Cardiovascular registry research comes of age

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No matter how beautiful the strategy, you should occasionally look at the results.

Winston Churchill

Registry research is gaining increasing visibility within cardiovascular medicine. Randomised controlled trials (RCTs) are rightly at the top of the hierarchy of evidence for determining clinical efficacy. However, the characteristic that makes the RCT so powerful in establishing internal validity—control—limits the ability to provide a comprehensive picture of clinical medicine as it is practised. As in the Churchill quote above, RCTs may be able to provide the basis for the most ‘beautiful’ management strategies, but determining how these strategies work in the ‘real world’ is critical. In addition to these limitations in external validity, practical problems such as cost, time horizon and breadth of questions leave a clear need for many types of observational research. Registries across the globe are actively examining many aspects of this need. As with all study types, critical assessment of the structure, strengths and weaknesses of registries is necessary in order to gain an appropriate perspective of where this research fits into the broad picture of cardiovascular medicine. To this end, Heart will publish a new series of articles describing some of the most important registries of patients with acute coronary syndrome and other cardiovascular disorders.

ROLE OF REGISTRIES

How can registry research contribute to filling the knowledge gap? In his 2000 editorial entitled ‘Are data from clinical registries of any value’, Alpert articulated a well-reasoned affirmative answer to this question.1 Gitt and colleagues recently published an updated defence of cardiac registries in evidence-based medicine.2 Briefly, registries have multiple purposes.

First, they can be designed to assess the translation of information from an RCT into clinical practice. For instance, many therapeutic strategies—reperfusion, aspirin, β blockers and angiotensin converting enzyme inhibitors—have been shown to reduce mortality in patients with ST-segment elevation myocardial infarction. However, registries have been instrumental in demonstrating low adoption rates of these strategies,3–5 in identifying potential strategies to deal with them6 and in showing improvement over time.7 8

Second, registries can evaluate how the efficacy of a treatment extends to populations not included, or not well represented, in the RCTs. Patients in clinical trials are not representative of the population—either in baseline characteristics or in outcomes.9 10 Also, large academic tertiary care hospitals are more likely to participate in RCTs. While this bias may be minimal for simple treatments such as administration of a pharmaceutical agent, any evaluation of a more complex intervention, such as PCI, may very well be influenced by operator and hospital experience.11

Third, registries can assess longer-term risks than clinical trials. Owing to the high expense of RCTs, the time horizon of the experimental phase rarely exceeds 3–5 years. The impact of a therapeutic strategy over a longer period may be critical for a true assessment of risk–benefit, and certainly, for cost–benefit analyses.

Fourth, owing to the ability to follow-up large groups of patients for extended time periods, registries can often identify low incidence but important risks that RCTs would not. For instance, cardiovascular mortality for treatment of non-cardiovascular conditions, such as non-steroidal anti-inflammatory agents for rheumatological conditions,12 are often difficult to ascertain in RCTs.

Fifth, registries can answer certain questions not easily addressed by RCTs. For instance, identifying optimal timing of intervention in patients with unstable angina or non-ST-segment elevation myocardial infarction was dealt with more feasibly in a ‘real-world’ registry13 than the controlled environment of an RCT.

A sixth area of potential registry impact is only emerging with the improved rigor of registry design and implementation—registries that reliably capture a defined population can be used for monitoring incidence of disease entities and evaluating potential aetiologies. For instance, the MINAP study includes all acute cardiac care hospitals in England and Wales. Trends in hospital admissions for acute coronary syndrome can reliably monitor trends in incidence for the population.

LIMITATIONS OF REGISTRIES

Registries certainly have a number of limitations and will never replace RCTs for determining the efficacy of management strategies in those patients meeting inclusion criteria defined by the trialists. Owing to the lack of experimental control in registry populations, internal validity can be significantly affected by indication bias—for example, an association between a treatment and an improved outcome might be due to higher-risk patients not receiving the treatment.

Second, external validity of registries can also be limited by selection bias just as with RCTs. Most registries do not capture 100% of the population with a specific condition—both through limited participation of sites (eg, hospitals) and incomplete capture of patients within a site.14 15 Even adequate representation of a defined population, such as England and Wales, does not guarantee validity for other populations around the world with different patient groups and different health systems.

Third, feasibility constraints limit the amount of information obtained for each participant. Collecting even the basic demographic and clinical data on patients creates significant administrative burden for the sites. An appropriate balance between completeness and feasibility needs to be obtained.

Fourth, the quality of the data collection is critical in limiting bias. Missing data can be a significant challenge as the assumption that data are missing at random is often questionable.

Fifth, multiple analyses in attempts to identify associations within a given dataset raise caution over the interpretation of results.

Sixth, as is well known positive associations are more likely to end in publication than negative ones, resulting in a publication bias. Thus, in order to provide credible evidence, just as with RCTs, investigators need to understand and deal with these limitations. Fortunately, with the
Syndrome (AMIS) is the oldest and the Swiss Registry of Acute Coronary
some of their strengths and limitations.
compared in table 2, which illustrates
registries that will be featured in
sented in registry research. Three of the
Acute coronary syndrome is well repre-

appropriate scientific rigor, steps can be
taken to improve the quality of registries
and are listed in table 1.

