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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

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ABSTRACT & COMMENTARY

Complete vs. Infarct-related, Artery-only Revascularization in STEMI

By Jeffrey Zimmet, MD, PhD

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

Dr. Zimmet reports no financial relationships relevant to this field of study.

SYNOPSIS: This trial randomized patients with ST elevation myocardial infarction and at least one noninfarct artery with angiographically significant stenosis to either fractional flow-reserve-guided complete revascularization by percutaneous coronary intervention or to no revascularization of noninfarct arteries. The primary composite endpoint was significantly lower in the complete revascularization group, driven by a reduction in later revascularization.

SOURCE: Smits PC, Abdel-Wahab M, Neumann FJ, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med* 2017;376:1234-1244.

Up to half of patients presenting with ST elevation myocardial infarction (STEMI) have angiographically significant stenoses in other vessels at the time of intervention. Guidelines from the American College of Cardiology, the American Heart Association, and the European Society of Cardiology recommend treatment of the infarct-related artery only. Several clinical trials over the past several years have challenged this concept. The PRAMI trial from 2013 randomized 465 patients with STEMI to infarct artery-only percutaneous coronary intervention (PCI) vs. "preventive" PCI of other angiographically significant lesions, and reported a significant benefit in terms of recurrent angina, nonfatal myocardial infarction (MI), and cardiac death. The DANAMI 3 trial, published in 2015, randomized 627 STEMI patients to either no further invasive treatment (beyond PCI of the infarct artery) or to complete fractional flow-reserve (FFR)-guided revascularization prior to discharge. This trial demonstrated a benefit in terms of major adverse cardiac events, but this was driven primarily by a reduction in the need for subsequent ischemia-driven revascularization. The CvLPRIT trial, pub-

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lished in 2015, enrolled 295 patients and showed a benefit in terms of the composite endpoint, but was too small to show a significant decrease in any individual components of this endpoint.

Smits et al conducted the largest trial to date looking at this question. Between mid-2011 and late 2015, 885 patients presenting with STEMI and multivessel disease were enrolled at 24 centers in Europe and Asia. Patients were randomized 1:2 to either FFR-guided complete revascularization or to treatment of the infarct-related artery only. In contrast to earlier studies, all angiographic stenoses of 50% or more were interrogated by FFR in all patients in both groups. However, intervention was performed only in the complete revascularization group, and the patient and outpatient providers were kept blinded to the FFR results (but not to the angiography results). The primary endpoint was a 12-month composite of all-cause death, any revascularization, and cerebrovascular events. Elective, clinically indicated PCI procedures performed within 45 days of the STEMI presentation were excluded (primarily lesions believed clearly to be angiographically severe at the time of the index procedure).

FFR was successfully performed in all but 18 of 885 patients. Among the complete revascularization patients, 158 of 292 (54.1%) exhibited at least one vessel with FFR < 0.80 and underwent PCI. More than 80% of these PCIs were performed during the index procedure, while the remainder were completed within three days. Among the infarct artery-only patients, 275 of 575 (47.8%) exhibited FFR-positive lesions, and 59 patients underwent staged elective revascularization within 45 days based on clinical and angiographic data; only 44 of these had positive FFRs.

At one year, 23 patients in the complete revascularization group (7.8%) and 121 patients in the infarct artery-only group (20.5%) experienced major adverse cardiac events (MACE, hazard ratio [HR], 0.35; $P < 0.001$). This difference was driven almost entirely by a higher incidence of revascularization in the infarct-only group. Mortality was not significantly different between groups. Although there was a trend toward a reduction in MI in the complete revascularization group, this did not meet statistical significance (HR, 0.50; 95% confidence interval, 0.22-1.13; $P = 0.10$). Among subsequent revascularization procedures, approximately one-third were for unstable angina.

The authors concluded that for patients presenting with STEMI and multi-vessel disease, FFR-guided complete revascularization in the acute setting resulted in a decrease in MACE, driven primarily by a reduction in subsequent revascularization procedures.

