

WJC 6th Anniversary Special Issues (5): Myocardial infarction

Clinical disease registries in acute myocardial infarction

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Received: December 28, 2013 Revised: February 18, 2014

Accepted: April 16, 2014

Published online: June 26, 2014

drome; Coronary artery disease; Health statistics; Ethics; Patient records; Audit; Research; Patient safety

Core tip: Clinical disease registries are one of the oldest types of research methodology. They have been particularly important in the researching and guiding the management of myocardial infarction. Registries in multi-site studies can often be cheaper and simpler to undertake and less demanding of patients, and allow huge volumes of data to be collected from which many landmark studies already have been published.

Ashrafi R, Hussain H, Brisk R, Boardman L, Weston C. Clinical disease registries in acute myocardial infarction. *World J Cardiol* 2014; 6(6): 415-423 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i6/415.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i6.415>

Abstract

Disease registries, containing systematic records of cases, have for nearly 100 years been valuable in exploring and understanding various aspects of cardiology. This is particularly true for myocardial infarction, where such registries have provided both epidemiological and clinical information that was not readily available from randomised controlled trials in highly-selected populations. Registries, whether mandated or voluntary, prospective or retrospective in their analysis, have at their core a common study population and common data definitions. In this review we highlight how registries have diversified to offer information on epidemiology, risk modelling, quality assurance/improvement and original research-through data mining, transnational comparisons and the facilitation of enrolment in, and follow-up during registry-based randomised clinical trials.

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Key words: Myocardial infarction; Acute coronary syn-

INTRODUCTION

Despite improvements in prognosis, myocardial infarction (MI) remains a major cause of death and morbidity^[1]. Significant structural, human and financial resources (nearly two billion euros/year in the United Kingdom) continue to be devoted to its management^[2]. This aspect of cardiological practice has been particularly well served by rigorous research using large randomised control trials (RCTs) of specific interventions or strategies-many of which have informed national and international guidelines^[3-5]. However, such guidelines are not automatically adopted. Clinicians may be slow to change, or uncertain where new findings fit into, their existing practice. They may fail to recognise, within a well-designed RCT, with its controlled environment, narrow inclusion criteria and intention to treat analyses, their own patient populations and complex (messy) working conditions, where what matters is not what treatment is “intended” but rather what is “given”, and the subsequent outcome. Registries

illuminate what is actually happening in practice.

Registries existed before the contemporary dominance of the RCT, and continue to flourish, as clinicians, researchers, healthcare companies, policymakers and patient advocacy groups recognise their importance. They complement the RCT, in as much as they allow an understanding of the extent to which the findings of RCTs are implemented in practice. Their analysis fills in some of the “gaps in evidence” concerning interventions for which RCTs have not been, or cannot be, performed or have not provided definitive answers. Additionally, they have a role in quality assurance, through clinical audit, and quality improvement initiatives and will play a central role in describing the outcomes of clinical care, from patient and payer perspectives.

There is no unified definition of a disease (or clinical) registry. While many registries fail to provide comprehensive outcome information the following two definitions highlight some of the key features:

“An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes”^[6].

“... a systematic collection of a clearly defined set of health and demographic data for patients with specific health characteristics, held in a central database for a pre-defined purpose”^[7].

So a registry is characterised by an intention to explore what is happening to patients with a particular condition or health need, pre-planning, explicit definitions of data items, a systematic approach to data collection, and a clear purpose.

In this anniversary edition, we review the historical background of registries, their characteristics, practical issues and future development in the management of myocardial infarction. Necessarily we will draw on our experience within the United Kingdom, but will also discuss other established national and international registries. We do not intend to provide an exhaustive catalogue of such registries, and mean no disrespect to colleagues whose registries we do not mention.

HISTORICAL DEVELOPMENT

The earliest registries were the personal records of individual physicians formed through their review of patient cases. These were presented and published as case series of particular conditions for the education of the wider medical community. The emphasis was on presentation and prognosis, rather than treatment of the recently recognised condition of coronary thrombosis. Examples of these early series, the precursors of the modern registry, can be found in the 1920s such as a seminal series of papers from Boston on MI and angina^[8]. By 1931, White and Bland^[9] were able to report on the prognosis of 200 cases of coronary thrombosis.

Collaborative, small scale, hospital registries began

to appear, normally containing observational reports on changing patterns of disease or outcomes of patients with MI^[10]. Interestingly, many of the most common clinical practices such as the use of the coronary care unit^[11] and description of Killip class^[12] were introduced following publication of analyses of disease registries.

