

Guideline adherence for antithrombotic therapy in acute coronary syndrome: an overview in Dutch hospitals

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Objective. To assess current Dutch antithrombotic treatment strategies for acute coronary syndrome (ACS) in light of the current European Society of Cardiology (ESC) guidelines. **Methods.** For every Dutch hospital with a coronary care unit (CCU) (n = 93) a single cardiologist was interviewed concerning heparin, thienopyridine and GP IIb/IIIa inhibitor (GPI) treatment. In each hospital, we randomly approached one cardiologist assuming equal policy among physicians employed at the same hospital. **Results.** The response rate was 90%. In 59% of hospitals, treatment of ST-elevation myocardial infarction (STEMI) occurred according to the 2008 ESC STEMI guideline, with unfractionated heparin. In contrast, although not recommended, low-molecular-weight heparin (LMWH) was used in 39% (enoxaparin 19%, dalteparin 12%, nadroparin 8%). In non-STEMI, low-molecular-weight-heparins (LMWHs) were used in 97% of all hospitals. Fondaparinux, agent of choice in a noninvasive strategy for the treatment of non-STEMI, was applied in only 2% of hospitals. Although recommended by the ESC, dose adjustment of LMWH therapy for patients with renal failure is not applied in 71% of hospitals. Likewise, LMWH dose adjustment is not applied for patients aged over 75 years in 92% of hospitals. **Conclusion.** To a great extent treatment of ACS in the Netherlands occurs according to

ESC guidelines. Additional benefit may be achieved by routine dose adjustment of LMWH for patients with renal insufficiency and aged >75 years, since these patients are at high risk of bleeding complications secondary to antithrombotic treatment. Periodical evaluation of real-life practice may improve guideline adherence and potentially improve clinical outcome. (*Neth Heart J* 2010;18:291-9.)

Keywords: Coronary Disease; Fibrinolytic Agents; Practice Guidelines; Thrombolytic Therapy

Plaque rupture or erosion with superimposed coronary thrombus formation is the instigating event in acute coronary syndrome (ACS). Total occlusion of the coronary artery is associated with ST-elevation myocardial infarction (STEMI), whereas partial or intermittent coronary occlusion is associated with unstable angina and non-ST-elevation myocardial infarction (UA/NSTEMI).^{1,2} Antithrombotic agents, divided in anticoagulant and antiplatelet agents, mitigate coronary thrombosis, prevent recurrent ischaemia and prevent thromboembolic complications related to percutaneous coronary intervention (PCI). Different antithrombotic agents have distinct efficacy and safety profiles. To aid physicians in making a decision in the selection of antithrombotic agents, guidelines for the management of ACS have been drawn up by expert committees of the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology (AHA/ACC). To investigate if these guidelines are actually applied in clinical medicine, we conducted a survey of antithrombotic treatment in current Dutch clinical practice for ACS.

Methods

Setting

There are 142 hospitals in the Netherlands collaborating in 93 healthcare organisations, each with a single coronary care unit (CCU). These 93 health-

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care organisations with a CCU were approached in the period from April to November 2008. In each hospital, we approached one cardiologist assuming equal policy among physicians employed at the same hospital. To reduce selection bias, we randomly approached a cardiologist per hospital.

Data collection

Data were acquired by approaching cardiologists by means of e-mail. The questionnaire that was sent is depicted in the appendix. Questions 1 to 6 were sent to all hospitals. Since GP IIb/IIIa inhibitors (GPI) are mainly used as part of reperfusion therapy we interviewed cardiologists employed at interventional hospitals regarding GPI use in STEMI and UA/NSTEMI (questions 7 to 12). In addition we interviewed all Dutch ambulance services regarding prehospital in-ambulance antithrombotic therapy (questions 13 to 16). When no response was received, cardiologists were interviewed by means of a telephone call. Either the physician on call was interviewed or a secretary was asked for an available physician. Interviews were conducted by a single research fellow. To standardise the interview process the questions were read from a printed questionnaire. This questionnaire was identical to the questionnaire sent by e-mail.

Assumptions

Antithrombotic therapy in ACS depends on the choice of reperfusion strategy. The questionnaire was developed on the basis of three assumptions regarding reperfusion strategies. These three assumptions reflect current clinical practice in the Netherlands:

1. We assumed primary PCI to be the standard reperfusion strategy. In the Netherlands patients with possible STEMI are triaged on site by ambulance personnel. If STEMI is confirmed or suspected and if symptoms are existent for less than 12 hours patients are transported to the nearest hospital with interventional facilities per protocol. We tested this assumption by interviewing all Dutch ambulance services (n=23).
2. In the unlikely event of STEMI patients presenting at emergency departments of regional non-interventional hospitals, without making use of ambulance services, they are transferred from these local non-interventional hospitals to interventional hospitals after triage. They are treated with PCI after which they return to the referring local hospital.
3. In UA/NSTEMI, patients are initially stratified according to risk, and subsequently qualify for early diagnostic work-up or receive medical

