

**TOM GERBER:** Hello, I'm Tom Guber one of the cardiologists here at Mayo Clinic in Rochester. I'm also a Professor of Medicine and Radiology at the Mayo Clinic College of Medicine. It's my privilege to discuss today the randomized, controlled trials that examine the use of coronary CT angiography in the evaluation of chest pain patients in the emergency department. As usual, I have no conflicts of interest to declare. I also won't discuss any uses of coronary CT angiography that are not FDA approved.

So as background, we all know that chest pain suggestive of an acute coronary syndrome is one of the most common and most vexing presentations in the emergency department. The current strategies that we have to rule out acute coronary syndromes are fairly inefficient. They lead to overcrowding in the emergency departments and often unnecessary admissions. Despite our low threshold to admit patients to the emergency department, up to 2% of patients with an acute coronary syndrome are missed.

So what would we expect of a strategy to rule out acute coronary syndrome in the emergency department? Firstly, we'd want it to be safe. That means good patient outcomes at 28 days to six months. We'd also want it to reduce admissions, both as a matter of patient satisfaction but also as a matter of cost. And we would want it to reduce overall cost.

Now as a little background, let's take you through the studies that established the diagnostic value of coronary CT angiography in the detection of coronary artery disease. It is important to remember that the good randomized controlled trials that we have for coronary CT angiography in outpatients with chest pain, used equipment that's really no longer state of the art. Nonetheless, across a variety of prevalence of disease, and across a variety of centers with differing levels of expertise, the sensitivity of coronary CT angiography and the negative predictive value of coronary angiography are very high.

A completely normal coronary CT angiogram rules out significant coronary arterial disease with very high likelihood. Conversely, sometimes because of problems with image quality, CT angiography does not optimally rule out significant stenosis and the positive predictive failure can be suboptimal. This is important because it could lead to further investigations and admissions that, in retrospect, turned out not to be necessary.

So with that background in mind, let's think about the multicenter randomized trials of coronary CT angiography in acute chest pain patients. In theory coronary CT angiography may allow earlier and safe triage, reducing hospital admissions and length of stay compared to standard of care. However, some preliminary retrospective analyses of Medicare data suggest that procedures and costs were double after a coronary CT angiography compared to standard functional testing.

So the randomized trials that we have are as follows-- the CT STAT trial enrolled 700 low-risk patients and compared CT angiography with myocardial perfusion imaging, the ACRIN PA study compared CT angiography with standard of care in 1,300 low-risk patients, and the probably best publicized and most detailed among these studies is the ROMICAT II study that compared CT angiography with standard of care in 1,000 intermediate-risk patients. This was an NIH sponsored study.

So here's a concise synopsis of these three trials. All three trials showed shorter length of stay and time to diagnosis in patients who underwent CT angiography compared to patients who had standard of care. Two of three trials showed less cost in the emergency department for patients in the CT angiography arm. And in terms of safety and procedures, at least taken individually, none of the three trials showed a higher rate of invasive angiography for patients who underwent CT. And also no difference in adverse outcomes at 28 days to six months.

Let's maybe, as one example for those studies, go through the ROMICAT II study in a little more detail. This study enrolled 1,000 patients and again compared coronary CT angiography to a standard of care. The majority of these patients had two or three coronary risk factors. And you will see that the completeness of follow-up was fairly high at 98, and 99% respectively.

Their primary outcomes measure was length of stay. And they found that 50% of the CT angiography patients were discharged at 8.6 hours, at which time less than 10% of the standard of care patients had been discharged. Overall they found a mean difference of length of stay of 7.6 hours between the CTA patients and the standard of care patients.

Among their secondary effectiveness end points, they showed a higher rate of direct discharge from the emergency department in patients who underwent CT angiography. They showed a shorter time to diagnosis in patients who underwent CT angiography, but there was no difference in repeat emergency department visits over 28 days between the two groups. In terms of secondary safety end points, there was no difference in missed acute coronary syndrome in periprocedural complications or adverse cardiac events at 28 days.

