Management of hypertension in CKD: What's different point among ARBs?

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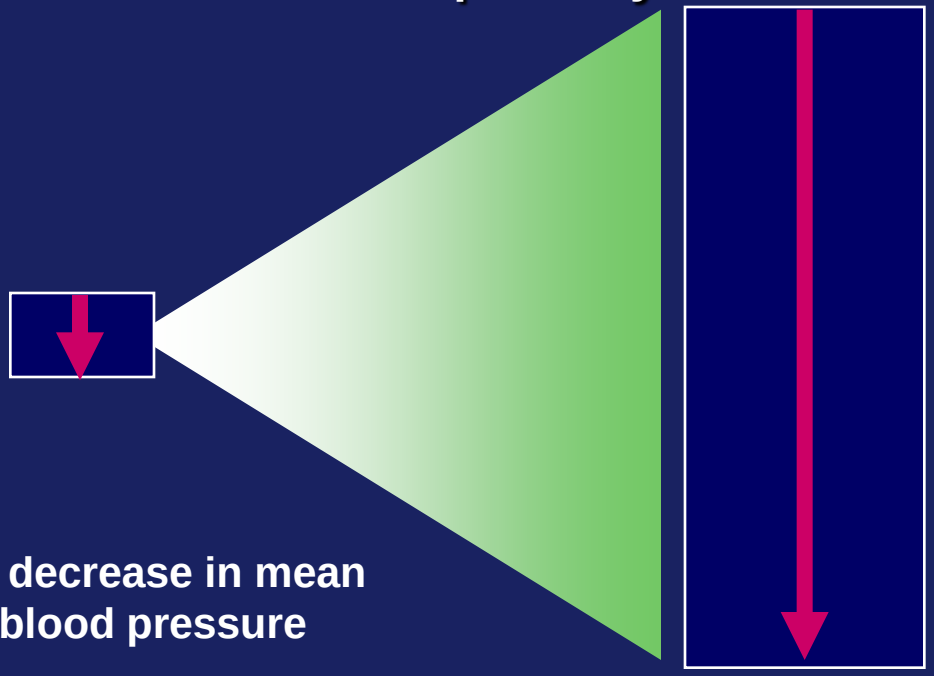
Topics

- Current guideline for HT management
- Role of RAS blockade in Cardio-Kidney Damage Continuum
- Review of Clinical Evidences of RAS Blockade Therapy focusing on Renoprotection
- Original vs Generic ARB: What is the difference?

Blood pressure reductions of as little as 2 mmHg reduce the risk of cardiovascular events by up to 10%

- Meta-analysis of 61 prospective, observational studies
- One million adults
- 12.7 million person-years



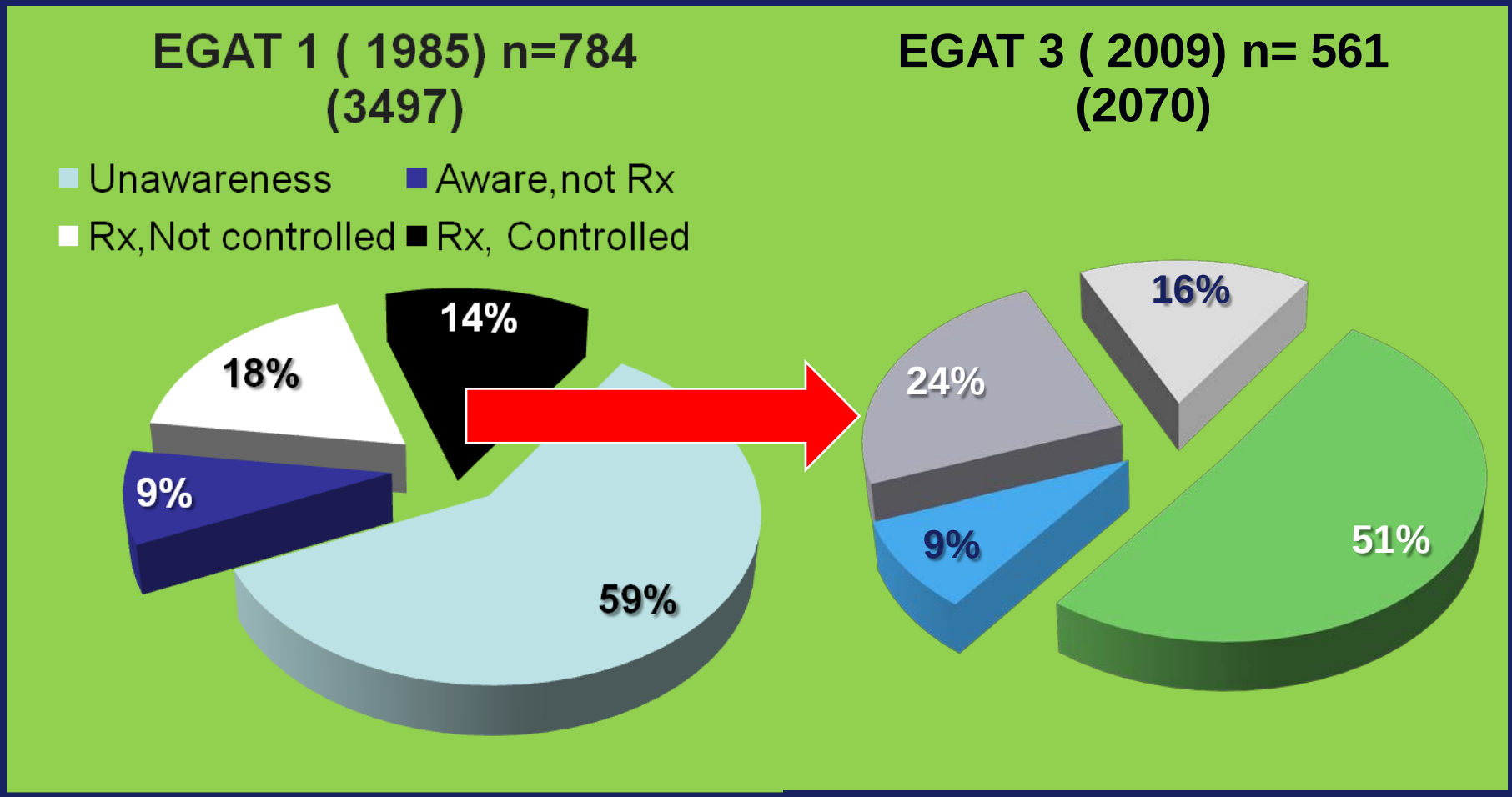
2 mmHg decrease in mean systolic blood pressure

7% reduction in risk of ischemic heart disease mortality

10% reduction in risk of stroke mortality

Lewington S et al. Lancet. 2002;360:1903–1913.

EGAT study: HT in real world



Sritara P, *et* al; 2010

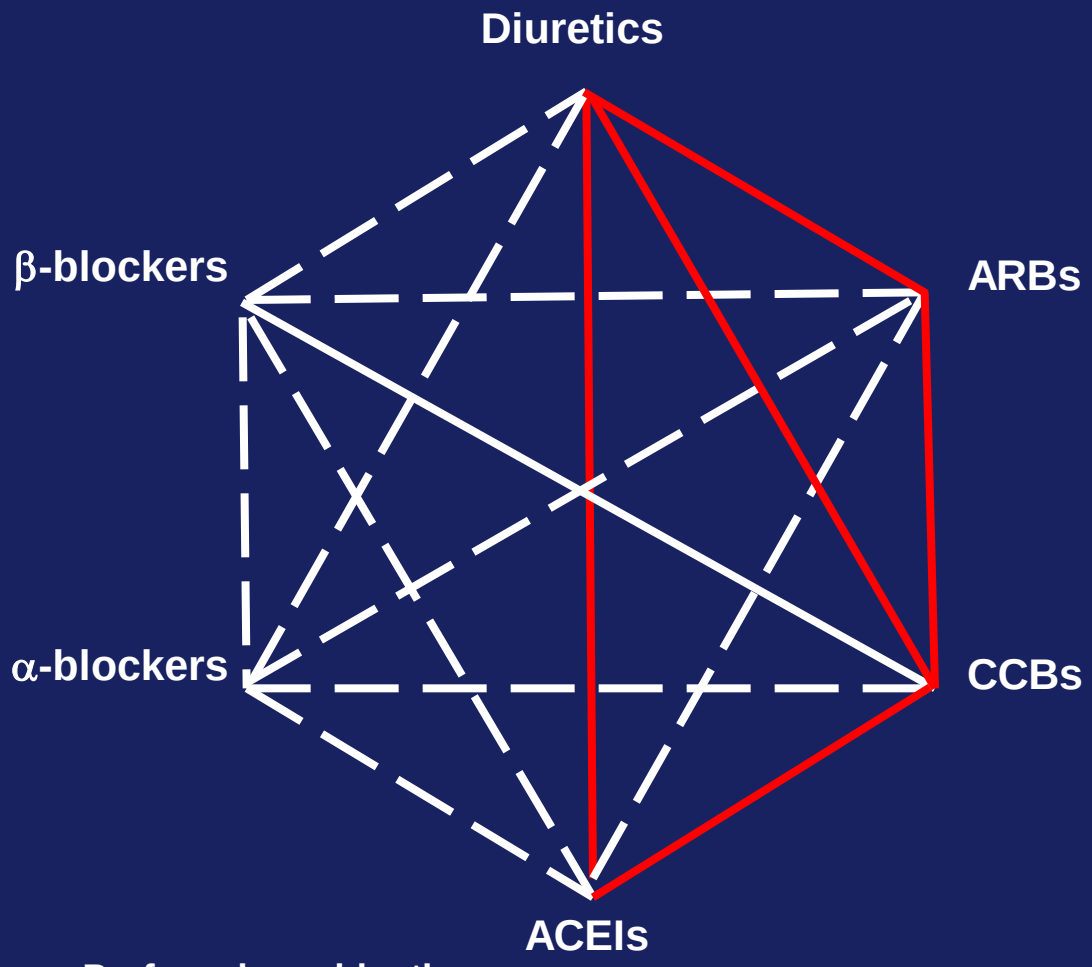
ESH–ESC Guidelines Recommend Target BP Goals of <140/90 mmHg for Uncomplicated Hypertension and <130/80 mmHg for Complicated Hypertension

Type of hypertension	BP goal (mmHg)
Uncomplicated	<140/90
Complicated	
Diabetes mellitus	<130/80
Kidney disease	<130/80*
Other high risk (stroke, myocardial infarction)	<130/80

***Lower if proteinuria is >1 g/day**

Task Force of ESH–ESC. J Hypertens 2007;25:1105–87

ESH–ESC Recommendations for Combining BP-lowering Drugs and Availability as Single-pill Combinations



- **ESH-ESC recommendations include**
  - **ARB + diuretic**
  - **ARB + CCB**
  - **CCB + diuretic**

Task Force for ESH–ESC. J Hypertens 2007;25:1105–87.

NICE Hypertension Guidelines

	Aged <55yrs	Aged ≥55yrs or Black AC
Step 1	A	C*
Step 2	A + C*	
Step 3	A + C* + D	
Step 4 Resistant Hypertension	A + C* + D + Further Diuretic[+] Consider specialist Advice	

A = ACEi or ARB

C = CCB

D = Thiazide-like diuretic

C* = CCB preferred but D is an alternative in people intolerant of C or at high risk of heart failure

Further Diuretic: Consider low dose spironolactine or higher dose thiazide

BHS British Hypertension Society

NICE hypertension guidelines 2011 http://guidance.nice.org.uk/CG127/QuickRefGuide/pdf/English accessed August 2011)

How about Thailand?

ตารางที่ 8 หลักการใช้ยาลดความดันโลหิต

	อายุ ≤ 55 ปี	อายุ > 55 ปี
Step 1	A	C/D
Step 2	A + C/D	C/D + A
Step 3	A + C + D	
Step 4	A + C + D	
	เพิ่ม diuretics เช่น spironolactone 25 มก./วัน หรือ furosemide ก่อนการให้ α-blocker หรือ β-blocker	

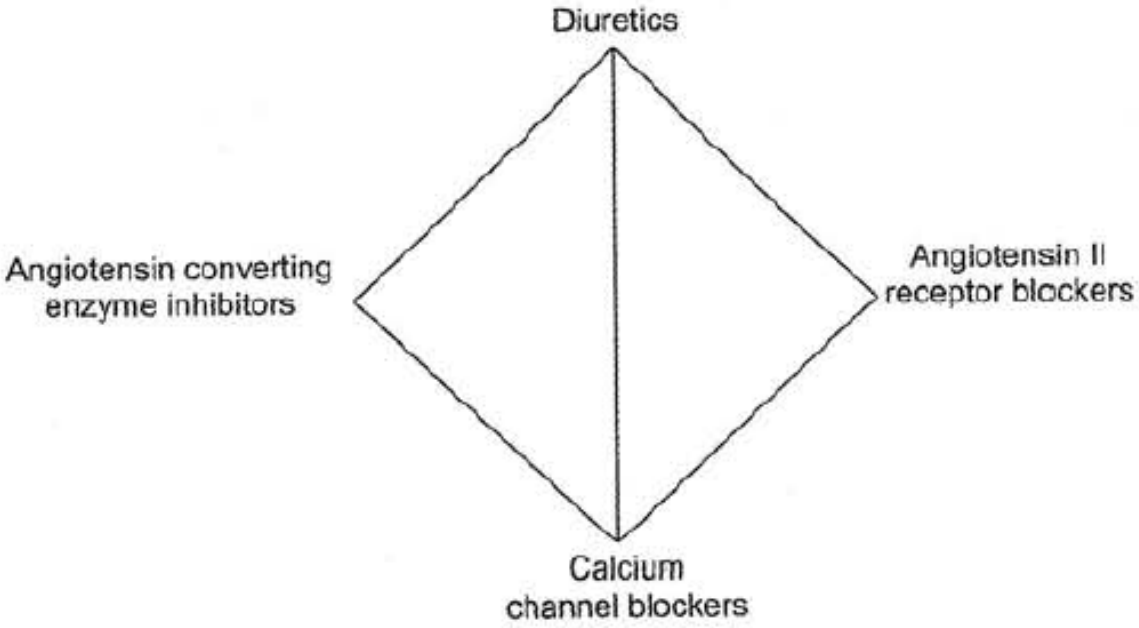
หมายเหตุ: A: ACEIs หรือ ARBs (ให้ใช้ ACEIs ก่อน หากเกิดอาการไอ จึงเปลี่ยนเป็น ARBs) (น้ำหนัก +/คุณภาพหลักฐาน I)

C: Calcium channel blockers (ให้เลือกใช้ก่อน diuretics) (น้ำหนัก +/คุณภาพหลักฐาน II)

D: Diuretic (ให้ระวังการใช้ในผู้ที่มีความเสี่ยงต่อการเป็นโรคเบาหวาน โรคเก๊าท์ และการเกิดภาวะเกลือแร่ผิดปกติในเลือดซึ่งมักพบในผู้สูงอายุ)

Thailand HT Guideline

รูปที่ 1 การเลือกใช้ยาลดความดันโลหิตที่สามารถเสริมฤทธิ์กัน



Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH; Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

JAMA. doi:10.1001/jama.2013.284427
Published online December 18, 2013.

2014 Guideline for Management of High Blood Pressure

Questions Guiding the Evidence Review

This evidence-based hypertension guideline focuses on the panel's 3 highest-ranked questions related to high BP management identified through a modified Delphi technique.[5] Nine recommendations are made reflecting these questions. These questions address thresholds and goals for pharmacologic treatment of hypertension and whether particular antihypertensive drugs or drug classes improve important health outcomes compared with other drug classes.

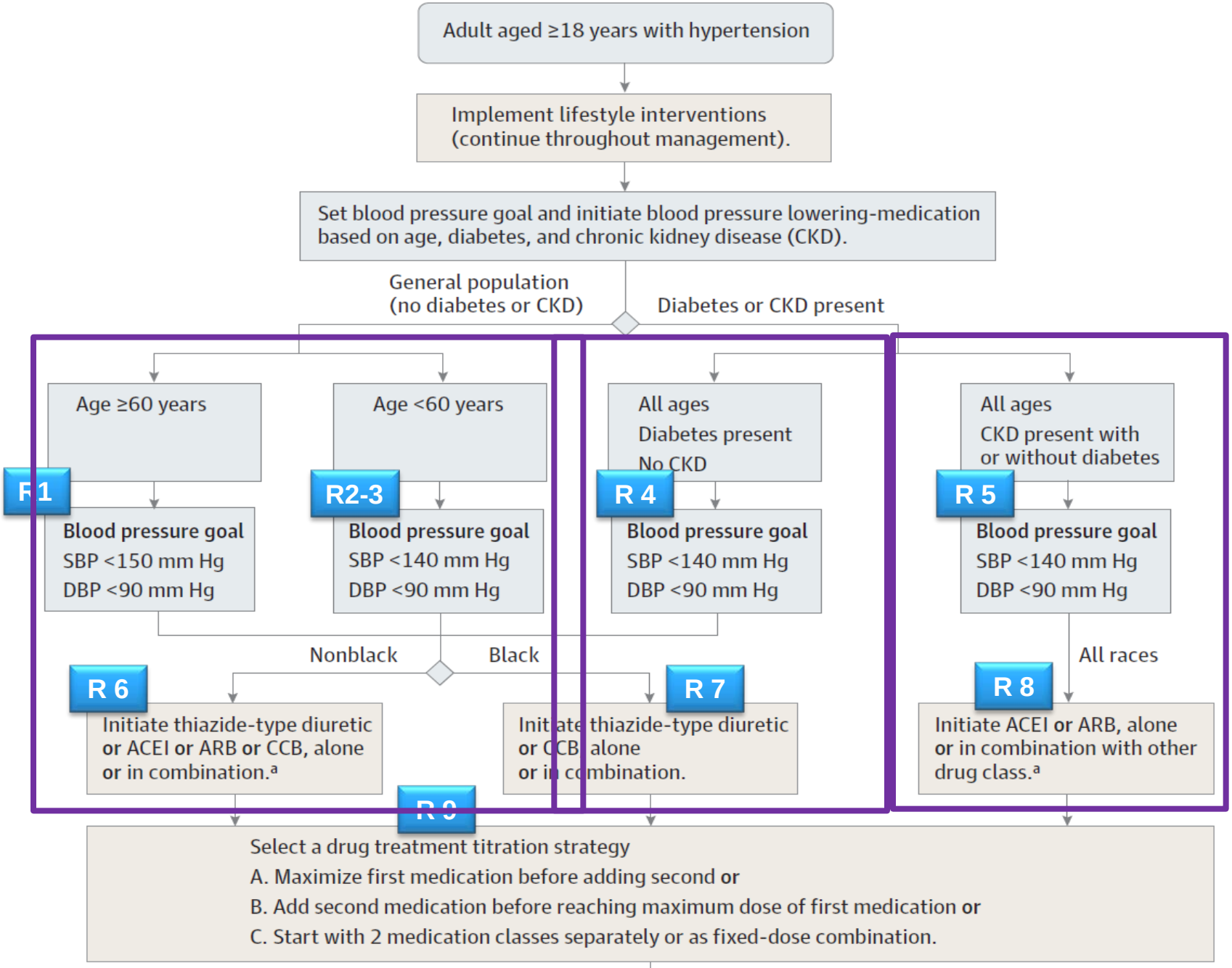
1. In adults with hype…nsive pharmacologic therapy… …health outcomes?
2. In adults with hyper…tension, does treatment with antihypertensive pharmacologic… …goal lead to improvements in heal…
3. In adults with hypertension, do various antihypertensive drugs or drug classes differ in … …s and harms on specific health outcomes?

THRESHOLD

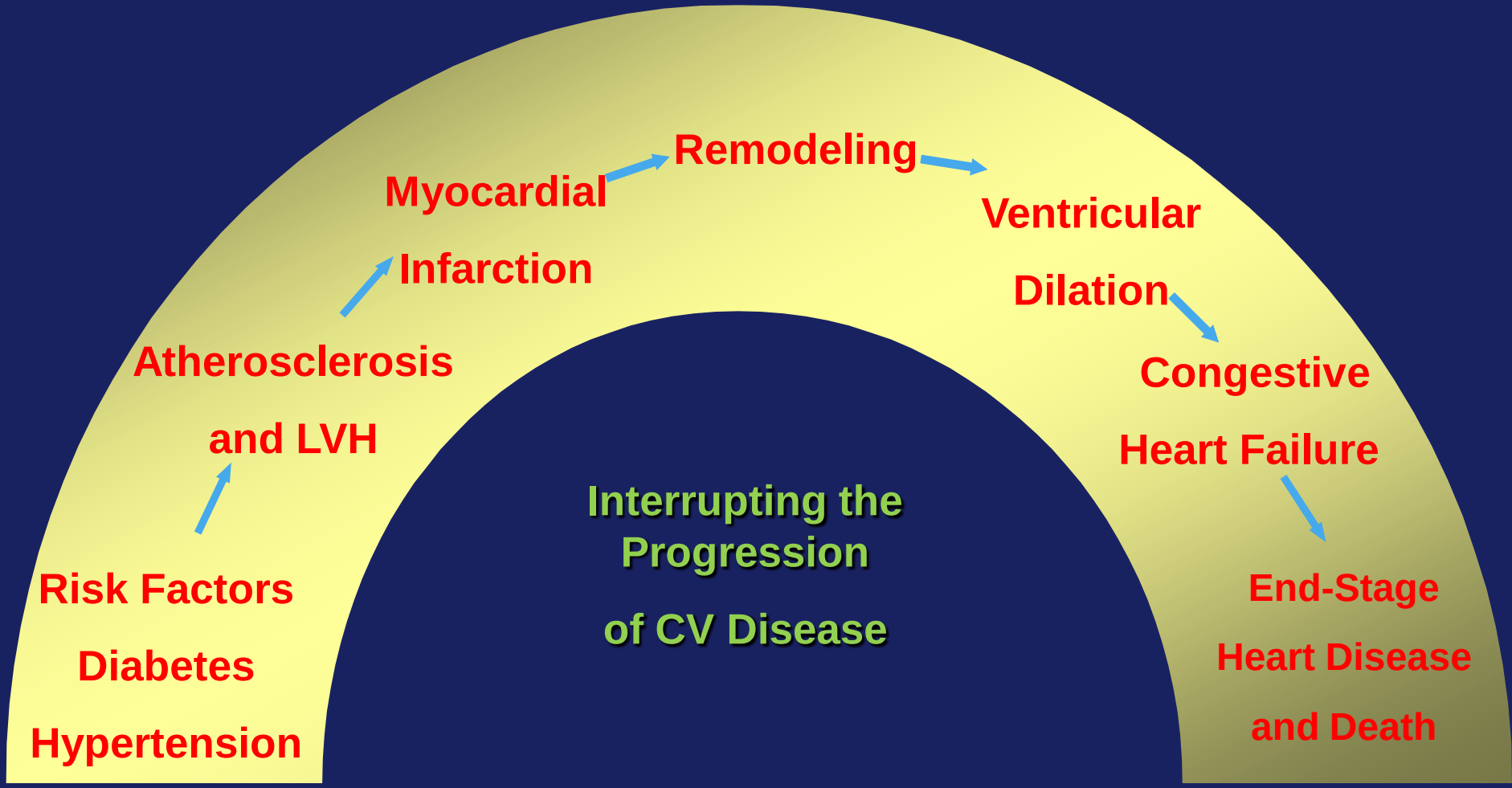
Goal?

