Still a long way to go to defeating atherosclerotic disease: a call to arms!

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This commentary refers to ‘Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry’, by M.J. Alberts et al., on page 2318

The REduction of Atherothrombosis for Continued Health (REACH) Registry is by far the largest international registry of patients with stable, chronic atherosclerotic disease, and Alberts et al. should certainly be commended for such an endeavour. The paper presents the 3-year outcome data in 32 247 patients with symptomatic disease, representing 81% of those eligible for follow-up. Although the proportion of patients lost to follow-up is definitively high, it nevertheless seems acceptable, granting the difficulty of such a worldwide study, and the conclusions from these analyses can certainly be considered solid evidence. The population is constituted of a majority with coronary artery disease, but also of patients with cerebrovascular disease or peripheral artery disease; ∼20% had involvement of several arterial territories. The mean age of the patients was 68.5 years at inclusion, two-thirds were men, and 37% were diabetic. Recruitment was contemporary, carried out between 2003 and 2004.

The information brought by this study can be categorized into three groups: medication prescription and compliance; inequalities in treatment and clinical outcomes; and rates of clinical outcomes in the whole population as well as in population subsets.

The data on medications yield mixed results; the baseline prescription rates were rather on the low side for patients with symptomatic vascular disease: 92% for antithrombotic agents, 68% for statins (73% for lipid-lowering agents); in addition 91% received antihypertensive medications, and a fair proportion of those received angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (nearly 70%) and/or β-blockers (slightly less than half of the population). The bright side, however, is that there seems to have been an excellent adherence with the medications initially prescribed. Use of antithrombotic agents was stable, and that of lipid-lowering medications increased to 76% at 3 years. This emphasizes the fundamental role of the initial prescription: once medications are started, they are generally continued over the subsequent years; conversely, lack of prescription when the patients are seen initially results in a lack of prescription over the long term. Although these results are at variance with some observations, recent reports from both sides of the Atlantic have also found that adherence to cardiovascular medications was usually high. It is important, however, to consider that prescription of recommended classes is, though necessary, not sufficient by itself: adequate doses have to be prescribed and therapeutic goals must be achieved. The analysis by Alberts et al. provides no insight into these important issues.

Several inequalities in treatment are pointed out by the authors: inequalities across regions are simply mentioned; they were more extensively described in the paper analysing the 1-year outcome of the whole population included in the registry, but we lack a precise description of regional differences in the treatments used in patients with symptomatic atherothrombotic disease. Also, importantly, women receive fewer recommended medications than men. The differences regarding either antithrombotic therapy or lipid-lowering medications, though highly statistically significant, are relatively small (from 2 to 3.5% in absolute terms) and, because women were probably older than men, these differences are probably attributable at least in part to an age bias rather than a gender bias. Whatever the case, though, modest inequalities in treatment do exist and it will be important in future analyses from the REACH registry to try and fully understand their causes.

The third type of findings are undoubtedly the most important and pertain to clinical outcomes. In this regard, considerable differences are observed from one region to another: Japan (not unexpectedly) and Australia have the lowest event rates, while the highest rates are found in Eastern Europe. Eastern European patients have a 3-year vascular death rate of 9.03%, compared with 5.79% for Western Europe; this difference is all the more striking when one considers that Eastern European patients enrolled in REACH were 63 years old on average, compared with 69 years for Western European patients. Of note, at baseline, Eastern Europeans initially included in the registry (i.e. both with and without symptomatic atherothrombotic disease) received statins and angiotensin receptor blockers less often, while they had...
more antiplatelet agents, β-blockers, and ACE inhibitors, compared with Western Europeans. The difference in the latter group of medications, however, may partly be explained by the higher proportion of patients with a history of atherothrombotic disease in the Eastern European countries. Beyond the prescription of medications, a detailed analysis of the causes of these differences in outcomes will be urgently needed. Understanding the causes of inequalities is, in fact, the necessary first step before taking public health measures to try and correct them.

Finally, the overall clinical outcomes of outpatients with symptomatic atherothrombotic disease are less favorable than might have been expected, and this is in spite of the fact that most patients received recommended medications. The annual vascular death rates ranged from 1.9% for patients with coronary artery disease to 2.9% in those with peripheral artery disease. These rates are slightly higher than those of the placebo groups of randomized trials which enrolled patients 15–20 years ago; thus, the cardiovascular death rates were 1.7% in the 4S trial and in the Heart Protection Study,6,7 and 1.6% in the Heart Outcomes Prevention Evaluation (HOPE) study. They are approximately double those found in more recent trials, such as the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA), the Prevention of Events With Angiotensin Converting Enzyme Inhibition (PEACE), or the A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system (ACTION) trials (1.0, 0.8, and 0.9% respectively).8,9 Likewise, the 3-year global cardiovascular events rates ranged from 25% to nearly 40%.

