Inter-regional differences in acute coronary syndrome trials

See page 1433 for the article to which this Editorial refers

The increasing international participation in clinical trials has made it possible to explore regional differences in baseline characteristics, management and clinical outcomes of patients with cardiovascular disease. Analyses published to date have highlighted significant country by country and regional (US vs non-US) differences in application of diagnostic and therapeutic strategies and short-term mortality. Variability in medical treatments and clinical outcome has also been observed in different regions or types of hospitals within the United States. Whether such variability is decreasing over time remains unclear, despite the presence of clinical practice guidelines, the influence of third-party payers and the increasing ease of global communication and transportation.

Prior to the presentation of the ESSENCE trial data in this issue, regional analyses of clinical outcomes had been published from only three other large randomized clinical trials: the Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial, the International Tissue Plasminogen Activator/Streptokinase Mortality Trial and the Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial. Among countries enrolling more than 100 patients in ESSENCE, the incidence of the triple end-point of death, myocardial infarction or recurrent angina ranged from 19% in the Netherlands to 31% in Argentina. This inter-country difference is much larger than the difference between enoxaparin and unfractionated heparin in the trial. In addition, a multivariable logistic model identified enrolment in Argentina and France as factors significantly associated with worse clinical outcome.

The patient demographics, risk factor profiles and concurrent treatments differed substantially among the six countries analysed. The authors’ assertion that the regional differences in outcome can be reasonably well explained by differences in patient characteristics seems a little strong given that the concordance of 62% achieved by their model is not much better than the 50% concordance that would be expected by chance alone. Furthermore, in searching for potential explanations for regional variations in outcome, the separation of baseline risk factors and process of care issues may be somewhat artificial. The relatively low rates of hypertension and hypercholesterolaemia seen in the U.K. patients enrolled in ESSENCE may reflect difficulties in the ability of the healthcare system to identify patients with these risk factors, rather than reflecting their true level in the community.

In 1988, Peto and colleagues sounded a note of caution regarding the clinical relevance of post-hoc subgroup analyses of large clinical trials when they showed that patients in the ISIS-2 trial born under the Gemini or Libra astrological birth signs had higher mortality after randomization to aspirin than similar patients randomized to no aspirin. All patients born under other signs had strikingly beneficial effects of aspirin. Comparisons among countries, regions or insurance plans are subject to the same risk of spurious ‘statistically significant’ differences.

In studies with large patient enrolment, small differences between groups will be highly significant by conventional use of P values, and the clinical importance of these differences can only be judged with clinical insight. This being said, certain trends in inter-regional differences are now becoming apparent. Patients enrolled in the United States are significantly heavier, taller, have more diabetes mellitus and, not surprisingly given the high rates of revascularization, are more likely to have undergone prior percutaneous coronary intervention or bypass surgery. Invasive cardiac procedures, including angiography and coronary revascularization, are used more frequently in the United States than elsewhere in the world. In trials of fibrinolytic therapy, non-US patients took significantly longer to present to hospital, had longer door-to-needle times and had significantly higher Killip classes at randomization.

Of particular concern is the repeated finding of poorer outcomes of patients enrolled in Latin America.
American countries in a broad range of acute coronary syndrome trials; in the ESSENCE trial, Argentinian patients had a 50% greater incidence of the triple end-point than American or Dutch patients, the worst outcome of all the enrolling countries[7]. Such a finding suggests that so far unidentified variables present in Latin America are contributing to worse clinical outcome. This is one issue that clearly warrants further research. It should be acknowledged, however, that only two countries in ESSENCE enrolled more than 300 patients each, raising concerns about the representative nature of the patient samples for each country as a whole. Furthermore, given the small numbers involved, the outcome differences may simply be due to chance or due to the particular centres that were chosen, rather than to country-wide practice differences.

