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To β-block or not to β-block?

Treating sympathetic overdrive

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Introduction

The adverse effects of sympathetic overdrive are commonly treated using β-blockers. By disrupting the binding of natural ligands to the β-receptors in the cell membrane, β-blockers induce various pharmacodynamic effects, including the reduction of blood pressure and heart rate. These agents are used to treat patients with cardiovascular disease such as heart failure (HF), atrial fibrillation (AF) and ischaemic heart disease (IHD).

There has recently been considerable debate around the use of β-blockers in hypertension. Some concerns have arisen from data indicating an increased risk of stroke, with a consequent alteration to some societies' guideline recommendations for managing hypertension. Based on risk-benefit assessment, the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) have retained the use of β-blockers in their recommendations for reducing the risk of cardiovascular events in hypertensive patients and for the treatment of hypertension in the presence of cardiac organ damage, HF, AF and IHD.

Click here – you need to watch the video in order to complete the CPD questionnaire.

LEARNING OBJECTIVES

You will learn:

- How disease modifies the sympathetic nervous system
- How the sympathetic nervous system of hypertensive patients is regulated and dysregulated by comorbidities in hypertensive patients
- New risk factor modifiers that increase cardiovascular risk and sympathetic overdrive
- How to interpret and apply β-blocker therapy in hypertensive patients with coronary artery disease and cardiac conditions such as atrial fibrillation

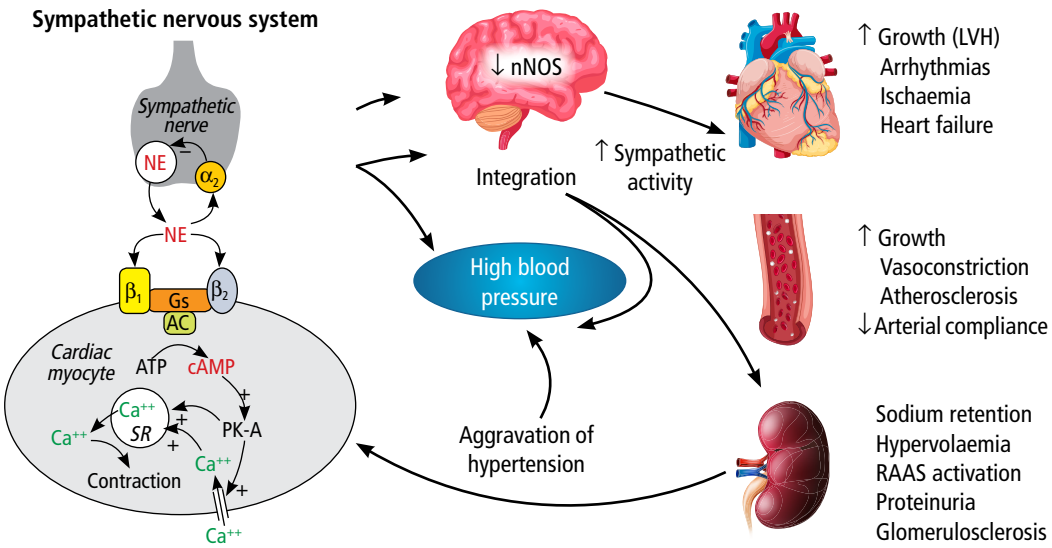

Figure 1. β-receptors can bind to other receptors to form heterodimers

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What is the mechanism of β-blocker action?

In recent years, there have been many new discoveries regarding the interaction between β-blockers and β-receptors on the heart and the blood vessels, and the different sub-types of β-receptors – β_1, β_2, and β_3. Not only do β-blocking agents limit the binding of the natural ligands, norepinephrine and epinephrine, to the β-receptors, but they also induce an effect or action, as seen when prescribing a β-blocker with intrinsic sympathomimetic activity.

