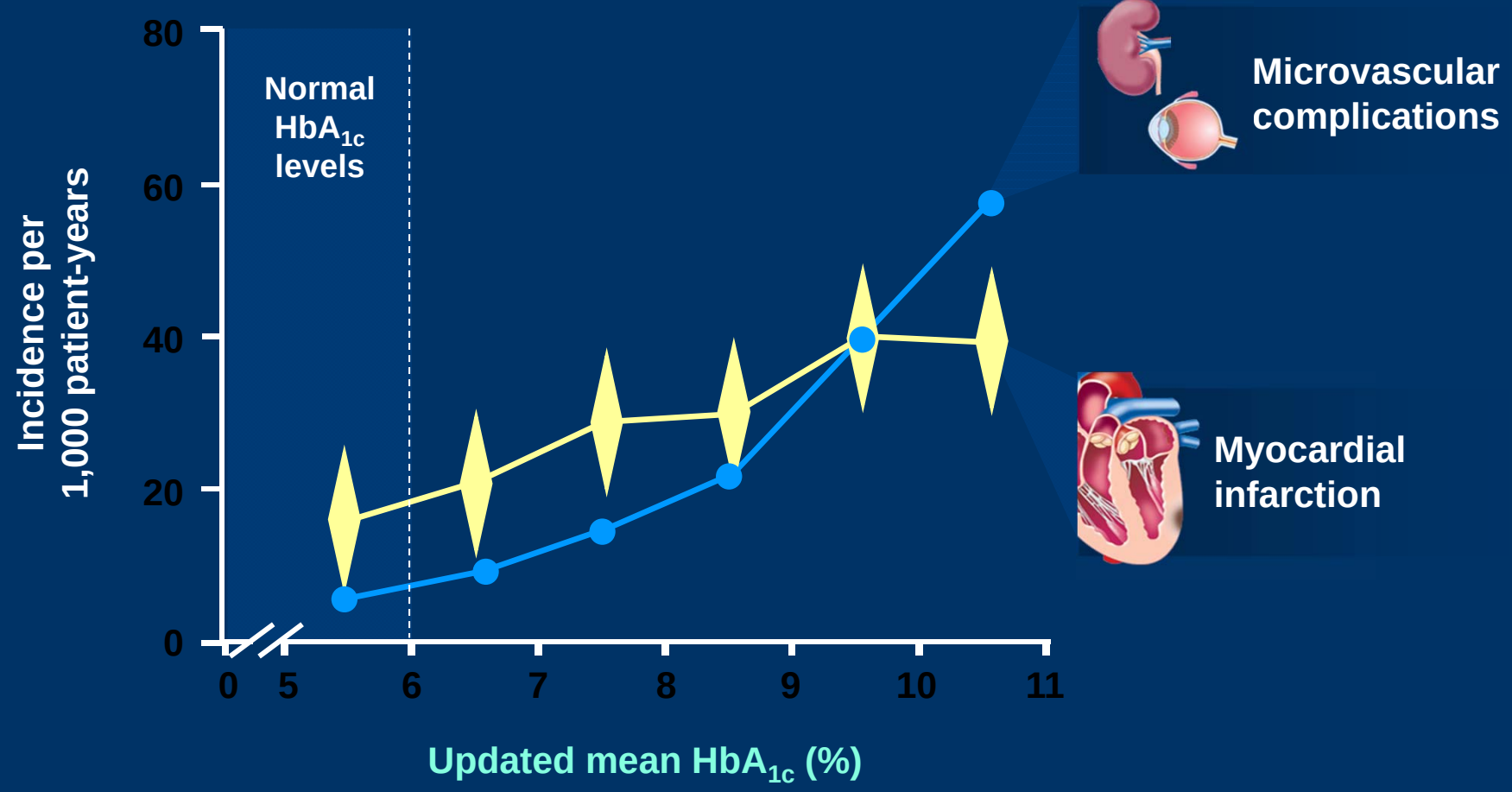
Stratton IM, *et al. BMJ* 2000; 321:

UKPDS: decreased risk of diabetes-related complications associated with a 1% decrease in A1C



