

The REGICOR Registry and the Epidemiology of Myocardial Infarction in Spain: Forging a Path

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Cardiovascular disease is currently the primary cause of death in the industrialized world and constitutes a serious healthcare problem consuming a substantial proportion of resources. The early decades of the twentieth century saw a progressive fall in mortality from infectious diseases and a considerable increase in coronary heart disease. This stimulated the implementation of the first large-scale epidemiologic studies aimed at increasing our knowledge of geographic distribution and other factors related to the appearance of ischemic heart disease. One of the first relevant results was confirmation of the great geographic variability in incidence and mortality, which in northern Europe are up to 5 times greater than in Spain.^{1,2} In this context, Spain occupies a privileged position having the second lowest rate of ischemic heart disease, only greater than that of France. Nonetheless, ischemic heart disease is an important cause of mortality which in Spain brought about the deaths of 22 072 men and 16 615 women during 2000, with overall mortality of 114 per 100 000 men and 82 per 100 000 women.^{1,2} The magnitude of the problem may go some way towards explaining the growing but somewhat overdue interest in obtaining data, especially in recent years.

Sources of information on ischemic heart disease include official statistics, population-wide registries, hospital registries, clinical trials, and post-hospital discharge data on morbidity.^{3,4}

Large-scale clinical trials frequently provide information about ischemic heart disease that surpasses their objectives and extends to patients' clinical characteristics, diagnosis and therapy. During recent decades, caring for the patient with acute myocardial infarction (AMI) has been enriched by new therapeutic procedures that successfully reduce mortality and severe

complications in the patients they have been administered to. Many of these achievements have been demonstrated in controlled clinical trials. Although the information obtained is useful when evaluating a specific intervention or studying other characteristics of the patients included, applying it to the population with AMI is difficult given the selection bias that frequently occurs in clinical trials,³⁻⁵ conditioned as it is by inclusion criteria and researchers' interests when enrolling patients. Several publications have demonstrated lower mortality and a more benign clinical profile in patients with AMI included in clinical trials and some subgroups of patients at greater risk, eg, women and older patients, are less common than in the "real world."³⁻⁵ Moreover, a considerable time lapse frequently occurs before clinical trial results materialize in the form of changes to patient care in daily clinical practice. Changes do not happen simultaneously and considerable variety in patterns of caring for patients with AMI can be found when comparing hospitals, cities and countries.⁶⁻⁸

Disease registries seem a necessary complementary strategy. They permit us to establish the external validity of clinical trials, as well as offering a global approach to studying the effectiveness of the treatment of patients and measuring the frequency of the illness and its characteristics. For AMI, hospital registries and population-wide registries are the most frequently used.^{3,4}

Hospital registries are limited to the admissions at a particular center. Detection is based on patients with a specific diagnosis (eg, AMI), admitted to a hospital or group of hospitals attending the population of a clearly delimited area.^{3,4}

Hospital AMI registries can provide valid, useful information about the clinical characteristics of patients admitted, procedures employed, and prognoses. However, comparison of data from various registries requires caution. Frequently differences in design, inclusion criteria and definitions of variables make comparisons difficult. Some registries remain active without interruption from their start^{9,10} whereas others are designed to obtain data at specific time intervals.^{7,8,11,12} Some registries establish no inclusion criteria on age limit¹⁰; others exclude older patients.^{2,9} Some registries include all patients admitted for AMI in the hospital⁷; others include only patients admitted to intensive coronary care units (ICCU).^{8,10,12} All this means differences exist between the populations

SEE ARTICLE ON PAGES 349-56

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included that cannot be ignored when attempting to make comparisons.

In Spain, information about in-hospital care of patients with AMI was scarce until quite recently. In 1978, at the Hospital Josep Trueta in Gerona, northeastern Spain, a registry of patients with AMI was begun: the REGICOR study.^{1,3,9} It remains active today and has given rise to numerous publications. In 1988, data from an AMI registry was published,⁴ including patients diagnosed with AMI at discharge from 12 hospitals in the city of Barcelona from 1 November 1983 thru 31 August 1984. In 1996, data of the pilot phase of the PRIAMHO registry,⁴ appeared, including patients with AMI in 32 Spanish hospitals. In 1997, results of the RICVAL study¹¹ appeared with data on 1124 patients with AMI admitted to hospitals in Valencia from December 1993 thru November 1994. Later, data from year 1 of the PRIMVAC study,¹⁰ which remains active after 12 years, and from the PRIAMHO I study,⁸ were published. In 2001, RISCII¹³ data were published with similar results to those reported by PRIAMHO over 5 years; in 2003, PRIAMHO II,¹² reported on 6221 patients with AMI admitted to 58 Spanish hospitals from 15 May to 15 December 2000. Data from the ARIAM study¹⁴ were published in 1999, although this was both a registry and an intervention study. Data from the hospital phase of the IBERICA registry⁷ were published in 2001. Despite their limitations, the development of hospital-based AMI registries in Spain is proof of the growing interest to obtain data “here and now” –an objective substantially achieved thanks to the efforts of researchers who have managed, moreover, to lay solid foundations for future studies.