It was well known that β-receptors are present as monodimers on the cell membrane, but it was only recently discovered that these β-receptors can bind to each other to create heterodimers, i.e. β_1-β_2, β_1-β_3, β_2-β_3 (Figure 1). They can also bind to the membrane receptors of other systems to create 'cross-talk' between, for example, the sympathetic nervous system and the renin-angiotensin system. The effects of β-blockers differ when binding to monodimers as opposed to heterodimers. This potentiates new therapeutic targets - drugs that act directly not only on β-receptors, but also on newly identified heterodimer receptors. "Although we know everything about β-blockers," says Professor Pathak, "this will probably change in the next 5-6 years."

Disease modifies the sympathetic nervous system

Disease, by itself, changes the way β-receptors react and interact, and this may modify the effect of β-blockers. We know, for example, that in the state of HF there will be a decrease in the number of adrenal β-receptors with a decrease in their sensibility for a certain period and then, when administering β-blockers, an upregulation of expression with an increase in their sensibility. Disrupting the binding of natural ligands induces the pharmacodynamic effects of reducing blood pressure and heart rate.

Where the sympathetic nervous system is concerned, it is not simply a case of the interaction between a ligand and a receptor, because this system is over-regulated by very complicated mechanisms beyond what is happening at the level of cells, tissue, organs or even disease (Figure 2).

"Although we know everything about β-blockers, this will probably change in the next 5-6 years."
Professor Pathak

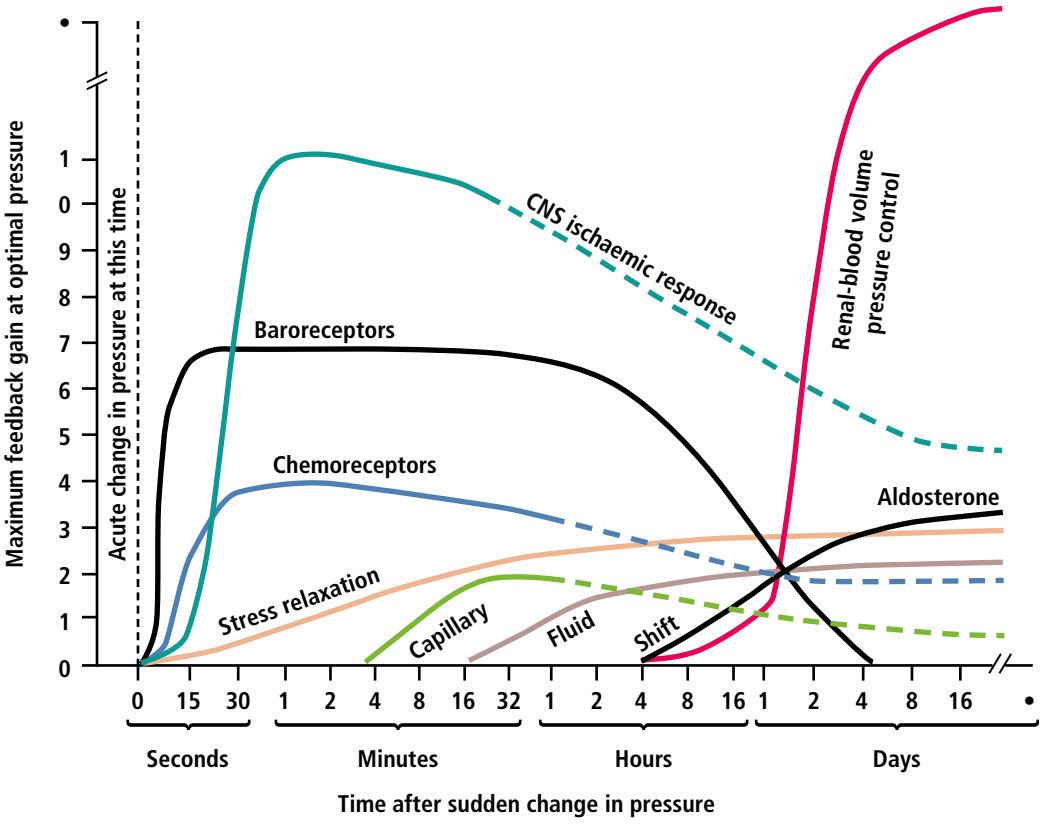


Figure 2. Factors influencing regulation of the sympathetic nervous system

How to identify a patient with sympathetic overdrive?

