Hypertension, P wave dispersion and risk of atrial fibrillation

Drs. Elibet Chávez González[a], Emilio González Rodríguez[b], Raimundo Carmona Puerta[c]
[a, c] Cardiac Electrophysiology Service and Stimulation. Cardiocentro Ernesto Che Guevara. Villa Clara, Cuba
[b] Department of Digital Researches. University "Marta Abreu" of Las Villas. Villa Clara, Cuba

To the Director

Hypertension (HTN) affects 26.4% of the population over 19 years of age and its risk of morbility and mortality is worsened when it is associated with cardiac arrhythmias. (1)

In Framingham heart study, a prevalence of double atrial fibrillation (AT) in HTN was shown. P wave dispersion (Pd) on the electrocardiogram (EGC) is mentioned as an aggravating factor. (2)

P Wave Dispersion in the Hypertensive Patient. Its Regression with Treatment

Since many years ago, several authors, in search to predict the risk of AF and continuing previous studies of P wave in ECG, have studied the duration of this wave in twelve derivations and they found a difference between the measured maximum and minimum value. This difference is named Pd and it is significantly higher in hypertensive patients with history of paroxysmal AF. Paroxysms of AF have been associated with increased risk of cardiovascular thrombosis. Therefore, AF increases the risk of HTN in patients with values of maximum P (134 ms) and Pd (46 ms). (3)

The risk of AF is reduced when Pd value decreases; this is obtained when the control of HTN is achieved. Higher values of Pd fall are achieved when medicines capable of blocking the rennin-angiotensin system are used in the treatment of HTN. This has been a research topic of several authors. Celik et al. (4) studied ramipril and telmisartan and they found a regression of P (maximum) and Pd values.

P Wave Dispersion and Prehypertension

Unpublished data, from our research group, have shown a significant increase in Pd in young hypertensive patients of recent clinical debut regarding normotensive controls. Recently, higher values of maximum P and Pd in prehypertensive patients have been proved. Celik et al., (5) in a comparison between prehypertensive and normotensive patients, found: Pd (65 ms) in prehypertensive patients against 35 ms in the control group ($p < 0.001$) and maximum P (110 ms) in prehypertensive patients against 80 ms in the control group ($p < 0.001$).

Due to proved evidences, we recommend the inclusion of P wave measurement in the EGC and Pd calculation in the examination of individuals with risk of suffering HTN or with diagnosis of HTN. This should be a usual practice that allows us to define groups in risk of suffering from AF in the future with the aim of avoiding this arrhythmia associated with sudden death.

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Authors' reply

Atrial fibrillation (AF) is the most frequent arrhythmia in the world population and one of the causes of morbimortality due to CVA and stroke.

Multiple onset and recurrence predictors of this arrhythmia were described. From the electrocardiographic point of view, several works have analyzed the presence of P wave dispersion, premature atrial extrasystoles, abnormal P wave axis, maximum wide of P and others such as onset and recurrence predictors of AF, from which P wave dispersion is one of the strongest predictors in AF; this dispersion is attributed to the heterogeneity in interatrial and intra-atrial electrical conduction. (1) Another studied parameter is the time measurement from the beginning of P wave until the beginning of the left atrial appendage ejection flow (measured by Doppler through a transesophageal echocardiogram), which shows an excellent correlation with P wave dispersion as predictor of AF onset in hypertensive patients. (2, 3)

The correlation between the diastolic dysfunction (characteristic alteration in patients with hypertension) and P wave dispersion has been studied; values in P wave dispersion in patients with diastolic dysfunction were higher than in patients with no diastolic dysfunction. (4)

The antihypertensive therapeutics, especially medicines that act in the renin-angiotensin system, decreases P wave dispersion and the probability of having AF. (5, 6) This is related to the fall in the left ventricular end-diastolic pressure, diastolic dysfunction or maybe a direct effect on angiotensin II receptor, which is involved in atrial electrical

remodeling responsible for electrical heterogeneity that allows us the perpetuation of AF. (7)

Bayes de Luna has described intra-atrial and interatrial disorders as mechanisms which predispose to AF. This even motivated, many years ago, the onset of electrical stimulation therapies for AF, as left atrial multisite pacemaker, its preferential stimulation, and present studies of our group of interatrial and intra-atrial synchronization to avoid dyssynchrony, homogenize refractory periods and avoid AF. (8, 10)

