

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
 - α -, β -reseptör
- 1950-1960: c-AMP: ikinci haberci
- 1960-1970:
 - **Propranolol**: ilk β -bloker
 - β_1 - β_2 subtipleri



James Black
1988 Nobel Tıp Ödülü
“Propranolol keşfi”

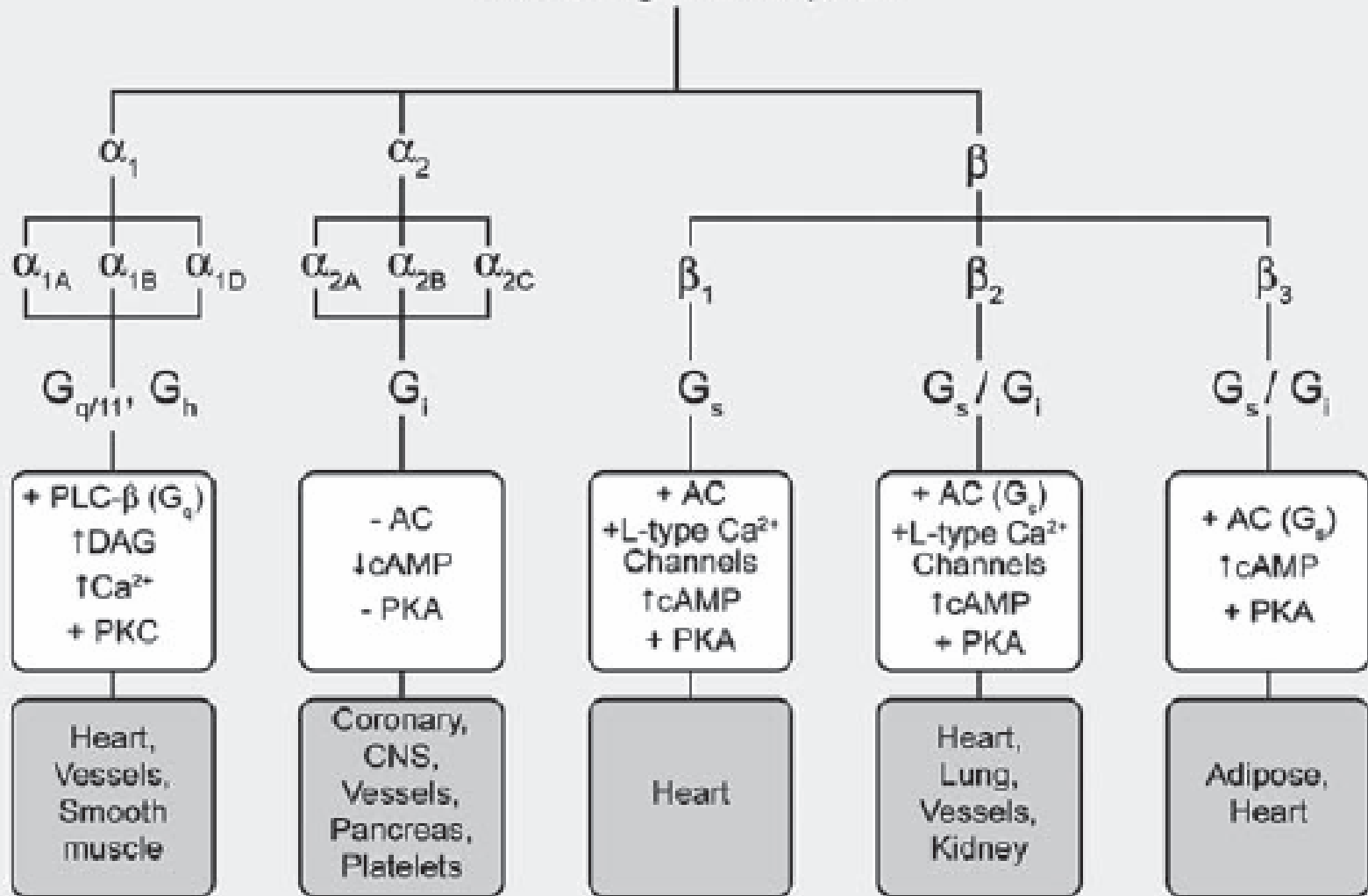
Geçen yüzyılda...

- 1970-1980: α_1 - α_2
- 1980-1990:
 - α_{1A} , α_{1B}
 - α_{1A} , α_{1B} , α_{2C}
 - β_3 klonlandı
- 1990-2000:
 - α_{1D} klonlandı
 - “Knock-out” modeller
 - Polimorfizmler
 - β_4 ?

1988



Adrenergic Receptors



Etkinliđi belirleyen...

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

β -reseptör aracılı etkiler...

Doku	Fonksiyon	Reseptör
Sempatik nöron	E/NE salınımı	β_2
Kalp	Kronotropi, İnotropi, dromotropi, batmotropi	$\beta_1 > \beta_2 > \beta_3$
Damar	Relaksasyon	$\beta_2 > \beta_1$
Böbrek	Renin salınımı	β_1
Karaciğer	Glikojenoliz	β_2
Pankreas	İnsülin	β_2

β -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 ₂ taşınımı ↑ O ₂ harcanmasını ↓
Kalp yetmezliği	Ani ölümden ↓

Beta blokerlerin sınıflandırılması...

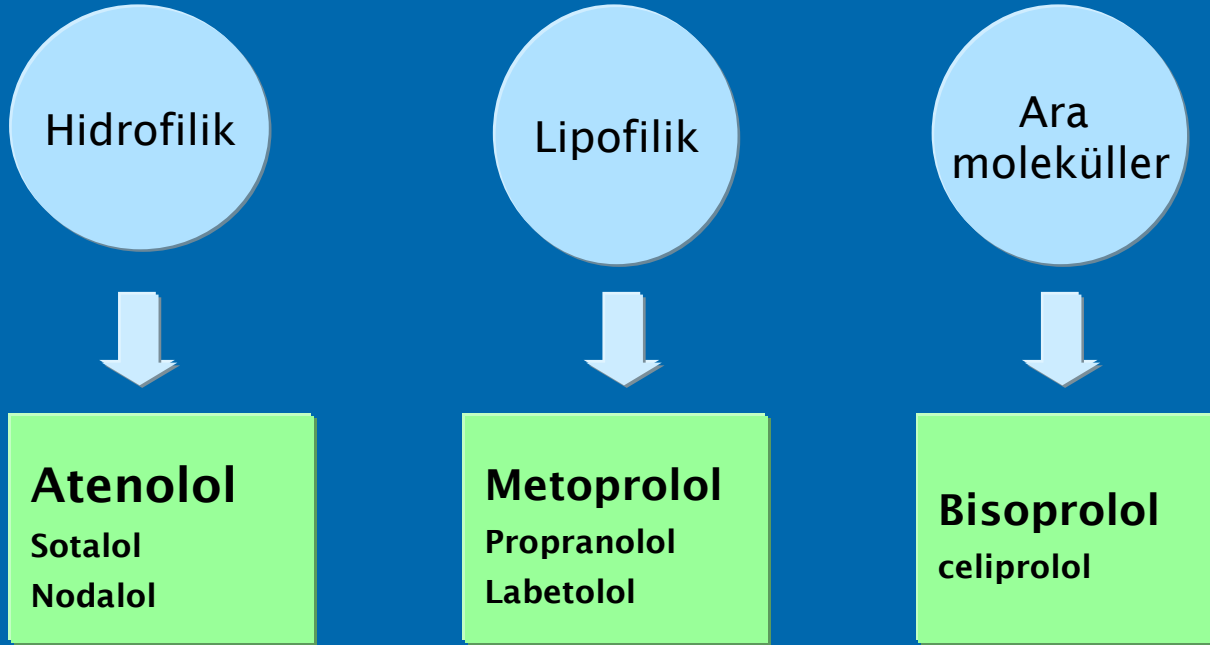
Seicilik

- β_1 : Kalp
- β_2 : Bronş, periferik damar, pankreas

- Nebivolol (β_1)
- Propranolol (non-selektif)

- β_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 β 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

- **α -antagonist:** Karvedilol, Labetolol
- **NO salınımı sağlayan:** Nebivolol
- **Vazodilatör ve antioksidan:** Karvedilol
- **K⁺-kanal antagonisti:** Sotalol