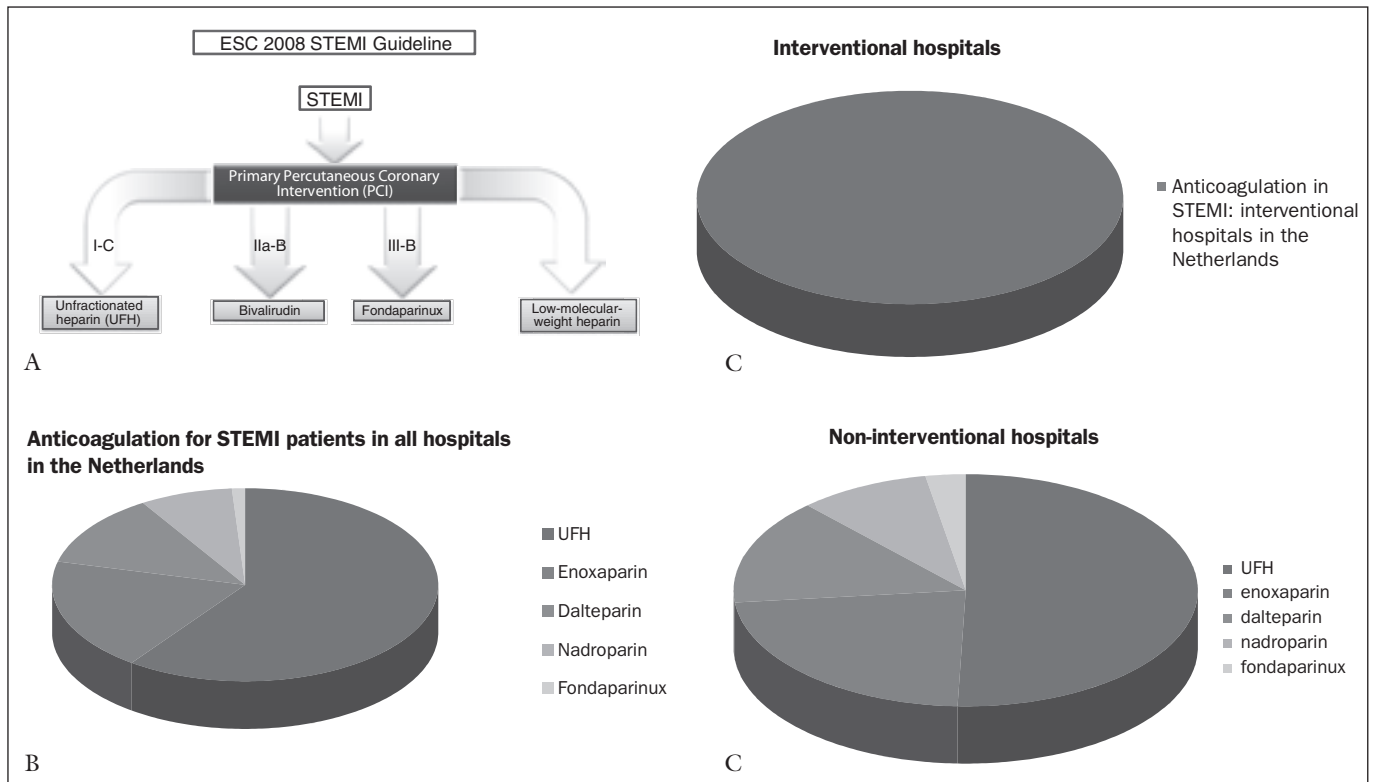


Figure 1. Anticoagulation in ST-elevation myocardial infarction. A) Flowchart displaying ESC guideline recommendations with level of evidence.⁴ * For patients with heparin-induced thrombocytopenia there is a Class I, Level of Evidence B recommendation. B) Actual clinical practice in all hospitals in the Netherlands. C) Actual clinical practice in interventional and non-interventional hospitals in the Netherlands.

treatment only. After early diagnostic work-up patients are treated by elective PCI, coronary artery bypass grafting (CABG) or conservative medical treatment. The choice of antithrombotic agent in NSTEMI-ACS is dependent on whether or not an invasive strategy is applied. To simplify the interview process we made no distinction for different treatment strategies.

Data analysis

Results were compared with the 2003 ESC STEMI guideline³ and the 2007 ESC UA/NSTEMI guideline.² Because the 2008 ESC STEMI guideline¹ was published during the study period we also included this guideline in our analysis. The results were divided for hospitals with facilities for performing PCI and for hospitals without these facilities. A total of 19 hospitals have facilities for performing PCI. Seventy-four hospitals with a CCU are not equipped with facilities for performing PCI. Data are given as percentages of interviewed hospitals.

Results

We had a total response rate of 90%. Figures 1 to 4 display current Dutch practice combined with flowcharts of ESC recommended therapy. For each of the antithrombotic agents a recommendation with level of evidence is depicted depending on treatment strategy.

STEMI

Thrombolysis in the ambulance is not part of treatment in the Netherlands. All interviewed ambulance services (21/21) treat STEMI patients with 5000 IU unfractionated heparin intravenously. Of interviewed ambulance services, 95% (20/21) treat STEMI patients with 500 mg acetylsalicylic acid intravenously. A total of 90% (19/21) of interviewed ambulance services apply a loading dose of 600 mg for STEMI patients in the ambulance. The remaining 10% (2/21) apply a 300 mg loading dose of clopidogrel. Anticoagulant treatment of STEMI patients in the Netherlands is summarised in figure 1.

