Right Beta Blockers for the Right Patients

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DISCLOSURE STATEMENT OF FINANCIAL INTEREST

• Nothing To Disclose
1948: Ahlquist classified adrenergic receptors into α and β receptors.

1958: Dichloroisoprenaline (DCI) – First BB

1963: Therapeutic breakthrough, Propranolol introduced by J.W. Black

1980: BB become the most popular antiHTNs after diuretics. Practolol – First β1 selective.

2003: BB become the most controversial antiHTNs!!

2019: ???????
Cardiovascular disease continuum: From risk factors to irreversible damage.
Cardiovascular disease continuum: The role of sympathetic overdrive

- Sympathetic overdrive
- Myocardial infarction
- Coronary thrombosis
- Neurohormonal activation
- Arrhythmias and loss of muscle
- Remodeling
- Ventricular enlargement
- Sudden cardiac death
- Remodeling
- End-stage heart disease
- Risk factors:
  - Dyslipidemia
  - Hypertension
  - Diabetes
  - Smoking
  - Obesity (visceral adiposity)
Autonomous nervous system – silent regulator of all bodily functions
Autonomous nervous system – silent regulator of all bodily functions

Parasympathetic system
"rest and digest"

Sympathetic system
"fight or flight"
How to measure activity of sympathetic system in humans?

- Sympathetic adrenergic neuroimaging
- Microneurography
- Regional and total norepinephrine spillover
- Plasma norepinephrine
- Power spectral analysis of heart rate
- Heart rate
SYMPATHETIC OVERDRIVE – AN IMPORTANT RISK FACTOR FOR HYPERTENSION AND CARDIOVASCULAR COMPLICATIONS PRESENTING WITH ELEVATED HEART RATE
Heart rate is associated with mortality
Chicago People Gas Company study, n=1233, 40–59
Elevated Heart Rate is a Risk Factor in patients with Heart Disease
CRUSADE Registry (n = 135 164)
Inverse linear relation between RHR and life expectancy in mammals and humans

Cook S et al. Eur Heart J 2006;27:2387-2393
Heart rate = 25/min

Life span = ?
Heart rate = 25/min

Life span = 150 years
Sympathetic Overdrive Is Common At Initial Stage of Hypertension
Elevated resting heart rate predicts development of hypertension in children. Suzhou Study
Elevated resting heart rate predicts development of hypertension in children. Suzhou Study

Every 10bpm increase in heart rate was associated with a 26% greater risk of hypertension development in boys.
Heart rate \( \geq 84 \) bpm is associated with increased mortality

LIFE Study

Peter M. Okin et al. All-cause and cardiovascular mortality in relations to changing heart rate during treatment of hypertensive patients with electrocardiographic left ventricular hypertrophy. European Heart Journal (2010) 31, 2271–2279
Management of the hypertensive patient with elevated heart rate: Statement of the Second Consensus Conference endorsed by the European Society of Hypertension


INTRODUCTION

In 2006, the European Society of Hypertension published an Expert Consensus Document titled ‘Identification and management of the hypertensive patient with an elevated heart rate’ [1]. This document summarized the available data on the association between high heart rate (HR) and the cardiovascular risk in hypertension. During the 9 years since the publication of the 2006 Consensus paper, research on high HR in hypertension and other clinical settings has actively been pursued. The results of many new important studies, including several large cohort studies and meta-analyses of clinical trials in hypertension focusing on the association between high HR and adverse outcomes, have been published. These studies have widened the information available in 2006 and have reinforced the evidence about the importance of high HR as a risk factor for cardiovascular diseases. Several issues were reviewed and discussed during a consensus meeting held under the auspices of the European Society of Hypertension, on 18...
In most studies of hypertension, HR was considered to be elevated when it was higher than 80–85 bpm.

Symptomatic tachycardia HR reduction by available drugs (mostly beta-1 selective beta-blockers) should be considered.
Tachycardia is frequent also in established hypertension (n=38,145)

Farinaro E et al, Nutr Metab Cardiovasc Dis 1999:9;196
Borderline hypertensives present exaggerated response to beta-blockers as compared to normotensives.

