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Clinical use of novel antithrombotic agents in the management of acute coronary syndromes

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Abstract
Among patients with ST elevation-acute coronary syndrome (ACS) novel thrombolytic agents can be given as a bolus (reteplase, tenecteplase) and their delivery is easier and may shorten the time to treatment, providing the ideal tool in the pre-hospital setting.
Reinfarction after thrombolysis occurs in the 3-5% range in all major trials. Reinfarction after thrombolysis rate may be reduced by abciximab and enoxaparin. However major hemorrhage is doubled by abciximab (but not by enoxaparin).
When primary angioplasty is preferred to thrombolysis, adjunctive abciximab decreases the need for urgent target vessel revascularization.
A whole body of literature tells that aspirin is not enough in patients without ST elevation ACS. Most patients benefit from concomitant clopidogrel. High-risk patients are candidate to the use GP IIb-IIIA blockers, particularly if they need coronary angioplasty.
All patients with glomerular filtration rate ≥ 30 ml / min should receive low molecular weight heparin. Evidence for that is mainly driven by studies using enoxaparin.

Great emphasis has been placed on the role of antithrombotic therapy in acute coronary syndromes over the last fifteen years, following the observation that coronary thrombosis is the usual precipitating factor [1,2]. As a result, the scientific community has witnessed an impressive escalation of trials with countless recruits, showing a progressively important role of anti-thrombotic drugs covering the whole spectrum of the disease, from its onset (pre-hospital) to the long-term follow-up.

Some manoeuvres are now so deeply-rooted(aspirin, thrombolytic therapy, thienopyridines after coronary stent implantation) that their use is taken as an indicator of quality treatment provided by health care systems [3]. Other antithrombotic drugs of proven efficacy lag behind (warfarin, direct thrombin inhibitors) mainly for the perception of their low benefit-to-risk ratio profile. Other drugs are used only in a fraction of patients (parenteral glycoprotein IIB-IIIA inhibitors) or have dramatically failed (oral glycoprotein IIB-IIIA inhibitors).

Despite the above ups and downs the "mobile average" is toward a progressive increase in the use of antithrombotic agents, with the term "increase" referring to the number of drugs being combined in the single patient, the duration of

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treatment, the identification of high-risk categories, the number-vs-intensity of treatment(s) issues and the like.

At the same time, hazards of antithrombotic treatments are increasingly scrutinized and are of major importance when it comes to the clinical use setting.

From a practical point of view acute coronary syndromes are divided among those patients showing persistent ST segment elevation in their presenting electrocardiogram and those without persistent ST elevation.

Acute coronary syndromes with persistent ST segment elevation

Thrombolytic therapy is the key treatment of patients with persistent ST segment elevation. The quick delivery of a lytic drug has been shown to save lives practically in almost all subgroups of patients admitted within 12 hours from symptoms onset [4]. One distinct feature of thrombolytic therapy is the strict inverse relationship between delay of treatment and capacity to reduce in-hospital and long-term mortality. The so-called "golden hour" identifies a subgroup of patients for whom thrombolytic therapy (delivered within 1 hour from the onset of symptoms) may save as many as 65 lives per 1000 treated patients [5].

The importance of time to treatment cannot be overemphasized because it has been confirmed in many ways and under different circumstances. Thus, it has been shown that the prehospital administration of thrombolysis reduces total mortality compared to in-hospital treatment [6], a performance that parallels that of primary angioplasty [7]. Actually, similar outcomes have been reported when prehospital thrombolysis and primary angioplasty have been compared directly [8].

The availability of new thrombolytic agents (reteplase, tenecteplase) that can be safely administered as a bolus not only decreases medication errors [9], but also speeds up drug delivery, allowing treatment in the emergency department environment [10]. Nurse-initiated thrombolysis is a distinct option being tested in the field [11] and further expands the room for implementing reperfusion in as many patients as possible.

Although logistics appear the main advantage of new thrombolytic agents, different pharmacologic profiles may result in selective clinical advantages. In the ASSENT-2 study the equivalence of tenecteplase and alteplase on mortality was nicely shown (6.18 vs 6.15 %, p = NS); however the need for blood transfusions was lower in the group receiving tenecteplase (4.25 vs 5.49 %, p = 0.0002) [12]. Particularly female patients at high risk for bleeding (> 75 years old and body weight < 67 kg) take advantage from the treatment [13]. Again, in the ASSENT-2 study it was shown that time-to treatment not only determines clinical outcomes but also the reperfusion efficacy itself [14], suggesting that fibrin cross-linking proceeds very quickly in the early phase of coronary thrombosis. Thus, not only "time-is-muscle" (being lost) but probably also "time is thrombus" (being accrued).

