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EDITORIAL COMMENT

Imaging Asymptomatic Individuals for Coronary Disease*

Darryl P. Leong, MBBS, MPH, MBiostat, PhD, Philip G. Joseph, MD, Salim Yusuf, MBBS, DPhil

Imaging for cardiovascular disease (CVD) poses a substantial burden on health budgets. Although the use of diagnostic imaging to confirm specific conditions is justifiable when uncertainty exists, can one justify their use more broadly to detect coronary artery disease (CAD) in asymptomatic subjects? In the United States between 1999 and 2008, Medicare claims grew by 44%. Cardiovascular imaging accounted for approximately one-third of all services provided (1); cardiac computed tomography use increased >6-fold and nuclear stress imaging increased 3.2-fold during that period (1). Cardiovascular imaging therefore has contributed significantly to the rising cost of health care in high-income countries such as the United States, where health expenditure as a percentage of gross domestic product rose from 5.0% in 1960 to 17.8% in 2015 (2), a trajectory that is unsustainable. Therefore, the evidence to support cardiovascular imaging for new indications must be rigorously examined prior to its widespread adoption.

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In a review published in this issue of *iJACC*, Rozanski et al. (3) summarize the few randomized trials that have evaluated imaging to screen for asymptomatic CAD. They identified 5 randomized trials of 4,615 subjects that evaluated whether imaging for the identification of asymptomatic CAD, or changes in therapy predicated on the results of such imaging, influenced clinical outcomes. These trials demonstrated that routine CAD imaging did not significantly reduce the incidence of clinical outcomes. So, is there a role for imaging to identify occult CAD in asymptomatic subjects?

The World Health Organization suggests 10 criteria that should characterize effective screening tests (**Table 1**) (4). The trials reviewed by Rozanski et al. (3) demonstrate that imaging to screen for asymptomatic CAD does not meet at least 3 of these criteria.

The first criterion is that there should be a treatment for the condition, which (we add) is dependent on the results of the screening test; although there are treatments for CAD, the imaging trials have not demonstrated that changes in management on the basis of imaging asymptomatic subjects lead to improved clinical outcomes. There are 2 principal reasons for these neutral findings. First, the treatment of CVD risk factors alone (without screening using cardiac imaging) leads to substantial reduction in CVD events (5). If subjects are appropriately treated for their CVD risk factors, further improvements in outcome from cardiac imaging will depend on identifying subjects for additional treatments that would reduce events; however, at present we have no evidence that there are incrementally effective interventions that could be applied to those with asymptomatic CAD detected by cardiac imaging. Second, even if there were interventions that could improve outcomes, these trials were too small to detect plausible reductions in the incidence of CVD events. The outcome event rates observed among control subjects in the trials cited by Rozanski et al. (3) ranged from 0.11% to 2.3% per year, and the studies were far too small to detect a plausible treatment effect (**Table 2**).

The second criterion is that there should be a latent phase of the disease. Unlike cancers such as breast and colon, for which small cancers detected by screening will progress over time to advanced cancers with poorer outlooks, or diseases such as Wilson's disease, for which there is a latent phase between the identification of the genotype and the clinical manifestation of the disease, stable asymptomatic CAD

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From the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Pamela Douglas, MD, served as the Guest Editor for this paper.

TABLE 1 Criteria for an Effective Screening Test

Criterion	Fulfilled by Coronary Imaging
The condition should be an important health problem	+
There should be a specific treatment for the condition (that would be applied on the basis of the test results)	±
Facilities for diagnosis and treatment should be widely available	±
There should be a latent stage of the disease	±
There should be a test or examination for the condition	+
The test should be acceptable to the population	+
The natural history of the disease should be adequately understood	+
There should be an agreed policy on whom to treat	±
The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole	±
Case finding should be a continuous process, not just a "once and for all" project	±

does not necessarily progress to myocardial infarction in a substantial proportion of patients. Although patients with a greater burden of atherosclerosis on cardiac imaging have a higher risk for future cardiac events, it is also recognized that a stable coronary plaque, which might be detected by imaging, is frequently not the direct cause of myocardial infarction (6). For example, in a multicenter registry of consecutive patients undergoing nonurgent coronary angiography, prior myocardial infarction was noted in only 40% of those with chronic total coronary occlusions (7). Therefore, although stable CAD detected by cardiac imaging is a risk factor for acute myocardial infarction in a population, it may not reliably predict future events in patients.

