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Critical analysis of the latest clinical research in cardiovascular medicine

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ABSTRACT & COMMENTARY

# Benefits of Early Coronary Angiography in Acute Heart Failure

*By Jeffrey Zimmet, MD, PhD*

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SYNOPSIS: For patients hospitalized with acute heart failure, invasive coronary angiography within 14 days was associated with higher rates of coronary revascularization and lower rates of all-cause death, cardiovascular mortality, and heart failure hospitalization.

SOURCE: Kosyakovsky LB, Austin PC, Ross HJ, et al. Early invasive coronary angiography and acute ischaemic heart failure outcomes. *Eur Heart J* 2021;42:3756-3766.

In adult patients with congestive heart failure, the presence of coronary disease carries a worse prognosis and demands different treatments, both in terms of medical therapy and in the possibility of mechanical revascularization by bypass surgery or percutaneous interventions (PCI). However, current guidelines offer only vague direction regarding the performance and timing of coronary angiography for these patients. The relative lack of good data explains this gap.

Kosyakovsky et al sought to address this knowledge gap through an analysis of patients presenting to Canadian hospitals with heart failure and at least one feature suggesting the possible presence of underlying coronary disease: prior myocardial infarction (MI), troponin elevation, or angina. They identified patients with either early coronary angiography (defined as angiography within 14 days of presentation) or not. The primary outcome was all-cause and cardiovascular mortality. Patients were excluded if a more-detailed chart review did not indicate heart failure, or if brain natriuretic peptide (BNP) or NT-proBNP values did not support this diagnosis. Patients were similarly excluded if they showed clear contraindications to cardiac catheterization, such as severe renal failure or contrast allergy, or if they had been hospitalized recently for a pure coronary event, such as acute MI or coronary revascularization.

Ultimately, 2,994 patients were included in the study, of whom 1,567 underwent early coronary angiography and 1,427 did not. As one would expect, these groups were fundamentally different in multiple respects. Patients offered early cardiac

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catheterization were younger and reported higher rates of personal history of MI, angina, troponin elevation, new ST-segment changes, and reduced ejection fraction. Patients were at lower risk of early angiography if they presented with comorbidities, including dementia, COPD, higher creatinine levels, and atrial fibrillation, as well as history of coronary bypass surgery and white race. The authors used inverse probability of treatment weighting (IPTW) to adjust for baseline differences. The resulting groups recorded no significant differences in the distribution of any baseline clinical characteristics.

After weighting, both all-cause mortality (HR, 0.74; 95% CI, 0.61-0.90; $P$ = 0.002) and cardiovascular death (HR, 0.72; 95% CI, 0.56-0.93; $P$ = 0.012) were lower among patients who had undergone early coronary angiography, as were rates of heart failure hospitalization (adjusted HR, 0.84; 95% CI, 0.71-0.99; $P$ = 0.042). Among patients undergoing early angiography, 58.5% were diagnosed with obstructive coronary artery disease, and just under 18% underwent revascularization within 90 days of angiography. Those undergoing early angiography recorded higher rates of coronary revascularization by PCI and bypass surgery, both at 90 days (HR, 4.69) and at two years (HR, 2.82; 95% CI, 2.06-3.86; $P$ < 0.001).

The authors concluded early angiography in acute heart failure patients was associated with improvements in cardiovascular and all-cause mortality as well as in subsequent heart failure hospitalization. Revascularization was significantly higher among these patients. They suggested early coronary angiography should be strongly considered at the initial presentation with heart failure in the presence of features suggestive of higher ischemic risk.

## ■ COMMENTARY

This study was not a randomized trial; therefore, it is subject to unmeasured confounding despite the relatively rigorous use of IPTW analysis. Still, the robust findings here of improvements in mortality and heart failure hospitalization, correlated with more coronary revascularization out to two years, certainly provides food for thought and supports the authors' general conclusions.

It might be best to initiate most or all components of guideline-directed medical therapy during initial hospitalization for heart failure. This could protect against subsequent outpatient providers who might be slow to add or further titrate heart failure medications downstream. The decision to offer early invasive angiography may be thought of in a similar context, where putting off this testing initially leads to inertia that is difficult to overcome later.