Interestingly enough, the two acute coronary syndromes that occurred in the CT angiography patients occurred in patients who had high grade disease on coronary CT angiography, but did not undergo invasive angiography because their stress tests were normal. In terms of costs of care, there was less cost for the CT angiography arm in the emergency department, but the total cost at 28 days was not different. Now this teaches us that it's important to not just look at the length of stay and time to diagnosis, but also at cost.

As one gold standard for chest pain patient trials, the Mayo CPU Trial still stands. This was published in the *New England Journal of Medicine* in 1998, and that trial looked at intermediate risk patients with unstable angina. And they were randomized either to admission or the chest pain unit. And in the chest pain unit, they underwent six hours of observation with serial biomarkers. And they underwent treadmill exercise testing or stress imaging. If the initial evaluation was unremarkable.

Now it's really important to recognize the cost structure for the different tests and procedures that could be done in patients with chest pain. In the Mayo CPU Trial the cost of a treadmill exercise test had a relative value of one. And you can see how the other tests and procedures stack up, ranging from other diagnostic modalities to revascularization procedures. The CPU investigators looked at overall cost at six months. And low and behold, the patients who were candidates for an exercise treadmill study fared the cheapest by far. Once a patient was not a candidate for a treadmill exercise test, they were much more likely to have an abnormal stress test, or requiring revascularization, and their cost was much higher.

Now what do we know about overall cost in these trials of CT angiography for chest pain patients? Well, not very much. Three of the trials that we have didn't report overall cost at all. And the ROMICAT II study, as I had mentioned earlier, showed no difference in overall cost at 28 days.

A recent meta-analysis of the four randomized controlled trials of CT angiography in the emergency department however, suggested that patients who underwent CT angiography had a higher rate of invasive angiography. Most of that was during their initial stay-- this is in yellow. Some of it though happened after discharge-- in orange. Most importantly, patients who underwent CT angiography in this pooled analysis had a higher rate of revascularization percutaneously or surgically. Even though the overall cost was not directly examined in this meta-analysis, you can imagine what this higher rate of revascularization procedures will do to overall cost of a CTA approach.

And finally, going back or including the older studies, including the ERASE trial that examined myocardial perfusion imaging as an initial strategy to deal with chest pain patients in the emergency department, not only is treadmill exercise testing the cheapest of the initial modalities it also has the best track record of preventing admissions. Even though myocardial perfusion imaging and CT angiography decrease the rate of admissions, their effect this much smaller.

Now the following are limitations of the studies that we have on the use of CT angiography in patients with chest pain. Firstly, the enrollment in these trials was limited to weekday business hours. Also none of these trials were really powered to show differences in clinical outcomes.

I would like to mention two points though that I think may have contributed to underselling the value of coronary CT angiography in the emergency department. Firstly, a possible difference in repeat emergency department presentations for patients in the CT angiography your arm has never been examined in detail. We all know that patients who come to the emergency department time and again with chest pain often undergo serial stress testing, because of concerns that a sub-clinical plaque doesn't take much volume change to go from sub-clinical to critical. If you had an anatomic test, a completely normal coronary CT angiogram, you could imagine how that could contribute to the reassurance of providers and the patient themselves about the absence of sub-clinical disease. Secondly, an update to the noninvasive imaging and women statement by the AHA from 2005 is about to be published, which reminds me that a potential difference in the efficacy of functional versus anatomic imaging in women with chest pain has never been explored in full.

But as conclusions at this point, I would offer that randomization trials in chest pain patients are very difficult to design, the preferred endpoints of such trials should be patient outcomes, reduced admissions, and reduced overall costs, and only the Mayo CPU trial showed a reduction admission in total costs. As a second set of conclusions, in the more contemporary trials of CT angiography, CT angiography significantly reduced the length of stay and time to diagnosis. It also increased direct emergency department discharge rates without an impaired increase in missed acute coronary syndromes. But it leads to more invasive angiography and revascularization.

And in keeping with that evidence base, treadmill exercise testing and stress imaging has a class I level of evidence C recommendations in the pertinent AHA and ACC guidelines. Whereas the recommendation for coronary CT angiography geography is a class IIA level of evidence B recommendation. And with that in mind, I thank you for your attention. Thank you again. Be in touch if you have questions.