Rationale and design of the ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries) project

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During the past 10 years, the health of people in Eastern Europe and the former Soviet Union has undergone changes very different from the health patterns seen in their Western counterparts. Mortality from cardiovascular disease has been decreasing continuously in the USA and many Western European countries, but it has increased or remained unchanged in many of the states of Eastern Europe. Analysis of this phenomenon has been hindered by insufficient information. The International Registry of Acute Coronary Syndromes registry study in Transitional Countries (ISACS-TC) is both a retrospective—over a 1-year period—and prospective study which was designed in order to obtain data of patients with acute coronary syndromes (ACSs) in countries with economy in transition in Central and Eastern Europe, and herewith control and optimize internationally guideline recommended therapies in these countries. Adhesion to the project was given by 112 Collaborating Centres in 17 countries with economy in transition (Albania, Bosnia and Herzegovina, Belarus, Bulgaria, Croatia, Hungary, Kosovo, Latvia, Lithuania, Macedonia, Moldova, Montenegro, Romania, Russian Federation, Serbia, Slovakia, Slovenia, and Ukraine). A total of 47 cluster sites in 11 countries in Central and Eastern Europe are currently collaborating in ISACS-TC. The registry encourages optimal individualization of evidence-based therapies and the international patient body ensures good representation of multiple practice patterns. It may help to make an additional improvement in clinical outcomes of countries with economy in transition.

KEYWORDS
Acute coronary syndrome; Evidence-based secondary prevention therapy; Cardiac catheterization and procedures

The collapse of the Berlin Wall brought with it massive economic, social, and political changes for the countries that emerged from the Socialist era. Currently, the predominant share of the global burden of cardiovascular disease (CVD) is concentrated in these countries.¹ The increase in CVD burden is largely the result of both an increase in the prevalence of the risk factors and a relative lack of access to well-recognized interventions that prolong survival once CVD is manifest. Extremely limited data are available about the mortality rates of acute CVD in Central and Eastern European countries,²–⁴ although the available data suggest higher proportion of in-hospital mortality deaths attributed to CVD in these countries when compared with the European member states.⁴

Focus on acute coronary syndromes

Because changes in the economic context of most countries come very quickly and often bring strict consequences,
reforms in clinical practice are particularly challenging in one of the most complex areas of CVD: the acute coronary syndromes (ACS). Acute coronary syndromes refer to a spectrum of clinical presentations of CVD ranging from ST-segment elevation myocardial infarction (STEMI) to non-STEMI (NSTEMI) or unstable angina (UA). In terms of pathophysiology, ACSs share common underlying mechanisms, being almost always associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the related coronary artery. Acute coronary syndrome is the leading cause of cardiovascular morbidity and mortality, resulting in substantial healthcare utilization and costs. Global data on the management and therapies of patients with ACS are needed to improve the outcomes of these patients, especially in countries with low-to-middle income economies.

From controlled randomized trials into routine clinical practice

Unfortunately, much of the data on the ACS are derived from the context of randomized trials, which may be subject to ‘narrow interpretation’ or ‘broad interpretation’. A very narrow interpretation would be that only patients similar to those enrolled in the trial would receive benefit. In a strict sense, the results of the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)—Thrombosis in Myocardial Infarction (TIMI) 28 Trial apply only to those patients aged 18–75 years who have been hospitalized within 12 h of onset of symptoms, do have STEMI, and receive fibrinolytic therapy. As well, the results of the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) were consistent only in patients treated with fibrinolytic therapy. A very broad interpretation of these trials would be that a more potent dual antiplatelet therapy leads to a reduction in coronary heart disease mortality in whatever subset of STEMI patients. The controversy over the high bleeding risk of dual antiplatelet therapy is less over the validity of the findings in the subjects randomized than over whether those findings can be generalized to other groups of patients. Accordingly, there are no randomized trials that have specifically evaluated the use of combined clopidogrel and aspirin in patients with STEMI undergoing primary percutaneous coronary intervention. Much more importantly, in the countries of Eastern Europe (ISACS-TC), a large proportion (41.9%) of patients does not undergo any reperfusion therapy. Differences in drugs’ efficacy and side effects make comparison of dual antiplatelet therapy particularly relevant for care of these patients, as they are at high risk for death, and anticoagulants carry a significant increase in bleeding risk. Translation of the extensive information built up from randomized controlled trials into routine clinical practice is incessantly warranted.

