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Is it possible to reduce time to appropriate treatment of acute coronary syndrome through a faster diagnosis?

Focus on future innovative technologies and related treatments

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ABSTRACT

Patients with chest pain represent 5% of the total Emergency Department (ED) presentations and among these only 5–15% receive a final diagnosis of acute coronary syndrome (ACS), while up to 2% are still discharged with a missed ACS diagnosis. The diagnosis of ACS depends on a combination of clinical symptoms, ECG findings, and cardiac biomarkers. ACS management starts from the pre-hospital setting, where the use of successful networks, efficient emergency medical systems and telemedicine, combined with patient education campaigns, has proved to improved survival. Unfortunately, at ED arrival, ACS diagnosis still represents a challenge for emergency physicians, whereas clinical presentations can be widely variable and the diagnostic tools available are still quite limited. While the 12-lead ECG is the first-line test, it could be often non diagnostic so the experimental use of innovative and more accurate device seems to overcome its limits. Moreover, the introduction of high-sensitivity or ultrasensitive troponins assays and point-of-care (POCT) testing for troponins have proved their utility, reducing the time to rule-in and to rule-out for patients presenting with chest pain since ED admission. As soon as ACS is diagnosed, it is mandatory to immediately start treatment, according to guidelines. This is even more important in the era of innovative and emerging P2Y12 inhibitors that have shown to play an important benefit for ACS treatment. The aim of this article is to show the ideal approach to ACS, from symptom onset to early treatment in the ED, to show innovative tools for ACS diagnosis and treatment in order to improve outcome for these patients.

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Introduction

The term 'acute coronary syndrome' (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) [1].

In the USA, more than 400,000 Americans die annually of coronary artery disease, and more than 1,000,000 have acute coronary syndromes (ACS) [2]. Moreover, between 2010 and 2030, the total direct medical costs in the USA for cardiovascular diseases are projected to triple from \$273 billion to \$818 billion [3]; consequently there is an urgent need to optimize ACS

management with an ideal approach in the early phase of the disease in order to reduce myocardium loss and to improve patient outcomes worldwide.

Chest pain patients presenting to the Emergency Department (ED) represent 5% of the total number of ED accesses. Among these patients, 5–15% receive a final diagnosis of ACS, but today still up to 2% are discharged with a missed ACS diagnosis [1].

The leading symptom that initiates the diagnostic and therapeutic cascade for ACS is chest pain, but the diagnosis of ACS depends variably on a combination of clinical symptoms, ECG findings, and cardiac biomarkers; classification of patients is based on the electrocardiogram (ECG) [1].

Management of ACS is targeted at restoring and maintaining coronary blood flow and improving myocardial oxygen balance [4]. Early diagnosis and treatment in ED is fundamental for improving patient survival.

Pre-hospital care

In the first hours from the onset of symptoms the possibility of saving lives decreases very quickly with time, while the length of the delay to treatment is inversely related to the number of saved lives, especially in patients with STEMI [5]. Pre-hospital care may be invalidated by two main causes of delay: ACS symptoms late acknowledgment by subject himself and patient's late transport to the hospital. In order to decrease these delays it should be important to contemporary train patients, EPs and paramedics, and to establish a network to improve ambulance response time [6]. The main features of a successful network include: a clear definition of the geographical areas of interest, targeted protocols according to risk stratification, and close cooperation among caregivers and institutions [7]. It has been demonstrated that these networks induce an increase in the number of reperfused patients, a reduction of heart failure and recurrent myocardial infarction and a decrease in both short and long term mortality [8].

Patient-related delay is the most difficult to be reduced: it is still very long and almost unchanged through the years [9]. Patients with longer decision times tend to be older, female, diabetics, with atypical symptoms. Patient education campaigns did not yield good results in the past [10], probably because of a short duration. Anyway, good results have been obtained by AHA Mission Lifeline in the USA [11] and by other initiatives in Europe [12, 13]. For example, in a randomized controlled trial, Mooney M et al. recently tested an educational intervention, composed by a 40-minutes individualized education session, enforced 1 month later by telephone call, and they demonstrated that median delay time was significantly lower in the

intervention compared to the control group (1.7 h v. 7.1 h; $p \leq 0.001$) [14].

