DIABETES LEADERSHIP EDGE

AAPA

The Cardiorenal Syndrome and New Concepts in Preventing Diabetic Kidney Disease

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  - None

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Ode to the Kidneys

Thou forgotten organs, fist sized hermits,
Admire thy bean shaped duality,
Thy filter half cup of blood per minute,
Rid body of waste, no venality,

Without such hushed evenness, you provide,
Balance lost, muscles fail, sickness ensues;
Left inside mummies, you were glorified,
Left without your nephrons, could not make do,

I thank thee, loyal filter architects.

Dr. Euro Lodgy (pen name) marking of World Kidney Day 2019

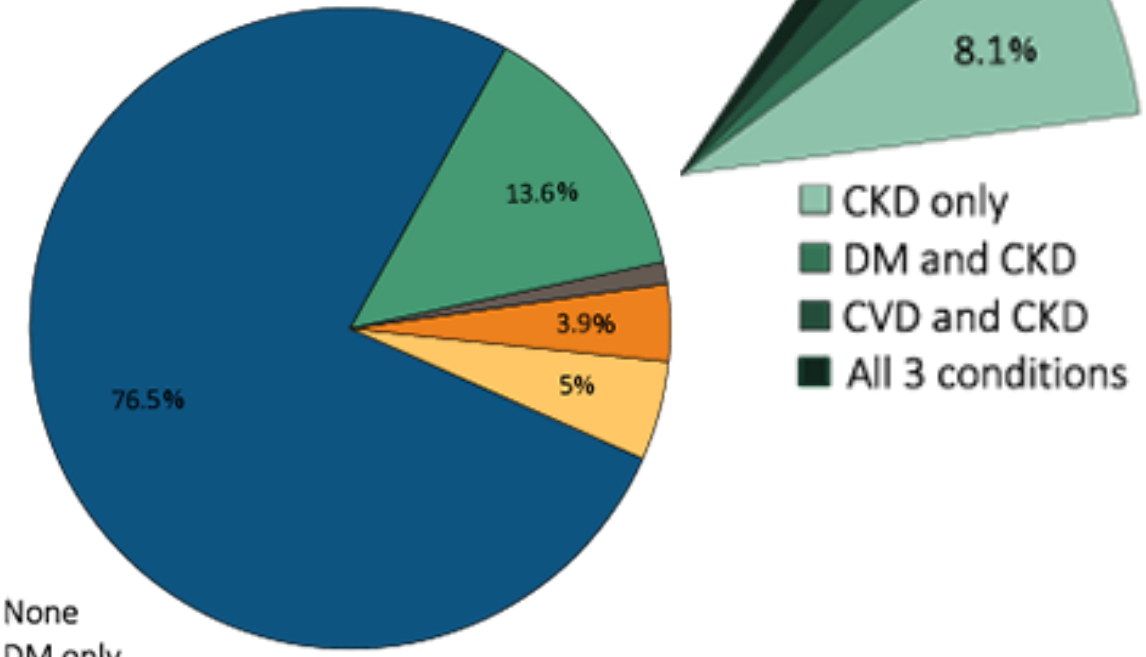
The Cardiorenal Syndrome and New Concepts in Preventing Diabetic Kidney Disease

At the end of this module, you'll be able to:

- Describe pathophysiological factors of diabetic kidney disease (DKD).
- Outline the interconnectivity of type 2 diabetes, DKD, and cardiorenal syndrome (CRS).
- Interpret screening results for and classify DKD.
- Analyze the results of recent trials as they relate to the treatment of DKD and CRS.
- Apply prevention and treatment strategies for DKD.

Diabetes and Chronic Kidney Disease in United States

Distribution of NHANES participants with diabetes, self-reported CVD, and CKD



NHANES (2007-2012)

Diabetes

	26.0	diagnosed
	9.4	undiagnosed
+	91.8	pre-diabetes
	127.2	million

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NIDDK Kidney Disease Statistics for the US. Available at https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease

Virani SS, et al. Circulation. 2020;141:e139–e596.

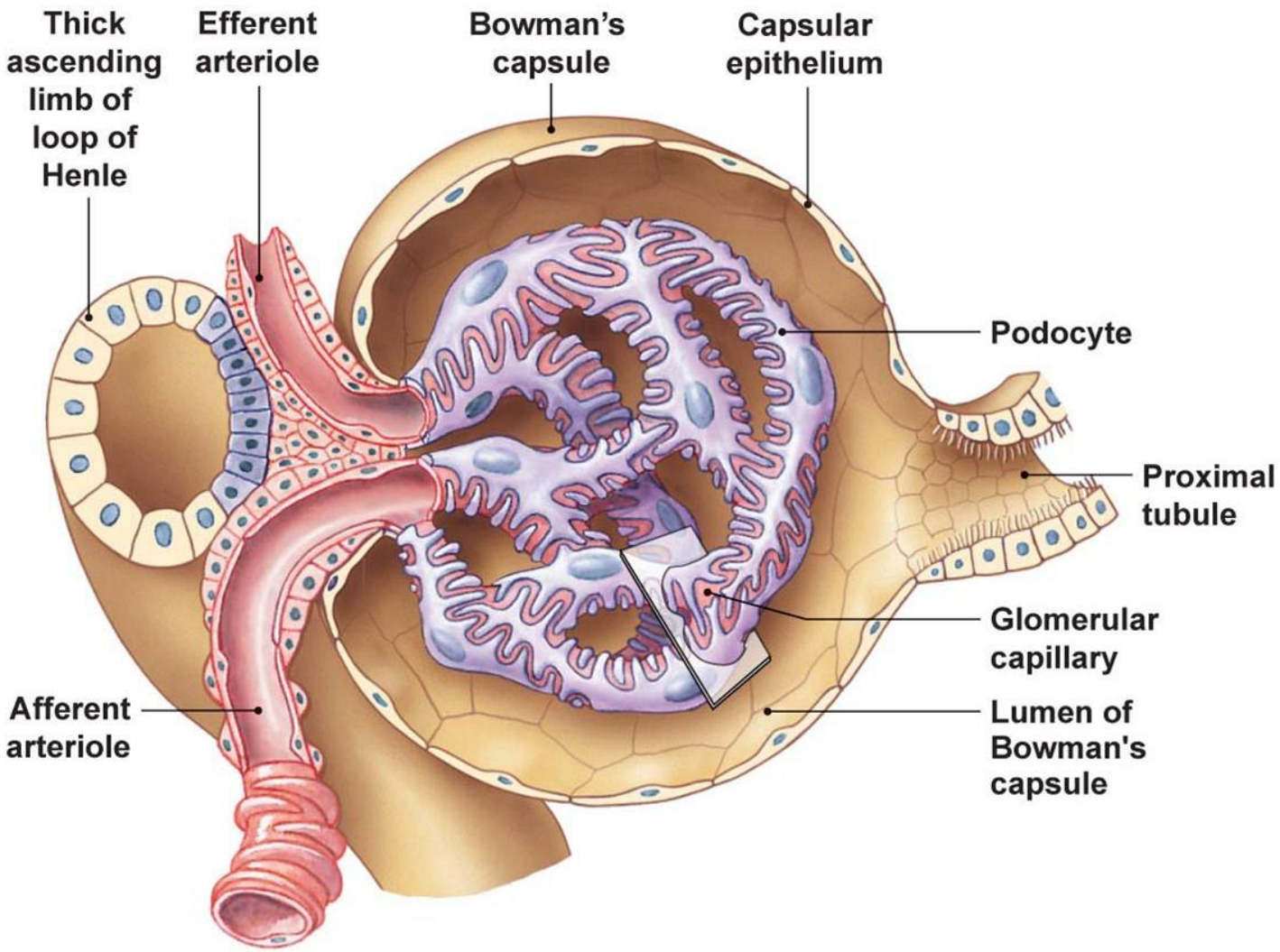
Diabetes and Kidney Disease in United States

- Hypertension, diabetes main causes of CKD
- Per CDC, ~1 in 3 adults ≥18 years or older have CKD
  - Diabetic kidney disease (DKD) most common CKD in industrialized world
- ~Half of patients with CKD also have diabetes and/or self-reported CVD
- Diabetes leading cause of kidney failure
  - Accounts for 38% of new cases annually

NIDDK Kidney Disease Statistics for the US. Available at https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease
CDC. Chronic Kidney Disease in the United States, 2019.
Burrows NR, et al. MMWR Morb Mortal Wkly Rep 2017;66:1165-70.

Pathophysiological Factors of Diabetic Kidney Disease

Glomerulus



(a) The epithelium around glomerular capillaries is modified into podocytes.

Diabetic Kidney Disease

- Defined by increased urinary albumin excretion in the absence of other renal diseases
- Follows classic step-by-step changes with some variation, *particularly in patients with diabetes*:

Early glomerular hyperfiltration ➔

Microalbuminuria ➔

Macroalbuminuria ➔

Declined GFR

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Gross JL, et al. Diabetes Care. 2005;28:164-76.
Lin YC, et al. J Formos Med Assoc. 2018;117:662-75.

Conceptual Model: DKD Natural History

Stages of diabetic nephropathy (DN)	Renal hypertrophy	Incipient DN	Overt DN	ESRD
Structural changes	Increased kidney and glomerular size GBM thickness	↑ GBM thickness Mesangial expansion	Inflammation Glomerulosclerosis Tubulointerstitial fibrosis	
GFR	High (↑ 20% - 50%)	Normal	Declines	<10 ml/min (ESRD)
Albuminuria	Microalbuminuria		Macroalbuminuria	
Blood pressure	Normal	Increased/hypertension		
Hyperglycemia	Present			
Concomitant disease				Cardiovascular disease Infections Death
Kidney complications			Anemia, bone and mineral metabolism, retinopathy, and neuropathy.	

Years	0 (diagnosis)	5	10	20	30

ESRD = end-stage renal disease; GBM = glomerular basement membrane; GFR = glomerular filtration rate.

