

Cardiovascular Protection and the RAS

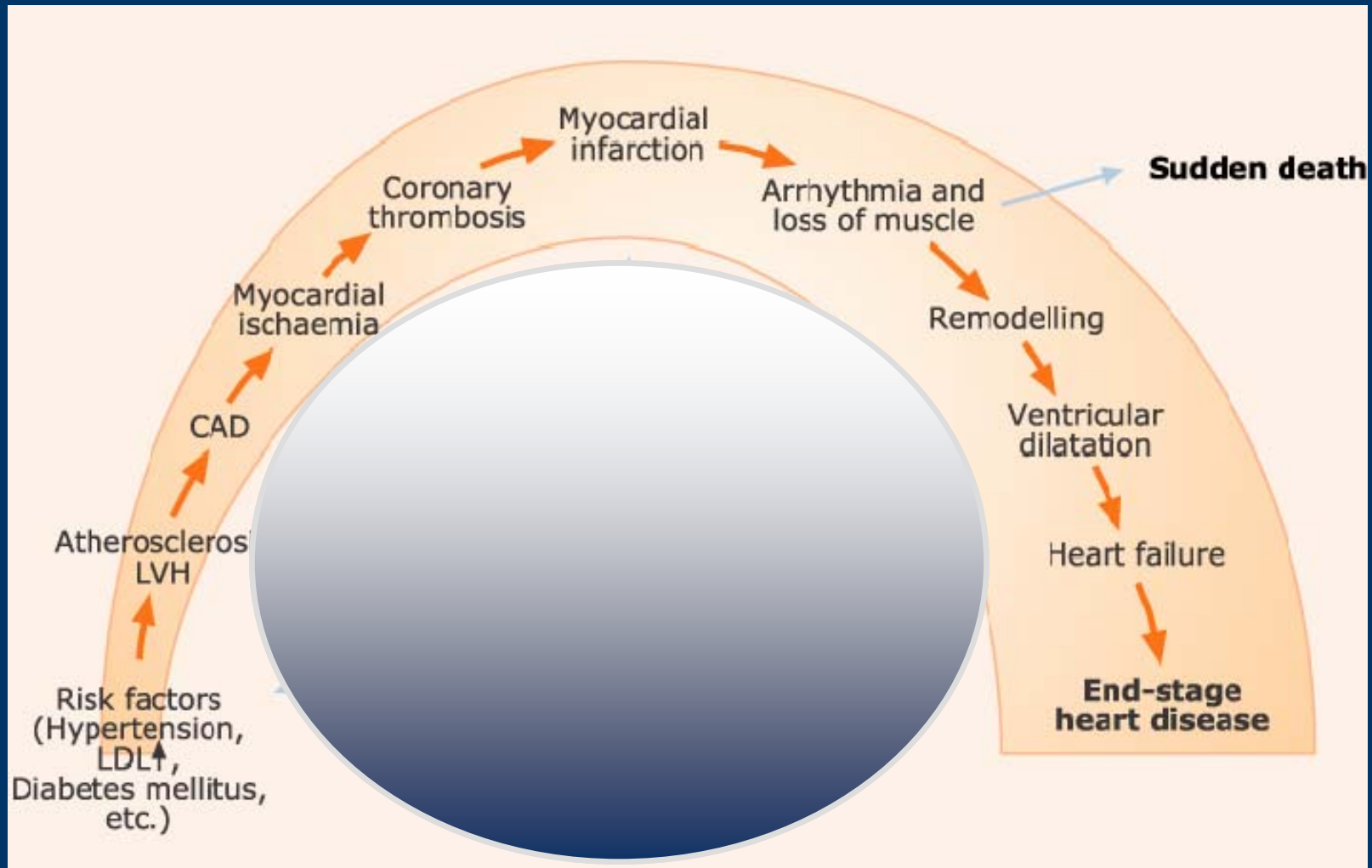
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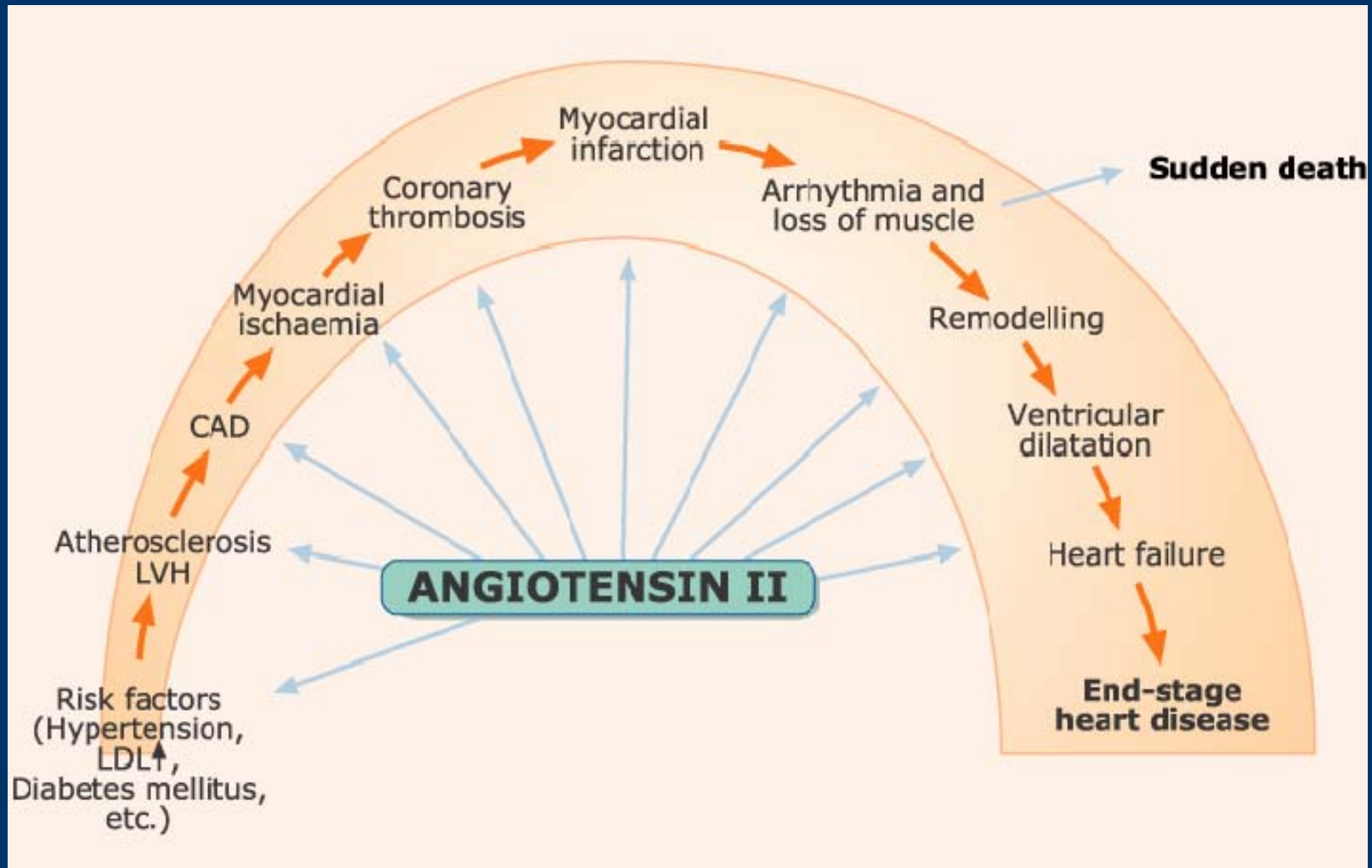
Cardiovascular Disease is a Major Health Concern