The third criterion is that the total cost of finding a case should be economically balanced in relation to medical expenditure as a whole: imaging must not only be justified in being effective but also cost-effective. Health economic analyses have come to inconsistent conclusions in this respect. In 2 U.S. cost-effectiveness analyses, Roberts et al. (8) suggested that coronary artery calcium scoring with statin initiation for a calcium score ≥100 is preferred to a clinical guideline-based approach to statin use, whereas Pletcher et al. (9) reported that coronary calcium scoring in intermediate-risk patients is cost-effective only if statins are costly or adversely affect quality of life. Statins are generic and thus are relatively inexpensive, and they are well tolerated. Also, one needs to consider the opportunity cost of funding imaging to screen for asymptomatic CAD; an alternative use of these funds might be to implement a clinical risk-based approach to population screening and treatment, which in contrast to imaging has been strongly shown to reduce adverse CVD outcomes (10).

There is also an inverse relationship between the risk for CVD or cardiovascular death in strata of patients and the numbers of patients at risk within each stratum. Those with high-risk characteristics may represent only a minority of those who will experience future events within the population, with a substantial proportion of events occurring in low- or moderate-risk populations. There is general agreement that those with established CVD be aggressively medically managed because the absolute risk for recurrent cardiovascular events is high, and even a modest relative risk reduction translates into important absolute benefits within this subgroup of the population. In those without established CVD, the case for screening on the basis of imaging can be justified only if the magnitude of increase in cardiovascular outcome risk in those with a positive test is

TABLE 2 Total Sample Size Required to Be Randomized 1:1 to an Imaging or a Nonimaging Strategy to Demonstrate a Clinically Plausible Effect Size, Assuming 85% Power, Average 4-Year Follow-Up With No Loss to Follow-Up, and Perfect Adherence to Intervention in the Imaging Group

Risk	Control Group Annual Cardiovascular Event Rate	Effect Size (Hazard Ratio in Imaging vs. Nonimaging Group)	Sample Size
Clinically low risk	0.5%	0.9	170,510
	0.5%	0.75	25,114
	0.5%	0.6	8,966
Clinically intermediate risk	1%	0.9	85,214
	1%	0.75	12,544
	1%	0.6	4,476

substantial and if this risk could not have been determined without the test. In a systematic review of prospective studies evaluating the risk for cardiovascular events in those with elevated coronary calcium scores, the pooled adjusted relative risk for coronary events for those with coronary calcium scores of 1 to 100 was 2.1 (95% confidence interval: 1.6 to 2.9) and for those with scores 101 to 400 was 4.2 (95% confidence interval: 2.5 to 7.2) (11). Notably, none of the studies in this meta-analysis evaluated the relationship between coronary calcium and clinical outcomes adjusted for treatment with blood pressure-lowering medications or statins; because these treatments lower the risk for CVD events, adjustment for them might be expected to attenuate the reported association between calcium score and coronary events. On the basis of an analysis of the PURE (Prospective Urban Rural Epidemiology) study—a large, prospective cohort study of adults from countries of all income strata—1 or more of hypertension, diabetes, smoking, or self-reported CVD is present in approximately one-half the middle-age adult population. Over 4 years, 84% of all major cardiovascular events occurred in this population (12). Therefore, if a simple approach based on easily ascertained clinical risk factors is effective, then the role of imaging to identify additional subjects for prevention is likely to be minimal.

In conclusion, the available evidence does not support the widespread use of coronary imaging for the identification of asymptomatic CAD. Further trials comparing the value of imaging with clinical risk stratification in reducing cardiovascular events will need to be much larger than previous studies (**Table 2**). Perhaps a decision-tree analysis will help decide which subgroup of subjects should be considered for additional screening with imaging, and such an algorithm can be tested prospectively in moderate-sized trials. Until the results of such studies demonstrate clear clinical benefit, it would be premature to recommend screening using imaging techniques in asymptomatic subjects as part of a routine clinical or a population health strategy.

ADDRESS FOR CORRESPONDENCE: Dr. Darryl P. Leong, C3-106 David Braley Building, Hamilton General Hospital, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada. E-mail: leongd@phri.ca.

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