Obviously, each case of acute heart failure needs to be considered individually, where the risks and potential benefits of coronary angiography are weighed carefully for each patient. In situations where patients are candidates for percutaneous or surgical revascularization, or where certainty regarding the presence or absence of ischemic disease will alter medical therapy, timely cardiac catheterization is worth thorough consideration at the time of acute heart failure presentation. ■

ABSTRACT & COMMENTARY

# The Limits of Shortened Antiplatelet Therapy in Acute Coronary Syndrome

***By Jeffrey Zimmet, MD, PhD***

*Associate Professor of Medicine, University of California, San Francisco; Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center*

SYNOPSIS: One month of dual antiplatelet therapy (DAPT) followed by clopidogrel monotherapy did not meet criteria for noninferiority vs.12 months of DAPT for a composite endpoint of ischemic and bleeding events.

SOURCE: Watanabe H. STOPDAPT-2 ACS: One-month dual antiplatelet therapy followed by clopidogrel monotherapy in acute coronary syndrome. Presented at European Society of Cardiology Annual Congress, Aug. 30, 2021. https://bit.ly/3FnfJCk

The authors of the original STOPDAPT-2 trial, published in 2019, investigated the use of one month of dual antiplatelet therapy (DAPT) followed by clopidogrel monotherapy in more than 3,000 patients with a mix of acute coronary syndrome (ACS) and stable presentations. That trial demonstrated a significantly lower rate of the composite of bleeding and cardiovascular events with shortened DAPT vs. 12 months of dual therapy.[1] Other trials, including TWILIGHT and the recently presented MASTER DAPT, have similarly suggested shortened DAPT could reduce bleeding with no apparent cost in terms of ischemic events.[2,3]

STOPDAPT-2 ACS was designed to test the short DAPT hypothesis in ACS patients specifically. Researchers recruited 3,008 patients from multiple centers in Japan. An additional 1,161 patients came from the ACS subgroup of the STOPDAPT-2 trial, for a total of 4,169 patients. Among the ACS patients enrolled, ST-elevation myocardial infarction (MI) patients represented 56% of the total. Subjects were randomized 1:1 to receive either one month of DAPT followed by clopidogrel alone or standard duration 12 months of DAPT. The aspirin dose was 100 mg per day. All patients had undergone PCI with a cobalt chromium alloy everolimus-eluting stent. Importantly, enrolled subjects were not high bleeding risk. Patients requiring oral anticoagulants were specifically excluded, as were those with any history of intracranial hemorrhage or serious in-hospital bleeding.

In the composite primary endpoint of cardiovascular death, MI, stroke, stent thrombosis, and thrombosis in MI major and minor bleeding, the short DAPT group failed to meet the defined criteria for non-inferiority. Overall event rates were relatively low: 3.2% in the one-month DAPT group and 2.83% in the 12-month group, which was not statistically different (HR, 1.15; 95% CI, 0.80-1.62). Although short DAPT resulted in lower rates of bleeding (0.54% vs. 1.17%; HR, 0.46; 95% CI, 0.23-0.94), this was achieved at a cost of a significant increase in MI (1.59% vs. 0.85%; HR, 1.91; 95% CI, 1.06-3.44). The composite ischemic endpoint of cardiovascular death, MI, stroke, and stent thrombosis trended toward benefit in the standard 12-month DAPT arm (2.8% vs. 1.9%; HR, 1.50; 95% CI, 0.99-2.26).

When he presented the findings at the European Society of Cardiology Annual Congress in August, Hirotoshi Watanabe, MD, said the results were inconclusive for the benefit of one-month DAPT vs. 12 months DAPT in ACS patients.

