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PERI-INTERVENTIONAL CARE:

Rationale for ACE manipulation

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PROGRAM GOAL:

Educational Goals

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

- Understand new data concerning the potential role of angiotensin-converting enzyme (ACE) and angiotensin II on the endothelium in acute coronary syndrome (ACS) pathophysiology
- Discuss the role of ACE inhibition for improving plaque stability and vascular biology in patients with ACS
- Describe new clinical trials supporting use of ACE inhibition in the peri-interventional period in a comprehensive secondary prevention regimen to reduce the risk of future vascular events

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PERI-INTERVENTIONAL

Cardiovascular (CV) disease is the leading cause of death and disability in the United States and the number one category for hospital discharges.[1,2] There are at least 1.1 million myocardial infarctions (MI) annually, of which 450,000 are recurrent MIs.[1] Many recurrent events could be avoided through more intensive secondary prevention, particularly if treatment is initiated in the hospital at the patient's "teachable moment."[3]

RATIONALE FOR ACE INHIBITION IN ACUTE CORONARY SYNDROMES

Widespread inflammation and unstable plaques in the coronary tree of patients with acute coronary syndromes (ACS) are a major cause of recurrent events.[4,5] In the peri-interventional period intensive secondary-prevention strategies directed to the vascular wall are essential to enhance plaque stability and reduce recurrent ischemic events *(Figure 1)*.[6] Angiotensin-converting enzyme (ACE) inhibitors possess plaque-stabilizing properties that contribute to their proven benefit in reducing recurrent coronary events. These favorable effects are in addition to those of lipid-lowering drugs and other concomitant medications.[6]

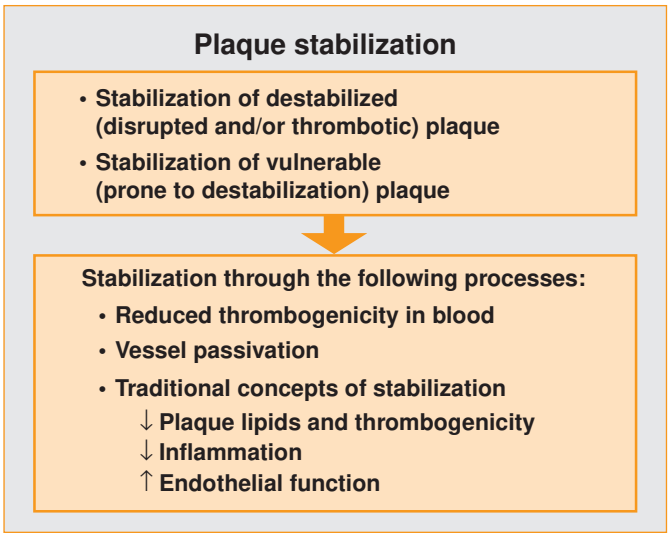

Figure 1. A new paradigm for plaque stabilization to prevent future coronary events. Adapted from Ambrose and Martinez.[6]

CARE: RATIONALE FOR ACE MANIPULATION

This monograph focuses on ACE inhibition in peri-interventional care, including:

- Mechanisms of ACE inhibition that benefit vascular function
- The evolution of ACE inhibition for treatment of high-risk patients
- Recent clinical trials that extend the benefits of ACE inhibition for secondary prevention of ischemic events

ROLE OF ACE, ANG II, AND BRADYKININ AT THE VESSEL WALL

CV risk factors (eg, hypertension, hyperlipidemia, and diabetes) trigger pathobiologic changes in the vessel wall that promote vascular disease. One of the first changes is increased oxidative stress, which disrupts vascular homeostasis of reactive oxygen species, inactivates nitric oxide (NO), and promotes endothelial dysfunction.[7] Activation of the vascular renin-angiotensin system (RAS) has been linked to increased oxidative stress. Overall, the RAS has an important role in modulating the atherogenic process.

ACE catalyzes formation of angiotensin (Ang) locally; Ang II is a potent inflammatory mediator. ACE also degrades bradykinin. Inflammation has a fundamental role in mediating all stages of atherosclerosis, from its initiation through progression and, ultimately, the thrombotic complications.[8] Ang II has important proinflammatory actions in the vascular wall, including the induction of reactive oxygen species, cytokines, and adhesion molecules, potentially acting through a positive-feedback mechanism *(Figure 2)*.[7]

Ang II increases vascular inflammation and induces endothelial dysfunction, enhancing atherogenesis and the risk of ischemia.