The Emergency Medical System (EMS) plays a key role in ACS management: it can receive the call for help through an emergency phone number, dispatch the proper ambulance and staff to the scene [15], rescue the patient, start the pharmacological therapy and transport the patient in the fastest way to the most suitable centre. Unfortunately, the utilization of the EMS in Europe is very variable, ranging from 18 to 85% of the STEMI cases in the different countries [16] and it has been shown that the lack of the EMS use is linked to longer delays in treatment and to worse outcomes [17]. There are basically two EMS models: with physicians-staffed ambulances; or with paramedics/nurses-staffed ambulances, working with protocols and physicians' support by telemedicine [18, 19]. Telemedicine integrates the use of telecommunication and of information technologies to eliminate distance barriers and facilitate real-time collaborative patient management. For example, the use of pre-hospital ECG (PHECG) has been shown to reduce the time to reperfusion [20], although high quality ECG recording is a specific process of care, requiring training [21]. The PHECG can be interpreted by the ECG machine automated software, by EMS personnel in the ambulance or by a reference centre after tele-transmission in order to reduce door-to-balloon (D2B) time and mortality [22]. The agreement on STEMI diagnosis on the ECG between well trained paramedics and physicians seems to be good [23], but it is important to underline that both knowledge and skills should not only be acquired but also maintained by physicians and paramedics. However, adherence to guidelines and protocols in the pre-hospital setting is still suboptimal and widely variable [24]. Regarding transport to the ED, there are two main transfer models: the hub-and-spoke transfer system [25] and the STEMI receiving centre (SRC) organization. In the first model, patients presenting directly to a non-PPCI capable centre are transferred to a PPCI centre, within the shortest interval and particularly with the shortest door-in-door-out time [26]. In the second transfer model, non-SRC are bypassed by the transport system, according to diversion protocols which allow a direct transfer of the patients from the field to a 24 h/7 days PPCI hospital [27]. In the experience of the city of Vienna, a partial rotating system in the function of SRC among different hospitals resulted in an increase of reperfused patients (from 66 to 87%), in an important reduction of mortality (from 16.0 to 9.5%), and in an equitable access to care among all STEMI patients [13]. Otherwise, a reduction of both short and long-term mortality was shown by other networks, as the one of Bologna in Italy [28].

There is a paucity of evidence-based data in pre-hospital ACS care, and high-quality research in

this field is mandatory and should be strongly encouraged. Chest Pain Clinical Database in the Emergency Department is an Italian registry proposal, an observational prospective study, with the aim to collect data about ED patients with chest pain suggestive of ACS. These patients differ from those of cardiological trials, because they are usually older and they have different comorbidities.

ED arrival: ACS diagnosis

At ED arrival ACS diagnosis needs to be performed as soon as possible since a delayed 'rule in' increases morbidity and mortality, leading to increased risk of complications, while delayed 'rule out' contributes to overcrowding in the ED, increasing patients' uncertainty and anxiety and resulting in a significant cost to the healthcare system.

Typical clinical presentation of ACS patients is represented by retrosternal pressure or heaviness ('angina') radiating to the left arm, neck, or jaw, which may be intermittent (usually lasting for several minutes) or persistent. Other common presentation symptoms are diaphoresis, nausea, abdominal pain, dyspnea, and syncope. However, 30% of STEMI patients arrive at ED presenting atypical symptoms [29] such as epigastric pain, indigestion, stabbing chest pain, chest pain with some pleuritic features, or increasing dyspnea (often observed in elderly patients, in women, and in patients with diabetes, chronic renal failure, or dementia). Moreover, the exacerbation of symptoms by physical exertion, or their relief at rest or after the administration of nitrates, supports a diagnosis of ischemia [7].

However, EPs well know that ACS patients may be totally asymptomatic and that chest pain can be a confusing symptom, and it can hide other life-threatening diseases, apart from ACS, such as pulmonary embolism, aortic dissection, pericarditis, valvular heart disease [30].

