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EDITORIAL COMMENT

Imaging for Improving Therapy

A Stop on the Way to Improve Outcomes?*

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Knowledge and timber shouldn't be much used till they are seasoned
—Oliver Wendell Holmes (1)

Despite rapid advances in diagnosis and greater availability of effective cardiac therapies, utilization rates for these evidence-based treatments have been suboptimal in most cardiac conditions. Less than optimal rates of drug prescription, use, and adherence contribute to this problem. Multiple studies, including the REACH (Reduction of Atherothrombosis for Continued Health) registry involving 67,888 patients, confirmed a concerning underutilization of many drugs shown to favorably alter

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cardiovascular outcomes (2). Various strategies have been proposed to improve evidence-based drug prescription and adherence, but most have had only modest success. Because a visual picture may be worth many thousand words of oral or textual description, 1 strategy that has evoked great interest is to use cardiac imaging to detect subclinical disease; moreover, displaying graphic evidence of coronary artery disease (CAD) that is likely to cause high-impact events in patients without evidence of CAD, may impact physician–patient behavior positively. Imaging not only provides a very refined risk assessment in CAD, but also offers detailed visual information of coronary pathology, including changes in the coronary wall—information not easily available with other modalities; such combined information might overcome some of the current limitations in medication use and adherence. There is preliminary evidence that visual images improve understanding of a threat, increase believability of the risk information, and encourage risk behavior modification (3). Studies with coronary calcium imaging show a benefit in terms of increase in statin use (4,5). Computed tomography angiography (CTA) (which presumably would be used in a "for-cause testing" population with an enriched pre-test probability compared with coronary calcium screening studies), with more detailed information, might be similar or better in changing physician–patient behavior. A study in this issue of *iJACC* is one such effort to study the effect of a positive coronary CTA scan on prescription patterns and change in cardiovascular risk factors. Cheezum et al. (6) retrospectively studied 1,125 patients without known CAD, low-risk scores, and mostly atypical chest pain coming for CTA. Pre- and post-CTA prescription patterns for aspirin, statins, and blood pressure medication (1 snapshot from databases in the 6 months pre- and post-CTA) and risk factors were evaluated. Similar to prior studies in symptomatic (7) as well as asymptomatic patients coming for screening (8), knowing CTA results increased the frequency of some appropriate prescriptions and resulted in improvement of lipid profiles. Not unexpectedly, the change was in proportion to the severity of the imaging abnormality. Similar to all other studies in this arena, the study was too small to evaluate outcomes.

Can Imaging Modify Physician and Patient Behavior?

Cardiac imaging in general results in increased therapy, and the increase is related to the severity of

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test results. This has been shown in many studies (4,5,9), many albeit mostly small and limited to single or few centers using multiple different imaging modalities and sources of data. Some studies directly worked on motivating the patient, whereas others had a more global strategy. Even in the positive studies, the magnitude of change in medication use still remains suboptimal, even in those groups with the highest risk. Nearly one-third of high-risk patients were not on guideline-recommended medications post-imaging in the SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease) study (9), and use of medication diminishes with time following an imaging test (8). Data in patients with lower risk are limited and varied, including in asymptomatic and symptomatic patients. One recent, well-done study showed that coronary artery calcium scanning in 2,137 highly motivated, well-educated, middle-aged asymptomatic volunteers was associated with better risk factor profiles at a single time point 4 years later. Outcomes, although the study was not powered for this endpoint, were not different (4).

However, results have not been unanimously consistent, especially in some of the more robust studies. A good-sized randomized trial using myocardial perfusion imaging in diabetic patients found that imaging did not markedly change the use of appropriate therapy (10). An older randomized study in active duty military personnel (somewhat similar risk as in the current paper (6), but younger age) did not show any benefit, in terms of altering modifiable risk, by their knowing whether they had coronary calcium or not. Although intensive case management helped in lowering modifiable risk, knowledge of coronary calcium did not add to it (11). Finally, another well-done randomized study of carotid plaque imaging failed to change smoking cessation rates or risk factor profiles even in motivated subjects (12). Notably, the test was positive in 58% of the subjects, thus avoiding the criticism of other studies that one cannot motivate a change in behavior if there is no high-risk indictor to start with. As a comparison, only 15% had a positive electron beam computed tomography scan in the O'Malley et al. study (11), and only 9% had >50% stenosis (and 55% had no CAD at all) in the current study (6). In a meta-analysis of 7 studies, intervention failed to show that cardiovascular imaging significantly influenced drug use, smoking cessation, or diet changes (13) but also demonstrated the scarcity of high-quality data addressing these issues. Despite imaging's attractiveness, its ability to refine cardiovascular risk, and encouraging current data, many limitations, including the use of highly selected patient populations, low prevalence of abnormal findings, and a lack of outcome data, preclude the drawing of firm conclusions on its broader utility for patient motivation or modifying physician prescription behavior. Some of these studies did not involve the patient's physician directly, did not suggest a pre-defined path for intervening, and the endpoint depended on recall or a long latency in follow-up, to a time point 4 years later. Typically, the effects of short-term counseling do not persist so long, and factors other than counseling might have played a role. Not surprisingly, given all these limitations, some have argued against widespread adoption of imaging to change behavior (14).

