

## Clinical Decision Making Based on Cardiac Diagnostic Imaging Techniques (II)

## Risk Stratification After Acute Myocardial Infarction

Jaume Candell Riera

Servei de Cardiologia. Hospital General Universitari Vall d'Hebron. Barcelona. España.

In recent years, the characteristics of patients who suffer acute myocardial infarction without complications during hospitalization have changed. In addition, the range of non-invasive studies available for evaluating left ventricular systolic function, residual myocardial ischemia, and myocardial viability in these patients has improved. Left ventricular systolic function and residual ischemia should be evaluated in all patients before release. The non-invasive technique used (exercise test, echocardiography, nuclear cardiology, magnetic resonance imaging) depends on availability, experience, and results at each institution. Coronary arteriography should be performed in patients with significant ischemia or severe left ventricular systolic dysfunction in non-invasive studies. In these cases coronary angiography must be performed to determine if coronary arteries are suitable for revascularization before performing a test of myocardial viability.

**Key words:** *Acute myocardial infarction. Prognosis.*

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## INTRODUCTION

Prognostic evaluation of ischemic heart disease should be basically aimed at stratifying the risk of complications during follow-up in groups of low, medium and high risk patients. A low risk group is characterized by less than 1% one year cardiac mortal-

This section is sponsored by Laboratorio Dr. Esteve

Correspondence: Dr. J. Candell Riera.  
Servei de Cardiologia. Hospital General Universitari Vall d'Hebron.  
P. Vall d'Hebron, 119-129. 08035 Barcelona. España.  
E-mail: [jcandell@hg.vhebron.es](mailto:jcandell@hg.vhebron.es)

**Estratificación pronóstica tras infarto agudo de miocardio**

Durante estos últimos años ha cambiado no sólo el perfil de los pacientes que han presentado un infarto agudo de miocardio, a consecuencia de los avances terapéuticos que se han ido implantando, sino también las exploraciones que permiten valorar la función ventricular y la isquemia residual en todos los enfermos que no han presentado complicaciones durante su ingreso, y la viabilidad miocárdica en aquellos con función sistólica ventricular deprimida y con arterias coronarias revascularizables. Sin entrar en preferencias por algún tipo concreto de exploración no invasiva (prueba de esfuerzo convencional, ecocardiografía, isótopos, resonancia magnética), porque esto va a depender de la disponibilidad, experiencia y resultados en cada centro, siempre debería valorarse antes del alta hospitalaria la función sistólica ventricular izquierda y la isquemia residual, reservando la coronariografía para cuando aparezcan signos de isquemia manifiesta en las exploraciones no invasivas o cuando la función sistólica esté gravemente deprimida, con la finalidad de analizar si el árbol coronario es adecuado antes del estudio de la viabilidad miocárdica.

**Palabras clave:** *Infarto agudo de miocardio. Pronóstico.*

ity, whereas a high risk group presents a 5% one year mortality.<sup>1</sup>

Post-infarction prognosis depends on multiple factors:<sup>2-36</sup> patient characteristics previous to the infarction (age, physical condition, previous infarctions, hypertension, diabetes, smoking and heart failure), instant when therapy was initiated, ventricular arrhythmias, left ventricular function and residual ischemia, amongst others. An exhaustive model for death risk prediction including 11 324 AMI patients followed-up during 4 years has been recently published, based on the GISSI<sup>37</sup> study. During this follow-up period, 1071 patients died (9.5%). Influence in mortality of non-modifiable risk factors (age and gender) and others, such as left ventricular dysfunction, electrical instabi-

lity, residual ischemia and cardiovascular risk factors, was studied using multiple regression models. After analyzing the results the following conclusions were drawn: *a)* age is the principal death prognostic factor; *b)* up to 60 years this risk is higher in males; *c)* diabetes is an important risk factor; *d)* intermittent claudication is also an important factor, indicating that clinical markers of arteriosclerosis should be included in the algorithms for diagnosis; *e)* total cholesterol and triglycerides, as opposed to HDL cholesterol (HDL-C), are not associated with an impaired prognosis in a population in its majority undergoing hypercholesterolemic therapy; *f)* post-infarction blood pressure does not have a prognostic value for mortality in a population already receiving antihypertensive treatment, although a history of hypertension does, and *g)* left ventricular dysfunction has more prognostic importance than residual ischemia.