■ COMMENTARY

With this, the fourth and largest trial to date of the complete vs. infarct artery-only revascularization saga, do we finally have an answer? This trial demonstrates that the strategy of FFR-guided complete revascularization is feasible, and for the most part can be accomplished safely, even during the index procedure. Remarkably, the average procedure time for the complete revascularization group was only six minutes longer than in the comparator group, and the mean volume of contrast was only 10% higher. For the relatively low-risk patients enrolled in this trial (hemodynamically stable, excluding Killip 3 and 4 patients, and following successful uncomplicated intervention of the infarct-related artery) subsequent FFR-guided interventions can be undertaken with an acceptable risk profile. That is not to say that it should be done, or that it is risk free. Notably, two very serious adverse events occurred during FFR in this trial. In one, the FFR wire led to dissection of the nonculprit right coronary artery, leading to MI and in-hospital death. In the other, the FFR wire led to occlusion of the nonculprit left anterior descending artery, requiring urgent intervention. Clearly, some judgment is required to decide when evaluation of a nonculprit vessel is indicated during the initial procedure. Middle-of-the-night STEMI interventions, potentially conducted by tired operators, should not be prolonged routinely by FFR of nonculprit vessels.

The finding that the strategy of FFR-guided complete revascularization led to lower rates of MACE at one year is compelling and adds to the body of evidence supporting revascularization of non-culprit vessels identified at the time of STEMI. However, the benefit in this case mainly was driven by reduced subsequent revascularizations, and most of these were not in the setting of acute coronary syndromes. Ultimately, even larger trials with sufficient power to speak to hard clinical endpoints (nonfatal MI and cardiovascular death) will be needed to answer this question fully, and to identify the patients who are most likely to benefit from immediate complete revascularization. ■

ABSTRACT & COMMENTARY

Predicting Electrical Cardioversion Failure

By Michael H. Crawford, MD, Editor

SYNOPSIS: A study of the 30-day success rate of electrical cardioversion of acute atrial fibrillation revealed five clinical predictors of recurrence. These were combined into a risk score that could be useful to avoid unnecessary cardioversions in the acute setting.

SOURCE: Jaakkola S, Lip GY, Biancari F, et al. Predicting unsuccessful electrical cardioversion for acute atrial fibrillation (from the AF-CVS score). *Am J Cardiol* 2017;119:749-752.

Electrical cardioversion (ECV) of atrial fibrillation (AF) is not always successful and exposes patients to thromboembolism when anticoagulation is inadequate. Thus, investigators from the FinCV study sought to derive and validate a clinical scoring system to predict ECV failure and early AF recurrence in acute AF patients (< 48 hours). This was a retrospective study of first EVCs in 2,868 patients with acute AF presenting to one of three Finnish hospitals and followed for 30 days after ECV. The population was divided into two cohorts: derivation (Western Finland) and validation (Eastern Finland). Failure was defined as unsuccessful ECV or recurrence in 30 days. A multivariate analysis of clinical variables believed to be associated with persistence of AF was performed on the derivation set and resulted in five independent variables: age group (< 45 years, 45-65 years, and > 65 years), not their first AF episode, congestive heart failure, vascular disease (coronary, peripheral, or aortic), and more than one month since prior episode. Points were assigned to each variable to derive an AF-CVS (acronym for the five factors, see Table 1) score. The overall AF event rate was about 40% in both cohorts. Those with < 3 points exhibited low failure rates (1.3-13%) and with > 5 points high rates (34-67%). The lowest rate was seen in young men (< 45 years) experiencing their first AF event (0-6% in both cohorts). The C-statistic for the AF-CVS score was 0.67. The accuracy of the AF-CVS score was independent of the use of antiarrhythmic drugs. The authors concluded that five simple clinical factors can predict the early failure of ECV in acute AF patients.

Table 1. Calculating the AF-CVS Score

Factors	Points	Hazard Ratio
Age 45-65 years	1	1.31
> 65 years	2	1.31
not **F**irst AF episode	2	1.55
Congestive heart failure	2	1.52
Vascular disease	1	1.38
Short interval from prior AF	3	2.31

■ COMMENTARY

Rapid cardioversion of new AF patients in the ED is becoming more popular as hospitals try to limit admissions to higher reimbursed patients. Also, ED doctors appreciate the extra procedural income. However, repeated ECV can result in prolonged atrial stunning and increase the risk of thromboembolism. Thus, it would be useful to create a method of identifying patients less likely to experience recurrent AF after ECV. This study is the first attempt to develop a risk tool for recurrent AF after acute ECV.

