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iVIEW

EDITOR'S PAGE

Risk Detection Among Asymptomatic Patients With Diabetes

Is It Time for a Varied Approach?

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This issue of *iJACC* highlights several papers on the utility of cardiovascular imaging in diabetes. Over the past decade, there has been a plethora of observational registries and randomized trials evaluating the utility of noninvasive imaging, with recent reports examining prognostic risk among asymptomatic patients with diabetes using coronary computed tomographic angiography (CTA) (1-8). We have seen an evolution in diagnostic and risk assessment approaches for patients with diabetes, and with the introduction of CTA over the past decade, newer series are adding to this evidence base (9). Given this resurgent interest in testing of patients with diabetes, it is worthwhile reviewing the historical approaches to screening and lessons learned from other modalities.

Importantly, very few asymptomatic subgroups of patients have appropriate indications for diagnostic testing. Overall, asymptomatic patients are often categorized as low risk on the basis of global risk score estimates. Testing of asymptomatic patients with diabetes, however, has historically been considered an exception to this rule, largely because of the perceived inordinately "high risk" for future events. Earlier data maintained that patients with diabetes have a risk equivalent to patients with established coronary artery disease (CAD) and, therefore, should all be classified as high risk (10). This coupled with silent myocardial ischemia due to prevalent neuropathy diminished symptom onset as indicators of CAD. However, lessons learned over the past decade have challenged this approach and now support that routine evaluation of asymptomatic patients with diabetes solely on the basis of a perceived lack of symptoms and elevated CAD risk has been shown to be misleading. A key to this shift in thought has been the focus on adherence to guideline-directed care for targeted glucose and related CAD risk factor control, and the yield of the screening tests for many asymptomatic patients with diabetes is expectedly low. Thus, in today's environment, a patient with diabetes is not always one with the highest risk, and all patients with diabetes are not at uniformly high risk (11,12).

A recent study by Kang et al. (9) reported in this issue of *iJACC* undertook what one might consider a historic approach to diagnostic testing for risk assessment purposes among asymptomatic patients with diabetes. They enrolled an unselected cohort of 591 asymptomatic patients with diabetes consecutively tested from 1 medical center. This report emulated earlier reports that showed effective risk stratification in large cohorts of patients undergoing stress myocardial perfusion imaging (3,7,13). Published research on myocardial perfusion imaging noted a graded increase in risk along with the extent and severity of myocardial perfusion abnormalities, and Kang et al.'s (9) series similarly found a graded increase in risk with CAD severity. How useful is this information? A critical view of this evidence base would conclude that almost any population, given a sufficient sample size and observed event rate, could prove useful for risk stratification purposes. Stated otherwise, provide any large sample size, and almost any imaging modality would incrementally improve risk stratification, even among asymptomatic

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populations. The question that still remains unaddressed is what to do with this information and how much it affects our ability to modify the natural history of CAD in patients with diabetes.

This assumption that all patients with diabetes, regardless of symptom status, are at high risk or risk equivalence to patients with known CAD has led to expanded imaging practices (10). Yet the body of imaging evidence has been misleading and has often included limited detail regarding glucose control, diabetes severity, or the concomitant presence of peripheral atherosclerosis. The evolution in thought regarding testing of patients with diabetes was further challenged with several recent randomized trials that revealed no improvement in CAD outcomes following randomization to stress nuclear imaging (DIAD [Detection of Ischemia in Asymptomatic Diabetics]) or CTA (FACTOR-64) among asymptomatic patients with diabetes (2,5). In both of these studies, a primary assumption was that early detection of CAD could lead to improved outcomes. From the FACTOR-64 trial, 900 asymptomatic patients with diabetes were randomized to CTA versus guideline-directed diabetes care. At 4.0 years of follow-up, the primary outcome (all-cause death, myocardial infarction, or unstable angina) did not differ between patients randomized to CTA and those randomized to optimal diabetes care (6.2% vs 7.6%; hazard ratio: 0.80; 95% confidence interval: 0.49 to 1.32; $p = 0.38$). Importantly, this trial focused on patients meeting targets for low-density lipoprotein cholesterol, blood pressure, and glucose consistent with guideline-directed care. It appears that both anatomic testing for CAD and physiological testing for ischemia as a consequence of CAD, for a number of reasons, are not pivotal in our ability to change outcomes in asymptomatic patients with diabetes. This approach led to a focus on effective diabetic and CAD risk factor management and has diminished the impact of diagnostic testing with CTA.

This evidence supports the notion that surely we can risk-stratify almost any subgroup of patients. However, the benefit of risk detection lies in the burden of observed events during follow-up. Too often, we have observed randomized trials with lower than expected event rates (2,14). Our focus on preventive management has produced populations that now require a more nuanced approach to testing. Broad statements about the need for asymptomatic testing among patients with diabetes have now been replaced with growing support for selective diagnostic testing.