The Achille's heel of thrombolysis is re-occlusion. Lysis and reocclusion take place simultaneously from the beginning and the net effect determines the ultimate patency.

Therefore, thrombolytic drugs need some form of adjunctive treatment. Aspirin is a must after the ISIS-2 trial [15]. Intravenous heparin is used with fibrin-specific lytic agents, although the evidence for heparin use is weak. The principal reason for using unfractionated heparin in combination with fibrin-specific drugs is that this combination was successful in reducing the mortality rate compared to streptokinase in the

Table 1. Novel adjunctive treatments in combination with thrombolysis in the ASSENT-3 Study 18

OUTCOME	UNFRACTIONATED HEPARIN (N = 2038)	ENOXAPARIN (N = 2040)	ABCIXIMAB (N = 2017)
30-day death / in-hospital reinfarction / refractory ischemia *	15.4 %	11.4 %	11.1 %
30-day death / in-hospital reinfarction / refractory ischemia / ICH / major bleed **	17.0 %	13.8 %	14.2 %
30-day death ***	6.0 %	5.4 %	6.6 %
In-hospital reinfarction ****	4.2 %	2.7 %	2.2 %
In-hospital refractory ischemia *	6.5 %	4.6 %	3.2 %
In-hospital ICH ***	0.9 %	0.9 %	0.9 %
Major bleeds (other than ICH) *****	2.2 %	3.0 %	4.3 %

ICH: intracranial haemorrhage
* p = 0.0001
** p = 0.0081
*** p = NS
**** p = 0.0009
***** p = 0.0005

Table 2. Trials on the use of glycoprotein IIB-IIIA blockers in conjunction with primary angioplasty 21.

STUDY (N° Patients)	PRIMARY END-POINT	ABCIXIMAB	PLACEBO	P
ADMIRAL (300) 41	D / RI / UTVR *	6.0 %	14.6 %	0.01
RAPPORT (483) 42	D / RI / TVR **	28.2 %	28.1 %	NS
ISAR-2 (292) 43	LUMEN LOSS ***	1.26 ± 0.85 mm	1.21 ± 0.74 mm	NS
CADILLAC (2082) 44	D / RI / DS / IDTVR **	15.8 %	13.4 %	NS

D : death ; DS : disabling stroke; IDTVR: Ischemia-driven target-vessel-revascularization; RI: recurrent infarction; (U)TVR: (urgent) target vessel revascularization
* at 30 days
** at 6 months
*** angiography at 6 months; binary restenosis rate 31.1 vs 30.6 %

GUSTO-I study [16]. Despite these achievements intravenous heparin therapy is affected by many drawbacks: poor anticoagulation control, particularly in the first 12 hours after thrombolytic therapy, a very narrow therapeutic index and the absolute need for the tight adherence to well-established infusion nomograms, based on careful monitoring of the aPTT level.

Unlike unfractionated heparin, low molecular weight heparins have more predictable kinetics, are less protein-bound, have less potential for platelet activation and do not require monitoring. Several mechanistic studies have shown the capacity of low molecular weight heparins to decrease coronary reocclusion or to increase late patency after thrombolysis; interestingly, this effect has been shown to occur even when the thrombolytic agent is not fibrin-specific (streptokinase) [17], contradicting the widespread opinion that an anticoagulant is not needed when there is a lytic state. Recently the ASSENT-3 investigators confirmed in a several-thousand patients trial that enoxaparin, compared to unfractionated heparin, is able to improve in-hospital prognosis of patients receiving tenecteplase (Table 1) [18]. Thus, enoxaparin opens a new way in the reperfusion treatment of acute myocardial infarction, for the first time allowing to reduce recurrent in-hospital infarction after thrombolysis, an achievement so far obtained mainly by primary angioplasty [7]. Ongoing trials are evaluating the capacity of enoxaparin to reduce 30-day re-infacrtion as well as other adverse outcomes in a more general way, including several different thrombolytic agents.