Bradykinin breakdown disrupts the vessel wall. Bradykinin degradation by ACE leads to a decrease in locally generated NO and prostacyclins, which are critical vasorelaxant and anti-inflammatory molecules.[7] Bradykinin degradation also impairs fibrinolysis, as bradykinin is a potent stimulus of tissue plasminogen activator (tPA).[9]

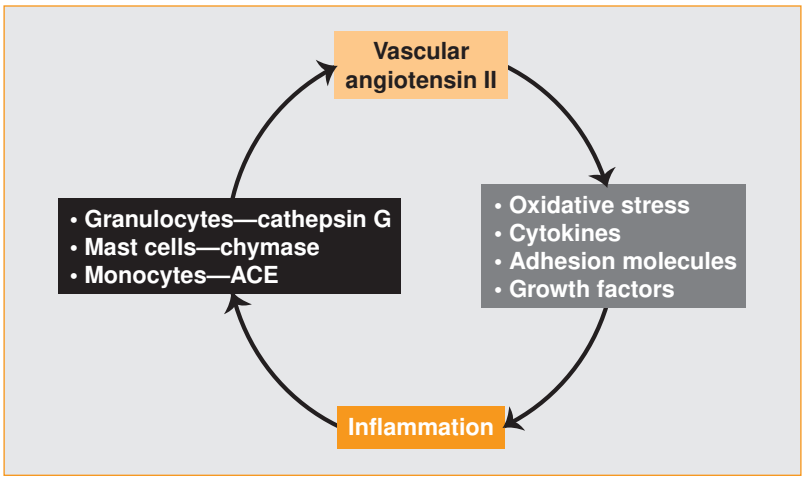

Figure 2. Activation of vascular ACE creates a positive-feedback mechanism for Ang II formation with subsequent induction of oxidative stress and inflammation. Dzau.[7]

ACE and Ang II: Levels of ACE and Ang II are elevated in culprit lesions. Human atherosclerotic lesions contain high levels of ACE and Ang II concentrated in the inflamed shoulder regions of vulnerable plaques.[10] ACE activity is increased in culprit lesions from patients with ACS, but not in lesions from patients with stable disease; therefore ACE activity may be related to the causative mechanism in ACS.[11]

"Angiotensin-converting enzyme (ACE) inhibitors possess plaque-stabilizing properties that contribute to their proven benefit in reducing recurrent coronary events."

Ang II may foster plaque instability and ischemia through multiple mechanisms[7]:

- Stimulates LDL oxidation and migration of lipid-rich macrophages and lymphocytes to vulnerable plaque shoulders
- Accelerates metalloproteinase release, which can break down extracellular matrix, weakening the vulnerable shoulder area
- Increases expression of inflammatory cytokines and leukocyte adhesion molecules
- Promotes thrombosis by stimulating production of plasminogen activator inhibitor-1 (PAI-1) and sensitizing platelets, altering fibrinolytic and clotting mechanisms[9]

ACE INHIBITION HAS MULTIPLE ANTI-ISCHEMIC EFFECTS

ACE inhibitors have a wide range of vascular protective actions.[12] ACE inhibition blunts atherogenic and ischemic processes in the vascular wall, which can lead to ACS development, including oxidation, inflammation, vascular smooth muscle cell proliferation, and thrombosis *(Table 1)*.[12] Inhibition of ACE reduces Ang II, blunting its multiple damaging effects, and prevents bradykinin degradation, which increases NO, the central regulator of CV homeostasis.

On the whole, research advances have increased understanding of ACE inhibition as a target for pharmacologic treatment.[7] The anti-inflammatory effect of ACE inhibition at the vascular wall may help to stabilize plaque, reducing the risk of rupture or thrombosis and the resulting acute ischemic episode.

