

2021 Dr. Pedro Cossio Foundation Award

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The 47th edition of the historical Annual Congress of the Argentine Society of Cardiology was held between October 14 and 16, 2021. For the second year in a row, it was entirely virtual, as almost everything that happened in the last 2 years. The presentation of the works selected to receive the Dr. Pedro Cossio Award had to be recorded and analyzed in this way by the Jury, without direct contact with the authors and without the contribution of expert commentators on the various core topics. We hope that our next Congress will be face-to-face again, as it was historically for decades. The Scientific Committee of the Congress selected 4 works as candidates to win this Award. Following the tradition initiated more than 30 years ago by Dr. Pedro Cossio Jr, we will make brief comments about them.

The following work was the winner:

Circulating Cardiac MicroRNAs as Biomarkers of Potential Diagnostic and Prognostic Value in Chagas Cardiomyopathy. A Prospective Study. Drs. Laura Antonietti, Manuela Santalla, María José Martínez, Diego Alfredo Kyle, Maximiliano de Abreu, Javier Mariani, Paola Ferrero, Carlos Tajer.

MicroRNAs (miRNAs) were discovered in 1993 and reported in the classical work of Rosalind Lee et al. (1) They are short (between 21 to 23 nucleotides) non-coding RNA molecules, which constitute an extensive family of post-transcriptional regulatory genes. They are involved in the regulation of several biological processes, such as cell differentiation, proliferation, apoptosis, and in embryonic and tissue development. They are present throughout the plant and animal kingdom and have become a subject of considerable interest and expansion in many fields of Biology and Medicine.

Briefly, inside the nucleus, the genes encoding for miRNAs are transcribed as long precursors, giving rise to the so-called primary miRNA, whose length varies by hundreds of nucleotide pairs. This precursor is cut by Drosha and Pasha ribonucleases into one or more hairpin-shaped RNA molecules, transforming it into pre-miRNAs of 60-70 nucleotides. Pre-miRNAs leave the nucleus towards the cytoplasm aided by ex-

portin-5, where the miRNAs maturation process will take place. They behave as endogenous epigenetic genes which can silence or activate genes, interfering with protein translation, and they can even affect some genes other than those from which they have been transcribed.

In the area of precision medicine, it is possible to detect circulating miRNAs that function as biomarkers capable of operating as precursors in the generation and development of cardiovascular diseases (2) and others such as cancer, diabetes, Alzheimer's disease, osteoarthritis, osteoporosis, etc. (3) They also have therapeutic implications; inclisiran is one of the examples in Cardiology, a synthetic miRNA that silences the formation of the PCSK9 protein, causing a great decrease in LDL cholesterol. (4)

This work carried out by a cooperative team from Hospital El Cruce, the Arturo Jauretche National University School of Health Sciences and the Cardiovascular Research Center "Dr. Horacio E. Cingolani" from the National University of La Plata investigated the value of circulating cardiac miRNAs for the early diagnosis of Chagas disease (CH). They prospectively included 104 participants enrolled between 2016 and 2020 and classified them into 4 groups: group 1 (G1): negative CH serology, asymptomatic and free from heart disease (healthy controls); group 2 (G2): positive CH serology and absence of cardiomyopathy; group 3 (G3): Chagas cardiomyopathy (CHCM), defined by positive serology for CH, left ventricular ejection fraction (LVEF) under 45%, and history of heart failure; group 4 (G4): ischemic-necrotic cardiomyopathy (INCM), defined by negative CH serology and documented coronary heart disease by coronary angiography or multislice computed tomography. An electrocardiogram and echocardiogram were performed, and the miRNAs were analyzed. A threshold ≥ 2 or ≤ 0.5 times of change in the overexpression or underexpression of the miRNAs found, respectively, was considered. Groups 1 and 2 had a higher proportion of women and younger age compared with groups 3 and 4. As expected, patients with INCM showed higher frequency of hypertension, diabetes, dyslipi-

demia, and smoking, and G3 patients presented more arrhythmias, especially ventricular, than the others. It was also expected that G3 and G4 patients would show increased left ventricular diastolic diameters and depressed LVEF.

