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Special Article

Management Strategies in Unstable Coronary Artery Disease—Current Problems and Future Directions

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Summary: Unstable coronary artery disease continues to pose a major challenge to clinicians. The advent of new therapies, such as percutaneous transluminal coronary angioplasty, low-molecular-weight heparins, and glycoprotein IIb/IIIa inhibitors, provides new management options for this indication but also raises new questions with regard to optimal management. Prospective randomized trials with well-defined, long-term outcome measures and a means of identifying which patients will derive most benefit from each treatment, together with a means of rapid and clear dissemination of study results and implications, are required in order to advance the management of unstable coronary artery disease.

Key words: unstable coronary artery disease, antithrombotic, revascularization, clinical trial, heparin

Unstable coronary artery disease, whether unstable angina or non-Q-wave myocardial infarction, poses a major challenge to clinicians. Among the key aims of management in the first few months of follow-up are the prevention of myocardial infarction and death through stabilization of the patient and institution of a long-term management plan. The standard therapeutic approach is to administer long-term oral aspirin, with unfractionated heparin administered intravenously for a few days in the acute phase of treatment. The advent of new therapies, such as percutaneous transluminal coronary angioplasty, glycoprotein IIb/IIIa inhibitors, and the low-molecular-weight heparins, has provided us with new management options and, inevitably, has raised new questions regarding the optimal management of unstable coronary artery disease. For example, what treatment or combination of treatments constitutes the most effective therapy? How long should antithrombotic treatment continue? Are there advantages to the adoption of an early invasive versus a conservative strategy? Can patients be stratified and treated according to level of risk?

Unstable coronary artery disease is due to subtotal or intermittent occlusion of the coronary artery as a result of plaque disruption in about 75%, and plaque erosion in about 25% of patients. From the work by Van Belle *et al.*[1] in France, it is known that intracoronary thrombus is still visible on angioscopy at 1 month after an acute episode in patients treated with thrombolytic agents and that this thrombus resembles an acute thrombus. This observation, together with the high incidence of reocclusion and the high ongoing-event rate after myocardial infarction, would in theory support the use of antithrombotic drugs for at least 3 months and possibly up to 6 months after the acute event.

The beneficial effects of aspirin in reducing the risk of death or myocardial infarction by around 50% in patients with unstable coronary artery disease are well established.[2–4] It is also clear from studies with aspirin in combination with anticoagulants, glycoprotein IIb/IIIa agents, or heparins that additional antithrombotic treatment can reduce further the ongoing-event rate and the number of invasive procedures performed. What is less clear, however, is whether there are clinically relevant differences between the alternative antithrombotic drugs available, and the duration for which antithrombotic therapy should be continued and at what dose.

Studies with low-molecular-weight heparins have shown that these agents have practical and safety advantages over unfractionated heparin: predictable pharmacokinetics, no need for laboratory monitoring, the possibility for self-administration by the patient at home, and reduced risk of thrombocytopenia and osteoporosis. Most data are available for dalteparin and enoxaparin, but there is to date no clinical evidence of any significant difference between the low-molecular-weight heparins in terms of anticoagulant efficacy.

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We must indeed be careful in comparing the results from clinical trials in unstable coronary artery disease, as they often differ in terms of inclusion criteria, control treatment strategies, and designated outcomes. Differences in patient selection, in terms of severity and definitions of disease, age, and gender, must have an impact on outcomes in these trials. In the Fragmin in Unstable Coronary Artery Disease (FRIC) trial,[5] for example, a differentiation was made between recurrent angina in hospitalized and in discharged patients, whereas a broader definition encompassing a variety of in- and outpatient settings was used in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial.[6] It is thus impossible to compare the recurrent angina outcomes between these two trials. Interpreting the results of clinical trials relies on the endpoints selected, and trial investigators often choose different endpoints to report on. Do we need to define some specific endpoints and look for these within each of the studies? Long-term outcome measures such as quality-of-life benefits, readmission rates, and overall health costs need to be incorporated into the design of clinical trials, as it is the ongoing-event rate that we are aiming to reduce in the management of patients with unstable coronary artery disease.

