

Glyburide for prevention of sudden cardiac death

To the Editor

Diabetes mellitus (DM) is considered a risk factor for cardiovascular disease, as there is a clear association between both conditions. A specific electric vulnerability has been suggested in these patients. (1) In an multivariate analysis, Morahem and Mazem found that DM was associated with greater risk of ventricular fibrillation (VF) independent of heart failure or coronary artery disease. (2) Glyburide, a second-generation sulfonylurea used in type 2 DM, has antiarrhythmic effects determined by the selective blockade of cardiomyocyte ATP-dependent potassium (KATP) channels.

Under physiological conditions, these channels are closed and do not contribute to repolarization of the cardiac action potential. However, ischemia decreases ATP levels and induces potassium efflux due to opening of KATP channels. Thus, action potential duration is shorter and the cells remain partially depolarized due to increased extracellular potassium concentrations. These elements, and the fact that ischemia is limited to an area of cardiac tissue increase the spatial heterogeneity of cardiac fibers and shorten the refractory period, predisposing to the development of reentrant arrhythmias, including VF.

Therefore, the ability of glyburide to block KATP channels has encouraged several studies about the possible antiarrhythmic effects of this drug. Lomuscui et al. demonstrated a significant reduction in the incidence of VF in non-insulin dependent diabetic patients with acute myocardial infarction. (3) Aronson et al. evaluated diabetic patients with heart failure using 24-hour Holter monitoring and found a reduction in the incidence of ventricular arrhythmias in patients receiving glyburide compared to those treated with other hypoglycemic drugs. (4) In 15 Langendorff-perfused human hearts explanted from patients with dilated cardiomyopathy, Farid et al. observed that KATP channel blockade by glyburide promoted spontaneous defibrillation by attenuating the ischemia-dependent spatiotemporal heterogeneity of refractoriness during early VF. (5)

These investigations demonstrate that the effectiveness of glyburide in DM complicated with coronary artery disease exceeds the benefits derived from endocrine control. The purpose of this letter is to raise awareness on the importance of conducting studies with large samples to definitely demonstrate the advantages of these findings.

Dr. Raimundo Carmona Puerta¹,

Dr. Yaniel Castro Torres², Dr. Zoila Armada Esmore²

¹Cardiocentro de Santa Clara "Ernesto Che Guevara", Cuba

²Universidad de Ciencias Médicas de Villa Clara

"Serafin Ruiz de Zárate Ruiz"

e-mail: raimundo@cardiovc.sld.cu

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Analysis and Dispersion of QT, JT and Tpeak-Tend Intervals in Elite Female Water Polo Players

To the Editor

We have read with great interest the article reported by Dr. Raimundo Carmona Puerta et al. (1) on the analysis and dispersion of QT, JT and Tpeak-Tend (Tp-Te) intervals in elite female water polo players.

The incidence of sudden death in athletes is low; however, the medical and social impact is high. Therefore, our efforts should focus on identifying the population at potential risk. Undoubtedly, this represents a great challenge and implies an adequate assessment of the athlete and a thorough evaluation plan (2)

In the absence of structural heart disease as hypertrophic cardiomyopathy or arrhythmogenic right ventricular dysplasia, electrical abnormalities play a key role in the development of malignant ventricular arrhythmias and risk of sudden death (SD) (3)

The QT interval classically represents ventricular repolarization and its prolongation or heterogeneity is recognized as an important risk marker. Long-QT syndrome is responsible for the development of complex ventricular arrhythmias and SD both in athletes and the normal population with a variable prevalence, ranging from 1 every 2500 to 10000 inhabitants. (4-6)

A small number of athletes (approximately 0.4%) present abnormal QT interval, probably due to the effect of delayed repolarization as a result of increased left ventricular mass. (3, 4) In addition, sinus bradycardia, first-degree AV block, type I second-degree AV block or incomplete right bundle branch block are common findings. (2) These variants are considered normal and it should be noted that Bazett's formula is not very useful in subjects with very slow heart rates. (4, 5)

The significance of QT-interval dispersion and changes in Tp-Te intervals in athletes is still unclear as there is no sufficient information derived from studies on this topic.

