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Editorial

REGICOR: 35 Years of Excellence in Cardiovascular Research

REGICOR: 35 años de excelencia en investigación cardiovascular

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REGICOR, acronym for *Registre Gironí del Cor* (Girona Heart Registry), is now 35 years old. The registry is thus now approaching 4 decades of high-level research into cardiovascular epidemiology by more than 50 investigators of the *Instituto del Hospital del Mar de Investigación Médica* (IMIM), Barcelona, the Cardiology Department of the Hospital Josep Trueta, Girona, and the Girona Primary Care Research Unit.

The initial idea for REGICOR was probably conceived on a Saturday afternoon of an otherwise unremarkable weekend sometime in 1978. A group of friends, Dr. Jaume Marrugat, Dr. Joan Sala, and Dr. Rafael Macià, later to be joined by Dr. Roberto Elosua, had the prescience to take advantage of the tremendous opportunities for conducting population-based studies in ischemic heart disease, risk factors, and cardiovascular prevention in general in the province of Gerona. The initial concept has morphed over the years into dozens of research projects grouped into different areas of interest, such as cardiovascular risk equations, population-based registries of myocardial infarction, nutritional studies, traditional risk factors and biomarkers, and cardiovascular genetics. The activity of REGICOR during these years has been characterized by the robustness of the epidemiological studies, the ability to form research networks with other Spanish and international groups, and prolific scientific output.

THE BEGINNINGS: POPULATION-BASED REGISTRY OF ACUTE MYOCARDIAL INFARCTION

In 1978, a hospital registry was started of all patients who were admitted to the University Hospital Josep Trueta in Gerona for myocardial infarction and continued to collect data until 2009. Over the 30-odd years that the registry was in operation, the results allowed analysis of changes in the management and treatment of patients with myocardial infarction.[1–3] This hospital database has been a model for other studies aiming to estimate the incidence, mortality, and lethality of myocardial infarction. To run such population-based registries, standardized methodology was required based essentially on a clear and stable definition. Moreover, definition of the disease under study should be standard, valid, reliable, and reproducible, and allow comparison of results across studies in different populations. Meeting all of these conditions, REGICOR began to operate in 1990. This registry prospectively collected sociodemographic and clinical data from all cases of myocardial infarction in the 600 000 inhabitants of the 6 districts that form the province of Gerona (*L'Alt Empordà, El Baix Empordà, La Garrotxa, El Gironès, El Pla de l'Estany*, and *La Selva*). During these years, information has been gathered from the registries of all the hospitals and clinics in these 6 districts, the ambulance service, and the official mortality registry, with the aim of making the data as exhaustive as possible.[4] This continuous registry has allowed changes in prognosis and in the effectiveness of treatments to be observed in all patients with the same diagnosis attended in a given health region.

The REGICOR investigators have demonstrated their ability to analyze epidemiologic data and make scientific predictions of what can be expected in the future. In particular, we wish to highlight a recent publication that suggests that there will be 115 752 cases (95% confidence interval [95%CI], 114 822-116 687) of acute coronary syndrome in Spain in 2013.[5] Of these, 30 426 will die before they reach hospital and 85 326 will require hospitalization. Of the hospitalized patients, 81.3% will be diagnosed with acute myocardial infarction and the remainder with unstable angina. Mortality in patients diagnosed with myocardial infarction will be 11.8% after 28 days. In 2021, the number of cases of acute coronary syndrome is predicted to be 109 772 (95%CI, 108 868-110 635). The trend in the number of cases of acute coronary syndrome between 2005 and 2049 will tend to stabilize in individuals aged 25 to 74 years and to increase significantly in individuals aged older than 74 years. The number of cases of acute coronary syndrome will increase through to 2049 due to population aging.

CARDIOVASCULAR RISK EQUATIONS

The REGICOR risk equations are probably what have given greatest visibility to the population-based registry. When the Framingham risk equations became popular at the end of the 1970s,[6] they were thought to be highly useful tools to guide decision-making in clinical practice for cardiovascular disease prevention and risk factor control. However, these equations had been derived within the framework of a high-risk population, and their validity in the Mediterranean population, with a much lower incidence of heart disease, was questionable. It was therefore essential to adapt the Framingham risk equations to the Spanish population using a well-defined methodology. The intention was to replace the incidence of the Framingham equation with that

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observed in the population of Gerona through the REGICOR population-based registry of cardiac disease. The prevalences observed in the cohort of individuals free of cardiac disease recruited in 1995 were recorded.[7] Tables were drawn up from the adapted equation. These were readily usable in clinical practice and showed the 10-year risk of infarction according to the risk factor profile. The data observed in REGICOR were validated for the entire Spanish population through the VERIFICA study.[8] This validation was achieved by collecting information from participants with different risk profiles from all over Spain. The risk predicted by the equation was very similar to the observed risk, whereas, as suspected, risk was clearly overestimated by the original Framingham equation. Studies with REGICOR have enabled the variables included in the Framingham equation to be refined by including antihypertensive and lipid-lowering therapies, something not contemplated in the original Framingham equation because few people were taking such agents at the time.

