

# **BÜTÜN BETA BLOKERLER AYNI MIDİR?**

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İç Hastalıkları A.D., Nefroloji B.D.

# Sunum Planı

- Tarihçe
- Sınıflama
- Klinik özellikler
- Diğer antihipertansif sınıflarla karşılaştırma
- Yeni (3. jenerasyon) moleküllerin farkı

# Geçen yüzyılda...

- 1900-1910: Epinefrin
- 1940-1950:
  - Norepinefrin
  - $\alpha$ -,  $\beta$ -reseptör
- 1950-1960: c-AMP: ikinci haberci
- 1960-1970:
  - **Propranolol**: ilk  $\beta$ -bloker
  - $\beta_1$ -  $\beta_2$  subtipleri

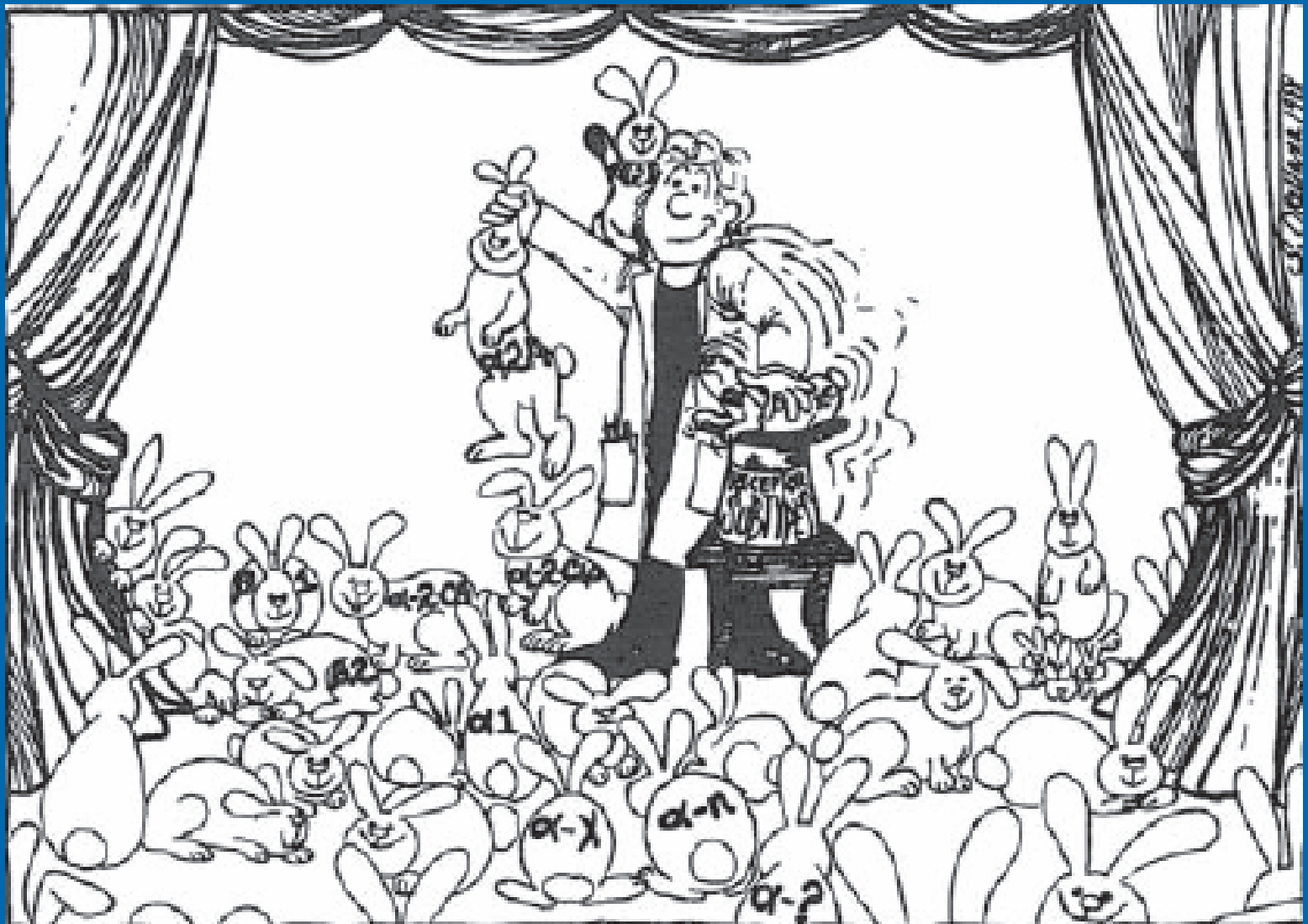


James Black  
1988 Nobel Tıp Ödülü  
“Propranolol keşfi”

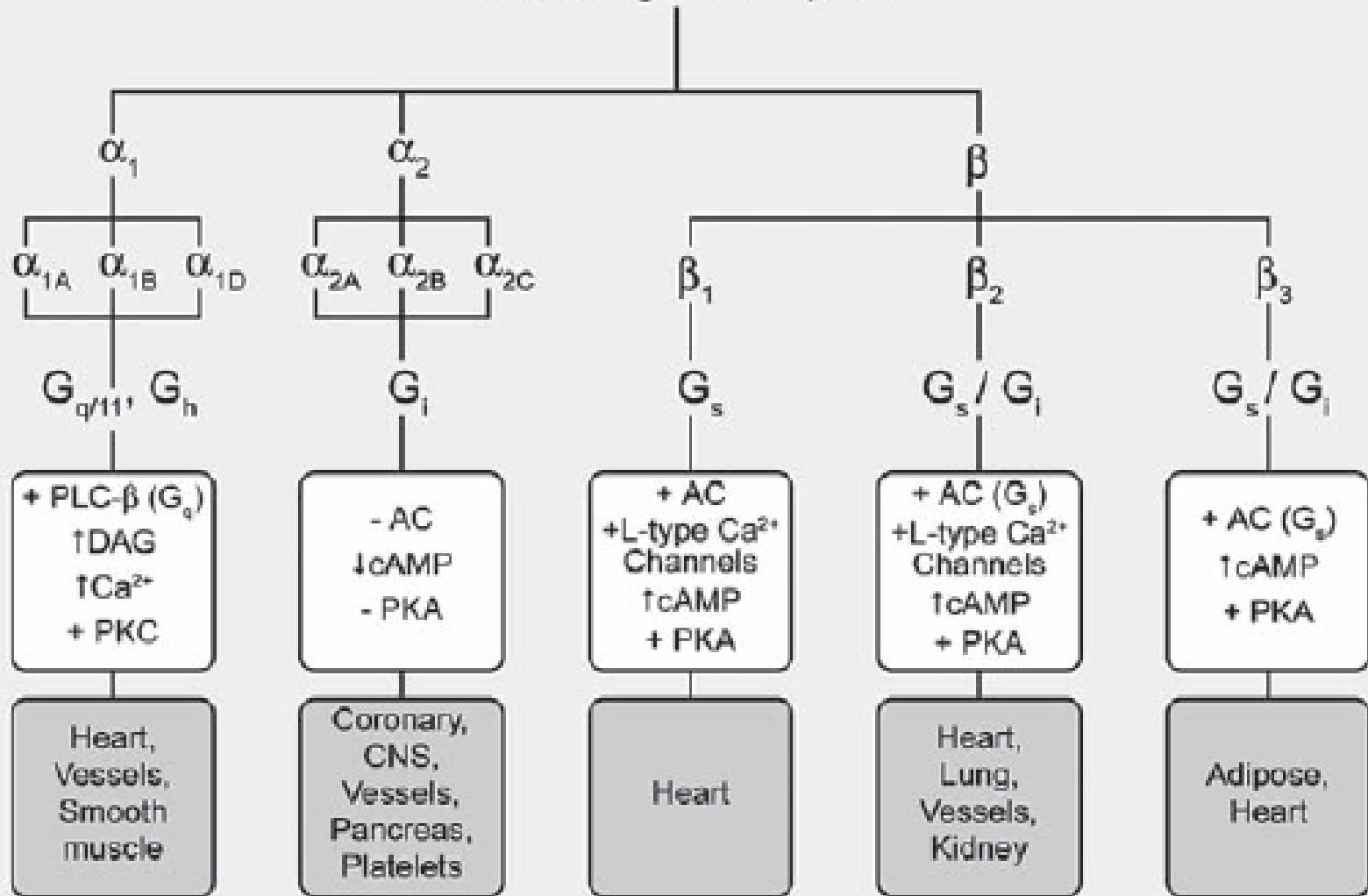
# Geçen yüzyılda...

- 1970-1980:  $\alpha_1$  -  $\alpha_2$
- 1980-1990:
  - $\alpha_{1A}$ ,  $\alpha_{1B}$
  - $\alpha_{1A}$ ,  $\alpha_{1B}$ ,  $\alpha_{2C}$
  - $\beta_3$  klonlandı
- 1990-2000:
  - $\alpha_{1D}$  klonlandı
  - “Knock-out” modeller
  - Polimorfizmler
  - $\beta_4$ ?

1988



# Adrenergic Receptors



## Etkinliđi belirleyen...

- Katekolaminlerin “dolařım” ve “dokudaki” düzeyleri
- Reseptör “dađılım” ve “miktarı”

# $\beta$ -reseptör aracılı etkiler...

Doku	Fonksiyon	Reseptör
Sempatik nöron	E/NE salınımı	$\beta_2$
Kalp	Kronotropi, İnotropi, dromotropi, batmotropi	$\beta_1 > \beta_2 > \beta_3$
Damar	Relaksasyon	$\beta_2 > \beta_1$
Böbrek	Renin salınımı	$\beta_1$
Karaciğer	Glikojenoliz	$\beta_2$
Pankreas	İnsülin	$\beta_2$