This certainly represents the major finding of the study: in spite of the considerable progress we have made in the past 20 years in the treatment of patients with cardiovascular disease, mortality and complications remain unacceptable high, even when the patients are (more or less) adequately treated. A further indication that currently recommended medications are not enough to prevent further cardiovascular events comes from the differential analysis of events occurring in men vs. women. In particular, the observed cardiovascular death rate at 3 years was 6.1% in men vs. 4.6% in women, a highly statistically significant difference after adjustment for age, and this in spite of the previously mentioned fact that men received slightly more recommended medications than did women. Likewise, mortality was higher in North America or Europe, compared with Australia or Japan, despite the higher use of recommended medications in the former regions.

The conclusion of these findings is simple to draw: currently recommended medications are not enough to stabilize the atherothrombotic process completely. Part of the explanation may come from the fact that the doses used in clinical practice are frequently lower than recommended,10 and that the recommended therapeutic targets are frequently not achieved,11 but it does not seem likely that such mechanisms can be the sole explanation for the current findings. Also, the importance of lifestyle changes in patients with recognized atherothrombotic disease should be emphasized; it is possible that cultural differences in the adaptation of the patients following discovery of their disease exist across regions and can account for part of the observed differences in clinical outcomes. However, the main explanation probably resides in the fact that the atherothrombotic process is complex and not fully understood yet, and that continued research efforts are needed in this field, with concomitant pharmacological research.12 Thanks to the progress made over the past two decades, coronary artery disease has become a chronic disease, and mortality, especially in younger patients (i.e. those usually included in controlled trials), has decreased remarkably. This, however, poses a problem for clinical research: randomized controlled trials should probably focus on the populations most at risk, i.e. those frequently excluded from such trials (e.g. the elderly, or patients with co-morbidities), and they may no longer be the only answer to document the benefit of new medications. New ways of exploring the very long-term (>10 years) effects of (new) medications should be sought; actually, many patients present with atherothrombosis disease at a young age, and we should aim at stopping the atherosclerotic process in order to improve their health status far beyond the usual 5 years which currently constitute the duration of long-term randomized trials. In order to go along this route, we are in need of surrogate markers in the field of atherothrombotic disease that might be used to test new medications, and potentially authorize their marketing (such as is done with the control of glycaemia for diabetes, that of LDL-cholesterol for lipid-lowering drugs, or that of blood pressure for antihypertensive agents). In parallel, conventional randomized trials should be aimed at populations at increased risk. Finally, scientific observation, over long periods of time, of cohorts of patients suffering from the target disease might be the best way to monitor both the true long-term efficacy and the safety of newly marketed medications, as used in a real-world setting; new statistical techniques appear remarkably reliable, and could be used for this purpose.13 The REACH registry may be considered one of the first steps in this direction.

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References
It is widely accepted that patients presenting with recent onset chest pain associated with ST-segment elevation should undergo emergent coronary reperfusion.

Recently, De Winter et al. (N Eng J Med 2008; 359:2071–2073) have convincingly pointed out that in few patients with acute LAD occlusion there is a peculiar pattern of upsloping ST-segment depression with tall, positive, and symmetrical T waves in the V leads. Since these patients require immediate reperfusion therapy, it is important to recognize their ECG pattern. A case we observed offers the opportunity to emphasize this matter.

A 61-year-old male presented to the emergency department with precordial chest pain of about 1 h duration. The ECG (Panel A) revealed upsloping ST-segment depression at the J point followed by positive, peaked T waves in the precordial leads, while lead aVR exhibited slight ST-segment elevation (Panel A). Emergent coronary angiography documented the proximal occlusion of the LAD (Panel B). Successful PTCA and stent implant (Panels C and D) were followed by a peak CKMB of 105 ng/L and a clinically benign course. At 6 months, the patient remained asymptomatic with a left ventricular ejection fraction of 50% (Panels E and F). While the electrophysiological basis of this ECG pattern is unclear, we believe that it is of great importance to recognize it promptly and thus to implement the appropriate therapeutic measures since it signifies the total occlusion of a major coronary artery. It is also of relevance that, in the work of De Winter, patients presenting with this ECG pattern suffered, despite successful reperfusion, considerable myocardial damage as shown by high CKMB level.