Do we need clinical registries?

Luigi Tavazzi*

Maria Cecilia Hospital, GVM Care&Research, E.S. Health Science Foundation, Cotingola, Italy

Online publish-ahead-of-print 7 September 2013

This editorial refers to ‘Heart failure in young adults: 20-year trends in hospitalization, aetiology, and case fatality in Sweden’, by A. Barasa et al., on page 25–32

In recent years the numbers of observational reports in the medical field have exploded. Several reasons might explain such a huge increase in observational clinical research. First, the increasing expectations of people regarding their national health systems associated with their exponential cost and, consequently, the need to know how the declining resources are used. Secondly, understanding the current epidemiology of diseases and therapies to make reasonable estimates of the needs for care and expenditure in the future. Thirdly, to allow physicians and scientists to learn more about the incidence and course of diseases by observing ‘clinical practice’.

What is ‘clinical practice’? Clarifying this is important in order to interpret the observational findings correctly. As elegantly reported by Gabbay et al.,1 the majority of clinicians rarely access and use explicit evidence from research or other sources directly. They instead rely on ‘mindlines’ generated by a number of sources of varying degrees of reliability, collectively reinforced, resulting in individual ‘internalized, tacit, guidelines’. These can be far removed from the official recommendations; however, they guide the physician in his clinical practice. A similar process also of course applies to the patient; mixing information obtained from different sources leads to individual beliefs guiding patient behaviour (i.e. acceptance of treatment and adherence both to prescribed medications and an appropriate lifestyle over time). All this results in so-called ‘clinical practice’, which is the object of observational medical research. On the therapeutic front, clinical practice lies in both physician prescriptions (adherence to guideline recommendations) and patient adherence to the prescriptions over time.

Some of the vast array of possible aims of observational medical research are reported in Table 1. The current limitations of post-marketing safety analyses of both drugs and devices deserves special consideration. Spontaneous reports contain only those events or reactions submitted voluntarily either to a regulatory authority or to the drug manufacturer by consumers and/or members of the health profession. The information is often incomplete and not verified scientifically or otherwise. Often there is no certainty that the suspected therapeutic agent caused the reported reaction, as physicians are encouraged to report suspected reactions. Accordingly, the reporting rate is subject to biases and various external factors, including an increased reporting during the first 2 years or so of the launch of a new therapeutic tool as compared with the remaining years of use. Specific observational networks with huge support from information technology have been structured or are being implemented in several countries, in particular in the USA,2 aimed at detecting and confirming signals rapidly and quantitatively.

According to the multiplicity of aims of observational research, a number of methodological approaches have been described and discussed. Recently an international initiative of epidemiologists, methodologists, researchers, and journal editors reformulated the principles of a methodological approach to different types of medical observational studies.3 Detailed recommendations on reporting observational longitudinal research have also been published.4 Adherence to multiple methodological rules, including systematic and accurate checking of data quality (both central checking and peripheral auditing), consecutiveness of patient enrolment, representativeness of the pre-defined setting of recruitment, to be balanced with the independence of the investigators from the funding sources, may be difficult for observational studies often not supported by adequate resources. However, it is necessary to be rigorous in order to avoid misleading and confounding findings. Precise and clear definition of the variables included in the data set is also essential to interpret the data correctly and to allow comparisons across different populations and settings. Imprecise definitions can lead to apparent inconsistencies of the findings, and changes in definitions adopted by the medical community with time can simulate even radical and abrupt epidemiological modifications. The choice of the variables to be collected, consistent with the observational nature and the aim of the study, may be critical. Frequently, a compromise is necessary between the number of desired variables and the workload needed to collect the requested information; in other words, to guarantee the feasibility of the study. The larger the network of...
The main findings were a marked increase in HF incidence (after 1992–1996) seen among persons aged 44–54 years, peaking in the mid-1990s, and contrasting with the decrease in the younger groups. An increase of HF incidence having stopped in the last decade is considered epidemiological change.

A few limitations of the reported analysis, in part acknowledged by the authors, should be considered. First, as mentioned above, the universal nature of the registry (all hospitals, all patients) results in simple data sets. This requires the difficult exclusion of important variables. For instance, most biological variables are not included in the reported registry; one above all, the left ventricular ejection fraction. In a time of intense research focused on HF with reduced vs. preserved ejection fraction, this lack may be felt as a serious limitation.

