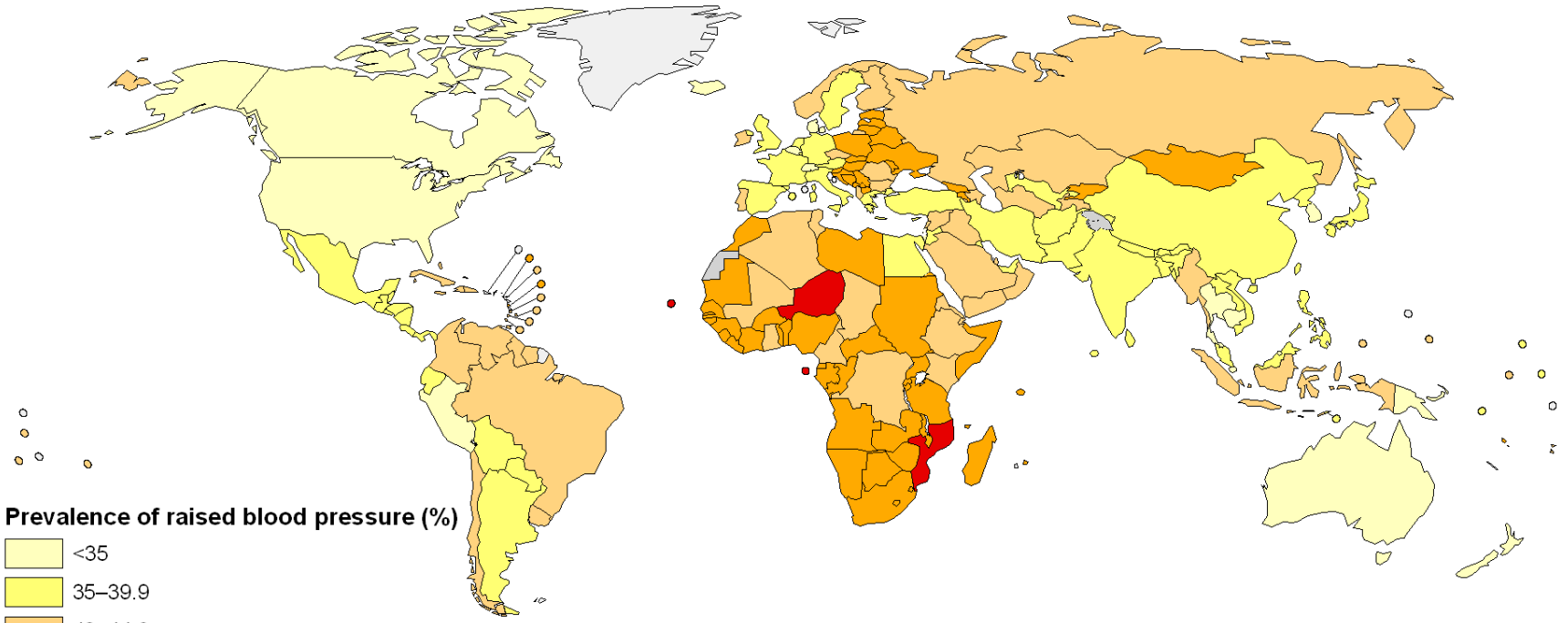
Έχουν θέση οι β-αποκλειστές στη θεραπεία της αρτηριακής υπέρτασης;

Ε. Τριανταφυλλίδη
Επιμελήτρια Α΄ Καρδιολογίας

Β΄ Πανεπιστημιακή Καρδιολογική Κλινική
Νοσοκομείο ΑΤΤΙΚΟΝ

Prevalence of raised blood pressure*, ages 25+, age standardized
Both sexes, 2008



Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

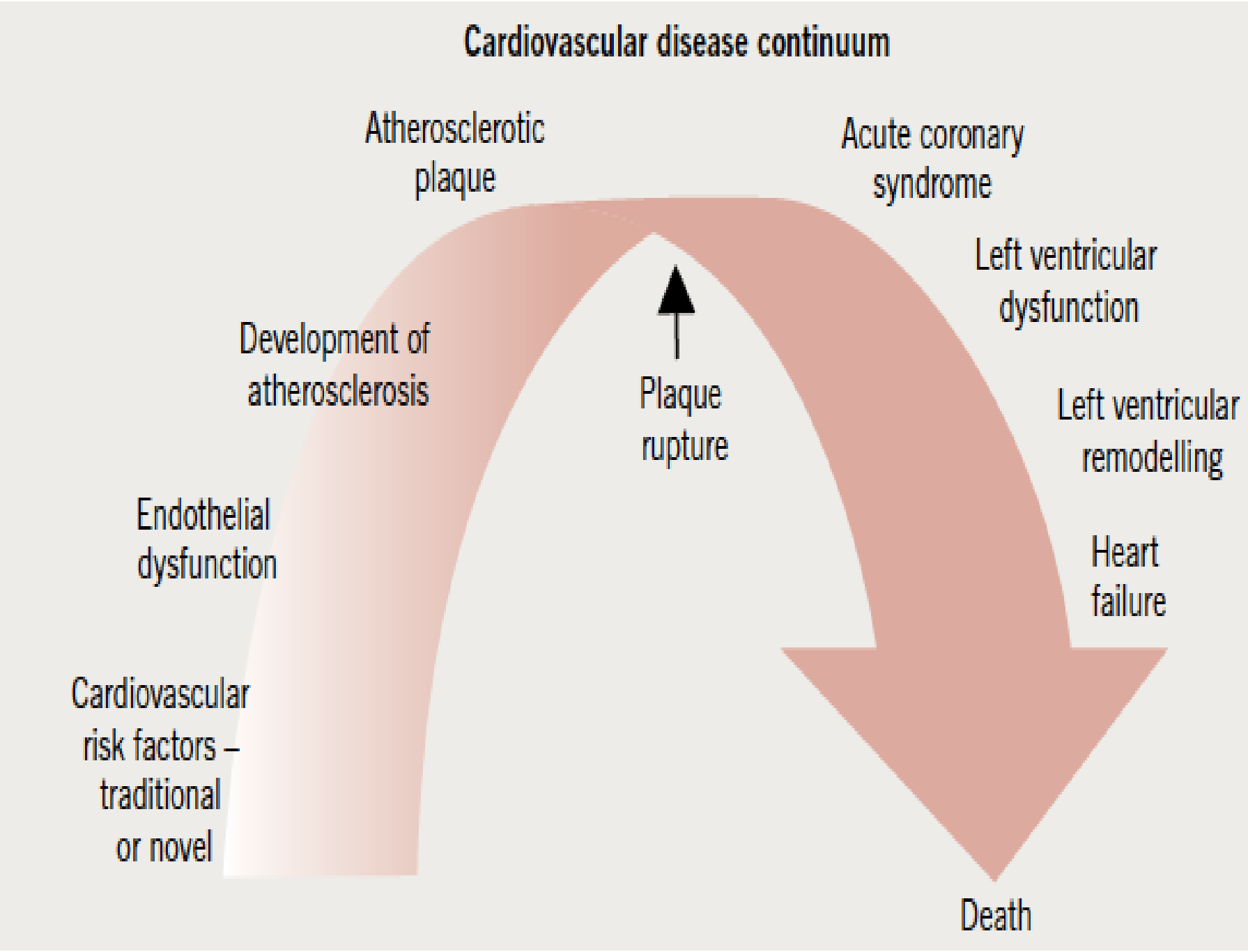

Cardiovascular disease continuum
Atherosclerotic plaque
Acute coronary syndrome
Left ventricular dysfunction
Development of atherosclerosis
Plaque rupture
Left ventricular remodelling
Endothelial dysfunction
Heart failure
Cardiovascular risk factors – traditional or novel
Death

