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Decision analytic model for evaluation of suspected coronary disease with stress testing and coronary CT angiography.

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Abstract

Rationale and Objectives: To apply a decision analysis model for evaluation of coronary artery disease (CAD) to define optimal utilization of cCTA and stress testing.

Materials and Methods: Our model assumes CAD is evaluated with a stress test and/or cCTA, and that a patient with a positive evaluation undergoes cardiac catheterization. Based upon values of sensitivity, specificity and radiation dose from the published literature and test costs from the Medicare fee schedule, a decision tree model was constructed as a function of disease prevalence.

Results: False negative rate (FNR) is lowest when cCTA is used as an isolated test. False positive rate (FPR) is minimized when cCTA is employed in combination with stress echocardiography. Effective radiation is minimized by use of stress ECG or stress echocardiography alone, or prior to cCTA. When the pretest probability of CAD is low, a strategy that employs stress echocardiography followed by cCTA minimizes FPR and effective radiation exposure, with relatively low imaging costs and with a FNR only slightly higher than a stress myocardial scintigraphy strategy. As the pretest probability of CAD increases above 20%, the FNR of stress echocardiography followed by cCTA increases by more than 5% relative to cCTA alone.

Conclusion: Effective radiation dose and imaging costs for the work-up of CAD may be minimized by an appropriate combination of stress testing and cCTA. A strategy that employs stress echocardiography followed by cCTA is appropriate for evaluation of the low risk CAD patient with a pre-test probability less than 20%, while cCTA alone may be more appropriate in the intermediate risk patient.

Introduction

Although the age-adjusted death rate from heart disease has been declining slowly over the past 50 years, heart disease remains the most common cause of death in the United States, and was responsible for 26% of all deaths in 2006.[1] Atherosclerotic disease of the coronary arteries remains the most important etiology of heart disease. The evaluation of suspected coronary artery disease (CAD) should always begin with an appropriate history, physical examination and ECG. In the stable, symptomatic patient evaluation for CAD often progresses to non-invasive stress testing. The stress test provides a physiological evaluation of cardiac function and serves as a diagnostic study and prognostic marker for future coronary events.[2]

Coronary computed tomographic angiography (cCTA) provides a non-invasive alternative to cardiac catheterization for visualization of coronary anatomy, and has demonstrated high sensitivity and specificity for the anatomic presence of CAD.[3,4] Although functional information about wall motion can be obtained during cCTA, the primary utility of cCTA is for imaging of the coronary arteries to define the presence of CAD. Stress testing provides additional information to predict the functional relevance of coronary stenosis with respect to myocardial ischemia.[5,6] When cCTA demonstrates coronary stenosis of uncertain hemodynamic significance, a follow-up stress test may evaluate the functional significance of CAD found by cCTA. Given the divergent emphasis of stress testing on functional physiology and cCTA on coronary anatomy, these two modalities may provide complementary information in the evaluation of CAD.[7]

Stress testing has served as the traditional test of choice to evaluate symptoms that may be related to CAD. Three broad categories of stress testing include stress ECG without imaging, stress echocardiography and the nuclear stress

test – myocardial perfusion scintigraphy (stress MPS). Although cCTA may be more accurate than stress testing for evaluation of "hemodynamically significant" coronary stenosis[8] and appropriateness criteria have been evaluated for the application of cCTA,[9] the precise role of cCTA (versus stress testing or in combination with stress testing) in the work-up of CAD remains poorly defined.

In this study, we apply a theoretical decision analytic model to evaluate the diagnostic accuracy, effective radiation dose and imaging costs associated with evaluation of CAD using various combinations of cCTA and stress testing. Our goal is to define the strengths and weaknesses of various testing strategies that may be employed in order to optimize evaluation of the symptomatic patient with suspected obstructive CAD.

