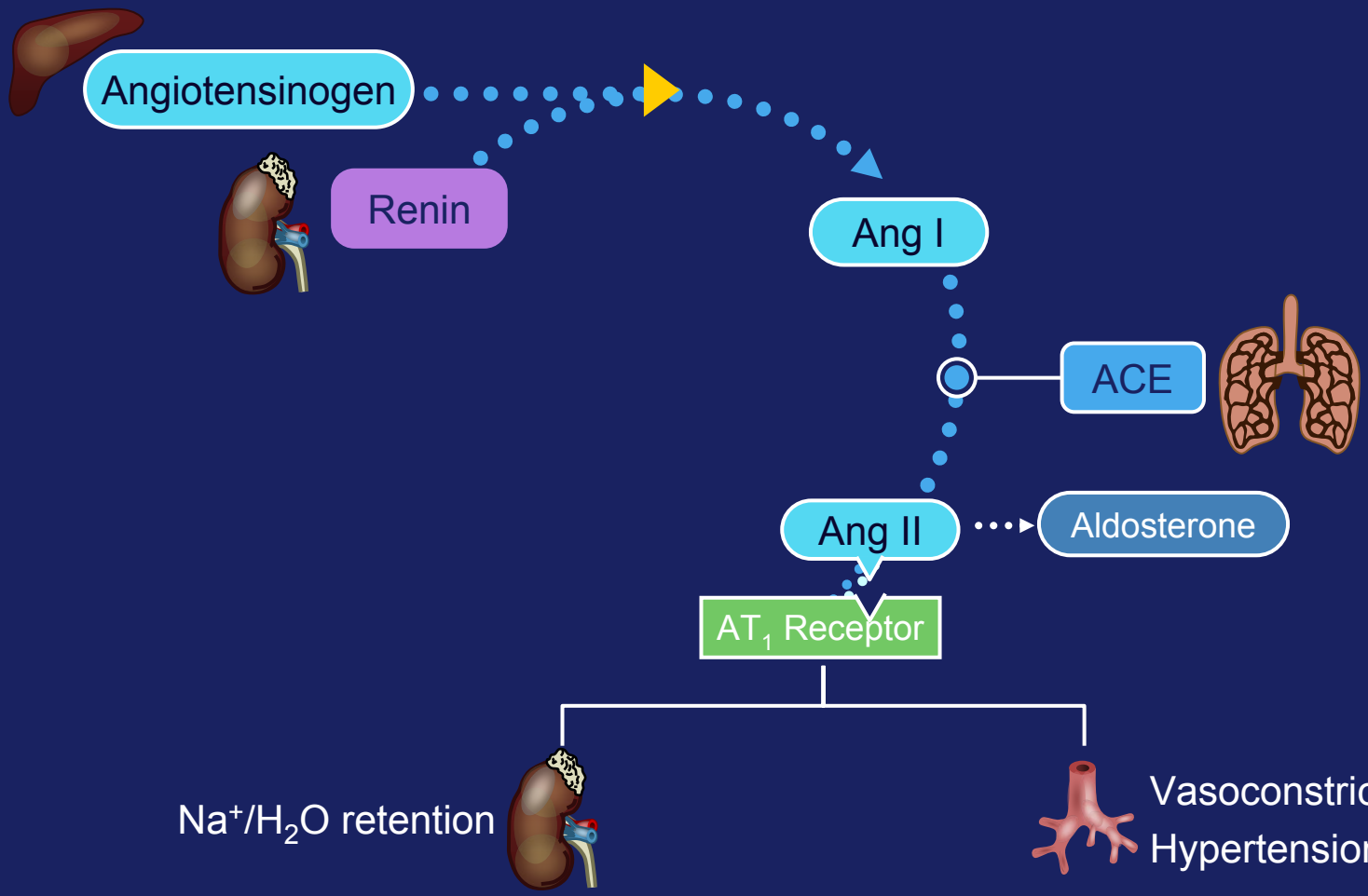
Renin sistemin tansiyondaki kontrol rolü ve kardiovasküler sistemindeki organ hedeflerin hasarı

Friedrich C. Luft, MD
Charité and Max-Delbrück Center
Campus Berlin-Buch
Berlin, Germany

Renin angiotensinogen'i Ang I catalize ediyor, sonunda tansiyon yükseliyor

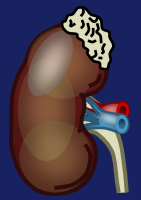


Chronic activation of the Renin System can lead to organ damage

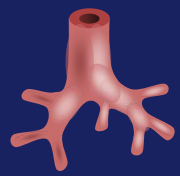
Adapted from: Weber MA & Giles TD. Rev Cardiovasc Med 2006;7:45–54

Renin sistemindeki organ hasarında Ang II kilit nokta

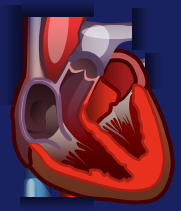
- Organ damage associated with excessive renin system activity and is mediated through Ang II.[1]
- Chronic dysregulation of Ang II is implicated in organ remodeling and restructuring.[2]



Kidney
- Dysfunction
- Glomerular sclerosis
- Fibrosis



Blood vessels
- Restenosis
- Atherosclerosis
- Thrombosis

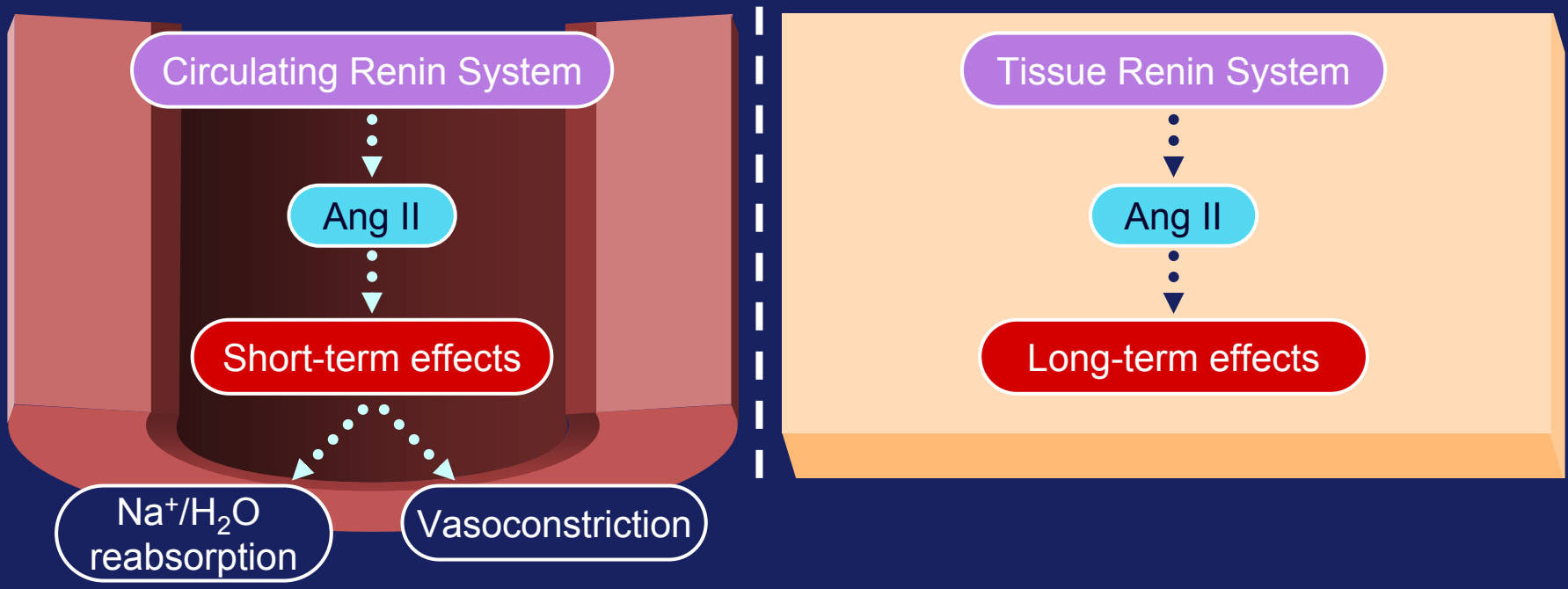


Heart
- Myocardial hypertrophy
- Systolic dysfunction

1. Müller DN & Luft FC. Clin J Am Soc Nephrol 2006;1:221–8
2. Weir MR & Dzau VJ. Am J Hypertens 1999;12:S205-S213

Dolaşan Renin sisteminden hariç, bölgesel bir yığın Renin sistemi dokuda var

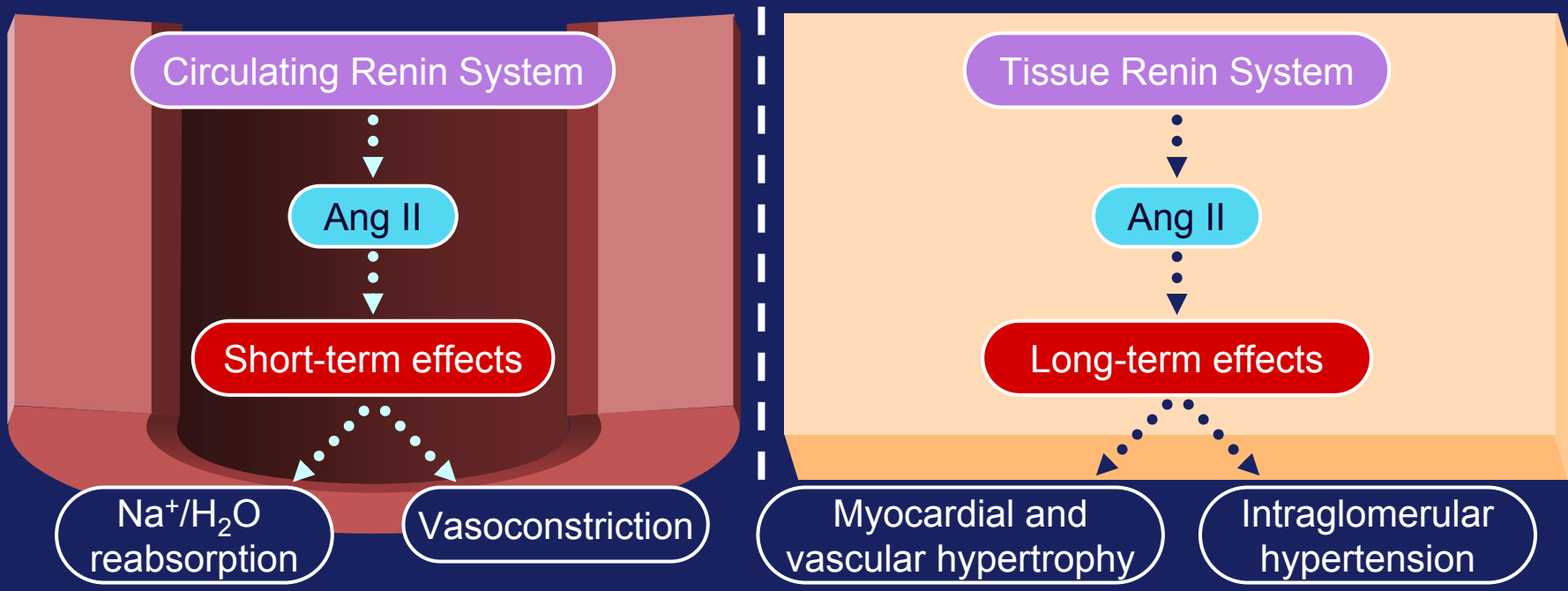
- Tissue Renin System activity can vary independently of circulating Renin System activity
  - tissue Renin Systems can regulate local concentrations of Ang II independently of the circulating Renin System



Re RN. Med Clin North Am 2004;88:19–38; Dzau VJ. Arch Int Med 1993;153:937–942

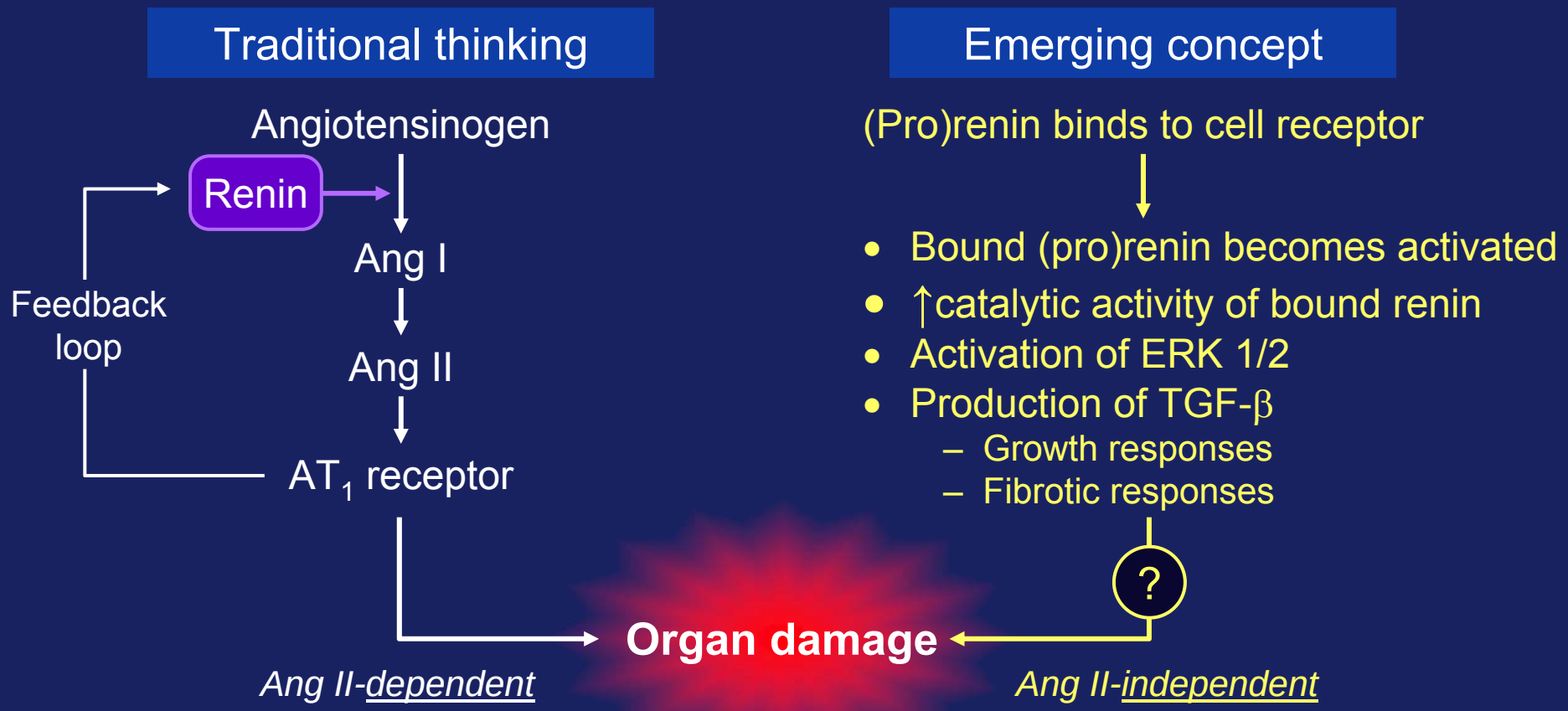
Renin sisteminin dokudaki görevleri detaylı bilinmiyor

- Over-activity of tissue Renin Systems has been implicated in the deleterious effects of hypertension
- How about the eye, the testis, or the mast cell?



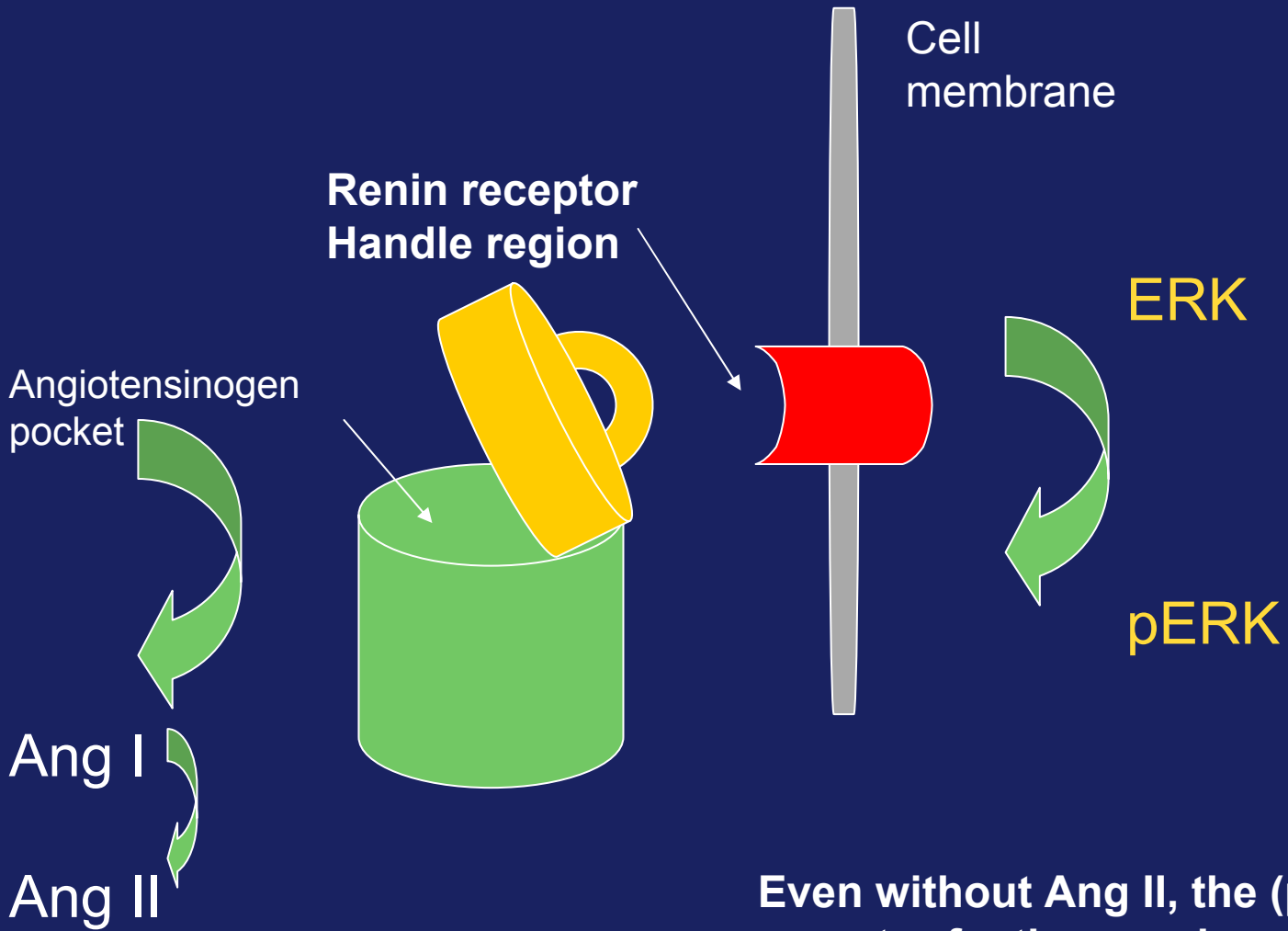
Re RN. Med Clin North Am 2004;88:19–38; Dzau VJ. Arch Int Med 1993;153:937–942