Drug?

Figure. 2014 Hypertension Guideline Management Algorithm

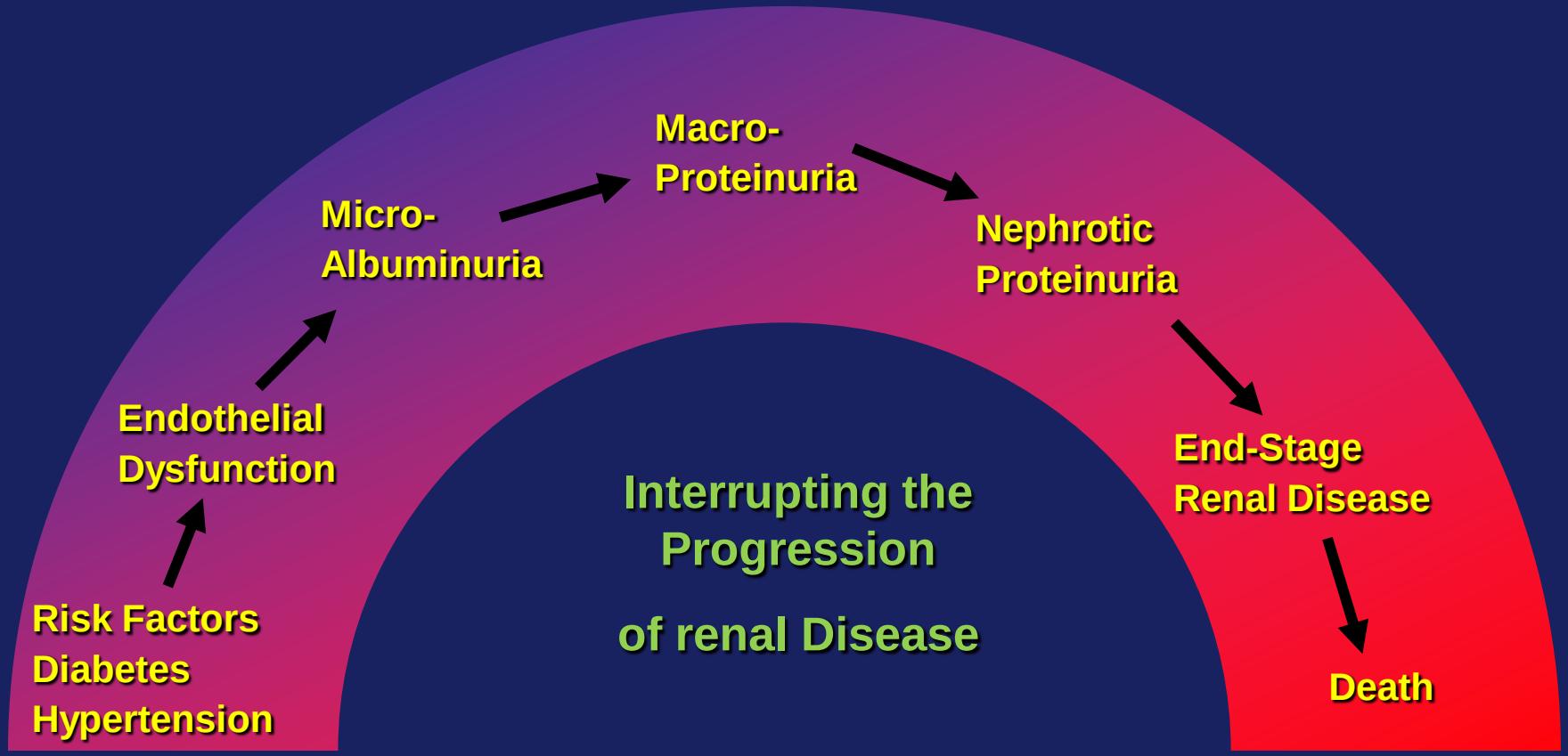


Morbidity and Mortality Along the Cardiovascular Continuum



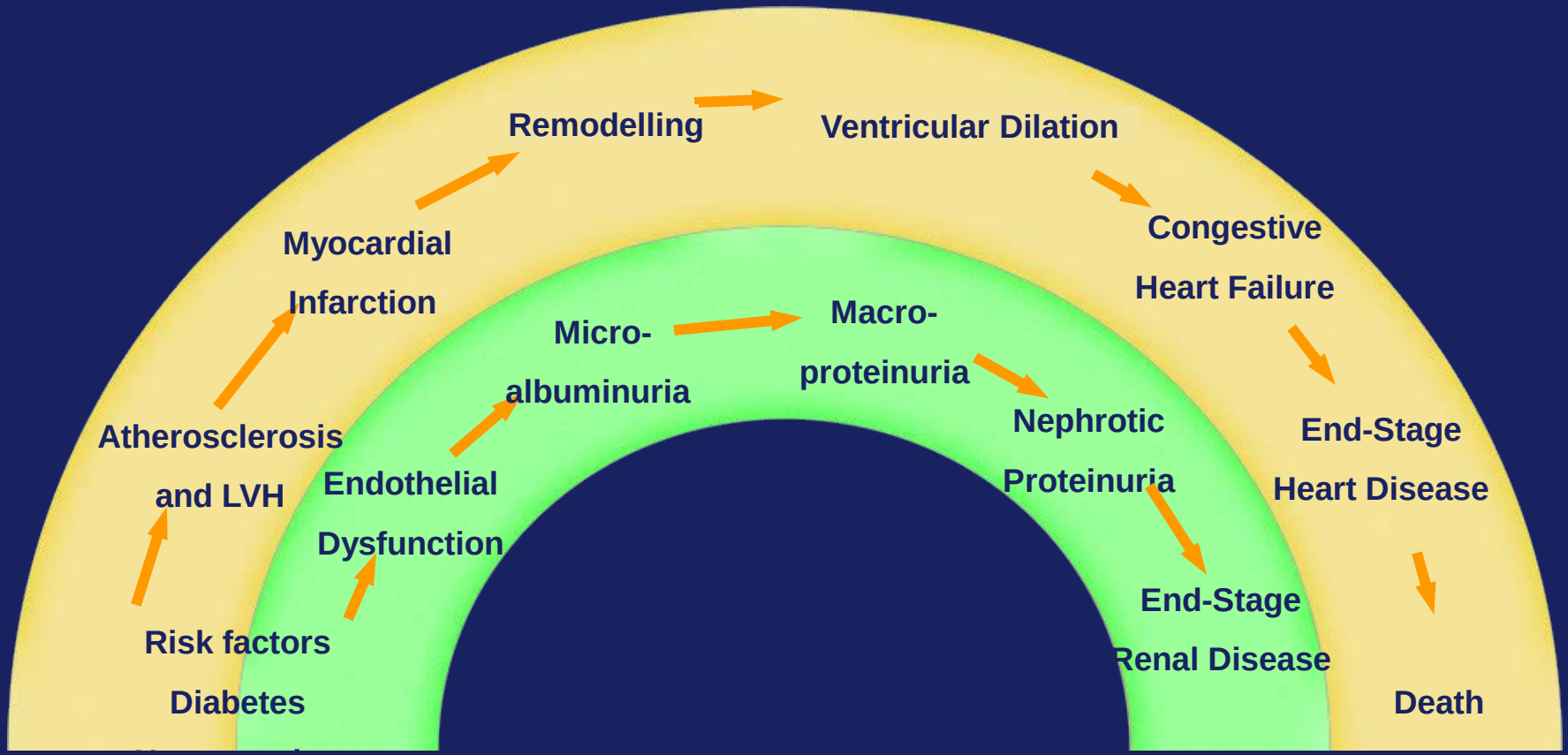
Adapted from Dzau V, Braunwald E. *Am Heart J*. 1991;121:1244-1263.

Morbidity and Mortality Along the Renal Continuum



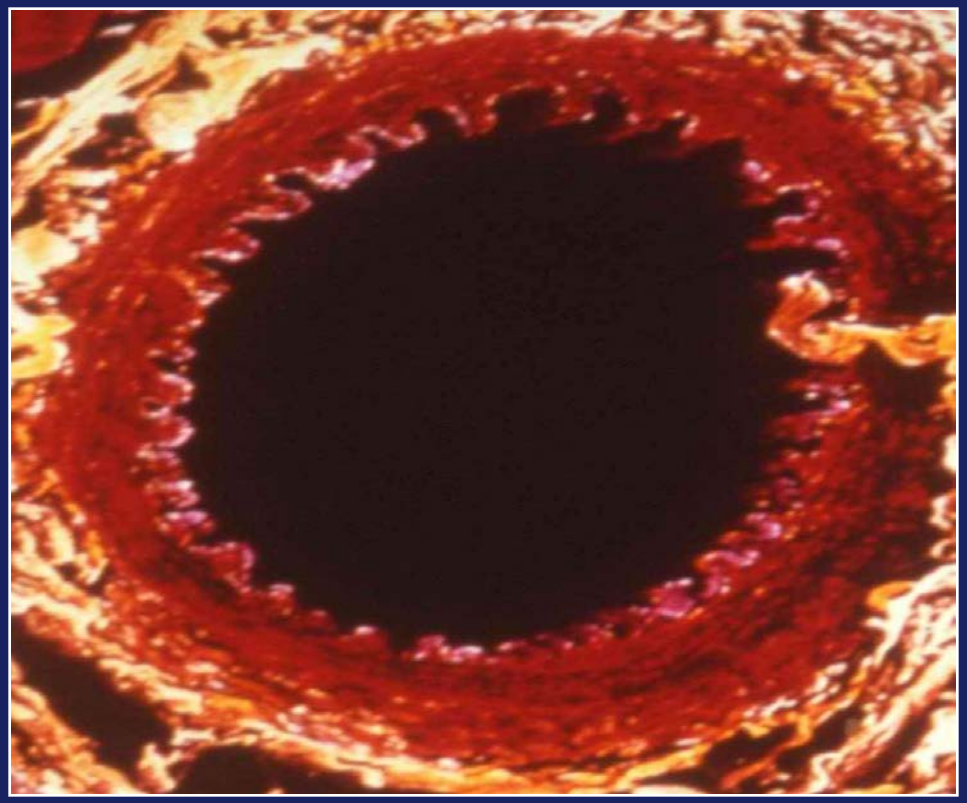
Adapted from Burgess

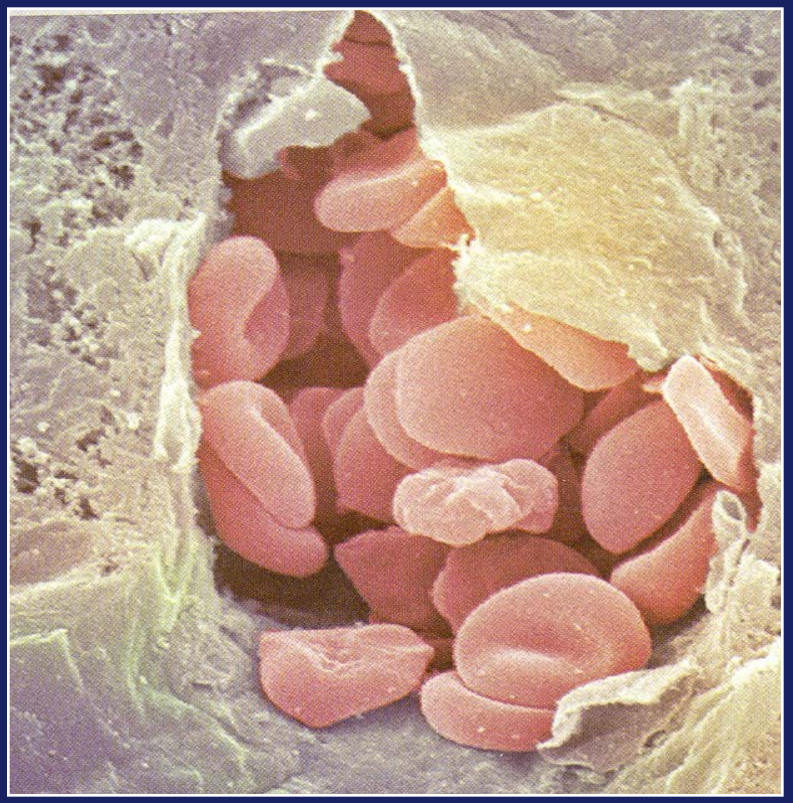
The Cardio-Kidney-Damage Continuum



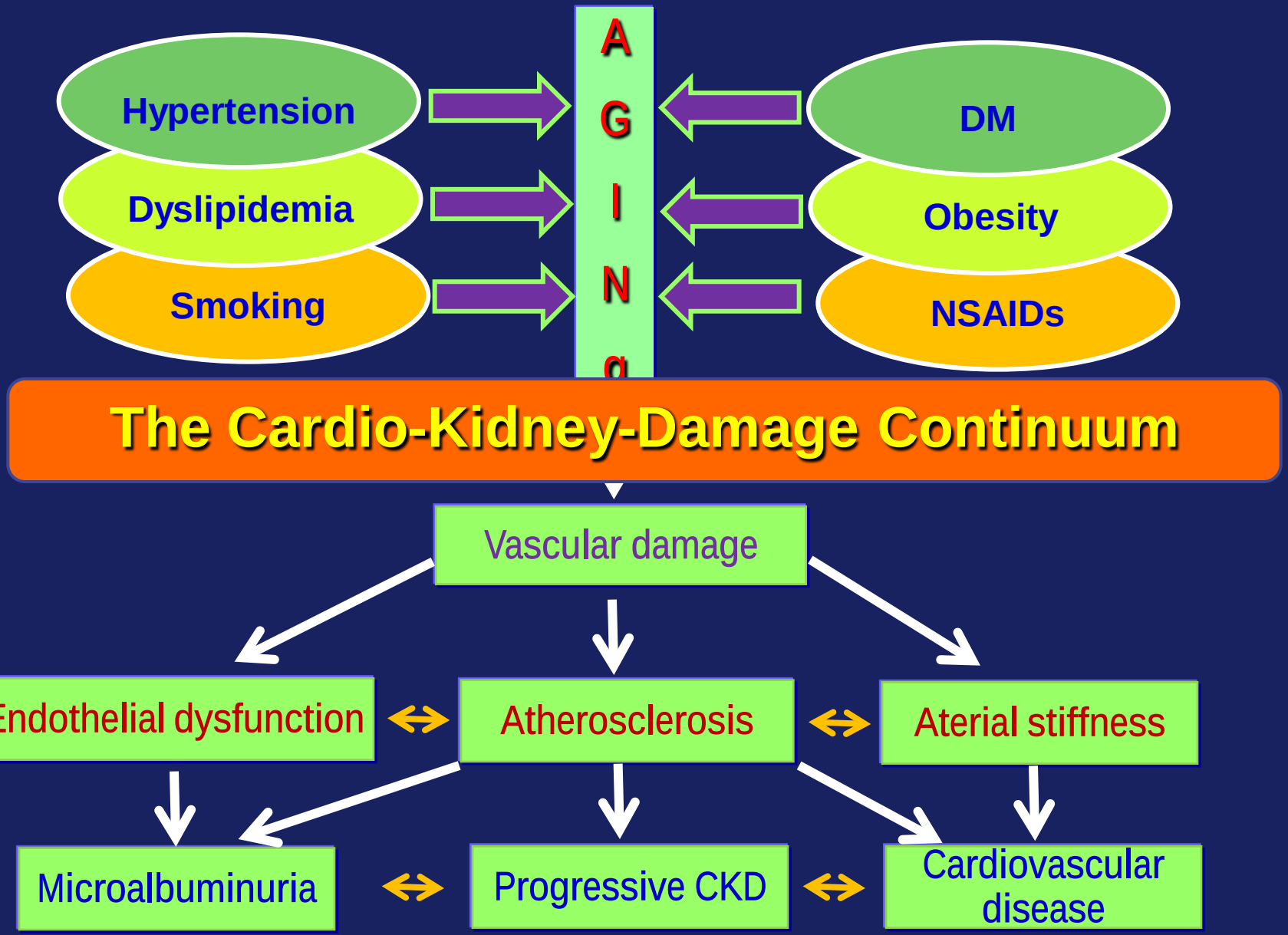
Adapted from Dzau, Braunwald. *Am Heart J* 1991;121:1244–1263

Endothelium





- Weight: 1.5 kg, surface: >800 m^2
- Produces >250 active substances
- Undergoes the life and death cycle



Adapted from El Nahas AM et al. Kidney Int. 2010;78(1):14-8.

คำแนะนำและข้อบ่งชี้ การใช้ยานอกบัญชียาหลักแห่งชาติ ที่มีราคาแพง

กลุ่มยา Angiotensin Converting Enzyme Inhibitor and Angiotensin Receptor Blocker

จัดทำโดย
คณะทำงานย่อยกำหนดคำแนะนำและ
ข้อบ่งชี้ การใช้ยานอกบัญชียาหลักแห่งชาติที่มีราคาแพง
กลุ่มยา Angiotensin Converting Enzyme Inhibitor and
Angiotensin Receptor Blocker

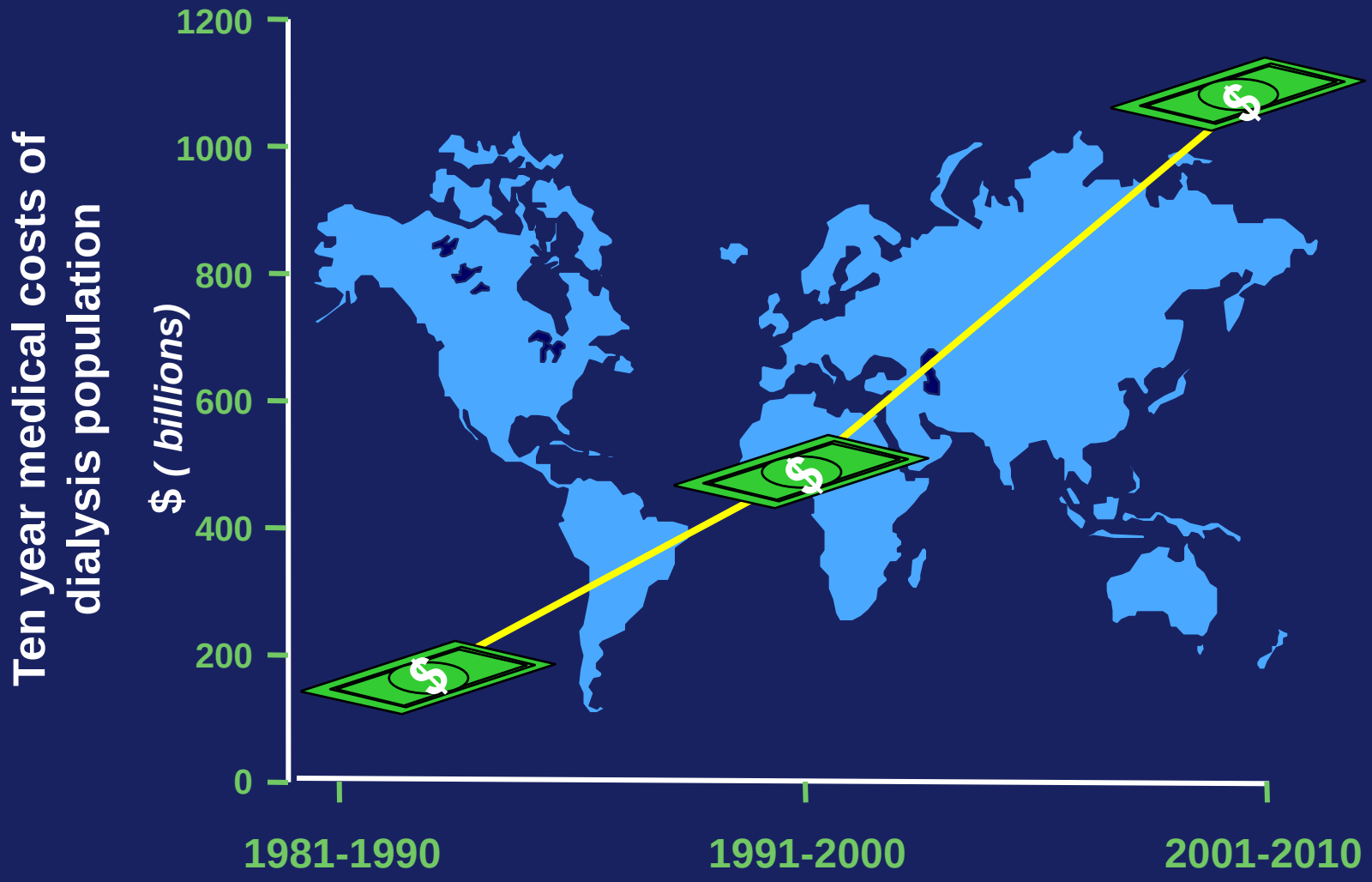
ตารางสรุปน้ำหนักของคำแนะนำและคุณภาพหลักฐานของการใช้ยากลุ่ม ACEI

