# Localization of Atherosclerosis

## *Role of Hemodynamics*

*Spiros G. Frangos, MD; Vivian Gahtan, MD; Bauer Sumpio, MD, PhD*

Atherosclerosis is a chronic disease attributed to risk factors that are systemic in nature. Yet the lesions involved do not occur in random fashion. The coronary arteries, the major branches of the aortic arch, and the abdominal aorta and its visceral and major lower extremity branches are particularly susceptible sites. Hemodynamic forces interacting with an active vascular endothelium are responsible for localizing lesions in a nonrandom pattern of distribution. Shear stress and cyclic circumferential strain are the predominant forces that have been characterized. The modification of endothelial cell structure and function by these mechanical forces sheds insight into the vasculature's propensity for atherogenesis. *Arch Surg. 1999;134:1142-1149*

**Statement of Clinical Relevance:** The irregular distribution of plaque results from the interaction of local hemodynamic forces with the vessel wall. The recognition of cyclic circumferential strain and shear stress as important modulators of endothelial cell structure and function has been uncovered with the improvement of in vitro models that can mimic specific hemodynamic milieu. An understanding of the intracellular events that link hemodynamic stimulus and endothelial cell response is prerequisite to the comprehension of the biochemical and pathophysiologic mechanisms of atherogenesis. As these mechanisms become further elucidated, this knowledge should allow for the design of preventive and therapeutic strategies to combat the disease early in its course. In the coming years, the nonrandom localization of atherosclerosis may necessitate a correspondingly precise delivery of atherolytic agents into specific vessel subsegments to most efficiently and effectively combat this chronic disease.

The lesions of atherosclerosis are distributed irregularly throughout the vasculature. Some vessels are characteristically spared, whereas other sites within the arterial tree commonly harbor lesions. The reaction to injury hypothesis, which states that vascular endothelial cells (ECs) lining the intima of arteries are exposed to multiple insults to their integrity, remains a widely accepted theory in the pathogenesis of atherosclerosis.[1] Recent experimental evidence supports this hypothesis for atherogenesis.

*From the Department of Surgery (Dr Frangos) and the Section of Vascular Surgery (Drs Gahtan and Sumpio), Yale University School of Medicine, New Haven, Conn.*

### LOCALIZATION OF CLINICAL LESIONS

Atherosclerotic lesions do not occur at random sites.[2] DeBakey et al[3] described 5 major categories of arterial plaque distribution. The coronary arteries, the major branches of the aortic arch, and the abdominal aorta and its visceral and major lower extremity branches are sites particularly susceptible to the atherosclerotic process (**Figure 1**).[3] Plaque localization in these sites accounts for most of the clinical manifestations of the disease. The patterns of arterial occlusive disease in these vessels determine the prognostic criteria and the available therapeutic options for these lesions.[3]

The coronary arteries (category 1)[3] retain a complex geometric configuration of branchings and curves and undergo mechanical torsions during the normal cardiac cycle; this may help explain the propensity for these vessels to develop clinically significant disease.[4] The left coronary artery bifurcation into left anterior descending and circumflex branches has a particular predilection for plaque formation. Lesions distribute mainly along the outer walls of the bifurcation, whereas the walls of the flow divider and the inner walls further downstream are less affected.[5]

The major branches of the aortic arch compose the second category of lesion localization.[3] The carotid arteries are especially prone to lesion formation. These vessels undergo the greatest amount of intimal thickness in the proximal internal carotid artery and midcarotid sinus locations.[6] Specifically, the region of maximal intimal thickening occurs opposite the flow divider, with minimal intimal thickening distal to the sinus.[6]

Category 3 consists of the visceral arterial branches of the abdominal aorta.[3] This category includes the celiac, superior mesenteric, inferior mesenteric, and renal arteries. A high probability of lesion formation is associated with the dorsal abdominal aorta and the proximal inflow tracts of the aforementioned arterial probability in regions distal to these ostia.[2]

