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Pre-hospital management of patients with chest pain and/or dyspnoea of cardiac origin. A position paper of the Acute Cardiovascular Care Association (ACCA) of the ESC.

Writing committee

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Abstract

Chest pain and acute dyspnoea are frequent causes of emergency medical services activation. The pre-hospital management of these conditions is heterogeneous across different regions of the world and Europe, as a consequence of the variety of emergency medical services and absence of specific practical guidelines. This position paper focuses on the practical aspects of the pre-hospital treatment on board and transfer of patients taken in charge by emergency medical services for chest pain and dyspnoea of suspected cardiac aetiology after the initial assessment and diagnostic work-up. The objective of the paper is to provide guidance, based on evidence, where available, or on experts' opinions, for all emergency medical services' health providers involved in the pre-hospital management of acute cardiovascular care.

Keywords

Pre-hospital, chest pain, dyspnoea

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Part I

Introduction

Chest pain and acute dyspnoea are among the most frequent causes of out-of-hospital emergency medical services (EMSs) activation. A recent publication of a Swiss population based registry (n=28,697 patients in 2010) shows that after trauma (29%) and coma (9%), chest pain (6%) and dyspnoea (6%) are the most common reasons to call the EMSs.[1]

After the reception of the call by the dispatching staff (whether integrated or not in the EMSs), the clinical presentation and the level of emergency need to be evaluated and decisions need to be made regarding the choice of the team to be dispatched. Once at the scene the team has to ensure initial management of the patient and secure patient transfer to adequate centres with appropriate facilities based on the individual patient's needs.

EMSs are extremely variable even across Europe, ranging from systems providing only basic life support to others with physicians on board and the possibility of providing advanced life support. Such disparity explains the difficulty in implementing guidelines in the pre-hospital setting homogeneously. Hence the organization of regional networks and the coordination between pre-hospital services and hospital departments involved in the management of acute cardiovascular emergencies appear as the most important base for providing continuous and consistent care to patients based on shared protocols.

The objectives of an EMS defined by the European Society of Cardiology (ESC) task force on the management of chest pain[2] (Table 1 in the Supplementary Material online) are to correct vital functions, stabilize the patient, start a diagnostic work-up, begin treatment in order to relieve symptoms, prevent development of complications and permanent damage and transfer the patient as soon as possible to an adequate health care facility.

With regard to the first two above-mentioned objectives (i.e. correct vital functions, stabilize the patient), specific guidelines for the management of vital emergencies requiring cardiopulmonary resuscitation, invasive ventilation and advanced life support are available and should be applied in all cases requiring such interventions.[3] For the very broad field of diagnostic work-up and triage we refer readers to the ESC textbook of intensive and acute cardiac care[4] and the Acute Cardiac Care Association (ACCA) decision making toolkit (http://www.escardio.org/communities/ACCA/education-research/awareness/Documents/ACCA-Toolkit-Abridged-version.pdf), which provide valuable information on the management of acute cardiovascular conditions. The ACCA toolkit is available in downloadable and smartphone app formats.

The scope of the present position paper is to focus on practical aspects of the last two specific objectives of the pre-hospital team, that is, the treatment on board and the transfer of patients with chest pain and dyspnoea of suspected cardiovascular origin. The aim of the current paper is not to replace high quality existing guidelines but to provide a symptom based document, based on recent evidence where available or expert opinions, for all EMS staff, focusing specifically on the pre-hospital management of patients after the initial assessment has oriented the diagnosis towards cardiovascular diseases.

1. Recommended competence and equipment on board

The recommended equipment and medication on board for an optimal pre-hospital medical management of acute cardiovascular conditions are depicted in Table 1. The use of many instruments and medications in the pre-hospital setting may require the presence of physicians or at least highly specialized and trained EMS paramedics or nurses on board. Unlike most EMSs worldwide, the majority of European countries' EMSs are physician-based. Although the presence of physicians is not mandatory in every emergency situation, in situations such as ST elevation myocardial infarction or respiratory distress, systems providing advanced life support may reduce delays in the diagnosis and the administration of appropriate treatment and subsequently improve outcome.[5,6]

Despite limited evidence, since a high level of pre-hospital care may require the presence of emergency physicians on-scene, consensus was reached in the study group to recommend a physician-based EMS organization with the availability of emergency physicians in the case of chest pain or acute dyspnoea of suspected cardiac origin. However, in countries where the presence of physicians on board is not possible, a certain level of advanced management – for example, resuscitation, inotropic support and fibrinolysis – may also be provided by trained non-physician paramedics or nurses in the pre-hospital setting, based on physician supervised checklists, approved protocols and/or teletransmission of clinical and ECG data and teleconsulting.[7,8] An alternative to the systematic presence of a physician on board may be the 'rendezvous' system developed in some countries, such as Austria, where an EMS team and a physician may meet on the scene. The benefit and the cost-effectiveness of each type of organization, however, need to be assessed by appropriate multicentre studies.

2. Management of chest pain of cardiac aetiology

The challenge of the pre-hospital management of chest pain, beyond rapid diagnosis, is the treatment and transfer of patients with major cardiovascular emergencies (i.e. ST elevation myocardial infarction, aortic dissection) to adequate centres. The level of evidence is quite high for the

Table 1. Recommended instrumentation (a) and medication (b) on board.

(a) Instrumentation

ECG recorder and monitor	Mandatory
ECG tele-transmission	Mandatory if no physician on board Recommended if physician on board
Blood oxymetry monitor	Mandatory
External cardioverter	Mandatory
External pacemaker	Highly recommended
Invasive ventilation	Recommended
Non-invasive ventilation/CPAP	Recommended
Chest compression devices	May be considered
Point of care biomarker systems (troponin)	May be considered
Ultrasound portable diagnostic devices	Recommended

(b) Medication

Medication for ACS

	STEMI		NSTE-ACS	
	PH fibrinolysis	PPCI	Urgent (<2 h) catheterization	Non-urgent catheterization
Fibrinolytics				
Tenecteplase[a]	Highly recommended	–	–	–
Reteplase	May be considered			
Alteplase	May be considered			
Streptokinase	Not recommended			
Anticoagulants				
Enoxaparin[b] and/or UFH	Mandatory	Recommended	Recommended	–
Fondaparinux	Not recommended	Not recommended	–	–
Bivalirudin	Not recommended	Recommended if high bleeding risk	–	–
Antiplatelets				
Aspirin	Mandatory	Highly recommended	Mandatory	Recommended
Clopidogrel	Mandatory	Recommended if prasugrel or ticagrelor unavailable or contraindicated	Recommended	–
Ticagrelor[c]	–	Recommended	Recommended	–
Prasugrel	–	Recommended	Not recommended	–
GP2b3a inhibitors (tirofiban, abciximab)	–	May be considered in early presenters	–	–
Anti-anginal/anti-ischaemic drugs				
GTN/ISDN	Not recommended	Not recommended	Recommended	Recommended
Beta-blockers	Recommended	May be considered	May be considered	May be considered

Other medication on board

Morphine	Mandatory
Amiodarone	Highly recommended
Lidocaine	Recommended
Adenosine	Recommended
Magnesium sulphate	Recommended
Furosemide	Mandatory
Atropine	Highly recommended
Epinephrine	Mandatory
Norepinephrine	Highly recommended
Isoprenaline	Recommended
Dobutamine	Recommended
Anti-hypertensive drugs (beta-blockers, GTN/ISDN, calcium channel blockers, sodium nitroprusside…)	Highly recommended

[a]Fibrin specifics are preferred to streptokinase and tenecteplase administered as a single bolus is the first line option in comparison with reteplase administered as a double 30-minute separated bolus and alteplase as a continuous intravenous infusion in the pre-hospital setting.

[b]Enoxaparin should be preferred to UFH especially in the setting of pre-hospital fibrinolysis.

[c]Ticagrelor is the only P2Y12 inhibitor with an adequately sized study showing its safety in the pre-hospital setting as compared with its catheterization laboratory administration.

PH: pre-hospital; PPCI: primary percutaneous coronary intervention; NSTE-ACS: non ST elevation acute coronary syndrome; UFH: unfractionated heparin; GP2b3a: glycoprotein 2b3a; GTN/ISDN: glyceryl trinitrate/isosorbide dinitrate.

Table 2. Time intervals in the pre-hospital setting management of STEMI.

Time	Definition	Ideal times/factors affecting delays
Patient delay	Between symptom onset and EMS call	–/Population education
'Field delay'[a]	Between EMS call and team on scene	<20 min/geography and logistics
Diagnosis delay	Between FMC and diagnostic ECG	<10 min/competence on board, ECG transmission
Time to reperfusion therapy	Between FMC and balloon or needle	FMC-wire/balloon: preferred ⩽ 90 min acceptable ⩽ 120 min door to wire/balloon ⩽ 60 min (PCI centres) door-in door-out ⩽ 30 min (non-PCI centres or EMS) FMC-needle ⩽ 30 min /STEMI network organization
System delay	Between EMS call and reperfusion	–/Global efficiency of the STEMI network

EMS: emergency medical service; FMC: first medical contact defined here by team on scene; PCI: percutaneous coronary intervention; STEMI: ST elevation myocardial infarction.
[a]This delay, depending also on the geographical situation and logistics, is not mentioned in the ESC guidelines. It directly reflects the accessibility to EMSs.

pre-hospital management of STEMI while for other cardiovascular causes of chest pain, most recommendations are opinion based.

2.1. ST elevation myocardial infarction

ST elevation myocardial infarction (STEMI) guidelines of the ESC published in 2012[9] include a full chapter on the logistics and organization of EMS and STEMI networks managing such conditions. The delays and ideal time intervals for diagnosis and intervention in the pre-hospital setting have been well defined (Table 2). Nevertheless, the practical aspects of STEMI management in the pre-hospital setting remain difficult to implement in many regions of the world because of the extreme variety of EMSs and the lack of universal STEMI networks despite guidelines clearly recommending their organization. A previous scientific statement of a study group of the ACCA has also reported on the management of STEMI in the pre-hospital setting.[10] The aim of this section is to provide recent evidence and practical decision-making tools for EMS personnel.