(Pro)renin reseptör-baglantisi organ hasarına sebep olabilir, Ang II den bağımsız



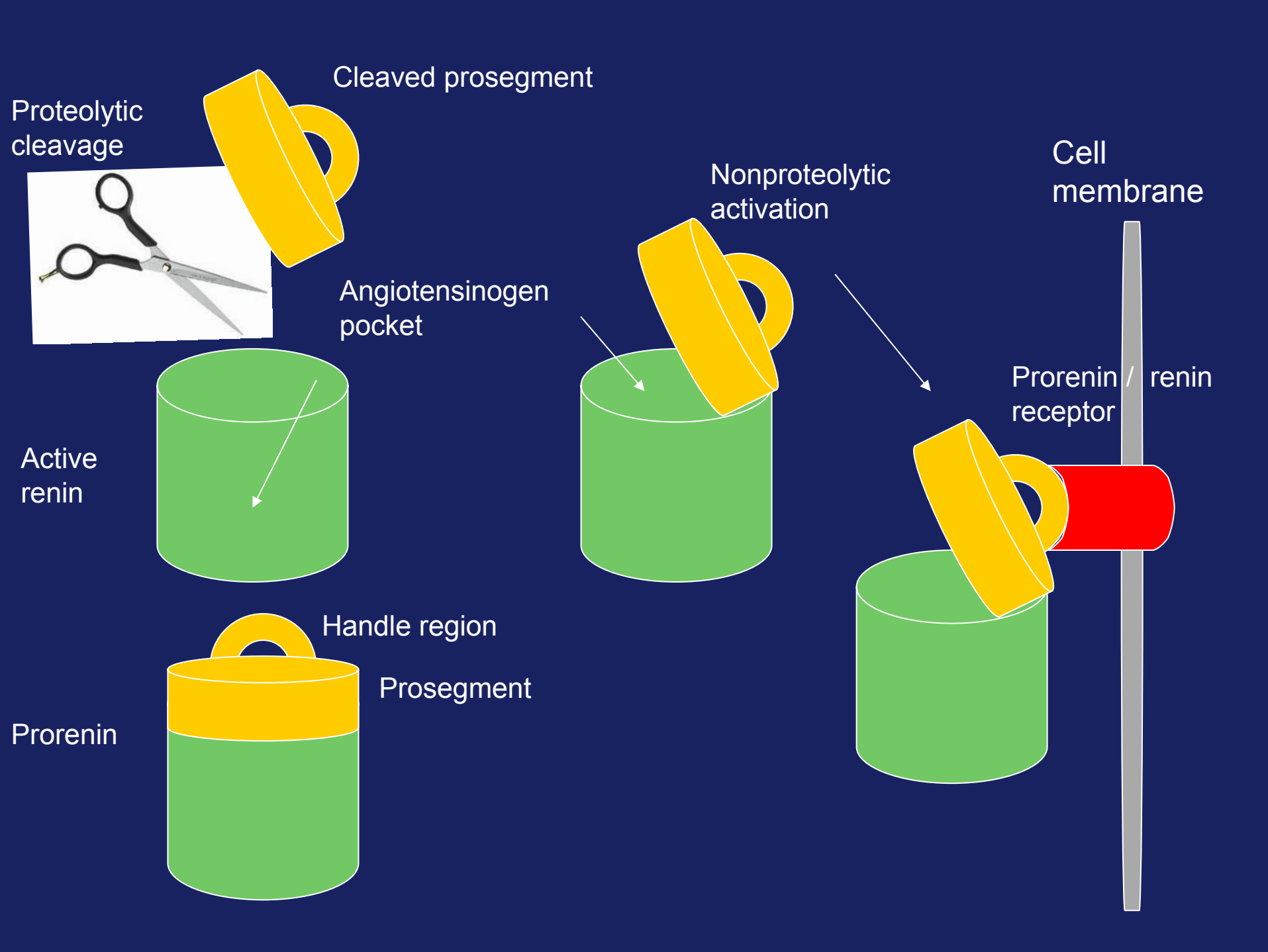
Nguyen G, *et al.* J Clin Invest 2002;109:1417–1427
Saris J, *et al.* Hypertension 2006;48:564-571
Huang Y, *et al.* Kidney Int 2006;69:105–113

(Pro)renin receptor: a 350 amino-acid protein, single transmembrane domain, activates prorenin and activates ERK1/ERK2 even with losartan present



Nyugen et al. J Clin Invest 2002

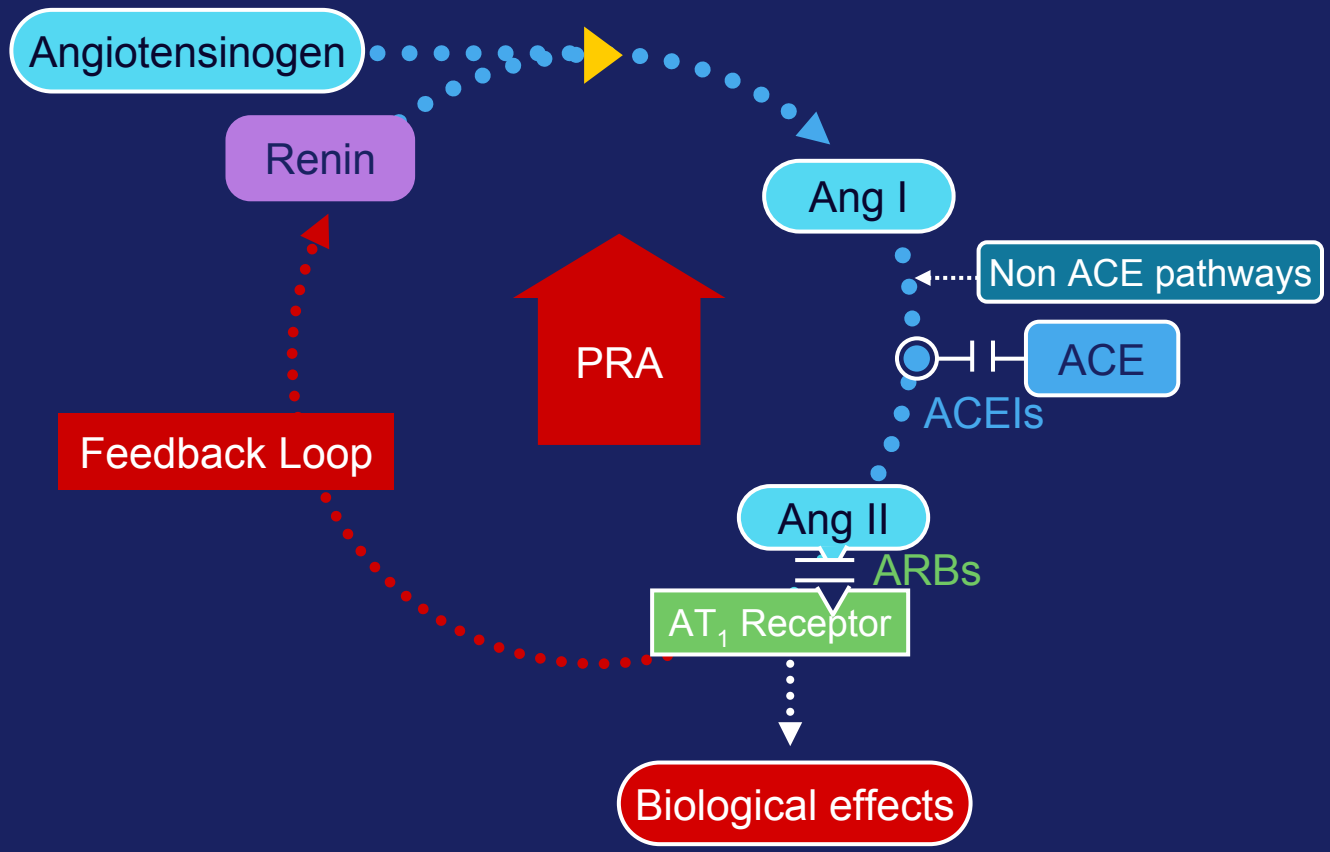
Even without Ang II, the (pro)renin receptor fuctions and activates ERK


Cleaved prosegment
Proteolytic cleavage
Angiotensinogen pocket
Nonproteolytic activation
Cell membrane
Prorenin / renin receptor
Active renin
Handle region
Prosegment
Prorenin

Direkt Renin engelleme girişimi Renin sistemini denetim altına ala bilir

Aliskiren is the first effective DRI;
we had to wait 30 years for this!

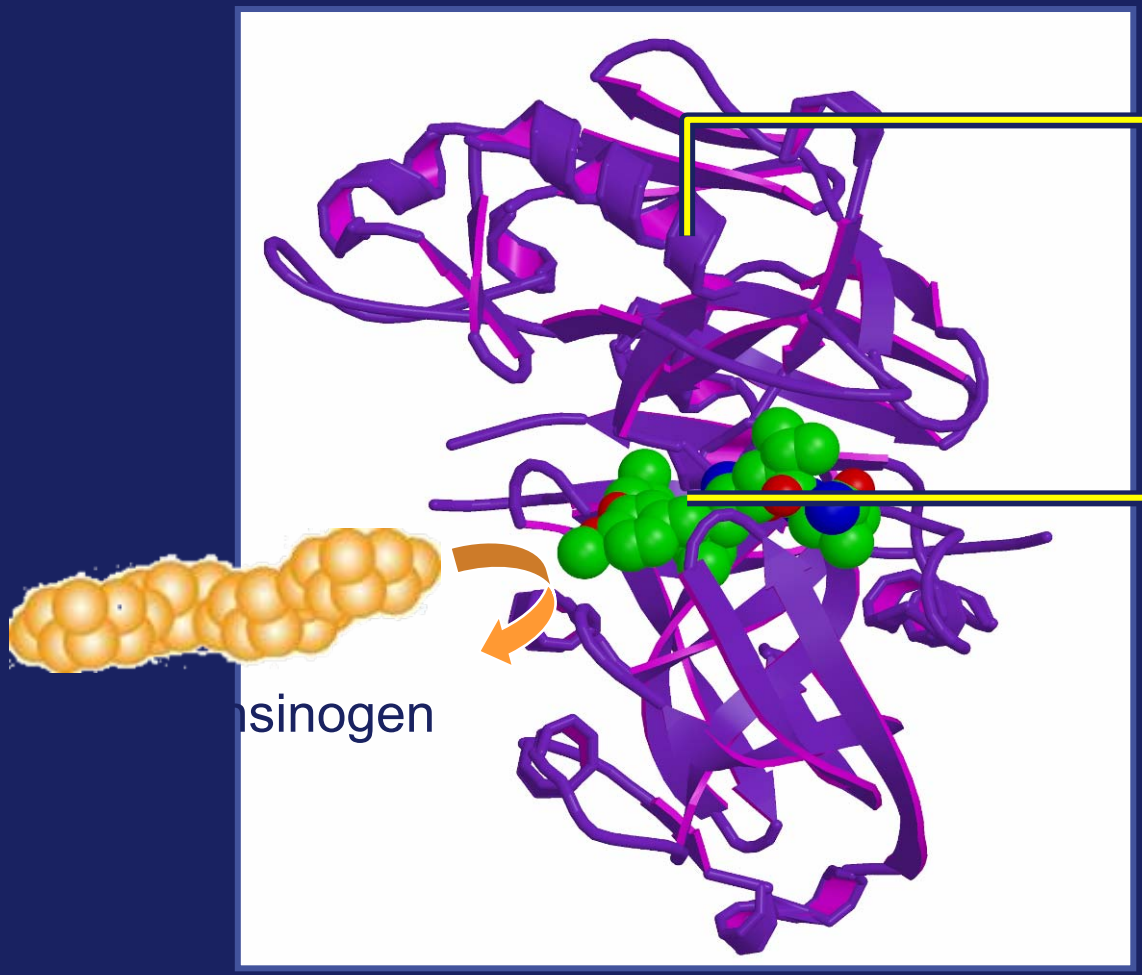
ACEIs ve ARBs stimülasiyonu Renin sistem faaliyetini ters tepki üzerinden tetikliyor



PRA: plasma renin activity

Adapted from: Weber MA & Giles TD. Rev Cardiovasc Med 2006;7:45–54

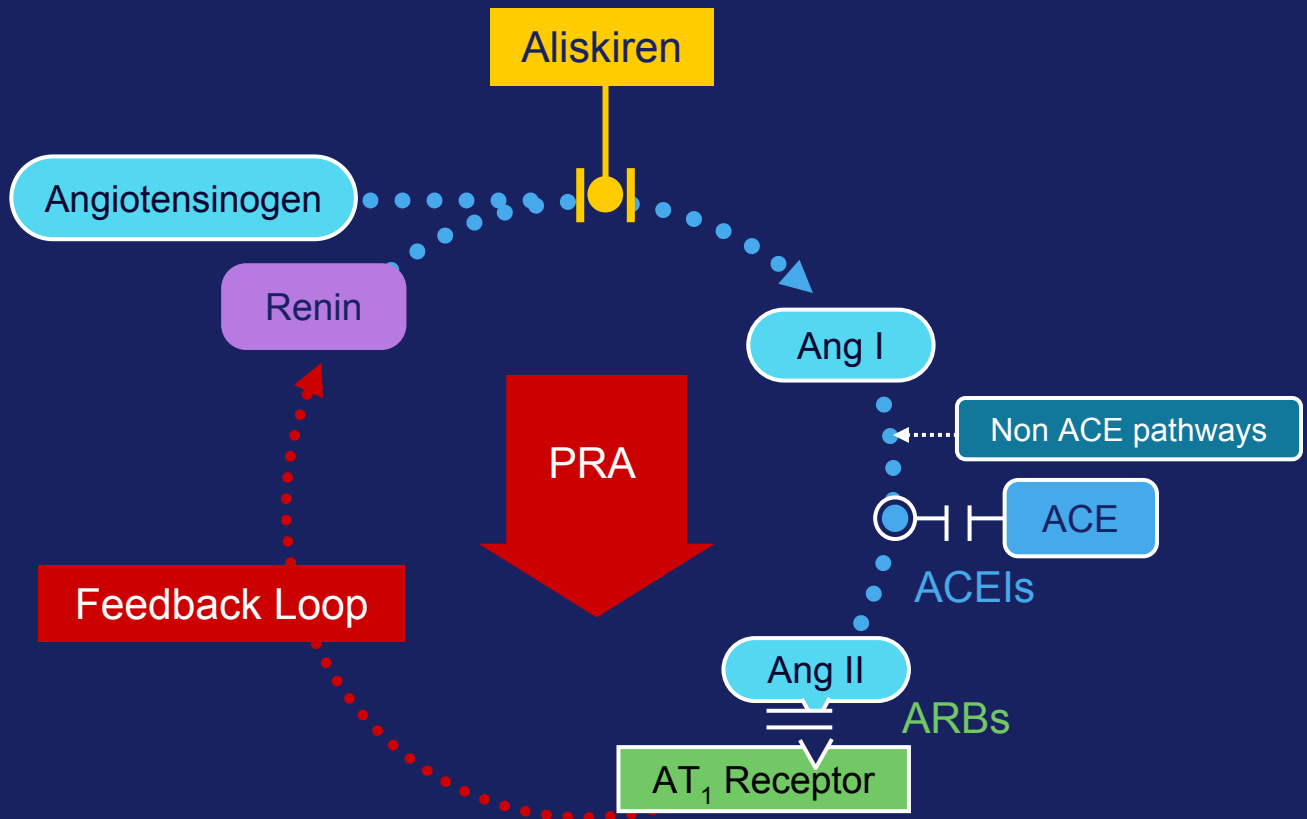
Direkt renin önleyici aliskiren renin sistemini aktiv yerleşim merkesinde bloke edip engelliyor



Aliskiren binds to a pocket in the renin molecule, blocking cleavage of angiotensinogen to Ang I

Adapted from Wood JM, *et al.* Biochem Biophys Res Commun 2003;308:698–705

D R I ile aliskiren etkisizleştiriyor



Adapted from: Weber MA, Giles TD. Rev Cardiovasc Med 2006;7:45–54

Aliskiren özellikle Ang I, Ang II ve PRAyi düşürüyor

	Ang I	Ang II	Renin	PRA
ACEIs	↑	↓	↑	↑
ARBs	↑	↑	↑	↑
Aliskiren	↓	↓	↑	↓

Reduced Ang I production limits the generation of Ang II via non-ACE pathways

Azizi M. J Hypertens 2006;24:243–256

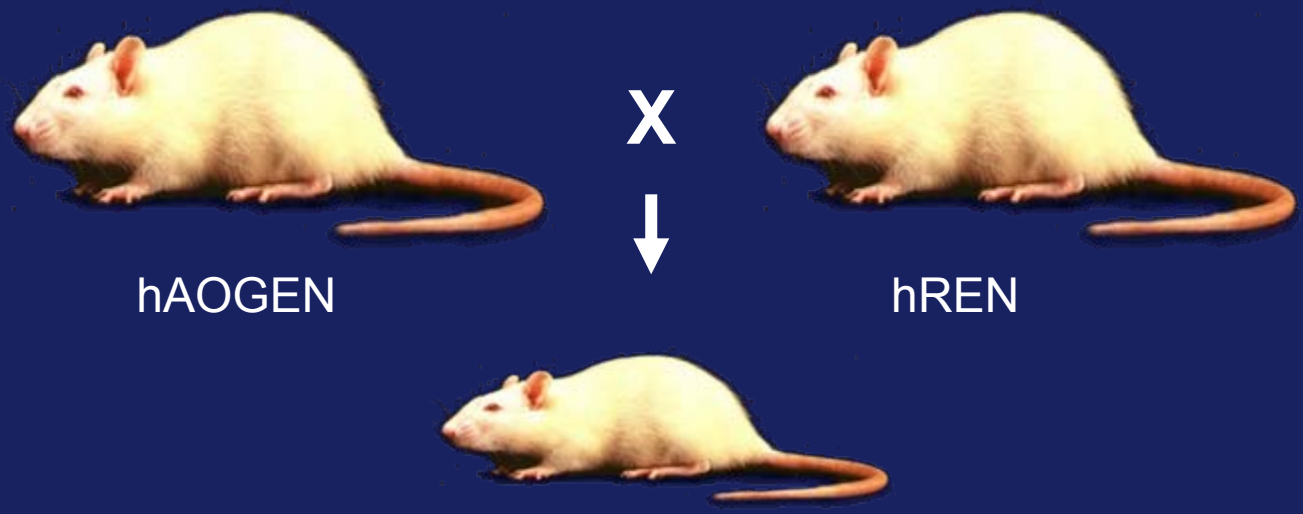
Gelişmiş Renin sistem kontrol – etkili ve gelişmiş organ koruma yöntemimi ?