Methods:

A decision tree was constructed to compare false negative rates, false positive rates, effective radiation exposure and imaging costs during the work-up of suspected coronary disease with stress testing and/or cCTA (figure 1). The decision tree begins with a decision node – the rectangular box – where a CAD work-up strategy is chosen. The work-up options include evaluation with a single stress test or by cCTA alone, as well as options for a combined evaluation with both stress testing and cCTA. Each individual test option is represented by a node – a circle – whose outcome is governed by the sensitivity and specificity of that particular test. The work-up strategy follows the upper branch out of the test node when the test is positive, and the lower branch out of the test node when the test is negative. For combined evaluations, the decision tree includes options that begin with a stress test and proceed to cCTA as well as options that begin with cCTA and proceed to a stress test. In order to minimize unnecessary cardiac catheterizations, patients in this model are referred to catheterization only when non-invasive diagnostic testing is positive. When an option for combined testing is chosen, the patient is referred for the second test only if the first test is positive, and is referred to catheterization only when both the stress test and the cCTA are positive.

Spreadsheet computations for expected rates (or proportions) of true and false diagnoses among the population presenting for diagnostic testing were implemented as follows:

True positive rate (TPR) = prevalence x sensitivity

False negative rate (FNR) = prevalence - True positive rate

True negative rate (TNR) = (1 – prevalence) * specificity

False positive rate (FPR) = (1- prevalence) – True negative rate

It is important to distinguish the positive and negative rates/proportions in a study population (as defined above) from the positive and negative rates of a diagnostic examination. With respect to a diagnostic examination, the TPR (sensitivity), FNR (1-sensitivity), TNR (specificity) and FPR (1-specificity) are defined independent of disease prevalence. However, the expected proportion of positive and negative tests in a population and are dependent upon disease prevalence. For the purpose of health care policy decisions, the proportion of correct diagnoses in a study population (TPR + TNR), the proportion of incorrect diagnoses in a study population (FPR + FNR) and the overall imaging costs in the population are of interest. The TPR, TNR, FPR, and FNR of individual diagnostic tests are only important in so far as they impact the proportion of correct and incorrect diagnoses in the population. For the remainder of this manuscript all references to positive and negative rates refer to proportions within the study population.

Although CAD may be defined by gradations of severity, we use a dichotomous definition for CAD to simplify the decision analysis. cCTA is defined as positive for the presence of atherosclerotic disease when there is more than 50% diameter narrowing. The results of cardiac catheterization (our "gold standard") are assumed to be correct. Expected rates of true and false diagnoses are propagated through the decision tree based upon a Bayesian analysis that depends only upon prevalence of disease in the study population (= pre-test probability of disease for the individual patient) and the sensitivity/specificity of each test. At each test-decision node within the tree, the expected rate of positive exams is calculated as the sum of the true positive rate + false positive rate while the expected rate of negative exams is calculated as the sum of the true negative rate + false negative rate.

For any particular work-up strategy in the decision tree, effective radiation dose is computed as the sum of the effective radiation dose for each test in the pathway multiplied by the proportion of patients who will be subjected to that test. Imaging cost is similarly computed as the sum of the imaging cost for each test in the pathway multiplied by the proportion of patients who will be subjected to that test. Since the cost of cardiac catheterization is far greater than the cost of stress testing and cCTA, a strategy that employs more testing can result in reduced imaging costs if the rate of cardiac catheterizations is reduced.

A range of values for the sensitivity and specificity of stress tests and cCTA are reported in the literature. The values used for this analysis are summarized in table 1. The values for stress testing are based upon published meta analyses of the literature for stress ECG testing[10] as well as stress echocardiography and stress MPS.[11] The sensitivity and specificity of cCTA for CAD with diameter stenosis greater than 50% were based upon a recent multicenter trial by Budoff.[12] A sensitivity analysis was performed by varying the sensitivity and specificity of cCTA according to values obtained in two other recent multicenter trials – one trial by Meijboom demonstrating lower specificity,[13] and a second trial by Miller demonstrating lower sensitivity.[14] Our primary analysis was based upon sensitivity/specificity data from the Budoff trial because these values are intermediate between those of Meijboom and Miller. Finally, although single center trials may overestimate the accuracy of a diagnostic study, several recent meta analyses of single center studies have suggested higher diagnostic accuracy than the multicenter trials referenced above.[3,4] Therefore, higher values of sensitivity and specificity were also tested based upon the analysis of Vanhoenacker.[3]

