HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 May 2010

ANGIOX 250 mg, powder for concentrate for solution for injection or infusion
Box of 2 vials (CIP: 566 203-6)
Box of 10 vials (CIP: 566 193-0)

Applicant: THE MEDICINES COMPANY FRANCE

Bivalirudin
ATC code: B01AE06

List I
Medicinal product reserved for hospital use

Date of first Marketing Authorisation: 20 September 2004 (centralised procedure)

Reason for request: Inclusion on the list of medicines approved for use by hospitals in the extension of indication: "ANGIOX is indicated as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), **including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI**." Marketing Authorisation amendment of 20 November 2009.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Bivalirudin

1.2. Indication

"ANGIOX is indicated as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), **including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI**. (extension of indication)

Note: Old text: "Anticoagulant in patients undergoing percutaneous coronary intervention (PCI)."

ANGIOX is also indicated for the treatment of adult patients with unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) planned for urgent or early intervention. ANGIOX should be administered with aspirin and clopidogrel."

1.3. Dosage

"ANGIOX should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures.

Patients undergoing PCI, including primary PCI

The recommended dose for patients undergoing PCI is an intravenous bolus of 0.75 mg/kg body weight followed immediately by an intravenous infusion at a rate of 1.75 mg/kg body weight/hour for at least the duration of the procedure. The infusion may be continued for up to 4 hours post-PCI as clinically warranted. After cessation of the 1.75 mg/kg /h infusion, a reduced infusion dose of 0.25 mg/kg/h may be continued for 4 – 12 hours as clinically necessary.

Patients should be carefully monitored following primary PCI for signs and symptoms consistent with myocardial ischaemia.

Renal insufficiency

- ANGIOX is contraindicated in patients with severe renal insufficiency (GFR<30 ml/min) and also in dialysis-dependent patients.
- In patients with mild or moderate renal insufficiency, the ACS dose (0.1 mg/kg bolus / 0.25 mg/kg/h infusion) should not be adjusted.
- Patients with moderate renal impairment (GFR 30-59 ml/min) undergoing PCI (whether being treated with bivalirudin for ACS or not) should receive a lower infusion rate of 1.4 mg/kg/h. The bolus dose should not be changed from the posology described under acute coronary syndrome (ACS) or PCI below.

During PCI, monitoring of clotting time such as the ACT is recommended in patients with renal insufficiency. The activated clotting time (ACT) should be checked at 5 minutes post bolus dose. If the ACT is less than 225 seconds, a second bolus dose of 0.3 mg/kg should be administered and the ACT re-checked 5 minutes after the administration of the second bolus dose.

Hepatic impairment

No dose adjustment is needed. Pharmacokinetic studies indicate that hepatic metabolism of bivalirudin is limited, therefore the safety and efficacy of bivalirudin have not been specifically studied in patients with hepatic impairment.

Elderly population

Caution should be exercised in the elderly due to age-related decrease in renal function.

Paediatric patients

There is no relevant indication for use of ANGIOX in children less than 18 years old.

Use with other anticoagulant therapy

- **In STEMI patients undergoing primary PCI, standard pre-hospital adjunctive therapy should include clopidogrel and may include the early administration of UFH** (see section 5.1 of the SPC). Patients can be started on ANGIOX 30 minutes after discontinuation of unfractionated heparin given intravenously, or 8 hours after discontinuation of low molecular weight heparin given subcutaneously.

- ANGIOX can be used in conjunction with a GP IIb/IIIa inhibitor (see section 5.1 of the SPC).

Method of administration: ANGIOX is administered as a weight based regimen consisting of an initial bolus (by rapid IV push) followed by an IV infusion."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

B	Blood and blood forming organs
B01	Antithrombotic agents
B01A	Antithrombotic agents
B01AE	Direct thrombin inhibitors
B01AE06	Bivalirudin

2.2. Medicines in the same therapeutic category

- Other antithrombotic direct thrombin inhibitors: none.

Note: The other direct thrombin inhibitors marketed in France have a different indication: REFLUDAN (lepirudin) has the following indication: "Anticoagulation in adult patients with heparin-induced thrombocytopenia (HIT) type II and thromboembolic disease mandating parenteral antithrombotic therapy"; REVASC (desirudin) has the following indication: "Prevention of deep venous thrombosis in patients undergoing elective hip or knee replacement surgery"; PRADAXA (dagibatran) has the following indication: "Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery."

