Percutaneous Coronary Intervention in Octogenarians and the Safety of Glycoprotein IIb/IIIa Inhibitors*

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“Seventy is old enough. After that there is too much risk.”
—Mark Twain (1)

Mark Twain’s 19th-century sentiment regarding old age is shared by many cardiologists in the current century when considering the use of invasive procedures or pharmacologic therapies in the elderly, particularly in those over 80 years of age. It is certainly true that advanced age leads to increased risk with coronary surgery, percutaneous coronary interventions (PCI), and the use of drugs such as thrombolytic agents. Paradoxically, these are precisely the patients that may benefit the most. Thus, it is important to understand the risks and benefits of these therapies in elderly persons before they are either widely used and assumed safe or summarily dismissed as being too risky.

This issue is of increasing importance in the U.S. and other nations faced with a progressive growth in the elderly population. Based on the year 2000 census, there are over 9 million Americans age 80 years or more and over 4 million age 85 years or more (2). Population projections suggest that over the next 50 years, the greatest growth will be in those aged 85 years and over, with an estimated 8.5 million Americans in this age group by 2030 and more than 18 million by 2050 (2). Given the marked prevalence of heart disease in the elderly, cardiologists face a future where a substantial number of their patients will be octogenarians or older.

Although coronary surgery can be performed safely in highly selected octogenarians, most patients age 80 years or more either have significant comorbid illness which makes surgery a prohibitive risk or they simply chose not to undergo this procedure. Percutaneous procedures are much more palatable to the mindset of the elderly as well as their physicians. How safe and effective are PCI procedures in elderly patients? Recently, the results of two registries reported the clinical outcomes from a total of nearly 11,000 PCI procedures in octogenarians in the current era (2,3). As might be expected, this population had a high frequency of comorbid illness such as diabetes (23%), previous bypass surgery (24%), previous stroke (18%), and renal failure (11%) (3). For the most part, PCI is performed for acute coronary syndromes or recent myocardial infarction (MI) rather than for elective, stable syndromes. Over half of these patients have multi-vessel coronary disease. Despite this, these studies confirm that PCI in octogenarians may lead to acceptable early results. Angiographic success is high, and the overall hospital mortality was 3.7% (3,4). Mortality was closely linked to timing of MI, with the lowest mortality (1.35%) seen if there was no MI, and the highest mortality (13.79%) seen if MI was within the past 6 h (4). Other significant in-hospital complications included stroke in 0.46% and 0.68% (3,4), renal failure in 2.15%, and major vascular complications in 3.73% (4).

The large-scale registries suggest that PCI can be performed in octogenarians with an acceptable risk. Whether this aged population actually achieves a longer term benefit from revascularization procedures is another question entirely. A large population study from Canada comparing the outcomes of revascularization versus medical therapy in elderly patients found that revascularization was associated with better survival in all elderly subgroups, but the greatest absolute survival difference was seen in patients over 80 years of age (5). Patients <70 years old had survival rates for bypass surgery, PCI, and medical therapy of 95%, 94%, and 91%, respectively, whereas patients more than 80 years of age had survival rates of 77% with surgery, 72% with PCI, and 60% with medical therapy.

Survival is probably not the most important outcome in the elderly. Patients in their 80s almost universally declare that quality of life takes precedence over measures that prolong survival. Few studies have specifically addressed quality-of-life measures in elderly patients receiving medical therapy versus PCI. In the Trial of Invasive versus Medical therapy in Elderly (TIME), 301 patients >75 years of age with chronic angina on at least two anti-anginal drugs were randomized to coronary angiography and revascularization versus optimized medical therapy (6). The primary end points were indices of quality of life and the presence of major adverse event (death, non-fatal MI, hospital admission for acute coronary syndrome) at six months. Although these patients likely represented a select group of elderly individuals, their clinical characteristics were similar to the large registries with similar proportions of comorbidities and multi-vessel coronary disease. Among the group randomized to an invasive approach, 109 (74%) underwent revascularization procedures, with PCI in 79 (72%) and coronary artery bypass graft surgery (CABG) in 30 (28%). Mortality related to revascularization was 2.5%. In both the invasive and medical groups, the indices of quality of life improved. Angina severity decreased in both groups but more significantly in patients randomized to an invasive...
approach. At six months, adverse cardiac events occurred in 49% of the medical group and 19% of the invasive group and were due primarily to higher rates of hospital admissions for acute coronary syndromes and non-fatal MI in the medical group. These data suggest that patients age 75 years or older with angina have less symptoms, less hospital readmissions, and a better quality of life after revascularization (primarily accomplished with PCI) compared with medical therapy.

The proportion of elderly patients who might benefit from PCI is not known. Many octogenarians might not be considered for an invasive procedure because of their associated illnesses or poor general health status. Even among those felt to be good candidates for revascularization, a sizeable proportion of patients are found to have untreatable coronary disease. As a clinician, it is hard to know which octogenarians should be chosen for an invasive approach. In the TTMI trial, 74% of patients randomized to an invasive strategy underwent revascularization, with most of these undergoing PCI. The remaining patients were treated medically either because of refusal (7/37), the identification of non-critical disease (11/37), or the presence of disease not amenable to either PCI or CABG (19/37). Thus, even in a select group, roughly one-quarter of elderly patients will either have disease not amenable to revascularization or will have insignificant disease.