# $\beta$ -reseptör antagonistleri ve kardiyovasküler etkileri...

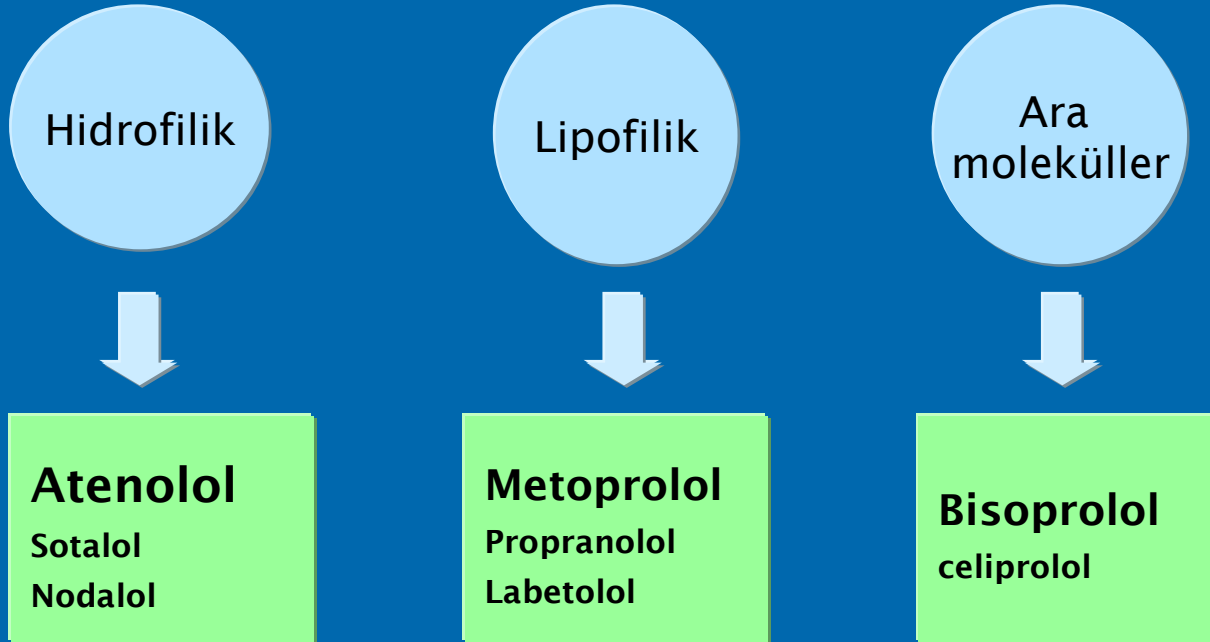
Hastalık	Etki
Aritmiler	SA ve Av ileti ↓
Arteriyel hipertansiyon	Kalp debisi ve Renin salınımı ↓
Koroner kalp hastalığı	Kalp hızını ↓ O <sub>2</sub> taşınımı ↑ O <sub>2</sub> harcanmasını ↓
Kalp yetmezliği	Ani ölümdede ↓

# **Beta blokerlerin sınıflandırması...**

# Seicilik

- $\beta_1$ : Kalp
- $\beta_2$ : Bronş, periferik damar, pankreas
  
- Nebivolol ( $\beta_1$ )
- Propranolol (non-selektif)
  
- $\beta_2$ 'yi de bloke edenler **YAN ETKİYİ OĞALTIR**
  - Bronkospazm
  - Periferik vazospazm
  - Diyabetojenik etkinlik

# Çözünürlük



**Hidrofilik**



İlk geçiş etkisi ve etki süresi ↑  
Kan-beyin bariyerini geçiş ↓  
Böbrekten atılım ↑

# Antagonist etkinlik

Pür  $\beta$  Antagonist

Metoprolol

Parsiyel agonist  
+  
ISA

Dinlenme fazında agonist  
Sempatik aktivitede antagonist

?

Acebutalol  
Pindolol



**TERCİH**

Periferik damar hastalığı  
DM  
Dislipidemi

# Etki süresi

- Çok kısa (Esmolol=9 dakika)
- Kısa (Metoprolol=4 saat)
- Orta (Atenolol=8 saat)
- Uzun (Acebutalol=12 saat)

# Birleşik etkinlik

- **$\alpha$ -antagonist:** Karvedilol, Labetolol
- **NO salınımı sağlayan:** Nebivolol
- **Vazodilatör ve antioksidan:** Karvedilol
- **K<sup>+</sup>-kanal antagonisti:** Sotalol

# **Hipertansif Hastalarda Klinik Kullanım**

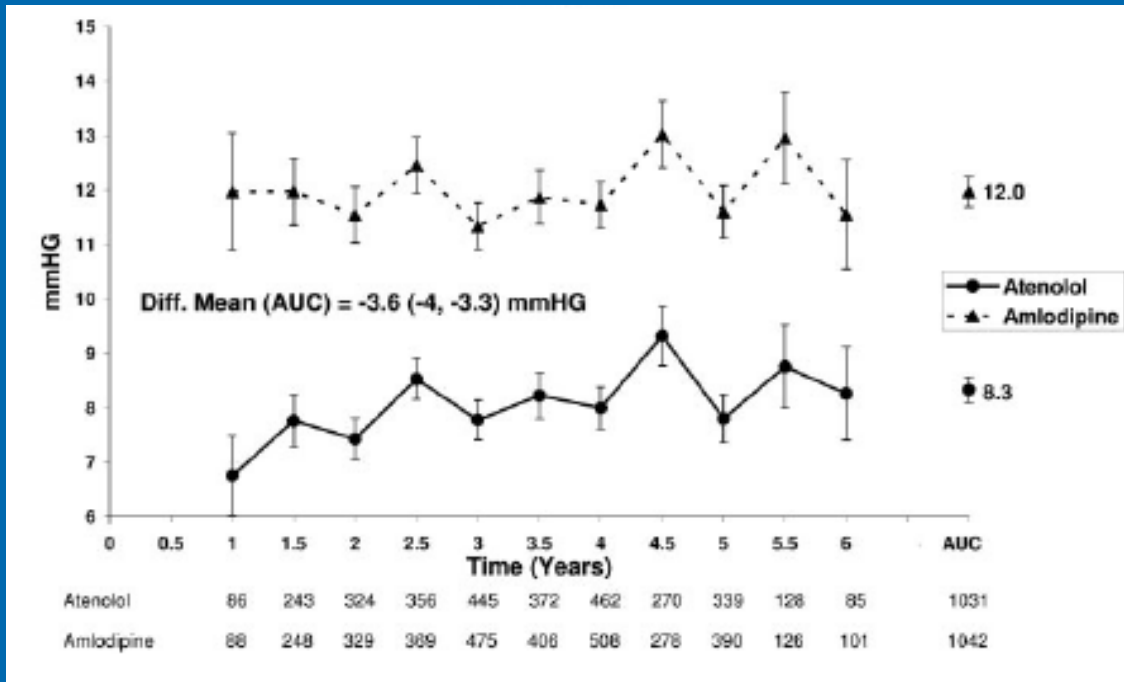


# Kullanım oranı

- ABD'de en sık reçete edilen **4. antihipertansif**
- 44 milyon reçete/yıl
- Ülkemizde durum?

# Kan basıncını düşürme etkinliği

- Zayıf.
- LIFE study
  - Hedef kan basıncı oranı: %10



Williams, Circulation, 2006  
ASCOT study

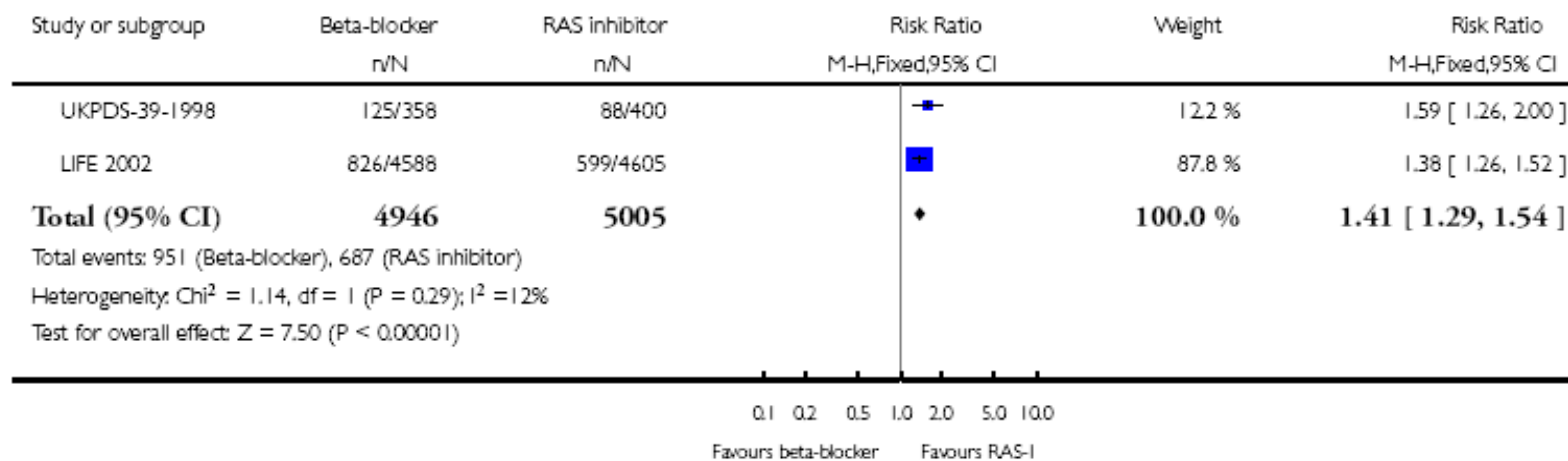
# Yan etki nedeniyle ilacı bırakma

## RAS inhibitörü / BB

Review: Beta-blockers for hypertension

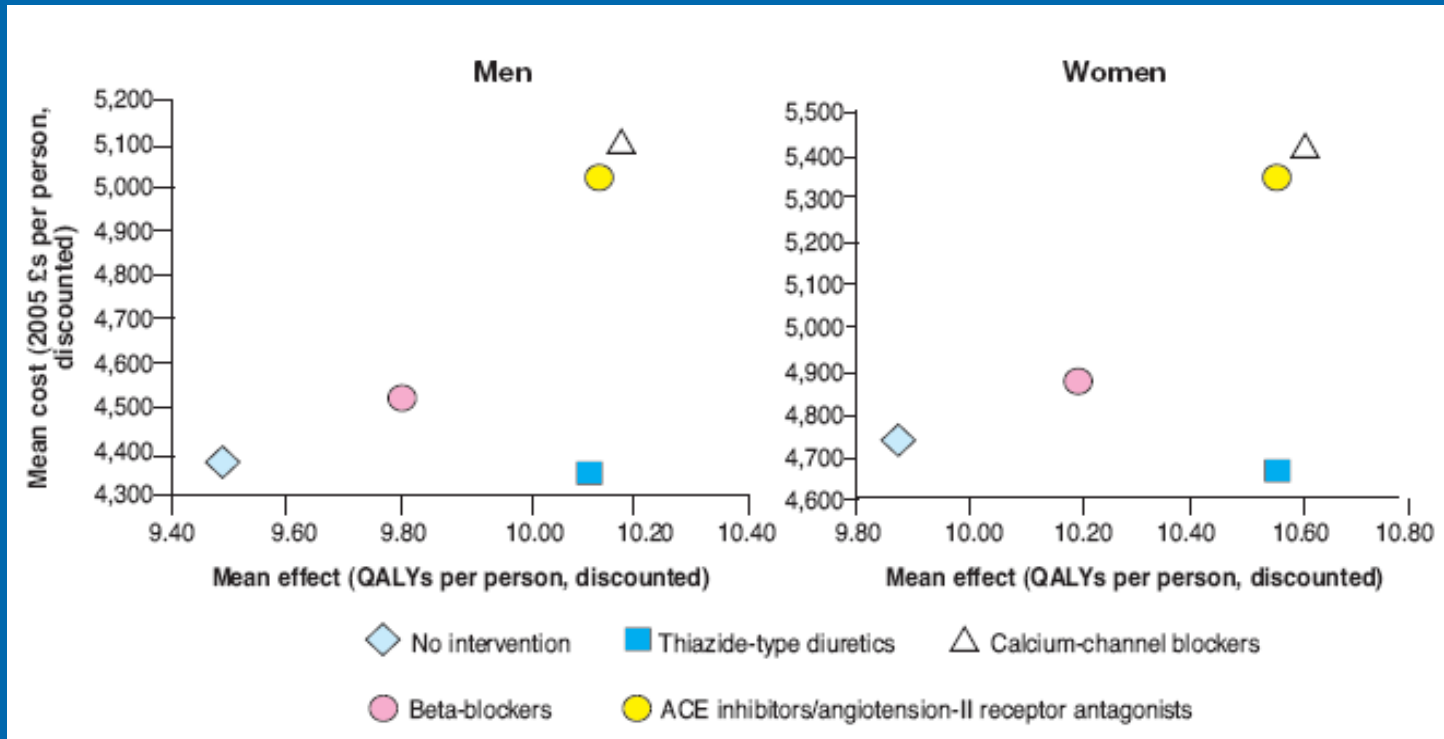
Comparison: 4 Beta-blocker versus RAS inhibitor

