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), antihypertensive drugs (OR, 1.05; 95% CI, 0.75-1.47), or antiplatelet agents (OR, 1.05; 95% CI, 0.84-1.32). Similarly, no effect was seen on dietary 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.


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-
MEASUREMENTS and RESEARCH 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: Aguston, computerized axial tomography, computed tomography, computed tomographic angiography, computerized tomography, CAC, CACS, CCTA, CT, CTA, CTCA, calcification score, calcium score, cardiac gating, cardiac gated, coronary artery calcification, coronary artery calcium, coronary calcification, coronary calcium, detector row, double helical, dual energy, dual source, electron beam, EBCT, EBT, MDCT, MSCT, 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.

RESULTS

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 completeness of follow-up, and crossover between groups. These features were rated using bias assessment guidelines developed by the Cochrane Collaboration.9 When information was missing or unclear, we contacted study authors for clarification. We also inquired about outcome measures not reported in the original publications.

STUDY METHODS

We included randomized trials that compared primary prevention patients undergoing application of noninvasive cardiovascular imaging with a control group receiving usual or standard care. Cardiovascular imaging comprised computed tomography, magnetic resonance imaging, echocardiography, positron emission tomography, arterial ultrasonography, nuclear myocardial perfusion imaging, exercise electrocardiography, and radionuclide angiography. Because our intent was to evaluate the effects of imaging on clinical care, we excluded trials that compared different imaging modalities in head-to-head fashion unless they also included control patients not receiving imaging. In addition, trials had to measure at least 1 of the following to be included: medication prescribing, lifestyle modification (smoking cessation, dietary modification, or exercise), the subsequent use of invasive (catheter-based) angiography in any vascular territory, or revascularization in any vascular territory. We focused on these outcomes because they represent anticipated sequelae of cardiovascular imaging or because they are regarded as performance indicators in cardiovascular prevention. Other care processes (eg, referrals to specialists, additional noninvasive imaging) and outcome measures (eg, cholesterol levels, blood pressure, cardiovascular events) were sparsely reported and therefore not included in our analyses.

Figure 1. Literature search and selection.


direct angiography, and revascularization.

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Figure 1. Literature search and selection.
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%-0.4%). 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%).

Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging</th>
<th>Setting and Intervention</th>
<th>Follow-up</th>
<th>Sample Age, y/% Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovet et al12</td>
<td>US</td>
<td>Carotid plaque screening in 153 adult cigarette smokers from the general population</td>
<td>6 mo</td>
<td>46/15</td>
</tr>
<tr>
<td>Faglia et al16</td>
<td>Echo, ETT</td>
<td>Screening of 141 patients with type 2 diabetes mellitus with additional cardiovascular risk factors but no known cardiac disease</td>
<td>53.5 mo</td>
<td>60/43</td>
</tr>
<tr>
<td>Lederman et al13</td>
<td>CT</td>
<td>Coronary calcium screening of 56 postmenopausal women without known CAD or breast cancer</td>
<td>12 mo</td>
<td>65/100</td>
</tr>
<tr>
<td>Martina et al17</td>
<td>Echo</td>
<td>Detection of target organ damage in 177 general medical outpatients with primary hypertension</td>
<td>6 mo</td>
<td>51/40</td>
</tr>
<tr>
<td>O’Malley et al15</td>
<td>CT</td>
<td>Coronary calcium screening of 450 asymptomatic active-duty army personnel without known CAD</td>
<td>12 mo</td>
<td>42/21</td>
</tr>
<tr>
<td>Obuchowski et al14</td>
<td>CT</td>
<td>Total-body imaging of 50 asymptomatic, medically insured adults without known CVD, cancer, or diabetes (including coronary calcium screening)</td>
<td>2 y</td>
<td>55/50</td>
</tr>
<tr>
<td>Young et al18</td>
<td>MPI</td>
<td>Screening of 1123 patients with type 2 diabetes without known CAD</td>
<td>4.8 y</td>
<td>61/54</td>
</tr>
</tbody>
</table>

Table 2. Methodological Quality Parameters

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomized</th>
<th>Concealed Allocation</th>
<th>Blindinga</th>
<th>Lost to Follow-up, %</th>
<th>Crossover, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovet et al12</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Faglia et al16</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lederman et al13</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Martina et al17</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>O’Malley et al15</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Obuchowski et al14</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Young et al18</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
<td>19</td>
</tr>
</tbody>
</table>
aBlinding of at least 1 study component (patients, physicians, outcome assessors).
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, 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>764</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</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</td>
</tr>
</tbody>
</table>

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

aPrescribing events (usual care and imaging groups pooled).

*Heterogeneity testing was not applicable, with n=1 for this category.

Figure 2. Effect of imaging on measures of care. Mantel-Haenszel random effects meta-analysis of the impact of imaging on various care measures. Data are plotted on a logarithmic scale. Trial odds ratios are represented by squares with 95% confidence intervals denoted by horizontal whiskers. The size of each square is proportional to the weight of the corresponding trial. The overall effect for each outcome is shown as a diamond.
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, 0.89; 95% CI, 0.44-1.88).56,58 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).

Accepted for Publication: January 7, 2011.

Published Online: March 14, 2011. doi:10.1001/archinternmed.2011.69

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Author Contributions: Dr Hackam had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hackam, Shojania, Spence, Alter, Dresser, and Goela. Acquisition of data: Hackam, Shojania, Spence, Alter, Beanlands, Dresser, Badano, Poldermans, Boersma, and Njike. Analysis and interpretation of data: Hackam, Shojania, Spence, Alter, Beanlands, Dresser, Goela, Badano, Poldermans, Boersma, and Njike. Drafting of the manuscript: Hackam, Shojania, Spence, Alter, and Dresser. Critical revision of the manuscript for important intellectual content: Hackam, Shojania, Spence, Alter, Beanlands, Dresser, Goela, Badano, Poldermans, Boersma, and Njike. Statistical analysis: Hackam and Shojania. Obtained funding: Hackam, Shojania, Spence, Alter, and Dresser. Administrative, technical, and material support: Beanlands, Goela, Badano, Poldermans, Boersma, and Njike. Financial Disclosure: Dr Spence has received grants from the Heart and Stroke Foundation of Ontario and Canadian Institutes of Health Research and Canadian Stroke Network. Dr Hackam was supported by a Canadian Institutes of Health Research New Investigator Award in Clinical Research. Dr Shojania was supported by the Government of Canada Research Chairs Program. Drs Alter and Beanlands were supported by Career Investigator Awards from the Heart and Stroke Foundation of Ontario.

Role of the Sponsors: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Additional Contributions: Don Redelmeier, MD, MSHSR, and Amit Garg, MD, PhD, provided constructive comments on the manuscript; neither were compensated for their contribution.

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