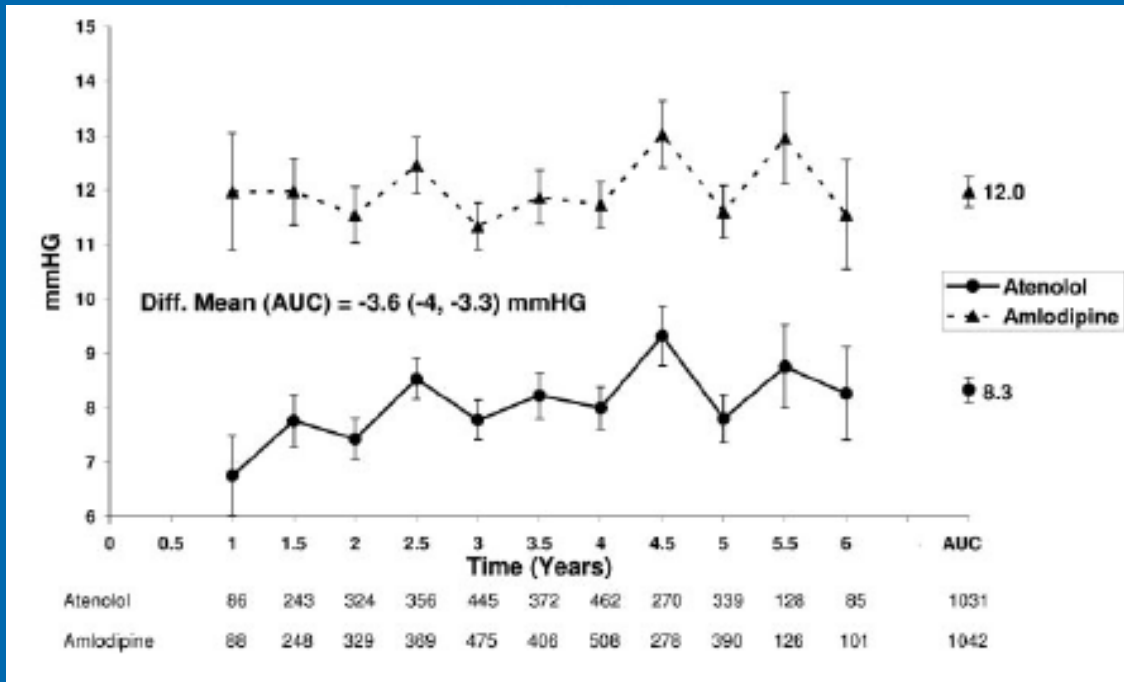
Hipertansif Hastalarda Klinik Kullanım

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

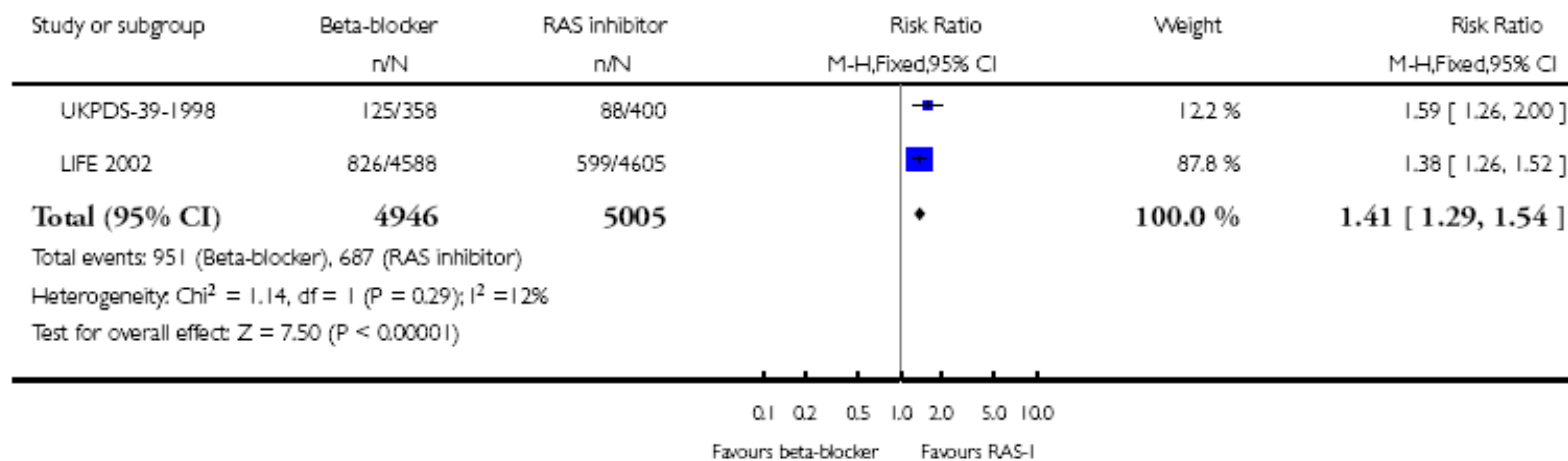
Yan etki nedeniyle ilacı bırakma

RAS inhibitörü / BB

Review: Beta-blockers for hypertension

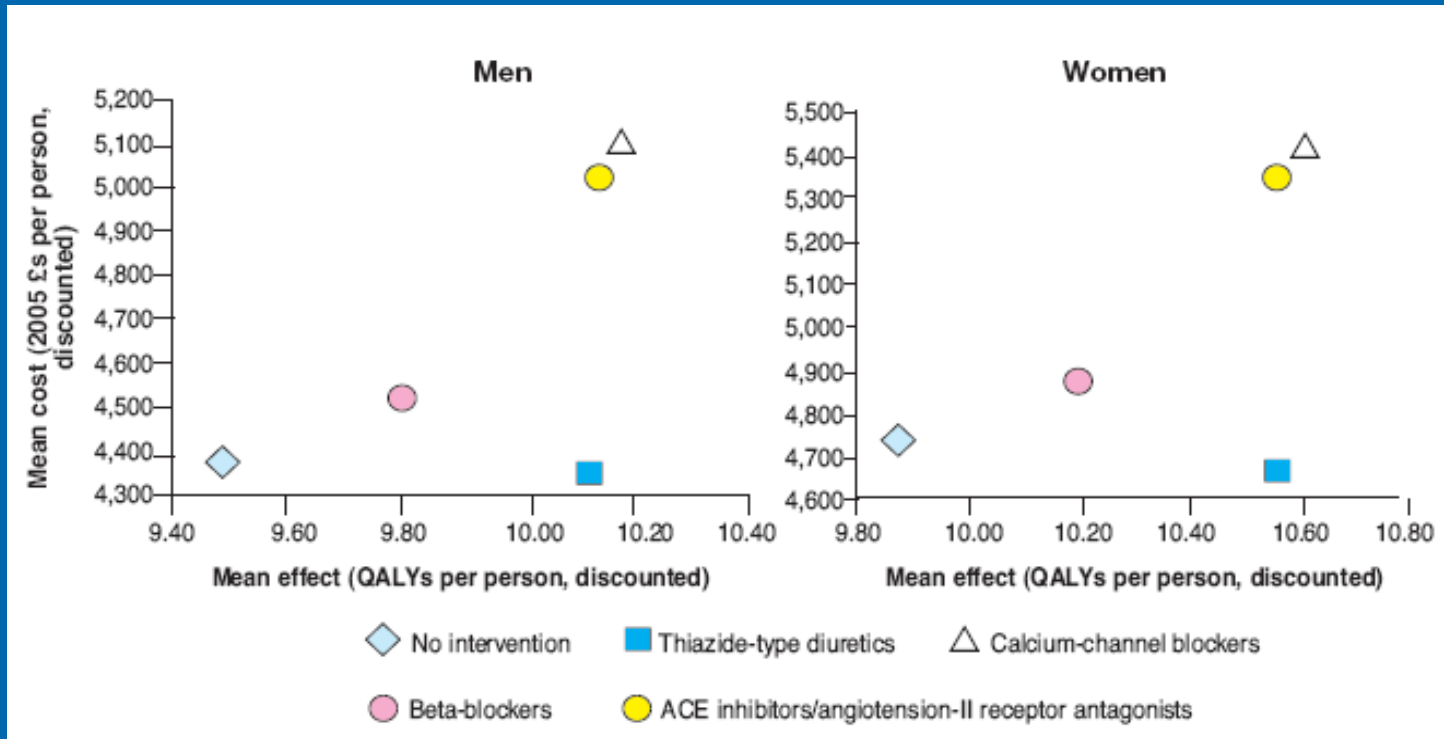
Comparison: 4 Beta-blocker versus RAS inhibitor