The expression profile of 417 circulating miRNAs was analyzed. G1 and G2 showed low amounts of differentially expressed miRNAs and there were no significant differences between them. On the contrary, 32 in the CHCM group (G3) and 20 in the INCM group (G4) differentially expressed miRNAs were identified. When the two groups of patients with CH were compared, those with CHCM had a higher number of overexpressed and underexpressed miRNAs than those of G2. Finally, of the total miRNAs analyzed, 16 miRNAs (13 overexpressed and 3 underexpressed) were found to be differentially expressed only in CHCM patients.

Routine serological diagnosis of CH disease is based on immunofluorescence or indirect hemagglutination tests. This interesting study offers a totally different panorama, that refers not only to diagnosis but to many other aspects of the pathophysiology and prognosis of CH disease. Despite the small sample, it is original and raises questions that should promote additional research in the future. Could differentiated miRNAs in patients with CH disease but without heart disease be early markers of cardiomyopathy? Could the expression of different miRNAs serve to identify different types of cardiomyopathies? These are just two examples among many others.

For the second consecutive year, the winners of the Dr. Pedro Cossio Foundation Award investigated aspects related to Chagas disease. It is stimulating to observe the interest in advancing research on this endemic disease that currently affects more than 1 500 000 people in Argentina, many of them undiagnosed, unmonitored and untreated.

The other works were the following:

Use of Lipid-lowering Agents and Compliance with Therapeutic Goals in Patients at High Cardiovascular Risk in the Argentine Republic. Drs. Alan Rodrigo Sigal, Melisa Antonioli, Pilar López Santi, Nicolas Aquino, Ezequiel Lerech, Fernando Botto. On behalf of the Argentine Council of Cardiology Residents (CON-AREC)

The introduction of statins during the 1990s constituted a true revolution in the treatment of atherosclerotic cardiovascular disease, the most frequent cause of death in most countries of the world. For the first time, pharmacological agents capable of reducing mortality and cardiovascular events between 20% and 30%, depending on the different clinical scenarios, were discovered. It was also shown that high doses are significantly more effective than low doses. (5) However, for different reasons, adherence to treatment is poor: in the US it is only 40% a year after prescription and 30% after 5 years, especially considering the use of high doses. (6) On the other hand, in an extensive

database of 347 104 veterans, it was found that non-adherent patients suffered 30% more ischemic events than those who maintained their adherence. (7) For these reasons, it is very relevant to stimulate and optimize the correct prescription and acceptance of these treatments.

This cross-sectional multicenter study included 1000 consecutive patients older than 18 years in secondary prevention of cardiovascular events (75.6% male, mean age 68 ± 12.6 years) treated between March and August 2020 in 24 hospitals with Medical Residency of Argentina, affiliated to the Argentine Council of Cardiology Residents (CONAREC). The primary endpoints were 4: 1) To assess how many patients at high cardiovascular risk in secondary prevention receive statins or other lipid-lowering treatments and at what dosage; 2) To evaluate the reasons why they do not receive lipid-lowering pharmacological treatment or receive it but at inadequate doses (atorvastatin < 40 or 80 mg, or rosuvastatin < 20 or 40 mg); 3) To evaluate how many patients meet the LDL therapeutic goals established by the Argentine Society of Cardiology (SAC) Guideline (8), and the European Society of Cardiology (ESC) Dyslipidemia Guideline (9), and 4) To evaluate the number of patients at high cardiovascular risk who would be candidates for treatment with PCSK9 inhibitors (PCSK9i) for not meeting the goals despite the best tolerated treatment. In 80% of cases patients had hypertension, 55.6% dyslipidemia, 33.7% diabetes and 20.5% were smokers. A total of 85.9% of patients received statins, 4.8% ezetimibe, 2.4% fibrates, and 13% received no treatment. Sixty-seven percent of those receiving statins (58% of all patients) did so at high doses. The most used drug was atorvastatin, followed by rosuvastatin and simvastatin. In 509 patients, information was obtained on LDL, HDL and triglyceride levels in the last 6 months. In this subgroup, the average LDL was 94.2 mg/dL, HDL 41.7 mg/dL and triglycerides 151.4 mg/dL. A total of 30% of patients met the goals according to the SAC guideline, and 16% according to the ESC guideline, but patients who received high-dose statins reached the goals in 40.6% of cases according to SAC guidelines and 20% corresponding to ESC guidelines. The main reasons for lack or deficient medication were adverse effects (especially muscular), lack of indication by the treating physician, refusal to take the medication, fear of adverse effects, and having run out of a prescription and not requesting its renewal. Three percent of patients meeting clear criteria for receiving PCSK9i, having LDL cholesterol greater than 100 mg/dL with a maximum tolerated dose of statins in combination with ezetimibe, or with intolerance undoubtedly attributed to statins, were identified.