2.1.1. Risk assessment in the pre-hospital setting of STEMI. Risk assessment in the pre-hospital setting is of major importance as it greatly influences the management and transfer of patients. It can usually be based on clinical score systems alone. Although the Thrombolysis In Myocardial Infarction (TIMI) and Mini-Global Registry of Acute Coronary Events (GRACE) scores (Supplementary Tables 2(a), and 2(c)) could be used for early risk assessment in the pre-hospital setting, all STEMI patients are considered as high risk patients requiring urgent reperfusion. Therefore such scores are unlikely to impact clinical decision making in the pre-hospital setting but may influence the choice of the health facility to which the patient is transferred. Hence the pre-hospital use of such scores may be considered if it does not delay reperfusion therapy.

The pre-hospital use of point-of care troponin tests among STEMI patients is not validated and therefore not recommended.[11] Furthermore, troponin tests have no prognostic role in the early phase of STEMI where ECG and clinical assessment should be used not only as diagnostic tools leading to early reperfusion but also as prognostic tools leading to different risk-based managements (e.g. reperfusion strategy, antithrombotic regimens, transfer to different health facilities).

The ECG (18 leads) is very useful in identifying high-risk patients based on features such as ST segment elevation in V1, aVR, V3R or V4R leads, Σ ST segment elevation > 8 mm, left bundle branch block or high degree atrioventricular block.[12–14] Furthermore ECG signs of proximal coronary artery occlusion in the absence of obvious ST segment elevation associated with an on-going chest pain should be detected in the pre-hospital setting.[15] Hence 18 lead ECG should be performed as recommended by ESC guidelines[9] within 10 min following first medical contact. Moreover specific training in ECG interpretation is mandatory for all EMS personnel in a position to provide care to STEMI patients.

In systems providing both primary percutaneous coronary intervention (PPCI) and fibrinolytic therapy the high risk situation of cardiogenic shock in which fibrinolysis has not been reported to improve outcome should preferentially lead to PPCI, unless PCI is not available in a timely fashion.[9]

The most important risk to assess in the pre-hospital setting is the bleeding risk as it directly determines the choice of reperfusion strategy as fibrinolysis is contraindicated in patients at high bleeding risk (Figure 1). The CRUSADE score (Supplementary Table 2(d)) used in the in-hospital setting requires biological parameters, which are usually unavailable out of hospital. The more easy to use HAS-BLED[16] bleeding risk used for the assessment of bleeding risk among patients with atrial fibrillation has not been validated in the setting of acute coronary syndrome (ACS).

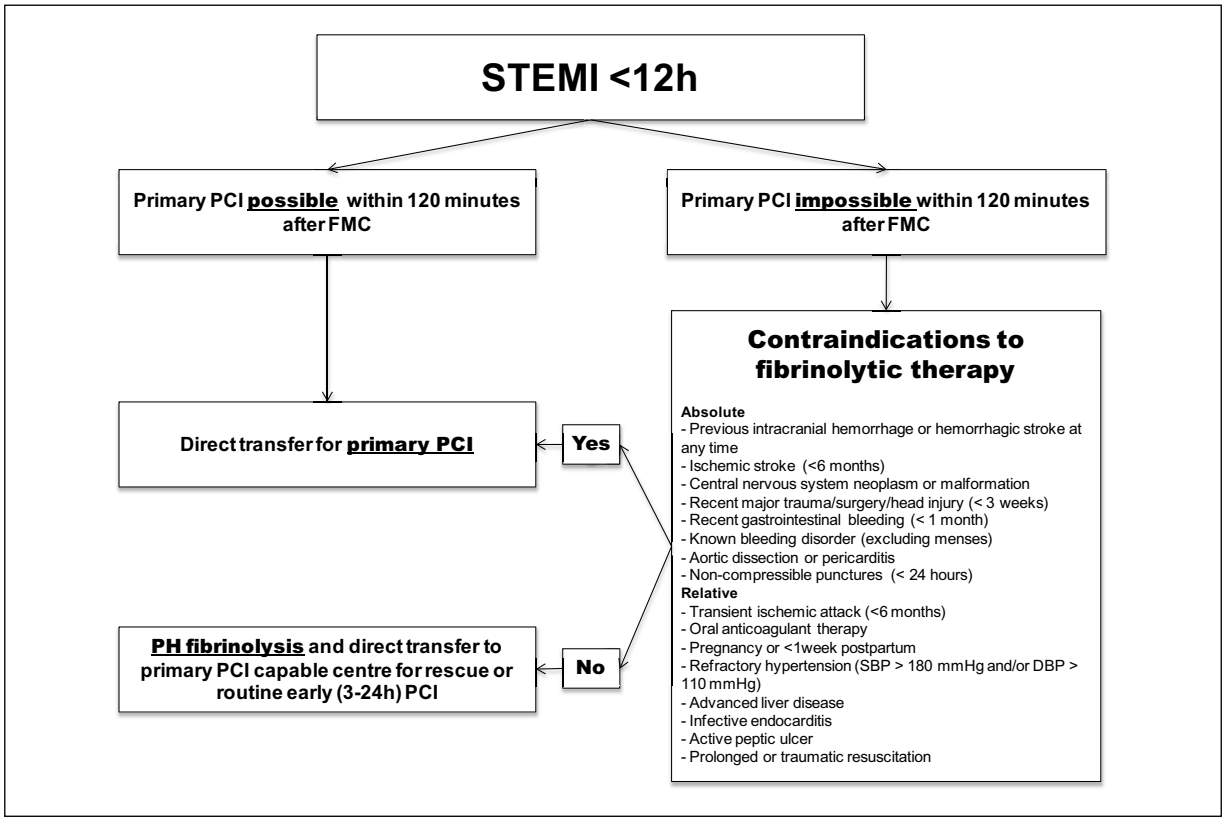

Figure 1. Pre-hospital reperfusion strategies.
For STEMI, within 12–24 h after symptom onset a PPCI strategy is recommended if the symptom is persistent.
PPCI: primary percutaneous coronary intervention; FMC: first medical contact; SBP: systolic blood pressure; DBP: diastolic blood pressure; PH: pre-hospital.

Table 3. Factors associated with high risk of bleeding in acute coronary syndromes based on the Global Registry of Acute Coronary Events (GRACE).[17]

Older age (especially >80 years)
Female gender
History of renal failure
History of bleeding
Low blood pressure
Treatments associated with higher risk of bleeding
Thrombolytics
Glycoprotein 2b3a antagonists
Dual antiplatelet therapy
Oral anticoagulants[a]
Non-steroid anti-inflammatory drugs[a]
Need for intravenous inotropics
Need for vasodilators

[a]These medications were not assessed in the GRACE registry.

EMS personnel should be thoroughly familiar with the contraindications for fibrinolytic therapy (Figure 1) and also be able to detect a high risk of bleeding in patients without obvious contraindication based on simple clinical and history data as validated in the GRACE ACS registry (Table 3).[17] Most clinical scores show that high risk of bleeding is associated with age > 80 years old, female gender, renal insufficiency, history of bleeding and treatment by antithrombotic (antiplatelets, anticoagulants) or non-steroid anti-inflammatory drugs. Therefore the presence of any of such parameters may identify a high risk of bleeding and assist in prudent balancing between advantages and risks of different reperfusion strategies and anti-thrombotic regimens. Pre-hospital fibrinolysis should be withheld if the bleeding risk seems to overbalance the expected benefit of fibrinolysis. Furthermore in the absence of clear

Table 4. Pre-hospital adjunctive therapy in a primary percutaneous coronary intervention strategy for ST elevation myocardial infarction.

Pain control
Titration of i.v. opioids (limited to the lowest dose required)

Anticoagulant
Enoxaparine: 0.5mg/kg or UFH **70–100 IU/kg** i.v. bolus only
(Bivalirudin may be considered in patients at high risk of bleeding.)

Antiplatelet therapy
- Aspirin LD 150–300 mg p.o. or 250–500 mg i.v.

And
- P2Y12 inhibitor
- Ticagrelor[a] 180 mg LD p.o.
  Or
- Prasugrel 60 mg LD p.o. (if no past history of stroke and age <75 years)
  Or
- Clopidogrel 600 mg LD p.o. *if ticagrelor and prasugrel unavailable or contra-indicated*

[a]Only the pre-hospital administration of ticagrelor has been compared with its in-hospital administration in an adequately sized random controlled trial (RCT) showing its safety. Small RCTs have assessed the pre-hospital administration of clopidogrel, and prasugrel's pre-hospital use has been assessed only in non-RCT cohort studies.
i.v.: intravenous; p.o.: per os; LD: Loading dose.

evidence for the benefit of pre-hospital versus in-hospital antithrombotic therapy, a fast transfer with no administration of any antithrombotic medication to a PCI-capable centre could be the most reasonable decision in patients with active bleeding or at very high risk of bleeding. Caution should be taken in general, based on the risk assessment, not to initiate a treatment pre-hospital which might be administered more safely in the hospital setting after further evaluation. In such situations a rapid and secure transfer in stable conditions to the appropriate facility is the best option.

Reperfusion therapy and STEMI networks. Reperfusion therapy is widely discussed in the ESC guidelines for the management of STEMI[9] and for myocardial revascularization.[18]

The care of STEMI in the pre-hospital setting should be based on regional STEMI networks. Such networks include one or more hospitals and EMS organizations which have a shared protocol for the choice of reperfusion strategy adjunctive therapy and patient transfer in order to provide consistent treatment to patients. Such protocols should be formally discussed between all components of the network and be available in writing.

