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CURRENT OPINION

The role of cardiac registries in evidence-based medicine

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Introduction

Cardiovascular disease remains the primary cause of mortality, and a major cause of disability in the developed world.[1] This significant burden necessitates ongoing improvements in patient management, to minimize the impact of cardiovascular conditions on both patients and healthcare systems. These improvements in cardiovascular care are promoted by an evidence-based approach, shaped by comprehensive clinical guidelines.

The scientific basis of recommendations is an important feature of clinical guidelines, and influences the degree to which they are followed in clinical practice.[2] Recent studies have assigned the highest evidence grading to randomized controlled trials (RCTs) that are clinically important, and representative of the clinical population covered by the guideline recommendation.[3] For example, this highest grading was assigned to a recommendation based on a meta-analysis of RCTs showing low-dose diuretics to be the most effective first-line treatment for cardiovascular event prevention in hypertensive patients. This study reviewed data from 42 RCTs which were, crucially, representative of the population that the recommendation was made for (i.e. hypertensive patients).[3,4]

The importance of the applicability of evidence to recommendations highlights the need to consider evidence from clinically relevant situations, not all of which have been assessed by RCTs. This evidence can originate from expert consensus, as well as non-randomized prospective studies. Although generally providing a lower evidence-level than RCTs,[3,5] observational studies can make an important contribution to the evidence base when the study outcomes are clinically important, and the populations involved are representative. Indeed, information from several registries was considered in the recent American Heart Association Acute Coronary Care in the Elderly Scientific Statement.[6]

Non-randomized prospective registries document the treatment and outcomes for consecutive patients in clinical practice. Therefore, data are gained from a 'real-world' selection of patients, many of whom would be excluded from RCTs, in a variety of clinical settings. RCTs are costly, which limits the size of the populations under study. In contrast, registries can survey large populations, providing a powerful scientific tool. For example, The Global Registry of Acute Coronary Events, launched in 1999, currently includes over 100 000 patients with acute coronary syndromes (ACS) in 30 countries worldwide.[7] The Reduction of Atherothrombosis for Continued Health (REACH) Registry set out to recruit 68 000 outpatients at risk for, or suffering from, atherothrombotic diseases from 44 countries worldwide.[8] The global nature of these surveys provide an unprecedented opportunity to study the epidemiology of atherothrombotic diseases and the varying use of management strategies, both between and within regions.

Within Europe, the Euro Heart Survey (EHS) programme comprises a series of surveys and ongoing registries investigating conditions including ACS, diabetes, heart failure, congenital heart disease, valvular heart disease, pregnancy in heart disease, chronic stable angina, secondary prevention, and atrial fibrillation, as well as treatments including coronary revascularization and percutaneous coronary interventions (PCIs). The programme has grown to include 182 hospitals from 35 countries, and individual surveys document up to 47 000 patients.[1] The European Society of Cardiology designed the EHS to assess the applicability of evidence-based medicine (RCTs), the application of guidelines in clinical practice and the outcome of different patient management

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strategies.[9] These and other registries are currently documenting the prevention, diagnosis and treatment of a variety of cardiovascular diseases in clinical practice throughout the region. The past and future findings of these studies have the potential to provide a link between RCTs and the 'real-world' situation.

Methodology and limitations of non-randomized prospective registries

Prospective registries involve the follow-up of a cohort of patients over time. This approach can be expensive and requires a long period of time to complete, but offers several advantages over cross-sectional surveys. For example, the temporal associations between baseline factors and outcomes can be assessed. Additionally, information about the patient's treatment and risk factors can be noted at the time at which they are measured, rather than relying on historical records, which might be incomplete.

Key attributes of an effective registry are summarized in *Table 1*. Standardized methodologies are crucial to the quality of registry data, and facilitate comparisons between the findings of different registries.[10–12] Standardized definitions and reporting systems are particularly pertinent when a large number of centres, countries, and languages are involved in a single registry. Additionally, a standardized system of cardiology data collection would avoid duplication of effort due to requests for differing data from different organizations.

