Influence of Noninvasive Cardiovascular Imaging in Primary Prevention

Systematic Review and Meta-analysis of Randomized Trials

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Background: Despite extensive use in practice, the impact of noninvasive cardiovascular imaging in primary prevention remains unclear.

Methods: We searched for randomized trials that compared imaging with usual care and reported any of the following outcomes in a primary prevention setting: medication prescribing, lifestyle modification (including diet, exercise, or smoking cessation), angiography, or revascularization.

Results: Seven trials were included. Trials screened patients for inducible myocardial ischemia (2 trials), coronary calcification (3 trials), carotid atherosclerosis (1 trial), or left ventricular hypertrophy (1 trial). Imaging had no effect on medication prescribing overall (odds ratio [OR], 1.01; 95% confidence interval [CI], 0.76-1.33) or on provision of lipid-modifying agents (OR, 1.08; 95% CI, 0.58-2.01), antiplatelet agents (OR, 1.05; 95% CI, 0.84-1.32). Similarly, no effect was seen on diet improvement (OR, 0.78; 95% CI, 0.22-2.85), physical activity (0.02 vs −0.08 point change for imaging vs control on a 5-point scale; P = .23), or smoking cessation (OR, 2.24; 95% CI, 0.97-5.19). Imaging was not associated with invasive angiography (OR, 1.26; 95% CI, 0.89-1.79).

Conclusions: We found limited evidence suggesting that noninvasive cardiovascular imaging alters primary prevention efforts. However, given the imprecision of these results, further high-quality studies are needed.

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The past 30 years have seen substantial improvements in the treatment of most major forms of cardiovascular disease. Despite this, significant gaps in the application of proven treatments remain; these include deficiencies in the use of evidence-based therapies and failure to provide and follow up on recommendations relating to diet, physical activity, and smoking cessation. For example, a large multinational registry of 67 888 patients with established atherosclerosis or multiple cardiovascular risk factors recently reported substantial underuse of statins, antiplatelet agents, and other evidence-based medications.1 Addressing these care gaps is a major goal advocated by scientific associations and embedded in a range of practice guidelines.2-5

It has been suggested that noninvasive cardiovascular imaging may improve primary prevention efforts.6 Such imaging may facilitate the prescription of evidence-based therapies and promote lifestyle modification through multiple pathways. Early detection and visualization of disease may represent a “teachable moment” for patients and health care providers alike. Conversely, the absence of demonstrated pathologic findings in some imaging studies might unduly reassure patients with risk factors but no manifest detectable disease, thereby retarding appropriate care. The explosive growth in the use of cardiovascular imaging suggests a need for research focused on the end results of imaging and specifically its influence on clinical care and prognosis.7 We therefore undertook a comprehensive systematic review and meta-analysis of noninvasive cardiovascular imaging with particular reference to effects on medication prescribing, lifestyle modification, inva-
SEARCH STRATEGY

We searched 11 electronic information sources for trials from their inception until November 1, 2010: Cardiosource Clinical Trials, the Cochrane Central Register of Controlled Trials, the Cochrane Health Technology Assessment Database, Excerpta Medica (EMBASE), Healthstar, the International Standard Randomized Controlled Trial Number Register, MEDLINE, National Institutes of Health ClinicalTrials.gov, UpToDate Online, Web of Science with Conference Proceedings, and What’s What Online. The search was developed and performed in concert with a health informatics specialist. We used search terms related to imaging technologies and cardiovascular disease or risk factors. For example, to identify articles on computed tomography, we used variants and combinations of the following terms: Agatston, computed axial tomography, computed tomodiography, computed tomographic angiography, computerized tomography, CCTA, CTA, CT, CTCA, ciconification score, calcium score, cardiac gating, cardiac gated, coronary artery calci- fication, coronary artery calcium, coronary clectron beam, EBCT, EBT, MDCT, MCTA, multidetector, multislice, sixteen slice, and sixty-four slice. We supplemented the electronic search by scrutinizing the reference lists of primary articles, review articles, editorials, and imaging guidelines, as well as consulting experts in the field and screening personal files. Finally, we performed a gray literature search of the Internet, thesis dissertations, and abstract listings to locate additional trials. Pairs of reviewers performed the search and adjudicated study inclusion based on a standardized eligibility rating form (D.G.H. with K.G.S., J.D.S., D.A.A., and G.K.D.). Disagreements between reviewers were resolved through consensus.

DATA EXTRACTION AND QUALITY ASSESSMENT

We extracted the following details from eligible studies: citation information, characteristics of the imaging procedure, sample and setting characteristics, and details related to follow-up and outcomes. Data for each study arm were cross-checked for discrepancies. We recorded 5 measures of methodological quality: adequate randomization, concealed allocation, blinding of patients, clinicians, or outcome assessors, completeness of follow-up, and crossover between groups. These features were rated using bias assessment guidelines developed by the Cochrane Collaboration.6 When information was missing or unclear, we contacted study authors for clarification. We also inquired about outcome measures not reported in the original publications.