TABLE 4. Factors—other than office BP—influencing prognosis; used for stratification of total CV risk in Fig. 1

Risk factors
Male sex
Age (men ≥55 years; women ≥65 years)
Smoking
Dyslipidaemia
Total cholesterol >4.9 mmol/L (190 mg/dL), and/or
Low-density lipoprotein cholesterol >3.0 mmol/L (115 mg/dL), and/or
High-density lipoprotein cholesterol: men <1.0 mmol/L (40 mg/dL), women <1.2 mmol/L (46 mg/dL), and/or
Triglycerides >1.7 mmol/L (150 mg/dL)
Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL)
Abnormal glucose tolerance test
Obesity [BMI ≥30 kg/m^2 (height^2)]
Abdominal obesity (waist circumference: men ≥102 cm; women ≥88 cm) (in Caucasians)
Family history of premature CVD (men aged <55 years; women aged <65 years)

Diabetes mellitus
Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) on two repeated measurements, and/or
HbA_{1c} >7% (53 mmol/mol), and/or
Post-load plasma glucose >11.0 mmol/L (198 mg/dL)

Asymptomatic organ damage
Pulse pressure (in the elderly) ≥60 mmHg
Electrocardiographic LVH (Sokolow–Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mV*ms), or
Echocardiographic LVH [LVM index: men >115 g/m^2; women >95 g/m^2 (BSA)][a]
Carotid wall thickening (IMT >0.9 mm) or plaque
Carotid–femoral PWV >10 m/s
Ankle-brachial index <0.9
CKD with eGFR 30–60 ml/min/1.73 m^2 (BSA)
Microalbuminuria (30–300 mg/24 h), or albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine)

Established CV or renal disease
Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack
CHD: myocardial infarction; angina; myocardial revascularization with PCI or CABG
Heart failure, including heart failure with preserved EF
Symptomatic lower extremities peripheral artery disease
CKD with eGFR <30 mL/min/1.73m^2 (BSA); proteinuria (>300 mg/24 h).
Advanced retinopathy: haemorrhages or exudates, papilloedema

Εκτίμηση καρδιαγγειακού κινδύνου

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to moderate risk	Moderate to high risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥ 4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

FIGURE 1 Stratification of total CV risk in categories of low, moderate, high and very high risk according to SBP and DBP and prevalence of RFs, asymptomatic OD, diabetes, CKD stage or symptomatic CVD. Subjects with a high normal office but a raised out-of-office BP (masked hypertension) have a CV risk in the hypertension range. Subjects with a high office BP but normal out-of-office BP (white-coat hypertension), particularly if there is no diabetes, OD, CVD or CKD, have lower risk than sustained hypertension for the same office BP.

2013 ESH/ESC Guidelines for the management of arterial hypertension

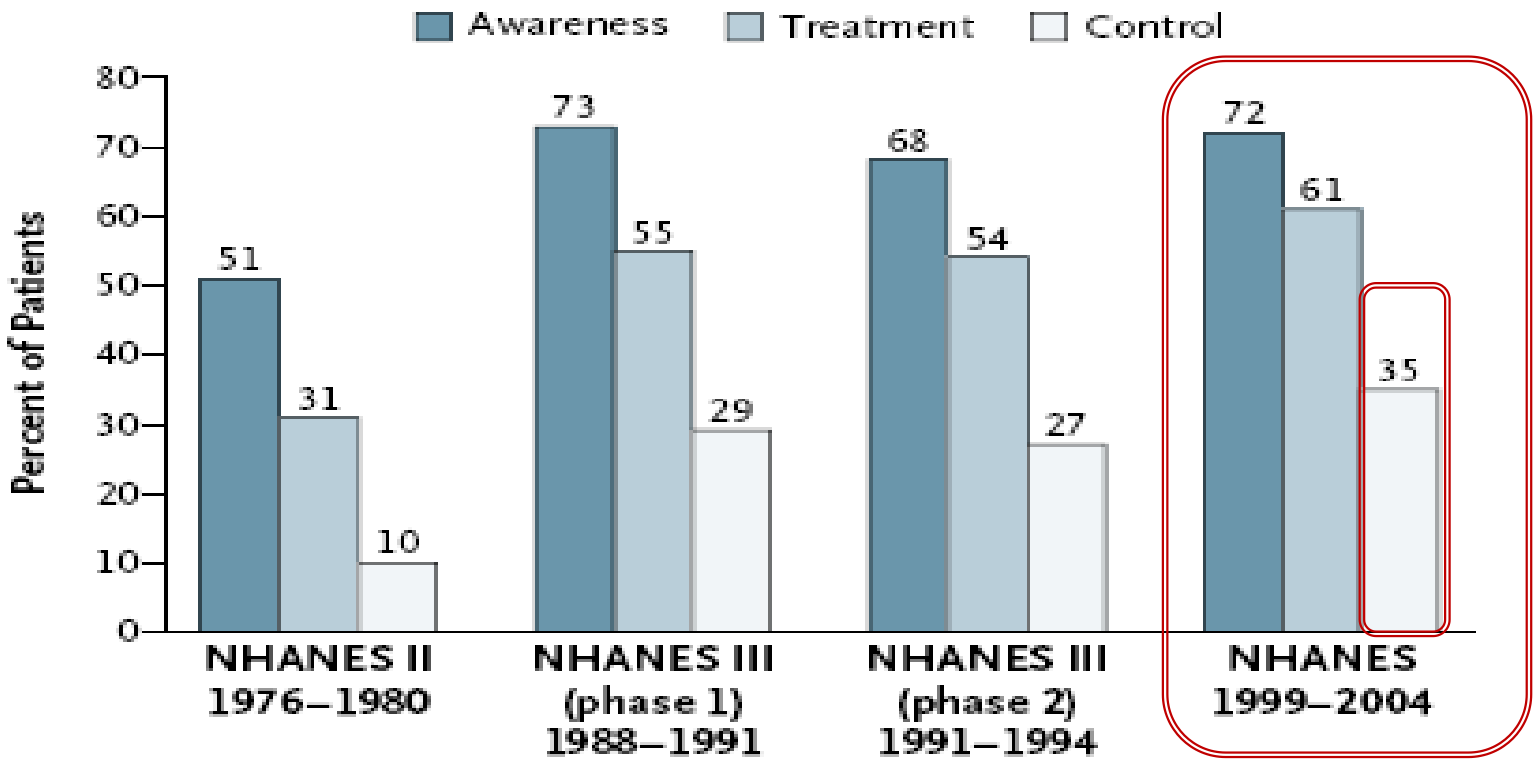
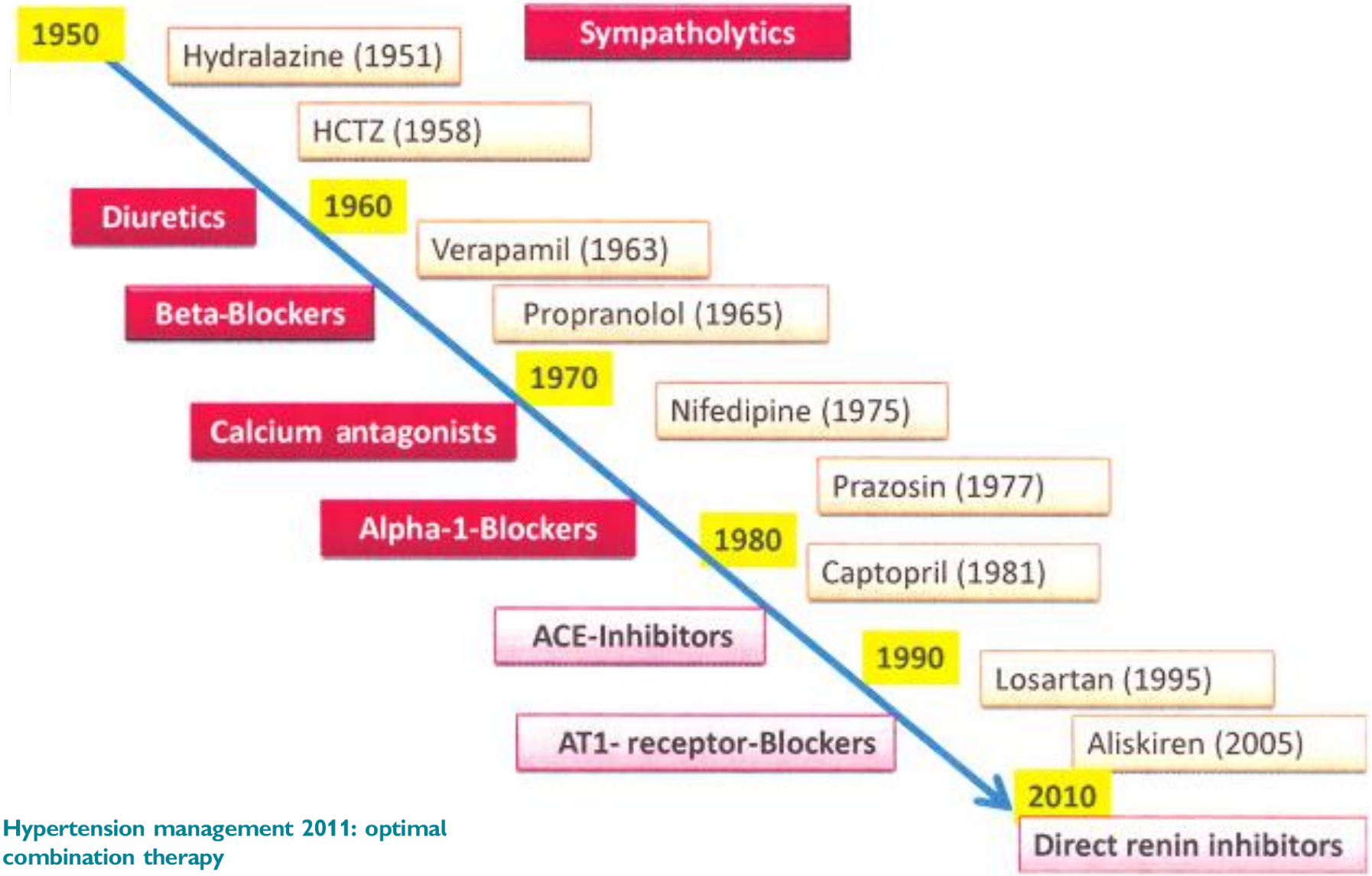


