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THE POTENTIAL ROLE OF BETA-BLOCKADE IN BLUNTING THE PROGRESSION OF ATHEROSCLEROSIS

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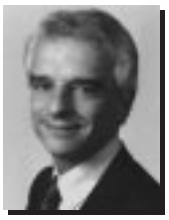

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PROGRAM GOAL:

Educational Goals

On successful completion of this continuing education activity, you should be able to:

- Understand the pathophysiologic role of sympathetic activation in heart failure, hypertension, and atherosclerosis
- Describe evidence linking stress to atherosclerosis
- Discuss recent clinical trials demonstrating the effects of β-blockade in blunting the progression of atherosclerosis
- Discuss the rationale for early initiation of β-blockers to prevent progression of hypertension to heart failure

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THE POTENTIAL ROLE OF BETA-BLO

An epidemic of heart failure (HF) is under way—in just the last decade HF prevalence tripled.[1] Of the nearly 5 million Americans with HF, about 75% are at least 65 years of age, and their numbers are expected to double within the next 40 years as the population ages.[2] The concentration of HF among older Americans is predictable, since it marks the end of a pathophysiologic progression that begins with hypertension and evolves over decades (Figure 1).[3] With increasing hemodynamic load, either systolic or diastolic dysfunction may develop and evolve to different forms of HF.[4]

On the positive side, survival with HF has improved in men and women since 1950 (Figure 2) and incidence has declined in women.[5] These favorable trends may be related to the relative contributions of conditions such as hypertension, coronary heart disease, and valve disease; changes in the pathophysiologic process (ie, the proportion of patients who have impaired versus unimpaired left ventricular [LV] systolic function); or greater use of pharmacologic therapies that extend survival in patients with HF due to LV systolic dysfunction. Nevertheless, HF remains a grave condition with less than 50% survival at 5 years.[5]

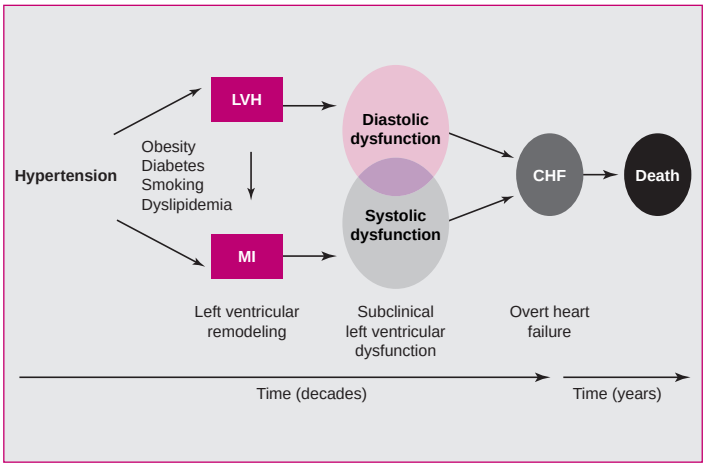

Figure 1. The progression of hypertension to heart failure. LVH = left ventricular hypertrophy; CHF = congestive heart failure. Vasan and Levy.[3]

"HF marks the end of a progression of cardiovascular disease that begins with hypertension and develops over decades."

The escalating HF epidemic and the serious prognosis for patients with HF underscore the need to intensify preventive efforts. This is particularly important for the growing number of elderly adults at increased risk of HF because of hypertension, coronary artery disease, or diabetes, as most cases are attributable to these three treatable or preventable conditions.[5] The rising prevalence of obesity, which increases the risk of hypertension, diabetes, and heart disease, adds to the prospect of HF as a major public health concern.[6,7]

This monograph focuses on the therapeutic mechanisms of β-blockers, notably the latest clinical studies demonstrating the antiatherosclerotic effects of β-blockade. It discusses recent findings on the role of sympathetic activation in the development of atherosclerotic disease. These new insights add to the logic for initiating β-blockade early in the course of atherosclerotic disease as part of treatment to avoid what, too often, is the inevitable progression of hypertension to HF in older patients.

