The Value of Stress Testing Following Invasive Treatments

To the Editor

I would like to give my views on the Director's Letter published in Volume 81, Issue 2, April 2013 of your *Journal*. (1)

The letter analyzes the value of stress testing following invasive treatments, providing comprehensive information on rules and studies which suggest that stress testing less than 2 years in some cases and 5 years in others following invasive treatment is inappropriate, because false positives may lead to reassess the patient and not find restenosis that requires subsequent intervention, which demonstrates the lack of value of these results.

The term 'false positive', as developed in the letter, springs from the Bayes' theorem.

In this regard, I would like to reiterate Dr. Mario Bunge's expression (2) in our *Journal*: "***Bayes' theorem does not apply to medical diagnosis because the disease-symptom relationship is causal rather than random.***" (This opinion is thoroughly analyzed in his book Emergence and Convergence.) (3) For those of us who agree with this criterion, because the test "is not convincing" due to either the "pretest or posttest probability", we should call these false positives "***abnormal of unknown origin***", as stated by Myrvin H. Ellestad. (4)

I am raising these points because I beg to disagree on the standardized criteria reported in the letter.

If, say, a patient is prescribed a post-angioplasty stress test and it shows ischemia, the fact that no reobstructions or critical lesions occur afterwards when a catheterization is performed does not undermine it: non-critical (but functionally critical) 40-50% lesions may be found. (5) Or 40-60% lesions of 10-15 mm extension with markedly reduced flow at the distal end. (6) Or seemingly insignificant lesions that are indeed significant, studied by IVUS. We should also consider different ischemic mechanisms, for example, vasospasm and/or endothelial dysfunction. Linked to this, the editorial by Dr. Juan C. Kaski, (7) published in the same issue of the Journal, states that: "*A proportion of patients have 'microvascular angina' (angina caused by coronary microcirculation dysfunction).*" Another element for consideration is that "*coronary angiography only shows a small part of actual coronary flow*". (8)

To be aware of those mechanisms –if any of them occurs– may help improve the treatment outcomes, because if remained untreated, they may, in the long term (say 8-10 years), cause ischemic dilated cardiomyopathy, with 'normal' coronary arteries.

On the other hand, the patient may have been performed catheterization and subsequent invasive treatment for any of those functional tests, when he/she was asymptomatic and presented no symptoms in the test, and you want to know the outcomes with the same method that led to the intervention, thus providing you with objective safety to reroute patient's life.

Mauricio Mandelman

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Reply to Mauricio Mandelman

I thank Dr. Mandelman for his interest in my letter published in Issue 2 of the Journal (April 2013), and in turn it allows me to clear up some confusion.

The first point is that what we want to predict is the so-called gold standard, which, in this situation, is restenosis in coronary angiography or the occurrence of a clinical coronary event, with a test used as screening.

In this situation, it is clear that the logic used for the "reverse conditional probability" of Bayes' theorem will be that when the pretest probability of restenosis in a "*population*" is low (10%), the posttest probability of restenosis will surely show that 2 out of 3 or 3 out of 4 *positive* stress tests will be *false* to visualize stent restenosis in the gold standard coronary angiography.

It is clear that probabilistic prediction only applies to "*populations*"; an "*individual*" does not have a 5% mortality risk due to a surgical procedure but only a binary possibility of surviving surgery or not. We can only say that 5 out of 100 patients in that situation (probability in a population) will not survive; but we cannot predict if that patient in particular will be included in the usual population (95%) of those who survive or in the scarce population (5%) of those who die.

Therefore, Mario Bunge's quote, "***Bayes' theorem***

does not apply to medical diagnosis because the disease-symptom relationship is causal rather than random" –highlighted in bold and italics like a neon sign–, *does not apply because we are not discussing the "disease-symptom relationship"*: we are discussing asymptomatic populations.