- 2009 AHA Statistics for the US:
 - CVD (80 mil)
 - MI (8 mil)
 - Stroke (6.5 mil)
 - Heart failure (5.7 mil)
 - CVD deaths (0.86 mil)
- Effective treatments are needed to reduce the risk of CV events

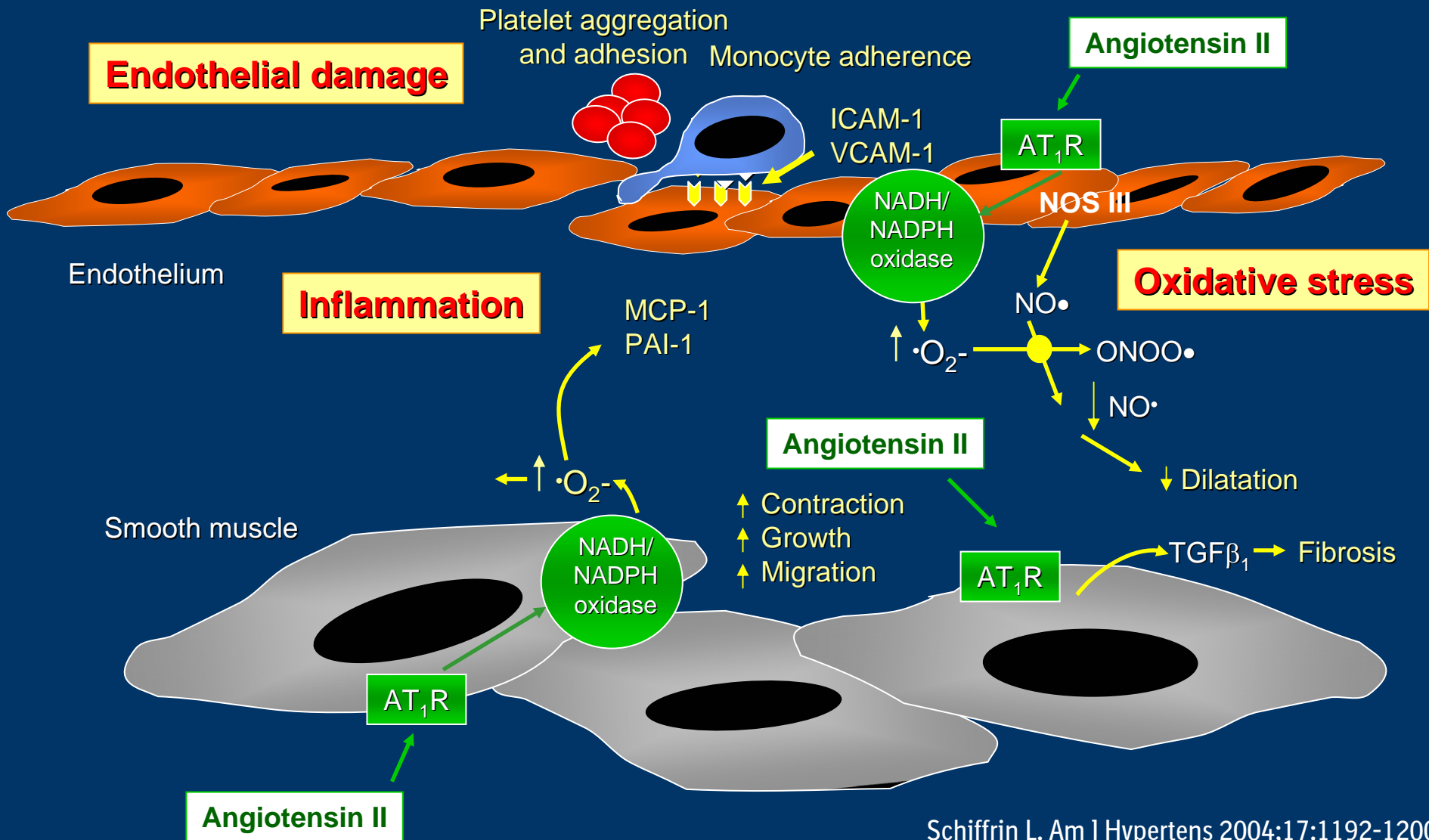
Cardiovascular Disease Continuum



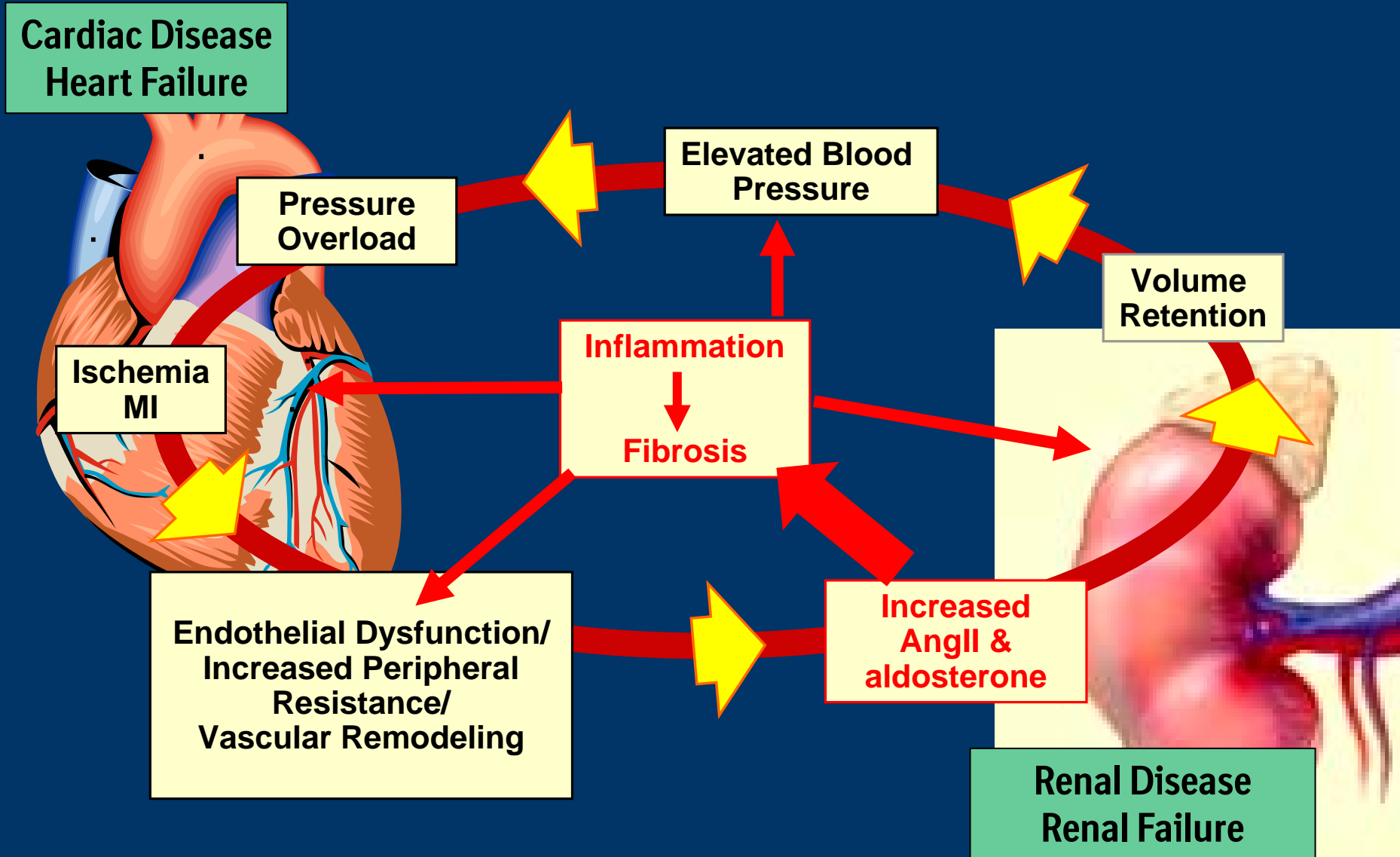
Angiotensin II is Involved in Progression of CAD from Multiple Risks to End-Stage