Over the past 20 years, there have been major advances in the treatment of HF. Current medical treatment slows the progression of HF by modulating the effects of activation of the renin-angiotensin-aldosterone system and sympathetic nervous system on HF pathophysiology.[8] A series of large clinical trials involving more than 10,000 patients has demonstrated the importance of β-blockade in improving survival in patients with HF caused by LV dysfunction.[9-12] Earlier clinical trials have also clearly shown that β-blockers are highly effective in the treatment of hypertension and of coronary heart disease, including patients with chronic angina and post-myocardial infarction (MI).[13,14]

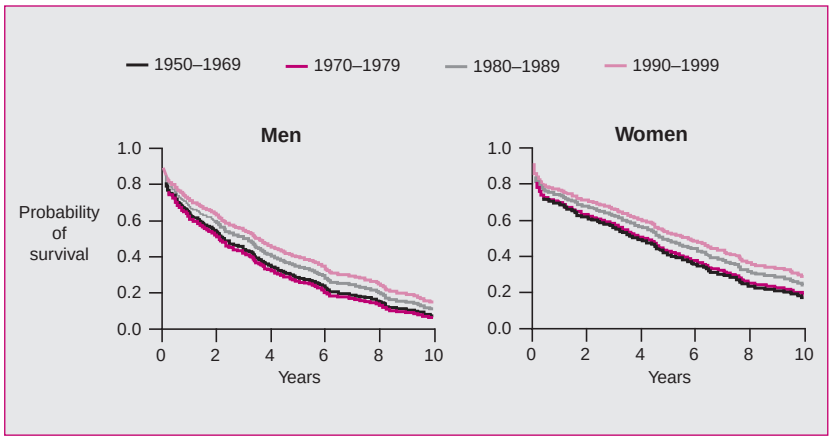

Figure 2. Trends in survival after the onset of heart failure show improved survival in men and women since 1950. Values are adjusted for age. Estimates shown are for ages 65 to 74 years. Levy et al.[5]

"The expanding HF epidemic and the serious prognosis for patients with HF underscore the need to intensify preventive efforts."

β-BLOCKADE AND THE ROLE OF SYMPATHETIC ACTIVATION

Sympathetic activation has been implicated in the pathophysiology of HF as well as in hypertension and atherosclerosis, providing the rationale for the use of β-blockade across the continuum of cardiac disease.

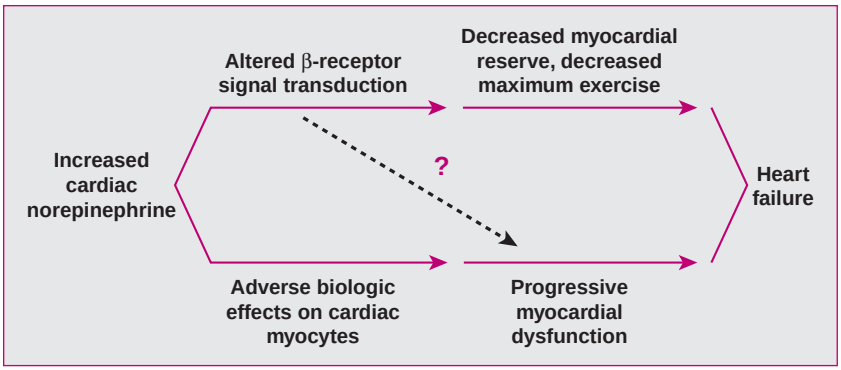

Figure 3. The adrenergic hypothesis of heart failure. Bristow.[16]