In general, PPCI is the reperfusion modality of choice if it can be performed in a timely manner. However, pre-hospital fibrinolysis remains a very important tool if transfer delays are prolonged, particularly among early presenters at low bleeding risk (Figure 1).

Tables 4 and 5 summarize simple examples of treatment protocols recommended by the study group for 'en route' therapy for PPCI and pre-hospital fibrinolysis.

Although the ESC guidelines still recommend fibrinolysis up to 12 h after symptom onset, the benefit of fibrinolysis remains modest >6 h after coronary occlusion.[19] EMSs that can provide both reperfusion strategies should balance the benefit and the risk of pre-hospital fibrinolysis >6 h after symptom onset. The choice between PPCI and fibrinolysis in the individual patient should be based on the estimated time for PCI (first medical contact to balloon time), the patient's bleeding risk, time since symptom onset, STEMI location and the haemodynamic status of the patient, as outlined in the ESC guidelines.[20] It is especially relevant in elderly patients with non-extensive STEMI to consider switching to a PPCI strategy if it can be done without an 'unacceptable' increase in reperfusion delay.

Direct telephone contact between the pre-hospital team, the emergency medical communication centre and interventional cardiology team, with ECG teletransmission if necessary, may be very useful in planning reperfusion therapy in the safest and most efficient way in borderline cases.

The use of nitrates and beta-blockers in the pre-hospital setting has not been studied and may be associated with hypotension and heart failure. The routine use of intravenous beta-blockers as well as routine oxygen supplementation early after myocardial infarction are associated with adverse events.[21,22] Therefore, the routine use of nitrates, beta-blockers and oxygen supplementation are not recommended in the pre-hospital setting.

2.1.2.1. PPCI strategy. PPCI is widely accepted as the preferred method of reperfusion in STEMI and should be preferred to fibrinolysis if it can be performed in a timely fashion.

2.1.2.1.1. Adjunctive therapy prior to PPCI. Unlike the setting of fibrinolysis, there are major gaps in the evidence for the benefit of pre-hospital versus in-hospital administration of adjunctive therapy in patients managed by a PPCI

Table 5. Pre-hospital fibrinolysis in ST elevation myocardial infarction.

Pre-hospital fibrinolysis strategy

Pain control
Titration of i.v. opioids (limited to the lowest dose required)

Age <75 years:
- Aspirin 150–300 mg p.o. or i.v.
- Clopidogrel *300 mg* p.o.
- Enoxaparin: 30mg i.v. + 1mg/kg s.c. (max 100mg) 15 min after i.v. bolus
- Tenecteplase weight adjusted dose[a]

Age ⩾75:
- Aspirin 150–300 mg p.o. or i.v.
- *Clopidogrel 75 mg* p.o.
- Enoxaparin: 1mg/kg s.c. (max. 75mg), no i.v. bolus
- Tenecteplase half weight adjusted dose[b]

In all cases a direct transfer to a PCI-capable centre for rescue PCI for fibrinolysis failure or routine PCI should be preferred to transfer to a non-PCI facility.

[a]Weight adjusted dose: 30mg ⩽60kg, 35mg >60 to ⩽70 kg, 40mg >70 to ⩽80 kg, 45mg >80 to ⩽90kg, 50 mg if >90 kg.
[b]Reducing the dose by 50% in elderly patients was associated with an improvement of outcome in the STREAM trial.
i.v.: intravenous; p.o.: per os; s.c.: subcutaneous; PCI: percutaneous coronary intervention.

strategy. However, early initiation of antiplatelet therapy at the time of PCI is associated with improved outcome and sets the basis of pre-hospital antiplatelet therapy.

2.1.2.1.1.1. Aspirin. Although historically used with high levels of recommendation, there are major gaps of evidence for the pre-hospital use of aspirin before PPCI for STEMI.

A small case versus control study showed that the pre-hospital administration of the combination of aspirin and unfractionated heparin (UFH) improved coronary artery patency when compared with in-hospital administration, although outcome was not affected.[23] Despite the lack of evidence, in light of its major impact on vascular mortality[24] and the low risk of its pre-hospital administration, aspirin's prompt use in the pre-hospital setting is recommended.

2.1.2.1.1.2. P2Y12 inhibitors. The pre-hospital versus in-hospital administration of clopidogrel has been assessed in two small sized studies showing its safety but no evidence of a clinical benefit.[25,26] However, a meta-analysis of pre-PCI versus post-PCI (although not pre-hospital versus in-hospital) administration of clopidogrel among STEMI patients has shown a significant reduction of mortality risk without an increase of bleeding risk in association with pre-PCI treatment.[27]

No study comparing pre-hospital versus in-hospital administration of prasugrel is available. A small sized trial showed the higher platelet reactivity inhibition after pre-PPCI administration of prasugrel compared with clopidogrel.[28] In the STEMI sub-group of the TRITON trial there was a benefit in favour of prasugrel in terms of the primary endpoint of the study (cardiovascular death, myocardial infarction or stroke) and early mortality without significant excess in bleeding. These results should be considered with caution as a major part of the benefit was driven by patients undergoing PCI several days after STEMI and most patients in the trial received their first dose of study medication during PCI.[29]

In the PLATO trial pre-PPCI ticagrelor tended to reduce the triple thrombotic primary endpoint (p=0.05) without significantly increasing bleeding.[30] The pre-hospital administration of ticagrelor in the setting of PPCI has been compared with its in-hospital administration in the adequately sized (n=1862) ATLANTIC trial.[31] Although the trial's co-primary endpoints – pre-PCI ST segment elevation resolution or TIMI grade 3 flow – were equally distributed between the pre-hospital and in-hospital groups, the pre-hospital administration of ticagrelor was not associated with an excess in bleeding complications, highlighting the safety of such a strategy. Furthermore, there was a marked and significant reduction in rates of definite stent thrombosis in the pre-hospital group. Although this finding should be considered more as hypothesis generating than as established evidence it might support the pre-hospital administration of ticagrelor in view of the absence of a safety issue with this strategy. Interestingly the crushing of ticagrelor tablets leads to an accelerated drug absorption and subsequent higher 1 h platelet reactivity inhibition compared with integral tablet administration.[32] Administration of crushed tablets may therefore be considered especially in STEMI patients with difficulties with swallowing tablets, such as those with prior stroke or dysphagia and those sedated, especially by opioids, and/or intubated.

Considering the likely benefit and the safety of pre-PCI P2Y12 inhibitors in the setting of STEMI, the extension of their use to the pre-hospital setting is recommended by the study group although the evidence in favour of this strategy

is limited. Such therapy should be withheld in the presence of high bleeding risk or uncertain STEMI diagnosis. As recommended by ESC guidelines[9] ticagrelor and prasugrel are to be considered as first line medications while clopidogrel should only be used when ticagrelor or prasugrel are unavailable or contraindicated. The study group did not reach consensus on the preferential use of one of the latter drugs over the other.

An unfavourable interaction between opioid use and the clinical effect of ticagrelor[31] and biological effects of both prasugrel and ticagrelor[33] has been reported in the setting of STEMI, questioning the safety of routine opioid use. Considering the importance of pain control, opioid use titrated according to pain evaluation is recommended but caution should be taken to limit the doses as much as possible.

2.1.2.1.1.3. Glycoprotein 2b3a inhibitors. The rationale for the use of glycoprotein 2b3a (GP2b3a) inhibitors was essentially based on the long delay between clopidogrel intake and maximum effect. The FINESSE trial failed to show a benefit of abciximab-facilitated PPCI compared with catheterization lab administration of the drug and although meta-analyses showed a benefit in coronary artery patency associated with GP2b3a inhibitor-facilitation, the clinical benefit of such strategy remained unproven.[34] A more recent meta-analysis comparing early versus late administration of abciximab in the setting of PPCI for STEMI showed a benefit of early strategy not only on coronary artery patency but also on mortality.[35] The ON-TIME-2 trial finally compared routine pre-hospital versus provisional in-hospital administration of high dose tirofiban associated with PPCI, showing a benefit of upstream GP2b3a inhibition on the primary thrombotic endpoint with no relevant excess in bleeding risk.[36]

The upstream use of 2b3a inhibitors seems to be especially interesting in high risk patients presenting early after symptom onset.[37,38]

The increased use of new more powerful P2Y12 inhibitors prasugrel and ticagrelor with more reliable and faster onset of action compared with clopidogrel has somewhat reduced the upstream use of GP2b3a inhibitors, which have only been assessed in association with clopidogrel. However, the delay in platelet reactivity inhibition may last several hours after oral P2Y12 inhibition in STEMI and such delay may be avoided by the use of GP2b3a inhibitors.[39]

Hence upstream GP2b3a inhibition in the pre-hospital setting may be considered in high risk patients (extensive infarct) presenting early (<2 h) after symptom onset. GP2b3a use may also be considered in self-presenters to spoke centres who satisfy the above-mentioned conditions before and during their transfer to hub centres for PPCI. Finally GP2b3a inhibitors may be used as an antiplatelet therapy bridge in patients unable to swallow oral P2Y12 inhibitors. The use of GP2b3a inhibitors in any case should be limited to patients at low risk of bleeding.

An alternative to GP2b3a inhibitors in the pre-hospital setting may be the intravenous P2Y12 inhibitor cangrelor, with a fast on–off effect, which has been associated with a reduction of thrombotic events in association with clopidogrel but not the newer oral P2Y12 inhibitors.[40] However, cangrelor use in the pre-hospital setting has not been yet validated.

2.1.2.1.1.4. Anticoagulants. The coordination between the pre-hospital and in-hospital therapies through shared protocols and real-time communication between teams is extremely critical with respect to anticoagulation regimen as switching between anticoagulants is associated with poor outcome and should be avoided.[9]

The pre-hospital administration of a combination of aspirin and UFH versus its in-hospital administration improved coronary artery patency in a small case versus control study.[23] The benefit of UFH administration in the emergency room as compared with the catheterization laboratory has also been reported in terms of coronary artery patency in another small sized case–control study.[41]

Despite the paucity of evidence, UFH is routinely given as soon as possible, including in the pre-hospital setting in many European EMSs.

