HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

2 April 2008

LOVENOX 6,000 IU anti-Xa/0.6 ml, injectable solution (S.C.) in prefilled syringe
Box of 2 (CIP: 364 690-3)
Box of 10 (CIP: 364 692-6)

LOVENOX 8,000 IU anti-Xa/0.8 ml, injectable solution (S.C.) in prefilled syringe
Box of 2 (CIP: 364 693-2)
Box of 10 (CIP: 364 694-9)

LOVENOX 10,000 IU anti-Xa/1 ml, injectable solution (S.C.) in prefilled syringe
Box of 2 (CIP: 364 688-9)
Box of 10 (CIP: 364 689-5)

LOVENOX 30,000 IU anti-Xa/3ml, injectable solution in multiple dose vial
Box of 1 (CIP: 561 070-8)

Applicant: SANOFI – AVENTIS FRANCE

Enoxaparin

ATC code: B01AB04

List I

Dates of the initial marketing authorisation (national procedure):
- 6,000 IU/0.6 ml; 8,000 IU/0.8 ml; 10,000 IU/1ml dosages: 17/03/1993
- 30,000 IU/3ml dosage: 06/08/1998

Modification of marketing authorisation of the extension of indication:
- LOVENOX 6,000 IU/0.6 ml: 09/07/2007
- LOVENOX 8,000 IU/0.8 ml; 10,000 UI/1ml; 30,000 IU/1ml: 10/07/2007

Reason for request: change to the conditions of registration: inclusion on the list of medicines approved for use by hospitals in the extension of indication **"treatment of acute myocardial infarction with ST segment elevation, in combination with thrombolytic treatment, for patients who may or may not be eligible for a secondary coronary angioplasty"**.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient

Enoxaparin

1.2. Indications

"Curative treatment of established deep-vein thromboses, with or without pulmonary embolism, with no signs of clinical severity, excluding pulmonary embolisms that are likely to respond to thrombolytic or surgical treatment.

- Treatment of unstable angina and non-Q-wave myocardial infarction in the acute phase, in combination with aspirin.
- **Treatment of acute myocardial infarction with ST segment elevation, in combination with thrombolytic treatment, in patients who may or may not be eligible for a secondary coronary angioplasty".**

1.3. Dosage

The recommended dosage for the treatment of acute myocardial infarction with ST segment elevation, in combination with thrombolytic treatment, in patients who may or may not be eligible for a secondary coronary angioplasty, is as follows:
Initial IV bolus of 3,000 IU of anti-Xa followed by an SC injection of 100 IU of anti-Xa/kg within 15 minutes and then every 12 hours (up to a maximum of 10,000 IU of anti-Xa for the first two SC doses).
The first dose of enoxaparin is administered in an interval running from 15 minutes before to 30 minutes after the start of thrombolytic treatment (which may or may not be fibrinospecific).

The recommended duration of treatment is eight days or until discharge from hospital, if the patient has spent less than eight days in hospital.

Associated treatment: aspirin must be introduced as soon as possible after the onset of symptoms and continued at a dosage of between 75 mg and 325 mg a day for at least 30 days, unless otherwise specified.

<u>In cases of coronary angioplasty</u>:
- if the most recent SC injection of enoxaparin was given less than eight hours before balloon dilation, it does not need to be administered again.
- if the most recent SC injection was given more than eight hours before balloon dilation, a bolus IV injection of 30 IU of anti-Xa/kg of enoxaparin must be administered.

<u>Patients aged 75 or over</u>:
- do not administer the initial IV bolus injection. Administer an SC dose of 75 IU of anti-Xa/kg every twelve hours (up to a maximum of 7,500 IU of anti-Xa for the first two injections only).

<u>Renal failure</u>: practitioners must assess the renal function of patients with renal failure before initiating LMWH treatment, especially in the cases of elderly patients aged over 75. Use Cockcroft's formula to calculate creatinine clearance, with recent data on the patient's weight. LMWH is contraindicated for curative indications in patients found to have severe renal failure (creatinine clearance of around 30 ml/min).