Mortality of patients suffering a myocardial infarction without acute phase complications is usually 1% to 5%. Therefore it is important to delimit high risk patients from others with uncomplicated infarction, since the former would benefit from coronary revascularization. The main physiological mechanisms that determine prognosis are left ventricular dysfunction and myocardial ischemia, and previous studies have demonstrated that outcome after a first uncomplicated infarct at one year<sup>38</sup> and at 5 years<sup>39</sup> is determined basically by these two factors. Since more than 80% of post-infarction severe complications occur during the first month, most post-infarction guidelines<sup>40,41</sup> recommend that the examinations for assessing these factors should be performed before hospital discharge.

### CHANGES IN THE INFARCT PATIENT PROFILE IN RECENT YEARS

New therapeutical approaches developed in recent years, such as fibrinolysis and primary percutaneous revascularization, and new drugs used in secondary prevention, have contributed to reduce post-infarction morbidity/mortality, but also to modify the planning of pre-discharge prognostic evaluation.<sup>42,43</sup>

In the last decade, we observed a significant increase in the use of fibrinolytic therapy and in the use of beta-blockers before hospital discharge (Table 1).<sup>38,44</sup> Two essential aspects of current post-infarct risk stratification are conditioned by a smaller number of patients with low EF, and a lower percentage of patients on whom residual ischemia is detected.<sup>45</sup> In our two series of patients with a first uncomplicated AMI followed-up during 10 years, we observed that the proportion of patients with a EF<40% had fallen from 48% to 11%, and that the proportion of patients with ST segment depression had fallen from 42% to 20%. These findings were observed despite submaximum

**TABLE 1. Outcome of AMI patients receiving fibrinolytics and treatment for angina before discharge at Hospital Vall d'Hebron during the past ten years<sup>38,44</sup>**

Year	1991	2001	P
Fibrinolysis	25 (22%)	48 (42%)	<.001
Beta-blockers	14 (12%)	89 (81%)	<.001
Calcium antagonists	21 (18%)	16 (15%)	.470
Nitrates	12 (10%)	15 (14%)	.444

**TABLE 2. Outcome of post-infarction low EF and residual ischemia patients before discharge at Hospital Vall d'Hebron during the past ten years<sup>38,44</sup>**

Year	1991	2001	P
EF<40%	55 (48%)	12 (11%)	<.001
ST depression>1 mm	48 (42%)	22 (20%)	<.001
Scintigraphic ischemia	78 (68%)	12 (11%)	.002

EF indicates ejection fraction.

stress tests were performed during the first study, and symptom-limited tests during the last one. The number of patients with residual ischemia detected by isotopic examinations is also less, even when the most recent study uses a highly sensitive tomographic technique (Table 2).<sup>38,44</sup> This last point can be partially explained by a limited increase in heart rate during the stress test due to the fact that 81% of patients were receiving beta-blocking treatment.

### ¿SHOULD ALL POST-INFARCTION PATIENTS BE CATHETERIZED ROUTINELY?

Some authors<sup>46</sup> recommend that a coronary angiography should be performed on all patients after an AMI. However, no significant differences were found in various series<sup>47-50</sup> between patients assigned to a routine coronary angiography or receiving a conservative treatment, with relation to mortality, infarction or need of revascularization.