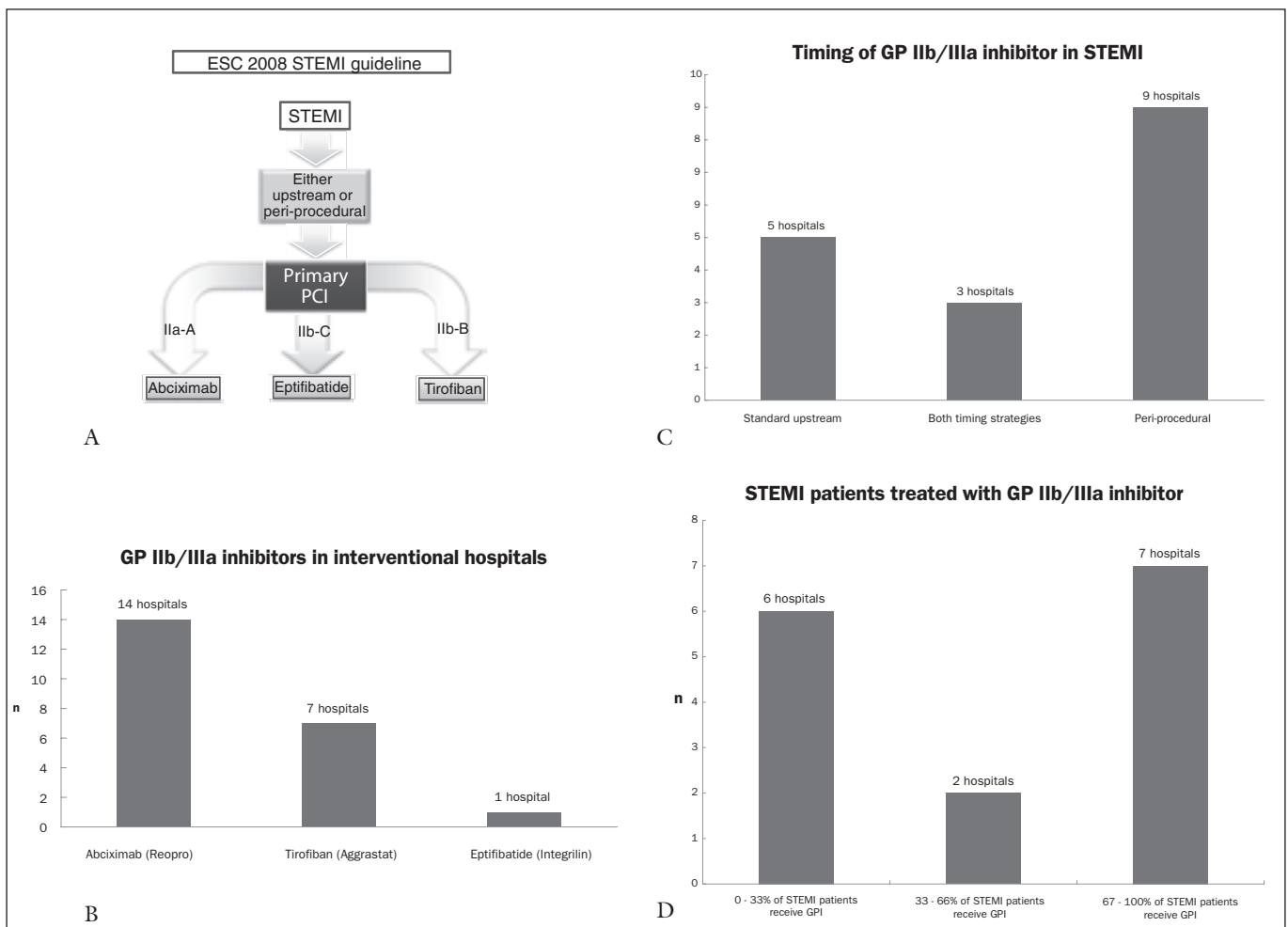


Figure 2. GP IIb/IIIa inhibitor therapy for STEMI patients. A) Flowchart displaying ESC guideline recommendations with level of evidence.⁴ B) Actual clinical practice in interventional hospitals in the Netherlands. C) Timing strategies in interventional hospitals in the Netherlands. D) Estimated percentages of STEMI patients receiving GPIs in interventional hospitals in the Netherlands.

