

From Clinical Trials to Registry: the PRIAMHO II Registry

Antoni Curós Abadal

Servei de Cardiologia, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain.

In recent years there has been marked progress in the treatment of cardiovascular disease and, more specifically, in the case of the different clinical entities that are currently known as acute coronary syndrome. A key, and indispensable, factor in treating our patients has been the implementation of the concept of evidence-based medicine (EBM), used and recognized universally as the best clinical method for demonstrating the efficacy of any treatment. Evidence-based medicine has been defined as the consistent and sensible use of the best evidence derived from clinical research on making decisions regarding individualized patient care, taking "evidence" to mean that which is verified or confirmed. More simply, this involves applying the most effective medical treatments to maximize the quality and quantity of life of the patients.

It is clear that randomized clinical trials provide the most robust scientific evidence we have regarding the efficacy of a therapeutic intervention. When conclusive clinical trials are unavailable, the level of evidence progressively decreases. In these cases, we use the information available, usually a metaanalysis (a statistical analysis that combines the results of different independent clinical trials, usually consisting of small samples, that are considered "combinable") or observational studies, especially registries. Inasmuch as they refer to the treatment administered, registries are studies of effectiveness rather than efficacy, like clinical trials, and they assess the effect of such treatment in real life.

There are several acute myocardial infarction (AMI) registries in Spain. The scope and duration of registries are different, making it possible to quite precisely

analyze the prognosis and care such patients receive in our setting. Thus, among these, there are the REGICOR registry,¹ done in the province of Gerona, the PRIMVAC registry² done in the Community of Valencia, the PRIAMHO I³ and PRIAMHO II registries⁴ done at the Spanish national level, and the IBERICA registry,⁵ which included patients from several Spanish regions. These registries have provided us with very useful information concerning knowledge of the disease and the results of our care work.

Among the other relevant contributions of these registries, we note that 28-day mortality in the patients with AMI admitted to our coronary care units between 1994-1995 and 2000 has been reduced from 14% to 11.4%.^{3,4} We have also found that in the hospital phase there is a progressive increase in the use of beta-blockers (BB) and angiotensin-converting enzyme inhibitors (ACE inhibitors), forming 51%-56% of prescriptions in the former and a similar percentage, 45%-50%, in the latter²⁻⁵ with a marked reduction in the percentage of variability in their use. Furthermore, we can verify that the percentage of candidates for reperfusion therapy has increased to 71%, although only 10.7% of primary angioplasties⁴ are carried out. Compared with another contemporary European registry,⁶ mortality in Spain is still high. In the therapeutic context, we use 25%-30% fewer BB and 10% fewer ACE inhibitors, and achieve good levels of reperfusion therapy, although primary angioplasty is employed less often (20% in the European registry). It is clear that, regarding knowledge provided by EBM, we should implement better primary angioplasty programs more often and increase the use of BB. There is a marked underuse of ACE inhibitors in our context in patients with ventricular dysfunction, presence of extensive previous anterior AMI, diabetes, or hypertension, although, as found in the PRIAMHO II substudy published in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA, they are, in fact, most used in these types of patients.⁷

Clinical trials have been decisive in establishing the therapeutic indications for certain drugs in patients with AMI. This has been the case with BB, which were found to reduce mortality by 20%-40% in these patients.⁸⁻¹⁰ The impact of the treatment is indisputable, since treating 42 patients with AMI over 2 years prevents one

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Correspondence: Dr. A. Curós Abadal.
Servei de Cardiologia, Unitat Coronària.
Hospital Universitari Germans Trias i Pujol.
Ctra. del Canyet, s/n. 08916 Badalona. Barcelona. España.
E-mail: acuros@ns.hugtip.scs.es

death. This benefit is much higher than with statins where 94 patients have to be treated to obtain the same results.⁸ It should be pointed out that in most clinical trials showing such benefits, patients had ST-segment elevation AMI (STEMI), beginning and duration of treatment ranged between the first days to weeks after the AMI and, in general, the patients did not receive ACE inhibitors or fibrinolytic agents. This means that the benefit is not uniform and depends on the time therapy is begun, its duration, AMI class, patient risk, and even the type of BB used.^{8,9} In patients at less risk, for example those treated with fibrinolytic agents, early treatment with BB reduces mortality, although to a lesser degree than in those at greater risk, such as patients who present heart failure or depressed ventricular function.⁸ In patients with STEMI with ventricular dysfunction treated with ACE inhibitors, the CAPRICORN clinical trial¹⁰ has demonstrated that treatment with BB initiated early in the hospital phase leads to an absolute reduction of 3% in mortality in those treated with carvedilol versus placebo. In other words, treating 33 patients with these characteristics for little more than 1 year prevents one death. There are no clinical trials with a similar design that demonstrate a benefit from combining BB with ACE inhibitors early after AMI in unselected patients with STEMI or at low risk, nor in those with AMI without ST-segment elevation. In this sense, some observational studies, such as the American Cooperative Cardiovascular Project registry,¹¹ which included 201 752 patients with AMI, have demonstrated reduced mortality attributed to treatment with BB for all types of AMI and in those who also receive ACE inhibitors. Thus, there is sufficient evidence to state that treatment with BB in the first days of AMI reduces mortality in patients who do not have contraindications, especially in those considered at greater risk. The level of evidence is lower in those receiving ACE inhibitors without having impaired ventricular function. This is the issue addressed by the PRIAMHO II study in this issue of the Journal.