Outcome: 6 Withdrawal due to adverse effect



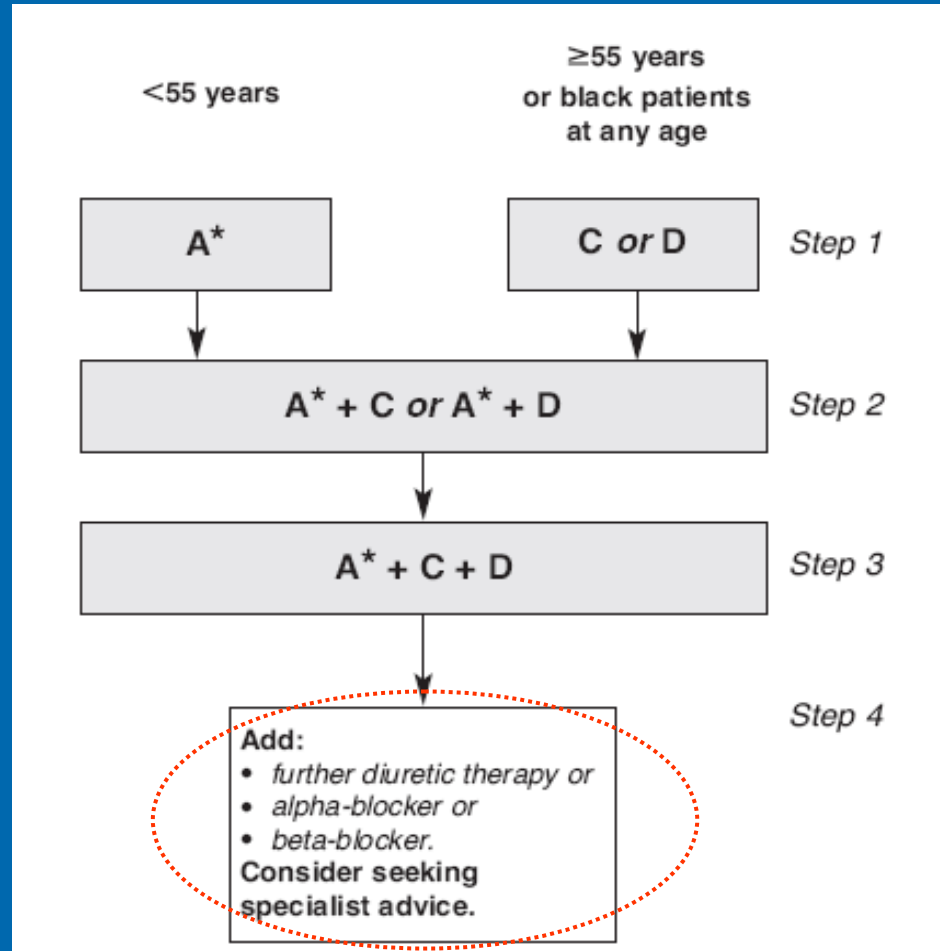
Cochrane Database of Systematic Reviews, Issue 1, 2009

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 β -blockers – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. β -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



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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)
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Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis



Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

Summary

Background: β 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 β blockers.

Methods: The Cochrane Library and PubMed were searched for β 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 β blockers with other antihypertensive drugs. Seven studies (n=27 433) were included in a comparison of β blockers and placebo or no treatment.

Findings: The relative risk of stroke was 16% higher for β blockers (95% CI 4–30%) than for other drugs. There was no difference for myocardial infarction. When the effect of β blockers was compared with that of placebo or no treatment, the relative risk of stroke was reduced by 19% for all β 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 β blockers is less than optimum, with a raised risk of stroke. Hence, we believe that β 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

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67573-3

See Comment page 1510

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β -bloker



β -bloker

**Diğer antihipertansif sınıflarla
karşılaştırma...**

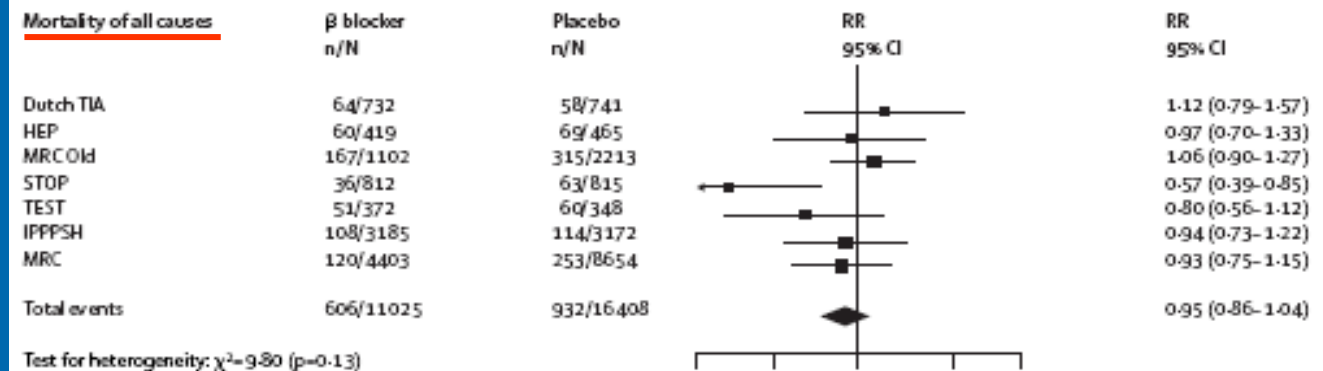
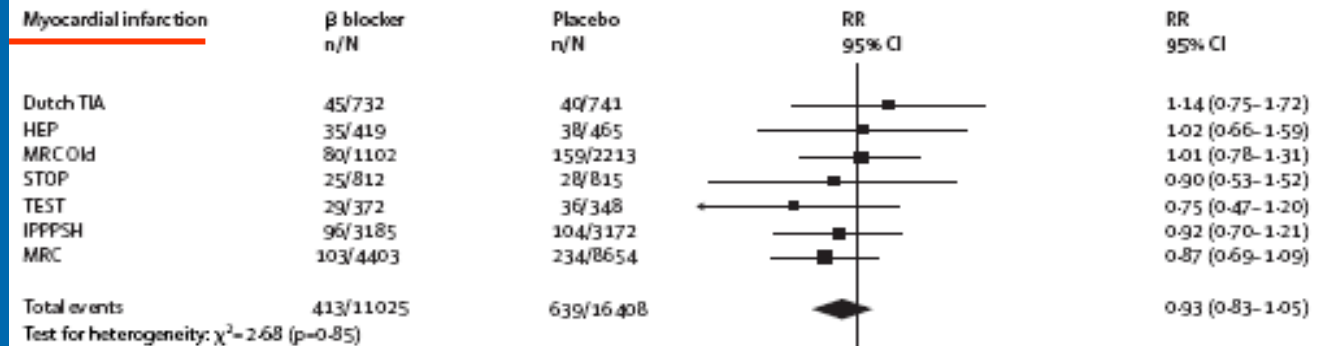
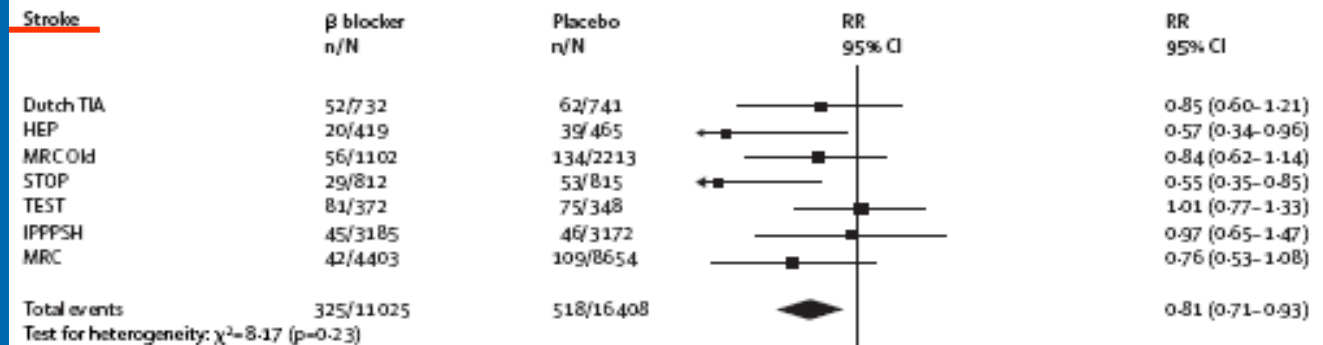
BB / Plasebo