One of the potential values in exploring regional differences in randomized clinical trials is the possibility of comparing the performance of different health care systems in a relatively controlled setting. This approach has been exploited particularly in comparison between the technology driven and multi-payer system in the US and the more conservative, government regulated system that operates in Canada. Mark et al., in an analysis of the GUSTO-I data, showed that Canadian patients had more cardiac symptoms and worse functional status one year after acute myocardial infarction than did US patients, having had fewer invasive cardiac procedures and fewer visits to cardiologists[14]. Others have shown that the more restrictive Canadian cardiac catheterization strategy in GUSTO-I was no more efficient in identifying severe coronary artery disease and may have failed to identify a substantial number of patients with high-risk anatomy, findings that will require long-term follow-up to define their impact on mortality[15]. Most studies have not found substantial differences in mortality, however, implying that the more invasive and expensive US approach may be a waste of money.

The ESSENCE study[7] demonstrates that this discussion can be broadened beyond US vs Canadian differences and beyond the merits and demerits of an aggressive revascularization policy post myocardial infarction. For example, the use of a variety of therapies based on evidence of true benefit differs considerably around the world. In reports that have included country-by-country analyses, including the ESSENCE analysis in this issue, the United Kingdom has consistently had the lowest use of beta-blocker therapy[7,16]. In PURSUIT, lipid-lowering therapy was prescribed for 24%, 16%, 6% and 6% of patients in North America, Western Europe, Eastern Europe and Latin America, respectively[11]. More recently, using data from GUSTO-I and III, Hudson et al. have shown that regional differences in patient management can affect outcome, demonstrating a clear relationship between increased intra-aortic balloon pump use in the United States and improved survival from post-myocardial infarction cardiogenic shock[17].

Perhaps so little has been published about these regional differences because they make us uncomfortable. The methodological uncertainties cited in this editorial leave us unclear about how to interpret such differences appropriately. Process of care differences may reflect differential access to expensive medications or revascularization procedures. These same economic issues, compounded by cultural patterns, may constrain our ability to change, even when we agree on the ‘best practice’ indicated by medical evidence.

These analyses demonstrate that there are important differences in patient characteristics, use of medications and invasive procedures and outcomes among regions and countries. These differences could affect the outcomes of patients as much as the intervention itself; almost nothing is known about possible interactions between treatment effect and these national and regional differences. The drive to develop global therapeutic approaches for widespread conditions such as acute coronary syndromes will require broad-based clinical trials. The regional differences highlighted in the ESSENCE trial and in this editorial underscore the need to develop methods for understanding regional differences. Perhaps more importantly, we need additional comparative data that will give us insight into the preferred practices of each country.

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Are data from clinical registries of any value?

See pages 1440, 1450 and 1458 for the articles to which this Editorial refers

‘The answer you get depends on the question you ask’

The question asked in the title of this editorial might be phrased differently: why bother to collect registry data at all? Is it of any use to clinicians and health care administrators/planners? Indeed, one might argue that only data from prospective, community-wide studies performed over decades such as the Framingham Heart Study are valid and therefore useful. However, my answer to these rhetorical questions is in the affirmative: collection of registry data does serve a number of useful purposes, but it is essential that we bring a critical understanding to the interpretation of such data. Let us examine the question further. I believe that registry data has at least 10 important functions:

1. Registry data reveal a cross-sectional view of multiple clinical and demographic aspects of a particular disease that can then be studied in greater detail in prospective, community-wide studies or by means of national health statistics.

2. Registries reveal the degree to which clinicians are managing a particular disease in accordance with the principles of evidence based medicine, information that is of great use to health care administrators/planners.

3. Registries are able to collect data on large numbers of patients rapidly and efficiently thereby producing a picture of a disease and its management at a particular moment in time. Repeated registry samples provide a dynamic estimate of changing patterns of disease demographics and therapy.

4. Registry data enable individual clinicians to compare their own patient population and therapeutic strategies with that of other practitioners possibly enabling these physicians to modify their practice patterns.