The GUSTO study,<sup>51</sup> including 23 105 North-American patients and 2898 Canadian patients, demonstrated that coronary angiography, angioplasty and revascularization surgery were practiced more frequently in the first series (72%, 29%, and 14%, compared to 25%, 11%, and 3%, respectively), although survival to one year was not significantly different between both series (90.7% compared to 90.3%, respectively). The SAVE study,<sup>47</sup> including 2231 patients with EF<40%, showed similar results. In the RESCATE study,<sup>49</sup> including first AMI patients, the incidence of the re-admission and death was not significantly different (24%

compared to 25%) between tertiary and non-tertiary institutions after 6 months follow-up. These findings were found despite patients admitted to tertiary hospitals underwent coronary angiography and revascularization in a higher proportion than patients admitted to hospitals without a cardiac catheterization laboratory (55% and 21% compared to 22% and 8%, respectively).

In Europe, the proportion of patients undergoing coronary angiography in the first 6 months after AMI is highly variable among countries between 8% and 61%.<sup>52</sup> In our institution, catheterization after a first uncomplicated AMI is indicated when a depressed EF or signs of significant residual ischemia exist, representing 35% of all cases.

### POST-INFARCTION PROGNOSIS BASED ON NON-INVASIVE TESTS

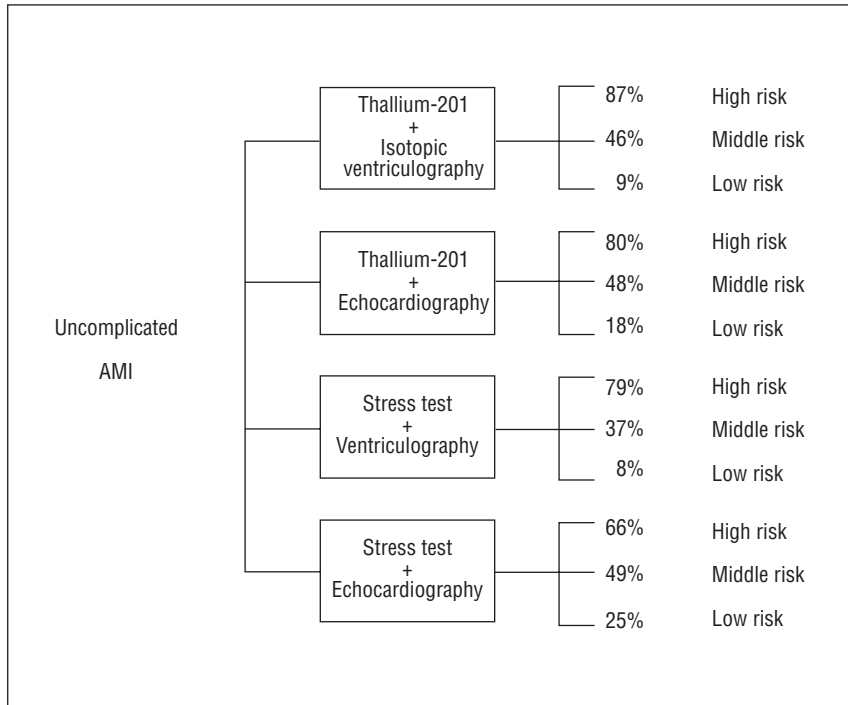
Non-invasive studies of patients suffering infarction without acute phase complications (angina, heart failure, malignant arrhythmias) provide essential prognostic information for evaluating the left ventricular systolic function and residual ischemia. A few years ago, residual ischemia could only be evaluated with the conventional stress test<sup>5,6,9</sup> or by planar myocardial perfusion scintigraphy,<sup>53-55</sup> whereas systolic function could be evaluated by echocardiography<sup>16,20,22</sup> and isotopic ventriculography.<sup>24,26</sup> Information obtained after combining together some of these examinations had proved very useful for post-infarction risk stratification.