2 SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2007)

B	Blood and haematopoietic organs
B01	Antithrombotic agents
B01A	Antithrombotic agents
B01AB	Heparin
B01AB04	Enoxaparin

2.2 Medicines in the same therapeutic category

2.2.1 Comparator medicines

For the same indication:

- Other low molecular weight heparins (LMWH): none.
- Unfractionated heparins (UFH): CALCIPARINE and HEPARIN CHOAY.

2.3 Medicines with a similar therapeutic aim

Adjuvant reperfusion treatments (involving fibrinolysis or primary coronary angioplasty) to be employed in cases of acute coronary syndrome with ST elevation:

- Antithrombotic drugs aimed at stopping the spread of an existing coronary thrombus or preventing excessive thrombotic reaction which could be encouraged by thrombolysis prior to admission or by a coronary angioplasty: aspirin +/- clopidogrel.
- *Glycoprotein IIb/IIIa antagonists[1] should not be used either in isolation because of their lack of efficacy or in combination with a fibrinolytic because they increase the risk of haemorrhage (grade B). Their use in the acute phase of ST+ ACS must only be considered before a primary angioplasty. Their risk/benefit ratio in the pre-admission phase, in combination with clopidogrel, is unknown. The recommended medication is abciximab at a dose of 250 µg/kg by IV administration followed by a continuous IV perfusion of 0.125 µg/kg/min up to a maximum of 10 µg/min".*

1 Consensus Conference. Prise en charge de l'infarctus du myocarde à la phase aigue en dehors des services de cardiologie [Management of acute myocardial infarction outside cardiology units]. French emergency medical services with the methodological and financial support of the Haute Autorité de Santé; 6 February 2007

3 ANALYSIS OF AVAILABLE DATA

Marketing authorisation was granted for enoxaparin (LOVENOX) in the acute phase of myocardial infarction (MI) in the light of the results of the ExTRACT-TIMI 25 study.

3.1 Summary of the ExTRACT-TIMI 25 study[2]

Objective: the aim of this study was to compare the efficacy and adverse effects of enoxaparin with those of an unfractionated heparin in patients with ST-elevation myocardial infarction, in addition to fibrinolytic treatment.

Methodology

Type of study: randomised, double-blind[3], multi-centre study versus unfractionated heparin.

Inclusion criteria: adult patients (aged 18 or over), with symptoms of ischaemia at rest for at least 20 minutes in the six hours prior to randomisation, with ST elevation of at least 0.1 mV in two peripheral leads or of 0.2 mV in at least two adjacent precordial leads or left branch block. Patients eligible for fibrinolytic treatment.

Exclusion criteria: contraindications for fibrinolytic treatment or low molecular weight heparin in the preceding eight hours, cardiogenic shock, pericarditis, aortic dissection symptoms, known renal failure (serum creatinine level above 220 µmol/l in men and above 175 µmol/l in women), life expectancy below 12 months.

Comparator treatments administered in combination with thrombolytic/fibrinolytic treatment[4]:

- enoxaparin: an IV bolus of 3,000 IU of anti-Xa followed immediately by an SC dose of 100 IU of anti-Xa/kg, then SC injection of 100 IU of anti-Xa/kg every 12 hours. Duration of treatment: until the patient leaves hospital or up to a maximum of eight days
- UFH: an IV bolus of 60 IU/kg (up to a maximum of 4,000 IU), followed by continuous perfusion of a dose suitable for the activated partial thromboplastin time (target APTT of 1.5 to 2). Duration of treatment: at least 48 hours.

The dosage regimen for enoxaparin has been adapted to take account of patients' ages and renal functions:

- **For patients aged under 75**: 30 mg (3,000 IU) as IV bolus followed 15 minutes later by SC injection of 1.0 mg/kg (100 IU/kg) every 12 hours.
- **For patients aged 75 or more**: no IV bolus and SC dose reduced to 0.75 mg/kg (75 IU/kg) every 12 hours.

In addition,

- For the first two SC injections: maximum dose of 100 mg (10,000 IU) (patients aged under 75) or 75 mg (7,500 IU) (patients aged 75 or over).
- in order to reduce the risk of haemorrhage, the IV bolus was not administered to patient who had received UFH on an open-label basis (at least 4,000 IU) in the three hours prior to randomisation.

2 Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M. et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006;354(14):1477-88.
3 A double-placebo technique was used.
4 Options for fibrinolytic treatment: streptokinase, tenecteplase, alteplase or retepase.