Outcome: 6 Withdrawal due to adverse effect



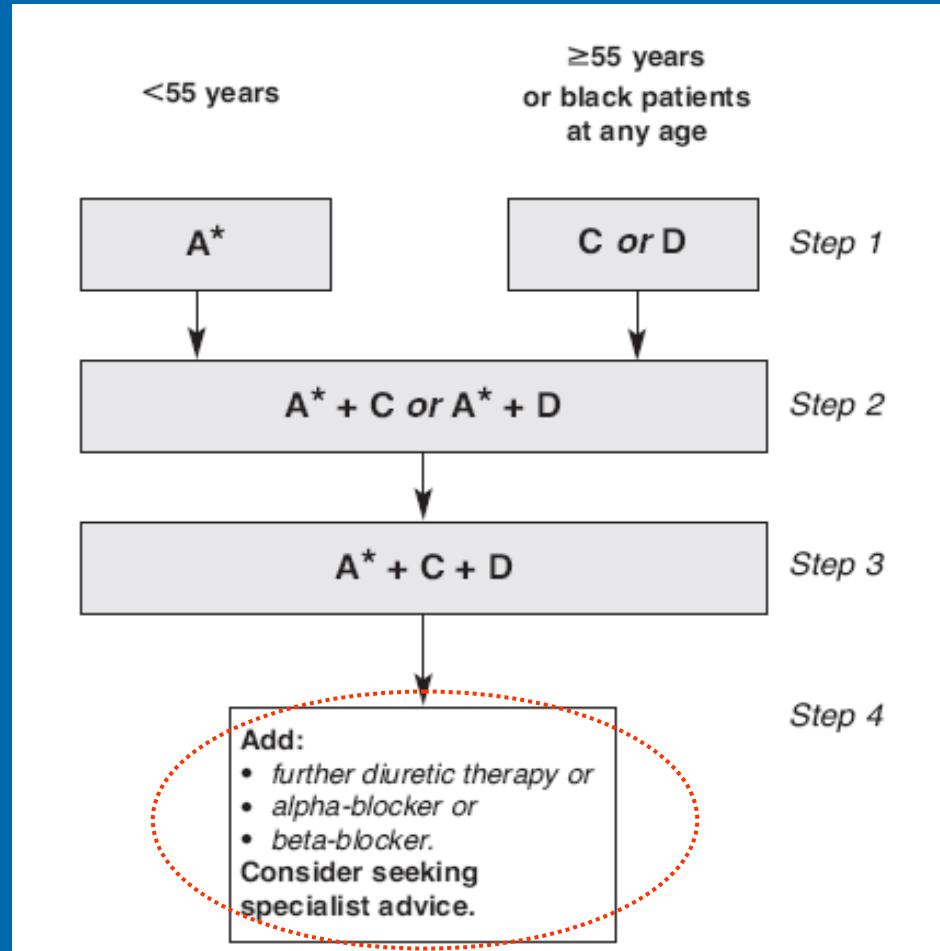
Cochrane Database of Systematic Reviews, Issue 1, 2009

# Maliyet



BHS&Royal College of Physicians Guideline 2004

# Kılavuzlara göre başlangıç seçeneği olarak beta bloker





## † 2007 Guidelines for the management of arterial hypertension

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

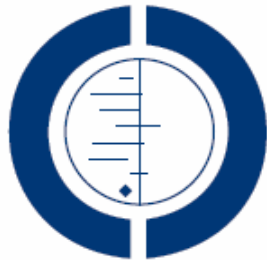
### *Box 10 Position statement: Choice of antihypertensive drugs*

- The main benefits of antihypertensive therapy are due to lowering of BP *per se*.
- Five major classes of antihypertensive agents – thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and  $\beta$ -blockers – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination.  $\beta$ -blockers, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes.
- Because in many patients more than one drug is

# Meta-analizler

## Beta-blockers for hypertension (Review)

Wiysonge CSU, Bradley HA, Mayosi BM, Maroney RT, Mbewu A, Opie L, Volmink J



THE COCHRANE  
COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

<http://www.thecochranelibrary.com>



Beta-blockers for hypertension (Review)  
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## Should $\beta$ blockers remain first choice in the treatment of primary hypertension? A meta-analysis



Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

### Summary

**Background:**  $\beta$  blockers have been used widely in the treatment of hypertension and are recommended as first-line drugs in hypertension guidelines. However, a preliminary analysis has shown that atenolol is not very effective in hypertension. We aim to substantially enlarge the data on atenolol and analyse the effect of different  $\beta$  blockers.

**Methods:** The Cochrane Library and PubMed were searched for  $\beta$  blocker treatment in patients with primary hypertension. Data were then entered into the Cochrane Collaboration Review Manager package and were summarised in meta-analyses. 13 randomised controlled trials (n=105 951) were included in a meta-analysis comparing treatment with  $\beta$  blockers with other antihypertensive drugs. Seven studies (n=27 433) were included in a comparison of  $\beta$  blockers and placebo or no treatment.

**Findings:** The relative risk of stroke was 16% higher for  $\beta$  blockers (95% CI 4–30%) than for other drugs. There was no difference for myocardial infarction. When the effect of  $\beta$  blockers was compared with that of placebo or no treatment, the relative risk of stroke was reduced by 19% for all  $\beta$  blockers (7–29%), about half that expected from previous hypertension trials. There was no difference for myocardial infarction or mortality.

**Interpretation:** In comparison with other antihypertensive drugs, the effect of  $\beta$  blockers is less than optimum, with a raised risk of stroke. Hence, we believe that  $\beta$  blockers should not remain first choice in the treatment of primary hypertension and should not be used as reference drugs in future randomised controlled trials of hypertension.

Lancet 2005; 366:1545–53

Published online  
October 18, 2005  
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See Comment page 1510

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$\beta$ -bloker



$\beta$ -bloker

**Diğer antihipertansif sınıflarla  
karşılaştırma...**



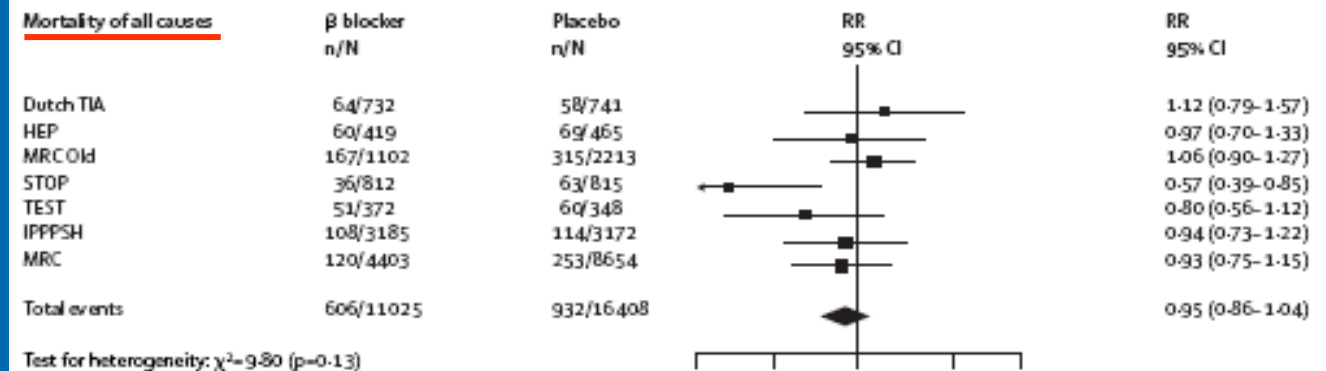
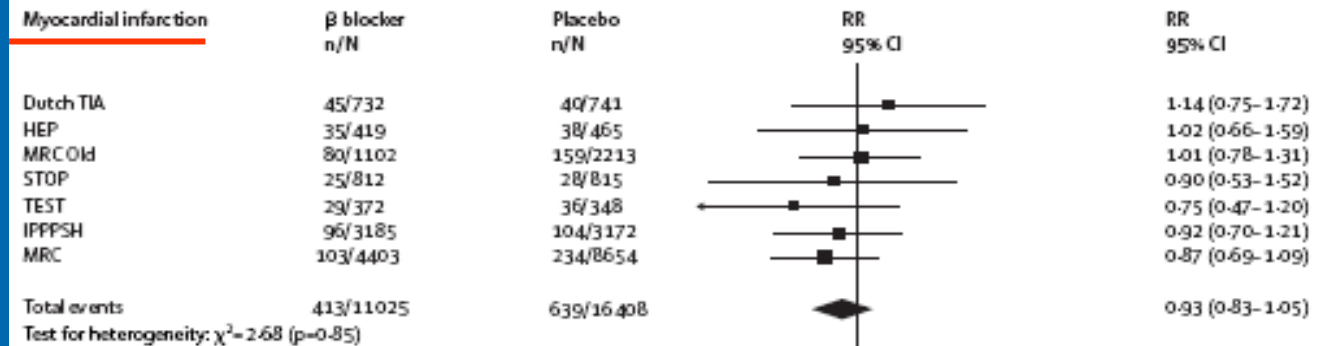
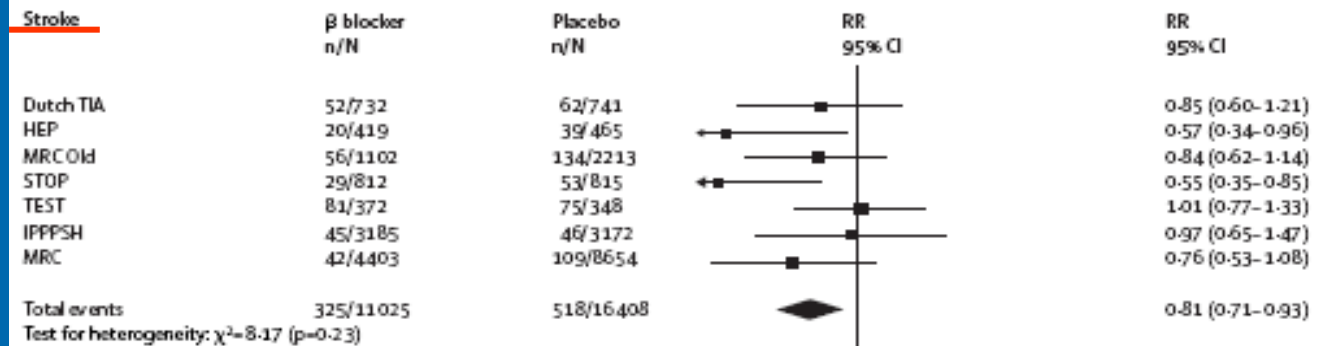
# BB / Plasebo