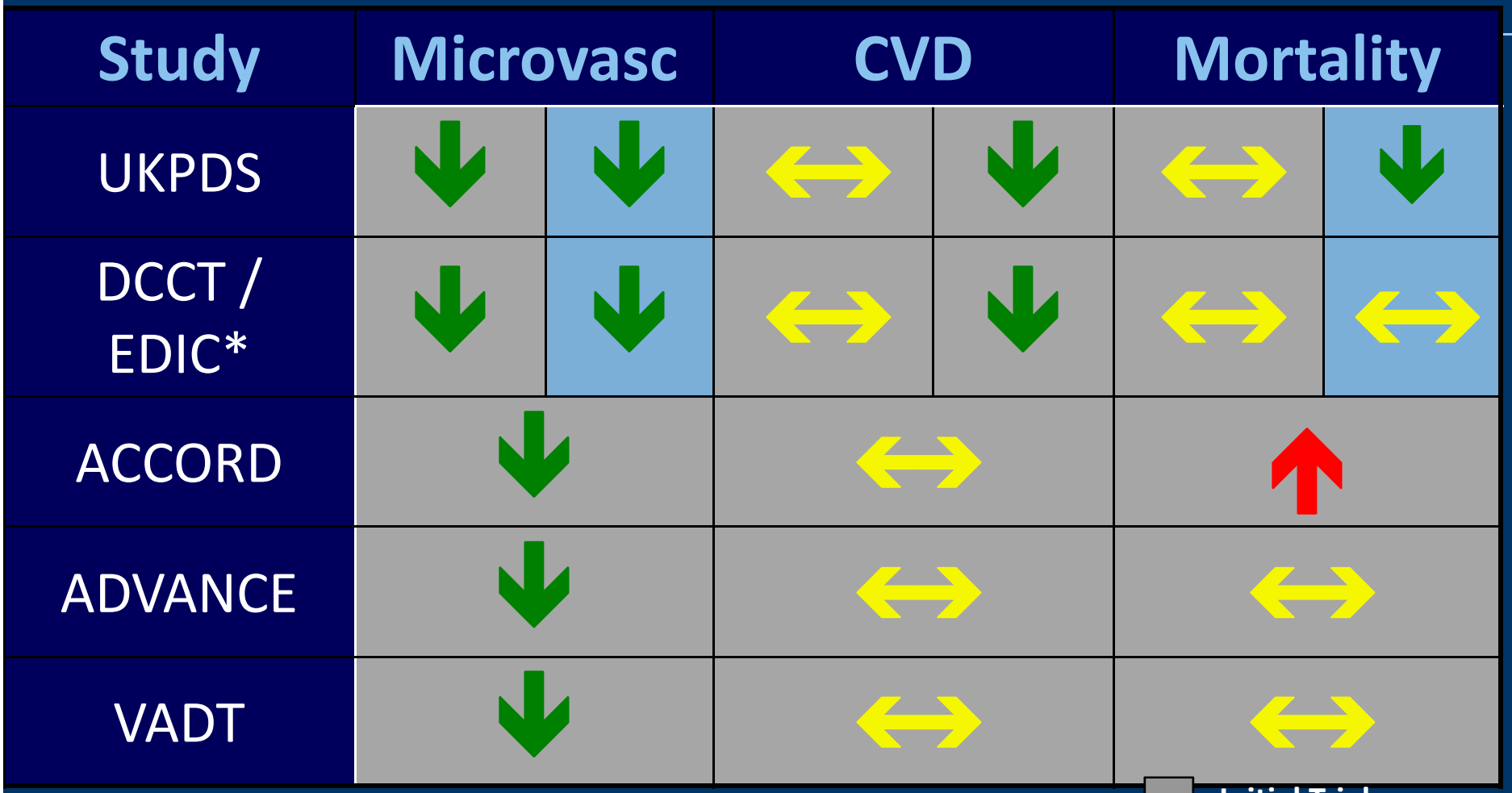
Adapted from Stratton IM, *et al.* UKPDS 35. *BMJ* 2000; 321:405–412.

Risk of complications decreases as HbA_{1c} decreases



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

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



Kendall DM, Bergenstal RM. © International Diabetes Center 2009

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329:977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129.
Moritz T. *N Engl J Med* 2009;361:1024)

Reducing Glycemia and CVS Risk

Type 2 Diabetes	Hba1c 'Conv' Gp	Hba1c 'Intv' Gp	Nephro-pathy	Neuro-pathy	Retino-pathy	CVS
UKPDS	7.9 %	7.0 %	33 %	-	21 %	16 % (ns)
Kumamoto	9.4 %	7.1 %	70 %	80 %	69 %	46% (ns)
Steno 2	9 %	7.8 %	61 %	63 %	58 %	
ADVANCE	7.3 %	6.5 % (<6.5 %)	21 %	-	5 % (ns)	6 % (ns)
ACCORD	7.5 %	6.4 % (<6 %)	-	-	-	10 % (ns)
VADT	8.4 %	6.9 % (<6 %)				13 % (ns)

Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

Aggregate Endpoint		**1997**	**2007**
Any diabetes related endpoint	*RRR:*	12%	**9%**
	P:	0.029	**0.040**
Microvascular disease	*RRR:*	25%	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	16%	**15%**
	P:	0.052	**0.014**
All-cause mortality	*RRR:*	6%	**13%**
	P:	0.44	**0.007**

Holman R, et al. *N Engl J Med* 2008;359.