Blood pressure is more sensitive to adrenergic blockade in obese than in lean hypertensive patients
Beta-blockers Reduce Sympathetic Overdrive In Hypertension With Clinical Benefits
Inhibition of sympathetic overdrive

- **Alpha2-agonists** (moxonidine)
- **Ganglion-blocking drugs** (trimetaphane)
- **Beta-blockers**
- **Alpha-blockers**
Beta-Adrenergic Blockers

Alpha-1
- Vasoconstriction
- Increased peripheral resistance
- Increased blood pressure

Alpha-2
- Inhibition of norepinephrine release
- Inhibition of insulin release
Beta-Blockers

Beta-1

• Tachycardia
• Increased lipolysis
• Increased myocardial contractility

Beta-2

• Vasodilation (in skeletal vasculature)
• Slightly decreased peripheral resistance
• Bronchodilation
• Increased muscle and liver glycogenolysis
• Increased release of glucagon
Properties

- Receptor Blockade
  - Nonselective $\beta$ blockade
  - Selective $\beta_1$ blockade
  - $\beta+\alpha$ blockade
  - Intrinsic sympathomimetic property-ISA (partial agonistic action)

- Membrane stabilising action-MSA (Local anaesthetic action-Na channel block)
Classification

Sympathetic drugs in hypertension

\[ \beta \text{ receptor antagonists} \]

Non-selective (First Generation)
- Nadolol
- Penbutolol
- Pindolol
- Propranolol
- Timolol
- Sotalol
- Levobunolol
- Metipranolol

\[ \beta_1 \text{-selective (2nd Generation)} \]
- Acebutolol
- Atenolol
- Bisoprolol
- Esmolol
- Metoprolol

Non-selective (3rd Generation)
- Carvedilol
- Bucindolol
- Labetalol

\[ \beta_1 \text{-selective (3rd Generation)} \]
- Betaxolol
- Celiprolol
- Nebivolol
Properties of β1 Selectivity

- Less broncho constriction
- Less interference with CHO metabolism → less hypoglycemia
  → preferred in diabetics
- Less chances of Raynaud's phenomenon
- Less deleterious effect on blood lipid profile
- Less impairment of exercise capacity
- Less effect on tremor
Properties of ISA (Intrinsic Sympathomimetic Activity)

- Less bradycardia
- Less rebound effect on withdrawal
- Less deleterious effect on blood lipid profile
- *Not effective in migraine prophylaxis*
- *Not suitable for secondary prophylaxis of MI*
# 3rd Generation Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>MSA</th>
<th>ISA</th>
<th>Beta blockade</th>
<th>Other properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>+</td>
<td>+</td>
<td>Non selective</td>
<td>α1 blockade</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>+</td>
<td></td>
<td>Non selective</td>
<td>α1 blockade, CCB Antioxidant</td>
</tr>
<tr>
<td>Bucindolol</td>
<td></td>
<td>+</td>
<td>Non selective</td>
<td>α1 blockade, β2, β3 agonism Increases HDL cholesterol</td>
</tr>
<tr>
<td>Celiprolol</td>
<td></td>
<td>+</td>
<td>β1 selective</td>
<td>β2 agonism NO release</td>
</tr>
<tr>
<td>Nebivolol</td>
<td></td>
<td></td>
<td>β1 selective</td>
<td>• NO release • Inhibits platelet aggregation</td>
</tr>
<tr>
<td>Bevantolol</td>
<td></td>
<td></td>
<td>Nonselective</td>
<td>α1 blockade CCB</td>
</tr>
</tbody>
</table>
USES

CARDIOVASCULAR

- Hypertension
- Angina
- Myocardial infarction
- Arrhythmia
- Cardiomyopathy
- CCF
- Dissecting aneurysm of aorta

NON - CARDIOVASCULAR

- Thyrotoxicosis
- Pheochromocytoma
- Migraine prophylaxis
- Essential tremor
- Glaucoma
- Anxiety
- Portal hypertension
- Anti psychotic induced akathisia
Acute coronary syndrome

• Beta-blockers reduce mortality and reinfarction by 20-25% in those who have recovered from an infarction [1].

• Oral treatment with beta-blockers should be considered for all ST-elevation myocardial infarction (STEMI) patients without contraindications (Class IIa, Level B) [2]. They are indicated if STEMI patients also have heart failure or LV dysfunction (Class I, Level A) [2].