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

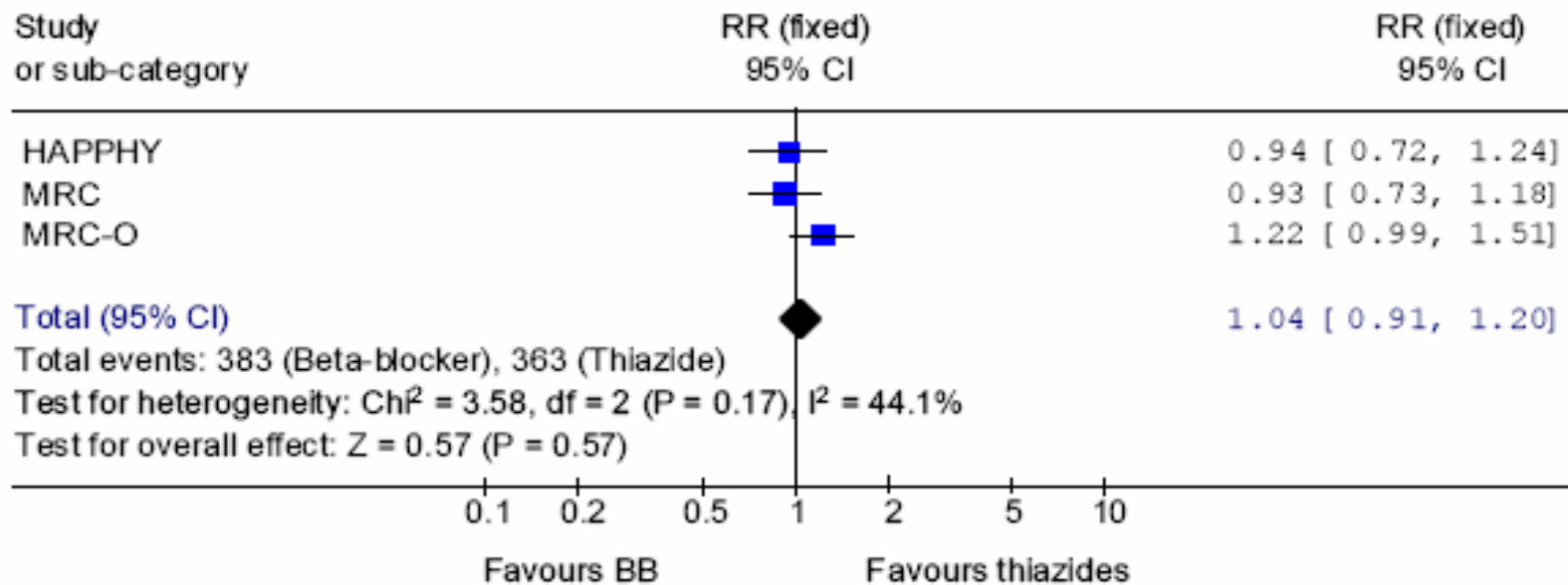
Berglund 1981	Propranolol	Diuretic	174.0/105.5	-4.0/+2.0
VA COOP 1982	Propranolol	Diuretic	146.3/101.5	+7.0/+1.6
MRC 1985	Propranolol	Diuretic	162.0/98.5	+3.5/+1.0
HAPPHY 1987	Atenolol or metoprolol or propranolol	Diuretic	166.0/107.9	0.0/-1.0
MRCOA 1992	Atenolol	Diuretic	184.0/91.0	+1.0/-0.5