Effective radiation dose for stress MPS, cCTA and diagnostic cardiac catheterization is a moving target with improvements in technology. Effective doses used for the current analysis are summarized in table 2. For stress MPS, the base value used for the analysis was 12mSv, based upon the reported dose for a Tc-99m sestamibi 1-day rest-stress protocol.[15] For the purpose of sensitivity analysis, the dose of a stress MPS examination was also varied down to 9.4mSv as reported in a more recent review of nuclear medicine studies.[16] In the interest of using an effective dose that is obtained with the latest generally available technology, we assume a 4.2mSv effective dose for prospectively ECG-gated cCTA based upon clinical reports.[17,18] For the purpose of sensitivity analysis, since many centers have not yet adopted prospectively gated cCTA, the effective dose of cCTA was also varied up to 10mSv as demonstrated in a recent multicenter trial using the more conventional helical CTA with tube current modulation.[19] The effective dose for diagnostic cardiac catheterization was set at 7mSv for the base analysis, but was varied down to 5mSv for the sensitivity analysis.[20,21]

Imaging/testing costs were computed as a combination of professional and technical fees as reported in table 3. For the purpose of cost comparisons, we refer to these costs as imaging costs even though the stress ECG study does not include an imaging component. Professional and technical fees for stress testing, cCTA and diagnostic cardiac catheterization were obtained from the 2009 physician Medicare fee schedule provided by our local carrier (Highmark Medicare; Camp Hill, PA). These fees are very similar to the 2009 national average Medicare payments (based upon the Nov 2008 Federal Register using a 2009 conversion factor – http://www.bostonscientific.com/Reimbursement). The facility fee for cardiac catheterization was not available in the 2009 physician medicare fee schedule

provided by our local carrier, and was therefore based upon the national average

facility fee from the Federal Register.

The decision tree model was implemented on a spreadsheet (Quattro Pro;

Correl Corp. Ottawa, Ontario). Computed values of false negative rates, false

positive rates, costs and radiation exposure were obtained for a disease prevalence

(= pre-test probability) that ranged from 0.01 to 0.60. The calculated values

represent expected mean values as a function of CAD prevalence. Results of this

analysis are presented in graphical format.

Results:

The imaging cost and expected effective radiation dose associated with each of the various work-up strategies for CAD are depicted to the right side of each terminal branch of the decision tree in figure 1. Figures 2 and 3 demonstrate the false negative and false positive rates for the diagnosis of CAD as a function of CAD prevalence, using our baseline assumptions of sensitivity and specificity (Budoff). Table 4 reports the values of these positive and negative work-up rates as a function of the prevalence of CAD. The order in which the stress test and cCTA are performed make no difference in this calculation. False negative rate (FNR) is proportional to CAD prevalence while false positive rate (FPR) is inversely related to CAD prevalence. FNR is lowest when cCTA is used as an isolated test. When a stress test is used in combination with cCTA, the FNR is slightly higher compared with the FNR when the same stress test is used alone. Specifically, the FNR of a combined approach including cCTA is increased by up to 3% relative to the FNR of a stress test alone as the prevalence of CAD approaches 60%. However, the FPR of the combined approach is reduced by 9-19% as the prevalence of CAD approaches 1%. FPR is minimized when cCTA is employed in combination with stress echocardiography.

Figure 4 demonstrates expected effective radiation dose as a function of CAD prevalence. Strategies that employ no advanced imaging (0.0mSv) or proceed directly to cardiac catheterization (7.0mSv) are not demonstrated in this figure since the effective radiation dose for these strategies is independent of CAD prevalence. Strategies that use stress MPS result in a higher effective dose than all other strategies. Stress MPS alone results in an effective dose that is approximately 8mSv

higher than cCTA alone. When a stress ECG or stress echocardiogram is added following cCTA, effective radiation dose is reduced by approximately 1mSv relative to cCTA alone. However, when a stress ECG or stress echocardiogram is added prior to cCTA, effective radiation dose is reduced by 4-5mSv because fewer cCTA studies are performed. A work-up strategy that employs stress ECG or stress echocardiography prior to cCTA minimizes effective radiation exposure compared to all other strategies that use cCTA and/or MPS. When the prevalence of CAD is below 47%, a strategy that employs stress echocardiography followed by cCTA will result in an expected effective radiation dose that is below that of a single cCTA (4.2mSv). When the prevalence of CAD is below 10%, a strategy that employs stress echocardiography followed by cCTA may actually result in an effective radiation dose that is lower than a strategy that uses stress echocardiography alone.