Trial identification	Beta-blocker	Comparison drug	Baseline BP (mmHg)	Mean BP difference*
Coope 1986	Atenolol	No treatment	196.7/99.7	-18.0/-11.0
MRCOA 1992	Atenolol	Placebo	184.0/91.0	-13.0/-7.0
MRC 1985	Propranolol	Placebo	162.0/98.5	-9.5/-5.0
IPPPSH 1985	Oxprenolol	Placebo	173.2/107.9	-4.1/-1.5

Cochrane Database of Systematic Reviews, Issue 1, 2009

# BB / Plasebo

Lindholm, Lancet 2005



# BB / Diüretik

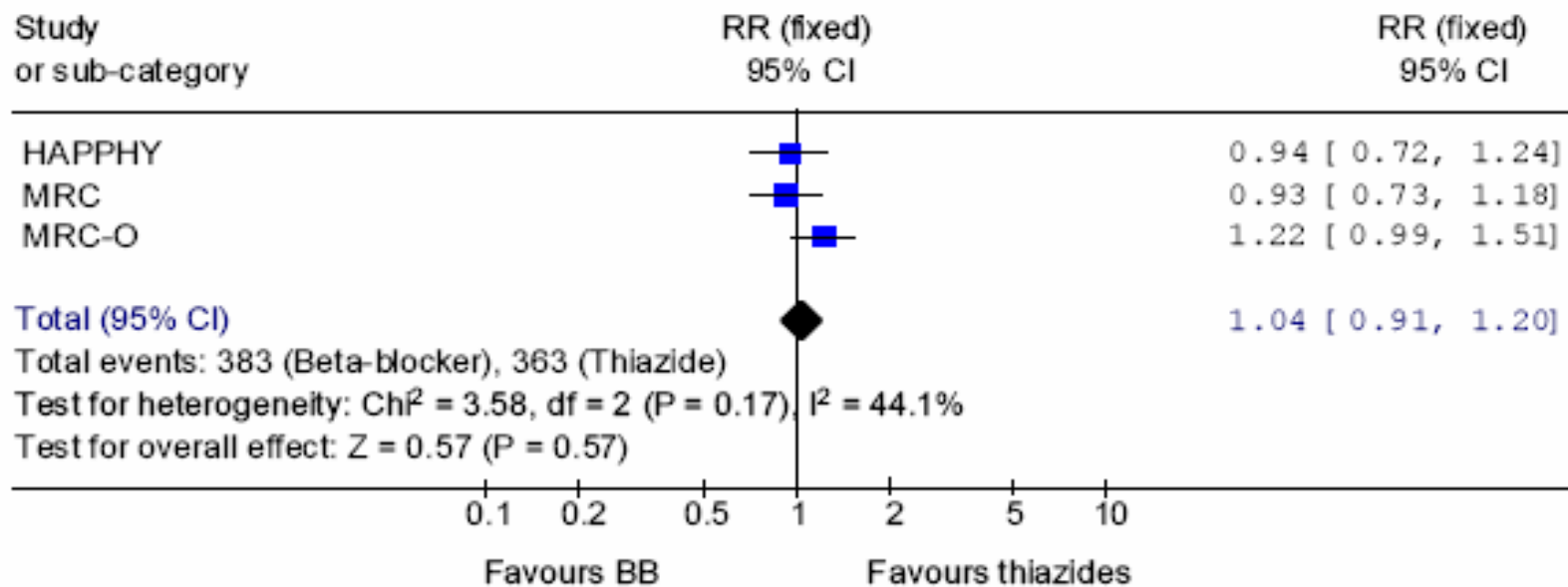
Berglund 1981	Propranolol	Diuretic	174.0/105.5	-4.0/+2.0
VA COOP 1982	Propranolol	Diuretic	146.3/101.5	+7.0/+1.6
MRC 1985	Propranolol	Diuretic	162.0/98.5	+3.5/+1.0
HAPPHY 1987	Atenolol or metoprolol or propranolol	Diuretic	166.0/107.9	0.0/-1.0
MRCOA 1992	Atenolol	Diuretic	184.0/91.0	+1.0/-0.5

Cochrane Database of Systematic Reviews, Issue 1, 2009

# BB / Tiyazid diüretik

Comparison: 01 Beta-blockers versus thiazides

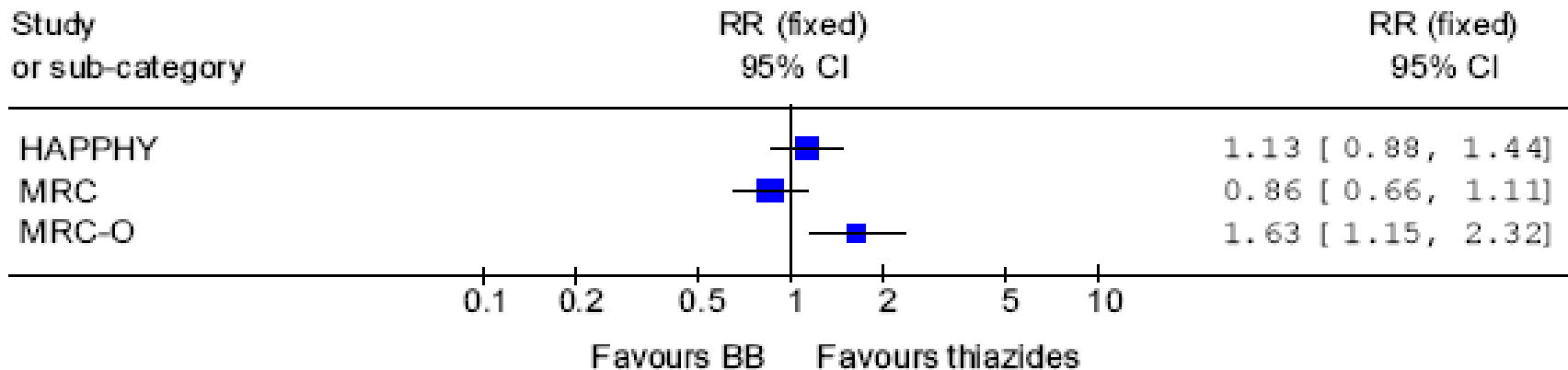
Outcome: 01 Mortality



# BB / Tiyazid diüretik

Comparison: 01 Beta-blockers versus thiazides

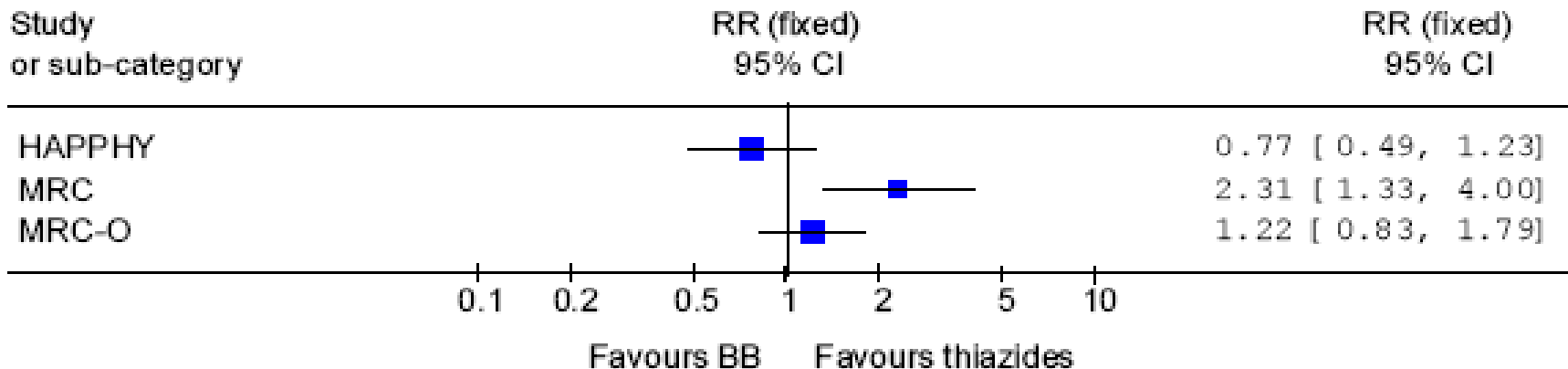
Outcome: 02 Myocardial infarction



# BB / Tiyazid diüretik

Comparison: 01 Beta-blockers versus thiazides

Outcome: 03 Stroke



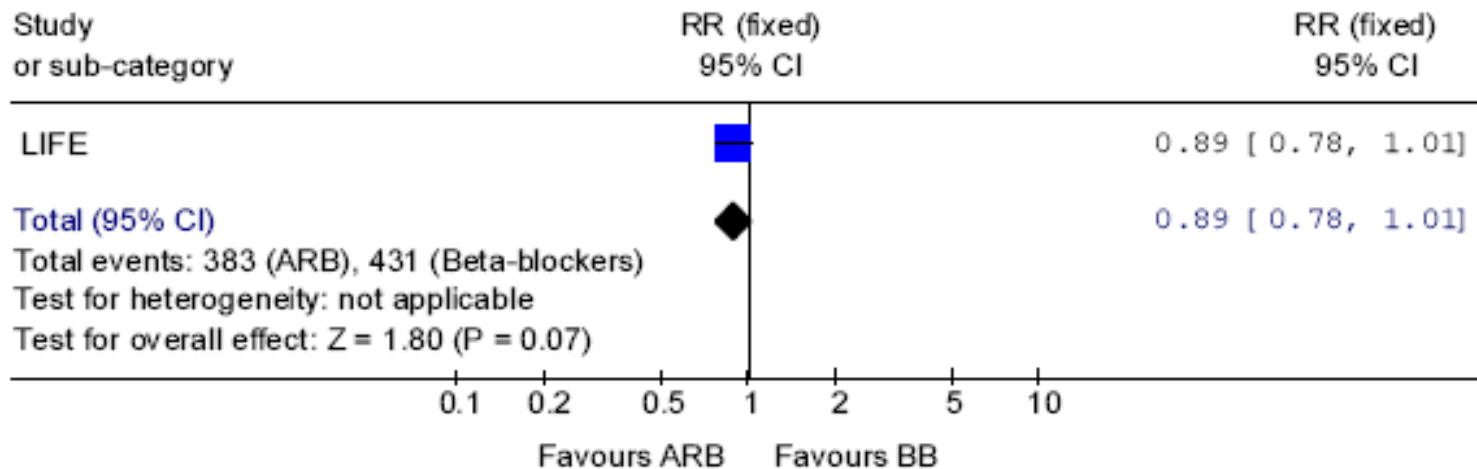
# BB / RAS inhibitörleri

UKPDS-39-1998	Atenolol	Renin-angiotensin system inhibitor (ACEI)	159.0/93.0	-1.0/-1.0
LIFE 2002	Atenolol	Renin-angiotensin system inhibitor (ARB)	174.5/97.7	+1.1/-0.2
AASK 2002	Metoprolol	Renin-angiotensin system inhibitor (ACEI)	150.0/96.0	0.0/-1.0