Role of observational databases in evaluating therapy

Our view is that observational registry databases can and should play an important role in the evaluation of therapy. By design, a registry database is relatively non-selective, so that the entire spectrum of patients with disease is represented. In some conditions, registries may be preferable designs for studies of effectiveness, that is, whether a drug, device, or procedure in fact achieves its desired effect in the real world. Many patients included in a clinical database would not be included in a randomized trial. In the Coronary Artery Surgery Study (CASS), a randomized trial and registry of coronary artery bypass surgery and medical therapy in the management of patients with mild or moderate stable angina pectoris or free of angina but with a documented history of myocardial infarction, only 21% of patients were actually randomized. The majority of patients met eligibility criteria for randomization but declined participation in the randomized study. Half the randomized patients were assigned to surgery and half to the medical group. Of the non-randomized patients, 43% started with surgical therapy and 57% constitute the medical group. Survival in the medically randomized and non-randomized patient groups was similar in the estimates at 5-year follow-up. A number of key distinguishing observational studies have been published from the registry of the Coronary Artery Surgery Study that have considerably enhanced the value of the overall investigation, including examinations of the efficacy of coronary bypass surgery in the elderly, those with poor left ventricular function, and those with severe angina.

One strategy does not fit all

The purpose of the ISACS-TC registry is to collect additional information regarding the effectiveness and the cost-effectiveness of the currently available drugs and technologies for treatment of ACS in selected broad populations of patients in 17 countries with economy in transition: Albania, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Hungary, Kosovo, Latvia, Lithuania, Macedonia, Moldova, Montenegro, Romania, Russian Federation, Serbia, Slovakia, and Ukraine. The concept of ‘one strategy fits all’ does not apply to all of these countries. A variety of factors, including national healthcare reform, austerity measures, stringent regulation, and a variety of cost issues related to specific geographical conditions, may significantly slow the use of technologies and drugs. Excluding Greece, all other Balkan countries (Croatia, Serbia, Montenegro, Bulgaria, Romania, Albania, Bosnia and Herzegovina, and Macedonia) have lower-to-middle-income economies. Regardless of this, drug costs in Balkan countries are similar to costs in industrialized European countries, which could produce differences in cost-utility of the same drug between industrialized European and Balkan countries. In this socioeconomic context, non-randomized comparisons either are sufficient to address the research question or, in some cases, may be necessary because of the following issues with randomized treatment. Can providers ethically introduce randomization between relatively new vs. old treatment when the treatments are not equivalent in terms of cost-utility? How can compliance and adherence to a treatment be studied, if not by observing what people benefit in real-world situations?
The ISACS Advisory Committee has identified five roles to promote health and prevent mortality from ischaemic heart disease in older adults: (i) to provide high-quality health information to public health professionals and consumers; (ii) to support healthcare organizations in prevention efforts; (iii) to integrate public health prevention expertise with a cardiology services network; (iv) to identify and implement effective prevention efforts; and (v) to monitor changes related to medications and coronary procedures in the health of older adults.

### Participating centres and sampling methods

The International Registry of Acute Coronary Syndromes registry study in Transitional Countries (ISACS-TC) is both a retrospective—over a 1-year period—and prospective study which was designed in order to obtain data of patients with ACSs, and herewith control and optimize internationally guideline recommended therapies in these countries with economy in transition. The Registry is designed with four aims: (i) documentation of the characteristics of all patients presenting to the enrolled centres with STEMI or non-ST-segment elevation myocardial infarction (UA/STEMI), (ii) documentation of in-hospital outcome, and outcome rates at 6 months and 1 year, (iii) documentation of interventional cardiac procedures and related complications, (iv) documentation of therapeutic regimens and investigation conformity of treatment with already established guidelines. The registry encourages optimal individualization of evidence-based therapies, and the international patient body ensures good representation of multiple practice patterns.