## ■ COMMENTARY

This is an interesting trial that contributes significantly to the body of knowledge concerning the optimal type and duration of antiplatelet therapy after PCI. Comparing this trial with its direct predecessor, STOPDAPT-2, the primary lesson appears to be ACS subjects are substantially different from stable angina patients in terms of their ischemic risk over time from the event. One prior trial from 2018, SMART-DATE, similarly demonstrated a higher MI rate with six months vs. 12 months of DAPT in ACS patients, using clopidogrel as the predominant P2Y12 agent.[4]

STOPDAPT-2 ACS was not a high bleeding risk trial. In fact, large subsets of patients at elevated bleeding risk were specifically excluded. Short DAPT led to many fewer bleeding events, but this did not counterbalance the higher risk of MI in the composite endpoint. The balance of bleeding and ischemic risk might trend differently in a high bleeding risk population. Another point worth noting is the choice of clopidogrel as the P2Y12 monotherapy agent. One might infer from this trial that 12 months of DAPT should remain the standard of care for ACS patients. This is true when clopidogrel is involved. But STOPDAPT-2 was performed in Japan,

where there is a higher prevalence of clopidogrel resistance genotype, and clopidogrel resistance was not assessed. Other trials, such as TWILIGHT, have demonstrated fewer bleeding episodes and noninferior ischemic outcomes using shortened DAPT with ticagrelor monotherapy. More potent and predictable P2Y12 inhibitors might show different outcomes vs. clopidogrel. However, this has not been tested in an ACS population like this one. ■


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ABSTRACT & COMMENTARY

# Using Cardiac MRI to Detect Suspected Tumors

***By Michael H. Crawford, MD, Editor***


SYNOPSIS: Among patients with suspected cardiac tumors, cardiac MRI was highly accurate at distinguishing tumor from thrombus and benign from malignant tumors, using subsequent clinical data over five years of follow-up as the diagnostic standard.


SOURCE: Shenoy C, Grizzard JD, Shah DJ, et al. Cardiovascular magnetic resonance imaging in suspected cardiac tumor: A multicenter outcomes study. *Eur Heart J* 2021; Sep 21:ehab635. doi: 10.1093/eurheartj/ehab635. [Online ahead of print].

Although believed to be the gold standard for diagnosing the etiology of cardiac masses, there is a paucity of data that correlates cardiac MRI findings with outcomes. Investigators from four large U.S. academic medical centers prospectively enrolled 935 patients referred to cardiac MRI for suspected cardiac tumors between 2003 and 2014. The authors collected clinical information and patients for the primary endpoint of all-cause mortality. All four sites used the Society for Cardiovascular Magnetic Resonance protocol, which included late gadolinium enhancement (LGE) imaging.

Cardiac MRI interpretations were conducted blinded to the clinical data and were categorized into five categories: no mass, pseudomass, thrombus, benign tumor, and malignant tumor. Pseudomasses were prominent normal structures, such as the crista terminalis in the right atrium. In 32 patients, the masses did not fit into the five categories (e.g., vegetations), and they were excluded. The median age of the remaining 903 patients was 60 years, and 36% were men. The most common preceding imaging study was echocardiography (78%).

The cardiac MRI diagnosis was no mass in 25%, pseudomass in 16%, thrombus in 16%, benign tumor in 17%, and malignant tumor in 23%. In comparison to the final clinical diagnosis, the cardiac MRI diagnosis was correct 98% of the time. One of the 236 patients categorized as no mass exhibited a small mobile mass on the mitral chordal apparatus that was diagnosed as a papillary fibroelastoma. All 149 patients categorized as pseudomass proved to be correct. Four of the 146 patients categorized as thrombus turned out to have benign tumors, three of which were myxomas. In the five patients incorrectly diagnosed as benign tumors, two that were called myxomas included thrombi and two were malignant tumors. The four of 213 called malignant tumors turned out to be benign.

During the almost five-year median follow-up, 376 patients died. In comparison to the no mass group, the pseudomass group recorded a similar mortality rate (HR, 1.03; 95% CI, 0.70-1.51), as did those with a benign tumor diagnosis (HR, 0.77; 95% CI, 0.50-1.17). Those with thrombus (HR, 1.46; 95% CI, 1.00-2.11; $P = 0.48$) and those with a malignant tumor (HR, 3.31; 95% CI, 2.40-4.57; $P < 0.001$) recorded higher mortality rates. Also, the cardiac MRI diagnosis provided incremental prognostic value vs. other clinical parameters, such as left ventricular ejection fraction and extracardiac malignancy. The authors concluded cardiac MRI carries a high rate of diagnostic accuracy for cardiac masses and is a strong independent predictor of mortality.