Stable coronary artery disease

- Beta-blockade is a very effective symptomatic treatment, alone or combined with another drug, for most of patients with classical angina [1].

- Beta-blockers and/or calcium channel blockers are first-line treatment to control heart rate and anginal symptoms (Class I, Level A) [3].


Heart Failure

• Beta-blockers have been shown to reduce mortality and heart failure readmissions in patients with heart failure with a reduced ejection fraction (HFrEF) [1].

• Beta-blockers are recommended, in addition to ACE inhibitors, for patients with stable, symptomatic HFrEF (Class I, Level A) [4].

• Bisoprolol, Carvedilol, Metoprolol and Nebivolol are licensed for use in HFrEF and should be preferred [4].


Beta-blockers can be used to slow the heart rate in patients with arrhythmias such as atrial flutter and/or atrial fibrillation [1].

They are effective in the control of ventricular arrhythmias related to sympathetic activation, acute coronary syndrome, and heart failure; including the prevention of sudden cardiac death [1].

Contraindications and side effects

• The most frequent side effects of beta-blockers include: hypotension, bradycardia, bronchospasm, cold extremities, fatigue, headache, sleep disturbances and increased insulin resistance [1].

• High-degree AV block is an absolute contraindication (if no pacemaker) [1].

• Use cardioselective beta-blockers in case of chronic obstructive pulmonary disease (COPD); start low and go slow [1].

• Asthma is a relative contraindication for the use of beta-blockers [4]. These drugs should be used with caution and preferably with specialist advice.

Beta-blockers are a diverse group of medicines and prescribers should consider their different properties, along with the presence of co-morbidities, to individualise care for patients with cardiovascular conditions.

When a beta-blocker is initiated, a slow upwards titration of dose is recommended to minimise adverse effects. Beta-blockers should also be withdrawn slowly, ideally over several months, to prevent rebound symptoms such as resting tachycardia.

Beta receptor selectivity enhances the beneficial effects of beta blockers and allows treatment of patients with co-morbidities.

New generation of Beta Blocker: β1 selective, NO production, anti oxidative properties.
THANK YOU
BACKUP SLIDES
### Treatment strategies and choice of drugs

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium</td>
<td>I</td>
<td>A</td>
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<tr>
<td>antagonists, ACE inhibitors, and angiotensin receptor blockers are all suitable</td>
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<tr>
<td>and recommended for the initiation and maintenance of antihypertensive treatment,</td>
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<tr>
<td>either as monotherapy or in some combinations with each other.</td>
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<tr>
<td>Condition</td>
<td>Drug</td>
<td></td>
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<td>-----------------------------------------------</td>
<td>-------------------------------------------</td>
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<tr>
<td>Asymptomatic organ damage</td>
<td></td>
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<tr>
<td>LVH</td>
<td>ACE inhibitor, calcium antagonist, ARB</td>
<td></td>
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<tr>
<td>Asymptomatic atherosclerosis</td>
<td>Calcium antagonist, ACE inhibitor</td>
<td></td>
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<tr>
<td>Microalbuminuria</td>
<td>ACE inhibitor, ARB</td>
<td></td>
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<tr>
<td>Renal dysfunction</td>
<td>ACE inhibitor, ARB</td>
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<tr>
<td>Clinical CV event</td>
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<tr>
<td>Previous stroke</td>
<td>Any agent effectively lowering BP</td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td><strong>BB</strong>, ACE inhibitor, ARB</td>
<td></td>
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<tr>
<td>Angina pectoris</td>
<td><strong>BB</strong>, calcium antagonist</td>
<td></td>
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<tr>
<td>Heart failure</td>
<td>Diuretic, <strong>BB</strong>, ACE inhibitor, ARB, mineralocorticoid receptor antagonists</td>
<td></td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td><strong>BB</strong></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, prevention</td>
<td>Consider ARB, ACE inhibitor, <strong>BB</strong> or mineralocorticoid receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, ventricular rate control</td>
<td><strong>BB</strong>, non-dihydropyridine calcium antagonist</td>
<td></td>
</tr>
<tr>
<td>ESRD/proteinuria</td>
<td>ACE inhibitor, ARB</td>
<td></td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>ACE inhibitor, calcium antagonist</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISH (elderly)</td>
<td>Diuretic, calcium antagonist</td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>ACE inhibitor, ARB, calcium antagonist</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>ACE inhibitor, ARB</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Methyl dopa, <strong>BB</strong>, calcium antagonist</td>
<td></td>
</tr>
<tr>
<td>Blacks</td>
<td>Diuretic, calcium antagonist</td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Blood pressure difference (mm Hg)</th>
<th>Coronary heart disease events</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Thiazides vs any other</td>
<td>-1.4</td>
<td>0.2</td>
</tr>
<tr>
<td>β blockers vs any other</td>
<td>1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors vs any other</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Angiotensin receptor blockers vs any other</td>
<td>-0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Calcium channel blockers vs any other</td>
<td>-0.4</td>
<td>-0.9</td>
</tr>
</tbody>
</table>
Superior blood pressure and heart rate control with bisoprolol ADLIB Trial (n=25, age 28 – 55 years)