Role of sympathetic activation in HF. Vascular dysfunction in HF is driven by the adverse effects of sympathetic activation (Table).[15] The adrenergic hypothesis of HF proposes that increased cardiac adrenergic drive contributes to the two hallmarks in the natural history of HF: impaired exercise capacity and progression of myocardial dysfunction (Figure 3).[16] In the short term, increased adrenergic activation may play a compensatory role by increasing heart rate and myocardial contraction. In the long run, chronic adrenergic activation may damage the heart by increasing afterload and precipitating cardiac arrhythmias. The increase in sympathetic tone intensifies myocardial contractility, tachycardia, atrial vasoconstriction (thus increasing cardiac afterload), and venoconstriction (which increases cardiac preload).[17]

In the failing heart, the continuously increased adrenergic drive conveys adverse biological signals to the cardiac myocytes via β_1- and probably β_2- and α_1-adrenergic receptors, with the majority mediated by β_1-receptors.[16] This is the fundamental reason for the use of antiadrenergic therapy in the treatment of chronic HF.

The evidence that β-blockers improve survival in patients with HF caused by LV dysfunction is compelling. β-Blockade with bisoprolol, carvedilol, and extended-release metoprolol succinate consistently improved survival in patients with mild to severe HF (New York Heart Association class II to class IV) in major mortality trials (Figure 4).[10-12] Only one study has failed to demonstrate a benefit: Bucindolol achieved favorable short-term effects (reductions in heart rate and HF symptoms and improved ejection fraction) but it did not reduce all-cause mortality in patients with class III or IV HF.[18]

Role of sympathetic activation in hypertension. The importance of sympathetic nervous activation in hypertension is well documented.[19] Younger individuals with essential hypertension have increased circulating catecholamine levels, sympathetic nervous hyperactivity in muscles, and increased vascular reactivity to α-adrenergic agonists.[4] The renin-angiotensin-aldosterone system may also be involved both as a direct pressor and as a growth promoter to produce LV hypertrophy (LVH). This was suggested in the LIFE (Losartan Intervention for Endpoint Reduction) trial by the superiority of losartan over atenolol in patients with hypertension and LVH.[20]

Table. Adverse Vascular Effects of Sympathetic Activation

↑ Endothelial injury
↑ Vessel wall permeability to lipid transport
↑ Release of growth factors
↑ Platelet activation (platelet-derived growth factor)
↑ Apoptosis (programmed cell death)
↑ Inflammatory changes in arterial wall
↓ Metabolic performance
↑ Risk for cardiovascular events

Adapted from Bondjers.[15]

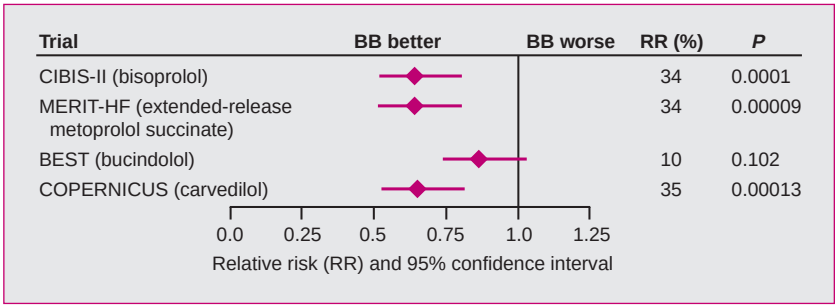

Figure 4. All-cause mortality results from the β-blocker mortality trials. BB = β-blockers. Adapted from CIBIS-II Investigators and Committee,[10] MERIT-HF Study Group,[11] Packer et al,[12] and the Beta-Blocker Evaluation of Survival Trial Investigators.[18]

In the treatment of hypertension, besides direct hemodynamic effects, β-blockers may exert hypotensive effects through resetting baroreceptors, reducing cardiac output, blocking the release of renin, blocking adrenergic neurons, reducing central sympathetic tone, and increasing vasodilator prostaglandins.[21] When hypertension is being treated, evidence of a beneficial effect on mortality and morbidity is clearest for β-blockers and diuretics.[22] β-Blockers are indicated for treatment of uncomplicated hypertension, along with diuretics. β-Blockers are recommended for hypertensive patients with concomitant coronary disease, including angina and particularly after an MI, and for patients with HF or tachyarrhythmias.[23] Although β-blockers were not tested in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), the results showed a relative equivalence among chlorthalidone, lisinopril, and amlodipine.[24]