The human aorta sustains atherosclerotic lesions throughout its length, but the infrarenal abdominal portion is most commonly victimized by the gross pathologic, clinically significant lesions.[4] The distal abdominal aorta and its ileofemoral branches compose category 4.[3] Atherosclerotic disease of the terminal abdominal aorta and its major lower extremity branches composed the highest proportion of patients of the 5 categories.[3] Symptomatic plaque in this region had the highest probability of being associated with symptomatic atherosclerotic disease elsewhere and had the greatest tendency for recurrence.[3]

Category 5 consists of patients in whom a combination of 2 or more of the aforementioned categories were diagnosed at the same time.[3] The systemic nature of atherosclerotic disease contributes to symptomatic plaque distributing in multiple categories.

Unlike these categories, the propensity for stenosis within the superficial femoral artery at the level of the adductor (Hunter) canal is unique in that there are no major branch points. This segment of artery is unable to undergo any substantial enlargement as a response to increased mural thickening because of the constrictions of the fasciomuscular boundaries of the canal.[7] Compensatory dilatation, as an adaptive response of vessels to preserve lumen circumference, is limited, and therefore an equivalent deposition of plaque more readily achieves a symptomatic stenosis at this site.

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**Figure 1.** *Predominant sites for the localization of atherosclerotic lesions. Reproduced with permission from DeBakey et al.[3]*

## THE PDAY STUDY

The multicenter study of the Pathobiologic Determinants of Atherosclerosis in Youth (PDAY) was designed to reveal the pathologic effects of major coronary artery disease risk factors on the arterial wall and to accumulate data on the responsible risk factors that contribute to the progression of atherosclerosis in young patients.[8] Patients who underwent autopsy were 15 to 34 years of age and included blacks and whites and both sexes. Intimal plaques at an early stage in their development would best be exemplified within this age range. The causes of death in these individuals were related to trauma.

Arterial specimens were evaluated for early lesion formation, and the various risk factors were assessed via laboratory studies. The thoracic and abdominal aortas and the coronary arteries were specifically investigated (**Table 1**). The pathologic specimens from the first 1532 persons studied revealed that the point prevalence of early lesions in the aortas of the youngest age subgroup (15-19 years) was 100%.[9] Approximately half of the right coronary artery samples showed evidence of early lesions in this same subgroup. The mean percentage of intimal surface affected by

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lesions increased rapidly with advancing age in aortic and coronary specimens (**Figure 2**).[9]

Findings from the PDAY Study support the fact that atherosclerosis has its origins in childhood, with fatty streaks existing as ubiquitous lesions within the aortas of young Americans.[8] The prevalence and extent of fatty streaks and fibrous plaques increases rapidly with increasing age,[10] although the disease rarely reaches an advanced level before 35 years of age.

## RISK FACTORS FOR ATHEROSCLEROSIS (PDAY STUDY)

The PDAY Study has provided valuable information on the relationship between coronary artery disease risk factors and the prevalence of early lesion formation. Multiple risk factors were measured post mortem in the PDAY Study. Using serum thiocyanate levels as a marker for smoking, a strong positive association between smoking and the prevalence of raised lesions was shown, particularly in the abdominal aorta. Elevated postmortem glycohemoglobin levels, as a marker for impaired glucose tolerance and diabetes, revealed a positive association with lesion severity despite controlling for other risk factors.[11] Very-low-density lipoprotein and low-density lipoprotein cholesterol levels had a positive correlation with the extent of atherosclerotic lesions in the right coronary artery and aorta specimens, whereas high-density lipoprotein levels were negatively correlated with these findings.[12,13]