Angiotensin II a Mediator for Oxidative Stress, Inflammation and Vascular Damage



Cardiac/Renal Protection- What To Target?



Chronic Kidney Disease

It begins with

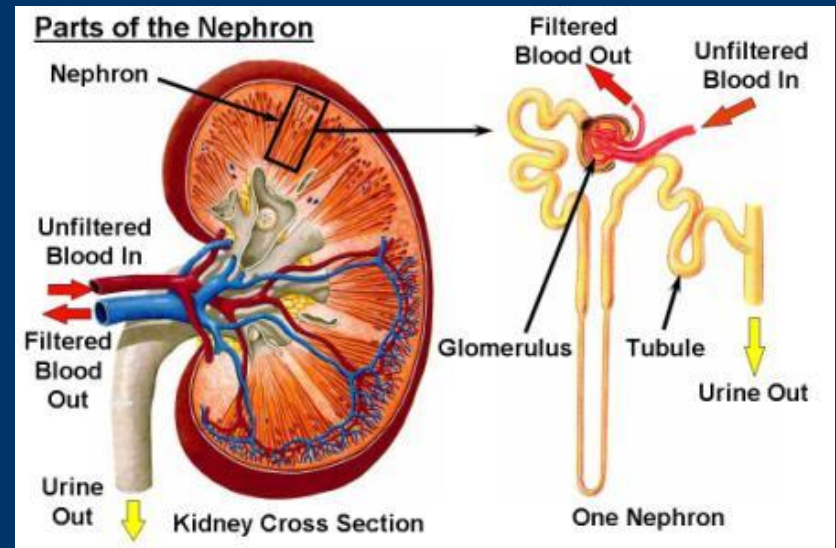
- Hyperfiltration (diabetes),
- Microalbuminuria,
- Hypertension, and/or
- Inflammation (nephritis)

Once present

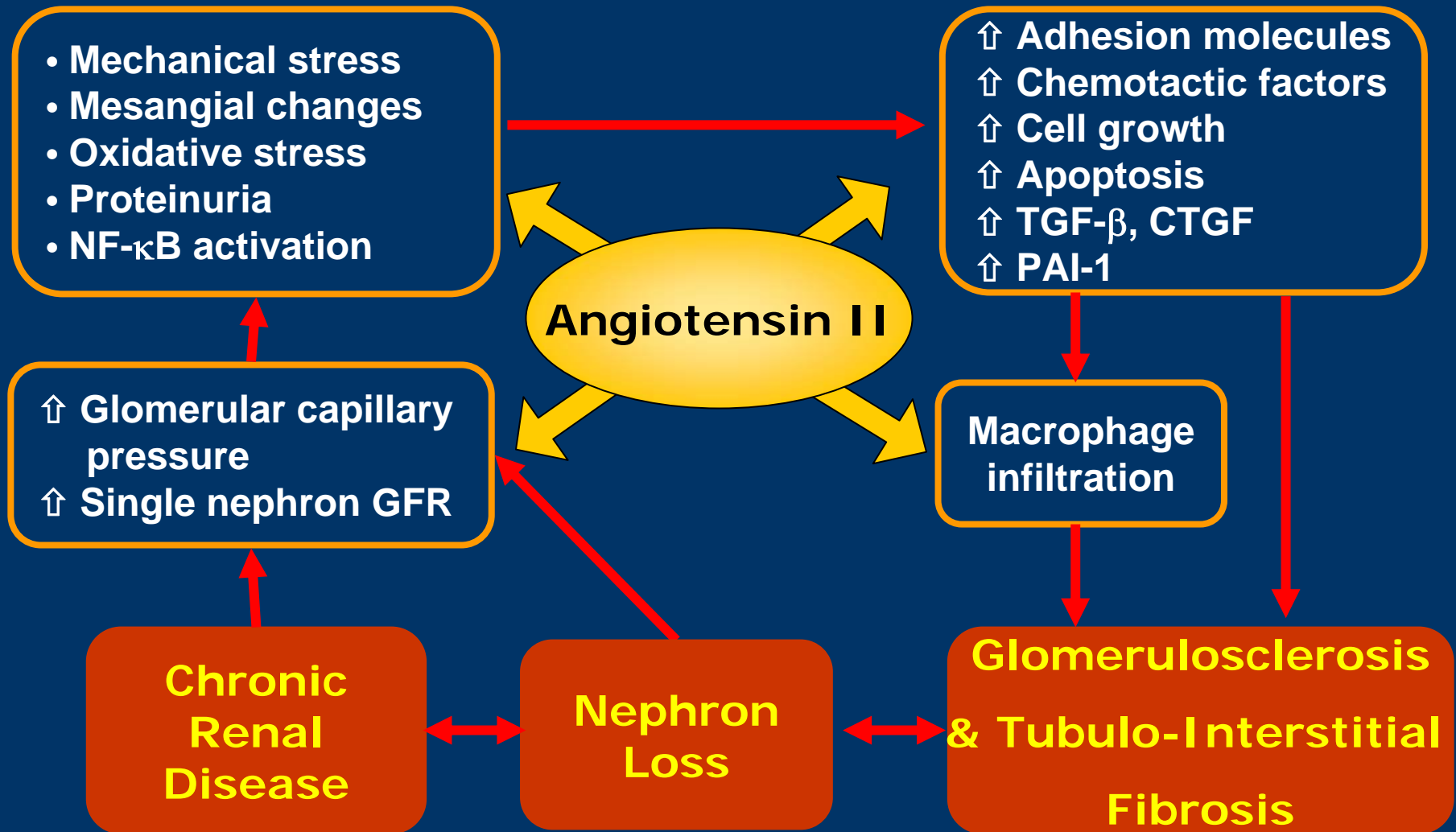
- Underlying pathophysiological mechanisms of disease progression are similar, irrespective of cause