However, the study by Dr. Carmona Puerta (1) undoubtedly provides novel information that may contribute to identify populations at greater risk in the future.

Dr. César R. Cáceres Monié, Dr. José F. Estepo^{MTSAC}

Hospital de Clínicas "José de San Martín", UBA
vivolberg@gmail.com

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Authors' response

We were pleased to read the letter by Dr. Cáceres Monié and Dr. Estepo about how complex it is to predict the risk of arrhythmias in elite athletes. Although the incidence of sudden death in athletes is very low, mortality rate is 2.8 times greater than that of non-athletes of the same age. (1) Moreover, the social connotation is significant. In our opinion, the risk of electric disease is the most difficult to determine as structural diseases are easier to detect and can be confirmed by image testing. The electric abnormalities are dynamic and constitute a perfect arrhythmogenic substrate. In most cases the fatal event is the first manifestation of these abnormalities. Occasionally, they are caused by an electric pattern with discrete abnormalities which are not understood yet. Scherr et al. (2) evaluated 198 healthy men before and at 0 h, 24 h and 72 h after participating in a marathon and found prolonged QTc and Tpeak-Tend intervals that were coincident with significant hypomagnesaemia and hypokalemia. Proinflammatory interleukin-6 was also increased. However, a significant association could not be demonstrated. This investigation demonstrated that abnormalities of ventricular repolarization after exercise are greater than those seen at baseline. Moreover, extracardiac anomalies

might produce extreme modifications in cardiac electrophysiology. Basavarajaiah et al. (3) followed-up four elite athletes with QTc values (derived using Bazett's formula) between 460 to 492 ms during three years. Athletes were encouraged to continue with active exercise practice. These athletes did not present adverse events during the follow-up period. In an editorial about this paper, Dr. Moss (4) considered that electrocardiographic normal standards, especially those for ventricular repolarization, do not exist for elite, highly trained, endurance athletes and need to be developed in future studies.

We consider that this type of studies is still in an initial stage as the electrophysiological limits (expressed in the electrocardiogram) between normality and abnormality in elite athletes are hardly clear yet. Our study was not designed to discern the real meaning of the observations, but we found prolonged ventricular repolarization in female water polo players. We know that the current knowledge can hardly explain the cases of sudden death of undetermined cause reported by some series (29% in Australia). (5) Is it possible that the undetermined cause is the lethal substrate that we still do not understand? Can this substrate, in combination with modifications occurring during or after the competition, be the final thrust provoking the mortal event? These are some of the questions-hypotheses to focus on in the future.

Dr. Raimundo Carmona Puerta¹,

Dra. Magda Alina Rabassa López-Callejas²,

Dra. Elibet Chávez González¹

¹ Servicio de Electrofisiología Cardíaca Clínica y Estimulación del Cardíaco "Ernesto Che Guevara". Santa Clara, Villa Clara, Cuba

² Centro Provincial de Medicina del Deporte. Villa Clara, Cuba

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Current trends of interventional studies in Argentina

To the Editor

Reading the detailed analysis made by Dr. Borracci in his article "Clinical Trials in Cardiovascular Pharmacology in Argentina Between 2006 and 2010" draws the attention on the current development of national research on interventional cardiology. Concentration is the common denominator emerging

from all the described instances: concentration of a few centers (mostly in the private sector); concentration of a few pharmaceutical laboratories sponsoring international trials; and concentration of clinical trial monitoring and follow-up in a few Bioethics Committees. In line with other countries (even those considered to be developed), independent multicenter research is becoming more uncommon in our setting. These initiatives used to have objectives arising from academic interests with different points of view responding to the specific needs of the local professional community. Unfortunately, nowadays, research developed by the “industry” has surpassed them in number and financial power. Concerning concentration of clinical trial approval and monitoring in a few Bioethics Committees, I shall only mention that our Argentine Society of Cardiology has a prestigious Bioethics Committee that fulfills all the necessary regulatory requirements; thus, institutions and multicenter groups should turn to this committee for the revision and monitoring of local and foreign clinical trials.