LANDMARK TRIALS: ACE INHIBITION IN POST-MI PATIENTS

Results of large randomized trials that evaluated ACE inhibition for patients with acute MI support the use of ACE inhibitors in the treatment of early MI. A multi-trial analysis involving 100,000 patients with acute MI shows that ACE inhibition given within

Table 1. Potential Vascular Protective Anti-ischemic Effects of ACE Inhibition

↑ Endothelial function
↑ Release of NO and prostacyclin
↓ Vascular remodeling
↓ LDL oxidation
↓ Macrophage migration and function
↑ Endogenous fibrinolysis
↓ PAI-1
↑ tPA
↓ Platelet aggregation
↓ Sympathetic activity
↓ Blood pressure
↓ Left ventricular mass

Ambrosioni et al.[12]

36 hours of onset and continued for 4 to 6 weeks reduces 30-day mortality by 7% (P = 0.004), with 85% of the benefit occurring during the first week *(Figure 3)*.[13] A broad range of patients benefited from treatment, but patients with left ventricular (LV) dysfunction had the greatest advantage.

Long-term studies of ACE inhibition in post-MI patients with LV dysfunction show not only that ACE inhibitors reduce mortality from heart failure, but that they reduce the risk of coronary ischemic events. Pooled results of three trials of ACE inhibition

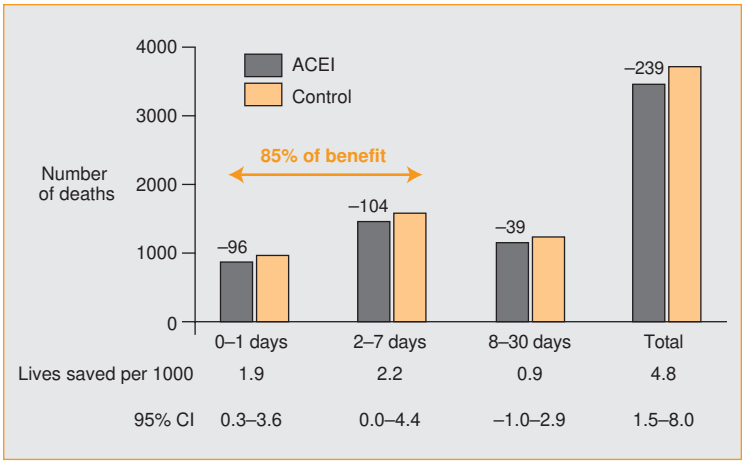

Figure 3. Multi-trial analysis demonstrates the positive effect of early ACE inhibition on deaths in acute MI patients (N = 100,000). ACE Inhibitor Myocardial Infarction Collaborative Group.[13]

in 6000 post-MI patients with reduced LV function or clinical heart failure, including SAVE (Survival and Ventricular Enlargement), AIRE (Acute Infarction Ramipril Efficacy), and TRACE (Trandolapril Cardiac Evaluation), demonstrated that ACE inhibition started as early as 3 days after an acute event and continued for a median of 31 months reduced deaths by 26%.[14] ACE inhibition was unexpectedly associated with a 20% reduction in MI that was unrelated to LV ejection fraction. These results were consistent with findings in the earlier SOLVD (Studies of Left Ventricular Dysfunction) trials in 6800 patients with LV dysfunction or clinical heart failure.[14] This observation suggested that ACE inhibition might prevent MI in a wide range of patients, not just those with reduced LV function—a hypothesis that has been verified in the HOPE (Heart Outcomes Prevention Evaluation) study.[15]

"This observation suggested that ACE inhibition might prevent MI in a wide range of patients, not just those with reduced LV function—a hypothesis that has been verified in the HOPE study."

ACE INHIBITION BENEFITS IN HIGH-RISK PATIENTS WITH NORMAL LV FUNCTION

The HOPE study showed that long-term ACE inhibition significantly reduces mortality and coronary events in a wide spectrum of patients with normal LV function who are at high risk for CV events.[15] HOPE evaluated the effect of ramipril 10 mg daily vs placebo in 9297 patients aged >55 years with LV ejection fractions of ≥40% and a history of coronary disease, stroke, peripheral vascular disease, or diabetes plus another CV risk factor. Treatment with ramipril reduced the combined primary outcome of MI, stroke, and CV death by 22% at 4.5 years. The benefit was evident at 1.5 years and progressively improved with duration of treatment.