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BB / Tiyazid diüretik

Comparison: 01 Beta-blockers versus thiazides

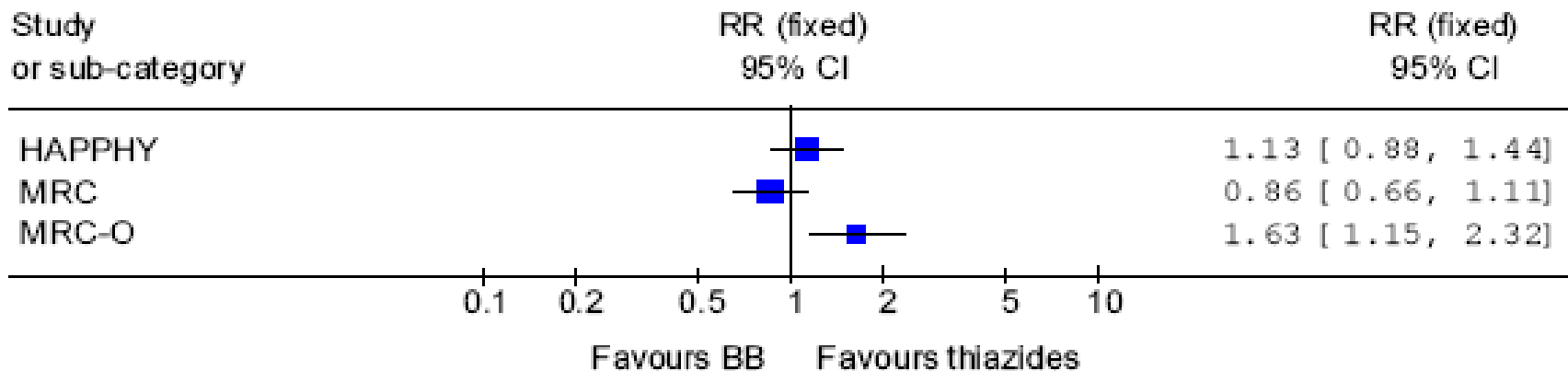
Outcome: 01 Mortality



BB / Tiyazid diüretik

Comparison: 01 Beta-blockers versus thiazides

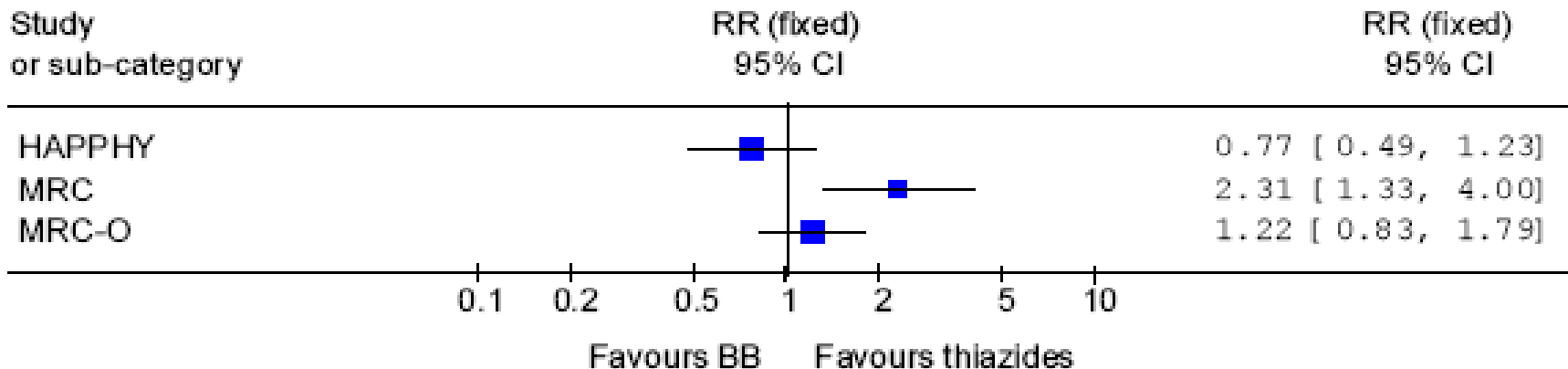
Outcome: 02 Myocardial infarction



BB / Tiyazid diüretik

Comparison: 01 Beta-blockers versus thiazides

Outcome: 03 Stroke



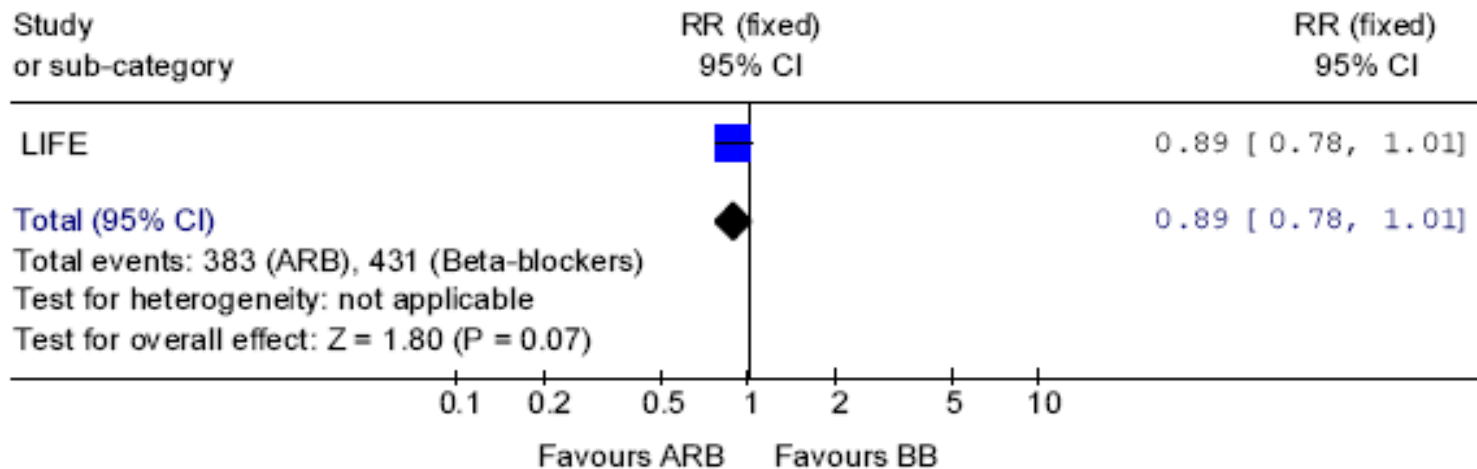
BB / RAS inhibitörleri

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

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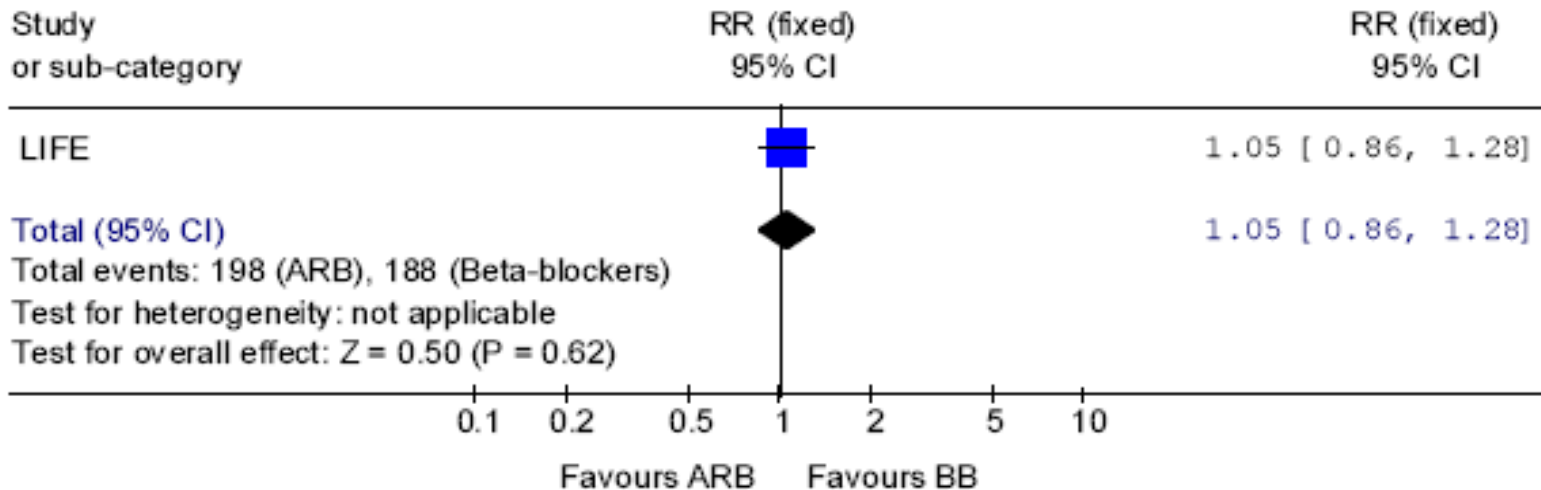
BB / ARB

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



BB / ARB

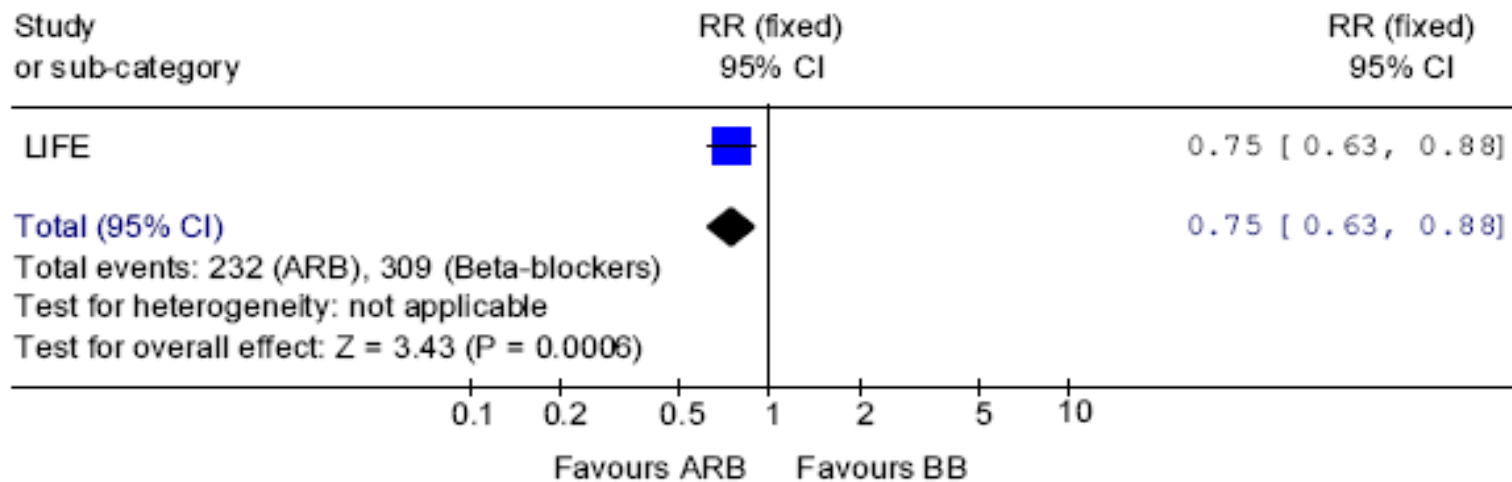
Comparison: 03 ARBs versus beta-blockers
Outcome: 02 Myocardial infarction



BB / ARB

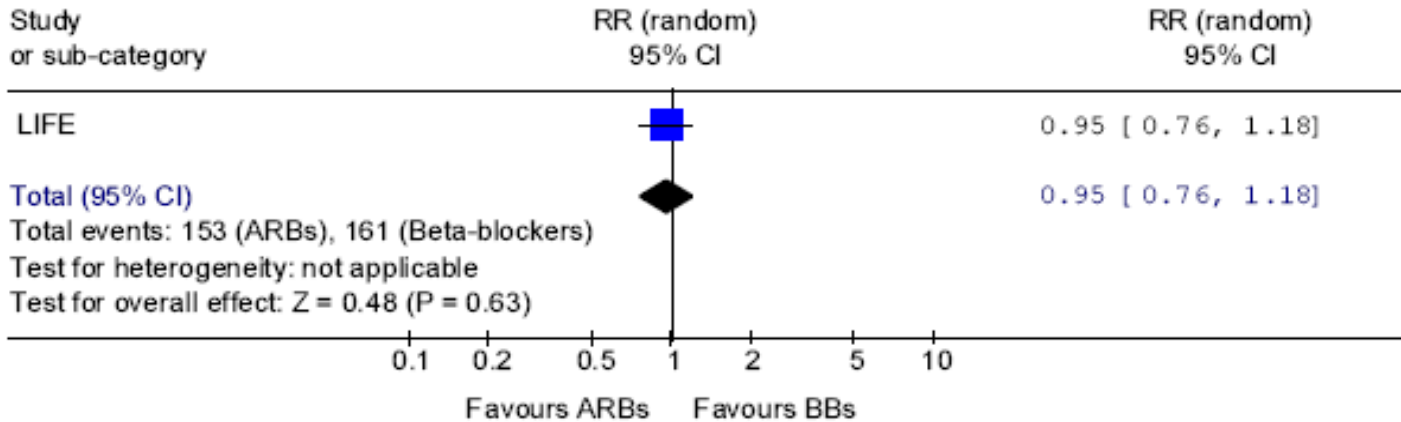
Comparison: **03 ARBs versus beta-blockers**