Bisoprolol and nebivolol: Blood pressure lowering

NEBIS trial

Czuriga I et al.. Comparison of the new cardioselective beta-blocker nebivolol with bisoprolol in hypertension: The nebivolol, bisoprolol multicenter study (NEBIS). Cardiovascular Drugs and therapy 2003: 17: 257-63
Cardiovascular disease continuum: The role of sympathetic overdrive

Myocardial infarction

Coronary thrombosis

Myocardial ischemia

CAD

Atherosclerosis

LVH

Risk factors
- Dyslipidemia
- Hypertension
- Diabetes
- Smoking
- Obesity (visceral adiposity)

Arrhythmias and loss of muscle

Remodeling

Ventricular enlargement

CHF

End-stage heart disease

Sudden cardiac death

Sympathetic overdrive

Neurohormonal activation
Increased plasma levels of adrenaline predict development of left ventricular hypertrophy
Twenty-year follow-up
Cardiovascular disease continuum: The role of sympathetic overdrive

Sympathetic overdrive

- Myocardial infarction
- Coronary thrombosis
- Neurohormonal activation
- Arrhythmias and loss of muscle
- Remodeling
- Ventricular enlargement
- CHF
- End-stage heart disease

Risk factors:
- Dyslipidemia
- Hypertension
- Diabetes
- Smoking
- Obesity (visceral adiposity)

CAD
Atherosclerosis
LVH
Sudden cardiac death
Reduction of atherosclerosis during beta-blocker therapy

**BCAPS**

All randomized (n = 793)

- Placebo
- Metoprolol CR/XL

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>18 months</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid Artery Bulb (Δ mm)</td>
<td>0.10</td>
<td>0.15</td>
</tr>
</tbody>
</table>

- p < 0.001
- p = 0.018

**ELVA**

- Placebo
- Metoprolol CR/XL 100 mg once daily

<table>
<thead>
<tr>
<th>Change in IMT Composite (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year Follow-up</td>
</tr>
</tbody>
</table>

- p = 0.004
- p = 0.011
Risk of plaque rupture triples in patients with tachycardia

### TABLE 6. Multivariate Analysis on Associations With Coronary Plaque Disruption

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular mass &gt;270 g</td>
<td>4.92 (1.83–13.25)</td>
<td>0.02</td>
</tr>
<tr>
<td>HR mean &gt;80 bpm</td>
<td>3.19 (1.15–8.85)</td>
<td>0.02</td>
</tr>
<tr>
<td>β-Blocker use</td>
<td>0.32 (0.13–0.88)</td>
<td>0.02</td>
</tr>
<tr>
<td>Wall thickness IVS</td>
<td>1.68 (0.57–9.91)</td>
<td>0.06</td>
</tr>
<tr>
<td>PPF</td>
<td>1.81 (0.67–4.90)</td>
<td>0.07</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>0.51 (0.19–1.34)</td>
<td>0.06</td>
</tr>
<tr>
<td>Statins</td>
<td>0.42 (0.16–1.22)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

HR indicates heart rate; IVS, interventricular septum; PPF, fractional pulse pressure; and ACE, angiotensin-converting enzyme.