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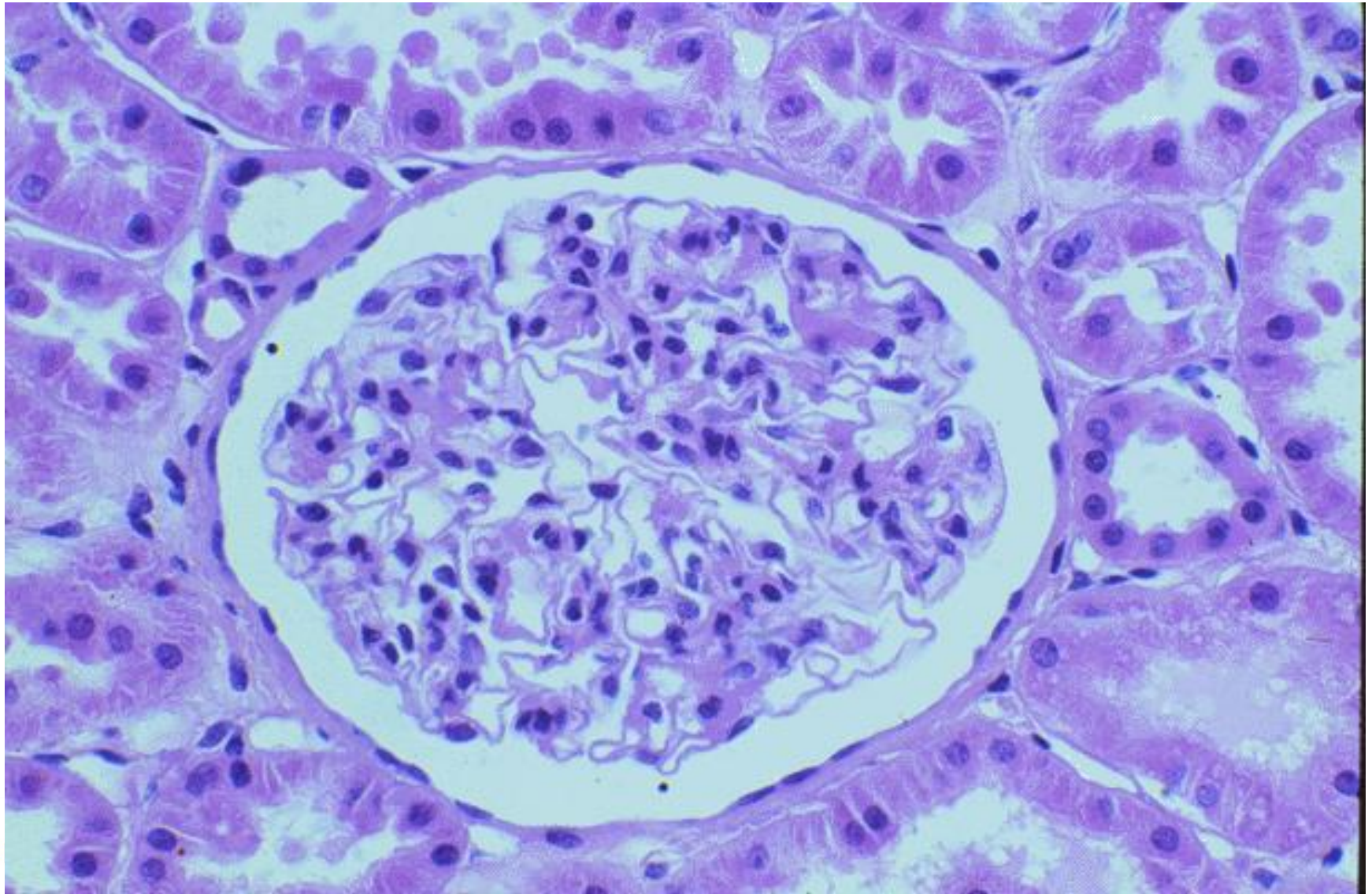
Adapted from Lin YC, et al. J Formos Med Assoc. 2018;117:662-75 and Alicic RZ, et al. Clin J Am Soc Nephrol. 2017;12:2032-45.

Normal Kidney



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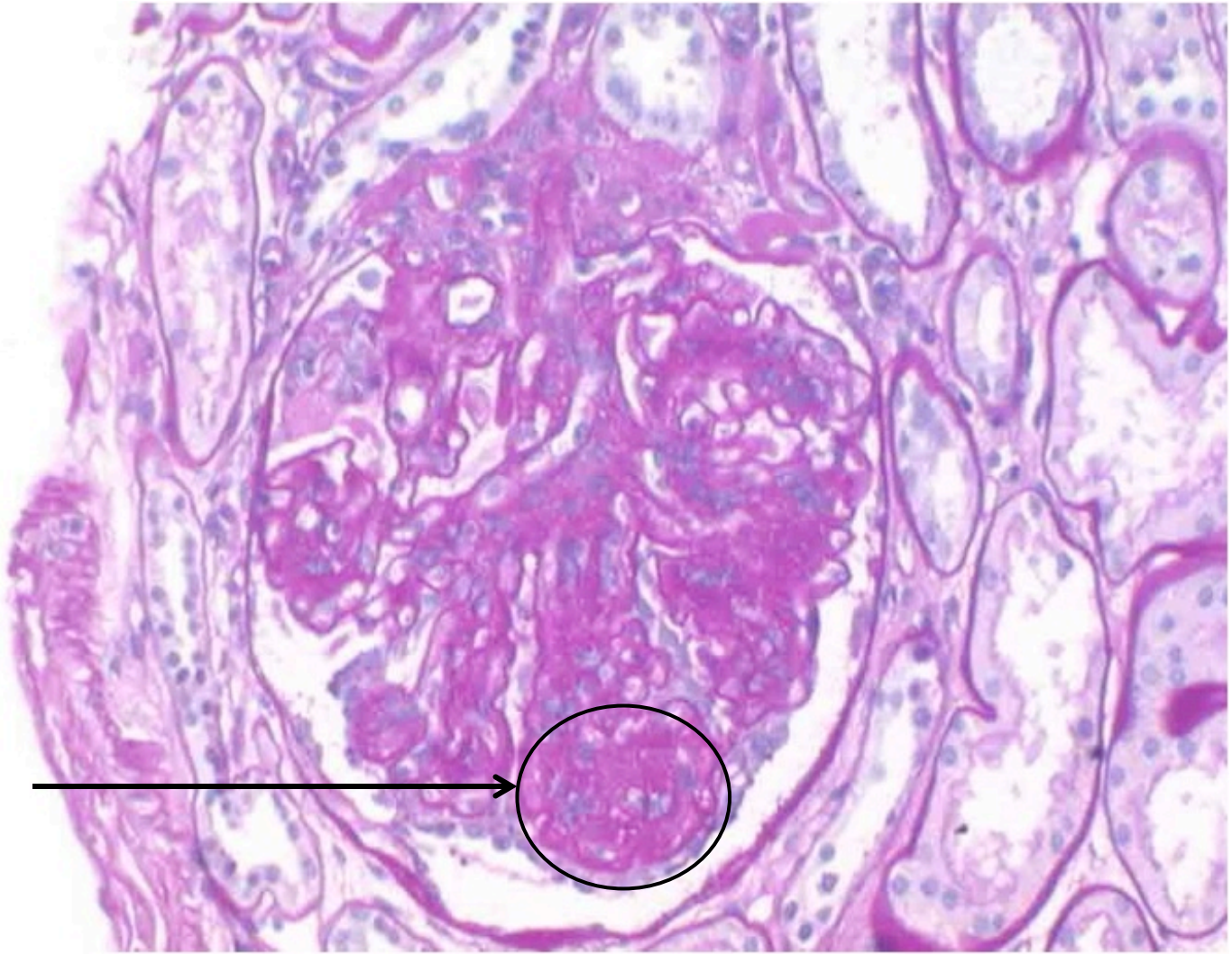
Diabetic Nephropathy



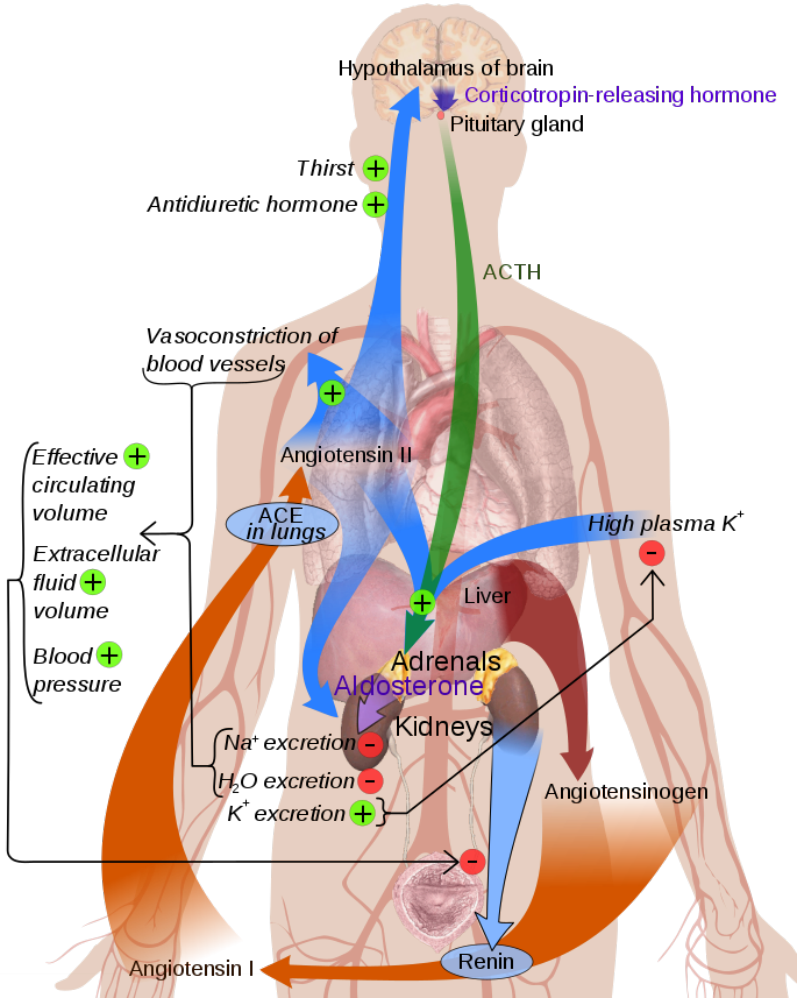
Pathophysiological Factors: Hypertension

- Defined as systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥ 80 mm Hg
- Associated with mortality, disability, CVD, and microvascular complications
- Prevalent in ≈30% of patients with CKD
- Can reduce the number/size/functionality of microvessels in kidneys

Whelton PK, et al. J Am Coll Cardiol 2018;71:e127–248. ADA. Diabetes Care 2020;43:S111-S134. de Boer IH, et al. Diabetes Care. 2017;40:1273-84. Zannad F, et al. Circulation. 2018;138:929-44. Climie RE, et al. Hypertension. 2019;73:1138-49.