5. Registries provide insights for clinical investigators that assist them in designing clinical trials. Indeed, registries are often the source of questions that lead to clinical trials.
(6) Registries provide a quick estimate of the morbidity, mortality, and resource utilization associated with a particular disease entity.

(7) Collection of registry data by clinicians often focuses the practitioner’s attention on specific aspects of a particular illness that might otherwise be overlooked. For example, what are the exact criteria for making a particular diagnosis?

(8) International registries enable clinicians and health care administrators to compare disease specific management and outcomes in their country with that of other nations. Discussion of such data might lead to changes in national health priorities or strategies of disease management.

(9) The media, general public, and politicians are often interested in various aspects of registry data. For example, are there gender, race, or ethnic differences in disease demographics and/or outcomes within a country?

(10) Registry data can serve as a focus for educational discussions with residents and students.

I am certain that with further thought, the readers of this journal will discover other valuable aspects of registry data.

This issue contains three interesting reports based on registry data \cite{1,2,3}. A comparison of these three studies reveals that the data from one registry does not always agree with information gleaned from the others.

One example will suffice: Bowker et al.\cite{1} found no difference in outcome for patients with unstable angina based on gender. Collinson et al.\cite{2} on the other hand, observed an increased risk of mortality for males even after correction by multivariate statistical analysis. What is one to conclude from this disparity? Is one registry correct and the other wrong? Was the data collection flawed?

The methodology for the two registries appears solid; however, there are important differences. For example, only the PRAIS-UK Registry\cite{2} employed standardized definitions for acute myocardial infarction and unstable angina. On the other hand SAMII data were collected differently, since the centres were a random selection of general hospitals from the whole of the U.K. and the patients were less than 70 years old. Thus, important differences in patient demographics could easily exist between the PRAIS-UK and the SAMII Registries leading to the disparate gender results.

Therefore, the reader must take great pains in reading these reports to examine the methods employed for data collection. Indeed, ‘the answer you get does depend on the question you ask’ as noted at the beginning of this essay. Another way to put the same aphorism is ‘the results you obtain depend on how you collect the data’. Each registry must define meticulously how the patient data was selected so that bias can be identified.

In an attempt to improve registry data, I would like to conclude with a series of 12 suggestions that should improve comparisons between registries in the future:

(1) Standardized disease definitions should be employed and stated clearly in the methods sections. All participants in the data collection should be completely familiar with these disease definitions.

(2) Sampling techniques should also be standardized and followed with great care.

(3) Randomized selection of hospitals or clinics is strongly encouraged. Community-wide data collection is even better.

(4) All participants should have a clear understanding of the information being sought for each entry on the data sheet. Although gender and age are self-explanatory, misunderstandings can easily arise when the data collection form requests information on ‘softer’ outcomes such as ‘the presence of refractory angina’.

(5) All collected data should be reported. Selection or exclusion of some centres or some data forms increases bias.

(6) All original data sheets or electronic submissions should be centralized. Analysis should be performed by a central data collection and analysis centre.

(7) A professional statistician should monitor the data collection and analysis.

(8) Each data sheet or electronic submission should be carefully examined by the central data centre to ascertain completeness and accuracy. Individual investigators should be promptly queried concerning incomplete or confusing responses.

(9) The registry protocol should be reviewed at each participating centre by an institutional review board for studies involving human subjects. Appropriate consent for participation must be obtained.

(10) The names of all participating investigators should appear in the published report of the registry.

(11) Sponsorship for the trial should be clearly stated in all published reports so that commercial bias can be easily identified.

(12) One principal investigator or a small steering committee should be designated to maintain administrative order, adjudicate disagreements, and encourage timely submission of documents and data analysis.
In conclusion, registry data is valid, interesting, and useful to physicians, clinical investigators, and health care administrators. Meticulous attention to methodology improves the quality of the data. Interpreting the implications of a particular registry’s data requires a thorough understanding of the techniques employed to collect the information reported.