In addition, with growing knowledge and the collection of genetic data in recent years, the extent to which prediction could be improved by adding genetic variants to the traditional risk factors is under assessment.[9,10] With the same aim, other biomarkers related to metabolism, inflammation, hemodynamics, hemostasis, and myocardial injury are also being evaluated.

TRADITIONAL RISK FACTORS AND BIOMARKERS OF CARDIOVASCULAR RISK

In addition to determining the incidence, mortality, and lethality of acute myocardial infarction, REGICOR has established the prevalence of cardiovascular risk factors in the same area and the degree of control of these factors. From 1994 to the present day, 3 cross-sectional studies have been performed to determine which factors are important in addition to traditional cardiovascular risk factors. These factors include physical activity, diet, biochemical biomarkers of lipid profile, insulin resistance, oxidation, inflammation, endothelial and cardiac function, hemodynamics, and hemostatic status.[11] These cross-sectional studies are characterized by recruiting participants using random sampling to avoid inclusion bias, thereby increasing their external validity. The studies have allowed trends to be identified in the prevalence of cardiovascular risk factors in the Spanish population.[12] Ten-year follow-up cohort studies have also been performed in participants recruited in the cross-sectional studies. In 2007, a collaboration was started with the Center for Environmental Epidemiology Research (*Centro de Investigación en Epidemiología Ambiental* [CREAL]) to investigate individuals previously included in the cross-sectional study of 2000, and to determine whether there is an association between carotid intima-media thickness and exposure to air pollution (REGICOR-2000-AIR).[13]

NUTRITIONAL STUDIES

The REGICOR investigators have shown particular interest in the scientific study of the protective effect of the Mediterranean diet against cardiovascular morbidity and mortality. Thus, interventional studies are being conducted to determine the effect of olive oils and functional olive oils (enriched with biologically active compounds). In particular, we would like to highlight the EUROLIVE study, a multicenter European study coordinated by the IMIM, in which an intervention with 3 olive oils with differing contents of antioxidant phenolic compounds is being investigated in 200 healthy volunteers.[14] In addition, to study the mechanisms underlying the benefit of a cardiac-healthy diet, several avenues of research are emerging, such as the functionality of high-density lipoproteins or nutrigenomic studies, that is, study of the changes in gene expression attributable to nutrients, as well as studies of the interaction between diet and intestinal flora.

CARDIOVASCULAR GENETICS

In the last 10 years, REGICOR investigators have started a new line of research in cardiovascular genetics. The main objective is to study the genetic variants associated with greater individual susceptibility to cardiovascular disease. In addition, the interaction between genetic and environmental factors is being analyzed, with particular emphasis on research into protective factors against cardiovascular disease.[9]

In the early years of the project, interest mainly centered on study of candidate genes such as *PON1* and *ESR1*. In a subsequent stage, made possible by collaboration with international groups, the Genome Wide Association Study has been undertaken, with publications in high-impact journals. Other studies along these lines include an assessment of the improvement in the predictive capacity of risk equations when genetic information is added. Finally, also under investigation is the impact of epigenetic variants (DNA changes that do not imply changes in the underlying DNA sequence, with DNA methylation being the main example) on the risk of cardiovascular diseases, and how lifestyle influences epigenetic variability.

Currently, the main objectives of this line of investigation are identification of genetic variants associated with cardiovascular characteristics (myocardial infarction, hypertension, and other cardiovascular risk factors), determination of the extent to which these variants increase the predictive capacity of traditional cardiovascular risk functions,[10] and, finally, assessment of the impact of epigenetic variants on cardiovascular characteristics.

WHAT THE FUTURE HOLDS FOR REGICOR

It will not be easy for REGICOR to maintain this level of excellence in cardiovascular research in the coming years. The economic crisis, which has reduced the funding available for projects, and strong international competition are 2 elements that will undoubtedly have an impact. However, the REGICOR investigators will surely not slacken in their determination to formulate hypotheses, collect and analyze data, and publish the findings of those analyses, whether working locally or in collaboration with dozens of international centers, while at the same time continuing their commitment to postgraduate teaching and innovation in research. We wholeheartedly thank and congratulate REGICOR for all the hard work that has helped medical progress in cardiovascular disease.

CONFLICTS OF INTEREST

None declared.

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