- Recent discussion of T2DM and CV disease has centered primarily upon the exciting results of large CV safety trials evaluating some of the newer glucose-lowering agents
- In addition to the positive CV results, the mechanisms underlying these benefits have elicited much interest, as have the implications of those results for clinical practice

CVOT (ADA 2018)

	DPP-4 inhibitors				GLP-1 receptor agonists			SGLT2 inhibitors		
	SAVOR-TIMI 53 (129) (n = 16,492)	EXAMINE (145) (n = 5,380)	TECOS (132) (n = 14,671)	ELIXA (140) (n = 6,068)	LEADER (138) (n = 9,340)	SUSTAIN-6 (139)* (n = 3,297)	EXSCEL (141) (n = 14,752)	EMPA-REG OUTCOME (133) (n = 7,020)	CANVAS (135) (n = 4,330)	CANVAS-R (135) (n = 5,812)
Intervention	Saxagliptin/ placebo	Alogliptin/ placebo	Sitagliptin/ placebo	Lixisenatide/ placebo	Liraglutide/ placebo	Semaglutide/ placebo	Exenatide QW/ placebo	Empagliflozin/ placebo	Canagliflozin/placebo	
Main inclusion criteria	Type 2 diabetes and history of or multiple risk factors for CVD	Type 2 diabetes and ACS within 15–90 days before randomization	Type 2 diabetes and preexisting CVD	Type 2 diabetes and history of ACS (<180 days)	Type 2 diabetes and preexisting CVD, kidney disease, or HF at ≥50 years of age or cardiovascular risk at ≥60 years of age	Type 2 diabetes and preexisting CVD, HF, or CKD at ≥50 years of age or cardiovascular risk at ≥60 years of age	Type 2 diabetes with or without preexisting CVD	Type 2 diabetes and preexisting CVD with BMI ≤45 kg/m^2 and eGFR ≥30 mL/min/1.73 m^2	Type 2 diabetes and preexisting CVD at ≥30 years of age or ≥2 cardiovascular risk factors at ≥50 years of age	
A1C inclusion criteria (%)	≥6.5	6.5–11.0	6.5–8.0	5.5–11.0	≥7.0	≥7.0	6.5–10.0	7.0–10.0	7.0–10.5	
Age (years)††	65.1	61.0	65.4	60.3	64.3	64.6	62	63.1	63.3	
Diabetes duration (years)††	10.3	7.1	11.6	9.3	12.8	13.9	12	57% >10	13.5	
Median follow-up (years)	2.1	1.5	3.0	2.1	3.8	2.1	3.2	3.1	5.7	2.1
Statin use (%)	78	91	80	93	72	73	74	77	75	
Metformin use (%)	70	66	82	66	76	73	77	74	77	
Prior CVD/CHF (%)	78/13	100/28	74/18	100/22	81/18	60/24	73.1/16.2	99/10	65.6/14.4	
Mean baseline A1C (%)	8.0	8.0	7.2	7.7	8.7	8.7	8.0	8.1	8.2	
Mean difference in A1C between groups at end of treatment (%)	−0.3^	−0.3^	−0.3^	−0.3^	−0.4^	−0.7 or −1.0^†	−0.53^	−0.3^‡	−0.58^	
Year started/reported	2010/2013	2009/2013	2008/2015	2010/2015	2010/2016	2013/2016	2010/2017	2010/2015	2009/2017	
Primary outcome§	3-point MACE	3-point MACE	4-point MACE	4-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	Progression to albuminuria**
	1.00 (0.89–1.12)	0.96 (95% UL ≤1.16)	0.98 (0.89–1.08)	1.02 (0.89–1.17)	0.87 (0.78–0.97)	0.74 (0.58–0.95)	0.91 (0.83–1.00)	0.86 (0.74–0.99)	0.86 (0.75–0.97)§	0.73 (0.47–0.77)
Key secondary outcome§	Expanded MACE	4-point MACE	3-point MACE	Expanded MACE	Expanded MACE	Expanded MACE	Individual components of MACE (see below)	4-point MACE	All-cause and cardiovascular mortality (see below)	40% reduction in composite eGFR, renal replacement, renal death
	1.02 (0.94–1.11)	0.95 (95% UL ≤ 1.14)	0.99 (0.89–1.10)	1.00 (0.90–1.11)	0.88 (0.81–0.96)	0.74 (0.62–0.89)		0.89 (0.78–1.01)		0.60 (0.47–0.77)

Table 9.4 Continued

	DPP-4 inhibitors			GLP-1 receptor agonists				SGLT2 inhibitors		
	SAVOR-TIMI 53 (129) (n = 16,492)	EXAMINE (145) (n = 5,380)	TECOS (132) (n = 14,671)	ELIXA (140) (n = 6,068)	LEADER (138) (n = 9,340)	SUSTAIN-6 (139)* (n = 3,297)	EXSCEL (141) (n = 14,752)	EMPA-REG OUTCOME (133) (n = 7,020)	CANVAS (135) (n = 4,330)	CANVAS-R (135) (n = 5,812)
Cardiovascular death§	1.03 (0.87–1.22)	0.85 (0.66–1.10)	1.03 (0.89–1.19)	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.62 (0.49–0.77)	0.96 (0.77–1.18)¶ 0.87 (0.72–1.06)#	
MI§	0.95 (0.80–1.12)	1.08 (0.88–1.33)	0.95 (0.81–1.11)	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.87 (0.70–1.09)	0.85 (0.65–1.11)	0.85 (0.61–1.19)
Stroke§	1.11 (0.88–1.39)	0.91 (0.55–1.50)	0.97 (0.79–1.19)	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	1.18 (0.89–1.56)	0.97 (0.70–1.35)	0.82 (0.57–1.18)
HF hospitalization§	1.27 (1.07–1.51)	1.19 (0.90–1.58)	1.00 (0.83–1.20)	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.65 (0.50–0.85)	0.77 (0.55–1.08)	HR 0.56 (0.38–0.83)
Unstable angina hospitalization§	1.19 (0.89–1.60)	0.90 (0.60–1.37)	0.90 (0.70–1.16)	1.11 (0.47–2.62)	0.98 (0.76–1.26)	0.82 (0.47–1.44)	1.05 (0.94–1.18)	0.99 (0.74–1.34)	—	
All-cause mortality§	1.11 (0.96–1.27)	0.88 (0.71–1.09)	1.01 (0.90–1.14)	0.94 (0.78–1.13)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.68 (0.57–0.82)	0.87 (0.74–1.01)‡‡ 0.90 (0.76–1.07)##	
Worsening nephropathy§‖	1.08 (0.88–1.32)	—	—	—	0.78 (0.67–0.92)	0.64 (0.46–0.88)	—	0.61 (0.53–0.70)	0.60 (0.47–0.77)	