Data collection activities began in October 2010 with the aim of collecting data on ~3000 patients hospitalized with ACS on an annual basis. Adhesion to the project was given by 112 collaborative centres in 18 countries with economy in transition (Table 1). A total of 57 cluster sites in 17 countries in Central and Eastern Europe are currently collaborating in ISACS-TC. Four countries (Bosnia and Herzegovina, Montenegro, Romania, and Serbia) have recruited relatively more study hospitals than other countries to provide a more descriptive overview of national practices in the management and outcomes of patients with ACS. Details on patients’ identification approaches are documented at NIH (NCT01218776). Examples of patient-reported data include health-related quality of life and symptoms. Examples of clinician-reported data include clinical diagnoses, clinical signs, laboratory results, medications, cardiac procedures, and biological specimens.

### Assessing the magnitude of bias

Alert for any source of bias is important, and the value of a registry is enhanced by its ability to provide a formal assessment of the likely magnitude of all potential sources of bias. Briefly, a special system of cardiovascular event monitoring was developed. Each collaborating centre of each country area served as a coordinating and data entry centre for the study (first level). Metropolitan hospitals under the responsibility of the Principal Investigator of the country formed the intermediate monitoring teams (second level). The basic unit of the system (third level) was at the data bank of the international coordinating center (CINECA). The diagnosis was validated according to ACC/AHA/ EHS diagnostic criteria and a standard event form was completed by the physician; the form was sent to the coordinating centre, where the case was reviewed again by a supervision group. After any possible errors in case registration were corrected, the final data

### Table 1 Collaborating countries in the prospective enrolment of the ISACS-TC registry

<table>
<thead>
<tr>
<th>Country</th>
<th>Hospitals type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belarus</td>
<td>Tertiary centres (n = 1)</td>
</tr>
<tr>
<td>Bosnia and Herzegovina</td>
<td>Secondary (n = 5) and tertiary centres (n = 2)</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Tertiary centre (n = 1)</td>
</tr>
<tr>
<td>Croatia</td>
<td>Tertiary centres (n = 1)</td>
</tr>
<tr>
<td>Hungary</td>
<td>Tertiary centre (n = 1)</td>
</tr>
<tr>
<td>Kosovo</td>
<td>Tertiary centres (n = 1)</td>
</tr>
<tr>
<td>Latvia</td>
<td>Tertiary centres (n = 1)</td>
</tr>
<tr>
<td>Lithuania</td>
<td>Tertiary centres (n = 1)</td>
</tr>
<tr>
<td>Macedonia</td>
<td>Tertiary centre (n = 1)</td>
</tr>
<tr>
<td>Moldova</td>
<td>Tertiary centres (n = 1)</td>
</tr>
<tr>
<td>Montenegro</td>
<td>Secondary (n = 7) and tertiary centres (n = 1)</td>
</tr>
<tr>
<td>Romania</td>
<td>Secondary (n = 10) and tertiary centres (n = 8)</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>Tertiary centres (n = 1)</td>
</tr>
<tr>
<td>Serbia</td>
<td>Secondary (n = 2) and tertiary centres (n = 5)</td>
</tr>
<tr>
<td>Slovakia</td>
<td>Tertiary centres (n = 1)</td>
</tr>
<tr>
<td>Ukraine</td>
<td>Tertiary centres (n = 1)</td>
</tr>
</tbody>
</table>

Secondary Centre: healthcare services offered by medical specialists (it includes acute coronary unit with or without cardiac catheterization laboratory). Tertiary Centre: healthcare services providing advanced medical investigation and treatment (it includes primary percutaneous intervention and/or cardiac surgery).

*List at the day 30 August 2013.
collaboration of every patient was sent to the international coordinating centre. In addition, several approaches were used to facilitate quality control and standardization of medical records in a systematic manner. First, national Principal Investigators and physicians responsible of the collaborating centres met twice a year to discuss technical and administrative issues of the study. Secondly, site visits were made by the national Principal Investigator staff to collaborating centres reporting technical difficulties or having problems with compliance. Thirdly, to ensure uniformity in the coding of cardiovascular events between the collaborating centres, quality control tests were held at regular intervals (usually once every 6 months). Tests were similar to those adopted by the MONICA Project.

Conclusion

ISACS-TC is a large international investigative effort that will evaluate the role of evidence-based therapies and interventional cardiac procedures over a 5-year period. It may help to make an additional improvement in clinical outcomes of countries with economy in transition.

Conflict of interest: None declared.

Appendix

ISACS-TC Investigators


ISACS-TC Administrative Committee

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Conflict of interest: None declared.
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References