In the late 1960s, there was great interest in a more collaborative international approach, to better understand the epidemiology of MI. The World Health Organisation (WHO) set up and co-ordinated a number of local MI registries (the MONICA project) which yielded much valuable information at a local level^[13]. This WHO initiative focussed on communities rather than hospitals, and was therefore able to capture information about those who died before reaching hospital and those who (as was common practice at that time) were managed at home by their general practitioners^[14]. Importantly, it promoted the collection of common datasets of information. The primary purpose remained “educational”-to more precisely describe the incidence of coronary events in a community, to categorise the various manifestations of heart attack and to compare fatality rates between communities. While others more recently have attempted to perform exhaustive community-based prospective studies of MI^[15,16] with an emphasis on expressing the “burden” of disease within a population-most existing registries are hospital-based (*i.e.*, patients are included/enrolled upon admission to hospital); the emphasis is on describing the provision of care and its effect on outcomes.

The need for a change in emphasis to allow such analysis was recognised by Hugh Tustall Pedoe in 1978 (echoing the thoughts of Osler, above): “The collection of information for its own sake is of doubtful value unless it is acted upon. Community registries should not become the equivalent of village war memorials”^[17].

He further stated that such information could be used in “monitoring the effects of treatment” and ensuring that it was “reaching those who needed it”. Here was an aspiration for registries to be used to assure provision of appropriate care and to record outcomes.

Long established, single-centre, registries (*e.g.*, the enduring Nottingham Heart Attack Registry, which began in 1972), instigated by interested clinicians rather than imposed by healthcare managers or professional bodies, provided fascinating insights into the changing management of MI^[18] but did not allow direct comparison with other units.

In some countries it was recognised that the administrative records generated to support well-developed insurance-based healthcare systems could be used for a secondary purpose: to create registries to compare care between hospitals (as “provider units”). In the United States, the Co-operative Cardiovascular Care project used billing information to investigate improvements in care, particularly for MI^[19]. The use of administrative data is now a common and cost-effective approach to data collection within registries.

More recently, there has been a general shift from registries as a mechanism for the “passive” reporting of

Table 1 Examples of key or historic exemplar registries of myocardial infarction

Registry/author	First publication year	Location	Setting	Key outcome
White ^[8]	1926	United States	Hospital	Prognosis of MI
Killip <i>et al</i> ^[12]	1967	United States	Hospital	Importance of coronary care unit
Tower Hamlets coronary project ^[14]	1972	United Kingdom	Community	Community based treatment and outcomes of MI
MONICA Project ^[23]	1987	Global	Various	Geographical variation, mortality and epidemiological trends
Second National Registry of Myocardial Infarction ^[24]	2000	United States	Hospital	Importance of door to balloon time in angioplasty
GRACE ^[25]	2002	Global	Hospital	Risk stratification in acute MI
EuroHeart Survey ^[26]	2002	European	Hospital	Quality improvement and assurance
MINAP ^[27]	2004	United Kingdom	Hospital	Epidemiology and quality improvement

MI: Myocardial infarction; MINAP: Myocardial Ischaemia National Audit Project; GRACE: Global Registry of Acute Coronary Events.

epidemiologic characteristics and the provision of treatments towards their use in an “active” process that assures and improves quality of care. Such an initiative can be appreciated in the Global Registry of Acute Coronary Events (GRACE)-a collaboration of over 100 volunteer hospitals in 14 countries to produce the largest multinational register of patients hospitalised with acute coronary syndrome^[20]. The development of this influential registry has been a milestone in the use of such data, not only in its “worldwide reach” but also in the underlying intention, to improve the care of MI.

Similar strategies of quality improvement and audit have been introduced in many countries. In the United Kingdom, the Myocardial Ischaemia National Audit Project (MINAP) began in 1998 with the intention to audit the management of all patients admitted to hospital in England and Wales following MI^[21]. The results of this project have allowed cardiologists to audit the performance of their hospital and focus on areas of inadequate performance in order to improve care^[22].

A selection of exemplar registries in MI through the years is shown in Table 1.

TYPES OF REGISTRY

MINAP is a (1) mandated, (2) continuous registry that uses a (3) unique data collection system to describe the (4) “whole-pathway” of care of acute coronary syndrome-from the onset of symptoms until discharge from hospital. It is designed to collect data on every case, regardless of where the patient is admitted within a hospital, though case ascertainment is incomplete. While some registries share these four attributes (*e.g.*, the Swedish SWEDE-Heart registry^[28]), others differ in this regard.

