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Current Therapeutic Options in Unstable Angina

C. T. Olariu¹, L. Olariu²

Unstable angina represents a serious challenge in everyday practice. In the past 10 years we have witnessed enormous progress in risk stratification and treatment of this kind of patient. This paper focuses on the current medical armamentarium against this acute coronary syndrome. While some old drugs like aspirin and beta-blockers had a well proved efficacy, the use of newer drugs such as low molecular weight heparins, glycoprotein IIb/IIIa receptor antagonists, thienopyridines is evolving with impressive results. The introduction of intravenous glycoprotein GP IIb/IIIa receptor antagonists represents the most important therapeutic advance especially in the setting of percutaneous coronary intervention. Surprisingly, the oral form of this class is a big therapeutic failure according to the present trials. Low molecular weight heparins (especially enoxaparine) appear to be a reasonable and efficient alternative to standard heparin. Other drugs such as direct thrombin inhibitors have not found a definite therapeutic niche whereas lipid lowering drugs (particularly statins) administered aggressively in high doses seem to win a more consolidated position as part of maximal therapy. *J Clin Basic Cardiol 2001; 4: 269–74.*

Key words: unstable angina, therapy, antiplatelets, GP antagonists, beta-blockers

As one of the acute coronary syndromes, unstable angina was the subject of some important trials and debates in the literature during the last decade. Despite the remarkable therapeutic achievements during the first year after the diagnosis, 12 % of patients will die and another 12 % will experience an acute myocardial infarction [1]. In this article we will focus on the present pharmacological armamentarium against unstable angina.

Antiplatelet Therapy

Antiplatelet drugs can be classified according to their mechanism of action (Table 1). Only four of these drugs are currently in use.

Aspirin

This compound acts as an irreversible inhibitor of cyclooxygenase to inhibit the generation of thromboxane A₂. Several well known studies (Veterans Administration Cooperative Study, Canadian Multicenter Trial, Montreal Heart Institute Study, RISC Group) confirmed that aspirin in doses of 75–300 mg/d reduces the risk of death and myocardial infarction by 50–70 % in patients with unstable angina [2, 3].

The effect is rapidly installed and the benefit is the same over all the dosages used but it should be noted that the higher doses are associated with more frequent side effects (mostly gastrointestinal). According to present guidelines, aspirin must be given to all patients with acute coronary syndromes in the absence of absolute contraindication (active bleeding, hypersensitivity) in doses of 75–325 mg/d. Patients without prior aspirin administration may receive a higher initial dose (160–325 mg) [3–5]. In some studies, 30–40 % of patients did not respond to moderate doses (80–325 mg) of aspirin [6]. It is possible that the remarkable effect of aspirin

is mediated through some other pathways such as endothelial function improvement [7]. Despite its salutary effects, aspirin is still underused so that in 1995 only 84 % of patients with ischaemic heart disease were using it regularly [8]. Patients who cannot tolerate aspirin should take ticlopidine or clopidogrel but not dipyridamole, which has a doubtful efficacy [9]. Moreover, aspirin associated with dipyridamole is not better than aspirin alone [10].

Ticlopidine

Ticlopidine is a thienopyridine derivative which interferes with ADP-induced platelet aggregation. It is not only a substitute for aspirin, but together with aspirin it is given to patients with intracoronary stents. The onset of action is delayed for 2–3 days after administration and the usual dosage is 2 × 250 mg/d [5, 11]. The Studio della Ticlopidina nell'Angina Instabile demonstrated a 46.3 % reduction in the incidence of death and non-fatal myocardial infarction in patients taking ticlopidine versus those receiving placebo (7.3 % vs. 13.6 %) [4]. It is generally accepted that ticlopidine is not better than aspirin in acute coronary syndromes, being reserved for patients intolerant to aspirin and for those receiving intracoronary stents to whom it is administered for one month. In this situation, ticlopidine is better than aspirin or aspirin plus warfarin [12]. Its widespread use is limited by some potentially severe side effects like neutropenia (which is reversible and has an incidence of 1–2.4 %) and thrombotic thrombocytopenic purpura necessitating complete blood cell counts every 2 weeks during the first months of therapy [4, 13].