Secondly, the main findings of the study rest on hospitalization for or with HF (first-ever HF diagnosis code in any position at discharge, not necessarily as the primary diagnosis). It is well known that in the long run changes in national health system structure and rules, availability of facilities, modifications of adopted diagnostic definitions, sensitivity of the physicians toward certain diseases, and so forth, can lead to changes in hospitalization rates for a disease, regardless of its incidence. Thus, taking the HF hospitalization rate as the metric of HF incidence can expose the data risk of non-marginal approximations. This can be managed in part by analytical adjustments, but not all variables can be easily adjusted in the analyses.

The authors are aware of this potential limitation of course, but they are confident that the reported changes in hospitalization reflect true epidemiological changes. Thirdly, the gradual increase over time, at any age, of the diagnosis of cardiomyopathy raises further questions. The huge heterogeneity in aetiology and phenotype of cardiomyopathies and the multiplicity of definitions released in the last 20 years by various bodies justifies a robust scepticism of the possibility of measuring true epidemiological changes based on relatively vague definitions of diagnostic discharge codes. For instance, the classification of cardiomyopathy released by the European Society of Cardiology (Working Group on Myocardial and Pericardial Disease) and the American Heart Association in the last few years differ substantially. The issue is not related only to the definition of cardiomyopathy given in the registry, but mostly to the ability of the physicians to interpret uniformly the diagnostic criteria of such a complex disease category. The rate of diagnosis of cardiomyopathy increased in Sweden, but in my view the reported findings do not offer enough evidence that this reflects an epidemiological change.

Conflict of interest: none declared.
Epsilon waves in giant-cell myocarditis

Dirk Vollmann1,*, Andreas Goette2, Reinhard Kandolf3, and Gerd Hasenfuss1

1Division of Clinical Electrophysiology, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Georg-August-University, Robert-Koch-Str. 40, 37075 Göttingen, Germany; 2Department of Cardiology and Intensive Care Medicine, St Vincenz-Krankenhaus, Paderborn, Germany; and 3Department of Molecular Pathology, University Hospital, Tübingen, Germany

* Corresponding author. Tel: +49 (0)5513910265, Fax: +49 (0)5513910268, Email: d.vollmann@med.uni-goettingen.de

A 44-year-old male with palpitations and dyspnoea presented with sustained ventricular tachycardia (VT) (Panel A). ECG during sinus rhythm (SR) showed late potentials after the QRS complex, particularly in the right precordial leads (Panel B, red arrows), consistent with epsilon waves. Echocardiography revealed moderate biventricular wall thickening, normal left ventricular (LV) size and systolic function but moderate right ventricular (RV) dilatation. Coronary angiography ruled out coronary artery disease. Cardiac magnetic resonance imaging findings (Panel C, short-axis, T1-weighted late gadolinium enhancement) were consistent with myocarditis with prominent RV involvement. Immunohistology of RV endomyocardial biopsies revealed active giant-cell myocarditis (Panel D, arrow: CD68-positive giant cells). Immunosuppression (steroids and cyclosporine) was initiated and ICD implantation planned. Upon placement of the transvenous ICD lead, only markedly delayed potentials of low amplitude (≤2.5 mV) could be acquired from different RV sites, making implantation of an epimyocardial LV pace-sense electrode necessary. Eleven weeks later, an invasive EP study was performed due to recurrent VT despite amiodarone therapy. During SR, electro-anatomical mapping (CARTO3, Biosense Webster, USA) of both ventricles showed large areas of diseased myocardium [local bipolar amplitude (Bip) <1.5 mV, Panel E] within the RV. Notable, marked RV activation delays (Panel F, LAT, local activation time with respect to QRS onset) correlated with epsilon waves on surface ECG (Panel G, MAP, mapping catheter signal).

When VT occurs in a mid-aged male with normal coronary arteries and evidence for prominent RV disease, ARVC, sarcoidosis and giant-cell myocarditis should be considered. Epsilon waves are a major diagnostic criterion for ARVC, but this case illustrates that also other cardiac pathologies such as giant-cell myocarditis can cause severe RV conduction disturbances manifesting with VT and epsilon waves on surface ECG.