Using changes in intimal thickness within small renal arteries as markers for blood pressure, the prevalence of raised lesions involving 5% or more of the intimal surface of aortic and right coronary artery specimens was 2-fold greater in hypertensive vs normotensive males in all age groups.[14] Similarly, obesity, as measured by body mass index and thickness of panniculus adiposus, was associated with more extensive atherosclerotic disease in the right coronary artery specimens in the 15- to 34-year-old age group.[10] Coronary artery specimens supplied by the PDAY Research Group have shown that *Chlamydia pneumoniae* can be found in a high proportion of plaque lesions, whereas no bacteria could be found in the tissue of age- and sex-matched controls without atherosclerosis.[15]

The PDAY research program has provided evidence that these aforementioned risk factors are influential in the development of early atherosclerotic lesions, before the development of clinical disease.[16] These are systemic factors, however, and do not readily explain why some regions within the vascular tree seem to be more affected by disease than others. The association of lesion severity with branch ostia, bifurcations, and bends suggests that hemodynamic factors have a role in the localization of atherosclerosis.[17] Hemodynamic forces seem to interplay with endothelial surfaces at the cellular and biochemical level and, in such a manner, contribute to the localization of plaque.

## HEMODYNAMIC FORCES AND THE ENDOTHELIUM

Vascular ECs line the luminal surface of blood vessels. Viewing the endothelium as merely a vessel lining is a misconception. It is an active participant in the interactions that occur between the vessel wall and the

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surrounding dynamic fluid environment.[18]

Pulsatile blood flow exerts various mechanical forces on the vascular endothelium. The biologic response of the endothelium to these hemodynamic forces is important in atherogenesis. Shear stress and cyclic circumferential strain (stretch) are 2 hemodynamic variables whose actions are focused primarily on the vascular endothelium. Recent research has centered on these 2 variables and their role in the pathophysiology of atherosclerosis.

### Shear Stress

Shear stress (**Figure 3**, left) is the tangential drag force of blood passing along the surface of the endothelium, with its magnitude being directly proportional to blood viscosity and inversely proportional to the cube of the vessel radius.[4]

Earlier studies[19,20] showed that by correlating measurements of vascular fluid mechanics with the distribution of early intimal lesions, the hemodynamic variables associated with atherogenesis could be elicited. By understanding the forces that lead to local endothelial damage, the pathophysiological mechanisms of atherosclerosis might be further uncovered.

One group[6] used anatomically accurate steady-flow models of the carotid bifurcation to investigate the hemodynamic forces that might contribute to regional plaque formation. They measured wall velocity gradients at various increments and determined the shear stress values. Subsequently, they compared these results with the corresponding wall regions of the pressure-fixed carotid bifurcation specimens. Greater wall shear stress values were found along the inner wall of the carotid sinus opposite the flow divider, and much greater values were found in the distal internal carotid artery. High shear stress was inversely proportional to the distribution of early nonstenosing intimal lesions within the corresponding pressure-fixed autopsy specimens. Intimal lesions seemed to localize in areas where shear stress is low, approaching zero, and high levels of shear seemed to protect against atherogenesis. Their data were contrary to those of earlier studies[21] that showed that high shear can lead to endothelial surface degeneration and erosion in animal models in the short term. The mechanism by which even low levels of shear stress might contribute to atherosclerosis remained purely speculative. The notion that ECs located in regions of low-velocity blood flow are exposed to atherogenic lipids, monocytes, and platelets for greater periods of time has been entertained.[22]

A similar study[20] reproduced pulsatile flow within a cast of a human aortic bifurcation that was affected by mild atherosclerotic disease. Comparing the cast wall shear stress profile with corresponding sites on the cadaveric aorta, the intimal thickening and wall shear stress values were again found to be inversely proportional, providing further evidence for a role for shear forces in atherogenesis. Furthermore, oscillatory shear stress along the endothelium, like low shear values, was believed to be a contributory factor.[23]

The walls of the flow divider of the left coronary artery and the inner walls further downstream have been shown to be less affected by lesions.[5] It is once again in the regions of low shear stress and low-velocity blood flow that lesions seem to localize.