Stress, sympathetic activation, and atherosclerosis. Although relatively little attention has been paid to the role of β-blockade in the atherogenic process, the level of evidence supporting the use of β-blockers in patients with a history of atherosclerotic cardiovascular disease is very strong.[13,14] Current secondary-prevention guidelines recommend indefinite use of β-blockers in all patients with coronary and other vascular diseases.[14] Potential mechanisms for the benefits of β-blockade have included antihypertensive effects, improvements in myocardial function, and antiarrhythmic effects—notably, a significant reduction in sudden death.[25] Now, accumulating evidence linking stress to coronary artery disease and atherosclerosis supports the hypothesis that β-blockers may exert antiatherosclerotic effects by antagonizing the sympathetic nervous system.

Job-related stress doubles the risk of cardiovascular death among healthy workers.[26] Humans who have an exaggerated blood pressure response to stress are more likely to have increased atherosclerosis.[27]

JNC-VI: HYPERTENSIVE RX CONSIDERATIONS

Recommendations in the sixth report from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) reflect growing evidence that selecting an antihypertensive agent that not only lowers blood pressure but also moderates the underlying pathophysiologic process may enhance the outcome of treatment.[25]

The antihypertensive drug selected should optimally be effective over 24 hours with once daily dosing, and with at least 50% of the peak effect persisting at the end of 24 hours. Long-acting agents are preferable to short-acting agents for the following reasons:

- Compliance is better with once-daily dosing
- Fewer tablets may reduce costs
- Hypertension control is continual with no interruptions
- May protect against the risk of sudden death and other cardiovascular events related to the abrupt early-morning increase in blood pressure

Experimental studies show that infusion of noradrenaline has an atherogenic effect in rhesus monkeys that may be inhibited by sympathectomy.[28] Psychosocial stress increases atherosclerosis in dominant cynomolgus monkeys, but these atherogenic effects are inhibited with β-blockade.[29] Psychosocial stress causes endothelial injury that is mediated by β_1-receptor activation and inhibited by the β_1-selective agents metoprolol and atenolol (Figure 5).[30] Together, these experimental studies support the idea of psychosocial stress via β_1-adrenergic activation as a major factor in precipitating and exacerbating atherosclerosis.

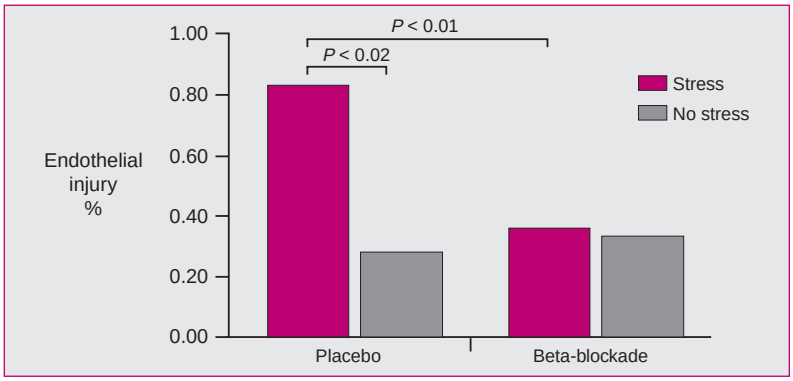

Figure 5. Psychosocial stress caused a significant increase in injured endothelial cells in circumostial areas of the descending thoracic aorta in cynomolgus monkeys. The effect of stress is mediated by β_1-receptor activation and inhibited by β_1-selective receptor antagonists. Skantze et al.[30]

"Experimental studies support the idea of psychosocial stress via β_1-adrenergic activation as a major factor in precipitating and exacerbating atherosclerosis."