Pathophysiological Factors: Angiotensin II

Renin-Angiotensin-Aldosterone System



Elevated angiotensin II:

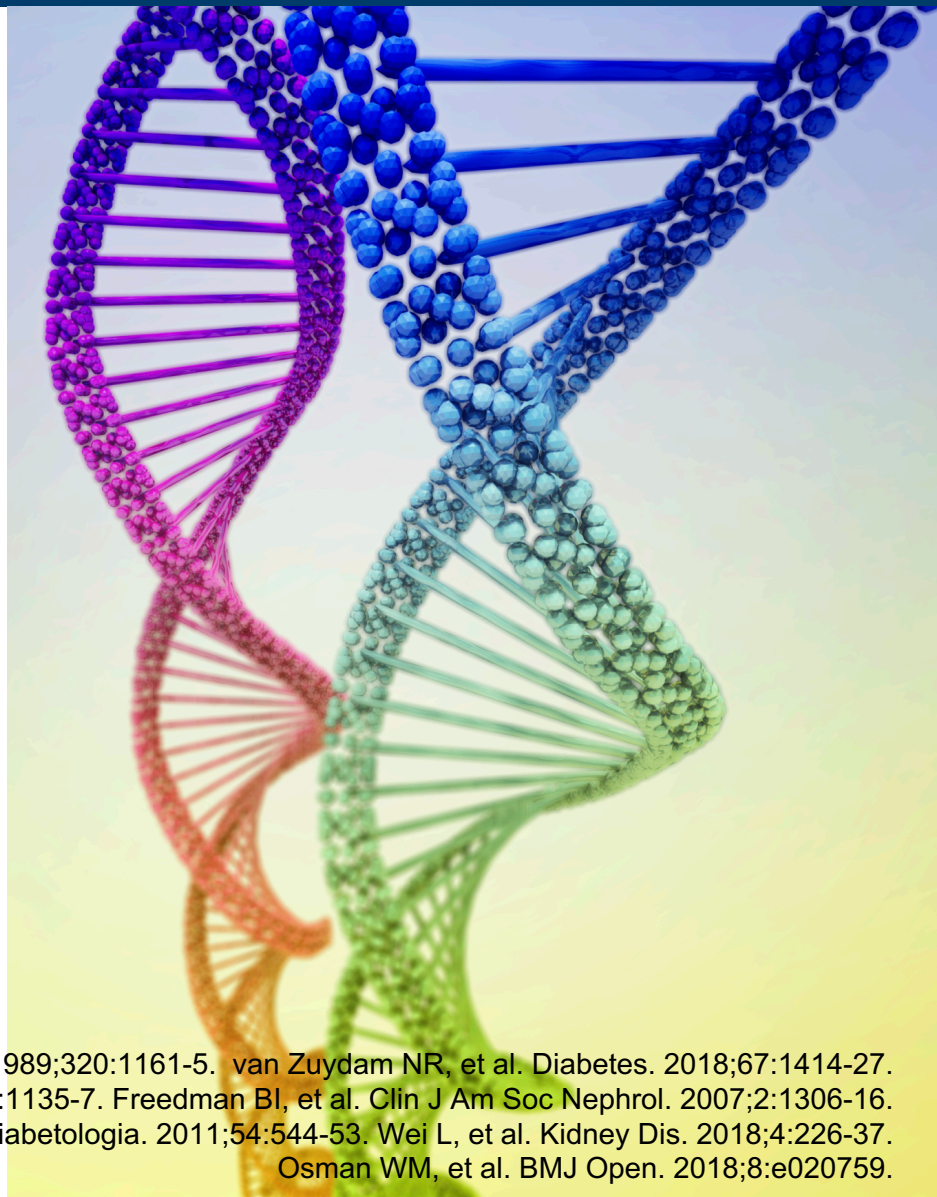
- Contributes to various renal and CV physiological/pathological mechanisms
- Exerts pressure on arteriolar muscle, causing increased vascular pressure
- Can cause efferent arteriolar vasoconstriction
- Associated with increased albuminuria
- Induces inflammation, apoptosis, cell growth, migration, and differentiation

Chawla T, et al. World J Diabetes. 2010;1:141-5.
Alicic RZ, et al. Clin J Am Soc Nephrol. 2017;12:2032-45.
Toth-Manikowski S, et al. J Diabetes Res. 2015;2015:697010.
Climie RE, et al. Hypertension. 2019;73:1138-49.

Pathophysiological Factors: Genetics

Concept that patients with diabetes may have a genetic susceptibility to diabetic nephropathy supported by:

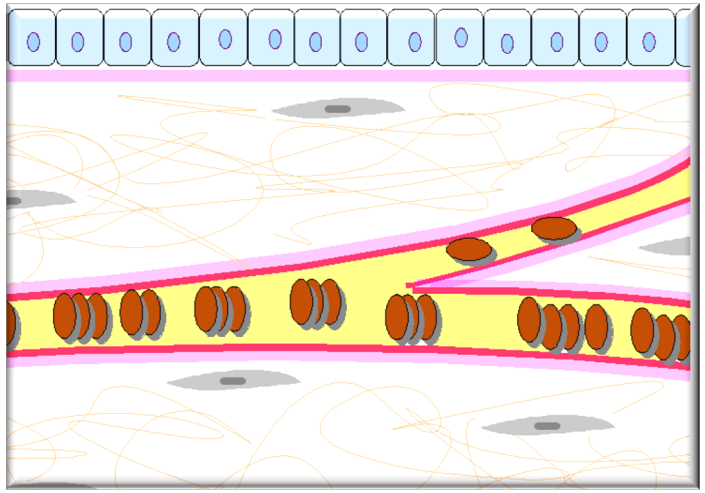
- Study of concordance rates among siblings
- Reports of the disease aggregating in families
- Variation in prevalence among different ethnic groups



Seaquist ER, et al. N Engl J Med. 1989;320:1161-5. van Zuydam NR, et al. Diabetes. 2018;67:1414-27.
Rich SS. Clin J Am Soc Nephrol. 2018;13:1135-7. Freedman BI, et al. Clin J Am Soc Nephrol. 2007;2:1306-16.
Mooyaart AI, et al. Diabetologia. 2011;54:544-53. Wei L, et al. Kidney Dis. 2018;4:226-37.
Osman WM, et al. BMJ Open. 2018;8:e020759.

Pathophysiological Factors: Extracellular Matrix

- Deposition of extracellular matrix (ECM) proteins leads to:
  - Thickening of glomerular and tubular basement membranes
  - Changes in mesangial tubulointerstitial matrices
- Changes in:
  - Basement membrane + glomerular hyperfiltration + increased glomerular hydrostatic pressure ➔ albuminuria
  - Mesangial matrix ➔ declining renal function
- As ECM formation progresses:
  - Interstitial fibrosis
  - Tubular atrophy
  - Glomerulosclerosis



Genovese F, et al. Fibrogenesis Tissue Repair. 2014;7:4.
Hu C, et al.. Curr Med Chem. 2015;22:2858-70.
Mason RM, et al. J Am Soc Nephrol. 2003;14:1358-73.
Kolset SO, et al. Histochem Cytochem. 2012;60:976-86.

Pathophysiological Factors: Glomerular Hyperfiltration

- Defined as an abnormally high whole-kidney GFR
- Ranges between 130-140 ml/min/1.73 m^2 for threshold

Proposed Mechanisms of Glomerular Hyperfiltration

Ultrastructural

- Kidneys increase in size due to expanded nephron size in response to hyperglycemia
- Increases in kidney size, filtration surface area linked to hyperfiltration

Vascular

- Imbalances of various vasoactive humoral factors that are responsible for controlling pre- and post-glomerular arteriolar tone become imbalanced, leading to hyperfiltration

Tubular

- Enhanced glucose-sodium reabsorption leads to a reduction of afferent arteriolar resistance and an increase in single-nephron GFR
- Imbalances lead to net increased gradients

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Helal I, et al. Nat Rev Nephrol. 2012;8:293-300. Tonneijck L, et al. J Am Soc Nephrol. 2017;28:1023-39.

DKD Progression

Glomerular Hypertrophy and Hyperfiltration

- Glomerular hemodynamic changes occur in response to nephron loss
- Compensatory glomerular hypertrophy eventually becomes unsustainable
- Glomerular hyperfiltration = absolute increase in GFR
  - Increases glomerular hydraulic pressure

Inflammation of Glomeruli and Tubulointerstitial Area

- Initial systemic inflammation in DKD
  - Affects molecular vascular regulators
  - Increases vulnerability
- Abnormal glomerular filtration, inflammation, fibrogenesis, and hypoxia contribute to tubulointerstitial injury
  - Stimulates further inflammation and damage
- Tubulointerstitial injury ↑ hypoxia, kidney damage

Apoptosis of Cells and Accumulation of Extracellular Matrix

- Inflammatory cytokines (e.g., interleukins) expressed in greater proportions in diabetes
- Induce apoptosis of endothelial cells
- Contribute to glomerular basement membrane thickening, ECM accumulation
- Transforming growth factor-β influences changes in gene expression

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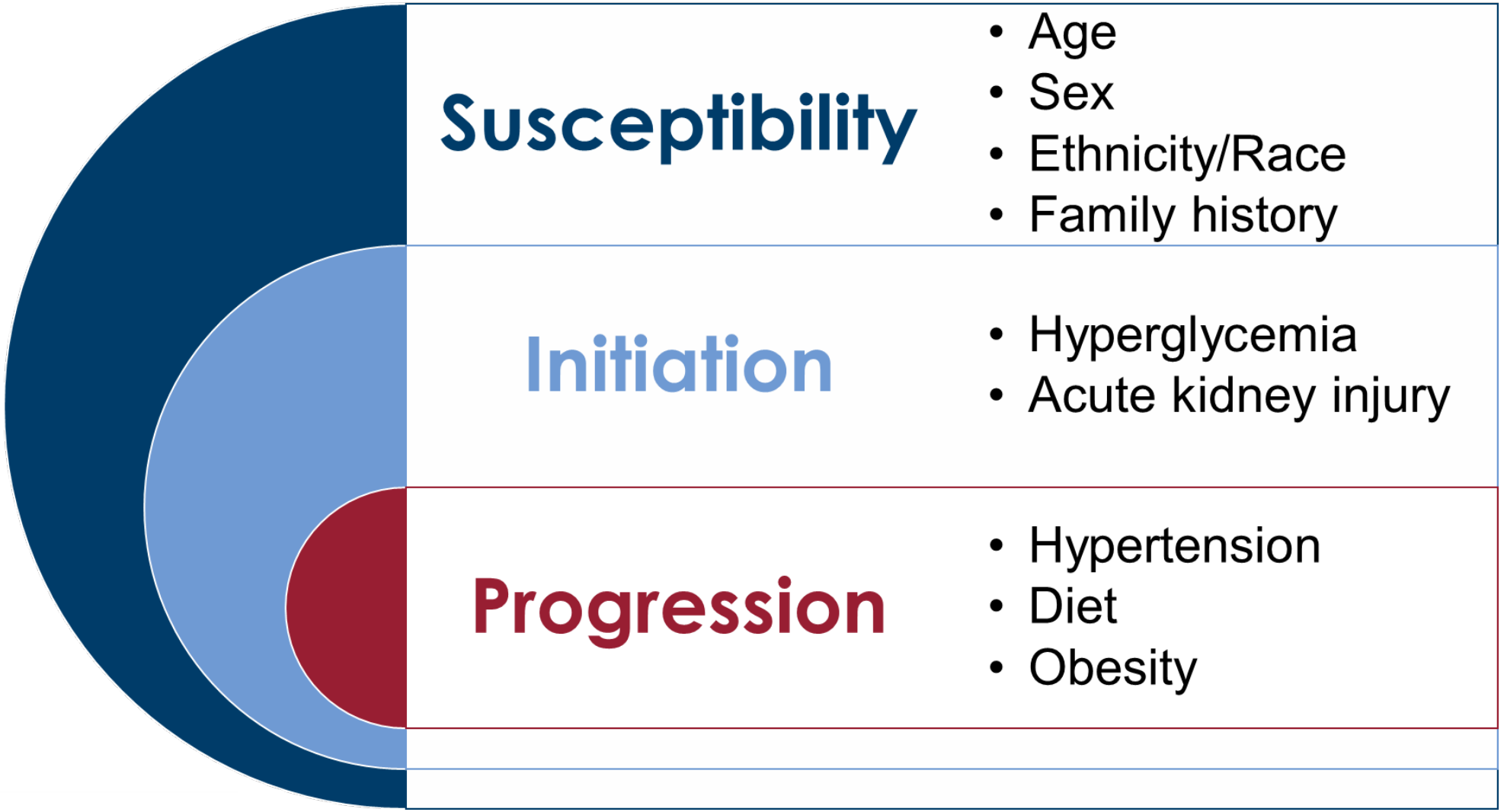
Helal I, et al. Nat Rev Nephrol. 2012;8:293-300. Trevisan R, et al. Nephron 2017;136:277-80. Mihai S, et al. J Immunol Res. 2018;2018:2180373. Toth-Manikowski S, et al. J Diabetes Res. 2015;2015:697010. Hodgkins KS, et al. Pediatr Nephrol. 2012;27:901-9.