STATISTICAL ANALYSIS

We conducted analyses according to a prespecified plan. All outcomes with the exception of physical activity were synthesized using Mantel-Haenszel random effect models to compute summary odds ratios (ORs) with 95% confidence intervals (CIs). Physical activity was reported in terms of the original units of the single trial that included this measure (change in activity points on a validated 5-point scale ranging from 0 to 5, with higher values indicating higher degree of activity).9 All data were analyzed according to the intention-to-treat principle. An OR greater than 1 indicated that the process or outcome measure improved in relation to imaging; for example, an OR of 1.25 for smoking cessation implied that the odds of quitting smoking were 25% higher in patients who underwent imaging than in patients assigned to usual care.

Heterogeneity was quantified using the I² statistic, a measure of variability in the pooled effect estimate arising from between-study heterogeneity rather than chance.10 As an approximate rule of thumb, an I² value lower than 30% denotes low heterogeneity, an I² value between 30% and 50% represents moderate heterogeneity, and an I² value higher than 50% denotes substantial heterogeneity.11 We tested for publication bias by visually assessing funnel plots for each outcome. A 2-tailed P value less than .05 was deemed statistically significant. All statistical analyses were performed using Cochrane Review Manager (Version 5.0.2; Nordic Cochrane Centre, Copenhagen, Denmark).

DESCRIPTION OF STUDIES

The literature search produced 60,299 citations, of which 1353 were potentially relevant and retrieved in full (Figure 1). Of these, 7 trials12-18 were eligible for the review; additional published information on 3 of these trials was available and abstracted (trial design articles and other secondary
we clarified study details with the corresponding authors of all trials; further, authors of 6 trials provided additional outcome data not provided in the original publications.13-18 Trials enrolled a median of 153 patients (interquartile range [IQR], 99-314 patients) with a median follow-up of 12 months (IQR, 9-39 months; Table 1). The median age of participants was 55 years (IQR, 49-60 years); overall, 45% were women. Computed tomography was the most common imaging modality (3 trials), followed by echocardiography (2 trials), ultrasonography (1 trial), and myocardial perfusion imaging (1 trial). Patients were screened for myocardial ischemia (2 trials), coronary calcification (3 trials), carotid atherosclerosis (1 trial), and left ventricular hypertrophy (1 trial). The median frequency of “positive” imaging results, suggesting the presence of cardiovascular disease, was 22% (IQR, 19%-28%).

Most studies scored well on the methodological quality indicators (Table 2). Randomization was adequately performed in all 7 trials, concealed allocation was attempted in 6 trials (86%) and blinding of at least 1 study component was used in 6 (86%). Median loss to follow-up was 7% (IQR, 3%-10%), with median crossover occurring in 0% (IQR, 0%-4.4%) Of the 7 trials, 5 did not formally assess the effects of noninvasive imaging on self-perceived health or well-being; of the 2 that did, differences in psychological parameters between screened patients and controls were not significant.14,15

STUDY OUTCOMES

Medication Prescribing

Four trials (n=1500 patients) reported medication use in relation to imaging, with a median of 258 prescribing events and 9 drug classes reported (Table 3).13,16-18 There was no effect of imaging on prescribing overall (OR, 1.01; 95% CI, 0.76-1.33; I2=0%; Figure 2, top) nor on most of the drug classes, with the possible exception of insulin prescribing (OR, 1.28, 1.00-1.64; P=0.05; I2=0%). Removal of 1 trial that did not report concealed allocation and had substantial attrition did not materially affect the results for medication prescribing (OR, 1.00; 95% CI, 0.75-1.32; I2=0%). Usual care prescribing rates for the various drug classes ranged from 13% for diuretics to 79% for oral hypoglycemic agents (median prescribing rate, 35%), indicating that the lack of influence of imaging was not due to a ceiling effect.

Lifestyle Modification

Four trials reported smoking cessation rates12-15 in a total of 198 baseline smokers; 1 trial each reported dietary modification13 and physical activity.15 We found no statistically significant effect of imaging on smoking cessation (OR, 2.24; 95% CI, 0.97-5.19; I2=0%; Figure 2, middle), dietary improvement (OR, 0.78; 95% CI, 0.22-2.85), or physical activity (0.02 vs −0.08 point change for imaging vs control on a 5-point scale; P=.23).