Figure 2. Rates of Awareness, Treatment, and Control of High Blood Pressure in the United States (1976–2004).

High blood pressure is defined as a reading of 140/90 mm Hg or more for persons between the ages of 18 and 74 years. Despite major improvements in blood-pressure therapies in recent years, some 28% of Americans with hypertension do not know they have the condition, 39% are receiving no therapy, and 65% have insufficient blood-pressure control. Data are from Chobanian et al.[12] and Cutler et al.[41] NHANES denotes National Health and Nutrition Examination Survey.

The history of antihypertensives

Reserpine, Pentolinium, Guanethidine, Methyl dopa (1950—1960), Clonidine (1980)



Hypertension management 2011: optimal combination therapy

Peter S. Sever[1]* and Franz H. Messerli[2]

European Heart Journal Advance Access published June 22, 2011

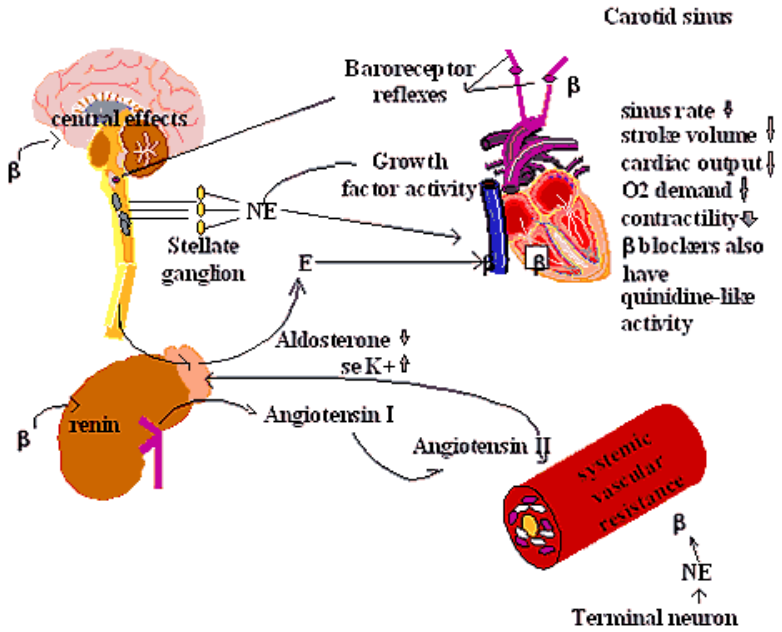
Beta adrenergic receptors

Specific actions of the β_1 receptor include:

- Increase cardiac output by increasing heart rate (positive chronotropic effect), conduction velocity (positive dromotropic effect), and stroke volume (by enhancing contractility—positive inotropic effect).
- Increase renin secretion from juxtaglomerular cells of the kidney.

