From Clinical Trials to Registry: the PRIAMHO II Registry
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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 “combinalbe”) 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,3 done in the province of Gerona, the PRIMVAC registry4 done in the Community of Valencia, the PRIAMHO I5 and PRIAMHO II registries6 done at the Spanish national level, and the IBERICA registry,7 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%.1,8,9 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 latter10 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 angioplasties5 are carried out. Compared with another contemporary European registry,4 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.10-13 The impact of the treatment is indisputable, since treating 42 patients with AMI over 2 years prevents one
death. This benefit is much higher than with statins
where 94 patients have to be treated to obtain the same
results.4 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, consequently, 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.6,9 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.5
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
death rate presented by the entire patient group in the
PRIAMHO II registry which compares 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,
它可以 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 registry7 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 fulfills 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,13 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
CARDIOLOGÍA1 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

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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 trials in real life. In fact, these show that is, the apparent reduction in mortality attributed 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. 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.

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REFERENCES