Compared with UFH enoxaparin provides a more reliable and stable anticoagulation with no need for biological monitoring to assess its efficacy. Enoxaparin has been compared with UFH in the setting of PPCI in the ATOLL trial, where almost 70% of patients were randomized in the pre-hospital setting.[42] The study showed an almost significant (p=0.06) trend in favour of intravenous enoxaparin (0.5 mg/kg) with respect to the primary endpoint and a significant benefit of enoxaparin on several secondary outcomes including death/myocardial infarction (MI) or urgent revascularization (p=0.04) as well as a trend towards lower mortality (p=0.08). A meta-analysis of published studies confirms the benefit of enoxaparin compared with unfractionated heparin in the setting of PPCI, where its use is associated with a reduction of mortality, MI and bleeding complications.[43] The ESC guidelines recommend enoxaparin over unfractionated heparin with a grade IIa B level of recommendation.[9]

Hence the pre-hospital use of enoxaparin as a first line therapy, or UFH if enoxaparin is not available, during the transfer for PPCI is recommended.

The direct thrombin inhibitor bivalirudin has been compared with UFH in the pre-hospital setting in the EUROMAX trial.[44] The study showed the superiority of bivalirudin on the primary endpoint of the study (death or non coronary artery bypass grafting (CABG)-related bleeding) (p=0.001). The benefit was driven exclusively by the reduction of bleeding events. Although the study is clearly in favour of bivalirudin two issues have been raised: first, the routine use of GP2b3a inhibitors in about 59% of patients in the UFH group versus 4% in the bivalirudin group and, second, the higher risk of acute stent thrombosis

(relative risk 6.11 (1.37–27.24)) in the bivalirudin arm. Several meta-analyses, including one in the specific setting of STEMI, have consistently confirmed the benefit of bivalirudin in reducing the rates of bleeding as well as the higher risk of acute stent thrombosis associated with its use compared with the combination of UFH and GP2b3a inhibitors.[45,46] The controversy regarding the benefit of bivalirudin over UFH alone in reducing bleeding rates is supported by the results of the HEAT trial where, with similar rates of GP2b3a inhibition in bivalirudin and UFH arms, rates of bleeding were similar in the two study arms whereas acute stent thrombosis was significantly increased in the bivalirudin arm.[47] A pre-specified analysis of the EUROMAX trial, however, showed that the benefit of bivalirudin over UFH is consistent whether GP2b3a inhibitors are used on a routine basis or in bailout situations in association with UFH.[48] Furthermore a longer infusion of bivalirudin (>4 h after PCI) was associated with a reduction in the rates of stent thrombosis in the BRIGHT trial.[49]

The cost of bivalirudin, especially in a prolonged infusion regimen, compared with UFH or enoxaparin raises the question of its cost-effectiveness in many countries and its use in European countries remains relatively restricted. In view of the benefit on bleeding the use of bivalirudin may be recommended as a first line anticoagulation regimen in the setting of STEMI among patients at high bleeding risk and/or the elderly. A >4 h infusion of bivalirudin is highly recommended after PPCI in such patients.

Finally fondaparinux (2.5–5 mg intravenous bolus followed by 2.5 mg subcutaneous daily for eight days) compared with UFH was associated with poor outcome and is not recommended for use in PPCI.[50]

2.1.2.1.2. Transfer for PPCI. The PPCI strategy requires a transfer to a 24/7 PCI-capable centre. The need for onsite surgery dose not appear mandatory because of very low rates of coronary bypass surgery in haemodynamically stable patients. However, unstable patients with cardiogenic shock or suspicion of mechanical complication should, if possible, ideally be transferred to centres with onsite PCI and possibility of circulatory assistance implantation in the intensive care unit and onsite cardiac surgery, and if such a transfer destination will not delay revascularization.

2.1.2.2. Pre-hospital fibrinolysis strategy. Pre-hospital fibrinolysis is associated with an excellent long term outcome[51] and recommended over in-hospital fibrinolysis (IIa A) by the ESC guidelines as a part of a pharmaco-invasive strategy which must include immediate transfer to a PCI-capable centre for immediate rescue PCI if reperfusion has failed and an early (3–24 h) invasive approach, in all based on solid evidence.[9,52]

2.1.2.2.1. Adjunctive therapy in combination with pre-hospital fibrinolysis. The need and the use of adjunctive antithrombotic regimens at the time of fibrinolysis have been widely studied and are well documented.

2.1.2.2.1.1. Antiplatelet therapy. The historical ISIS 2 trial demonstrated the benefit of aspirin in combination with fibrinolysis with streptokinase in STEMI patients.[24] Hence aspirin administration at the time of fibrinolysis is mandatory.

The additional benefit of clopidogrel, the only P2Y12 inhibitor assessed in the setting of fibrinolysis, was demonstrated in patients <75 years old receiving aspirin and a clopidogrel loading dose of 300mg.[53] The 75mg dose in elderly patients is an expert-decided extension based on the all-coming STEMI COMMIT trial.[21] The newer P2Y12 inhibitors prasugrel and ticagrelor have not been assessed in combination with fibrinolysis and should not be used.

The use of clopidogrel (300 mg loading dose in <75 years old and 75 mg dose in ≥ 75 years old) in combination with fibrinolysis is mandatory.

2.1.2.2.1.1. Anticoagulation. The benefit of enoxaparin over UFH in combination with fibrinolysis by fibrin-specific agents is well documented.[54] Hence, enoxaparin should be the anticoagulant of choice in this setting as recommended by ESC guidelines (IA).[9] Following the use of the non-fibrin specific streptokinase, no anticoagulation is routinely required. EMS using the latter agent, despite the grade IB ESC recommendation in favour of fibrin specific agents, may not need to use concomitant anticoagulation. Although some data are available with bivalirudin and fondaparinux mainly in combination with streptokinase, their use in this setting has not been validated and is not recommended.[50,55]

2.1.2.2.2. Choice of fibrinolytic agent. The combination of tenecteplase, enoxaparin, aspirin and clopidogrel is the most widely studied and validated within the pharmaco-invasive strategy and may be preferably recommended. Tenecteplase is administered as a single weight-adjusted intravenous bolus, and is therefore the most convenient in the pre-hospital setting.

The STREAM trial, showing similar results between pre-hospital fibrinolysis and PPCI in early presenters who could have not undergone PCI within 60 min, highlighted the fact that a 50% reduction in the dose of tenecteplase in elderly patients (>75 years) is associated with a significant reduction of rates of stroke, translating to an improvement in mortality rates. Although the delay for PPCI after first medical contact was relatively important in the study (117 min) it was in the range of the ESC guidelines, and lower than what is reported in real life registries. These results published after the publication of the ESC guidelines for STEMI appear important enough to be translated into practice.[56]

A weight adjusted dose of tenecteplase as the first line fibrinolytic regimen is recommended if PPCI is not available in a timely fashion, with a half dose regimen in > 75 years old.

2.1.2.2.3 Transfer after pre-hospital fibrinolysis. Patients undergoing pre-hospital fibrinolysis should be directly transferred to a PCI-capable centre for early (3–24 h) angiography in the case of successful (ST segment elevation resolution > 50% and chest pain resolution within 60 min after fibrinolysis) and urgent rescue PCI in the case of unsuccessful fibrinolysis.[9]

2.1.2.3. Transfer for in-hospital fibrinolysis. Although quite rare, in some European regions both pre-hospital fibrinolysis and PPCI are still not available. Patient transfer to non-PCI-capable centres for in-hospital fibrinolysis is not recommended but remains the usual strategy in such regions with a 'scoop and run'-based EMS organization. The benefit of pre-hospital adjunctive antithrombotic therapy (aspirin, clopidogrel and anticoagulants) in these situations remains unknown, but such therapy may be started in the pre-hospital setting in the absence of any contraindication. These patients, as well as self-presenters to non-PCI-capable centres, should undergo reperfusion therapy by fibrinolysis as soon as possible in the emergency department and be immediately transferred to a PCI-capable centre. In such cases the organization of a true hub and spoke network between hospitals with and without catheterization facilities linked by an efficient transportation organization is highly recommended.[57–59]

Part 2

2.2. Non ST elevation ACS (NSTE-ACS)

The diagnosis of non ST elevation ACS (NSTE-ACS) in the pre-hospital setting is often challenging in the absence of routine use of biomarkers and imaging modalities. The difficulty is emphasized by the fact that some differential diagnoses such as aortic dissection and pericarditis are contra-indications to antithrombotic therapy. Thrombotic and bleeding risk assessment based on similar clinical findings and scores (Supplementary Table 2(b) to (d) and Supplementary Table 3) as for STEMI are highly recommended in the setting of NSTE-ACS where the balance between such risks leads the decision of invasive approach and antithrombotic regimen. Point of care troponin tests as well as trans-thoracic echocardiography may also be considered to help diagnosis and risk assessment in this setting.[60,61] However, their routine use requires more extensive clinical validation.

2.2.1. Treatment on board. Neither ESC nor American Heart Association/American College of Cardiology (AHA/ACC) guidelines specifically address the pre-hospital management of NSTE-ACS.[62,63] The timing of antiplatelet therapy also remains unclear in the guidelines with no timing recommended for aspirin and 'as soon as possible' recommended for a P2Y12 inhibitor in addition to aspirin.[63]

The benefit of pre-hospital antithrombotic therapy in the pre-hospital management of NSTE-ACS remains totally unknown even in such high-risk patients. There are no data demonstrating the benefit of pre-hospital versus in-hospital administration of aspirin or anticoagulants.