Potential antiatherosclerotic mechanisms of β-blockade. The atherogenic effect of sympathetic activation is probably the result of complex interactions between hemodynamic and biochemical effects. In the central nervous system, β-blockade promotes a decrease in sympathetic nervous discharge and improves cardiac hemodynamics by reducing heart rate, blood pressure, and contractility. At the vascular wall, β-blockade may reduce atherosclerosis by such mechanisms as decreasing endothelial injury, increasing production of prostacyclins (which relax vascular smooth muscle), inhibiting platelet accumulation, and decreasing the binding of low-density lipoprotein cholesterol (LDL-C) to proteoglycans in the vessel wall (Figure 6).[15,31]

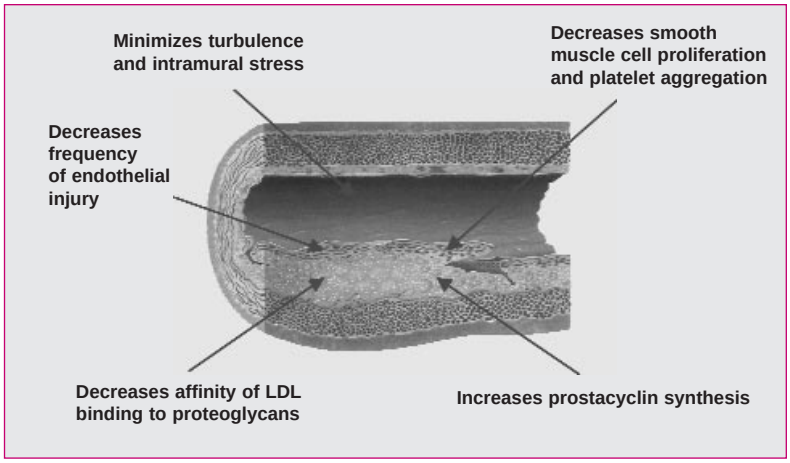

Figure 6. Long-term β-blockade interferes with key steps in the development of atherosclerosis. LDL=low-density lipoprotein. Adapted from Bondjers[15] and Kaplan and Manuck.[31]

Clinical trial evidence for β-blockade blunting progression of atherosclerosis

The growing evidence supporting an anti-atherosclerotic effect of β-blockade provided the stimulus for two primary-preventive, randomized placebo-controlled ultrasound studies of the effect of β-blockade on atherosclerotic progression.

BCAPS: the β-blocker Cholesterol-lowering Asymptomatic Plaque Study

Briefly, the aim of BCAPS was to investigate the antiatherogenic effect of a low dose of extended-release metoprolol succinate (25 mg once daily) on the progression of carotid atherosclerosis in asymptomatic adults with carotid artery plaque.[32] The study enrolled 793 subjects (mean age 60 years). Follow-up was 3 years. Most subjects had normal cholesterol levels on entering (mean 6 mmol/L). The main outcomes of the study were the changes in mean carotid intima-media thickness (IMT) and maximal IMT (IMT_{max}) in the bulb.

Summary of BCAPS results

- In the extended-release metoprolol succinate group, mean heart rate was markedly reduced (–2.5 beats/min; $P = 0.006$) compared with placebo, whereas systolic blood pressure was not (–1.3 mm Hg; NS).
- Lipid levels, lipoproteins, or other metabolic variables in the placebo and treatment groups were similar.
- The progression of IMT_{max} in the carotid artery bulb as shown in Figure 7 was reduced significantly in the extended-release metoprolol succinate group at 18 months (–0.058 mm/y) and at 3 years (–0.028 mm/y).
- The combined outcome of all-cause mortality or nonfatal MI or nonfatal stroke was significantly lower in the extended-release metoprolol succinate group, which had 8 events versus 19 in the placebo group (Figure 8).

"The progression of IMT_{max} in the carotid artery bulb was reduced significantly in the extended-release metoprolol succinate group."