Indications	Captopril	Enalapril	Lisinopril	Quinapril	Ramipril	Perindopril	Imidapril
High risk population (e.g.HT,DM,LVH,MetS)	-	-	-	-	++,1	+, 1	-
Acute coronary syndrome	++,1	+/-,1	++,1	-	++,2	+, 1	-
Stable coronaryheart disease	-	+/-,2		+/-,1	++,1	++,1	
Congestive heart failure (lowEF)	+, 1	++,1	+/-, 2	-	-	-	-
Congestive heart failure (NormalEF)	-	-	-	-	-	+/-,2	-
Diabetic kidney disease (Microalbuminuria)	+/-,1	-	-	-	++,1	-	-
Diabetic kidney disease (Macroalbuminuria)	++,1	-	-	-	-	-	-
Non-Diabetic kidney disease (Proteinuria > 1 g/day)	-	-	-	-	++,1	-	-
STROKE (secondaryprevention)	-	-	-	-	+, 2	+, 1	-

ตารางสรุปน้ำหนักของคำแนะนำและคุณภาพหลักฐานของการใช้ยากลุ่ม ARB

Indications	Losartan	Irbesartan	Valsartan	Candesartan	Telmisartan	Olmesartan
Highriskpopulation (e.g.HT,DM,LVH,MetS)	++,1	-	+, 1	+/-,1	++,1	+/-,1
Acutecoronarysyndrome	+/-,1	-	++,1	-	-	-
Stable coronaryheart disease	-	-	-	-	++,1	-
Congestive heart failure (lowEF)	+/-,1	-	+, 1	++,1	-	-
Congestive heart failure (NormalEF)	-	+/-,1	-	+/-,1	-	-
Diabetic kidney disease (Microalbuminuria)	-	++,1	+/-,2	-	+, 2	-
Diabetic kidney disease (Macroalbuminuria)	++,1	++,1	-	-	-	+/-,1
Non-Diabetic kidney disease (Proteinuria > 1 g/day)	+,1	-	+, 2	-	-	-
STROKE (secondaryprevention)	-	-	-	+/-,1	+/-,1	

PREDICTED DIALYSIS COST FOR THE COMING DECADE



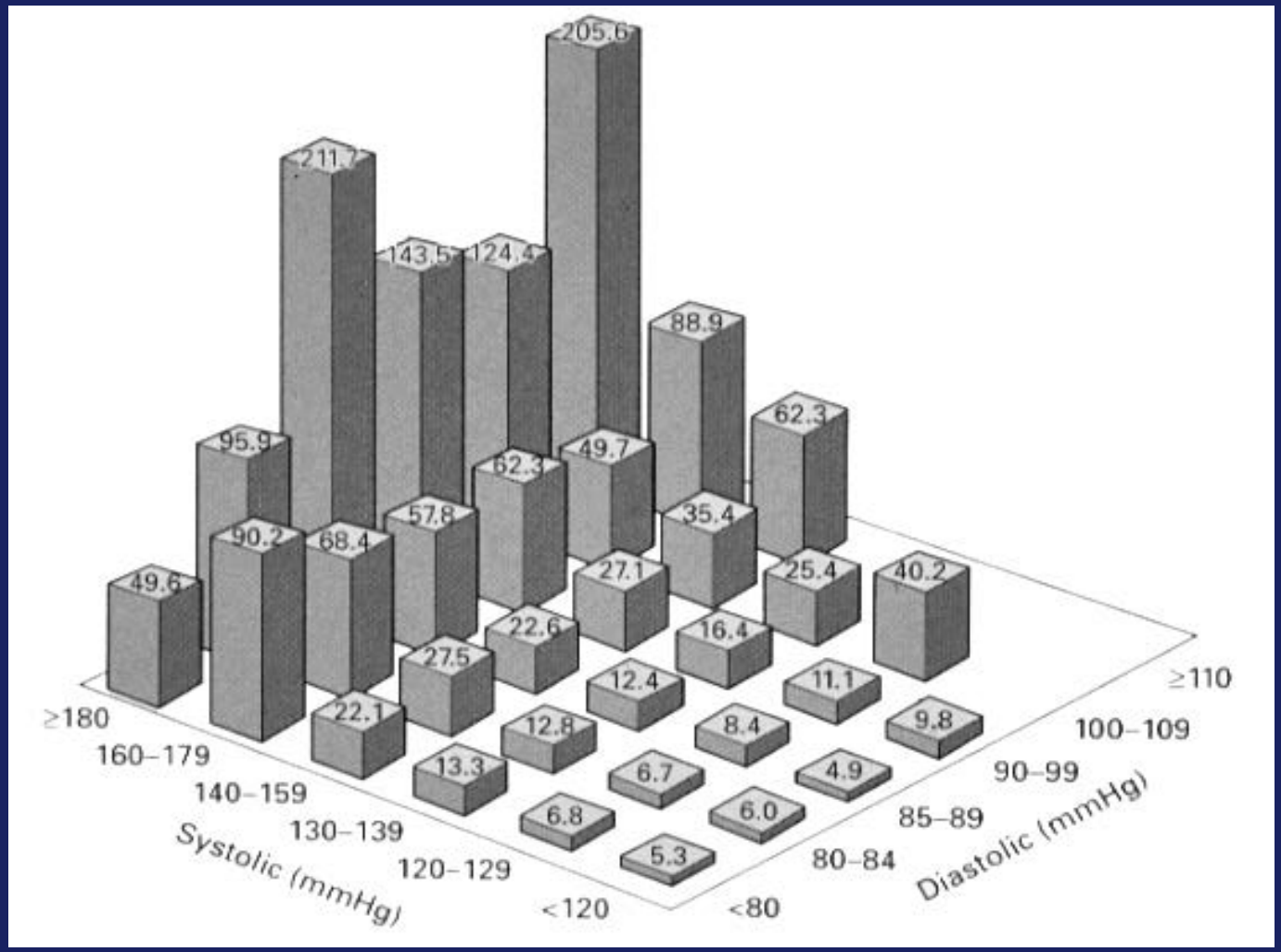
Lysaght et al., *J Am Soc Nephrol,* 2002

Prevalence of CKD: Thai SEEK Study

Stage	Description	GFR (mL/min/1.73 m^2)	
1	Kidney damage with normal GFR	> 90	8.9%
2	Mild renal insufficiency	60-89	
3	Moderate renal insufficiency	30-59	8.7%
4	Severe renal insufficiency	15-29	
5	Kidney failure	<15 (or dialysis)	

Ingsathit A et al., *Nephrol Dial Transplant.* 2010; 25(5):1567-75

Age-adjusted rate of ESRD per 100,000 patient-years

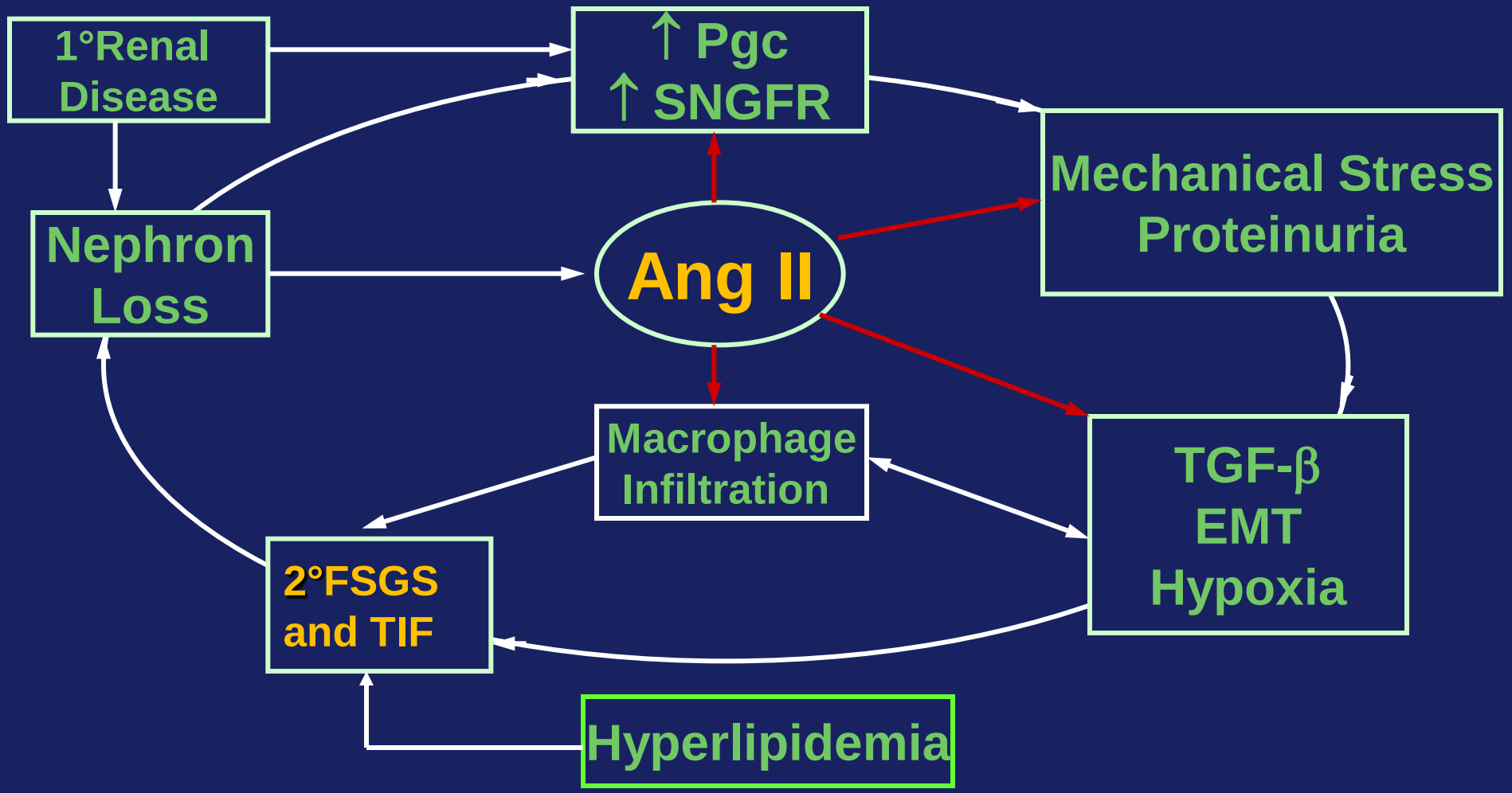


N = 332,544

Age : 35-57 yr

MRFIT Study. Klag MJ, et al : NEJM 1996.

CKD Progression



Role of Proteinuria in Progression of CKD

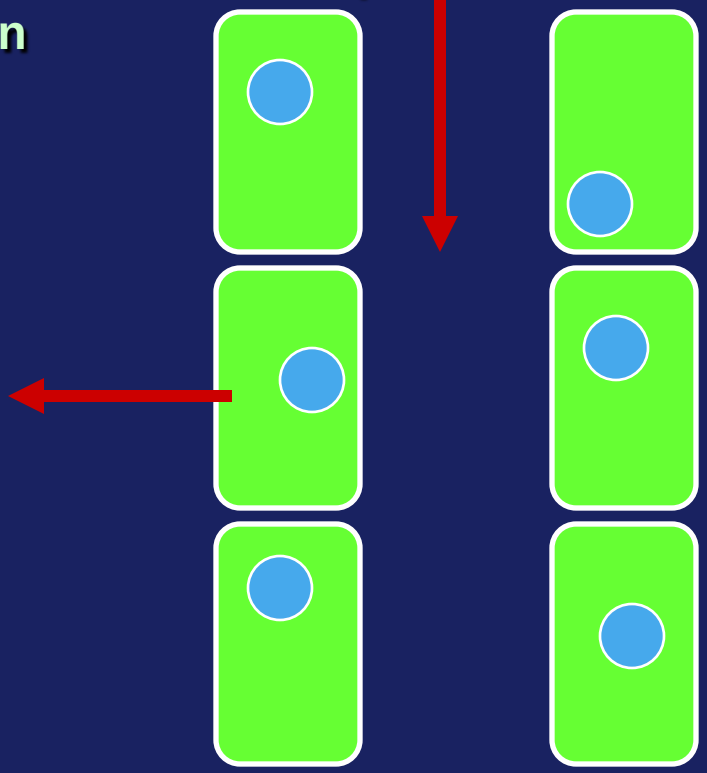
Inflammation

Interstitial Fibrosis

Mesangial expansion

Hypertension

Excess filtered protein



MCP-1, RANTES

Endothelin

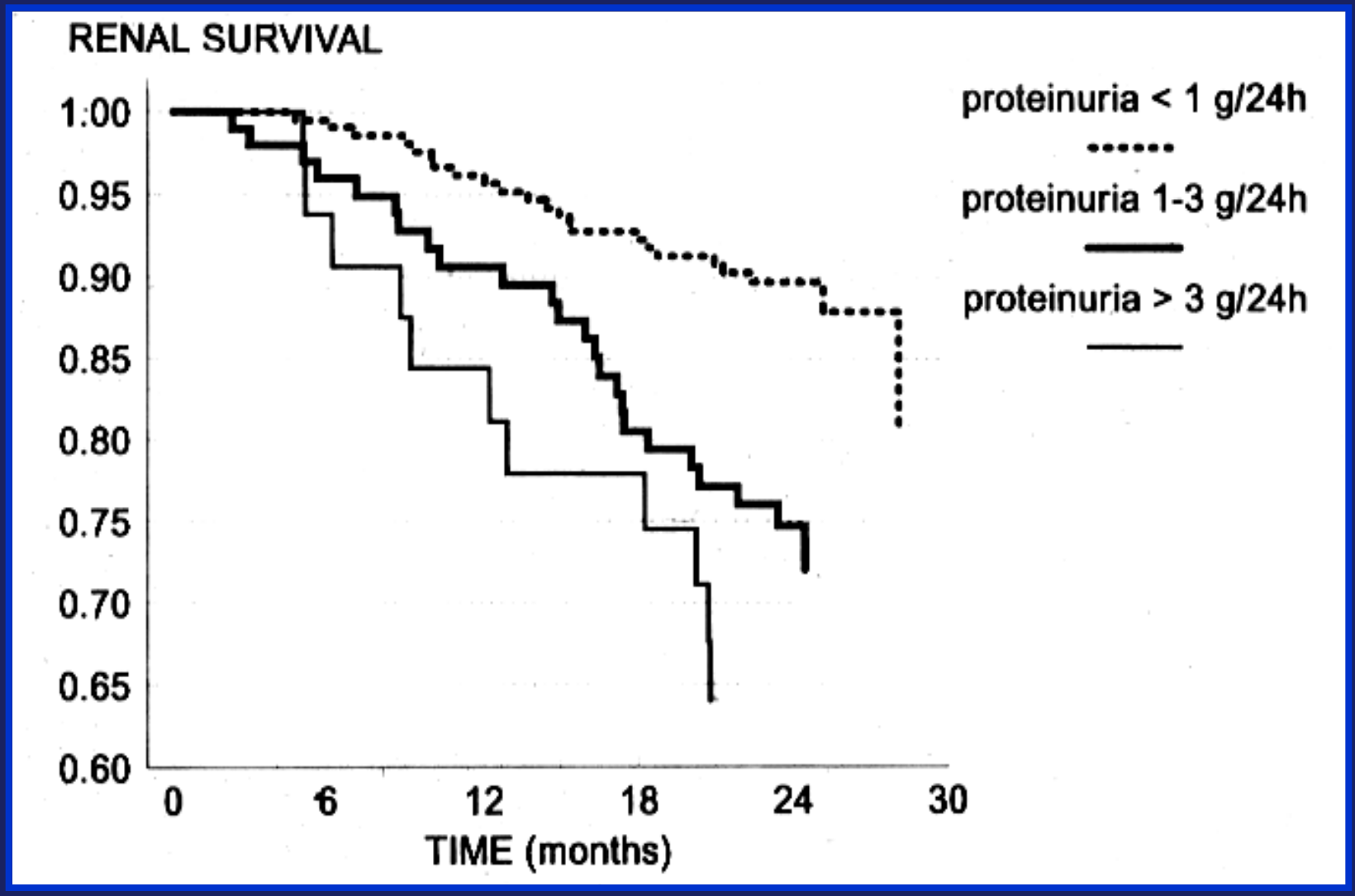
TGF-β, Collagen

Remuzzi et al.

NEJM 339:1448-56

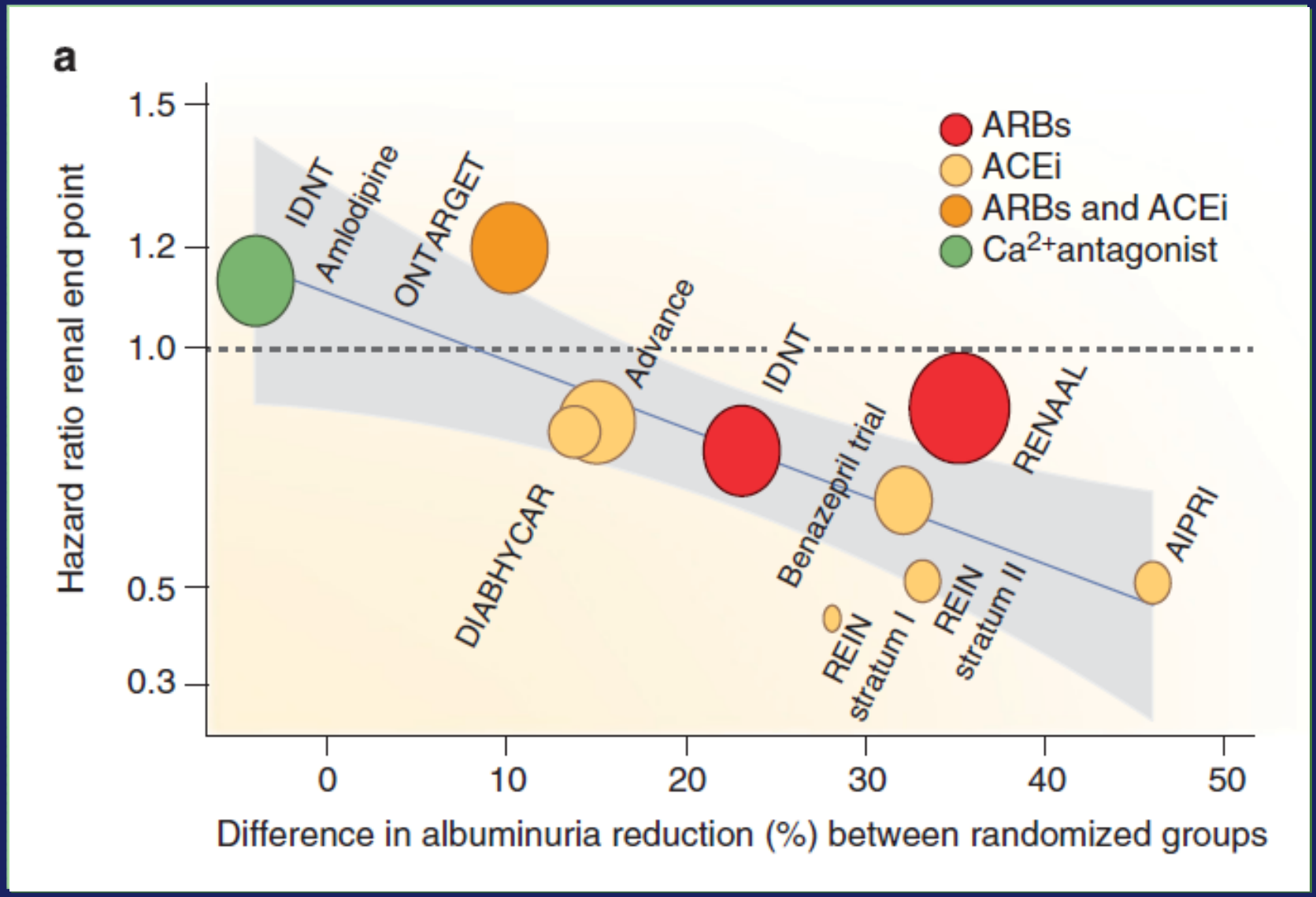
1998

Proteinuria: REIN Study



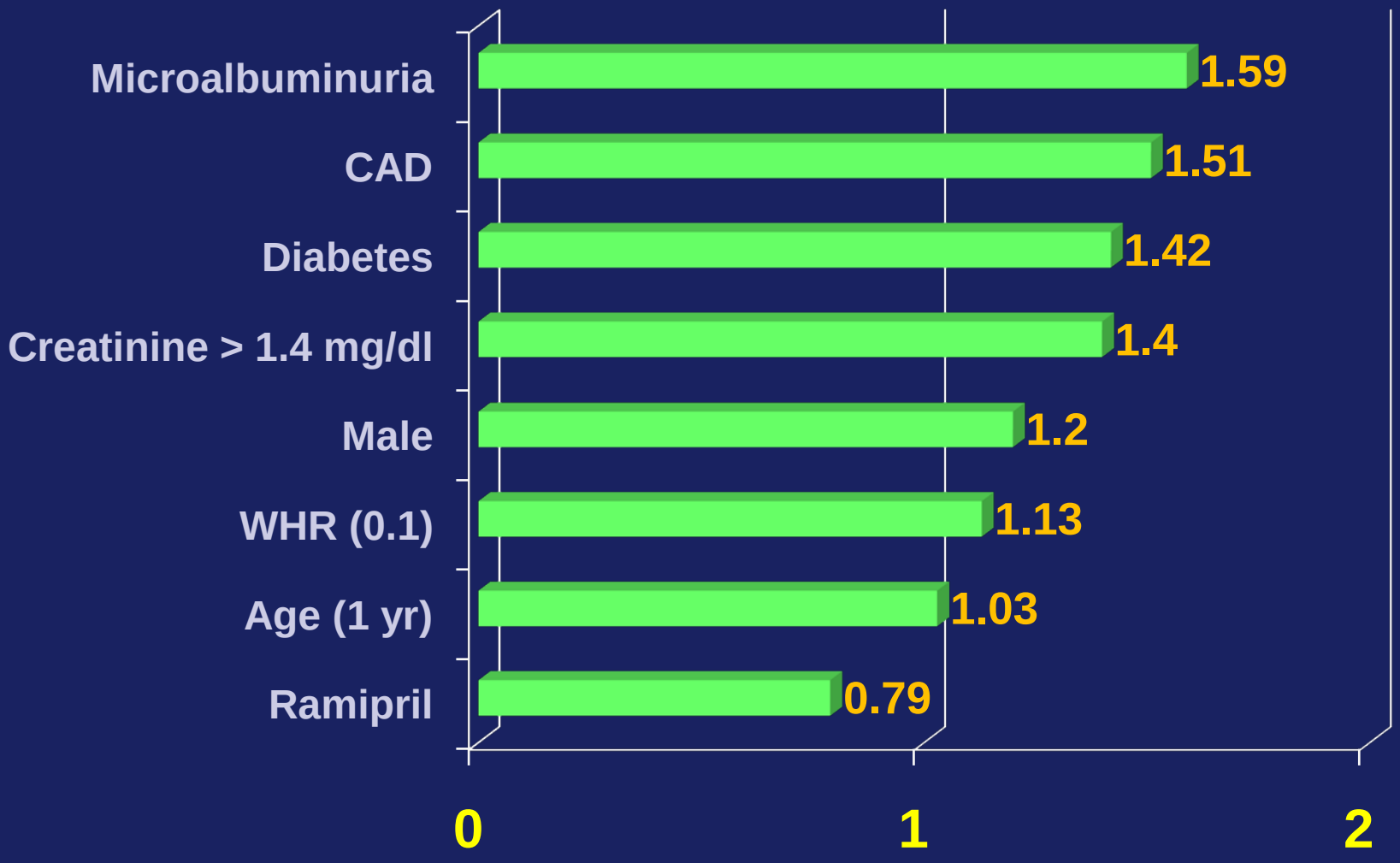
Ruggenenti P et al. Kidney Int Suppl 1997;63:S54-7.