The correlation of atherosclerosis with regions of disturbed blood flow suggests that changes in local hemodynamic forces may modify cellular response patterns. A major emphasis has emerged in developing in vitro systems that can recreate these forces and apply them directly on cultured vascular ECs (**Figure 4**, left). In vitro studies on cultured cells are better equipped to provide data on the structural and functional responses of ECs to hemodynamic forces.

Results of cell culture studies showed that ECs respond to shear stress in a variety of ways (**Table 2**). Endothelial cells subjected to shear forces sustained morphologic changes implying[24] cytoskeletal reorganization. They underwent changes in their orientation with alignment in the direction of the shear flow.[25] It became apparent that ECs underwent a reorganization of their F-actin filament containing cytoskeletons in response to shear,[26] allowing for the aforementioned motions to occur. Results of related studies[27] showed that shear stimulated migration and proliferation of ECs within cell cultures.

In vitro techniques have shown that shear stress affects the synthesis and secretion of macromolecules. Prostacyclin, a potent vasodilator and platelet antiaggregator, was produced at a greater rate within human ECs subjected to pulsatile shear stress vs static control cell cultures.[28,29] Similarly, the rate of secretion of the fibrinolytic protein tissue-type plasminogen activator was greater in ECs subjected to shear.[30] Extrapolating from these data, there are obvious implications about the increased atherogenicity of a low-shear environment depicted in the earlier studies.

Alterations in shear stress affect the rate of fluid-phase endocytosis of bovine aortic ECs (BAECs) in vitro.[31] Similarly, shear stress within physiologic levels was shown to enhance the binding and internalization of low-density lipoprotein in BAECs.[32] The effects of shear on the macromolecular transport of atherogenic substances in vitro provides evidence to correlate hemodynamic forces with atherosclerosis.

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**Figure 2.** *Bar graphs showing the percentage of intimal surface involved with fatty streaks and raised lesions for segments of aorta and right coronary artery by sex, race, and age. Reproduced with permission from the PDAY (Pathobiologic Determinants of Atherosclerosis in Youth) Research Group.*[8]

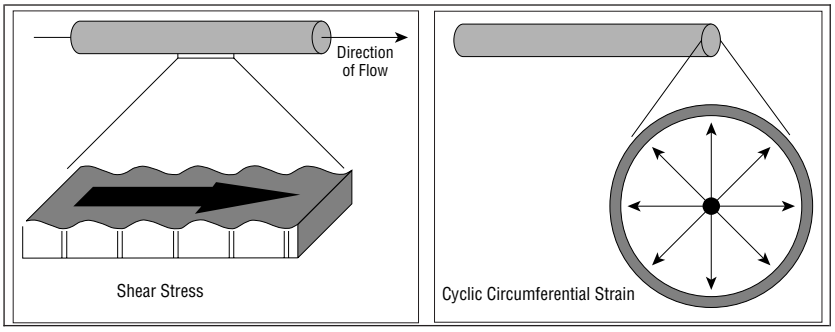


**Figure 3.** *Left, Shear stress: the tangential drag force of blood passing along the lumenal surface of the endothelium. Right, Cyclic circumferential strain (stretch): the repetitive pulsatile pressure distention on the vessel wall.*

Regional flow differences can affect receptor-mediated events within ECs. The signal transduction mechanisms by which ECs recognize variable levels of shear stress and provide a response remain largely unknown. In vitro studies[33] have emerged that show increases in levels of the second messenger inositol triphosphate in response to elevated wall shear stress, implying a possible role for inositol triphosphate in signal transduction from stimulus to response. A similar role has been proposed regarding calcium as a second messenger mediating responses to shear stimuli.[34] A potassium selective ionic current has been identified in vascular ECs stimulated by shear stress and represents one of the earliest couplings of hemodynamic stimulus with EC response.[35]