Preliminary data from the Fragmin and/or Early Revascularization during Instability in Coronary Artery Disease (FRISC II) trial[7] have, for the first time, clearly demonstrated that prolonged treatment with a low-molecular-weight heparin may reduce the risk of death or myocardial infarction. In this study, patients who continued to receive dalteparin beyond the standard 5–7-day acute-treatment period had a 43% lower rate of further events (death or myocardial infarction) at Day 45 compared with patients who received placebo in the long-term phase. At 90 days, the benefit dropped to an 18% reduction. The FRISC II trial also appears to support a strategy of aggressive medical treatment in conjunction with early intervention, compared with a conservative strategy. Full analysis of the data is eagerly awaited.

Earlier trials investigating the utility of longer-term antithrombotic treatment (e.g., FRISC),[8] Organization to Assess Strategies for Ischemic Syndromes (OASIS) pilot,[9] FRIC,[5] Williams *et al.*,[10] Thrombolysis in Myocardial Infarction (TIMI) 11B,[11] Fraxiparine in Ischemic Syndrome (FRAXIS)[12] tended to use lower doses of antithrombotic agent during the longer-term, out-of-hospital phase, compared with doses used for acute management. Results of these trials have been inconclusive. It may be that the doses used were too low to show a consistent benefit across the whole spectrum of patients with unstable coronary artery disease, although they were high enough to increase bleeding.

There is currently a vast and expanding array of agents for treating patients with coronary artery disease, and as yet there is no standardized protocol for optimal medical therapy or lifestyle interventions in the trials of new therapies in unstable coronary artery disease. Given that there are so many treatment strategies available, how should we define maximal medical therapy for unstable coronary artery disease in 1999? This could include anti-ischemic drugs (to the maximum doses tolerated by the patient), lipid-lowering therapy, aspirin, glycoprotein IIb/IIIa receptor inhibitors,[13] angiotensin-converting enzyme inhibition for left ventricular dysfunction, beta blockers, control of diabetes and blood pressure, as well as lifestyle changes—smoking cessation, weight reduction, and programmed physical activity. Similarly, optimal angioplasty or coronary artery bypass surgery has not been fully defined; in recent years there have been several advances in these techniques, which means that the trials are not always comparing like with like. There remains the question of whether it is possible to identify which patients might benefit most from intervention.

If the preliminary results of FRISC II are borne out in the final analysis of the data, all patients with unstable coronary artery disease should undergo early revascularization. Logistically, this has enormous implications for clinical practice, particularly in Europe, where resources do not currently support such a strategy. It should be mentioned that early invasive treatment in the FRISC II trial was 3 days after hospitalization, a rather conservative approach that allowed sufficient time for risk stratification of patients. Fortunately, FRISC II suggests that prolonged treatment with dalteparin provides a protective window of 45 days within which to plan surgical intervention.

It may be that we need to define subsets of patients who will derive most benefit from each treatment strategy in order to prescribe the most beneficial and cost-effective therapy for each patient. Several clinical trials have shown a poorer prognosis in those patients with unstable coronary artery disease who have specific adverse indicators.[14–18] These indicators, which seem to be useful in identifying high-, intermediate-, and low-risk patients, include previous and present symptoms, response to medical therapy, recurrent ischemia on ST-segment monitoring or exercise stress testing, and elevation of cardiac-specific troponins or creatine kinase MB. In the FRISC study there was evidence that elevation of troponin-T to ≥ 0.1 μg/l during the acute unstable coronary artery disease episode identified a subgroup of patients in whom prolonged antithrombotic treatment (with the low-molecular-weight heparin dalteparin) was beneficial in reducing the incidence of death or myocardial infarction at 40 days.[18]

Clearly, new prospective randomized studies, including prespecified risk groups and well-defined outcome measures, are required to provide the evidence base for tailoring a treatment approach to the individual patient. As so many unanswered questions remain in unstable coronary artery disease, it is vital that the latest research findings are disseminated rapidly to clinicians to ensure that patients are receiving optimal management based on informed clinical judgment.

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