Across the natural history of cardiovascular disease development - risk factors, complications such as left ventricular hypertrophy and acute myocardial infarction (MI), or HF followed by sudden death – there is some kind of sympathetic overactivity. Sympathetic overdrive can initiate disease, trigger a complication, or even worsen a patient's condition (Figure 3).[1] This explains why patients with elevated sympathetic activity have HF or chronic kidney disease (CKD). Professor Pathak maintains that while it's very easy to recognise that any patient at risk of, or with, cardiovascular disease will have some kind of sympathetic overactivity, the challenge is, that upon investigation and measurement, sympathetic overdrive is more complicated than it appears.

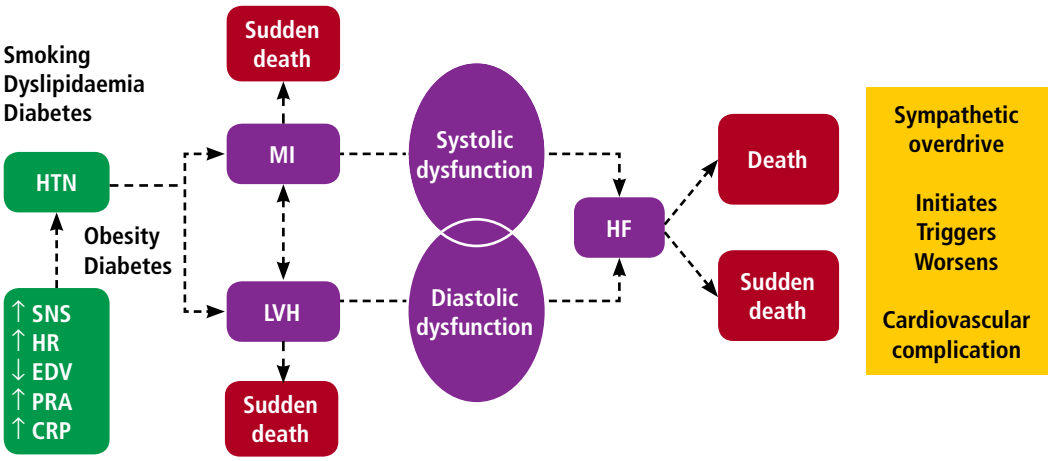


Figure 3. Sympathetic overdrive and the cardiovascular continuum[1]
HTN: hypertension; MI: myocardial infarction; LVH: left ventricular hypertrophy; SNS: sympathetic nervous system; HR: heart rate; EDV: endothelium dependent vasodilation; PRA: plasma renin activity; CRP: C-reactive protein; HF: heart failure

Elevated heart rate increases the risk of mortality

It is very difficult to identify those patients with sympathetic overdrive. One way is to measure sympathetic activity, but this is very complicated; another option is to assume, because of the association, that every patient with cardiovascular disease has sympathetic overdrive. A simple marker that might be used is heart rate. There is a very strong association between increased mortality and increased heart rate, with studies indicating that the higher the baseline heart rate in young men, the greater the rate of cardiovascular mortality and the higher the risk of sudden cardiac death (Figure 4).[2]

