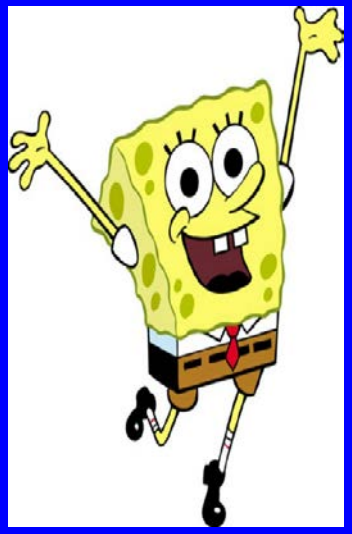


Drugs to Treat Type 2 DM Demonstrate Reductions in Major Adverse Cardiovascular Events





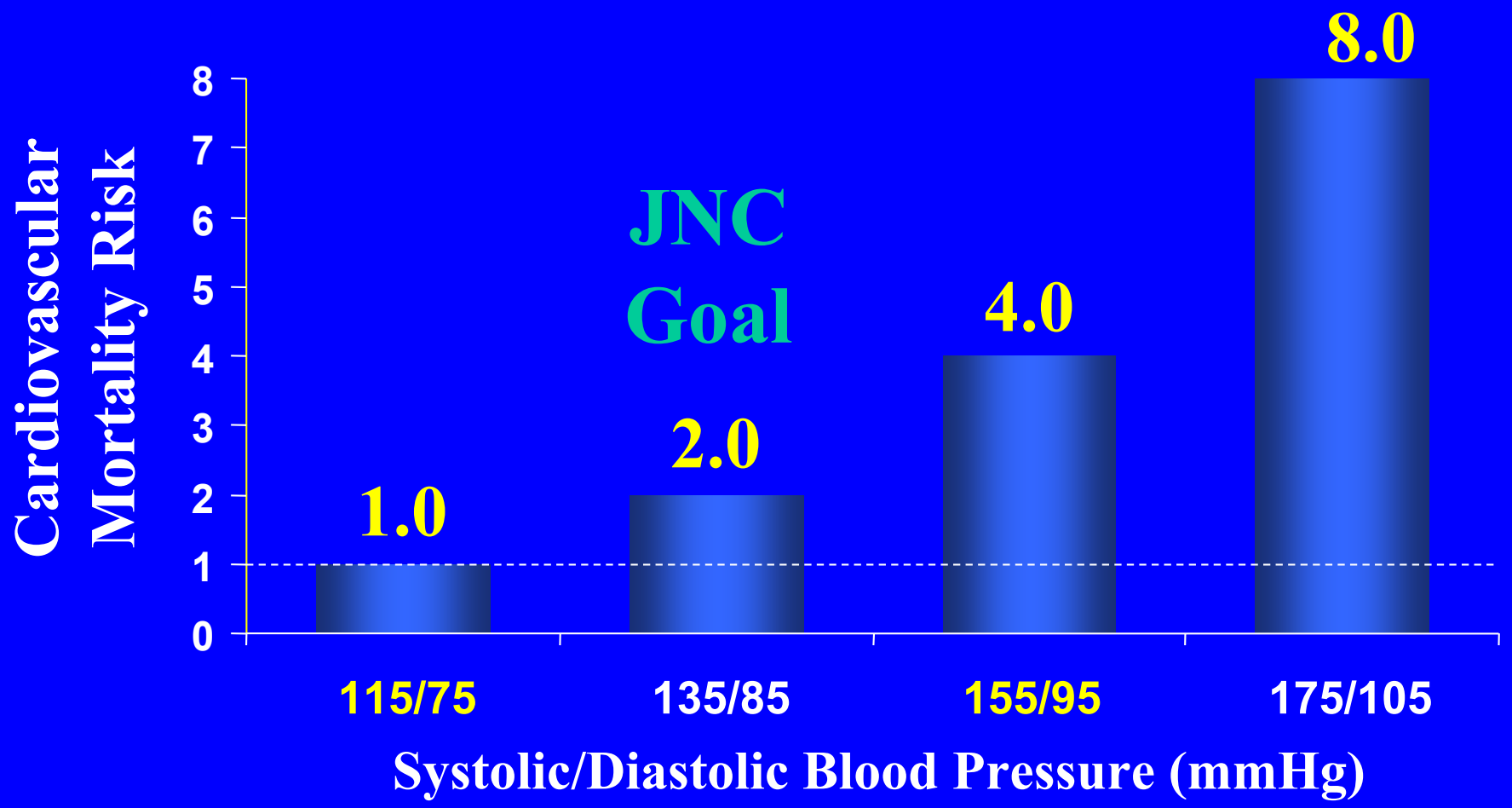


How does all this play out when it comes to treating patients with type 2 DM who have chronic kidney disease?