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National and regional registries: what good are they?

See pages 1440, 1450 and 1458 for the articles to which this Editorial refers

Three registries on patients with acute coronary syndromes are reported in this issue that provide useful insights into the patient populations and practice patterns of Europe. While it might seem self-evident, the value and application of registry data will play critical roles in the future refinement of medical practice. Two conclusions can be extrapolated from the fascinating detailed information contained in this series of papers. First, acute coronary syndrome patients seen in European practices are similar to those in clinical trials designed to test therapies for acute coronary syndrome manifestations, and second, care of these patients falls far short of what would be considered ‘best practice’ for both male and female patients.

Despite evidence that the mortality from acute coronary syndromes is being reduced by effective treatments, the public health implications remain staggering. It is the leading cause of death worldwide[1] and it is projected to remain the leading cause of death through to the year 2020[2]. In the U.K. it has been estimated that approximately 300 000 people suffer a myocardial infarction annually and 1-4 million people have angina[3]. This report also suggests that morbidity may be rising despite the rapid decline in mortality. The economic burden for the care of coronary heart disease is responsible for a large portion of national health care budgets. The cost of hospital care for acute coronary syndromes in the U.K. alone was about £1600 million in 1996[4].

In an ideal world, clinical trials would be done to determine whether proposed diagnostic and therapeutic strategies provided a clinical benefit at a reasonable cost. Practitioners would become aware of these ‘best practices’ by reading evidence summaries and clinical practice guidelines that weave the evidence into strategic algorithms for treating common medical problems. Given sufficient data and clear dissemination strategies, few patients would be denied adequate therapy or would be ‘over-treated’ with therapies that are ineffective or too expensive for routine treatment.

For years, registries and administrative databases in the U.S. and Europe have documented substantial variations in medical care as a function of location and individual patient characteristics. The value of registry trials lies in the ability to identify significant systematic differences in patient care. Such registries are valuable for a variety of reasons. A large size registry offers a powerful research tool to examine the course of a disease process, to understand factors that influence the clinical course, to analyse the efficacy of new therapies, and to study regional differences in delivery of care. Registries provide a snapshot into clinical management, such as resource utilization, and serve as important gauges in the translation of clinical evidence into clinical practice. While registries are intrinsically interesting for intellectual thought and discussion, our belief is that such targeted registries should be an integral part of the clinical practice framework and that constant sampling should provide the basis for evaluating the quality of medical care as it relates to diagnostics and therapeutics.
Substantial geographic variation was demonstrated within Europe for each component of acute coronary syndrome treatment and evaluation in the ENACT Registry\textsuperscript{8}. However, both this registry and the PRAIS-UK Registry\textsuperscript{9} documented a disturbing shortfall in the use of therapies that are known to be beneficial in acute coronary syndromes. The SAMII Study provides evidence that the inadequacies of therapy in the U.K. are shared equally between male and female patients\textsuperscript{7}. Multiple recent studies have pointed out the appallingly common failure to prescribe aspirin and beta-blockers in the acute setting.

The lower use of ACE inhibitors and statins may reflect a more expensive therapy, but both medications have extensive support for an incremental cost-effectiveness ratio that is well within an acceptable range in all societies represented in these reports. Additionally, the ubiquitous fascination with variations in invasive procedures continues to play out in these three reports. Since no consensus currently exists regarding appropriate indications for revascularization in acute coronary syndromes, the registries serve as more of a reminder of the need for larger and more definitive clinical trials than as a monitor of quality.

