International differences: selection, noise, or real?

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A number of recent studies have reported international differences in both the treatment effect and the outcome of patients with acute myocardial infarction, and several studies have reported that these differences persisted even after adjustment for baseline patient characteristics and revascularization rates in patients treated with thrombolytic therapy\(^1\)-\(^4\). Small international differences in the treatment effects of thrombolytic strategies are most likely due to chance\(^2\). International differences among patients presenting with unstable angina have not been closely studied.

The Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial investigators examined regional differences in the effect of eptifibatide on the primary 30-day end-point of death or non-fatal myocardial infarction in patients presenting with acute coronary syndromes without persistent ST-segment elevation\(^5\). There were differences in patient outcome, and on univariate analysis there were large differences in the point estimate of the relative treatment effect depending on the definition of infarction in patients randomized in North America (23–35%), Western Europe (17–42%), Eastern Europe (0–33%) and Latin America (55–82%).

After further analysis, most of the international differences in the efficacy of eptifibatide were attributed to regional variations in the baseline demographics of the patients, the frequency of coronary interventions, and the ascertainment and adjudication of myocardial infarction.

Are the authors being Procrustean in attempting to explain away possible international differences by these factors? [Procrustes was a legendary ancient Greek brigand, who tied his captives to a bed and then either stretched or amputated their legs to fit the bed.]

The North American patients in the PURSUIT trial were 2 years younger, weighed more, and had a higher frequency of diabetes than those in Europe. There are many baseline demographic factors that are not measured in a large international trial, and there were regional variations in medical management, such as the rate of interventional procedures and the use of adjunctive heparin (including the type of heparin and the route of administration). Within the 72-h study drug infusion period, percutaneous interventions were performed in 25% of North American patients, 7% of Western European patients, 2% of Eastern European patients and 4% of Latin American patients.

The effects of the glycoprotein IIb/IIIa receptor antagonists are incremented if these agents are used prior to and with percutaneous coronary interventions\(^6\)-\(^8\). The PURSUIT investigators found that eptifibatide improved 30-day outcomes by reducing not only the occurrence of events prior to interventions, but also the periprocedural infarction rate. The absolute and relative treatment effects of eptifibatide were greater in patients undergoing early percutaneous coronary interventions, and patients in countries with higher intervention rates would therefore be expected to show larger treatment effects. However, coronary interventions are post-randomization events, and bias in the selection of lower-risk patients for interventions\(^9\) may confound the association between revascularization rates and outcome.

For the ascertainment of the end-point of myocardial infarction by the PURSUIT adverse events committee, new Q-waves or various elevations of creatine kinase or creatine kinase MB levels were required. Usually an adverse events committee improves the specificity of adverse events by excluding events that have been reported by investigators but do not fit the strict trial definition, whereas the PURSUIT adverse events committee reviewed laboratory reports of cardiac enzymes and found more infarctions than the investigators reported. The relative benefit of eptifibatide was larger when the investigators’ assessment was used for end-point definition in North America and Western Europe. Some of the differences between regions could also be due to the varying accuracy of laboratory results. If reproducibility is poor, the sensitivity and specificity of the diagnosis of myocardial infarction will vary between centres and potentially between countries. Furthermore, the longer hospital stays in Eastern Europe (median 13 days)
compared with North America (median 6 days) may have resulted in an ascertainment bias in that the Eastern European patients had a greater opportunity to have electrocardiograms recorded and cardiac enzymes measured.

There are a number of other factors that may explain differences in outcome or treatment effects in an international trial, such as the selection of the sites. The threshold for admission to a coronary care unit differs between countries\[10\], and the sites participating in an international trial may be highly selected and not representative of centres throughout the country. They also vary in terms of size, location (whether metropolitan or rural), the capacity to perform angiography and revascularization procedures, and whether or not they are academic institutions. Sites with catheterization laboratories are more likely to perform procedures\[11\], thereby increasing the benefit of treatments that reduce the incidence of periprocedural infarction. The patients randomized may also be highly selected within a site. Registries are useful for recording information that may be valuable in determining the applicability of the trial results to a wider patient population\[12\], but they are costly. No registry is available from the PURSUIT trial.

Sites may also vary depending on whether they are staffed by cardiologists or general physicians. It has been shown that cardiologists are more likely than general physicians to use beneficial treatments, and less likely to use treatments showing no evidence of benefit in the management of acute myocardial infarction\[13\]. Patients managed by cardiologists also have a lower mortality rate than those managed by internists or primary care physicians\[14,15\]. In a prospective cohort study of patients with unstable angina, those managed by internists received fewer medications that have been shown to be beneficial, and there was a trend towards a higher hospital mortality rate\[16\].

The degree of coronary artery disease may differ between populations, and consequently the risk of events among patients in different countries may also differ. The prevalence of traditional risk factors for coronary artery disease such as smoking, hypertension, dyslipidaemia, glucose intolerance, obesity and other anthropometric measures vary among populations, as do other factors shown to be associated with a higher risk of coronary heart disease such as less education, lower social class, overcrowding, lower income and deprivation in utero\[17\]. Beneficial factors such as a moderate alcohol intake and the amount of exercise also differ between countries.