Therapeutic Approaches to Treating CKD in Type 2 DM

- Management of diabetic kidney disease must focus on treatment of hyperglycemia and hypertension with a foundation of inhibition of the Renin-Angiotensin Aldosterone System
- Intensifying management of glycemia produces small reductions in albuminuria, but has not decreased risk of death, CVD, or ESRD
  - Risk of hypoglycemia often outweighs benefit
- Hypertension is the #1 cause of death in the world
  - JNC8 defines normal blood pressure at 120/80 mm/Hg, so anything higher than that is unacceptable, especially in patients with type 2 DM and CKD

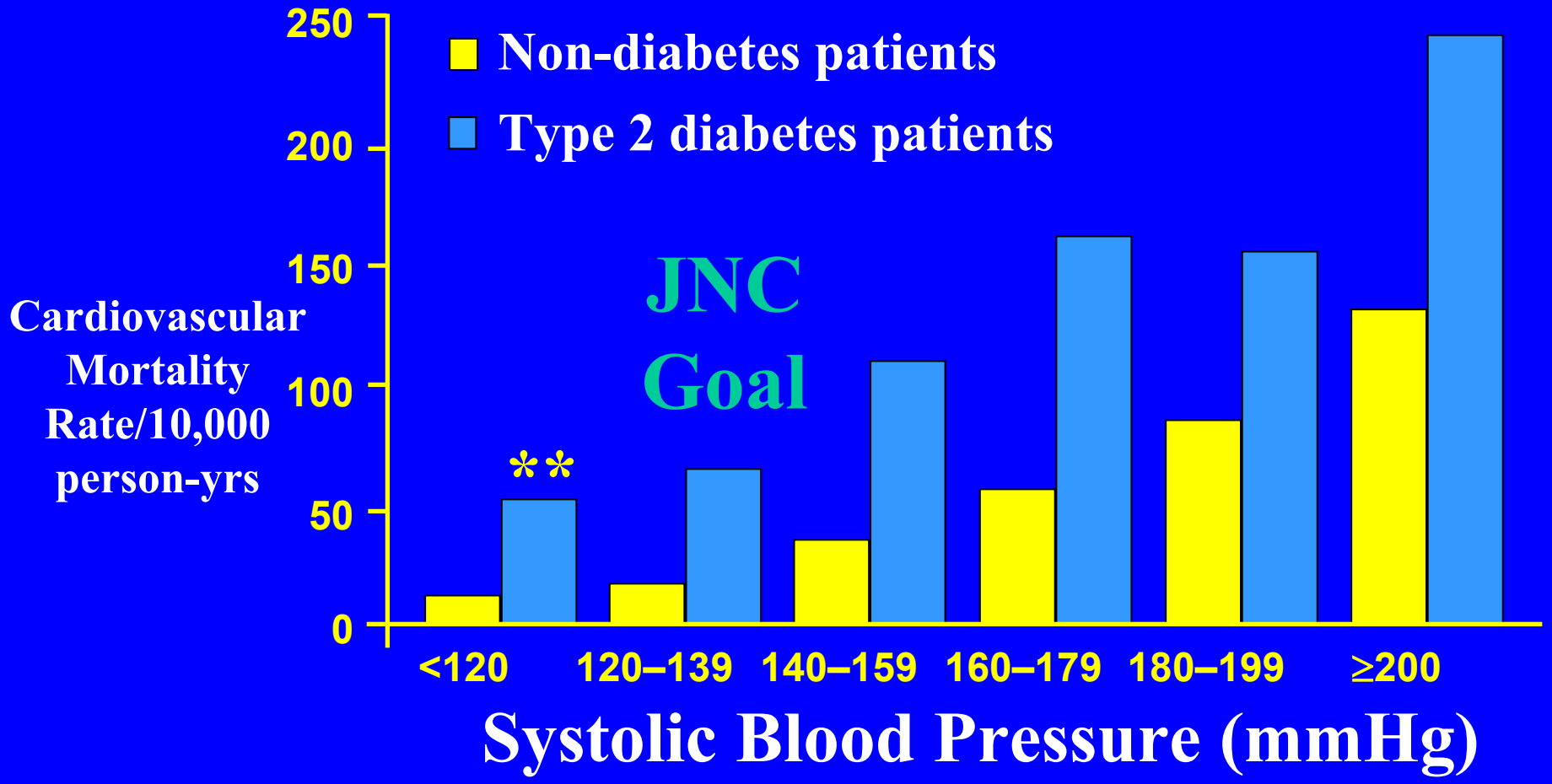
Cardiovascular Mortality Doubles with each 20/10mmHg Blood Pressure Increment Starting at 115/75mmHg