In a prospective series of 115 uncomplicated AMI patients studied before hospital discharge using sub-maximum stress tests, echocardiographic examination, planar thallium-201 scintigraphy, isotopic ventriculography, Holter and cardiac catheterization, after multivariate analysis we observed that impaired prognostic predictive factors during the first year of outcome were: *a*) for the stress test, not reaching the 75 W ergometric bicycle maximum load and not exceeding 150 mm Hg maximum systolic blood pressure; *b*) for the echocardiographic examination, EF<45% and the presence of a ventricular aneurysm; *c*) for thallium-201 scintigraphy, presence of more than one ischemic segment, more than 5 necrotic segments (over a total of 15 segments) and presence of pulmonary captation; *d*) for isotopic ventriculography, EF<40%, and *e*) for catheterization, >70% stenosis of three vessels and the presence of a ventricular aneurysm. For this series, mortality was 2.6% and the incidence of severe complications (angina III-IV, heart failure III-IV, revascularization, reinfarction and death) was 20%. Associating a test for evaluating the ventricular function with a test for residual ischemia allowed to calculate the probability of severe complications. It also allowed to stratify the patients in low, medium and high risk

groups. Performing a cardiac catheterization did not improve the predictive value of non-invasive tests.<sup>38</sup> The prognostic stratification value of these non-invasive tests was also validated for a follow-up period of 5 years (Figure 1).<sup>39</sup>

Currently, the most important post-AMI prognostic variable is left ventricular EF.<sup>56</sup> As already mentioned, the number of low EF patients has fallen, turning more relevant the detection of residual ischemia. Right ventricular EF is depressed in complicated inferior infarcts during, but during the first year of outcome, did not add prognostic information to left ventricular EF<sup>57</sup> in multivariate analysis. Nevertheless, other authors<sup>58</sup> have observed that right ventricular dysfunction is a death event and heart failure predictor when associated with post-infarction left ventricular dysfunction. Holter<sup>38,39</sup> and electrophysiological studies<sup>59</sup> seem less important in post-infarction risk stratification, as left they do not provide independent predictive variables when evaluated together with EF and the presence of residual ischemia in multivariate analysis.<sup>60</sup>

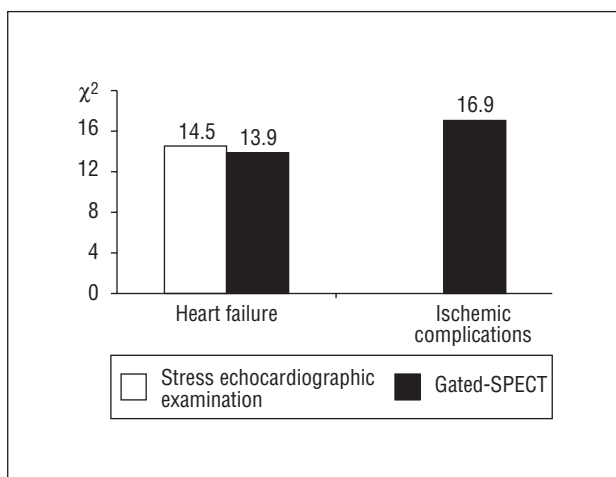
Nowadays, ventricular function and residual ischemia can be evaluated simultaneously by using stress echocardiography<sup>61-64</sup> or synchronized myocardial perfusion scintigraphy (gatedSPECT).<sup>44,65-70</sup> With the aim of comparing the prognostic value of gated-SPECT and stress-echo tests after a first uncomplicated AMI, we studied 103 consecutive patients. A gatedSPECT with 99m Tc-tetrofosmine, and a symptom-limited stress-echo exam, were performed before discharge. During a 12 months follow-up period, two patients died, nine developed heart failure, and 29 presented ischemic complications (four, reinfarction, and 25, angina). The only heart failure predictive factor in multivariate analysis was EF<40%, determined either by echocardiography or gatedSPECT. The only ischemic complications predictive variable was an ischemic area extension >15% with respect to the entire left ventricle in the gated-SPECT polar map. To this regard, both the stress-echo test and the gated-SPECT exam predicted heart failure, but only the gated-SPECT predicted ischemic complications as well (Figure 2).<sup>44</sup> This does not match results of other series by which ischemia detected by stress-echo was predictive of ischemic complications,<sup>61-64</sup> but confirms Brown's opinion<sup>71</sup> after analyzing two revised extensive series.<sup>72,73</sup> For Brown, ischemia detected by stress-echo did not demonstrate a significant prognostic value for post-infarction risk stratification. This is in agreement with other publications that describe the higher sensitivity of perfusion scintigraphy for detecting multivessel disease<sup>74,75</sup> and post-infarction complications.<sup>76</sup> In our series, gated-SPECT demonstrated a high sensitivity for detecting residual ischemia: in the stress-echo exam, only 20% of patients presented new contractile alterations, whereas gated-SPECT detected