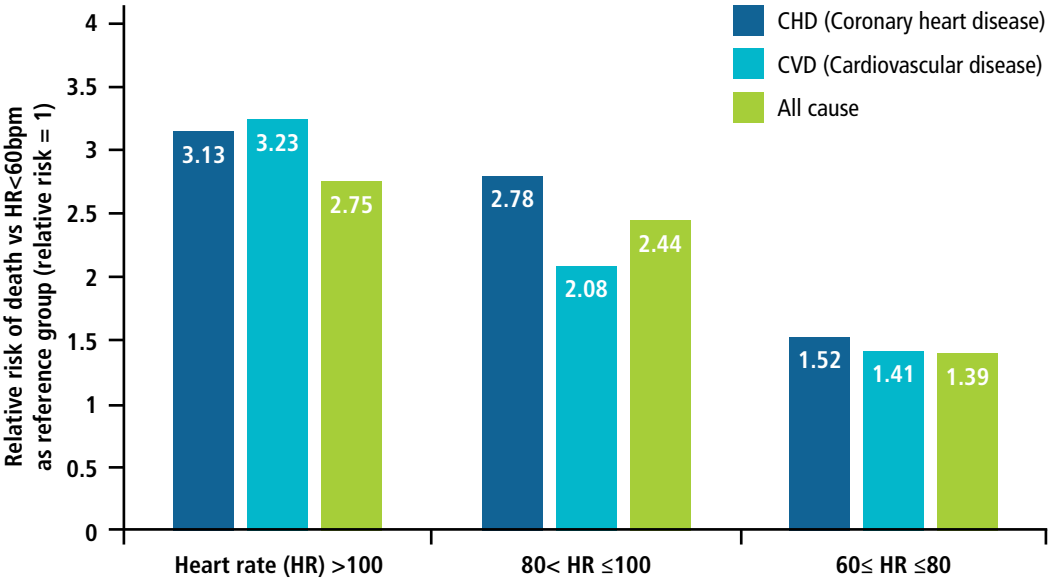


Figure 4. Elevated heart rate increases the risk of mortality in young men[2]

Estimating cardiovascular risk - the SCORE system

Newly identified cardiovascular risk factors have been included in the SCORE system. Circumstances such as psychosocial stress, burnout and social deprivation are associated with elevated sympathetic activity and increased cardiovascular risk (Table 1). So, beyond measuring blood pressure and heart rate, beyond investigating risk factors, complications or heart failure, remember that the individual's environment and circumstances - pollution, burnout, being happily married or not, laughing a lot, being a sad person, being stressed - also have an effect on sympathetic overdrive.

Table 1. Factors increasing cardiovascular risk as determined using the SCORE system

Social deprivation – the origin of many causes of cardiovascular disease
Obesity (measured by BMI) and central obesity (measured by waist circumference)
Physical inactivity
Psychosocial stress, including vital exhaustion
Family history of premature cardiovascular disease (occurring at age <55 years in men and <60 years in women)
Autoimmune and other inflammatory disorders
Major psychiatric disorders
Treatment for infection in human immunodeficiency virus
AF
Left ventricular hypertrophy
CKD
Obstructive sleep apnoea syndrome

What is the definition of hypertension?

The ESC and ESH[3] have retained the classic hypertension definition of 140/90mmHg office blood pressure. Included in this guidance are blood pressure values when measured using ambulatory blood pressure monitoring or home monitoring (Table 2). The patient with a mean blood pressure ≥140/90mmHg is considered hypertensive and treatment should be initiated. There is an exception in the case of elderly hypertensive patients; in those older than 80 years, treatment should be initiated only if systolic blood pressure (SBP) is ≥160mmHg (Table 3).

Although the ESH/ESC guidelines use 140/90mmHg as a diagnostic threshold, they acknowledge that with treatment, blood pressure should be targeted at <130/80mmHg, but not lower than 120/70mmHg. The reasoning behind this narrow target range is the J curve phenomenon – although cardiovascular risk decreases with blood pressure, there is a point where, if the blood pressure is too low, there is an increased risk of ischaemic heart disease and other negative effects, especially in patients with IHD.