The benefit of pre-PCI treatment by clopidogrel in NSTE-ACS is also less obvious than in STEMI. The above-mentioned meta-analysis of randomized and non-randomized studies shows a reduction in major cardiac events – but not mortality – associated with clopidogrel pretreatment with no significant increase of the bleeding risk.[27] Nevertheless about 40% of suspected NSTE-ACS patients[64] do not undergo PCI and about 5% have coronary artery bypass surgery during the index hospitalization with an associated risk of CABG-related bleeding if a P2Y12 inhibitor is used. Another meta-analysis[65] of studies in the general setting of NSTE-ACS failed to show any mortality benefit and reported a significant increase in the risk of bleeding from thienopyridine pre-treatment (clopidogrel and prasugrel). The results of the latter study were, however, mostly driven by the ACCOAST trial comparing pre- versus post-angiography treatment by prasugrel while clopidogrel pre-treatment may have no significant effect on the risk of bleeding.[66] In this trial half dose prasugrel given before angiography, with another half given during the procedure, was compared with pre-angiography placebo and full procedural loading. Importantly, the median time to intervention in this trial was about four hours, much earlier than is often the case in usual daily practice.[67] Although the benefit of full dose prasugrel and a later angiography timing cannot be fully excluded, prasugrel should not be used in the pre-hospital setting as assessed in the ACCOAST trial prior to coronary angiography.

Finally the PLATO trial[64] compared ticagrelor and clopidogrel in a pre-treatment strategy across the full ACS spectrum (STEMI or NSTE-ACS managed with an invasive or medical strategy), showing a benefit in terms of cardiovascular mortality in favour of ticagrelor. However, the benefit of ticagrelor administration in the pre-hospital setting versus its in-hospital administration in the setting of NSTE-ACS remains unassessed.

Considering the lack of evidence and the risk of misdiagnosis of NSTE-ACS in the pre-hospital setting and the further possibility of cardiac surgery, the role of pre-hospital antithrombotic therapy remains a matter of debate and could be reduced to no therapy or aspirin alone in the absence of persistent chest pain and the need for urgent (<2 h) invasive assessment.

The ESC guidelines for NSTE-ACS[63] recommend urgent (<2 h) invasive assessment of coronary anatomy in patients with refractory angina despite optimal medical therapy associated with signs and symptoms of acute heart failure, haemodynamic instability or ventricular arrhythmia. In EMSs where emergency physicians are on board and where the diagnosis of high risk NSTE-ACS is highly

Table 6. Aortic dissection detection score of probability.[72]

High risk conditions and history	Marfan, Loeys–Dietz, Ehlers–Danlos, Turner syndrome, or other connective tissue disease. Patients with mutations in genes known to predispose to thoracic aortic aneurysms and dissection. Family history of aortic dissection or thoracic aortic aneurysm. Known aortic valve disease. Recent aortic manipulation (surgical or catheter-based). Known thoracic aortic aneurysm.
High risk pain features	Pain that is abrupt or instantaneous in onset. Pain that is severe in intensity. Pain that has a ripping, tearing, stabbing, or sharp quality.
High risk examination features	Pulse deficit. Systolic blood pressure limb differential greater than 20 mmHg. Focal neurologic deficit. Murmur of aortic regurgitation (new). Hypotension or shock.

Scoring: one point for the presence of one of the characteristics in any category.
Patients with a score > 0 are considered at high risk for aortic dissection (sensitivity 91%).

probable and an early invasive strategy is chosen, an antithrombotic regimen including aspirin, ticagrelor or clopidogrel loading dose and anticoagulation by enoxaparin or UFH may be considered. ECG teletransmission may be useful for the management of such patients in the absence of trained physicians on board. NSTE-ACS patients with cardiogenic shock, life-threatening arrhythmias and persistent ischaemia despite initial management should be managed similarly to STEMI patients. Despite limited evidence, consensus was obtained within the study groups to recommend pre-hospital anti-thrombotic therapy (aspirin, P2Y12 inhibitors, anticoagulants) and immediate invasive strategy in such patients.

Other anticoagulation regimens based on fondaparinux, preferably used in medically managed patients,[68] or bivalirudin, validated against a routine GP2b3a inhibitor + heparin regimen,[69] have not been assessed in the pre-hospital setting of NSTE-ACS and are not recommended.

2.2.2. Transfer. In most cases, patients with suspected NSTE ACS may be transferred to an emergency department or a chest pain unit when available for further diagnostic assessment (troponin, ultrasound) and therapeutic decision. In selected high-risk cases with haemodynamic instability or signs of heart failure patients may be transferred to intensive care or cardiac care units. Patients with persistent symptoms despite initial therapy should be transferred directly to a catheterization laboratory. High-risk patients should be directed by the EMS to facilities with on-site 24/7 interventional cardiology capability.

NSTE-ACS patients with cardiogenic shock should ideally be transferred to centres with onsite interventional cardiology, intensive cardiac care and possibility of circulatory support and cardiac surgery.

2.3. Suspected aortic dissection

Aortic dissection and other acute aortic syndromes are the most potentially lethal causes of chest pain. Aortic dissection should be considered not only in patients with chest pain but also those with abdominal or back pain, syncope, unexplained hypotension and focal neurological disorders. In the pre-hospital setting the diagnosis is based only on medical history and clinical findings. ECG, performed as for any chest pain, is usually normal. The presentation may be non-specific[70] (Supplementary Table 3) and aortic dissection is suspected at initial presentation in only 20% of those with a final diagnosis of aortic dissection.

Focused echocardiography (FoCUS) may be helpful to support the diagnosis of aortic dissection in the pre-hospital setting especially in cases where ECG signs of myocardial ischaemia are present.[71,72] The aortic dissection detection (ADD) score summarized in Table 6 is a useful tool for the pre-hospital orientation of diagnosis and its use in the pre-hospital setting is highly recommended.[73] While patients with an ADD score of 0 have a low probability of aortic dissection, those with a score ≥ 1 in the pre-hospital setting should be considered at high risk.

2.3.1. Treatment on board. The treatment during transfer in suspected aortic dissection is limited to pain relief and blood pressure control. The target heart rate and systolic blood pressure are <60 beats/min and 100–120 mmHg respectively in the absence of neurological complications. Intravenous beta-blockers (first choice), nitrates, sodium nitroprusside or calcium channel blockers are adequate options. Beta-blockers should be started before other antihypertensive drugs in order to avoid reflex tachycardia.

In the case of complications (stroke, tamponade, mesenteric ischaemia, acute aortic regurgitation, MI, cardiogenic shock) the treatment may be extremely complex but in the

pre-hospital setting limited to life support. The mortality rates even after adequate surgical or endovascular treatment remain extremely high in the presence of complications.

Withholding antithrombotic therapy in suspected aortic dissection complicated by ischaemic events is mandatory and requires careful and cautious diagnostic reasoning.

2.3.2. Transfer. Patients with a very high probability of aortic dissection (ADD score >1) should ideally be transferred to a centre with 24/7 available aortic imaging, that is, computed tomography, magnetic resonance imaging, trans-thoracic and trans-oesophageal echocardiography (TEE) and cardiac surgery.

As performed in some regions, aortic imaging/and cardiac surgery may be activated by the EMS during transfer and the patient admitted directly to radiology before proceeding to the operating theatre. In some cases imaging (TEE) may be performed in the operating theatre in a sedated patient. Transfer to a non-surgical centre for imaging before transfer to a facility with cardiac surgery will jeopardize the patient and should be avoided when the probability of aortic dissection is high. However, the latter statement may apply only to physician-based EMS.

2.4. Suspected pulmonary embolism

Pulmonary embolism may present as chest pain, dyspnoea, syncope, haemoptysis, cardiac arrest or a combination of these. Symptoms and signs are highly non-specific and may be found in many other cardiac or pulmonary conditions.[74] The use of clinical prediction scores (Table 7)[75] developed to determine the likelihood of pulmonary embolism is highly recommended in the pre-hospital setting. The positive diagnosis of pulmonary embolism requires pulmonary perfusion imaging.

The assessment of the severity of pulmonary embolism is highly recommended based on the presence of hypotension or signs of shock. The use of the simplified pulmonary embolism severity index (Supplementary Table 4) may be considered in the pre-hospital setting. However, it has been validated only in the setting of proven pulmonary embolism. ECG signs of right ventricular overload (inversion of T waves in leads V1–V4, QR pattern in V1, S1Q3 pattern, and incomplete or complete right bundle-branch block) are usually seen in more severe cases and the most frequent ECG signs are limited to sinus tachycardia or atrial fibrillation.

The use of point of care D-dimer assays to rule out pulmonary embolism as well as cardiac ultrasound detecting signs of acute pulmonary hypertension are neither validated in the pre-hospital setting nor available in most EMSs.

2.4.1. Treatment on board. In stable patients the treatment of pulmonary embolism can usually be delayed from the pre-hospital to the hospital setting after definitive diagnosis. The on board management of such patients requires continuous ECG and blood oxygen saturation monitoring and intravenous access.

Risk stratification in pulmonary embolism is essentially based on the presence or absence of haemodynamic compromise (i.e. cardiogenic shock, hypotension) that may require supportive measures (i.e. vascular expansion and inotropes) in the pre-hospital setting.

