Management of acute chest pain: A major role for coronary CT angiography


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Abstract Most patients presenting with acute chest pain (ACP) at the emergency unit do not have any marked electrocardiogram abnormalities or known history of heart disease. Identifying the few patients who have, or will actually develop acute coronary syndrome in this group that is considered to be at low risk, is an actual clinical challenge for emergency department physicians. In these patients, the goal of complementary non-invasive morphological or functional imaging tests is to exclude heart disease. The diagnostic values of coronary CT angiography include a sensitivity of 96% and a negative likelihood ratio of 0.09, which are highly contributory to the diagnosis, and the integration of this imaging test into a decision tree algorithm appears to be the least expensive strategy with the best cost/effective ratio. Coronary CT angiography is indicated in the presence of ACP associated with an inconclusive electrocardiogram, in the absence of any other obvious diagnoses, when the ultrasensitive troponin assay is negative or the dynamic changes are modest, slow and/or inconclusive. Ideally, coronary CT angiography should be performed within 3 to 48 hours after the initial consultation.

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State of the art

Acute chest pain (ACP) represents 30% of the consultations in emergency units [1]. Approximately 5% of the patients who present with this symptom in the emergency unit will develop segment elevation (ST+) myocardial infarction (STEMI) and will be treated by a coronary reperfusion strategy [2]. Another quarter of these subjects will progress to non ST+ Acute Coronary Syndrome (ACS). This includes non ST+ segment elevation myocardial infarction (NSTEMI), which is generally rapidly diagnosed and treated by early revascularization, and unstable angina, defined as an authentic transitory myocardial ischemia without necrosis, which is often more difficult to diagnose [3]. Analysis of these results shows that most patients consulting for ACP in the emergency room have no marked changes in ECG or history of heart disease. These studies, which are already quite dated [4–6], classified these patients as “low risk” based on a short-term STEMI rate of 2%, NSTEMI rate of 1 to 6% and unstable angina of 4%. Thus, the primary goal of an emergency physician in the management of ACP is to stratify patients in relation to their level of risk while eliminating ACS from other severe diagnoses. This goal is usually reached by using standardized protocols familiar to specialists [7,8]. To identify the few patients who actually have ACS in what is considered a low risk group is still a real clinical challenge for emergency physicians. They have therefore developed the precautionary principle of “Rule Out Myocardial Infarction” (in fact “rule out ACS”) resulting in a very low risk threshold, whose excellent sensitivity is obtained at the expense of specificity. The result of this approach is that a large number of patients are admitted into monitoring units for additional tests, increasing the probability of false positives (and all of the potential associated iatrogenic complications) as well as added expense. Thus, in the United States, nearly 80% of the patients consulting for ACP are kept for observation, even in the absence of any real change in ECG or elevated cardiac enzymes. Less than 15% of these hospitalized patients have confirmed ACS, while the annual diagnostic cost of ACP in emergency units is around 12 million dollars. On the other hand, although all existing emergency unit assessment and triage strategies tend to be somewhat overcautious, 2% of these individuals still leave the hospital too early with undiagnosed ACS and a risk of morbidity and mortality that is two-fold [9]. These “errors” are the source of 20% of the medicolegal complaints for malpractice in the United States.

Existing practices

To meet this challenge numerous diagnostic strategies are now available, including chest pain centers, the use of cardiac biochemical markers, new risk scores, accelerated diagnostic protocols and non-invasive imaging of the heart and coronary arteries [10,11]. Guidelines for the stratification of risk in non ST+ ACS recommend the use of the GRACE score [12]. This includes the Killip classification (Evaluation of Left Ventricular Systolic Dysfunction) based on the importance of rales and crackles during the clinical work-up, systolic pressure, heart rate, age, creatinine levels, the presence of cardiac arrest at admission, ST segment abnormalities or elevated cardiac biomarkers. It should be calculated at admission as well as when the patient is discharged. With the GRACE score, low risk (<108), intermediate risk (between 109 and 140), and high risk (>140) subgroups can be identified. The probability of mortality at 6 months for each of the three subgroups (low, intermediate and high risk) was 3%, 6% and 8% respectively. The GRACE register, which includes results for 12,000 patients in 14 countries and reports intrahospital events at 6 months, has shown that identification of unstable angina is associated with a readmission rate of 16% at 6 months, revascularization in 8%, death in 2.2% and myocardial infarction in 0.2% [13,14].