Overall imaging costs are summarized in figure 5 as a function of CAD prevalence. A strategy that tests all patients with cardiac catheterization is not demonstrated in figure 5 as this strategy would result in a fixed imaging cost of $2948, independent of CAD prevalence. As long as the pre-test probability of CAD is below 75%, the cost for each of the remaining strategies is below the cost of proceeding directly to cardiac catheterization. When the prevalence of CAD is below 45%, a strategy that employs stress MPS together with cCTA will result in lower rates of cardiac catheterization and lower imaging costs as compared to a strategy that uses either MPS or cCTA alone. Imaging costs are minimized by a strategy that employs stress ECG followed by cCTA. This combined strategy saves at least $400 per patient relative to a strategy that combines stress MPS with cCTA. From the imaging cost perspective, a strategy that employs stress echocardiography followed by cCTA is the second best strategy provided the prevalence of CAD is

below 20%. As demonstrated in figures 2 and 3, the diagnostic accuracy (FPR and FNR) of a strategy that employs stress echocardiography followed by cCTA is superior to that of stress ECG followed by cCTA.

Figure 6 demonstrates a sensitivity analysis for effective radiation dose. Figure 6A demonstrates effective radiation based upon a lower assumption of dose for stress MPS (9.4mSv) and cardiac catheterization (5mSv), while figure 6B demonstrates effective radiation based upon a higher assumption of dose for cCTA (10.0mSv). Figure 6C demonstrates the effective radiation dose based upon a combination of the lower dose assumptions for stress MPS and cardiac catheterization with the higher assumption for cCTA. Although the overall effective radiation doses are different from those demonstrated in figure 4, there is a similar pattern in the relative ordering of work-up strategies with respect to effective dose. Strategies that employ stress ECG or stress echocardiography alone or followed by cCTA continue to result in the lowest effective radiation dose. Similar graphs of effective radiation dose were produced when the diagnostic accuracy of cCTA was based upon the data of Miejboom (figure 6D) or Miller (figure 6E).

Figure 7 demonstrates a sensitivity analysis for expected imaging costs based upon various diagnostic accuracies of cCTA. The Miejboom values (figure 7A - lower specificity of cCTA) result in a higher FPR for cCTA, more cardiac catheterization procedures and higher overall imaging costs associated with options that include cCTA evaluation. The Miller values (figure 7B - lower sensitivity of cCTA with higher specificity) result in a lower FPR for cCTA and are associated with lower overall imaging costs. Notwithstanding the differences in absolute imaging costs, analyses based upon both the Miejboom and Miller data both

demonstrate that imaging costs are minimized by a strategy that employs stress ECG followed by cCTA. A strategy that employs stress echocardiography followed by cCTA is the second best strategy from a cost prospective in the setting of low CAD prevalence. When the sensitivity and specificity of cCTA are set to higher values based upon the meta analysis of Vanhoenacker (figure 7C) overall imaging costs with a cCTA work-up are reduced in comparison to the baseline analysis (figure 5).

Discussion:

We have applied a decision theoretic model to define the optimal roles of stress testing and cCTA in the work-up of the symptomatic patient with CAD. Our model demonstrates that when a stress ECG or stress echocardiogram is added prior to cCTA, the number of unnecessary cardiac catheterizations, the effective radiation dose and the imaging costs of the work-up may be minimized. The combination of stress echocardiography followed by cCTA results in a FNR that is slightly higher than stress MPS alone (up to 8% higher at a CAD prevalence of 50%), but it minimizes the FPR of CAD diagnosis (by approximately 20% relative to MPS alone at a CAD prevalence of 10%). Previous studies have noted that stress testing and cCTA provide complementary functional and anatomic information.[7] Our study demonstrates that a combination of stress testing and cCTA may be complementary from the viewpoint of minimizing effective radiation dose and imaging costs.