It is further asserted that: "*We should also consider different ischemic mechanisms, for example, vasospasm and/or endothelial dysfunction*." As if denying that situation. Obviously, he did not read the Director's Letter from Issue 4, which states: "For many years, and even now, we took it for granted that to label a chest pain as due to an ischemic heart disease, even if it is a typical angina pain, the patient should present with a significant obstructive lesion in the coronary angiography. Maybe because we believe at face value in experimenting on animals that Gould and Lipscomb described in 1974, in which '... a ≥ 50% occlusion limited maximum vasodilating capacity and ≥ 85% occlusion limited resting coronary blood flow'."

"... Based on this mechanism, these lesions were converted into "ischemic stenosis" and this prevented acknowledging –what was evident before our eyes– that a considerable number of patients presenting with typical pain, ST segment depression or perfusion or exercise motility disorders… but had normal or completely normal coronary arteries, were therefore, not sick." (1)

After the detailed description of the different compartments of coronary circulation, he states: "But as sensitivity and specificity of challenge tests are based on the presence or absence of at least one significant coronary lesion and, actually, not in true evidence of myocardial ischemia, these tests are labeled as '*false positives*'."

"Therefore, all known tests in which the gold standard is coronary angiography will have low '*specificity*' due to the presence of 'false positives' for significant lesion, even when the patient may present a true myocardial ischemia due to microcirculatory alterations. Hence, when these tests are used, we should say that they have low specificity and a high proportion of false positives '*only*' for the presence of significant coronary lesions. However, none of these tests canrule out that the patient has symptoms and a positive challenge test due to myocardial ischemia elicited by another mechanism." (1)

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About the Brugada Syndrome Unmasked by Drugs or Fever and Brugada Phenocopies

To the Editor

We have read the clinical report by González et al about a patient with Brugada pattern unmasked by fever, recently published in the Argentine Journal of Cardiology. It has been of great interest to us, and we would like to discuss certain aspects of the publication. (1)

First of all, the classification used to describe the ECG patterns of the Brugada syndrome (BrS) is based on the second consensus on this syndrome. The latest consensus considers only two patterns: type 1 and type 2. Pattern type 1 is marked by J-point elevation (at least 2 mm) with ST segment depression and negative T-wave in right precordial derivations. Pattern type 2, with ST segment elevation (at least 0.5 mm) and positive T-wave, includes patterns type 2 and 3 from the old classification. (2)

We would like to expand on the authors' comment about the diverse situations causing electrocardiographic manifestations of Brugada syndrome in patients without the typical genetic condition of that syndrome. We are referring to **Brugada phenocopies** (BrP). They involve manifestation of Brugada ECG pattern in the absence of the true syndrome. (3) Phenocopies secondary to different etiologies have been described and classified as: 1) metabolic conditions; 2) mechanical compression; 3) ischemia & pulmonary embolism; 4) myocardial & pericardial disease; 5) ECG modulation; 6) miscellaneous. (3, 4) Diagnostic criteria for BrP have been recently reviewed and are summarized as follows: 1) The ECG pattern has a type 1 or type 2 Brugada pattern; 2) the patient has an identifiable reversible condition; 3) the ECG pattern resolves after resolution of the underlying condition; 4) low clinical pre-test probability for true BrS; 5) negative provocative testing with sodium channel blockers; 6) provocative testing with sodium channel blockers not mandatory if surgical right ventricular outflow tract manipulation has occurred within the last 96 hours; 7) the results of genetic testing are negative (not mandatory because the SCN5A mutation is identified in only 25-30% of patients affected by true BrS). (3, 4) We consider that the term BrP should be used to refer to cases meeting these criteria.

The patient presented here is not a case of phenocopy but of true BrS unmasked by flecainide (due to chronic use of this drug), and possibly aggravated by fever, since sodium channels are temperature dependent. (5) Monitoring temperature is very important in these patients, as is discontinuation of flecainide treatment. In addition, an ECG and genetic screening of the family group are necessary to identify carriers of the syndrome.

Unlike the true syndrome, the arrhythmic risk and natural evolution of phenocopies are not defined. A

database is being developed with this purpose and will be uploaded online at www.brugadaphenocopy.com; it will include cases meeting the BrP criteria in order to determine the long term prognosis of this entity.