So, for example, in Italy the BLITZ programme consists four separate voluntary, time-limited, “snapshot” audits of care provided to a limited number of patients admitted to cardiac care units-the most recent being for a 10 wk period in 2010^[29]. In France the FAST-MI audit programme has, every five years since 1995, organised a month-long, nationwide, voluntary registry of consecutive patients admitted, with either STEMI or NSTEMI, to cardiac or intensive care units, within 48 h of symptom onset^[30]. The Acute Coronary Syndrome Israeli Survey is a biennial nationwide survey of acute coronary syndrome patients admitted to all 26 public hospitals in Israel dur-

ing a 2 mo period^[31]. An advantage of such intermittent (snapshot) data collection is the ability to collect very detailed and extensive data for a limited number of patients over a relatively short time (*e.g.*, 3079 patients over 1 mo in FAST MI 2010 compared with 79863 in the 12 mo from April 2010 in MINAP^[32]) without causing undue fatigue for data collectors. The long interval between snapshots allows adequate time for follow up of patients, for careful analysis of results and for the re-design of the next registry.

Some registries are designed to capture data for only certain sub-groups of patients with MI. So the ALERT-CZ registry reported on aspects of the pre-hospital treatment of patients admitted to 32 non-interventional hospitals in the Czech Republic^[33]; The Austrian Acute Percutaneous Coronary Intervention (PCI) Registry restricts analysis to those patients with acute coronary syndrome undergoing PCI, and so can provide accurate data on particular adjunctive drug treatments during such interventions^[34]; The Spanish EPICOR, a large registry sponsored by a pharmaceutical company, concentrates only on survivors of MI^[35].

As mentioned earlier, while many registries require active collection of data as an additional task, others use (or “mine”) routinely-collected administrative data, either as the sole data source, or, as in the case of MINAP, as the mechanism to provide basic follow-up information. Using administrative data restricts the types of question that can be answered through subsequent analysis, but considerably reduces the effort involved in collection. In many cases, at the local (hospital) level, there is no financial incentive to collect data and so anything that makes data collection less onerous is greatly advantageous.

Provision of data to registries may be voluntary on the part of the patient, such as the STENT registry on treatment of vein graft disease^[36], voluntary on the part of the hospital such as the Danish registry on mortality in ST-elevation and non-ST elevation MI^[37] or mandatory as part of a local legal or business framework-in some cases the successful completion of data is necessary if a hospital is to receive payment for the care provided.

FUNCTIONS OF REGISTRIES

Epidemiological information

Provision of epidemiological information-incidence and

prevalence, patient characteristics, intervention rates-the national Swiss AMIS Plus, and CZECH 1 and CZECH-2, being key examples of projects that can evaluate changes in epidemiology^[38,39].

Risk modelling and prognostication

Risk modelling and prognostication-as in the national MINAP registry^[40] and the multi-national GRACE-risk scores derived from such registries, and validated in others^[41], allow interventions to be targeted at those at highest risk, and therefore most likely to benefit, and, through use in case-mix adjustment, allow meaningful comparisons between hospitals and health systems.

Quality assurance

Quality assurance-registries can be used to measure performance against “best practice”, as described in national or international guidelines. In Europe, the first Euro Heart Survey on acute coronary syndromes was a large registry that looked prospectively at adherence to guidelines^[26] a second survey, repeated several years later, showed improved guideline adherence and superior outcomes^[42]. This has been confirmed in the Swedish registry where the adoption of evidence-based interventions (those shown to be beneficial in randomised trials) was shown to be associated with increased survival in those with STEMI^[43], and in MINAP where delivery of best and timely care (as expressed by a composite performance score) was associated with improved outcomes^[44].

Quality improvement

Quality improvement-registries can be designed, or opportunistically used, to monitor changes in process and outcomes of care, and so provide a good platform for assessing the effectiveness of quality improvement initiatives^[45]. Rather than being a passive tool to facilitate quality improvement, or a surrogate marker of a willingness to improve care (whereby voluntary participation in the registry is a sign of openness to change for the better), some have suggested that registries themselves provide the stimulus for instigating such initiatives. Major improvements in hospital performance and mortality rates have been reported following the public disclosure of hospital-specific results, with a substantial narrowing of the gap between the best and worst performing hospitals^[46].