Point of care focused echocardiography in the pre-hospital setting may help demonstrate right ventricular enlargement and D-shaping of the left ventricle, suggesting high-risk pulmonary embolism.[72,75] Under these circumstances echocardiography allows also identification or exclusion of other differential diagnoses (tamponade, aortic dissection, acute left ventricular dysfunction, right ventricular infarction, mechanical complications of STEMI…). Echocardiographic findings in a patient with suspected pulmonary embolism and shock or cardiac arrest are sufficient to lead to reperfusion therapy by fibrinolysis or surgical or endovascular embolectomy.[76] Although not validated and not routinely performed, echocardiography guided reperfusion therapy in the pre-hospital setting may be considered in EMSs with trained operators in the field. Nevertheless

Table 7. Clinical prediction scores for pulmonary embolism.[75]

Wells' rule	Simplified scoring
Previous PE or DVT	1
Heart rate >100 beats/min	1
Surgery or immobilization within the past four weeks	1
Haemoptysis	1
Active cancer	1
Clinical signs of DVT	1
Alternative diagnosis less likely than PE	1
Clinical probability	
PE unlikely	0–1 criterion
PE likely	⩾2 criteria
Revised Geneva score	
Previous PE or DVT	1
Heart rate, beats/min	
75–94	1
⩾ 95	2
Surgery or fracture within the past month	1
Haemoptysis	1
Active cancer	1
Unilateral lower limb pain	1
Pain on lower limb deep venous palpation and unilateral oedema	1
Age >65 years	1
Clinical probability	
PE unlikely	0–2
PE likely	⩾3

PE: pulmonary embolism; DVT: deep vein thrombosis.

echocardiography should not delay the transfer of an unstable patient to the appropriate facility.

Finally, although D-dimer, plasma troponin and B-type natriuretic protein (BNP) tests are useful for the diagnosis or risk stratification of pulmonary embolism, the use of rapid assays in the pre-hospital setting is not validated and cannot be recommended at this point.

2.4.2. Transfer. Stable patients with pre-hospital suspicion of pulmonary embolism may be transferred to emergency departments or chest pain units for further diagnosis and treatment.

Patients with massive pulmonary embolism diagnosed by the presence of right ventricular enlargement and those with severe symptoms or haemodynamic instability (cardiac arrest, syncope, shock) should be transferred to intensive care units in tertiary centres equipped for thrombectomy.

2.5. Suspected pericarditis

Pericarditis is one of the common causes of chest pain, sometimes mimicking ACS. The diagnosis is suspected based on the clinical background (e.g. recent symptoms of viral infection), characteristics of the chest pain (modified by posture and breathing), physical findings (pericardial friction rub) and ECG findings (diffuse ST segment elevation without reciprocal ST depression, PR segment depression…). Positive diagnosis, usually based on biological signs of inflammation and possible pericardial effusion on echocardiography, cannot be confirmed in the pre-hospital setting. However, it is critical to consider pericarditis in every patient in whom fibrinolysis is considered for presumed STEMI.

2.5.1. Treatment on board. Stable uncomplicated pericarditis does not need any specific management during pre-hospital transportation. Pain relief by intravenous minor (paracetamol) or major (opiates) analgesics may be considered.

2.5.2. Transfer. Patients should be transferred to appropriate units (emergency department, chest pain unit, cardiology unit) in facilities where echocardiography and pericardiocentesis are available (cf. cardiac tamponade).

Part 3

3. Management of acute dyspnoea of cardiac origin

3.1. Suspected acute heart failure

Acute heart failure (AHF) is a frequent life-threatening condition requiring urgent management and hospitalization.[77,78] The correct diagnosis of AHF is challenging and requires cautious clinical reasoning. Patients with dyspnoea due to AHF have a high risk of early in-hospital death.

As recommended by the ESC guidelines,[79] the assessment of AHF is based on clinical and ECG findings as well as biomarkers and imaging data.

The pre-hospital management of AHF depends on its severity, cause and precipitating factors.

Recently a consensus paper on the pre-hospital and early in-hospital management of AHF from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine has been published.[80] Another position paper from ACCA has also set the basis of the interdisciplinary management of acute heart failure.[81] We refer readers to these valuable documents for their clear decision making algorithms and avoid providing details in this paper. Many aspects of the practical early in-hospital management of AHF, as depicted in the above papers, may be performed in the pre-hospital setting especially if emergency physicians are on board.

Risk assessment in the pre-hospital setting is mandatory as it directly impacts on the management of AHF. It is based on the presence or not of cardiogenic shock, haemodynamic instability (heart rate > 130 beats/min or <40, systolic blood pressure <90 mmHg), respiratory distress (respiration rate > 25, blood oxygen saturation <90%) and ECG findings (ventricular or supraventricular arrhythmia, bradycardia, ongoing ischaemia, i.e. STEMI, NSTE-ACS).

Focused ultrasound allows correct detection of pulmonary oedema, ascites, inferior vena cava and cardiac chambers dilatation and may be considered in the pre-hospital setting if competent staff are on board.

The point-of care BNP tests may also be used in the pre-hospital setting to confirm or exclude heart failure. Although feasible, neither ultrasound nor BNP testing in the pre-hospital setting should delay patient transfer, as their impact on outcome is still unknown.

3.1.1. Treatment on board. In the absence of cardiogenic shock the recommended treatment is:

- Oxygen with a target saturation >94%;
- Sublingual/intravenous nitrates titrated according to blood pressure;
- Intravenous diuretics (furosemide).

In the case of haemodynamic compromise and respiratory distress the recommended treatment comprises:

- Non-invasive ventilation (pre-hospital continuous positive airway pressure should be initiated promptly immediately if respiratory distress is detected);
- Invasive ventilation in the case of unsuccessful or contra-indicated non-invasive ventilation;
- Inotropic or vasopressor support.

Specific management of precipitating or causal factors is mandatory:

- Electrical cardioversion in the case of ventricular arrhythmia or rapid supraventricular tachycardia associated with haemodynamic and/or neurological compromise is mandatory;
- Antiarrhythmic drugs (amiodarone) in the case of well tolerated ventricular arrhythmia may be considered;
- Intravenous atropine and/or isoprenaline and/or external pacemaker – if available – may be considered in the case of severe bradycardia;
- Specific treatment of STEMI or NSTE-ACS.

These interventions require the presence on board of either an emergency physician or trained emergency medicine technicians or nurses using checklists under medical supervision and possibly teleconsulting.

3.1.2. Transfer. Stable patients who appear to respond rapidly to initial treatment may be transferred to emergency departments, chest pain units, or cardiology or medicine wards.

Unstable patients (i.e. haemodynamic instability, respiratory distress) and/or those who fail to respond adequately to the treatment should be transferred to emergency departments with critical care facilities and/or to intensive cardiac care units. Patients with refractory heart failure and cardiogenic shock may be more adequately transferred to centres with onsite possibility of circulatory assistance.

3.2. Suspected tamponade

Tamponade is a consequence of cardiac compression related to increased intrapericardial pressure by fast occurrence of a significant pericardial effusion. The ESC taskforce on pericardial disease distinguishes the 'surgical tamponade', that is, compression within minutes to hours (e.g. bleeding) requiring urgent pericardiocentesis, and 'medical tamponade', that is, compression developing within days to weeks (e.g. inflammatory process), which may be initially medically managed in the absence of haemodynamic compromise.[82]

The pre-hospital risk assessment is mandatory. It is based on the detection of signs of shock, haemodynamic instability, respiratory distress, acute right ventricular compression and increased systemic venous pressure (jugular vein distension), quiet heart sounds and low voltage and/or electrical alternans on the ECG.

Although the diagnosis of cardiac tamponade is clinical, echocardiography is the diagnostic tool allowing exclusion of other causes of increased systemic venous pressure and visualization of pericardial effusion with diastolic compression of the right heart chambers, inferior vena cava distension, and respiratory variations of mitral, aortic and/or tricuspid flow. It may also show the aetiology of the tamponade (aortic dissection, left ventricular wall rupture…). Hence the pre-hospital use of echocardiography in this setting may be considered, if expertise is available and if it does not delay patient transfer.

3.2.1. Treatment on board. The emergency treatment of tamponade is pericardiocentesis.

Echocardiography allows guiding of urgent percutaneous pericardiocentesis when indicated.[83,84] However, the presence of ultrasound devices and emergency physicians is mandatory if such interventions are to be performed in the pre-hospital setting.

Blind pericardiocentesis may be performed by trained operators in the absence of ultrasound in severe cases with cardiac or 'near-cardiac' arrest with very high likelihood of tamponade (e.g. known pericardial effusion). However, blind pericardiocentesis is associated with significantly higher risk of complications and is not recommended.[83]

In most EMSs the suspicion of tamponade should be treated by vascular expansion, inotropic/vasopressor support, oxygen/ventilation if needed and fast transfer to the appropriate facility.

3.2.2. Transfer. The patient with suspicion of tamponade should be transferred, in the 'sitting position', to the nearest centre with the possibility of ultrasound-guided pericardiocentesis, ideally with on-site cardiac surgery.

4. Management of chest pain and/or acute dyspnoea caused by cardiac arrhythmias and conduction dysfunction

Chest pain and dyspnoea may occasionally be caused by cardiac arrhythmias.

ECG teletransmission by EMS teams not including emergency physicians skilled in identification of dysrhythmias may be extremely useful for a rapid diagnosis and treatment of principal arrhythmias and is therefore recommended.

Simple algorithms may facilitate the distinction between supraventricular arrhythmia, characterized by narrow QRS complexes, and ventricular arrhythmia suspected in the presence of wide-QRS regular tachycardia until proven otherwise (cf. ACCA toolkit).

Continuous ECG monitoring and venous access is mandatory in all patients with any type of cardiac arrhythmia.

Both supraventricular and ventricular arrhythmias, associated with haemodynamic instability, loss of consciousness or resistant angina pectoris should be promptly treated with electrical cardioversion.

Pharmacological treatment of cardiac arrhythmias in the pre-hospital setting may be considered in selected conditions.

The use of intravenous amiodarone may be associated with side effects and has relatively limited efficacy for the management of ventricular tachycardia in the pre-hospital setting.[85,86] It should be reserved for patients with resuscitated cardiac arrest as a prevention of recurrent life-threatening arrhythmia.