Dr. Claudio C. Higa

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Optimal Medical Treatment of Multivessel Stable Coronary Disease: The Controversy Continues

To the Editor

I appreciate the interesting comments on my letter made by Dr. Roberto Battellini (1) and Dr. Jorge Belardi (2) and I agree with most of their opinions. However, the topic is controversial and I would like to put forward some considerations regarding the following statements.

Firstly, the author states that “in general, surgeons receive patients who have already been submitted to optimal medical treatment (OMT); may we say the same about patients undergoing angioplasty?” (1) In this sense, the EUROASPIRE III trial detected that in the subgroup of patients with ischemic heart disease (which included patients with history of surgery and/or angioplasty, among others), optimal control of risk factors as hypertension, hypercholesterolemia and diabetes mellitus was respectively achieved only in 50%, 49% and 35% of the patients. (4) Therefore, it seems that in the “real” world most patients undergo revascularization strategies (angioplasty and surgery) with no subsequent OMT, particularly in medium and long-term periods.

In the second place they state that “It would be medically inadequate to treat patients with multivessel disease (MVD) and left main coronary

artery (LMCA) disease, with evocative tests revealing high risk ischemia, only with MT, without indicating a revascularization strategy although they are clinically stable.” (2) Regarding this statement, the last Guidelines on myocardial revascularization developed by The Task Force on Myocardial Revascularization of the European Society of Cardiology indicated that most meta-analyses reported no mortality benefit, increased nonfatal periprocedural myocardial infarction, and reduced need for repeat revascularization with percutaneous coronary intervention compared to OMT. Moreover, this guideline points out that in patients with stable angina and no limiting symptoms with OMT, revascularization has a class III recommendation. (5) Therefore, in clinically stable patients with MVD and LMCA disease (a subgroup of patients not included in the COURAGE study), (6) the Heart Team would not consider the indication of OMT alone as an inadequate medical decision, especially for subjects who do not have an optimal control of their cardiovascular risk factors.

Thirdly, “all current OMT potentialities were used in the COURAGE study”. (2) In this respect, I would like to point out that three biochemical variables are not enough to demonstrate that all OMT potentialities have been used, as this type of treatment also includes factors related to lifestyle changes, such as physical activity, healthy diet, smoking cessation and body weight control, among others. For example, the prevalence of sedentary life and smoking reported by the COURAGE trial after one year follow-up was 57% and 20%, respectively, while the body mass index (BMI) was in the overweight range and even slightly increased from 28.9 (at baseline) to 29 (at one year). (6) Cameron et al. have recently reported the number of deaths that could be prevented in the United States if the prevalence of sedentary life, smoking habits and overweight, among other factors, was reduced to 0%. (7)

Finally, I remain at the disposal of the Argentine Journal of Cardiology to continue debating in the future -as agonist- on such controversial topics as “OMT as the only therapeutic option in stable MVD” and the Heart Team.

Dr. Alberto Morales Salinas

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Advanced Atherosclerotic Lesions in Patients with Apparently Healthy Hearts

To the Editor

I have read with great interest the article published by Duronto et al. (1) about the presence of neovascularization in advanced atherosclerotic plaques from apparently healthy hearts of brain dead patients due to stroke or traumatic brain injury, who were excluded for heart transplantation but were suitable for providing valves for homograft transplantation. Hearts from patients with diabetes, history of myocardial infarction or symptomatic atherosclerotic disease and any other chronic disease were excluded from the study.