In conclusion, this study (sponsored by a pharmaceutical company producing PCSK9i) revealed that in Argentina (as in many other developed or underdeveloped countries around the world), slightly over half of the patients in secondary prevention receive

high intensity statins, with poor therapeutic goal achievement. In these conditions, opportunities to significantly reduce risk and cardiovascular events is lost. It is essential to make physicians aware about the available scientific evidences and their application. Healthcare systems should reduce the barriers that hinder the compliance of the goals. Patients should avoid myths such as information from spurious sources (family, friends, non-specialized press) or that produced by the “nocebo effect”, which contrary to “placebo”, appears when a person feels adverse effects only because they believe they may occur.

This is another of the extensive series of surveys performed by CONAREC revealing cardiovascular disease realities in Argentina, though as in all of them, the sample analyzed corresponds to centers with Cardiology residency, that is, moderate or high-complexity academic institutions that may not be representative of the general population. Most of the patients analyzed were in coronary care unit, and although ambulatory patients were also included, perhaps this could have affected the external validity of the results. Plasma lipid values were obtained in only half of the population. Another possible limitation is that patient recruitment was carried out during the pandemic in Argentina and worldwide, so it is possible that this might have changed the characteristics of patient access to medical treatment, influencing the results obtained.

Symptomatic Unruptured Abdominal Aortic Aneurysm: Results from Endovascular and Surgical Repair in a University Hospital of the Autonomous City of Buenos Aires. Fernando Garagoli, Norberto Fiorini, Martín Rabellino, José Chas, Alberto Domenech, Vadim Kotowicz, Rodolfo Pizarro, Ignacio Bluro.

Abdominal aortic aneurysm (AAA) is considered when its diameter is greater than 3 cm. Its prevalence is 1% in patients between 55 and 64 years and increases with age, reaching 7% for those over 70 years. It has a strong association with tobacco smoking, and most are of atherosclerotic etiology, infrarenal, and fusiform in shape. Among its 3 types of presentation, symptomatic unruptured AAA (urAAA) represents an intermediate state between asymptomatic and ruptured states regarding risk of rupture and mortality. Moreover, the long-term post-operative evolution after urAAA is also intermediate between asymptomatic AAA and ruptured AAA. (10)

According to the European Society of Vascular Surgery, urAAA must be operated on urgently, though “some suggest to reasonably postponing the procedure to allow a complete assessment of risk, optimization of the state of the patient and adaptation of the moment of surgery to the presence of the team and experienced personnel that can significantly improve the results”. (11)

Few reports in the literature analyze this particular group of patients. The present work from Hospital Italiano de Buenos Aires is a retrospective

