

Antithrombotics in Acute Coronary Syndromes: Actual Guidelines and New Evidences*

Antitrombóticos nas Síndromes Coronarianas Agudas: Diretrizes Atuais e Novas Evidências

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SUMMARY

BACKGROUND AND OBJECTIVES: Acute coronary syndromes (ACS) are one of the most common causes of ICU admissions. New drugs have been developed for management of ACS. These drugs reduced morbidity and mortality; however their adverse effects or their incorrect use may cause excessive bleeding. The objective of this review is to present the principal peculiarities, doses, and indications of these drugs in ACS settings.

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METHODS: Original articles were retrieved crossing the terms acute coronary syndromes and antithrombotic therapy in the MedLine database as well as search for Brazilian and international guidelines in <http://sumsearch.uthscsa.edu>.

RESULTS: In the treatment of acute coronary syndromes with non-ST-segment elevation enoxaparin was as efficient as UFH, but with a simpler management (SYNERGY and A to Z studies). In this same setting, fondaparinux was non inferior to enoxaparin and had lesser bleedings (OASIS 5), bivalirudin, combined or not with GPIIb/IIIa blockers, was not inferior when compared with other heparins (ACUITY). In ST-segment elevation ACS, enoxaparin was superior to HNF in patients treated with fibrinolysis (EXTRACT TIMI 25); in OASIS 6 fondaparinux was superior to UFH in patients treated with thrombolytic therapy and not submitted to reperfusion.

CONCLUSIONS: The correct management and individual combination of antithrombotic drugs are mandatory for decreased mortality and of major cardiovascular events, reducing the undesirable risk of additional bleeding.

Key Words: antithrombotics, bivalirudin, enoxaparin, fondaparinux, heparin

RESUMO

JUSTIFICATIVA E OBJETIVOS: As síndromes coronarianas agudas (SCA) estão entre as principais causas de admissão em unidades de terapia intensiva (UTI). Novos fármacos vêm sendo desenvolvidos para o manuseio das SCA. O uso combinado destes medicamentos tem reduzido de forma considerável a morbimortalidade desta síndrome, no entanto seus efeitos adversos ou mesmo seu manuseio incorreto podem levar à maior incidência de sangramento. O

objetivo deste estudo foi apresentar os principais aspectos terapêuticos, indicações e manuseio dos fármacos em síndromes coronárias agudas.

MÉTODO: Foi realizada uma busca por artigos originais cruzando os unitermos *acute coronary syndromes* e *antitrombotic therapy* na base de dados MedLine; busca de artigos e diretrizes nacionais e internacionais no endereço eletrônico: <http://sumsearch.uthscsa.edu>.

RESULTADOS: No tratamento de angina instável e infarto sem supradesnivelamento de ST, a enoxaparina mostrou-se tão eficaz quanto à heparina não fracionada (HNF) e de manuseio mais simples (estudos SYNERGY e A a Z). Neste cenário, o fondaparinux também não foi inferior à enoxaparina e; no entanto, promoveu menor taxa de sangramento (OASIS-5), a bivalirudina também foi não inferior combinada ou não ao GPIIb/IIIa comparada a outras heparinas (ACUITY). No infarto com supradesnivelamento do segmento ST, a enoxaparina foi superior à HNF em pacientes submetidos à trombólise (EXTRACT TIMI 25), e no estudo OASIS 6, o fondaparinux foi superior a HNF em pacientes submetidos à trombólise e os não submetidos à reperfusão.

CONCLUSÕES: A correta administração das doses dos antitrombóticos e a escolha individualizada da combina-

ção de fármacos são imprescindíveis para a redução de óbito e eventos cardiovasculares maiores, reduzindo o desconfortável risco de sangramento adicional.

Unitermos: antitrombóticos, bivalirudina, fondaparinux, enoxaparina, heparina.

INTRODUCTION

Although significant advances in the treatment of acute coronary syndromes (ACS) have been made in the last years, they still remain one of the major causes of admission and death in the intensive care units (ICU). Better knowledge of ACS physiology has allowed development of new drugs, especially anticoagulants and anti-platelets agents. The combination of this drugs with strategies of early invasive treatment (coronary cine-angiography in the first 48 hours) are helping to reduce clinically relevant events.