The authors' findings become more relevant due to the thorough methodology used, including "state of the art" immunohistochemical techniques as well as the most refreshing (yet unfortunately uncommon) purpose of evaluating high-risk plaques in patients dying from non-cardiac causes.

There is ample evidence supporting the concept that about two thirds of acute coronary thrombotic events originate from angiographically non significant lesions. Actually, in about 50% of previously asymptomatic subjects with a history of normal function tests, myocardial infarction or sudden death are the first manifestations of coronary artery disease.

Despite the great progress in diagnostic methods, the natural history of high-risk plaques is still almost unknown. Thin fibrous cap atheroma (TFCA) is a type of lesion of considerable prevalence and responsible for 60% acute coronary thrombosis. (2) Although most of TFCAs have similar phenotypic characteristics, a small number of them present plaque rupture and most of them do not elicit clinical events. Effectively, not only the direct association between plaque accident and clinical association is unpredictable but also the chronology between both events, as reported in at least 50% of patients with ST-segment elevation myocardial infarction in whom coronary thrombi have been developing for days or weeks. (3) Rioufol et al. were the first to report the prevalence of plaque rupture in patients with acute coronary syndrome using intravascular ultrasound (IVUS) of the three coronary arteries, with an average of 2.1 ruptured plaques per patient. Eighty percent of these patients had ruptured plaques outside the culprit lesion and nearly 70% of ruptured plaques were in non-culprit

arteries. (4) In a more recent publication, use of IVUS-Virtual Histology demonstrated plaque rupture in 31% of patients with chronic stable angina. (5)

Other histopathological studies had already demonstrated advanced lesions in patients dying from non-cardiac causes. Arbustini et al. evaluated 132 hearts from patients who died during hospitalization due to non-cardiac causes and found coronary atherosclerotic lesions in 110 hearts, critical stenosis or occlusion in 42% of the cases and thrombosis in 10 vessels of 9 hearts. Plaque rupture without thrombosis was also reported in 5 hearts. (6) More recently, Sato et al. found coronary artery thrombosis in 10% of patients dying from non-cardiac causes. (7)

The important progress in invasive diagnostic tools as IVUS, virtual histology, optical coherence tomography, thermography, palpography and angiography has allowed identifying the high prevalence of advanced atherosclerotic lesions even in non-culprit vessels. (8, 9)

In the article published in this Journal, Duronto et al. reported the presence of 143 advanced lesions in 121 apparently healthy hearts, 50 of which had angiogenesis. It is noteworthy, though in line with previous findings, that most underlying lesions were non-obstructive (median luminal obstruction 25% and 40-50% in plaques with angiogenesis). As with any histopathological study, the prevalence of atherosclerotic lesions might be underestimated, since the coronary arteries were evaluated with cross sections every 3 mm and it has been described that a lesion may be as small as a few hundred microns in length. In effect, this statement does not limit the findings by Duronto et al.; on the contrary, they are reinforced by confirming not only the great prevalence of high-risk plaques in subjects without history of coronary artery disease but also how unpredictable the natural history of the vulnerable plaque is.

Dr. Gastón A. Rodríguez-Granillo^{MTSAC}

Sanatorio Otamendi, Buenos Aires
Clínica La Sagrada Familia, Buenos Aires

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Advanced Atherosclerotic Lesions in Patients with Apparently Healthy Hearts

To the Editor

The article of González et al (1) concludes that sudden death in the “indeterminate form” (sic) of Chagas disease is infrequent.

I do not agree with the denomination and the derived conclusions, but also with the vision of Chagas disease and the interpretation of statistical results, which lead to a different medical attitude towards patients and diseases.

The authors must know that I undertake writing these lines with the same loyalty for which they thank me at the end of their article, an acknowledgment I am also grateful for.

This letter can only express in general terms my disagreement with the authors' conclusions. Therefore I commit myself before them and the readers to express my controversy in a future full article.