## ■ COMMENTARY

The persistent problem with new cardiac imaging techniques that tout better diagnostic accuracy and improved patient outcomes is deciding what gold

standard to use for comparison. Often, there is not such a standard, but because the pictures look better, some might believe it must be a superior technique. This is certainly the case for cardiac MRI for the diagnosis of suspected cardiac tumors.

Although believed to be the best current imaging technique for this purpose, there is a lack of solid clinical research to back this up. Thus, this multicenter study, which included an analysis of subsequent clinical data (biopsies and a five-year follow-up to validate the imaging diagnoses of masses suspected to be tumors), is of interest. Not surprisingly, diagnostic accuracy was high, but examining the errors is instructive. One of the 236 patient masses categorized as no mass was incorrect and was caused by a mobile mass attached to the mitral chordae, which was shown to be a papillary fibroelastoma at surgery. This mobile mass appeared on echocardiography but not on the cardiac MRI, probably because of motion averaging. Thus, echo might be a better tool to identify mobile masses.

None of the 149 patients categorized as pseudomasses were incorrect. The most common pseudomasses were hypertrophied interatrial septum, prominent epicardial fat pad, prominent Eustachian valve, prominent crista terminalis, and hiatal hernia. Perhaps a more robust echo lab would have prevented a cardiac MRI for these patients. Four patients diagnosed as thrombus were incorrect; four were benign tumors, of which three were myxomas. Five of 159 patients diagnosed as benign tumor were incorrect; two were thrombi diagnosed as myxomas, and two were malignant tumors. Therefore, the distinction between myxomas and thrombus may be a weak area. This is important because the treatment of thrombi and myxomas is different. However, the investigators excluded patients with obvious thrombi to prevent overloading the study population with the more common thrombi, which makes the distinction between tumor and thrombus more challenging. For example, the post-myocardial infarction patient with an apical aneurysm and a mass would have been excluded as obvious thrombus. Four of the 213 patients diagnosed as malignant tumor all had benign tumors, mainly myxomas. Although most myomas are benign, they can be friable and result in systemic emboli, the work up for which is often how they are discovered.

All that said, the authors did not systematically compare echo vs. cardiac MRI. Only patients referred for cardiac MRI were included, so there is a selection bias for suspected tumors. There are no data on primary vs. metastatic malignant tumors. Also, researchers only examined all-cause mortality, not diagnosis-specific mortality. In addition, T1 and T2 mapping were not used, as this technique was not available for the entire study period and may have helped better examine the tissue characteristics of the masses, but probably would not have altered the basic distinction between tumor and thrombus much. Overall, the study demonstrated a 99% accuracy for distinguishing tumor from thrombus and a 98% accuracy for distinguishing benign from malignant tumors. Thus, for discriminating between cardiac masses, cardiac MRI clearly is robust. ■

ABSTRACT & COMMENTARY

# Mammograms as a Cardiometabolic Disease Prevention Tool

***By Michael H. Crawford, MD, Editor***

SYNOPSIS: In a study of women undergoing routine mammographic screening for breast cancer, mammographic features, such as microcalcifications and breast density, were associated with the risk of developing cardiovascular disease.

SOURCE: Grassmann F, Yang H, Eriksson M, et al. Mammographic features are associated with cardiometabolic disease risk and mortality. *Eur Heart J* 2021;42:3361-3370.

The identification of prevalent cardiovascular disease is challenging, especially in women, for whom the incidence is lower than men until later in life. Although controversial, mammographic screening programs have been shown to reduce mortality from breast cancer. Mammography not only detects early cancer, but other features of the images have been shown to be associated with an increased risk of cardiovascular disease (CVD).