New antithrombotic drugs have shown a more selective binding to antithrombin III (fondaparinux) in relation to the UFH (UFH) and, like bivalirudine, direct action on the factor II (thrombin). Such effects have led to a lower incidence of undesirable effects such as heparin-induced thrombocytopenia (HIT) and less bleeding (Figure 1).

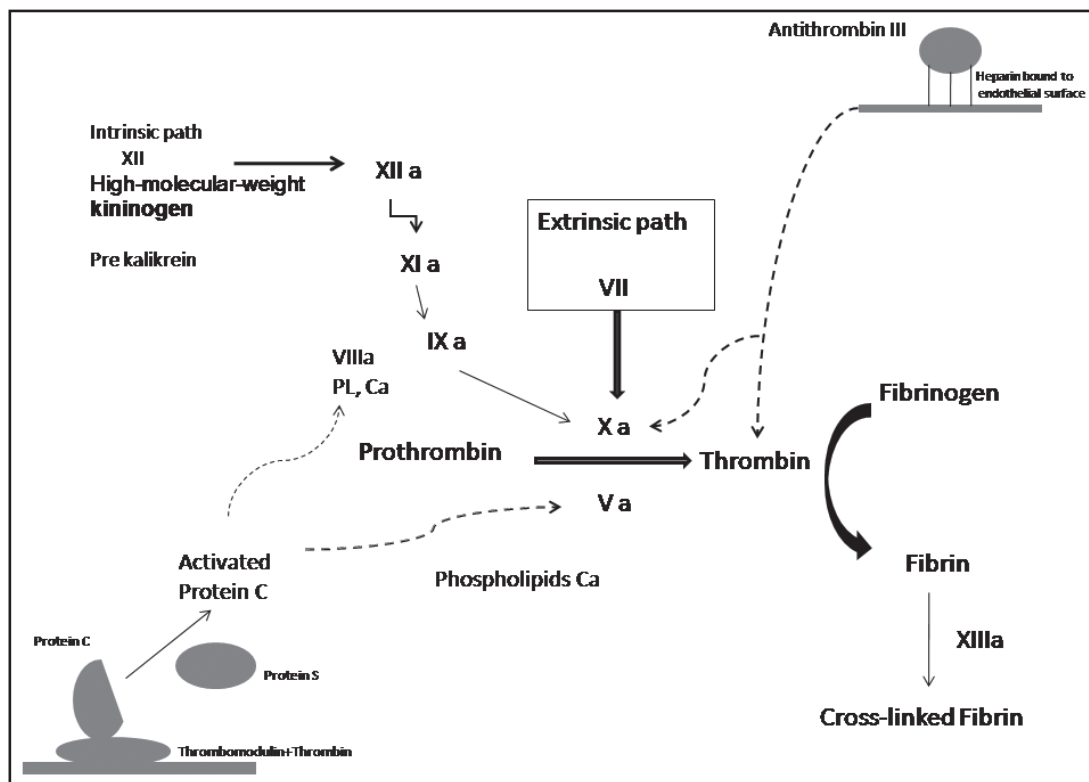


Figure 1 – Cascade of Coagulation. Intrinsic, Extrinsic and Common Routes full lines = activate coagulation; traced lines = inhibit coagulation

On the other hand, the combination of antithrombotic drugs induces an increase of undesirable events, especially hemorrhages¹, increasing intra-hospital mortality of these patients, even six months after use. Therefore, to reduce risk and improve treatment of these patients, doses, adjustments and indications of each drug in the ACS setting must be well known.

The objective of this study was to present the essential evidences for indication and prescription of antithrombotic and anti-platelet drugs in the setting of ACS.

METHODS

Articles published from 1990 to 2007 were selected in the MedLine database, using the key words acute coronary syndrome, antithrombotic therapy. Initially a total of 392 articles was found. Upon a second more restricted evaluation, articles of therapeutical intervention and systematic reviews were selected by means of a search based on the link - clinical queries, of the above mentioned system comprising 47 articles. The articles were assessed by analysis of the methods and design limitations. A search for Brazilian and international guidelines in the portal <http://sumsearch.uthscsa.edu> was also carried out. As this is not a meta-analysis, but a descriptive study, the more relevant conclusions of the main studies and meta-analyses found will be presented without a direct interference from the authors' personal analysis.