- in patients with creatinine clearance below 30 ml/min, the dosage was altered to 1.0 mg/kg (100 IU/kg) every 24 hours.

The study protocol specified that a percutaneous coronary procedure[5] could be performed if fibrinolysis failed or as an emergency to treat a further episode of ischaemia or MI, and that the procedures scheduled would be postponed to at least 48 hours after randomisation.

All patients were also given aspirin for at least 30 days.

Primary endpoint: a compound efficacy endpoint including the following events: recurrence of myocardial infarction[6] and death from any cause in the 30 days following inclusion.
This study was designed to detect, with a statistical power of at least 90%, a 13% reduction in the relative risk of the primary efficacy endpoint occurring among patients taking enoxaparin. It has been estimated that approximately 21,000 patients would need to be randomised in order to achieve a figure of 2,080 events.

- Several secondary endpoints were assessed, including:
  - death from any cause, recurrence of myocardial infarction,
  - compound criterion comprising death from any cause**,** non-fatal recurrence of myocardial infarction and recurrence of myocardial ischaemia requiring emergency revascularisation[7] during the 30 days after inclusion.
  - occurrence of bleeding/haemorrhage classified according to the TIMI criteria.

Results:
- Of the 20,506 patients randomised, 20,479 were included in the population that was analysed on an "intention to treat" basis. The characteristics of patients in both arms at the time of inclusion were similar.
- The median interval between the onset of symptoms and the start of fibrinolytic treatment was 3.2 hours.
- The median duration of hospitalisation of the population studied was 10 days (interquartile range: from 7 to 17 days).

Details of treatment
- The median duration of treatment with enoxaparin was 7 days (2 days for UFH).
- 74.3% of patients had drug treatment alone for MI.
- 23% of patients (4,716 patients) underwent a percutaneous coronary procedure (coronary angioplasty). In 2.8% of cases this was a rescue treatment, and in 20.2% of cases it was an emergency or scheduled procedure. 2.8% of patients had an aortocoronary bypass.

Drug co-administration:
- fibrinolytics for 99.7% of patients,
- platelet anti-aggregants:
  - aspirin: for almost 95% of patients and for at least 30 days,
  - clopidogrel: for 28% of patients, as an alternative to or in combination with aspirin.

5 Patients due to undergo a percutaneous coronary procedure would be given antithrombotic treatment in addition to the blinded drug used. This treatment could be stopped after simple procedures according to the investigator's decision.
6 The term "non-fatal myocardial infarction (MI)" indicates that the patient had a recurrence of MI and was still alive at the stated date.
7 The term "emergency revascularisation" refers to episodes of recurrence of myocardial ischaemia (without infarction) treated by coronary revascularisation during the same hospital stay.

Other drugs:

- a beta-blocker (in almost 85% of patients),
- an ACE inhibitor or a sartan (in almost 95% of patients),
- a statin (in almost 70% of patients).