Albuminuria Reduction Predict Renal Protection



Roscioni SS et al. Kidney Int. 2014;86(1):40-9.

Multivariate Hazard Ratios for Primary Outcome in HOPE Study



HOPE Study Investigators. N Engl J Med 2000;342:145-153

GFR Categories in CKD: KDIGO 2012

Stage	GFR (mL/min/1.73 m^2)	Terms
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

KDIGO CKD Work Group. Kidney Int 2013; 1(Suppl).

Albuminuria Categories in CKD: KDIGO 2012

Categories	Albuminuria (mg/day)	ACR (mg/g)	Terms
A1	< 30	< 30	Normal to mildly increased
A2	30 - 300	30 - 300	Moderately increased
A3	> 300	> 300	Severely increased

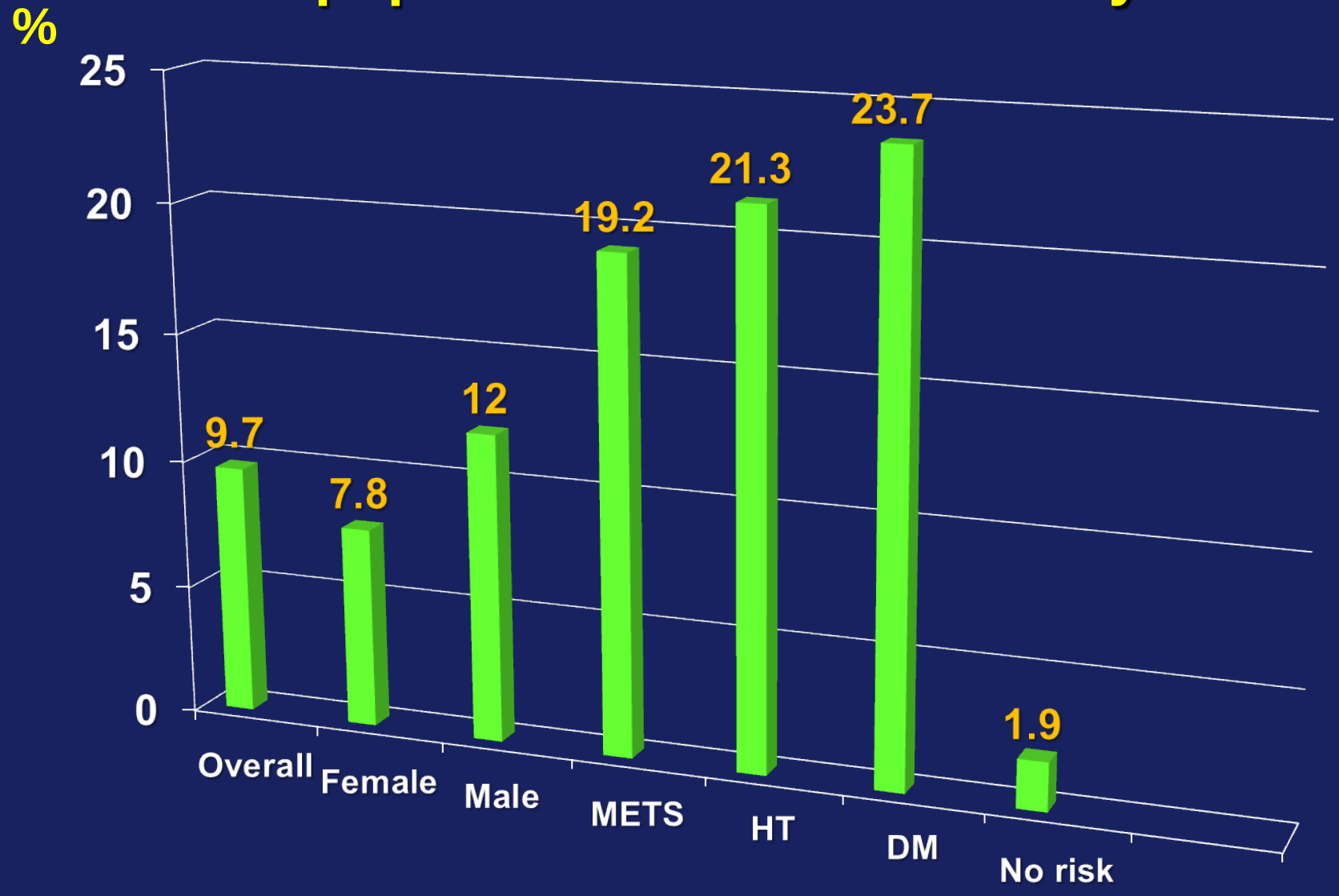
KDIGO CKD Work Group. Kidney Int 2013; 1(Suppl).

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/1.73m²) Description and range				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
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

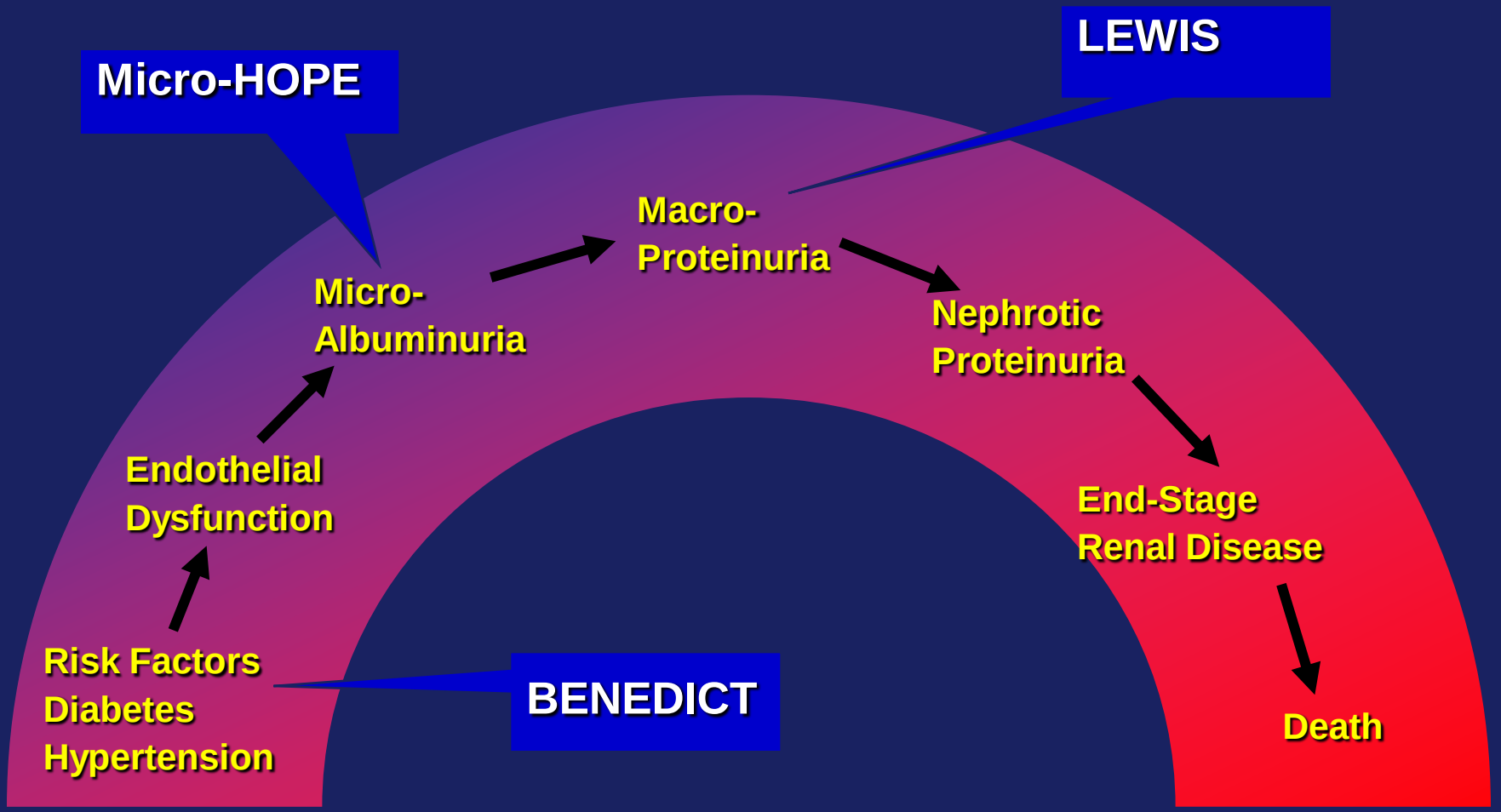
KDIGO CKD Work Group. Kidney Int 2013; 1(Suppl).

Prevalence of microalbuminuria in specific population: Thai SEEK Study



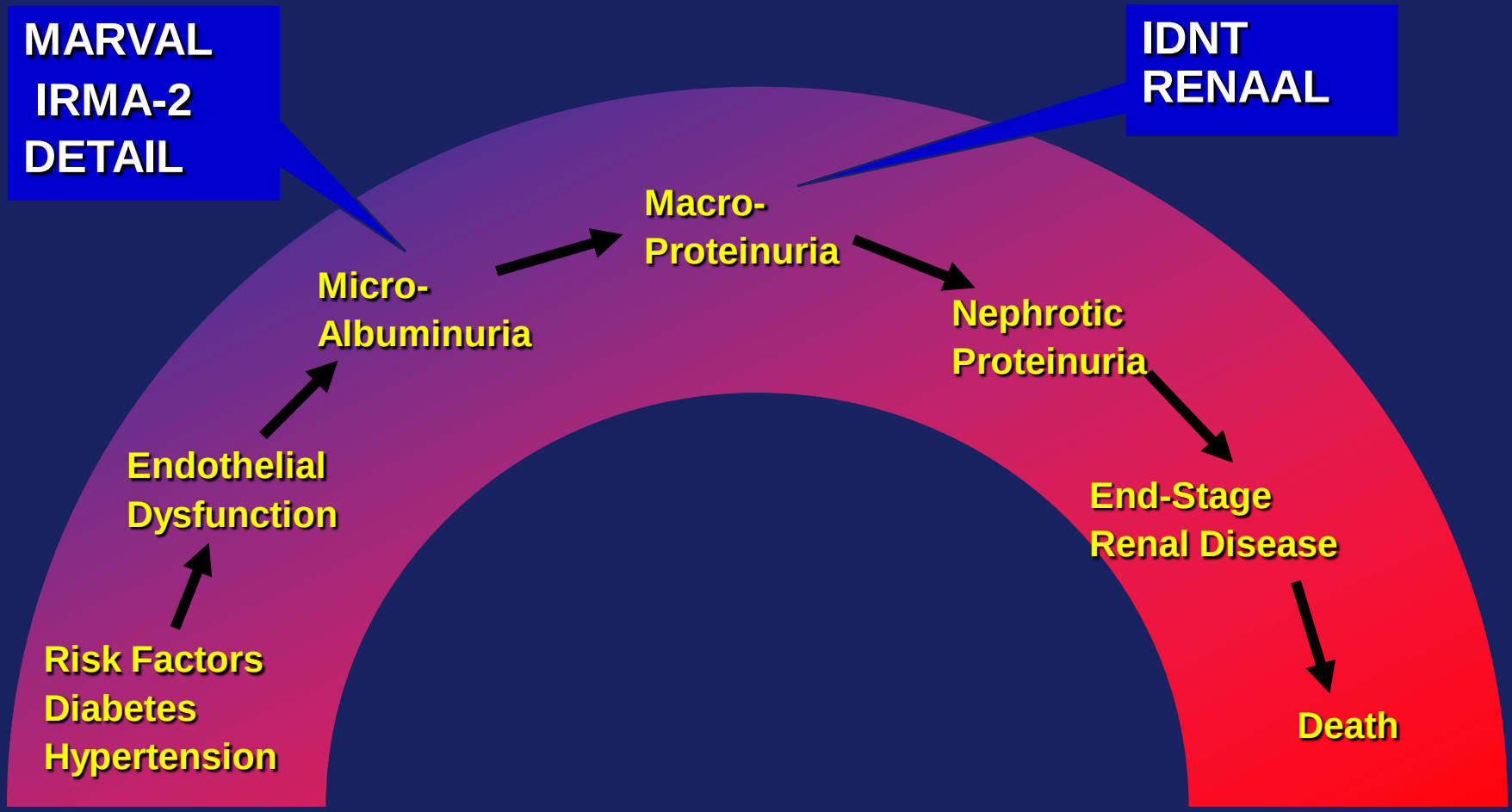
Gojaseni et al. Thai SEEK group. Unpublished data.