RESULTS

Studies with Enoxaparin

First clinical studies with enoxaparin in ACS were carried out in the nineties. The ESSENCE trial² compared enoxaparin (1 mg/kg), subcutaneous (SC) every 12 hours with intravenous UFH, to maintain the APTT between 55 and 85 seconds in patients with acute coronary syndrome, with non ST segment elevation (ACS NSTEMI). This was a randomized double blind controlled study, encompassing 3171 patients. The primary endpoint analyzed was the combination of death, infarction, or reinfarction and recurring angina at 14 days. This endpoint took place in 16.6% of the enoxaparin and 19.8% of the UFH (OR 0.81; CI 95% 0.68 to 0.96; p = 0.016) groups. This difference remained unchanged in the 30 days analysis. The authors concluded that treat-

ment with enoxaparin is superior to that with UFH in patients with ACS NSTEMI.

The TIMI 11-b³ trial compared use of enoxaparin in a long term strategy (bolus 30 mg intravenous, 1mg/kg SC every 12 hours, for up to eight days and 40 to 60 mg, applied SC per day, for 35 days), versus UFH (dose for maintenance of APTT between 1.5 and 2.5 times the control for three days). A total of 3910 patients (ACS NSTEMI) with high risk of cardiovascular events were randomized. The primary endpoint was mortality for all causes, re-infarction and emergency revascularization at 8 to 43 days. At eight days, incidence of primary endpoint was 12.4% in the enoxaparin group and 14.5% in the UFH (OR 0.83; CI 95%: 0.69 a 1.00; p = 0.048). Analysis of the prolonged phase did not disclose additional benefit of use between 8 and 43 days.

Both studies showed a superiority of enoxaparin in comparison to UFH for patients with ACS NSTEMI). In these studies patients had been managed with a conservative strategy (coronary cine-angiography only for patients with symptoms of refractory ischemia), therefore safety and efficacy of enoxaparin in a setting of early invasive strategy, associated or not to glycoprotein IIb/IIIa inhibitors, had not been tested.

Next, the SYNERGY trial⁴ selected patients with high risk ACS NSTEMI for enoxaparin or UFH associated with early invasive strategy and GPIIb/IIIa inhibitors. Enoxaparin was used (1 mg/kg) every 12 hours or UFH in continued intravenous infusion to achieve an APTT of 1.5 to 2 times the reference value. It is noteworthy that patients receiving enoxaparin did not receive UFH during the catheterism or angioplasty procedures, but considering the interval of the last dose of enoxaparin, a bolus of the drug could or could not be administered (Table 1). Included were 10027 patients in 467 hospitals in 12 countries. The endpoint death or nonfatal acute myocardium infarction (AMI) took place in 14% for the enoxaparin group and in 14.5% for the UFH group (OR 0.96 CI 0.86-1.06; p = 0.4). A higher incidence of bleeding was observed in the enoxaparin group (9.1%) compared with the control group (7.6%), p= 0.008.) The authors concluded that in high risk patients, treated with early invasive strategy, enoxaparin was not inferior to UFH. Such results were consistent for up to six months and one year. However, in the SYNERGY trial patients were randomized independent of prior use of any antithrombotic (75% of patients had already received some kind of heparin at pre-randomi-

zation) in addition UFH was used in 12% of patients of the enoxaparin group and enoxaparin was used in 4% of patients of the UFH group after randomization (crossover). These findings brought about strong and consistent criticism in literature about the true validity of the study.

Analysis of patients according to contamination, that is to say, the excessive crossing of heparin or enoxaparin pre or post-randomization disclosed the added finding that the major risk of bleeding was related to concomitant or crossed use of UFH with enoxaparin during treatment.