**Fig. 1.** Decision trees for combining four non-invasive techniques, that show the probability of severe complications to five years after an uncomplicated infarction depending on results of both branch studies. Positive results in both studies = high risk; positive results in one study = medium risk; negative results in both studies = low risk 39. AMI indicates acute myocardial infarction.

reversible perfusion defects in 48% of patients. Quiñones et al,<sup>77</sup> comparing stress echocardiography and thallium-201 SPECT in a series of 292 patients, did not find significant differences in coronary disease diagnostic sensitivity of both techniques. But stress-echo detected a 36% less ischemic segments than gated-SPECT. Other studies in which stress echocardiography and perfusion scintigraphy techniques are

compared in the same series of patients have obtained similar results.<sup>75,78-80</sup> This could be explained by two facts. First, contractile abnormalities are always preceded by hypoperfusion. And second, technical difficulties of echocardiographic examination may not allow to visualize correctly all the left ventricle segments. In our study,<sup>44</sup> as in previous publications,<sup>81-85</sup> twenty-one of the 103 echocardiographic studies were considered suboptimal. Tauke et al<sup>84</sup> observed that TEE detected 33% more ischemic segments than TTE, and Amanullah et al,<sup>80</sup> in a series of 796 patients with contractile dysfunction at rest, found that SPECT-dobutamine evidenced ischemia in 65% of cases and dobutamine-echocardiography only in 33% of cases. Thus, the second technique would only distinguish one half of the ischemic segments viewed using perfusion gated-SPECT.



**Fig. 2.** Heart failure predictive value during first year of follow-up after a first uncomplicated infarction is similar for stress echocardiographic examination and for gated-SPECT when EF<40%. Only myocardial perfusion gated-SPECT (reversible defect extension >15% respect to all left ventricle) has predictive value for ischemic complications<sup>44</sup>.

### POST-INFARCTION PROGNOSIS AND MYOCARDIAL VIABILITY

Severe left ventricular systolic dysfunction, specially when associated to heart failure, is associated with impaired prognosis. Nevertheless, surgical revascularization has provided a noticeable improvement of survival<sup>86-88</sup> in the subgroup of patients with viable dysfunctioning myocardium (hibernated and/or stunned). To distinguish ventricular dysfunction secondary to necrosis from viable myocardium caused ventricular dysfunction is clinically important for treating these patients. In the medical literature, there



is a consensus about post-infarction patients with severe systolic dysfunction, severe angina (with or without heart failure), and adequate coronary arteries. These patients will have a better outcome if they undergo revascularization, although a significant baseline EF improvement<sup>89</sup> will not be confirmed later. After revascularization, patients with signs of predominant heart failure and left ventricular dysfunction secondary to extensive areas of viable dysfunctioning myocardium not only usually improve clinically, but also improvements in regional and total systolic function are frequently observed.<sup>90</sup>