The clinical application of our results is best illustrated by an example. Assume that we have a symptomatic patient with a 10% pre-test probability of clinically significant CAD (a reasonable assumption for many patients who present to the emergency department with chest pain). The least expensive options for evaluation as demonstrated in figure 5 begin with a stress ECG followed by cCTA at an expected imaging cost of $591 or with stress echocardiography followed by cCTA at an expected cost of $807. If the evaluation is performed only with cCTA the expected cost rises to $1412. If the evaluation is performed only with a nuclear stress MPS test the expected cost rises to $1532. The estimated FNR for these approaches is 3.6% for stress ECG + cCTA, 2.8% for stress echocardiography +

cCTA, 1.2% for stress MPS alone and 0.6% for cCTA alone (figure 2). The FPR (=
the rate of unnecessary cardiac catheterizations) is 3.5% for stress ECG + cCTA,
1.8% for stress echocardiography + cCTA, 21% for stress MPS alone and 15% for
cCTA alone (figure 3). Expected effective radiation dose would be minimized to
1.4mSv by evaluation with stress echocardiography + cCTA while dose is
maximized to 14.1mSv by evaluation with stress MPS alone (figure 4). The lower
radiation dose and costs associated with stress ECG + cCTA or stress
echocardiography + cCTA are related to the decreased FPR and greatly reduced
number of unnecessary cardiac catheterizations. These cost savings and the lower
morbidity related to fewer cardiac catheterizations must be weighed against a 1.6%
increase in the FNR of the work-up with stress echocardiography + cCTA relative to
stress MPS alone.

The most appropriate testing strategy for the work-up of symptomatic CAD
depends upon the pre-test probability of disease which can be estimated on the basis
of clinical presentation.[22] When the pre-test probability of disease is very high the
patient should be triaged directly to cardiac catheterization. For the patient
described above with a low pre-test probability of disease (≤ 20%), the
combinations of stress ECG + cCTA or stress echocardiography + cCTA provide
optimal options as judged by cost and radiation dose, while stress echocardiography
+ cCTA is optimal as judged by FPR. As the pre-test probability of CAD increases,
FNR becomes a greater consideration. For a symptomatic patient with a pre-test
probability of disease approaching 60%, the least expensive option for evaluation is
stress ECG at $1,584, but stress ECG is associated with a FNR of 19% and is
probably not appropriate. Stress ECG + cCTA has an estimated cost of $1,639 and
is associated with a FNR of 22%, while stress echocardiography + cCTA has an

estimated cost of $2,059 and is associated with a FNR of 17%. Evaluation with stress MPS alone has an estimated cost of $2,490, a radiation dose of 16.3mSv and a FNR of 7.2%. Evaluation with cCTA alone has an estimated cost of $2,562, a radiation dose of 8.7mSv and a FNR of 3.6%. Our analysis demonstrates that evaluation by cCTA alone is superior to all other non-invasive testing options in terms of FNR, and thus may be a more appropriate option for the patient with an intermediate pre-test probability of disease (> 20%).

In our clinical experience the MPS study is the most common form of stress test requested for evaluation of suspected CAD. Stress MPS is often advocated as superior to stress echocardiography because it is less operator dependent. Large studies suggest that the overall diagnostic performance of stress echocardiography is equivalent to that of stress MPS in the diagnosis of CAD.[23] Furthermore, as demonstrated in our analysis, use of stress echocardiography reduces the false positive rate, effective radiation dose and imaging costs relative to stress MPS. Our decision analysis suggests that a combination of stress ECG with cCTA or stress echocardiography with cCTA provides an optimal work-up for symptomatic CAD in a low prevalence population, while cCTA alone may be more appropriate in an intermediate prevalence population. For the low prevalence population, if one wishes to minimize radiation dose, the stress test should be performed prior to cCTA. If the referring physician wishes to know about the anatomic presence of CAD – irrespective of whether the disease is hemodynamically significant - it may be reasonable to begin the work-up with cCTA and progress to a stress test based upon a positive cCTA.