2.3. Medicines with a similar therapeutic aim[1]

Other anticoagulants indicated in patients with STE ACS (ST segment elevation acute coronary syndrome):

- Unfractionated heparins (UFH): CALCIPARINE and Héparine sodique CHOAY

- Adjuvant therapies to reperfusion (by fibrinolysis or primary coronary angioplasty) to be deployed for STE ACS:
  - Medicines intended to prevent the spread of a coronary thrombus that has already formed or an excessive thrombotic reaction promoted by prehospital thrombolysis or coronary angioplasty: aspirin + clopidogrel (according to expert opinion).
  - *"Glycoprotein IIb/IIIa inhibitors[2] do not have a place either on their own, because of lack of efficacy, or in combination with fibrinolysis, because of the increased risk of haemorrhage (grade B). Their use in the acute phase of STE ACS should only be considered prior to primary angioplasty. Their risk/benefit ratio in the prehospital phase, in combination with clopidogrel, is not known. The substance recommended is abciximab at a dosage of 250 µg/kg i.v. followed by a continuous intravenous infusion of 0.125 µg/kg/min up to a maximum of 10 µg/min".*

[1] 1 Enoxaparin and fondaparinux are thus not indicated for primary angioplasty in the MA.

[2] 2 Consensus Conference. Management of acute myocardial infarction outside cardiology units. SAMU de France [French emergency medical service], with the methodological partnership and financial support of the Haute Autorité de santé; 6 February 2007

3. ANALYSIS OF AVAILABLE DATA

Summary of the conclusions of the previous assessments

Bivalirudin has been granted MA as an “anticoagulant in patients undergoing percutaneous coronary intervention (PCI)” since September 2004. This indication is based chiefly on the results of the randomised comparative REPLACE-2 study (patients with stable angina). The REPLACE-2 study showed bivalirudin therapy to be non-inferior to the combination of heparin and a GP IIb/IIIa inhibitor in regard to "death, myocardial infarction, urgent fresh revascularisation because of ischaemia at 30 days" and “major haemorrhages in hospital”. An advantage in favour of bivalirudin was found in REPLACE-2 in regard to the reduction of the risk of major haemorrhages (2.4% versus 4.1%, $p < 0.001$) but the Committee was of the view that this result was hard to carry over into French practice as French practitioners used introducers with a smaller diameter, made more frequent use of radial access, and prescribed unfractionated heparin at low doses in comparison with the treatment protocol evaluated in the REPLACE-2 study[3]. The Committee had concluded that ANGIOX brought a considerable improvement in actual benefit (level II) as an anticoagulant in patients with a history of HIT (heparin-induced thrombocytopenia) undergoing percutaneous coronary intervention as it is able to meet a real therapeutic need, even though the available data in this regard are from only a very limited number of patients. In patients without a history of HIT, it was of the view that ANGIOX did not bring an improvement in actual benefit in comparison with combination therapy consisting of a GP IIb/IIIa inhibitor and unfractionated heparin in patients pretreated with aspirin and clopidogrel.
In the context of the extension of the indication to “Treatment of patients with acute coronary syndrome (ACS; unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI)) planned for urgent or early intervention. ANGIOX should be administered with aspirin and clopidogrel”, the Committee concluded (opinion of 29 April 2009) that ANGIOX did not bring an improvement in actual benefit (IAB V) in the strategy for the management of non-ST segment elevation acute coronary syndromes. The randomised, open, multicentre ACUITY study carried out in 13,819 patients with UA/NSTEMI showed that bivalirudin in combination with a GP IIb/IIIa inhibitor was non-inferior to the combination UFH+GP IIb/IIIa inhibitor on a composite ischaemic endpoint at 30 days (death, MI, or unplanned revascularisation because of ischaemia: 7.7% versus 7.3%) and major haemorrhages (5.3% versus 5.7%).

On the basis of **new data (HORIZONS study)**, an extension of indication has been obtained for bivalirudin as an anticoagulant in patients with ST-segment elevation myocardial infarction (STE ACS) undergoing primary percutaneous coronary intervention (PCI).

3.1. Efficacy data from the HORIZONS study

The aim of the HORIZONS study was to establish the tolerance of use and the efficacy of bivalirudin in patients with STEMI undergoing a primary PCI with placement of a stent, either a stent that slowly releases paclitaxel (TAXUS™-eluting stent) or a similar, uncoated stent (Express2™ bare metal stent). The patients were randomised according to the anticoagulant therapy received (pharmacological randomisation) and to the type of stent used (second randomisation).