Echocardiographic techniques, dobutamine-echocardiography in particular, are a widely used for the diagnosis of viable myocardium. Dobutamine administered in low doses (5-10 µg/kg/min) and high doses (20-40 µg/kg/min) is the most common procedure, and a biphasic response (increased contractility at low doses and reduced contractility at high doses) is most specific for predicting viable myocardium improvement after revascularization.<sup>91-94</sup> After an AMI, concordance between dobutamine-echocardiography and positron emission tomography [PET]) is 79% for the diagnosis of viability.<sup>95</sup> The specificity values of dobutamine-echocardiography for the diagnosis of viable myocardium are close to 80%, usually higher than for isotopic techniques. The specificity of the latter techniques oscillate between 60% and 70%, whereas sensitivity is between 80%-90%, slightly higher than for dobutamine echo.<sup>96</sup> Viable myocardium of patients receiving beta-blockers can present an attenuated response to low doses of dobutamine.<sup>97</sup> Furthermore, and that even low doses of dobutamine may produce myocardial ischemia in the presence of a critical coronary stenosis. These facts may explain the lower sensitivity of stress echo to detect viability.

Amongst the recent and mostly used isotopic techniques used are the methods based on thallium-201 with delayed rest-redistribution and stress-redistribution image acquisition,<sup>98</sup> although the technetium compounds<sup>99</sup> with or without previous administration of nitroglycerin<sup>100</sup> are currently also widely accepted. Ischemia detected in stress studies (either exercise or drugs) is a sign of viability sign. Therefore, these studies are always recommended in patients requiring the diagnosis of viability.<sup>101</sup> The mismatch pattern (absence of contractility and preserved metabolism) in PET studies has been used as the gold standard in many myocardial viability studies, and an 88% concordance with thallium<sup>102</sup> re-injection has been observed. Identical results have been obtained using technetium compounds with the advantage of<sup>103</sup> improved image quality. The high costs of PET studies and the lack of a demonstrated clinical advantage over gated-SPECT has limited its use in a few centres for experimental purposes. Magnetic resonance has a good negative predictive value for the diagnosis of

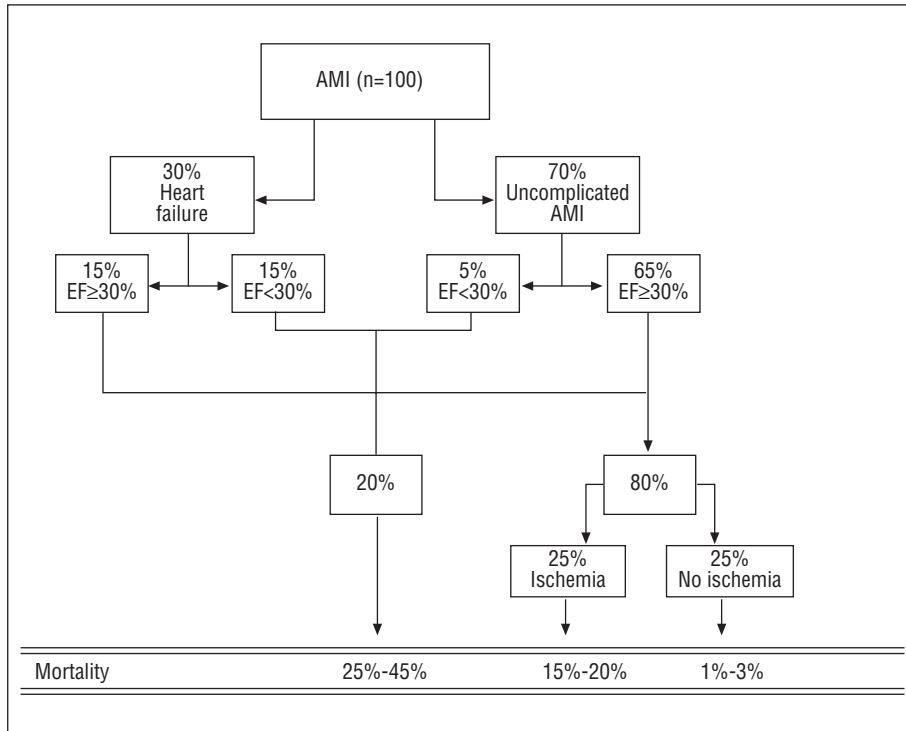
myocardial viability, specially when delayed positive regions following the administration of gadolinium are found.<sup>105</sup>