Outcome: **03 Stroke**

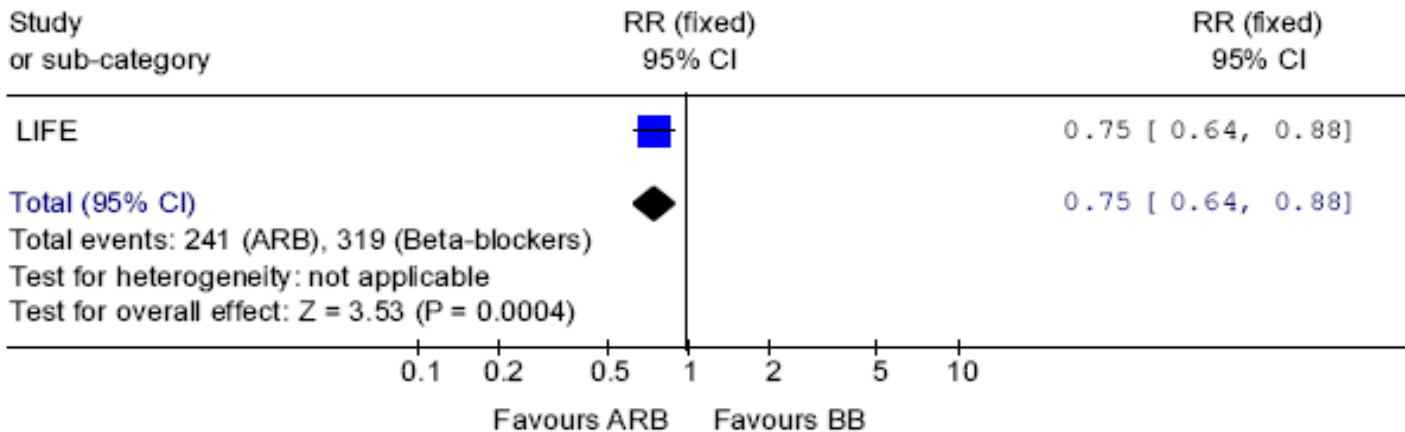


BB / ARB

Comparison: 05 ARBs versus beta-blockers
Outcome: 05 Heart failure



Comparison: 03 ARBs versus beta-blockers
Outcome: 05 Diabetes



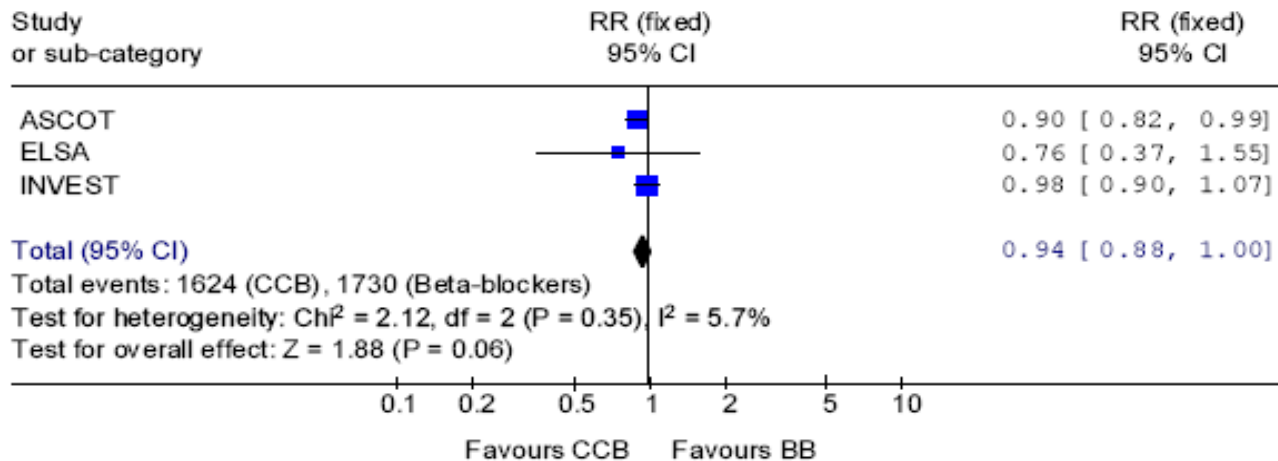
BB / KKB

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

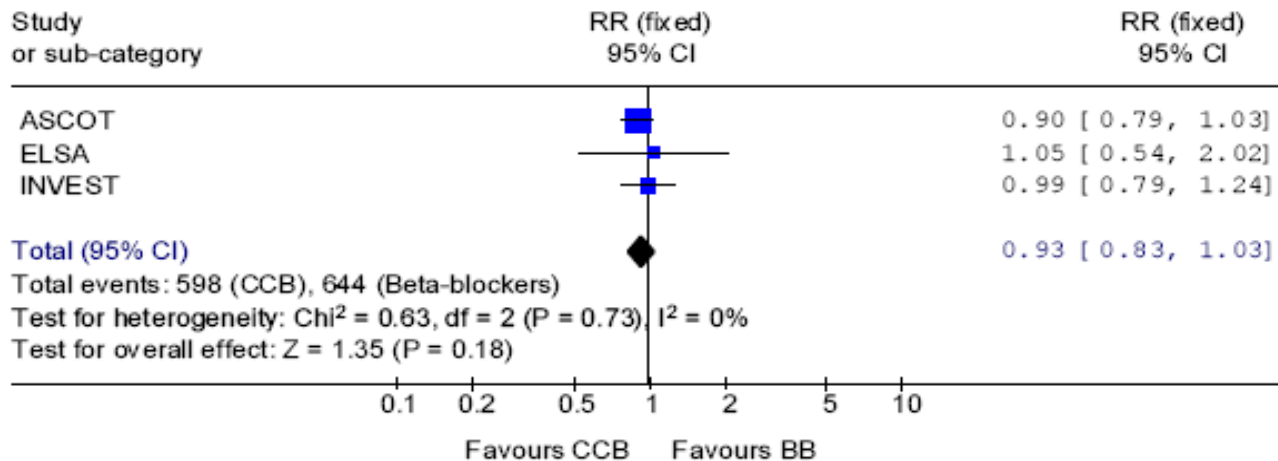
Cochrane Database of Systematic Reviews, Issue 1, 2009

BB / KKB

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



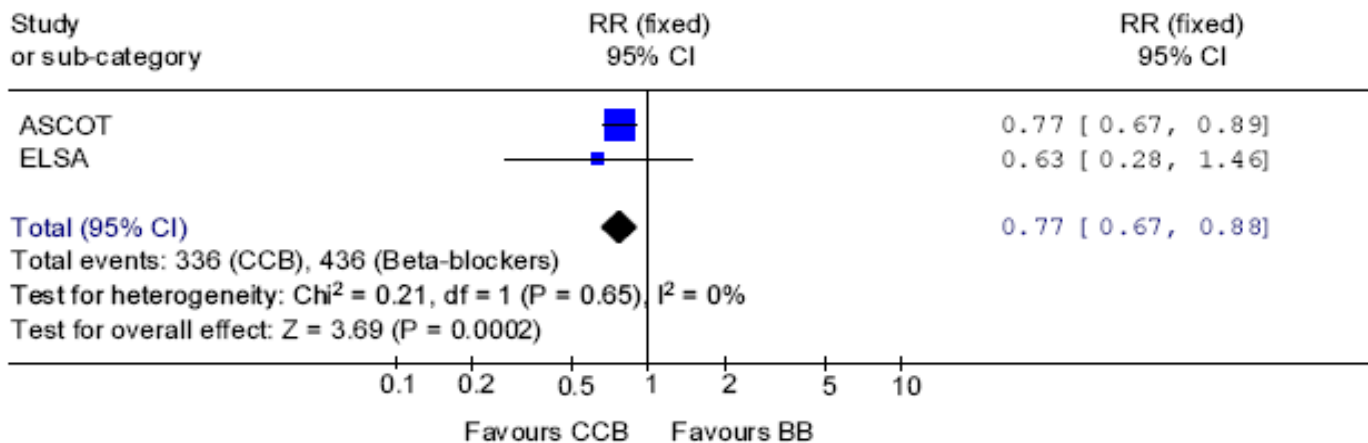
Comparison: 06 Calcium-channel blockers versus beta-blockers
Outcome: 02 Myocardial infarction (including silent MI)



BB / KKB

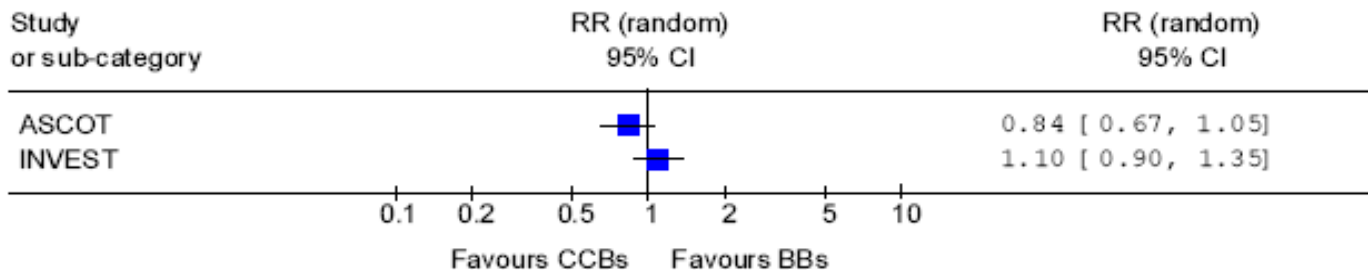
Comparison: 06 Calcium-channel blockers versus beta-blockers