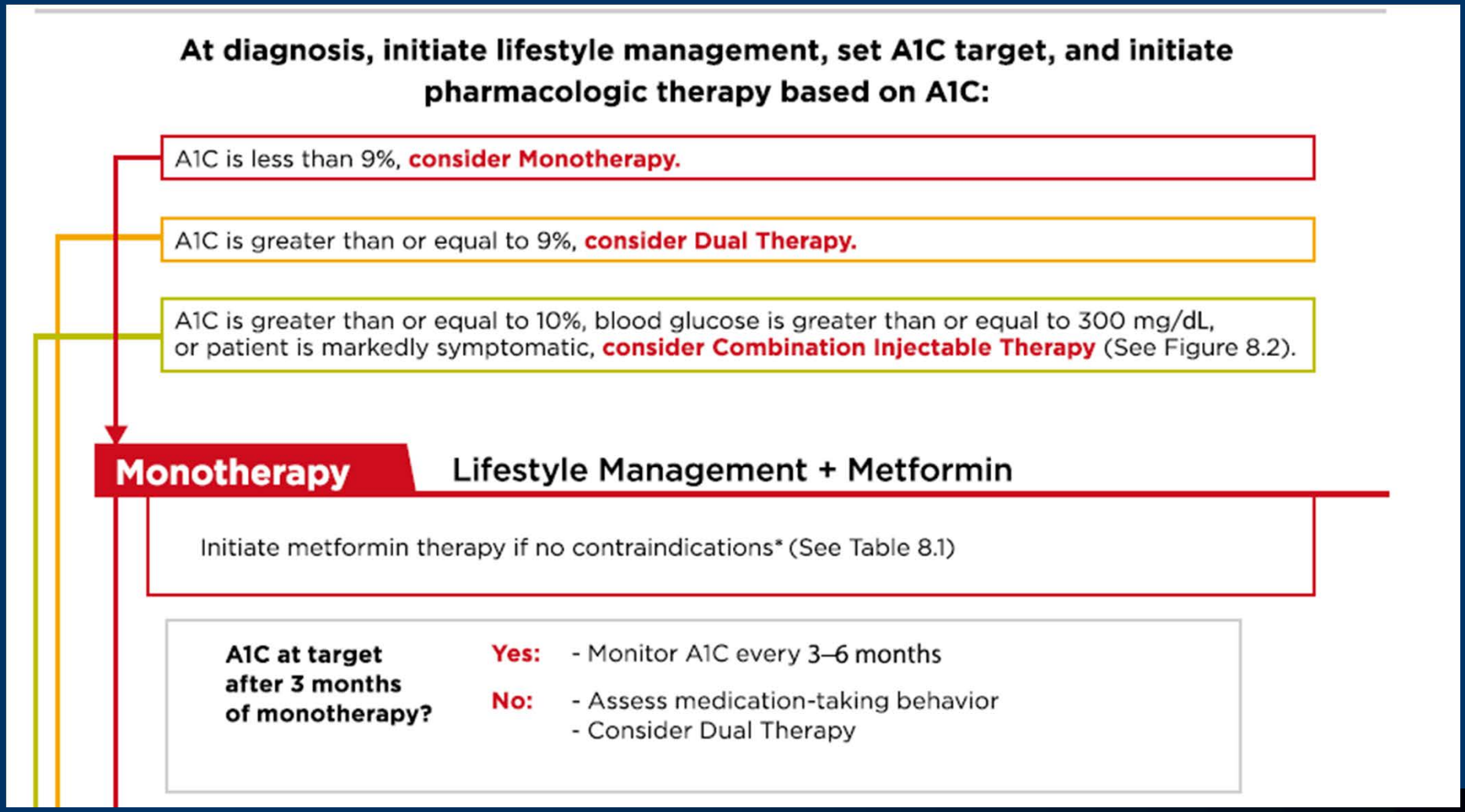
CVD and Renal as main factors to be consider