Diabetic Kidney Disease
Landmark Renal Outcome Trial of ACEIs



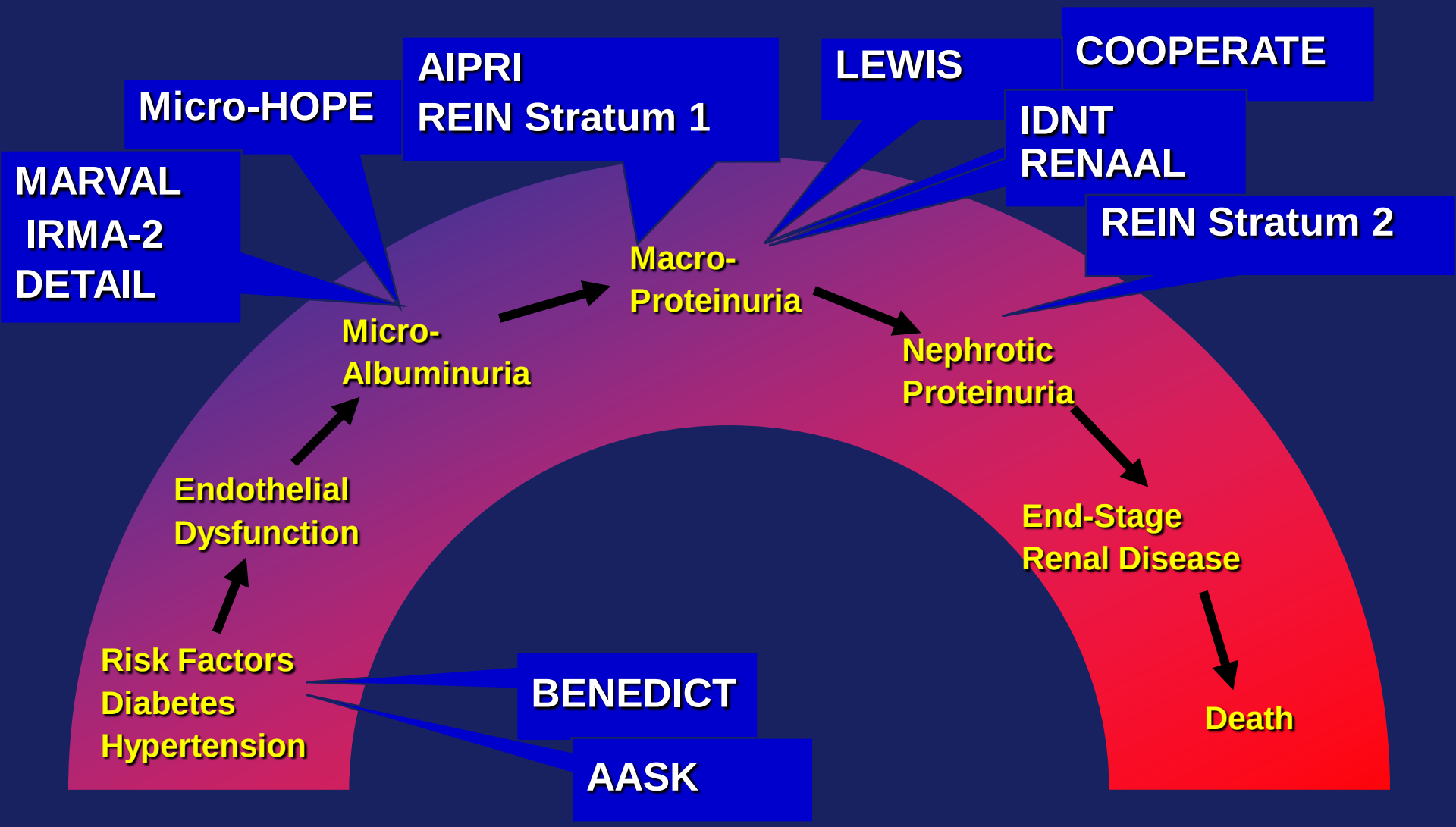
Adapted from Burgess

Diabetic Kidney Disease
Landmark Renal Outcome Trial of ARBs



Adapted from Burgess

Summary: Chronic Kidney Disease Landmark Renal Outcome Trial of ACEIs/ARBS



Adapted from Burgess

IRMA 2
Study design

590 patients with type 2 diabetes,

MAU (albumin excretion rate 20 – 200 mg/min),

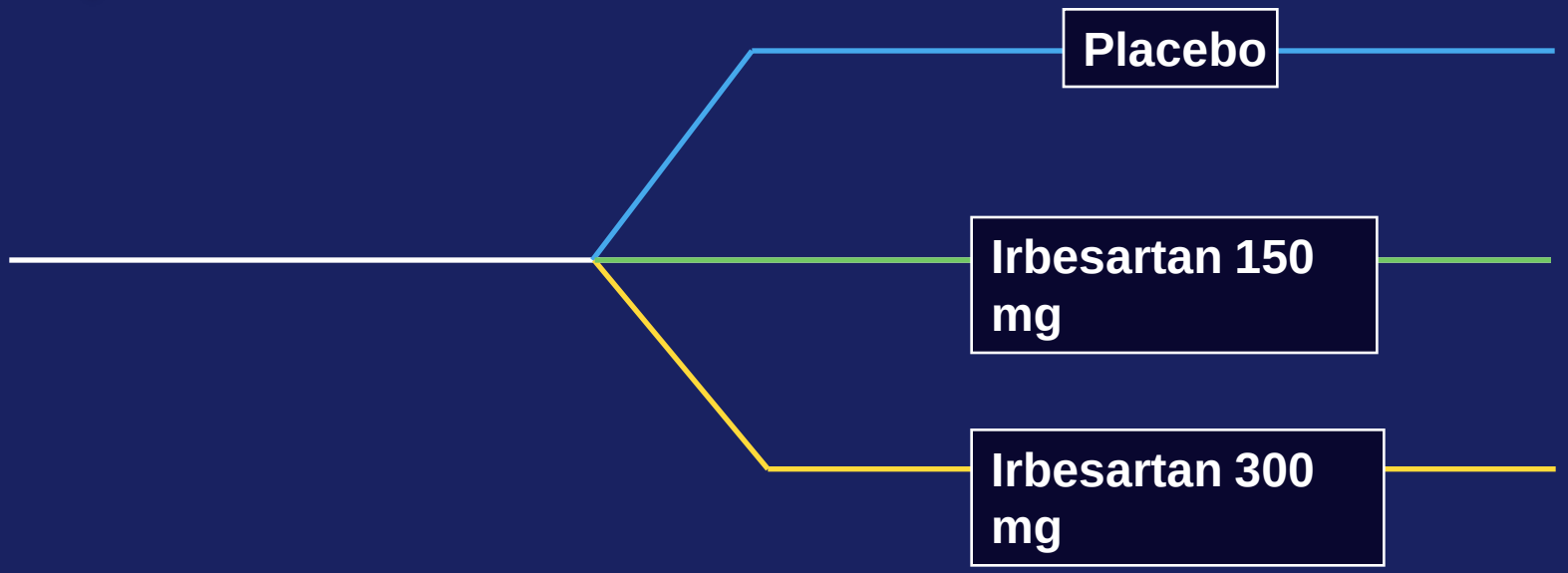
normal renal function, and hypertension

Follow-up: 2 years

Screening/Enrollment

Up to 5 weeks

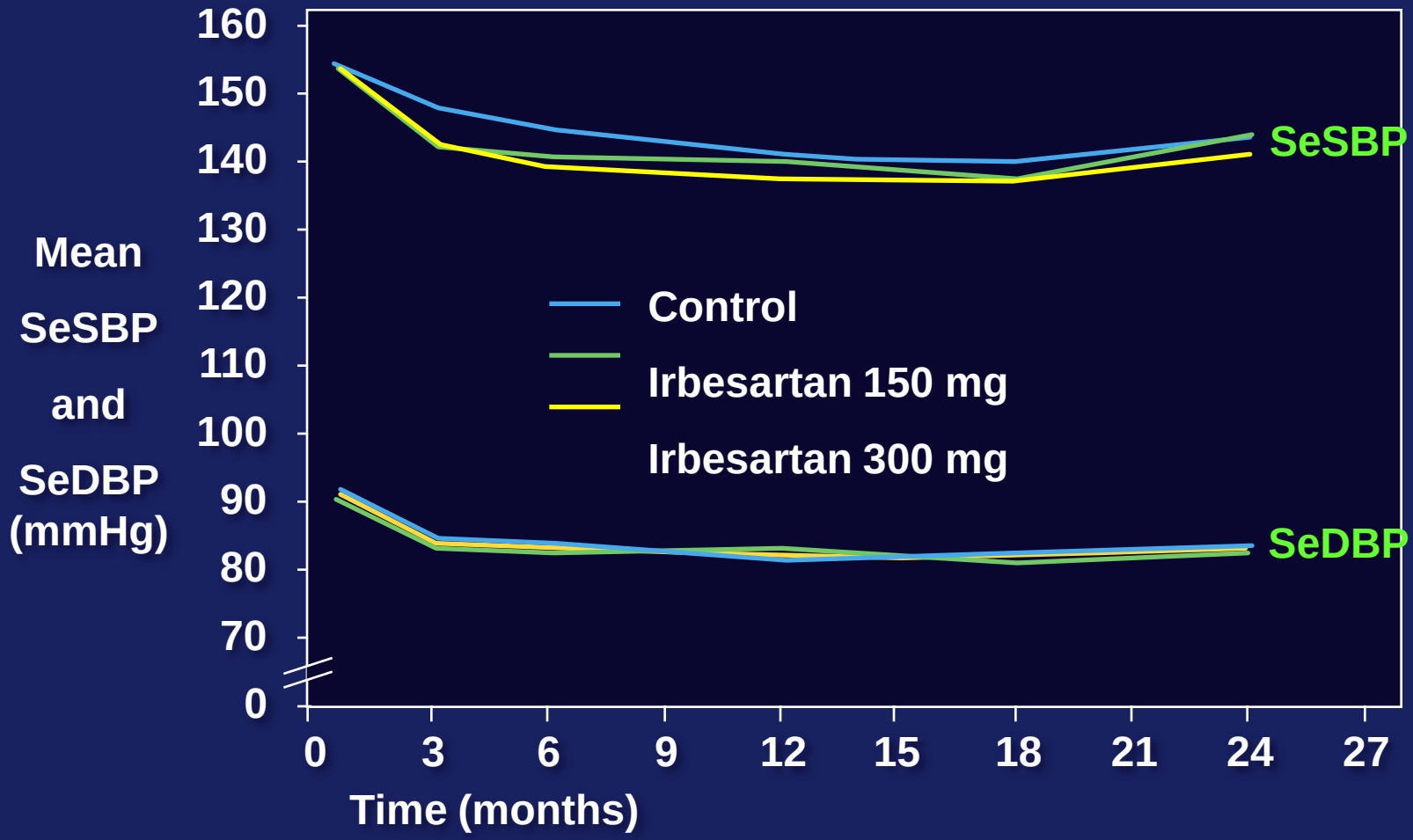
Double-blind Treatment



* Adjunctive antihypertensive therapies (excluding ACE inhibitors, angiotensin II receptor antagonists, and dihydropyridine calcium channel blockers) could be added to all groups to help achieve equal blood pressure levels.

Parving H-H et al. *N Engl J Med* 2001;345:870–8.

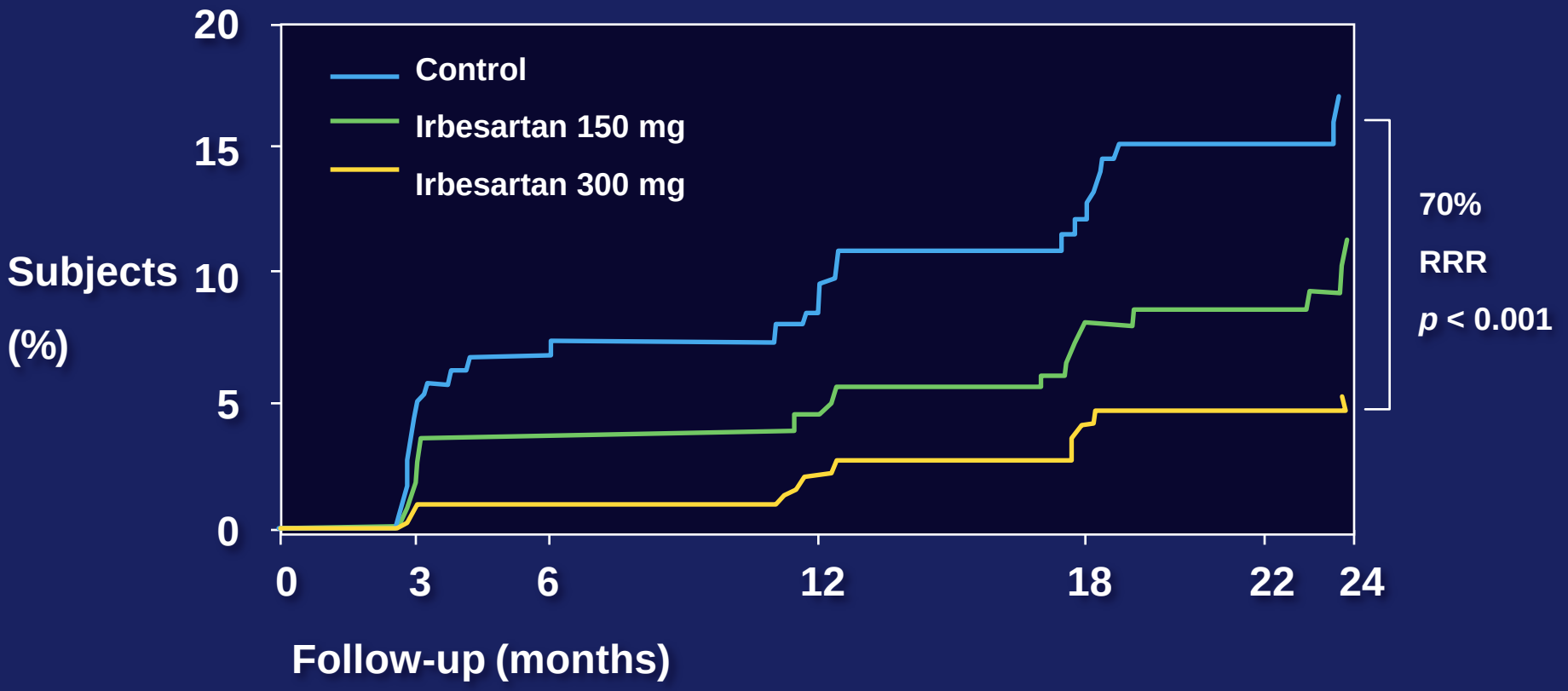
IRMA 2
Blood pressure response



Concomitant antihypertensive agents received by 56% of patients in the control group, 45% in the irbesartan 150 mg group, and 43% in the irbesartan 300 mg group

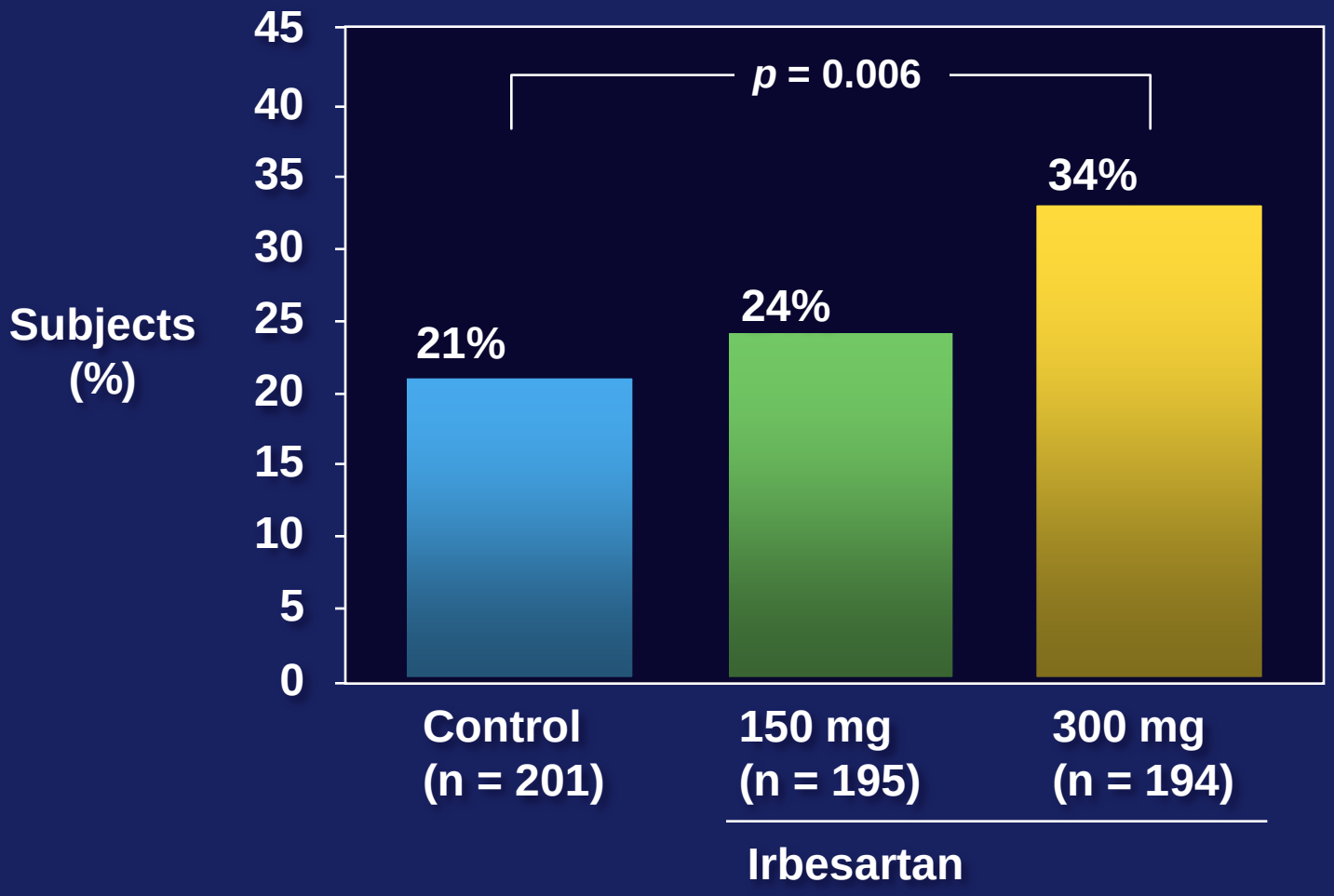
Parving H-H et al. *N Engl J Med* 2001;345:870–8.

IRMA 2
Primary endpoint: Time to overt proteinuria



Parving H-H et al. *N Engl J Med* 2001;345:870–8.

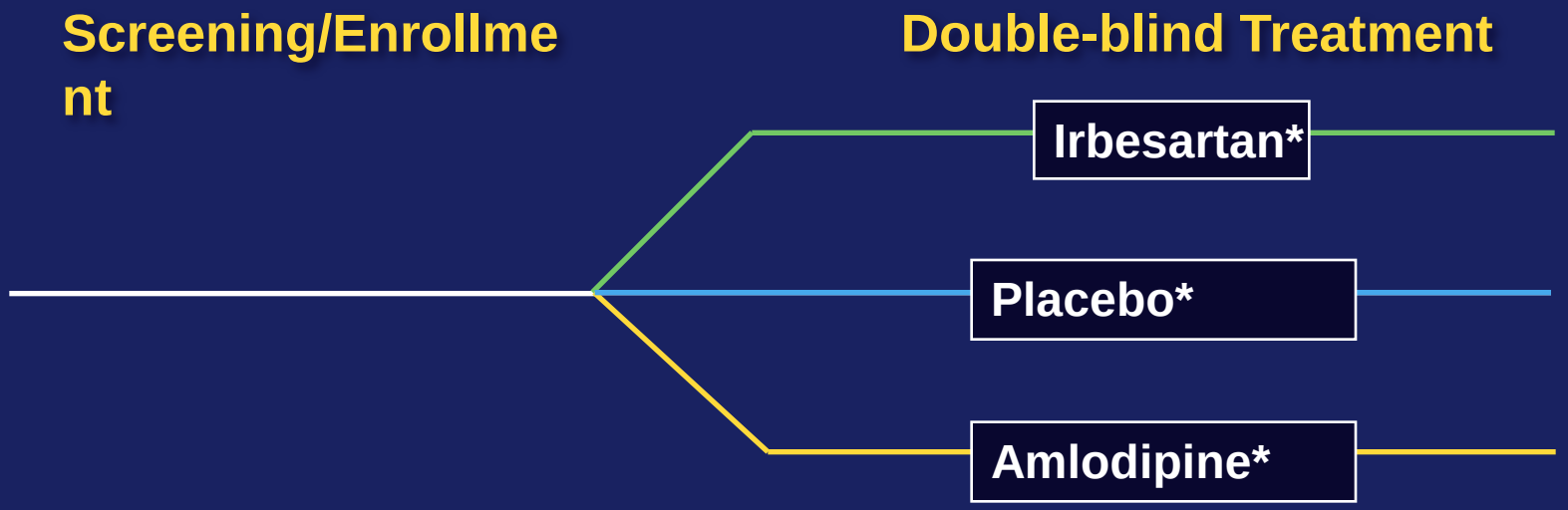
IRMA 2
Normalization of Urinary Albumin Excretion Rate



Parving H-H et al. *N Engl J Med* 2001;345:870–8.

IDNT
Study design

1,715 patients with type 2 diabetes, proteinuria > 900 mg/d, and hypertension

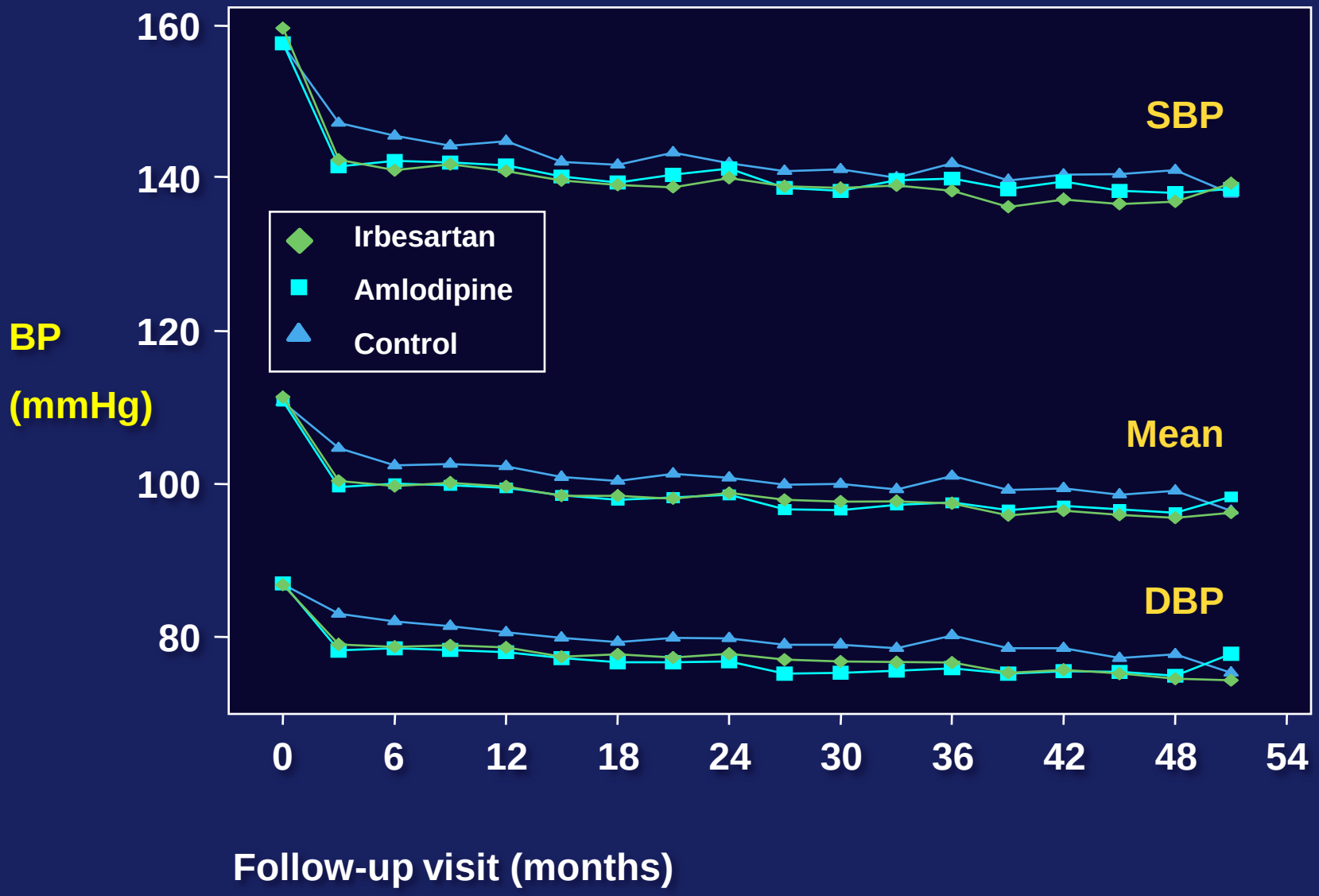


* Adjunctive antihypertensive therapies (excluding ACE inhibitors, angiotensin II receptor antagonists, and calcium channel blockers)

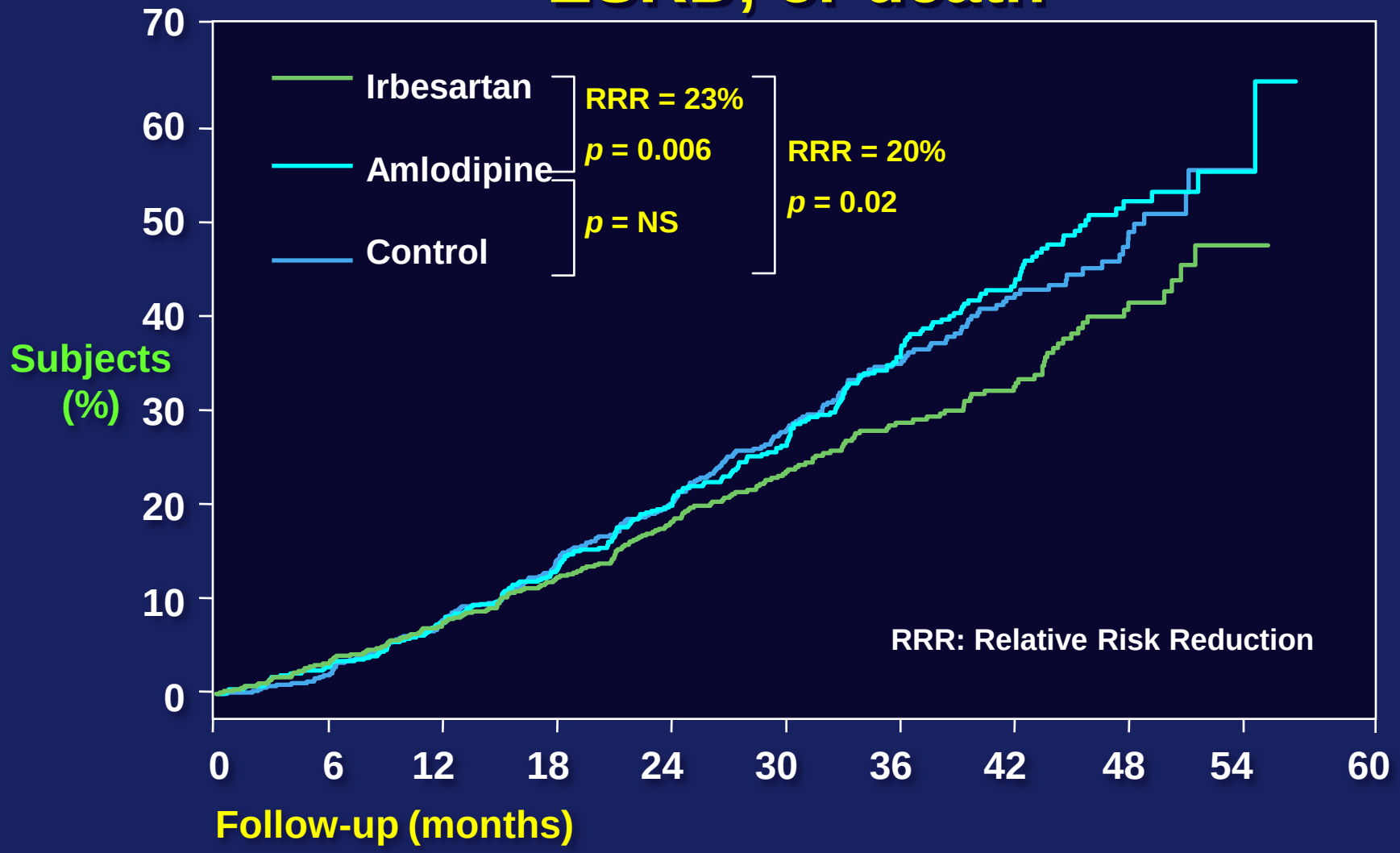
added to each arm to achieve equal blood pressure reduction

Lewis EJ et al. *N Engl J Med* 2001;345:851-860.