Individuals aged 40-70 years, starting at blood pressure 115/75 mmHg

Lancet 2002;360:1903-1913; JAMA 2003;289:2560-2572

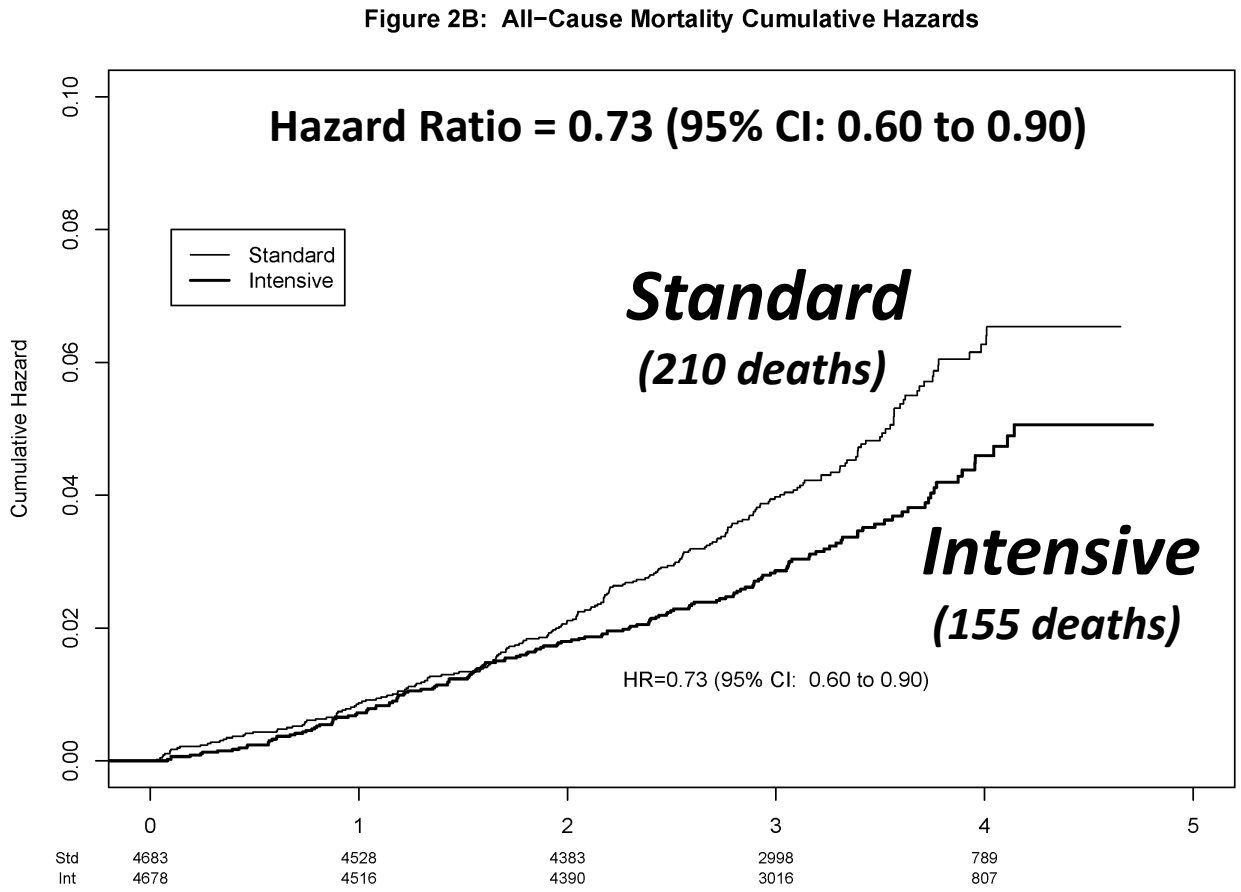
Increased Cardiovascular Mortality in Type 2 Diabetes Even at Systolic BP <120 mmHg



Why should we accept anything less than NORMAL in patients with type 2 DM?

