

The Disconnect Between Practice Guidelines and Clinical Practice—Stressed Out

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DESPITE INCREASING EVIDENCE SUPPORTING plaque instability as the proximate cause of atherosclerotic events,^{1,2} treatment strategies continue to focus on the anatomic stenosis.³ This preoccupation with coronary luminology causes clinicians to perform stress tests and angiograms to identify flow-limiting lesions, even among asymptomatic patients, and to mitigate the effects of these lesions by direct mechanical or surgical intervention. As a result, clinical practice guidelines currently recommend revascularization when stress testing reveals demonstrable myocardial ischemia despite optimal medical management.^{3,4}

Unfortunately, the guidelines are not as clear as they might be on this matter. For example, one guideline reads as follows³:

[Percutaneous coronary intervention] may be considered in patients with [Canadian Cardiovascular Society] class III angina and no evidence of ischemia on noninvasive testing or who are undergoing medical therapy and have 2- or 3-vessel [coronary artery disease] with significant proximal [left anterior descending coronary artery disease] and treated diabetes or abnormal [left ventricular] function.

Clinicians reading this guideline may fail to make sense of the convoluted sequence of *and*'s and *or*'s in this sentence, resulting in a fair amount of wiggle room for well-intentioned interpretation.

It is not surprising, then, that Lin et al,⁵ in this issue of JAMA, demonstrate that noninvasive testing is not routinely used to document myocardial ischemia prior to elective percutaneous coronary intervention (PCI). Rather, noninvasive testing was used less than half the time among 23 887 Medicare fee-for-service beneficiaries aged 65 years and older undergoing elective PCI in 2004. The rate of stress testing varied geographically and correlated with a variety of patient characteristics. Rates were lower among those with prior catheterization or older female patients with comorbid conditions, and higher among African American patients or patients with chest pain or cancer. Physician characteristics played an additional role: younger physicians and those performing

a high volume of PCIs were less likely to use stress testing.

As noted by the authors, these findings are not necessarily probative of misutilization. Administrative databases such as this do not include a variety of clinical factors that might explain and justify the observed patterns of utilization. Nevertheless, the analyses that were performed leave the clear impression that referral for PCI was influenced less by objective evidence of ischemia than by incidental factors. The wide geographic variation in rates of stress testing before PCI further supports this conclusion.

To some extent, this should not be news. Fifteen years ago, Topol et al⁶ reported similar observations among 2101 privately insured patients undergoing coronary angioplasty during 1988-1989. Only 29% of these patients had exercise testing before angioplasty. As in the study by Lin et al, women were less likely to undergo stress testing than men were.

Some of this variability is understandable. Stress testing is generally thought to be less reliable in women than in men.⁷ On the other hand, chest pain in women is also less predictive of obstructive coronary disease,⁸ implying that stress testing should be used more frequently in women. This example demonstrates that the underutilization of stress testing prior to revascularization has no straightforward, rational basis.

How much does this matter? If PCI is effective, then it is no wonder that physicians prefer to skip the preliminaries and "cut to the chase." But what does "effective" mean? A substudy of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial evaluated the effectiveness of PCI as an adjunct to optimal medical therapy (OMT) using myocardial perfusion scintigraphy (MPS).⁹ Of 2287 patients, 314 underwent MPS before treatment and 6 to 18 months thereafter. At follow-up, the reduction in ischemia was greater with PCI and OMT than with OMT alone (-2.7% vs -0.5%; $P < .001$), and more patients in the PCI and OMT group exhibited at least 5% ischemia reduction (33% vs 19%; $P = .0004$).

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See also p 1765.

However, ischemia reduction did not lower the risk of death or myocardial infarction after adjustment for other factors. These findings are consistent with those of Mahmarian et al¹⁰ showing that intensive medical treatment was comparable to revascularization with respect to cardiac events even in high-risk stable postinfarction patients with ischemic perfusion defects. On the other hand, both trials were nonrandomized and underpowered for this purpose. While 2 other trials have reported a reduction in risk using PCI in asymptomatic patients with exercise-induced myocardial ischemia,^{11,12} the intensity of medical therapy was not as rigorous as in COURAGE.^{13,14} The COURAGE trial therefore provides the best evidence in support of guideline recommendations to the effect that “the majority of patients . . . should be treated medically,” and that revascularization is best reserved for patients with objective evidence of ischemia despite ongoing intensive medical therapy.³

However, the guidelines fail to define the appropriate intensity of anti-ischemic medical therapy. In one study of patients with chronic stable angina who were referred for coronary angiography,¹⁵ intensity averaged only 15 on a scale from 0 to 100—equivalent to an average dose of a single antianginal drug—and 15% were not being treated with any antianginal medications. These findings have important implications regarding the management of stable coronary disease and the associated national costs of health care. Quite simply, the erroneous conclusion may be that medical therapy fails a large number of patients when, in fact, those patients never received enough medical therapy to make that determination.