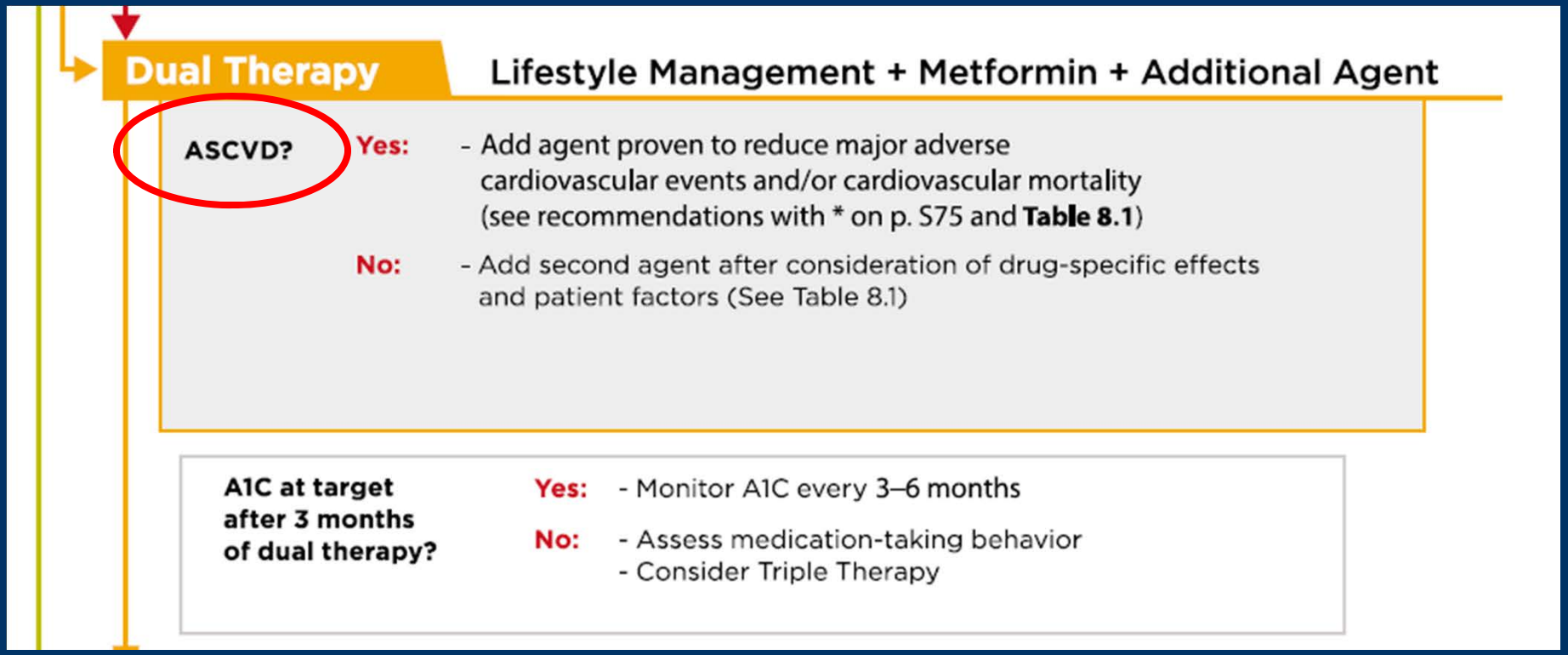
Table 8.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

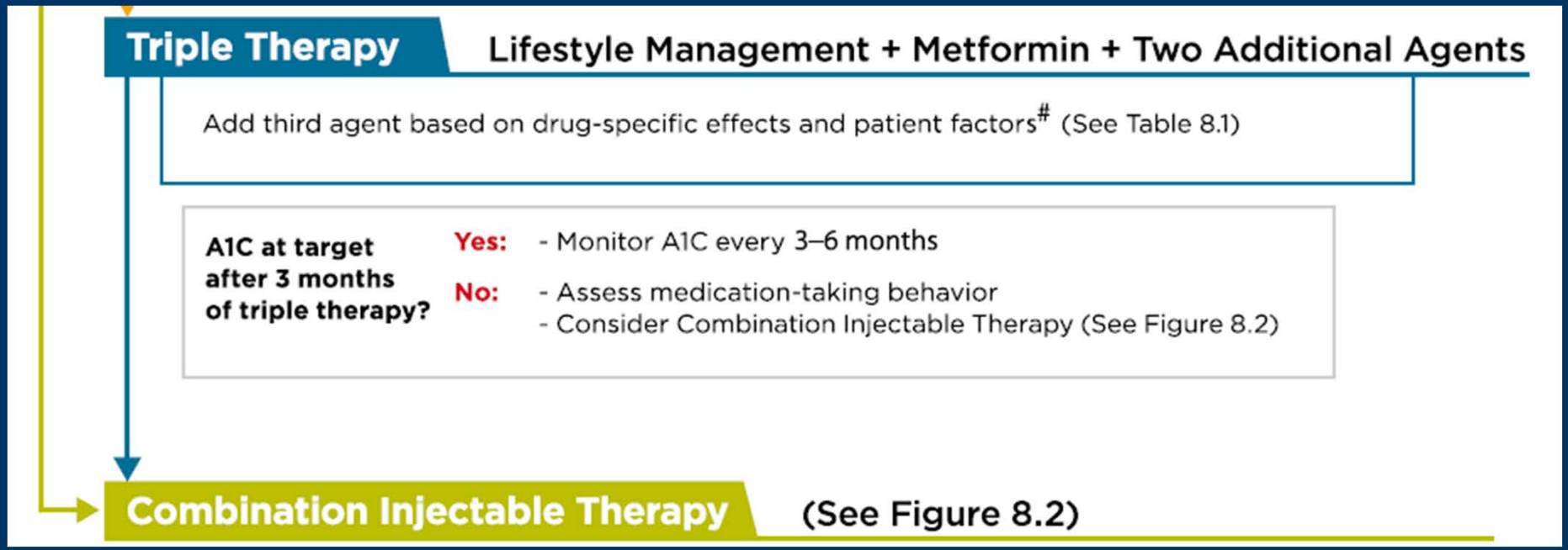
	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additi
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastro (diarrhe ▪ Potenti
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30	▪ FDA Bl amputa ▪ Risk of (canagl ▪ DKA ris T2DM) ▪ Genito