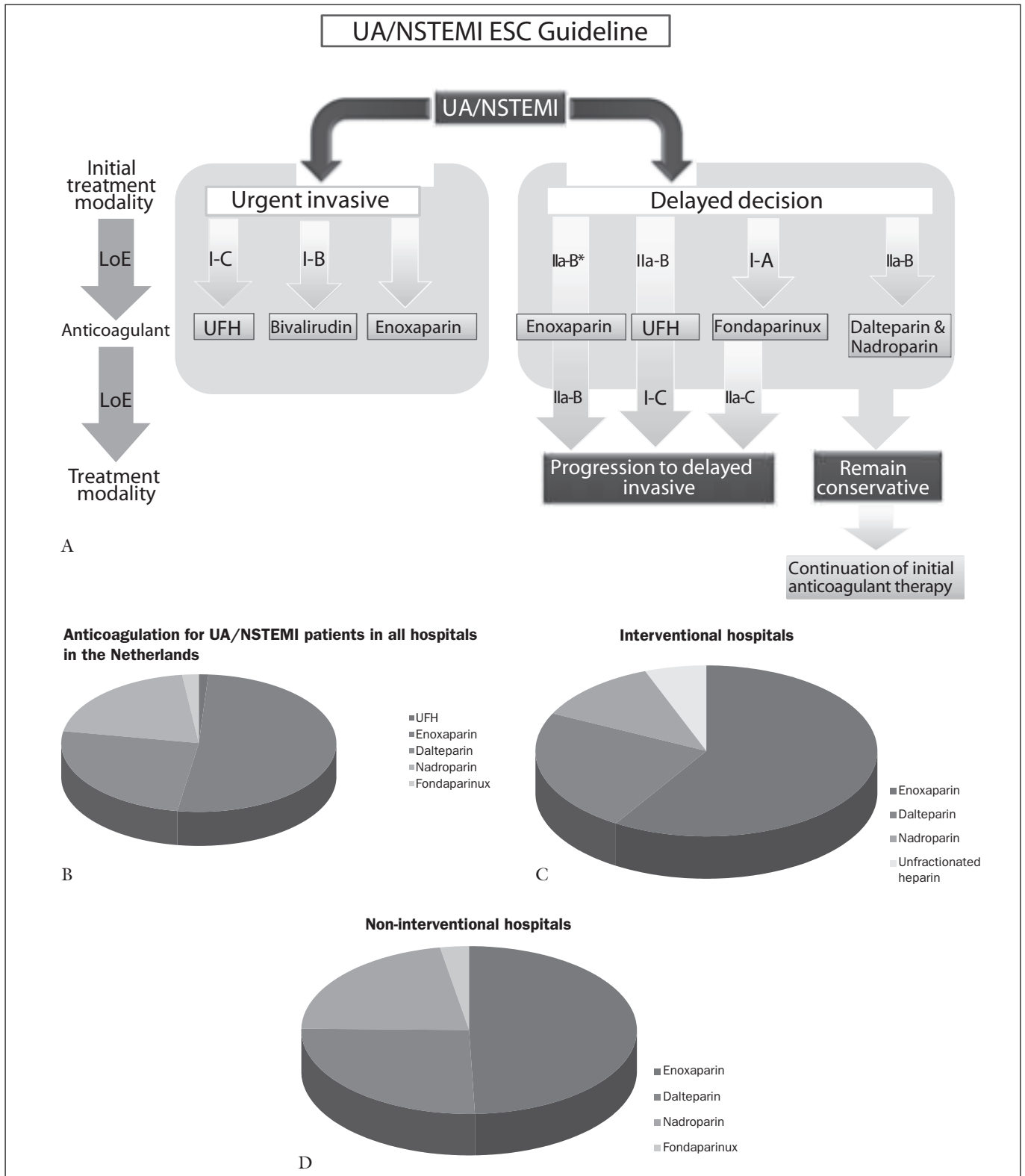


Figure 3. Anticoagulation in non-ST-elevation myocardial infarction. A) Flowchart displaying ESC guideline recommendations with level of evidence.¹ LoE = Level of evidence. When no decision had been made for a delayed invasive approach or a conservative approach, enoxaparin may be administered when the bleeding risk is low. †When fondaparinux is administered and a delayed invasive approach is applied, unfractionated heparin should be added to the antithrombotic therapy. ‡Dalteparin and nadroparin should not be preferred over fondaparinux as their efficacy and safety profile have not been tested compared with fondaparinux. B) Actual clinical practice in all hospitals in the Netherlands. C and D) Actual clinical practice in interventional and non-interventional hospitals in the Netherlands.

Unfractionated heparin is currently used in 59% (54/91) of all Dutch hospitals. Enoxaparin is used in 19% (17/91), dalteparin in 12% (11/91), nadroparin in 8% (7/91) and fondaparinux in 1% (2/91) of all Dutch hospitals in STEMI (figure 2B). We found bivalirudin to be used in 2% of all hospitals (combined with unfractionated heparin during catheterisation procedures). In all interviewed interventional hospitals STEMI patients eligible for PCI receive unfractionated heparin (18/18). The bolus infusion administered in the catheterisation laboratory varies between 5000 IU (74%, 13/18), 10,000 IU (21%, 4/18) or in a weight-dependent fashion (70 IU/kg) (5%, 1/18).

When self-referring patients present to non-interventional hospitals, they are treated with unfractionated heparin in 49% (36/73) of the

non-interventional hospitals, enoxaparin in 23% (17/73), dalteparin in 15% (11/73) nadroparin in 10% (7/73) and fondaparinux in 3% (2/73) (figure 2C). When comparing these data with the 2008 ESC STEMI guideline, 51% (37/73) of treatments in non-interventional hospitals are not in accordance with the guidelines, since LMWHs and fondaparinux are not recommended for treatment of STEMI patients. However, at the time of interviewing, the 2008 STEMI guideline was not yet published. If the data are compared with the 2003 STEMI guideline, 21% of all hospitals are not guideline adherent. Figure 1A depicts the ESC recommended treatment pathway for STEMI patients along with actual Dutch treatment.