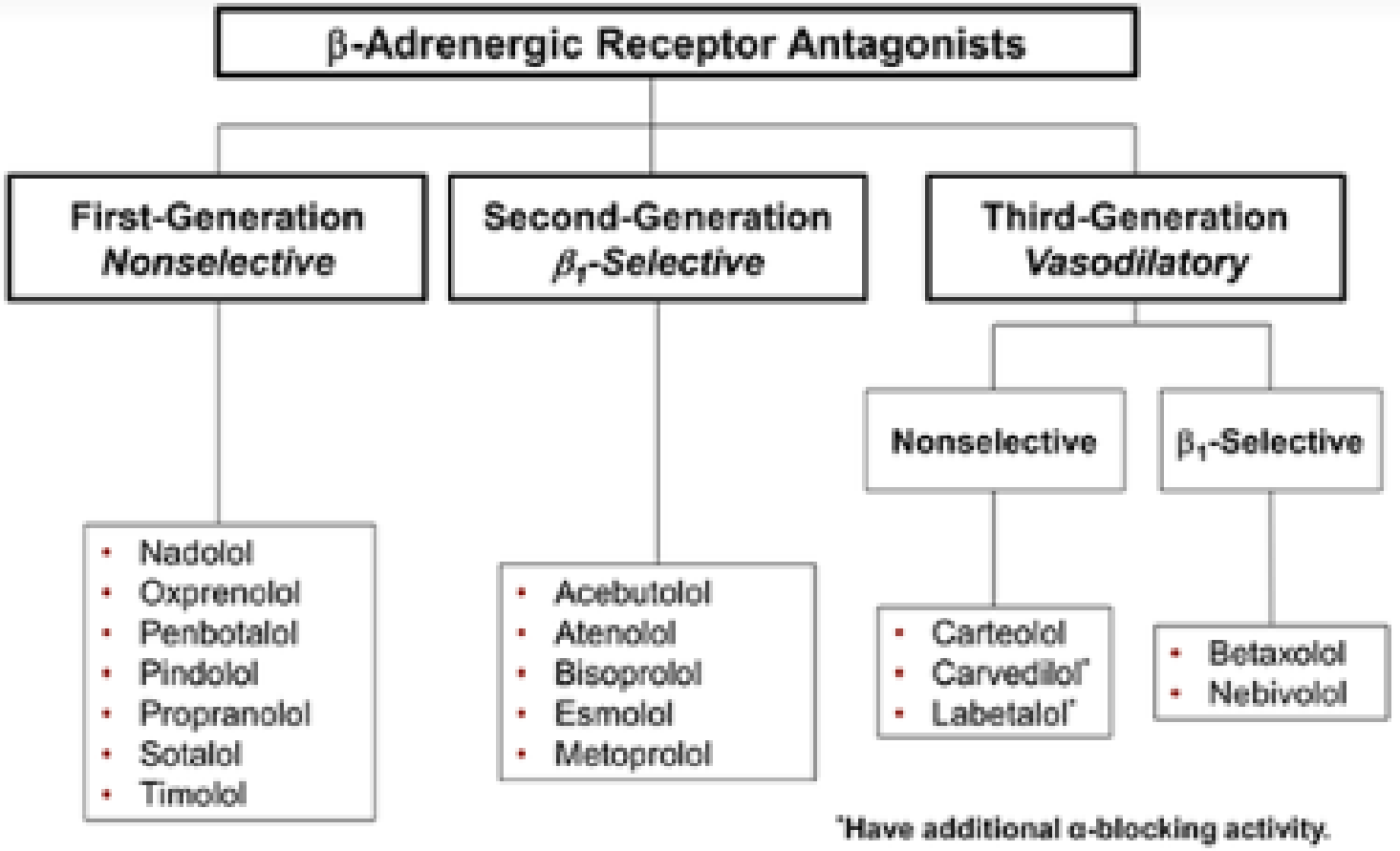
Specific actions of the β_2 receptor include the following:

- Smooth muscle relaxation, e.g. in bronchi,[9] GI tract (decreased
- Lipolysis in adipose tissue.[11]
- Dilate arteries to skeletal muscle



Effects of the sympathetic nervous activity which can be influenced by beta receptor blockers

3 Generations of β-blockers



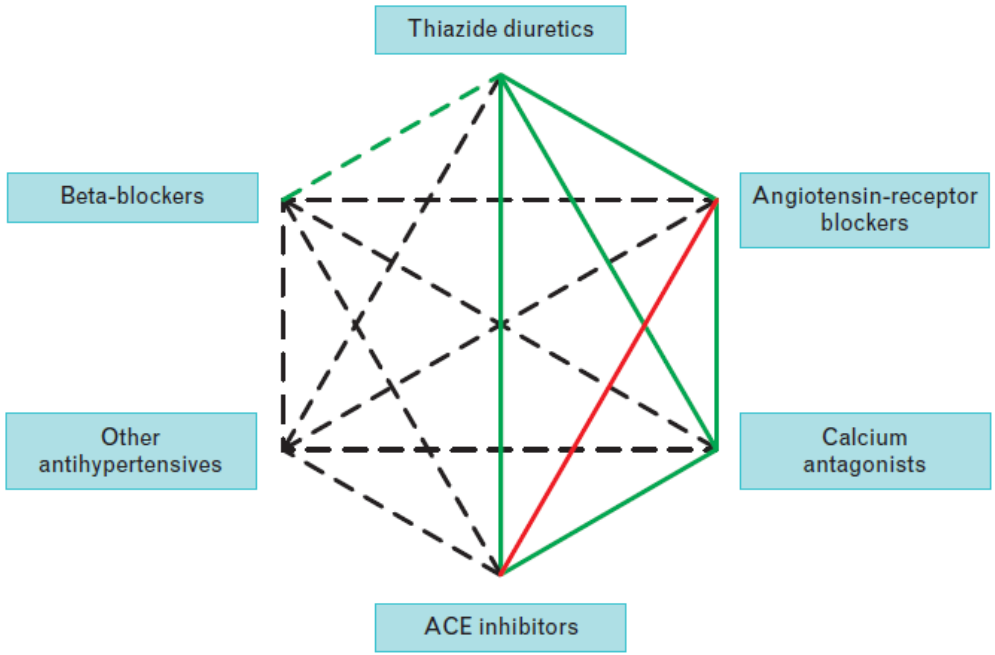
Manrique C, et al. *J Clin Hypertens*. 2009;11:369-375.[1]

Nebivolol: Βελτιώνει την αρτηριακή σκληρία, μειώνει την κεντρική αορτική πίεση και τις περιφερικές αντιστάσεις.

Carvedilol: Μειώνει το μεταφορτίο στην καρδιακή ανεπάρκεια και στην μετεμφραγματική δυσλειτουργία της αριστερής κοιλίας.

First choice antihypertensive treatment

2013 ESH/ESC Guidelines for the management of arterial hypertension



ACE = angiotensin-converting enzyme.

FIGURE 4 Possible combinations of classes of antihypertensive drugs. Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); black dashed lines: possible but less well tested combinations; red continuous line: not recommended combination. Although verapamil and diltiazem are sometimes used with a beta-blocker to improve ventricular rate control in permanent atrial fibrillation, only dihydropyridine calcium antagonists should normally be combined with beta-blockers.

Current guidelines reconfirm that diuretics (including thiazides, chlorthalidone and indapamide), **beta-blockers**, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers **are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations**

Clinical Review & Education

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. LaFavre, 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

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. Patients want to be assured that blood pressure (BP) treatment will reduce their disease burden, while clinicians want guidance on hypertension management using the best scientific evidence. This report takes a rigorous, evidence-based approach to recommend treatment thresholds, goals, and medications in the management of hypertension in adults. Evidence was drawn from randomized controlled trials, which represent the gold standard for determining efficacy and effectiveness. Evidence quality and recommendations were graded based on their effect on important outcomes.