Practice patterns vary between and within countries. United States patients may be prescribed anti-ischaemic medications more frequently and undergo less exercise testing, but are more likely to have angiography, percutaneous coronary interventions or bypass surgery\[2,3,18\]. These international differences in procedure use exist even in patients who are initially admitted to hospitals without cardiac catheterization laboratories\[18\]. Recurrence of ischaemia in patients with non-ST-elevation acute coronary syndromes results in a substantially higher incidence of infarction and death\[19\]. With respect to outcomes, it may not be the number of interventions performed that is important, but the capacity to respond quickly to the occurrence of ischaemia or worsening clinical features, and to expeditiously perform appropriate revascularization procedures. It has been shown that procedures are performed earlier in the United States than they are elsewhere\[20\], but there is little information about the coupling of interventions to the occurrence of ischaemia.

Compliance with medications may vary internationally. Although this is unlikely to be a major factor with intravenous infusions, as used in the PURSUIT trial, it may be an important issue with other medications, such as aspirin, that have been shown to be beneficial in patients with acute coronary syndromes.

International differences in the selection and management of patients would be expected to produce differences in absolute event rates, and thus in the number of patients that need to be treated to prevent one event. However, differing event rates would not be expected to affect the relative effect of a treatment. The most reliable way to estimate the effect of a treatment in any subgroup is generally to apply the overall relative effect to that subgroup unless there is compelling statistical evidence of a different treatment effect and an a priori reason (preferably prespecified) for that difference. When numerous subgroups are examined, it is highly likely that a subgroup will be found where the effect is larger or where there is no apparent effect. Unless there is statistical evidence of a significant treatment difference due to the interaction of baseline characteristics, and a good rationale for the finding, subgroup differences are most likely due to chance. The authors of the PURSUIT trial have appropriately emphasized the consistency in the pattern and directionality of the treatment effect among the four different regions rather than the magnitude of the treatment effect itself.

However, given the ethnic, social, dietary, economic and other environmental differences between countries, it is possible that antithrombotic treatment
could have differing effects in different populations. Genetic factors interacting with environmental factors and patient characteristics may particularly affect the coagulation and fibrinolytic pathways. The degree of prothrombotic and endogenous fibrinolytic activity following plaque fissuring or rupture may also vary between populations. Elevated levels of fibrinogen[21,22] and von Willebrand factor[23] have been identified as risk factors for myocardial infarction, and abnormalities can occur in plasminogen activator inhibitor-1[24]. Polymorphism in genes for endothelial nitric oxide synthase (eNOS) is associated with decreased endothelial function[25]. The response to fibrinolytic[26] and antithrombotic agents may also differ between populations. For example, major bleeding has been shown to be more common with the use of tissue plasminogen activator in African populations[27].

The PURSUIT investigators[5] identified differences in baseline characteristics, adjunctive therapy and adjudication processes as factors to consider when regarding differences in patient outcome and the consistency of the treatment effect in international trials. These factors are certainly important, but our understanding of them is incomplete.

There are now many rich international databases, some of which have genetic material available, where the unravelling of potential international differences in outcome and treatment effects will be possible in the very near future.

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[8] The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with epti...
Aortic stiffness: a predictor of acute coronary events?

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Epidemiological studies of patients with coronary heart disease have identified a number of risk factors for fatal and non-fatal myocardial infarction including diabetes, hypertension, tobacco use, elevated plasma lipids and a family history of precocious coronary artery disease. Of equal importance is the observation that the incidence of myocardial infarction can be favourably modulated by cessation of smoking, reduction in plasma cholesterol, optimal treatment of hypertension and appropriate glycaemic control. While primary prevention of coronary heart disease remains the ideal, the majority of clinical cardiovascular specialists treat patients who have already manifested coronary disease or related complications. In symptomatic or asymptomatic patients with evidence for coronary heart disease, another tier of information, regarding further long-term prognostic stratification is a prerequisite for optimal patient management.

Clinical trials of survivors of acute myocardial infarction have been a rich substrate for prospective acquisition of baseline measurements of ventricular topography, ejection fraction, coronary anatomy, pulse pressure and ambulatory electrocardiographic evidence of ischaemia, and have all provided incremental prognostic information above that available from baseline demographics. The purpose of characterizing objective measures of prognosis is to identify individual patients at high, moderate and low risk of future adverse events and tailor treatment strategies to minimize risk of adverse events which include recurrent infarction, congestive heart failure and stroke. Attenuation of left ventricular remodelling with angiotensin converting enzyme inhibitors, beta adrenergic receptor blockade and aggressive reduction of plasma cholesterol in post-infarction patients represent three different treatment strategies that have proved efficacious in reducing the incidence of adverse cardiovascular events[1–3]. The aim now and into the millennium is to anticipate adverse cardiovascular consequences of coronary artery disease and intervene rather than stratify risk after complications have occurred.

Over the last decade, attention has focussed on the central vasculature and in particular upon assessing plaque stability, lipid content, biophysical properties of the fibrous cap and estimation of the shear forces necessary to trigger plaque rupture, thrombosis, vessel occlusion and myocardial infarction[4]. The specific aim of these studies has been to recognize abnormal vessel structure and function early, so that consequent irreversible loss of cardiomyocytes can be avoided. The myocardium may be regarded as a target organ with limited ability to autoregulate its epicardial and intramural coronary blood flow when subjected to acute reduction in coronary flow by sudden thrombotic occlusion of a previously haemodynamically unimportant stenosis as well as during perturbations in systolic and diastolic load. Risk factors for coronary heart disease mediate their effect by altering the structure, properties and function of the medial and endothelial components of the arterial wall which vary among different vascular beds. In addition, age-related changes in the composition and material properties of the arterial wall in individuals without atheromatous disease are associated with increased systolic blood pressure and increased pulse pressure and reflect increased arterial stiffness or reduced arterial distensibility.