We were unable to ascertain the duration of heparin therapy in STEMI patients, since the re-

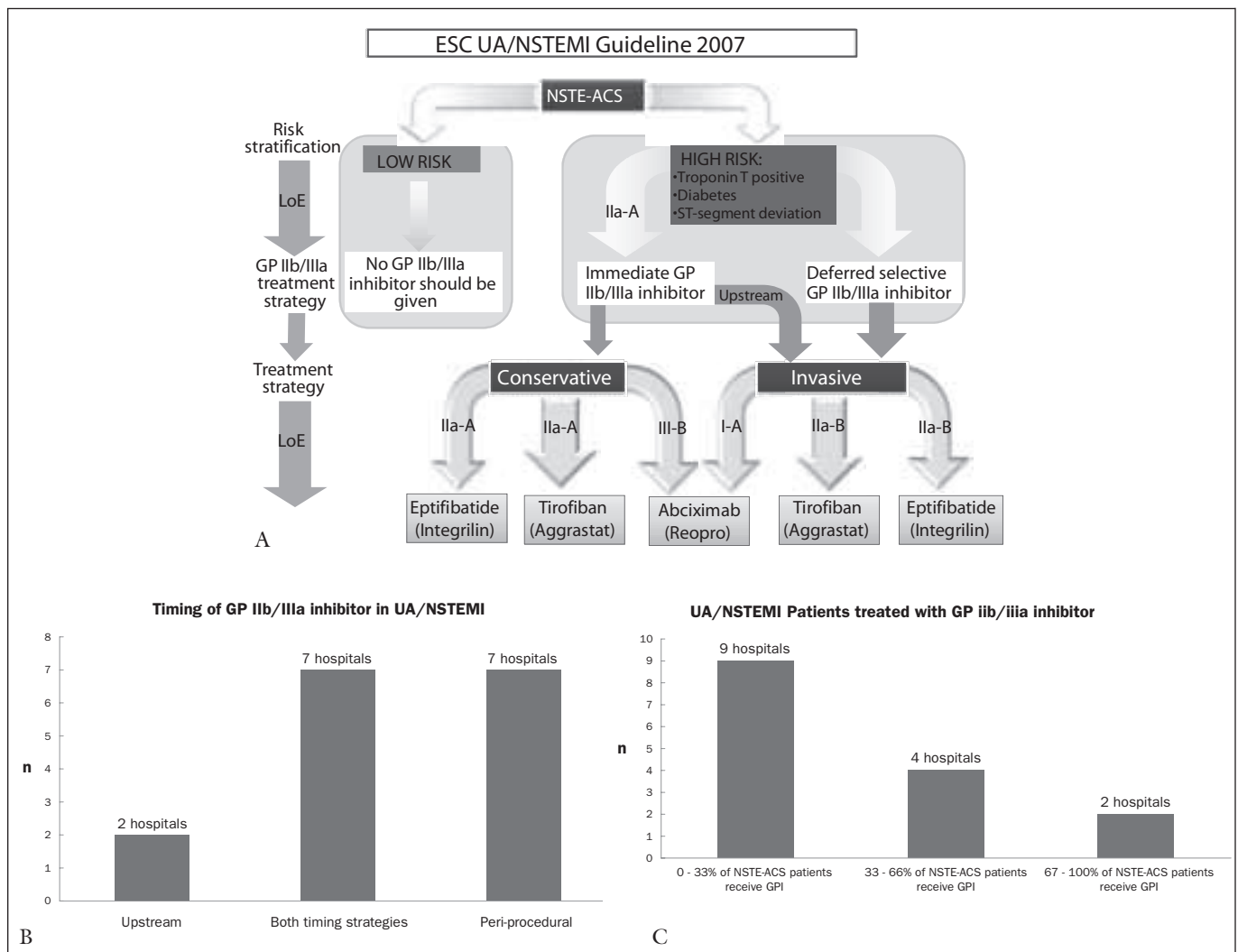


Figure 4. GP IIb/IIIa inhibitor therapy for UA/NSTEMI patients. A) Flowchart displaying ESC guideline recommendations with level of evidence.¹ Patients with UA/NSTEMI are stratified according to risk. A GPI may be administered preceding the diagnostic angiogram ('upstream', level of evidence IIa-A), or periprocedurally, depending on angiographic results. Next, in the flowchart, the recommendations and levels of evidence (LoE) are displayed for each agent depending on invasive or conservative approach. B) Timing strategies of GPI in interventional hospitals in the Netherlands. C) Estimated percentages of STEMI patients receiving GPIs in interventional hospitals in the Netherlands.

ferred STEMI patients treated with PCI frequently return to the referring hospital. The patients are then treated according to local practice.