Preclinical cardio-renal protection with aliskiren

Your average unfriendly marmoset
IC50 (nM):
Man 0.6
Monkey 2.0
Mouse 11
Rat 80
Cat 8500

Insan DRIs için Hayvan modeli
Double transgenic rats (dTGR)

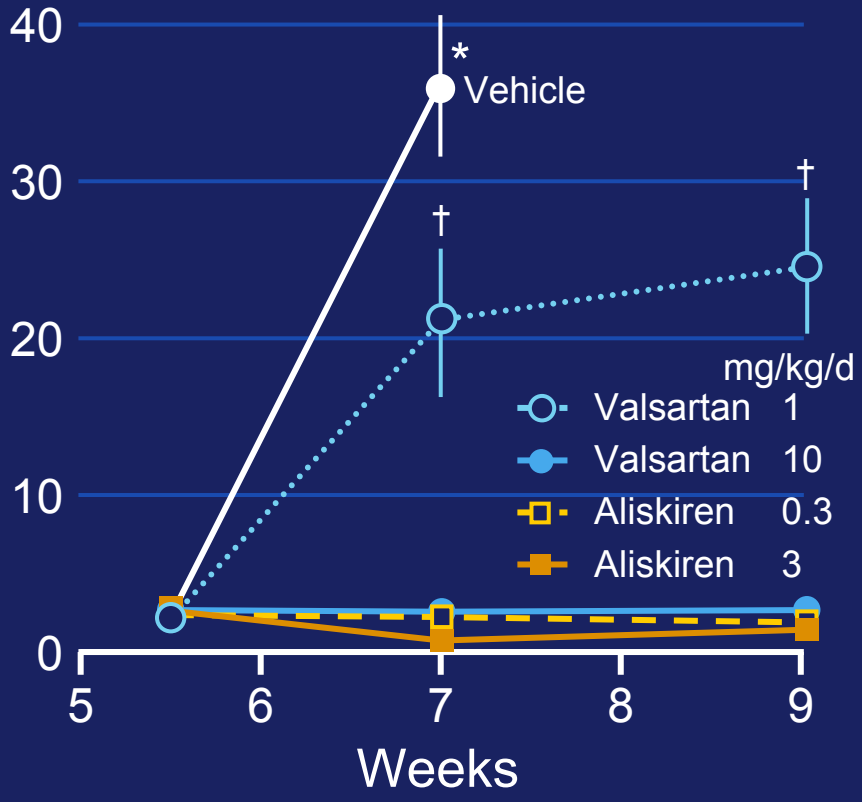
- dTGR model
  - Expresses genes for human renin and human angiotensinogen
  - Animals develop severe hypertension and end-organ damage
  - They die at 7 weeks of age!



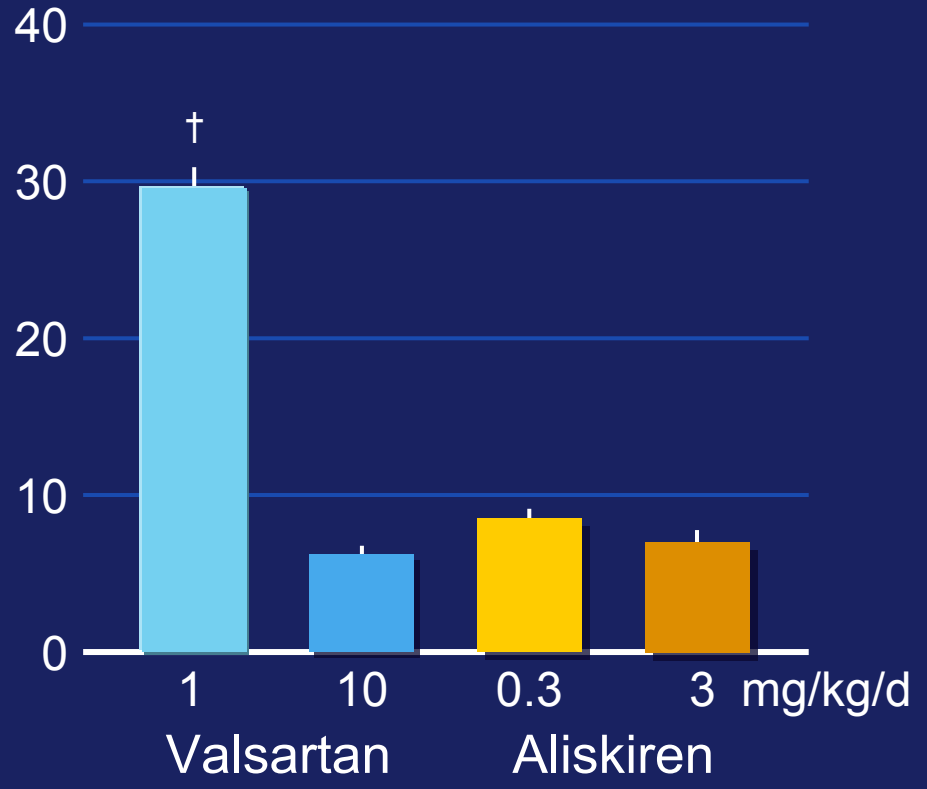
Bohlender J *et al.*, Hypertension. 1997;29:428–434

Aliskiren albuminuria önlüyor ve böbrek iltihapını engelliyor

Urinary 24-h albumin excretion in dTGR (mg/d)



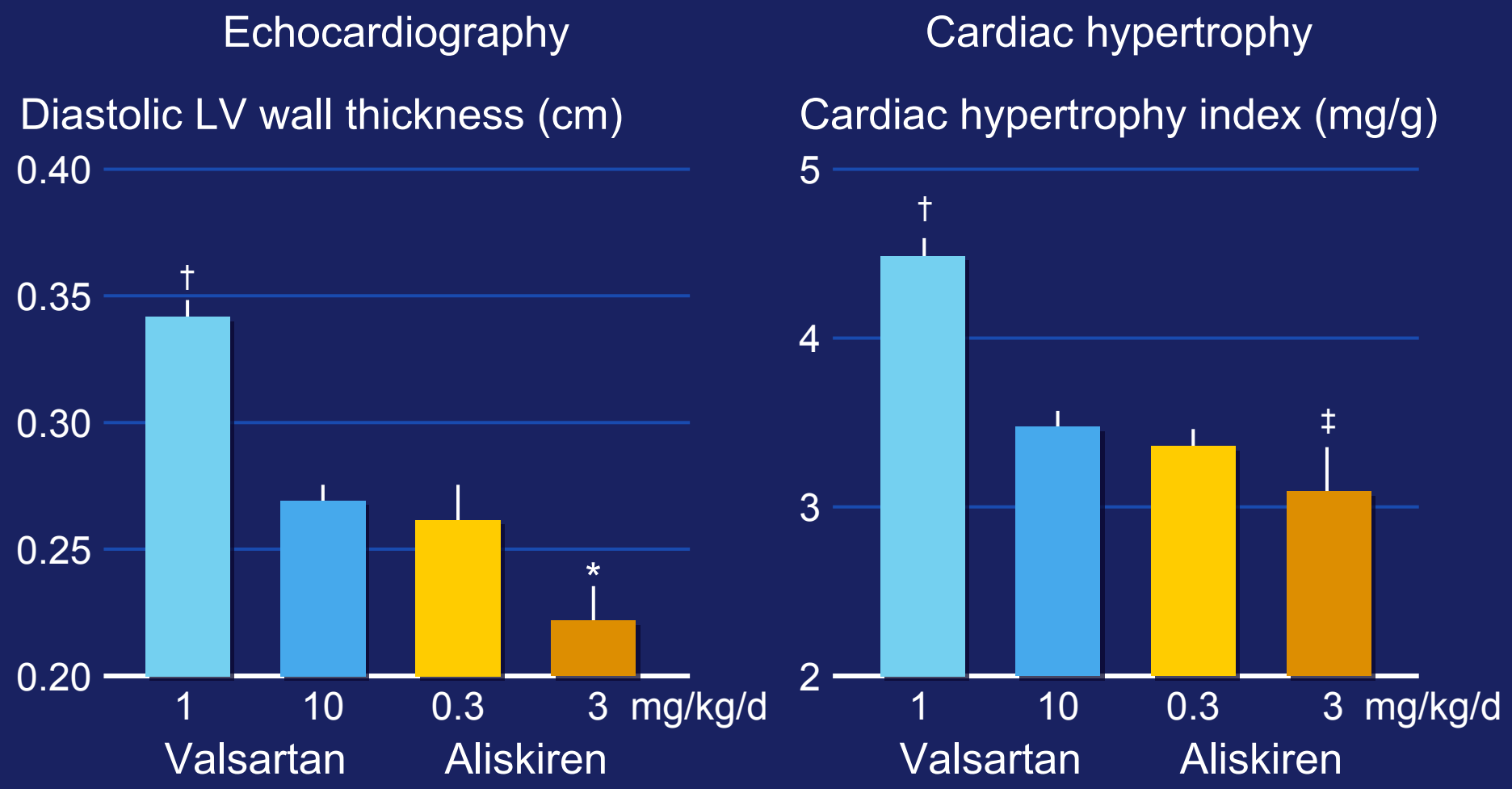
Renal macrophage infiltration in dTGR



*P<0.05 vs all other groups;
†P<0.05 vs other groups.
dTGR, double-transgenic rats. Untreated rats died by Week 8.
Error bars indicate standard error of the mean.

Pilz B *et al.*, Hypertension. 2005;46:569–576

Aliskiren LVHyı dTGRde onlüyor

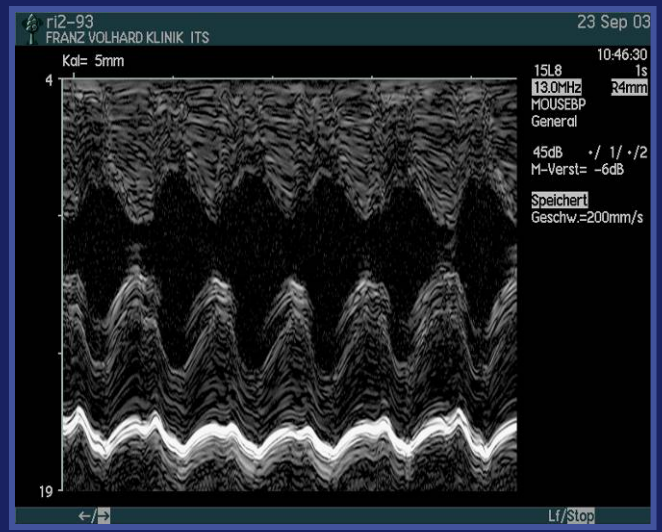


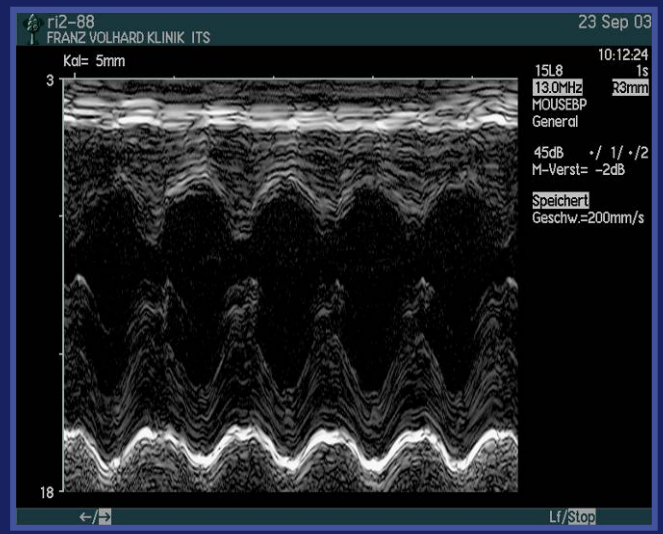
*p<0.05 vs other groups; †p<0.05 vs other groups; ‡p<0.05 vs valsartan 10 mg.
dTGR, double-transgenic rats. Untreated rats died by Week 8
Error bars indicate standard error of the mean.

Pilz B *et al.*, Hypertension. 2005;46:569–576

Ekokardiografi aliskirenin kalp hipertrofisini azaltığını gösteriyor

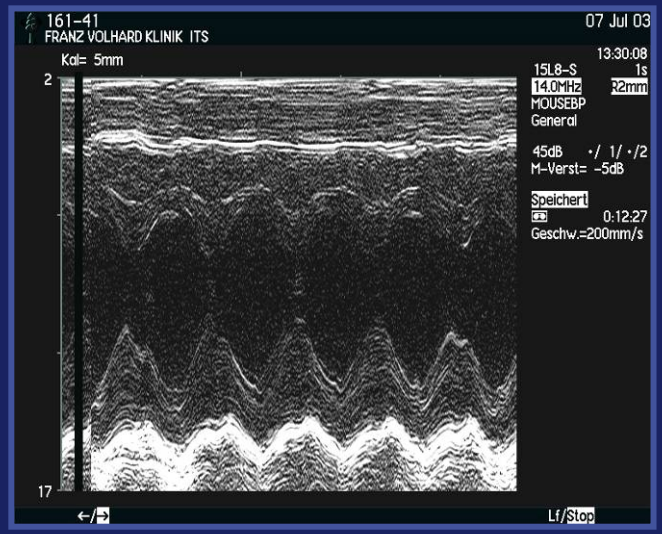
Valsartan
1 mg/kg/d

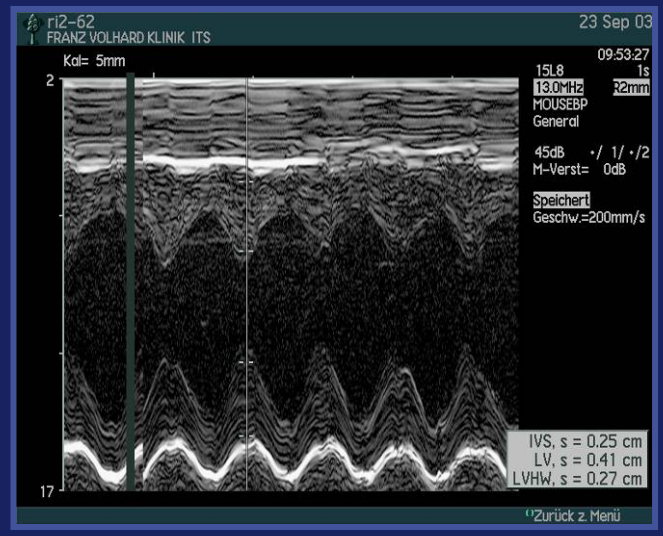




Aliskiren
0.3 mg/kg/d

Valsartan
10 mg/kg/d

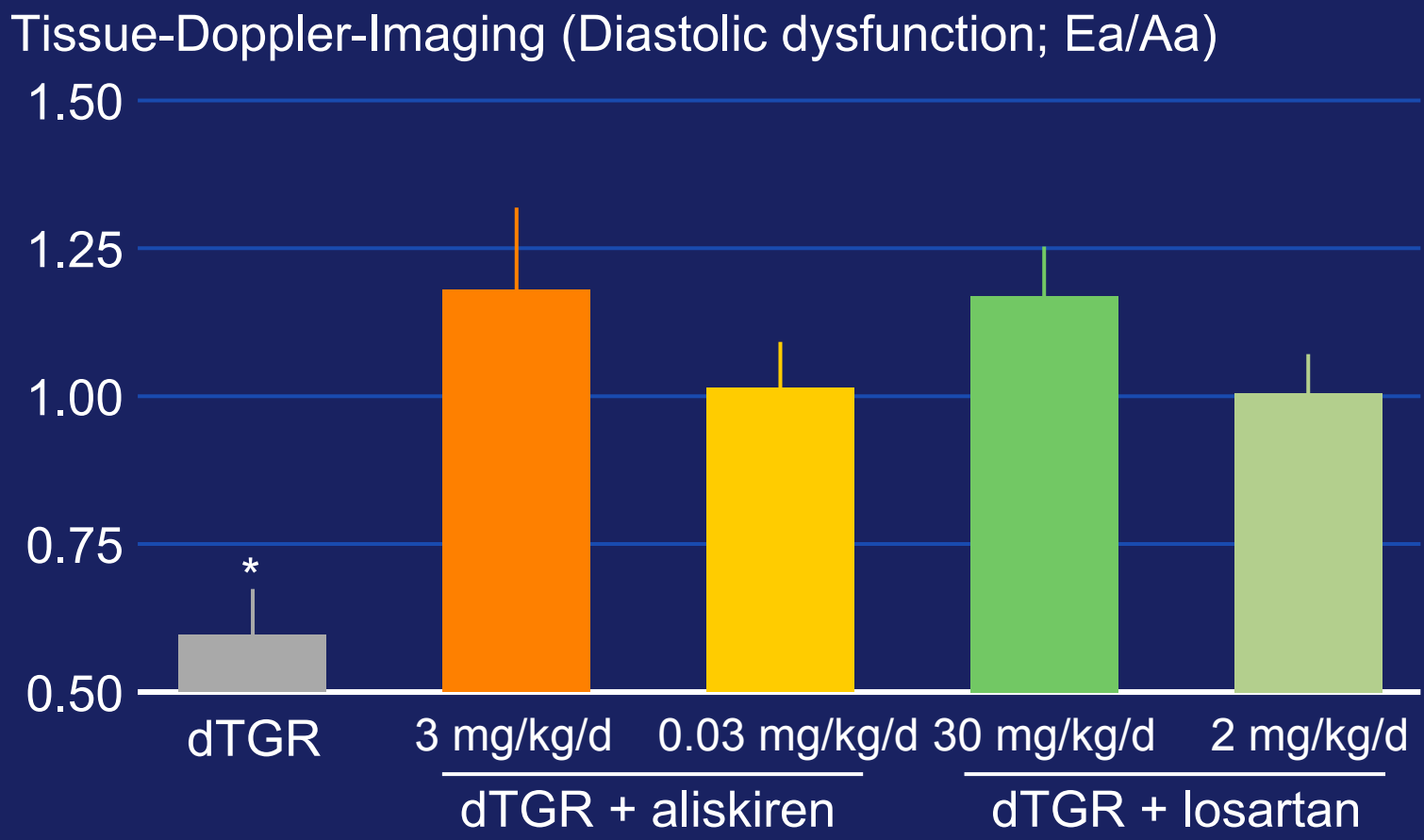




Aliskiren
3 mg/kg/d

Pilz B *et al.*, Hypertension. 2005;46:569–576

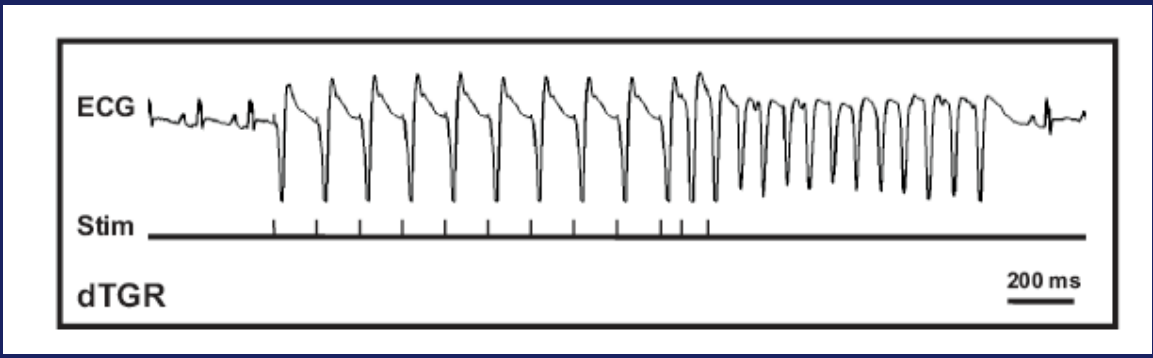
Aliskiren diastolik fonksiyon bozukluğunu dTGRde düzeltiyor