ECG

A 12-lead electrocardiogram (ECG) is the single, first-line, most important test in the initial evaluation of patients with ACS, and it should be obtained within 10 minutes from the first medical contact [31]. ECG recordings should be repeated at least at 3 h, 6–9 h and 24 h after first presentation, and immediately in the case of recurrence of chest pain or symptoms [7]. However, it is well known that 12-lead ECG is often non diagnostic. Moreover, it should be remembered that the posterior and lateral walls are not adequately represented on the 12-lead ECG and therefore it may not completely exclude ischemia in those territories. These considerations lead to the introduction of a new, more accurate ECG device with 80 Leads ECG (HeartScape). This system utilizes 80 data collection points, including 58 anterior leads, 12 lateral leads, and 10 posterior leads, that provide a 360-degree view of the electrical activity of the heart. The increased spatial view of the heart can assist EPs to better diagnose chest pain patients in the ED. The device is easy-to-use and directly shows on the monitor a 3D Colour-coded Torso Map, built using data from a single beat taken at each electrode. Red colour represents a positive deflection above isoelectric, blue colour a negative deflection below isoelectric, while green colour means no deflection (Fig. 1).

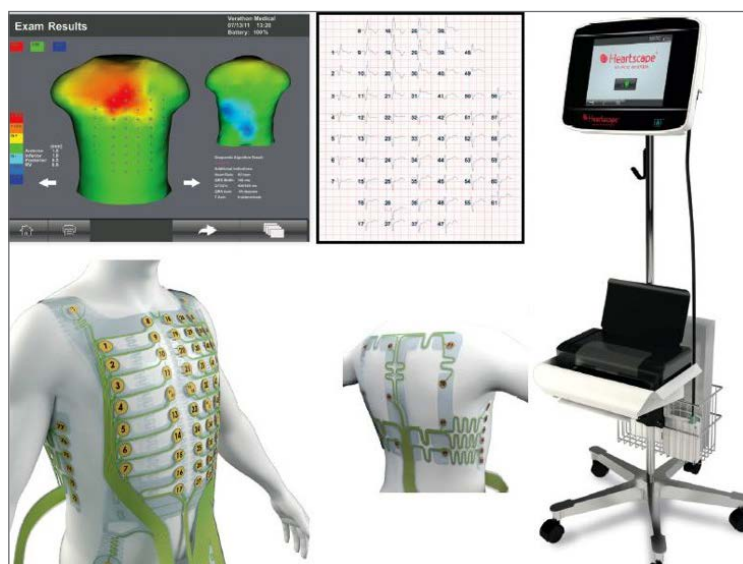


Figure 1. 80-lead 3D ECG System

The OCCULT-MI trial [32] showed the incremental benefit of HeartScape in detecting ACS in patients without ST-elevation myocardial infarction, compared to traditional 12-lead ECG. The sensitivity of the 80L for ACS had a relative increase of 73% and an actual increase of 5.2% ($p = 0.0025$). The absolute reduction in specificity was less than 3%, not clinically significant [32].

Troponins

The second pivotal tool to achieve ACS diagnosis includes cardiac troponin measurement, indifferently T or I troponin [33, 34]. Elevation of cardiac troponins reflects myocardial cellular damage [35]. Troponin increase occurs within 4 h after symptom onset and it may remain elevated for up to 2 weeks. The diagnostic cut-off exceeds the 99th percentile of a normal reference population [36]. However, troponin evaluation requires long time to make ACS diagnosis, thus contributing to ED overcrowding and patients' anxiety. Thus, the recent introduction of high-sensitivity or ultrasensitive assays, that have a 10- to 100-fold lower limit of detection, has already shown its utility in the ED [37, 38]. The negative predictive value with a high-sensitivity or ultrasensitive troponin single test on admission is $> 95\%$ and it improves to 100% with the second sample within 3 h [39, 40]. Even though other clinical conditions, apart from ACS, may lead to troponin elevation, it is important to remember that any increase of troponin value is associated with worse prognosis [41–43].