It is "progressive"

- Progresses (at variable rates) to end-stage renal disease (ESRD) requiring dialysis or transplantation
- However, CKD patients are more likely to die from CV disease



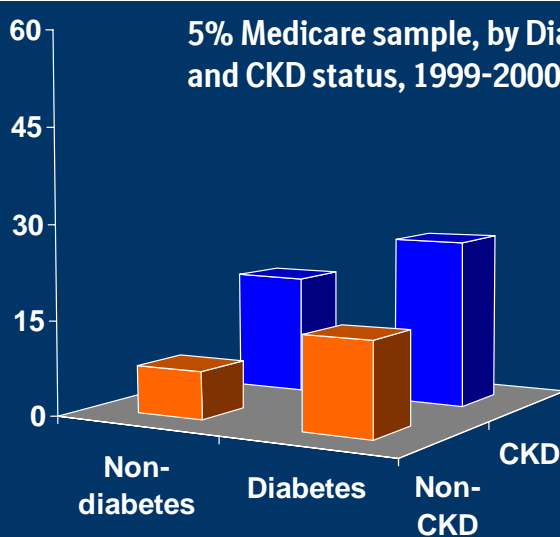
Role of Angiotensin II in Chronic Renal Disease



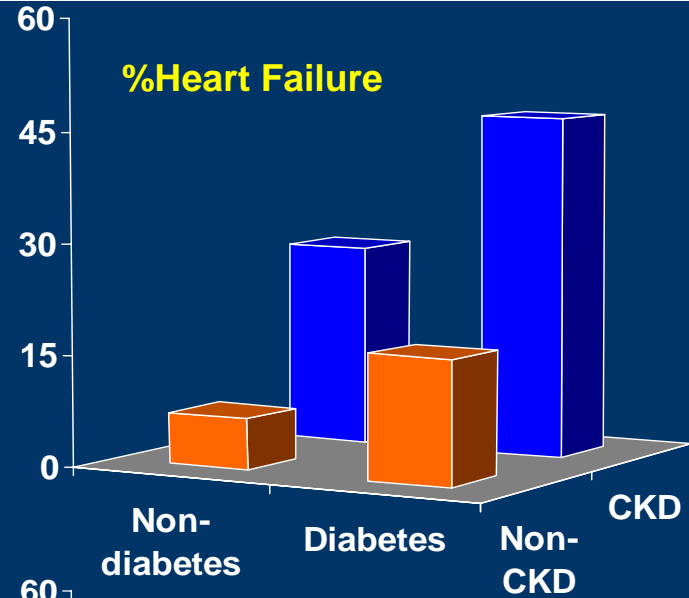
Comorbidities: Diabetes and CKD Significantly Contribute to CVD Morbidity

