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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Stress Myocardial Perfusion Scintigraphy for Tracking Prognosis and Monitoring the Success of Anti-ischemic Therapies in Stable Survivors of AMI The INSPIRE Trial

Originally presented by: John J Mahmarian, MD

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Reported and discussed by:
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The in-hospital investigation and subsequent decisions regarding revascularization management of patients with acute myocardial infarction (AMI) remains controversial.[1-9] There is an ever increasing frequency of utilization of early angiography and intervention in all subsets of patients with AMI, with little evidence that this utilization is based on risk or improves outcome.[1-4] Although recent studies highlight the clinical benefit of this approach in patients with high-risk acute coronary syndrome (ACS) and ST depression and/or enzyme elevation,[5,6] or those with significant ischemia post-thrombolysis,[7] there is no prospective evidence that this early invasive approach is of benefit in stable patients with Q-wave MI,[1-3] patients treated with thrombolytic therapy for ST elevation AMI,[1-3] or those with intermediate and low risk ACS.[8-9]

Exercise and pharmacologic perfusion imaging have been extensively evaluated and have proven value in assessing prognosis in patients with ACS[10] and those with Q-wave MI without,[11-14] or with thrombolytic therapy.[15-27] Stress imaging can be safely performed 1 to 4 days early post-AMI.[14] These studies concluded that patients with minimal ischemia are at low risk for a cardiac event and can be managed conservatively with aggressive risk factor modification, beta-blockers, aspirin, and ACE inhibitors. The data shows that patients with demonstrable ischemia are at significant risk of a cardiac event and coronary angiography with appropriate revascularization is commonly performed in these high-risk patients. The value of this strategy of risk assessment and subsequent intervention in improving outcome has not been prospectively evaluated in clinically stable patients post-AMI.[16] Preliminary data from Mahmarian,[21,22] that provides the foundation of the INSPIRE trial, showed that patients could be accurately stratified into low, intermediate, and high-risk groups based on quantitative total and ischemic perfusion defect size. Patients can be further stratified by calculation of left ventricular ejection fraction (LVEF) by gating the myocardial perfusion study.

Since preliminary data demonstrated that aggressive medical therapy can reduce ischemic defect size and potentially improve survival to a similar degree as intervention post-AMI,[28] the INSPIRE trial[29] was initiated to address the relative efficacy of these 2 approaches in reducing ischemia as determined by sequential adenosine sestamibi single-photon emission computed tomography (SPECT). In addition, the study was powered to address the ability of sestamibi SPECT to effectively stratify patients according to risk and to compare strategies of intensive medical therapy and/or coronary revascularization for reducing myocardial ischemia and improve clinical outcome. Specifically, the goals of the INSPIRE trial were to evaluate:

- the degree to which the detection of perfusion defect size predicts prognosis

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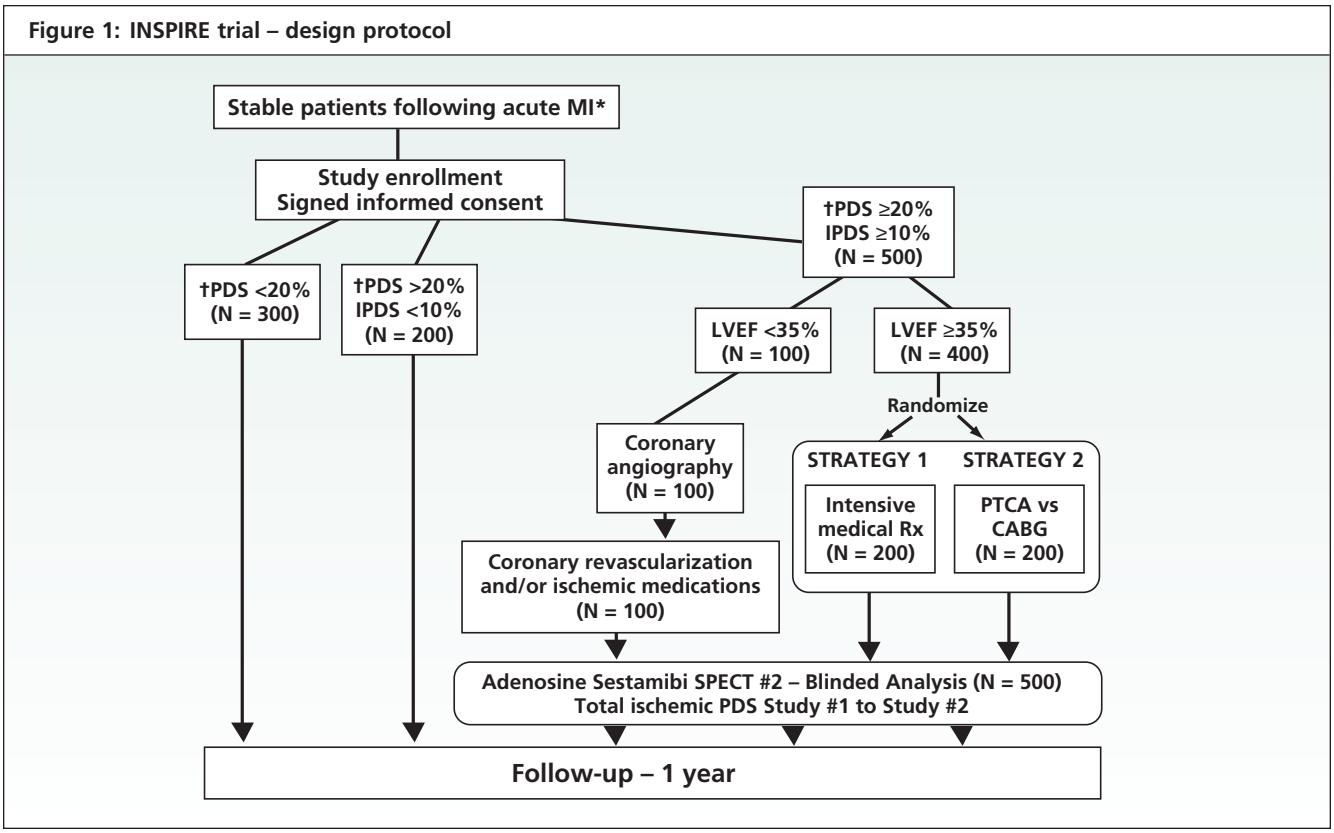
Figure 1: INSPIRE trial – design protocol



PDS = perfusion defect size; IPDS = ischemic perfusion defect size

• whether maximal medical therapy is as effective as coronary revascularization for reducing ischemia and improving outcome in a randomized subset of high-risk patients with MI.

Study protocol

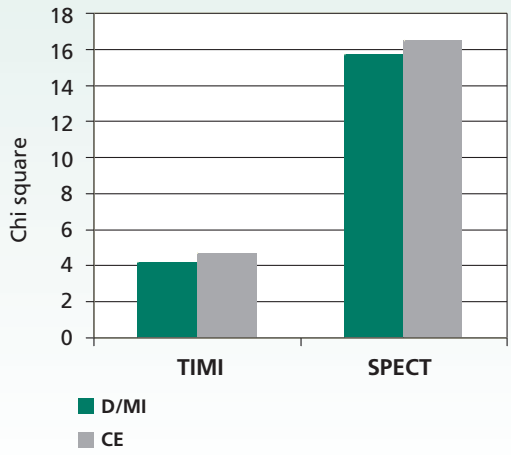
The INSPIRE trial was a multicentre, prospective, randomized trial of patients with documented AMI who remained stable early in their hospitalization. After informed consent, all had adenosine and rest sestamibi SPECT imaging 1 to 10 days after presentation. Therapeutic strategies were based on the quantitative assessment of perfusion defect size (PDS), the ischemic PDS (IPDS), and the EF as shown in Figure 1. The number of patients expected to fall into each subgroup is shown. All patients were followed for 1 year and identification of cardiac events, including cardiac death, reinfarction, and rehospitalization for ACS or congestive heart failure. A second SPECT was performed after each assigned anti-ischemic therapy was optimized.

INSPIRE findings

INSPIRE enrolled 728 stable AMI patients at multiple centres; all underwent adenosine sestamibi SPECT imaging within 10 days of their MI. The average age was 63, 69% were male, 48% had Q-wave AMI, and 35% received thrombolytic therapy. All patients with primary angioplasty were excluded. Approximately 70% of patients underwent baseline SPECT by day 4 and each was designated as being at low, intermediate, or high risk on the basis of their PDS and IPDS from the SPECT results. High-risk patients were then assigned on the basis of LVEF to either coronary angiography (if their LVEF was <35%) or medical therapy or coronary revascularization by percutaneous transluminal coronary angiography (PTCA) or coronary artery bypass graft (CABG) (if their LVEF was >35%), on top of optimal medical therapy. Imaging procedures were then repeated following the assigned treatment and patients from all risk categories were followed for 1 year.