Table 2. ESC/ESH definition of hypertension[2]

Category	SBP (mmHg)		DBP (mmHg)
Office blood pressure*	≥140	and/or	≥90
Ambulatory blood pressure			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep) mean	≥120	and/or	≥70
24-hour mean	≥130	and/or	≥80
Home blood pressure mean	≥135	and/or	≥85

*Conventional office blood pressure rather than unattended automated office blood pressure

Table 3. ESC/ESH treatment thresholds stratified by age and comorbidity

Age group	Office SBP treatment threshold (mmHg)					Diagnostic treatment threshold (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/ TIA	
18-65 years	≥140	≥140	≥140	≥140	≥140	≥90
65-79 years	≥140	≥140	≥140	≥140	≥140*	≥90
≥80 years	≥160	≥160	≥160	≥160	≥160	≥90
Diastolic treatment threshold (mmHg)	≥90	≥90	≥90	≥90	≥90	

*Treatment may be considered in these very high-risk patients with high-normal SBP (i.e. SBP 130-140mmHg)
CAD: coronary artery disease; TIA: transient ischaemic attack

Lowering blood pressure

The clinician should consider β-blockers at any treatment step, when there is a specific indication for their use

With regard to hypertension, much the same as with diabetes, 50% of patients are diagnosed, 50% of these are treated and 50% of treated patients reach target. In order to improve the low numbers of patients that reach therapeutic target, ESC/ESH guidelines recommend a single-pill approach and, as often as possible, a formulation of combination dual therapy. A renin-angiotensin-aldosterone system (RAAS) blocker, such as an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), is recommended in combination with a calcium channel blocker (CCB) or diuretic. If step-up is required, a combination of all three agents is recommended. If triple therapy is insufficient, add spironolactone. Furthermore, the ESC/ESH hypertension guidelines recommend that the clinician should consider β-blockers at any treatment step, when there is a specific indication for their use such as HF, AF and IHD (Figure 5).

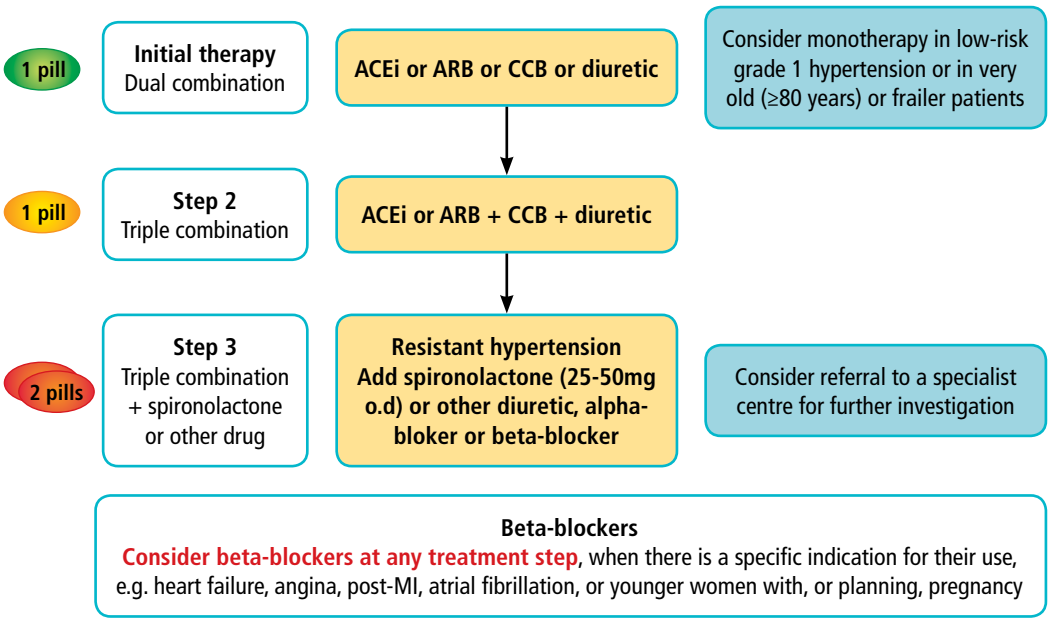


Figure 5. ESC/ESH drug treatment strategy for uncomplicated hypertension
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker

Exploring the role of β-blockers in hypertension with existing cardiovascular disease[4-8]

For the treatment of hypertension in the patient with CAD, the ESC/ESH recommends a dual combination of a β-blocker with a CCB or a diuretic or a RAAS blocker as initial therapy. Further step-up recommendations are outlined in Figure 6.