Diabetes Care 1993;16:434-444

SPRINT Trial: All Cause Mortality



Number Needed to Treat to prevent one death was 90

N Engl J Med 2015;373:2103-2116

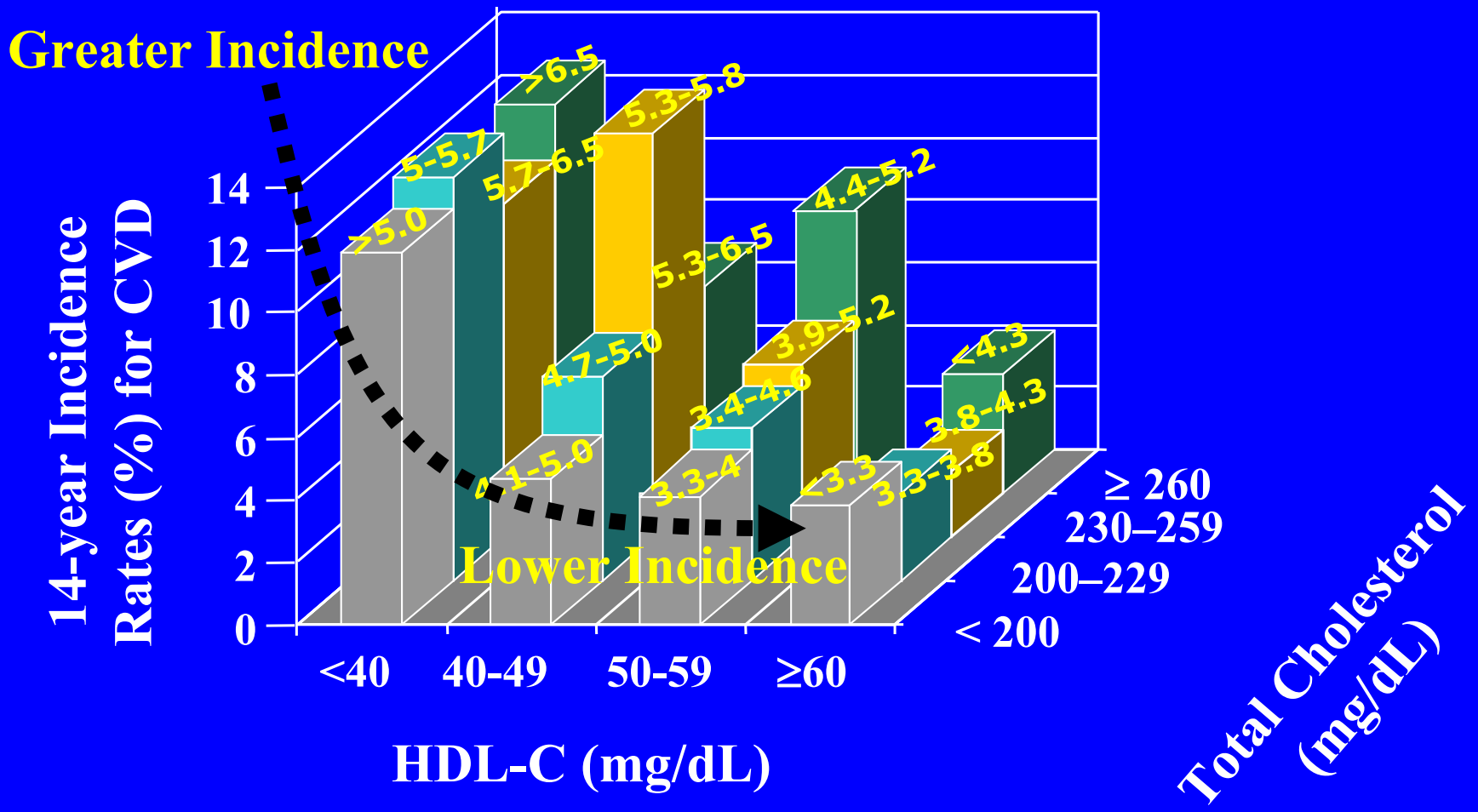
Therapeutic Approaches to Treating CKD in Type 2 DM (cont.)

- Dyslipidemia is frequently associated with CKD, but LDL-C does not reliably discriminate because many of the patients have lower HDL-C and higher triglycerides
  - Lipid goal should be a total cholesterol/HDL-C ratio < 4
  - For patients on dialysis, statins should NOT be initiated
- Albuminuria is a powerful independent risk factor for progression of CKD and CVD.
  - While. many trials looked at reductions in albuminuria, primary outcomes were not designed to study that relationship
  - Future study designs must look at albuminuria as a primarily end point to prove (of refute) the validity of albuminuria as a target in reducing CKD and CVD.

Total Cholesterol/HDL-C Ratio

High Cardiovascular Disease Risk when Ratio > 5

Risk Attenuates Once Ratio ≤ 5



NOTE the curvilinear risk of CVD when TC/HDL-C ratio is > 5 vs. ≤ 5.

JAMA 1986;256:2835-38

21 Statin vs. Control Studies

Lancet 2012;380:581-590

Study	n =	TC/HDL	Ratio-Pre	Ratio-Post	LDL-Pre	LDL-Post	Drug (s)	↓Mortality
BASELINE PRE TC/HDL-C RATIO > FIVE								
1. WOSCOPS	6595	272/44	6.18	4.71	192	142	Pravastatin	31%
2. AFCAPS	6605	221/36	6.14	4.71	150	115	Lovastatin	37%
3. LIPID	9014	218/36	6.06	4.74	150	113	Pravastatin	24%
4. 4D	1255	218/36	6.05	4.24	125	72	Atorvastatin	None
5. 4S	4444	261/46	5.67	3.97	188	122	Simvastatin	42%
6. ALLIANCE	2442	226/40	5.65	4.04	147	95	Atorvastatin	9%
7. HPS	20536	228/41	5.57	4.67	131	104	Simvastatin	18%
8. CARE	4159	209/39	5.36	4.08	139	100	Pravastatin	24%
9. LIPS	1677	200/38	5.26	3.48	131	96	Fluvastatin	31%
BASELINE PRE TC/HDL-C ≤ FIVE								
10. GISSI-P	4271	230/46	5.00	4.28	152	123	Pravastatin	None
11. ALERT	2102	251/51	4.90	3.90	160	109	Fluvastatin	None
12. ALLHAT	10355	224/48	4.67	3.69	146	104	Pravastatin	None
13. PROSPER	5804	220/50	4.40	3.15	147	100	Pravastatin	24%
14. CORONA	5011	210/48	4.40	3.08	138	76	Rosuvastatin	None
15. ASCOT	10305	212/50	4.26	3.26	133	90	Atorvastatin	10%
16. MEGA	8214	248/58	4.22	3.55	158	129	Pravastatin	None
17. ASPEN	2410	194/47	4.12	3.25	113	80	Atorvastatin	None
18.GISSI-HF	4574	192/48	4.00	3.45	123	90	Rosuvastatin	None
19. AURORA	2773	176/45	3.91	2.80	100	57	Rosuvastatin	None
20. CARDS	2838	207/54	3.83	3.31	118	82	Atorvastatin	None
21. JUPITER	17802	185/49	3.80	2.60	108	55	Rosuvastatin	20%