*Circulation; 104:1477-1482, 2001.*
Cardiovascular disease continuum: The role of sympathetic overdrive

- Sympathetic overdrive
  - Myocardial infarction
  - Coronary thrombosis
  - Myocardial ischemia
  - CAD
  - Atherosclerosis
  - LVH
  - Risk factors: Dyslipidemia, Hypertension, Diabetes, Smoking, Obesity (visceral adiposity)
  - End-stage heart disease
  - CHF
  - Remodeling
  - Ventricular enlargement
  - Arrhythmias and loss of muscle
  - Sudden cardiac death
Cardiac remodeling: mechanism behind heart failure

Acute myocardial infarction

Hours - days
Expansion of hypokinetic segment, thinning of heart wall

Days - months
Continues remodeling

Necrosis
Sympathetic system in heart failure

- Sympathetic overactivity
- Decreased cardiac neuronal density
- Reduced beta-receptor density
- Aggrevated norepinephrine release
Inhibition of sympathetic overdrive

- Alpha2-agonists (moxonidine)
- Beta-blockers
- Alpha-blockers
- Ganglion-blocking drugs (trimetaphane)
Higher mortality in heart failure patients treated with moxonidine ... 

**MOXCON trial**

...despite lower plasma norepinephrine concentration

MOXCON trial
Beta-blockers reduce mortality in heart failure due to systolic dysfunction.
No reduction in mortality in patients with heart failure treated with bucindolol

*BEST trial*

No reduction in mortality in patients with heart failure treated with nebivolol

SENIORS trial

MD Flather et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS) Eur Heart J 2005; 26: 215
Cardiovascular disease continuum: How can we stop it?
The Impact Of Sympathetic Overdrive In The Cardiovascular Continuum

- Sympathetic overdrive initiates and accelerates cardiovascular continuum
- Heart rate is a sensitive marker of sympathetic overdrive
- Only cardioselective beta-blockers safely reduce sympathetic overdrive with clinical benefits
Advantages of selective $\beta_1$-receptor blockade

- Heart rate ↓
- Contractility ↓
- Blood pressure ↓
- Less bronchoconstriction
- Fewer peripheral effects
- Less metabolic effects
- Less circulatory side effects

Species-selective ($\beta_1$-selective)

Nonselective ($\beta_1 + \beta_2$)

- Similar cardiac and nearly similar antihypertensive effects
- More marked pulmonary and peripheral effects
Bisoprolol: $\beta_2/\beta_1$ Selectivity Ratio at Human $\beta$-receptors *In Vitro*
Bisoprolol needs no dose adjustment in patients with mild to moderate, Renal or Hepatic dysfunction
Plasma concentration profiles after administration of metoprolol succinate CR and bisoprolol (3/12 subjects were CYP2D6 “poor” metabolizer)

Individual plasma concentration profiles of metoprolol and bisoprolol after single administration of one metoprolol 100 mg controlled release tablet and one bisoprolol 10 mg normal release tablet
BETA-BLOCKERS AND ASTHMA, COPD
β-Adrenergic blocking agents increase airway resistance and should not be administered to patients with asthma or other reversible airways disease. Only in selected instances of coexisting cardiac conditions, may β-adrenergic blocking agents be considered for trial (levels B-I, C).

Some studies support the concept that cardioselective β-adrenergic blocking agents exert less effect than nonselective agents on pulmonary function in patients with reversible airways disease. If an asthmatic patient with severe systemic hypertension is unable to tolerate other classes of antihypertensive medications, a trial of a cardioselective β-adrenergic blocker could be attempted while maintaining optimal treatment with bronchodilators. Cardioselectivity may be lost at higher doses of these agents (levels
Beta-blockers in COPD patients: Reduced mortality

Beta-blockers in COPD patients: Reduced mortality

Figure 1. Cumulative survival of patients with chronic obstructive pulmonary disease according to β-blocker use.

Beta-blockers in COPD patients: Reduced mortality
Pulmonary specialists in COPD patients: Reduced survival

Figure 1. Cumulative survival of patients with chronic obstructive pulmonary disease according to β-blocker use.

Figure 2. Cumulative survival of patients with chronic obstructive pulmonary disease according to referral to a pulmonologist.