This evolution in evidence has identified an important trend for cardiac imaging that remains a vital consideration for risk stratification and risk reduction. First of all, for any disease state that ultimately ends in an elevated CAD risk, there are important considerations regarding adherence to care and subsequent diabetes control. Second, prognostication is limitless with large patient sample sizes. However, a lack of consideration of the impact of adherence to guideline-directed care and a focus on disease state solely will be misleading. In our example from Kang et al. (9), patient enrollment based only on diabetes may not be justified, and selective eligibility based on risk factor and diabetes control is an important covariate. Finally, our discussion illustrates that risk stratification and risk reduction are 2 very different approaches.

In an updated testing strategy, a focus on selective compared with routine testing of asymptomatic patients with diabetes could be more fruitful. In the report by Kang et al. (9), only 12 CAD deaths or myocardial infarctions were observed over 5 years of follow-up, and CTA did not risk-stratify using this hard endpoint ($p > 0.10$). An expanded endpoint that added unstable angina, however, did result in effective risk stratification for patients with diabetes, with events rates from 0.6% for no CAD to 7% for obstructive CAD ($p = 0.003$, $n = 20$ events). These approaches that rely on combined event analysis to enhance risk detection harken back to earlier stress imaging approaches. Careful consideration of the limited number of documented events provides us with a signal that this population, too, may not be ideal for testing of asymptomatic patients with diabetes. Foremost in this unselected cohort is the evidence that a sizable proportion of this cohort had well-controlled diabetes and a predicted low CAD risk. However, an additional subgroup had long-standing diabetes, with many patients who were not well controlled, including average glycated hemoglobin values of >7% and elevations in blood pressure and low-density lipoprotein levels. Thus, a more selective approach to diagnostic testing including patients with diabetes with reduced rates of adherence to guideline-directed care could have elevated CAD risk and resulted in more refined risk stratification. This selective testing approach enriches the eligible patients with those who are at higher risk and may identify a subgroup for whom future randomized trials may reduce risk.

An alternative approach is to exclude the lower risk subgroups who do not benefit from diagnostic testing. In this series, nearly half of these patients with diabetes had no to minimal coronary artery calcium (CAC) (scores of 0 to 10). Alternative approaches that apply sequential imaging strategies, such as that used in the CRESCENT (Computed Tomography Versus Exercise Testing in Suspected Coronary Artery Disease) trial

(15), may have improved the detection of at-risk patients but also improved efficiency and reduced costs associated with the diagnostic evaluation. In the latter trial, an index CAC score was used and followed by CTA only for patients with detectable CAC. There were no CAD events over 1 year of follow-up among patients with CAC scores of 0; by excluding the low-risk patients with CAC scores of 0 to 10, the remaining cohorts had an elevated CAD risk.

Both of these strategies of enhancing the pool of higher risk patients or excluding those at low risk are based on more than a decade of learning regarding optimal risk detection strategies. Unselected risk assessment can be undertaken but may mislead readers that the results apply uniformly to all asymptomatic patients with diabetes. By applying selective approaches, a greater depth of understanding may be garnered as to how to detect risk but also would form the basis for future randomized trials. Recall that risk stratification is only important as a means to target patients at high risk and ultimately improve outcomes. We must now be more prudent in our registry analyses in order to inform future trial design. Our ultimate goal for patient-centered imaging is that screening tests must be applied to guide clinical management that improves patient outcomes.

A critical analysis will have to conclude that we are not there yet as far as routine screening of asymptomatic diabetes is concerned. Screening asymptomatic subjects with diabetes, as currently envisaged, starts with a big disadvantage: it violates many of the accepted principles of screening (16). Screening fundamentally assumes that detecting an abnormality early would allow us to target and change natural history. In a disease such as diabetes, the target itself is rather nebulous and our ability to influence it weak. We probably address a number of different targets when we screen asymptomatic subjects, and we do not know which one if vital; are we screening for disease (e.g., with CAC or CTA), disease-causing advanced plaque and stenosis (e.g., with CTA or similar anatomic testing), or CAD-causing ischemia that may also cause events (e.g., with physiological testing such as myocardial perfusion imaging) or purely targeting the risk for hard events such as death and myocardial infarction (e.g., with risk scores or CAC). Perhaps that is why these repeated efforts have been rather fruitless so far.

Screening fundamentally assumes that detecting an abnormality early will allow us to target it and change natural history. Diabetes will be a mammoth problem in the future, from the current 415 million worldwide to more than 642 million projected by 2040 (17), and being able to channel efforts to those who will benefit most will become crucial. It is time to stop focusing on small studies trying to screen patients with diabetes for high risk, in a piecemeal modality-specific fashion, and focus on larger scale efforts at first identifying the risk target correctly before embarking on efforts to attenuate it. For now, addressing risk via risk score strategies such as pooled cohort equation or SCORE risk profiles, perhaps buttressed with CAC, might be superior to anatomic or physiological approaches.

Newer technologies, such as CTA, should not embark on clinical research endeavors based on the concept of a blank slate or tabula rasa, a core principle of Lockean empiricism. The blank-slate philosophy states that all humans enter the world without knowledge and that only through personal experiences does one gain knowledge. Although this was meant to contemplate individual experiential learning, its application to clinical research is one worth considering. Certainly our individual knowledge is formed experientially, but learning for the purpose of adaptation and advancement (from past experience) must be a fundamental principle for rapid evolution and refined diagnostic approaches within cardiovascular imaging.

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