There is no clear evidence that pre-hospital cardioversion of well-tolerated supraventricular arrhythmia may improve survival and outcomes. Hence a direct transfer to adequate centres (emergency department, chest pain unit, intensive/cardiac care unit) for anti-coagulation and possible anti-arrhythmic therapy following current ESC guidelines[87] is recommended in the absence of the above-mentioned signs of poor tolerance. Amiodarone may be considered in prevention of recurrent supraventricular arrhythmia with haemodynamic compromise after urgent electrical cardioversion in the pre-hospital setting.

The pre-hospital use of adenosine may be considered in selected cases of re-entrant supraventricular tachycardia.[88,89] If used, a 6–12 mg intravenous bolus should be injected directly and rapidly.

Special care should be taken in the pre-hospital setting in patients with very rapid, irregular wide QRS tachycardia, which may represent atrial fibrillation in a patient with pre-excitation. The use of AV slowing agents (e.g. verapamil, adenosine, digoxin) is contraindicated in these patients and electrical cardioversion is usually the treatment of choice.

Although evidence is almost limited to pre-hospital feasibility studies, atropine, adrenaline, isoprenaline and external pacing are recommended in the pre-hospital setting in patients with severe bradycardia associated with haemodynamic instability (hypotension, shock) and/or loss of consciousness.[90,91]

Patients with well-tolerated arrhythmia do not require any specific treatment.

However, all patients with symptomatic cardiac arrhythmia should be first transferred to a facility with continuous ECG monitoring (emergency department, chest pain unit, intensive or continuous care unit).

5. Future perspectives

5.1. Filling gaps in evidence

The challenge of cardiovascular emergencies in the pre-hospital setting is to provide early diagnosis and treatment where diagnostic tools, therapeutic options and specialist consultation are limited.

There is a need for the systematic evaluation of pre-hospital compared with in-hospital therapies, similar to what has been done for fibrinolysis or bivalirudin and more recently for ticagrelor in the setting of STEMI based on adequately designed randomized trials. Research also has to be promoted for the evaluation of pre-hospital diagnostic tools. Although the pre-hospital feasibility of point-of care tests (troponin, BNP, haemoglobin, D-dimers) and focused cardiac and pulmonary ultrasound have been reported, it is critical to assess their benefit in terms of outcome and their cost-effectiveness before their routine use. It is also important to assess and define adequate transfer destinations.

Timeframes, in addition to those already defined by the ESC guidelines, should be defined to assess the patient-related time and the EMS call to first medical contact time to evaluate and improve the population awareness and the regional effectiveness of the EMS.

In order to provide strong evidence, it is also important to define and assess the levels of competence required for the pre-hospital teams. Although the study group recommends the 'European model' of EMSs with routine or provisional emergency physicians on board, its evaluation compared with 'scoop and run' systems in terms of quality of care and cost-effectiveness by adequate prospective trials and not only registries is critical to provide the most effective care in the pre-hospital setting.

5.2. Acute cardiovascular care networks

There is a need for well-defined hub and spoke networks similar to those already existing for STEMI[59] for all other cardiovascular emergencies (e.g. acute heart failure, aortic dissection, etc.) with an organized multidisciplinary approach.[92] Such networks may include general practitioners who may manage patients not transferred to the hospital after initial evaluation and treatment by the EMS and help reduce the frequent crowding of emergency departments and cost. Many patients with acute heart failure may benefit from such strategies backed by telemedicine.

The wide availability of information technologies and fast communication networks has opened the door for the teletransmission of medical data, teleconsulting and telemedicine. The evaluation of technology, however, lags behind its evolution. There is a clear need for assessment and validation of such technologies not only in terms of patient outcome but also in terms of confidentiality of medical information and medico-economics.

Specific and homogenous education programmes for physicians, paramedics, nurses, dispatchers and emergency technicians as well as quality of care indicators and programmes are needed within networks in order to assess and improve the quality of care in the pre-hospital setting.

Finally, population educational campaigns should be a part of the acute cardiovascular network initiatives in order to reduce the patient-related delays.

6. Conclusions

Despite the variety of pre-hospital care organizations, standardized high-quality care of patients with chest pain

and acute dyspnoea in the pre-hospital setting is mandatory. While the organization of STEMI networks is well defined, other acute cardiovascular conditions lack specific pre-hospital evidence and guidelines. There is a need for clear action plans in the pre-hospital setting with immediate management and secure transfer to centres adapted to specific patient conditions.

The ACCA has gathered, through the ACCA toolkit and the present work, important diagnostic and therapeutic pathways in the work-up of such patients. However, many questions on the scientific and practical aspects of pre-hospital care of acute cardiovascular conditions remain to be addressed in well powered, clinical trials in the near future.

Conflict of interest

The conflict of interests of co-authors are reported at the study groups page at http://www.escardio.org/The-ESC/Communities/Acute-Cardiovascular-Care-Association-(ACCA)/About/Pre-hospital-Care-Study-Group.

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Summary of recommendations

Levels of recommendation

- *Mandatory*: the treatment or procedure is considered as the only option based on strong evidence and/or general consensus. Alternatives do not exist or may jeopardize quality of care.
- *Highly recommended*: the treatment or procedure is considered as the best option in comparison with alternatives based on moderate to strong evidence and/or general consensus.
- *Recommended*: the treatment or procedure is a good option in comparison with alternatives based on limited evidence but general consensus.
- *May be considered*: the treatment or procedure is acceptable and/or feasible with conflicting evidence and/or opinion on the benefit. Its application is limited to specific situations.
- *Not recommended*: the treatment or procedure is associated with harm or cost with no improvement of outcome based on evidence or general consensus.

Competence and equipment on board

- The organization of networks between pre-hospital services and hospital departments involved in the management of acute cardiovascular emergencies based on shared protocols is *mandatory*.
- Physician-based EMSs with the availability of emergency physicians in the case of chest pain or acute dyspnoea are *recommended.*

STEMI

Risk assessment in STEMI

- The use of clinical findings and ECG for the risk assessment is *mandatory.*
- Recording 18-lead ECG within 10 minutes following first medical contact is *mandatory.*
- Specific training in ECG interpretation for all EMS personnel in a position to provide care to STEMI patients is *mandatory.*
- The pre-hospital use of mini-GRACE or TIMI scores *may be considered* if it does not delay reperfusion therapy.
- The pre-hospital use of troponin point-of care tests is *not recommended* in STEMI.
- Perfect knowledge of contraindications for fibrinolytic therapy is *mandatory* for all EMS personnel who may provide fibrinolysis.
- The ability to detect a high risk of bleeding based on simple clinical and history data is *mandatory* for all EMS personnel who may provide fibrinolysis or antithrombotic therapy.
- Withholding all antithrombotic medication and rapid transfer to a PCI-capable centre in patients with active bleeding or at very high risk of bleeding is *mandatory.*

STEMI networks and reperfusion therapy

- Organization of regional STEMI networks with a shared written protocol for the choice of reperfusion strategy, antithrombotic therapy and patient transfer is *mandatory.*
- PPCI is *recommended* over fibrinolysis if it can be performed in a timely manner.
- Pre-hospital fibrinolysis is *highly recommended* if first medical contact time to PCI is prolonged, particularly among early presenters at low bleeding risk.
- The assessment of the balance between the benefit and the risk of pre-hospital fibrinolysis >6 h after symptom onset in EMSs that can provide both reperfusion strategies is *highly recommended.*
- In elderly patients (>75 years) presenting >6 h after symptom onset with non-extensive STEMI and who are potential candidates for fibrinolysis, switching to a PPCI strategy *may be considered.*
- Direct telephone contact between the pre-hospital team, the emergency medical communication centre and interventional cardiology team with ECG teletransmission is *recommended* for planning reperfusion therapy in borderline cases.
- The routine use of nitrates, beta-blockers and oxygen supplementation is *not recommended* in the pre-hospital setting.

PPCI strategy

- Recommended examples of pre-hospital adjunctive therapy are reported in Table 4.
- Pre-hospital use of aspirin is *recommended* prior to PPCI.
- Pre-hospital loading doses of P2Y12 inhibitors in the setting of STEMI is *recommended* prior to PPCI.
- Ticagrelor and prasugrel with respect to their contraindications are *recommended* as first line P2Y12 inhibitors.
- Clopidogrel is *recommended* when ticagrelor or prasugrel are unavailable or contraindicated.
- Withholding pre-hospital antithrombotic therapy in the presence of high bleeding risk or uncertain STEMI diagnosis is *highly recommended*.
- Opioid use titrated according to pain evaluation is *recommended* but caution should be taken to limit the doses as much as possible in light of its potential interaction with oral antiplatelet therapy.

- Upstream GP2b3a inhibition *may be considered* prior to PPCI in high risk patients (extensive infarct) presenting early (<2 h) after symptom onset, in self-presenters to spoke centres who satisfy the above-mentioned conditions and who are to be transferred to hub centres for PPCI, and as an antiplatelet therapy bridge in patients unable to swallow oral P2Y12 inhibitors.
- The use of GP2b3a is only *recommended* in patients at low risk of bleeding.
- The pre-hospital use of enoxaparin as a first line therapy, or UFH if enoxaparin is not available, during the transfer for PPCI is *recommended*.
- Bivalirudin is *recommended* as a first line anticoagulation regimen in the setting of STEMI among patients at high bleeding risk and/or the elderly.
- A >4h infusion of bivalirudin is *highly recommended* after PPCI in such patients.
- Fondaprinux is *not recommended* for use in PPCI.
- The routine transfer to facilities with 24/7 PPCI is *mandatory*.
- The routine transfer to facilities with onsite surgery is *not recommended.*
- Transfer of unstable patients with cardiogenic shock or suspicion of mechanical complication to centres with onsite PCI and possibility of circulatory assistance implantation in the ICU and optimally onsite cardiac surgery is *recommended* if such a transfer destination will not delay revascularization.