There is strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90 mm Hg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mm Hg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than 140/90 mm Hg for those groups based on expert opinion. The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years. There is moderate evidence to support initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy. There is moderate evidence to support initial or add-on antihypertensive therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in persons with CKD to improve kidney outcomes.

Although this guideline provides evidence-based recommendations for the management of high BP and should meet the clinical needs of most patients, these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient.

Editorial pages 472, 474, and 477

Author Audio Interview at jama.com

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and CME Questions page 522

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Paul A. James, MD, University of Iowa, 200 Hawkins Dr, 01286-D FFP, Iowa City, IA 52242-1097 (paul-james@uiowa.edu).

JAMA. 2014;311(5):507-520. doi:10.1001/jama.2013.284427
Published online December 18, 2013.

Recommendation 6

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB).

Moderate Recommendation – Grade B

- The panel did not recommend β-blockers for the initial treatment of hypertension.
- The panel suggests that any of these 4 classes would be good choices as add-on agents.

Clinical Review & Education

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. LaFavre, 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

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. Patients want to be assured that blood pressure (BP) treatment will reduce their disease burden, while clinicians want guidance on hypertension management using the best scientific evidence. This report takes a rigorous, evidence-based approach to recommend treatment thresholds, goals, and medications in the management of hypertension in adults. Evidence was drawn from randomized controlled trials, which represent the gold standard for determining efficacy and effectiveness. Evidence quality and recommendations were graded based on their effect on important outcomes.

There is strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90 mm Hg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mm Hg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than 140/90 mm Hg for those groups based on expert opinion. The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years. There is moderate evidence to support initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy. There is moderate evidence to support initial or add-on antihypertensive therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in persons with CKD to improve kidney outcomes.

Although this guideline provides evidence-based recommendations for the management of high BP and should meet the clinical needs of most patients, these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient.

Editorial pages 472, 474, and 477
Author Audio Interview at jama.com
Supplemental content at jama.com
CME Quiz at jamanetworkcme.com and CME Questions page 522

Author Affiliations: Author affiliations are listed at the end of the article.
Corresponding Author: Paul A. James, MD, University of Iowa, 200 Hawkins Dr, 01286-D FFP, Iowa City, IA 52242-1097 (paul-james@uiowa.edu).

JAMA. 2014;311(5):507-520. doi:10.1001/jama.2013.284427
Published online December 18, 2013.

Recommendation 9

The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using the drugs in recommendation 6 because of a contraindication or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed.

Expert Opinion – Grade E

α-Blockers,
dual α1-+β-blocking agents (carvedilol)
central α2-adrenergic agonists (clonidine)
adrenergic neuronal depleting agents (reserpine)

direct vasodilators (hydralazine),
vasodilating β-blockers (nebivolol)
aldosterone receptor antagonists
loop diuretics (furosemide)

B-Blockers pharmacokinetic (hydrophilicity versus lipophilicity)

1. ***Blood levels and length of action***. Hydrophilic b-blockers (atenolol and nadolol) have less blood levels variation compared with liver metabolized agents (propranolol, metoprolol). Being unmetabolized and renal-excreted, hydrophilic b-blockers have a long biological action which enables a low dose, once daily basis, 24-hour cover.

2. ***The brain***. Atenolol has a brain/blood ratio of 0.1:1, compared to 17:1 and 14:1 with propranolol and metoprolol, respectively. This possibly accounts for the low incidence of CNS side effects.

3. ***The kidney***: a. Atenolol and nadolol are excreted virtually unmetabolized by the kidney. Significant accumulation occurs in moderate to severe renal failure (GFR=10-35 ml/minute) so the daily dose should be halved. b. Propranolol and metoprolol, have a tendency for increased blood levels in severe renal failure (due to the accompanying liver dysfunction).

4. ***The elderly***. The elderly and young subjects handle and tolerate hydrophilic b-blockers similarly. However, due to the aging liver dysfunction, lipophilic b-blockers achieve blood levels in the elderly up to fourfold higher than in younger subjects.

Η θέση των β-αναστολέων στην αρτηριακή υπέρταση

Ανεπιθύμητες ενέργειες

I. Ληθαργικότητα, κατάθλιψη και διαταραχές ύπνου
II. Αίσθημα κόπωσης
III. Επιδείνωση βρογχικού άσθματος
IV. Ψυχρά άκρα, φαινόμενο Raynaud
V. Διαταραχές στύσεως
VI. Επιδείνωση μεταβολικού profile
VII. Βραδυκαρδία- διαταραχές κολποκοιλιακής αγωγιμότητας

Table 14 Compelling and possible contra-indications to the use of antihypertensive drugs

Drug	Compelling	Possible
Diuretics (thiazides)	Gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcaemia Hypokalaemia
Beta-blockers	Asthma A–V block (grade 2 or 3)	Metabolic syndrome Glucose intolerance Athletes and physically active patients Chronic obstructive pulmonary disease (except for vasodilator beta-blockers)
Calcium antagonists (dihydropyridines)		Tachyarrhythmia Heart failure
Calcium antagonists (verapamil, diltiazem)	A–V block (grade 2 or 3, trifascicular block) Severe LV dysfunction Heart failure	
ACE inhibitors	Pregnancy Angioneurotic oedema Hyperkalaemia Bilateral renal artery stenosis	Women with child bearing potential
Angiotensin receptor blockers	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	Women with child bearing potential
Mineralocorticoid receptor antagonists	Acute or severe renal failure (eGFR <30 mL/min) Hyperkalaemia	

A-V = atrio-ventricular; eGFR = estimated glomerular filtration rate; LV = left ventricular.

Beta-blockers for hypertension.

Wiysonge CS[1], Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH.

Author information

Cochrane Database Syst Rev. 2012 Nov 14;11

Abstract

BACKGROUND: This review is an update of the Cochrane Review published in 2007, which assessed the role of beta-blockade as first-line therapy for hypertension.

OBJECTIVES: To quantify the effectiveness and safety of beta-blockers on morbidity and mortality endpoints in adults with hypertension.

SEARCH METHODS: In December 2011 we searched the Cochrane Central Register of Controlled Trials, Medline, Embase, and reference lists of previous reviews; for eligible studies published since the previous search we conducted in May 2006.

SELECTION CRITERIA: Randomised controlled trials (RCTs) of at least one year duration, which assessed the effects of beta-blockers compared to placebo or other drugs, as first-line therapy for hypertension, on mortality and morbidity in adults.

DATA COLLECTION AND ANALYSIS: We selected studies and extracted data in duplicate. We expressed study results as risk ratios (RR) with 95% confidence intervals (CI) and combined them using the fixed-effects or random-effects method, as appropriate.