Clopidogrel

Clopidogrel is an analogue of ticlopidine given in a single daily dose of 75 mg [6, 12]. Administration of a loading dose (300 mg) followed by 75 mg/d is associated with a more rapid inhibition of platelet aggregation [11]. Its safety profile is at least equal to that of aspirin and superior to ticlopidine. Neutropenia and thrombotic thrombocytopenic purpura are rare [12–14]. In the Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) study which involved 19,185 patients with ischaemic stroke, ischaemic heart disease and peripheral arterial disease the end-point, a composite of ischaemic stroke, myocardial infarction and vascular death, occurred in 5.3 % of those given clopidogrel versus 5.8 % aspi-

Table 1. Mechanism of action of antiplatelet drugs

- Drugs acting on arachidonic acid metabolism (aspirin, triflusal, indobufen)
- Drugs that increase platelet cAMP (triflusal, dipyridamole, iloprost)
- Antagonists of ADP receptors on platelet membranes (ticlopidine, clopidogrel)
- Antagonists of GP IIb/IIIa receptors

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rin patients [15]. According to the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) study the combination of clopidogrel plus aspirin is superior to aspirin alone. The addition of clopidogrel (300 mg load followed by 75 mg daily) to aspirin in patients with acute coronary syndromes significantly reduced the risk of cardiovascular death, myocardial infarction and stroke by 20 %, cardiovascular death, myocardial infarction, stroke and refractory ischaemia by 1/6. The benefits begin to accrue very early (within 2 hours of the loading dose) [F. Jafary, oral presentation at ACC Scientific Sessions, 2001]. Aspirin plus ticlopidine seems to be equally as effective as aspirin plus clopidogrel [13]. Clopidogrel is preferred to ticlopidine because it more rapidly inhibits platelets and appears to have a more favourable safety profile [16]. Based on the available data, dual antiplatelet therapy (eg aspirin plus ticlopidine) may be warranted in patients with multiple vascular bed involvement, resistance to aspirin or with ischaemic stroke despite aspirin therapy, in patients with heart failure who require an angiotensin converting enzyme inhibitor, in those with end-stage coronary disease or after stent placement [17].

Triflusal

Triflusal is structurally related to aspirin. Administered in a dose of 900 mg/d to patients with unstable angina triflusal determined at 6 months, a 66 % reduction of the risk of non-fatal myocardial infarction versus placebo [18]. However, its place in the treatment of unstable angina is not well established.

The impact of antiplatelet therapy in unstable angina resulted in 50 major vascular events being prevented by treating 1000 patients for 6 months [2].

Platelet Glycoprotein IIb/IIIa Receptor Antagonists (GP IIb/IIIa Antagonists)

Contrasting with the above mentioned drugs, GP IIb/IIIa antagonists inhibit platelet aggregation irrespective of the agonist by preventing the binding of fibrinogen to its receptor on platelets and so interfere with the final common pathway of aggregation [3, 4, 12]. This group of drugs has 4 main representatives: Abciximab, which is a Fab fragment of the chimeric human-murine monoclonal antibody, binds with high affinity to GP IIb/IIIa and vitronectin receptors; eptifibatide, a synthetic heptapeptide; and tirofiban and lamifiban which are non-peptide products. These latter agents are specific an-

tagonists of GP IIb/IIIa receptor only [4, 12, 19]. Abciximab has a longer plasma half life, is antigenic and the platelet function returns to normal 12–36 hours after the administration of the drug was stopped. Tirofiban and eptifibatide have a shorter half life and the platelet function recovers within 4 hours after drug discontinuation [12, 20].

These drugs are administered intravenously. They were studied in patients with acute coronary syndromes without persistent ST segment elevation (unstable angina or non-Q-wave myocardial infarction) treated conservatively or interventionally [4, 12, 20]. There are also agents from this class for oral administration (xemilofiban, orbofiban, sibrifiban, lotrafiban) but their efficacy and superiority over classical agents could not be proved in clinical trials [21].