Pharmacologic Approaches to Glycemic Treatment Diabetes Care Volume 41, Supplement 1, January 2018

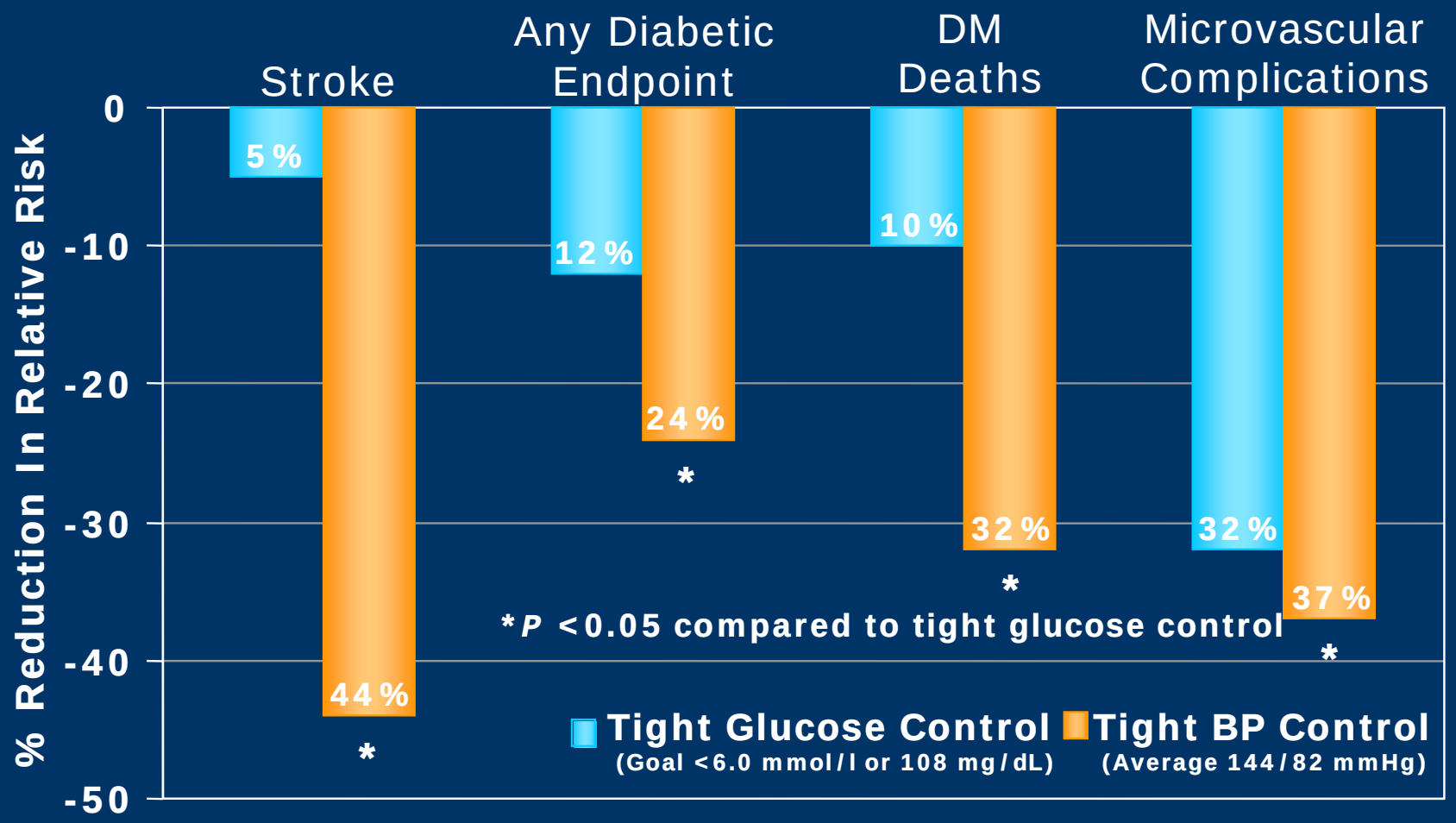
Antihyperglycemic therapy in adults with T2DM