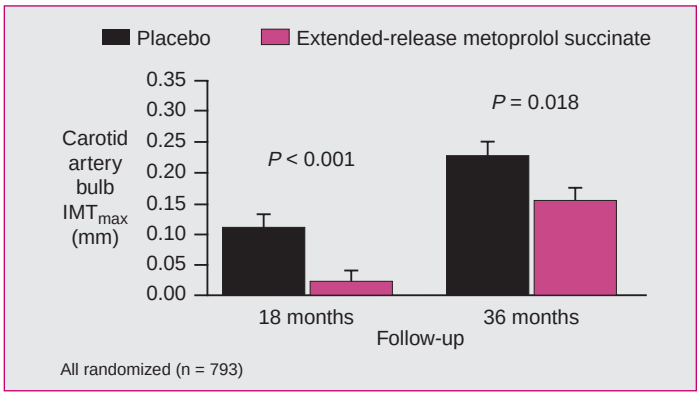

Figure 7. BCAPS: Changes in maximal intima-media thickness (IMT_{max}) in the carotid artery bulb at 18 months and 36 months compared with baseline. Adapted from Heblad et al.[32]

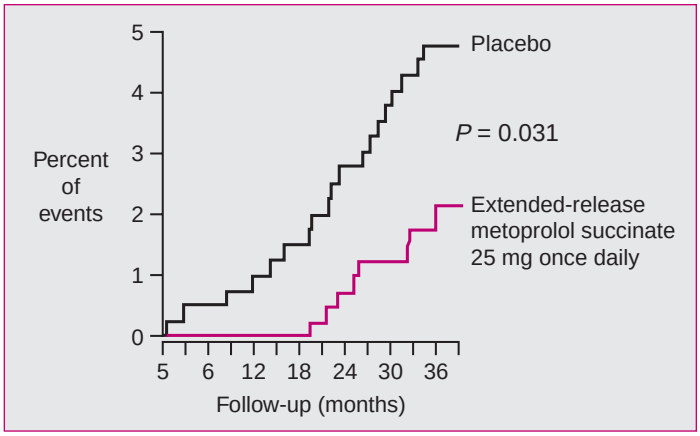

Figure 8. BCAPS: Kaplan-Meier estimates of the combined outcome of all-cause mortality or nonfatal myocardial infarction or stroke (time to first event). Heblad et al.[32]

ELVA: Antiatherogenic Effect of β-Blockade in Hypercholesterolemia

ELVA (Effect of Long-Term Treatment with Metoprolol CR/XL on Surrogate Variables for Atherosclerotic Disease) was a 3-year trial to compare the effect of β-blockade with extended-release metoprolol succinate 100 mg once daily and placebo on IMT in the carotid artery in patients with hypercholesterolemia on concomitant lipid-lowering therapy.[33] The aim was to determine whether β-blockade provided an added antiatherosclerotic effect to that provided by statins. The study included 92 subjects with hypercholesterolemia (mean age 60 years). Study participants had total cholesterol levels ≥6.5 mmol/L, LDL-C >5.0 mmol/L, and signs of early carotid artery atherosclerosis. Most patients were also prescribed a statin.

Summary of ELVA results

- Heart rate decreased 5.1 beats/min in the β-blocker group.
- There was no significant difference between groups in blood pressure (net difference 3.8 mm Hg), probably because subjects entering the study were normotensive (mean blood pressure 138/80 mm Hg).
- Lipid levels were similar in the treatment and placebo groups; in both groups, cholesterol levels were reduced to 6.4 mmol/L (Figure 9).
- There was a highly significant difference in the progression of carotid bulb IMT plus common carotid IMT between the extended-release metoprolol succinate and placebo groups after 1 year (–0.08 vs –0.01 mm) and the benefit persisted at 3 years (–0.06 vs +0.03 mm) (Figure 10).
- The decrease in carotid IMT was not secondary to an increase in lumen diameter, which actually decreased slightly during follow-up.[33]

Significance of BCAPS and ELVA Results

The BCAPS and ELVA studies provide the first evidence that β-blockade reduces progression of atherosclerosis in the vascular tree in humans, indicating that these agents may lower the risk of developing atherosclerosis. The results point to an important role of the autonomic nervous system in atherosclerosis. The findings are consistent with the hypothesis that long-term β-blockade retards atherosclerosis and may do so independently of an antihypertensive effect.