To address this issue, the Cardiology Audit and Registration Data Standards (CARDS) have been developed to encourage uniform data collection across countries within Europe. Variables, definitions, and coding were defined for patients with suspected ACS, patients undergoing PCI, and patients using a pacemaker or implantable cardioverter defibrillator and undergoing an ablation procedure. These standards cover demographics, past history, risk factors, presenting symptoms, procedure or event details, outcome, discharge details, and follow-up. The CARDS were approved by all member states of the European Union in 2004, and it was reported that most EU countries would be likely to adopt them in future cardiology health information systems.[12]

As first outlined by Alpert in 2000, a useful prospective registry requires several other characteristics. To ensure the quality of registry data, standardized sampling techniques, randomized selection (or inclusion of all) clinical centres, thorough understanding of definitions by participants, reporting of all collected data, and continual improvement of submitted data were suggested. In addition, proper analysis procedures were encouraged through centralized compilation and analysis of data, and involvement of a professional statistician. For transparency, it was proposed that the names of all participating investigators and details of funding should appear in all publications. Furthermore, a single principal investigator or small steering committee was recommended to maintain momentum and ease the resolution of any issues that might arise in such a large undertaking. Finally, it was noted that proper ethical review procedures are necessary.[10,11]

Even when these criteria are met, care should be taken when interpreting findings from prospective registries. Most importantly, patients included in prospective registries experience 'real-world' therapy choices, and are not randomized to treatments. This means that care must be taken when drawing conclusions regarding treatment effectiveness, for which RCTs are the gold-standard. Careful registry design and robust statistical methods can help to improve the strength of registry findings. As well as being uniform in definition, the variables collected must be appropriate to the aim of the study. Several years ago, a process of optimizing and prioritizing variables collected in registries of patients undergoing coronary artery bypass grafting (CABG) was carried out using existing registry data. Only after new data were prospectively collected with these variables could they be used for risk adjustment.[13]

Table 1 Key attributes of an effective clinical registry

1. Standardized data collection with definitions and reporting (CARDS approved by all EU countries)
2. Integrated tools for rapid feedback to participating institutions
3. Appointment of a single principal investigator or a small steering committee
4. Proper ethical review procedures
5. Electronic data capture with clear, simple explanations of definitions and instructions for participants, and plausibility controls to highlight incorrectly entered data
6. Randomized selection of centres (ideally, 100% participation)
7. Consecutive enrolment of patients for representativity
8. Audit of at least a small group of randomly selected centres
9. Centralized data compilation and statistical analysis, performed by professional statisticians
10. Reporting of all collected data, with conclusions appropriate to study the design
11. Transparent reporting of investigators and funding sources in all publications

The main goal of evidence-based medicine is to guide therapeutic decisions. As a scientific basis for recommendations, information about the causal effects of relevant treatments is needed, i.e. the differences in outcomes of patients if they receive one or the other therapy. The best evidence comes from studies where both (or all) treatment groups are representative of the population that is to be treated. A crucial problem of many RCTs is that the treatment groups are similar to each other but not to the patient population that appears in clinical practice. However, in observational studies, characteristics and risk profiles of the treatment groups are usually different, so estimates and statistical tests of treatment effects may be biased. This bias pertains only to situations where the registry is regarded as an observational study to estimate treatment effects, not as a survey, for instance.

Imbalances in risk factors between treatment groups can confound the effect of the treatment and its estimation. Regression modelling (usually logistic or Cox regression) and matching are statistical methods to adjust the effect estimates for imbalances in observed confounders, and to control this overt bias. The selection of patients into treatment groups can be explored by a propensity analysis, and the calculated propensity score can be used for regression, stratification, or matching. These methods are

demonstrated by a series of publications from the New York cardiac reporting systems.[14–17] However, it should be noted that with any registry analysis, unforeseen confounders are always possible. Therefore, although registries provide important additional information, they do not replace RCTs, and can be considered unsuitable for inclusion in meta-analyses of RCT data.[18]

There is also a possibility that centres that are more compliant with guidelines might be more likely to participate, resulting in selection bias. Moreover, since the populations included in registries can be specific (e.g. confined to one country), the findings might not be extrapolated to other populations. When a registry is well-designed and any differences between baseline patient characteristics are taken into consideration and corrected for as far as possible, the 'real-world' nature of registry data can generate important hypotheses regarding everyday treatment use and outcomes.