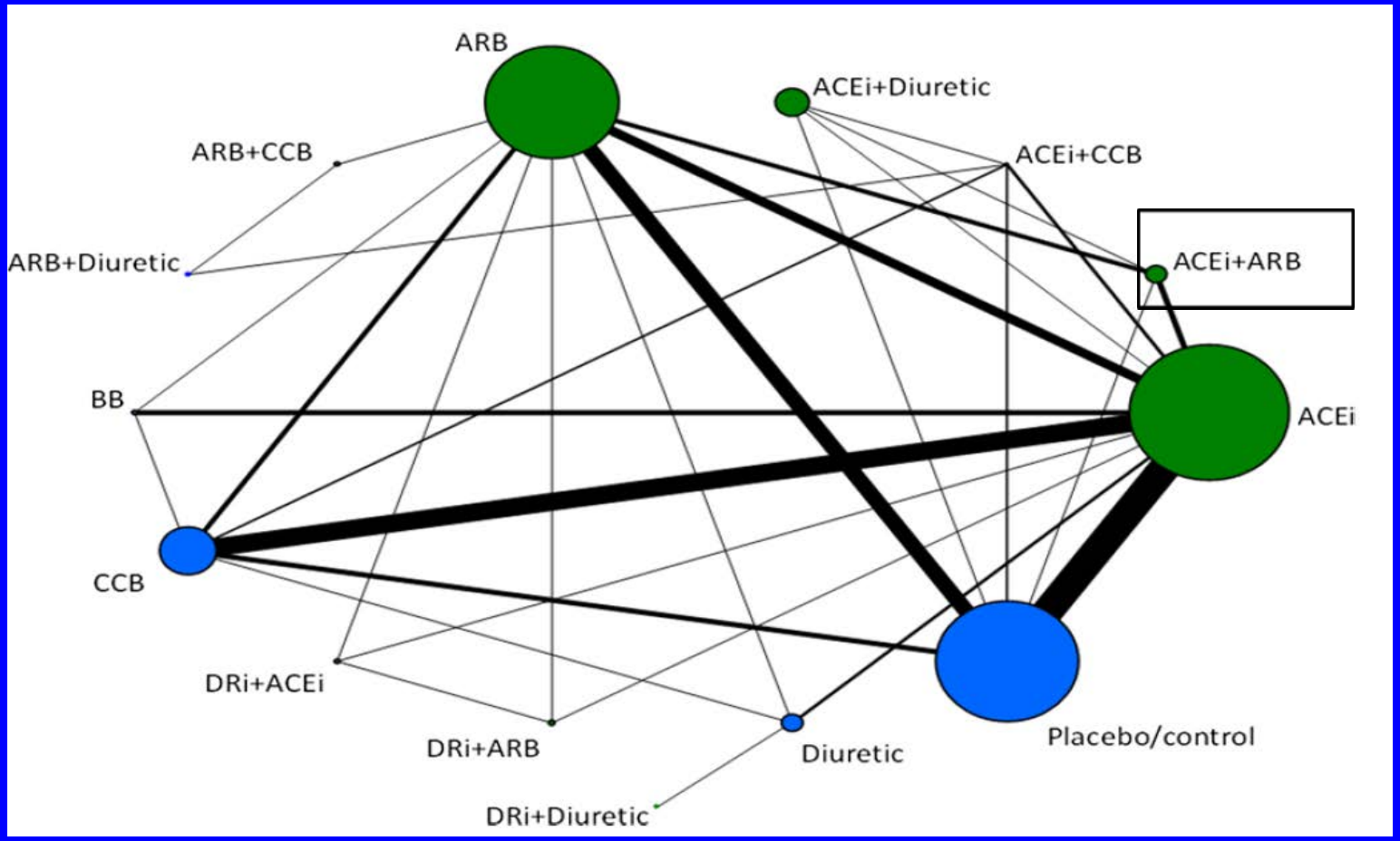
Pharmacologic Approaches to Treating CKD in Type 2 DM

1. Metformin must be considered cornerstone of treatment, when not contraindicated (eGFR <30)
2. For patients not at goal on metformin monotherapy, adding $SGLT_2$ inhibitors, like empagliflozin, is warranted when not contraindicated (eGFR <45). (+) CVD benefit ?Class effect?
3. For patients not at goal with metformin + $SGLT_2$ inhibitor, adding liraglutide or semaglutide is warranted when not contraindicated (eGFR <30). (+) CVD benefit NOT a GLP-1 agonist class effect
4. Approaches #2 and #3 are interchangeable based on personal preference; Remember: $SGLT_2$ inhibitory ↑glucagon
5. What impact does Cycloset have on the progression of CKD?