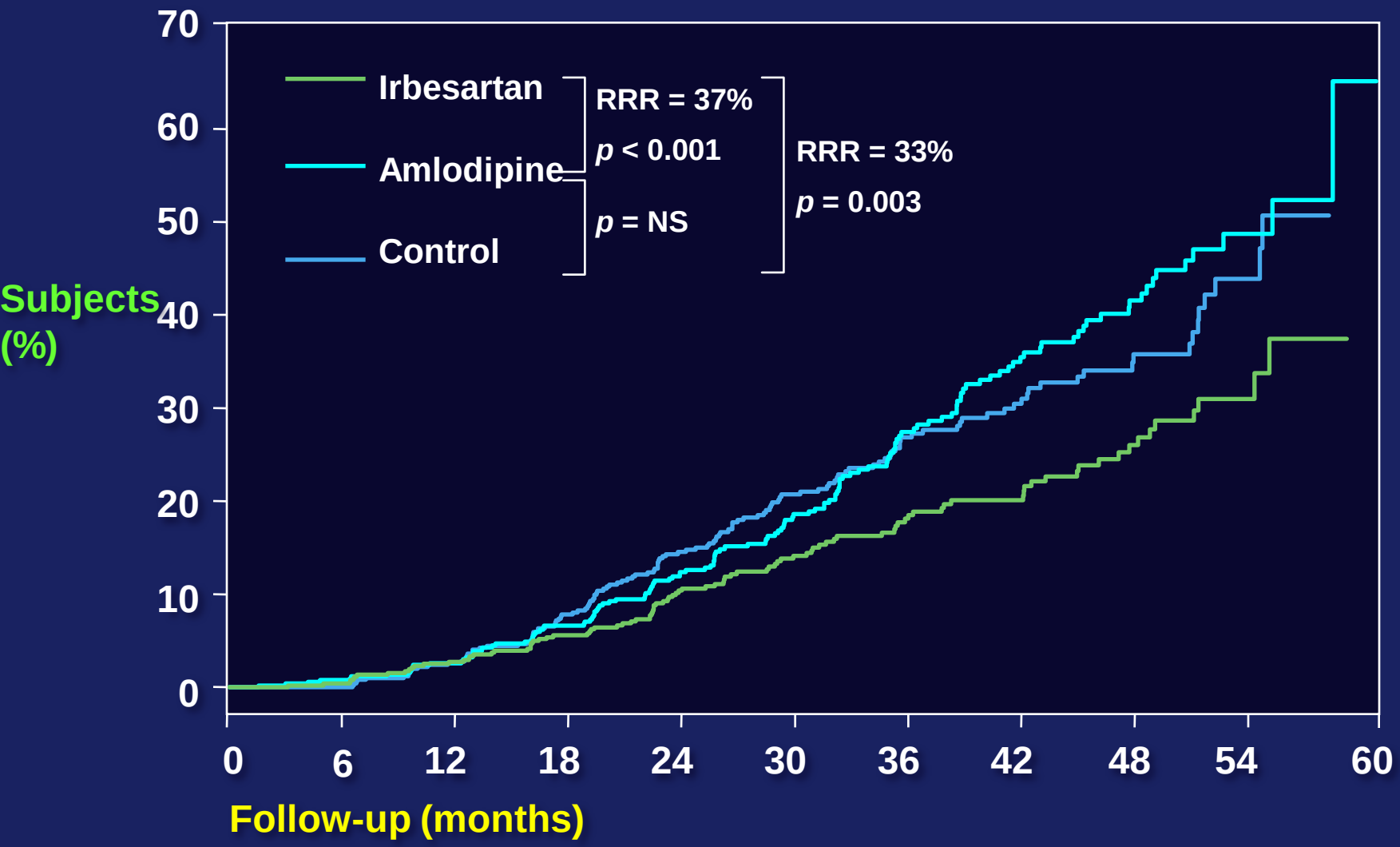
IDNT
Systolic, mean, and diastolic BP response



IDNT primary endpoint
Time to doubling of serum creatinine, ESRD, or death

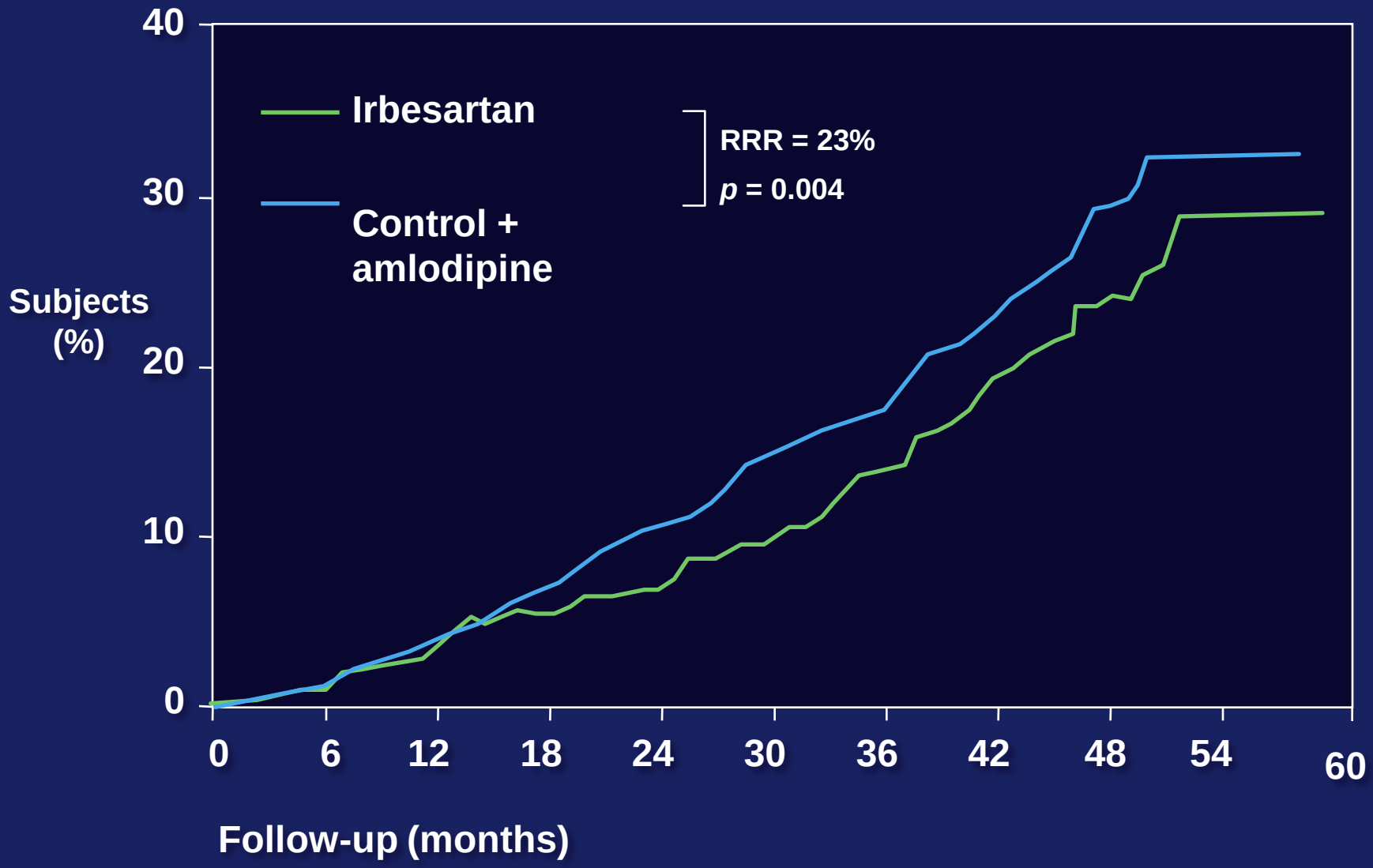


IDNT
Time to doubling of serum creatinine



Lewis EJ et al. *N Engl J Med* 2001;345(12):851–60.

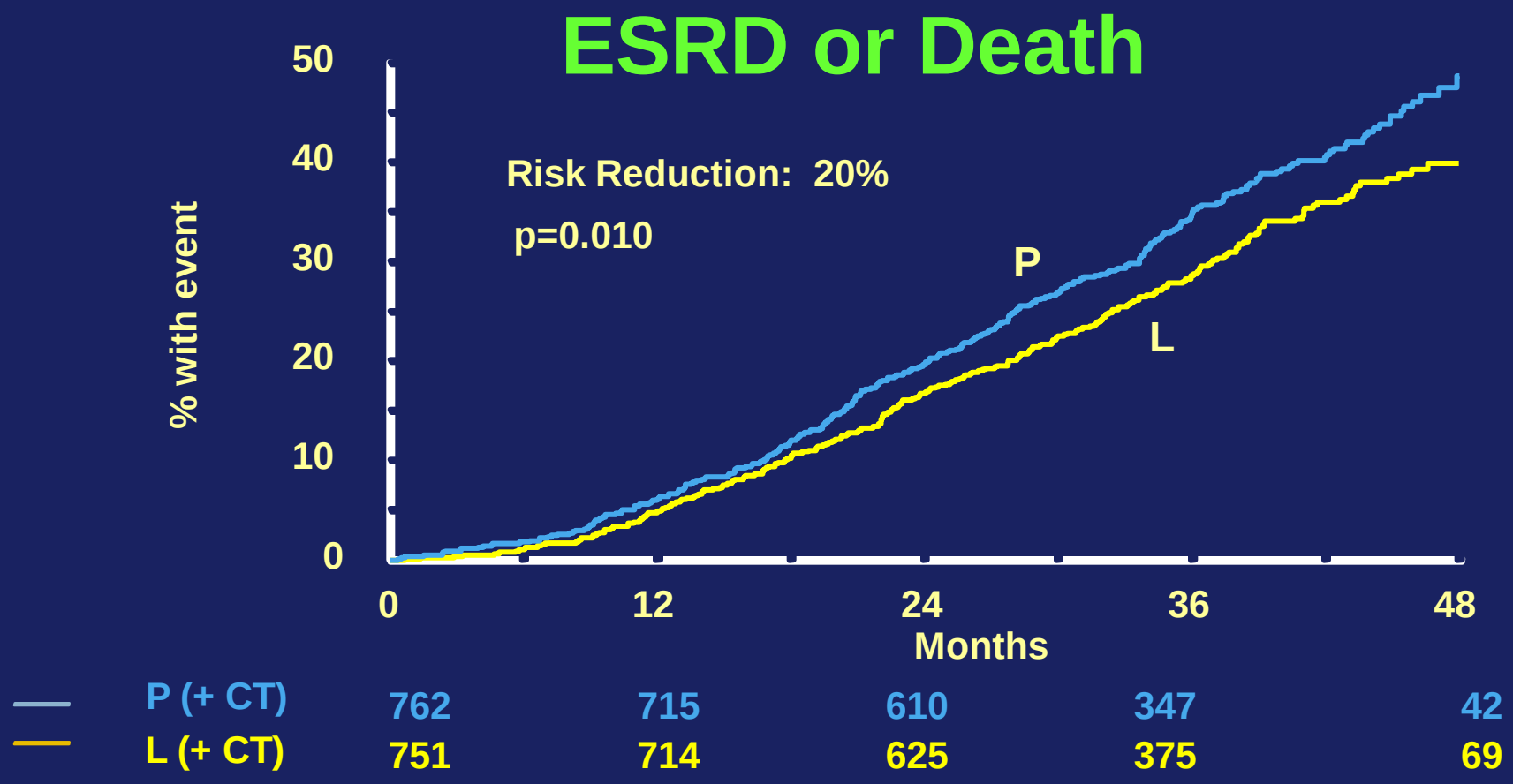
IDNT
Time to ESRD



Lewis EJ et al. *N Engl J Med* 2001;345(12):851–60.

RENAAL: Reduction of Endpoint in NIDDM with the Angiotensin II Antagonist Losartan

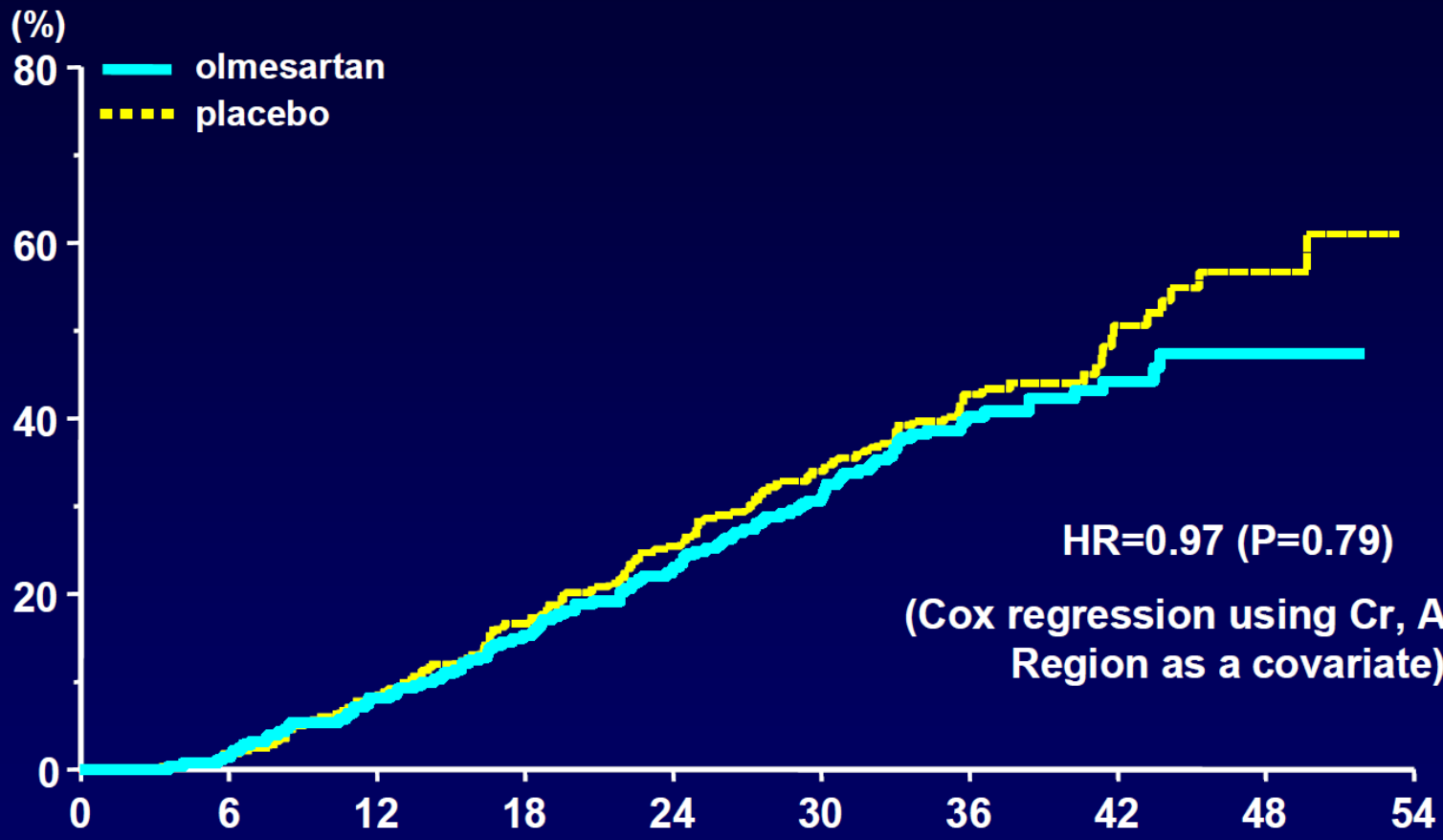
1513 Patients with type 2 diabetes, hypertension and macroproteinuria



Brenner BM et al . New Engl J Med 2001;345(12):861-869.

Kaplan-Meier Curves of Primary Composite Renal Outcome

ORIENT
Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial



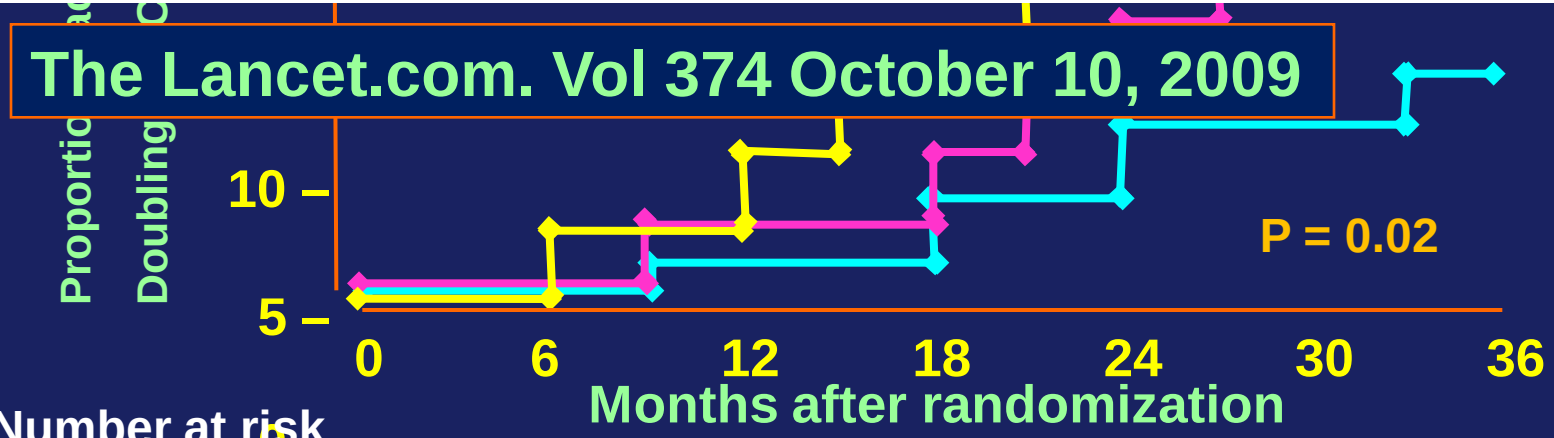
NO. AT RISK									
olmesartan	282	278	259	238	217	184	107	44	17
placebo	284	279	259	236	211	176	102	41	17

COOPERATE

Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease

Retraction—Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial

The Lancet.com. Vol 374 October 10, 2009



Number at risk

Losatan	89	88	84	79	65	59	47
Trandolapril	86	85	83	75	72	63	58
Combination	88	87	86	83	76	73	67

Naoyuki Nakao, et al. Lancet 2003; 361:117-24

ONTARGET Renal Outcome

	Ramipril n (%)	Telmisartan n (%)	Ramipril+ telmisartan n (%)	Telmisartan vs ramipril HR (95% CI)	p	Ramipril+ telmisartan vs ramipril HR (95% CI)	p
All dialysis, doubling, death	1150 (13·4)	1147 (13·4)	1233 (14·5)	1·00 (0·92–1·09)	0·968	1·09 (1·01–1·18)	0·037
All dialysis and doubling	174 (2·03)	189 (2·21)	212 (2·49)	1·09 (0·89–1·34)	0·420	1·24 (1·01–1·51)	0·038
A							133
A							144
Doubling	140 (1·63)	155 (1·81)	166 (1·95)	1·11 (0·88–1·39)	0·378	1·20 (0·96–1·50)	0·110
Acute dialysis	13 (0·15)	20 (0·23)	28 (0·33)	1·55 (0·77–3·11)	0·221	2·19 (1·13–4·22)	0·020
Chronic dialysis	33 (0·39)	31 (0·36)	34 (0·40)	0·94 (0·58–1·54)	0·817	1·05 (0·65–1·69)	0·854

No proven benefit of dual blockade in both diabetic and non-diabetic kidney disease

Dialysis=at least one dialysis. Chronic dialysis=more than 2 months. Acute dialysis=2 months or less. Doubling=doubling of serum creatinine from baseline values. HR=hazard ratio. Reasons for acute dialysis were reported as severe infection (n=22), volume depletion (n=9), post-surgery (n=7), drugs (n=5), specific renal diseases (n=5), and other reasons (n=23). In three of 165 originally reported cases of dialysis,[6] detailed analysis revealed that no dialysis took place. In three of the 162 cases of dialysis, we got no information on duration of dialysis. Investigators could report several reasons for acute dialysis.