### Cyclic Circumferential Strain

Curves and branch points in the vasculature are regions that succumb to an altered mural tensile stress.[17] The potential for this factor to contrib-

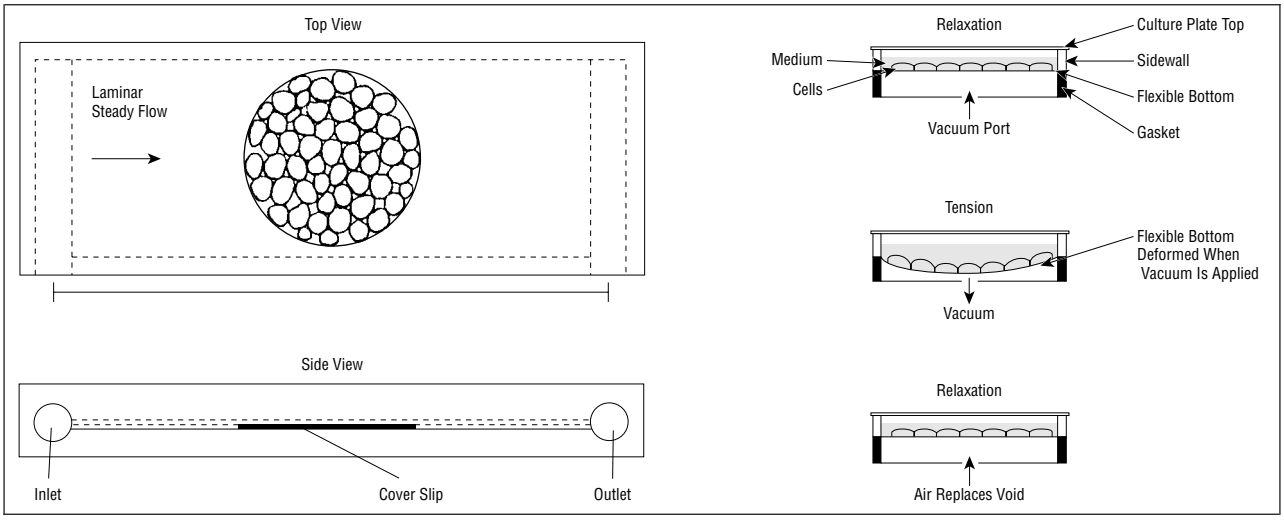


**Figure 4.** *Left, Schematic of a parallel plate, channel flow device that can expose cultured endothelial cells to measurable amounts of wall shear stress in vitro. Reproduced with permission from Levesque and Nerem.[25] Right, Schematic of a flexible-bottomed plate during vacuum deformation; a device such as this provides an in vitro model that mimics cyclic circumferential strain in vivo. Reproduced with permission from Sumpio et al.[37]*

**Table 2. Endothelial Cell Response to Hemodynamic Forces**

| | Shear Stress | Cyclic Circumferential Strain |
|---|---|---|
| Morphologic changes | + | + |
| Cell proliferation | + | + |
| Cell migration | + | + |
| Synthesis/secretion of macromolecules* | | |
| tPA | + | + |
| PDGF | + | + |
| NOS | + | + |
| ET | + | – |
| PGI2 | + | + |
| Intracellular signaling | + | + |
| Endocytosis | + | – |
| Transcription factors | + | + |

**tPA indicates tissue-type plasminogen activator; PDGF, platelet-derived growth factor; NOS, nitric oxide synthase; ET, endothelin; and PGI2, prostacyclin.*

ute to lesion formation has received increasing attention; simultaneous to the cell culture studies investigating the effects of shear, the ability of cyclic strain to similarly induce cellular responses within cultured vascular cells underwent investigation.