Dual Therapy
Lifestyle Management + Metformin + Additional Agent
ASCVD?
Yes:
- Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and Table 8.1)
No:
- Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)
A1C at target after 3 months of dual therapy?
Yes:
- Monitor A1C every 3–6 months
No:
- Assess medication-taking behavior
- Consider Triple Therapy


Triple Therapy
Lifestyle Management + Metformin + Two Additional Agents
Add third agent based on drug-specific effects and patient factors# (See Table 8.1)
A1C at target after 3 months of triple therapy?
Yes:
- Monitor A1C every 3–6 months
No:
- Assess medication-taking behavior
- Consider Combination Injectable Therapy (See Figure 8.2)
Combination Injectable Therapy
(See Figure 8.2)

Diabetes: Tight Glucose & Blood Pressure Control and CV Outcomes



Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661.

comprehensive list ADA 2018

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
LABORATORY EVALUATION	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year			
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides#	✓		✓^
	• Liver function tests#	✓		✓
	• Spot urinary albumin-to-creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate†	✓		✓
	• Thyroid-stimulating hormone in patients with type 1 diabetes#	✓		✓
	• Vitamin B12 if on metformin (when indicated)	✓		
	• Serum potassium levels in patients on ACE inhibitors, ARBs, or diuretics†	✓		✓
ASSESSMENT AND PLAN	**Goal setting**			
	▪ Set A1C/blood glucose target and monitoring frequency	✓	✓	✓
	▪ If hypertension diagnosed, establish blood pressure goal	✓		✓
	▪ Incorporate new members to the care team as needed	✓	✓	✓
	▪ Diabetes education and self-management support needs	✓	✓	✓
	Cardiovascular risk assessment and staging of CKD			
	▪ History of ASCVD	✓	✓	✓
	▪ Presence of ASCVD risk factors (see Table 9.2)	✓	✓	✓
	▪ Staging of CKD (see Table 10.1)†	✓	✓	✓

- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven *to reduce major adverse cardiovascular events and cardiovascular mortality* (currently empagliflozin and liraglutide), after considering drug-specific and patient factors