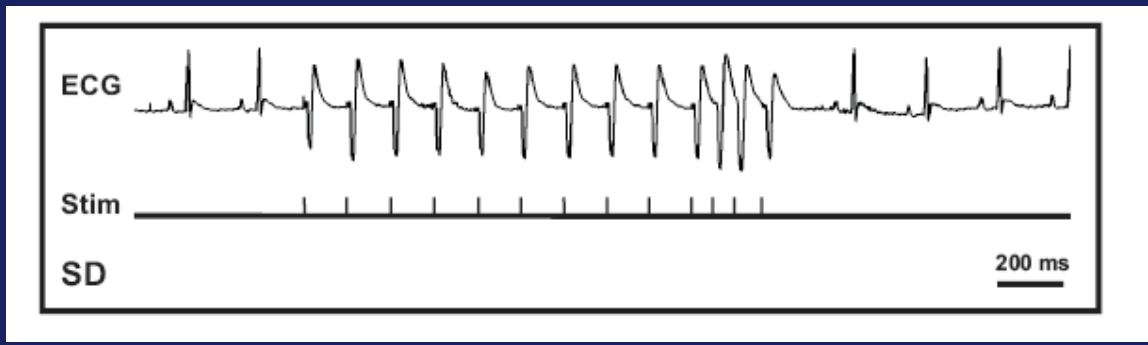


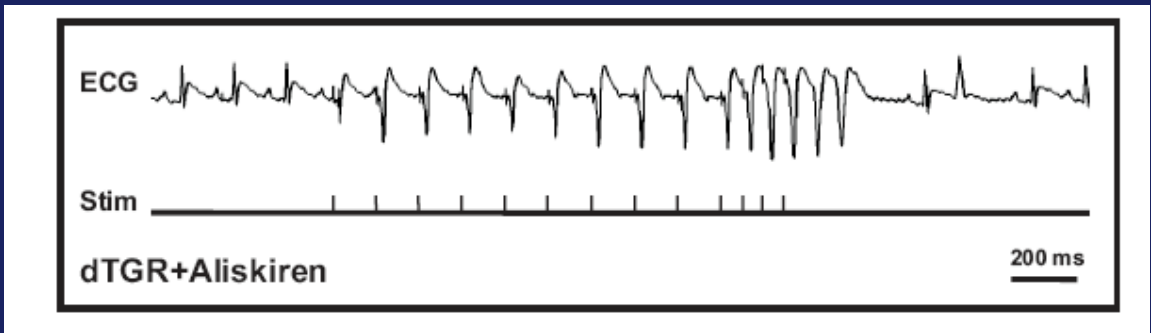
Tissue-Doppler imaging
*p<0.05 vs other groups

Dechend R, *et al.* JRAAS 2007;8:81–84

Hayvanlar VTden ölüyor

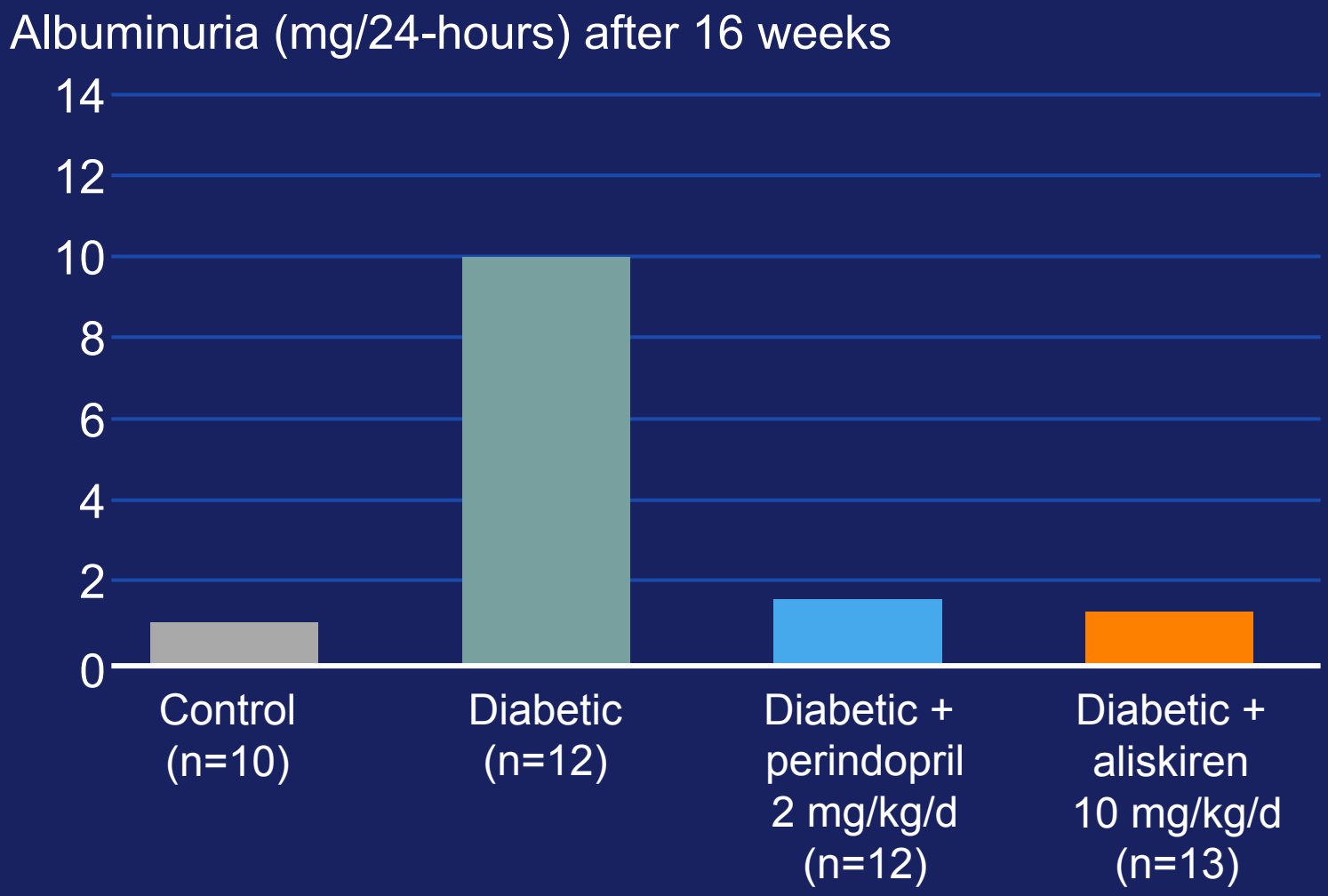






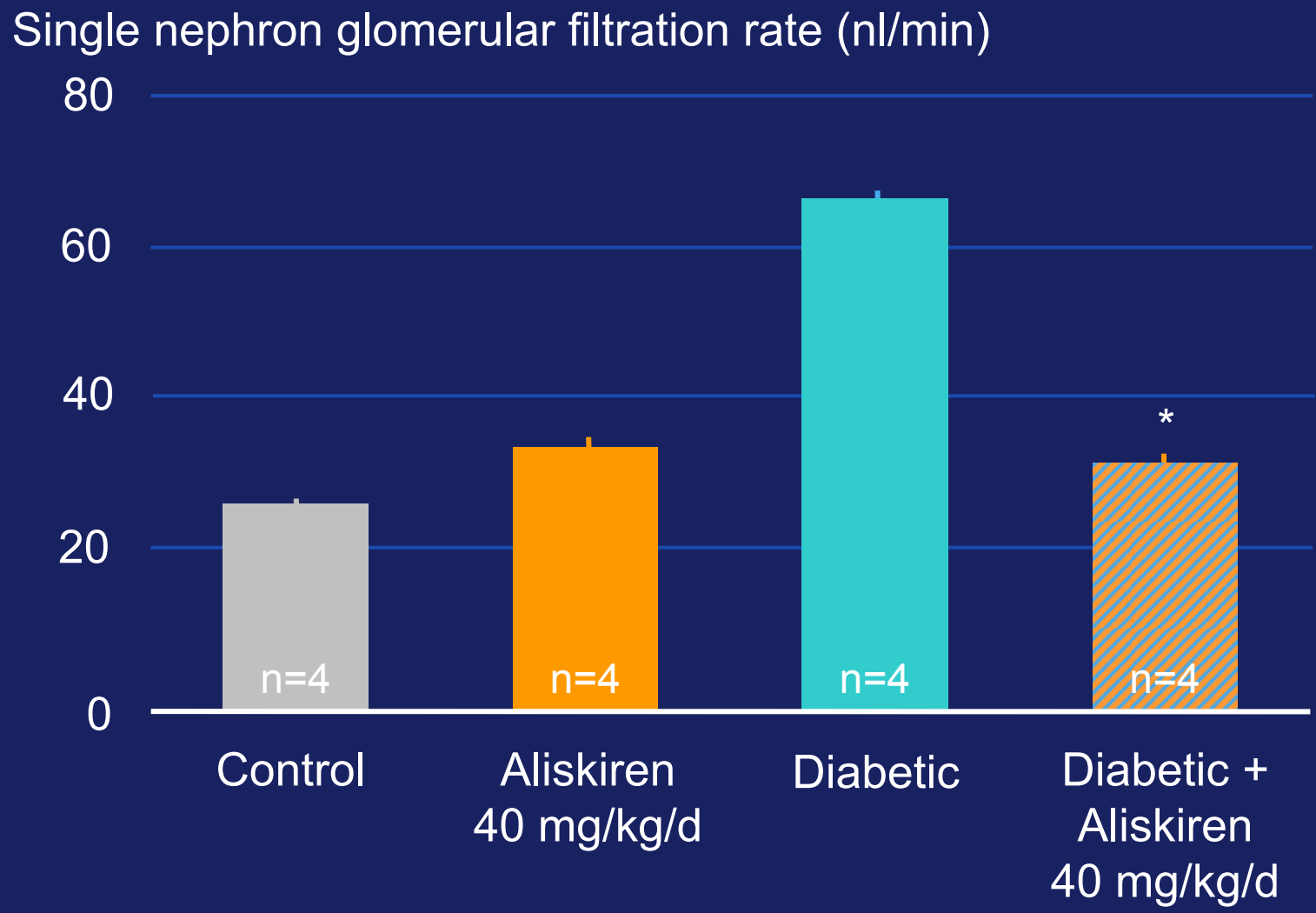
Fischer et al.
Hypertension (submitted)

Aliskiren albuminüriyi devamlılık belirten diyabetik nefropatide modelinde azaltıyor (streptozotocin-uyarılmış (mRen-2)27 fare)



Kelly DJ & Zhang J. Presented at ASN 2006; SA-FC006

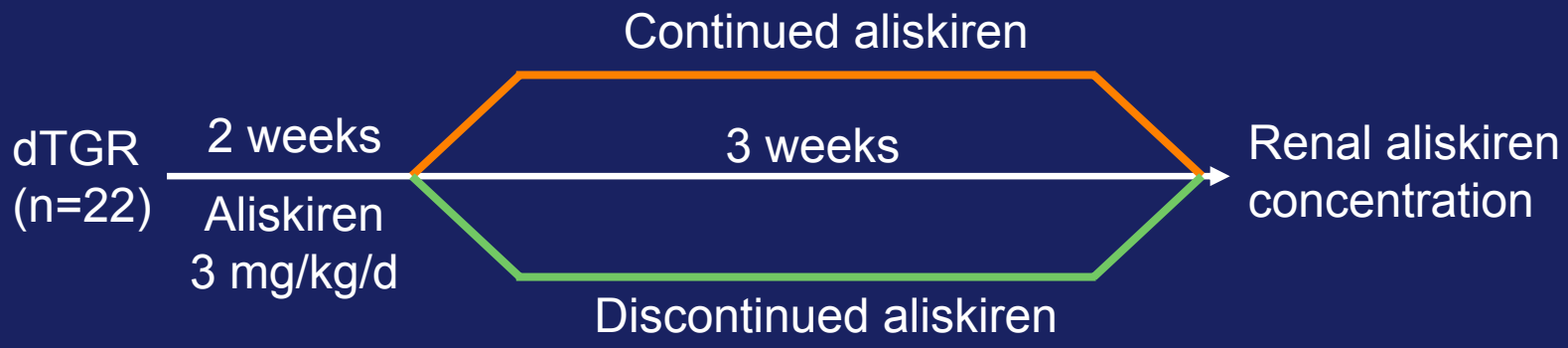
Aliskiren diyabetik hipertansiyon farede glomerular süzmeyi düzeltiyor