Transferability of randomized controlled trial findings into clinical practice

As well as being performed in high-volume, experienced centres, RCTs enrol highly selected patient populations. Indeed, it is estimated that less than a third of heart failure patients in clinical practice would qualify for inclusion in RCTs,[19,20] due to factors including age and concomitant disease, resulting in a potentially lower-risk population than is seen in clinical practice. Prospective registries can be used to assess whether RCT findings in these selected populations can be transferred to the unselected clinical population. This can be achieved in two ways; firstly, the characteristics of patients included in registries can be assessed to determine whether they are similar to those included in clinical trials; and secondly, they can show whether RCT findings are maintained in the unselected (or excluded) clinical population.

It should, however, be noted that prospective registry populations are not randomized, and findings regarding treatment efficacy should therefore be treated with caution. Indeed, small imbalances in unmeasured confounders that have a strong relationship with outcomes can have a large confounding impact on the relationship between treatment and outcomes. The contradictory findings from two analyses of the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) provide a good example of the importance of approaching registry findings (and, indeed, any individual study) with caution. The initial analysis of the 2003/2004 SCAAR cohort indicated increased mortality rates associated with drug-eluting stents compared with bare metal stents,[21] which was reversed in a recent analysis of the 2003–06 cohort.[22] Suggested reasons for this reversal included an improved balance in lesion and stent characteristics between the two groups in the latter study,[22] highlighting the potential impact of unforeseeable confounders.

The European Network for Acute Coronary Treatment (ENACT) and European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) registries revealed similar rates of risk factors, including smoking and diabetes, among European coronary heart disease populations.[23,24] These rates can be compared with the baseline demographics of RCTs to help assess whether the selected population can be considered truly representative. It is interesting to note that a survey of nearly two thousand consecutive acute myocardial infarction (AMI) patients admitted to coronary care units in Italy reported that over a quarter were over 75 years of age.[25] In RCTs, patients in this high-risk age group have been far fewer,[26] or even excluded from participation.[27]

If higher-risk patients are not adequately represented in RCTs, registries have an important role in validating trial findings in groups that are excluded or under-represented. However, it is important that the potential confounding associated with the analysis of non-randomized populations is considered. In the case of comparing outcomes following PCI or thrombolysis after AMI, registry data have confirmed that the superiority of PCI is not restricted to selected, relatively lower-risk patient sub-groups. Indeed, the superiority of PCI has been shown to be maintained in groups including the elderly, patients who had undergone resuscitation, and patients with cardiogenic shock (*Figure 1*).[28] A recent study has further confirmed this finding in a high-risk diabetic population.[29]

RCTs comparing PCI with CABG have also been assessed for their applicability to clinical populations. The characteristics and outcomes of patients who participated in 14 major RCTs were compared with those of over 4000 patients enrolled in the EHS on Coronary Revascularization, and in concordance with other studies, nearly two-thirds of the Survey participants would have been ineligible for trial participation. Patients in clinical practice were shown to be both older, and more likely to be suffering comorbid conditions. Interestingly, the RCTs showed no difference between PCI and CABG in outcomes, a finding that was replicated in the trial-eligible Survey patients. However, in the trial ineligible patients, a clear 1-year survival benefit was reported for PCI over CABG. This resulted in a significant benefit for PCI in the overall Survey population.[30] The conflicting results from an analysis of a New York registry[15] might be explained by this contrast between trial eligible and trial ineligible patients.