5% Medicare sample, by Diabetes and CKD status, 1999-2000

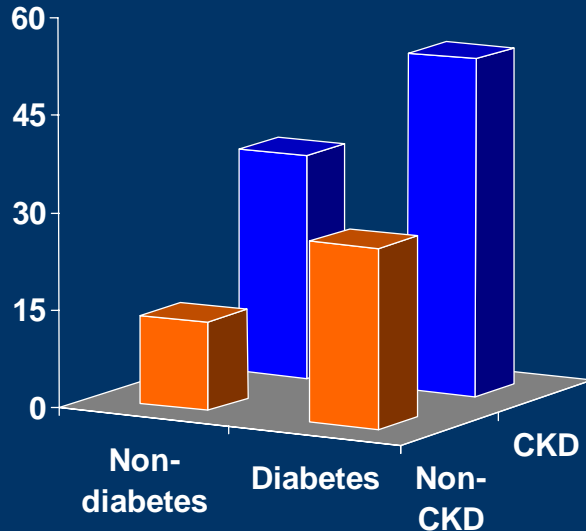
%Stroke/TIA



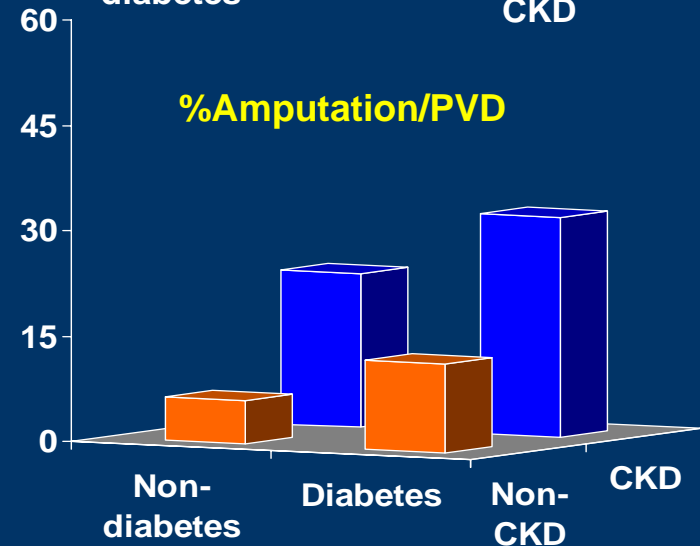
%Heart Failure



%ASHD



%Amputation/PVD



Optimal Cardio-Vascular Protection

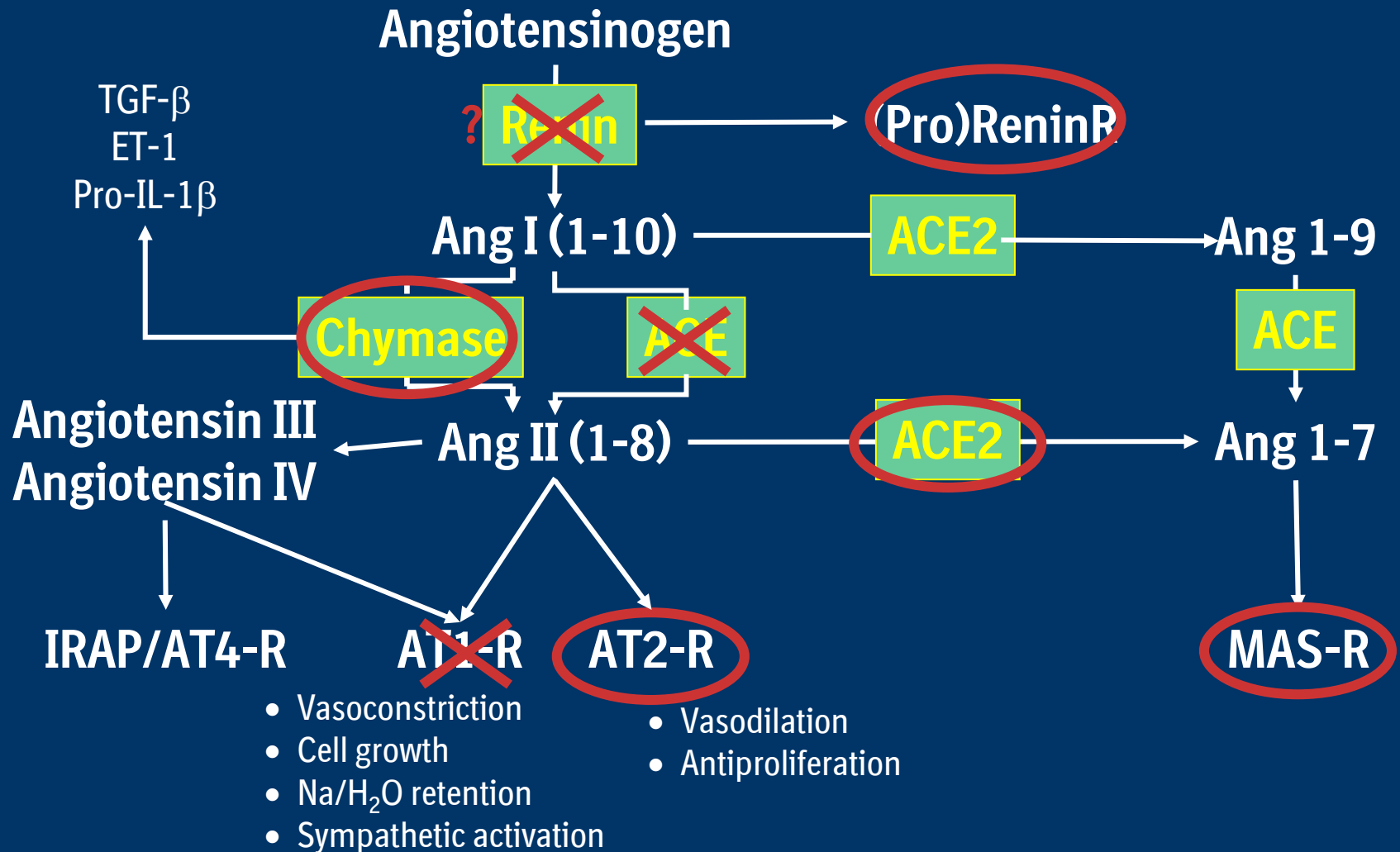
There is a continuous relationship between
BP, cholesterol, glucose
and CV events!

Optimal Cardio-Vascular Protection

Earlier and more aggressive
BP, lipid and glucose control

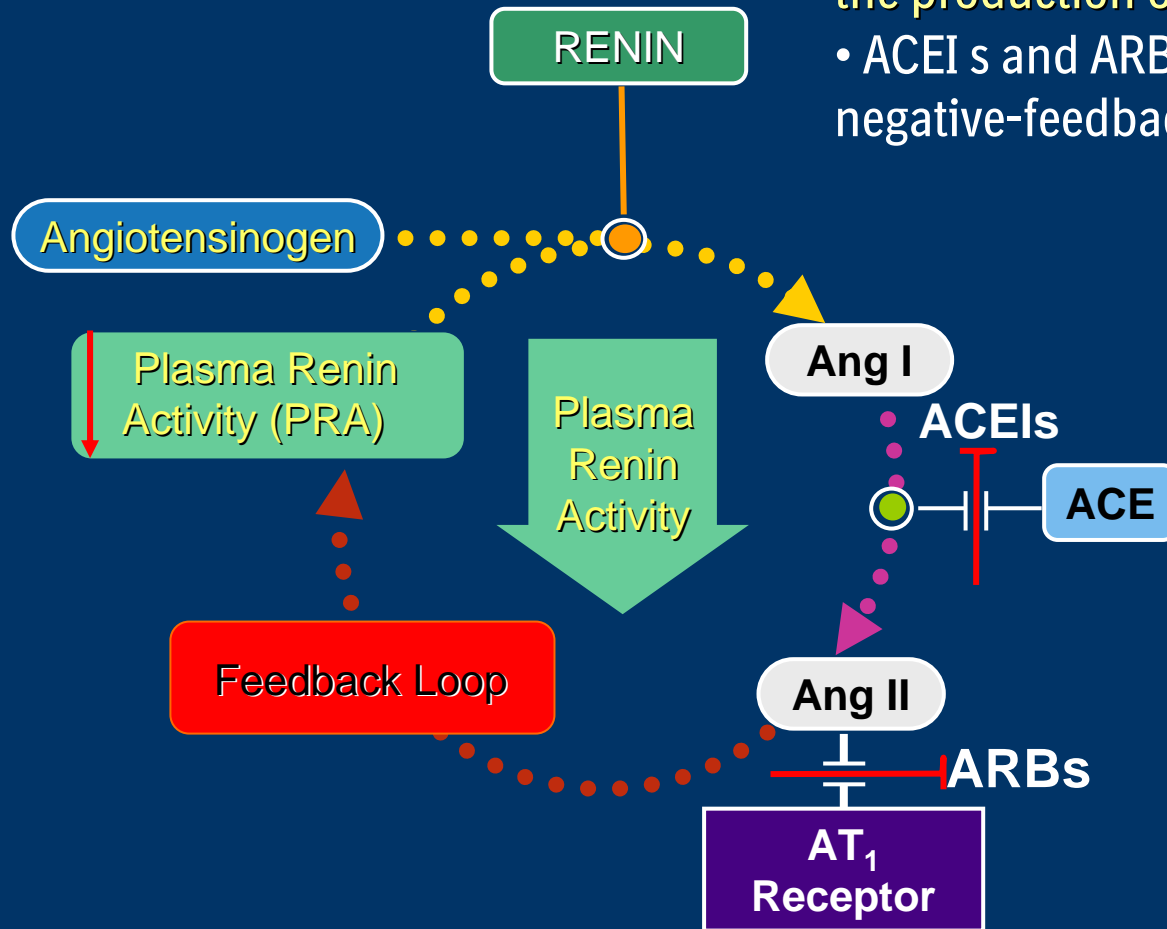
Pharmacologic blockade of the RAS

Growing Complexity of the RAS



The RAS Is Controlled by a Negative-Feedback Loop

- Angiotensin II formation decreases the production of renin
- ACEIs and ARBs interrupt the RAS' negative-feedback loop