HOPE: ANTI-ISCHEMIC EFFECTS OF ACE INHIBITION

Long-term treatment with ramipril reduced coronary events, including reductions of 21% in total MI *(Figure 4)*, 16% in fatal MI, 23% in nonfatal MI, 12% in new or worsening angina, and 18% in the need for coronary revascularizations.[16] Significant risk reductions were noted in high-risk subgroups and in patients taking antiplatelet agents, β-blockers, and lipid-lowering therapy, indicating that the favorable effects are independent of and additive to agents with known cardioprotective benefits.

Benefit is in addition to BP reduction. Only part of the benefit of ACE inhibition observed in HOPE is attributed to blood pressure (BP) reduction, as the mean BP reduction was slight (~3/2 mm Hg). The majority of patients entering the study had normal BP and the remainder had controlled hypertension: The mean baseline BP was 139/79 mm Hg. Therefore, the clinical benefit of ACE inhibition is likely to be related to multiple vascular protective actions in addition to BP lowering.[12]

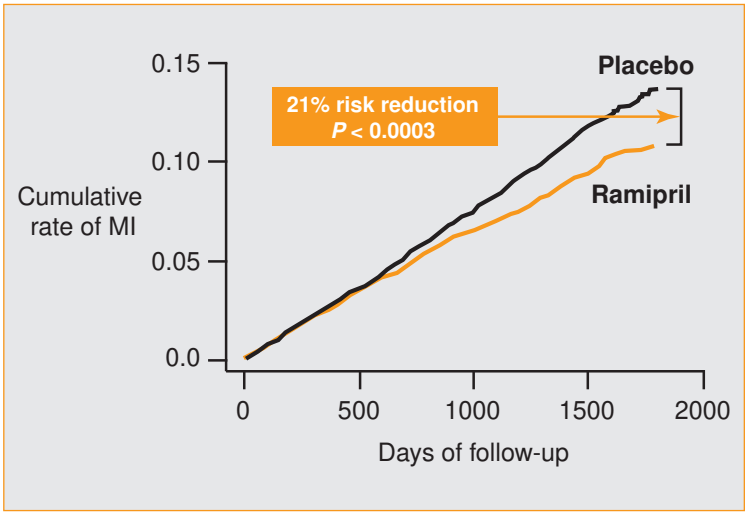

Figure 4. HOPE: Cumulative rate of fatal/nonfatal myocardial infarction with ramipril vs placebo.
Dagenais et al.[16]

Similar benefits of ACE inhibition in women and men. The HOPE study provides strong evidence for the role of ACE inhibitor therapy in post-menopausal women at high risk for CV events. HOPE shows that ramipril significantly reduces the risk of major vascular events in women (n = 2480).[17] Treatment resulted in reductions of 23% in the combined outcome of nonfatal MI, stroke, and CV death, 38% in CV death, and 36% in stroke (all $P < 0.05$ vs placebo). There were trends towards reduced rates of MI, heart failure, and all-cause death. The beneficial effects of ramipril appear to be similar in women and men *(Figure 5)*.

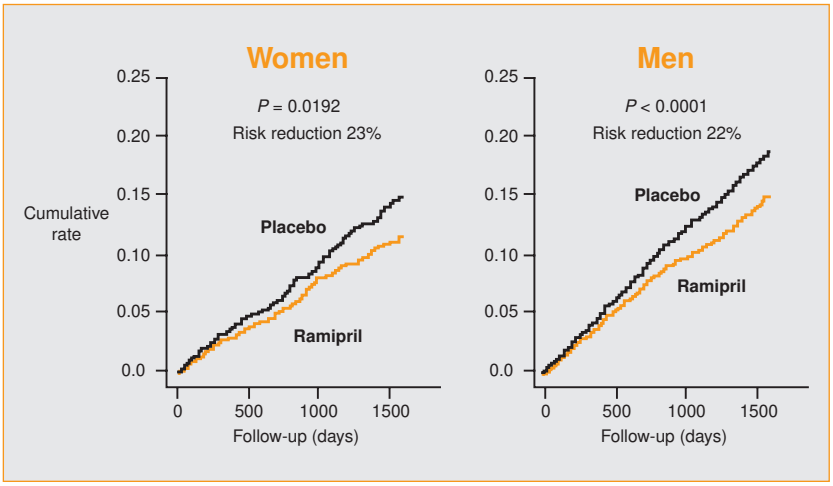

Figure 5. HOPE: Primary composite outcome of MI, stroke, or CV death in women and men. Lonn et al.[17]

"Long-term ACE inhibition may improve clinical outcomes in patients with stable coronary artery disease who undergo revascularization."