Pharmacologic Approaches to Treating CKD in Type 2 DM (cont.)

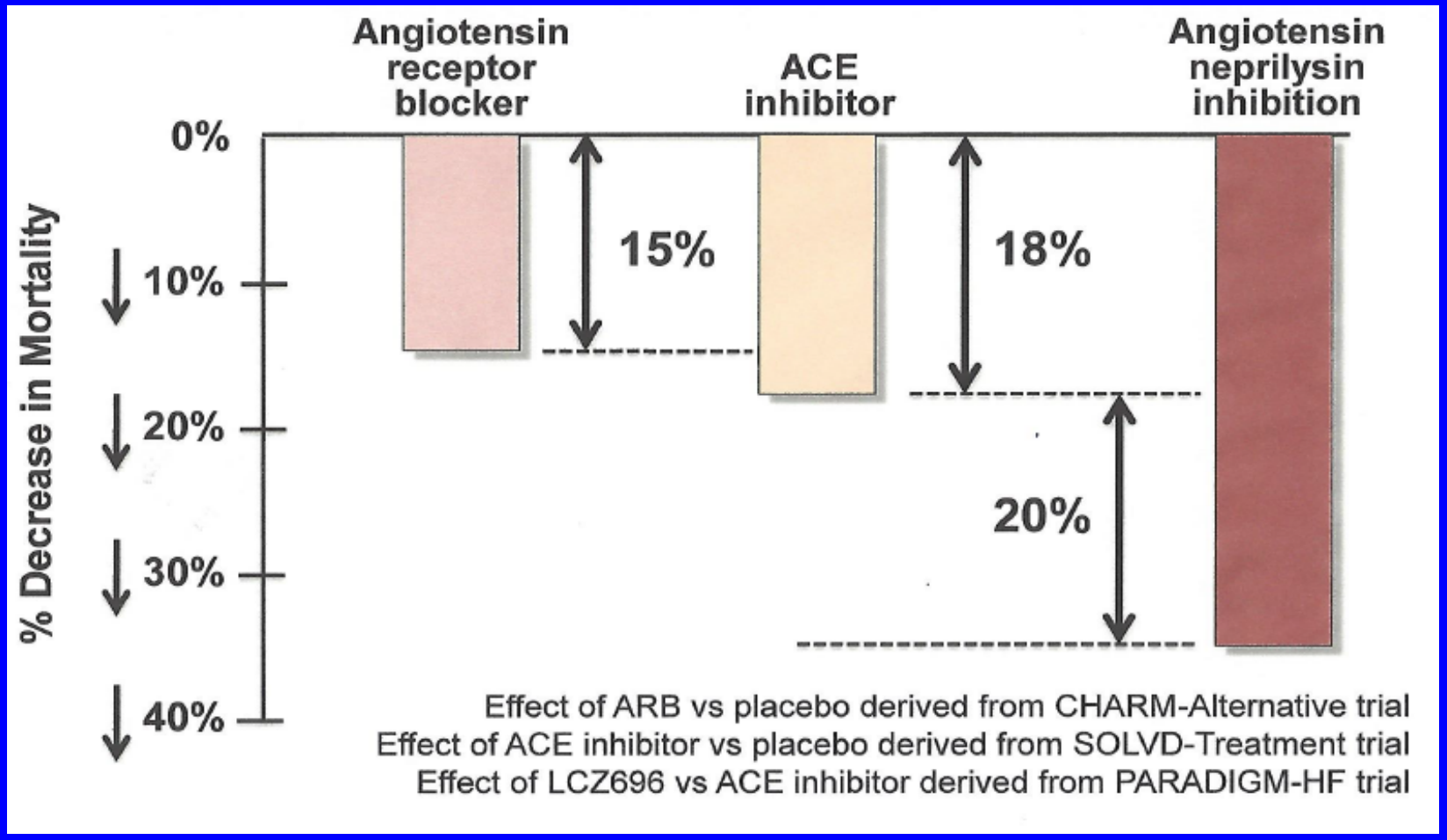
- Goal for blood pressure in patients with type 2 DM, with or without CKD, should be <120/80 mmHg
  - Blood pressure goal should be 5 mmHg above syncope if albuminuria is present!!
- Renin-Angiotensin System (RAS) inhibition is the cornerstone of treatment
- The UACR goal is less than 7.5 for women and less than 4.0 for men (based on muscle mass)
- Patients who are not at UACR goal despite acceptable blood pressure (or at risk of syncope), off-label higher dosing of an ACE inhibitor or ARB is warranted
  - "Duel" ACE inhibitor + ARB is also another option

