In Western countries, persons 75 years of age or older constitute ~5% of the population but account for more than one third of those with acute coronary syndromes. In addition, one third of this elderly population has exercise-induced silent ischemia. The elderly population is projected to be more than 3 times larger in 2050 as today. The lower fertility rate and reduced mortality account for the aging of global population now and during the coming 50 years. However, this problem is not a problem for the richest countries only, and, according to the World Health Organization, the developing countries are actually more vulnerable to cardiovascular diseases, which have increased by more than 120% in the last 30 years compared with a 50% increase in developed countries over the same period. Better information and education of the elderly population, better access to healthcare services, earlier detection of coronary artery disease, better quality of care delivered to the elderly, and extrapolation to older persons of modern, evidence-based medicine, and often of modern aggressive care successfully tested in younger populations, are leading to dramatic changes in the management of this segment of the population. The painful consequence is that health systems will be stretched as the number of elderly patients increases. There will be a need for more investment in treatments of coronary artery disease, development of more aggressive prevention, and evaluation of the best cost-effective measures in this group of patients.

Most randomized, clinical trials have enrolled few older persons, and, as a result, fewer data are available to firmly guide clinical practice. Despite a distinct profile with more frequent comorbidities, a limited life expectancy, reductions in volume of distribution, hepatic, and renal functions, as well as pathophysiological changes that affect dosing, efficacy, and toxicity of drugs, several studies have confirmed in the elderly the benefit of drugs or even invasive strategies that have proven efficacy in younger populations.

Inhibition of platelet aggregation is one of the most important therapeutic advances in the field of coronary artery disease. Clinical trials have consistently demonstrated a benefit from platelet glycoprotein (GP) IIb/IIIa receptor inhibition in patients undergoing high-risk percutaneous coronary intervention (PCI). Recent evidence has supported this strategy even when strong oral antplatelet therapy with high-dose clopidogrel and aspirin is used in patients with non-ST elevation acute coronary syndrome. This demonstration has been obtained with abciximab, the most potent GP IIb/IIIa inhibitor (and the most expensive, also). The ISAR (Intracoronary Stenting and Antithrombotic Regimen) Investigators, who are among the smartest scientists in the field, had the understandable desire to know more about the risk/benefit ratio of the patients enrolled in the ISAR Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) study. They focused on the elderly subgroup, concluding in a study published in this issue of Circulation that the efficacy of abciximab is age-dependent, with no effect in patients >70 years of age. Our first reaction might be to accept this finding as it is, that is, as evidence of another subgroup in which the drug or even the class will not work, clouding a little more the understanding that we have of the optimal use of these drugs. Indeed, previous studies have also suggested that GP IIb/IIIa inhibitors may not improve clinical outcome of PCI performed in elective cases, low-risk ST-elevation myocardial infarction, bypass grafts, diabetic patients . . . leading to a naive question: “When does this drug really work in PCI?”

We have to recall here that, in a positive study, when we identify a subgroup in which these drugs do not work, it means that it improves outcome considerably in the opposite subgroup. In addition, patients belong to different subgroups, with diverging records for efficacy. What shall we do, for example, in the case of an elderly diabetic patient presenting with an ongoing anterior ST-elevation myocardial infarction? Do we need a special palm pilot program to weigh all the subgroups before deciding? This is not to mention the genotype information that we will soon get with the ECG.

