A half century ago, Goldblatt described the effect of renal ischemia on blood pressure. Motivated by inadequate pharmacological therapies for hypertension (HBP), the substantial risks of persistently elevated blood pressure, and the possibility of curing an important disease, clinicians soon thereafter sought to apply Goldblatt’s findings, initially by removal of suspected culprit kidneys and later by attempts to relieve stenoses in renal arteries. Even in 1989, patients with renovascular hypertension (RVH) have blood pressure that often remains relatively difficult to control, continue to be at risk for a deterioration of renal function (especially if they have atherosclerotic disease), and are subjected to an array of side effects and complications, some of them from modern antihypertensive agents. And so the “which” hunt continues: which patients, which tests, which etiologies, and which therapies.

Although more specific and less toxic pharmacological therapies for HBP should, in isolation, decrease the motivation for identification of patients with RVH from the perspective of blood pressure control, over the years surgical therapy for RVH has improved in efficacy and decreased in risk. New percutaneous approaches to relieving arterial obstruction have evolved, mitigating, in part, the advantage of newer drugs compared with revascularization in the achievement of blood pressure control. Furthermore, aggressive therapy may better preserve renal function and eliminate the patient’s lifelong struggle with compliance to pharmacological programs that, in the short run, diminish the patient’s quality of life. Notwithstanding the lack of prospective, randomized, controlled studies, if we could accurately, safely, and cheaply identify our hypertensive patients who would respond, revascularization would still be the strategy of choice in 1989. Unfortunately, the accuracy, safety, and expense of the many available approaches to case finding continue to be as problematic as in the mid-1970s when McNeil and colleagues and Weinstein and Stason published cost-effectiveness analyses. Even a more recent analysis by England et al did not include new diagnostic modalities, such as the captopril-stimulated peripheral and renal vein renin analysis, renal scans after the administration of converting enzyme inhibitors, and digital subtraction angiography. If the accuracy of diagnostic studies is increasing as their risks decrease, the spectrum of patients subjected to those strategies should enlarge. Indeed, proponents of individual screening tests, proponents of a very aggressive approach, and national study groups have not been shy about providing algorithms and making suggestions, based on clinical judgment, consensus, and personal opinion.

Consider, in this context, the general issues of screening, assuming, of course, that renal revascularization provides some benefit in the setting of RVH. First, the criteria for establishing the diagnosis must be considered. In the case of renovascular disease, two disparate definitions exist: the presence of anatomic obstruction of a renal artery and the improvement of hypertension after relief of such an obstruction. Having defined the disease, we must next consider why it is important to identify patients in that category; whether it is in terms of survival, diminished vascular complications, better preservation of renal function, or an improved quality of life, their prognosis after screening, with presumably altered treatment, must in some way be improved. Of course, few treatments provide benefits without concomitant risks and costs, and renal revascularization is no exception. Both surgery and angioplasty involve some risk to life and kidney; those risks are immediate, whereas the consequences of persistent RVH can be delayed many years. The tradeoff between the risks and benefits of revascularization can be used to define a threshold probability of RVH above which it would be reasonable to treat the patient.

With that threshold probability in mind, the alternative diagnostic strategies that would raise an individual patient’s likelihood of RVH above that threshold, or decrease that likelihood to the point that no further evaluation is reasonable should next be considered. Although a variety of such strategies are available (each consisting of one or more diagnostic tests and criteria for action based on combinations of the test results), each must be evaluated...
variety of combinations of tests are reported, pre-
diagnostic studies, even in this limited set of patients. With knowledge about both the benefits and risks of treatment and the risks, sensitivity, and specificity of the testing strategy, it is possible to calculate two additional thresholds: for all patients whose probability of disease falls between those thresholds, diagnostic evaluation would improve outcome; for patients in whom the probability of disease is below the testing threshold, conservative therapy would be best; for patients in whom the probability of disease is above the test-treatment threshold, treatment (in the case of RVH, renal arteriography and possible revascularization) would be best.

Of course, we have not yet considered the issue of cost. We no longer have the luxury of practicing in a world of seemingly infinite resources. Even strategies that in net provide better patient outcomes may not be feasible if their cost is too high or the benefit they provide too low. We must consider the marginal or extra cost for each unit of net improved outcome we provide. As clinicians, we must implicitly or explicitly consider all these factors (and presumably many others) when we decide which patients to evaluate for RVH and which tests to perform. Obviously, such considerations depend critically on the availability of adequate information.

In this issue of Hypertension, Laura Svetkey and her colleagues report 2 years of experience at Duke with a select population of 66 patients with a relatively high prevalence of RVH. These patients had each undergone a variety of diagnostic approaches, including captopril-stimulated renin determination and digital subtraction angiography, thus providing an opportunity for comparison of several tests in the same patient. The authors include in their article receiver-operator curves of three of the tests that can be reported quantitatively, thus making their comparison relatively independent of the choice of a specific cutoff criterion (e.g., 4 ng/ml/hr for peripheral vein renin determinations). Furthermore, the sensitivity and specificity of a variety of combinations of tests are reported, precluding the need to assume that various test results are independent when the usefulness of complex strategies is considered. These investigators deserve substantial credit for comparing prospectively the performance of many of the currently available diagnostic studies, even in this limited set of patients.