The Orbofiban in Patients with Unstable coronary Syndromes (OPUS-TIMI 16) trial was prematurely terminated because of increased mortality in the treatment group. The Sibrifiban versus aspirin to Yield Maximum Protection from ischaemic Heart Events Post-acute Coronary Syndromes (SYMPHONY) trial showed no additional benefit of sibrifiban over aspirin in the incidence of the primary end-point (composite of all-cause mortality, non-fatal myocardial infarction or severe recurrent ischaemia) and there was a trend towards more events in the sibrifiban group. The SYMPHONY2 trial also showed an increased mortality rate in the treatment group [22]. The Blockade of the glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial testing the effect of lotrafiban in patients with ischaemic heart disease, cerebrovascular disease and peripheral vascular disease was also stopped because the rate of end-points (all-cause mortality, non-fatal myocardial infarction, urgent revascularisation) was higher in the lotrafiban group.

The Fibrinogen Receptor Occupancy Study (FROST) reported the effect of lefradafiban versus placebo in a small number of patients with unstable angina and myocardial infarction without persistent ST-segment elevation. In the group receiving 30 mg lefradafiban there was a 24 % relative reduction in the composite end-point of death, myocardial infarction or myocardial revascularisation at the cost of increased bleeding events. Anyhow, these results need confirmation in large scale clinical trials [23].

Pooled analysis of oral inhibitors trials shows a 33 % increased mortality with long-term follow-up [24].

There are 6 studies including more than 30,000 patients (Table 2) with unstable angina or non-Q-wave myocardial in-

Table 2. Clinical trials with GP IIb/IIIa antagonists in unstable angina.

Trial	Patients	Agent	Study groups	GP IIb/IIIa**	Control	P value
PRISM	3231	Tirofiban	A + H T + A	5.8 %	7.1%	0.11
PRISM PLUS	1915	Tirofiban	A + HT + A T + H + A	8.7 %	11.9 %	0.03*
PARAGON A	2282	Lamifiban	A + H LDm + A/H LDM + A/H	10.6 % 12 %	11.7 %	0.55
PARAGON B	5225	Lamifiban	L+A+H A+H	12.8 %	11.8 %	0.32*
PURSUIT	10948	Eptifibatide	A + (H)# E + A (H)	14.2 %	15.7 %	0.04
GUSTO IV	7800	Abciximab	Ax 24 h Ax 48 h PI	8.2 % 9.1 %	8 %	NS

A = aspirin; Ax = abciximab; H = heparin; T = tirofiban; E = eptifibatide; L = lamifiban; LDm = lamifiban low dose; LDM = lamifiban high dose, NS= non-significant, PI= placebo; * not statistically significant; # heparin was optional; ** end-point (death, infarction or reinfarction) at 30 days; PRISM = Platelet Receptor Inhibition in Ischemic Syndrome Management; PRISM PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs; PARAGON = Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in the Global Utilization Network; PURSUIT = Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy, GUSTO = Global Utilization of Streptokinase and tPA for Occluded coronary arteries trial IV in Acute Coronary Syndromes

fraction treated empirically which evaluated GP IIb/IIIa antagonists. The largest trial was PURSUIT. These trials had comparable entry criteria but the PRISM trial patients were at lower risk. The therapeutic strategies were quite different. All the patients received aspirin but the administration of heparin was different [20]. Only 3 out of the four studies proved the superiority of the study drug in comparison to placebo. In PURSUIT trial eptifibatide administration determined a 1.2–1.5 % absolute reduction in the rate of death and myocardial infarction at 96 hours, 7 days, one and 6 months. In PRISM PLUS trial tirofiban plus heparin was associated with a significant and durable reduction of the ischaemic end-points in comparison to heparin alone. The composite end-points (death, myocardial infarction, refractory ischaemia) were reduced at 7 days and this effect was preserved at 30 days although the pre-established level of significance was not reached. Administration of tirofiban without heparin was accompanied by a rise of the rate of death at 7 days and this arm of the study was stopped. In the PRISM study the risk of death, myocardial infarction or refractory ischaemia was significantly reduced at 48 hours. In the PARAGON A trial the benefit of lamifiban was present only after 30 days and was significant at 60 days for those receiving low-dose of the drug [4, 6, 12, 20, 26]. In PARAGON B trial a non-significant clinical benefit was noted at 30 days for lamifiban group versus placebo [Williams DO – oral presentation at ACC Scientific Session, 2000]. GUSTO IV was a randomized, placebo-controlled trial comparing the safety and efficacy of 24 or 48 hour infusion of abciximab in patients with non-ST-segment acute coronary syndrome who were not undergoing a planned percutaneous coronary intervention. Abciximab did not reduce 30 day major adverse cardiac events but did increase bleeding when given for longer than 24 hours. It should be mentioned that this population was a low risk one [27]. In the above mentioned trials the hemorrhagic risk was higher for treated patients but the rate of intracerebral bleeding was similar to placebo [20].