All these findings support the line of research carried out by Dr. Elibet Chávez González and his group from the Cardiocentro Ernesto Che Guevara and the University "Marta Abreu" of Las Villas, in hypertensive and prehypertensive patients, which add more merit to his researches. Likewise, the existing evidence reinforces the recommendation given by this group about the execution of P wave dispersion measurement in patients with risk of suffering from HTN and in prehypertensive patients, since it is a simple and economic method and it allows specialists to guide the preventive therapeutics in those groups which are more prone to present AF. On the other hand, as an interventionist electrophysiologist with experience in different types of non-invasive treatments for this arrhythmia, I see the possibility to foresee and avoid, with preventive measures, morphological and structural changes, which in the near future will develop this type of arrhythmias. These ones will force us to carry out aggressive therapeutics for subgroups of patients with bad clinical evolution.

Dr. Luis Dante Barja
Chief of Electrophysiology of the Hospital Universitario Austral. Pilar, Province of Buenos Aires, Argentina

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Sildenafil improves exercise capacity in patients with chronic heart failure

To the Director

Curotto Grasiosi et al.'s work "Sildenafil improves exercise capacity in patients with chronic heart failure", (1) deserves a liminary reflection. Considering that the advance of therapeutic technology improves every day, but our patients' scope to such progresses is far from improving with the same tendency, this work reveals something valuable to us: the use of a drug at our patients' hand. Most of the people who suffer from chronic heart failure are treated in centers which are far from having advanced and complex technologies, hence the importance of this work results.

The increase of the functional capacity with an only dose of 50 mg of sildenafil, apart from offering a functional improvement, it allows us to deduce that with its application we could complement cardiovascular rehabilitation optimizing the performed exercise, achieving a better fitness that would redound in a better response of the skeletal muscle system, generally damaged and unfitted in these patients.

Sildenafil was initially designed for hypertension and coronary heart disease; however, its effectiveness was observed in erectile dysfunction.

Subsequently, its use was known in pulmonary hypertension, alone or combined, well-tolerated in most of the patients. (2) Due to its clinical effectiveness, tolerance profile and oral administration, sildenafil and tadalafil are among the first-line therapies recommended for patients with pulmonary hypertension in functional class II-III by the World Health Organization. (3)

In a controlled and randomized study during 12 weeks of treatment with sildenafil in patients with chronic heart failure and secondary pulmonary hypertension (4) Lewis et al. conclude that the inhibition of phosphodiesterase type 5 with sildenafil improves the exercise capacity and the quality of life of these patients.

Blum says that therapy with sildenafil improves the exercise capacity and the quality of life in patients with chronic heart failure, especially in those that had secondary pulmonary hypertension, it also improves the peak oxigen consumption, reduces the scope of the ventilatory equivalent for CO2, has a selective pulmonary vasodilator effect during exercise in patients with heart failure and pulmonary hypertension. Sildenafil improves endothelial dysfunction, muscle

perfusion and ventilatory efficiency; it is a potential and new indication in chronic heart failure. (5)

Guazzi et al. informed that 40 patients with chronic heart failure treated with sildenafil during 6 months improved the recovery of the heart rate (first minute of post-effort), important prognosis marker. (6)

New ways of research are opened. Sildenafil, phosphodiesterase type 5 inhibitor, with vasodilator action, reduces peripheral resistance, afterload, wall stress and myocardial oxigen consumption improving the cardiac performance. Long-term studies would evaluate the effect in heart function and morbimortality. Besides, short and long-term differences in patients with chronic heart failure, with secondary pulmonary hypertension or without it could be determined.

Dr. Roberto Luis Tortorella

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Authors' reply

We thank the interest and the appropriate observations of Dr. Roberto Luis Tortorella in relation to our work. Besides, we are pleased to hear from you that you are agreed with our conclusions. The aim of the study was to examine the effect of sildenafil, compared to placebo, over the exercise capacity in patients with chronic heart failure in functional class II-III.