Efficacy results

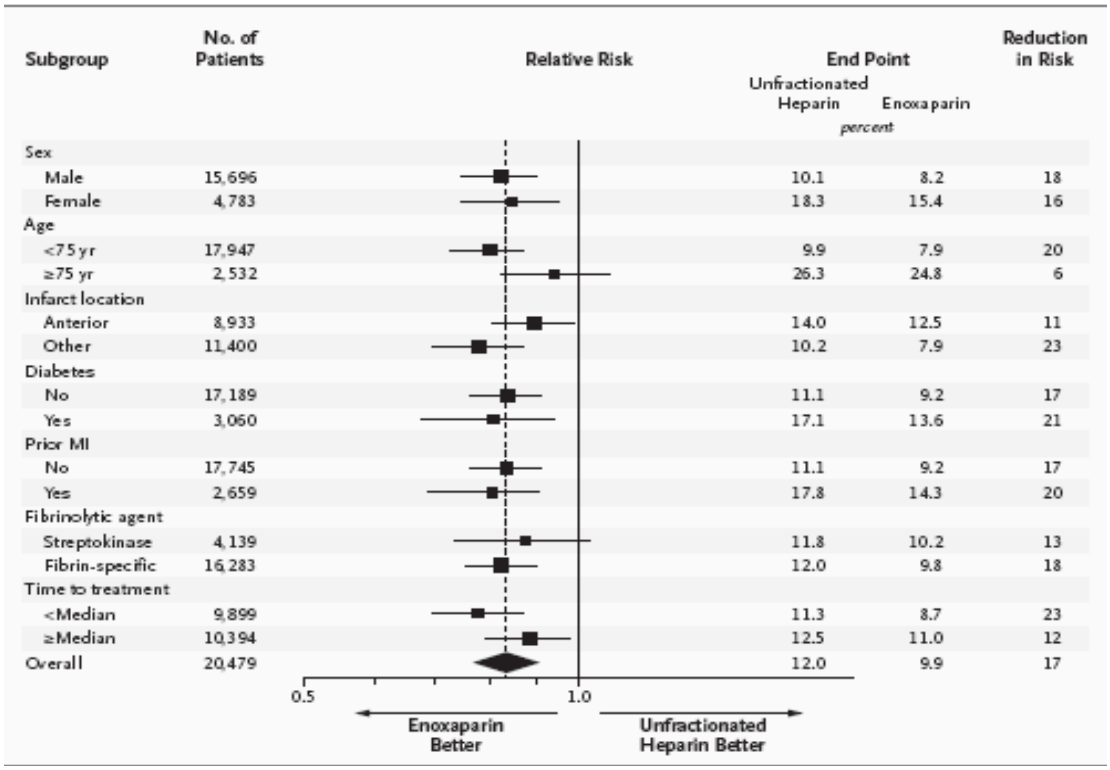
Primary endpoint: 1,017 events (recurrence of myocardial infarction or death from any cause after 30 days of treatment) were observed in 10,256 patients treated with enoxaparin (9.9%) versus 1,223 events in 10,223 patients treated with UFH (12%), p< 0.001. Enoxaparin (LOVENOX) did therefore reduce the occurrence of the primary efficacy endpoint, but the extent of this effect (absolute reduction of 2.1% and relative reduction of 17%) was relatively modest.

Secondary endpoints:
- recurrence of myocardial infarctions was less frequent in the enoxaparin group (3.4%) than in the UFH group (5%), p<0.001, RRR of 31%,
- there was no difference in the frequency of deaths from any cause between the two treatments.

Efficacy results after 30 days of the Extract-TIMI study

Results	**Enoxaparin (n= 10,256)**	**unfractionated heparin (n= 10,223)**	**Relative risk (95% CI)**	**p value**
		Number (%)		
Results after 30 days				
Primary efficacy endpoint (death or non-fatal MI)	**1.017** (9.9)	**1,223** (12.0)	0.83 (0.77-0.90)	< 0.001
Death	708 (6.9)	765 (7.5)	0.92 (0.84-1.02)	0.11
Non-fatal MI	309 (3.0)	458 (4.5)	0.67 (0.58–0.77)	<0.001
Emergency revascularisation	213 (2.1)	286 (2.8)	0.74 (0.62–0.88)	<0.001
Death, non-fatal MI or emergency revascularisation	1,199 (11.7)	1,479 (14.5)	0.81 (0.75–0.87)	<0.001

The effect of enoxaparin (LOVENOX) on the primary endpoint has been investigated in several sub-groups based on age, gender, location of the myocardial infarction, past history of diabetes or myocardial infarction, administration of thrombolytic drugs, interval between the first clinical signs and the start of treatment:



Results for the primary efficacy endpoint after 30 days in the various sub-groups

It can be observed that:
- enoxaparin was shown to be more effective than UFH on the primary endpoint - in patients who had undergone a percutaneous coronary procedure (coronary angioplasty) in the 30 days after randomisation (10.8% versus 13.9%, 23% reduction in the relative risk) and - in patients who received drug treatment (9.7% versus 11.4%, 16% reduction in the relative risk, interaction p=0.33);
- in patients aged over 75 (2,532 patients out of the 20,479 assessed as a sub-group in this analysis), no difference between enoxaparin and UFH in terms of efficacy was found for the primary efficacy endpoint.