The first discrepancy is regarding the “indeterminate form”. The 2010 Argentine Federation of Cardiology (FAC) International Consensus on the Indeterminate Form postulated the elimination of this denomination, a proposal confirmed by the Argentine Society of Cardiology (SAC) Chagas Disease Council together with other Latin American Societies of Cardiology. (2) The authors took into consideration the Guidelines of the Brazilian Society of Cardiology (3) which, though written after the International Consensus, preserved this denomination. It would have been commendable to discuss this discrepancy, which is not semantic and besides, completely modifies their previous position.

Considering the official numbers in our country, 1600000 persons are parasitized by *T. cruzi*. Seventy percent of them would present the erroneously called indeterminate form, which according to the cited 2010 Consensus should be called chronic phase without cardiomyopathy manifestations (evidenced by ECG and X rays). There would be 1120000 affected persons in this stage.

Based on the analysis of 15 studies, the authors conclude that mortality among asymptomatic patients with normal ECG would be 0.92%, and thus they claim that sudden death would be infrequent.

Ninety two percent of 1120000 patients correspond to 10304 patients that will die.

Do not 10000 deaths, though statistically infrequent, deserve employing all the necessary means for the early detection of disorders, such as endothelial dysfunction and dysautonomy (4) as postulated by the cited Consensus? (2) It is evident, that a normal ECG was unable to predict mortality in these patients. The authors claim not “alarming them (these patients) unnecessarily about their condition or indicating sophisticated and expensive studies”.

This reasoning is erroneous because it reverses the burden of proof. It tries to reassure the other 1110000 patients who will not die, in whom the “sophisticated” studies will be normal and detect those in whom adequate measures can be adopted.

Following this line of thought, the authors should advocate against the systematic serologic test on the annually 700000 pregnant women in Argentina, given that only 2000 infants will be born with congenital Chagas (0.28%). Or to avoid wasting millions in performing cholesterol tests in the healthy population as the “annual infarct risk was of 9 cases every 10000 persons per year and its mortality reached 9%”.(5)

Dr. Edgardo Schapachnik

Tel. 4361-2505 / Cel. 15-4927-5421 / Fax 4361-2505
e-mail: edgardoschapachnik@grupoakros.com.ar

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To the Editor

The text of Gonzalez et al. Published in RAC (1) is full of errors which motivate these comments.

I will proceed to analyze only one of the references on which he bases his conclusions. Pinto Dias (reference 23) studies the relationship in 387 electrocardiographically assessed patients, from a total of 1088

Chagasic patients, between 1949 and 1967. (2)

He divides the assessed patients into three groups: from 0-29, from 30-49 and over 50 years of age.

In the first group 38 out of 179 (21.8%), in the second group 55 out of 138 (39.8%) and in the third group 39 out of 70 (55.7%) patients died. Between the first and the second group 24% of the assessed patients with an average age < 50 years died and those with an average age of 60 years had an additional 10% death rate. Read carefully: 34% of the assessed patients had already died and among the 254 survivors 40% had pathologic ECG recordings.

With reference to parasitized subjects with a normal ECG, Pinto Dias sustains that in the 387 assessed patients, 133 (34.3%) died and that **37 of them had a normal ECG** (27.8% of the dead patients and not 19.2% as sustained by Milei). Likewise, when analyzing ECG evolution, Pinto Dias states that from 105 subjects (100% of assessed patients) 10 years after their death, **33 (31.5%) had a normal ECG**. In the 127 subjects (100% of assessed patients) who had 5-9 years recordings before dying **28 (22.1%) had a normal ECG**. In the 334 subjects (100% of assessed patients) who had recordings between 0 and 4 years before dying **20 (6%) had a normal ECG**. These results which give 81 cases with normal ECG do not support the authors' statement claiming that from 566 dead subjects, only 14% might be considered indeterminate at study initiation. In fact, after 10 years or more there were 31.5% subjects with normal ECG.