The major determinants of early recurrence are a short interval from a prior episode of AF and experiencing a prior episode in general. The other three factors are components of the CHA_2DS_2-VASc score. Interestingly, sex, which is important in the CHA_2DS_2-VASc score, did not quite make significance in this study (female sex, $P = 0.065$). The AF-CVS has a C-statistic of 0.67, which is similar to that of the CHA_2DS_2–VASc score.

Recurrence of AF in 30 days was about 40%, which may be an underestimation since patients were not monitored for asymptomatic events. This score only is applicable to patients with acute AF of <

48 hours duration. Recurrences after longer time intervals may have different predictors, such as left atrial size. Previous studies have shown that the use of antiarrhythmic drugs and beta-blockers reduces recurrences. Although antiarrhythmic drug use was evaluated in this study, it did not affect the accuracy of the AF-CVS score. Older literature has identified the ECG characteristics of AF as a predictor of recurrence. Those with coarse AF waves on the ECG were less likely to recur than those with very fine waves. This may have something to do with the health of the atria. ECG characteristics were not evaluated in this study. Despite these limitations, I believe this score will be useful for identifying the appropriate candidates for acute ECV in the ED. ■

ABSTRACT & COMMENTARY

Cardiac Resynchronization Therapy Reduces New Onset Ventricular Arrhythmias

By Joshua D. Moss, MD

Associate Professor of Clinical Medicine, Cardiac Electrophysiology, Division of Cardiology, University of California, San Francisco

Dr. Moss reports no financial relationships relevant to this field of study.

SYNOPSIS: In an analysis of the landmark Resynchronization in Ambulatory Heart Failure Trial, patients without prior ventricular arrhythmias randomized to cardiac resynchronization therapy experienced significantly less new onset ventricular arrhythmias than those randomized to implantable cardioverter defibrillator alone.

SOURCE: Sapp JL, Parkash R, Wells GA, et al. Cardiac resynchronization therapy reduces ventricular arrhythmias in primary but not secondary prophylactic implantable cardioverter defibrillator patients: Insight from the Resynchronization in Ambulatory Heart Failure Trial. *Circ Arrhythm Electrophysiol* 2017 Mar;10(3). pii: e004875. doi: 10.1161/CIRCEP.116.004875.

The positive effects of cardiac resynchronization therapy (CRT) in patients with significant left ventricular (LV) dysfunction, congestive heart failure (CHF), and widened QRS have been well demonstrated. Amelioration of symptoms, reduction in heart failure admissions, and improved survival are well documented in prospective, randomized, controlled trials, such as COMPANION, CARE-HF, REVERSE, and MADIT-CRT. However, there have been conflicting data on the effects of CRT on the incidence and frequency of ventricular arrhythmias (VA).

In the Resynchronization in Ambulatory Heart Failure Trial (RAFT), 1,787 patients with New York Heart Association (NYHA) class II or III heart failure, LV ejection fraction (EF) ≤ 30% and intrinsic QRS duration ≥ 120 msec or paced QRS duration ≥ 200 msec, were randomized to either implantable cardioverter defibrillator (ICD) alone or ICD plus CRT (CRT-D). After mean follow-up of 40 months, mortality was significantly lower in the CRT-D group (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.62-0.91; $P = 0.003$). Heart failure hospitalizations also were reduced significantly, although adverse events (particularly lead dislodgement) were higher in the first 30 days post-implant.

In this post hoc analysis of RAFT, the authors evaluated data on VAs detected by the implanted devices. Device interrogations were performed one month after implant and every six months thereafter, and device data were available for 1,764 of 1,787 patients implanted. All devices were programmed with ventricular tachycardia (VT) detection at 150 bpm (or slower if clinically indicated), with a threshold of 16 beats for initial detection.

VAs were common, occurring in 49.4% of patients over a mean follow-up of 40.7 ± 19.2 months, and occurred significantly more in patients who had a history of pre-implant VA ("secondary prophylaxis" indication) vs. those who did not ("primary prophylaxis"). In the entire cohort, the time to occurrence of VA was not different significantly in patients with CRT-D vs. ICD alone. However, among the primary prophylaxis patients, CRT-D was associated with significant prolongation in time to VA compared with a simple ICD (HR, 0.86; 95% CI, 0.74-1.00; $P = 0.044$). There was not the same protective effect among the secondary prophylaxis patients. The mean number of VA or ICD therapies per person per year at risk was 5.91 in secondary prophylaxis patients with CRT-D, significantly more than the 3.36 in patients with an ICD alone. This resulted in a trend toward more anti-tachycardia pacing therapies,

though not more ICD shocks. The authors concluded that in heart failure patients without prior VA who met criteria for CRT, significantly fewer new onset VAs were observed in those treated with CRT than those treated with ICD alone.