This was an open prospective randomised multicentre comparative study with two arms: 11 countries involved, 57% of patients included in Europe (no patients recruited in France). Two randomisations were carried out, one prior to angiography for the pharmacological randomisation, the other after angiography for the patients eligible for PCI for randomisation according to stent type. This was a non-inferiority study, with possible performance of a superiority test.

[3] 3 Cf. Opinion on ANGIOX given on 13 April 2005.

Endpoints (day 30)

For the comparison of the anticoagulant treatments, the aims were to demonstrate, at 30 days (day 30), that bivalirudin in comparison with the combination UFH + GP IIb/IIIa inhibitor would make it possible to obtain:
a- non-inferior rates of the composite endpoint "major adverse ischemic/cardiac events" (MACE) and of its individual components (death form any cause, reinfarction, CVA, target-vessel revascularisation because of ischaemia);

The events of the MACE endpoint were defined as follows:
- death from any cause (cardiac and non-cardiac). A cardiac death was defined as one due to an acute MI, cardiac perforation or pericardial tamponade, arrhythmia or conduction abnormality, a CVA in the 30 days after the procedure or suspected to be connected with the procedure, a procedural complication, or any death for which a cardiac cause could not be ruled out.
- reinfarction: re-elevation of troponin or CK-MB or CPK (>3 x upper normal limit) in the 24 h following PCI in patients whose initial level was normal; but also: CK-MB or CPK level (≥10 x upper normal limit) in the 24 h following ACB and which was at least 50% above the most recent pre-ACB levels, in patients who had had an ACB,
- CVA or revascularisation of the target vessel because of ischaemia: all repeat PCIs of the target vessel or an ACB of the target vessel because of ischaemia.

b- non-inferior or decreased rates of major haemorrhagic complications not related to an aortocoronary bypass (ACB);

c- non-inferior or decreased rates of the composite endpoint "MACE and major haemorrhages not related to an ACB" (net adverse clinical events [NACE]).

The duration of the follow-up period was 30 days and one year. The Marketing Authorisation registration dossier was based on the 30-day (day-30) data.

The primary endpoint was a composite endpoint (NACE) combining MACE and major haemorrhage (not related to an ACB) at 30 days: a case rate of 3332 patients gave a power of 80% for demonstrating non-inferiority, assuming rates of 12% in the two groups and a non-inferiority margin of $\delta = 3.2\%$. For the MACE endpoint, the prespecified non-inferiority margin (2.2%) was calculated from the non-inferiority margin of 27% calculated for the primary composite endpoint (corresponding to a relative difference of 44% and considering an upper limit of the 95% CI for a putative placebo of 51%). These margins were prespecified in the protocol.

The NACE and "major haemorrhage" endpoints were analysed in a hierarchical manner for non-inferiority then superiority in the same population. The order of the analyses was as follows: 1) test of non-inferiority for NACE, 2) test of non-inferiority for major haemorrhages, 3) test of superiority for major haemorrhages, 4) test of superiority for NACE. The analysis of the primary endpoint, NACE, was carried out on the FAS (modified ITT population), PP, and PCI populations, using the percentage of events.

Treatments received by the patients:

- medicine assessed: same dose of bivalirudin as that used in the REPLACE-2 study: bolus of 0.75 mg/kg i.v. followed by an infusion of 1.75 mg/kg/h as soon as possible (rate adjusted according to status of renal function in Europe) and at least until the end of the PCI. The bivalirudin was to be administered before the PCI was performed, irrespective of the administration times of previous boluses of UFH.

Note: Patients could also be given a GP IIb/IIIa inhibitor during the PCI in the event of a giant thrombus adjacent to the stent or in the coronary vessel or in the event of a sustained absence of reflow.

- reference treatment: UFH at a dose of 60 U/kg as an intravenous bolus administered as soon as possible and then according to ACT results (target ≥ 200 sec). The GPIIb/IIIa inhibitor, abciximab or eptifibatide, was started in the emergency department or, failing that, 3 min before the first dilation of the balloon (bolus, then intravenous infusion according to the dosage employed locally) and halted 12 h (abciximab) to 18 h (eptifibatide) after the end of the PCI.