Abciximab is the most commonly used GPI in Dutch interventional hospitals (in 88%, 14/16). Tirofiban is the second most applied GPI (44%, 7/16) followed by eptifibatide (6%, 1/16). In five hospitals multiple GPIs are used. Treatment strategies vary: in 29% (5/17) of interventional hospitals GPI is administered as standard upstream treatment, prior to coronary angiography, to STEMI patients. In 18% (3/17) GPI is administered both periprocedurally and standard upstream, at the discretion of the treating physician. In 53% (9/17) of interventional hospitals the diagnostic coronary angiogram is awaited before administering GPI. In a periprocedural strategy, the following indications were given: in case of angiographic evidence of intracoronary thrombus, no-reflow or in case of angiographic suspicion of a thrombotic dissection. Figure 2 displays the ESC recommended GPI treatment strategies for STEMI patients and actual Dutch GPI treatment.

The estimated percentage of STEMI patients in interventional hospitals receiving GPI varied from 0% (not at all) to 100% (all STEMI patients). In 24% (4/17) of these hospitals an anticoagulant is administered after cessation of GPI treatment. In 12% (2/17) of interventional hospitals an anticoagulant is administered in combination with GPI treatment. In 59% (10/17) no anticoagulant is used in combination with GPI treatment (with the exception of periprocedural unfractionated heparin).

STEMI patients are pretreated with 300 mg clopidogrel in 22% (4/14) of interventional and 39% (28/72) of non-interventional hospitals. The 600 mg loading dosage is applied in 72% (14/18) of interventional and 61% (44/72) of non-interventional hospitals. Both loading dosages are in accordance to the guideline.

UA/NSTEMI

Figure 3 depicts the evidence-based anticoagulant treatment pathway based on the 2007 ESC Guideline for UA/NSTEMI along with actual anticoagulant treatment of UA/NSTEMI in the Netherlands. In our study, unfractionated heparin is used in 1% of all hospitals (1/90), enoxaparin in 51% (46/90), dalteparin in 26% (23/90), nadroparin in 20% (18/90) and fondaparinux in 2% (2/90) of all hospitals. Patients with NSTEMI-ACS are treated with unfractionated heparin in 2% (1/17) of interventional hospitals, enoxaparin in 59% (10/17), dalteparin in 24% (4/17) and nadroparin in 12% (2/17) (figure 3C). Enoxaparin is used in 49% (36/73) of non-interventional hospitals, dalteparin in 26% (19/73), nadroparin in 22% (16/73) and fondaparinux in 3% (2/73) of non-interventional hospitals. An overview of anticoagulant therapy for UA/NSTEMI

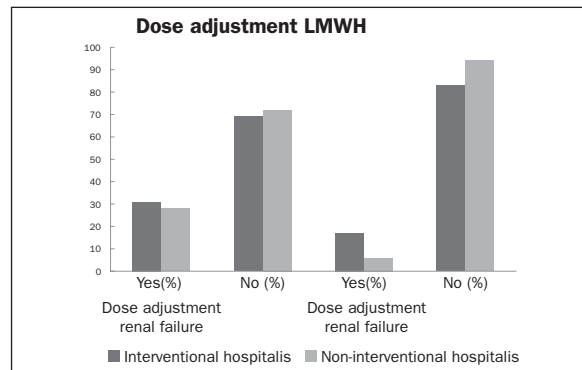


Figure 5. Dose adjustment LMWH for patients with renal failure and aged >75 years.

patients in the Netherlands is given in figures 3B and C. When anticoagulant treatment strategies in the Netherlands are compared with the ESC UA/NSTEMI guideline, one can conclude that treatment occurs according to the guideline.

The loading dose of clopidogrel seemed to vary depending on treatment strategy. A dose of 600 mg clopidogrel is preferred in case of an early invasive approach whereas a 300 mg dose is used in a conservative approach. Physicians reported that the loading dose for clopidogrel sometimes varied among cardiologists within their department. Hence, exact numbers and percentages on this subject are not reported. Both dosing regimens are in accordance with current guidelines.

In UA/NSTEMI the estimated percentages of application of GPI vary between 5 and 90%. Some cardiologists indicated that there was variation between GPI treatment strategies for NSTEMI patients treated within the same hospital. In 13% (2/16) of interventional hospitals GPI is administered as standard upstream treatment to UA/NSTEMI patients. In 44% (7/16) GPI is administered both periprocedurally and early upstream, depending on the risk stratification of patients. In 44% (7/16) of interventional hospitals the diagnostic coronary angiogram is awaited before administering GPI. An overview of GPI therapy for UA/NSTEMI patients in Dutch interventional hospitals is given in figure 4. Figure 4A displays the flowchart for GPI treatment according to the ESC UA/NSTEMI guideline with recommendations and level of evidence. When comparing our findings with the guidelines, one can conclude that treatment for patients with UA/NSTEMI occurs according to guidelines.

Dose adjustment for patients with renal failure or aged over 75 years

In a total of 31% (5/16) of the interventional hospitals and in 28% (21/73) of the non-interventional hospitals, routine dose adjustment for low-molec-

ular-weight heparin therapy is applied for patients with renal failure. Conversely, in 69% (11/16) of interventional hospitals and in 72% (54/73) of non-interventional hospitals routine dose adjustment of low-molecular-weight heparin does not occur for patients with renal failure.