However, these registries advance current knowledge regarding acute coronary syndrome management strategies in Europe and the U.K. The next challenge is to address these shortcomings and maximize the standard of care in patients presenting with an acute coronary syndrome. Currently, The Global Registry of Acute Coronary Events (GRACE) registry is enrolling patients. GRACE is a population-based approach to an international registry designed to collect treatment options, practice patterns, and long-term outcomes in acute coronary syndrome management\textsuperscript{10}. The acute coronary syndrome inclusion criteria for GRACE are strictly defined, as compared to the local diagnostic approach applied in the pan-European ENACT, but taken together, these three registries should provide an excellent backdrop for reference when GRACE is completed.

To put these data in context, the Institute of Medicine in the United States has recently increased the alarm about not providing therapies with proven efficacy by producing a report entitled 'To Err is Human\textsuperscript{11}'. This report focuses on the issue of medical errors. Their definition of a medical error, borrowed from other high-risk industries, is either having the wrong plan or failing to execute the right plan. Bluntly stated, failure to give an acute coronary syndrome patient aspirin and a beta-blocker (unless a contradiction exists) is a medical error, and a patient who dies without the benefit of such therapy is an accident victim. We now have evidence that thousands of such accident victims are included in our patients with acute coronary syndrome.

While the registries make a valuable contribution by calling our attention to the issue, individual publications will never make a major difference. Rather, we need systems that ensure delivery of proven cost-effective therapies. This goal can be achieved in one of several ways. Ideally, medicine will finally join the computer revolution and create computerized physician order entry systems that are linked with computerized problem lists. Artificial intelligence could be used to remind practitioners of needed therapies and track adherence to standards of care. While we wait on this new world, serial sampling of practices can be used in a continuous quality improvement model to provide feedback to practitioners about their performance relative to standards. The National Dialysis Program and the Professional Review Organizations (PROs) currently use this approach for Medicare in the United States.

The motivation for such programmes is perplexing at first glance. One might think that informed clinicians, armed with definitive quantitative data, would march forth with computers in hand as a matter of conscience. However, the complexities of reimbursement, coupled with poor medical school teaching about quantitative issues in human therapeutics, leave us with few such operating systems and even fewer examples of successful maintenance of quality initiatives. Indeed, it is not unheard of for government and hospital officials to passively resist such efforts because of the increased cost associated with administration of appropriate therapies, and at the same time, doctors often resist the scrutiny of their practice quality.

Ultimately, as the world shrinks due to the Internet, patients will demand the type of quality that we know can be provided. In the U.S., patients are represented by third-party payors. Medicare (the largest insurer) and the National Committee on Quality Assurance (health care system accreditation) are measuring adherence to standards of care. In addition, the concept of 'patient activation' has become a progressive movement, thus, a very important consideration. Increasingly, patients will be informed of effective therapies over the Internet and personally demand these treatments of their physicians. This 'patient activation' occurs through direct to consumer advertising by the medical products industry, but it can also be an effective tool when the source is a physician group, a professional society, or a payor intent on empowering patients to demand high quality care.

In the very near future, information systems will be designed to integrate evidence into clinical practice that will benefit both provider and consumer. The access target of these systems will be insurance payors, integrated health care delivery networks,
Chest pain and a non-diagnostic ECG: trying not to be frustrated

See page 1464 for the article to which this Editorial refers

Persistent ST-segment elevation on the ECG is highly specific for acute myocardial infarction, and identifies a group of patients who will unequivocally benefit from prompt recanalization of the occluded coronary artery. However, only a minority of all patients presenting with acute chest pain are defined in this way. ST-segment depression, or T-wave inversion,
while suggestive of myocardial alterations induced by ischaemia, may bear no direct relationship to acute occlusion of a coronary artery. An ECG which is apparently normal, or which shows only non-specific changes, is also frequently seen in patients presenting in the CCU with chest pain. These situations still present a major challenge to the cardiologist.

The modern approach to treating acute coronary syndromes has become increasingly effective, but the potentially harmful side effects of treatment, the complexity of invasive procedures, and overall costs, require that these interventions be deployed only after a reasonably certain diagnosis has been established.