Where central laboratory requires too much time to measure troponin level, point-of-care (POC) tests for troponins allow to save about 1 h of wasted time [44] and to rapidly rule-out low risk group within 2 h [45]. However, POC tests showed to have worse analytic reliability and poor sensitivity, compared to central

laboratory tests. The ASPECT study showed that only 9.8% of 3.582 patients with suspected ACS could be safely discharged 2 h after presentation, using POC troponin test [46]. This finding suggests that POC troponin tests application could be more useful for patient's disposition than for ACS diagnosis: if the rapid POC test is positive, hospitalization is needed, while if the POC test is negative (as occurs in nearly 90% of patients), the patient may be admitted to the chest pain unit (CPU) to continue his serial testing with the higher sensitivity central laboratory troponin test [47]. Compared to central laboratory troponin, the use of POC tests has already proved to be very useful in shortening ED stay [48]. However, its use is still limited and further researches are needed to confirm preliminary results and to standardize its application in the ED [48].

ACS treatment in ED

As soon as ACS is diagnosed, it is mandatory to start treatment immediately in the ED, according to ESC guidelines [7, 49], to which we refer for better insights (Fig. 2).

The first approach includes the use of an initial dose of 150–500 mg orally or 250 mg *i.v.* of aspirin [7, 49] and a loading dose of a P2Y12 inhibitor. The PLATO study and the TRITON study provided evidence that the more potent effect of ticagrelor as well as prasugrel on P2Y12 inhibition results in a significant reduction of athero-thrombotic events as compared to clopidogrel in patients with ACS [50, 51]. Ticagrelor is indicated in all-comers, prasugrel only prior PCI in patients without prior stroke/TIA whose anatomy is known, clopidogrel if ticagrelor and prasugrel are not available [47, 52]. While clopidogrel and prasugrel need to form the active metabolites in the liver [53, 54], ticagrelor and

