Acute Coronary Care and Beyond: The Expanding Role of Low-Molecular-Weight Heparin

Introduction

Freek W. A. Verheugt, M.D., F.A.C.C., F.E.S.C., AND JAMES H. CHESEBRO, M.D.*

Heartcenter, University Medical Center, University of Nijmegen, Nijmegen, The Netherlands; *The Cardiovascular Institute, Mount Sinai Hospital, New York, New York, USA

There have been many periods of excitement and innovation in cardiology in the last 50 years, but we are now entering an era in which a whole spectrum of new therapeutic concepts is emerging.

For many years, heparin has been widely used as an anticoagulant in the treatment of coronary artery disease. With the realization that the biological activity of heparin is encoded in pentasaccharide segments of the molecular structure, smaller molecules were derived from unfractionated heparin (UFH) by depolymerization and fractionation. These low-molecular-weight heparins (LMWHs) retain the antithrombotic qualities of the parent compound but also possess extra beneficial pharmacokinetic and pharmacodynamic properties and are now playing an integral role in the current rapid evolution of cardiology. The advantages of LMWH over UFH include a longer half-life; a more predictable dose response that reduces the need for laboratory monitoring; and greater bioavailability following subcutaneous administration, allowing a more convenient mode of administration without the restrictions of an intravenous line. Research with LMWH has made significant progress, and an increasing number of clinical benefits of LMWH treatment are now emerging. As more is learned about the physiologic and clinical profile of the LMWHs, the range of possible indications for these agents is expanding.

This forms the theme of the papers included in this supplement, in which the potential wider role of LMWH in cardiology is evaluated, focusing on unstable coronary artery disease (UCAD: unstable angina and non-ST-segment-elevation myocardial infarction), acute myocardial infarction (AMI), and atrial fibrillation.

The results of randomized clinical trials using different forms of LMWH, dalteparin, enoxaparin, and nadroparin¹⁻⁴ have provided solid evidence that, in terms of acute-phase treatment for UCAD, LMWH treatment is as effective as UFH treatment in reducing the risk of death or myocardial infarction (MI).⁵ Aided by their ease of administration, LMWHs have now gained acceptance as first-line antithrombotic agents in the treatment of patients with UCAD.⁶ However, as increased coagulant activity may persist for a long time in these patients, and reactivation of the disease may occur after initial treatment, an important issue has been to determine whether the early benefits of LMWH treatment are sustained by extended therapy.⁷ This important question was addressed in the Fragmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) trial,⁸ which also investigated the merits of an early invasive strategy to treat patients with UCAD compared with a noninvasive therapy.⁹ Kontny (pp I-3-I-7) reports that, while the lowest rate of death and MI was seen in patients managed invasively, treatment with dalteparin for up to 45 days provided a protective "bridge" to revascularization for patients when early revascularization was not possible. Further subgroup analyses of results from the FRISC II trial concerning the relevance of identification of high-risk groups of patients, also discussed, are of value as we seek to refine the management of UCAD.

The use of a new class of antiplatelet agents, the glycoprotein (GP) IIb/IIIa inhibitors, in combination with aspirin and antithrombotic agents, has improved the outcome of patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI).^{6, 10} At present, there is some confusion about the combined use of UFH and GP

Address for reprints:

Professor Freek W. A. Verheugt
Heartcenter
University Medical Center
University of Nijmegen
PO Box 9101
6500 HB
Nijmegen, The Netherlands

IIb/IIIa inhibitors in these patients as UFH activates platelets. This may make the effects of GP IIb/IIIa inhibitors harder to predict and dosing regimes more difficult to plan.¹¹ Data showing the favorable anticoagulation response when UFH is replaced with dalteparin (which does not activate platelets), in combination with the GP IIb/IIIa inhibitor abciximab, are reported by Fry (pp I-8–I-11). A reduced risk of thrombocytopenia appears to be one of the advantages of LMWH over UFH when used with abciximab during PCI.

A new direction for dalteparin therapy as an adjunct to recombinant tissue-plasminogen activator (rt-PA) and aspirin to improve patency in AMI is explored by Wallentin and colleagues (pp I-12–I-14). The possibility that dalteparin may be a more effective adjuvant to rt-PA than UFH in reperfusion treatment of AMI is discussed.

Patients with atrial fibrillation should be cardioverted as promptly as is safely possible to prevent unfavorable electrophysiologic remodeling. The high compliance for dalteparin therapy in ambulant patients, and relative ease of maintenance of effective antithrombotic levels, make it an attractive agent to reduce the risk of thromboembolic complications and allow for a reduction in the time to cardioversion in patients with atrial fibrillation. Studies using transesophageal echocardiography to identify patients with atrial fibrillation who are thrombus free and suitable for direct cardioversion, and dalteparin antithrombotic cover before, during, and after cardioversion, have yielded encouraging results. These results, described by Camm (pp I-15–I-19), present a promising new direction for LMWH therapy.

There is increasing clinical evidence to support a wider role for LMWH in cardiology in the future. Indeed, in several countries dalteparin has been approved for extended use in patients with UCAD scheduled for revascularization on the strength of FRISC II evidence. This supplement offers a timely insight into the expanding role of LMWH in acute coronary care and beyond.

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