- Before transfer to the cardiac catheterisation laboratory, the patients received two other platelet aggregation inhibitors: aspirin (chewable: 300 to 325 mg) and clopidogrel (300 or 600 mg as a loading dose) or, failing that, ticlopidine.
A beta blocker (propranolol, atenolol, metoprolol i.v.), trinitrine i.v., an analgesic, and low-flow nasal oxygen were also administered according to local practice.

After leaving the cardiac catheterisation laboratory, the patients received:
- aspirin: 300 to 325 mg/day whilst in hospital then 75 to 81 mg/day
- clopidogrel: 75 mg/day for at least 6 months
- a beta blocker, an ACE inhibitor, and a statin if necessary.

The randomisation was stratified according to whether or not patients were pretreated with an UFH, according to the loading dose of clopidogrel (300 or 600 mg or ticlopidine 500 mg), according to the GP IIb/IIIa inhibitor administered (abciximab or eptifibatide), and according to the geographical location of the study centre (United States of America or elsewhere).

Characteristics of the evaluated population

Between 25 March 2005 and 7 May 2007, 3602 STEMI patients scheduled for a PCI were randomised to the bivalirudin group (1800 patients) or the unfractionated heparin + GP IIb/IIIa inhibitor group (1802 patients).

Primary PCI was performed in 92.9% of the patients. Follow-up on day 30 was undertaken in 99.3% of the patients.

Patients receiving 600 mg clopidogrel as a loading dose were twice as numerous (approximately 64%) as those receiving a 300 mg loading dose.

It should be noted that nearly 66% of the patients were pretreated with unfractionated heparin (cf. stratified analysis in this regard) and that PCI by the femoral route was performed in the majority of the patients.
Nearly 16% of the included population had renal impairment (creatinine clearance < 60 ml/min).
The groups were balanced in terms of concomitant treatments.

Efficacy

For the primary endpoint, the non-inferiority hypotheses are confirmed in the PP population and the superiority tests are significant in all the populations, according to the hierarchical analysis plan. However, the result appears to be influenced by whether or not the patients received UFH therapy during the procedure according to a subgroup analysis (specified by the protocol).

The results at 30 days for the intent-to-treat (ITT) population are set out in the table below.

Table of results of the HORIZONS study at 30 days (intent-to-treat population)

Endpoint	**Bivalirudin (%)**	**Unfractionated heparin + GP IIb/IIIa inhibitor (%)**	**Absolute benefit [95% CI]** **Relative risk [95% CI]**	**p value (superiority test)**
	1800 patients	1802 patients		
Primary endpoint at 30 days				
NACE	**168 (9.3)**	**228 (12.7)**	**- 3.3** **[- 5.4 ; - 1.2]** **0.74** **[0.61 ; 0.89]**	**0.0015**
Composite endpoint at 30 days				
MACE	98 (5.4)	100 (5.5)	- 0.1 [- 1.6 ; + 1.4] Non-inferiority was defined as a 95% CI upper limit < 2.2%. 0.98 [0.75 ; 1.29]	NS
Components of the MACE composite endpoint				
Deaths from any cause	37 (2.1)	56 (3.1)	- 1.1 [- 2.1 ; 0.0] 0.66 [0.44 ; 1.0]	0.0465
- Cardiac deaths	32 (1.8)	52 (2.9)	-1.1 [- 2.1 ; - 0.1] 0.62 [0.40 ; 0.95]	0.0276
- Non-cardiac deaths	5 (0.3)	4 (0.2)	0.1 [- 0.3 ; + 0.4] 1.25 [0.34 ; 4.65]	NS
Reinfarction	34 (1.9)	32 (1.8)	0.1 [- 0.8 ; + 1.0] 1.06 [0.66 ; 1.72]	NS
Revascularisation of the ischaemic target vessel	45 (2.5)	35 (1.9)	0.6 [- 0.5 ; + 1.6] 1.29 [0.83 ; 1.99]	NS
Cerebrovascular accident	14 (0.8)	12 (0.7)	0.1 [- 0.5 ; + 0.7] 1.17 [0.54 ; 2.52]	NS
Tolerability results				
Major haemorrhage not related to bypass (ACB)	92 (5.1)	159 (8.8)	- 3.7 [- 5.4 ; - 2.0] 0.58 [0.45 ; 0.74]	<0.0001
Major haemorrhage not related to bypass (ACB), excluding haematoma > 5 cm	87 (4.8)	149 (8.3)	- 3.4 [- 5.1 ; - 1.8] 0.58 [0.45 ; 0.76]	0.0001

If account is taken of administration of an UFH during the procedure (2253 patients, 1182 of them in the bivalirudin group, 65%), superiority is established only in the group of patients that received the UFH during the procedure; the degree of significance of the interaction test is 0.0628.