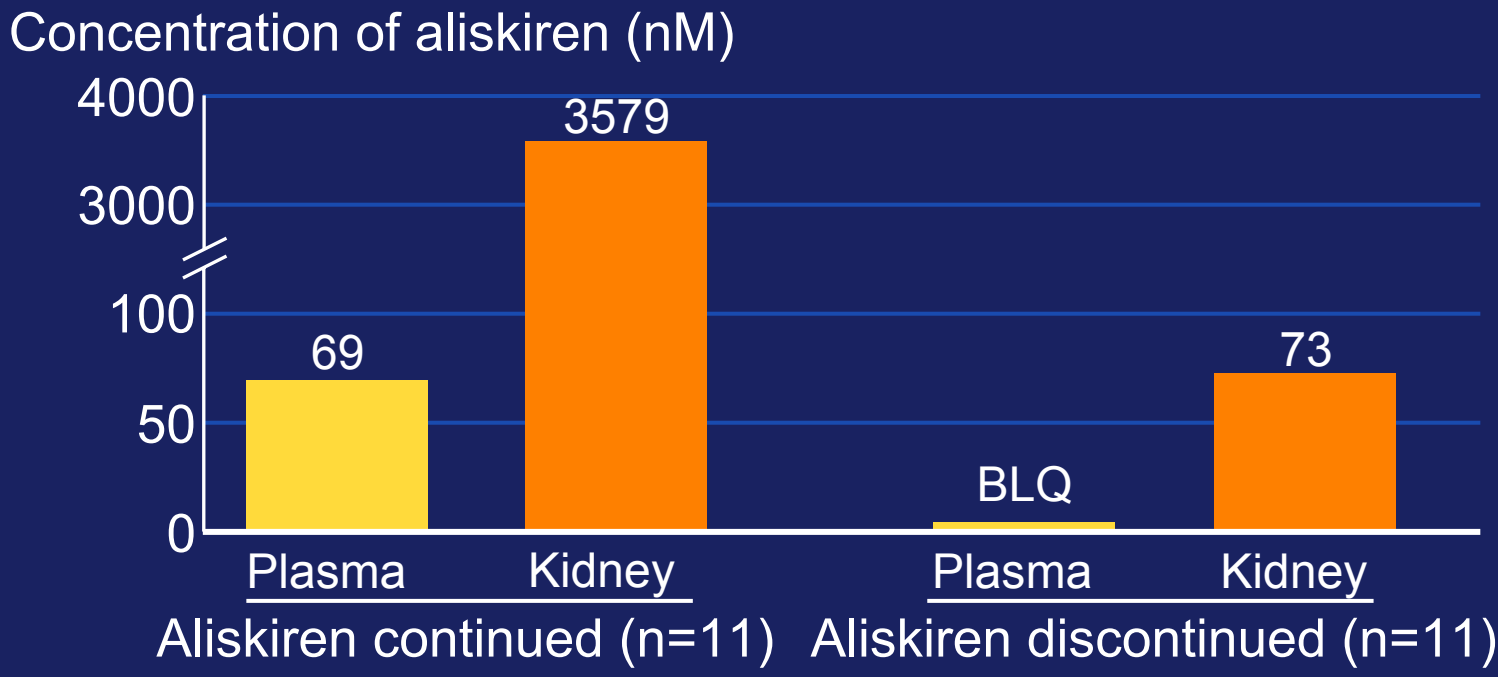


*p<0.05 vs. diabetic group

Kang JJ, *et al.* Presented at ASN 2006;F-PO290

Aliskiren tedavi bırakıldıkdan veya ara verildiginden sonra böbrekte kalır

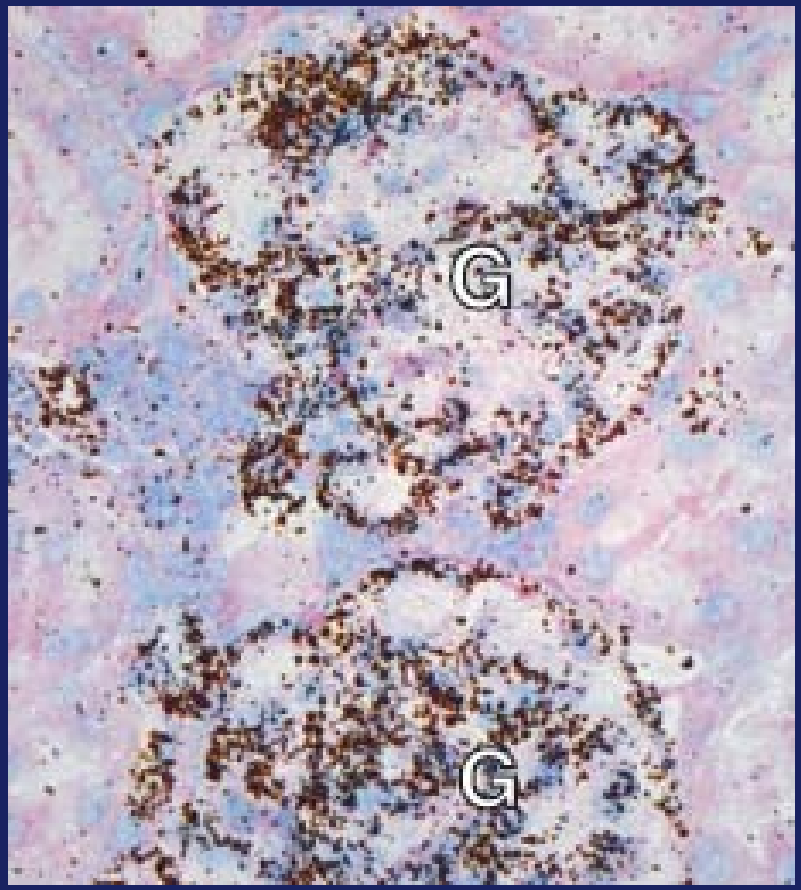


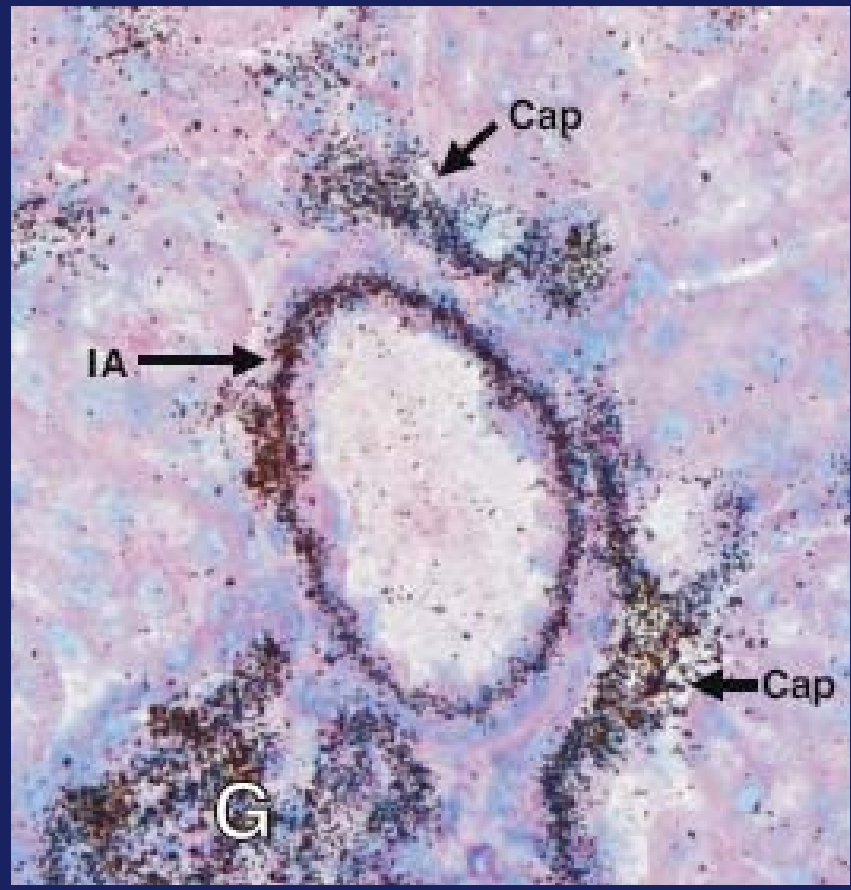


BLQ: below level of quantification

Feldman *et al.* J Clin Hypertens 2006;8:A80-81 P178

Böbrekteki Aliskiren bölümleri (double-transgenic fare)



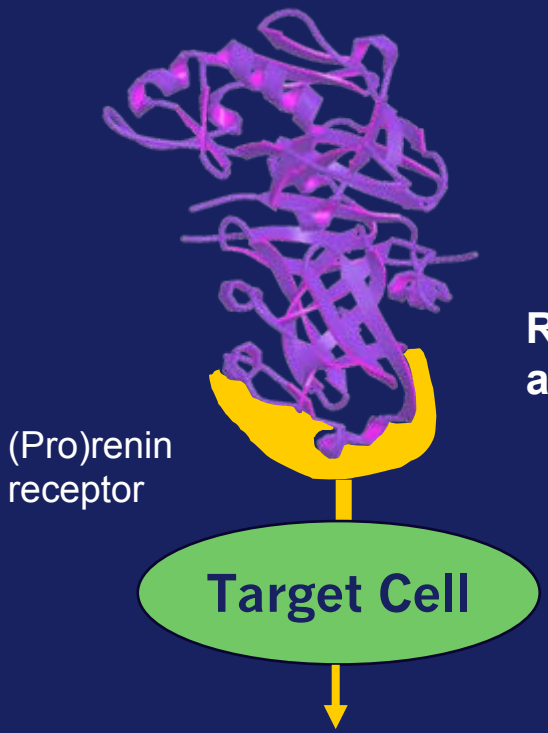


G = glomerulus
IA = interlobular artery
Cap = Capillaries

Feldman *et al.* J Clin Hypertens 2006;8:A80-81 P178

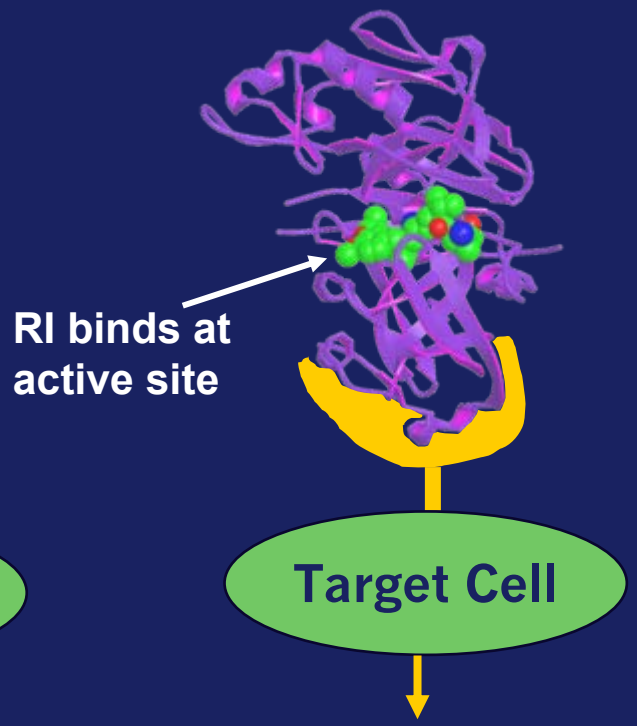
Direkt renin inhibitor bloku renini (pro)renin receptorundan bloke edebilir mi?

Renin binds to (pro)renin receptor



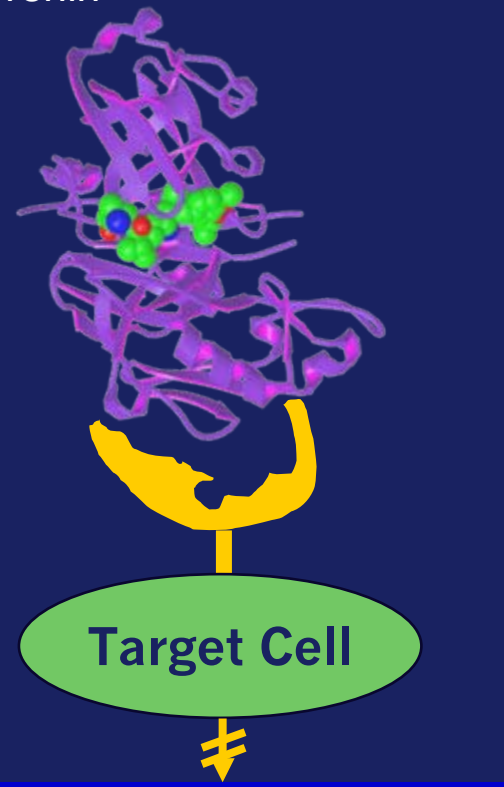
Binding domain ≠ active site

- Normal receptor binding in presence of remikiren

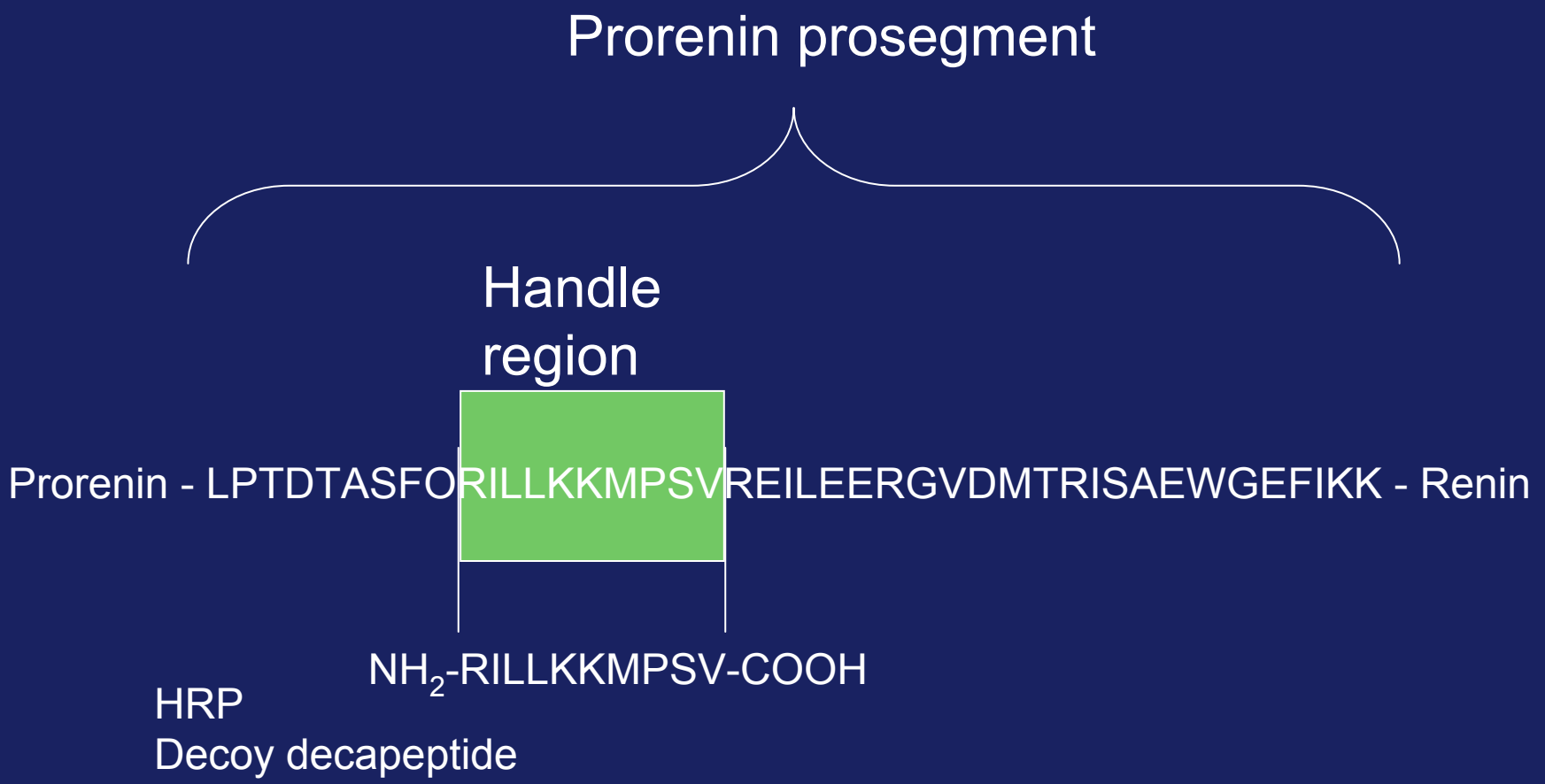


Does aliskiren block (P)RR:

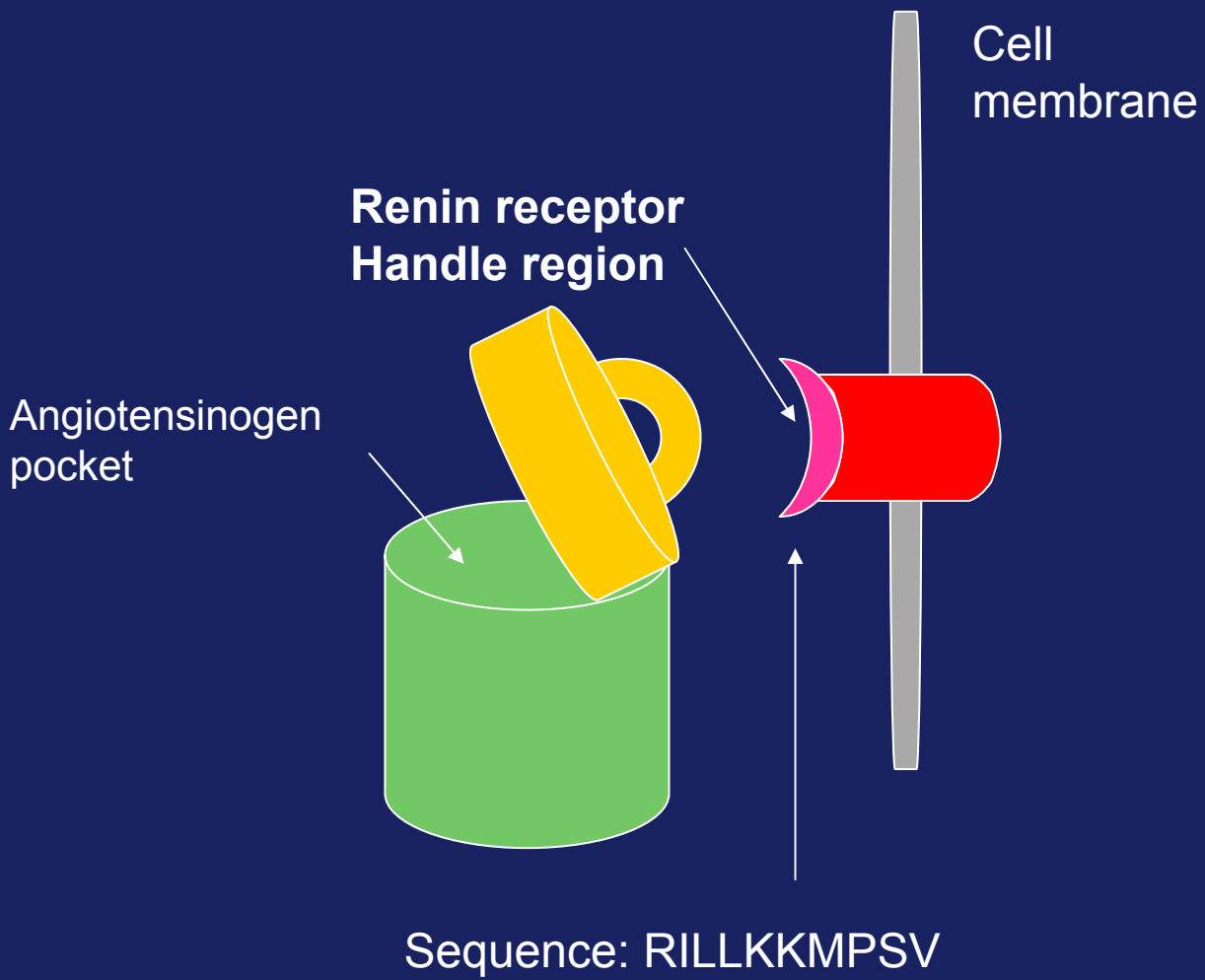
- RI must change conformation of renin



Adapted from Rahuel J *et al.*, J Struct Biol. 1991;107:227–236


Prorenin prosegment
Handle region
Prorenin - LPTDTASFORILLKKMPSVREILEERGVDMTRISAEWGEFIKK - Renin
NH2-RILLKKMPSV-COOH
HRP
Decoy decapeptide

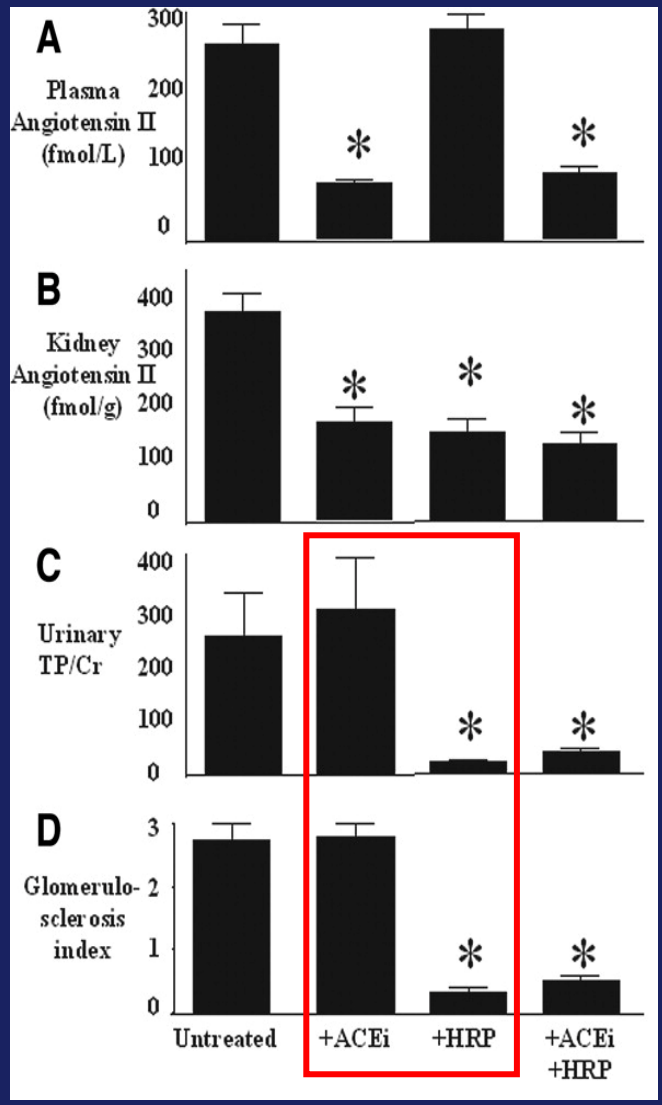
Handle region peptide (HRP)
blocks the (pro)renin receptor