Multiple variables examined during the exercise test in patients with heart failure (HF) give important clinical information. A series of researches have discovered that ventilatory efficiency and aerobic capacity are closely related to the prognosis of these patients. (1) On the other hand, aerobic capacity responds favorably to several interventions. (2)

In chronic heart failure, the attention has been centered in the skeletal muscle as a fatigue mediator and a source of excessive ventilatory stimulus which is subjectively interpreted as dyspnea. The abnormal signaling in skeletal muscles, due to stimulation by metabolic subproducts, and effective interventions to reduce peripheral stimulus could be an important concept to consider in our search to understand and treat this disease. (3) The contribution of muscular reflex over ventilation may be reduced through an improvement of endothelial function and, in that way, to improve muscle perfusion, since vasodilation mediated by nitric oxide is diminished in the skeletal muscle of patients with chronic HF in comparison with normal individuals. (4) Sildenafil increases nitric oxide availability and vasodilation due to nitric oxide in patients with HF. In studies with acute patients, sildenafil increased myocardial contractility, reduced adrenergic stimulus and left ventricular overload, improved diffusion capacity, pulmonary hemodynamics, and effectiveness of ventilation during exercise and aerobic performance. (5)

Our work consists of a small number of patients; however, its power makes it reliable. We know that this drug shows a high security profile in a wide group of patients, which added to the aforementioned, cheers us to study long-term benefits of sildenafil, as other groups of study have begun to do it, not only to evaluate the improvement of functional capacity but also for probable changes in the ventricular function and morbimortality.

We coincide with Dr. Tortorella's appreciations that the use of sildenafil is at every patients' hand and could complement the work of cardiovascular rehabilitation.

Dr. Jorge Curotto Grasiosi,
Dr. Antonio Paragano[MTSAC]

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The role of natriuretic peptides in renovascular hypertension and its correlation with the evolution of myocardial hypertrophy

To the Director

Natriuretic peptides, polypeptide hormones (atrial natriuretic peptide [ANP] and B natriuretic peptide [BNP] included in the natriuretic polypeptide system in the myocardium, taking part of the "endocrine myocardium", have an important role in cardiovascular

homeostasis. Both peptides are markers of myocardial differentiation and their expression is strongly regulated during the embrionary development of the heart. After birth, their expression may be increased in heart failure (HF) and in left ventricular hypertrophy (LVH). This system acts as a counterregulatory mechanism of the myocardial hypertrophy response; their inappropriate response favors LVH and, in the long-term, left ventricular dilatation and onset of HF. (1, 2)

Based on the experimental model, 1-kidney 1-clip Goldblatt model, Cerrudo et al. (3) evaluated secretion profiles of ANP and BNP in an evolutionary and differential way during acute and chronic periods of the development of LVH. Authors show the steps in the evolution of cardiac hypertrophy and evaluate the sequential and differential expression of both peptides during the development of the myocardial response considering the hemodynamic overload which imposes the development of renovascular hypertension, that is, during the development of LVH and, in some way, they establish a physiopathological correlation between the expression of these peptides and the evolutionary process of the development of LVH.

In the conclusion, authors say that the expression of these peptides would respond in a differential way, increasing prematurely BNP and belatedly ANP. This sequence would allow us "to suppose" that BNP would be an early marker for future development of LVH and that ANP would be generated lately, but with a greater correlation with the development and severity of LVH.

As a cardiologist, I have to adapt these results to clinical medicine. The prevalence of LVH in hypertensive patients ranges between 15% and 20%; its development depends on several factors. Not all patients develop LVH at the same time and with the same degree of severity or evolution time of the disease and its onset changes radically the patient's prognosis and the present methods of diagnosis are late. Therefore, as an example, if we find 5 hypertensive patients with similar clinical characteristics, we may say that only one patient will develop LVH and, as a consequence, he will modify his prognosis; the early identification of this patient would be useful. The use of these peptides as early risk markers in the development of LVH would be a useful tool in this population, modifying our therapeutic behavior. It is desirable the fact that the continuous development of this research line performed by Cerrudo et al. allow us to find these early markers of target organ damage in HTN. (4)

Sadly, authors' data were not obtained in plasma. Future studies, which evaluate the behavior of these peptides in plasma during the different stages of the model development, may constitute a logical continuation of the researchers' line.

Finally, the analysis of this basic research work and its theoretical extrapolation to clinical medicine reinforces the vital importance that "bidirectional" communication has between basic and clinical researchers in medicine.