Table 1 – Adjustment of the Enoxaparin Dose for Angioplasty (ATCS)

Last dose < 8h	ATCS with no new bolus
Last dose > 8h	0.3 mg/kg, intravenous pre-ATCS

Continuing along the same research line, the A to Z⁵ trial selected high risk patients with ACS NSTEMI for use with heparin versus UFH associated to GPIIb/IIIa inhibitor. Included were 3987 patients, 340 hospitals in 41 countries. More than half of the patients were treated following the early invasive strategy. Occurrence of death, new AMI or refractory ischemia at seven days was of 8.4% in the enoxaparin and 9.4% in the control group (OR 0.88 CI 0.71-1.08; p = ns). This study showed that enoxaparin was not inferior to UFH. Incidence of major bleeding was of 0.9% in the enoxaparin and of 0.4% in the control group (p = 0.05). The authors concluded that enoxaparin was inferior to heparin for treatment of high risk patients with ACS NSTEMI using GPIIb/IIIa inhibitors.

In a meta analysis⁶ that included studies with enoxaparin in conservative strategy (ESSENCE TIMI 11B, INTERACT⁷ and enoxaparin in early invasive strategy (ACUTE II⁸, SYNERGY, A to Z) there was no difference in mortality when analyzed separately, but there was a decrease of the combined endpoint of death and nonfatal AMI, in favor of enoxaparin (10.1% versus 11% OR 0.91 CI 0.83-0.99). There was no difference regarding bleeding or need for blood transfusion among groups. For patients not treated with another antithrombotic prior do randomization, decrease in the occurrence of combined endpoint was higher (OR 14.6%).

In the setting of acute coronary syndromes, with ST segment elevation (ACS STEMI) the new AHA/ACC guidelines⁹ recommend use of anticoagulants asso-

ciated with fibrinolytics.

To evaluate use of enoxaparin adjuvant to thrombolysis in (ACS STEMI) the EXTRACT TIMI 25¹⁰ studies was designed. This study selected patients with (ACS STEMI) elected for treatment with fibrinolytics (streptokinase, tenecteplase, Tpa, R-Tpa) and ranked them for use of enoxaparin (30 mg intravenous in bolus and 1mg/kg every 12 hours for seven days) or UFH (60 UI/kg in *bolus* and 12 UI/kg/h, APTT 50-75^{''} for 48 hours). To avoid risks of major bleeding in the elderly and patients with chronic renal disease, enoxaparin doses were adjusted for these groups (Table 2).

Table 2 – Adjustment of Enoxaparin Dose in EXTRACT-TIMI 25

Depuration < 30	1 mg/kg day
Age > 75 anos	Not administer bolus, dose 0.75 mg/kg, every 12 hours (maximum of 75 mg/dose)
Received UFH	Not administer bolus intravenous

Combined endpoint of death and nonfatal AMI was analyzed in 20,506 patients, during 30 days. Primary endpoint occurred in 9.9% of patients in the enoxaparin group and in 12% of the control group (OR 0.83 CI 0.77-0.90 p < 0.001). The rate of major bleeding was of 1.4% in the control group and of 2.1% in the enoxaparin group (p < 0.001). The authors further surveyed the total benefit rates (death, AMI, and bleedings) and in this survey enoxaparin remained superior (11% versus 12.8% OR 0.86 CI 0.80-0.93, p < 0.001). It was concluded that during hospital stay due to ACS STEMI treated with fibrinolysis, use of enoxaparin was better than UFH. Accordingly it was projected that, for each 1000 patients treated, six episodes of death would be saved at the expense of four major nonfatal bleeding episodes.

Studies with Bivalirudine

Bivalirudine is a direct thrombin inhibitor. The ACUITY¹¹ trial randomized patients with ACS STEMI (from moderate to high risk) for one of three groups: (UFH or enoxaparin + GPIIb/IIIa, inhibitor, bivalirudine + GPIIb/IIIa, inhibitor and bivalirudine alone. Doses are shown in table 3.