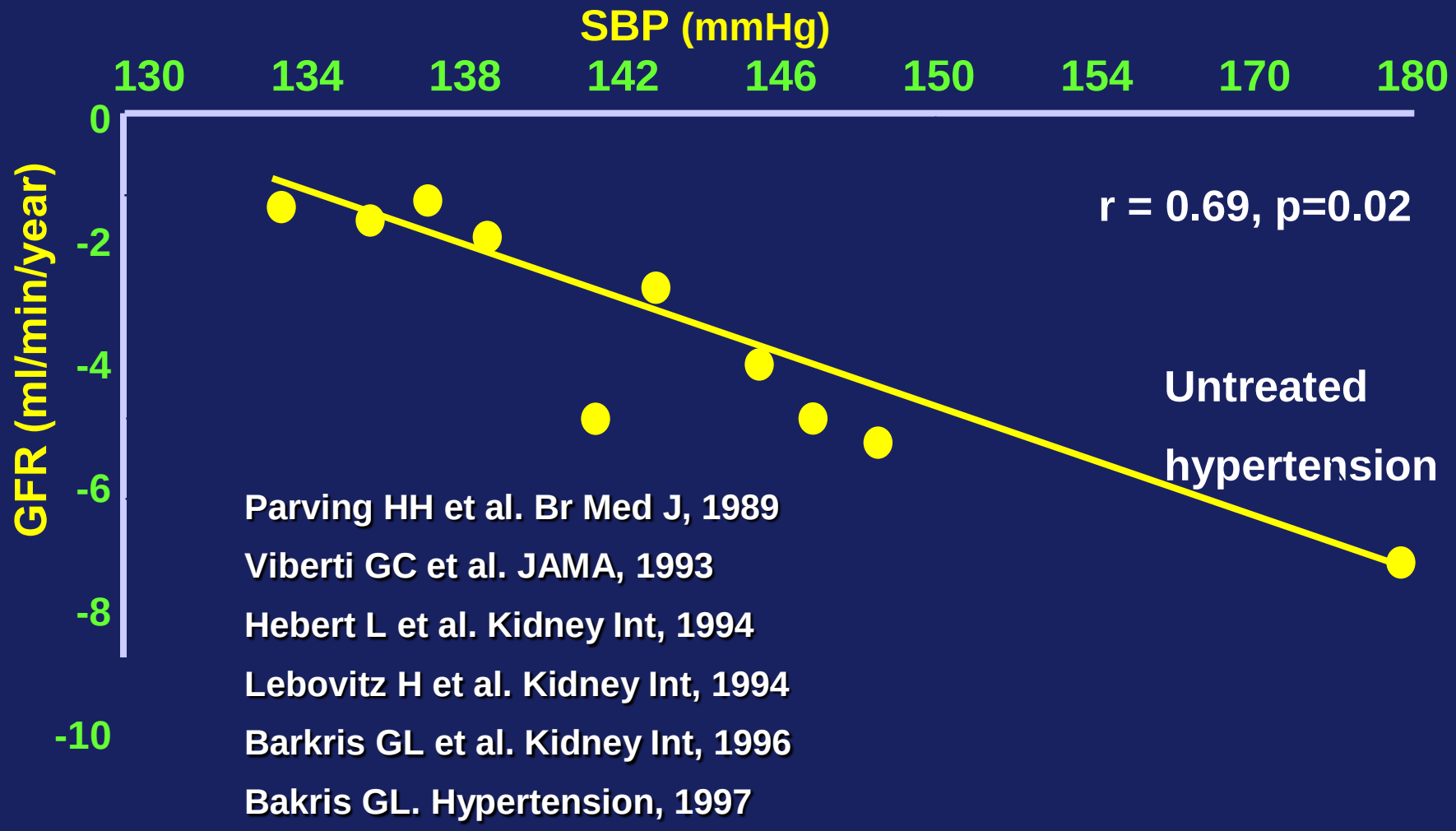
Table 2: Incidence of primary and secondary renal outcomes and of its components

Mann JF et al. Lancet. 2008 Aug 16;372(9638):547-53.

KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease

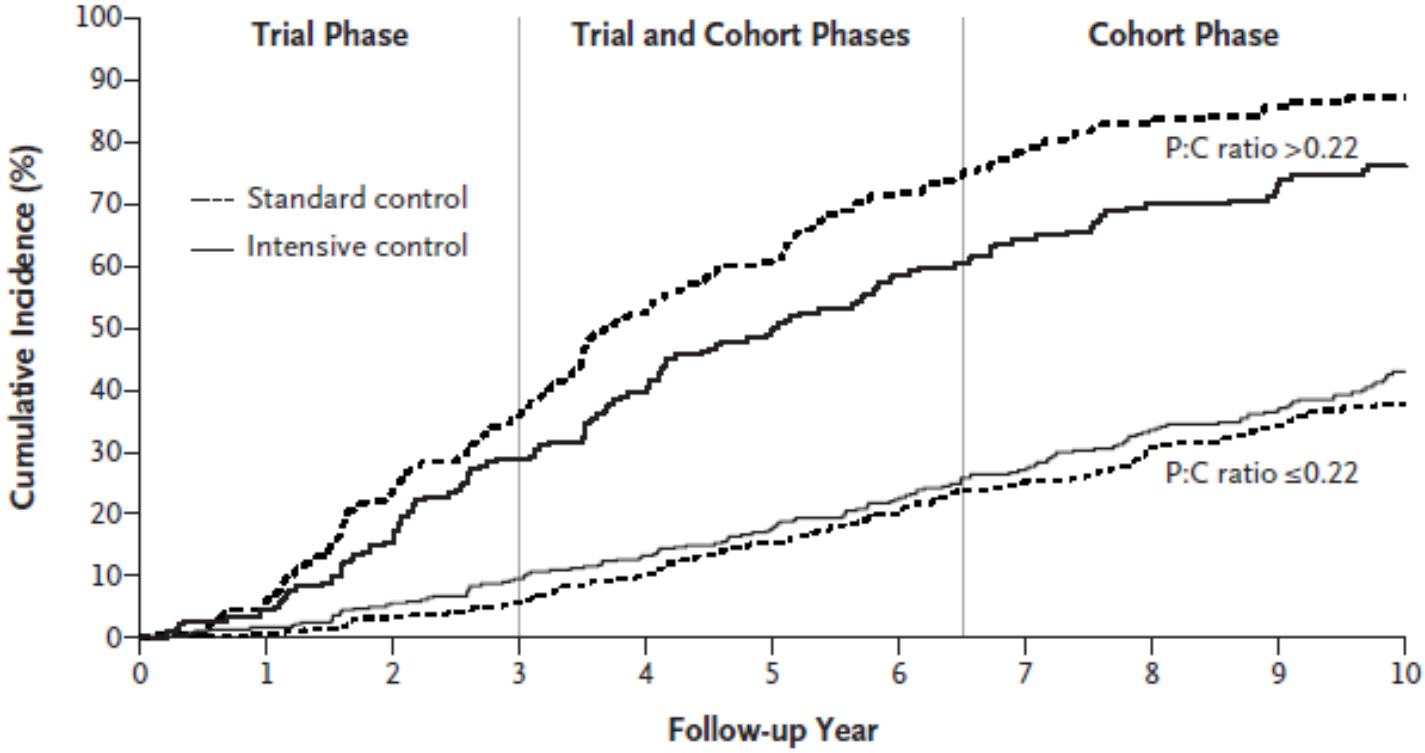
KDIGO Blood Pressure Work Group. Kidney Int 2012; 2(Suppl): 337–414.

Rates of Decline in GFR vs SBP in Type 2 DM and CKD in RCT Extending ≥ 3 Years



Bakris. Arch Intern Med, 161(22): 2661-2667; 2001.

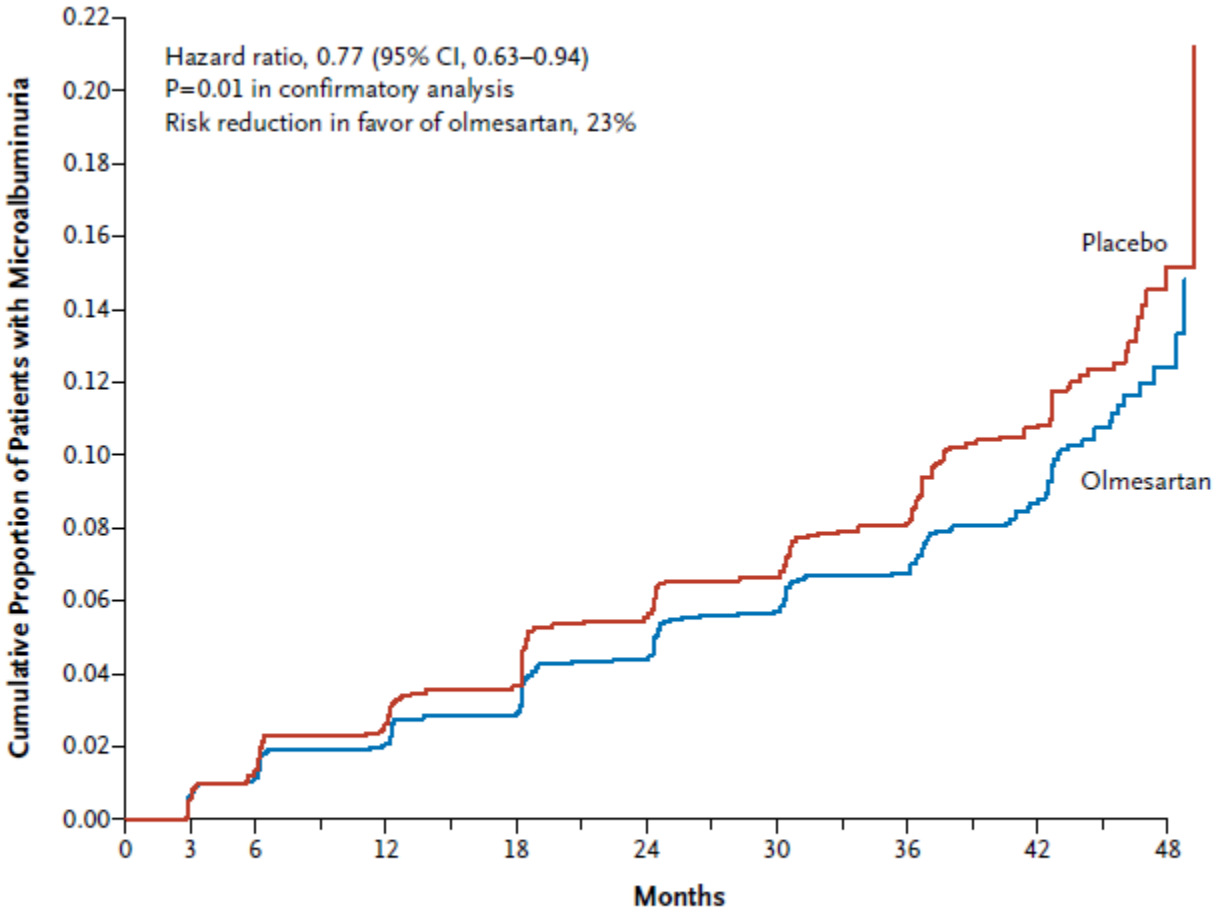
Intensive Blood-Pressure control in Hypertensive Chronic Kidney Disease: AASK Follow-up Data



P:C Ratio >0.22											
Standard control	176	165	134	113	81	66	45	32	26	22	13
Intensive control	181	172	151	128	109	87	67	56	47	40	25
P:C Ratio ≤0.22											
Standard control	376	373	362	353	332	302	267	234	214	196	128
Intensive control	357	350	335	321	306	282	254	228	206	189	128

Appel LJ et al. New Engl J Med 2010:363:918

Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes.



Haller H et al. N Engl J Med. 2011;364(10):907-17.

Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes.

Table 2. Secondary Efficacy End Points during the Double-Blind Treatment Period.*

End Point	Olmesartan (N=2232)	Placebo (N=2215)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Composite of cardiovascular complications or death from cardiovascular causes	96 (4.3)	94 (4.2)	1.00 (0.75–1.33)	0.99
Composite of death from any cause	26 (1.2)	15 (0.7)	1.70 (0.90–3.22)	0.10
Death from cardiovascular causes	15 (0.7)	3 (0.1)		
Death not related to cardiovascular causes	8 (0.4)	10 (0.5)		
Death from unknown cause	3 (0.1)	2 (0.1)		
Composite of death from cardiovascular causes	15 (0.7)	3 (0.1)	4.94 (1.43–17.06)	0.01
Sudden cardiac death	7 (0.3)	1 (<0.1)		
Death due to fatal myocardial infarction	5 (0.2)	0		
Evidence of recent myocardial infarction on autopsy	0	0		
Death due to congestive heart failure	0	0		
Death during or after percutaneous transluminal coronary angioplasty or CABG	1 (<0.1)	0		
Death due to fatal stroke	2 (0.1)	2 (0.1)		
Composite of cardiovascular complications, excluding new-onset atrial fibrillation and transient ischemic attack	63 (2.8)	71 (3.2)	0.87 (0.62–1.22)	0.42
Composite of new-onset atrial fibrillation or transient ischemic attack	19 (0.9)	28 (1.3)	0.67 (0.37–1.19)	0.17
Composite of all cardiovascular complications	81 (3.6)	91 (4.1)	0.87 (0.65–1.18)	0.37

Haller H et al. N Engl J Med. 2011;364(10):907-17.

Blood Pressure Management in CKD ND Patients with Diabetes Mellitus

Albuminuria (mg/day)	BP Target (mmHg)	Preferred Agents
< 30	≤ 140/90 *(1B)*	None
30 - 300	≤ 130/80 *(2D)*	ARB or ACE-I *(2D)*
> 300	≤ 130/80 *(2D)*	ARB or ACE-I *(1B)*

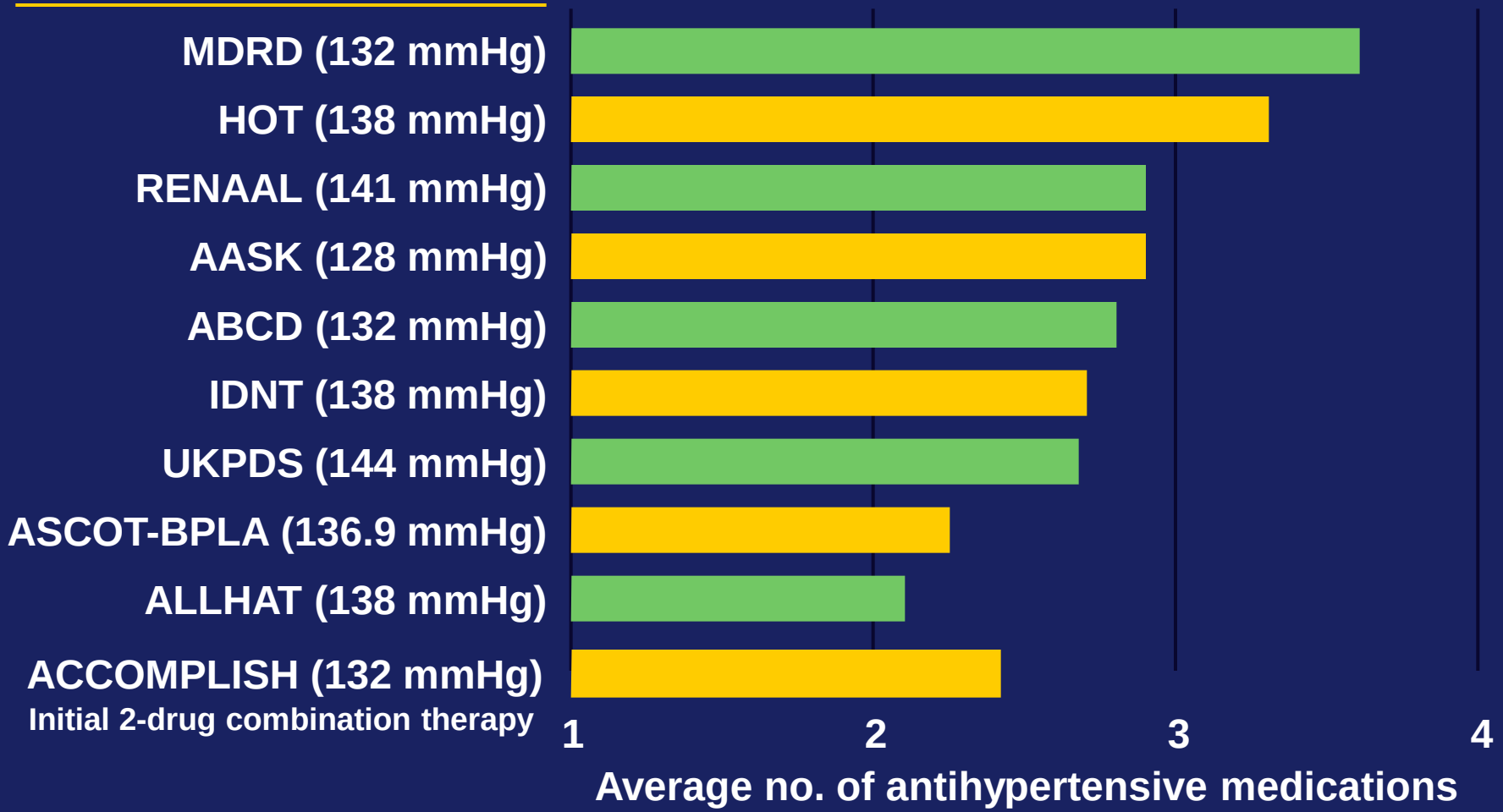
KDIGO CKD Work Group. Kidney Int 2012; 2(Suppl): 337–414.

Blood Pressure Management in CKD ND Patients without Diabetes Mellitus

Albuminuria (mg/day)	BP Target (mmHg)	Preferred Agents
< 30	≤ 140/90 *(1B)*	None
30 - 300	≤ 130/80 *(2D)*	ARB or ACE-I *(2D)*
> 300	≤ 130/80 *(2D)*	ARB or ACE-I *(1B)*

KDIGO CKD Work Group. Kidney Int 2012; 2(Suppl): 337–414.

Multiple Antihypertensive Agents are Needed to Reach BP Goal



Bakris et al. Am J Med 2004;116(5A):30S–8; Dahlöf et al. Lancet 2005;366:895–906
Jamerson et al. Blood Press 2007;16:80–6; Jamerson et al. N Engl J Med 2008;359:2417–28

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 4, 2008 VOL. 359 NO. 23

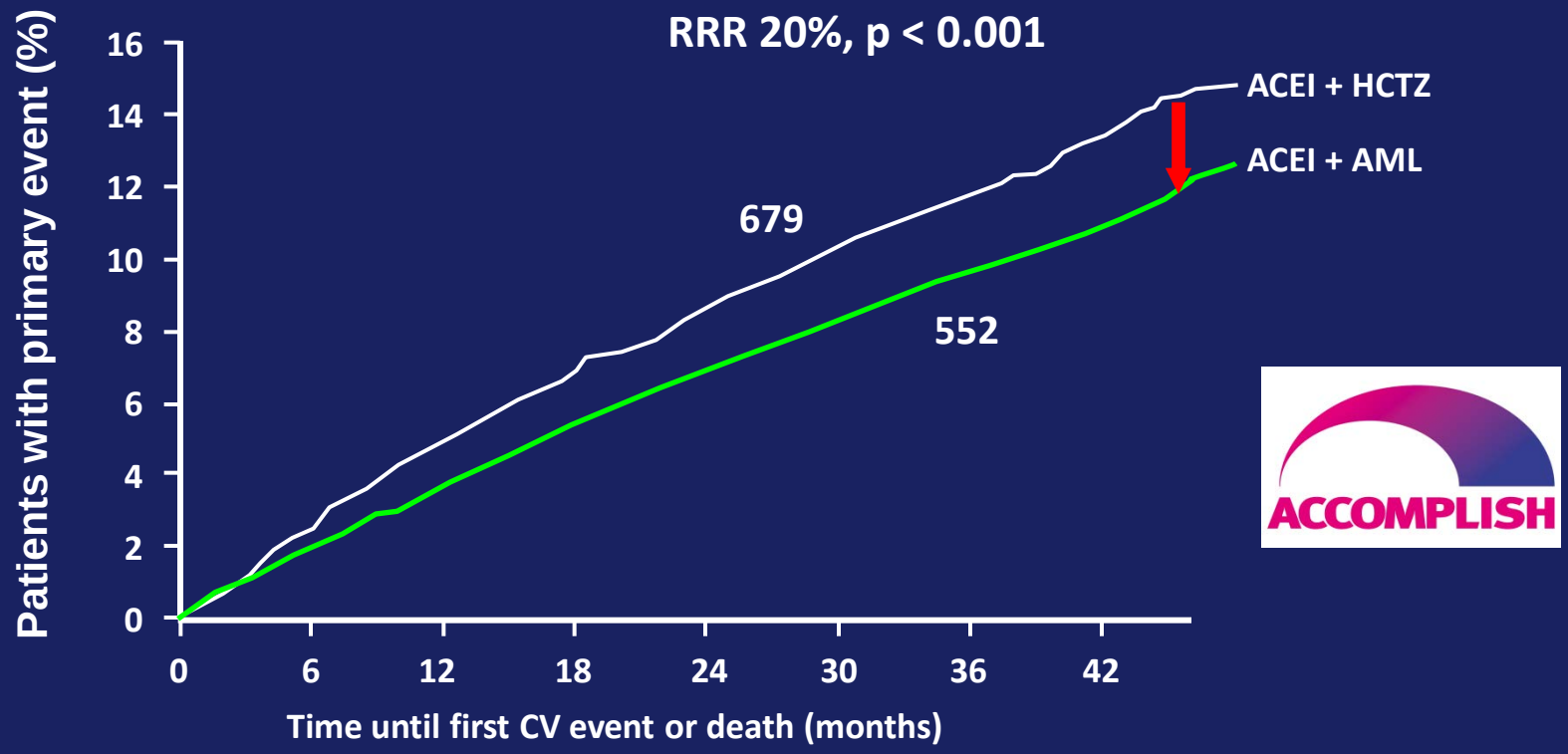
Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