MAIN RESULTS: We included 13 RCTs which compared beta-blockers to placebo (4 trials, N=23,613), diuretics (5 trials, N=18,241), calcium-channel blockers (CCBs: 4 trials, N=44,825), and renin-angiotensin system (RAS) inhibitors (3 trials, N=10,828). Three-quarters of the 40,245 participants on beta-blockers used atenolol. Most studies had a high risk of bias; resulting from various limitations in study design, conduct, and data analysis.Total mortality was not significantly different between beta-blockers and placebo (RR 0.99, 95%CI 0.88 to 1.11, I(2)=0%), diuretics or RAS inhibitors, but was higher for beta-blockers compared to CCBs (RR 1.07, 95%CI 1.00 to 1.14; I(2)=2%). Total cardiovascular disease (CVD) was lower for beta-blockers compared to placebo (RR 0.88, 95%CI 0.79 to 0.97; I(2)=21%). This is primarily a reflection of the significant decrease in stroke (RR 0.80, 95%CI 0.66 to 0.96; I(2)=0%), since there was no significant difference in coronary heart disease (CHD) between beta-blockers and placebo. There was no significant difference in withdrawals from assigned treatment due to adverse events between beta-blockers and placebo (RR 1.12, 95%CI 0.82 to 1.54; I(2)=66%).The effect of beta-blockers on CVD was significantly worse than that of CCBs (RR 1.18, 95%CI 1.08-1.29; I(2)=0%), but was not different from that of diuretics or RAS inhibitors. In addition, there was an increase in stroke in beta-blockers compared to CCBs (RR 1.24, 95%CI 1.11-1.40; I(2)=0%) and RAS inhibitors (RR 1.30, 95%CI 1.11 to 1.53; I(2)=29%). However, CHD was not significantly different between beta-blockers and diuretics, CCBs or RAS inhibitors. Participants on beta-blockers were more likely to discontinue treatment due to adverse events than those on RAS inhibitors (RR 1.41, 95% CI 1.29 to 1.54; I(2)=12%), but there was no significant difference with diuretics or CCBs.

AUTHORS' CONCLUSIONS: Initiating treatment of hypertension with beta-blockers leads to modest reductions in cardiovascular disease and no significant effects on mortality. These effects of beta-blockers are inferior to those of other antihypertensive drugs. The GRADE quality of this evidence is low, implying that the true effect of beta-blockers may be substantially different from the estimate of effects found in this review. Further research should be of high quality and should explore whether there are differences between different sub-types of beta-blockers or whether beta-blockers have differential effects on younger and elderly patients.

Cochrane Database Syst Rev. 2012 Nov 14;11:CD002003. doi: 10.1002/14651858.CD002003.pub4.

Beta-blockers for hypertension.

Wiysonge CS[1], Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH.

Author information

[1]Division of Medical Microbiology & Institute of Infectious Disease andMolecular Medicine, University of Cape Town, Observatory,South Africa. charles.wiysonge@uct.ac.za

B-blockers may be **inferior** to some other drug classes regarding morbidity and mortality:

1. Total mortality and CV events: **worse** than CaB (**but not** vs. diuretics and RAAS blockers)

2. Stroke: **worse** than CaB and RAAS blockers

3. Coronary Heart Disease: **equal** to CaB, RAAS blockers and diuretics

Cochrane Database Syst Rev. 2012 Nov 14;11:CD002003. doi: 10.1002/14651858.CD002003.pub4.

Beta-blockers for hypertension.

Wiysonge CS[1], Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH.

Author information

[1]Division of Medical Microbiology & Institute of Infectious Disease andMolecular Medicine, University of Cape Town, Observatory,South Africa. charles.wiysonge@uct.ac.za

AUTHORS' CONCLUSIONS

1. Initiating treatment of hypertension with beta-blockers leads to modest reductions in cardiovascular events and no significant effects on mortality.

2. These effects of beta-blockers **are inferior** to those of other antihypertensive drugs.

3. Further research of high quality should explore whether there are differences **between different sub-types of beta-blockers** or whether beta-blockers have differential effects on younger and elderly patients.

BMJ. 2009 May 19;338:b1665. doi: 10.1136/bmj.b1665.

Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies.

Law MR[1], Morris JK, Wald NJ.

Author information

Abstract

OBJECTIVES: To determine the quantitative efficacy of different classes of blood pressure lowering drugs in preventing coronary heart disease (CHD) and stroke, and who should receive treatment.

DESIGN: Meta-analysis. Data source Medline (1966-2007).

STUDY SELECTION: Randomised trials of blood pressure lowering drugs recording CHD events and strokes. 108 trials studied differences in blood pressure between study drug and placebo (or control group not receiving the study drug) ("blood pressure difference trials"), and 46 trials compared drugs ("drug comparison trials"). Seven trials with three randomised groups fell into both categories. The results were interpreted in the context of those expected from the largest published meta-analysis of cohort studies, totalling 958 000 people.

PARTICIPANTS: 464 000 people defined into three mutually exclusive categories: participants with no history of vascular disease, a history of CHD, or a history of stroke.

RESULTS: In the blood pressure difference trials beta blockers had a special effect over and above that due to blood pressure reduction in preventing recurrent CHD events in people with a history of CHD: risk reduction 29% (95% confidence interval 22% to 34%) compared with 15% (11% to 19%) in trials of other drugs. The extra effect was limited to a few years after myocardial infarction, with a risk reduction of 31% compared with 13% in people with CHD with no recent infarct (P=0.04). In the other blood pressure difference trials (excluding CHD events in trials of beta blockers in people with CHD), there was a 22% reduction in CHD events (17% to 27%) and a 41% (33% to 48%) reduction in stroke for a blood pressure reduction of 10 mm Hg systolic or 5 mm Hg diastolic, similar to the reductions of 25% (CHD) and 36% (stroke) expected for the same difference in blood pressure from the cohort study meta-analysis, indicating that the benefit is explained by blood pressure reduction itself. The five main classes of blood pressure lowering drugs (thiazides, beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers) were similarly effective (within a few percentage points) in preventing CHD events and strokes, with the exception that calcium channel blockers had a greater preventive effect on stroke (relative risk 0.92, 95% confidence interval 0.85 to 0.98). The percentage reductions in CHD events and stroke were similar in people with and without cardiovascular disease and regardless of blood pressure before treatment (down to 110 mm Hg systolic and 70 mm Hg diastolic). Combining our results with those from two other studies (the meta-analyses of blood pressure cohort studies and of trials determining the blood pressure lowering effects of drugs according to dose) showed that in people aged 60-69 with a diastolic blood pressure before treatment of 90 mm Hg, three drugs at half standard dose in combination reduced the risk of CHD by an estimated 46% and of stroke by 62%; one drug at standard dose had about half this effect. The present meta-analysis also showed that drugs other than calcium channel blockers (with the exception of non-cardioselective beta blockers) reduced the incidence of heart failure by 24% (19% to 28%) and calcium channel blockers by 19% (6% to 31%).

CONCLUSIONS: With the exception of the extra protective effect of beta blockers given shortly after a myocardial infarction and the minor additional effect of calcium channel blockers in preventing stroke, all the classes of blood pressure lowering drugs have a similar effect in reducing CHD events and stroke for a given reduction in blood pressure so excluding material pleiotropic effects. The proportional reduction in cardiovascular disease events was the same or similar regardless of pretreatment blood pressure and the presence or absence of existing cardiovascular disease. Guidelines on the use of blood pressure lowering drugs can be simplified so that drugs are offered to people with all levels of blood pressure. Our results indicate the importance of lowering blood pressure in everyone over a certain age, rather than measuring it in everyone and treating it in some.

BMJ. 2009 May 19;338:b1665. doi: 10.1136/bmj.b1665.

Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies.

Law MR[1], Morris JK, Wald NJ.