Cochrane Database of Systematic Reviews, Issue 1, 2009

# BB / ARB

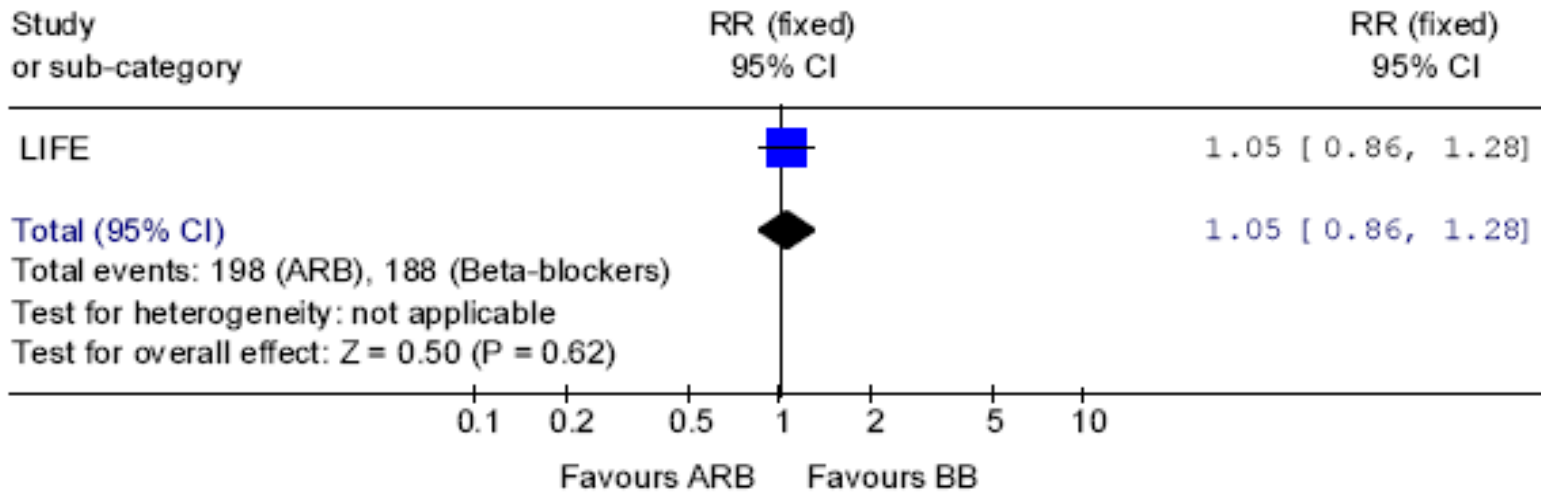
Comparison: 03 ARBs versus beta-blockers  
Outcome: 01 Mortality





# BB / ARB

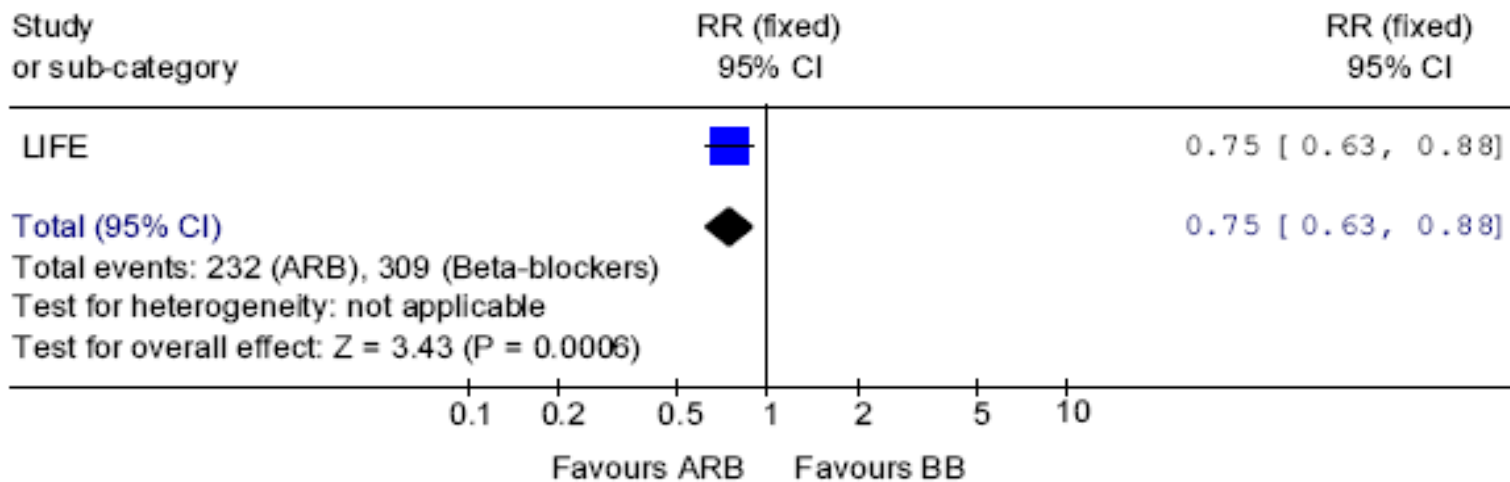
Comparison: 03 ARBs versus beta-blockers  
Outcome: 02 Myocardial infarction



# BB / ARB

Comparison: **03 ARBs versus beta-blockers**

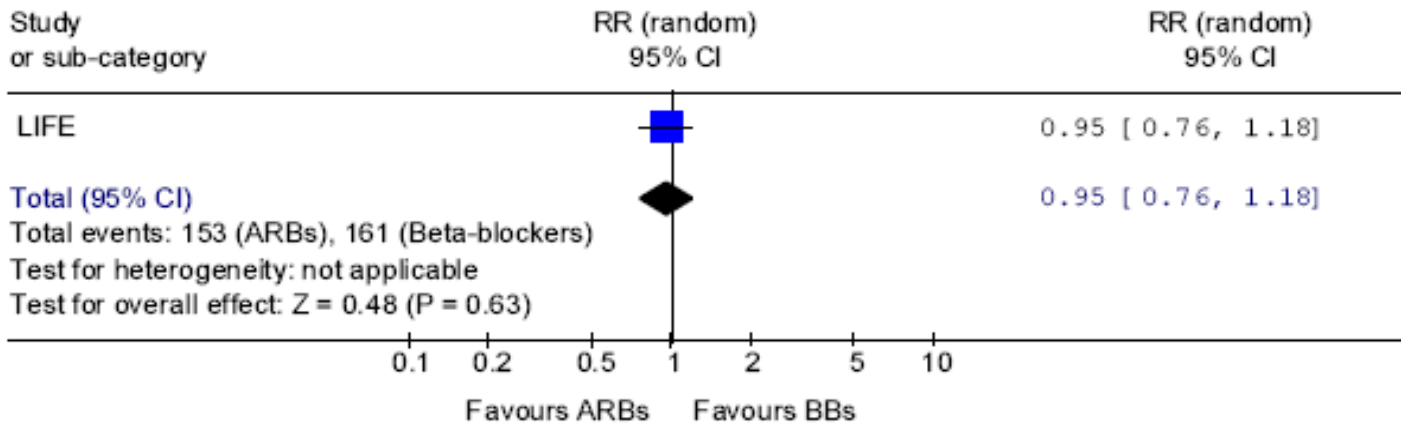
Outcome: **03 Stroke**



# BB / ARB

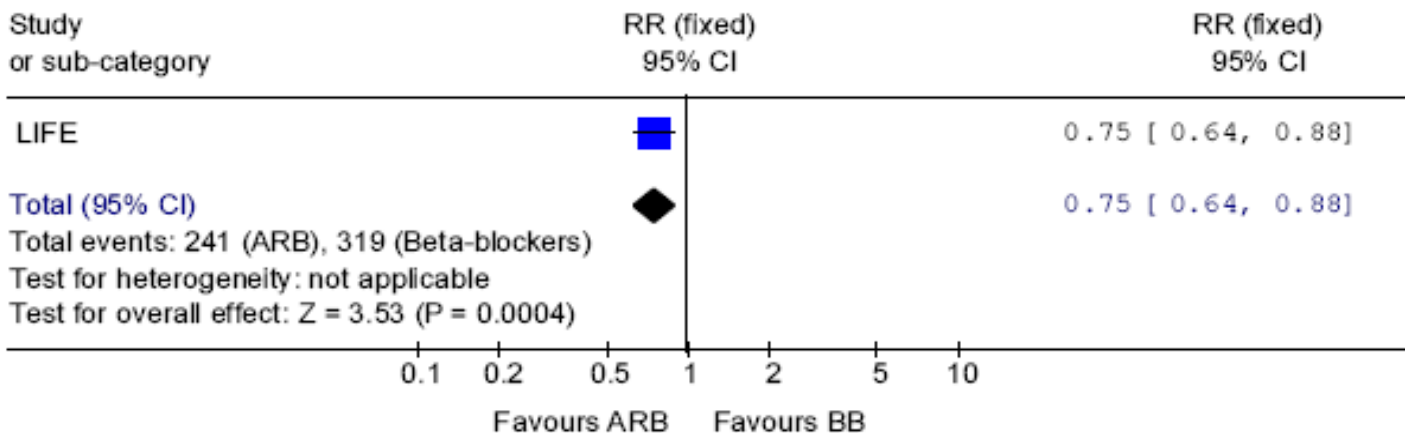
Comparison: 05 ARBs versus beta-blockers