Outcome: 04 Stroke



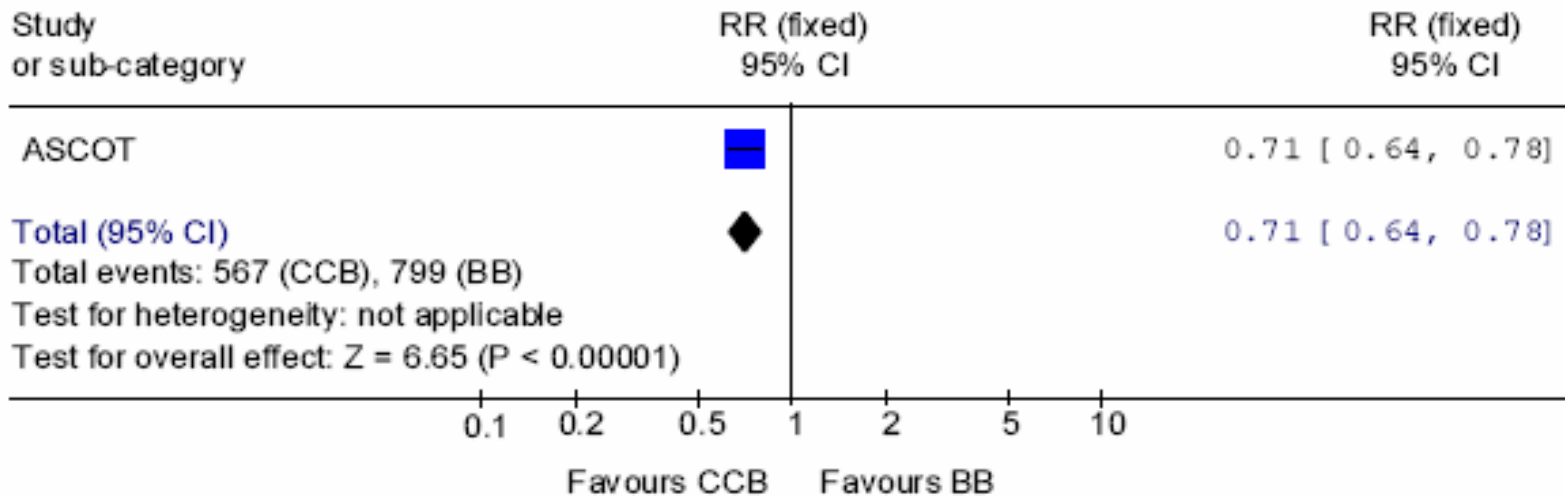
Comparison: 06 Calcium-channel blockers versus beta-blockers

Outcome: 06 Heart failure



BB / KKB

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



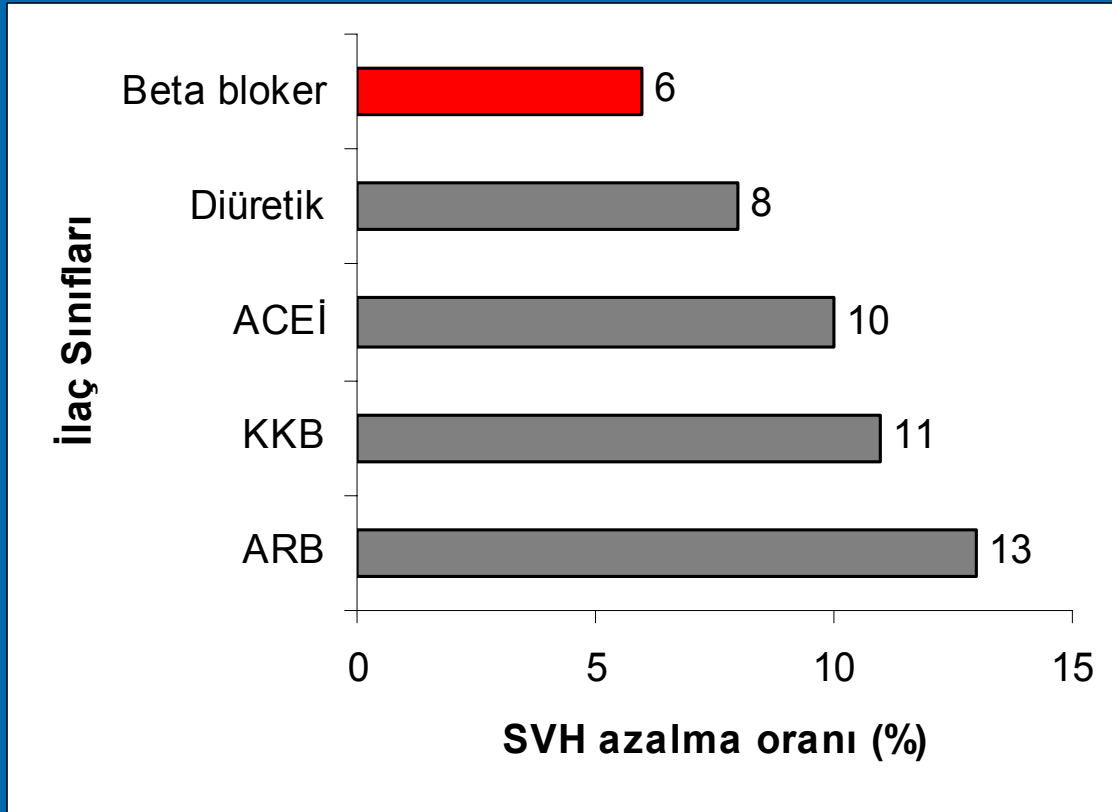
Perioperativ BB kullanımı

- 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
 α_1 -blokaj

||

ACEİ / KKB

Diyabetik hipertansiflerde

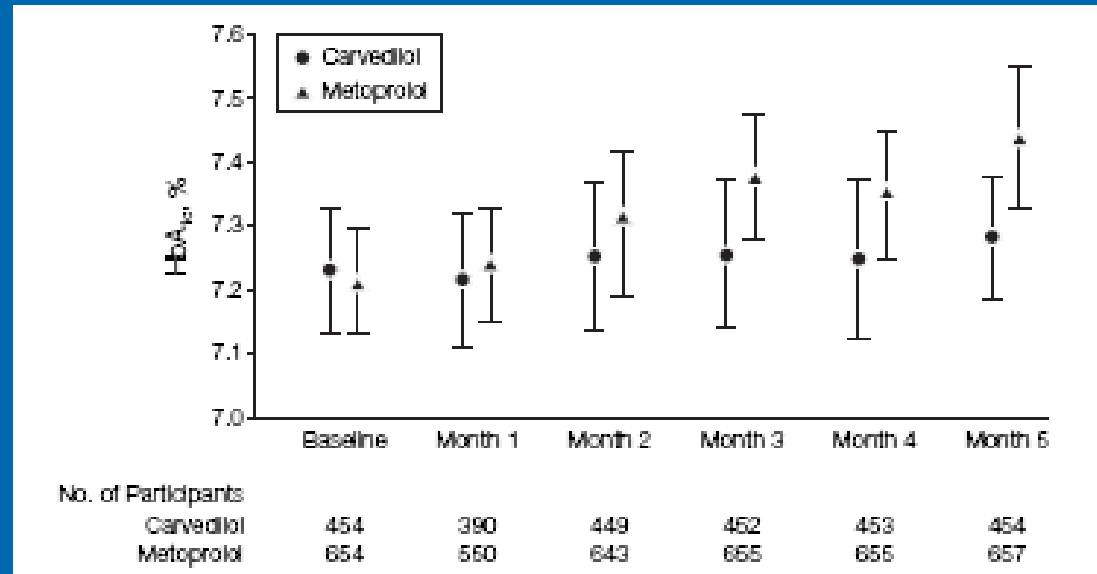
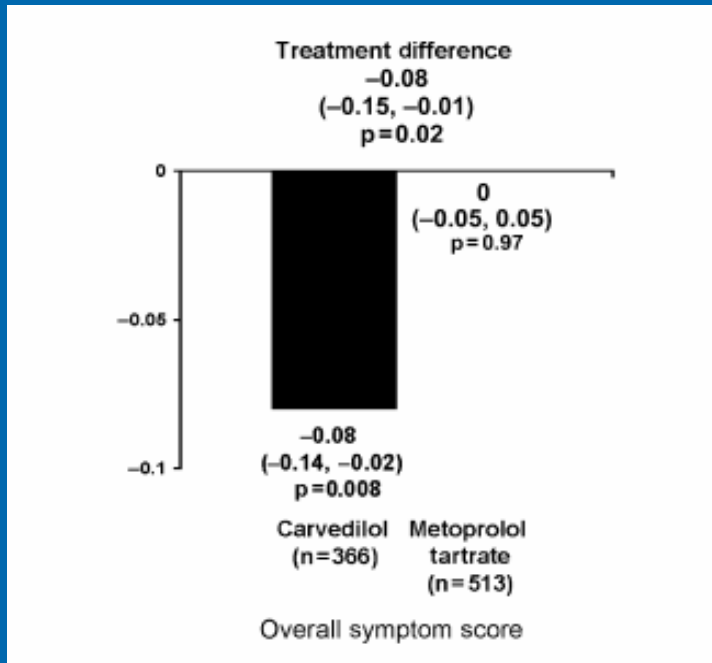
Karvedilol > Diğer kardiyoselektif BB?

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 β 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 β blocker	1.31 (1.09–1.57)
No β 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

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Published by Elsevier Inc.