Risk Factors for DKD



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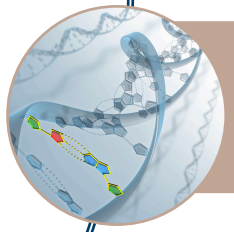
Alicic RZ, et al. Clin J Am Soc Nephrol. 2017;12:2032-45.

Non-modifiable Risk Factors

Race/Ethnicity – DKD ~2- to 3-fold higher in blacks, Hispanics, and Asians and up to 18-fold higher in Native Americans than whites

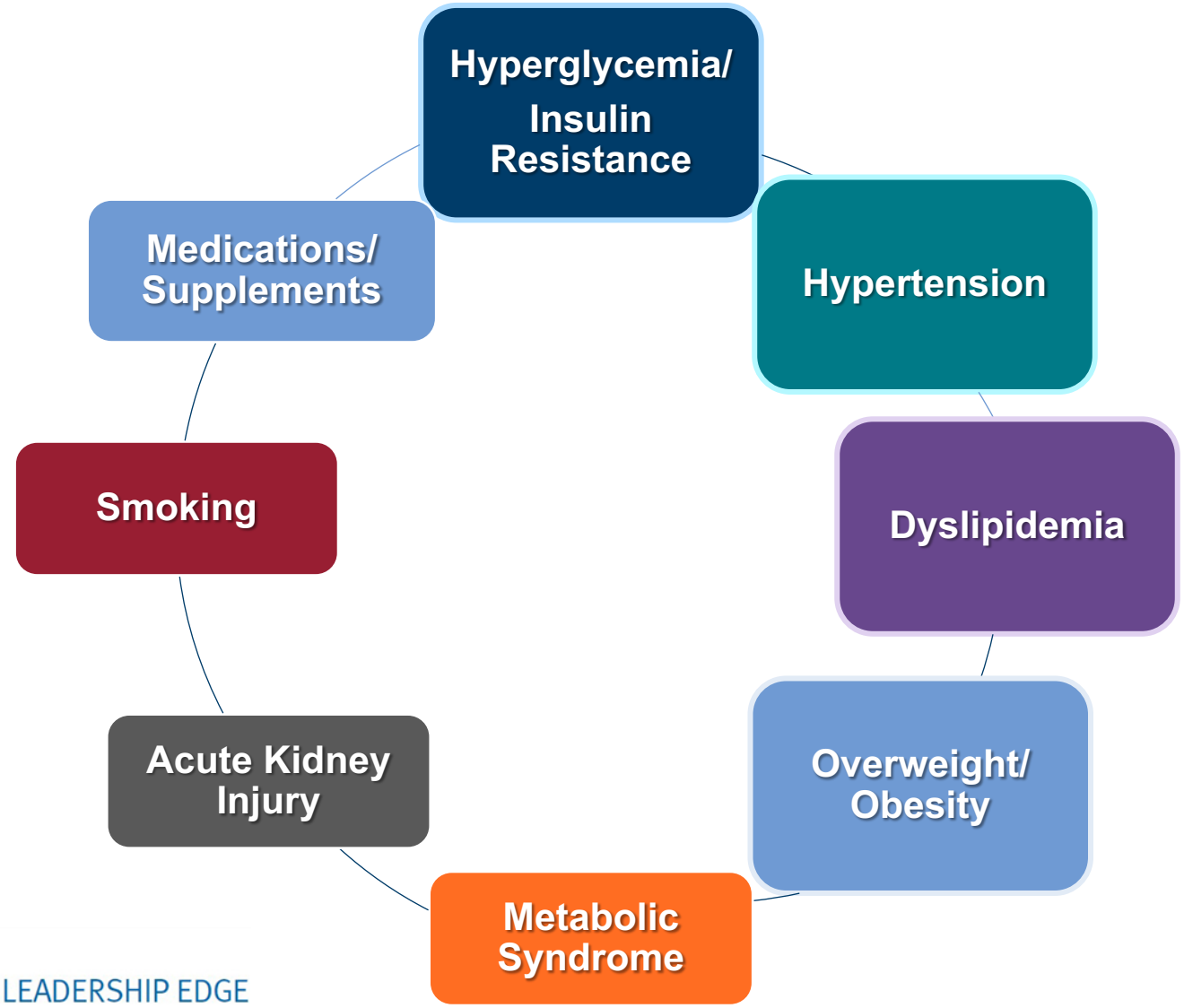
Sex – DKD appears to run a more aggressive course in males with diabetes; studies show a greater prevalence of albuminuria in males



Family History/Genetics – Family clustering in DKD reported; parental history of diabetes, CVD, hypertension = risk factors for DKD in patients with diabetes

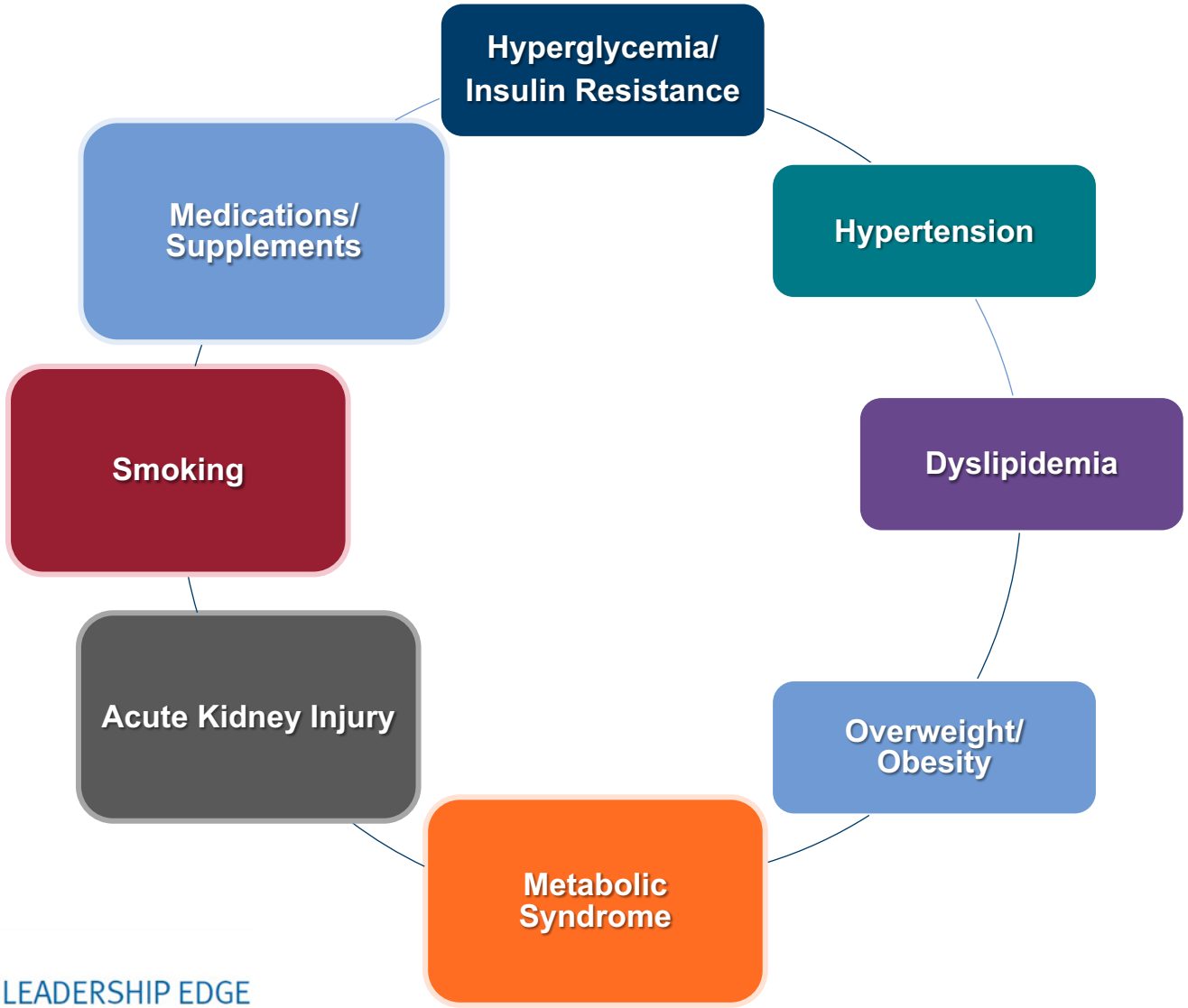
Age/Disease Duration – Renal blood flow, GFR diminish with aging; vascular changes compound histological changes; longer duration = risk factor for DKD

Modifiable Risk Factors



- Poor glycemic control prominent major risk factor
  - Well-established benefit of glucose lowering
- Hypertension: interactive relationship with kidneys
- Obesity risk factor for type 2 diabetes, hypertension, ESRD

Modifiable Risk Factors



- Metabolic syndrome characterized by several individual risk factors for DKD
- AKI ➔ kidney dysfunction, development of CKD
- Smoking independently associated with microalbuminuria

Interconnectivity: Diabetes, DKD, and CRS

Cardiorenal Syndrome

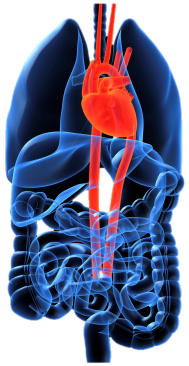
- Defined as disorders of the heart and kidneys whereby dysfunction in one may induce dysfunction in the other
- Converge and promote organ damage/dysfunction in the heart and kidney
  - Poorly managed diabetes may also induce dysfunction in both
- Deleterious outcomes reinforced in a feedback cycle with accelerated progression

Ronco C, et al. Eur Heart J. 2010;31:703–711.
Karnib HH, et al. Diabetes Res Clin Pract. 2010;89:201-8.
Song MK, et al. J Diabetes Res. 2014;2014:313718.