3.2 Adverse events

Patients taking enoxaparin experienced more haemorrhages than those taking UFH.
- The incidence of major haemorrhages (including intracranial haemorrhages) according to the TIMI criteria[8] after 30 days was 2.1% in patients taking enoxaparin and 1.4% in patients taking UFH. This equates to a 0.7% increase in the absolute risk of haemorrhage and a 53% in the relative risk, p<0.001.
- The risk of occurrence of minor haemorrhage was also higher in patients taking enoxaparin.
- The incidence of gastrointestinal haemorrhage was 0.5% in patients taking enoxaparin and 0.1% in patients taking UFH.
- The incidence of intracranial haemorrhage was 0.8% in patients taking enoxaparin and 0.7% in patients taking UFH.

Assessment of the efficacy/haemorrhagic risk ratio

An assessment of the net benefit has been suggested. It was defined using three composite criteria consisting of three relevant clinical events: death from any cause, recurrence of MI,

8 TIMI: Thrombolysis in Myocardial Infarction

and either a cerebrovascular accident, a major haemorrhage or an intracranial haemorrhage. The next benefit came down on the side of enoxaparin in each case ($p<0.001$).

3.3 Conclusion

According to the results of the EXTRACT-TIMI study performed on 20,506 patients in the acute phase of an ST segment elevation myocardial infarction and receiving medication to restore arterial patency (administration of a fibrinolytic), enoxaparin (LOVENOX) administered for a median duration of seven days was more effective than unfractionated heparin (UFH) administered for a median duration of two days in reducing the occurrence of events featuring in a composite assessment criteria consisting of myocardial infarction recurrence and death from any cause in the thirty days after inclusion.

The size of this effect was modest: the relative risk fell by 17% and the absolute benefit amounted to 2.1%. The clinical benefit was due mainly to a reduction in myocardial infarction relapses. A sub-group analysis failed to find clear evidence of this clinical benefit of enoxaparin (LOVENOX) among patients aged over 75.

Enoxaparin also caused more major and minor haemorrhages (TIMI criteria) than UFH. Analysis of the composite criteria measuring the net clinical benefit, taking the haemorrhagic risk into account, confirmed an expected benefit for enoxaparin compared to UFH.

However, most of the patients in this study received only one platelet anti-aggregant. The results of two recent clinical studies (CLARITY study[9] and COMMIT study[10]) indicate that patients are likely to gain an additional clinical benefit[11] from being treated with two platelet anti-aggregants in combination: aspirin and clopidogrel. The impact of this practice recommended in the light of the findings of the EXTRACT-TIMI study is unknown, particularly with regard to haemorrhagic risk.

N.B.: The clinical superiority of enoxaparin to a UFH observed in the EXTRACT-TIMI study could be the result of three factors: that enoxaparin has a more pronounced antithrombotic effect; that antithrombotic treatment with enoxaparin was administered for longer; or that there was a surge in antithrombotic events when UFH was stopped.

9 Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; 352:1179-89

10 COMMIT collaborative group. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controled trial. *Lancet* 2005; 366:1607-21

11 See the Committee's opinion dated 6 June 2007 for PLAVIX (clopidogrel) in this indication.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit in the extension of the indication

All acute coronary syndromes must be dealt with as an emergency by a specialised team. An electrocardiogram (ECG) is the only way of identifying a myocardial infarction requiring reperfusion as rapidly as possible to remove the coronary artery obstruction. LOVENOX is indicated in the acute phase of a myocardial infarction with ST segment elevation: these infarctions, known as ST+ ACS, are associated with total occlusion of a coronary artery. Patients should also benefit from reperfusion as an extremely urgent procedure because of the consequences for this action on their morbidity and mortality. Coronary reperfusion is achieved by angioplasty (cardiac surgery) or fibrinolysis (drug treatment). These serious clinical situations have an impact on the patient's vital prognosis.

Practitioners are advised to prescribe LOVENOX only in the acute phase of ST+ ACS MI as an adjuvant treatment to fibrinolysis. The aim of the treatment is to prevent re-occlusion of the coronary artery after fibrinolysis and to prevent aggravation of the infarction.
A different anticoagulant adjuvant treatment may be prescribed: unfractionated heparin (drug alternative). Practitioners should consider prescribing this form of treatment particularly in the case of patients with renal failure and patients aged over 75. UFH is the only possible choice in the case of first-intention angioplasty.