BETA-BLOCKERS AND LIPIDS
HDL-cholesterol during treatment with different beta-blockers

- Mepindolol 10 mg/day (n = 16)
- Bisoprolol 10 mg/day (n = 17)
- Propranolol 160 mg/day (n = 15)
- Atenolol 100 mg/day (n = 22)

Δ% HDL-cholesterol vs. baseline

*p<0.05  **p<0.01

Bisoprolol: $\beta_1$-selectivity and Lipid Metabolism in Long-term Therapy

Frithz G. Cardiovasc Drugs Ther 1993;7(suppl 2):424
BETA-BLOCKERS AND DIABETES
Risk of *de novo* diabetes mellitus during anti-hypertensive therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Odds Ratio (95% CI) p-value</th>
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</thead>
<tbody>
<tr>
<td>ARB</td>
<td>0.57 (0.46–0.72) p&lt;0.0001</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>0.67 (0.56–0.80) p&lt;0.0001</td>
</tr>
<tr>
<td>CCB</td>
<td>0.75 (0.62–0.90) p=0.002</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.77 (0.63–0.94) p=0.009</td>
</tr>
<tr>
<td>β blocker</td>
<td>0.90 (0.75–1.09) p=0.30</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Referent</td>
</tr>
</tbody>
</table>

Incoherence=0.000017

Treatment with valsartan and risk of *de novo* diabetes mellitus
(NAVIGATOR trial)

![Graph showing incidence of diabetes over years since randomization with valsartan and placebo.](image)

**A Incidence of Diabetes**

Hazard ratio, 0.86 (95% CI, 0.80–0.92)
P<0.001

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Valsartan</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>0</td>
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<td>0</td>
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<td>6</td>
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**No. at Risk**

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<tbody>
<tr>
<td>Valsartan</td>
<td>4631</td>
<td>3784</td>
<td>3335</td>
<td>2857</td>
<td>2511</td>
<td>2208</td>
<td>1533</td>
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<tr>
<td>Placebo</td>
<td>4675</td>
<td>3743</td>
<td>3248</td>
<td>2717</td>
<td>2366</td>
<td>2070</td>
<td>1403</td>
</tr>
</tbody>
</table>
Treatment with valsartan and cardiovascular complications (NAVIGATOR trial)

B  Extended Cardiovascular Outcome

Hazard ratio, 0.96 (95% CI, 0.86–1.07)  
P=0.43

Placebo
Valsartan

Extended Cardiovascular Outcome (%)

Years since Randomization
Concomitant therapy and the risk of de novo diabetes

**NAVIGATOR Trial**

Shen L, Shah BR, Reyes EM et al. Role of diuretics, β blockers, and statins in increasing the risk of diabetes in patients with impaired glucose tolerance: reanalysis of data from the NAVIGATOR study. BMJ 2013;347:f6745
**β₁-selectivity and glucose metabolism in patients with DM type 2 and concomitant hypertension**

![Graph showing glucose and HbA1c levels](graph.png)

- **Glucose**
  - A: initial value
  - B: after 2 weeks of bisoprolol
  - C: after 2 weeks of placebo
  - (P_{C-B} > 0.05)

- **HbA1c**
  - A: initial value
  - B: after 2 weeks of bisoprolol
  - C: after 2 weeks of placebo
  - (P_{C-B} > 0.05)

n = 20

BETA-BLOCKERS AND PAD
Beta Blockers for Peripheral Arterial Disease

S.C.V. Paravastu a,1, D.A. Mendonca b,2, A. da Silva c,∗

Conclusions: Currently, there is no evidence to suggest that beta blockers adversely affect walking distance in people with intermittent claudication. Beta blockers should be used with caution if clinically indicated, especially in patients with critical ischaemia where acute lowering of blood pressure is contraindicated.

There has been concern that the use of beta-blockers in patients with PAD may worsen the symptoms of claudication. Two meta-analyses of studies published in PAD patients with mild-to-moderate limb ischaemia did not confirm the intake of beta-blockers to be associated with exacerbation of PAD symptoms [589,590].
Use of beta-blockers was associated with a 53% significant reduction in the incidence of new coronary events.
Freedom from MALE was significantly higher in the bisoprolol-treated group than in the carvedilol group

MALE = major adverse limb events incl. any repeated revascularization [any endovascular procedure, any surgical revision or the use of thrombectomy or thrombolysis] and major amputation
BETA-BLOCKERS AND ERECTILE DYSFUNCTION
Self-reported erectile dysfunction during 6-14 weeks of antihypertensive therapy