A different reaction would be to closely examine the data presented before accepting them as a definitive demonstration. Several aspects of the study require attention: (1) The findings were not anticipated, and this subgroup analysis was not prespecified. (2) The elderly (like women) are commonly underrepresented in clinical trials, whereas they are at greater risk of both ischemic events and bleeding complications from GP IIb/IIIa inhibitors. Intriguingly, in the current study, older patients had a lower ischemic event rate than young ones, especially in the placebo arm with a primary end point rate steadily going down from ~17% to ~8% in patients <50 years of age to patients 70 to 80 years of age, and abciximab did not cause more major and minor bleedings in the elderly than in the younger patients. This may be accounted for by...
the play of chance, so frequently encountered in subgroup analyses, but could the age-dependent effect of abciximab described in the study be also a chance finding, despite the apparently solid data and cautious statistical analysis? (3) Are the results plausible? Retrospectively, they support a few plausible hypotheses: In the elderly, the thrombotic burden would be less serious, and alteration of the microcirculation would be less related to embolization. However, contradicting this hypothesis, the angiographic presence of thrombus and Thrombosis In Myocardial Infarction (TIMI) 0/1 flow were as frequent in the 2 age groups. Moreover, other plausible explanations could have been advanced that would not have been correct: For example, bleedings have been shown to trigger major ischemic events and drive later mortality in acute coronary syndromes, but abciximab did not cause more bleedings and did not affect mortality in the elderly group. (4) Are the results new or consistent with previous data? This issue on the elderly occurs after more >10 years of clinical trials testing abciximab with several tens of thousands of randomized patients; all the previous subgroups analyses have not consistently shown such an age-dependent effect of this drug. On the other hand, never before has such a thorough analysis of the relation between age and the abciximab effect been performed. However, in a meta-analysis of 4 major trials evaluating abciximab in a total of 7860 patients undergoing PCI, all age groups showed the same beneficial effect of the drug on ischemic end points, including the group >70 years of age (death/myocardial infarction and urgent revascularization rate of 11.8% placebo versus 7.2% abciximab, P<0.001).9 Similar benefits were observed in the elderly with other GP IIb/IIIa inhibitors in randomized studies performed in acute coronary syndromes.10-12 In addition, in these studies, bleeding complications occurred more frequently among the elderly and were triggered by GP IIb/IIIa inhibitors. Thus, recognizing the quality of Dr Ndrepepa’s work, we may interpret it as a new and intriguing hypothesis that needs to be retested.

In reporting this unexpected failure of abciximab in the elderly, the investigators add to the risk of undertreating older persons, in whom evidence-based therapy is already underused. They also add to the mixed track record of the class of GP IIb/IIIa inhibitors. Oral GP IIb/IIIa blockers and long infusions of abciximab have increased mortality rates in patients with acute coronary syndromes, and this untoward effect is likely related to proinflammatory and/or agonist effects of subthreshold GP IIb/IIIa receptor blockade. Uncertainties on the optimal dose of these blockers, failure in some clinical situations or subgroups of patients, cost, success of high-dose adenosine diphosphate antagonists, and the possible alternative of GP IIb/IIIa–sparring strategies with new, expensive anticoagulants have led to variable degrees of distrust in GP IIb/IIIa inhibitors. On the other hand, abciximab is remarkably effective in patients with ST-elevation or non-ST-elevation myocardial infarction undergoing PCI at reducing hard ischemic outcomes (including mortality), whereas new anticoagulants for PCI have shown safety benefits for low-risk patients.3,13,14 In this time of uncertainties for GP IIb/IIIa inhibitors, how do we contend with all the scientific information and marketing related to these drugs? Have we ushered in an age of fearing to use the most potent antithrombotic drugs in the catheterization laboratory because we are too safety oriented and not adequately open to the possibilities of preventing hard ischemic events? Are we too compliant, too willing to surrender an impact on death or reinfarction for vague promises on bleeding? The truth may come from practice, skills, and knowledge. There is a way to perform high-risk PCI with triple antiplatelet therapy while reducing bleeding complications by 80%, including in the elderly. However, for this benefit, there is no drug or device to buy, no marketing, and unfortunately almost no teaching. The radial access for PCI offers the best safety at the least cost without jeopardizing efficacy.15,16 In 2005, radial PCI was performed more often than femoral PCI in France. It is in a way reassuring to see that a technique can help stay the course in the catheterization laboratory.

Disclosures
Dr Montalescot received research grants from Eli Lilly, Guerbet, Sanofi-Aventis, and GSK, and honoraria from Astra-Zeneca, Eli Lilly, GSK, MSD, Schering Plough, Medicines Company, Sanofi-Aventis, and BMS.

References


Keywords: Editorials | anticoagulants | coronary disease | platelets
Glycoprotein IIb/IIIa Inhibitors in the Elderly: Fear of Age or Age of Fear?
Gilles Montalescot

doi: 10.1161/CIRCULATIONAHA.106.658245
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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