The follow-up SPECT study was performed a median of 66 days after the baseline SPECT. Aggressive medical therapy included ASA 325 mg/day, imdur titrated from 60 mg/day to 120 mg/day, atenolol 50 mg/day titrated up to 200 mg/day, plus angiotensin-converting enzyme (ACE) inhibitors and statins, both titrated to maximum dose. In patients with EF >40%, diltiazem could be given and titrated from 180 mg/day to 300 mg/day.

Figure 2: Determining risk of death or MI at one year based on SPECT and TIMI scores



D = death, MI = myocardial infarction, CE = cardiac events

Patients classified as low risk (n=242) had a death or AMI rate of 3%. The total event rate of death and AMI in the intermediate- (n=213) and high- (n=273) risk patients, based on the SPECT total and ischemic LV-PDS, was 10%; the rate was similar in both groups. Thus, the PDS successfully stratified the patients into low- and high-risk populations. When baseline SPECT imaging findings were considered in relation with baseline TIMI risk scores, SPECT was additive in predicting one-year risk as shown in Figure 2.

Of the 273 high risk patients, 68 had an EF <35% and underwent cardiac catheterization. The second component of the study compared total PDS and IPDS in the remaining 205 high-risk patients who were randomized to medical therapy or revascularization. The comparison of these 2 randomized groups is shown in Table 1. Aggressive medical therapy for treatment of ischemia reduced the PDS, ischemic burden, and scar to the same extent as revascularization. Both strategies had a similar improvement in EF and there was no difference in cardiac events.

Implications for clinical practice

The INSPIRE study suggests that greater use of state-of-the-art nuclear imaging could reduce the frequency of invasive coronary angiography and unnecessary revascularization post-AMI, with similar outcomes, improved safety, and reduced costs. Dr Mahmarian stated: "Based on the INSPIRE population, somewhere between one-half and two-thirds could be eliminated from having coronary angiography as a preliminary test. From this point of view, therefore, this study has very important implications in terms of what should be the first-line approach."

Table 1: Comparison of change in PDS and IPDS in high-risk patients randomized to medical therapy or revascularization

Randomized group	Medical therapy	Revascularization
Revascularization	22%	74%*
Change in PDS	-16.2	-17.8
Change in IDS	-15.0	-16.2
Change in Scar	-1.2	-1.6
% with 9% decrease PDS	75	79
% with 9% decrease IPDS	80	81
Death/MI	6%	6%
Total CE	8.6%	8.8%
Change in LVEF	4.7%	4.6%

* = p<0.001 vs medical therapy, all other comparisons NS

While provocative, the sample size in the randomized comparison group was small, making the conclusions less convincing; therefore, it might be suggested that the results should be interpreted with caution and viewed as hypothesis-generating. The surrogate endpoint of ischemic defect size was assessed and was similarly reduced by medical therapy as intervention. However, clinical events were also the same in both groups. It is possible that a larger sample size may show a difference, but the event rates were so similar in these 2 treatment groups that a very large study would be required to demonstrate the superiority of either strategy.

This study confirms the prognostic value of perfusion imaging in stable patients early post-MI. Risk stratification can be performed early and can positively impact on resource utilization. PDS, extent of ischemia, and LVEF were predictive of outcome and superior to a common, clinically-utilized, scoring system post-AMI. Thus, a significant reduction in PDS with aggressive medical therapy could be interpreted as evidence for reduced cardiac events.

These data do not apply to patients with high clinical risk post-AMI. Patients with congestive heart failure, EF <35%, significant arrhythmias, or post-AMI angina were excluded. In addition, patients with ACS with ST depression and positive cardiac enzymes warrant early coronary angiography and intervention rather than adenosine sestamibi SPECT imaging. A patient with Q-wave AMI, whether treated with thrombolytic therapy or not, warrants serious consideration for exercise or pharmacologic stress perfusion imaging as first-line investigation post-AMI. This can be performed early and the size of the perfusion defect and EF can

stratify the patient into low-risk or high-risk categories. Low-risk patients should be treated with proven medical therapy and high-risk patients should receive aggressive medical therapy with anti-ischemic therapy, with or without coronary angiography.

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