Kenneth Jamerson, M.D., Michael A. Weber, M.D., George L. Bakris, M.D., Björn Dahlöf, M.D., Bertram Pitt, M.D., Victor Shi, M.D., Allen Hester, Ph.D., Jitendra Gupte, M.S., Marjorie Gatlin, M.D., and Eric J. Velazquez, M.D., for the ACCOMPLISH trial investigators*

Jamerson et al. *N Engl J Med* 2008;359:2417–28

ACCOMPLISH Main endpoint (cardiovascular events/death)

Benazepril + Amlodipine vs. Benazepril + HCTZ in high-risk patients



RRR, relative risk reduction; ACEI, angiotensin converting enzyme inhibitor; AML, amlodipine; HCTZ, hydrochlorothiazide

Jamerson et al. *N Engl J Med* 2008;359:2417–28

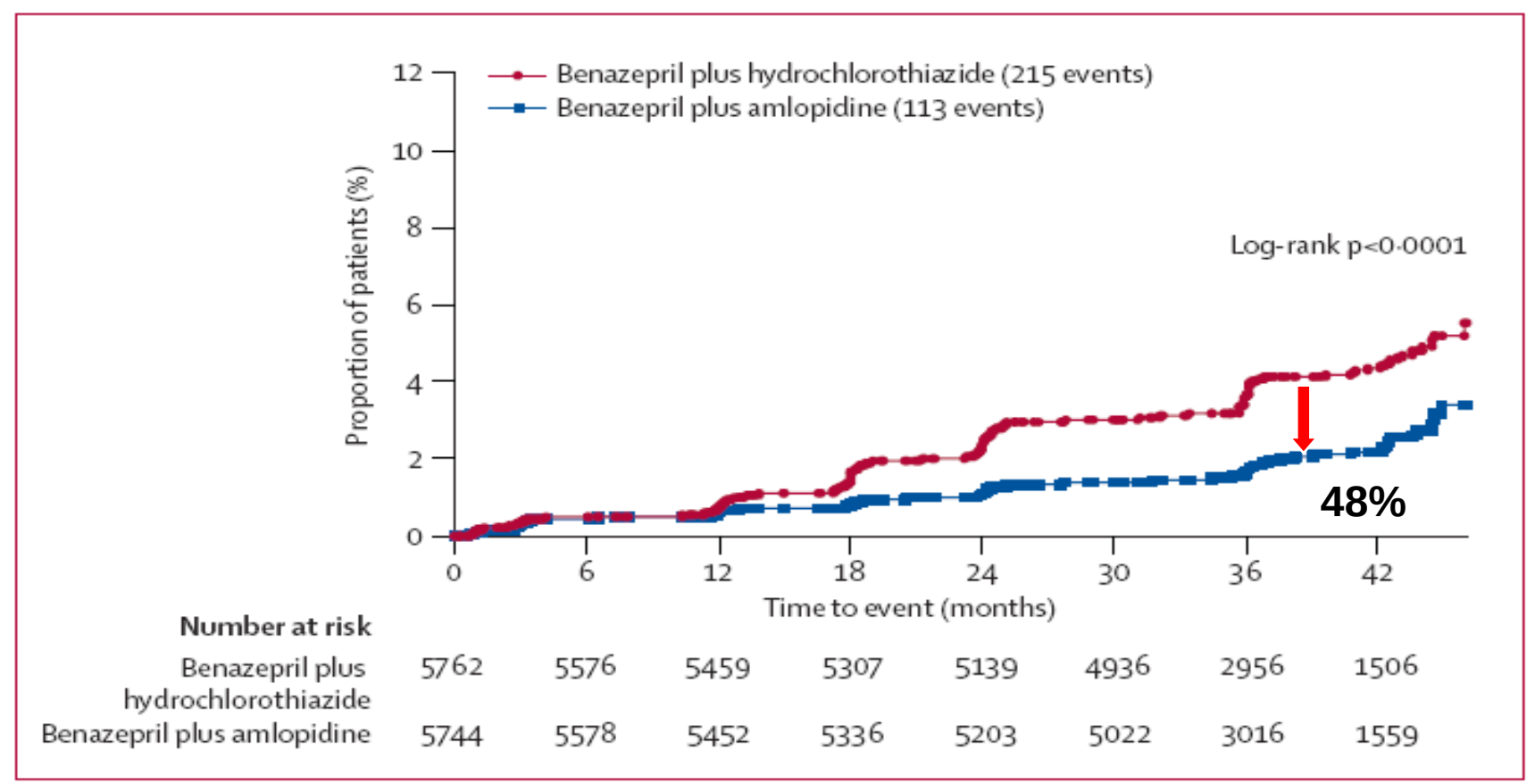
Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial

George L Bakris, Pantelis A Sarafidis, Matthew R Weir, Björn Dahlöf, Bertram Pitt, Kenneth Jamerson, Eric J Velazquez, Linda Staikos-Byrne, Roxzana Y Kelly, Victor Shi, Yann-Tong Chiang, Michael A Weber, for the ACCOMPLISH Trial investigators*

Published online February 18, 2010 DOI:10.1016/S0140-6736(09)62100-0

CKD progression

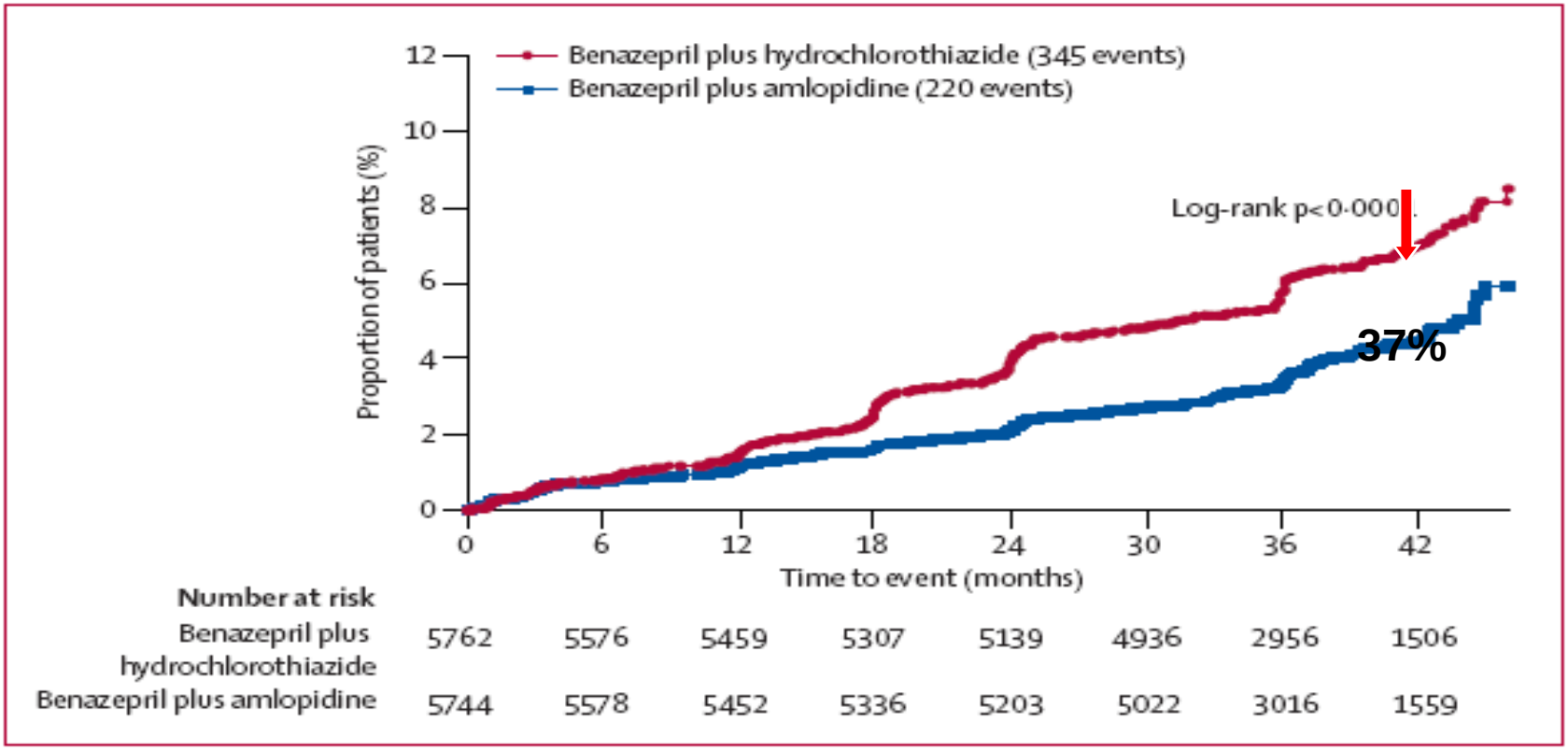
- Fewer chronic kidney disease events in the **benazepril plus amlodipine** group



Lancet. 2010 Apr 3;375(9721):1173-81

CKD progression + CV Death

- Fewer combined cardiovascular deaths and chronic kidney disease events in the **benazepril plus amlodipine** group



Lancet. 2010 Apr 3;375(9721):1173-81

ACEIs & ARBs in Thailand

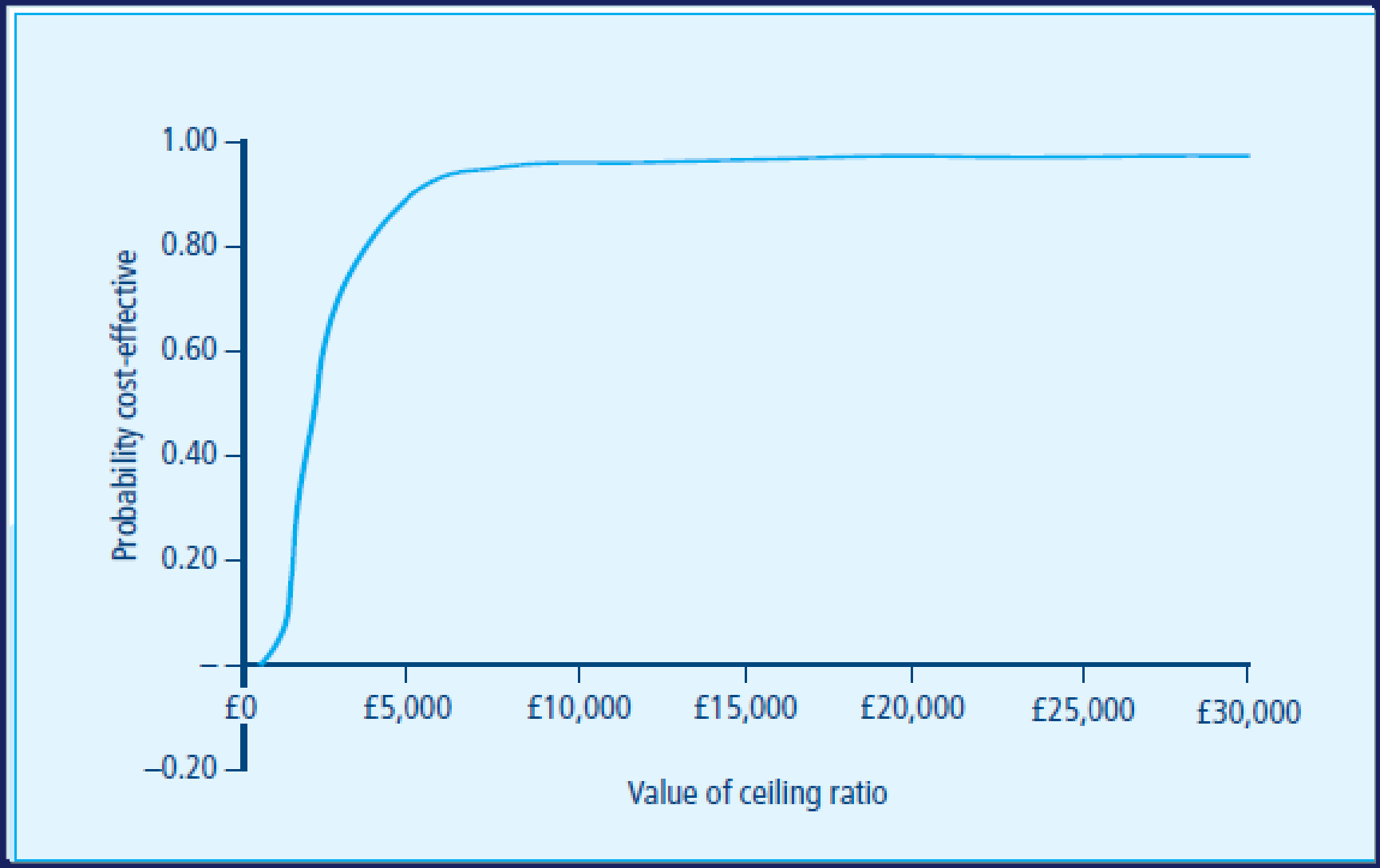
ACEI	ARB
Enalapril	Losartan
Captopril	Irbesartan
Lisinopril	Valsartan
Ramipril	Candesartan
Quinapril	Telmisartan
Perindopril	Olmesartan
Imidapril	

Cost-effectiveness Analysis: ICERs

$$\text{CE ratio} = \frac{\text{cost}_{\text{new strategy}} - \text{cost}_{\text{current practice}}}{\text{effect}_{\text{new strategy}} - \text{effect}_{\text{current practice}}}$$

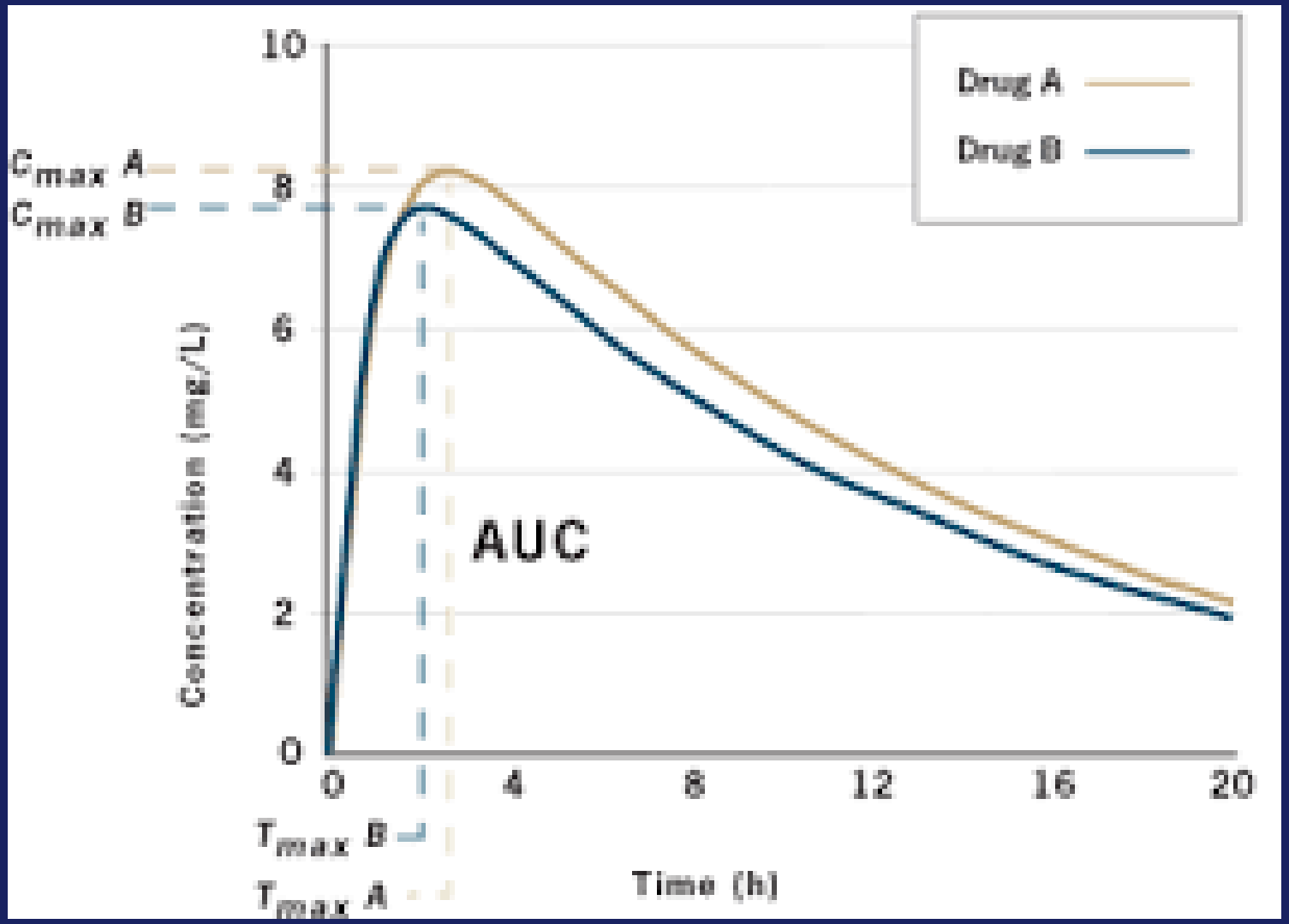
Figure 7 Cost-effectiveness Matrix

Cost-effectiveness Acceptability Curve

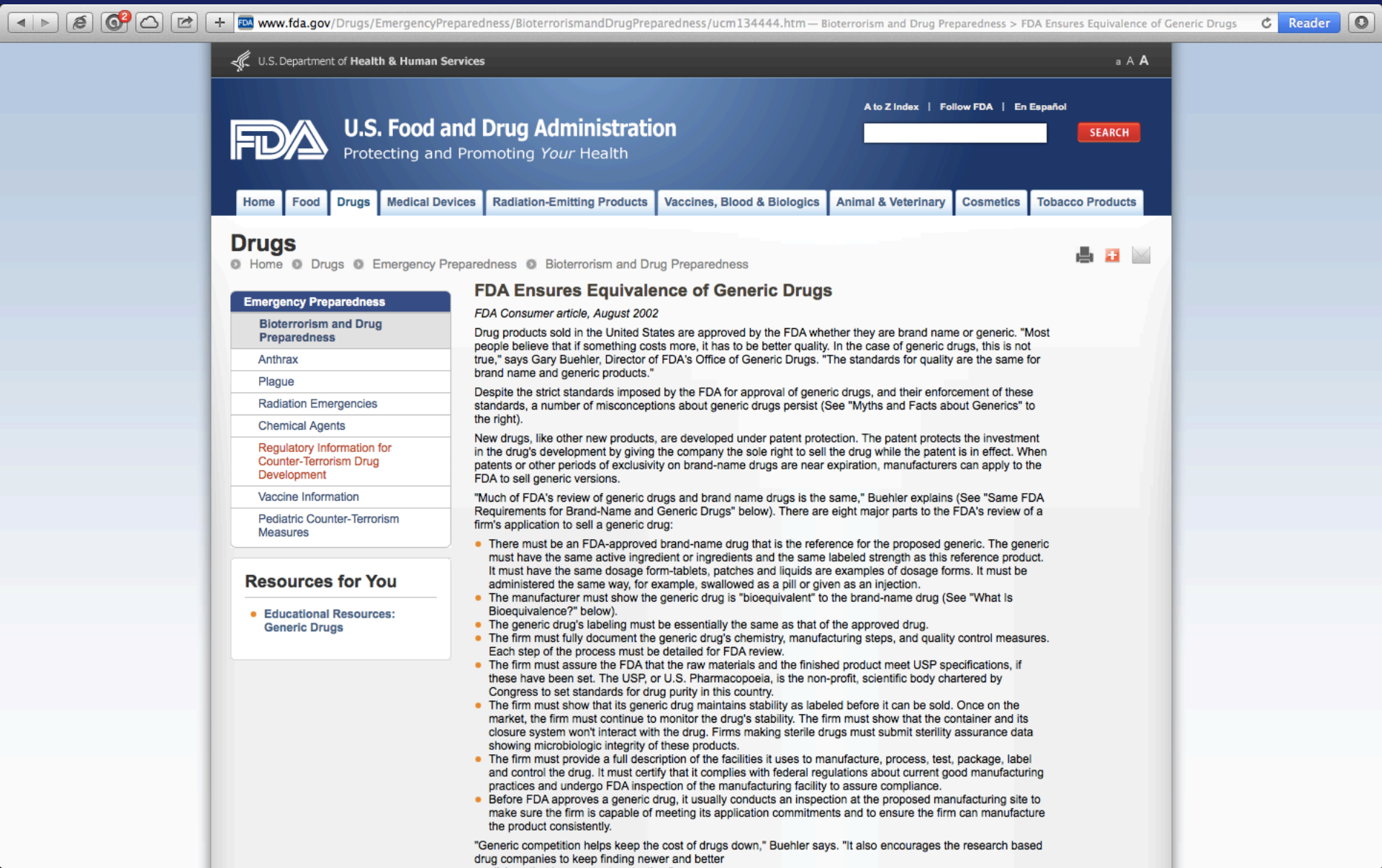


ACEIs & ARBs in Thailand

Do We Need a Clinical Trial for Generic Drugs?



Bioequivalence and Interchangeability of Generic Drugs



When Generic Substitution May Not be Appropriate

- Drugs on the market before 1938
- Drugs with a narrow therapeutic index (anticonvulsants, anticoagulants)
- Some antihypertensive agents (reserpine)
- Some oral antiasthmatic agents (theophylline, aminophylline)
- Corticosteroid creams, lotions and ointments
- Corticosteroid tablets (dexamethasone)
- Hormones (esterified estrogen, medroxyprogesterone)
- Antipsychotic drugs (chlorpromazine)
- Colchicine

Thank You