There are also 6 trials evaluating these drugs in the setting of coronary percutaneous interventions in more than 15,000 patients with unstable angina or non-Q-wave myocardial infarction (Table 3). With the exception of two studies (RESTORE and IMPACT II), the studied drug was abciximab and besides CAPTURE in all trials the drug was started immediately prior to the revascularisation, being continued for 12–36 hours. EPIC, EPILOG and EPISTENT trials proved an absolute reduction with 4.5–6.5 % of the end-points at 30 days. This benefit was confirmed by CAPTURE where the correspondent figure is 4.6 %. It is to be mentioned that in EPISTENT only 20 % of the stented patients had unstable angina within 48 h of the procedure [16]. IMPACT II (eptifibatide) and RESTORE (tirofiban) trials were associated also with a reduction of the rate of ischaemic periprocedural events but the magnitude of this effect was smaller compared to abciximab (1.5–2.5 %) and did not reach the conventional level of statistical significance. It should be mentioned that the early benefit of GP IIb/IIIa antagonists is long lasting [20, 24, 25, 28]. The bleeding risk in the interventional studies was not significantly increased [20].

To conclude, all the above mentioned trials showed that this new class of antiplatelet agents are of benefit in patients with unstable angina. The maximum benefit is to be expected in the setting of percutaneous intervention with 65 ischaemic events prevented by treating 1000 patients. This benefit is additive to that achieved by the administration of aspirin and thienopyridines with 50–60 % of risk reduction of ischaemic complication. In the empiric therapy, the benefit is smaller, in the range of 15–32 ischaemic events prevented

for 1000 treated patients, which means an up to 30 % risk reduction of ischaemic complication. Here also the benefit is additive to that obtained by the administration of aspirin and heparin. According to the present data abciximab is recommended for patients undergoing interventional procedures while eptifibatide and tirofiban are better for patients treated conventionally. The target population is represented by patients at high risk (rest angina, dynamic ECG modifications, ischaemic heart failure, haemodynamic instability, positive troponin, elevated creatin kinase). Up to date there is only one study comparing two of these drugs. Do Tirofiban And Reopro Give similar Efficacy outcomes Trial (TARGET) compared the effectiveness and safety of abciximab and tirofiban in patients undergoing coronary stenting having an acute coronary syndrome or not. The primary end-point of death, myocardial infarction or urgent revascularization at 30 days occurred in 7.55 % of the tirofiban group and 6 % of the abciximab group (p = 0.037). These results high light the fact that abciximab is the standard for percutaneous interventions [Topol EJ – oral presentation at AHA Scientific Sessions, 2000]. The bleeding risk is not increased and thrombocytopenia is rare but potentially severe. Its maximum rate is found with abciximab (up to 1.1 %). These agents should be administered together with aspirin, heparin and maybe thienopyridines at all times. Unfortunately, in some countries, the cost of GP IIb/IIIa is prohibitive [3, 20, 25, 28]. At this moment the huge difference between the intravenous and oral glycoprotein IIb/IIIa antagonist experience is perplexing and could be not adequately explained [24].

Anticoagulant Therapy

This therapy has three representatives: unfractionated heparin, low-molecular-weight heparins and direct anti-thrombins. Unfractionated heparin is the standard anticoagulant. It is made up of polysaccharide chains with molecular weight ranging from 3000 to 30000 Da. For the realisation of its effect the presence of antithrombin III is mandatory [4].