Pursuit of research

Pursuit of research-while not their primary purpose, most registries lend themselves to the creation of generalizable knowledge^[47] and so to observational research. Such research, while adequate for hypothesis generation, for example the link between non-steroidal anti-inflammatory drugs and adverse cardiovascular events^[48], lacks the power to prove causality, but can be used to support findings from RCTs by reproducing the results of a trial in the large unselected captured in a registry population^[49]. However, analysis of registry data is complex, and often requires sophisticated multivariate analysis, sensitiv-

ity analysis and, because of incomplete data collection, imputation of missing values^[50] or propensity analysis^[51]. Notwithstanding these difficulties, the large volume of data held within a registry may be mined to yield important information. So, confirmation that earlier reopening of a coronary occlusion is beneficial was obtained not from a randomised trial of early *vs* delayed primary percutaneous intervention but from analysis of a registry that recorded door-to balloon times^[24]. Also, many registries have been used to show which pharmacological treatments are important in the MI population and how discontinuation can have significant negative outcomes for patients and have used this as a driver for improved post MI care^[22,52].

KEY PRACTICAL ISSUES IN REGISTRIES

With most registries there is a “trade-off”, or balance, between the richness of the data and data completion and case ascertainment rates. As the amount of information required for each case increases so do the demands placed upon local data collectors and, unless there is an explicit link between reimbursement for care and data collection, the likelihood that some cases will be included with incomplete data, and others will be missed altogether. This is of importance because there is evidence that those hospitals with poorer recording systems are also those with poorer outcomes^[53]. The extent of missing data is associated with 30-d mortality for STEMI and NSTEMI^[54]. This is less likely to be problematic in snapshot-type registries. Others have responded to this by introducing differing levels of participation, (*e.g.*, ACTION Registry-GWTG Premier and Limited levels of participation-the latter having 50% reduction in the amount of data collected^[55]) to allow centers that are experiencing particular problems with data entry to continue to register patients.

Some of the key properties of good registry design and performance and their practical aspects are shown in Table 2. A review of the advantages and disadvantages of the most common registry types is shown in Table 3.

ETHICAL AND GOVERNANCE ISSUES IN REGISTRIES

Data that can be collected from administrative records or medical case notes can be recorded without the individual patient’s knowledge or consent. Is this ethical? This is a point of significant controversy. Consideration of the principle of individual autonomy and right to personal privacy balanced against the greater good of future patients, as well as national statute, lead to significant variation in practice. Patients who refuse to give consent are systematically different from those who do not and their exclusion from registries is likely to skew findings^[59]. For this, and other reasons, some authors have argued that a regulatory insistence on individual choice is counterproductive, and that the standards suggested for

Table 2 Some key attributes of good registry design

Attributes of a good registry	Practical aspects
Standardised data collection and definitions	Pre-project agreement of common data definitions (<i>e.g.</i> , use of the Cardiology Audit and Registration Data standards ^[56]) and, where possible, standardised data collecting techniques
Rapid data collection	Computer web based data collection allowing rapid data accrual and transmission; agreed timeliness of data entry
Case ascertainment/ data completeness	Built in data checking during submission; regular data validation exercises (<i>e.g.</i> , the NCDR Data Quality Program ^[57]); comparison of case numbers with some other measure of unit activity; regular audit of participating sites to identify areas for improvement; explicit definition of participation in the registry and of a minimum dataset for each record; linkage to other complementary dataset ^[58]
Sequential enrolment	Allows for representative data without cherry-picking
Appointment of key stakeholders to a formal Steering Committee	Effective coordination of registry with oversight to share good practice and important results; guarantee analyses; clinical leadership and endorsement by professional bodies; regular revisions of the dataset reflect changes in practice
Random multi-site collection or mandated participation	Reduces the risk of population or site bias (as is common with RCTs in large academic city centres); enables comparisons between sites
Appropriate ethical considerations	Addresses both legal and ethical issues of patient consent; confidentiality; anonymity; data linkage (see below)
Clear and comprehensive result presentation	Clear and full results with meaningful and appropriate conclusions that reflect the findings and are presented in a way the target audience understands (<i>e.g.</i> , funnel plots); easy access to data and reports; clear explanations of any statistical adjustments
Transparent study background and funding	Prospective declarations of any issues

RCTs: Randomised control trials.