Population-wide registries are more expensive and difficult to organize than in-hospital studies, making them much less common. The construction of a complex, multidisciplinary organizational structure involving cardiologists, intensive care specialists, specialists managing care in ER and epidemiologic services is almost always needed. Though the effort is rewarded as it facilitates the establishment of rates of attack, incidence, mortality, and fatality, as well as providing information about trends in timing of incidence, mortality and fatality if the registry is continued.^{3,4}

The MONICA-Cataluña² project is a population-wide registry begun in 1984 to determine trends in the timing of mortality from coronary heart disease, morbidity, acute coronary care and risk factors in a population of 479 000 individuals, aged 35 to 74, residing in and around Barcelona. The study has given rise to numerous publications and its methodology has served to guide other studies.

The Registre Gironí del Cor (REGICOR) group^{3,4,9} is one of the pioneers among Spanish registries of ischemic heart disease. The group was initially a hospital-based registry, and has gradually grown to cover part of Gerona province. All in all, it is a well-established workgroup

that has made important contributions to cardiovascular epidemiology.

In this issue of *Revista Española de Cardiología*,⁹ the REGICOR project researchers publish an “Analysis of the trend in fatality, incidence and mortality from myocardial infarction in Gerona between 1990 and 1999.” They constructed a registry of all episodes of AMI in 6 districts of Gerona province with a population of 227 598 inhabitants, aged 35 to 74. Rates of attack, incidence, recurrence, hospitalization and mortality, and population-wide and intrahospital fatality were determined from 1990 thru 1999. Results provide data of great interest that should be a cause for reflection among clinical cardiologists. In contrast with the excessively optimistic interpretation of results of some clinical trials, REGICOR data show that AMI still has a high level of fatality. Among 35-74 year-old patients with AMI, 20% who arrive at hospital alive, die following admission (in-hospital fatality). Almost half (42.1%) of all 35-74 year-old patients presenting with AMI die at ≤1 month (population-wide fatality at 28 days) and two thirds of these deaths occur without patients obtaining specialized hospital care. In Spain, another population-wide registry, MONICA-Cataluña,² offers similar figures, and the IBERICA study¹ indicated 38% population-wide fatality, in 1997. The RICVAL registry,¹¹ with no patient age limit, recorded 16.1% intra-ICCU fatality in 1994, PRIMVAC¹⁰ showed 14.1% mortality in ICCU in 1995 and IBERICA,⁷ with patients aged 25 to 74, showed 16.2% mortality at 28 days, in 1997. All these data confirm the high mortality from AMI between 1990 and 2000; much higher than that indicated in clinical trials. Other data of interest are the higher mortality in women and the substantial increase in mortality with age, also reported elsewhere.^{1,2,10,11}

One advantage of active, uninterrupted registries is that they facilitate study of the evolution over time of a series of parameters of great interest to clinicians. Sadly, registries like this are infrequent in Spain. The REGICOR study is a fortunate exception that has permitted the study of variations over time of rate of attack, incidence, recurrence, hospitalization and mortality, as well as population-wide and intrahospital fatality. Information about these variations can be useful when approaching results of therapeutic interventions for AMI. It is generally admitted that primary prevention would reduce the incidence of new cases of AMI, and secondary prevention would reduce the number of recurrent events.¹ Treatment in the acute phase of myocardial infarction would fundamentally affect intrahospital fatality. All therapeutic strategies would produce a beneficial reduction in rate of mortality and population-wide fatality.¹