NACE at day 30

Group	Bivalirudin (%)	UFH + GP IIb/IIIa inhibitor **(%)**	Relative risk	p value in interaction test
UFH, yes (n = 2253)	8.6	13.2	0.65 [0.52, 0.82]	NS
UFH, no (n = 1042)	10.7	11.0	0.97 [0.68, 1.39]	

For the haemorrhages endpoint, no interaction is observed.

3.2 Adverse effects

Data from the HORIZONS study: according to the SPC, adverse effects were more common in the heparin + GP IIb/IIIa group than in the bivalirudin group. A total of 55.1% of the patients who received bivalirudin had at least one adverse event and 8.7% had an adverse effect connected with the product. The most commonly observed adverse effects were haematomas of less than 5 cm at the puncture site. The rate of stent thromboses and the incidence of minor haemorrhages at the arterial puncture site and haemorrhages according to TIMI (Thrombolysis In Myocardial Infarction) and GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) criteria were secondary endpoints (day 30).

Haemorrhagic risk

- Major and minor bleeding were common (≥ 1/100 and <1/10). The incidence of major bleeding is presented in the table of results above. Major haemorrhage occurred most commonly at the puncture site.

The incidence of major and minor bleeding was lower in patients treated with bivalirudin than in those treated with the unfractionated heparin + GP IIb/IIIa inhibitor combination.

- There is no known antidote to bivalirudin; its effect wears off quickly (half-life of 35 to 40 min).

Thrombocytopenia: thrombocytopenia was reported in 26 patients (1.6%) treated with bivalirudin and 67 patients (3.9%) treated with heparin plus a GP IIb/IIIa inhibitor. In the bivalirudin group, all these patients received concomitant treatment with aspirin, all but one received clopidogrel, and 15 patients received a GP IIb/IIIa inhibitor.

Early stent thromboses (or acute stent thromboses)

- In STE ACS patients treated with primary PCI, early coronary stent thromboses were observed under bivalirudin.
In the first 24 h, their incidence was 1.5% in patients given bivalirudin and 0.3% in patients given UFH + GP IIb/IIIa inhibitor (p = 0.0002). Between 24 h and 30 days (subacute stent thromboses), the incidences were 1.2% with bivalirudin and 1.9% with UFH + GP IIb/IIIa inhibitor (p = 0.1553). At 30 days (p = 0.3257) and at 1 year (p = 0.7754), there was no difference between the two study arms; three patients who received bivalirudin and the UFH + GP IIb/IIIa inhibitor combination died after a stent thrombosis.

Monitoring for at least 24 h in a clinical department able to treat ischaemic complications is recommended.
- ANGIOX must not be used during gamma brachytherapy procedures on account of the risk of a thrombus.

Hypersensitivity reactions: Reports of allergic-type reactions to bivalirudin are uncommon in the clinical studies, with anaphylactic reactions being reported in ≤ 1/10,000.

Limitations of the study

- For the evaluation of clinical efficacy, the calculation of the number of subjects was based on a composite endpoint comprising death from any cause, MI, and revascularisations (subjective endpoint). The clinical relevance of these clinical events differs and the study was an open one.

- There were fewer cardiac deaths in the bivalirudin group. Given that the deaths could have been due to a CVA or an MI and that these events occurred in the same proportion between the two groups, the question of the cause of the cardiac deaths arises. A reduction of deaths from any cause and of cardiac deaths, which are secondary endpoints, has not been established.
- A reduction of the risk of major and minor haemorrhage by bivalirudin is established in the HORIZONS study. It should, however, be noted that there are several data that raise the question of whether the results of the HORIZONS study can be carried over into French practice, principally because there is no consensus on the benefit of combination with aspirin, clopidogrel, and UFH and a GP IIb/IIIa inhibitor[4].
- Radial arterial access was only used in 5.9% (214/3597) of the patients in the study (and in 9.7% (200/2055) of the patients included in the EU). According to the company, this rate, which reflects current practice in the European centres that took part in the study, is much lower than the estimated rate of radial access in France, which is 50% [Monsegu, 2007]. Radial access is recommended because it enables the risk of haemorrhage to be reduced.
- Nearly 65% of the patients in the bivalirudin group also received a UFH in the course of their care. The clinical benefit (NACE endpoint) is established only in patients who received a UFH in addition to bivalirudin. Pretreatment with UFH is carried out in 2/3 of the French patients.