Recurrent infarction after thrombolysis may also be curbed by the adjunctive infusion of glycoprotein IIB-IIIA receptor antagonists. However this combination resulted in major haemorrhage excess not only in the ASSENT-3 trial (Table 1), but also in the large GUSTO-V study [19]. Particularly those patients more than 75 years-old experienced almost a doubling of intracranial haemorrhage following the infusion of abciximab combined with half-dose thrombolytic agent. The bleeding excess was also confirmed in the INTRO-AMI study, evaluating the combination of alteplase with eptifibatide [20]. For these reasons the combination of a lytic drug with a glycoprotein IIB-IIIA blocker is not presently recommended by the European guideline on management of patients with persistent ST segment elevation [21].

The use of abciximab in the context of primary angioplasty is recommended by the European guideline (Class I when stenting is not used, Class IIa with stent implantation) [21] (table 2).

Acute coronary syndromes without persistent ST segment elevation

These syndromes encompass a whole spectrum of clinical situations with different clinical risk. They range from a low-risk population for which early discharge after the observation for 12 hours in a chest pain unit is feasible, to very high-risk patients with ongoing Ischemia, hemodynamic compromise, malignant arrhythmias for whom an aggressive strategy of revascularization is needed. The basic tenet is the occurrence of a mural coronary thrombus (or alternatively of an occlusive thrombus in a collateralised vessel). Consequences are strictly dependent on vessel size, concomitant other coronary obstructions, collaterals development, the degree of myocardial damage and the residual left ventricular pump function. Other important covariates affecting risk are: age, diabetes mellitus, previous vascular events, prior aspirin use, renal insufficiency, the occurrence of ST segment depression in the electrocardiogram, the positivity in the troponin assay and left ventricular ejection fraction [22-24].

Although aspirin is the mainstay of antithrombotic therapy of all types of acute coronary syndrome, evidence is mounting that aspirin alone “is not enough”. Most subgroups, also including low-risk categories, take advantage of the concomitant use of clopidogrel. In the CURE study the intention to treat for 1 year with the combination of aspirin plus clopidogrel resulted in the 20 % reduction in the composite of death, non-fatal myocardial infarction and stroke ($p < 0.0001$) [25]. The recent European guideline on management of non-ST segment elevation acute coronary syndromes places clopidogrel

Table 3. Rate of death / non-fatal myocardial infarction in trials of glycoprotein IIB-IIIA receptor blockers in acute coronary syndromes without persistent ST segment elevation 44

TRIAL (drug)	ACTIVE GROUP	CONTROL GROUP	OR (95 % CI)
PRISM (tirofiban) 46	5.8 %	7.1 %	0.80 (0.60-1.06)
PRISM-PLUS (tirofiban) 47	8.7 %	11.9 %	0.70 (0.50-0.98)
PARAGON-A (lamifiban) 48	11.6 %	11.7 %	0.99 (0.68-1.44)
PURSUIT (eptifibatide) 49	14.2 %	15.7 %	0.89 (0.79-1.00)
PARAGON-B (lamifiban) 50	10.6 %	11.5 %	0.92 (0.77-1.09)
GUSTO-IV-ACS (abciximab) 51	8.2 % * 9.1 % **	8.0 %	1.02 (0.83-1.24) * 1.15 (0.94-1.39) **
OVERALL	11.3 %	12.5 %	0.91 (0.85-0.99)

* Abciximab infusion: 24 hours
** Abciximab infusion: 48 hours

Table 4. Short-term rate of death / non-fatal myocardial infarction in trials of low molecular weight heparins in acute coronary syndromes without persistent ST segment elevation

STUDY (DRUG)	TIMING OF THE END-POINT	LMWH	UFH	OR (95 % CI)
FRIC (dalteparin) 52	0-6 days	3.9 %	3.6 %	1.07 (0.63-1.80)
ESSENCE (enoxaparin) 53	14 days	4.6 %	6.1 %	0.75 (0.55-1.02)
TIMI-11B (enoxaparin) 54	14 days	5.7 %	6.9 %	0.81 (0.63-1.05)
ESSENCE + TIMI-11B 55	14 days	5.2 %	6.5 %	0.79 (0.65-0.96) *
FRAXIS (nadroparin) 56	14 days	4.9 %	4.5 %	1.08 (0.72-1.62)
OVERALL				0.86 (0.72-1.02)

LMWH : low molecular weight heparin; UFH: unfractionated heparin
* p = 0.02

(plus aspirin) at the very early step, before risk stratification [26]. A further advantage of this strategy is that clopidogrel pre-treatment in patients deserving of coronary angioplasty results in the 30 % reduction of peri-procedure adverse events during the first 30 days following the manoeuvre [27].