Pre-hospital fibrinolysis strategy

- A recommended pre-hospital fibrinolysis regimen is reported in Table 5.
- Pre-hospital fibrinolysis is *highly recommended* over in-hospital fibrinolysis.
- Pre-hospital fibrinolysis with immediate transfer to a PCI-capable centre is *highly recommended.*
- Aspirin administration at the time of fibrinolysis is *mandatory.*
- Clopidogrel (300 mg loading dose in <75 years old and 75 mg dose in ≥ 75 years old) in combination with pre-hospital fibrinolysis is *mandatory.*
- A weight adjusted dose of tenecteplase as the first line pre-hospital fibrinolytic regimen is *recommended* with a half dose regimen in > 75 years old.
- Anticoagulation is *mandatory* at the time of pre-hospital fibrinolysis with fibrin specific agents.
- Enoxaparin is *highly recommended* as the anticoagulant of choice in this setting.
- Bivalirudin and fondaparinux are *not recommended* in combination with pre-hospital fibrinolysis.

NSTE-ACS

- Thrombotic and bleeding risk assessment is *highly recommended* in the setting of NSTE-ACS.
- Point of care troponin tests *may be considered* in the setting of NSTE-ACS.
- In the case of chest pain at first medical contact, sublingual or intravenous nitrates titrated to blood pressure are *recommended.*
- Transfer to the appropriate facility without any 'en route' treatment or aspirin alone is *recommended* in the absence of need for urgent (<2 h) invasive assessment.
- In EMSs where emergency physicians are on board and in the case of an early invasive strategy (<2 h), an antithrombotic therapy including aspirin, ticagrelor or clopidogrel loading dose and anticoagulation by enoxaparin or UFH *may be considered.*
- The use of prasugrel in the pre-hospital setting is *not recommended.*
- A management similar to STEMI is *recommended* in NSTE-ACS patients with cardiogenic shock, life-threatening arrhythmias or persistent ischaemia despite initial management, with an antithrombotic regimen including aspirin, ticagrelor or clopidogrel loading dose and anticoagulation by enoxaparin or UFH, and immediate invasive strategy.
- In the case of stable NSTE-ACS, transfer to an emergency department or a chest pain unit is *recommended* for patients with suspected NSTE-ACS.
- In high-risk patients with haemodynamic instability or signs of heart failure a transfer to emergency departments with possibility of critical care or intensive cardiac care units is *recommended*. In such patients a transfer to facilities with on-site 24/7 interventional cardiology capability is *recommended*.
- In patients with persistent symptoms despite initial therapy a direct transfer to a catheterization laboratory is *recommended.*
- In the case of NSTE-ACS with cardiogenic shock transfer to centers with onsite interventional cardiology, intensive cardiac care and possibility of circulatory support and cardiac surgery is *recommended.*

Aortic dissection

- The use of ADD score in the pre-hospital setting is *highly recommended.*
- FoCUS echocardiography *may be considered* to support the diagnosis of aortic dissection in the pre-hospital setting.
- A treatment limited to pain relief and blood pressure control is recommended in suspected aortic dissection.
- The *recommended* target heart rate and systolic blood pressure are <60 beats/min and between 100 and 120 mmHg respectively in the absence of neurological complications.

- Intravenous beta-blockers, nitrates, sodium nitroprusside or calcium channel blockers are *recommended* for blood pressure control.
- Starting beta-blockers before other antihypertensive drugs is *highly recommended.*
- In the case of complications life support and rapid transfer are *recommended.*
- Withholding antithrombotic therapy in suspected aortic dissection is *mandatory.*
- Transfer of patients with a very high probability of aortic dissection (ADD score ≥ 1) to a centre with 24/7 available aortic imaging and cardiac surgery is *mandatory.*
- Activation of aortic imaging and cardiac surgery and admission directly to radiology before proceeding to the operating theatre *may be considered.*
- Transfer to a non-surgical centre for imaging before transfer to a facility with cardiac surgery is *not recommended.*

Pulmonary embolism

- The use of clinical prediction scores developed to determine the likelihood of pulmonary embolism is *highly recommended*.
- The use of point of care D-dimer, troponin and BNP tests is *not recommended.*
- In patients with suspected pulmonary embolism continuous ECG and blood oxygen saturation monitoring, and an intravenous access during transfer are *highly recommended.*
- Point of care FoCUS echocardiography *may be considered* in the pre-hospital setting for evaluation of the severity of pulmonary embolism.
- Transfer to emergency departments or chest pain units is *recommended* for stable patients with suspicion of pulmonary embolism.
- Transfer of patients with severe symptoms or haemodynamic instability (cardiac arrest, syncope, shock) or right ventricular enlargement on echocardiography – if performed – to intensive care units in centres equipped for thrombectomy is *highly recommended.*
- Echocardiography guided reperfusion therapy in the pre-hospital setting *may be considered*, if expertise is available, in patients with haemodynamic instability.

Pericarditis

- It is *recommended* to consider pericarditis in every patient in whom fibrinolysis is considered for presumed STEMI.
- Specific management of stable uncomplicated pericarditis during the pre-hospital transportation is *not recommended.*
- Pain relief by intravenous minor (paracetamol) or major (opioids) analgesics *may be considered.*
- Transfer to appropriate units (emergency department, chest pain unit, cardiology unit) in facilities where echocardiography and pericardiocentesis are available is *recommended.*

AHF

- Risk assessment in the pre-hospital setting based on the following characteristics is *mandatory*:
  - Presence of cardiogenic shock; haemodynamic instability (heart rate > 130 beats/min or <40, systolic blood pressure <90 mmHg); respiratory distress (respiration rate > 25, blood oxygen saturation <90%); ECG findings (ventricular or supraventricular arrhythmia, bradycardia, on-going ischaemia (i.e. STEMI, NSTE-ACS)).
- FoCUS pulmonary and cardiac ultrasound *may be considered* in the pre-hospital setting if competent staff are on board.
- The point-of care BNP tests *may be considered* in the pre-hospital setting.
- Delaying transfer for ultrasound or BNP testing in the pre-hospital setting is *not recommended.*
- In the absence of cardiogenic shock the *recommended* treatment is:
  - Oxygen with a target saturation >94%;
  - Sublingual/intravenous nitrates titrated according to blood pressure;
  - Intravenous diuretics (furosemide).
- In the case of haemodynamic compromise and respiratory distress the *recommended* treatment is:
  - Non-invasive ventilation;
  - Invasive ventilation in the case of unsuccessful or contra-indicated non-invasive ventilation;
  - Inotropic or vasopressor support.
- Specific management of precipitating or causal factors is *mandatory*:
  - Electrical cardioversion in the case of ventricular arrhythmia or rapid supraventricular tachycardia associated with haemodynamic and/or neurological compromise;
  - Intravenous atropine and/or isoprenaline and/or external pacemaker if available in the case of severe bradycardia;
  - Specific treatment of STEMI or NSTE-ACS.
- Transfer to emergency departments, chest pain units, cardiology or medicine wards is *recommended* in stable patients who respond rapidly to initial treatment.
- Transfer to emergency departments with critical care facilities and/or to intensive cardiac care units is

highly recommended for unstable patients and/or those who fail to respond to initial treatment.
- Transfer to centres with onsite possibility of circulatory assistance *may be considered* in patients with refractory heart failure and cardiogenic shock.

Tamponade

- The pre-hospital risk assessment based on the following characteristics is *mandatory*:
  - Presence of cardiogenic shock; haemodynamic instability (heart rate > 130 beats/min or <40, systolic blood pressure <90 mmHg); signs of acute right ventricular compression and increased systemic venous pressure (jugular vein distension); respiratory distress (respiration rate > 25, blood oxygen saturation <90%); low voltage, and/or electrical alternans on the ECG.
- The pre-hospital use of echocardiography in this setting *may be considered* if expertise is available and if it does not delay patient transfer.
- Ultrasound-guided pericardiocentesis *may be considered* in the pre-hospital setting if ultrasound devices and medical expertise are available on board.
- Blind pericardiocentesis *may be considered* by highly trained medical operators in the absence of ultrasound in severe cases with refractory cardiac or 'near-cardiac' arrest with very high likelihood of tamponade.
- Rapid transfer of patients with suspicion of tamponade to the nearest centre with the possibility of ultrasound-guided pericardiocentesis and/or cardiac surgery on-site is *mandatory*.

Chest pain or dyspnoea in relation with cardiac arrhythmia

- Continuous ECG monitoring and venous access are *mandatory* in all patients with any type of cardiac arrhythmia.
- Specific ECG training and ECG tele-transmission by EMS teams not including emergency physicians skilled in identification of dysrhythmias is *highly recommended*.
- Pre-hospital electrical cardioversion is *recommended* in patients with rapid ventricular or supraventricular arrhythmias associated with haemodynamic instability, loss of consciousness or resistant angina pectoris.
- Pharmacological treatment of cardiac arrhythmias in the pre-hospital setting *may be considered* in selected conditions.
- Intravenous amiodarone *may be considered* for patients with resuscitated cardiac arrest as a prevention of recurrent life-threatening ventricular arrhythmia.
- Intravenous amiodarone *may be considered* in prevention of recurrent supraventricular arrhythmia with haemodynamic compromise after urgent electrical cardioversion.
- Intravenous adenosine *may be considered* in selected cases of re-entrant supraventricular tachycardia.
- In the case of very rapid, irregular wide QRS tachycardia – possible atrial fibrillation with pre-excitation – the use of AV slowing agents is *not recommended* (contraindicated). In these patients electrical cardioversion is recommended.
- Atropine, adrenaline, isoprenaline and external pacing are *recommended* in the pre-hospital setting in patients with severe bradycardia associated with haemodynamic instability (hypotension, shock) and/or loss of consciousness.
- A direct transfer of well tolerated arrhythmia without any specific treatment to adequate structures is *recommended*.
- Transfer to a facility with continuous ECG monitoring (emergency department, chest pain unit, intensive or continuous care unit) is *mandatory* for all patients with symptomatic cardiac arrhythmia.