The “Clinical Prediction Rules” are applied at the patient’s bedside to assist the clinician in decision-making. They are based on prospective and retrospective databases and include different variables from the clinical history, the physical examination and basic laboratory tests [15]. A recent review of the literature [16] evaluating the diagnostic value of the various propositions concluded that these “clinical rules” are heterogeneous, have major methodological limitations and have not been systematically and especially prospectively studied in routine clinical practice. It is therefore recognized that the information obtained from the clinical investigation, the initial ECG and a single enzymatic assay to detect myocardial ischemia is not sensitive enough to identify patients who can safely be discharged from the hospital.

Guidelines for the diagnosis and stratification of these patients [10,14] include performing an ECG within 10 minutes after the first medical contact to be interpreted by a doctor experienced in reading right chest and back leads V3R – V4R – V7-V9, to be repeated 6 and 24 hours later and before discharge from the hospital. Blood samples must be rapidly obtained to perform troponin I and T assays. The results should be available within the hour after the test, and be repeated 6 and 12 hours later if the first test is negative. A GRACE type score should immediately be determined.

An echocardiogram is recommended to exclude any possible differential diagnoses in patients without recurrent pain, with normal ECGs and with repeatedly negative cardiac troponin assays. A non-invasive test to provoke ischemia is indicated before discharge (guideline Ia). These guidelines state that an exercise ECG stress test should be performed in patients with a strictly normal baseline ECG who are capable of physical exercise (class Ic). In the other patients, a pharmacological stress test either in the form of cardiac scintigraphy (SPECT), stress cardiochography or MRI should be considered (guideline 1c). Ideally a confirmation test should be available at all times, to continue assessment in the observation unit to increase safety and rapid discharge following an accelerated protocol. An alternative strategy suggests having selected low risk patients (repeatedly negative ECG and cardiac biomarkers) perform a stress test as outpatients. For optimal safety and usefulness, this outpatient stress test should be performed within 72 hours and preferably within 24 hours after discharge with guaranteed follow-up after the test with close communication between the cardiac observation unit, the patient and the patient’s general practitioner (Fig. 1).
The role of ‘‘new’’ Troponin (Tn) assays

The options proposed by existing guidelines do not take into account ‘‘revolutionary’’ contemporary ultrasensitive cardiac troponin T or I assays that could further accelerate the protocols to ‘‘rule out ACS’’ [17]. Until recently most assays could not reliably or reproducibly detect low levels of troponin (<0.04 ng/mL). Several technological advances have decreased detection thresholds by 10 to 50 times. The most effective assays can now detect troponin in the serum of healthy subjects in the 99th percentile (0.010 ng/mL) with a detection limit of 0.0005 ng/mL. These assays provide precise and early evaluation of variations in troponin during ACS. The negative predictive value (NPV) of a single test at admission with these new troponin assays (with a threshold value of 14 pg/mL) has been shown to be above 95% [18–20]. Only patients presenting extremely early escape detection, but by performing a second test after three hours the sensitivity is nearly 100% [21–23]. A test result that is elevated and above 50 pg/mL for the initial test and/or that doubles between the first and second test three hours later, is a sign of ACS [20]. Thus reducing the delay between the two tests from 6 to 3 hours with ultrasensitive troponin (Tn US) provides faster assessment of patients.

A new decisional tree algorithm is already being used in certain emergency units. Low risk patients can be discharged after 3 hours following a single normal test result (<14 pg/mL) if the pain occurred more than 6 hours before the consultation, or after a 2nd normal test result is obtained 3 hours after the first, if the pain was less than 6 hours before. Myocardial ischemia stress testing is practiced on an outpatient basis.

Interpretation of the ultrasensitive cardiac troponin (US Tn) assay results should include a clinical picture that suggests a diagnosis of ACS, because although elevated US Tn is extremely specific for the presence of myocardial injury, it is not automatically suggestive of an ischemic etiology [24]. Numerous other clinical situations besides ACS could result in initial and dynamic changes in US Tn, which is generally modest and slow, even very slow. Acute/chronic renal failure, severe acute/chronic heart failure/insufficiency, sudden increase in blood pressure, tachy- or brady-arrhythmia, a pulmonary embolism, severe pulmonary hypertension, inflammatory disease, myocarditis, stroke, intracranial hemorrhage, aortic dissection, and acute diseases, in particular respiratory failure or sepsis can be the cause.