In a seminal sociological dissection of the medical profession, Freidson¹⁶ identified 5 traits characteristic of the typical clinician that help explain the disconnect between practice guidelines and clinical practice. (1) Physicians believe in what they are doing; (2) physicians prefer action, even with little chance of success, over no action at all; (3) physicians see apparent cause/effect relationships even in their absence; (4) physicians depend more on personal judgment than on empirical evidence; and (5) when things go wrong, physicians chalk it up to chance. Thus, when practicing cardiologists were presented hypothetical scenarios of patients with stable coronary disease, their treatment recommendations were biased toward PCI by an “oculostenotic reflex” in which angiographic narrowing trumped the demonstration of ischemic dysfunction.¹⁷ The practice of medicine, like nearly everything else in modern society, is a heady brew of science, politics, business, and industry, and a desire to satisfy patient expectations, and the patient’s well-being often gets lost in the mix.

Properly designed economic incentives might balance these competing influences.¹⁸ The Centers for Medicare & Medicaid Services, for example, might set reimbursement for evidence-based care at a higher level than for non-evidence-based care. Thus, a cardiologist performing PCI for a patient

with objective evidence of ischemia despite an appropriate intensity of medical therapy would be paid more than for the same patient without such evidence. Unlike “pay-for-performance”¹⁹ these evidence-based reimbursement incentives target individual physician decisions rather than aggregate patient outcomes, are based on empirical data rather than consensus opinion, and are relatively large in size and immediate in effect.^{20,21}

If evidence-based reimbursement policies such as this were adopted, dramatic changes in utilization could be realized virtually overnight (as happened in the 1980s with the advent of diagnosis related groups). The COURAGE trial shows that these changes would place the patient at no additional clinical risk,¹³ and the data from Lin et al suggest a substantial economic savings.⁵

Is this approach too drastic? Similar comments surrounded the original Medicare law. Its passage instantly ensured the elderly of unfettered access to health care, but the price paid was a gradual disconnect (arguably now a chasm) between what clinicians should do (according to the best available scientific evidence) and what they are paid to do (according to operative reimbursement policies). As a result, a national health care system that encourages suboptimal patterns of utilization has evolved. The potential mismanagement of patients with stable coronary disease as suggested by the findings of Lin et al is but one example.^{5,17}

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B Vitamins for Prevention of Cognitive Decline

Insufficient Evidence to Justify Treatment

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STROKE AND DEMENTIA ARE AMONG THE MOST COMMON diseases affecting the brain in older persons and account for most cases of disability requiring nursing care in this age group.¹ The incidence of these diseases increases exponentially with age. Consequently, improvements in life expectancy have resulted in a substantial increase in the absolute number of individuals with dementia and cognitive impairment in recent decades. Dementia is characterized by an insidious, slowly progressive memory loss with alteration of higher intellectual function and cognitive abilities. Among the subtypes of dementia, Alzheimer disease and vascular dementia have distinct clinical and pathological features, but these 2 disorders frequently co-exist and the combination is associated with a greater severity of cognitive impairment.²

Population-based studies, such as the Rotterdam study,² have demonstrated that indicators of atherosclerosis were associated with Alzheimer disease and that the prevalence of Alzheimer disease increased with the degree of atherosclerosis. The odds ratio for Alzheimer disease in those patients with severe atherosclerosis was 3.0 (95% confidence interval, 1.5-6.0) compared with those without atherosclerosis. Participants with at least 1 apolipoprotein E (ApoE) $\epsilon 4$ allele and atherosclerosis had a nearly 5-fold increased risk of Alzheimer disease compared with those with no $\epsilon 4$ allele²; cigarette smokers had twice the risk of Alzheimer disease compared with nonsmokers³; and individuals with

diabetes mellitus had 3 times the risk of Alzheimer disease compared with those without diabetes.⁴

The hypothesis that homocysteine may be a risk factor for Alzheimer disease and that B vitamins might be neuroprotective was prompted by the observation that patients with a histological diagnosis of Alzheimer disease, irrespective of whether there was concomitant histological evidence of cerebrovascular disease, had higher plasma levels of homocysteine than did age-matched controls.⁵ Homocysteine is a potentially harmful sulfur-containing amino acid derived from methionine and has been previously linked with an increased risk of cardiovascular disease.^{6,7} B vitamins, such as folic acid and vitamin B₁₂, are needed to transform homocysteine into the important one carbon donor S-adenosylmethionine (required for methylation reactions) and into glutathione (required to protect the cells from oxidative stress).⁸ The vitamin B₁₂-dependent reaction by which homocysteine is converted to methionine (and thereby removed from the bloodstream) is inactivated by oxidation.⁸

More convincing evidence for the importance of increased homocysteine levels and risk of dementia was provided by an 8-year follow-up of 1092 dementia-free elderly participants in the Framingham study,⁹ which reported that increased homocysteine levels (>14 $\mu\text{mol/L}$) were associated with a 2-fold higher risk of dementia and Alzheimer disease. These associations persisted after adjustment for age, sex, ApoE $\epsilon 4$ genotype,

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