

## THE INVEST TRIAL AFTER TEN YEARS; THREE ACES FOR PEPINE

### EL ESTUDIO INVEST DIEZ AÑOS DESPUÉS, TRÍO DE ASES PARA PEPINE

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#### To the Editor:

In the last months of 1999, young cardiologists were involved in the Community Projection of Cardiology (PROCCARD, for its acronym in Spanish). Their enthusiasm for the prevention of cardiovascular disease was due to the resounding success of the eminent Spanish cardiologist Valentin Fuster Carulla in the United States of America (USA) for his innovative concepts of "vulnerable atherosclerotic plaque" in the pathogenesis of ischemic heart disease, which enriched the Interventional Cardiology, and reaffirmed the importance of controlling coronary risk factors to prevent it.

Dr. Fuster put forward openly his principles before eminent and recognized personalities such as Eugene

Braunwald and L. Spencer King, in the never forgotten "Cardona Talks". Consequently and in recognition of his research, the Prince of Asturias Award for Technical and Scientific Research<sup>1</sup> was given to him in 1996.

Amid these changes, several professionals were selected by the Department of Public Health to participate in the INVEST study (INternational VErapamil Study), designed by the talented cardiologist Carl J. Pepine from the University of Florida (UF). This study involved 862 centers in 14 countries, and its main goal was to compare the effectiveness of Calcium Channel Blockers (CCBs) with beta-blockers (BB) in Hispanic patients over 50 years with heart artery disease and hypertension (HT). These were boom years for other vasodilators competing with CCBs, but Pepine had the "hunch", a strictly cardiology hypothesis, that by placing trandolapril in both groups, CCBs could be as effective as BB for blood pressure control and consequently the number of episodes of angina and fatal cardiovascular events, which was one of the pleasant surprises found in the results<sup>2</sup>. *Pepine's First Ace!*

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Although everything had been planned so thoroughly, an unpleasant drawback comes amid the recruitment period of cases: the possibility that the number of patients could not reach the 20,000 expected. There was no time then to redesign the study or meeting again with researchers working at a distance. Once again, Pepine must turn to a trump, a trump card for some, for others, intuition without fear of criticism, and he proposes the logical but bold idea - at a working meeting right at UF- to invite Cuba. Many of those present heard it and left, but his main collaborators stood firm. According to one of them, his attitude was that of a person who is very sure of what he did: he played the jazz "Rhapsody in Blue" by George Gershwin, sat down and said a sublime statement for Cubans ... "*They will come back*". A few days later he received permission to travel to Cuba, a task assigned to one of his assistants.

For the first time in the history of the Revolution a joint study between the UF and a Cuban institution was carried out, in this case, the Institute of Cardiology and Cardiovascular Surgery of Havana. The principal investigator for our part was Professor Dr. David Garcia Barreto, who is recognized for his professional qualifications and extensive knowledge in Pharmacology and Cardiology. Without a break, he organized an excellent team, young and inexperienced but eager for teachings. He also transmitted the necessary confidence, trained his staff in the most diverse issues, and multiplied knowledge, which still remains as a school. So Cuba could recruit 1872 patients in less than a year, was second behind the United States, and gave credit to its prestige in the organization of primary health care. Finally, the INVEST sample reached 22,576 patients thanks to the participation of our nation; which caused this Study to become the largest trial of hypertensive patients with ischemic heart disease to date<sup>3-4</sup>. Pepine's Second Ace!

There were many novelties in this investigation that led to regard it as the modern model for mega-studies. Among the novelties we could mention the recruitment of cases made directly through the Internet, and the use for the first time of a computer, perhaps the first non-human researcher of history, which would perform the randomization of cases with the exception that patients with chronic bronchial obstructive disease would be located directly in the CCBs group; at the same time, they could consult any drug interactions or get updated on the widest variety of studies. Also, drug distribution and remote control of over 800 different sites was facilitated. There was no chance whatsoever that anyone dared to contradict Pepine.

Murray Campbell was an eminent mathematician and programmer from IBM (International Business Machine), and also designer of Deep Blue, in 2007. Ten years after Deep Blue defeated world chess champion Garry Kasparov in the second match, Campbell denied the possibility of a rematch because he had decided to start a public health project<sup>5</sup>. Will anyone think that it was the powerful new computer of INVEST? The reality is that Deep Blue is in a museum today and INVEST in a gold jewelry box for science, as its author considers it one of his major achievements in his career and the best tribute to his mentor, Pepine's father, who with his advice "*don't look back*," raised him as a researcher from home<sup>6</sup>.

However, one of the most interesting aspects of this investigation was precisely that for the first time the design provided that all patients had hypertension and chronic ischemic heart disease. But why to choose a Hispanic population for the INVEST study?

Undoubtedly, Pepine must have moved in a scenario that might seem easy for a politician, an ethnologist or even to a baseball talent hunter. Each of them had separately focused his role very well as far as ethnicity is concerned, according to their scope. However Pepine, as a researcher, was particularly and rightly selective, and credited -through the neutral language of science- the growing phenomenon of "*Hispanic in the United States*" under this original demographic concept, never before applied in a multicenter study. He predicted that the INVEST results would be valid for future generations without a costly and strict monitoring, as the one carried out in the Framingham population, and time proved him right<sup>2-4,7</sup>. Pepine's Third Ace!

After ten years of the publication of INVEST first results we are still moved by its validity. Hypertension is a major health problem worldwide and in Latin America, the region that this accredited researcher turned into a protagonist. Hypertension is currently considered as an epidemic in progress that could acquire an intensive character of unpredictable consequences if measures involving the active participation of governments through far-reaching health policies in society are not taken, without waiting for the Eighth Report on Hypertension<sup>8-10</sup>.

We are deeply grateful here for the possibility given to us to be part of such an important project to science, and for working under the guidance of one of our most beloved teachers who also educated us on the research and editorial culture, Dr. David Garcia Barreto. Another well-deserved recognition goes to the Director of Cardiocentro "Ernesto Che Guevara," Dr.

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