Outcome: 05 Heart failure



Comparison: 03 ARBs versus beta-blockers

Outcome: 05 Diabetes



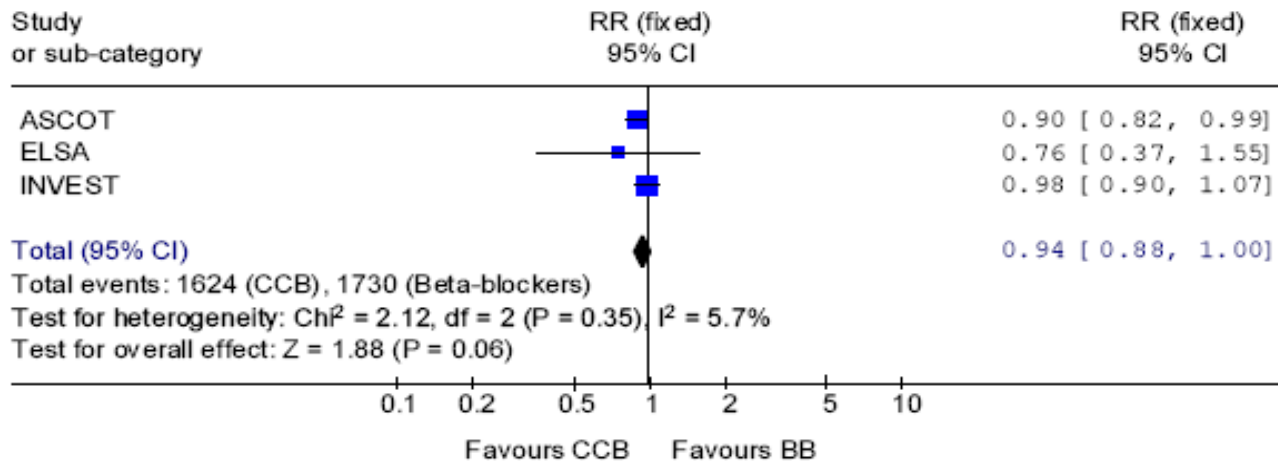
# BB / KKB

AASK 2002	Metoprolol	Calcium channel blocker	150.0/96.0	+2.0/0.0
ELSA 1992	Atenolol	Calcium channel blocker	163.1/101.3	+0.2/-0.1
INVEST 2003	Atenolol	Calcium channel blocker	150.8/87.2	+0.3/+0.2
ASCOT 2005	Atenolol	Calcium channel blocker	164.0/94.7	+1.6/+1.8

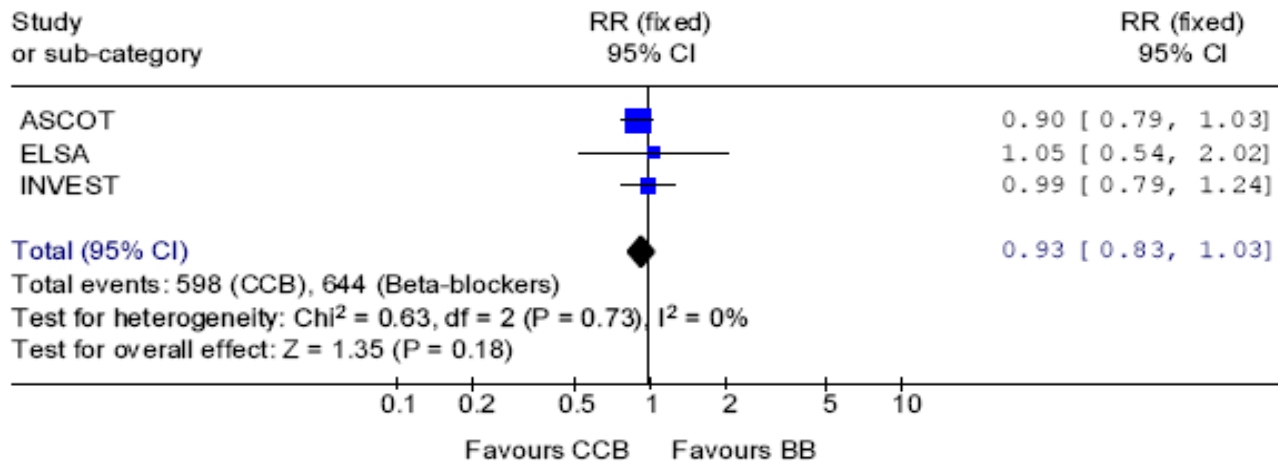
Cochrane Database of Systematic Reviews, Issue 1, 2009

# BB / KKB

**Comparison:** 06 Calcium-channel blockers versus beta-blockers  
**Outcome:** 01 Mortality



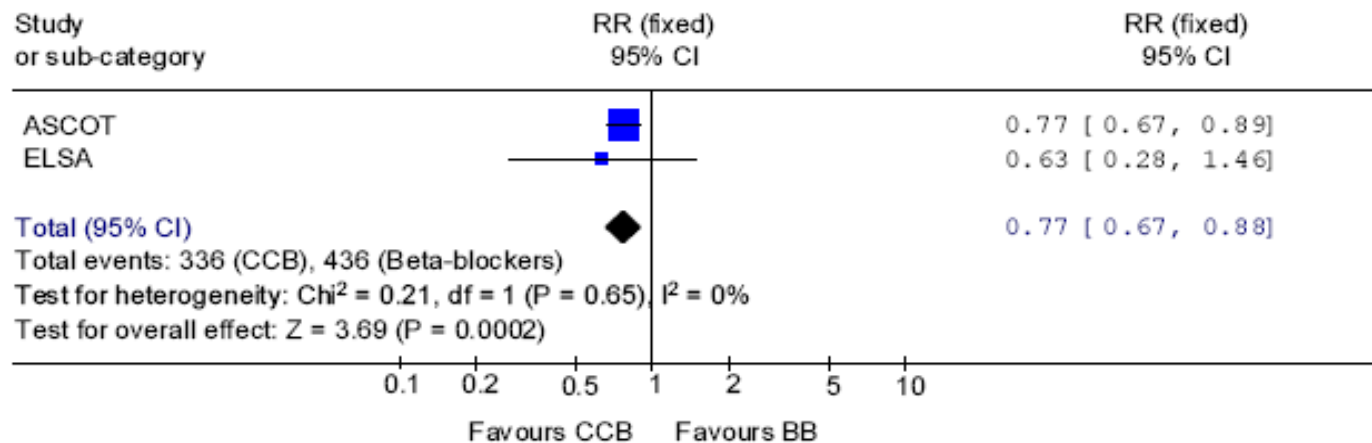
**Comparison:** 06 Calcium-channel blockers versus beta-blockers  
**Outcome:** 02 Myocardial infarction (including silent MI)



# BB / KKB

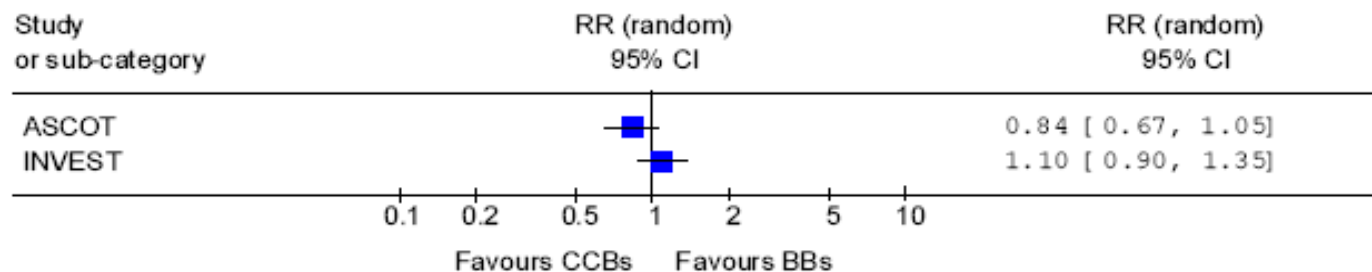
**Comparison:** 06 Calcium-channel blockers versus beta-blockers

**Outcome:** 04 Stroke



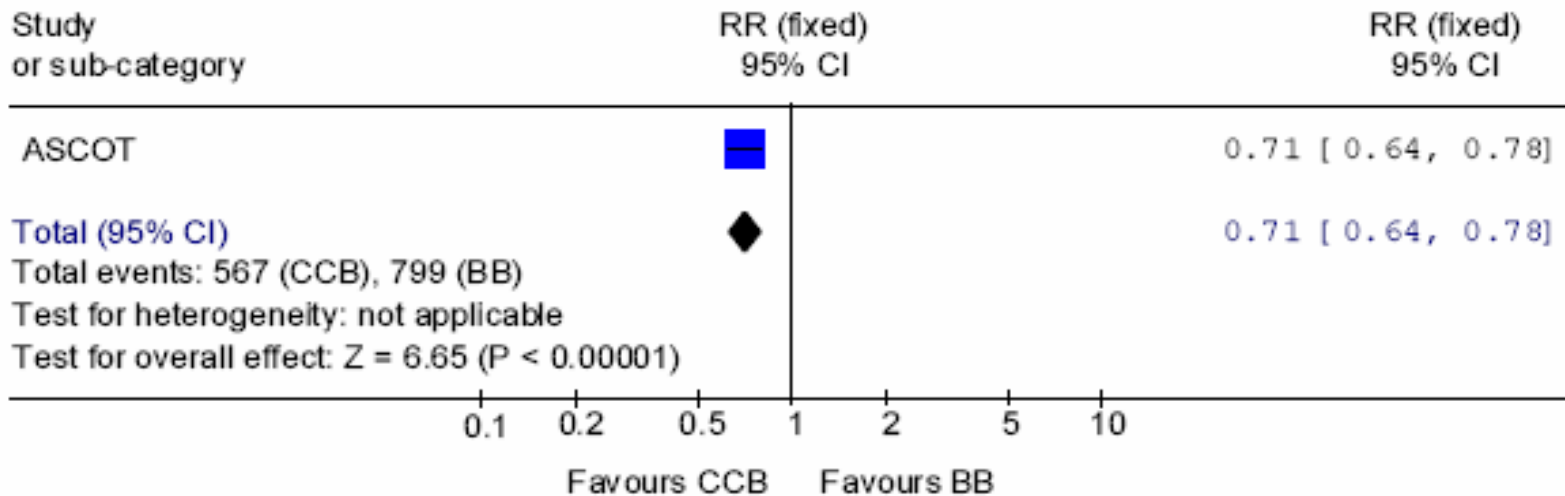
**Comparison:** 06 Calcium-channel blockers versus beta-blockers