observational study of 29 consecutive patients (20 male) recruited between May 2011 and July 2020. The inclusion criteria was the presence of infrarenal AAA with no evident rupture (urAAA) according to tomographic image, associated with abdominal, lumbar or dorsal pain, with exclusion of other causes. Among these patients, 15 underwent endovascular repair (ENDO) and 14 underwent surgery (SURG). Both groups had similar age: 75.3 vs. 74.7 years, respectively. Patients in the SURG group presented with larger aneurysm diameter (77.6 ± 17.0 vs. 62.6 ± 20.1 mm; $p=0.04$) and more hypertension (78% vs. 60%), chronic obstructive pulmonary disease (18.6% vs. 6.7%), chronic kidney disease (14.3% vs. 6.7%), coronary heart disease (42.9% vs. 13.3%), peripheral artery disease (14.3% vs. 0.0%), and heart failure (50.0% vs. 33.3%), but ENDO patients had more diabetes (20.0% vs. 7.1%) and dyslipidemia (73.3% vs. 35.7%). In-hospital mortality was 10.3% (3 patients): one death in the ENDO group and 2 in the SURG group. The causes were multiorgan failure in two cases and septic shock and prosthesis infection in the other. The most frequent postoperative complications were: acute kidney failure (15 cases), 10 in the SURG group and 5 in the ENDO group ($p=0.04$); ileus in 7 cases: 6 in the SURG group and one in the ENDO group ($p=0.02$); and minor bleeding, which was more frequent in the ENDO group: 4 cases vs. 0 in the SURG group ($p=0.02$). Length of hospital stay was lower in patients of the ENDO group (4 vs. 7.5 days; $p=0.04$). At a mean follow-up of 25 months, 2 SURG patients and one ENDO patient were lost. Long-term mortality was 6.3% per year. Three patients in the ENDO group and 4 in the SURG group died ($p=ns$). Five cases underwent a redo procedure in the ENDO group and one in the SURG group ($p=ns$). In a multivariate analysis, presurgical AAA diameter was the only independent predictor of long-term mortality (OR 1.14; 95% CI 1.01-1.31; $p=0.04$) and reinterventions (OR 1.19; 95% CI 1.01-1.41; $p=0.04$).

Regarding the choice of method for urAAA repair, international recommendations suggest that the decision on SURG or ENDO preference must be jointly taken by the patient and his physician after evaluating a series of factors, including: aneurysm size and morphology (fusiform or saccular), the anatomical feasibility for ENDO repair, patient's age and hence his/her life expectancy, surgical risk, comorbidities, hospitalization and recovery times and the experience of the treating team. The authors of the present work do not clarify the criteria to choose one procedure over the other in each patient. Moreover, the heterogeneity of the groups analyzed and the reduced number of patients in the sample do not allow drawing valid conclusions from the comparison between both groups. This study has the merit of being the first to report the outcomes of urAAA endovascular and surgical procedures in Latin America.

Cardiovascular Involvement in Patients Recovered from COVID-19: Reality or Fiction? Martin Ruano, Julieta Denes, María C. Carrero, Gerardo Masson, Iván Constantin, Carla Pessio, Luciano De Stefano, Pablo G Stutzbach

In the last year, ambulatory consultations for post-COVID-19 controls represented a large proportion of the total number of consultations. After discharge from an acute episode of COVID-19, many patients suffer different pathologies or symptoms that last weeks or months. This condition has been termed "long COVID". Researchers from the Johns Hopkins Hospital consider as such the persistence of symptoms for more than 3 weeks and chronic COVID when they last more than 12 weeks. (12) Given the brief observation period since the emergence of this disease, we ignore if some individuals will remain with abnormalities during years or perhaps during their whole life. Several organs and systems are affected, but the most frequent are the respiratory, cardiovascular, gastrointestinal, musculoskeletal, organoleptic (taste/smell) and neuropsychic (depression, anxiety) systems. Cardiovascular complications are frequent and well-known through numerous publications from different parts of the world, which describe them with adequate precision. Conversely, there are few studies analyzing the incidence of heart diseases during follow-up after discharge from COVID-19, especially in our setting.