CRS Classification

Type 1: Acute Cardiorenal

- Acute worsening of heart function
- Acute coronary syndrome (ACS) ➔ acute kidney injury (AKI)

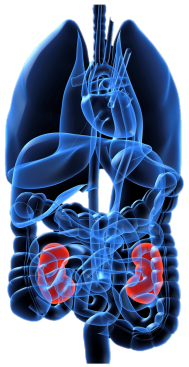


Type 3: Acute Reno-cardio

- AKI ➔ heart injury
- Dysfunction (ACS, acute heart failure, arrhythmias)

Type 2: Chronic Cardiorenal

- Chronic abnormalities in heart function
- Coronary heart disease ➔ CKD



Type 4: Chronic Reno-cardio

- CKD contributing to ↓ cardiac function, cardiac hypertrophy, left ventricular remodeling

Type 5: Secondary CRS

- Characterized by systemic conditions (e.g., diabetes, sepsis, amyloidosis) leading to simultaneous heart and kidneys injury/dysfunction

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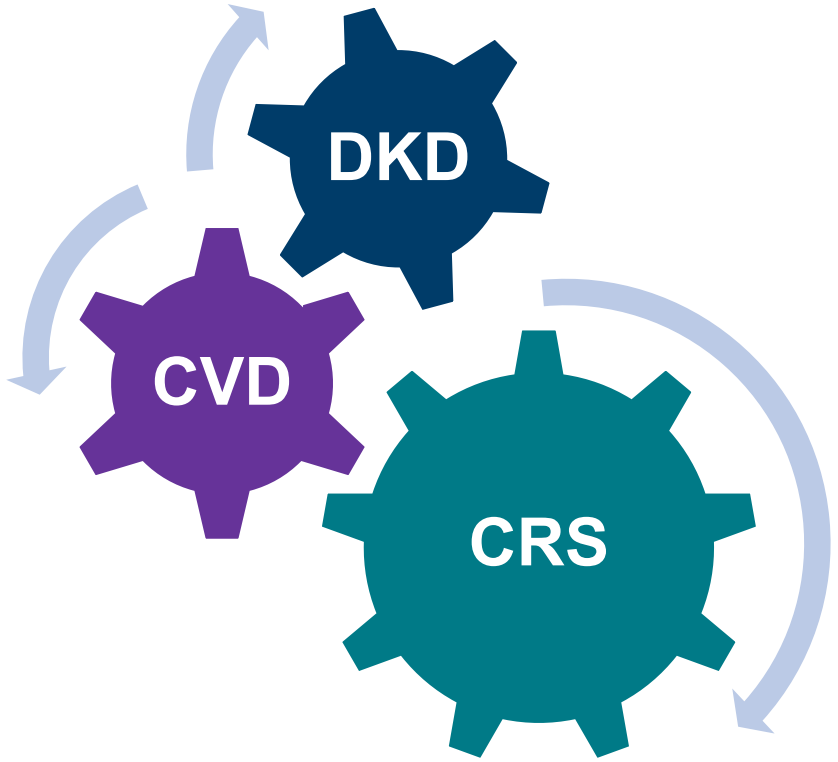
Ronco C, et al. J Am Coll Cardiol. 2008;52:1527-39.
Kulkarni M. J Nephrol Ther 2016;6:1000233.

Interconnectivity: Risk Factors

- DKD/CVD/CRS all evolve from vascular complications
- Nearly all risk factors that ↑ risk for DKD also increase risk for CVD, especially
  - Dyslipidemia
  - Hypertension
  - Obesity
  - Hyperglycemia
- Diabetes strongest risk factor for CVD



Sicree R. Diabetes Atlas, 3rd ed., Brussels: International Diabetes Federation; 2008.
Buse JB, et al. Circulation 2007;115:114–26.

Albuminuria

- Albuminuria commonly associated with diabetes, hypertension, AKI, CKD
  - Also connected to renal disease/dysfunction
  - Influential risk factor for CV death and all-cause mortality
- Microalbuminuria:
  - Increased risk for CV events and two-fold increased risk for CV mortality compared to normoalbuminuria
  - Adverse prognostic indicator for clinical CVD outcomes and all-cause mortality in patients with diabetes
- Prevalence of albuminuria in heart failure (HF) patients without renal dysfunction or diabetes and hypertension suggest it may help identify patients with CRS overlooked using eGFR alone

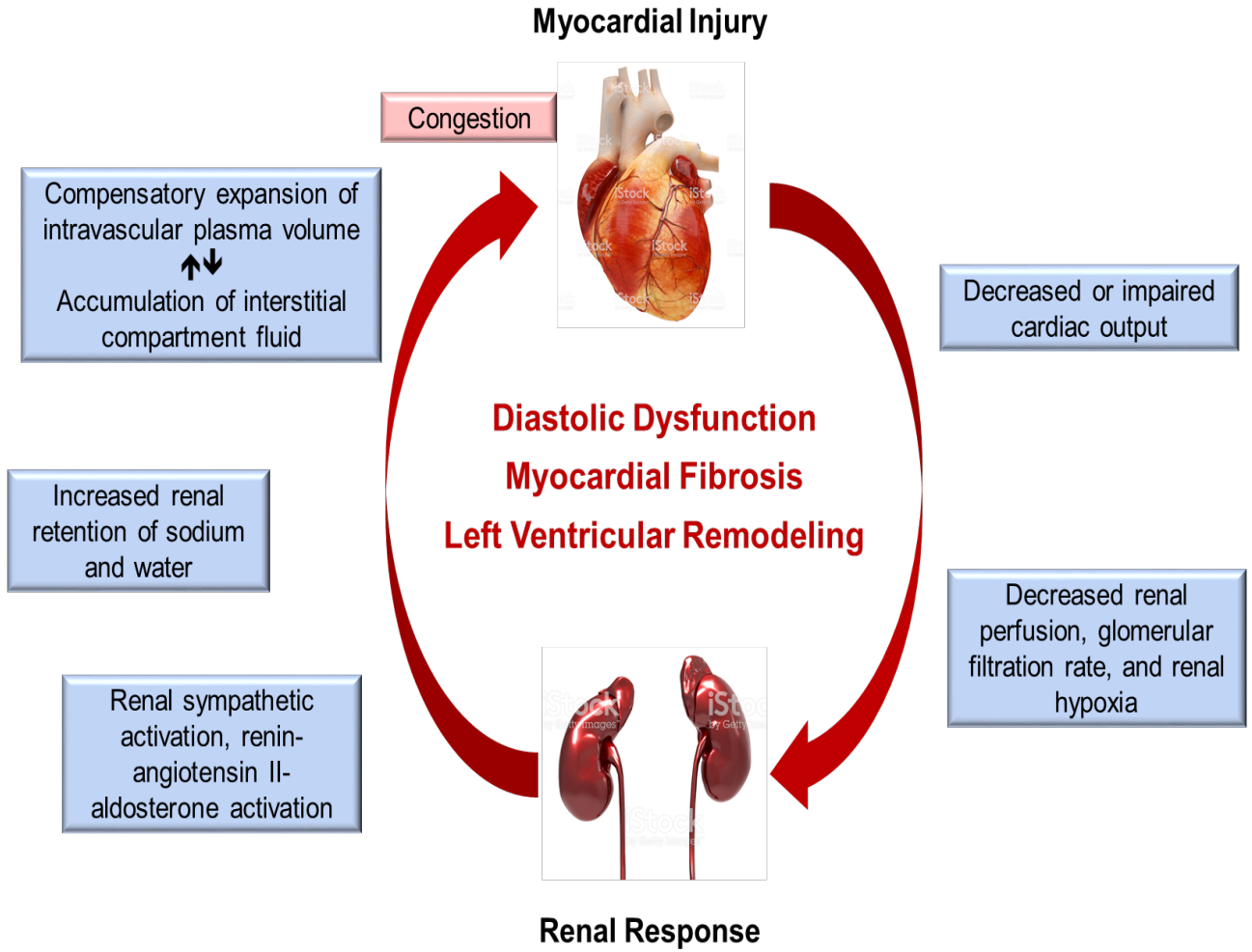
Rossing P, et al. BMJ.1996;313:779-84. Dinneen SF, et al. Arch Intern Med. 1997;157:1413-8. Masson S, et al. Circ Heart Fail. 2010;3:65-72. Anand IS, et al. Circulation. 2009;120:1577-84. Jackson CE, et al. Lancet. 2009;374:543-50. Gerstein HC, et al. JAMA. 2001;286:421-6. Karnib HH, et al. Diabetes Res Clin Pract. 2010;89:201-8.

eGFR and Outcomes

- Major studies – ARIC, CHS, HOT – brought eGFR into focus as factor to assess when evaluating CV risk, particularly in general population
- **ARIC:** Baseline eGFR 15-59 ml/min/1.73 m^2 ↑ risk of CVD 38% over baseline eGFR 90-150 ml/min/1.73 m^2
- **CHS**: 22% of participants had CKD at baseline; researchers determined by multivariate analysis that traditional risk factors, including diabetes, were significant predictors of CV mortality (all $p < 0.05$) but no novel factors (e.g., CRP) elevated risk
- **HOT**: Patients with reduced renal function (creatinine clearance ≤60 ml/min) demonstrated significantly greater risk for CV events than those with creatinine clearance >60 ml/min

Manjunath G, et al. J Am Coll Cardiol. 2003;41:47-55.
Shlipak MG, et al. JAMA. 2005;293:1737-45.
Ruilope LM, et al. J Am Soc Nephrol. 2001;12:218-25

Renal Dysfunction and Heart Failure



Connection between renal dysfunction and heart failure (HF) critical:

- Kidneys affected by DKD can be overwhelmed, unable to detoxify or excrete waste products
- Two-thirds patients have at least mild renal impairment
- 7% increase in mortality for every 10 ml/min reduction in estimated GFR

Verbrugge FH, et al. Cardiorenal Med. 2014;4:176-88.
Miller WL. Circ Heart Fail. 2016;9:e002922.
Smith GL, et al. J Am Coll Cardiol. 2006;47:1987-96.
Hillege HL, et al. Circulation. 2006;113:671-8.