Grassmann et al aimed to further develop the relationship between mammography features and CVD in a large prospective study of mammographic screening: the Karolinska Mammography Project for Risk Prediction of Breast Cancer, or KARMA. *(Learn more at: www.karmastudy.org.)* Between 2011 and 2013, the KARMA creators enrolled more than 70,000 women in Sweden, then followed this group through 2018. Those with breast cancer (BC)

diagnosed before or during the trial period were excluded, as were any subjects who underwent breast surgery before enrollment or for whom there were missing data. This resulted in a total study population of 57,867 women who underwent computer-aided detection of microcalcifications (MC) and breast density (BD) on routine mammographic images.

Those with BD greater than the mean value were considered to have dense breasts. Other data collected included family history of BC and a genetic risk score for BC. Various comorbidities were recorded, such as risk factors for CVD (identified by ICD-10 codes), and death caused by CVD was ascertained. They found increases in MC or BD were associated with the development of BC, as expected. Increases in MC were associated with the development of CVD, especially in women with a pre-existing CVD. In women without a prior CVD, MC was associated with hypertension and heart failure. By contrast, higher BD in women with a preexisting CVD was not associated with CVD. In women without a prior CVD, it was associated with a lower rate of CVD independent of MC, reproductive history, and lifestyle factors.

By the end of 2018, 233 women had died. Increased MC was associated with a CVD death (HR, 1.46; 95% CI, 1.10-1.94; $P = 0.01$) in the total study population, but not in women without prior CVD. Increased BD in the total study population was associated with a lower CVD mortality (HR, 0.64; 95%CI, 0.46-0.90; $P = 0.01$). Also, a family history of BC and a genetic risk score for BC were associated with a lower risk of CVD. The authors concluded MC and BD on mammography are associated with CVD and CVD mortality. These features on routine screening mammography may be of value for fine-tuning the risk of CVD in women.

■ COMMENTARY

The work by Grassmann et al was a well-conducted observational study that amplifies the associations between mammographic features and CVD that has been seen in smaller studies and strengthens the concept that mammogram results should be considered when risk-stratifying women.

Grassmann et al defined CVD rather broadly and included diseases that might be considered risk factors themselves, such as diabetes and renal failure. In addition, there was considerable granularity in that conditions such as cardiac conduction disorders and cardiac dysrhythmias were included. Another strength was the fact the Swedish health system provided the investigators with detailed information about all participants.

Standard formulae for estimating the risk of developing CVD to fine-tune prevention measures fail to consider important known risk factors, such as family history of early CVD, the detection of vascular calcium on CT scans, and prior radiation therapy. It seems we should add the presence of MC on routine mammograms to the list of other considerations when deciding whether a young woman should take a statin.

The association of low-density breasts with a higher risk of CVD is more problematic since low-density breasts contain more fat; obesity could be a confounder here. Another issue is the current algorithm for quantifying MC cannot distinguish between breast tissue and vascular calcification. The former is associated with the development of BC, but there was no difference in the study results in those who developed BC.

Another strength of the Grassmann et al study, other than the use of a large cohort of subjects, is the fact that the investigators identified and studied the sisters of the KARMA participants. Doing so led to the discovery of similar results. Whether this was because of like environments or family genetics is unclear. Nevertheless, all this indicates this was a robust study. ■

ABSTRACT & COMMENTARY

# A Simple Way to Measure Frailty Before Aortic Valve Replacement

***By Michael H. Crawford, MD, Editor***

SYNOPSIS: An analysis of transcatheter vs. surgical aortic valve implantation showed modified BMI, a measure of frailty, predicted one-year all-cause mortality and postoperative complications.

SOURCE: Driggin E, Gupta A, Madhavan MV, et al. Relation between modified body mass index and adverse outcomes after aortic valve implantation. *Am J Cardiol* 2021;153:94-100.

Although clinical frailty is known to be associated with worse survival rates after transcatheter or surgical aortic valve implantation (TAVI and SAVI), it is not measured routinely, in large part because of the lack of a standardized metric that is easy to use. So-called modified BMI (mBMI), which is BMI × serum albumin × 10, has been advanced as a simple-yet-accurate estimate of frailty.