Author information

[1]Centre for Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine, Queen Mary University of London, London EC1M 6BQ. m.r.law@qmul.ac.uk

Beta-blocker-initiated therapy seems to be:

(i) **equally** as effective as the other major classes of antihypertensive agents in preventing **coronary** outcomes and

(ii) **highly effective** in preventing CV events in patients with a **recent myocardial infarction and those with heart failure.**

BMJ. 2009 May 19;338:b1665. doi: 10.1136/bmj.b1665.

Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies.

Law MR[1], Morris JK, Wald NJ.

Author information

[1]Centre for Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine, Queen Mary University of London, London EC1M 6BQ. m.r.law@qmul.ac.uk

CONCLUSIONS

all the classes of blood pressure lowering drugs have a similar effect in reducing CHD events and stroke for a given reduction in blood pressure so excluding material pleiotropic effects.

Exceptions:

A. extra protective effect of beta blockers given shortly after a myocardial infarction and

B. the minor additional effect of calcium channel blockers in preventing stroke

Beta-blockers and…. stroke

A slightly lower effectiveness of beta-blockers in preventing stroke has been attributed to a lesser ability to reduce central SBP and pulse pressure.

However, a lower effectiveness in stroke prevention is also shared by ACE inhibitors, although these compounds have been reported to reduce central BP better than beta-blockers.

Canadian Journal of Cardiology 30 (2014) S47–S53

Systematic Review/Meta-analysis

Atenolol vs Nonatenolol β-Blockers for the Treatment of Hypertension: A Meta-analysis

Laura M. Kuyper, MD,[a] and Nadia A. Khan, MD, MSc[a,b]

[a] Division of General Internal Medicine, University of British Columbia, Vancouver, British Columbia, Canada

[b] Center for Health Evaluation and Outcome Sciences, Vancouver, British Columbia, Canada

Conclusions**

- In the **young**, both atenolol and non-atenolol b-blockers are effective in reducing cardiovascular end points for hypertension without compelling indications.

- **Atenolol** is associated with **increased stroke in the elderly** but whether this extends to non-atenolol b-blockers remains uncertain due to no data.

QUESTION: **Is age a more important factor in b-blocker efficacy than specific b-blocker type?**

**21 hypertension trials with data on 145,811 participants were included

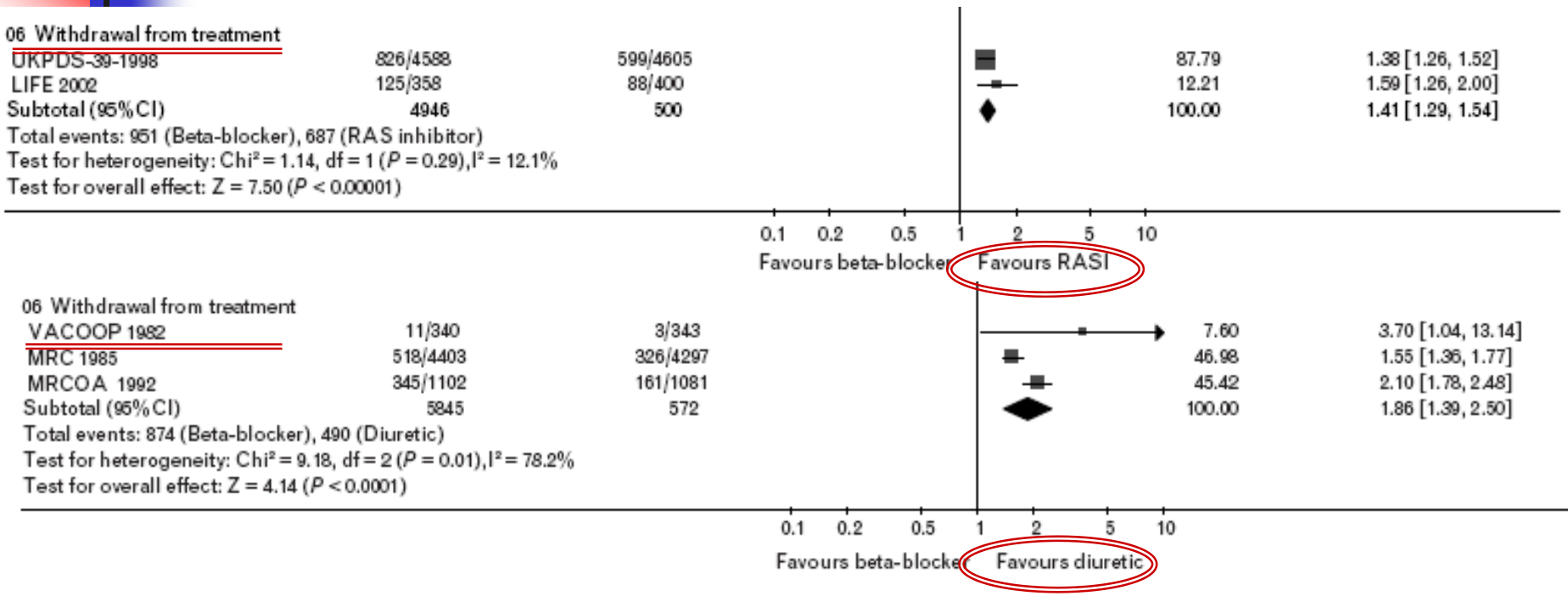
Beta-blockers and…. Target organ damage

Beta-blockers seems to be somewhat less effective than RAS blockers and calcium antagonists in regressing or delaying TOD (LVH, carotid IMT, aortic stiffness).

However, some of the vasodilating beta-blockers, such as celiprolol, carvedilol and nebivolol, more widely used today reduce central pulse pressure and aortic stiffness better than atenolol or metoprolol.

2013 ESH/ESC Guidelines for the management of arterial hypertension

Beta-blockers and…. Side effects



Beta-blockers also appear to have more side-effects which lead to the change of therapy.

However, the difference with other drugs is less pronounced in double blind studies.

How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and meta-analysis

Hazel A. Bradley[a,*], Charles Shey Wiysonge[b,*], Jimmy A. Volmink[c], Bongani M. Mayosi[b] and Lionel H. Opie[d]

Journal of Hypertension 2006, 24:2131–2141

Beta-blockers and…. Weight/diabetes

Beta-blockers tend to increase body weight and, particularly when used in combination with diuretics, to facilitate new-onset diabetes in predisposed patients.

However, vasodilating beta-blockers, such as celiprolol, carvedilol and nebivolol, affect insulin sensitivity less than metoprolol. Nebivolol has recently been shown not to worsen glucose tolerance compared with placebo and when added to hydrochlorothiazide.

2013 ESH/ESC Guidelines for the management of arterial hypertension

Beta-blockers and…. Lung disease

Beta-blockers have recently been reported not to increase, but even reduce, the risk of exacerbations and to reduce mortality in patients with chronic obstructive lung disease.

2013 ESH/ESC Guidelines for the management of arterial hypertension

Beta-blockers and…. pregnancy

Beta-blockers (possibly causing fetal growth retardation if given in early pregnancy) and diuretics (in pre-existing reduction of plasma volume) should be used with caution.

2013 ESH/ESC Guidelines for the management of arterial hypertension

Beta-blockers and…. Sexual dysfunction

Display Settings: Abstract Send to:

Cardiovasc Ther. 2010 Spring;28(1):15-22. doi: 10.1111/j.1755-5922.2009.00123.x.