The analysis of high-risk sub-groups using registry data are particularly important given the increased rate of complications in these patients, and the potential for therapies to cause harm. Indeed, due to an absence of RCTs evaluating the efficacy of thrombolysis in elderly patients, a large retrospective cohort study was performed in the USA to investigate the treatment in this population. The study showed that thrombolysis actually led to a reduction in survival, rather than benefitting the elderly.[31] A study investigating these interventions in a similarly elderly European population also found that thrombolysis did not improve in-hospital mortality, although 1-year mortality was improved. In this study, PCI improved both hospital and 1-year outcomes.[32] However, in a systematic overview of large randomized trials, a benefit of thrombolysis therapy was shown in elderly patients.[33] Indeed, when the population aged $\geq$75 years meeting the current eligibility criteria for reperfusion (presenting within 12 h with ST-segment elevation or bundle-branch block only) was analysed, a significant 15% relative reduction in mortality was shown.[34] These findings highlight the dangers inherent in extrapolating RCT findings between different populations, and

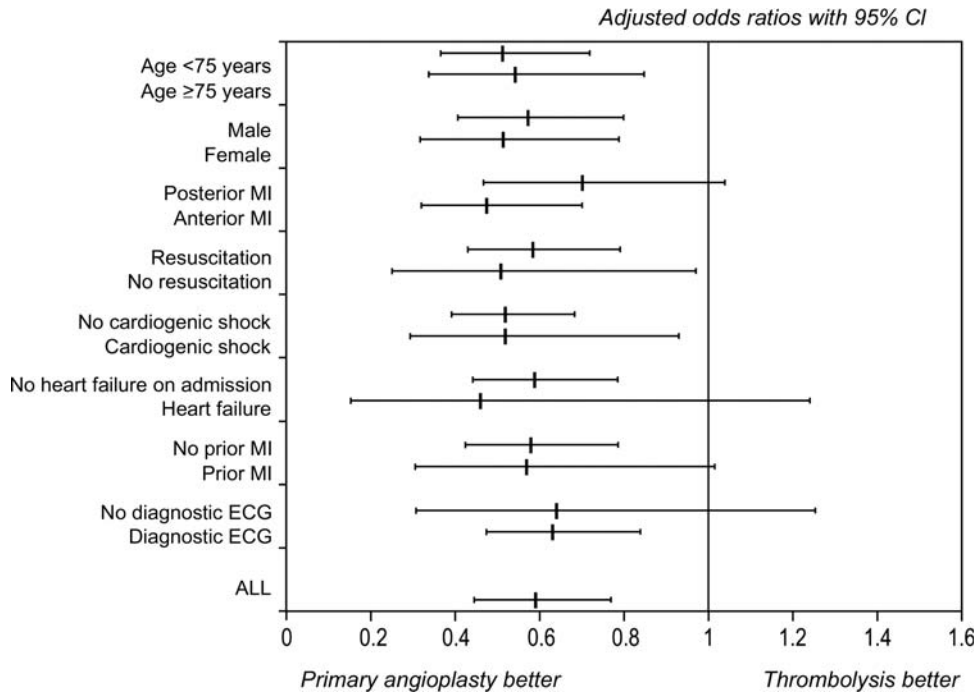

Figure 1 Multivariate analysis of hospital mortality following percutaneous coronary intervention or thrombolysis, performed following acute myocardial infarction in different patient sub-groups.[28]

also demonstrate the importance of assessing prospective registry findings using RCTs wherever possible.

Hypothesis generation from registry findings

Prospective registries can produce a wealth of data regarding characteristics, treatments, and outcomes for large numbers of patients. Analyses of these data can aid investigation of a range of questions that cannot be addressed by RCTs due to ethical considerations. Furthermore, registries can identify novel associations, generating hypotheses for future RCTs to confirm or disprove. A well-known example is the reduced rate of cardiovascular disease in women following post-menopausal oestrogen, identified by several observational studies dating from the mid-1980s.[35] The Heart and Estrogen/progestin Efficacy Study (HERS), a randomized, blinded, placebo-controlled trial, was designed to assess whether this association could be attributed to the treatment itself, and was not a product of confounding factors. Ultimately, HERS failed to show a reduction in cardiovascular events between the treatment and placebo arms.[36] Therefore, the observational study findings could not be attributed to the therapy itself, at least in the post-menopausal with established coronary heart disease population studied by HERS.