Table 3 Advantages and disadvantages of common registry types

Registry type	Benefits	Negatives
Academic	Limited external pressures for study; more flexibility in developing the dataset; lends itself to research; collaboration with many academic institutions and with Professional Bodies	Access to data provided by external sites may be limited; potentially limited funding; danger of “mission creep”-increasing data required; participating clinicians may become divorced from the academic group; difficult to enforce participation
Insurance	Ready access to data through billing information; large amounts of data held; potential for internal data linkage; large populations to study; excellent case ascertainment	Inability to expand dataset outside that determined by insurance company/HMO; difficult to influence/alter datafield definitions; full access to data may not be available due to commercial sensitivity
Industry sponsored	Well-funded; support for training of data collectors and encouragement of data entry; often based on access to new treatments	Limited sites; confidentiality clauses may restrict dissemination of findings; not all data widely available; may have strict patient selection (restricted to those receiving particular intervention); often time limited; less direct clinician control
Government	National “reach”; can promote and mandate high levels of participation and data collection; collaboration between multiple agencies; large population for study	Limited sense of clinical ownership

HMO: Health maintenance organization.

fully informed consent are too stringent and harm both research and public health^[60-62]. In the United Kingdom, the impact is low on patients whose data is included in a registry whose primary purpose is quality assurance and improvement and in which there is no intention to treat differently by virtue of participation, and so written consent is not required. The MINAP group, for example, has a legal exemption to hold patient-identifiable data without direct consent. As a result third party research access requires formal application of proposals to an academic steering committee and then only anonymised or pseudo-anonymised data is released after full academic review.

FUTURE DEVELOPMENTS

Registries will continue to develop beyond their original functions, becoming increasingly influential with respect

to quality improvement, regulation and research. This is predicated on an increased emphasis on professional accountability, the provision of safe, effective patient-centred care, and a shift of focus from the performance of particular interventions to the outcomes of the entire process of care. Increasingly, comparisons between clinicians, institutions and healthcare systems will be enabled through the implementation of common definitions for particular data fields across a range of registries. An international consortium of policy makers, clinicians, patient advocates and academics has identified registries as the mechanism through which to measure and report specific outcomes of the care of patients with coronary artery disease (including acute myocardial infarction) in a standardised way^[63], pointing to the need to share and to publicly report risk-adjusted data. Such transnational comparisons have recently been published following

painstaking analysis of two large national registries^[64]. Further, by understanding more about outcomes and costs of care it is hoped that patients will derive the maximum possible value of their interactions with clinicians in what has been called a “value-based” system^[65].

In addition to hard, readily/reliably measureable outcomes, such as death or length of stay in hospital, patients will be encouraged to report on their own outcomes following, and experiences of, care using a number of generic or disease-specific tools. These patient reported outcome measures or patient reported experience measures could potentially be gathered *via* integrated web services (with patient prompts), and provide a method of identifying important late complications which maybe outside the original data capture window^[66]. Furthermore, the social and emotional information contained within patient feedback may prove useful for the future design of services, and help understanding of adverse outcomes or difficulties in compliance with treatment.

If the ethical, legal and practical issues concerning the linkage of cases held in large datasets^[67] can be overcome, there will be further opportunities to appreciate the experiences and health needs of patients both before their index admission and thereafter. For example, the continuation of secondary preventive drugs following discharge from hospital with acute coronary syndrome has been assessed through linking the MINAP registry to a primary care dataset^[22]. It should be possible to link registries of heart attack to those of heart failure and cardiac rehabilitation, and so understand more fully the longer-term consequences of myocardial infarction.

Just as registries can provide information regarding the effects of quality improvement initiatives, so they can provide both a platform for enrolment and a mechanism for follow-up of patients participating in randomised trials of particular interventions; for example the TASTE trial of routine aspiration of intracoronary thrombus during primary percutaneous intervention^[68]. This technique, of registry-based randomised clinical trials, will significantly reduce the cost of interventional studies (to as little as 10% of the probable cost of an orthodox RCT in the case of TASTE) and maximise recruitment, while readily demonstrating the selective nature of the participating population through comparing the characteristics and outcomes of those enrolled with those excluded. The reduction in cost might also make possible important investigations of the utility of interventions for which there is no financial interest of the pharmaceutical or device industry—the usual sponsors of large trials—such as the role of supplemental oxygen in acute myocardial infarction^[69]. More investigator-initiated (either prospective/open-ended or time-limited/fixed-term) registries will be instigated to monitor the implementation of new technologies and to answer specific clinical questions^[70].

CONCLUSION

Registries have evolved greatly over the years from sources of epidemiological information to datasets whose analy-

sis can provide key information to clinicians, patients, researchers and medical policy makers. Registries will continue to provide important information on disease epidemiology, treatment and guideline adherence while being integral to quality improvement strategies in many disease states, as is already the case for MI.

ACKNOWLEDGMENTS

We acknowledge Emmanouil Lazarides and Polly Mitchell for helpful discussions and background research about the ethical dimensions of registries.

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