What is the all comment made in the document under discussion?

PintoDias et al. (reference 23) found very high mortality in patients with normal ECG (19.2%) across the study, but the causes of death were not reported. Of the 566 patients who died during the study, only 81 (14%) had a normal ECG at study initiation (bold writing corresponds to my remarks), therefore, most of the dead subjects did not correspond to the indeterminate form of the disease." Gonzalez aims to disqualify the accurate data reported by Pinto Diaz by assuming that at study initiation there were a few patients with the indeterminate form of Chagas disease and that causes of death were not reported.

An innocent question: what other pathology might have caused the death of 21.7% of subjects with an average age of 30 years? Pinto Diaz gives a sign when he reports that all deaths occurring in Bambui between 1963 and 1966 had the following age distribution: 10% in those between 10 and 30 years, 32% in those between 30 and 50 years and 58% in those over 50 years. This is a similar distribution to that observed for the death of subjects infected with *T. cruzi*

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Authors' response

We answer the comments of Dr. Schapachnik y Yanovsky to our systematic review recently published in the RAC (1). The first of them expresses that "... from the analysis of 15 studies, the authors conclude that mortality among asymptomatic patients with normal ECG would be 0.92%, and thus they claim that sudden death would be infrequent.

Ninety two percent of 1120000 patients correspond to 10304 patients that will die..." He then suggests that "...though statistically infrequent, these patients deserve employing all the necessary means (numerous sophisticated and expensive studies, difficult to perform in endemic areas) for the early detection of disorders, such as endothelial dysfunction and dysautonomy".

Absolutely not, because there was no level of evidence A for these dysfunctions in the Consensus. That is, there are no firm evidences, stemming from randomized clinical studies or from adequately designed cohorts to reach statistically correct and biologically significant conclusions on these markers. The expert opinion consensus (evidence C) is not enough to scientifically support that a certain diagnostic procedure/treatment is beneficial, useful and effective for patients with the indeterminate or chronic form without demonstrable pathology.

Even more, in a recent article, Marin Neto (2) states that theirs is the first therapeutic intervention study that will be made to reduce or revert microvascular myocardial ischemic alterations in patients with chronic Chagas disease. It is not advisable for a Consensus to indicate the indiscriminate study of patients without having a clear horizon of the benefits to start a therapy.

Regarding "... the authors should advocate against the systematic serologic test on the annually 700000 pregnant women in Argentina, given that only 2000 infants will be born with congenital Chagas (0.28%)...", this comment is not sustainable, as in this case there is ample evidence of treatment effectiveness.

A flagrant mistake of our colleague is when he suggests that according to our ideas we should "avoid wasting millions in performing cholesterol tests in the healthy population as the "annual infarct risk was of 9 cases every 10000 persons per year and its mortality reached 9%". These determinations must be performed with scientific criterion, not through "experience", since a multicentric study on 20913 patients with AMI and 95407 healthy controls, recently published in *The Lancet*, (3) demonstrated with genetic

studies that the increase in HDL was not in itself a condition leading to reduce cardiovascular risk. It is worth mentioning that this marker does not uniformly translate in a reduction in the number of AMI. Diagnostic and therapeutic strategies will then be in accordance with these studies.

On the contrary, neither the endothelial, autonomic or asymptomatic diastolic dysfunctions in the indeterminate form have merited studies on their clinical implications, and much less on the efficacy of their theoretical treatments.

Concerning the Dr. Yanovsky's letter, he curiously ends it with "... An innocent question: what other pathology might have caused the death of 21.7% of subjects with an average age of 30 years? Pinto Díaz gives a sign when he reports that all deaths occurring in Bambuí between 1963 and 1966 had the following age distribution: 10% in those between 10 and 30 years, 32% in those between 30 and 50 years and 58% in those over 50 years. This is a similar distribution to that observed for the death of subjects infected with *T. cruzi*", (references?)