Table 3. Clinical trials with GP IIb/IIIa antagonists for coronary interventions

Trial	Patients	GP IIb/IIIa*	Control	P value
EPIC	2099			
Abciximab B		11.4 %	12.8 %	0.43
Abciximab B+I		8.3 %	12.8 %	0.008
EPILOG	2792			
Abciximab LD		5.2 %	11.7%	< 0.001
Abciximab SD		5.4 %	11.7%	< 0.001
EPISTENT	2399			
Abciximab+stent		5.3 %	10.8 %	< 0.001
Abciximab+P		6.9 %	10.8 %	0.007
IMPACT II	4010			
Eptifibatide 135/5#		9.2 %	11.4 %	0.063
Eptifibatide 135/.75#		9.9 %	11.4 %	0.220
RESTORE	2139			
Tirofiban		8 %	10.5 %	0.052
CAPTURE	1265			
Abciximab		11.3 %	15.9 %	0.012

B= bolus; B+I= bolus plus infusion; P= coronary angioplasty; LD= low dose; SD= standard dose; * Composite end-points at 30 days (death, infarction, urgent revascularisation); # drug dosage. EPIC= Evaluation of C7E3 for Prevention of Ischemic Complications; EPILOG= Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade; EPISTENT= Evaluation of Platelet Inhibition in STENTing; IMPACT= Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis; RESTORE= Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis; CAPTURE= C7E3 AntiPlatelet Therapy in Unstable REfractory angina

According to present guidelines heparin should be given to all intermediate and high-risk patients with unstable angina. Initial dosage is 80 U/kg bolus followed by i.v. infusion of 18 U/kg/hour. The infusion rate will be changed with the goal of keeping the activated partial thromboplastin time (APTT) between 46 and 70 seconds or 1.5–2.5 times control [5]. It should be mentioned that keeping the APTT at higher levels exposes the patients to the risk of bleeding and also diminishes the efficacy of the drug [8]. At this time the continuous i.v. administration of heparin seems not to be superior to intermittent i.v. administration at 4 hours [4]. In a study which compared aspirin versus heparin in unstable angina, heparin reduced the risk of myocardial infarction by 78 %. It is proven that while aspirin reduces the risk of ischaemic complication in unstable angina by 50 % the same figure for heparin is 75 % [29]. The combination of aspirin with heparin is better than the administration of either drug alone in unstable angina being followed by a 56 % reduction in the risk of death or infarction in comparison to aspirin alone [29]. Withdrawal of heparin can be followed by an ischaemic rebound which could be prevented by the co-administration of aspirin [4, 25, 26]. Optimal duration of heparin therapy is not well settled but the drug should be given for 2 to 5 days or until a revascularisation procedure is performed [4, 30, 31]. The principal adverse effects of heparin therapy are bleeding and thrombocytopenia. The main limitations of heparin therapy include: low bioavailability after subcutaneous administration, unpredictable dose-effect relation, monitoring of coagulation parameters and hospitalisation [6].

Low-molecular-weight Heparins

Low-molecular-weight heparins (LMWH) are fragments of unfractionated heparin produced by chemical or enzymatic depolymerization [6, 32]. They have a significantly lower molecular weight than standard heparin ranging from 4.3 to 5.8 kDa, but like heparin, LMWH require the presence of antithrombin III for the anticoagulant effect [32, 33]. In contrast to standard heparin which exhibits an equivalent anti-factor Xa and IIa activity, LMWH have a much higher anti-Xa activity [34]. Anti-Xa/IIa ratio varies among agents. Those preparations which have a higher ratio exhibit superior pharmacologic efficacy than standard heparin while agents with a lower ratio have similar outcomes to heparin [4]. LMWH have some potential advantages over standard heparin including a higher bioavailability (> 90 %) after subcutaneous administration, longer duration of action with a persistent anticoagulant effect allowing a once or twice daily dosing, a predictable anticoagulant effect, a lower risk of bleeding, osteoporosis and thrombocytopenia; laboratory monitoring is not necessary and the therapy can be given on an outpatient basis with a reduction in costs even though LMWH are much more expensive than heparin [12, 35]. Among currently used agents [33] (enoxaparin, nadroparin, dalteparin, ardeparin, tinzaparin, certoparin, reviparin) only enoxaparin, dalteparin and nadroparin were studied in acute coronary syndromes. In a small study of 219 patients with unstable angina nadroparin significantly reduced the risk of myocardial infarction, recurrent angina and revascularisation compared to heparin. All the patients were given aspirin. This was the first evidence of the utility of LMWH in acute coronary syndromes [6, 34]. However, later, in the much bigger trial FRAXIS (FRAXiparin in Ischaemic Syndrome) the initial benefits were not confirmed [6, 32, 36]. The Fragmin During Instability in Coronary Artery Disease (FRISC) trial compared dalteparin (2 × 120 U/kg/d for 6 days then 7500 U/d 6 weeks) versus aspirin in patients with unstable angina. At 6 days a significant reduction in the rate of death and infarction was