Reducing Stroke in High-Risk Patients

Stroke is the third leading cause of death in the United States and a leading cause of disability.[1] Although the stroke death rate declined by 13% over the last decade, the actual number of stroke deaths rose by 8.6%.[1] For survivors, stroke-related complications present a major personal and economic burden. While lowering blood pressure can prevent stroke, a large proportion of strokes occur among normotensive patients.[18] Therefore, additional therapies are needed that lower the probability of stroke across a broad range of patients at high risk.

The efficacy of ACE manipulation in preventing stroke in high-risk patients is demonstrated in two recent studies.

PROGRESS (Perindopril Protection against Recurrent Stroke Study) evaluated the effect of BP reduction with perindopril 4 mg plus or minus indapamide 2.0–2.5 mg on recurrent stroke in a 4-year study of 6100 patients with a history of stroke or transient ischemic attack (TIA).[19] Patients had a wide range of baseline BP. The perindopril plus indapamide regimen reduced BP by 12/5 mm Hg. The benefits were largely seen in those taking both drugs, which reduced stroke recurrence by 43%. Benefits were seen in both hypertensive and nonhypertensive patients. Overall, BP declined by 9/4 mm Hg with active treatment, and stroke recurrence was reduced by 28% ($P < 0.0001$).

In the HOPE study, in a broad group of high-risk patients with relatively normal BP, prolonged treatment with ramipril reduced TIA and fatal and nonfatal stroke, including strokes of ischemic and hemorrhagic origin.[20] In the ramipril group, there was a 32% relative risk reduction in all strokes ($P = 0.0002$); 156 patients had a stroke compared with 226 in the placebo group. Cognitive impairment was reduced by 39% among ramipril patients with nonfatal stroke. Benefits with ramipril were consistent across all baseline BP levels, all high-risk subgroups, and in patients using aspirin, other BP-lowering medications, or lipid-lowering drugs.

Benefits of ACE inhibition post-revascularization

Two earlier studies indicate that long-term ACE inhibition may improve clinical outcomes in patients with stable coronary artery disease who undergo revascularization.

In APRES (Angiotensin-Converting Enzyme Inhibition Post-Revascularization Study), 159 patients with stable angina and LV ejection fractions of 30% to 50% who were given ramipril following percutaneous coronary intervention or coronary artery bypass surgery (CABG) had a 58% reduction in the triple composite outcome of cardiac death, MI, or congestive heart failure after 3 years (P = 0.03 vs placebo). Benefits were consistent whether LV ejection fraction was above or below 40%.[21]

In the QUO VADIS (Quinapril on Vascular ACE and Determinants of Ischemia) study (N = 149), 1 year of ACE inhibition with quinapril reduced clinical ischemic events in patients undergoing CABG. Clinical ischemic events—defined as death, revascularization, MI, recurrence of angina pectoris, ischemic stroke, or TIA—occurred in 15% of patients on placebo versus 4% of patients on quinapril, a 77% risk reduction (P = 0.02).[22]

In-hospital initiation of secondary prevention: Capturing the patient's teachable moment

In ACS patients, the use of aggressive risk factor modification is a critical component of medical management.[23] All patients with ACS, including patients treated medically or undergoing coronary angioplasty, are rightly recognized as having diffuse vascular disease that requires early and intensive secondary prevention to reduce the risk of recurrent events.[24]

"Guidelines for patients with atherosclerotic CV disease advise that all post-MI patients should be treated indefinitely with ACE inhibition."

ACE inhibition: part of a total secondary-prevention regimen

ACE inhibition plays an important role in current recommendations for high-risk patients. Guidelines for long-term medical therapy in ACS patients advise ACE inhibition for all patients with heart failure, LV dysfunction (ejection fraction <0.40), hypertension, or diabetes as part of a comprehensive secondary-prevention regimen.[25] Guidelines for patients with atherosclerotic CV disease advise that all post-MI patients should be treated indefinitely with ACE inhibition.[26] Treatment should start early in stable high-risk patients (anterior MI, previous MI, Killip class II [S_3 gallop, rales, radiographic heart failure]), and be considered as chronic therapy for all patients with coronary or other vascular disease unless contraindicated.[26] ACE inhibitors reduce mortality in patients with MI or who recently had an MI and have LV systolic dysfunction, and in a broad spectrum of patients with high-risk chronic coronary artery disease, including patients with normal LV function, as demonstrated in HOPE.[15,25]

"All patients with ACS are rightly recognized as having diffuse vascular disease that requires early and intensive secondary prevention to reduce the risk of recurrent events."