Diyabetik nefropatide (P)RRin bloker rolü

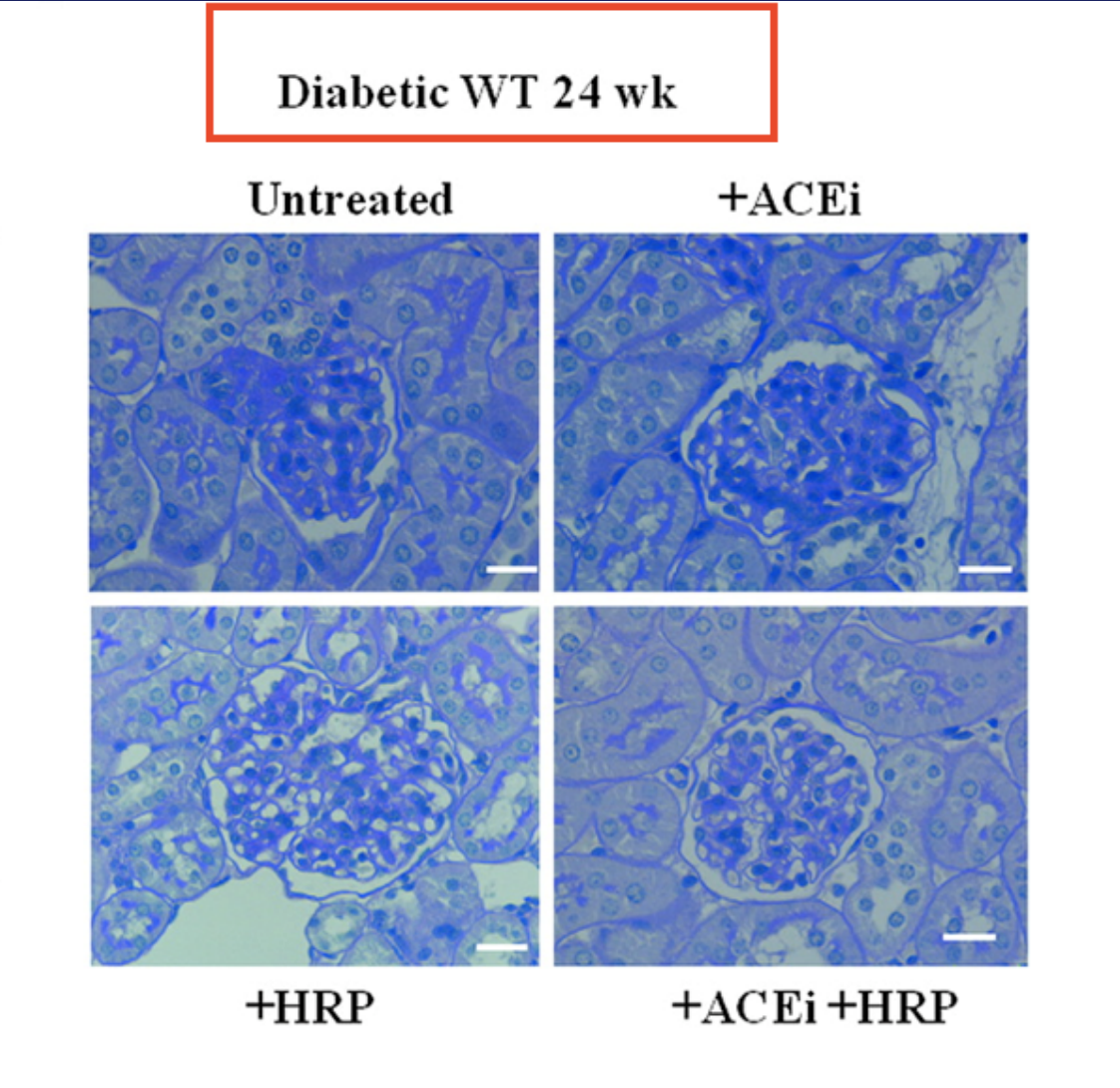
HRP works while ACEi does not in AT1a KO (abnormal) mice

AT1 receptor KO mice



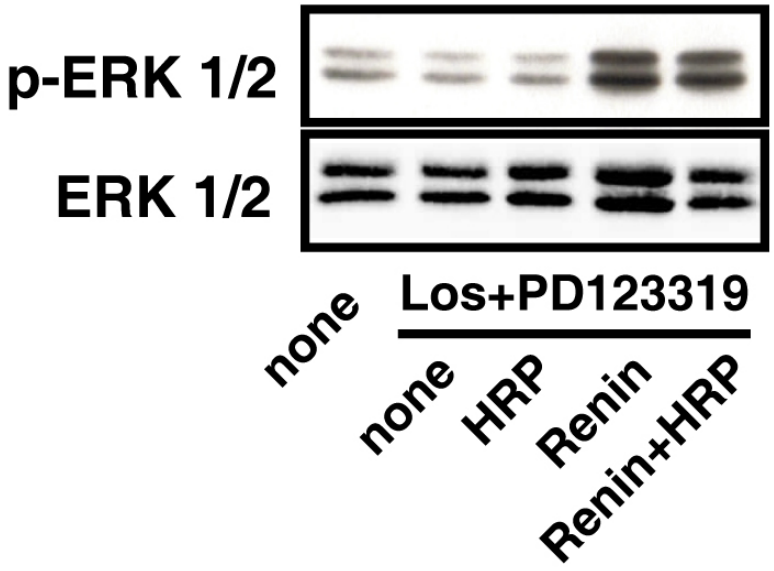
Ichihara et al. J Am Soc Nephrol 2006

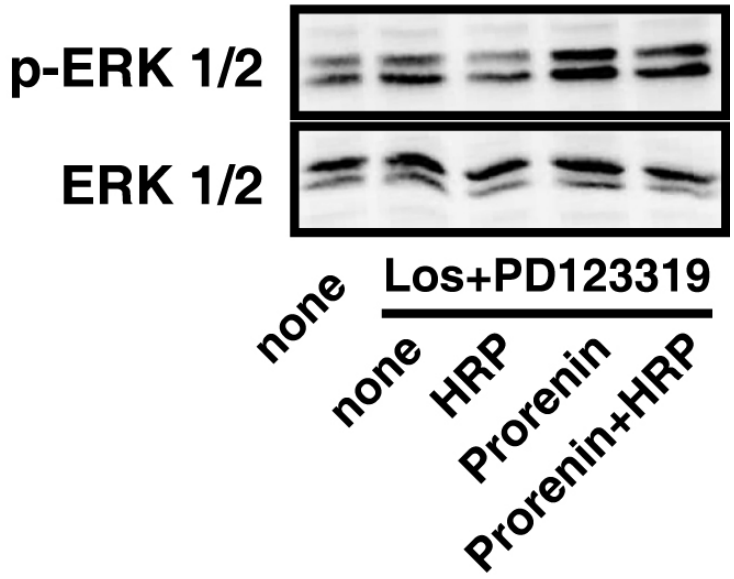
(P)RRin ablukası ve diyabetik nefropatid: HRP tedavi



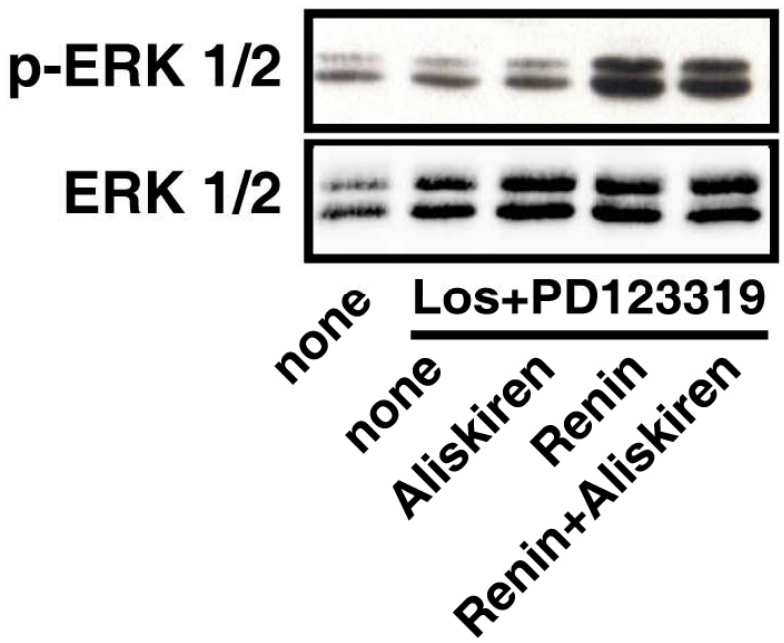
Ichihara et al. J Am Soc Nephrol 2006

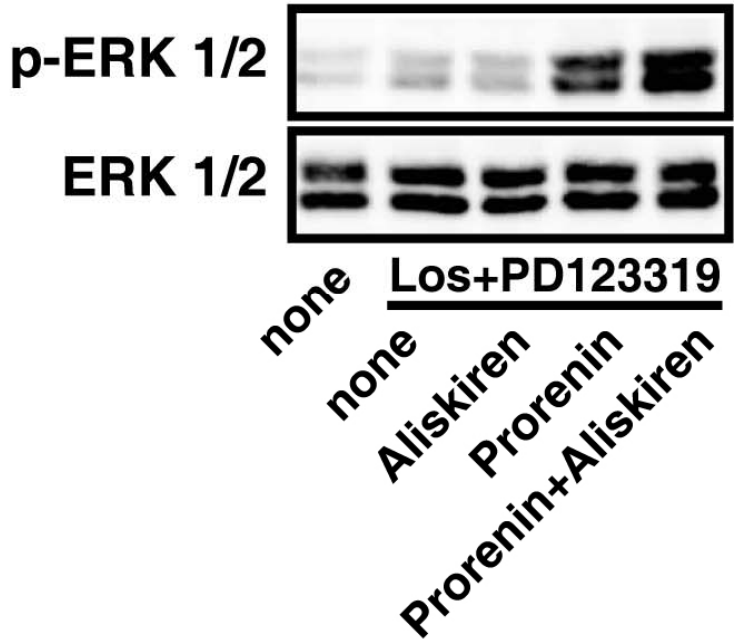
HRP, VSMC signal transduktion'de (pro)renin-tetiklemede bloke etmiyor





Aliskiren, VSMC signal transduktion'de (pro)renin-tetiklemede bloke etmiyor



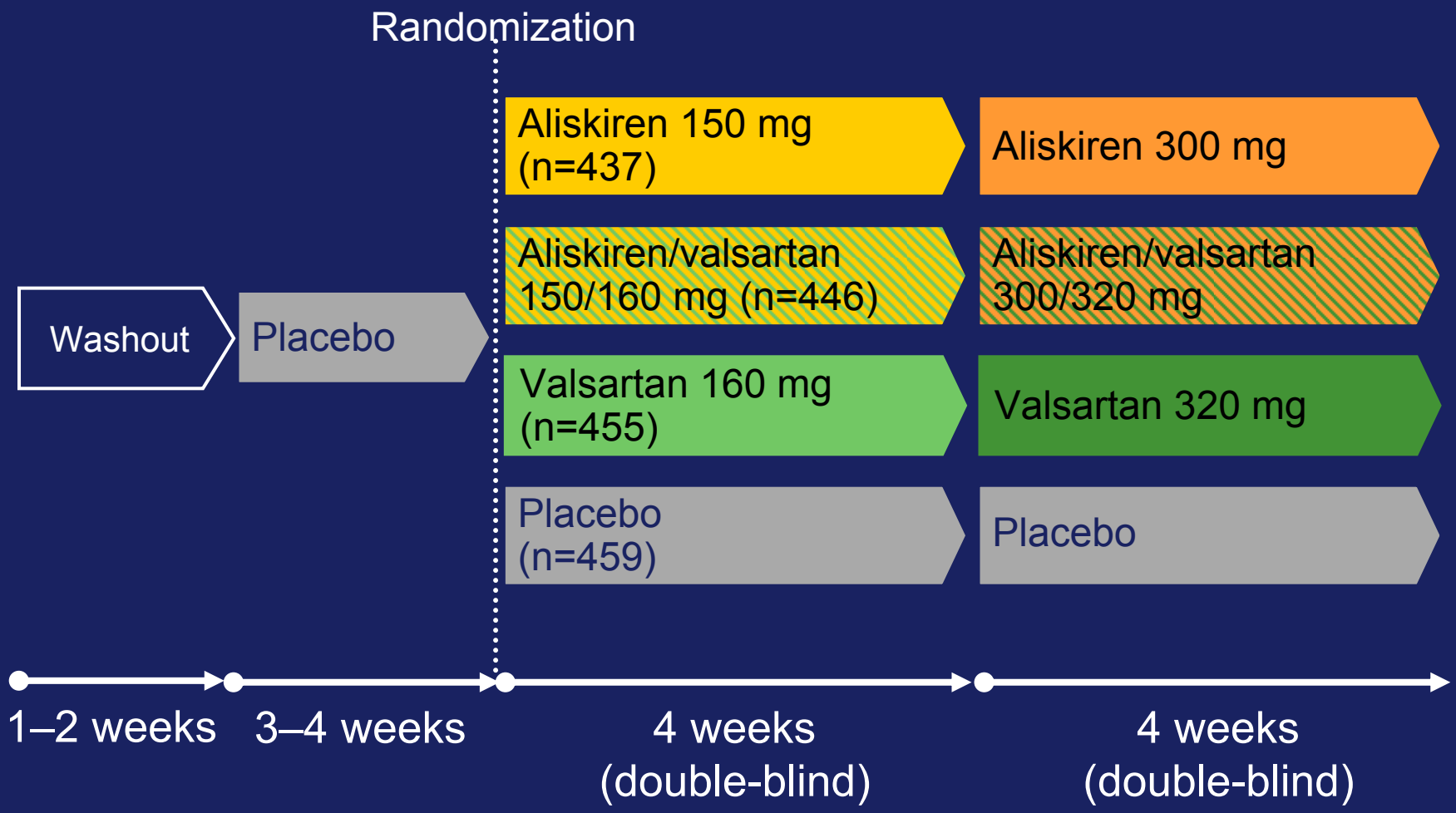


Prorenin signaling is NOT blocked by aliskiren

Aliskiren pharmakokinetik ve metabolik profil

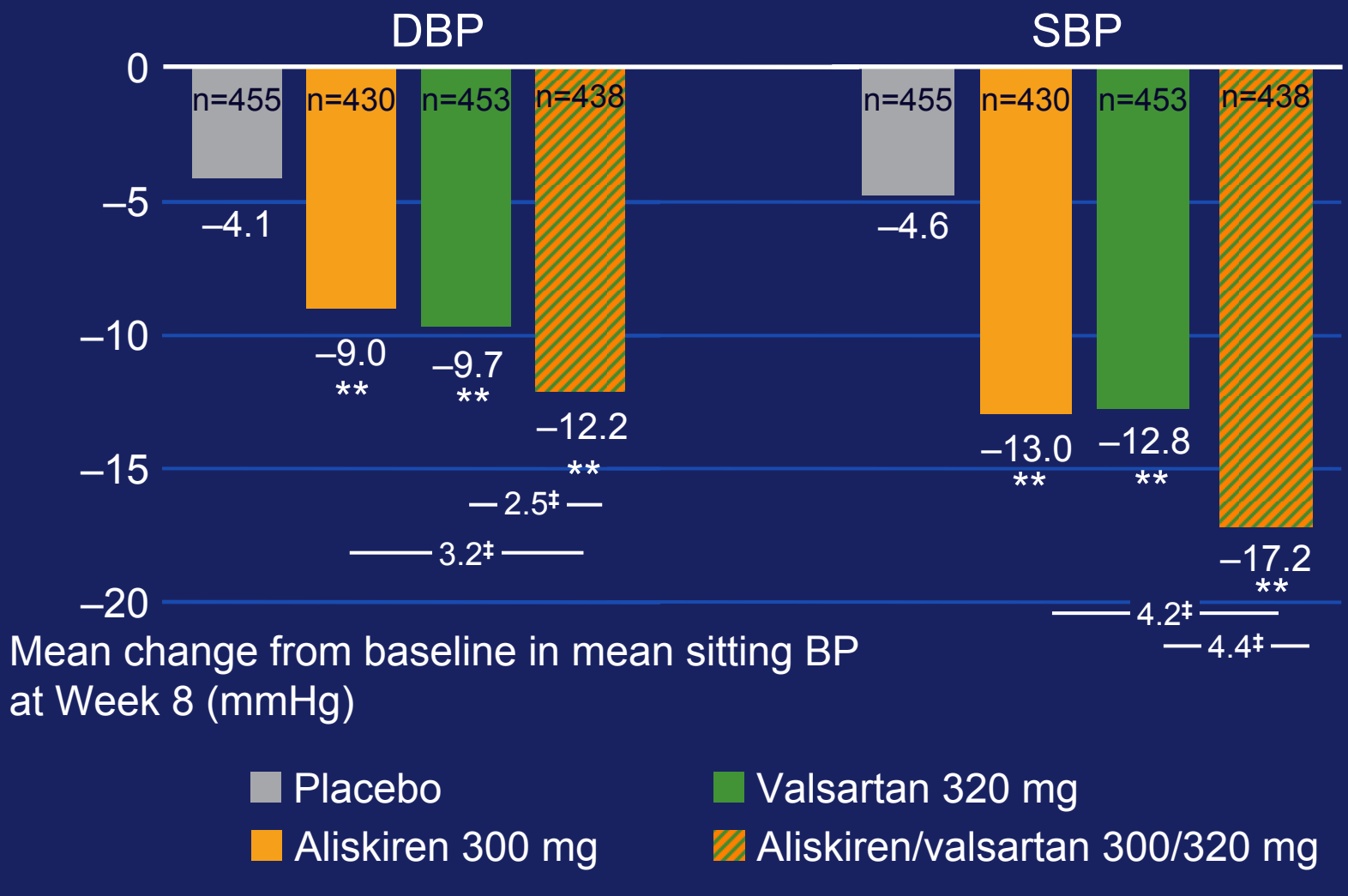
- Aliskiren has a half-life of 40 h
  - Not influenced by renal function
  - Not influenced by liver function
  - Not influenced by age, sex, ethnic group
  - No dose adjustments necessary
- Aliskiren is not metabolized by P450 (CYP) enzymes
  - Thus, no interaction with any other drugs
  - Side effect profile is similar to placebo in all studies to date
  - Like ACEI and ARB, aliskiren should not be given in pregnancy