Rationale for a More Complete RAS Blockade

- The RAS is one of the most detrimental neurohormonal pathways in the CV system
- Part of the target organ protection appears to be blood pressure independent highlighting the role of a local RAS
- The increasing appreciation of the complexity of the RAS suggests that present treatment modalities only incompletely inhibit the system
- Renin inhibitors are currently under development and their place in target organ protection needs to be determined in outcome studies
- Combination of ACEI and ARB treatment has been investigated for superior target organ protective properties

How to Achieve Optimal RAS Protection?

Optimal dosing of RAS blockers

- Highest doses approved by FDA for BP reduction appear to be the best doses

Targeting renin

- Blockade of the complex RAS at its initial point of activation without increased plasma renin activity

Combining RAS (ACEI + ARB) blockers

- More complete blockade of the pathway - ONTARGET trial

The ONTARGET Trial Program

ONTARGET

TRANSCEND

Screening

Run-In (n = 29,019)

Run-In (n = 6,665)

If ACEI intolerant

Randomization (n = 25,620)

Randomization (n = 5,926)

n = 8542

Telmisartan
80 mg/day +
placebo

n = 8576

Ramipril
10 mg/day +
placebo

n = 8502

Telmisartan
80 mg/day +
ramipril
10mg/day

n = 2,954

Telmisartan
80 mg/day

n = 2,972

Placebo

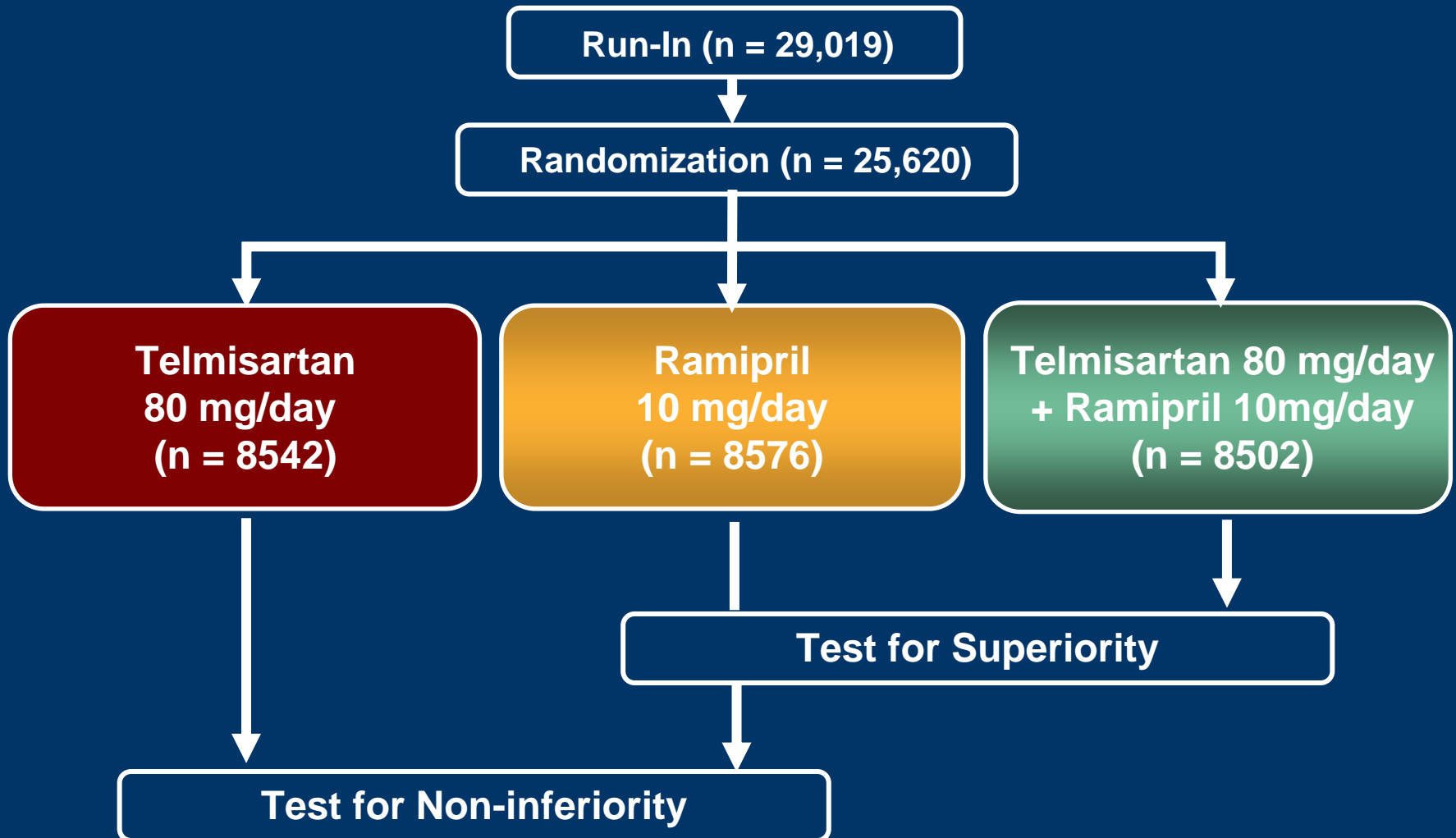
Follow-up at 6 weeks

Follow-up at 6 weeks

Follow-up at
6 months for 5.5 years

Follow-up at
6 months for 6 years

Design of the ONTARGET Trial

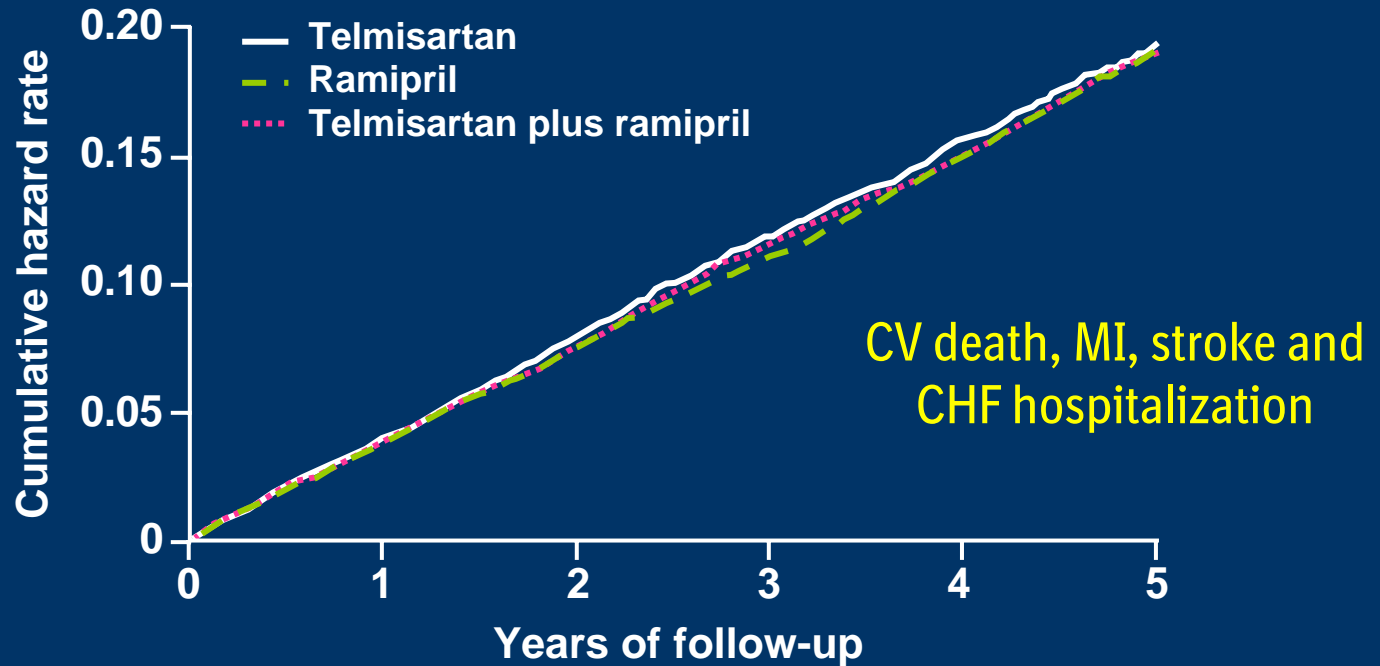


Comparison of Baseline Characteristics in HOPE and ONTARGET

	ONTARGET	HOPE
	25,620	9,297
Age (yrs)	66	66
% Women	27	27
% Coronary artery disease	75	80
% Peripheral artery disease	14	44
% Stroke/TIA	19	11
% Diabetes	38	38
% Hypertension	69	47
Blood pressure (mmHg)	142/82	139/79
% Statins	62	29
% Antiplatelet	76	76
% Diuretics	28	15
% β -blocker	57	40

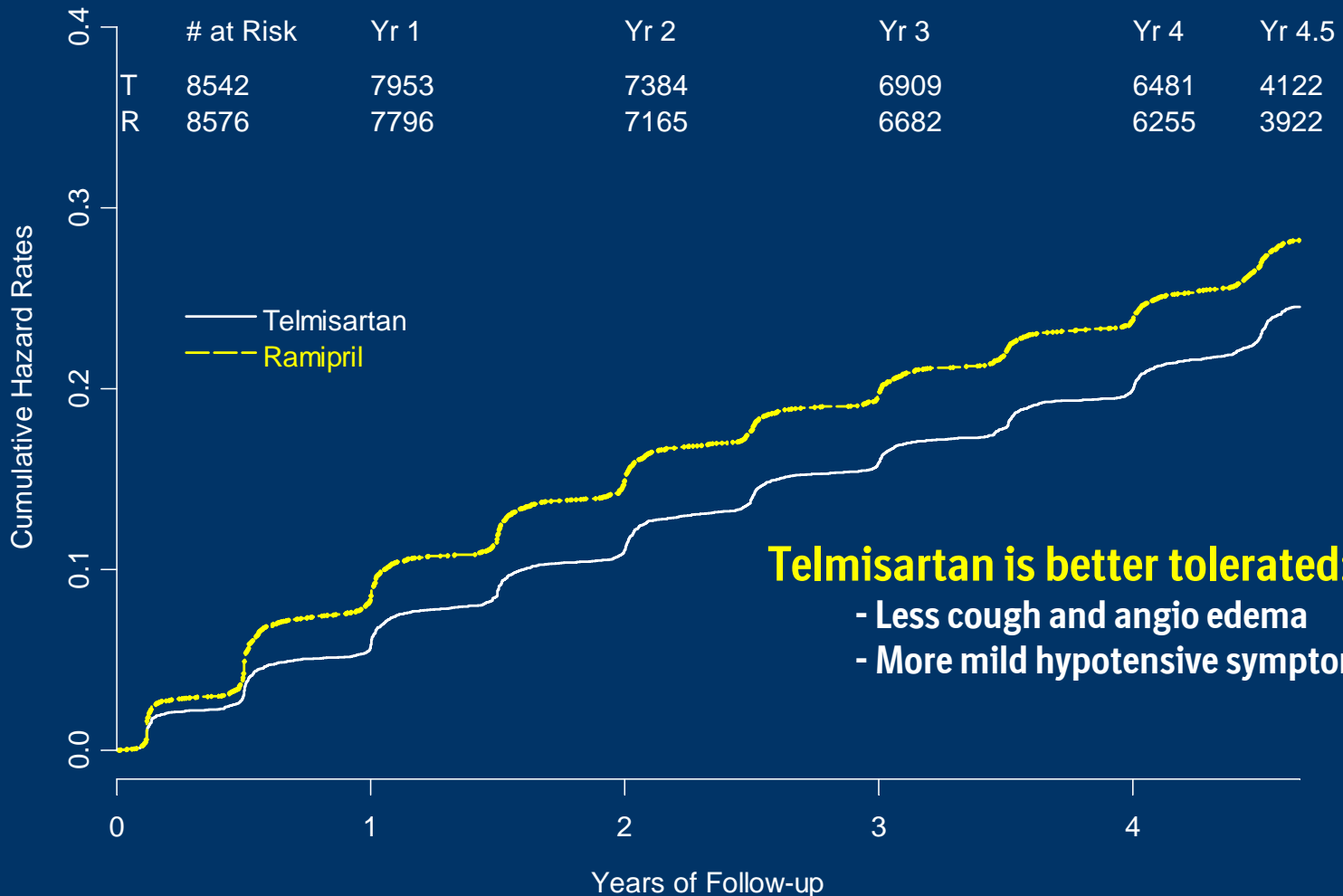
ONTARGET
patients had less
vascular disease
and were better
treated than HOPE
patients