"β-Blockade reduces progression of atherosclerosis in the vascular tree in humans, indicating that these agents may lower the risk of developing atherosclerosis."

In BCAPS, atherosclerosis was regressed with a very low dose of extended-release metoprolol succinate that did not decrease blood pressure in asymptomatic middle-aged and older men and women with a carotid plaque but no other symptoms of carotid artery disease. The BCAPS findings may be relevant for a very large population, since more than 50% of the people over age 60 who were screened for the study had a carotid plaque.[32]

The findings in ELVA indicate that in hypercholesterolemic patients, β-blockers have an antiatherosclerotic effect in addition to that of statins—which suggests that statins and β-blockers affect different mechanisms in the atherosclerotic process. The subjects in the study covered a wide spectrum of patients: hypercholesterolemia ranged from mild to severe and IMT thickening ranged from mild to extended plaques. Therefore, the findings with extended-release metoprolol succinate may be relevant for many patients with high cholesterol levels and therefore at risk for heart disease or stroke.[33]

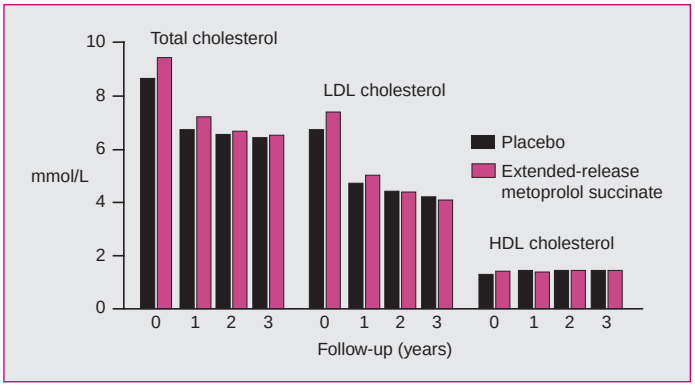

Figure 9. ELVA: Lipid levels at entry to the study and at 1, 2, and 3 years of follow-up. Most patients received statin therapy during follow-up. Wiklund et al.[33]

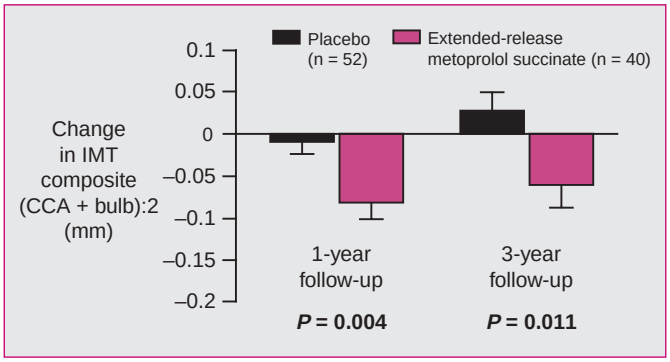

Figure 10. ELVA: Changes in intima-media thickness (IMT) composite of common carotid artery (CCA) and carotid artery bulb at 1 and 3 years of follow-up. The absence of an increase in IMT during year 1 in the placebo group probably relates to use of open-label statin therapy after randomization. Wiklund et al.[33]

Clinical Summary

- The autonomic nervous system may have an important role in atherosclerosis. Long-term β-blockade may retard the atherosclerotic process by interfering with key steps in atherosclerotic development.
- The results of BCAPS and ELVA provide the first evidence that β-blockade slows progression of atherosclerosis in humans. These findings extend the clinical benefits of β-blockers from hypertension, coronary artery disease, and HF to also include asymptomatic patients with carotid atherosclerosis.
- The results are the first to show an added antiatherosclerotic effect of β-blockade in patients who are also taking statins, which suggests that statins and β-blockers impact different mechanisms in the atherosclerotic process and have additive effects.
- Extended-release metoprolol succinate reduced atherosclerotic development and cardiovascular events in asymptomatic adults with carotid plaque, suggesting the importance of initiating β-blockade early in the course of atherosclerotic disease to blunt progression and reduce the risk of cardiac events.