As mentioned by Di Carli,<sup>106</sup> after studying the results of 9 series<sup>107-115</sup> in which the outcome of 634 patients with hibernated myocardium was assessed, symptom improvement, less complications and longer survival is found in patient who are revascularized, compared to those undergoing medical treatment. This is particularly evident when revascularization is performed as early as possible in the absence of an extreme left ventricular dilation.<sup>116,117</sup> For Yoshida y Gould,<sup>118</sup> the size of necrotic and viable myocardium in the arterial regions at risk was predictive of death with 3 years follow-up, mainly in low EF patients. Paolini et al<sup>119</sup> observed in multivessel disease patients with an EF<30%, without angina and evidence of viability in a significant number of myocardial segments, that after two years all revascularized patients were alive and showed functional class improvement, whereas more than one half of non-revascularized patients had died, awaited transplantation or showed progression of heart failure symptoms.

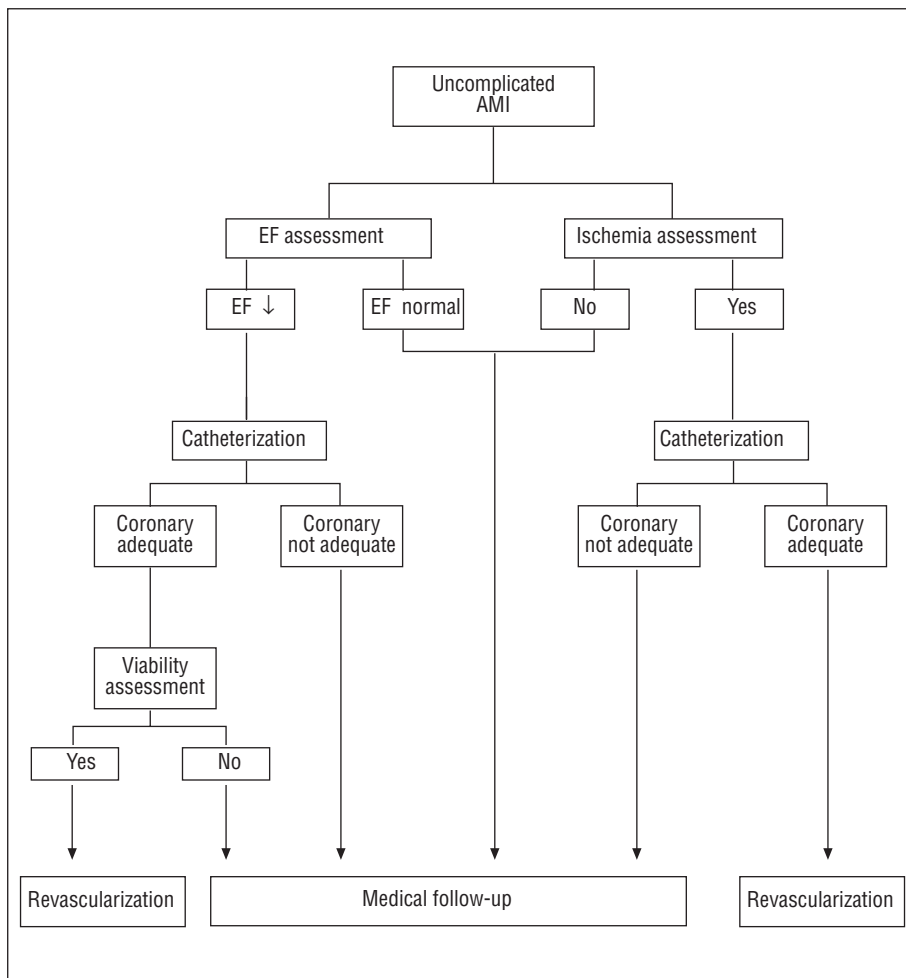
Although these publications confirm the tendency towards a better prognosis of revascularized patients, more studies are still necessary to demonstrate that myocardium viability is an independent prognostic variable *per se*, as accepted for systolic function and presence of myocardium at risk. We should remember that an hibernated myocardium is insufficiently irrigated chronically, so it could be included under myocardium at risk. Currently, the examinations aimed to detect and quantify the extent of myocardial viability should only be indicated after an extensive infarction, or for clinical decision making in ischemic cardiomyopathy.