A total of 17% (2/12) of Dutch interventional hospitals use an adjusted dose protocol for patients older than 75 years of age. This was also the case in 7% (4/67) of non-interventional hospitals. The majority (83% (10/12) to 93% (63/67)) of all hospitals do not adjust the heparin dose regimen for patients above 75 years of age. An overview of dose adjustment for low-molecular-weight heparin in Dutch hospitals is shown in figure 5.

Discussion

STEMI

Dutch physicians generally adhere to the current guidelines in antithrombotic treatment of STEMI patients. Nevertheless, a few remarks can be made. Dalteparin and nadroparin were used in 21% of all hospitals, although not recommended by ESC guidelines at the time of interview.⁴ A possible explanation for this may be the perceived interchangeability of low-molecular-weight heparins. Both the 2007 ACC/AHA STEMI guideline and the ESC Working Group on Thrombosis state that LMWHs and unfractionated heparin are not interchangeable.^{4,5} Different LMWHs should be considered as different entities, and trial results of one LMWH should not be extrapolated to the other LMWHs.^{4,6-9} LMWHs have different anti-Xa and anti-IIa potency when given in a dose recommended by the ESC. Dalteparin has the highest anti-factor Xa and anti-factor IIa activity, and nadroparin the lowest.^{5,10} Whether these differences have implications for clinical effects, efficacy and safety remains unclear. However, the 2003 ESC STEMI guideline does not recommend dalteparin and nadroparin for treatment of STEMI patients.^{3,4} Furthermore, in the most recent ESC STEMI guideline, LMWHs are not recommended at all for STEMI patients.¹ With respect to this point, improvement in clinical care in the Netherlands may be achieved.

Several trials have studied the effect of GPI when combined with heparin and aspirin (triple therapy) in the setting of PCI, showing a reduction in 30-day and long-term mortality effectuated by treatment with GPI.¹¹ However, there is little evidence for improved survival when GPI is accrued to standard pretreatment with heparin, aspirin and clopidogrel.¹² This may account for the broad variation of GPI use in STEMI.

Another unsolved issue surrounding GPI treatment in STEMI is timing of administration. In STEMI, the immediate upstream and standard application of GPI improves coronary patency after

angiography but has not been proven to be superior to periprocedural treatment in terms of clinical outcome, although a nonsignificant trend towards an improved clinical outcome was seen in some trials.^{13,14} Additionally, superiority in cost-effectiveness of either strategy remains unclear. Few trials have addressed this issue and clinical trials assessing cost-effectiveness should be interpreted with care as these trials often encompass a selected patient population. The ESC makes no specific recommendation for timing strategy.¹ This may explain the considerable variation in timing of application of GPI in interventional hospitals in the Netherlands.

UA/NSTEMI

The abovementioned potential reasons for the diversity in GPI treatment strategies in STEMI may similarly account for the observed diversity of GPI use in UA/NSTEMI. The lack of evidence of improved survival of GP IIb/IIIa inhibitor therapy in conjunction with standard care – heparin, aspirin and clopidogrel – accounts for low estimated percentages of GPI use in NSTEMI-ACS. The immediate upstream administration of GPI to UA/NSTEMI patients is superior to deferred selective treatment in terms of clinical outcome.¹⁵ The beneficial effect is larger when an invasive approach is applied in combination with GPI. In the ESC UA/NSTEMI Guideline, a recommendation is made for the upstream administration of GPI.² Nevertheless in 40% of interventional hospitals the diagnostic angiogram is awaited before treating with GPI.

The OASIS-5 trial resulted in a Class I, level of evidence A recommendation for the application of fondaparinux in a conservative approach for patients with UA/NSTEMI and a Class IIa, level of evidence C recommendation for application during an invasive approach.² In the OASIS 5 and 6 trials treatment with fondaparinux alone led to an increase of catheter thrombosis during coronary catheterisation procedures.^{16,17} Therefore, when deciding on an invasive approach, unfractionated heparin should be added to the antithrombotic therapy to prevent catheter thrombosis. The OASIS 5 and 6 trials showed improved survival explained by a reduction in bleeding complications. This demonstrates the favourable safety profile of fondaparinux and underlines the importance of reducing bleeds. Fondaparinux is currently applied in only two hospitals in the Netherlands.

There are two subpopulations in which Dutch physicians are not fully adherent to the guideline in the treatment of UA/NSTEMI patients. In patients with renal failure and in patients older than 75 years of age, there is room for improvement in the clinical care in these high-risk patients.