In the CURE study a statistically significant 1 % absolute excess in major bleeding was observed in the clopidogrel group (p = 0.001), but there was no excess in life-threatening bleeding or intracranial haemorrhage. Authors did not include bleeds in the primary end-point because they placed more emphasis on the clinical weight of hard vascular events. It should be realised, however, that approximately 3 to 5 % of patients need urgent-to-emergent cardiac surgery after hospital admission, a situation particularly at higher risk of bleeding following the aspirin-clopidogrel combination. It is recommended both to avoid clopidogrel when early surgery appears likely and to post-pone surgery (if clinically feasible) for at least 5 days after clopidogrel discontinuation.

The role of antiplatelet therapy in acute coronary syndromes is further witnessed by the reduction in major clinical outcomes obtained by using parenteral glycoprotein IIb-IIIA receptor blockers. Different agents belong to this class of drugs, with considerably different chemical composition, molecular weight, receptor affinity, specific activity and ultimately pharmacodynamic and pharmacokinetic profile. With these considerations in mind, a meta-analysis of studies addressing the role of these agents appears legitimate, yet somewhat "naïve". Small-molecule glycoprotein IIB-IIIA blockers (tirofiban, eptifibatide, lamifiban) appear to work in patients admitted to the coronary care unit (PRISM, PRISM-PLUS, PURSUIT, PARAGON), whereas large chimeric antibodies such as abciximab are useless outside the catheterization laboratory (GUSTO-IV-ACS) (Table 3). The European guideline recommends the use of glycoprotein IIB-IIIA blockers in patients judged to be at "high risk" (recurrent ischemia, early post-infarction angina, troponin positivity, hemodynamic instability during the observation period, major arrhythmia, i.e. ventricular tachicardia / fibrillation, diabetes mellitus, baseline ECG changes that preclude the ST segment analysis) [26]. Following this suggestion it happens that many patients will receive both the aspirin plus clopidogrel combination and a GP IIB-IIIA blocker. However, the evidence for using this "cocktail" is not firm. Actually, the use of GP IIB-IIIA inhibitors during the previous three days was an exclusion cri-

terion for enrolling in the CURE study. The efficacy and safety of this potent triple antiplatelet therapy has been shown in the subgroup of patients submitted to coronary angioplasty [28] but has not been addressed specifically in the larger population of all comers to the hospital with an acute coronary syndrome.

Mural coronary thrombus has also a red-tail, whereby blood coagulation should be inhibited. Traditionally, this has been achieved by the infusion of intravenous unfractionated heparin, but the evidence is weak [29].

More recently a much stronger evidence for using low molecular weight heparins has emerged [30]. The meta-analysis of thousands patients enrolled in different studies show not only that low molecular weight heparins are better than placebo in acute coronary syndromes, but also that they are at least as effective as intravenous unfractionated heparin, with the advantage of a more practical use, with no need of an intravenous infusion and no need of laboratory monitoring. Actually, for one of these agents (enoxaparin), it has been shown in two different studies (ESSENCE and TIMI-11B) [31,32] the superiority of low molecular weight heparin in the triple end-point (death / myocardial infarction / refractory ischemia) reduction; when the two studies were combined [33] also the double-end point (death / myocardial infarction) was reduced by enoxaparin (Table 4). It is presently discouraged to use low molecular weight heparin in patients with glomerular filtration rate ≤ 30 ml / min, for the risk of drug accumulation and the inherent difficulty to neutralize the persistent anticoagulant effect [34].

The need for long-term antithrombotic treatment

Angioscopic studies show the persistence of coronary thrombus for more than 1 month after myocardial infarction [35]. Although most coronary events occur in the first month after presentation, considerable attrition is observed thereafter, despite of the use of aspirin. Event rates appear related to the persistence of intravascular markers of ongoing thrombosis [36]. An apparent relapse of ischemic episodes is observed after heparin discontinuation [37] as well as after long-term treatment with low molecular weight heparin [38].

Therefore, it appears conceptually obvious that some form of long-term anti-thrombotic adjunct to aspirin should be advised. So far, the evidence for this long-term covering is still largely circumstantial. In the CURE study, clopidogrel addition results in event curves diverging immediately but with further separation going on continuously during the following 9 months [25]; these data have been largely confirmed in patients undergoing coronary angioplasty and 12-month combined treatment with aspirin plus clopidogrel in the CREDO study [39]. Furthermore, the combined use of warfarin (with or without aspirin) determines progressive reductions of new events over 4 years of treatment after the index episode of acute coronary syndrome (WARIS-2) [40].

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