■ COMMENTARY

Nearly every electrophysiologist who implants CRT devices has treated patients who seemed to develop new or more frequent VA after initiating biventricular pacing. Discontinuation of LV pacing often is considered in such patients, particularly in the setting of VT storm when multiple treatment strategies often are employed simultaneously.

The Sapp et al study adds valuable information to our knowledge about the pro-arrhythmic and/or antiarrhythmic effects of biventricular pacing, information that, at a minimum, will help facilitate conversations with patients about the potential risks and benefits of CRT. Particularly, in what are more often "borderline" candidates for CRT based on current guidelines — for example, non-left bundle branch block pattern on ECG or QRS durations only slightly longer than 120 msec — the longer implant procedure time, added hardware, and reduced battery life of CRT devices may make some patients and physicians lean toward a simple ICD. Knowing that there may be a benefit with CRT in a primary prophylaxis indication could be an additional incentive to proceed with the more complex device.

The major strengths of the study are the large patient population and the randomized distribution of simple ICDs vs. CRT-D devices. However, important limitations must be considered. Multivariate analysis was not performed to eliminate potential confounding effects. The actual percentage of time patients with a CRT-D device had biventricular capture (not just delivery of a pacing stimulus by the device) probably is not known. The presence or absence of VA was based entirely on device detection, which is limited by device programming — particularly in the secondary prophylaxis group, where amiodarone use was significantly higher and slower arrhythmias may have been missed. Also, the devices were implanted before the era of quadripolar LV leads and multisite pacing, both of which allow for more CRT "customization" and may further affect VA burden.

It will be important to determine if there are more specific predictors for new onset or increased burden of VA after CRT initiation, such as proximity of the pacing electrodes to areas of scar, timing of LV vs. RV pacing, or inducibility of VA with programmed stimulation from either the chosen LV or RV pacing sites. The data presented here should serve to further encourage referral for consideration of CRT in appropriate patients, including those with a secondary prophylaxis indication. Still, helping our patients understand potential risks and benefits associated with implanted device therapy and minimizing the morbidity associated with ICD shocks should remain priorities. ■

ABSTRACT & COMMENTARY

Can Echo/Doppler Accurately Estimate LVEDP in Pulmonary Hypertension Patients?

By Michael H. Crawford, MD, Editor

SYNOPSIS: In patients with pulmonary hypertension evaluated in a specialty clinic, echo/Doppler estimation of left ventricular end-diastolic pressure is not reliable for the determination of pre- vs. post-capillary pulmonary hypertension.

SOURCE: Cameron DM, McLaughlin VV, Rubenfire M, et al. Usefulness of echocardiography/Doppler to reliably predict elevated left ventricular end-diastolic pressure in patients with pulmonary hypertension. *Am J Cardiol* 2017;119:790-794.

If left ventricular end-diastolic pressure (LVEDP) can be estimated accurately by echocardiography/Doppler techniques, it could obviate the need for heart catheterization to distinguish pre- and post-capillary pulmonary hypertension (PH) and to determine volume status in PH patients. Cameron et al retrospectively evaluated 161 consecutive PH patients undergoing clinically indicated heart catheterization who were subjected to an echo/Doppler within three months of the cath and had no changes in medications or rhythm during the interval between tests. The 2009 American Society of Echocardiography (ASE) guidelines were used to identify patients with elevated LVEDP (> 15 mmHg). To improve the performance of the 2009 ASE guidelines, a new model also was developed using multivariate binary logistic regression analysis. The study patients exhibited a median mean pulmonary artery pressure of 34 mmHg and a pulmonary vascular resistance of 3.7 Wood units. An LVEDP > 15 mmHg was found in 81 patients. Median time between echo and cath was 23 days.