Renal failure

LMWHs exert their anticoagulant effect by inhibiting

factor Xa and factor IIa activity. Reduced glomerular filtration rates (GFR), particularly below 30 ml/min, induce accumulation of anti-factor-Xa and anti-factor-IIa activity during treatment with LMWH.¹⁸ As a result, patients with renal insufficiency are at increased risk of bleeding complications secondary to LMWH treatment.¹⁹ This is accordingly true for unfractionated heparin, bivalirudin, fondaparinux, and GP IIb/IIIa inhibitors. Dose adjustment should be made for these agents.² Although the ESC recommends dose adjustment, the ESC makes no unequivocal recommendation for the optimal dosage of LMWHs. The available current evidence shows that half-dose LMWH in patients with GFR below 30 ml/min and 75% dose for patients with GFR below 60 ml/min is recommended.²⁰ Dutch cardiologists, however, do not routinely restrict the dose of LMWH in patients with renal insufficiency. As a result patients may be at an increased risk of bleeding complications. Several trials have shown bleeding complications to be a more powerful predictor of mortality than ischaemic complications such as reinfarction.^{21,22} As known from the GRACE registry score for NSTEMI, renal failure is one of the most important predictors for in-hospital mortality and major bleeding.¹⁹ Patients with renal insufficiency form a large portion of the ACS patient population, with a prevalence varying from 13.2% for patients with GFR below 30 ml/min to 42% for patients with GFR between 30 and 70 ml/min.^{23,24} Furthermore, it has been shown that patients with renal failure benefit from an invasive strategy, although they are in fact at higher risk for bleeding, especially when dose restriction is not applied.²⁵

Patients aged 75 years and above

Age above 75 years has been shown to be an independent risk factor for bleeding complications and worse outcome.^{21,26} Dose adjustment of LMWH for patients older than 75 years of age is therefore recommended.²⁶⁻²⁸ Dutch physicians do not routinely adjust anticoagulation dosing for these patients. A possible explanation is that age is assessed in a broader clinical perspective instead of as an independent risk factor. The age of 75 years may be considered an arbitrary cut-off point. Renal function, liver function and varying volume of distribution contribute to altered pharmacokinetics and pharmacodynamics among the elderly and these parameters vary greatly among these patients.²⁹ Although the age cut-off may seem somewhat arbitrary,

a standard cut-off age of 75 years for dose adjustment of antithrombotic agents in a real-life setting should be routinely applied according to the guidelines. This simple measure is likely to reduce bleeding complications in this patient population.

Limitations

This study merely presents a description of current clinical practice in Dutch hospitals with respect to antithrombotic therapy in acute coronary syndromes. It does not describe the outcome and complications of these treatment methods. The study does not profess to give an estimation of complication rates for individual hospitals. However, the study does demonstrate that there is room for improvement in adherence to current clinical guidelines. This is particularly the case in the implementation of dose adjustment of anticoagulation for patients with renal failure and patients aged ≥ 75 years.

Another limitation was that we approached only one cardiologist per hospital assuming that cardiologists belonging to a single hospital and organisation apply the same guidelines. Although the direct interviewing may have impacted on the given response, it enabled clarification of the questions asked. In our opinion, this led to a more comprehensive and well-considered response of those interviewed.

Conclusions

To a great extent treatment of acute coronary syndromes in the Netherlands occurs according to current guidelines. Antithrombotic therapy was found to vary widely. Implementing dose adjustment of antithrombotic therapy for patients with renal insufficiency and aged over 75 years may reduce bleeding complications in these very high-risk ACS patients. In 39% of Dutch hospitals LMWH was used for STEMI. Based on the ESC 2008 STEMI guideline this is not recommended. GP IIb/IIIa inhibitor application in both STE-ACS and NSTEMI-ACS was found to be limited and both timing and drug of choice differed strongly. Finally, despite established scientific evidence, recommendations do not always find their way to real-life practice. This supports periodical evaluation of daily clinical practice among physicians.

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Appendix. Questionnaire

Antithrombotic treatment for patients with Acute Coronary Syndrome

Please answer the questions for practice applied in your hospital/institution.

For all hospitals

1. Which anticoagulant agent is administered to patients with acute ST-elevation myocardial infarction (STEMI) in your hospital regardless of type of reperfusion therapy (e.g. unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), bivalirudin or fondaparinux)?
2. Which anticoagulant dose regimen is applied in STEMI patients treated with primary Percutaneous Coronary Intervention (PCI)?
3. Which anticoagulant agent is administered to patients with acute non-ST-elevation myocardial infarction or unstable angina (UA/NSTEMI) in your hospital regardless of reperfusion therapy (e.g. UFH, LMWH, bivalirudin or fondaparinux)?
4. Which loading dose for clopidogrel is applied in your institution in STEMI and UA/NSTEMI?
5. Is routine dose-adjustment of antithrombotic regimen applied for patients with renal insufficiency?

6. Is routine dose-adjustment of antithrombotic regimen applied for patients aged 75 or older?

For hospitals equipped with PCI facilities:

7. Which GPI is administered in your institution?
8. What are the indications for GPI therapy in STEMI patients?
9. How many STEMI patients do you estimate are treated with GPI within your department?
10. What are the indications for GPI therapy in patients with UA/NSTEMI?
11. How many NSTEMI-ACS patients do you estimate are treated with GPI within your department?
12. Is GPI combined with anticoagulant therapy such as heparin? What is the administered dosage of this anticoagulant agent?

For ambulance services:

13. Is thrombolysis applied on your ambulance service for STEMI patients? (yes/no)
14. Which dose of unfractionated heparin is given to STEMI patients?
15. Which loading dose of acetylsalicylic acid is given to STEMI patients?
16. Which loading dose clopidogrel is given to STEMI patients?