**Outcome:** 06 Heart failure



# BB / KKB

Comparison: **06 Calcium-channel blockers versus beta-blockers**  
Outcome: **06 Diabetes**



# Perioperativ BB kullanımı

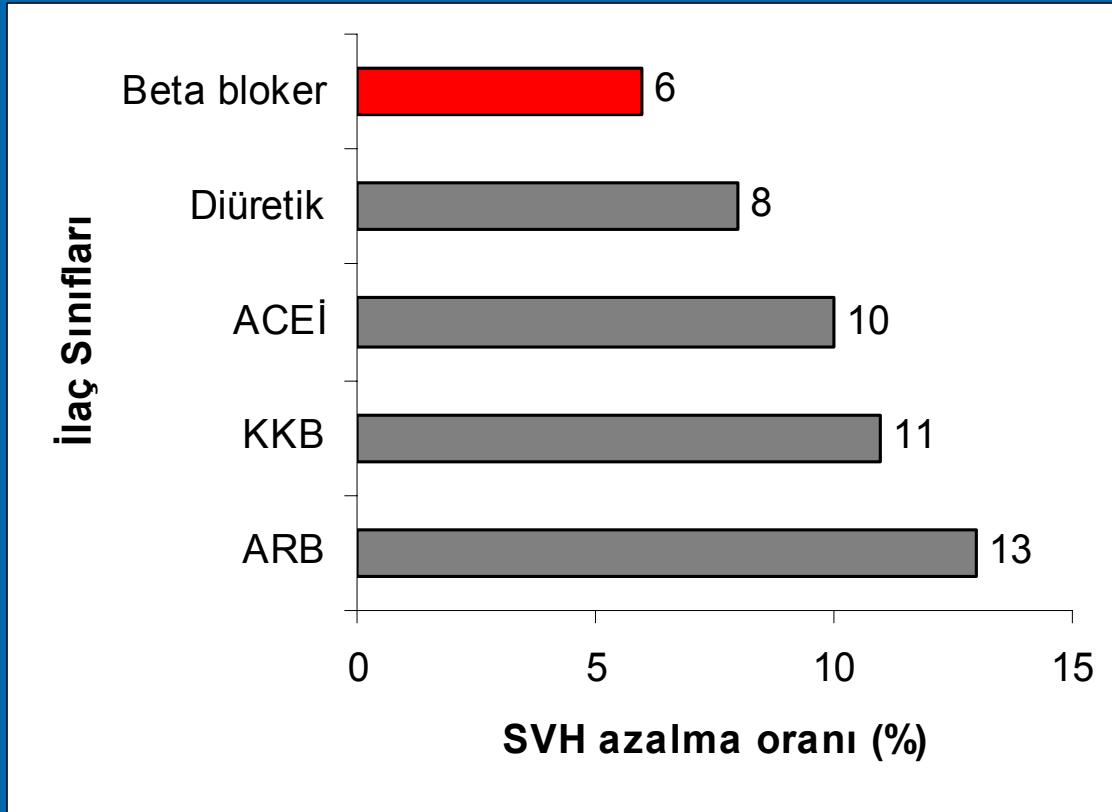
- BB kullanan her 1000 hastada;
  - MI'dan koruma: 15
  - Ağır İnme: 5
  - Ölüm: 8



POISE trial, Lancet 2008



# Sol ventrikül hipertrofisini geriletme



Klingbeil, Am J Med, 2003

# SONUÇ

Veriler beta blokerlerin “komplike olmayan hipertansiyonda” “ilk seçenek” ilaç olmasını desteklemiyor !

# Dayanak

- Plaseboya göre KAH için primer önleyici etkisi yok.
- Diğer ilaçlarla kıyaslandığında KB düşürücü etkisi geride!
- İnme ve toplam mortalite diğer sınıflara göre anlamlı yüksek
- Hedef organ hasarında düzelme oranı düşük
- Yan etkileri daha fazla

# Kanıtlar yetersiz!

- Gençlerdeki etkinlik?
- Farklı beta bloker ilaçlar için de sonuç aynı mı?  
(Özellikle 3. jenerasyon?)

## 3. Jenerasyon BB farkı

Karvedilol

Nebivolol

Arter Kan Basıncı = Kalp debisi x Toplam periferik direnç

Geleneksel  
BB

3. jenerasyon  
BB  
“Karvedilol”  
“Nebivolol”

“NO” salınım artışı  
 $\alpha_1$ -blokaj

||

ACEİ / KKB

# Diyabetik hipertansiflerde

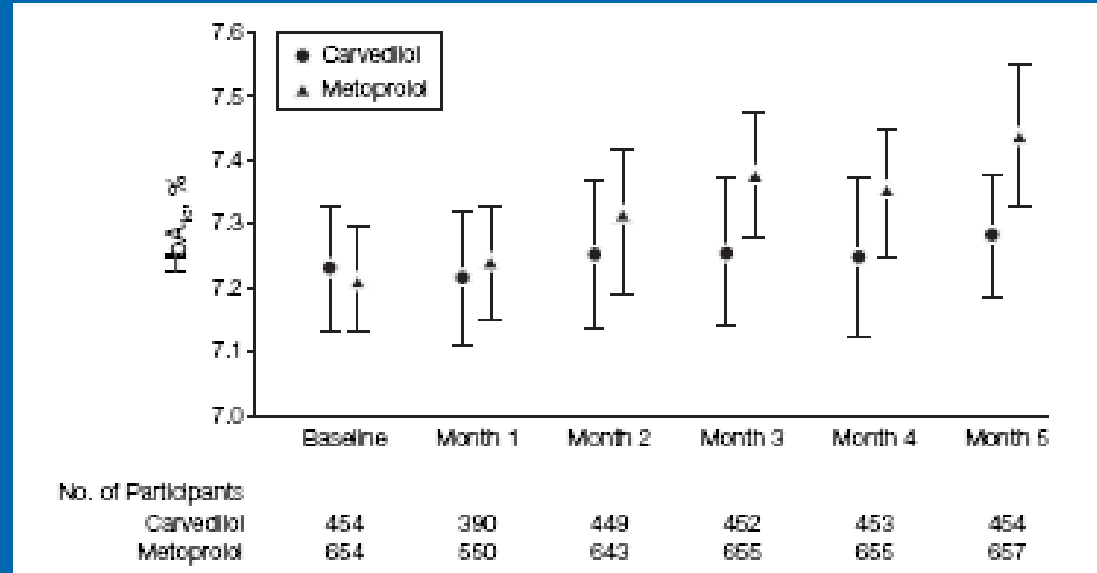
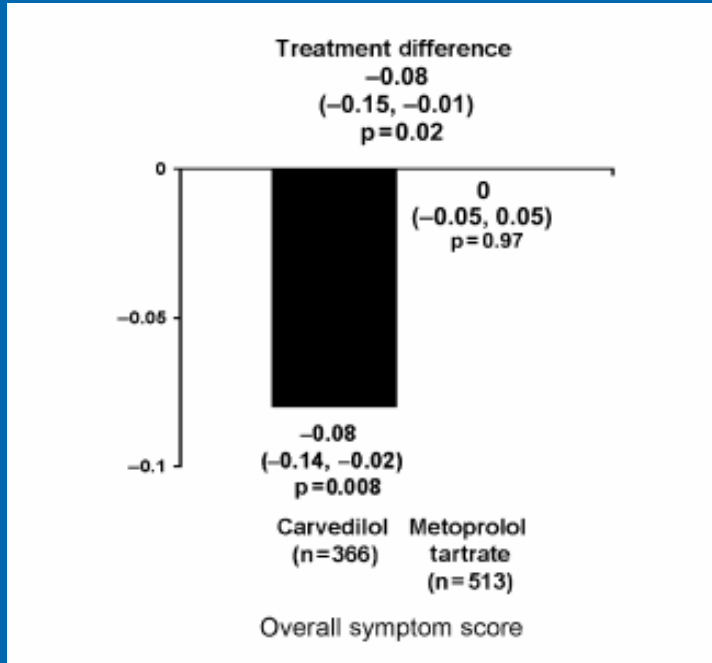
## Karvedilol > Diğer kardiyoselektif BB?

KARVEDİLOL ÜSTÜN!  
Etkinlik↑  
Yan etki profili↓

Fardoun, Pharmacotherapy, 2006

# Diyabetik hastalar: Karvedilol > Metoprolol

## Glisemi kontrolü ve semptomlar



GEMINI study, JAMA, 2004

GEMINI study, Diabetes, Obesity and Metabolism, 2007



# Yeni DM gelişimi

## Karvedilol > Geleneksel BB

- Karvedilol alanlarda %22 ↓

Poole-Wilson: COMET trial, Lancet, 2003

# Beta blokerlerin KY'de karşılaştırılması

## Karvedilol > Diğer BB

Type of $\beta$ Blocker	Rehospitalization for HF Adjusted Hazard Ratio (95% Confidence Interval)*
Atenolol	Reference
Metoprolol tartrate	0.95 (0.85–1.06)
<u>Carvedilol</u>	<u>0.92 (0.74–1.14)</u>
Other $\beta$ blocker	1.31 (1.09–1.57)
No $\beta$ blocker	1.12 (1.03–1.22)

Go, Am J Cardiol, 2007

# Hipertansif nefropatili hastalarda

Karvedilol > Metoprolol

- Mikroalbuminüriye transferi daha çok azaltır (%6 / %10)
- Uzun dönem etki?

GEMINI study, JAMA, 2004

# Kalp yetmezlikli diyaliz hastalarında beta bloker

Journal of the American College of Cardiology  
© 2003 by the American College of Cardiology Foundation  
Published by Elsevier Inc.