To determine its prognostic value in patients undergoing AVI, researchers assessed the tool in patients recruited for the PARTNER trials I, II, and S3, which were comparisons of TAVI to SAVI.[1-3] These trials included patients with severe aortic stenosis (AS) randomized to the two implantation methods. There were 6,593 patients in the pooled analysis, after the exclusion of valve-in-valve implantations. All patients were deemed acceptable for surgery, albeit at high risk for some. The mBMI calculation was the product of BMI in kg/m$^2$ and serum albumin in g/L. The lower the resulting number, the more frail the patient. Also, the Clinical Frailty Index (CFI) score was calculated based on gait speed, grip strength, serum albumin, and disability in activities of daily living (ADL). The primary outcome was all-cause mortality at one year following AVI. The authors also assessed a variety of secondary clinical endpoints.

Patients were divided into quartiles of mBMI to compare clinical characteristics. Eighty-four percent of patients underwent TAVI, the mean age was 83 years, and 57% were men. As mBMI decreased, the patients were older, there were more women, there were more symptoms, and the surgical risk scores were higher. Laboratory data with decreasing mBMI exhibited higher brain natriuretic peptide and lower hemoglobin. Echocardiography with a lower score showed smaller valve areas and lower left ventricular ejection fractions. In addition, lower mBMI patients stayed in the hospital longer or spent more time on the ICU. Overall mortality at one year was 16.5% and was highest in the lowest mBMI quartile at 26% (out of four total quartiles). As the mBMI values increased across the remaining three quartiles, the mortality rates progressed from 17% to 13% to 11% at the highest mBMI. Compared to the claims-based CFI, the C-statistic for mBMI was 0.68. The authors concluded since mBMI performs similarly to the more complicated CFI, mBMI is a simple, easily assessed measure of frailty in patients under consideration for TAVI.

## ■ COMMENTARY

The mBMI was independently associated with one-year all-cause mortality and a higher incidence of adverse clinical outcomes following the intervention. The importance of frailty as a contraindication to

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AVI is widely recognized because outcomes can be anticipated to be worse than in non-frail individuals. However, how best to measure it is unclear. Current techniques run the gamut from the complex CFI to the simple 0, 1, 2 scale, where 0 is the patient cannot perform any ADL; 1 is can perform some ADL; and 2 is can perform all ADL. The CFI includes gait speed and grip strength, which require special equipment. The Essential Frailty Toolset requires a Mini-Mental State Examination, which involves taking time to answer 30 questions.

None of these are entirely satisfactory for routine clinical use. Thus, the mBMI is attractive because it is simple yet quantitative. Also, it predicts higher one-year mortality and more postoperative complications, such as longer ICU stays and the need for mechanical circulatory support. In addition, it predicts higher rates of major adverse events, such as stroke and need for reintervention. Surprisingly, mBMI did not predict rehospitalization, perhaps because of longer initial hospital lengths of stay and the high mortality in the lowest quartiles. Considering the PARTNER participants all were at least intermediate surgical risk patients, they were older, with more comorbidities. A frailty measurement would be more discriminating in such a group. Consequently, the mBMI may not be as useful in younger, healthier patients undergoing AVI, but then no index of frailty would be useful for these patients. ■

## REFERENCES

1. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187-2198.
2. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609-1620.
3. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J* 2016;37:2252-2262.

## CME/CE QUESTIONS

**1. A retrospective, observational study of patients hospitalized for acute heart failure showed early coronary angiography resulted in:**

a. lower mortality rates.
b. higher stroke rates.
c. more bleeding.
d. shorter hospital lengths of stay.

**2. A simple measure of frailty (BMI × serum albumin × 10) in patients undergoing aortic valve implantation was independently associated with:**

a. rehospitalization.
b. all-cause mortality.
c. the extent of myocardial ischemia.
d. pulmonary emboli.

**3. A higher risk of cardiovascular disease in women is observed with which mammography finding?**

a. Evident breast cancer
b. Increased breast density
c. Increased microcalcifications
d. Increased breast volume

**4. Mono antiplatelet therapy one month after coronary stenting is reasonable in which type of patient?**

a. STEMI
b. Non-STEMI
c. Unstable angina
d. Chronic stable angina

**5. The accuracy of cardiac MRI for distinguishing between cardiac tumors and thrombi is:**

a. 85%.
b. 90%.
c. 95%.
d. 99%.