Table 3 – Doses of Bivalirudine in the ACUITY

UFH	60 UI/kg bolus + 12 UI/kg/h APTT 50-75 ^{''} ACT 200-250 ATCS
Enoxaparin	1 mg/kg 12/12h + 0.3 mg, intravenous in ATCS (> 8h) 0.75 mg, intravenous in ATCS (> 16h)
Bivalirudine	0.1 mg/kg, intravenous bolus + 0.25 mg/kg/h + 0.5 mg/kg bolus and 1.75 mg/kg/h if ATCS

The primary endpoint of efficacy combined was death, AMI and non-planned revascularization at 30 days. Data of 13819 patients were analyzed and when comparing the bivalirudine + GPIIb/IIIa and UFH + GPIIb/IIIa groups, there was no difference in the combined endpoint (OD 1.07 CI 0.92-1.23, $p = 0.39$) but bivalirudine was not inferior to standard treatment. There were no differences in bleeding rates (5.3% versus 5.7%, $p = 0.38$) or of combined endpoint associated to bleeding (11.8% versus 11.7%, $p = 0.93$). In the comparison between the bivalirudine alone and control there was no difference in the occurrence of primary endpoint (7.3% versus 7.8% RR 1.08 CI 0.93-1.24 $p = 0.32$) however bivalirudine alone reached the limit for non-inferiority. The higher incidence of bleeding was lesser in the bivalirudine group alone versus UFH + GPIIb/IIIa (3% versus 5.7% OR 0.53 CI 0.43-0.65 $p < 0.001$). Bivalirudine was better when the combined endpoint associated to major bleeding was analyzed (10.1% versus 11.7% OD 0.86 CI 0.77-0.97 $p = 0.02$). A larger number of ischemic events was perceived in patients who used bivalirudine alone or when not combined with tienopiridin derivatives (clopidogrel) before angioplasty (7.1% versus 9.1% OR 1.29 CI 1.03-1.63). Authors concluded that, in patients with ACS NSTEMI and treatment with invasive strategy, bleeding rates and ischemic events were similar among the groups using bivalirudine or heparin associated to GPIIb/IIIa inhibitor. When comparing bivalirudine with heparin and GPIIb/IIIa inhibitor, incidence of events was equal, however with lower bleeding rates in the bivalirudine group.

Studies with Fondaparinux

Fondaparinux is a pentasaccharide that acts directly on antithrombin III inhibiting the Xa factor and therefore inhibiting thrombin, avoiding formation of a thrombus. Studies on prevention of thromboembolism in patients of large size surgeries, clinical high risk patients, treatment of deep venous thrombosis (DVT) and in pulmonary thromboembolism have shown their efficacy and mostly their clinical safety¹²⁻¹⁴.

OASIS-5 was a randomized, multicentric, double blind non-inferiority study comparing fondaparinux to enoxaparin in patients with AMI STEMI¹². Patients were allocated for fondaparinux (2.5 mg, subcutaneously once a day) or enoxaparin (1mg/kg every 12 hours). Doses were adjusted in patients with altered renal function and those scheduled for angioplasty (Table 4).

Table 4 – Adjustments of Dose in the OASIS-5

Depuration < 30	Enoxaparin (1 mg/kg/d)
Angioplasty	Enoxaparin < 6h with no new dose > 6h 0.013 mL/kg with GPIIbIIIa 0.02 mL/kg Without GPIIbIIIa Fondaparinux < 6h 2.5 mg, intravenous > 6h 5 mg, intravenous or 2.5 mg, intravenous if GPIIbIIIa

The primary goal for efficacy showed non-inferiority of fondaparinux in preventing the combination of death, AMI and refractory ischemia at nine days and primary analysis of safety disclosed higher bleeding at nine days by means of intention to treat (ITT). This study included 20078 patients. Endpoint of primary efficiency took place in 5.8% of the fondaparinux group and 5.7% of the enoxaparin group (OR 1.01 CI 0.90-1.13), showing non-inferiority. When endpoints at 30 days (secondary goal) were analyzed, there was no difference (4.1% versus 4.1% OR 0.99 CI 0.86-1.13). Primary analysis of safety showed a lesser incidence of major bleeding in the fondaparinux group (2.2% versus 4.1% OR 0.52 CI 0.44-0.61 $p < 0.001$).

Patients with major bleeding had an increased mortality, independent of group. OASIS 6¹⁴ a randomized, multicentric double blind study that evaluated patients with ACS STE with a symptom onset in up to 12 hours. A total of 12092 patients was divided into 2 groups classified according to indication or not of UFH: stratum 1 (5658 patients) – with no indication for UFH; stratum 2 (6434 patients) – with indication for UFH those using fibrin-specific thrombotics, scheduled for primary angioplasty and those not submitted to reperfusion. In stratum 1, patients were randomized by administration of fondaparinux (2.5 mg subcutaneous or placebo for eight days. In stratum 2, patients were randomized for administration of fondaparinux (2.5 mg intravenous followed subcutaneous) or UFH (60 UI bolus and 12 UI/kg/h, APTT of 1.5-2.5). Patients scheduled for angioplasty had doses adjusted by previous use of UFH and GPIIbIIIa inhibitor (Table 5).