Cyclic circumferential strain (Figure 3, right) refers to the repetitive pulsatile pressure distention on a vessel wall. Experimental models that apply mechanical deformation to cells in culture are superior to previous artificially static ones that do not reflect the dynamic in vivo environment. The development of a device that enables repetitive deformation of a cell monolayer[36,37] allowed for such studies to occur (Figure 4, right). Flexible-bottomed plates inserted into this device are able to undergo vacuum deformation at repeating cycles of alternating elongation and relaxation. The ensuing studies help to prove that cyclic strain plays a role in the structural and functional events of in vitro ECs.

Cell culture studies have shown the variety of responses of ECs to cyclic strain. Cultured BAECs, exposed to an environment of applied cyclic tensional deformation and relaxation, are stimulated to increase synthesis of DNA and to increase their rate of proliferation.[37]

A similar regimen of in vitro cyclic stretch on BAECs confirms that they undergo changes in their cellular morphologic features compared with static controls. Tensional deformation leads to a more organized distribution of actin stress fibers perpendicular to the force vector, followed by cellular alignment in the same direction as the actin filaments.[38,39] Furthermore, it seems that the stretch stimulus leads to discrete differences in protein synthesis compared with the control group.[38]

These and similar studies raise questions (similar to those encountered with shear stress) regarding the signals that are conveyed from the cell membrane to the cell nucleus on the application of cyclic strain. What biochemical pathways are being activated by cell stretch that lead to differences in gene expression and protein elaboration and that culminate in a cellular response?

Macromolecule production and release has been studied with regard to cyclic stretch. The addition of arachidonic acid stimulates increased prostacyclin production in cyclically stretched cells vs static controls.[40] The secretion of tissue-type plasminogen activator is enhanced by cyclic strain,[41] once again an event that may contribute to endothelial nonthrombogenicity in vivo. Cyclic strain increases the activity of endothelial nitric oxide synthase and subsequent production of nitric oxide,[42,43] a potent relaxant of smooth muscle and a mediator of vascular tone. It also has been shown that cyclic strain stimulates the expression of intracellular adhesion molecule-1 on ECs,[44] an event that may enhance plaque formation by allowing adhesion of atherogenic blood cells.

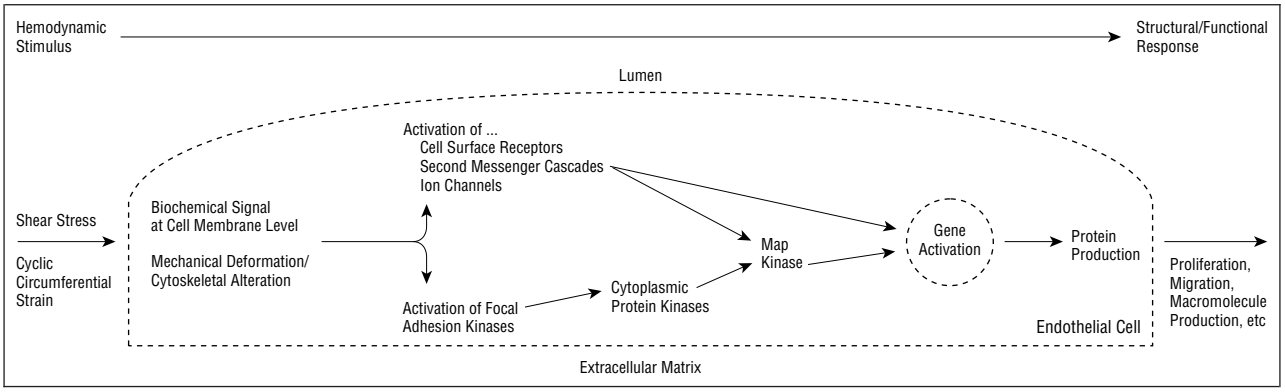


**Figure 5.** *A schematic of the activation and response of an endothelial cell to the mechanical forces in the surrounding dynamic fluid environment.*