Fibrosis

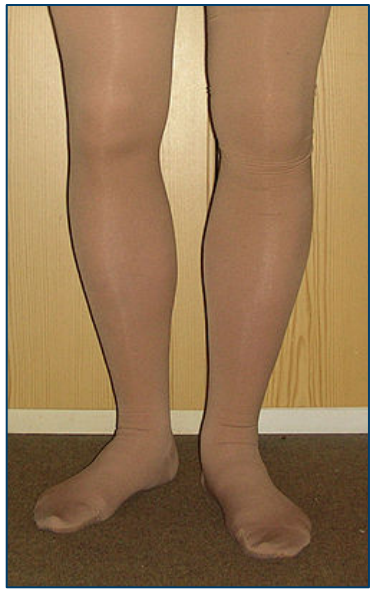
Myocardial Fibrosis →	Renal Fibrosis →
Atrioventricular block	Glomerular sclerosis
Bundle branch block	Reduced renal filtration function
Atrial fibrillation	Rapidly progressing CKD
Ventricular arrhythmias	
Systolic and diastolic dysfunction	
Heart failure	

Travers JG, et al. Circ Res. 2016;118:1021-40.
Ham O, et al. Sci Rep. 2018;8:16087.
Zannad F, et al. Circulation. 2018;138:929-44.
Hundae A, et al. Nephron Clin Pract. 2014;127:106-12.

DKD Classification and Trials Relating to DKD and CRS

Signs and Symptoms of DKD

- Nephropathy: 3% of patients with newly diagnosed type 2 diabetes already have overt nephropathy
- DKD relatively asymptomatic in early stages
- Peripheral edema: usually first sign; occurs in late stages
- Additional signs and symptoms
  - Hypertension
  - Elevated A1C
  - Dyspnea
  - Fatigue
  - Nausea
  - Hematuria
  - Dysgeusia



Persson F, et al. Kidney Int Suppl. 2018;8:2-7.

Screening: Albuminuria and eGFR

Albuminuria

UACR	Creatinine
Normal	<30 mg/g
Increased	≥30 mg/g

Urinary albumin-to-creatinine ratio via random spot urine collection

eGFR

	eGFR
Normal	≥60 ml/min/1.73 m^2
Abnormal	<60 ml/min/1.73 m^2

Calculated using validated formula, preferably CKD-EPI equation

- Diagnosis based on:
  - Measurement of albuminuria
  - Estimated GFR
  - Clinical features, such as diabetes duration and presence of diabetic retinopathy
- Screening recommended at least once a year

CKD Progression Risk

Risk of CKD Progression, Frequency of Visits, and Nephrology Referrals per GFR and Albuminuria

				Albuminuria Categories Description and Range		
Green = low risk Yellow = moderately increased risk Orange = high risk Red = very high risk (Numbers = numbers of visits per year)				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR Categories (ml/min/1.73 m²) Description and Range	G1	Normal or high	≥90	**1 if CKD**	**Treat 1**	**Refer 2**
	G2	Mildly decreased	60-89	**1 if CKD**	**Treat 1**	**Refer 2**
	G3a	Mildly to moderately decreased	45-59	**Treat 1**	**Treat 2**	**Refer 3**
	G3b	Moderately to severely decreased	30-44	**Treat 2**	**Refer 3**	**Refer 3**
	G4	Severely decreased	15-29	**Refer 3***	**Refer 3***	**Refer 4+**
	G5	Kidney failure	<15	**Refer 4+**	**Refer 4+**	**Refer 4+**

*Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treatment or referrals.

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KDIGO CKD Work Group. Kidney Int Suppl. 2013;3:1-150. Fox CS, et al. Lancet 2012;380:1662-73.
ADA. Diabetes Care. 2020;43:S135-S151. Vassalotti JA, et al. Am J Med 2016;129:153-162.e7.

Diabetes, DKD, and CRS: Setting the Stage

- Key trials have demonstrated impact of intensive glucose lowering in treatment of type 2 diabetes
- Hypothesized intensive glucose control also prevent renal disease
- Meta-analysis of 7 trials (N = 28,065) of intensive vs. conventional glucose control therapy that compared surrogate (micro- and macroalbuminuria) and clinical (doubling of serum creatinine, ESRD, death from renal disease) renal endpoints
  - Intensive therapy reduced risk for surrogate but not clinical renal endpoints

UK Prospective Diabetes Study Group. Lancet. 1998;352:837-53.
ADA. Diabetes Care. 2002;25:s33-s49.
Gerstein HC, et al. N Engl J Med. 2008;358:2545-59.
Coca SG, et al. Arch Intern Med. 2012;172:761-9.

Cardiovascular Outcomes Trials

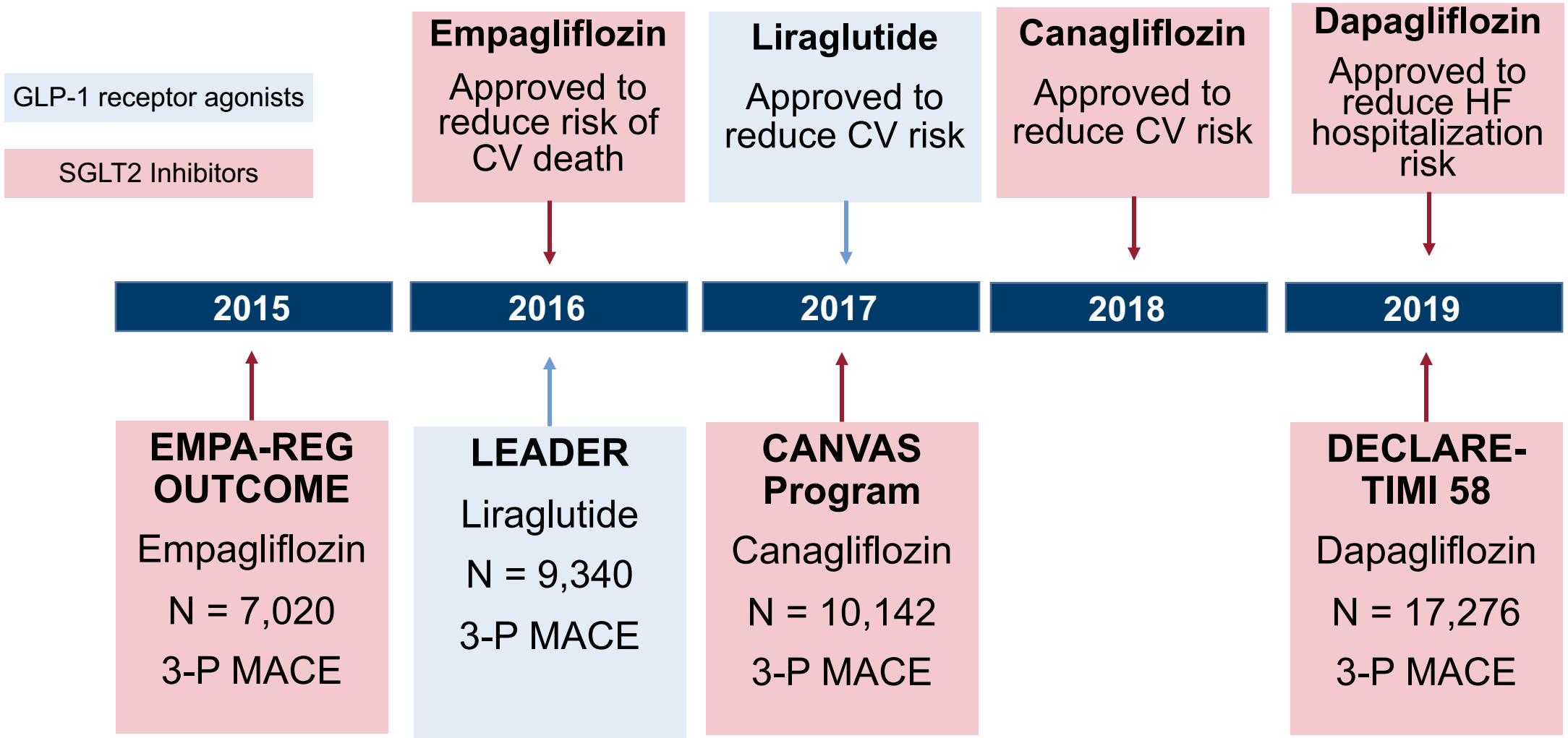
- Since FDA issued guidance >25 CVOTs have launched
- Primary endpoint: major adverse cardiac events (MACE)
  - 3-point MACE = cardiovascular death, nonfatal myocardial infarction, nonfatal stroke
  - 4-point MACE = 3-point MACE + additional CV endpoint (acute coronary syndrome or hospitalization for heart failure or unstable angina)

Major Drug Classes Studied

DPP-4 Inhibitors	GLP-1 Receptor Agonists	SGLT2 Inhibitors
• Alogliptin • Linagliptin • Saxagliptin • Sitagliptin	• Albiglutide • Dulaglutide • Exenatide • Lixisenatide • Liraglutide • Semaglutide	• Canagliflozin • Dapagliflozin • Empagliflozin • Ertugliflozin

- DPP-4 inhibitors: Increase incretin levels, reducing release of glucagon and increasing insulin secretion
- GLP-1 receptor agonists: Stimulate glucose-dependent insulin release and inhibit glucagon secretion
- SGLT2 inhibitors: Interfere with glucose reabsorption and prevent renal reuptake of glucose from the glomerular filtrate

Agents Approved for CV Outcomes



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Zinman B, C, Lachin JM, et al. N Engl J Med. 2015;373:2117-28. Marso SP, et al. N Engl J Med. 2016;375:311-22.
Neal B, et al. N Engl J Med. 2017;377:644-57. Wiviott SD, et al. N Engl J Med. 2019; 380:347-57.