Closing the Treatment Gap

Despite compelling evidence from clinical trials and recommendations in national guidelines, preventive care is widely underutilized. National data on the use of preventive therapies in post-MI patients reveal that a large gap persists between what is known about the benefits of treatment and the clinical reality *(Figure 6)*.[27] Among ACS patients who are considered most likely to benefit from ACE inhibition, about 42% receive an ACE inhibitor on hospital discharge.[28] The odds of receiving ACE inhibition are greatest in patients with an LV ejection fraction of ≤40%, anterior MI, chronic heart failure/pulmonary edema, hypertension, an intra-aortic balloon pump, or diabetes.[28]

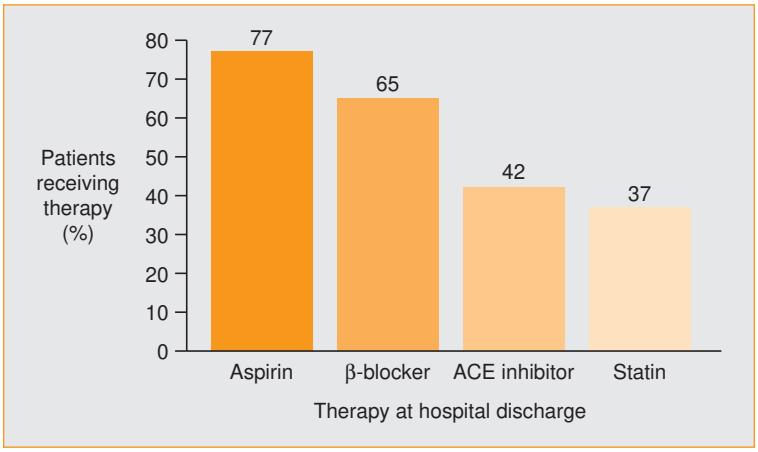

Figure 6. National Registry of Myocardial Infarction-3 data on the use of preventive therapies at hospital discharge indicate that many post-MI patients are not receiving optimal therapy. Beller.[27]

The goal during hospitalization is to ensure the initiation and maintenance of evidence-based therapies. The hospital is the ideal point for initiating treatment—it provides a teachable moment and predicts long-term compliance.[3] A systematic approach to secondary prevention can utilize a simple alphabetical checklist developed for the patient, including A: Aspirin and ACE inhibition; B: β-blockade; and C: Cholesterol-lowering therapy, as well as lifestyle recommendations; D: Diet and Don't smoke; and E: Exercise.[29] When used together, in appropriate patients, the medications prescribed can potentially prevent about 75% of recurrent events *(Table 2)*.[30] The challenge is to be certain that post-discharge regimens provide all of the appropriate therapies to all patients who can benefit from them. The goal is to prevent recurrent events in patients with atherosclerotic CV disease.

"The hospital is the ideal point for initiating treatment—it provides a teachable moment and predicts long-term compliance."

Table 2. Potential Cumulative Impact of Secondary-Prevention Treatment for Cardiovascular Disease

Treatment	Relative risk reduction (%)	2-Year CVD event rate (%)
None	–	8
Aspirin	25	6
β-Blockers	25	4.5
Lipid lowering (by 58 mg/dL)	30	3
ACE inhibitors	25	2.3
All four drugs	75	–

Yusuf.[30]

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Peri-Interventional Care: Rationale for ACE manipulation

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. Cardiovascular disease is the leading category for hospital discharges in the United States.
   a) True
   b) False

2. How many of the 1.1 million heart attacks that occur each year in the United States are recurrent events?
   a) 150,000
   b) 450,000
   c) 600,000
   d) 250,000

3. Cardiovascular risk factors trigger oxidative stress, which disrupts the balance between reactive oxygen species and nitric oxide at the vessel wall and promotes endothelial dysfunction.
   a) True
   b) False