Studies of large registry populations are also ideally placed to assess the incidence of rare adverse events that might not be identified by RCTs, particularly within high-risk groups. Post-marketing surveillance is very important given the short duration and specialized settings of RCTs, and the FDA recognizes the importance of integrating cardiac registries into their adverse event reporting systems.[37] These changes will make large populations of patients in a 'real-world' setting available for adverse event monitoring.

Quality assurance in cardiovascular medicine

Prospective registries provide a unique opportunity to accurately assess current clinical practice and outcomes, and compare these with other institutions and clinical practice guidelines. These data contribute to an ongoing process of quality assurance, indicating areas where education is necessary (*Figure 2*). It is therefore important that registries include integrated tools for rapid feedback to participating institutions.

The Swedish national Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) provides instant on-line access to reports regarding selected patient groups, as well as analysis and anonymous comparison of care consumption, treatments, and short and long term outcomes. Changes over time in comparison with other hospitals can also be viewed.[38] This is particularly useful given the greater than 90% participation of hospitals in the country.[39] Investigators at a new coronary intensive care unit in France used data from the Global Registry of Acute Coronary Events (GRACE) registry in this manner. The authors were able to confirm that treatment and outcomes for ACS patients at their institution were similar to those achieved by experienced

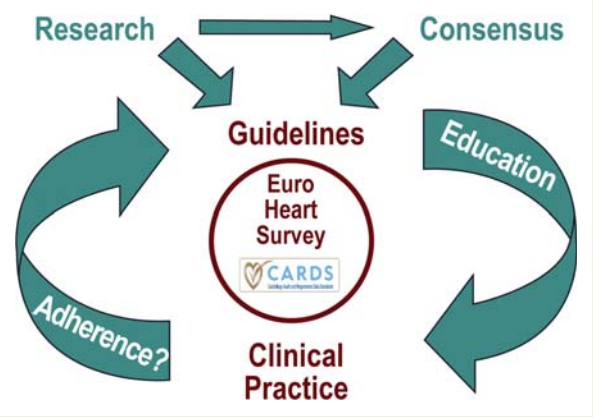

Figure 2 The European Society of Cardiology prospective surveys/registries quality cycle.[1]

institutions in the region.[40] Similarly, the EHS programme offers a benchmarking service for quality assurance for participating hospitals, and the ESC Working Groups and Associations.[1]

Registry data have also been used to determine areas in which treatment practices are suboptimal or conflicting with guideline recommendations,[41–45] or vary substantially between geographical areas[23,46] or between patient sub-groups.[43] Moreover, inadequate adherence to guidelines has been shown to translate into reduced survival rates for AMI patients.[44] An encouraging increase in adherence to guidelines was identified by the second Euro Heart Survey on Acute Coronary Syndromes (EHS–ACS-II) when compared with EHS–ACS-I, which was completed 4 years earlier.[47] Use of primary reperfusion therapy increased from 56 to 64%, and mortality rates fell by ~20%, both in hospital and at 30 days follow-up. Patient characteristics were similar between the two surveys, and 34 of 190 centres participated in both EHS–ACS-I and EHS–ACS-II. Interestingly, patients treated at centres that participated in EHS–ACS-I were even more likely to receive evidence-based medicine during EHS–ACS-II than the survey population as a whole, and the reduction in mortality was even greater at these centres. The primary reasons for patients not receiving evidenced-based medicines were contraindications, or lack of indication for treatment within current guidelines. Therefore, this data could help to indicate to future writing committees where current guidelines might be lacking, and where gaps in guidance need to be filled.

Conclusions

A range of prospective registries are currently providing a wealth of standardized data regarding patient characteristics, clinical practices and outcomes, both within Europe and worldwide. This important resource should be used to its full potential, informing and assessing the implementation of clinical practice guidelines, and providing important epidemiological insights that can inform future RCTs. It should also be used appropriately, with careful attention to design, analysis, and interpretation. These registries should be regarded as a key source of data for quality assurance in cardiovascular medicine.

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