Renal Outcomes in CVOTs

- **DPP-4 inhibitors**
  - Inconsistent results on renal outcomes
  - Most produced no significant differences in prespecified endpoints, but some reduced UACR
- **GLP-1 receptor agonists**
  - Results varied among agents in which renal endpoints were studied
  - Most had reduced or similar rates of adverse renal events versus placebo
- **SGLT2 inhibitors**
  - Effects expected as agents act on glucose reabsorption in the kidney
  - Results showed relative risk reductions, some significant, with various renal endpoints

CREDENCE

Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation

In people with type 2 diabetes, eGFR 30 to 90 ml/min/1.73 m^2, and UACR 300 to 5000 mg/g receiving standard of care, CREDENCE assessed whether canagliflozin compared with placebo reduces

Primary:

- Composite outcome of ESRD, doubling of serum creatinine, or renal or CV death

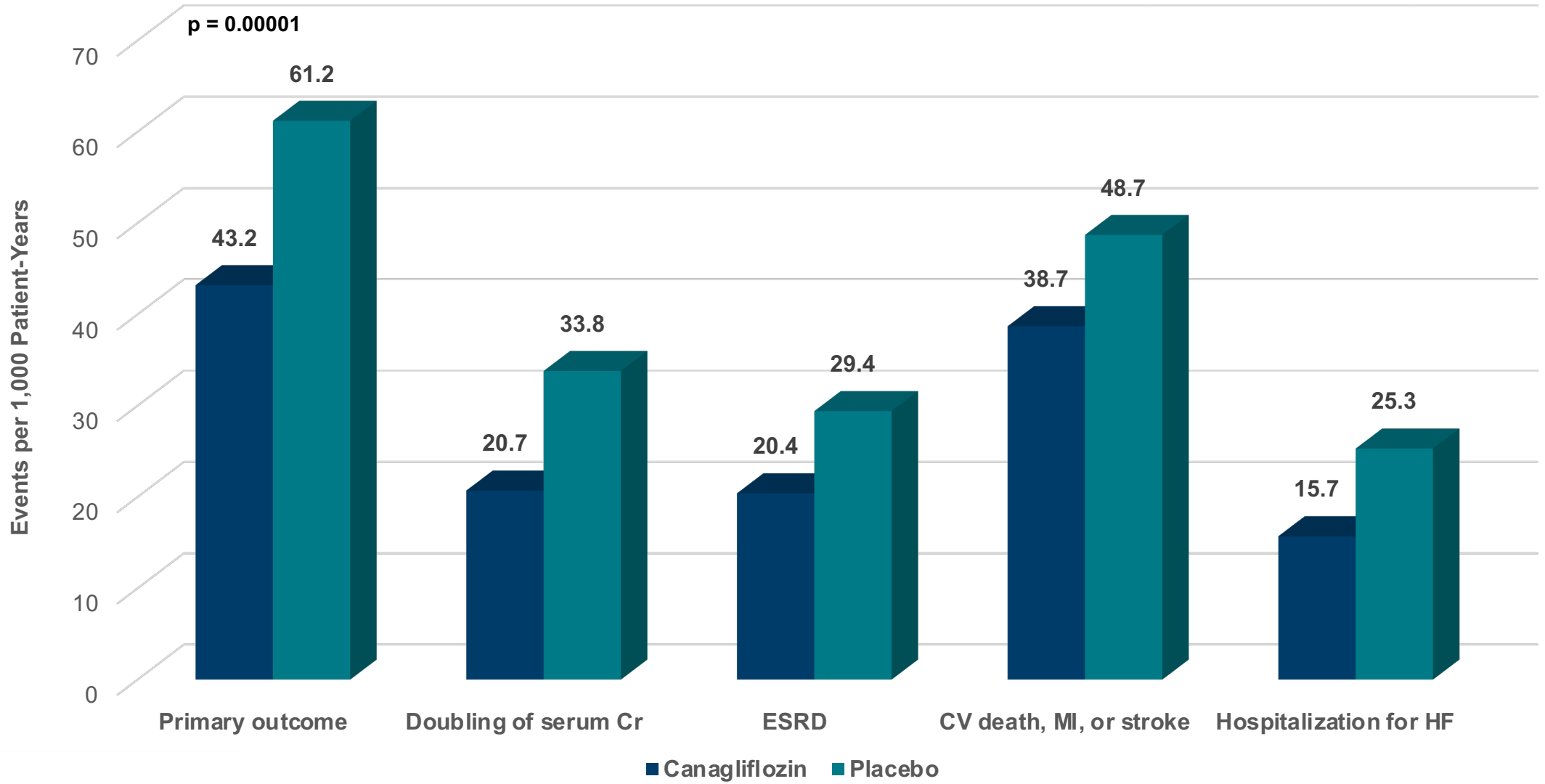
Secondary:

- CV death or hospitalization for heart failure
- Major cardiovascular events (3-point MACE: CV death, MI, or stroke)
- Hospitalization for heart failure
- ESRD, doubling of serum creatinine, or renal death
- CV death
- All-cause mortality
- CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina

DIABETES LEADERSHIP EDGE

Perkovic V, et al. N Engl J Med. 2019;380:2295-306.

CREDENCE

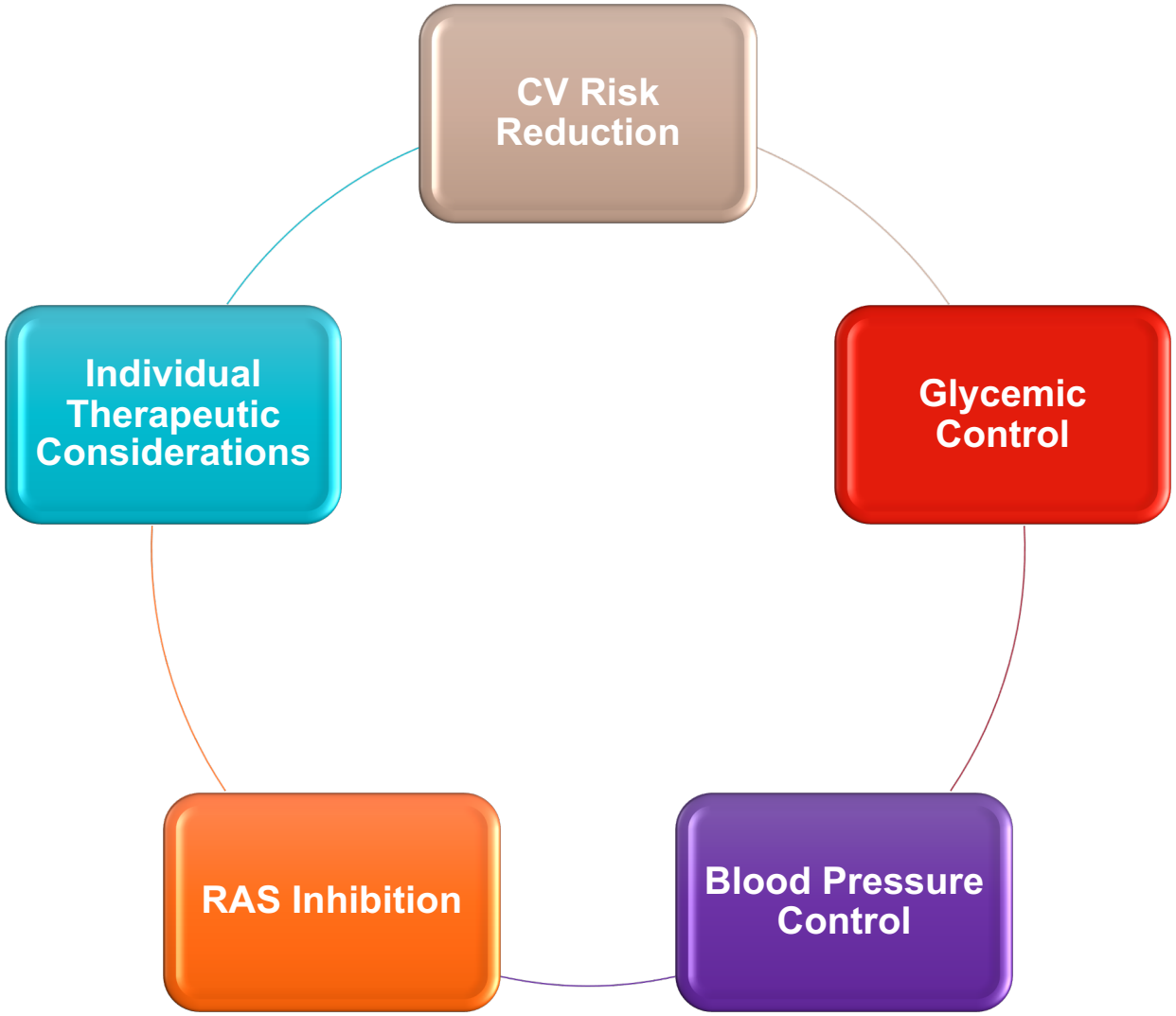


DIABETES LEADERSHIP EDGE

Perkovic V, et al. N Engl J Med. 2019;380:2295-306.