Men aged 35 to 64 present a statistically significant reduction in rate of attack, incidence, recurrence and hospitalization and this holds for the 65-74 year age group. Mortality does not vary between groups. Intrahospital fatality fell significantly in men, especially those aged 65-74, but population-wide fatality remained

stable in both groups. Reduced in-hospital fatality from AMI has been highlighted by other hospital registries such as RISCII,¹² which reported a fall in intra-ICCU fatality from 11.4% in 1995 to 9.3% in 1999. In the PRIMVAC registry, we observed a fall in intra-ICCU fatality from 14.1% in 1995 to 8.9% in 2004 (unpublished data). The comparison of in-hospital fatality recorded in PRIAMHO I and PRIAMHO II also showed a significant fall,¹⁵ although a comparison between different studies means conclusions must be considered with caution. However, the apparently consistent reduction in in-hospital fatality in Spain should reassure clinicians. We know that a scientific truth confirmed by different methods is considered more sound than if it is only verified by a single approach.⁴ Given that the clinical characteristics defining the seriousness of AMI appear unchanged and that in REGICOR and in other registries the therapeutic strategy in AMI seems to have evolved according to clinical guideline recommendations, the improved in-hospital prognosis has been attributed to better treatment.^{1,9}

However, REGICOR introduces some worrying elements that cast a shadow on clinicians' confidence in their own success: although in-hospital fatality has fallen, population-wide fatality is unchanged. In other words, the magnitude of the reduction is small and is rather lost in overall fatality figures, which have not varied in this period. So, we have to think about redirecting or diversifying our efforts: how can we influence the 66.8% of deaths that occur before patients reach hospital? Arrival times have not changed in recent years despite informative campaigns; only in fibrinolytic treatment does door-to-needle time seem to have been reduced. In-hospital medicine consumes more and more resources and, although we can feel happy about having reduced in-hospital fatality from AMI, we need to take a step further, by diversifying our efforts and paying more attention to primary prevention, in an attempt to diminish AMI incidence and the total number of deaths. We cannot justify forever-increasing hospital costs unless they are accompanied by a significant, relevant impact on the health of the population.²

One further interesting aspect of our analysis of REGICOR is that improvements in rate of attack, incidence and recurrence occur in men aged 35 to 64 and not in those aged 65 to 74. This suggests we are simply witnessing (or contributing to) a delay in the age of appearance or recurrence of AMI. Fortunately, even without variations in population-wide fatality, this older age group benefits more from in-hospital therapeutic strategies, but we do not know if this benefit extends to patients aged ≥ 74 who, in some hospital registries (PRIMVAC, unpublished data), account for $\geq 25\%$ of patients hospitalized in the ICCU with AMI.

The REGICOR study constitutes an important contribution to knowledge of AMI epidemiology in Spain where, except for MONICA-Cataluña,² there are no other active, population-wide registries that facilitate analysis

of trends. However, we must recognize that its scope is limited to part of Gerona province and its results cannot necessarily be extrapolated to the rest of Spain. Clinical characteristics, risk factors, in-hospital treatment and mortality from AMI differ greatly in the different Spanish regions.^{1,7,8} In some regions, mortality from AMI is twice that of others.¹ Sadly, except for some hospital registries, most of which have been of limited duration, and the IBERICA registry,⁷ which despite its importance does not cover all Spanish regions, the path walked by these registries has not been taken elsewhere. Multicenter registries are sometimes difficult to initiate and maintain, we know. Keeping them going over long periods finally disheartens researchers who lose their enthusiasm.^{3,4} Given the importance of patient registries, we need to develop financial and organizational mechanisms to facilitate their extension and maintenance.³

Patients aged >74 years are not analyzed in this study by REGICOR. The exclusion of older patients in some hospital AMI registries constitutes a considerable limitation. We feel that, in many registries, older patients constitute a substantial proportion of AMI admissions.^{1,4} Patients aged >74 years present very high population-wide and in-hospital fatality.¹ The Spanish population is getting older and, if the delay in appearance of AMI is confirmed, we should expect the proportion of older patients admitted with AMI to increase.¹ We need to know its clinical characteristics and whether the trend towards greater benefit from treatment in 65-74 year-olds also occurs in older patients, despite the very high fatality.

Analysis of the study ends in 1999, shortly before the new definition of AMI based on troponin values was introduced. The coming years will witness an increase in AMI admissions to hospitals that will push figures even higher if new, even more sensitive, biological indicators of necrosis appear. This raises the issue of how to analyze trends if diagnostic criteria of AMI change frequently.

The REGICOR group figures among those who have opened up new paths in Spanish cardiology. Their study, its contributions and the path of their research confirm the words of a great, Spanish language poet: in Spain, very often, "you make the path as you walk."

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