The present study (6), despite being retrospective, has some novelty even with the prior presence of at least 3 other studies. The authors used information from clinical indication–driven CTA in a larger group of patients than in many prior studies. Second, the patient population was unique in that the subjects were confined to 1 insurance system with generous benefits, and all their medical data were largely captive within that health system. Unlike previous studies, this study did not need to use recall or similarly less robust strategies to capture data (5). Finally, they were not subject to the confounding influence of variable levels of insurance and drug availability.

Does Using Imaging to Modify Physician and Patient Behavior Change Outcomes?

Even with many studies showing some benefit of cardiovascular imaging in modifying physician and patient behavior, one important unanswered question is whether CTA information just provokes more action, or whether the action is associated with better outcomes. It is worthwhile to remember that sometimes efforts at more intensive case management, based on a limited set of indicators, have resulted in adverse outcomes despite overwhelming benefit shown in small preliminary studies (15). Surrogate measures such as increased medication use or adherence to a prescription strategy may not reveal what will happen in the long run. Similarly, studies in other fields have shown that increased adherence and behavior change with intervention did not necessarily change outcomes (16). Primary prevention studies are notoriously affected by low event rates and need a very large number of patients to show a benefit—indeed, even the 2,137 patients in the EISNER (Early Identification of Subclinical

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Atherosclerosis by Noninvasive Imaging Research) study were insufficient to show an outcome difference even with imaging information (4). Although many guidelines support lipid-lowering therapy for primary prevention, some have also questioned whether we may have sufficiently robust data to subject tens of millions of asymptomatic subjects to such therapy (17). Future studies will have to show that acting based on imaging results in unquestionable benefits in smaller, better risk-triaged subgroups, and randomized outcome studies are needed before widespread acceptance. The population studied in the current study (6) was low risk: one-half did not have any CAD, and the prescription changes in the group with CAD were small; similar to other previous efforts, the current study had very few events and thus could not provide meaningful outcome data. Lipid changes were more substantial, but the mean changes, especially when only 37% had both, the pre-CTA and follow-up lipids, fail to reveal whether the benefit was from a small group of patients treated aggressively or from a larger population treated more modestly. Finally, this snapshot study cannot answer the more important question about durability of this effect. Adherence to medication has been notoriously difficult, adherence diminishes with time (8), and lack of adherence is a strong factor in suboptimal outcomes (18). Furthermore, benefits of lipid lowering take a long time to show up in chronic CAD, and an increase in 6-month prescription rates might not hold up long enough for sustained benefit. Thus, the short-term increase in medication rates in this study may not be predictive of desirable longer-term outcomes.

Does Using Imaging to Modify Physician and Patient Behavior Result in a More Appropriate Therapeutic Response?

The premise of using imaging for modifying physician/patient behavior, prescription, and adherence rests upon appropriate downstream action on the part of both. Imaging should increase the use of evidence-based therapies in the high-risk group while it should also logically avoid unnecessary therapeutics in the reclassified low-risk group. Although it is logical to think that the current study is primarily evaluating the effect of CTA, it is more likely evaluating: 1) a strategy where the "value proposition" assigned by treating physicians to CTA results is a major factor; and 2) the physician's idea of the "hierarchy of benefit" when treating various risk factors. Although patient preference may also have played a role in this strategy outcome, this study does not allow one to separate that contribution from the role of the treating physician. In the current study, it appears that the cardiologist performing the CTA did not directly influence the treating physician or the patient—only their report conveyed the threat assessment following CTA. It is not clear whether the recipients were cardiologists or primary care physicians—their understanding of what a CTA report means and what "threat value" it assigns would have been variable. No formal therapeutic strategy was guiding subsequent treatment; despite being a highly logical option, currently, there is scant evidence-based data to support the use of CTA-detected CAD as a pivotal point to initiate or withhold therapy for risk factors. Thus, physicians were free to initiate downstream actions as they chose.