A decision analysis model is only as good as the probability values that are

used to define the test nodes. We have chosen generally accepted values based upon large meta analysis studies for the sensitivity and specificity of stress testing.[10,11] With respect to cCTA, there is much controversy in the published literature about the true diagnostic accuracy of the technique. Furthermore, given the rapid pace of technological progress in cCTA, these numbers are constantly improving. Because the reported sensitivity and specificity with this relatively new technology varies among different centers, we chose to base our analysis on recently published multicenter trials of cCTA with cardiac catheterization as the gold standard. Unfortunately, these multicenter trials also differ in the reported values of sensitivity/specificity for cCTA. We chose to use the sensitivity/specificity values reported by Budoff for our primary calculations,[12] but performed a sensitivity analysis with the values reported by Meijboom demonstrating higher sensitivity with lower specificity,[13] as well as the values reported by Miller demonstrating lower sensitivity with higher specificity.[14] Finally, because cCTA is a rapidly improving technology, we performed an additional analysis based upon the higher values of sensitivity/specificity reported in recent meta analyses of single center studies.[3,4]

When interpreting a stress test or cCTA, results are often presented on a spectrum that extends from a truly negative test to a grossly positive test. Clearly, a stress MPS study that demonstrates an ECG abnormality along with a large reversible perfusion defect is more definitive than a study that demonstrates only a small fixed perfusion deficit. Likewise a cCTA that suggests a 90% stenosis of the proximal left anterior descending artery may be more definitive than a study that suggests a 50% lesion in the sub-optimally visualized mid-portion of the right coronary artery. In some patients, diagnostic testing with a stress test or cCTA may

provide an indeterminate result. Nonetheless, since sensitivity/specificity values for
stress testing and cCTA are available only for dichotomous test results, our decision
analysis assumes a dichotomous test result (normal versus abnormal study) for
stress testing, cCTA and cardiac catheterization.

Much of the cost savings of noninvasive testing results from avoiding cardiac
catheterization in patients without true CAD. In addition to the benefits of reduced
radiation exposure and costs, fewer cardiac catheterizations will result in reduced
complications from interventional angiography. In the clinical setting, however, a
mildly abnormal stress test or cCTA that does not indicate multivessel disease may
not proceed to cardiac catheterization. Results of the COURAGE trial suggest that
non-invasive medical therapy may be an equally appropriate option for these patients
when judged in terms of mortality and future coronary events.[24] Nonetheless, among
the subgroup of COURAGE patients evaluated with stress MPS, patients who
proceeded to cardiac catheterization and angioplasty demonstrated a reduced
ischemic burden.[25] Furthermore, a subsequent quality of life analysis among
COURAGE participants demonstrated a small, but significant early improvement in
quality of life among symptomatic patients who proceeded to cardiac catheterization
and angioplasty.[26] Although mildly abnormal test results may not proceed to further
testing in all patients, our analysis required a standard dichotomous decision model to
compute diagnostic accuracy, expected radiation exposure and costs. Based upon the
results reported in the subgroup of COURAGE patients evaluated with stress MPS,
we assume that a positive stress test in a symptomatic patient should trigger the
performance of another test, potentially culminating in cardiac catheterization so that
the patient may be treated with a stent or surgery for symptomatic relief.

With respect to cCTA, we chose to apply a cutoff of 50% diameter stenosis as the distinction between normal and abnormal. In the cardiac catheterization laboratory, a cutoff value of 70% is more commonly used to trigger a decision for angioplasty or surgery. In many cases, the decision for intervention is based on measurement of a pressure gradient that cannot be directly predicted from the degree of anatomic stenosis. For the purpose of the current analysis, however, we are limited by the fact that most studies document the sensitivity and specificity of cCTA to predict a 50% diameter stenosis. Little data is available on the accuracy of cCTA for other levels of arterial stenosis. Of note, the Budoff study that we used to provide our baseline values for sensitivity and specificity reports the diagnostic accuracy of cCTA for both 50% and 70% diameter reduction. The sensitivity of cCTA to detect a stenosis with ≥ 50% diameter reduction is 95% while the sensitivity of cCTA to detect a stenosis with ≥ 70% diameter reduction is 94%. The specificity was constant at 83% for both levels of stenosis.[12] Based upon our sensitivity analysis, it is clear that this difference of 1% in sensitivity would make little difference in our overall analysis.