3.3 Conclusion

In the HORIZONS study, bivalirudin was compared “on an open basis” with a combination of UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide):

Bivalirudin, in comparison with the combination of UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide), was associated with a reduction of events of the NACE composite endpoint on day 30 (primary endpoint) in all the populations analysed (9.3% versus 12.7% in the ITT population; p = 0.0015).

The analysis of the components of this composite endpoint breaks down into an analysis of efficacy (with a MACE composite endpoint) and an analysis of tolerance (haemorrhage):

- in terms of efficacy, bivalirudin, in comparison with the UFH + GP IIb/IIIa inhibitor therapy, is associated with non-inferiority on the MACE composite endpoint (5.4% versus 5.5% on ITT basis) but superiority is not demonstrated (p = 0.8901): the reduction of deaths from any cause (2.1% versus 3.1%) and of cardiac deaths (1.8% versus 2.9%) is thus of descriptive value only.
- In terms of tolerability (day 30): bivalirudin, in comparison with the UFH + GP IIb/IIIa inhibitor, is associated with a statistically significant reduction in the rate of major haemorrhage not related to an ACB (5.1% versus 8.8%; p < 0.0001), remaining significant when only haemorrhage outside the site of access (mostly femoral) is considered (2.6% versus 4.6%; p = 0.0011). Bivalirudin was associated with an increase in the global rate of acute stent thromboses (1.4% versus 0.2%) in the first 24 h, with an incidence of 1.5% in patients given bivalirudin and 0.3% in patients given UFH + GP IIb/IIIa inhibitor (p = 0.0002). Between 24 h and 30 days (subacute stent thromboses), the incidences were

[4] 4 UFH is considered the standard anticoagulant in STEMI patients reperfused by primary PCI [HAS, 2006]; in the French prospective FAST-MI registry in 2005 70% of these patients received a GP IIb/IIIa inhibitor [Danchin, 2008].

1.2% with bivalirudin and 1.9% with UFH + GP IIb/IIIa inhibitor (p = 0.1553). At 30 days (p = 0.3257) and at 1 year (p = 0.7754), there was no difference between the two arms of the study.

To sum up, the HORIZONS study is a non-inferiority trial involving a test of superiority on a composite primary endpoint comprising efficacy (a composite endpoint) and risk (major haemorrhage). Superiority on the NACE composite endpoint is established, with better tolerability, even when only haemorrhage outside the access site is considered. On the other hand, bivalirudin was non-inferior to the combination of UFH + GP IIb/IIIa inhibitor on the composite efficacy endpoint (MACE) but was not more effective. Thus the “benefit” (with substantial inaccuracy) in terms of reduction of mortality is of descriptive value only (open trial also).

Whether these results can be carried over into practice is a hard question to answer, as 65% of the subjects randomized to the bivalirudin group were also pretreated with UNF. Furthermore, there is no consensus regarding combination of a GP IIb/IIIa inhibitor with UFH + aspirin + clopidogrel. The thromboaspiration undertaken in certain patients also needs to be taken into account.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit in the extension of the indication

All acute coronary syndromes call for emergency treatment by a specialist team. Myocardial infarction necessitating reperfusion as soon as possible to remove the obstruction of the coronary artery can be identified by means of an electrocardiogram (ECG). These infarctus, known as STE ACS, are associated with total occlusion of a coronary artery. Patients must therefore undergo coronary reperfusion as a matter of extreme urgency in order to reduce the risk of death or recurrence of an MI in particular. Coronary reperfusion is obtained through angioplasty (interventional cardiology or percutaneous coronary intervention - PCI) or through fibrinolysis (thrombolysis by intravenous route). These serious clinical situations are life-threatening.
ANGIOX is henceforth indicated in the acute phase of STE ACS MI as an anticoagulant in cases of initial reperfusion by means of angioplasty (primary PCI). It is a first-line medicine.