REGISTRIES IN ACUTE CORONARY
SYNDROME
Acute coronary syndrome is well repres-
ented in registry research. Three of the
registries that will be featured in Heart are
compared in table 2, which illustrates
some of their strengths and limitations.
The Swiss Registry of Acute Coronary
Syndrome (AMIS) is the oldest and
provides 3- and 6-month questionnaire
data as well as inpatient data. However,
AMIS is small and voluntary. GRACE-2 is
multinational, with participants from 14
nations in five continents, has regular site
audits and has blood samples from a
subset of the participants. However,
GRACE has voluntary site participation,
incomplete enrolment within site and
only limited 6-month follow-up. MINAP
is the largest, is population based,
routinely audited, government funded and
has long-term continuous overall
mortality outcomes. However, MINAP
only includes England and Wales, has
limited breadth of clinical information
and has no blood samples. Thus, each has
significant information to contribute as
long as sufficient caution is used in its
presentation and interpretation.

FUTURE CONSIDERATIONS
Linkage of datasets is currently being
exploited. Horizontal linkage of clinical
datasets will enable a sharing of rich
clinical information with subsets of
participants with blood samples. Vertical
linkages will enable better elucidation of
the patient journey—sharing information
from primary care datasets with those of
disease-specific datasets, such as acute
coronary syndrome. Ultimately, the Holy
Grail of registries will harness the vast
information available in electronic health
records to truly study a representative
sample of the population with coordi-
nated horizontal and vertically rich clin-
cal information.

The quality of RCTs has improved
dramatically over the past four decades
with institution of standardised, rigorous
protocols. In much the same fashion,

Table 1 Potential biases and strategies to improve the validity of registries

<table>
<thead>
<tr>
<th>Bias</th>
<th>Strategies to limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection Site</td>
<td>Optimally design registry to include a defined area; alternatively, select sites within a defined area randomly</td>
</tr>
<tr>
<td>Patient</td>
<td>Adequate design and resources to capture all patients</td>
</tr>
<tr>
<td>Ascertainty 'Missingness'</td>
<td>Timely identification of missing data with feedback to sites</td>
</tr>
<tr>
<td>Misclassification</td>
<td>Rigorous assessment of impact of 'missingness' and appropriate statistical methods for imputation</td>
</tr>
<tr>
<td>Analytical Multiple analyses</td>
<td>A priori publication of analytical protocols</td>
</tr>
<tr>
<td>Publication Publication</td>
<td>A priori freely accessible study registration</td>
</tr>
<tr>
<td>Other</td>
<td>Transparent identification of funding source in all publications</td>
</tr>
</tbody>
</table>

Table 2 Selected registries on patients with acute coronary syndrome (ACS)

<table>
<thead>
<tr>
<th>AMIS</th>
<th>GRACE</th>
<th>MINAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full name</td>
<td>Swiss Registry of Acute Coronary Syndrome</td>
<td>Global Registry of Acute Coronary Events</td>
</tr>
<tr>
<td>Purpose</td>
<td>To describe the epidemiology, quality of care, and major in-hospital, 3-, and 6-month outcome for patients with ACS</td>
<td>To provide a multinational ACS registry to define patient characteristics and outcomes and to derive predictive risk scores</td>
</tr>
<tr>
<td>Funding</td>
<td>Industry</td>
<td>Industry, British Heart Foundation, Chief Scientist Office, Scotland.</td>
</tr>
<tr>
<td>Location</td>
<td>Switzerland</td>
<td>Multinational (N and S America, Europe, Australia, New Zealand (GRACE2 includes Asia)</td>
</tr>
<tr>
<td>Year started</td>
<td>1997</td>
<td>1999 (GRACE2 in 2001)</td>
</tr>
<tr>
<td>Setting</td>
<td>76 Hospitals, voluntary</td>
<td>GRACE: 123 hospitals (GRACE124 additional hospitals), Voluntary, with clusters of hospitals within a geographical region</td>
</tr>
<tr>
<td>Population (recruitment rate)</td>
<td>32 500 patients (~3000/year)</td>
<td>102 341 patients (~10 000/year)</td>
</tr>
<tr>
<td>Target population</td>
<td>All patients with suspected ACS</td>
<td>Patients with presumptive diagnosis of ACS</td>
</tr>
<tr>
<td>Data fields (N)</td>
<td>230 In-hospital data. 6 month patient contact and subsequent mortality. No blood resource</td>
<td>192 (with subfields). In-hospital and 6 month data. Blood/ genetic resource and 2-year follow-up in substudies</td>
</tr>
<tr>
<td>Data capture</td>
<td>Internet- or paper-based questionnaire by treating doctor or study nurse</td>
<td>Electronic data entry by study co-ordinators</td>
</tr>
<tr>
<td>Data quality control</td>
<td>Data checked centrally. Incomplete questionnaires returned for completion</td>
<td>All sites audited locally and 10% of individual patient records audited in a 2 y cycle</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Inpatient, 3-month, 6-month events and mortality, plus quality of life</td>
<td>Inpatient and 6-month events and mortality</td>
</tr>
<tr>
<td>Linkages</td>
<td>None</td>
<td>None. (Scottish data linked to Office of National Statistics for mortality)</td>
</tr>
<tr>
<td>Data access</td>
<td>Analysis proposals by members of AMIS plus steering committee</td>
<td>Analysis proposals considered, in competition, by an independent publications committee</td>
</tr>
</tbody>
</table>
techniques are creating vastly more reliable and powerful registries. No longer will it be acceptable to report registry results without the same level of scientific rigor required of other study designs. In this regard, registry research certainly has come of age.

Competing interests None.

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