Angiography and Revascularization

Two trials in 1173 patients reported rates of angiography and revascularization.14,18 We found no significant association between imaging and angiography (OR, 1.26; 95% CI, 0.89-1.79; I2=0%) or revascularization (OR, 0.71; 95% CI, 0.44-1.14; I2=0%).
We found limited evidence supporting a major influence of noninvasive cardiovascular imaging on markers of care in primary prevention settings. We included a diverse range of trials reflecting a number of major noninvasive cardiovascular imaging modalities in use today. Samples were equally diverse, ranging from asymptomatic middle-aged patients with no history of cardiovascular disease to patients with major cardiovascular risk factors. However, our results have a number of important limitations.

Of particular note, most trial samples were relatively small, potentially limiting our ability to detect clinically important effects on markers of care. The 95% CIs for medication prescribing and smoking cessation, for example, do not exclude increases of up to 1.33-fold and 5.2-fold, respectively. Furthermore, despite the fact that all trials were enrolled in primary prevention settings, several trials found substantial improvements in care in both groups over the course of follow-up, which is consistent with successive iterations of treatment guidelines recommending progressively lower treatment targets as well as a broader range of available medical therapies.13,16-18

Other limitations relate to potential reporting biases in individual trials. For example, of the 7 trials included in this review, only 4 listed medication prescribing at follow-up assessments after imaging. One trial reported medication prescribing at baseline but not after imaging, and 2 other trials did not record any drug prescribing. It must be appreciated that studying the impact of imaging on practice parameters such as medication prescribing might not have been a goal of investigators at the time trial designs were being conceived, and thus this information was simply not collected. In addition, 78% of patients had no identifiable imaging abnormalities, meaning that at most only 1 in 5 patients had an “actionable” test result mandating intensification of therapy (with some of these patients likely already receiving treatment).

Table 3. Effect of Imaging on Drug Prescribing by Individual Class

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Trials, No.</th>
<th>Events, a No.</th>
<th>Patients, No.</th>
<th>Prescribing Rate, Usual Care, %</th>
<th>OR (95% CI)</th>
<th>P, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All medications</td>
<td>4</td>
<td>258</td>
<td>1500</td>
<td>17</td>
<td>1.01 (0.76-1.33)</td>
<td>0</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>2</td>
<td>799</td>
<td>1267</td>
<td>62</td>
<td>1.05 (0.84-1.32)</td>
<td>0</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>3</td>
<td>225</td>
<td>1444</td>
<td>16</td>
<td>1.01 (0.76-1.34)</td>
<td>0</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>3</td>
<td>754</td>
<td>1323</td>
<td>57</td>
<td>1.08 (0.58-2.01)</td>
<td>55</td>
</tr>
<tr>
<td>ACE inhibitors or ARBs</td>
<td>3</td>
<td>609</td>
<td>1444</td>
<td>42</td>
<td>1.18 (0.80-1.75)</td>
<td>44</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>3</td>
<td>241</td>
<td>1444</td>
<td>17</td>
<td>1.03 (0.78-1.37)</td>
<td>0</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1</td>
<td>20</td>
<td>177</td>
<td>13</td>
<td>0.75 (0.29-1.91)</td>
<td>NA b</td>
</tr>
<tr>
<td>Any antihypertensive agent</td>
<td>3</td>
<td>829</td>
<td>1356</td>
<td>61</td>
<td>1.05 (0.75-1.47)</td>
<td>20</td>
</tr>
<tr>
<td>Insulin</td>
<td>2</td>
<td>374</td>
<td>1267</td>
<td>27</td>
<td>1.28 (1.00-1.64)</td>
<td>0</td>
</tr>
<tr>
<td>Oral hypoglycemics</td>
<td>1</td>
<td>891</td>
<td>1123</td>
<td>79</td>
<td>1.04 (0.71-1.52)</td>
<td>NA b</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CI, confidence interval; NA, not applicable; OR, odds ratio.

a Prescribing events (usual care and imaging groups pooled).

b Heterogeneity testing was not applicable, with n=1 for this category.
scale screening, screening in individually selected cases may provide reassurance to anxious patients, risk stratification for provision of cardioprotective therapies (in particular in intermediate-risk patients), or assist in “fine tuning” the management of a specific clinical problem (eg, echocardiographic screening for target organ damage in sustained hypertension).

Randomized trials with allocation to imaging in primary prevention settings do not typically report cardiovascular events or mortality. Two randomized trials included herein that screened asymptomatic diabetic patients for inducible cardiac ischemia found conflicting results: a small pilot trial (n=141) suggested a very large reduction in major cardiovascular events (relative risk, 0.07; 95% CI, 0.01-0.57), while a larger randomized trial (n=1123) confirmed no such effect on the same end point (hazard ratio, 0.88; 95% CI, 0.44-1.88).10,11 Given the low rate of cardiovascular events in most primary prevention populations accrued in the modern era, imaging trials powered for cardiovascular events will either need to include very large populations or induce greater shifts in the intensity and prevalence of evidence-based medical therapies (a phenomenon not evident from the trials conducted to date).

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