Public health benefit

The public health burden of ischaemic heart disease is high. That of ST elevation myocardial infarction (STEMI) requiring emergency or early intervention (PCI*) is considered small due to the more limited number of patients affected.
Improving the secondary prevention of these clinical situations continues to be a public-health need.
On the basis of the data from the HORIZONS study versus unfractionated heparin (UFH) + GPI [superiority of ANGIOX on a composite efficacy-haemorrhagic risk endpoint (NACE) and on major haemorrhage, non-inferiority only in terms of ischaemic efficacy (MACE)],
it is not expected that the proprietary medicinal product ANGIOX will have an additional impact on morbidity/mortality in comparison with existing therapies.
Furthermore, there is no guarantee that the results of this study can be carried over into actual practice in France, as it is an international study (global data) that does not necessarily reflect French practice: the organisation of emergency care, greater use of radial access – with less risk of a haemorrhage, more infrequent use of GPI therapy, the percentage of patients pretreated with UFH (high in the trial: 65%).
Aside from cases where there is a history of heparin-induced thrombocytopenia (less than 1% of angioplasty patients), it is not thought that the proprietary product ANGIOX can make an additional contribution towards meeting the identified public-health need.
Consequently, in the current state of knowledge and in view of the treatments available at present, it is not expected that ANGIOX will benefit public health in this indication.

The efficacy/undesirable effects ratio of bivalirudin as an alternative to a therapy combining a Gp IIb/IIIa inhibitor with UFH and in combination with aspirin and clopidogrel is high. There is an alternative anticoagulant therapy: UFH (+/- a Gp IIb/IIIa inhibitor).

The actual benefit of ANGIOX in this extension of the indication is substantial.

4.2. Improvement in actual benefit (IAB) in the extension of the indication (STE ACS with reperfusion by primary angioplasty)

ANGIOX does not provide any improvement in actual benefit (IAB level V) in comparison with the usual therapeutic management when indicated as an anticoagulant therapy in STEMI patients reperfused with primary angioplasty, given the heterogeneous nature of practice and prehospital prescription practice in France. Bivalirudin (ANGIOX) is nevertheless considered a useful additional therapeutic tool.

4.3. Therapeutic use of ANGIOX in ST segment elevation myocardial infarction

According to a recent French consensus conference[5], early restoration of coronary patency in the acute phase of STE ACS MI helps to improve 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. Primary angioplasty must be considered if it can be performed within 90 to 120 minutes of first medical contact and by an experienced team. It is recommended in particular in the presence of signs of poor haemodynamic tolerance, contraindications to fibrinolysis, presentation beyond the 3rd hour after the onset of symptoms, or doubt over the diagnosis.

Mechanical reperfusion is associated with the use of adjuvant treatment with antithrombotics, anticoagulant(s), and platelet aggregation inhibitor(s).

When antithrombotic treatment is required, its main aim is to prevent the spread of an intracoronary thrombus that has already formed or prevent an excessive thrombotic reaction promoted by prehospital thrombolysis or primary angioplasty and thus prevent reocclusion of the artery.

- The use of heparin is considered beneficial in the management of acute coronary syndromes with ST segment elevation:

  - in the case of angioplasty, there are no arguments in favour of LMWH over UFH, which remains, in this situation, the standard therapy.
  - as regards fibrinolysis, enoxaparin is superior to unfractionated heparin (UFH) in patients under 75 years of age with normal renal function (grade B). The recommended low molecular weight heparin (LMWH) is enoxaparin, administered as an initial intravenous bolus of 30 mg, followed by subcutaneous injections of 1 mg/kg every 12 h.
  - In subjects over 75 years of age and subjects with renal insufficiency, UFH is the recommended heparin (grade B). The dosage of UFH is 60 IU/kg for the initial direct intravenous bolus (without exceeding 4000 IU) with a maintenance dosage of 12 IU/kg/h (maximum 1000 IU/h).

- The use of clopidogrel (PLAVIX) is recommended in the early phase of ST segment elevation acute coronary syndromes, either in combination with aspirin or alone if aspirin is contraindicated.

A GP IIb/IIIA is only recommended in cases of coronary reperfusion by primary PCI. It is preferable to use abciximab.

Place of ANGIOX in coronary reperfusion by angioplasty

In patients who do not have renal impairment and who are eligible for the use of the combination UFH + GP IIb/IIIa inhibitor, bivalirudin is a useful alternative, particularly in patients at high risk of haemorrhage.