For the patient with hypertension and HF with reduced ejection fraction (HFrEF), initiate treatment with a β-blocker, a RAAS blocker and a diuretic, usually a loop diuretic. To step-up, add spironolactone (Figure 7).

In the patient with AF, the aim is to reduce heart rate and blood pressure. This patient will also benefit from combination therapy based on a β-blocker (Figure 8).

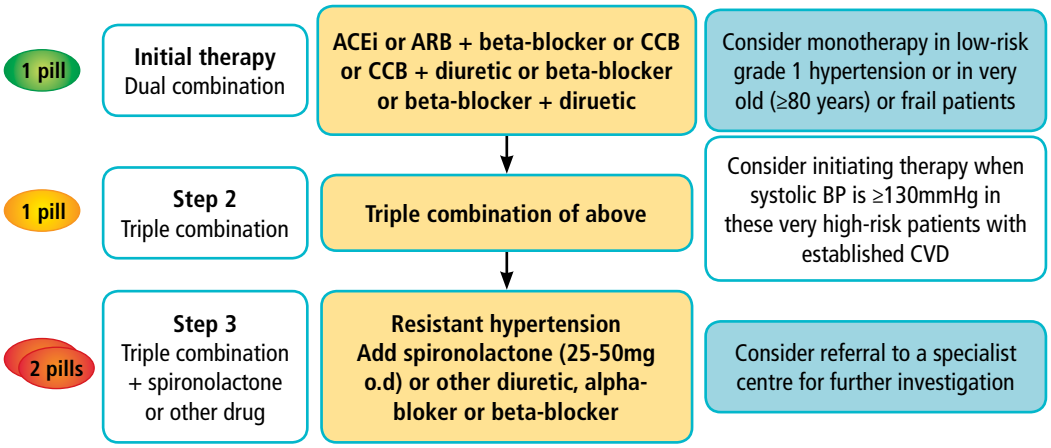
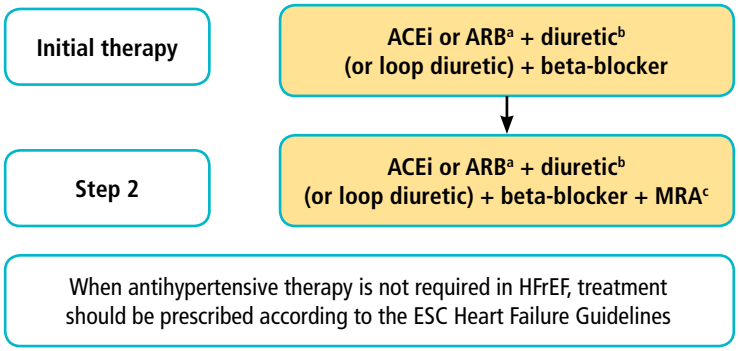
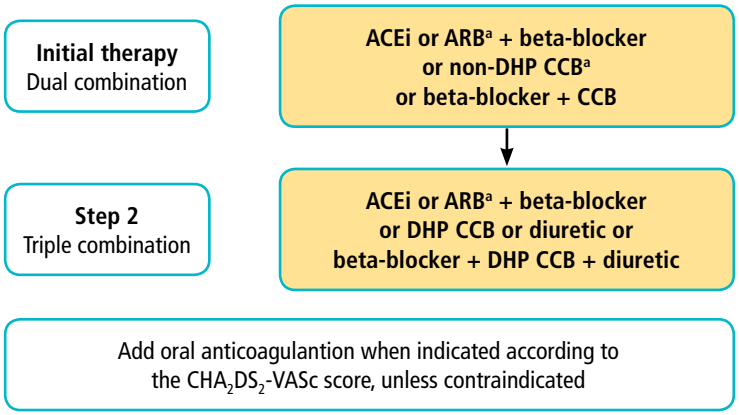


Figure 6. ESC/ESH treatment strategy for hypertension and coronary artery disease
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker



[a] Consider an angiotensin receptor/neprilysin inhibitor instead of ACEi or ARB per ESC Heart Failure Guidelines
[b] Diuretic refers to thiazide/thiazide-like diuretic. Consider a loop diuretic as an alternative in patients with oedema
[c] MRA (spironolactone or eplerenone)

Figure 7. ESC/ESH treatment strategy for hypertension and HFrEF
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ESC: European Society of Cardiology; MRA: mineralocorticoid receptor antagonist



[a] Routine combination of beta-blockers with non-dihydropyridine CCBs (e.g. verapamil or diltiazem) is not recommended due to a potential marked reduction in heart rate

Figure 8. ESC/ESH treatment strategy for hypertension and AF
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; DHP: dihydropyridine; CCB: calcium channel blocker

Factors influencing cardiovascular risk in patients with hypertension

The ESC and ESH have compiled a list of demographic characteristics and laboratory parameters associated with increased cardiovascular risk in the hypertensive patient (Table 4). Professor Pathak underscores a resting heart rate >80bpm. This indicates a patient with sympathetic overdrive, who is at high risk of a cardiovascular event and may be a candidate for β-blocker therapy.

Table 4. Factors influencing cardiovascular risk in patients with hypertension

Demographic characteristics and laboratory parameters
Sex (men > women)
Age
Smoking – current or past history
Total cholesterol and HDL-C
Uric acid
Diabetes
Overweight or obesity
Family history of premature CVD (men aged <55 years and women aged <65 years)
Family or parental history of early onset hypertension
Early onset menopause
Sedentary lifestyle
Psychosocial and socioeconomic factors
Heart rate (resting values >80 beats per min)

The β_1-selectivity of bisoprolol results in minimal effects on lung function in patients with stable angina pectoris and chronic obstructive lung disease

β-blockers can intervene at many points in the cardiovascular continuum

To β-block or not to β-block? There are specific and nonspecific indications for the use of β-blockers along the continuum of cardiovascular disease: targeting heart rate or blood pressure, risk reduction in the patient accumulating risk factors, and treatment of existing cardiovascular disease all have supporting trial evidence with use recommended by international guidelines.[9,10] Recommendations include:

- First-line treatment for the relief of angina symptoms
- Prevention of MI or death in all patients with normal left ventricular function after MI or acute coronary syndrome, and all patients with left ventricular systolic dysfunction (EF ≤40%) with HF or prior MI
- Hypertension and the hypertensive patient with cardiac comorbidities
- AF patients
- HF patients.

Which β-blocker should you use?

When deciding to use a β-blocker, Professor Pathak advises that evidence from the fields of hypertension and other diseases should be considered. His recommendations:

- Never use atenolol to treat a hypertensive patient. There is an increased risk of stroke with atenolol, and atenolol is always worse than its comparator in RCTs
- There are no morbidity or mortality data for nebivolol, but a single study, the SENIORS trial, showed that nebivolol is the only β-blocker tested in elderly HFrEF patients that is not able to show reduction in morbidity and mortality. All other trials with β-blockers in the setting of HF (carvedilol, metoprolol, bisoprolol) showed benefit

- Carvedilol is a very good agent, but it's an α_1-β-blocker and the α-blocking properties may give rise to orthostatic hypotension in some patients
- Metoprolol is a very good β-blocker with a high level of evidence in HF and IHD
- Bisoprolol has been studied in HF and ischaemic heart disease and the β_1-selectivity of bisoprolol results in minimal effects on lung function in patients with stable angina pectoris and chronic obstructive lung disease. Bisoprolol is not associated with orthostatic hypotension and shows no renal clearance.

KEY LEARNINGS

- Sympathetic overdrive leads to elevated heart rate and blood pressure in hypertension, HF and coronary artery disease, increasing the risk of cardiovascular and all-cause mortality in patients
- β-blockers help to prevent the adverse effects of sympathetic overdrive and reduce the risk of recurrent cardiovascular events and death
- Elevated heart rate is associated with increased mortality
- β-blockers can be used along the continuum of cardiovascular disease in the hypertensive patient

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