Cyclic strain applied to BAECs leads to activation of the adenylate cyclase–cyclic adenosine monophosphate–protein kinase A signal transduction pathway[45] and the inositol triphosphate–diacylglycerol pathway.[46,47] Similarly, it leads to an elevation of cytosolic calcium concentration.[48] Second messengers such as these may have a contributory role in the signal transduction process between stimulus (cyclic strain) and cell response (DNA synthesis, proliferation, macromolecule secretion, etc). The mitogen-activated protein kinase family also seems to contribute significantly to the transduction of signals from the cytoplasm to the cell nucleus (**Figure 5**).[49] The stimulation of transmembrane proteins such as focal adhesion kinase and platelet-EC adhesion molecule initiates the activation of various intracellular kinases that activate mitogen-activated protein kinase and culminate in a cellular response.

## CONCLUSIONS

The intracellular mechanisms that regulate EC adaptation to external forces have only recently begun to come to light.[50] As the pathways that link EC stimulus and response become more clear, the biochemical and physiologic activities of this dynamic barrier will be more readily understood. Eventually, this knowledge will allow for a greater understanding of EC response in pathologic states and might provide clues toward the development of preventive strategies in the face of disease.[50]

*We thank Panayiotis Tzoannos, BS, and Spyros Tzoannos, MS, for their assistance in the preparation of the figures.*

*Corresponding author: Bauer Sumpio, MD, PhD, Section of Vascular Surgery, Yale University School of Medicine, 333 Cedar St, FMB 137, New Haven, CT 06510 (e-mail: bauer.sumpio@yale.edu).*

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## IN OTHER AMA JOURNALS

### ARCHIVES OF INTERNAL MEDICINE

**Effectiveness of *Helicobacter pylori* Therapies in a Clinical Practice Setting**

*M. Brian Fennerty, MD; David A. Lieberman, MD; Nimish Vakil, MD; Nathan Magaret; Douglas O. Faigel, MD; Mark Helfand, MD*

**Background:** Whether eradication rates for *Helicobacter pylori* treatment regimens obtained in controlled clinical trials (efficacy) can also be obtained in clinical practice (effectiveness) is unknown because no such trials have been reported in the United States.
**Objectives:** To determine the eradication rates of *H pylori* in a community practice setting and the effects of practice variation in the choice of treatment regimen on patient outcome (*H pylori* infection cure) and cost.
**Methods:** Between February 1 and December 30, 1996, 38 community-based gastroenterologists in the Portland, Ore, metropolitan area enrolled a total of 250 patients infected with *H pylori*, as determined by endoscopic or noninvasive methods. Various therapeutic regimens aimed at eradicating *H pylori* were used by the gastroenterologists, and a posttreatment urea breath test was used to determine *H pylori* infection cure. Compliance and incidental effects were also measured and decision analysis was used to estimate the cost of treatment.
**Results:** The regimens used varied considerably. Patients receiving a 2- or 3-times-a-day treatment regimen were significantly more compliant ($P = .01$) than those receiving a 4-times-a-day regimen. Proton pump inhibitor–based triple-therapy regimens were significantly more effective than all other treatment regimens combined (87% vs 70%; $P = .001$) in eradicating *H pylori*. These proton pump inhibitor–based triple-therapy regimens were also more cost-effective by decision analysis for a hypothetical cohort of patients with duodenal ulcer disease.
**Conclusions:** The considerable variation in the choice of treatment regimens affects the clinical and economic outcomes of patients undergoing therapy for *H pylori* infection. Whether these data reflect the outcome in other communities is unknown but should be determined. It will be necessary to determine if the dissemination of these data results in a reduction of practice variation and improvement in clinical and economic outcomes of patients being treated for *H pylori* infection in clinical practice. (*1999;159:1562-1566*)

*Corresponding author: M. Brian Fennerty, MD, Division of Gastroenterology, Oregon Health Sciences University, PV-310, 3181 SW Sam Jackson Park Rd, Portland, OR 97201-3098 (e-mail: fennerty@ohsu.edu).*