Renin-Angiotensin System (RAS) Treatment Comparions

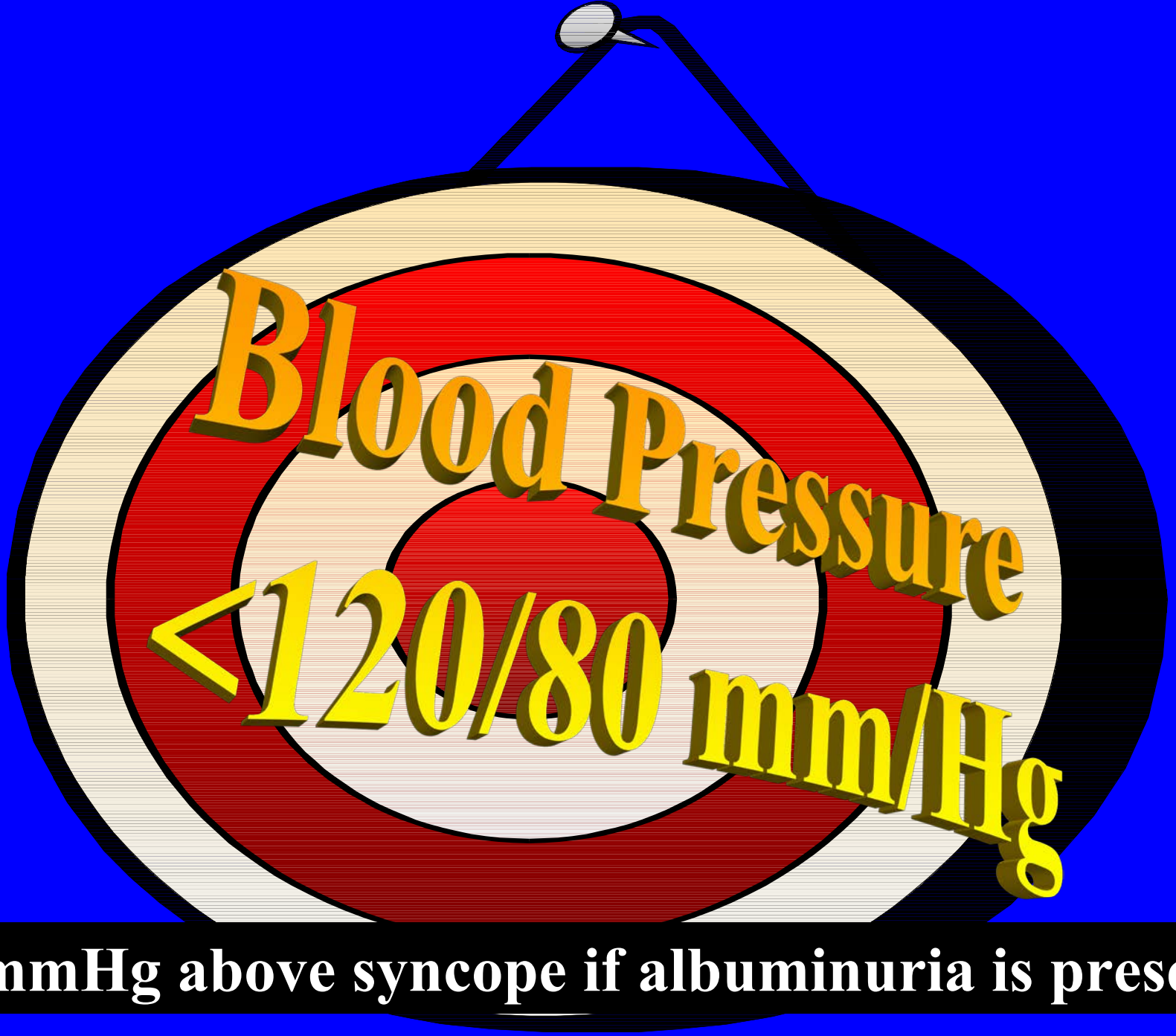


PLOS Medicine | DOI:10.1371/journal.pmed.1001971 March 8, 2016

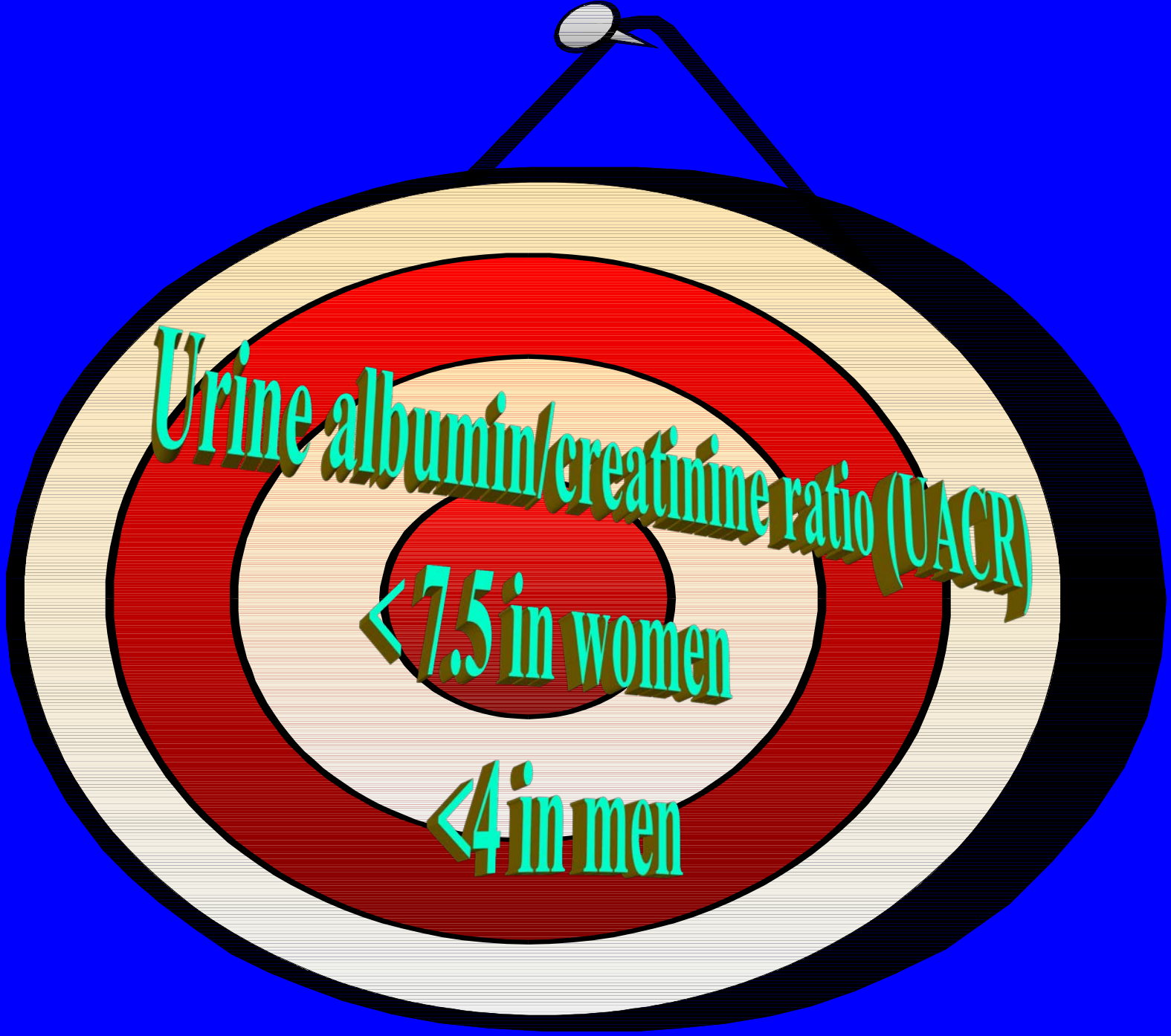
Angiotensin–Neprilysin Inhibition Superior to ARB or ACEi



N Engl J Med 2014;371:993-1004



5 mmHg above syncope if albuminuria is present!!


Urine albumin/creatinine ratio (UACR)
<7.5 in women
<4 in men

Pharmacologic Approaches to Treating CKD in Type 2 DM (cont.)

- Mineralocorticoid receptor antagonists (MRA) reduce albuminuria and total mortality when combined with RAS inhibition
- However, MRA increases risk of hyperkalemia in patients with stage 3b (eGFR 30-44) or higher stage CKD
- When contraindications, such as co-medication with potassium-sparing diuretics, are respected and renal function and potassium levels are closely monitored, patients with mild to moderate renal insufficiency appear to gain similar reductions in mortality and hospitalization by MRA as CHF patients with normal renal function
- Patiromer (Veltassa) and sodium zirconium cyclosilicate
  - Still determining ability to treat hyperkalemia and allow increased use of MRA (and RAS inhibition)

Circulation 2012;125:271-279

Teaching Tool—
Treating CKD in Type 2 Diabetes

- Hypertension and albuminuria are both independent variables that predict long-term decline in renal function
  - goal for blood pressure should be <120/80 mm/Hg
  - UACR goal <7.5 in women and <4.0 in men
- RAS is the cornerstone of treatment CKD
- Critical that future studies focus on albuminuria as a primary end-point
  - need to prove (or refute) the validity of albuminuria as a target in reducing CKD and CVD
- Total cholesterol/HDL-C should be <4
  - Statin therapy should NOT be started in patients receiving dialysis
- Metformin, cycloset, empagliflozin, liraglutide and semaglutide are drugs that benefit patients with type 2 diabetes
- Whether other drugs in the pipeline prove beneficial for patients with CKD remains to be seen