This study conducted at Instituto Cardiovascular San Isidro prospectively included 668 consecutive ambulatory patients ≥ 18 years between September 2020 and March 2021. They were all diagnosed with infection for COVID-19 confirmed by positive RT-PCR in a respiratory tract sample. The objective was to evaluate the occurrence of cardiovascular disease in patients recovered from COVID-19. The prevalence of symptoms (dyspnea, palpitations, angina and/or syncope) and electrocardiographic or echocardiographic abnormalities were analyzed, and the presence of myocarditis by gadolinium-enhanced cardiac magnetic resonance imaging (CMR) was investigated in patients with these findings. Mean age was 42.9 ± 14.9 years (56.9% female), 57.6% did not present cardiovascular risk factors, 19.5% had dyslipidemia, 12.9% hypertension, 9.6% smoked, 6.9% were obese and 4.3% diabetic. In 4.2% of cases, patients had a history of cardiovascular disease, with coronary heart disease as the most common presentation. During the acute phase of COVID-19, 489 patients (73.2%) presented mild disease, 109 (16.3%) required hospitalization for a median of 6 days and 7 (1.05%) intensive care with mechanical respiratory assistance. The latter were older, more obese and more frequently of male gender. Seventy-two percent of patient underwent computed tomography without contrast, and among them, 25.1% presented pneumonia. During convalescence 187 patients (27.9%) declared persistent dyspnea, 40 (5.9%) palpitations and 12 (1.8%) precordial chest pain. In the electrocardiogram (ECG), 24 patients (3.6%) showed already known conduction abnormali-

ties, 12 (1.8%) presented arrhythmias and 12 (1.8%) repolarization abnormalities. In the echocardiogram, 5 patients (0.7%) exhibited not previously described wall motion abnormalities and 3 (0.4%), pericardial effusion. Patients reporting symptoms or presenting echocardiographic and/or ECG abnormalities, underwent CMR with IV gadolinium. Among the 12 patients with precordial chest pain during the evolution, 4 had confirmed ventricular repolarization abnormalities and 1 presented pericardial effusion. In 4 patients belonging to this group, CMR demonstrated findings compatible with myocarditis. There was another case with myocarditis diagnosis confirmed by CMR who underwent the study due to frequent arrhythmias and elevated cardiac enzymes. Among the different electrocardiographic and echocardiographic abnormalities, the two variables showing association with the presence of myocarditis were repolarization abnormalities in the ECG and pericardial effusion in the echocardiogram ($p < 0.0001$).

Recently, the group of Lezicardio published in this Journal the analysis of 600 convalescent patients from COVID-19 with ambulatory care between September 2020 and May 2021. The primary objective of this study was to assess the prevalence of cardiac involvement in the convalescence stage of COVID-19 disease, through a transthoracic Doppler echocardiogram. Mean age was 41 ± 14.8 years and 48% were male. In 28.6% of cases, patients referred persistent symptoms (15.5% asthenia, 12.1% dyspnea, 6.4% palpitations and 4% precordial pain). New pathological echocardiographic findings were observed in 4.8% of patients. The CMR performed on these patients (at the discretion of the treating physician) and on those with arrhythmias showed some finding compatible with cardiac involvement after COVID 19 in 65.2% of cases: intramyocardial late gadolinium enhancement with non-ischemic pattern, left ventricular dysfunction or pericardial effusion. (13) A study including 2433 patients from Wuhan, China, revealed that one year after hospital discharge, 45% of cases presented at least one residual manifestation, the most frequent being fatigue, anxiety and respiratory symptoms. Cardiovascular manifestations were precordial oppression in 13% of patients, palpitations in 4.2% and dyspnea in 2.7%. (14) Several studies used CMR to detect myocarditis post COVID-19, especially in athletes. Daniels et al. performed CMR on 1597 symptomatic and asymptomatic university athletes, revealing findings compatible with myocarditis in 2.3% of these patients. (15) In another study, 145 young competitive athletes who had suffered mild to moderate COVID-19 without hospitalization were analyzed with CMR, and the rate of myocarditis was 1.4%. (16) The subsequent evolution of these cases was benign. Current evidence suggests that myocarditis is uncommon after COVID-19. The indication of CMR to confirm it is justified in cases of acute severe infection, elderly patients, those with prior cardiovascular disease, symptoms and new ECG or echocardiographic abnormalities.

The Jury of the 2021 Dr. Pedro Cossio Foundation Award was completed with former presidents of the Argentine Society of Cardiology, Dr. Eduardo Mele and Dr. Ricardo Migliore, whom I thank their expert and responsible participation.

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