The sensitivity and specificity as well as the positive and negative predictive values for detecting LVEDP > 15mmHg by the 2009 ASE criteria ranged from 54-66%. Only grade 3 diastolic dysfunction had an LVEDP significantly different from the other two grades (22 vs. 16, 15, 17 mmHg for grades 0, 1, 2, respectively; $P < 0.05$). The new model with the best performance yielded higher values between 63-68%, with sensitivity at 68%. This model used only three variables: left atrial diameter, E/A wave mitral valve inflow velocities, and E/e' tissue Doppler velocities on the septal side of the mitral annulus. The receiver operating curve for this model was 0.70. The authors concluded that echo/Doppler estimation of LVEDP in patients with PH does not perform adequately enough to identify patients with elevated LVEDP.

■ COMMENTARY

This paper offers important clinical implications. Even though many echo/Doppler diastolic parameters correlate statistically with LVEDP, in the setting of patients referred to a specialty clinic to determine the etiology of PH, these parameters alone or in combination failed to reliably identify patients with post-capillary PH. This is important because the treatment of post-capillary PH is different from that of other causes. Although many echo/Doppler measures are associated with LVEDP, the correlations are weak. In fact, mitral inflow velocity E/A demonstrated the best correlation coefficient at R = 0.19. Also, one would expect the LVEDP to rise with ascending levels of diastolic dysfunction. However, only the highest grade (3) was significantly associated with elevated LVEDP. Cameron et al tried to develop a better model to predict LVEDP and found a three-variable model that was somewhat better than the ASE criteria, but it was not reliable enough (sensitivity 68%, specificity 63%). In 2016, the ASE revised the diastolic function guidelines. The changes were small and using these new criteria the performance was somewhat worse (sensitivity 51%, specificity 67%).

There are some limitations to this study. The echo and cath were not performed simultaneously or even on the same day. Thus, it is possible that lifestyle changes could have affected LVEDP between the two tests. However, patients were excluded who had any change in diuretics or PH medications and if they went into atrial fibrillation. Also, not all patients underwent left heart catheterization, so it was assumed that pulmonary capillary wedge pressure was a reasonable approximation of LVEDP. In addition, the authors did not adjudicate the classification of the PH patients, but relied on the caring clinicians' determination. The largest of the PH groups were WHO class one (44%), but about one-third of these patients also exhibited an elevated LVEDP. This could have been a misclassification or, since this was a referral specialty clinic for PH, some may have had very high right ventricular pressures, which caused compression of the left ventricle, elevating its filling pressure. The bottom line is that echo/Doppler is not a reliable substitute for heart catheterization in distinguishing pre- from post-capillary PH. ■

ABSTRACT & COMMENTARY

Tolvaptan Fails to Improve Dyspnea in Acute Heart Failure

By Van Selby, MD

Assistant Professor of Medicine, University of California, San Francisco Cardiology Division, Advanced Heart Failure Section

Dr. Selby reports no financial relationships relevant to this field of study.

SYNOPSIS: In patients hospitalized for acute heart failure, adding tolvaptan to furosemide lead to increased weight and fluid loss, but did not improve dyspnea at 24 hours.

SOURCE: Felker GM, Mentz RJ, Cole RT, et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017;69:1399-1406.

Tolvaptan is an oral vasopressin-2 receptor antagonist that inhibits antidiuretic hormones and promotes free water elimination (aquaresis). Although it has been shown to increase fluid loss in patients suffering from acute heart failure (AHF), no clinical trial has shown clear improvements in symptoms or long-term outcomes. However, subgroup analyses of several trials suggested that patients with hyponatremia and those who received tolvaptan earlier in their hospital course may have experienced clinical benefit.

To determine whether more targeted use of tolvaptan in AHF could improve outcomes, the creators of the Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure (TACTICS-HF) trial randomized 257 patients hospitalized for AHF to oral tolvaptan (30 mg) vs. placebo in addition to a fixed-dose furosemide regimen. All patients were identified within 24 hours of hospitalization and were required to demonstrate dyspnea at rest or, with minimal exertion, elevated natriuretic peptide levels and at least one additional sign or symptom of congestion. Patients also were required to exhibit a serum sodium level < 140 mmol/L. The primary endpoint was the proportion of patients with at least moderate improvement in dyspnea at both eight and 24 hours ("responders").