Dr. Mónica Díaz[MTSAC]

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Authors' reply

In the first place, we want to thank Dr. Mónica Díaz for her special attention to our work. For us, the suggestions and concepts offered in her letter are very important.

The extrapolation of the results found through basic research, which was done in experimental animals versus human beings, is a difficult matter to assert and of eternal discussion. The events that take place in mammals, which register biological parameters similar to those in human beings, have a high and significant probability of being repeated.

Another topic to consider is that the experimental animal allows the researcher to obtain more precise data that the ones obtained by the clinical researcher. That is why, he has to explore in blood, urine and other humor samples in which substances are modified by several circumstances (metabolism, etc.).

In our work, we have directly registered the evolution of the production of natriuretic peptides by cardiomyocites in cardiac cavities. This allowed us to find more easily a correlation with myocardial hypertrophia and with indexes of heart function. Plasma concentration of natriuretic peptides is mainly a sample of their secretion and not a sample of their synthesis. Secretion is related to their synthesis and secretory stimuli. Once the peptidic hormone is secreted, its plasma concentration will depend on other factors, such as catabolism, renal elimination, and extracardiac production (although it is disposable in normal conditions), which conditions its bioavailavility. Due to that, synthesis, secretion and plasma availability do not always go in parallel. In our case, the first contribution for physiopathological knowledge of myocardial hypertrophy was to study in situ peptide production. We have advanced the study with dosage of ANP and BNP plasma concentration in these experimental models and although a same

tendency to the one registered with synthesis is observed, results are not so clear and significant, that is why the problem is still studied.

Carolina S.Cerrudo, Belisario E. Fernández

Prognostic value in the serological response to *Helicobacter pylori* in the long-term outcomes of acute coronary syndrome

To the Director

Medical pathologies of chronic development as atherosclerosis used to hide one or several ties with infectious noxas in their origin or in the course of their evolution.

This association is not a hazardous fact. Cells involved in those processes used to be the same in any disease. In this way, chronic hepatitis, conjunctive tissue pathologies, and affections, which are expressed through hormonal modifications and even cancer of any kind, have in common the active participation of structures involved in immunity. It is curious that nature gives, to these cells, a great part of the inflammatory processes which, as a last resort, are inherent to "chronicity" of any medical pathology.

These biological phenomena may be gathered with a simple blood collection with the aim of examining the antibody titration generated by the organism in response to an alleged infectological aggression.

In this way, immunoglobulin concentration, which indicates a contact in the course of life with a particular bacterium, is turned into a testimony of a possible etiogenic or pathogenic tie or even in a mere finding with no relationship with the studied pathology, argument supported by several colleagues until now.

During the nineties, we worked arduously in this topic. (1-5) Controversy reached international clinical trials which were methodologically questionable. We should accept the fact that evidences found by these trials did not give a reasonable association between infection and atherosclerosis in particular

Macín et al.'s work (6), which was published in the *Journal* that you edit, justifies such scientific question.

A phenomenon indicating high titration of a condition such as *Helicobacter pylori* is separated from other biological phenomena to indicate a risk of undesirable vascular events against those individuals that do not have them.

The work would have had more merit if authors would carried out a pharmacological intervention to eradicate the infection in the same way that is carried out today with disorders caused by the same germ in the digestive tube.

This is simply a speculation but, concomitantly, it is also a challenge.

After working 15 years in this area, we may recognize the results of our colleagues from Corrientes.

Such process has a biological echo in vascular structures which modifies its behavior and facilitates complications that may arise.

Results from findings in Dr. Macín's group indicate that to the present day, the hypothesis which says that an infectious noxa could be associated with such chronic process could not be rejected.

Drs. Enrique Gurfinkel[MTSAC], Gerardo Bozovich, Branco Mautner[MTSAC]

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Authors' reply

We thank the interest and comments from Drs. Gurfinkel, Bozovich and Mautner about our article "Prognostic value in the serological response to *Helicobacter pylori* in the long-term outcomes of acute coronary syndrome" that allow us to complete some ideas.