Public health benefit

In terms of public health, ischaemic heart diseases represent a major burden. That of myocardial infarction with ST elevation eligible for thrombolytic treatment is small due to the limited number of patients affected..
Improving the secondary prevention of MI is still a public health need.
A review of the available data and existing treatments shows that this medicinal product is expected to have a low impact in terms of morbi-mortality.
However, it is not certain that this data can be transposed, since:
- the population suitable for treatment with LOVENOX in practice will include more patients who are more vulnerable (elderly or with renal failure), patients already taking a combination treatment of PLAVIX+ASPIRIN, and patients with a secondary angioplasty (up to 30 days).
- This will reduce the expected impact in practice.
Furthermore, this data is transposable only in the case of patients being treated by fibrinolysis. Emergency management of MI in France varies from one region to another: some regions prefer angioplasty, while others are more likely to use fibrinolysis. The impact of LOVENOX is therefore likely to vary according to the region.
It therefore seems unlikely that LOVENOX will be able to provide a response to the identified public health requirement.
Consequently, in the current state of knowledge and in view of the existence of other currently available treatments, LOVENOX is not expected to benefit public health in this indication.

The efficacy/adverse effects ratio of enoxaparin is high.

The actual benefit of LOVENOX is substantial.

4.2 Improvement in actual benefit in the extension of the indication

Enoxaparin (LOVENOX) has been found to be superior to UFH in reducing the risk of recurrence of myocardial infarction, but this clinical effect was modest, with no impact **on mortality, and was obtained at the cost of an increased risk in major haemorrhage. Furthermore, the benefit of LOVENOX treatment has not been established in patients**

aged over 75, obese patients, patients with renal failure or patients requiring a secondary angioplasty in the thirty days following fibrinolysis in the event that this intervention fails.

In view of the clinical data available, the Committee is of the opinion that LOVENOX is an additional therapeutic option and so does not confer any improvement of actual benefit (IAB V) compared to UFH for this extension of indication.

4.3 Therapeutic use

According to a recent French consensus conference[12], early restoration of coronary patency in the acute phase of ST+ ACS MI contributes to improving the prognosis for patients. The choice between the two available techniques (angioplasty or fibrinolysis) is made with regard to the clinical situation, above all as a function of the time elapsed since the appearance of symptoms. Fibrinolysis is recommended if the interval that will inevitably pass between the first contact with medical help and arrival at the interventional cardiology department is thought likely to exceed 45 minutes. After fibrinolysis, the patient must be taken to a centre that has a diagnostic and interventional coronarography room. In other cases, the reperfusion strategy will depend on when the symptoms started. Fibrinolysis is an option if the attack started less than three hours before the patient first received medical help.

<u>On the use of antithrombotics</u>:
If antithrombotic treatment has to be introduced, its main objective is to prevent the extension of an intracoronary thrombus that has already been formed, or to prevent excessive thrombotic reaction encouraged by pre-hospital thrombolysis or primary angioplasty" and thus to prevent arterial re-occlusion.

- The use of clopidogrel (PLAVIX) is recommended in the early stage of acute coronary syndrome with ST segment elevation, either in combination with aspirin or alone if aspirin is contraindicated. The initial recommended oral dose (loading dose) is 300 mg in patients aged under 75 and 75 mg in patients over 75.

- The use of heparins is regarded as beneficial when managing acute coronary syndromes with ST segment elevation:

- In cases of fibrinolysis, enoxaparin is superior to unfractionated heparin (UFH) in patients under 75 with normal renal function (grade B). The recommended low molecular weight heparin (LMWH) is enoxaparin, at an initial IV bolus dose of 30 mg, followed by subcutaneous injections of 1 mg/kg every 12 hours.

N.B.: Since the publication of the results of the CLARITY study validating the use of clopidogrel in combination with aspirin, the benefit of combing aspirin, clopidogrel and enoxaparin or UFH with fibrinolysis remains to be clarified.

- In cases of angioplasty, there is no argument in favour of LMWH rather than UFH, which remains the standard treatment here.
- UFH is the recommended heparin (grade B) for subjects aged over 75 and subjects with renal failure. The dosage of UFH is 60 IU/kg for the initial bolus by the direct IV route (not exceeding 4,000 IU) with a maintenance dosage of 12 IU/kg/h (up to a maximum of 1,000 IU/h).