Table 5 – Adjustment of Dose in Primary ATCS OASIS-6

	Fondaparinux	UFH
UFH + GPIIbIIIa	2.5 mg intravenous + 2.5 mg subcutaneous for 8 days	dose < 65 UI/kg
UFH	5 mg, intravenous + 2.5 mg subcutaneous for 8 days	dose up to 100 UI/kg
GPIIbIIIa	2.5 mg, intravenous + 2.5 mg subcutaneous for 8 days	dose < 65 UI/kg
None	5 mg, intravenous + 2.5 mg subcutaneous for 8 days	dose up to 100 UI/kg

Table 6 – Indications and Levels of the Principal Antithrombotics Recommended in ACSA

Drugs	Initial dose	PCI with/ Previous TT	PCI without Previous TT	Post-PCI	Conservative Treatment	Discontinue - Surgery	Indication
Bivalirudine	0.1 mg/kg bolus 0.25 mg/kg/h infusion	0.5 mg/kg bolus + 1.75 mg/kg/h	0.75 mg/kg bolus + 1.75 mg/kg/h	Maintain for 4h	Maintain for 72h	In 3 h	IB
Dalteparin	120 UI/kg SC 12/12h	with/ GPIIb/IIIa: UFH ACT 200; Without/ GPIIb/IIIa: HNF ACT 250-300	With/ GPIIb/IIIa 60-70 UI/kg UFH; without/ GPIIb/IIIa 100-140 UI/kg	Without addi- tional TT	-	-	-
Enoxaparin	Bolus 30 mg IV optional; 1 mg/kg SC 12/12h	Last dose < 8h Without new dose last dose > 8h 0.3 mg/kg IV	0.5-0.75 mg/kg IV bolus	Without addi- tional TT	Maintain for 8 days	12-24h	IA
Fondaparinux *	2.5 mg SC/d	50-60 UI/kg IV UFH bolus #	50-60 UI/kg IV UFH bolus #	Without addi- tional TT	Maintain for 8 days	24h	IB
UFH	60 UI/kg IV bo- lus; 12 UI/kg/h IV infusion	With/ GPIIb/IIIa ACT 200” Without/ GPIIb/IIIa ACT 250-300”	With/ GPIIb/IIIa 60-70 UI/kg IV bo- lus; Without/ GPIIb/IIIa 100-140 UI/kg IV bolus	Without addi- tional TT	Maintain for 48h	Continue	IA

TT = treatment; SC = subcutaneous; IV = intravenous route; ACT = Activated time of coagulation

* Patients in conservative strategy and with risk of bleeding fondaparinux is preferable with level of evidence IB.

Adapted from ACC/AHA Guidelines for diagnosis and treatment for Unstable Angina/non ST elevation Myocardial Infarction, published on line Circulation Aug 6, 2007

Personal communication OASIS 5 Investigators July 7, 2006.

The combined primary goal was that of death or new AMI within 30 days. Thrombolitics were used in 45% of patients; primary angioplasty in 28.9% and 23.7% remained with no reperfusion treatment. Primary endpoint took place in 9.7% of the fondaparinux group and in 11.2% of the control group (OR 0.86 CI 0.77-0.98, $p = 0.008$). Analysis of isolated mortality was also lesser in the fondaparinux group (7.8% versus 8.9%, $p = 0.003$). No difference was found regarding bleeding incidence. Subgroup analysis showed decrease of death and/or reinfraction in patients who were not given reperfusion treatment, but utilized fondaparinux (relative risk reduction of 23%). However patients that were submitted to angioplasty did not benefit from fondaparinux (also in subgroup analysis). There was a higher rate of thrombosis and in the indications for angioplasty and coronary complications (dissection, new thrombus and abrupt occlusion) in the fondaparinux group, although there was no sign of clinical significance.