Complaints on erectile dysfunction and knowledge on the type of drug and side effects

% patients

3,1%
Complaints on erectile dysfunction and knowledge on the type of drug and side effects

% patients

- 3,1% „Blinded”
- 15,6% Known drug

Complaints on erectile dysfunction and knowledge on the type of drug and side effects

Patients who reported erectile dysfunction responded similarly to sildenafil and placebo

**β-Blocker Therapy and Symptoms of Depression, Fatigue, and Sexual Dysfunction**

- Beta-blocker therapy was not associated with a significant absolute annual increase in risk of reported depressive symptoms (6 per 1000 patients; 95% CI [-7 to 19])

- Beta-blockers were associated with a small significant annual increase in risk of reported fatigue (18 per 1000 patients; 95% CI, [5-30])

- Beta-blockers were also associated with a small, significant annual increase in risk of reported sexual dysfunction (5 per 1000 patients; 95% CI, [2-8])

- None of the risks of adverse effects differed significantly by degree of β-blocker lipid solubility

- The risk associated with reported fatigue was significantly higher for early-generation than for late-generation beta-blockers ($P=.04$).
**β-Blocker Therapy and Symptoms of Depression, Fatigue, and Sexual Dysfunction**

- Beta-blocker therapy was not associated with a significant absolute annual increase in risk of reported depressive symptoms (6 per 1000 patients; 95% CI [-7 to 19]).

- Beta-blockers were associated with a small significant annual increase in risk of reported fatigue (18 per 1000 patients; 95% CI, [5-30]).

  The conventional wisdom that beta-blocker therapy is associated with substantial risks of depressive symptoms, fatigue, and sexual dysfunction is not supported by data from clinical trials.

  The risk was not associated with lipid-solubility but low β1-selectivity.

- The risk associated with reported fatigue was significantly higher for early-generation than for late-generation beta-blockers ($P=.04$).
Erectile dysfunction and treatment with different beta-blockers (MR NOED study)

Brixius K et al.. Clin Exp Pharmacol Physiol 2007; 34: 327-31
BETA-BLOCKERS AND STROKE
Systolic blood pressure and risk of stroke

(Prospective Cohort Study Collaboration)

Lancet 2002; 360: 1903
Hypertensive therapy: effects calculated on BP reduction

Beta-blockers and stroke prevention
Evidence-based on clinical trials

- Atenolol (once daily) was used in 80% of clinical trials
- Atenolol (once daily) is a weak antihypertensive drug
- Risk of stroke is mostly related to blood pressure level
Beta-blockers reduce risk of stroke
Hypertensive treatment lowers cardiovascular risk in young and middle-aged population
BETA-BLOCKERS AND ACC/AHA AND NICE GUIDELINES
OMRON

INSTRUCTION MANUAL

Automatic Blood Pressure Monitor
with IntelliSense™

Model HEM-711
Difference between automated BP readings and measurement by medical personnel
(SMOB, self-measurement by the patient at the office)

141,0±18/85,4±9,9 - 140,3±18/86,3±9,5
ASCOT BPLA trial: unmet primary clinical endpoint

<table>
<thead>
<tr>
<th>Primary endpoints</th>
<th>Amloidine-based regimen (n=903)</th>
<th>Atenolol-based regimen (n=902)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Rate per 1000</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction (including silent) (n=14)</td>
<td>435 (5%)</td>
<td>8.2</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal myocardial infarction (including silent) (n=14)</td>
<td>360 (4%)</td>
<td>7.4</td>
</tr>
<tr>
<td>Total cardiovascular events and procedures (n=27)</td>
<td>753 (8%)</td>
<td>14.6</td>
</tr>
<tr>
<td>All-cause mortality (n=11)</td>
<td>718 (8%)</td>
<td>13.9</td>
</tr>
<tr>
<td>Cardiovascular mortality (n=26)</td>
<td>213 (3%)</td>
<td>4.4</td>
</tr>
<tr>
<td>Total and non-fatal stroke (n=43)</td>
<td>327 (3%)</td>
<td>6.2</td>
</tr>
<tr>
<td>Total and non-fatal heart failure (n=53)</td>
<td>134 (1%)</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Tertiary endpoints