Choice of the technique for restoration of coronary patency

Given that:

- in the first 3 hours after the start of the symptoms, it has been demonstrated (grade B) that primary angioplasty and fibrinolysis are evenly matched in terms of reduction of mortality at 30 days, provided that this strategy can be deployed with a “first medical contact to balloon expansion” time of less than 90 min. The rate of haemorrhagic cerebrovascular accidents is lower with primary angioplasty than with fibrinolysis.
- beyond the 3rd hour, the benefit of fibrinolysis fades in favour of primary angioplasty.

Primary angioplasty should therefore be preferred, whilst remembering that the speed of deployment of a reperfusion technique continues to influence the prognosis. Primary

[5] Consensus Conference. Management of acute myocardial infarction outside cardiology units. SAMU de France [French emergency medical service] with the methodological partnership and financial support of the Haute Autorité de santé ; 6 February 2007

angioplasty must thus be carried out with 90 min at most; if angioplasty cannot be performed within 90 min, fibrinolysis should be undertaken provided that it is not contraindicated.
- Beyond the 12th hour, it is accepted that emergency reperfusion reduces neither mortality nor morbidity from STE ACS. Certain situations may lead to late reperfusion being considered, however cardiogenic shock or persistence of chest pain. Angioplasty is to be preferred.
PCI is thus the option of choice if it can be performed within 90 minutes of first medical contact and by an experienced team.

Note: The European Society of Cardiology (ESC) has updated its recommendations on the management of patients with STE ACS[6] who are treated with primary PCI. The results of the HORIZONS study were taken into account. For antithrombin treatment, it recommends that heparin (grade IC), bivalirudin (grade IIaB), or fondaparinux (grade IIIB) be used. The following are also recommended: aspirin (grade IB), clopidogrel (grade IC with a loading dose of at least 300 mg and preferably 600 mg), a GPIIb/IIIa inhibitor - using abciximab (grade IIaA) in preference to tirofiban (grade IIbC) and to eptifibatide (grade IIbC).

4.4. Target population in the extension of the indication (STEMI)

The target population for ANGIOX is patients with a myocardial infarction with ST segment elevation, managed with percutaneous coronary intervention (primary PCI).
Estimation of the target population for ANGIOX (Project leader: Marion PINET)
On the basis of the FAST-MI registry (French registry of ST or non-ST segment elevation acute coronary syndromes) it is possible to estimate the incidence of STEMI in France[7]. This registry included 1617 patients hospitalised with a diagnosis of STEMI during October 2005 in 233 cardiological intensive care units (CICUs), which corresponds to 60% of the total in French CICUs. According to these data, the total annual number of patients admitted to CICUs with a diagnosis of STEMI would be approximately 32,000 (1617 x 12 x 100/60).
According to PMSI MCO [medical/surgical/obstetric] data, in 2008 in France, there were 69,959 hospital stays in which the principal diagnosis was acute myocardial infarction[8].
Thus the number of patients hospitalised for STEMI in France is estimated to be between 32,000 and 70,000 per year. According to FAST-MI registry data, 34.8%[1] of patients with STEMI were treated with primary PCI and 70%[9] of these received a GPIIB/IIIA inhibitor in combination with the anticoagulant therapy.
The target population of ANGIOX in “patients with ST-segment elevation myocardial infarction (STEMI) undergoing a primary percutaneous coronary intervention (PCI)” is estimated to be between **7800 and 17,000 patients per year**.

4.5. Conclusion

The Transparency Committee recommends inclusion of ANGIOX on the list of medicines approved for use by hospitals and various public services, “as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.”

[6] Van de Werf F et al. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology Management of acute myocardial infarction in patients presenting with ST segment elevation. European Heart Journal 2008;29:2909-2945.
[7] Cambou JP, Simon T, Mulak G, Bataille V, Danchin N. The French registry of Acute ST elevation or non-ST-elevation Myocardial Infarction (FAST-MI): study design and baseline characteristics. Arch Mal Coeur Vaiss. 2007;100:524 –534.
[8] 8 number of stays in MCO [medical/surgical/obstetric] short-term care involving an ICD-10 code of acute transmural infarct as the prinicipal diagnosis (ICD-10 codes I21.x) (source: www.atih.sante.fr)
[9] Danchin N, Coste P, Ferrières J, et al for FAST-MI Investigators. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data from the French registry on acute ST-elevation myocardial infarction (FAST-MI). Circulation 2008;118:268-76.