Table 6 summarizes the main evidences of this study and the levels of recommendations.

DISCUSSION

Use of potent antithrombotics in the attempt to reduce cardiovascular mortality in a universe of ACS led

to the increase of undesirable effects such as hemorrhages. It is known that bleeding is associated to a six times increase in mortality, after hospital dismissal and the utilization of new anticoagulants and/or antiplatelet agents. A lesser incidence of these factors may consequently afford a greater safety for patients. The decrease of morbidity mortality in ACS using combined treatment and early invasive strategy was of such impact that, to prove superiority of a new drug, trials with an increasingly large number of patients are required. That is why; in the last articles the concept of non-inferiority of a new drug in relation to the standard therapy is more frequently addressed. Drugs that are easy to handle and safe are sought.

The SYNERGY trial disclosed that “crossed use” of enoxaparin and UFH led to a higher rate of bleeding in these patients. Based upon this evidence, the non use of UFH has been recommended, mainly during invasive procedures, for patients previously treated with enoxaparin and vice-versa. As such, patients forwarded to hemodynamics using enoxaparin should be treated according to adjustment of the dose, as shown on table 1.

Further, elderly patients and those with chronic renal dysfunction are more inclined to bleeding while using enoxaparin. When this drug is elected, dose adjust-

ment is relevant as shown in table 3.

During use of bivalirudine, associated administration of antiplatelets agents, in addition to aspirin: clopidogrel and/or GPIIb/IIIa inhibitors, is required. This drug cannot be used alone with aspirin, due to higher risk of new ischemic events. Fondaparinux has proven to be an alternative in treatment of ACS, especially in relation to decrease of major bleeding. No advantages of use were found in the case of primary angioplasty. Correct choice of the best drug and the best handling of the dose for each subgroup of patients are absolutely necessary. Table 6 shows recommendations for dose of anticoagulants in acute coronary syndromes with no ST segment elevation, according to the guidelines of the American Heart Association (AHA) / American College of Cardiology (ACC)¹⁴.

The AHA and ACC published in 2007 an up-dating of the American College of Acute Myocardial Infarction with ST Segment Elevation¹⁴ with special attention to use of antithrombotics. Cited as relevant in this recommendation are:

1) Patients under fibrinolysis:

- Antithrombotics must be used for at least 48 hours and ideally for 8 days in patients treated with fibrinolysis (recommendation IA);
- Enoxaparin can be used with a 30 mg intravenous bolus followed by 1 mg/kg subcutaneous every 12 hours. Dose must be adjusted for depuration < 30 mL/min (mg/kg day) and for patients > 75 years (0.75 mg/kg every 12 hours) in addition to skipping the venous bolus. Treatment should extend from 48h to 8 days (recommendation IA);
- A dose of 2.5 mg of fondaparinux intravenous, followed by 2.5 mg subcutaneous per day. Use should be continued during the entire hospital stay or for 8 days (recommendation IB).

2) Patients submitted to primary angioplasty:

- If UFH was previously used – use UFH as support to the procedure with dose adjusted with or without use of GP IIb/IIIa. Bivalirudine may also be used (recommendation IC);
- If enoxaparin was previously used – if the last dose was given less than 8h ago, other treatment is not needed. If the last dose was given from 8 to 12h ago, administer *bolus* of 0.3 mg/kg intravenous (recommendation IB);
- If previously treated with fondaparinux – associate dose of other antithrombotics with anti-IIa action, considering simultaneous use or not of GPIIb/IIIa (recommendation IC) isolated use of fondaparinux du-

ring angioplasty received recommendation IIIc, that is to say must be avoided.

New drugs are continuously developed for treatment of ACS as for instance the new direct inhibitors of thrombin rivaroxaban, apixaban, dabigatran, as well as drugs with direct synergic block on thrombin and Xa factor such as the Org42675 still under investigation.

In the setting of the ACS, besides the assurance of adequate reperfusion and its maintenance, the risk of more severe adverse events such as bleeding must be taken into account and reduced to the maximum in patients using various anti-platelet and antithrombotic agents. As such, the correct handling of doses and the individual choice of the combination of drugs is mandatory and the intensive care physician must be familiar with it.

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