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Authors' reply

First of all, I would like to thank Dr. Genaro, Dr. Anselm, and Dr. Baranchuk for their interest and for their excellent briefing on Brugada phenocopy. We offer our congratulations and thanks to them.

Moreover, we could not agree more with the arguments expressed in their letter. In fact, for reasons of space, we removed a paragraph from the first draft, precisely on Brugada phenocopy. The briefing by Dr. Genaro et al is an excellent summary of the subject; we cannot add anything to it but our entire agreement.

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About the Brugada Syndrome Unmasked by Drugs or Fever and Brugada Phenocopies

To the Editor

We have read with great interest the opinion article by Dr. Maximiliano de Abreu and Dr. Carlos Tajer (1), published in Volume 81, Issue 5 of the Journal. We believe that the level of this analysis contributes to the prestige of the publication and its coveted international recognition.

There are some points regarding the text that we would like to share:

1. Role of the event adjudication committees: these committees reclassify the events in internation al multicenter studies. Given the importance of the events for the outcomes, the idea is to monitor the criteria of the different researchers, some times from all over of the world, with different academic medical backgrounds, experience, etc. Besides, for a site researcher, reporting an event involves recognizing a failure in the treatment, and additional workload with forms, explanations, etc., whereas the committee is more objective. One of the authors of this letter participated in one of these committees (MT, HOPE Study); he was surprised at how thoroughly and meticulously each case was analyzed, easily surpassing the dedication of researchers from the centers. A sponsor's influence is out of question, any discussion is totally forbidden and blind as to the study drug. We find it difficult to accept that these rules have not been respected in the studies discussed in the article.
2. Risk of bleeding: we strongly agree that new antiplatelet agents are not for everyone, and that it is necessary to stratify the risk for ischemia and bleeding before deciding on a dual antiplatelet therapy and its treatment. The problem is that both risks often run in parallel (for example, age). If the two scores recommended by the European Society of Cardiology (GRACE for ischemic risk and CRUSADE for bleeding risk) are compared, some parameters increase both risks (age, heart rate, creatinine, and heart failure), only the risk for ischemia (ST segment shifts, biomarkers, and cardiac arrest), or only the risk for bleeding (hypertension, diabetes, anemia, or vascular disease). If cautions for the use of a drug are included, the best combination for each patient can be selected.
3. Our experience: based on these selection parameters, in the latest 2013 SAC Congress we introduced data of our centers about the use of clopidogrel or new antiplatelet agents in patients with acute coronary syndrome treated with coronary angioplasty. We observed a reduction in ischemic events, but the strongest independent predictor of bleeding was the use of new antiplatelet agents (mainly prasugrel), interestingly remaining stable over time, supporting the trend to reduce the time for dual antiplatelet therapy to its minimum.

Once again, we wish to congratulate the authors, and we appreciate the opportunity to have our opinion published.

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Authors' reply

We would like to thank Dr. Marcelo Trivi, Dr. Diego Conde and Dr. Leandro Rodríguez for their contribution to the conceptual discussion about selection of antiplatelet therapy, and we would like to make some brief comments.

Honesty and thoroughness of the event adjudication committees in the PLATO study are unquestionable; however, the possible magnitude and tendency of the discrepancy between what researchers report and what committees evaluate cannot be attributed to chance. We have no explanation for this finding, which is still impressive and disturbing. In the evaluation of prasugrel, institutes such as NICE have prioritized "clinical infarctions" reported by researchers over those adjudicated as clinical effectiveness criteria, highlighting the complexity of an unresolved issue.

Regarding bleeding, we agree that some variables associated with increased risk of major events during follow-up are also associated with greater risk of bleeding. However, we consider that the real problem is not just the increase of cardiovascular events or bleeding associated with demographic variables. The important problem is that dual antiplatelet therapy in the presence of these variables generally increases bleeding in a higher proportion than the reduction in cardiovascular events, decreasing or reversing the net clinical benefit.

We believe that experience in follow-up is of great value and conceptually helps to make decisions. We therefore appreciate the concepts expressed in the letter.

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