noted in the dalteparin group (1.8 % vs. 4.8 %) and this benefit was maintained at 40 days. However, at 150 days no differences could be ascertained between groups. The FRagmin In unstable Coronary artery disease (FRIC) study evaluated the efficacy of dalteparin versus unfractionated heparin in patients with unstable angina or non-Q-wave myocardial infarction. Dalteparin was as effective as heparin concerning the rate of death, myocardial infarction or recurrent angina [12, 29]. The FRagmin during InStability in Coronary artery disease (FRISC) II trial included patients with unstable angina or non-Q-wave myocardial infarction.

All patients initially were given dalteparin (2 × 120 U/kg/d for 5 days) or heparin. Then they received dalteparin (2 × 7500 U/d for 3 months) or placebo. In the dalteparin group the rate of death and myocardial infarction was reduced significantly at 30 and 45 days but not at 3 months. At 90 days the composite end-point of death, myocardial infarction and myocardial revascularisation was significantly reduced [37]. Evidence from FRIC, FRISC and FRISC II trials support the usefulness of dalteparin as a safe and effective alternative to heparin in unstable angina or non-Q-wave myocardial infarction [34]. The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial compared enoxaparin (2 × 1 mg/kg/d for 2–8 days) versus heparin in patients with unstable angina or non-Q-wave myocardial infarction. In the enoxaparin group there was a significant reduction in the rate of death, myocardial infarction and recurrent angina versus the heparin group at 14 days (16.6 % vs. 19.8 %) and at 30 days (19.8 % vs. 23.3 %) [38]. The benefits were still present at 1 year (32 % vs. 35.7 %) [6]. The Thrombolysis In acute Myocardial Infarction (TIMI) 11B study evaluated the efficacy of enoxaparin (30 mg i.v. bolus then 2 × 1 mg/kg/d subcutaneously for 8 days followed by 2 × 40 mg/kg/d for patients < 65 kg or 2 × 60 mg/kg/d for those > 65 kg up to 43 days) versus standard heparin. At 14 days enoxaparin significantly reduced the rate of death, myocardial infarction and of recurrent angina necessitating urgent revascularisation (14.2 % vs. 16.6 %). The benefit was evident at 48 hours and was maintained at 43 days. As in the ESSENCE trial in this study the maximum benefit was noted in patients with EKG alterations and in those with prior aspirin consumption [34, 39]. The meta-analysis of ESSENCE and TIMI 11B trials emphasize a significant reduction of about 20 % in the rate of death and infarction [40]. All the available evidence shows that LMWH are at least as effective as standard heparin in reducing the rate of death and recurrent infarction in patients with unstable angina or non-Q-wave myocardial infarction. The risk of bleeding for LMWH seems to be similar to that for heparin but minor hemorrhages are more frequent. Among the studied agents only enoxaparin proved in well conducted trials to be superior to heparin in reducing the rate of death, infarction and recurrent angina in patients with unstable angina or non-Q-wave myocardial infarction [34] and for these reasons may be considered as an effective therapeutic alternative to heparin [40]. Unfortunately, the relative efficacy of LMWHs can not be evaluated in the absence of head to head studies [41].

Concerning the role of LMWH in patients receiving GP IIb/IIIa antagonists according to the recently presented results of the GUSTO IV substudy of LMWH it seems that dalteparin has effects similar to unfractionated heparin in a low risk population with acute coronary syndromes treated with abciximab [27].

Direct Thrombin Inhibitors

These drugs do not need the presence of antithrombin III for their anticoagulant activity. They work by inactivation of thrombin precluding its interaction with its own substrate. These agents do not bind to plasma proteins and have a more

predictable anticoagulant effect compared to heparin, and in contrast to heparin they also inactivate fibrin bound thrombin [3, 42]. The prototype agent is hirudin but there are also other representatives (bivalirudin, argatroban, etc.). The Global Utilisation of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) II B trial did not exhibit any significant difference between heparin and hirudin in reducing the rate of death or myocardial infarction in patients with acute coronary syndromes without ST segment elevation. The Organisation to Assess Strategies for Ischaemic Syndrome (OASIS) 1 and 2 trials in which the efficacy of heparin versus hirudin was compared in patients with unstable angina or non-Q-wave myocardial infarction proved a 20 % lower rate of death, infarction or refractory angina at 7 days with hirudin [43]. However, today the role and place of these agents in the therapy of unstable angina is not settled. Hirudin has been approved for patients with heparin-induced thrombocytopenia [16, 44].