Erectile dysfunction in high-risk hypertensive patients treated with beta-blockade agents.

Cordero A, Bertomeu-Martínez V, Mazón P, Fácila L, Bertomeu-González V, Conthe P, González-Juanatey JR.

Department of Cardiology, Hospital Universitario de San Juan, Alicante, Spain. acordero@coma.es

Abstract

BACKGROUND: Erectile dysfunction (ED) is a multifactorial disease related to age, vascular disease, psychological disorders, or medical treatments. Beta-blockade agents are the recommended treatment for hypertensive patients with some specific organ damage but have been outlined as one of leading causes of drug-related ED, although differences between beta-blockade agents have not been assessed.

METHODS: Cross-sectional and observational study of hypertensive male subjects treated with any beta-blockade agent for at least 6 months. ED dysfunction was assessed by the International Index of Erectile Dysfunction (IIEF).

RESULTS: 1.007 patients, mean age 57.9 (10.59) years, were included. The prevalence of any category of ED was 71.0% (38.1% mild ED; 16.8% moderate ED; 16.1% severe ED). Patients with ED had longer time since the diagnosis of hypertension and higher prevalence of risk factors and comorbidities. The prevalence of ED increased linearly with age. ED patients received more medications and were more frequently treated with carvedilol and less frequently with nebivolol. Patients treated with nebivolol obtained higher scores in every parameter of the IIEF questionnaire. The multivariate analysis identified independent associations between ED and coronary heart disease (OR: 1.57), depression (OR: 2.25), diabetes (OR: 2.27), atrial fibrillation (OR: 2.59), and dyhidopiridines calcium channel blockers (OR: 1.76); treatment with nebivolol was associated to lower prevalence of ED (OR: 0.27).

CONCLUSION: ED is highly prevalent in hypertensive patients treated with beta-blockade agents. The presence of ED is associated with more extended organ damage and not to cardiovascular treatments, except for the lower prevalence in nebivolol-treated patients.

Compared with older antihypertensive drugs, newer agents (RAAS inhibitors, CaB and vasodilating b-blockers) have neutral or even beneficial effects on erectile function.

Beta-blockers and ..Peripheral artery disease

There has been concern that the use of beta-blockers in patients with PAD may worsen the symptoms of claudication.

However, meta-analyses in PAD patients with mild-to-moderate limb ischemia did not confirm the intake of beta-blockers to be associated with exacerbation of PAD symptoms.

Beta-blockers and…. Kidney disease

SNS is activated in CKD and acts as a key player in the progression of renal dysfunction. **It was believed** that reduction of the cardiac output and the consequent **impairment of renal perfusion caused by b-blockers might be harmful in patients with CKD** (renal protection, sudden death prevention)

Recent guidelines recommended **RAAS blockers** as the agents of first choice for the management of hypertension in patients with CKD, because of the significant renal-protective effects of this class of drugs.

The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend that beta-blockers be used as the third-line antihypertensive agents in patients with proteinuria.

However, as compared to other antihypertensive agents, except RAAS blockers, it has been confirmed that there are no demerits to using b-blockers for renal protection. In addition, **vasodilatory b-blockers may also have beneficial renal protective effects.**

The hemodialysis (HEMO) study suggested a trend towards the benefit of b-blockers **for the prevention of sudden cardiac death in patients with CKD/CAD**, but not in CKD patients without CAD.

A Comparison of Vasodilating and Non-vasodilating Beta-Blockers and Their Effects on Cardiometabolic Risk

Icilma V. Fergus[1] · Kenneth L. Connell[2] · Keith C. Ferdinand[3]

Table 2 Compares the use of beta-blockers and diuretics in the major guidelines

Guideline	NICE 2011	ESC/ESH 2013	AHA/ACC/CDC 2013	ASH/ISH 2014	Hypertension guidelines "JNC 8" 2014
Beta-blockers first line?	No	Yes	No	No	No
Diuretics	Chlorthalidone, indapamide	Thiazide, chlorthalidone, indapamide	Thiazides	Thiazide, chlorthalidone, indapamide	Thiazide, chlorthalidone, indapamide

With wider documented benefits on cardiovascular outcomes, **it can be expected** that guidelines may evolve as well, with **recommendations based on sound evidence for vasodilator BBs to be used as first-line agents, as opposed to conventional BBs.**

Επιλογή b-blockers ως φαρμακευτική αγωγή

Condition	Drug
Asymptomatic organ damage	
LVH	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB
Clinical CV event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
Aortic aneurysm	BB
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist
Atrial fibrillation, ventricular rate control	BB, non-dihydropyridine calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist
Other	
ISH (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

2013 ESH/ESC Guidelines for the management of arterial hypertension

Συμπεράσματα

Worldwide, B-blocker use as first-line therapy in the treatment of hypertension without compelling indications remains controversial.

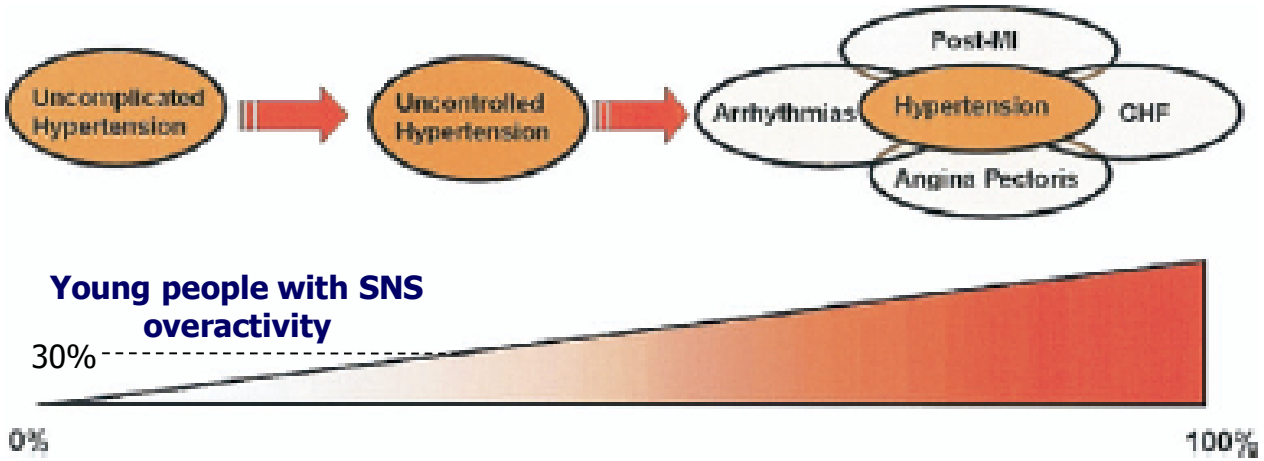


Figure 3 **Proposed Use of Beta-Blockers for Hypertension**

In patients with uncomplicated hypertension, beta-blockers should not be used as first-line agents. However, in patients with uncontrolled hypertension on various other antihypertensive agents and in those with complicated hypertension, beta-blockers should be considered in the armamentarium of treatment. CHF = chronic heart failure; MI = myocardial infarction.

JACC Vol. 50, No. 7, 2007
August 14, 2007:563–72