Interestingly, something similar occurs with ACE inhibitors when compared to BB. The results of the studies also varied depending on the ACE inhibitors used, the time of beginning treatment, its duration and the fact that only a small percentage of patients received BB at the same time. A metaanalysis¹² that included the main studies, such as GISSI-3 and ISIS-4, carried out in an unselected population of patients with AMI treated very early with ACE inhibitors, demonstrated a 0.5% absolute reduction in mortality versus controls. This means that 200 patients need to be treated for 30 days to prevent one death, assuming that some of these patients will suffer undesirable side effects or experience no benefit. Furthermore, it was proved that the reduction in mortality was strongly influenced by the greater benefit (the so-called dilutional effect) in patients with a worse prognosis, such as those who had a previous heart attack, anterior

AMI, Killip class I, diabetes, hypertension, or tachycardia (approximately 70 patients with any of these characteristics should be treated to prevent one death). Another metaanalysis¹³ was even more conclusive in this regard. It included the main studies, such as SAVE, AIRE and TRACE, which assessed the efficacy of treatment in the longer-term with different ACE inhibitors in patients with AMI with ventricular dysfunction or heart failure, finding that only 18 patients needed to be treated for approximately 2.5 years to prevent 1 death. We do not discuss some recent studies with ACE inhibitors that included patients with ischemic heart disease, among others, who received late treatment after AMI and not in the hospital phase. Thus, it can be concluded that treatment with ACE inhibitors initiated in the first days after AMI reduces mortality, although the effect only has high clinical importance in patients considered to be at high-risk.

The PRIAMHO II registry⁴ has received well-deserved recognition in Spain. It included 6221 patients with Q-wave AMI or non-Q-wave AMI admitted over 6 consecutive months in 2000 in 58 of the 165 coronary care units in Spanish state hospitals. Patients were randomly selected for voluntary inclusion in the registry. The PRIAMHO II registry strictly fulfils all the requirements needed to be a good registry, such as the systematic, prospective, and long-term data collection on all patients with AMI cared for in the selected coronary care units. Despite its smaller sample size compared to other registries, its characteristics, already highlighted by other authors,¹⁴ such as an external audit, excellent coverage, ascertainment and concordance rates, and 93% 1-year follow-up, make it a benchmark study in Spain.

The present issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA⁷ presents a subanalysis of the data obtained by the PRIAMHO II registry which compares 1-year survival in patients treated with combined BB and ACE inhibitors to those who received BB only, ACE inhibitors only or neither. In spite of the limitations of the study, well described by the authors themselves, the analysis is interesting, given the scarcity of data in this regard. They conclude that in an unselected patient population with AMI, combined treatment with BB and ACE inhibitors does have additive effects on 1-year survival.

In the first place, we confirm that, given the mortality rate presented by the entire patient group in the PRIAMHO II registry, this is a low to moderate risk group, which clearly can affect the interpretation of the results. The study shows that mortality is greatest in the group consisting of high-risk patients treated with ACE inhibitors, and is lowest in those patients at lower risk treated with BB only, an expected outcome according to the usual prognostic stratification of patients with AMI. On the other hand, the group of patients treated with BB and ACE inhibitors had a greater percentage of primary reperfusion (52%) and included up to 25% of patients

with Killip class I or ejection fraction <40%. This could lead to a positive treatment bias (the dilutional effect mentioned above), although in the statistical analysis the authors take these possible confounding variables into account.

The barely significant reduction in mortality in the total group receiving ACE inhibitors could instead be due to the rather short duration of treatment and the small sample size which could not show the low benefit observed in the large clinical trials in patients with similar characteristics (low or moderate risk), but which included far more patients. The same occurs in the total group treated with BB. In any case, this result suggests carrying out a confirmational clinical trial of the apparent reduction in mortality attributed to treatment with ACE inhibitors combined with BB in all AMI definitively started in the hospital and followed up for at least 6 weeks. It is reasonable to assume that this type of trial could be carried out only with difficulty, given the abundance of current studies already available on ACE inhibitors and BB. Such a trial would need to include a very high number of patients if we take into account that several thousands were needed to demonstrate the benefit of BB or ACE inhibitors in the low-risk patients that currently constitute the main group.

We consider that it was a good idea to analyze the influence of treatment on survival after dividing the patients into high- and low-risk groups. The results of such an analysis validate the findings of the clinical trials in real life. In fact, these show that is, the reduction in mortality due to early treatment with BB, ACE inhibitors, or both, in high-risk patients with AMI and the null or limited benefit in low-risk patients. These results are another proof of the quality of the PRIAMHO II registry, which not only describes in detail the clinical characteristics of our patients and the level of compliance with therapeutic recommendations, but is a clear proof of the necessary complementarity of the results of clinical trials and registries, thus helping to improve our knowledge and, therefore, patient care. Although, for one or another of the reasons mentioned above, the vast majority of our patients with AMI will receive treatment with ACE inhibitors, we adhere to the opinion of cardiologists such as Pfeffer, Domanski, and Braunwald,¹⁵ who recommend the prescription of ACE inhibitors in every patient with ischemic heart disease depending on the risk-benefit relationship and cost-effectiveness in every specific case.

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