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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
Secondary End Points				
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
- β -reseptör uyarımı azalır

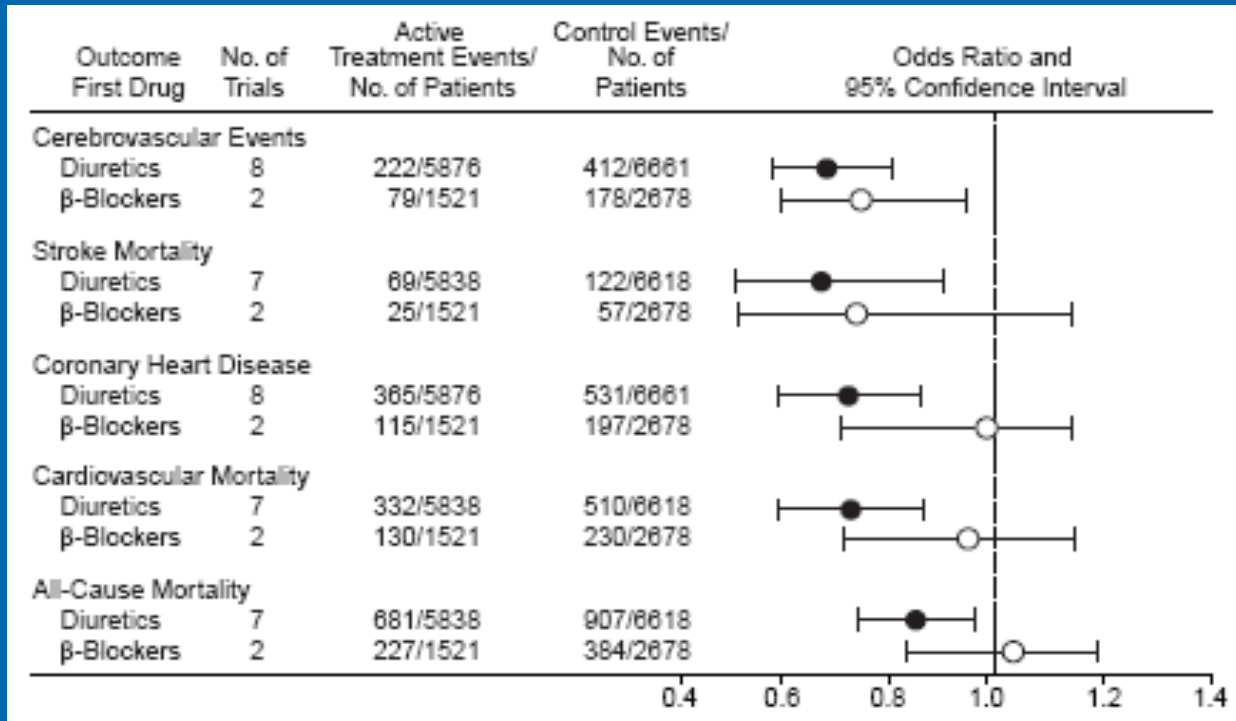


β -blokaj etkisi

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

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 β -blockers – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. β -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

ATENOLOL / METOPROLOL !!!

Hangi durumlarda kullanalım?

Kanıt durumu

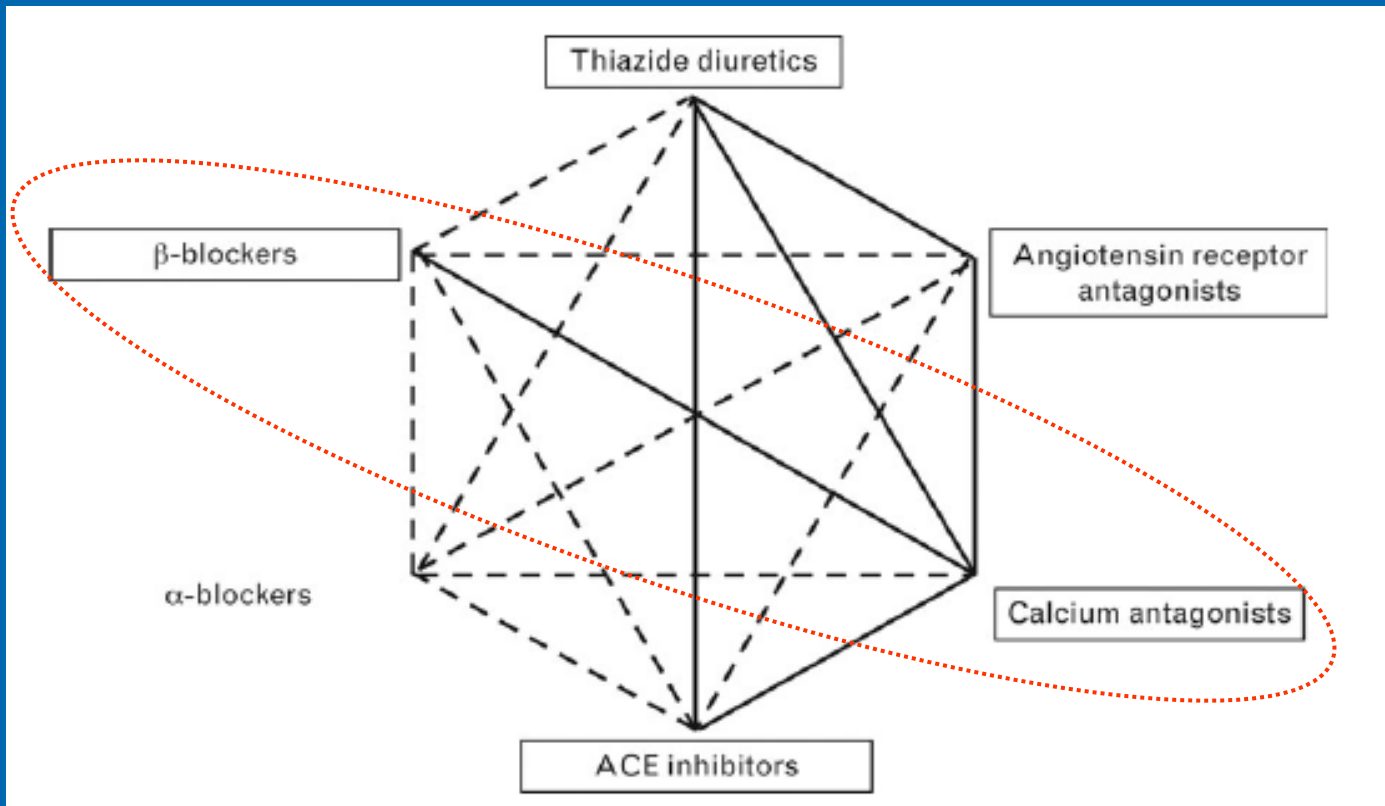
Durum	Zayıf/Yok	Kanıt var	Güçlü kanıt
Hipertansiyon	☹️		
Kalp yetersizliği			😊
Akut koroner sendrom		☹️	
Post-MI			😊
Stabil angina		☹️	
Perioperatif		☹️	
Hipertrofik KMP		☹️	

Kontrendikasyon!

- Astım
- AV Blok

ESH/ESC Guideline 2007

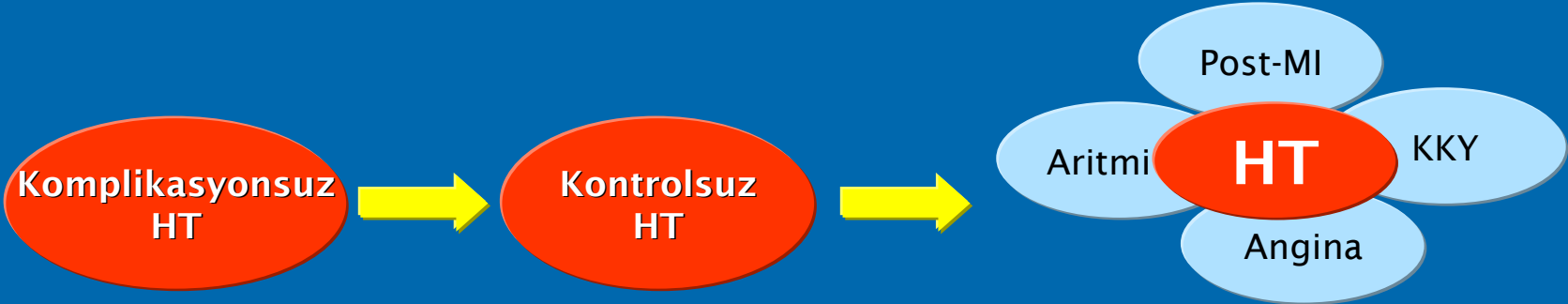
Önerilen tek kombinasyon!



ESH/ESC Guideline 2007

β-GEN TÜRK

ÖZETLE...



%0

KLİNİK KANIT DÜZEYİ

%100

ÖZETLE...

- Kullanılacaksa:
 - 3. jenerasyon BB tercih edilmeli