Annoying answers-questions: Could you provide the complete autopsies of dead patients? How do you know they were all due to the indeterminate form of Chagas disease? Fifty eight percent of the patients died after 50 years of age; how many from AMI, stroke, degenerative diseases?

Let us drop the riddles and the "personal experiences"

Elimination of Chagas disease is a State matter and depends on political decision. It is the government who should summon the best brains, provide the financing and us, the physicians, scientific societies and the community (not only the Chagasic one), should actively cooperate. Otherwise, 97 years from now, in the bicentennial anniversary of its discovery, we will continue to discuss classifications without a scientific basis.

Dr. Julián González, Dr. Francisco Azzato,

Prof. Dr. José Milei ^{MTSAC}

Instituto de Investigaciones Cardiológicas
"Prof. Dr. Alberto C. Taquini"- UBA- CONICET (ININCA)

Marcelo T. de Alvear 2270. Buenos Aires

ininca@fmed.uba.ar

<http://www.fmed.uba.ar/taquini/>

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National registry of hypertension. Awareness, treatment and control of hypertension. The RENATA study

Authors answer

We thank Drs Carol Kotliar and Sebastian Obregón's observations with reference to our work in the former number of our journal (1): National Registry of Hypertension. Awareness, Treatment and Control of Hypertension. The Renata Study. In their letter they observe the strengths and weaknesses of our study. Indeed, among the strengths we claim that it is the first epidemiologic study performed in 7 cities of Argentina, with 3 arterial blood pressure measurements recorded with an automated validated instrument thus avoiding subjectivity interpretations and involuntary bias.

In their observations they point out the "lack" of an accurate arterial hypertension diagnosis (HT), as a weakness or limitation. However, as seen in Dr Martín Salazar's Editorial, HT diagnosis in epidemiologic studies is not equivalent to that performed in the clinical practice.(3) As in any population review, the purpose of the RENATA study is neither, to estimate the final HT diagnosis nor to follow-up patients with HT detection after an interview. We agree that HT detection in the daily practice is more complex, given the wide blood pressure variability; the alert phenomenon, white coat effect and its counter face: occult or concealed HT.

With reference to HT prevalence increase in the RENATA study in comparison with the REDIFA study (2001), this is confirmed in the two National Surveys of Risk Factors (ENFR) with self-reported HT. In the first ENFR (2005) the prevalence was 34.5% and in the second ENFR (2009) the prevalence was 34.8%. It is interesting to underline that as in the RENATA study, in the second ENFR there were notorious differences according to the city assessed. Thus, for example, in the RENATA study CABA (Autonomous City of Buenos Aires) had the lowest HT prevalence (28.1%) and Mendoza the highest (37.2%). These findings agree with the second ENFR (CABA: 29.3% and Mendoza: 38%) (4)

The stratification of the assessed population is mentioned as a possible weakness, observing/pointing out that 80% of the population had secondary studies. The population was randomly selected and the number of subjects in each age-group was proportional to the amount of individuals according to the 2001 census. The fact that more than 50% of the population was under 44 years of age somehow explains the completion of secondary studies. The larger proportion of subjects with primary studies was observed in the elderly population. The menopause condition in women was not considered. The BP levels were analyzed both in men and women in different age-groups, observing a significant statistical difference in the first three age-groups, which disappears after 55 years of age.

Likewise, the HT prevalence is significantly higher in young men under 25 years of age: (men: 20.6% vs. women 2.8%). Similar data were seen in Dr Ennis et al. study in 3154 medical students, where the general prevalence was 12% (men: 20% vs. women 6%).(5)

We agree that the RENATA study, in contrast to other epidemiological studies is a survey model, which

has a low-cost design, allowing us to use it as an epidemiological observation tool.

Dr. Marcos Marin
Dr. Guillermo Fabregues
Dr. Pablo D. Rodriguez