Once a physician has decided to perform PCI in an octogenarian, the next decision regards the use of adjunctive pharmacology. The randomized controlled trials have established that adjunctive glycoprotein (GP) IIb/IIIa inhibitors reduce MI and death in numerous clinical subsets involving PCI (7–14). Importantly, they have been shown to be safe with low rates of major bleeding, especially when heparin is discontinued after the procedure (14). Because randomized trials represent only a small fraction of the total population being treated, the conclusions made from these studies may be difficult to extrapolate to specific patient subsets that were either excluded or underrepresented in the randomized trials. This is particularly true with elderly patients. At least one major trial of GP IIb/IIIa inhibitors in PCI excluded patients age >80 years (7), and the mean age of patients in all the other trials was only about 60 years.

There are no randomized comparisons determining the efficacy of GP IIb/IIIa inhibitors versus placebo in octogenarians undergoing PCI. Thus, the utility of these agents in this population is unknown. Subgroup analysis from the randomized trials provides some insights into this question. Several studies specifically analyzed the primary end point in patients more than 65 years old and showed a benefit of GP IIb/IIIa inhibitors compared with placebo (Figs. 1 and 2). The absolute benefit appeared greatest in younger patients in some studies (Evaluation of 7E3 for the Prevention of Ischemic Complications [EPIC], Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade [EPILOG], Evaluation of Platelet IIb/IIIa Receptor with Integrilin Therapy [EPISTENT]) (Fig. 2) but was greatest in older patients in others (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy [ESPRIT], Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis II [IMPACT II]) (Fig. 1). No efficacy data are available specifically for octogenarians, and no safety data were presented in any of these analyses.

The absence of published data regarding the safety of GP IIb/IIIa inhibitors in octogenarians leads to a clinical dilemma for many cardiologists. Because of advanced age and greater comorbidity, many clinicians are rightly concerned that these drugs might have prohibitive risk in the very elderly and might be associated with an increased risk of intracranial bleeding, a problem not seen in the younger patients enrolled in the randomized trials. The study by Sadeghi et al. (15), published in this issue of the Journal, helps alleviate these concerns and is thus an important contribution. In addition to the large size of the octogenarian cohort, one of the strengths of this study is that it represents a “real world” experience of PCI in the very elderly. These data are much more helpful to clinicians trying to make difficult decisions than data from random-
ized trials, because these data reflect common clinical practice.

The main risk of parenteral platelet inhibitors is bleeding, and this can be defined in many ways. Sadeghi et al. (15) defined access site bleeding as any hematoma ≥3 cm. Using this definition, Sadeghi et al. (15) found more access site bleeding in patients treated with GP IIb/IIIa inhibitors (26% vs. 20%). These numbers sound high and are greater than bleeding rates reported in the randomized trials; however, those trials had different definitions of bleeding. It is unclear how many of these hematomas were “significant” in terms of patient discomfort or led to a delayed discharge. To gain a sense of perspective regarding these bleeds, the investigators reported other indices of bleeding. Although there were more bleeds defined as a hematocrit drop of more than 10% (7.8% vs. 4.2%), there was no difference in transfusion requirements between the groups, suggesting that “serious” bleeding was not greatly increased in the parenteral platelet inhibitor group. Non-access site bleeding was also higher in the parenteral platelet inhibitor group, but the absolute numbers did not appear alarming (5.2% vs. 2.6%) and consisted mostly of gastrointestinal and genitourinary bleeds. Importantly, there was no intracranial bleeding, and there was no difference in the incidence of retroperitoneal or pulmonary hemorrhage. Few patients were treated with heparin post-intervention, which has been recognized as an important strategy to prevent bleeding with these drugs (14).

This study does not address the issue of efficacy. There was a higher event rate in the GP IIb/IIIa inhibitor group, but this is almost certainly due to the higher risk profile of those selected for use of these drugs. The parenteral platelet inhibitor group was more likely to have an acute coronary syndrome or MI and more likely to undergo multi-vessel PCI. No data on lesion type or complexity were reported, and this may have been an important additional criterion leading to the use of parenteral platelet inhibitors.

There are several important limitations of this study. First, patients were selected for parenteral platelet IIb/IIIa inhibitor use by unclear criteria (“at the operator’s discretion”), and thus broad application of these data to all octogenarians is not appropriate. It is certain that non-quantifiable variables involving common sense and sound clinical judgment were involved in selecting patients for this treatment, and it is imperative that clinicians wishing to apply these data to their own patients do the same. The bleeding complications were not prospectively defined, and no standardized system for data collection was performed. Bleeding events were either reported by operators or obtained by chart review, and this may have led to their underestimation. Finally, this is a study primarily of eptifibatide; the results may have been different if a greater proportion of patients were treated with abciximab or tirofiban.

Although these data add substantially to our knowledge regarding the use of this important class of drugs in an ever-increasing and high-risk group of patients, there does appear to be a need for a randomized trial to establish the safety and efficacy of these drugs in this age group. This will likely never be done. In the future, it is hopeful that additional registry and outcome data will supplement the study by Sadeghi et al. (15), providing information helpful to clinicians caring for the very aged. For the time being, it appears that the platelet GP IIb/IIIa inhibitors can be used safely in selected octogenarians chosen to undergo PCI.

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REFERENCES