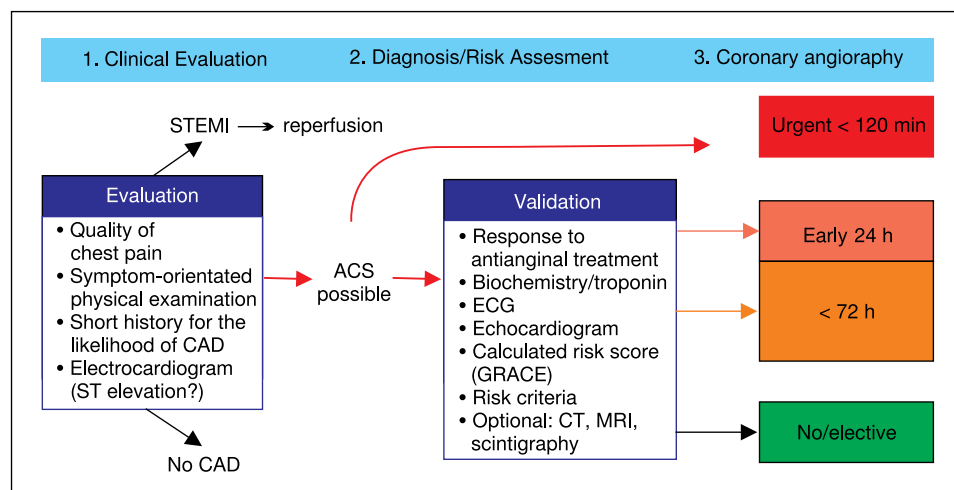


Figure 2. ACS management

new P2Y₁₂ inhibitors, such as cangrelor and elinogrel, are direct, reversible antagonists [55–57]. There are several limitations of P2Y₁₂ orally administered inhibitors especially if used in patients with ACS treated with PCI [58–60]. Oral P2Y₁₂ inhibitors cannot provide reliable inhibition in patients who are unable to swallow or rapidly absorb medication taken orally such as patients who are sedated, intubated, in shock, or those with nausea or vomiting [61, 62]. Cangrelor has the advantage over all orally administered agents of being a very potent, quickly reversible and direct-acting P2Y₁₂ antagonist reaching consistent optimal platelet inhibition within minutes after the start of the infusion [60, 63]. Cangrelor does not require hepatic activation [64]. The drug is rapidly metabolized through dephosphorylation by an endonucleotidase located on the surface of vascular endothelial cells with an elimination half-life of 2.9 to 5.5 min [65, 66]. Lack of interaction between cangrelor and ticagrelor may suggest choosing the last one for maintenance treatment if cangrelor was used in the acute setting, but this should be clinically tested. Cangrelor was not superior to clopidogrel in reducing the incidence of ischemic events in neither of the CHAMPION trials: CHAMPION PLATFORM [67] and CHAMPION PCI [68]. On the other hand, CHAMPION PHOENIX trial showed that the primary composite efficacy end point of death from any cause was significantly lower in the cangrelor group than in the clopidogrel group, not accompanied by a significant increase in severe bleeding or in the need for transfusions as compared to patients on clopidogrel [69]. Moreover, only 1 h is required in patients treated with cangrelor to return to baseline platelet function. Unfortunately, cangrelor is not available yet, however its pharmacodynamic properties (prompt and potent onset of action and fast offset) make it a desirable drug in the emergency setting.

Another masterpiece of ACS treatment is anticoagulation and different strategies are available: fondaparinux 2.5 mg/daily subcutaneously, that has the best benefit/risk profile, enoxaparin 1 mg/kg twice daily subcutaneously for low bleeding risk patients, UFH *i.v.* bolus 60–70 IU/kg (maximum 5000 IU) followed by infusion of 12–15 IU/kg/h (maximum 1000 IU/h) titrated to aPTT 1.5–2.5 × control [7, 49], or bivalirudin, indicated only in patients with a planned invasive strategy [70]. Glycoprotein IIb/IIIa is recommended only in high risk PCI patients, particularly in those not treated with P2Y₁₂ inhibitors [71]. Furthermore, nitrates (oral or intravenous) are usually administered to relieve angina, especially in patients with hypertension or heart failure but they are contraindicated in case of hypotension, right ventricular infarction or use of phosphodiesterase type 5 inhibitors in the previous 48 h [49]. In addition,

beta-blockers are indicated in patients with tachycardia, hypertension, and/or left ventricular dysfunction, while non-dihydropyridine calcium channel blocker may be considered in patients without heart failure already treated with beta-blockers or with contraindication to beta-blockers. In STEMI patients primary PCI is recommended within 120 min [49, 72], otherwise fibrinolytic therapy is indicated within 12 h of symptom onset in patients without contraindications [73]. Approximately 10–25% of patients with ACS eventually require non-invasive ventilator support for acute respiratory failure secondary to acute pulmonary edema, cardiogenic shock or cardiac arrest. Two randomized trials from Japan have analyzed the effect of continuous positive airway pressure (CPAP) in patients with AMI [74, 75], showing a reduction in the endotracheal intubation rate and faster improvement in acute respiratory failure. However, no study has specifically evaluated the usefulness of bilevel pressure support ventilation (NIPSV) compared to conventional oxygen therapy yet, but a possible adverse effect of the higher positive intrathoracic pressure generated by bilevel NIPSV, leading to hypotension and a decrease in coronary blood flow, was suggested [76]. A recent retrospective series of 206 patients has shown that patients with AMI treated with non-invasive ventilation (NIV) tended to have a higher mortality rate, confirming the evidence that the prognosis depends primarily on the severity of the myocardial injury rather than the degree of acute respiratory failure [77]. Unfortunately, most of the series of patients with AMI and NIV are retrospective and do not analyze ventilator parameters in detail. In accordance with previous data, mortality risk is better predicted by co-morbidities than by respiratory or direct cardiac parameters. NIV could be an independent risk factor of mid-term mortality [78]. It is likely that complications related to NIV, mainly ventilator-associated pneumonia, may explain these findings.

Conclusions

A fast diagnosis for patients with ACS is a challenging issue in order to start appropriate treatment. Innovative, accurate, rapid and easy-to-use tools are emerging to solve this problem. Pre-hospital care, ED arrival, and ACS treatment should be considered a *continuum* of the same rapid, accurate and effective ACS management. A shared protocol between EP physicians and cardiologists together with the use of innovative diagnostic approach, such as high sensitive ECG and troponin assessment, could lead to a shorter time to diagnosis and therapeutic strategies resulting in better outcome for these patients.

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