4. Which of the following mechanisms of Ang II promote plaque instability and ischemia?
   a) Ang II stimulates LDL oxidation
   b) Ang II stimulates migration of lipid-rich macrophages and lymphocytes to vulnerable plaque shoulders
   c) Ang II accelerates metalloproteinase release
   d) Ang II increases expression of cytokines and adhesion molecules
   e) All of the above

5. What vascular effect results from the prevention of bradykinin degradation by ACE inhibition?
   a) Nitric oxide increases
   b) Ang II increases
   c) Tissue plasminogen activator decreases
   d) None of the above

6. The anti-inflammatory effects of ACE inhibition at the vascular wall may help stabilize plaque, reducing the risk of an ischemic event.
   a) True
   b) False

7. ACE inhibition given within 36 hours after an acute MI has been shown to reduce 30-day mortality. How much of the observed benefit occurred within 7 days of treatment?
   a) 25%
   b) 40%
   c) 75%
   d) 85%

8. Which of the following risk reductions did the HOPE study demonstrate in patients treated with ramipril?
   a) Total MI
   b) Nonfatal MI
   c) Coronary revascularization
   d) New and worsening angina
   e) All of the above

9. The HOPE study supports a role for ACE inhibition in postmenopausal women at high risk for cardiovascular events. Benefits are similar to those in men.
   a) True
   b) False

10. APRES reported that ACE inhibition improves outcomes in patients with asymptomatic, moderate LV dysfunction who undergo revascularization.
    a) True
    b) False

11. In the PROGRESS study, BP reduction with perindopril plus indapamide reduced recurrent stroke by 43% compared with a 5% reduction in patients taking only perindopril.
    a) True
    b) False

12. In the HOPE study, significantly fewer patients on ramipril who experienced stroke had cognitive or functional impairment.
    a) True
    b) False

13. Patients with ACS have widespread inflammation and unstable plaques in the coronary tree that are a major cause of recurrent events.
    a) True
    b) False

14. Initiation of treatment for secondary prevention in the hospital is likely to improve long-term compliance.
    a) True
    b) False

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Peri-Interventional Care: Rationale for ACE manipulation

Answer Key

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

1.	A	B				6.	A	B				11.	A	B
2.	A	B	C	D		7.	A	B	C	D		12.	A	B
3.	A	B				8.	A	B	C	D	E	13.	A	B
4.	A	B	C	D	E	9.	A	B				14.	A	B
5.	A	B	C	D		10.	A	B						

Activity Evaluation

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

	Excellent				Poor
Quality of monograph	5	4	3	2	1
Relevance to practice	5	4	3	2	1
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

Overall rating of monograph (5 = excellent; 1 = poor): _____

Does the monograph cover the educational objectives stated? Yes _____ No _____

If no, what areas were not covered?

_____

_____

Would you read monographs on other topics as a form of continuing education? Yes _____ No _____

If yes, what topics would you like to learn about?

_____

_____

What form of educational activity do you find most useful?

_____

It took me _____ hour(s) and _____ minutes to read the monograph and complete the self-assessment questions.

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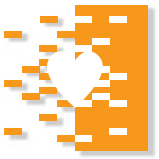

Vascular Biology in Clinical Practice™

Peri-Interventional Care: Rationale for ACE manipulation

Instructions for obtaining continuing medical education credit

To obtain a certificate for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association (AMA) for completing the activity **Peri-interventional care: Rationale for ACE manipulation,** please complete the self-assessment questions, fill out the correct answers on the Answer Key, and mail the Activity Evaluation and Answer Key to:

Office of Continuing Medical Education
University of Florida College of Medicine
PO Box 100233
Gainesville, FL 32610-0233

Telephone: (352) 265-8081
Fax: (352) 265-8082

For All Continuing Medical Education Respondents:

This is to attest that I have participated in the University of Florida College of Medicine **Peri-interventional care: Rationale for ACE manipulation** monograph. I have successfully reviewed all the materials and answered the self-assessment questions. I understand that a certificate for 1 credit hour in Category 1 of the Physician's Recognition Award of the AMA will be mailed to me upon receipt of this form, provided I receive a passing score of 70% or higher. I also understand that a $15.00 processing fee is required for me to receive credit. This fee may be paid by check or credit card.

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