## POST-INFARCTION DECISION TREES

After considering the publications that included AMI patient mortality during the first year of outcome, Epstein et al<sup>120</sup> established various post-infarction patient risk level subgroups depending on the degree of left ventricular dysfunction and presence of residual ischemia (Figure 3). Using the same scheme, these authors proposed an examination strategy aimed at identifying patients that would benefit from catheterization. This was indicated immediately for patients presenting angina, whereas ventricular function was evaluated first in the remaining patients. If ventricular function was severely impaired, the Holter was used for assessing presence of arrhythmias. In absence of arrhythmias, ischemia was discarded performing the conventional stress test or stress isotopic ventriculography. Catheterization was indicated when ST depression  $\geq 1$  mm or a low stress EF was observed.



**Fig. 3.** Post-infarction mortality to one year depending on ejection fraction and residual ischemia. EF indicates ejection fraction; AMI, acute myocardial infarction.



**Fig. 4.** Study algorithm recommended for risk stratification of patients with uncomplicated acute myocardial infarction. EF indicates ejection fraction; AMI, acute myocardial infarction.

Many authors<sup>121-133</sup> have used this algorithm to propose several decision trees that include performance of non-invasive examinations with the final aim of indicating catheterization only for patients with a high risk of complications during outcome. These would be the patients that benefit from coronary revascularization. In this direction, Crawford and O'Rourke<sup>122</sup> suggested performing examinations depending on the clinical manifestations: catheterization for angina, echocardiography or isotopic ventriculography for heart failure, Holter in case of arrhythmias, and stress tests if complications did not appear. Nienaber and Bleifeld<sup>123</sup> proposed a scheme mainly based on the conventional stress test, whereas myocardial perfusion scintigraphy and isotopic ventriculography were only indicated when the stress tests showed undetermined results. Iskandrian et al<sup>124</sup> published a similar algorithm with isotopic ventriculography at rest as an important factor in initial selection of patients. DeBusk et al<sup>126</sup> recommended another scheme that included performance of two stress tests; a submaximum test during the second week of outcome, and a symptom-limited test during the third or fourth week. The same recommendation was later adopted by the American College of Cardiology.<sup>134</sup> We have already mentioned that most complications after a first uncomplicated infarction appear in the first month of the first year of outcome. In consequence, our opinion is that risk stratification should always be done before hospital discharge, with the purpose of indicating catheterization during admission if necessary.

In this article, we have described repeatedly how the profile of AMI patients has recently changed due to therapeutical advances. Other reasons are that current evaluation tests allow to assess ventricular function and residual ischemia evaluation in patients without complications at admission, as well as myocardial viability in patients with impaired systolic ventricular function and coronary arteries suitable for revascularization. Without stating any preferences about the different types of non-invasive tests (conventional stress test, echocardiography, isotopic, magnetic resonance), that actually depend on availability, experience and results at each institution, our opinion is that left ventricular systolic function and residual ischemia should be evaluated always before discharge. Performing angiography should be conditioned to evident signs of ischemia appearing in non-invasive tests, or for severely impaired systolic function, with the purpose of analyzing if there is an adequate coronary tree before studying myocardial viability (Figure 4).

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