Unfortunately, Svetkey’s study is not without problems. The population is small and highly select. The definition of RVH includes response to surgery or percutaneous transluminal renal angioplasty, thereby inexorably linking the apparent accuracy of the diagnostic tests to the adequacy of therapy. Of the six patients who underwent angioplasty, two suffered thromboses and pseudoaneurysms developed in two, bringing into question the adequacy of the “gold standard” for diagnosis, response to therapy. Changes in the definition of disease, which would move some patients from the RVH category to the No RVH category, would change both specificity and sensitivity, potentially altering the comparison among tests. If therapy were suboptimal, then the pool of true RVH patients might be larger (i.e., the gold standard would be more lax). If that caused the inclusion of some patients with less severe disease, then sensitivity might be diminished and specificity enhanced. On the other hand, occasional patients appear to be cured by revascularization when, in fact, the procedure has merely produced total infarction of the ischemic kidney. Thus, the separation of anatomically successful revascularization from mitigation of HBP may be important. Certainly, limiting the definition of success to anatomic improvement would be wrong, but the clinician might wish to consider two separate outcomes: anatomic revascularization and the efficacy of that anatomic success in alleviation of the patient’s HBP.

A related concern arises from the manner in which some provocative tests were performed: diuretics were discontinued for only 2 days, samples were collected in the supine rather than the seated position, and precaptopril levels were not assayed. Similarly, if the peripheral vein renin data reported in 605 patients from the University of Indiana Hypertension Center (RVH prevalence 16%) were plotted on the ROC curve in Figure 1A of Svetkey’s study (RVH prevalence 17%), the characteristics of the Duke test would appear inferior, again bringing into question whether Svetkey’s comparison can be generalized to other settings. The performance of the renal vein renin test in the Duke study at a cutoff ratio of 1.5 (sensitivity 0.64, specificity 0.50) is also substantially below the Indiana test (0.95 and 0.79, respectively) and somewhat worse than the average data (sensitivity 0.80, specificity 0.62) summarized by Kaplan. Of course, the confidence intervals in Table 3 of the Duke data include the other tests’ performance, so the differences are not significantly different, but the comparisons in Svetkey’s report were based on the reported Duke data. The rather broad confidence intervals underscore the small size of the Duke experience. Calculations of sensitivity were based on no more than 11 patients. The 100% sensitivity reported for digital subtraction angiography is at variance with the 7–25% incidence of uninterpretable studies reported elsewhere, in part because equivocal studies were considered abnormal. Another approach would be to consider such intermediate results as a separate category, calculating their likelihood among patients with and without
RVH. By combining these disparate diagnostic results into a single “abnormal” category, the Duke clinicians might be discarding some useful data.

Quite correctly, Svetkey and her colleagues\(^9\) used Bayes’ rule to adjust predictive values and estimate test performance in a lower risk population (Table 4). Two concerns arise from that approach, however. First, is the 5% prevalence reasonable, particularly for patients known not to have the high risk clinical characteristics (severe, uncontrolled, accelerated, or recent onset HBP and abdominal or flank bruit)? Second, diagnostic tests might have improved specificity (in patients without RVH) and diminished sensitivity (in patients with RVH) if those patients had a milder form of HBP than the patients reported here. Conversely, the data Svetkey et al\(^10\) report in Table 5 suggest that, among patients with renal artery stenosis, positive results in three of four of the captopril-stimulated tests are slightly predictive of the absence of RVH, defined as response to revascularization, that is, the calculated likelihood ratios (true-positive rate/false-positive rate) are all less than or equal to one. Thus, the extrapolations of test performance to patients free of findings that strongly suggest RVH must be considered very soft.

Certain data have not been reported directly. Because some clinicians would argue that high risk patients, such as those in the Duke series, should proceed directly to conventional renal arteriography,\(^2\) we might ask how successful that approach would be. All 66 of the reported patients underwent arteriography, so we might ask what was the sensitivity and specificity of the arteriogram in predicting a response to revascularization. Although we are told that six of the 11 patients who eventually improved after revascularization underwent angioplasty percutaneously, we are not apprised of the frequency of revascularization in the patients whose blood pressure did not respond, that is, patients without RVH. Presumably the renal arteriogram, the basis for therapeutic decisions in this study, was not perfect in predicting blood pressure response, and revascularization may have been attempted in some patients without RVH as defined in this series.

Decisions about diagnostic evaluation cannot be based on test performance alone; data concerning the risks (mortality and especially short-term morbidity) of the tests, the true financial costs of the tests, and the benefits and risks of the various alternative therapies are also essential. In the case of RVH, where each of these tests is only a prelude to more invasive renal arteriography, the risks and costs of that final test must also be considered. The Duke report is silent on these issues. Their conclusions about which strategy is best in which prevalence groups can only be viewed as speculation; they cannot flow logically from the performance data reported here.

One hundred forty years after Alphonse Karr noted that “the more things change, the more they remain the same,” we find that turn of phrase relevant to screening for RVH in 1989. We have better therapies and better tests, but we still must continue our “which” hunt. Physicians must still apply careful clinical judgment, considering both medical nuances and patients’ individual preferences, when deciding which hypertensive patient should be subjected to which tests and be continually encouraged to comply with which therapy. It is not yet time to elevate one test or one strategy to the throne of the standard of care.

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