Letters to the Editor


A better control for ICD patients?

We read with interest the clinical perspective ‘Is prophylaxis the best use of the ICD?’ by Nisam and Farre[1]. There is no doubt that ICDs save lives and are certainly a great advance in the treatment of heart disease in this century.

The MADIT-II results[2] were published recently and are likely to bring about an exponential increase in the use of the device. However, some of the aspects of MADIT-II deserve a closer look before the results of the study are applied to all patients with prior myocardial infarction and left ventricular dysfunction.

In MADIT-II[3], the authors had used an antiarrhythmic drug (amiodarone) limb, in which 7% were also given beta-blockers vs 27% in the placebo limb: there was a high withdrawal rate of antiarrhythmic drug, many patients being left on no therapy. In MADIT-II, curiously, placebo replaced the amiodarone treatment limb. There have been data suggesting that amiodarone and beta-blockers combined may be synergistic on arrhythmic events as revealed in the EMITAT and CAMIAT studies[4]. Should a combination arm of beta blockers and amiodarone have served a more reasonable control group than placebo in MADIT-II?

Secondly, it is not clear why patients with prior revascularization in the previous 3 months were excluded in MADIT-II. Increasingly, most MADIT-II type patients now undergo revascularization, usually in close proximity to their infarct. The CABG-Patch trial[5] showed that in such patients there is no survival benefit with the AICD emphasizing the benefit of coronary revascularization. There is no doubt that treating large territory inducible ischemia with percutaneous or surgical revascularization would decrease the risk of life threatening ventricular arrhythmias. Conversely, not treating the ischemic burden with revascularization therapy is likely to cause the magnitude of the beneficial effect of the ICD to be exaggerated, as these patients are likely to suffer a greater incidence of life threatening ventricular arrhythmias.

Would the results of MADIT-II have reached statistical significance (showing benefit from AICD) if all the patients had been offered revascularization therapy (by percutaneous intervention or surgery, as appropriate) after their myocardial infarction and if the control limb had been given the benefit of amiodarone and beta-blocker therapy?

Maybe, we should await the outcome of the ongoing SCD-HEFT study[6], in which the effects of placebo, amiodarone, and the AICD therapy are being compared in a similar population.

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References


The need for European Registries in inherited cardiomyopathies

Cardiomyopathies (CMPs) are primary myocardial diseases that are not caused by congenital, valvular, vascular, or systemic disorders[7]. Their incidence is largely unknown as the available data are outdated, incomplete and mainly non-European[2–4] and the National Institutes of Health do not have any epidemiological data based on contemporary scientific knowledge.

The health impact of CMPs is influenced by the age of the patients (who are often young adults), the familial or sporadic presentations and the clinical expression that may range from asymptomatic to congestive heart failure, life-threatening arrhythmias and conduction disturbances[8–12]. The current diagnostic and management strategies, which include the implantation of devices (for arrhythmias, end-stage heart failure or conduction disturbances) and the multidrug medical approach, vary from one European country to another, as does the timing of follow-up visits.

The approach to patient screening and management, and the ethical rules followed during the genotyping process, also vary and often fail to respect the guidelines and good clinical practice recommendations of scientific societies. Most of these guidelines are excellent in terms of content, but their efficacy in this specific field is untested and their use is poorly controlled. The application of clinical trials could ensure identical enrolment criteria and a uniform approach to management, but there are few trials specifically dedicated to dilated or hypertrophic cardiomyopathy. Furthermore, the guidelines are often generated by small nuclei of experts without the active participation of the community cardiologists and family physicians who have to apply them.

Our working hypothesis is that interactive collaboration on specific topics among European countries (in our case, involving cardiological communities) could provide an infrastructure for establishing large databases based on uniform diagnostic criteria and a uniform therapeutic approach. The efficacy of this collaboration can be evaluated when systematically organised and maintained over a period of time that is sufficient to transfer the diagnostic and management methodology. The organization of a European network of tertiary centres with specific expertise in the field of inherited cardiomyopathies could provide the first standardized registries of CMP patients, which
would enable the comparison of different management strategies and their related outcomes.

The choice of inherited cardiomyopathies as the first diseases to be assessed is based on two major considerations:

- Although they are specific diseases, their management is entirely based on phenotypes (congestive heart failure, arrhythmia, conduction disturbances) that are common to other more common diseases (ischaemic, valvular, hypertensive, etc.).
- The diagnostic criteria can be accurately defined in order to limit diagnostic errors to less than 5%.

By concentrating on inherited cardiomyopathies with an evidence-based familial origin, the registries will provide the first systematic data concerning asymptomatic patients, who are unaware of their disease and only discovered by screening, healthy subjects who are candidates for developing the disease, and also healthy carriers of known gene defects.

We believe that identical diseases should be diagnosed and treated according to identical rules and guidelines in different countries. If this is done, the rates of related deaths, major events or complications, hospitalizations, direct and indirect costs should be the same in the different countries when normalized for population data, which would allow the programming of public health strategies with European-wide applications.

Our first effort will be aimed at diluted cardiomyopathies (DCM) and hypertrophic cardiomyopathies (HCM): the former because only 25% of the cases can currently be defined familial[11–13], and the latter because the majority of cases are familial[13–15]. A growing number of cases can be genetically characterized, which thus ensures a prospective proportion of healthy carriers who can therefore provide information concerning their natural histories[19,20].

In general terms, the two registries could first provide a database of patients with truly identical diseases, thus allowing the definition of their pathophysiological, genetic and clinical characteristics, and providing data for future aetiology-based clinical trials. One example of a registry recently established at the European level is the EUROGENE Heart Failure Study, which is supported by grants from the LEDUCQ Foundation and coordinated by the Department of Cardiology of Pitie-Salpetriere Hospital (Paris, France). Its aim is to study the genetic factors involved in patients with familial or sporadic forms of dilated or hypertrophic cardiomyopathy (the DNA of more than 1000 subjects has been included in a period of ten months) (INSERM Contract No. RBM, 00-39). This registry could form the basis for a genetic study registry that the Myocardium and Pericardial Working Group is proposing to the European Community for the VI European Framework.

Further reasons for considering HCM and DCM are:

- A number of HCM patients progress to a dilated phase in the late stages of the disease, which means that HCM may be confused with DCM[6,9,11].
- Both types of cardiomyopathy are genetically heterogeneous, and constitute a group of diseases for which appropriate molecular testing recommendations are still debated. A typical example is Marfan disease, for which the identification of the FBN1 gene defect is one of the major diagnostic criteria[21], thus underlining the need for precise recommendations concerning molecular genetic analysis. There are currently no guidelines concerning the identification of a genetic defect in the list of the diagnostic criteria, and the application of genetic testing is still confined to a few research centres.
- Defects in the same genes may cause either HCM or DCM[21–23], and so it is essential to use the same resources in an effort to improve our understanding of the molecular basis of the two diseases.

The Myocardial and Pericardial Disease Working Group is therefore launching a call for participation in this initiative, which constitutes the subject of a proposal to be submitted to the European Union. It also supports the approach of the Italian Registry of HCM run by Cecchi and Olivotto (Editorial submitted to Eur. Heart J.) and offers a reminder of the ongoing ‘Eurogene Heart Failure’ Project as example of how European tertiary centres can actively collaborate. It also recalls the shared database specifically developed for HCM patients and their families in Israel, which was successfully applied by 14 Cardiology Centres, leading to the standardization of the phenotyping process and facilitating centralized genotyping efforts. About 400 individuals (150 with HCM) have so far been evaluated in the framework of ISAAC (Israeli Shared Action for Advancement of Cardiomyopathies)[24].

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