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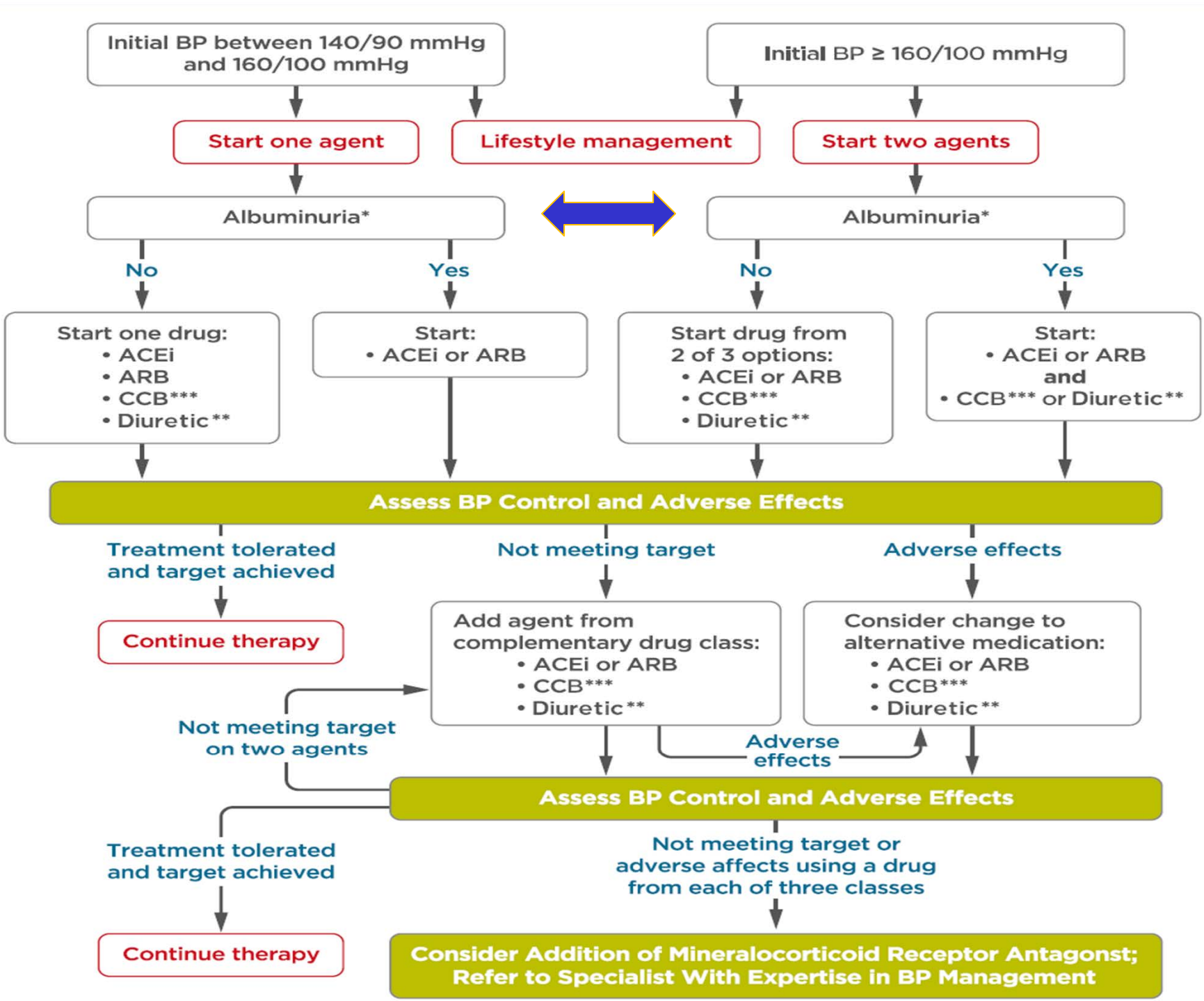
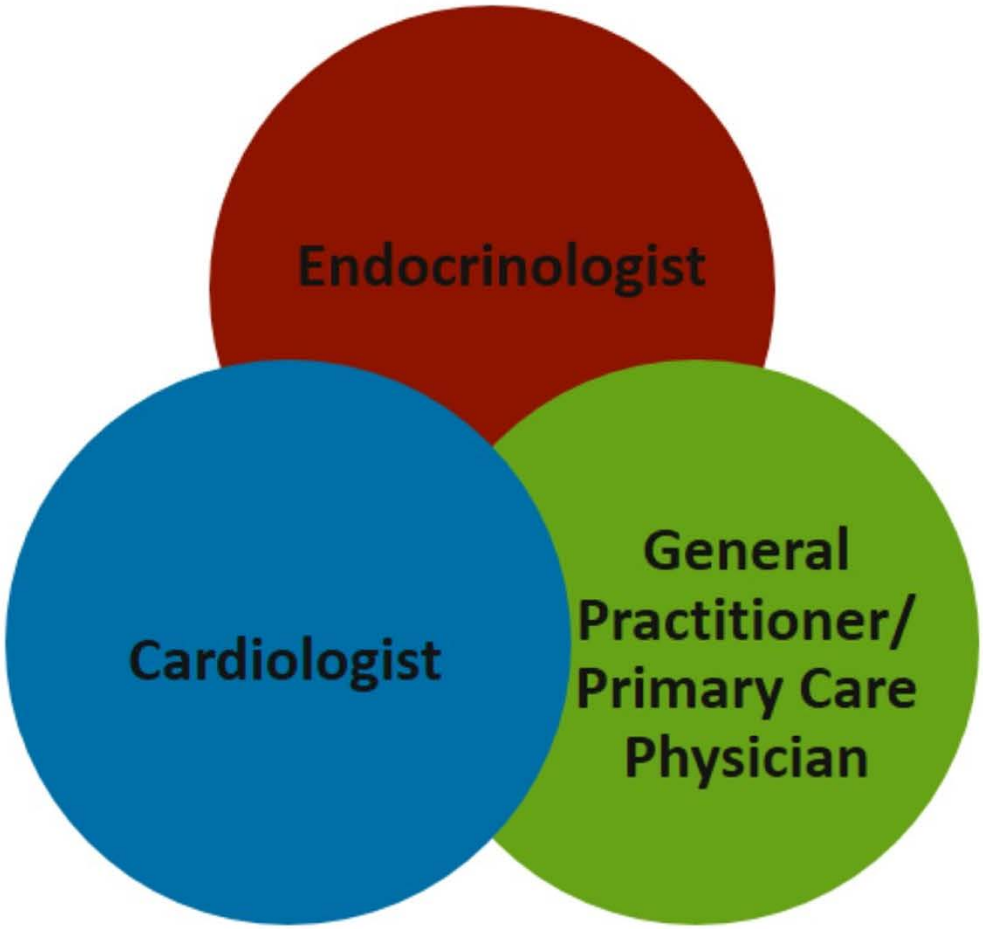

Initial BP between 140/90 mmHg and 160/100 mmHg
Initial BP ≥ 160/100 mmHg
Start one agent
Lifestyle management
Start two agents
Albuminuria*
Albuminuria*
No
Yes
No
Yes
Start one drug:
• ACEi
• ARB
• CCB***
• Diuretic**
Start:
• ACEi or ARB
Start drug from 2 of 3 options:
• ACEi or ARB
• CCB***
• Diuretic**
Start:
• ACEi or ARB
and
• CCB*** or Diuretic**
Assess BP Control and Adverse Effects
Treatment tolerated and target achieved
Not meeting target
Adverse effects
Continue therapy
Add agent from complementary drug class:
• ACEi or ARB
• CCB***
• Diuretic**
Consider change to alternative medication:
• ACEi or ARB
• CCB***
• Diuretic**
Not meeting target on two agents
Adverse effects
Assess BP Control and Adverse Effects
Treatment tolerated and target achieved
Not meeting target or adverse affects using a drug from each of three classes
Continue therapy
Consider Addition of Mineralocorticoid Receptor Antagonst; Refer to Specialist With Expertise in BP Management

T2DM and CVD: A Collaboration of Care Needed



- Knowledge of the most current data related to the management of patients with T2DM and CVD is essential for optimal patient outcomes
- Each type of physicians sees different types of patients; optimal care requires team work