In what the physician believed was the highest-risk group post-CTA (>50% stenosis, 9% of the population), statin use increased from 69% to 86% at >6 months post-CTA; about one-half of the patients had an increase in dose, and one-quarter had new prescriptions. However, the majority of patients in this group were hyperlipidemic to start with before CTA, and many of these patients, who as a group had the highest Framingham risk score in this study, may have had an independent reason to start statins; CTA could just have provided urgency to the physician to pull the trigger to treat these patients. Future CTA studies in this arena will have to show an added value over and above traditional risk stratification techniques. Interestingly, the odds ratio for statin use, adjusted for baseline risk factors and medications, was more pronounced in obstructive versus nonobstructive CAD. Aspirin use behaved similarly. The treating physician was probably assigning a different degree of "threat value" to nonobstructive CAD compared with obstructive CAD, despite data showing that the presence of nonobstructive plaque can account for a significant proportion of events (19). Compared with statins and aspirin, increased utilization of blood pressure medications was less pronounced. It is possible that the physician understood CTA plaque and subsequent events to be primarily dependent upon lipids/platelets that needed intensified treatment compared with blood pressure, once again highlighting the role of what the physician thought was the hierarchy of benefit. In this regard, the SPARC study also showed a modality-dependent preference for change in medications—a positive result on a CTA was more likely to result in

a statin prescription compared with a similar result from perfusion imaging, whereas beta-blocker use was independent of test modality (9).

The no CAD group (defined as no atherosclerosis and no stenosis) also presents very interesting data. One benefit of imaging should be the reassurance provided by not having CAD or, better yet, not having any visible plaque. Because not having CAD portends a very good prognosis, it is logical that low-risk patients with atypical chest pain and a negative CTA scan might not need aggressive risk factor therapy. The no CAD group in this study was at very low risk for events even before CTA (Framingham risk score 2.7 ± 3.7, low-density lipoprotein of 116 ± 31 mg/dl, high-density lipoprotein 55 ± 18 mg/dl). Far from any reduction in statin or aspirin use with a negative CTA, use of imaging surprisingly resulted in an intensification of statin therapy in a quarter of patients. This is different from that seen in other studies where statin use decreased following a negative test in asymptomatic patients coming for screening as a part of a large study (8). It appears that a positive imaging test is interpreted as needing more aggressive therapy, whereas a negative test may be accorded less credence for therapeutic decisions. This is consistent with the highly variable response to CTA information among a diverse group of physicians. Because these kinds of patients may form the bulk of patients in the general population, this dichotomy in decision making is concerning. Moreover, the risk-to-benefit ratio of statins might be suboptimal in this subset of patients in the primary prevention universe, and the effect of aspirin may even be somewhat detrimental. More data evaluating the safety of downsizing therapy in patients with a negative imaging test are clearly indicated. CTA might not be the best test for this purpose, but other imaging, for example, coronary calcium, might have an important role in filtering to a manageable size the millions of patients currently recommended for aggressive therapy for primary prevention.

Studies evaluating the effect of imaging on downstream risk factor levels and outcome are dependent upon a variety of variables and thus difficult to perform cleanly in environments like the present study (6) that are not a part of a randomized trial. A number of steps need to be reconciled appropriately, including interpreting and acting appropriately on the imaging report (not always done consistently as shown by the SPARC study), availability of adequate evidence-based guidelines, instituting changes of adequate magnitude and duration covering multiple nonrelated risk factors (a problem without a priori treatment algorithms), monitoring for the minimal necessary change in the target parameters (difficult even in the present study, where the population was largely captive in terms of insurance and provider choice—only 37% had both, pre-CTA and post-CTA lipid levels), sustaining the improved medication use for the necessary duration (not available in this study), and finally, showing changes in outcomes (very few events were seen, hard events were even fewer, but the study was not powered to evaluate outcomes). The population was probably a more disciplined group with access to high-quality insurance without significant out-of-pocket expenses and might represent a better-case scenario. How CTA-based information would perform in a more real-world group of patients is debatable. Nevertheless, the authors are fair in discussing their limitations, and this study is a useful addition to understanding the role of CTA in deciding risk-factor control strategies. That said, we now have a sufficient corpus of uncontrolled studies to move from "imaging for optimum therapy" to "imaging for optimum outcomes"—a far more pressing clinical question. All future investigations in this area will need to address whether imaging can change outcomes, and randomized trials with outcome endpoints will be very welcome.

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