Aliskiren ve valsartan kombinasyon terapi
Study design



Oparil S, *et al*. Lancet 2007

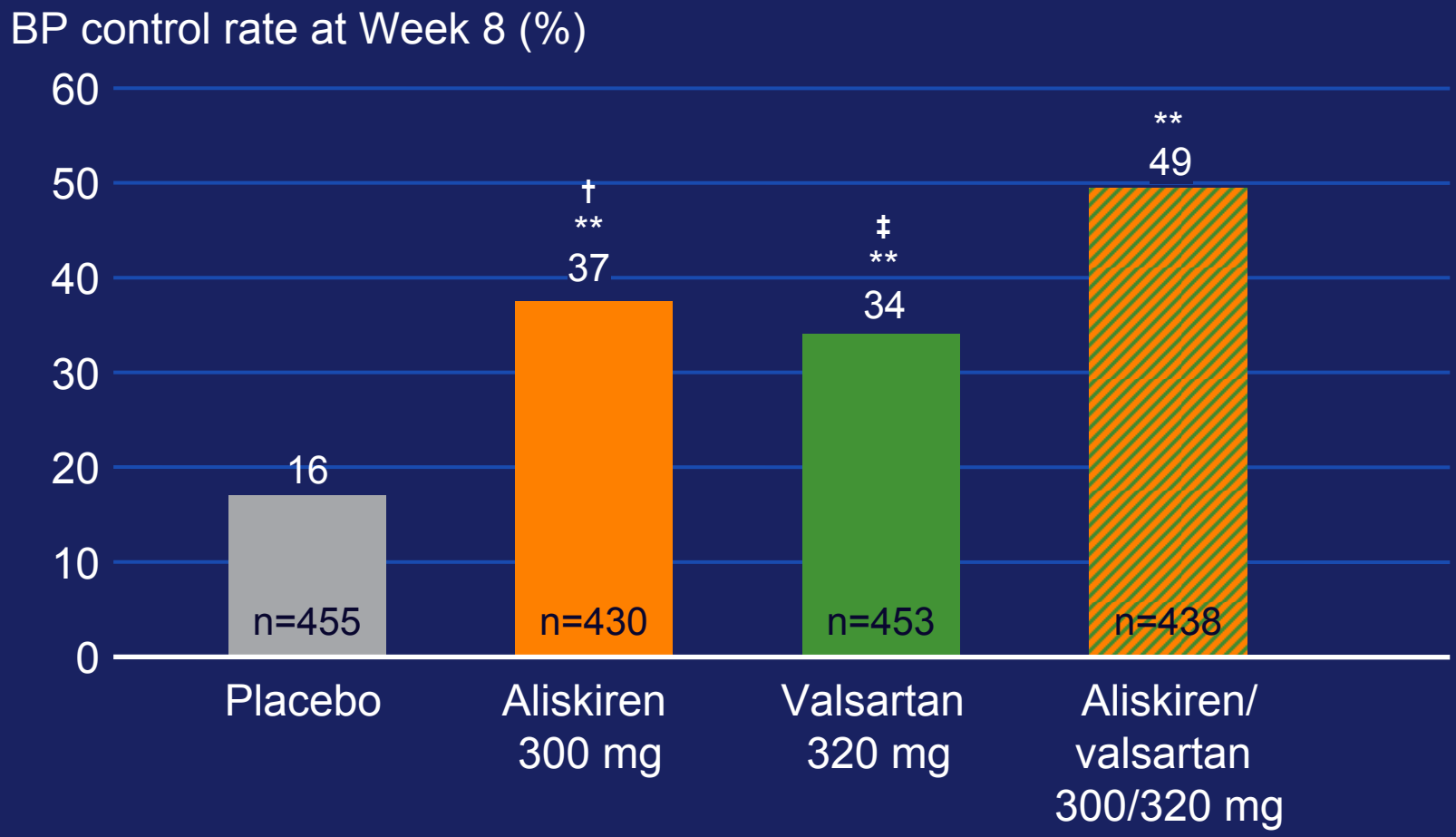
Aliskiren/valsartan kombinasyon terapisi tansiyonun düşüşünü sagliyor



**p<0.0001 vs placebo; ‡p<0.0001 vs aliskiren/valsartan combination therapy

Oparil S, *et al*. Lancet 2007

Aliskiren/valsartan tansiyon kontrolünü düzeltiyor her ikisini teker karşılaştırdığımızda

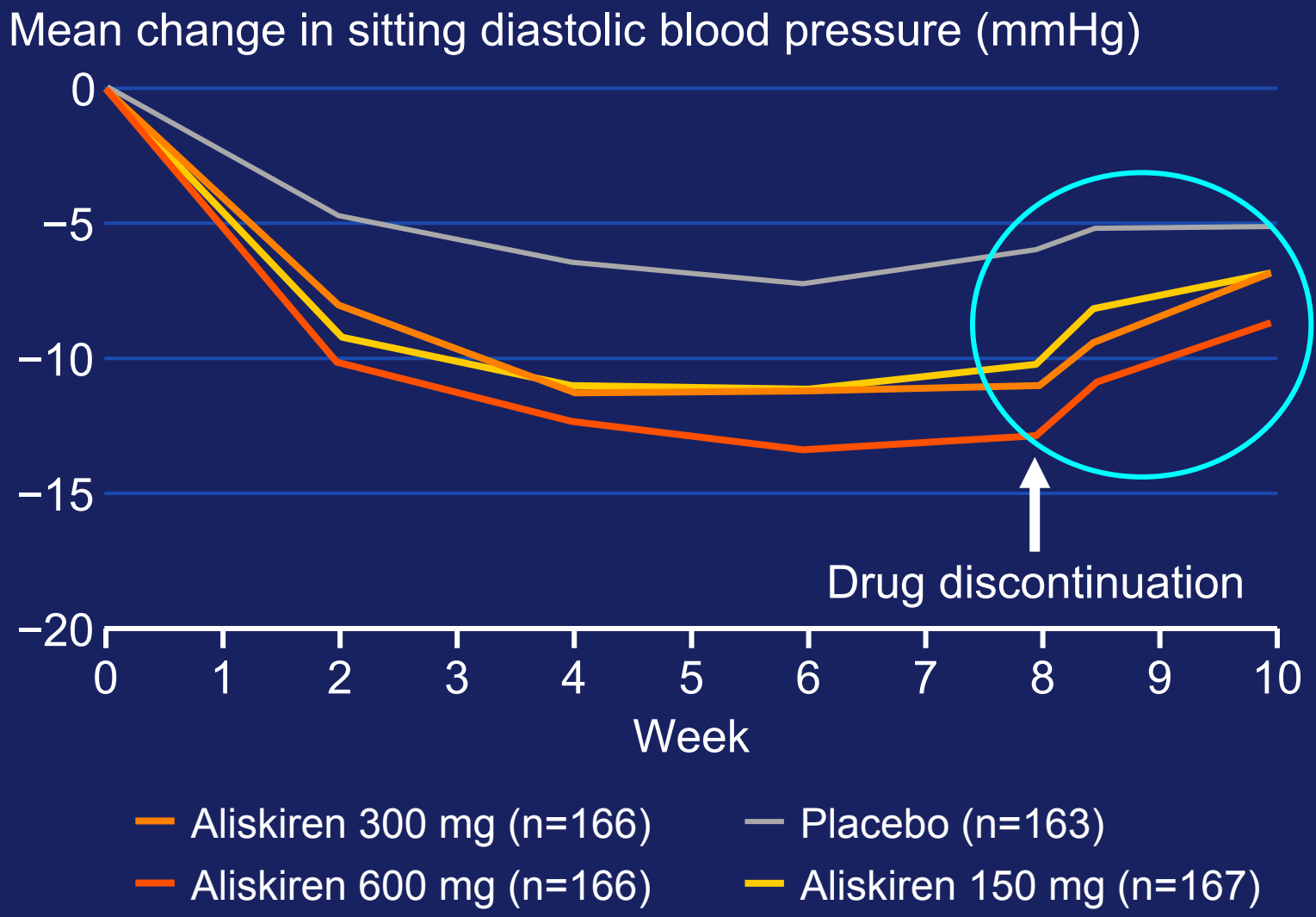


BP control defined as BP <140/90 mmHg

**p<0.0001 vs placebo; †p<0.001, ‡p<0.0001 vs aliskiren/valsartan combination

Oparil S, *et al*. Lancet 2007

Aliskiren uzun düşük tansiyon saglıyor

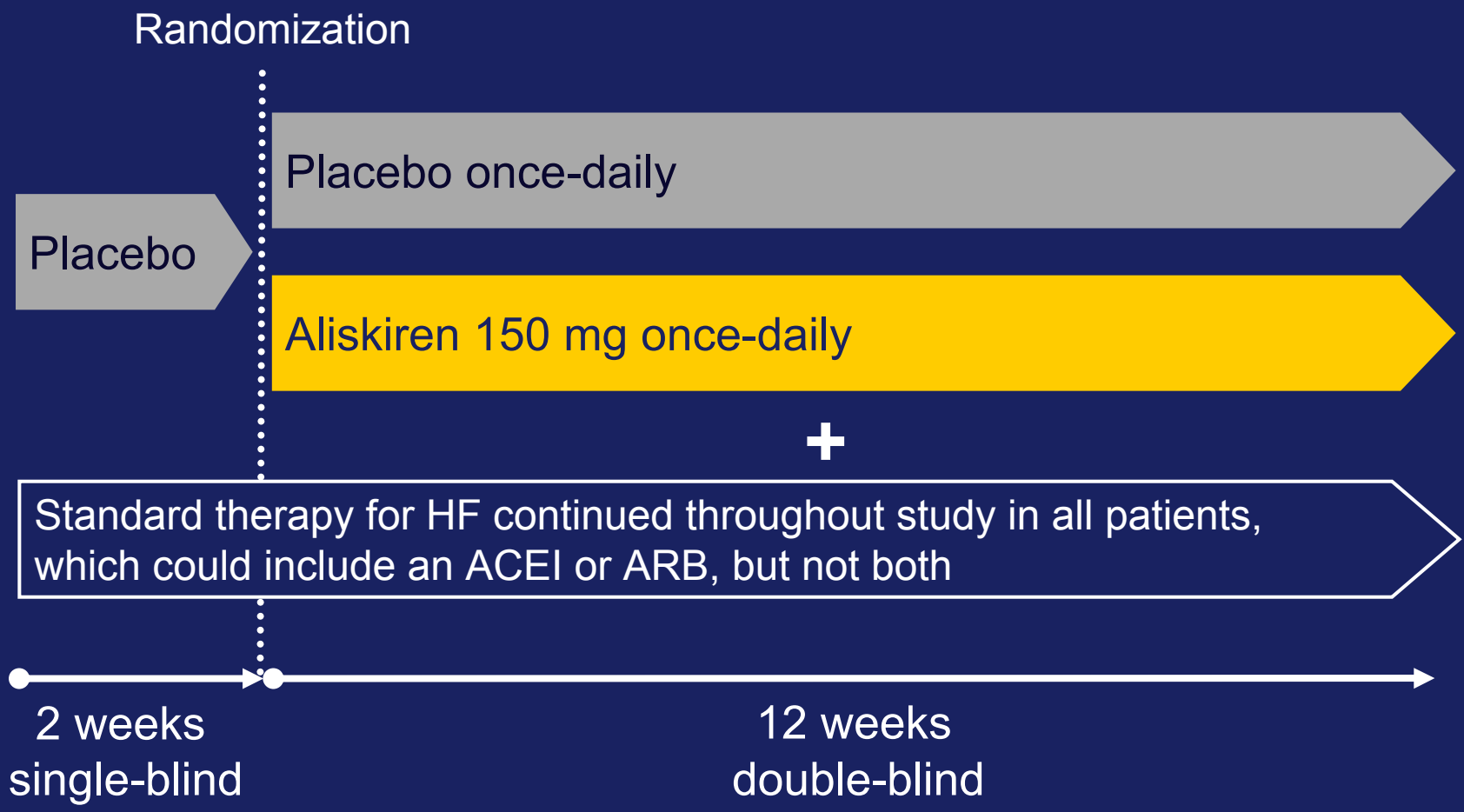


Herron J, *et al*. J Am Coll Cardiol 2007

Kıyaslamalı araştırmalarda yararlı
Summary

- Aliskiren lowers SBP and DBP about 10 mm Hg
- Aliskiren effectively combines with ARB
- Aliskiren effectively combines with HCTZ and amlodipine (not shown)
- Maximum dosage 300 mg/day
- Side effect profile similar to ARB and better than placebo (because of reduced headaches)
- When aliskiren is discontinued, there is no rebound - instead, BP takes 2 weeks to come back up

Aliskiren kalp hastalıkları tedavisindeki gözetleme (ALOFT) – Study design overview



McMurray JJV. ESC 2007 (ALOFT)

ALOFT
Population and objectives

Study population:

- Patients with NYHA II-III HF, prior or current hypertension, B-type natriuretic peptide (BNP) >100 pg/mL, and β-blocker with either an ACEI or an ARB

Primary objective:

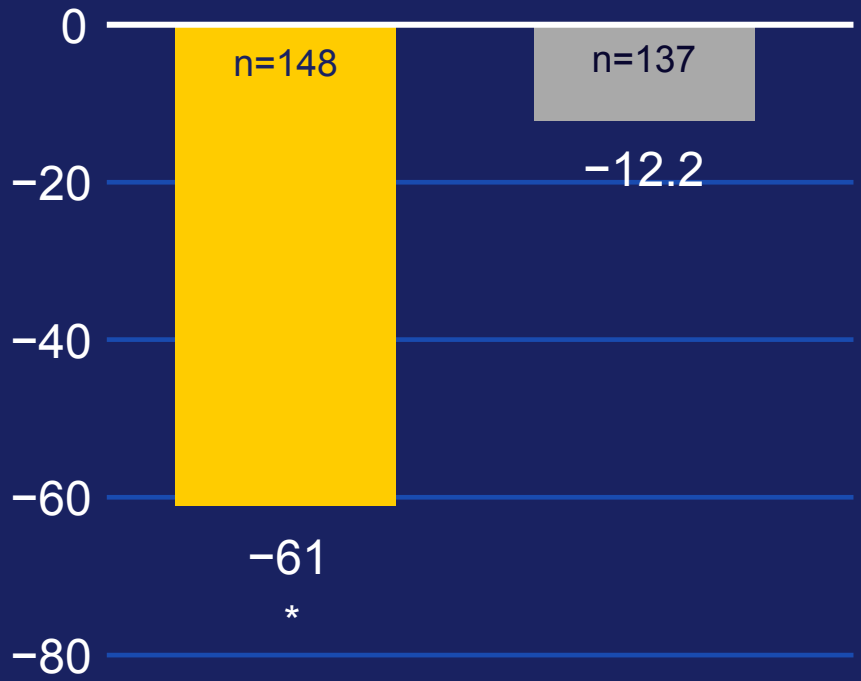
- Safety and tolerability of aliskiren 150 mg

Secondary objectives include:

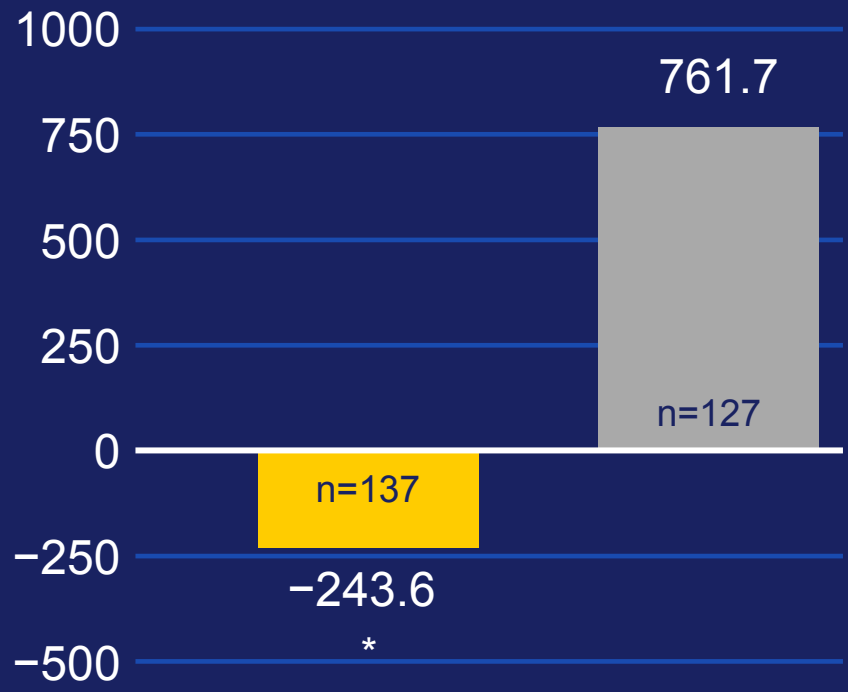
- Effect of aliskiren on BNP, N-terminal proBNP (NT-proBNP), aldosterone levels, echocardiogram, signs and symptoms of HF, and blood pressure

McMurray JJV. ESC 2007 (ALOFT)

Aliskiren BNP ve NT-proBNPı indiriyor placebo ile karşılaştırdığımız zaman (kalb hastalarında)



Mean change from baseline† in plasma BNP at Week 12 (pg/mL)



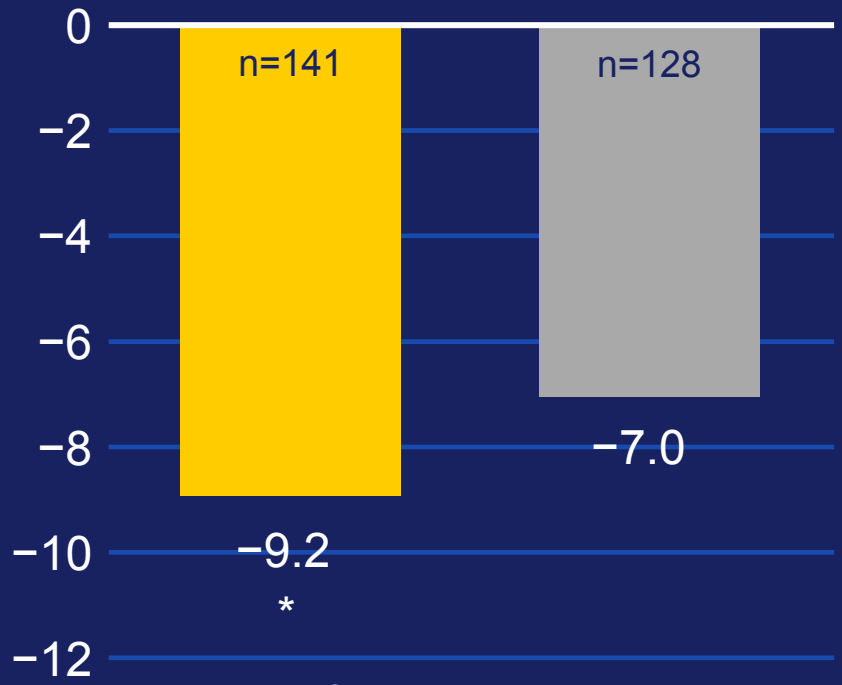
Mean change from baseline‡ in plasma NT-proBNP at Week 12 (pg/mL)

Standard HF therapy
- + aliskiren 150 mg
- + placebo

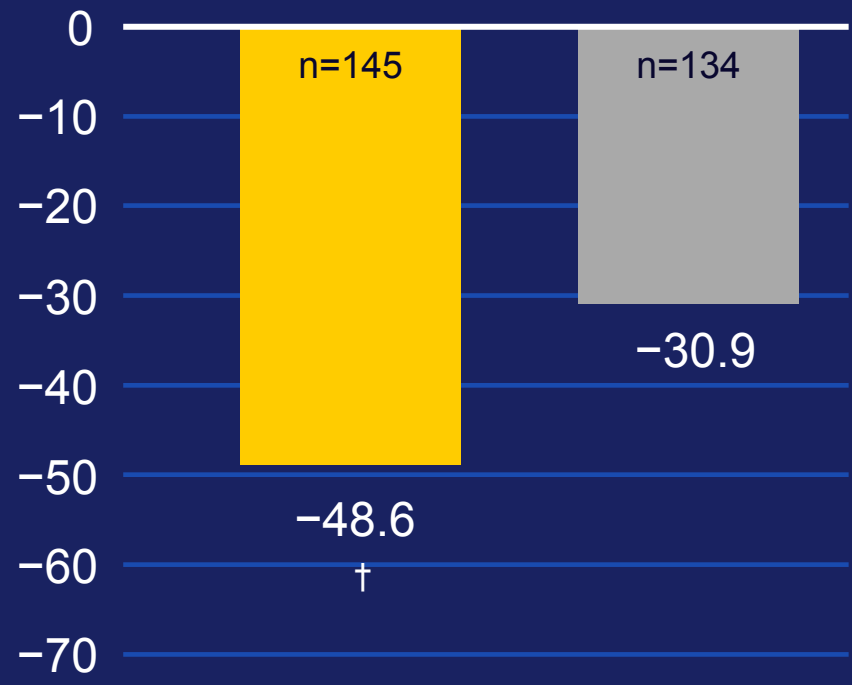
†Baseline BNP values – aliskiren 301 pg/mL, placebo 273 pg/mL
‡Baseline NT-proBNP values – aliskiren 2158 pg/mL, placebo 2123 pg/mL
*p<0.05 vs placebo