For the primary outcome of dyspnea relief, there was no significant difference between those randomized to tolvaptan vs. placebo (50% responders for tolvaptan and 47% for placebo at 24 hours; P = 0.80). Patients randomized to tolvaptan experienced significantly greater weight and fluid loss at 48 hours compared to those who received placebo. Tolvaptan also was associated with an increased incidence of worsening renal function (39% vs. 27%; P = 0.037). There was no difference in hospital length of stay or post-discharge event rates. The authors concluded that adding tolvaptan to a standard furosemide regimen does not significantly improve dyspnea at 24 hours despite greater weight and fluid loss.

■ COMMENTARY

Tolvaptan currently is approved for the treatment of hyponatremia, and there has been substantial interest in expanding its use to AHF. The pathophysiologic basis is sound, with the hope that adding a potent aquaretic would reduce the required dose of loop diuretics, avoiding some of the drawbacks of loop diuretics such as resistance and neurohormonal activation as well as preserving renal function. The TACTICS-HF trial built on data from previous trials, attempting to target subgroups in whom there was previously a suggestion of benefit. Unfortunately, TACTICS-HF (as well as the SECRET of CHF, another negative trial of tolvaptan for AHF published alongside TACTICS-HF) only adds to a growing list of trials showing that although tolvaptan effectively promotes fluid loss, this does not translate to clinically meaningful improvements.

It is not entirely clear why there is such a disconnect between fluid loss and clinical improvement in patients treated with tolvaptan. It may be that the type of fluid removed is important. In other words, losing free water is not as beneficial as losing fluid with a more physiologic electrolyte balance. That said, even trials of alternative fluid removal strategies, such as aggressive loop diuretics or ultrafiltration, have failed to show clear improvements in long-term outcomes despite successful volume removal. AHF clearly remains an incompletely understood syndrome. As a result, identifying effective therapies has proven very challenging.

Overall, TACTICS-HF was a well-conducted trial with few major limitations. The dose of furosemide used was relatively low compared to what has been used in previous trials, and may have reduced the proportion of patients who were adequately decongested. The study also was powered inadequately to identify differences in survival and rehospitalization. Another consideration in all AHF trials is the difficulty determining an appropriate primary endpoint. Although TACTICS-HF missed the primary endpoint of dyspnea relief at 24 hours, there was a non-statistically significant trend toward reduced dyspnea in the tolvaptan group at 48 and 72 hours. A similar delayed effect was seen in the SECRET of CHF. This may reflect the time needed for fluid to distribute out of the lungs and extravascular space into circulation before a patient experiences clinical benefit. In any case, the primary outcome of both trials was negative, and these secondary findings only can be considered hypothesis-generating.

Based on the results of TACTICS-HF and prior clinical trials, routine use of tolvaptan in AHF cannot be recommended at this time, especially given the high price of the drug. It is possible that further studies targeting even more specific subgroups of AHF patients will identify a role for tolvaptan. For now, we must continue searching for an intervention that clearly improves outcomes in patients hospitalized for AHF. ■

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CME/CE QUESTIONS

1. **One effect of implantable cardioverter defibrillator (ICD) plus cardiac resynchronization therapy placement in appropriate heart failure patients without prior ventricular arrhythmias is:**

   a. a reduced incidence of atrial fibrillation.

   b. more anti-tachycardia pacing episodes.

   c. more ICD shocks.

   d. fewer episodes of ventricular arrhythmias.

2. **In a large acute myocardial infarction (MI) trial, complete percutaneous revascularization compared to infarct artery-only primary percutaneous coronary intervention resulted in a reduction in:**

   a. stroke.

   b. MI.

   c. subsequent revascularization.

   d. mortality.

3. **The most important predictor of recurrent atrial fibrillation early after acute cardioversion is:**

   a. female sex.

   b. previous atrial fibrillation.

   c. a history of vascular disease.

   d. age 45-65 years.

4. **The best measurement to identify post-capillary pulmonary hypertension is:**

   a. echocardiography/Doppler mitral inflow velocity E/A.

   b. tissue Doppler E/e'.

   c. left atrial size.

   d. invasive pulmonary capillary wedge pressure.

5. **Studies in acute heart failure patients show that tolvaptan:**

   a. increases fluid loss.

   b. improves symptoms.

   c. increases serum sodium.

   d. Both a and c