Vol. 41, No. 9, 2003  
ISSN 0735-1097/03/\$30.00  
doi:10.1016/S0735-1097(03)00241-9

## CLINICAL RESEARCH

## Clinical Trials

### Carvedilol Increases Two-Year Survival in Dialysis Patients With Dilated Cardiomyopathy

A Prospective, Placebo-Controlled Trial

Gennaro Cice, MD,\* Luigi Ferrara, MD,\* Antonello D'Andrea, MD,\* Salvatore D'Isa, MD,\*  
Attilio Di Benedetto, MD,† Antonio Cittadini, MD,‡ Pina Elvira Russo, MD,\* Paolo Golino, MD, PhD,\*  
Raffaele Calabrò, MD\*

*Naples, Italy*

	Placebo (n = 56)	Carvedilol (n = 58)	Hazard Ratio (95% CI)	P Value
<b>Secondary End Points</b>				
All-cause mortality	41 (73.2%)	30 (51.7%)	0.51 (0.32–0.82)	< 0.01
All-cause hospital admission	33 (58.9%)	20 (34.5%)	0.44 (0.25–0.77)	< 0.005
All cardiovascular deaths	38 (67.9%)	17 (29.3%)	0.32 (0.18–0.57)	< 0.0001
Non-fatal myocardial infarction	1 (1.8%)	0 (0%)	0.81 (0.61–1.34)	0.31
Combined end point	39 (69.6%)	17 (29.3%)	0.76 (0.47–1.22)	0.22
Permanent treatment withdrawals	15 (26.8%)	17 (29.3%)	1.12 (0.84–1.24)	0.68

# Yaşlılarda BB kullanımı

- Kalp hızı azalır
- Kalp kasılma gücü azalır
- $\beta$ -reseptör uyarımı azalır

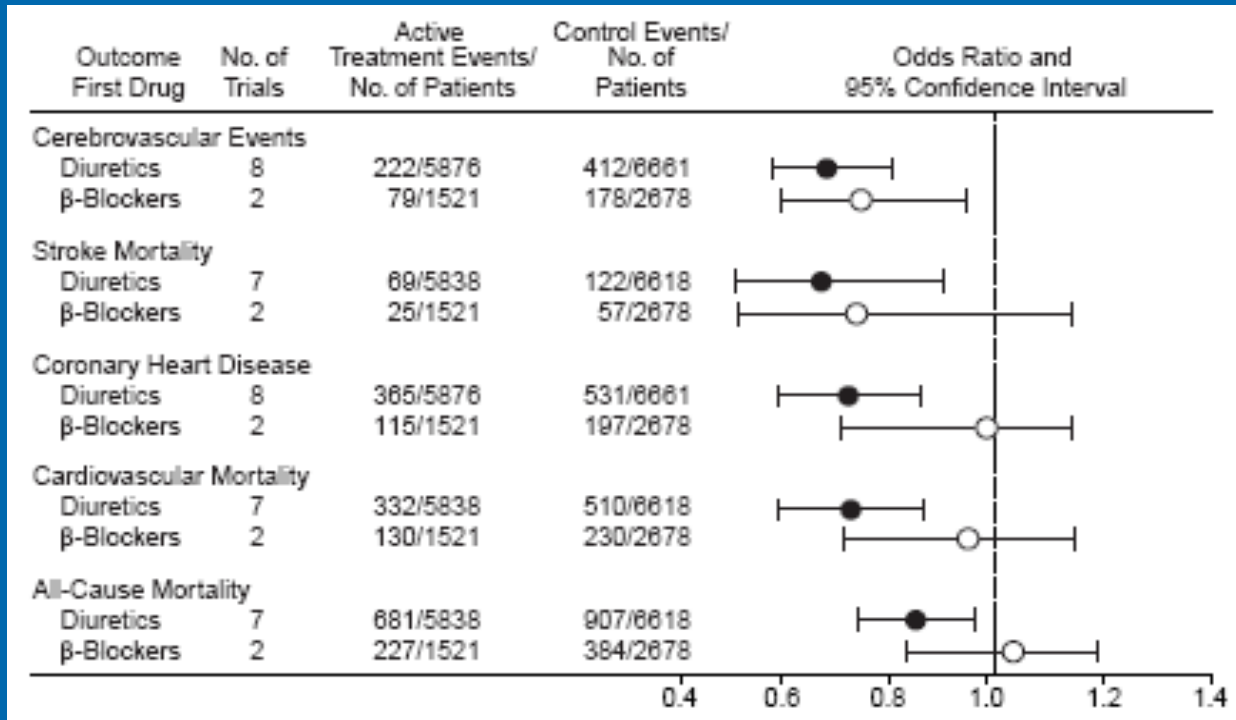


$\beta$ -blokaj etkisi

Fleg, J Appl Physiol. 1994

# Yaşlılarda beta bloker?

>65 yaş, n=16000, 1 yıl



Messerli, JAMA, 1998

**Karvedilol ?**

**Nebivolol (Ortostatik KB ↓ yok!) ?**

# Yan etki

## Karvedilol / Geleneksel BB

**Avantajlı**

Diyabetes Mellitus  
Periferik arter hastalığı  
Dislipidemi

**Fark yok!**

Yorgunluk  
Bronkospazm  
Depresyon  
Empotans

Staphylas, Vascular Health and Risk Management, 2008  
Saraphidis&Bakris, QJM, 2006  
Messerli&Grossman, Am J Cardiol, 2004

# Karvedilol mü Nebivolol mü?

- Hipertansiyon çalışması yok!
- Kalp yetmezliği:
  - Karvedilol > Nebivolol?

Patrianakos, Am Heart J, 2005  
Lombardo, Am J Cardiovasc Drugs, 2006



## † 2007 Guidelines for the management of arterial hypertension

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

*Box 10 Position statement: Choice of antihypertensive drugs*

**ATENOLOL / METOPROLOL !!!**

The main benefits of antihypertensive therapy are due to lowering of BP *per se*.

- Five major classes of antihypertensive agents – thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and  $\beta$ -blockers – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination.  $\beta$ -blockers, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes.
- Because in many patients more than one drug is

**Hangi durumlarda kullanalım?**

# Kanıt durumu

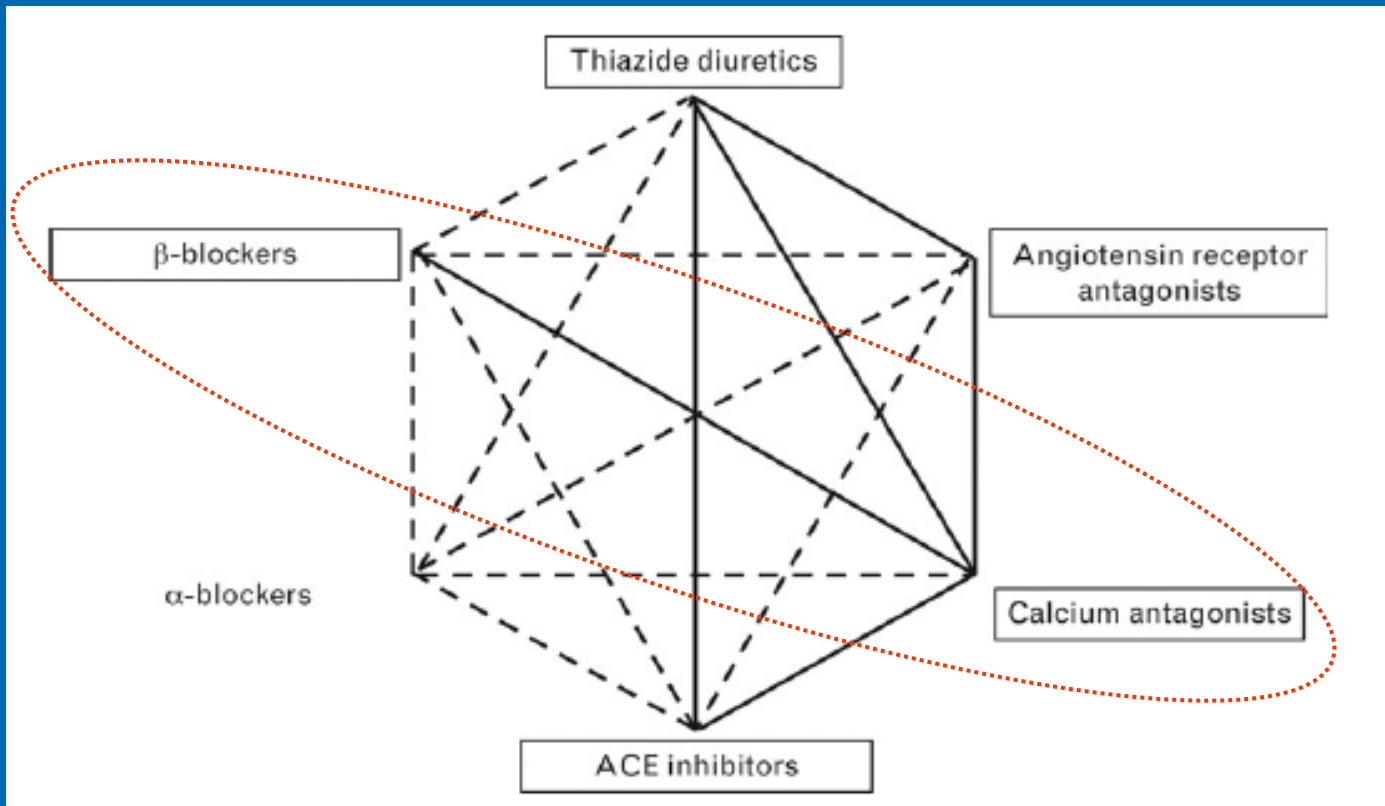
Durum	Zayıf/Yok	Kanıt var	Güçlü kanıt
Hipertansiyon	☹️		
<b>Kalp yetersizliği</b>			😊
Akut koroner sendrom		☹️	
<b>Post-MI</b>			😊
Stabil angina		☹️	
Perioperatif		☹️	
Hipertrofik KMP		☹️	

# Kontrendikasyon!

- Astım
- AV Blok

ESH/ESC Guideline 2007

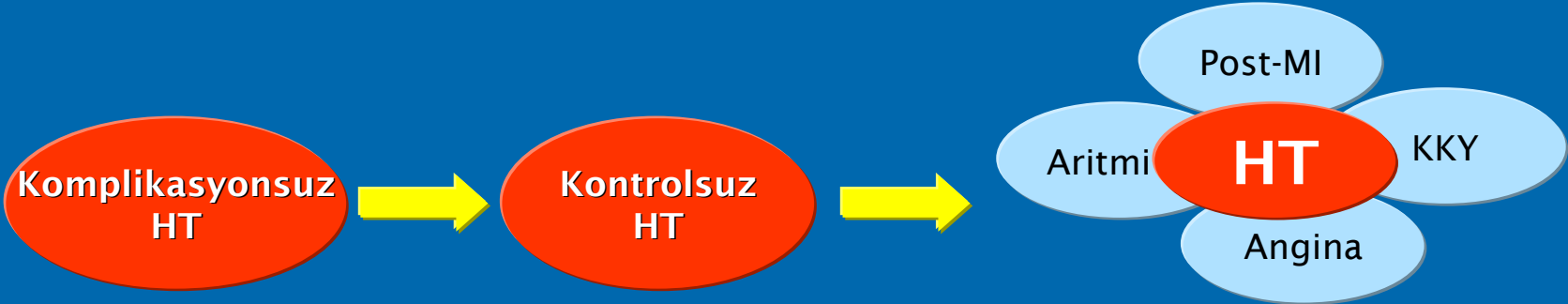
# Önerilen tek kombinasyon!



ESH/ESC Guideline 2007

**β-GEN TÜRK**

# ÖZETLE...



%0

KLİNİK KANIT DÜZEYİ

%100

# ÖZETLE...

- Kullanılacaksa:
  - 3. jenerasyon BB tercih edilmeli