Measurement of plasma concentrations of various biochemical markers of myocardial cell necrosis has gained wide acceptance as a ‘quick fix’ to the problem of ruling in/out whether in a given patient chest pain is attributable to acute myocardial infarction or not. However, the problem remains within the relatively large subgroup of patients in whom symptoms are due to unstable angina, which entails a different therapeutic approach as compared to acute myocardial infarction. All too often patients receive a final diagnosis of either myocardial infarction or unstable angina only retrospectively. In addition, there is at least one report that troponin T may also be elevated in patients with acute episodes of cardiac failure, a relatively common cause of admission for chest discomfort with a non-diagnostic ECG. In a prospective study of 30 consecutive admissions with NYHA class IV cardiac failure, but without evidence of acute ischaemia, Collinson[3] found that increased troponin T concentrations predicted an adverse outcome. One year mortality in those who were troponin T negative was 10%, compared with 40% in those who were troponin T positive, at a cut-off of 0·2 ng. l−1.

Thus, in spite of the availability of a vast array of biochemical markers, there is often no substitute for carefully watching the patient in the CCU. If extra ‘value’ (i.e. information) can be gained from the time spent monitoring a patient this will alleviate the frustration of cardiologists, and will provide an additional rationale for having patients in a high-cost environment, particularly in these cost-conscious days. In this issue, the group in Uppsala provide a clever approach to this problem[2]. The same authors have recently reported on the feasibility and usefulness of on-line ST-segment monitoring in improving risk stratification in patients admitted with chest pain and a non-diagnostic ECG[3]. Similarly, several studies had already shown that measurement of cardiac troponins are of value in predicting outcome in patients with acute coronary syndromes in whom acute myocardial infarction is ruled out on conventional grounds and who require risk stratification into low- and high-risk groups[4–8]. In their study[2], Jernberg et al. combined both approaches to get better risk stratification in this category of patients. Both a troponin-T ≥ 0·10 µg. l−1 and occurrence of ST-segment changes predicted worse outcome in a 6-month follow-up. When analysed by multivariate analysis, both parameters were independent predictors of cardiac death or myocardial infarction. The novel observation is that when troponin-T and ST-segment status were combined, patients could be further stratified into low-, intermediate-, or high-risk groups. This observation has potentially important clinical implications, as the ability of this combined strategy to differentiate high- and low-risk groups in patients presenting with suspected acute coronary syndromes may offer a tool for development and selection of tailored therapeutic and management pathways. The advent of newer therapeutic options for patients with myocardial infarction and unstable angina, such as primary angioplasty, low molecular weight heparins and platelet glycoprotein IIb/IIIa antagonists, is accompanied by increasing cost at a time of increasing pressure on resources. In this respect, the VANQWISH study has shown the inadequacy of current clinical methods of selection for intervention[9].

The paper by Jernberg et al. also provides information which may be of interest from a pathophysiological point of view. In this study, a sizeable proportion of patients, who presented on admission with increased troponin T concentrations, did not develop ST-segment changes during subsequent monitoring. One might be tempted to dismiss this finding merely as the result of ischaemic episodes having occurred prior to admission, which may have resolved while leaving behind cell injury. However, an additional 8% of patients who presented with negative troponin T values eventually went on to show a positive marker over 6 h, even though ST-segment monitoring showed no changes. Similarly, there could be patients with ST-segment changes on monitoring who did not show any increase in troponin T. These findings could be due to lack of sensitivity of either methodology. But they could also be a further indication that the patients with chest pain and a non-diagnostic ECG were a heterogenous group and that we have to learn more about the pathophysiology of acute ischaemic syndromes.

In short, there is still much to be learned from careful observation of patients in the CCU. Being able to gain additional information from the appropriate combination of electrocardiographic and biochemical alterations may make the time spent in
the CCU even more relevant for patients with a non-diagnostic ECG, and for the cardiologist as well.

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