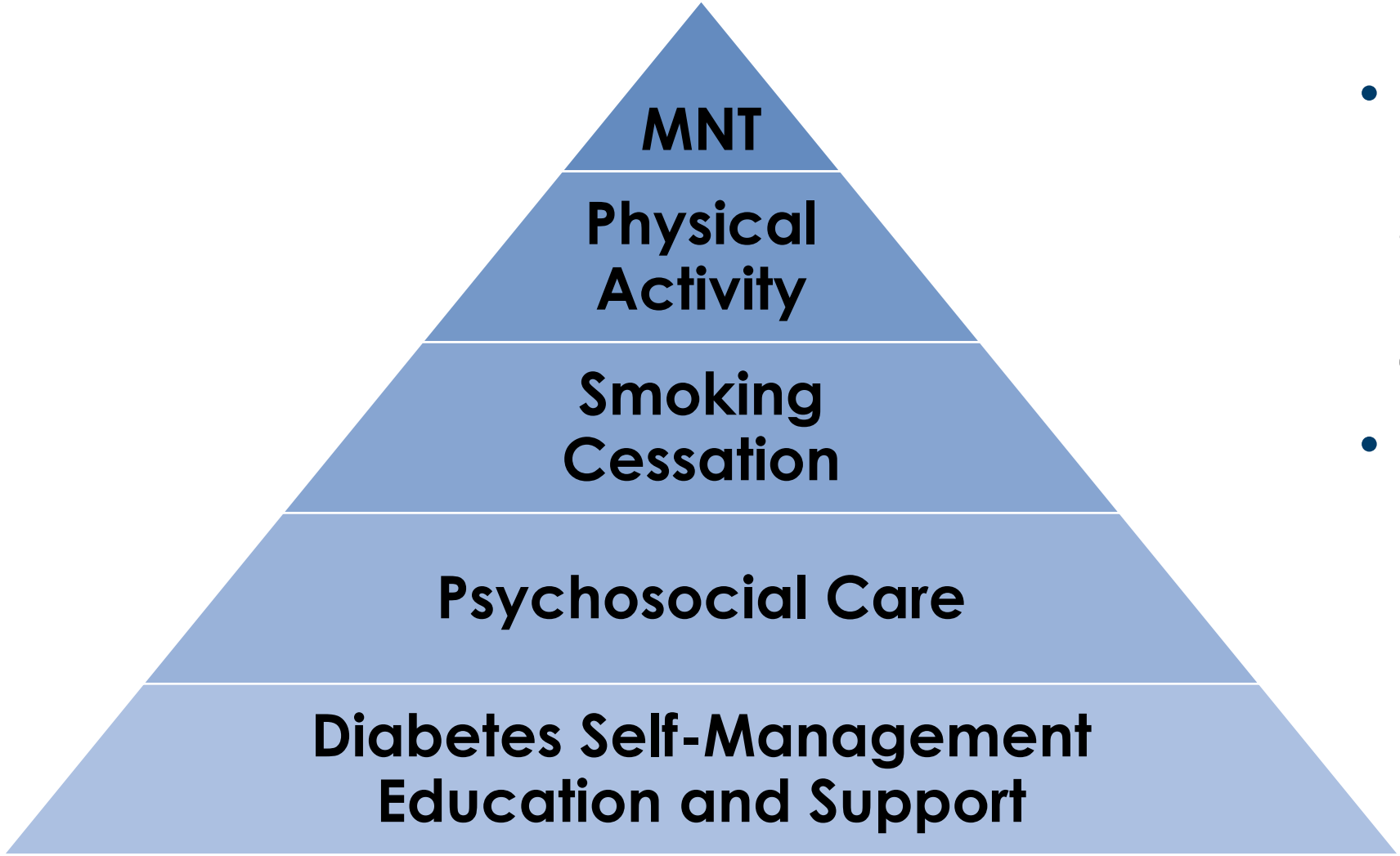
Management of DKD

Multifaceted Management Strategies



DIABETES LEADERSHIP EDGE

Lifestyle Modification and Patient Education



- Facilitating behavior change and well-being to improve health outcomes
- Patient-centered care with individualized management plan

DIABETES LEADERSHIP EDGE

ADA. Diabetes Care. 2020;43:S37-S47. ADA. Diabetes Care. 2020;43:S48-S65.
Evert AB, et al. Diabetes Care. 2019;42:731-54. Powers MA, et al. Diabetes Care. 2015;38:1372-82.

Appropriate Blood Pressure Control

- Blood pressure should be maintained at <130/80 mm Hg to prevent microvascular changes
  - Monitor at every clinical visit
- ACE inhibitors/ARBs reduce BP, decrease albuminuria
  - Also first-line therapy for HF, other CV comorbidities
- Combination therapy often needed
  - Other classes to consider per ADA: diuretics, calcium-channel blockers
- Choice of agent(s) dependent on patient preferences, comorbidities, concomitant therapy, and potential adverse effects

ADA. Diabetes Care. 2020;43:S111-S134.
Whelton PK, et al. J Am Coll Cardiol. 2018;71:e127-e248.
Van Buren PN, et al. Adv Chronic Kidney Dis. 2011;18:28-41.

Mineralocorticoid Receptor Antagonists

- MRAs block epithelial and nonepithelial actions of aldosterone
- Spironolactone and eplerenone decrease BP, provide protection in CKD and HF
  - May ↑ hyperkalemia risk in patients with stage 3+ CKD
- Trial data
  - EMPHASIS-HF: patients with diabetes, eGFR <60 had a benefit for CV mortality, HF hospitalization with eplerenone
  - RALES: mortality benefit from aldactone for patients with reduced EF, median creatinine ≥1.2 mg/dl
  - ARTS: finerenone reduced albuminuria in patients with CKD and HF
  - ARTS-DN: finerenone reduced UACR
- No specific recommendations for use

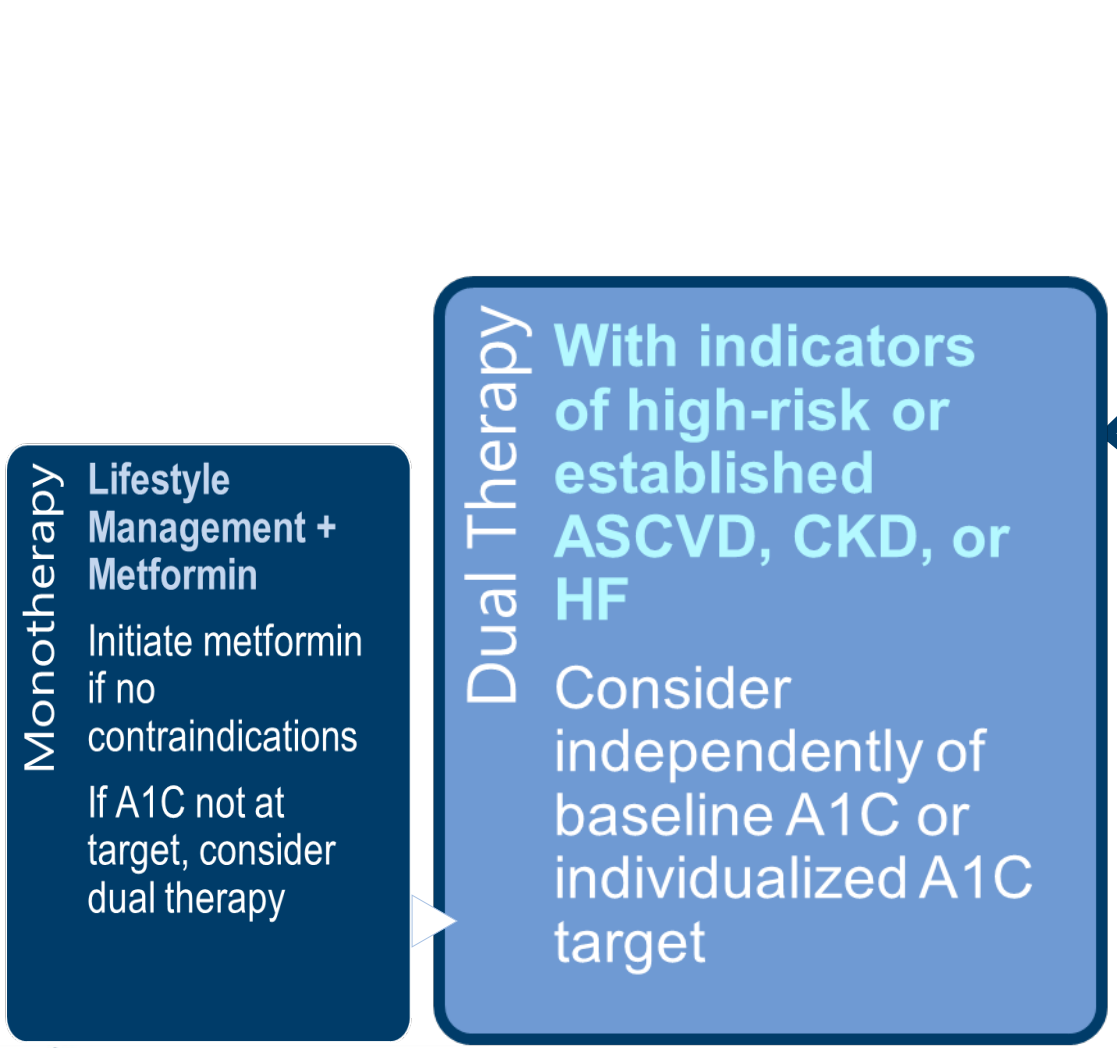
Sica DA. Methodist Debakey Cardiovasc J. 2015;11:235-9. Cooper LB, et al. J Am Heart Assoc. 2017;6.pii:e006540.
Pitt B, et al. N Engl J Med. 1999;341:709-17. Zannad F, et al. N Engl J Med. 2011;364:11-21.
Filippatos G, et al. Eur Heart J. 2016;37:2105-14. Bakris GL, et al. JAMA. 2015;314:884-94.

Dyslipidemia Management

- Diabetes associated with substantially increased risk of premature atherosclerotic CVD
  - In patients with type 2 diabetes, increased CV risk often precedes onset of hyperglycemia
- Stepwise approach to statin therapy to match patient's risk
  - Younger patients with no ASCVD – moderate-intensity statin therapy
  - Patients with multiple ASCVD risk factors – high-intensity statin therapy
- Other agents
  - Ezetimibe
  - PCSK9 inhibitors
  - Icosapent ethyl

ADA. Diabetes Care. 2020;43:S111-S134.
Grundy SM, et al. J Am Coll Cardiol. 2019;73:e285-e350.

SGLT2 Inhibitors and GLP-1 Receptor Agonists



ASCVD Predominates

PREFERABLY

- **GLP-1 receptor agonist** with proven CVD benefit* **OR**
- **SGLT2 inhibitor** with proven CVD benefit (if eGFR adequate)*

HF or CKD Predominate

PREFERABLY

- **SGLT2 inhibitor** with evidence of reducing HF and/or CKD in CVOTs if eGFR adequate† **OR**
- If SGLT2 inhibitor not tolerated or contraindicated or if eGFR less than adequate, add **GLP-1 receptor agonist** with proven CVD benefit*

***Proven CVD benefit** = label indication of reducing CVD events (canagliflozin, empagliflozin, liraglutide; dapagliflozin for HHF)

†Evidence from CVOTs = empagliflozin, canagliflozin, and dapagliflozin have shown ↓ HF and CKD progression

DIABETES LEADERSHIP EDGE

ADA. Diabetes Care. 2020;43:S98-S110.

Summary

- Numerous pathophysiological and risk factors of diabetic kidney disease have been shown to underlie cardiovascular disease.
- The interconnection of type 2 diabetes, cardiovascular disease, and diabetic kidney disease manifests in macrovascular and microvascular complications that can affect management of all three diseases.
- Screening for diabetic kidney disease focuses on albuminuria and estimated glomerular filtration rate
- The connection between renal dysfunction and heart failure has been shown to be critical as heart failure is a disease of volume overload and congestion characterized by renal retention of sodium and water.
- Trials using new and established drug classes are demonstrating safety and efficacy in cardiovascular and renal outcomes.

Paraphrased Excerpts from “An Ode to the Nephron”

Like [we do with our] experiences of life, [the nephron] filter[s] and retain[s]…

Struggles, yearns and lives a purposeful life…

There is only so much it can handle, only so much agony and so much pain…

Oh, how much like one’s life, what a masterpiece is a nephron.

Asudani, Deepak. An Ode to a Nephron. Am J Nephrol 2004;24:162–163.

AAPA Learning Central

The Diabetes Leadership Edge modules (7) are currently available on AAPA's Learning Central at www.cme.aapa.org