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For more information about the Vascular Biology Working Group, go to www.vbwg.org.

Vascular Biology in Clinical Practice™

The Potential Role of Beta-blockade in Blunting the Progression of Atherosclerosis

Self-assessment questions

Please check the appropriate answer for each question on the Answer Key.
Instructions for obtaining CME credit are provided on the back of the Answer Key.

1. Approximately how many Americans currently have HF?
   a) 1 million
   b) 3 million
   c) 5 million
   d) 15 million

2. Approximately 75% of Americans with HF are age 65 or older.
   a) True
   b) False

3. People with heart failure are living longer than 50 years ago and incidence has decreased in women.
   a) True
   b) False

4. What is the rate of 5-year survival with HF?
   a) <30%
   b) <40%
   c) <50%
   d) <60%

5. Which of these adverse effects may result from sympathetic activation?
   a) Increased endothelial injury
   b) Increased permeability of vessels to lipid transport
   c) Increased release of growth factors
   d) Inflammatory changes
   e) All of the above

6. The adrenergic hypothesis of HF proposes that increased adrenergic drive contributes to impaired exercise capacity and progression of myocardial dysfunction.
   a) True
   b) False

7. In major HF survival studies, which of these β-blockers did not improve all-cause mortality?
   a) Carvedilol
   b) Extended-release metoprolol succinate
   c) Bucindolol
   d) Bisoprolol

8. Younger patients with essential hypertension have increased circulating catecholamine levels.
   a) True
   b) False

9. Antihypertensive agents with once-daily dosing may offer protection against risks associated with the abrupt increase in blood pressure early in the morning.
   a) True
   b) False

10. In the BCAPS study, extended-release metoprolol succinate 25 mg daily reduced the progression of atherosclerosis in the carotid bulb. What was the patient population in the study?
    a) Hypercholesterolemic patients
    b) Asymptomatic patients with carotid plaques
    c) Patients with a history of angina

11. In BCAPS, β-blockade was associated with a reduction in all-cause mortality, or nonfatal stroke, or myocardial infarction.
    a) True
    b) False

12. In the ELVA study, extended-release metoprolol succinate 100 mg daily reduced carotid atherosclerotic progression in patients with high cholesterol levels. Which of the following results was observed?
    a) Antiatherosclerotic effect was in addition to statin therapy
    b) Benefit of treatment was seen at 18 months and 3 years
    c) Lipid levels were similar in the β-blocker and placebo groups
    d) All of the above

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Answer Key

Please check the correct box for each question. There is only 1 correct response for each question.

1.	A	B	C	D		5.	A	B	C	D	E	9.	A	B	
2.	A	B				6.	A	B				10.	A	B	C
3.	A	B				7.	A	B	C	D		11.	A	B	
4.	A	B	C	D		8.	A	B				12.	A	B	C	D

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Your input will help us improve our educational activities.
Please rate this monograph in the following areas:

	Excellent				Poor
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Value of content	5	4	3	2	1
Readability and presentation	5	4	3	2	1
Usefulness of illustrations	5	4	3	2	1
	Agree				**Disagree**
Importance to physicians	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Did not promote particular product or company	5	4	3	2	1

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To obtain a certificate for 1 category 1 credit toward the Physician's Recognition Award of the American Medical Association (AMA) for completing the activity, ***The potential role of beta-blockade in blunting the progression of atherosclerosis,*** please complete the self-assessment questions, fill out the correct answers on the Answer Key, and mail the Activity Evaluation and Answer Key to:

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