<u>Choice of the technique for restoration of coronary patency</u>

12 Consensus Conference. Prise en charge de l'infarctus du myocarde à la phase aigue en dehors des services de cardiologie [Management of acute myocardial infarction outside cardiology units]. French emergency medical services with the methodological and financial support of the Haute Autorité de Santé; 6 February 2007

Bearing in mind that:
- In the first three hours after the onset of symptoms, it has been shown (grade B) that primary angioplasty and fibrinolysis are equivalent in terms of reducing mortality after 30 days, provided that this strategy can be implemented within an interval of 90 minutes between the first contact with medical services and expansion of the balloon. Primary angioplasty exposes patients to a lower rate of haemorrhagic cerebrovascular accidents than if they undergo fibrinolysis.
- After three hours have passed, fibrinolysis is less beneficial to the patient than primary angioplasty.
Preference must therefore be given to primary angioplasty, not forgetting that the speed with which continuous reperfusion is started will continue to affect the prognosis. The primary angioplasty must therefore be carried out within 90 minutes at the most; if this is not possible, then fibrinolysis should be performed unless it is contraindicated.
- After 12 hours have passed, it is accepted that urgent reperfusion does not diminish mortality or morbidity associated with ST+ ACS. However, late reperfusion can be considered in some cases: cardiogenic shock or persistent chest pain. Preference should be given to angioplasty.

In view of these elements, the consensus conference jury recommends the following initial strategy:

- if the "door-to-door cardio" interval[13] is greater than 45 minutes, the likelihood that the overall "first contact with medical services to expansion of the balloon" interval will exceed 90 minutes is too great, and this justifies fibrinolysis for any patient whose symptoms started within the past 12 hours, with the same strategy being followed within a three-hour tolerance either way.
- if the "door-to-door cardio" interval is less than 45 minutes and the total interval ("door to cardio balloon")[14] is less than 90 minutes, the strategy depends on when the symptoms started:
    - if this interval is less than three hours, the doctor treating the patient may suggest either fibrinolysis or primary angioplasty depending on assessed written procedures. These procedures applied by cardiologists and emergency physicians must take account of the preference of the informed patient and certain clinical characteristics (in particular, age, previous necrosis location, whether the patient received medical help within one hour, etc.);
    - preference is given to primary angioplasty if the interval from the onset of symptoms is between three and twelve hours.

4.4 Target population for the extension of indication

Definition: the target population is represented by patients experiencing myocardial infarction with ST segment elevation who are eligible for thrombolytic treatment.
It can be estimated on the basis of the following data:

- According to PMSI 2004 data supplied by the firm, this situation affects approximately 56,000 patients per year in France.
- One in three of these is currently being receiving thrombolytic treatment with or without subsequent angiography.

13 The "door-to-door cardio" interval must be estimated by the doctor in charge of the patient at the time on the basis of how long it is likely to take to prepare the patient for the journey, place him or her on a stretcher and transport him or her to the diagnostic and interventional coronarography room (DICR). This information is passed on to the doctor in charge of the case.
14 The "door to cardio balloon" interval must be estimated by the doctor overseeing the case in the light of when an angioplasty table and team will be available, as determined by a prior call to the DICR. It is also estimated on the basis of data from shared records. This interval must be formally agreed by the teams. If it is not possible to estimate the "door to cardio balloon" interval, as DICR availability is uncertain, it must be considered to be over 45 minutes.

On the basis of this data, the target population for LOVENOX in this indication has been estimated as up to 18,000 patients (see Opinion on PLAVIX [15] for the same indication).

4.5. Conclusion

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the "treatment of acute myocardial infarction with ST segment elevation, in combination with thrombolytic treatment, in patients who may or may not be eligible for secondary coronary angioplasty" (extension of indication).

15 See Opinion of the Transparency Committee dated 6 June 2007 for PLAVIX in the indication: "Acute myocardial infarction with ST-segment elevation, in combination with ASA in patients treated medically and eligible for thrombolytic treatment". "The target population is represented by patients experiencing myocardial infarction with ST segment elevation who are eligible for thrombolytic treatment.