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Foreword

Platelet aggregation is a major factor in acute ischaemic syndromes (unstable angina and myocardial infarction) and excessive platelet aggregation can complicate coronary interventions. In clinical practice, platelet aggregation is usually initiated by spontaneous rupture of a coronary plaque, or by iatrogenic rupture (dissection) during coronary intervention. Current treatment of unstable angina and myocardial infarction includes aspirin, a weak platelet aggregation inhibitor, and heparin as anticoagulant. Similarly aspirin and heparin are used routinely to avoid thrombotic complications during coronary intervention. In spite of such combination therapy, platelet aggregation remains a major clinical problem in subgroups of patients with unstable angina and during coronary intervention.

Recently several new approaches have been taken to avoid platelet aggregation, including development of specific platelet GP IIb-IIIa receptor blockers and the development of specific thrombin inhibitors. During a symposium at the European Heart House on 16–18 February 1995 these developments were reviewed. This supplement contains the papers discussed at the symposium focusing on: the pathophysiology of plaque disruption, platelet aggregation; developments in antiplatelet and antithrombotic therapy; identification of patient subgroups at low risk and high risk for thrombotic complications during coronary interventions; current experience with c7E3 (ReoPro), a platelet GP IIb-IIIa receptor blocker which has recently been introduced in clinical practice; an overview of other antiplatelet agents and specific antithrombins; clinical application of platelet GP IIb-IIIa receptor blockers and (in the future) specific antithrombins including a discussion of bleeding risks and cost efficacy of such therapy; finally, guidelines for prevention and management of thrombotic complications during coronary interventions are discussed.

The rapid developments and challenges in this field are best illustrated by two trials which have been presented and published recently. The EPIC trial, as summarized by Califf in this supplement, demonstrated that administration of the c7E3 antibody reduced thrombotic complications during and after coronary angioplasty. A significant reduction of events was achieved early after the intervention, at 30 days, and at 6 months follow-up. In fact, further separation of the event-free survival curves up to 6 months suggested that short-term administration (12 h) of c7E3 might have a long-term effect and might reduce the rate of restenosis. Unfortunately, angiography was not repeated at 6 months in the EPIC study. Further studies are ongoing to assess the mechanism of this observation[1–3].

The HELVETICA study, with recombinant hirudin, enrolled patients with characteristics similar to those in EPIC (Table 1). Inhibition of anticoagulation and platelet aggregation by the specific antithrombin yielded a similar clinical effect at 30 days as observed with c7E3 in EPIC (Table 2). However, at 6 months follow-up, no difference was found in event rates in patients receiving hirudin or heparin[4,5].

The similarity of the early reduction of events by c7E3 and hirudin, and the apparent difference in late effect is intriguing. Several possibilities to explain this discrepancy should be considered. First, both studies confirm that inhibition of platelet aggregation (and anticoagulation) offers a major benefit with reduction of thrombotic events in patients undergoing coronary intervention, without excessive bleeding risk. Second, it is possible that the difference in long-term efficacy of both compounds is a chance finding. In fact, the number of events during follow-up is small in both studies, and the confidence intervals for the late effects are wide. Third, several mechanisms have been proposed which might explain a long-term effect of c7E3, including inhibition of vitronectin receptor mediated intimal hyper-

Table 1 Comparison of patients in the EPIC study (c7E3 for high risk PTCA procedures) with the HELVETICA study (hirudin for unstable angina). In both studies, three patient groups were compared. This table contains data from patients in the control group (placebo and heparin in EPIC and HELVETICA, respectively) and patients with the highest dose of c7E3 (bolus + infusion) and hirudin (infusion + subcutaneous administration). Patient characteristics among the two studies were similar

	EPIC		HELVETICA	
	Placebo	c7E3	Heparin	Hirudin
Patients	696	708	382	378
Age (years)	61		58	
Male (%)	72		79	
Previous MI (%)	57		40	
Previous PTCA (%)	23		17	
Previous CABG (%)	15		3	
Acute unstable angina (%)	43		29	

MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass surgery.

Table 2 Comparison of outcome at 30 days and 6 months in the EPIC and HELVETICA studies (see Table 1). Note a remarkable similarity in reduction of events during the first 30 days among the two studies. (HELVETICA data at 30 days kindly provided by the investigators). At 6 months follow-up, a further reduction in events by c7E3 in EPIC was reported, while event rates in the two treatment groups in HELVETICA were similar. Several explanations for this contrast between early and late effects of c7E3 and hirudin are discussed

	EPIC		HELVETICA	
	Placebo	c7E3	Heparin	Hirudin
Patients	696	708	382	378
30 days				
Death (%)	1.7	1.7	0.8	1.1
Infarction (%)	8.6	5.2	4.7	3.4
PTCA (%)	4.5	0.8	4.5	2.1
CABG (%)	3.6	2.4	3.1	2.4
Any event (%)	12.8	8.3	12.8	7.7
6 months				
Death (%)	3.4	3.1	1.0	2.9
Infarction (%)	10.5	6.9	4.5	4.0
PTCA (%)	20.9	14.4	19.6	19.3
CABG (%)	10.9	9.4	7.6	5.8
Any event (%)	35.1	27.0	32.7	32.0

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plasia. Further studies are required and are being conducted to investigate these issues.

The papers presented in this supplement provide an overview of the various approaches to prevent thrombotic complications during coronary interventions. A synthesis of these approaches, with practical guidelines, is presented in the concluding paper distilled from the final discussions of the symposium.

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