- Myocardial infarction
- Unstable angina
- Chronic stable angina
- Peripheral arterial disease
- Life-threatening arrhythmias
- Development of diabetes mellitus
- Development of renal impairment

Post hoc endpoints

Primary endpoints: coronary revascularization procedures
Secondary endpoints: death or myocardial infarction/stroke


ASCOT BPLA trial: unmet primary clinical endpoint

<table>
<thead>
<tr>
<th>Primary endpoints</th>
<th>Amlodipine-based regimen (n=9639)</th>
<th>Atenolol-based regimen (n=9618)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Rate per 1000</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction (including silent)+ fatal CHD</td>
<td>429 (5%)</td>
<td>8.2</td>
</tr>
</tbody>
</table>

Cardiovascular death 283 (3%) 4.4 267 (3%) 5.0 0.76 (0.62–0.95) 0.0192
Total and non-fatal stroke 327 (3%) 6.2 422 (4%) 8.1 0.77 (0.66–0.90) 0.00009
Total and non-fatal heart failure 134 (1%) 2.5 159 (2%) 3.6 0.84 (0.66–1.05) 0.127

Tertiary endpoints

| Non-fatal myocardial infarction | 47 (0.4%) 0.8 33 (0.3%) 0.6 1.27 (0.80–2.00) 0.309 |
| Unstable angina                 | 73 (1%) 1.4 106 (1%) 2.0 0.60 (0.31–1.12) 0.115 |
| Chronic stable angina           | 295 (2%) 5.9 268 (2%) 4.0 0.90 (0.52–1.53) 0.832 |
| Peripheral arterial disease     | 133 (1%) 2.5 103 (1%) 3.5 0.60 (0.27–1.33) 0.0016 |
| Life-threatening arrhythmias    | 27 (0.3%) 0.5 25 (0.3%) 0.5 1.10 (0.42–2.81) 0.0099 |
| Development of diabetes mellitus| 182 (2%) 3.5 208 (2%) 3.0 0.70 (0.43–1.13) 0.109 |
| Development of renal impairment | 405 (4%) 7.7 499 (5%) 9.1 0.85 (0.75–0.97) 0.0017 |

Post hoc endpoints

| Primary endpoints coronary | 136 (5%) 2.7 118 (1%) 1.3 0.86 (0.72–1.03) 0.078 |
| percutaneous procedures      | 136 (5%) 2.7 118 (1%) 1.3 0.86 (0.72–1.03) 0.078 |
| Non-fatal myocardial infarction | 295 (3%) 15.4 953 (10%) 18.4 0.82 (0.76–0.89) 0.000125 |
Why atenolol?

Why once daily?

Why 50 mg?
Bisoprolol and atenolol in hypertensive subjects > 60

Bisoprolol – most effective in reduction of diastolic blood pressure (PATHWAY-2)
Bisoprolol was most effective in patients with high-renin resistant hypertension (PATHWAY-2)
UKPDS at 20-year follow up: significant reduction in mortality in patients treated with beta-blocker.
Relation of Beta-Blocker–Induced Heart Rate Lowering and Cardioprotection in Hypertension

Sripal Bangalore, MD, MHA, Sabrina Sawhney, MD, Franz H. Messerli, MD

New York, New York
Beta-blocker-induced heart rate lowering and cardiovascular outcomes

Objections

- No data on basal heart rate
- Heart rate as an indicator of higher doses = more severe hypertension
- Heart rate < 50/min is not normal (!)
- Mostly (78% patients) studies with atenolol
- Relationship not observed in placebo studies
- Outcomes in the trials mostly affected by BP difference
- Beta-blocker are not given in hypertensive pts according to HR
In patients with prior MI use of beta-blockers was not associated with a lower risk of composite cardiovascular events

*Propensity score analysis of data from REACH Registry*

In patients with prior MI use of beta-blockers was not associated with a lower risk of composite cardiovascular events

*Propensity score analysis of data from REACH Registry*

- Mostly (78% patients) studies with atenolol
- Observational study
  - 36% patients on beta-blockers
  - 74% without beta-blockers
- Unobserved confounding by atrial fibrillation, renal dysfunction, COPD
- Comparing current users with nonusers and past users
Chocolate Consumption, Cognitive Function, and Nobel Laureates

THANK YOU