McMurray JJV. ESC 2007 (ALOFT)
McMurray *et al*. 2008 (ALOFT)

Aliskiren idrar ve plazma aldosteronu azaltıyor placebo ile karşılaştırdığımız zaman HF hastalar arasında



Mean change from baseline in urinary aldosterone at Week 12 (nmol/day)



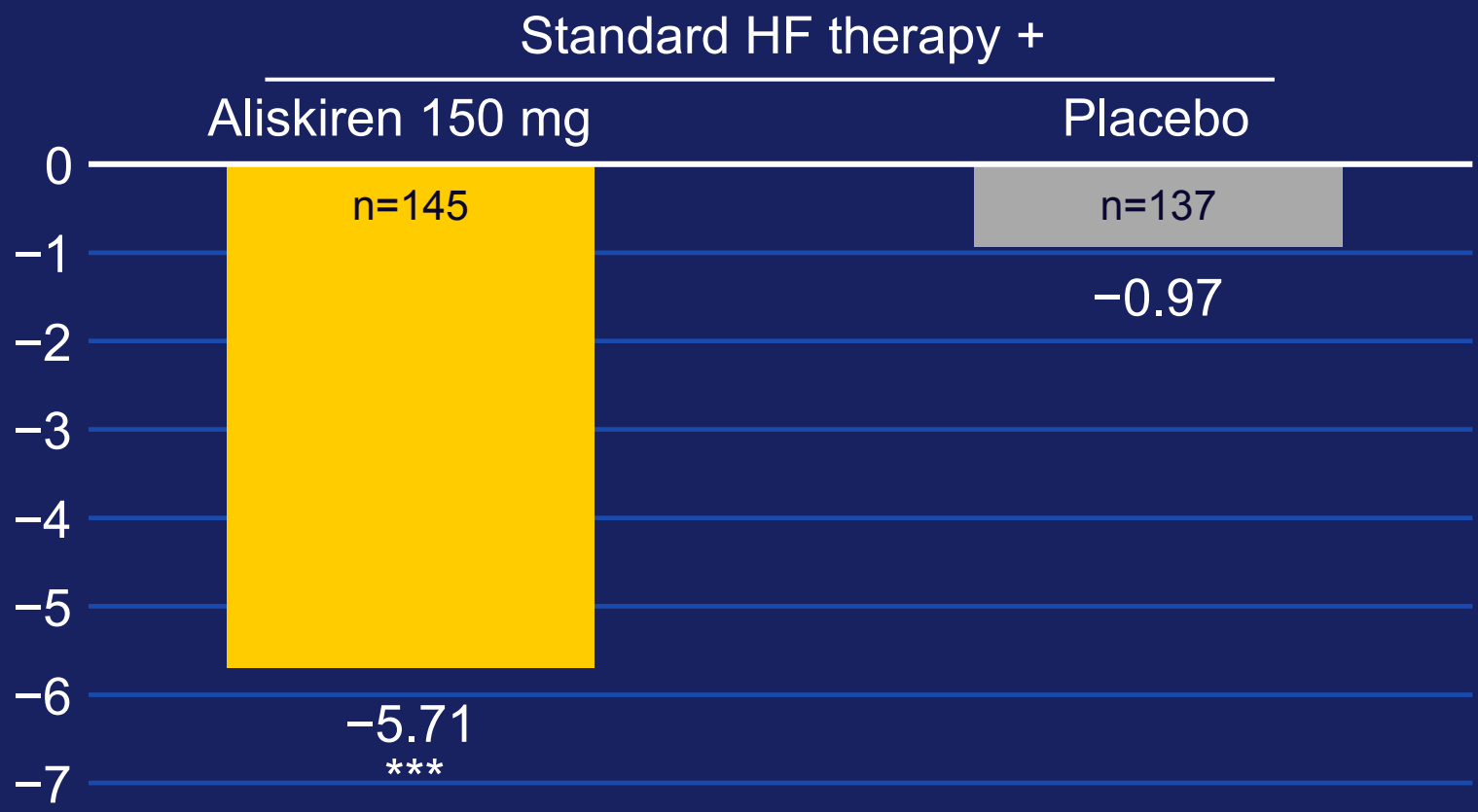
Mean change from baseline in plasma aldosterone at Week 12 (pmol/L)

Standard HF therapy
+ aliskiren 150 mg
+ placebo

*p<0.05 vs placebo; †not statistically significant vs placebo

McMurray JJV. ESC 2007 (ALOFT)

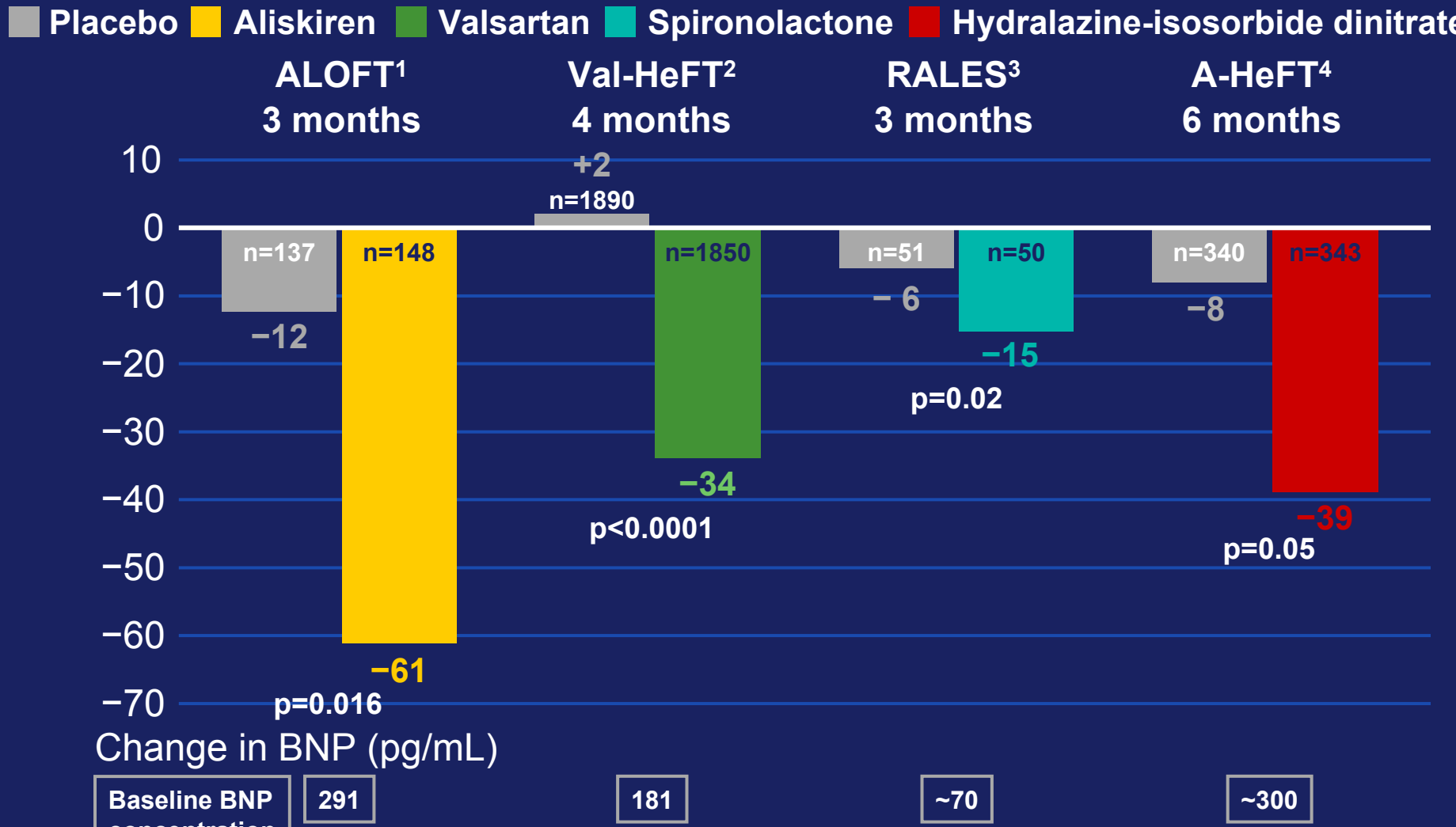
Aliskiren PRA düşürüyor placebo ile karşılaştırdığımız zaman HF hastalar arasında



***p<0.0001 vs placebo
PRA, plasma renin activity

McMurray JJV. ESC 2007 (ALOFT)

Aliskirenin diger antihypertensivler ile araştırmalara karsi izlenimi

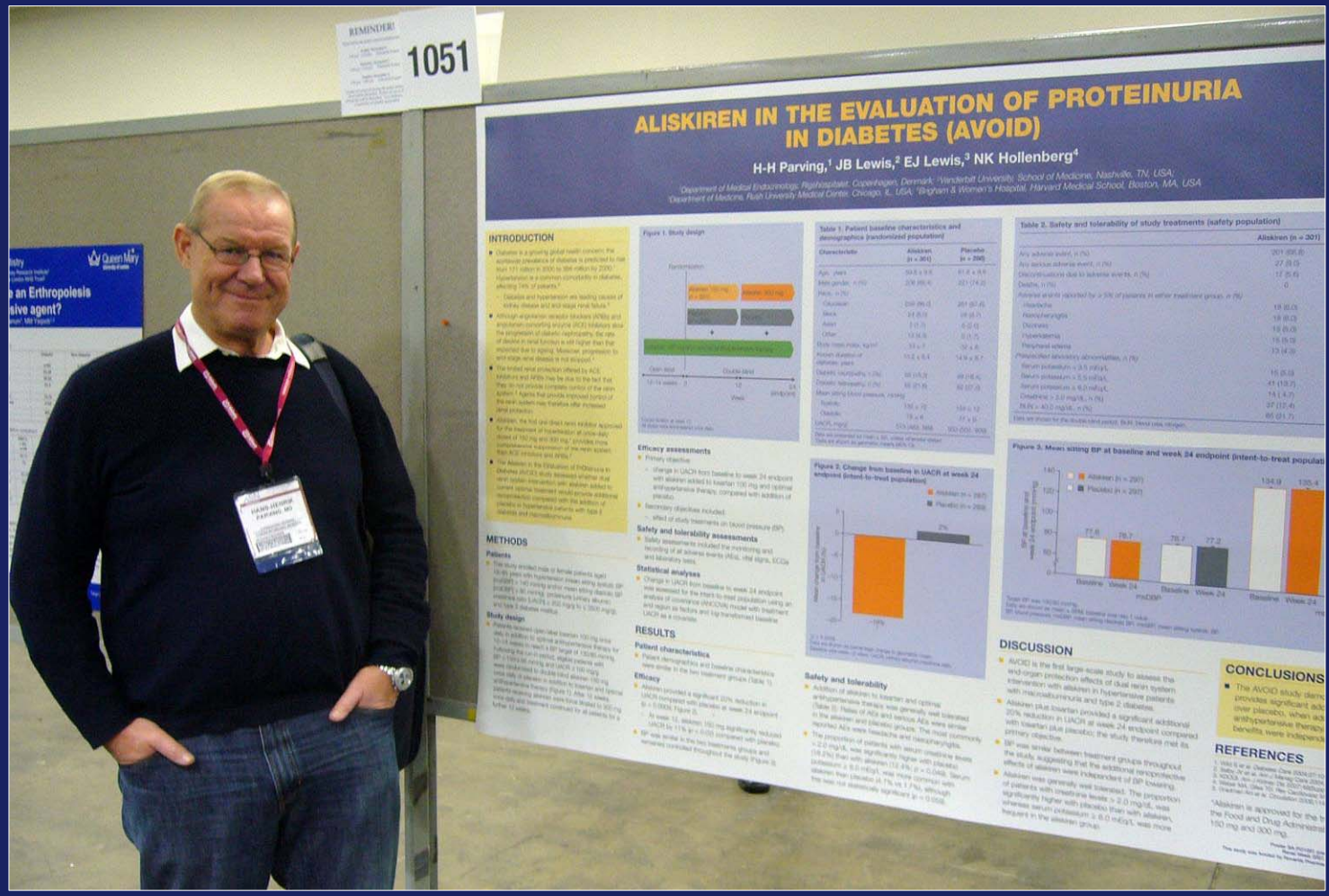


1. McMurray JJV. 2007; 2. Latini R, *et al*. 2002;
3. Rousseau MF, *et al*. 2002; 4. Cohn JN, *et al*. 2007

ALOFT
Summary

- In patients receiving standard therapy for HF:
  - Aliskiren has a placebo-like tolerability profile
  - Aliskiren significantly reduces BNP and NT-proBNP compared with placebo
  - Aliskiren reduces urinary aldosterone compared with placebo
  - Aliskiren provides significant reductions in PRA compared with placebo
  - Aliskiren provides significant improvements in some echocardiographic assessments of LV function

AVOID Study
Proteinuria reduction in DM nephropathy

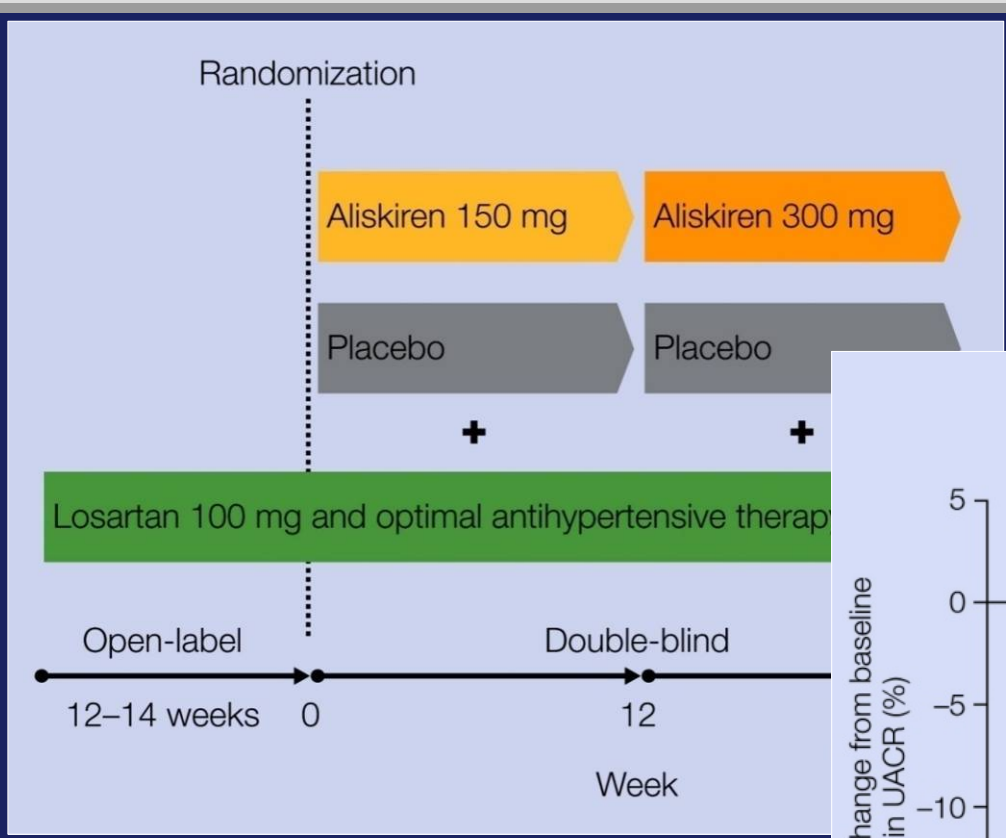


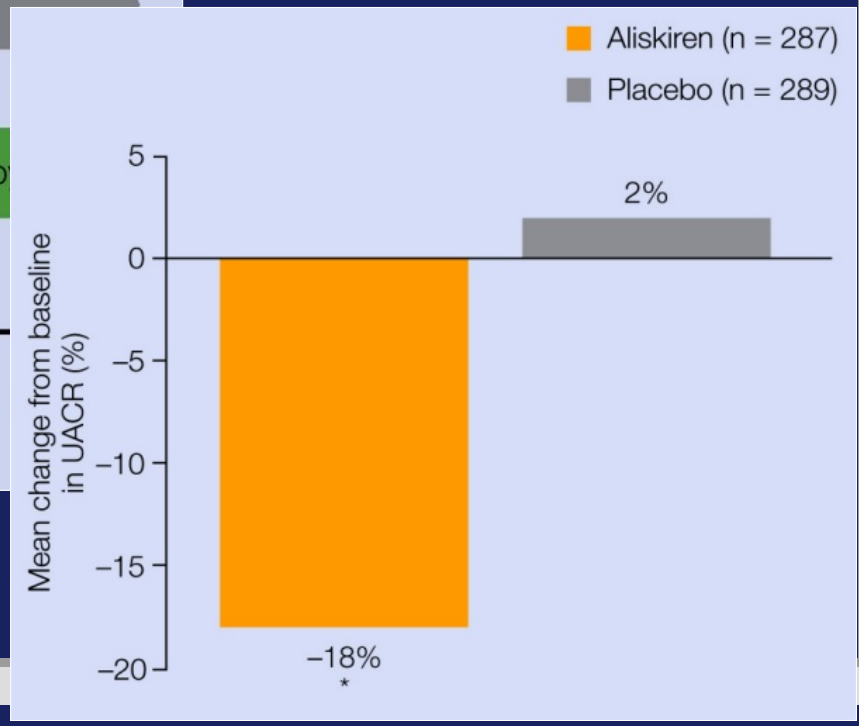
ASN Renal Week 2007
October 31 - November 5, 2007
San Francisco, California

ASN THE AMERICAN SOCIETY OF NEPHROLOGY

Parving, et al. , ASN 2007

Aliskiren „on top“ of losartan lowered proteinuria another 20%





Parving, et al. , ASN 2007

Renin: the key to cardiovascular pathology
Conclusions

- Chronic Ang II generation in the circulating or tissue renin systems causes organ damage
- Inhibition of the Renin System with either ACEIs and ARBs causes a compensatory rise in PRA
- Aliskiren targets the Renin System at its point of activation, providing more complete control
- Aliskiren reduces levels of Ang I and Ang II, and neutralizes the rise in PRA induced by other antihypertensives
- Aliskiren works in hypertension (alone or combined), heart failure, and diabetic renal disease