During the last fifteen years, many observations have linked the presence of Helicobacter pylori with coronary disease through inflammation, platelet aggregation and thrombosis. (1) Although the results are contradictory, *H. pylori* is associated with a severe gastric disease, through a stimulation of the immune system, as it happens in most of the chronic inflammatory diseases. There is a profound interaction among different pathogens and a variety of host characteristics, such as susceptibility to infection, magnitude of the inflammatory response and predisposition to develop an autoimmune response. (1, 2) Several studies have shown that *H.pylori* strains increase the risk of myocardial infarction when they are compared with healthy individuals (3) and a recent meta-analysis revealed that the infection suffered by these strains may be considered a marker of vascular damage. (4) Over the base of these considerations, the hypothesis of cross-reactivity between *H. pylori* antibodies and endothelial cells, which in presence of other cardiovascular risk factors could contribute to the initiation and growth of atherosclerotic plaques, has been developed. (4) Taking into account that

this pathogen may be eradicated by treatment with specific antibiotics, this concept has clinical relevance and it establishes the theoretical precept that the elimination of *H. pylori*, as a contributory measure to reduce the atherosclerotic disease, may contribute to stop its progression and improve the evolution of acute coronary syndrome. (2, 3)

Some *H. pylori* strains are joined with Von Willebrand factor and they interact with glycoprotein IIb to induce platelet aggregation in human beings as a contributory mechanism. (1)

As Drs. Gurfinkel, Bozovich and Mautner discuss, the work would have had more merit if a pharmacological intervention had taken place to eradicate the infection. The work was carried out to establish the relationship between serological response to *H. pylori* and events and to identify the best cut-off point of antibody titer in a non-selected population of patients with acute coronary syndrome, in order to plan an intervention. However, in our country not all treatment projects may be carried out due to lack of resources.

The future challenge is to gain more knowledge in this field, evaluate the pharmacological response in this group of patients with high immunoglobulin antibody titers and, in this way, use this information for the clinical practice.

Drs. Stella M. Macín, Eduardo R. Perna

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Use of aspirin in the public primary care level. Experience of the Remediar Program, Argentina

To the Director

In general, scientific evidences allowed us, in the field of cardiovascular and cerebrovascular prevention, to improve recommendations about detection and treatment of risk factors and to reject other promissory interventions as antioxidants, vitamins, hormone replacement therapy, etc.

The first measure should be the adoption of healthy habits, since they are pillars of vascular prevention, as the abolition of tobacco (even the passive smoker), an appropriate healthy diet, weight control and appropriate and regulated physical activity. (1) There is increasing interest in the need to *stratify* (guides) patients according to risk level and to define the *intensity* of the intervention with individuals' *probability* to suffer from cardiovascular or cerebrovascular events. (2)

With data from Framingham heart study, a score, which allows us to evaluate the cardiovascular risk in individuals, was created. This evaluation has limitations (according to races and ethnic groups), but this study has a great spreading and application. (3)

Bernztein and Drake's study (4) states that aspirin would reduce 25% of events and the study is indicated when cardiovascular risk (CVR) at 10 years is above 10%. The Remediar program provides aspirin to patients with no medical coverage in the public primary care level. (5)

The aim of this study was to analyze the use of aspirin and estimate its effectiveness, with the expectation of reducing morbimortality due to cardiovascular disease (CVD). Between March 2005 and February 2006, 15001041 prescriptions were analyzed; there were 225411 aspirin prescriptions, with a frequency of 1.5%. (5)

The distribution of the use of aspirin according to age was 12.8% in patients under 16 years of age and in patients over 50 years of age, the diagnoses were: hypertension 60.1%, other cardiac diseases 8%, diabetes 7.4%, pain 6.5%, heart failure 5.8%, ischemic heart disease 4.5%, cerebrovascular disease 0.4%.

From the analysis arises an *overprescription* of aspirin in patients under 16 years of age (risk of Reye's syndrome and, besides, we must be cautious in the use of aspirin in regions with endemic infectious diseases, as dengue).

On the other hand, with the prescription of 12.8% of aspirin in patients under 16 years of age, 6.8% due to pain and 60.1% in hypertension, these three markers are 79.7%, that is 80% of indications were in primary prevention and only 4.8% in ischemic heart disease.

The importance of the work lies in that it is the first Latin American population study in the use of aspirin in the prevention of CVD. Its great limitation is the lack of persistence in treatments which has been low to obtain conclusions.