Although our decision tree considers the imaging costs included in the non-invasive (stress test, cCTA) and invasive (cardiac catheterization) work-up of suspected CAD, the analysis does not include future outcomes associated with correct and incorrect diagnoses of CAD. The various work-up options on the tree will result in different frequencies of cardiac catheterization and therefore in different treatment decisions for a small minority of patients. Although we present the FPR and FNR associated with each testing strategy, we do not attempt to define the cost of false positive and false negative test results. Ignoring these future costs is

a major limitation of this study. However, although the cost of ultimate outcomes is important, this cost is very difficult to define. There is no published data to define the benefit of coronary intervention with angioplasty or surgery in patients with stenosis identified by cardiac catheterization but who have a negative stress test and/or negative cCTA. As suggested by the COURAGE trial, there is probably little mortality benefit from invasive therapy for single vessel CAD, though there may be some benefit in terms of ischemic burden and quality of life.[25,26] We believe that there is insufficient data to allow an accurate cost-effectiveness analysis of stress testing versus cCTA based upon long term outcomes. We have therefore decided to limit our analysis to the radiation dose and costs associated with the non-invasive and invasive diagnostic imaging components of the work-up for CAD.

In conclusion, when considering the work-up of CAD in the symptomatic patient, the FNR of cCTA is below that of stress testing at all levels of CAD prevalence. The combination of cCTA with any stress study results in a decreased FPR relative to a stress study alone. The FPR of a CAD evaluation is minimized when cCTA is employed in combination with stress echocardiography. Radiation dose is minimized by starting the work-up with stress ECG or stress echocardiography prior to cCTA. Finally, when the clinical scenario warrants further diagnostic testing for CAD, a work-up strategy that employs stress echocardiography followed by cCTA is an excellent approach to evaluate the low risk CAD patient, while cCTA alone may be more appropriate in the intermediate risk patient.

Figure Captions:

Figure 1. Decision tree for the work-up of symptomatic CAD. The decision tree begins on the left side with a decision node – the rectangular box – where a CAD work-up strategy is chosen. The option at the very top of the tree corresponds to no advanced testing such that all patients are treated medically. The option at the bottom of the tree corresponds to cardiac catheterization for all patients. The remaining work-up options include evaluation with a stress test and/or cCTA. Each non-invasive test is identified by a round "chance" node which uses the sensitivity and specificity associated with the test to propagate positive and negative detection rates down the tree. At the terminal points of the tree (marked by arrows) the effective radiation dose and imaging cost for each pathway is computed. The focus of this study is to distinguish the strengths and weaknesses of these various work-up options.

Figure 2. False negative work-up rates for the diagnosis of CAD using baseline assumptions of sensitivity and specificity from the study of Budoff.

Figure 3. False positive work-up rates rates for the diagnosis of CAD using baseline assumptions of sensitivity and specificity from the study of Budoff.

Figure 4. Effective radiation dose for the evaluation of suspected CAD using baseline assumptions of sensitivity and specificity from the study of Budoff and effective radiation doses of 4.2mSv for cCTA, 12mSv for stress MPS and 7mSv for cardiac catheterization.

Figure 5. Imaging costs for the evaluation of suspected CAD using baseline assumptions of sensitivity and specificity from the study of Budoff.

Figure 6. Sensitivity analysis for effective radiation dose in the evaluation of CAD.

(A) Presents expected dose using lower estimates for effective radiation for stress MPS (9.4mSv) and cardiac catheterization (5mSv).

(B) Presents expected dose using a higher estimate for effective radiation of cCTA (10.0mSv).

(C) Presents expected dose using lower estimates for effective radiation for stress MPS (9.4mSv) and cardiac catheterization (5mSv) in combination with a higher estimate for effective radiation of cCTA (10.0mSv).

(D) Presents expected dose based upon the data of Miejboom and our baseline assumptions of effective radiation doses of 4.2mSv for cCTA, 12mSv for stress MPS and 7mSv for cardiac catheterization.

(E) Presents expected dose based upon the data of Miller and our baseline assumptions of effective radiation doses of 4.2mSv for cCTA, 12mSv for stress MPS and 7mSv for cardiac catheterization.

Figure 7. Sensitivity analysis for expected imaging costs in the evaluation of CAD.

(A) Presents expected imaging costs based upon the sensitivity and specificity data of Miejboom.

(B) Presents expected imaging costs based upon the sensitivity and specificity data of Miller.

(C) Presents expected imaging costs based upon higher values of sensitivity and specificity in the meta analysis of Vanhoenacker.

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