Beta-Blocking Agents

According to current guidelines, beta-blockers should be given orally to low and intermediate risk patients and intravenously to high risk patients. The target heart rate with this therapy is about 50–60/minute [3, 5]. There are only few studies to support the beneficial effect of beta-blockers in unstable angina. An old meta-analysis on 4700 patients revealed a 13 % reduction of the risk of myocardial infarction [45]. The similar pathophysiology of unstable angina and acute myocardial infarction and extrapolation from myocardial infarction studies are the substrate of the unanimous recommendation of these drugs in unstable angina [4, 44]. The choice of a specific drug is not important as all agents seem to be equally efficient. The most used is metoprolol (3×5 mg i.v. at 5 minutes intervals then 100–200 mg/d orally). Contraindications should be avoided [5].

Nitrates

These drugs have an antiischaemic action and are currently used in the therapy of unstable angina despite the lack of convincing data concerning the beneficial effect on mortality or the incidence of infarction [4]. The initial dosage of nitroglycerine is 5 to 10 mg/minute by continuous infusion with titration up to 10 mg/minute every 5–10 minutes until relief of pain or limiting side-effects (most importantly hypotension with systolic pressure < 90 mmHg or more than 30 % below starting mean arterial pressure level). As a general rule perfusion should not be maintained beyond 72 hours. Patients should be switched on to oral therapy once they have been symptom-free for 24 hours. Care should be taken to provide a 6 to 8 hours free nitrate interval in order to prevent tolerance [4, 5, 8].

Calcium Channel-Blockers

These agents are not first line drugs with the exception of Prinzmetal angina. They are employed in cases in which nitrates and beta-blockers do not control symptoms or in patients who cannot tolerate them. In any instance nifedipine should not be used in the absence of concurrent beta-blockade. Patients intolerant to beta-blockers should be given non-dihydropyridine agents (verapamil, diltiazem). The benefit of this class is mainly symptomatic of the same magnitude as beta-blockers [4–6].

Lipid Lowering Agents

Among lipid lowering drugs only statins have a definite role in secondary prevention of ischaemic heart disease. Recommendation from the U.S.A. [47] settled a target level for low density lipoprotein cholesterol (LDL) < 100 mg% and for total cholesterol < 200 mg% while European guidelines [48] recommend lowering of total cholesterol < 190 mg% and of LDL < 115 mg%. In 1997 the American Heart Association recommended that LDL values > 130 mg% should be reduced with medication and for LDL values between 100 to 129 mg% a trial of diet modification should be attempted. If this is unsuccessful, the drug therapy is left to the judgement of the physician [6]. Among statins simvastatin and pravastatin were proven in large and well conducted trials to reduce total mortality, cardiovascular mortality, the rate of strokes and the necessity of myocardial revascularisation [46]. According to the results of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial treatment with Atorvastatin (80 mg/d) initiated during the acute phase of unstable angina or non-Q-wave myocardial infarction irrespective of the baseline LDL cholesterol levels significantly reduces early ischaemic events [Schwartz GG – oral presentation at AHA Scientific Sessions, 2000].

The management of patients in whom the principal disturbance is a low level of high density lipoprotein cholesterol (HDL) is not established. Recent data from Veterans Affairs HDL Intervention Trial (VA-HIT) showed that in patients with ischaemic heart disease, low HDL (≤ 1.03 mmol/l) and low LDL (≤ 3.6 mmol/l) 1200 mg gemfibrozil daily versus placebo was associated with a 6 % increase in HDL, 31 % decrease in triglycerides and a 22 % reduction of the relative risk of death and non-fatal myocardial infarction. These data may suggest that another class of lipid lowering drugs besides statins, the fibrates, could be effective for the secondary prevention of ischaemic heart disease [49].

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