Comment: ASA was introduced in the clinical practice in 1890 to treat a great variety of inflammatory processes; its antiplatelet activity was recognized after 80 years. Aspirin in low doses (75-162 mg) is beneficial for several patients that already have occlusive vascular disease. In primary prevention, with no history of disease, the value of aspirin is clearly "uncertain".

Dr. Eulalio Bereziuk[MTSAC]

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Authors' reply

The letter from Dr. Bereziuk recovers the information and discussion of our work "Use of aspirin in the public primary care level. Experience of the Remediar Program, Argentina". As regards the statement that in primary prevention, with no history of occlusive vascular disease, the value of aspirin is clearly "uncertain" I may say that several systematic revisions and meta-analysis show that the treatment with aspirin in low doses during the whole life would be very effective in primary and secondary prevention of the cardiovascular disease. The last meta-analysis, (1) based on patients' data, also mentioned by Dr. Bereziuk, shows that although greater effects are produced in secondary prevention, there was a relative reduction of 12% of serious vascular events in primary prevention (aspirin, 0.51% vs. 0.57% control per year; p = 0.0001 [RR 0.88 CI 95% 0.82-0.94]), with a small absolute reduction (only 0.07% per year). This difference was similar in those patients with different risk of coronary disease (from 2.5% to more than 10% after 5 years) in men and women. In primary prevention, aspirin reduced 18% the relative risk of greater coronary events (0.34% per year; RR 0.82 [CI 95% 0.75-0.90]; p < 0.0001), but with a small absolute reduction. This was at the expense of the reduction of non-fatal acute myocardial infarction, with no clear impact on coronary mortality; there was no significant net effect in cerebrovascular accident. In order to establish the benefit- risk relationship of aspirin in the primary prevention with more certainty, we have to wait for the results of future researches.

We thank the statement that it is the first Latin American population study in the use of aspirin in the prevention of cardiovascular disease. But we do not agree with the fact that "the greater limitation in the study is the lack of persistence in treatments, which has been low to obtain conclusions". Such lack of persistence, with lack of duty of an annual minimum of effective treatments, is one of the main conclusions of this work. If we want to improve health, it is necessary to provide medication and implement actions such as continuous medical education, formulation, development, implementation and spreading of clinical practice guidelines based on evidence, adequacy of the supply at health centers in different jurisdictions, according to population needs, and integration of information systems related to diagnoses and prescriptions. Likewise, the use of the Program database would be convenient to study the way in which diagnoses and prescriptions are performed throughout the country. In that way, the Remediar program would increase effectiveness.

Dr. Ricardo Bernztein, Lic. Ignacio Drake

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Terminological standardization in cardiology

To the Director

I have read with great interest Yurima de la Rosa et al.'s article (1) and I would like to express certain worry as regards the abundance of anglicisms in oral and written production among Argentinian doctors, phenomenon that is shared with Spanish-speaking colleagues.

The same concern was expressed by Cruz Fernández in the presentation of Thesaurus of the Spanish Society of Cardiology. (2) We may not ignore that most of the scientific works are published in English and in several occasions it is very hard to find an appropriate term in our language. However, there are lots of words in English that have their translation in Spanish and which, nevertheless, are ignored and replaced by anglicisms. Botella de Maglia (3) gave several examples, but I would like to mention some terms that are frequently used in Argentine works:

1. Randomize, and its variants, instead of randomly assign. (4)
2. *Versus*, a Latin word which means towards and that in English is used to compare a thing with another. (2)
3. Endpoint which in the context of clinical trials is synonym of variable outcome and it has its equivalent in Spanish: assessment variable, assessment criterion. (5)

The list is really long and coincides with the concern of authors and doctors who are devoted to scientific translation or simply with the concern of those professionals who enjoy the reading of an excellent scientific article written in Spanish. The fact that, Argentine scientific societies in general, and

the Argentine Society of Cardiology in particular will try to reach a consensus on a terminology in Spanish to avoid falling into anglicisms and false friends, which are so frequent in local productions, would be enriching. No doubt, the publication of this article in the *Argentine Journal of Cardiology* indicates that this topic is interesting and opens several doors to future discussions.

Dra. Rita B. Tepper

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