ONTARGET: First Primary Event (4 fold) Telmisartan, Ramipril & Combination



No. at risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

Time to Permanent Discontinuation of Study Medication



ONTARGET Conclusions

1. **Telmisartan is similarly effective as ramipril:**
 - Primary composite outcome ($p = 0.0019$)
 - HOPE primary outcome ($p = 0.0004$)
 - Most of the benefits of ramipril are preserved
2. **Consistent results on a range of:**
 - Secondary outcomes
 - Subgroups
3. **Telmisartan is better tolerated:**
 - Less cough and angioedema
 - More mild hypotensive symptoms

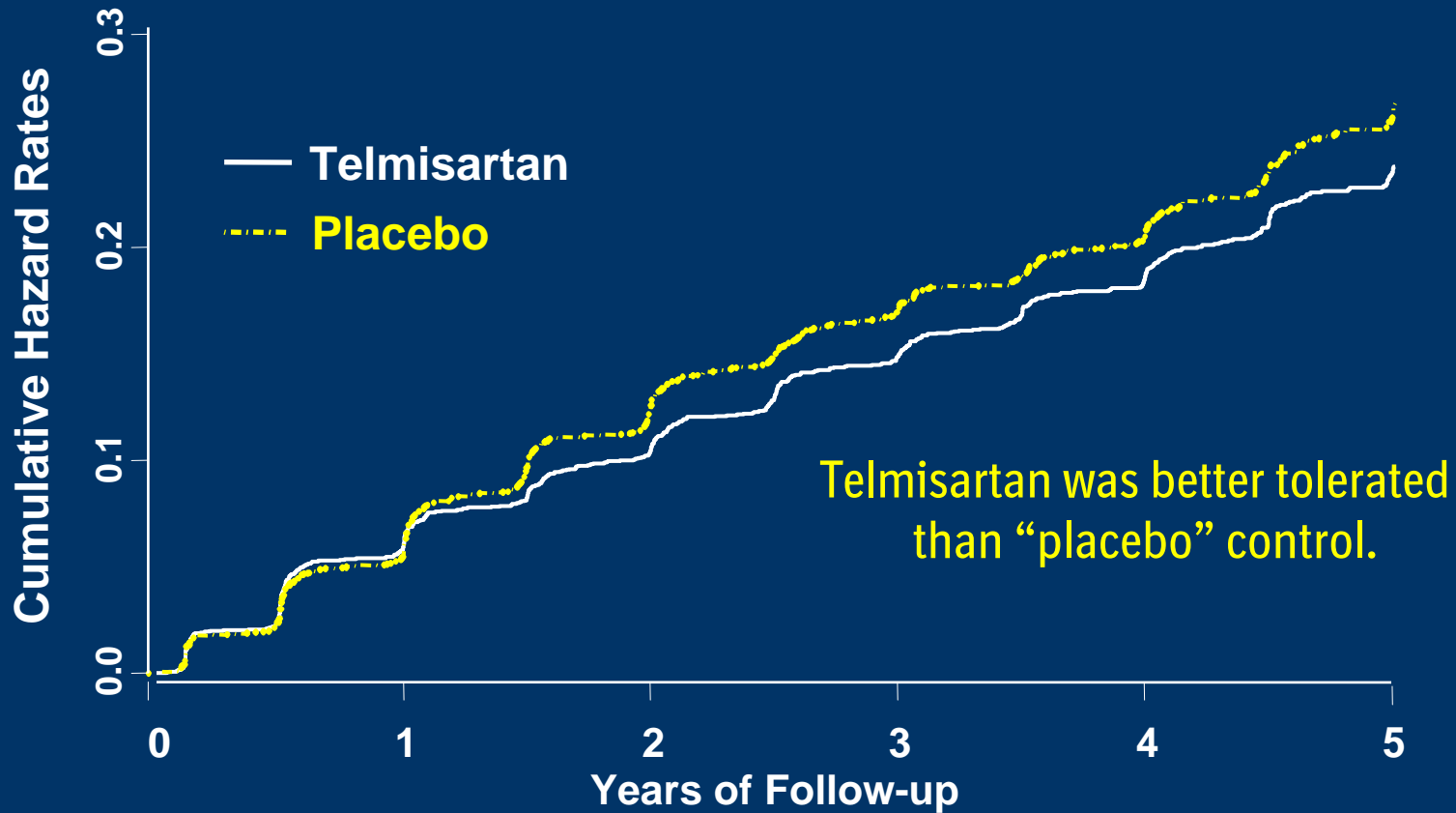
TRANSCEND:

Effect of Telmisartan on Primary Endpoint

	Telmisartan		Placebo	
Randomized	2954		2972	
CV death, MI, stroke and CHF hospitalization	465	15.7%	504	17.0%
CV death	140	4.7%	137	4.6%
Nonfatal MI	106	3.6%	136	4.6%
Non-fatal stroke	106	3.6%	127	4.3%
Hospitalization for CHF	123	4.2%	112	3.8%
Hazard ratio vs. placebo (95% CI) for primary endpoint	0.92 (0.81, 1.05) p = 0.22			

TRANSCEND

Permanent Discontinuation of Study Medication



	# at Risk	Year 1	Year 2	Year 3	Year 4	Year 5
T	2,954	2,784	2,663	2,547	2,271	1,086
PI	2,972	2,814	2,629	2,509	2,242	1,063

Baseline Characteristics Different in ONTARGET and TRANSCEND

	ONTARGET	TRANSCEND
N	25,620	5926
% Women	27	43
% Asians	14	21
% Hypertension	69	76
% Statins	62	55
% Diuretics	28	33
% CCBs	24	31

Renin Angiotensin System Inhibition

	ACE-I	ARB	Combination	Renin-I
HBP: Reduce BP	✓	✓	++	✓
Heart Failure	✓	✓	++	?
Myocardial Infarction	✓	✓	NAB	?
Chronic Kidney Disease	✓	✓	NAB	?
Vascular Disease	✓	✓	NAB	?

NAB = no added benefit

Conclusion

- Clinical studies indicate RAS inhibitors are very effective for reducing blood pressure
- The organ-protective benefits of ACEIs and ARBs are not synergistically enhanced by addressing the incomplete RAS suppression by combination treatment
- It remains to be shown in large outcome trials, whether renin inhibitors cause cardiovascular benefit
- Telmisartan appears to be as effective as Ramipril in cardiovascular protection based on the ONTARGET trial results



Signaling Pathways Include Oxidative Stress, Inflammation, Remodeling and Hypertrophy