Diagnostic value of coronary CT angiography

In patients with a low risk of ACS (GRACE score <108), the goal of an additional non-invasive, morphological or functional imaging test is to exclude the diagnosis of coronary disease: based on a highly sensitive technique with the lowest possible negative likelihood ratio (LR— is the relationship between the probability of having a negative test result when the patient ‘‘is ill’’ and the probability of presenting a negative test result when the patient is not ‘‘ill’’). For example a LR— of 0.1 means that there is 10 times more chance of having a negative test result when the person is not ill than when s/he is ill. The diagnostic value of a negative result therefore increases as the negative likelihood ratio decreases and approaches 0 (Fig. 2). Dobutamine
stress echocardiogram has an excellent LR− for the absence of coronary artery stenosis as well as important prognostic value for immediate and late events. Cardiac scintigraphy (SPECT) at rest, when there is no perfusion anomaly, is associated with a very low clinical risk so that the patient can be discharged quickly to undergo a treadmill stress test as an outpatient.

Since the development of multidetector CT (MDCT) and its use in cardiology (originally by retrospective then prospective ECG-gated), numerous publications have focused on the potential role of this technique in the triage of patients consulting for chest pain in emergency units. Coronary CT angiography is a rapid, non-invasive, anatomic technique (approximately 15 min to perform a test, interpretation after about the same amount of time) that is precise enough to exclude suspected heart disease with significant certainty. In cases of chronic heart disease, all comparative studies and meta-analyses have confirmed the excellent specificity and LR− for the diagnosis of coronary stenosis compared to coronary angiography. Two meta-analyses [25,26] have evaluated the diagnostic value of coronary CT angiography for the specific problem of ACP. These two meta-analyses both included studies performed with 16-, 40- or 64-slice CT devices, different methods of comparison (coronarography or clinical follow-up) and heterogeneity of included patients in terms of pre-test risk of ACS. In the most recent analysis by Athappan et al. [26], a systematic review of the literature was performed between 1995 and 2008 with 16 studies evaluated, including 9 that were performed with 64-slice coronary CT angiography, and including approximately 1120 patients. The diagnostic value had a sensitivity of 96% and a specificity of 92%, a LR+ of 10, and a LR− of 0.09, all of which show that the diagnostic value of this technique was highly contributive. These diagnostic values are not significantly different from those using other techniques for the functional exploration of myocardial ischemia. In this situation, clinical data on efficacy and safety do not discriminate between the different values of coronary CT angiography, cardiac scintigraphy, echocardiography or stress MRI (Fig. 3).

The ROMICAT [27] study published in 2009 provides a particularly clear picture of the value of CT in the triage of patients presenting in the emergency unit for ACP. The included population (368/1869 or 20% of those consulting for ACP) represents a "real life" group of low or intermediate risk patients with no known coronary/heart risks (bypass, stent), ECG or biological anomalies or inclusions not based on clinical scores that are unfamiliar to emergency room physicians. Eight percent of the population was found to have ACS in the immediate follow-up, including 75% with unstable angina. All patients received coronary CT angiography within the hours following their arrival in the hospital, and the results of this test, which were not provided to the clinicians, were expressed as the presence or not of plaque (yes/no) and stenosis (plaque > 50%). Thirty-four of the 368 tests (9%) were inconclusive (mainly due to significant calcifications) and were included for the global analysis in the group of patients considered to have stenosis (18% of the total). None of the patients without plaque (50% of the total population), presented with ACS (100% sensitivity and LR− of 0!). On the other hand, the specificity and positive likelihood value were modest in the presence of plaque as numerous patients presented with plaque but did not develop ACS. The sensitivity of the absence of significant stenosis was limited (77%) with 7 patients without identified stenosis who developed ACS, due to the presence of non-obstructive lesions or on secondary vessels detected on coronaryangiography; specificity was "satisfactory" (87%) as most patients with stenosis developed ACS. The authors concluded that 50% of the patients who presented to the emergency room could have immediately been discharged from the hospital because a normal coronary CT angiography was never associated with ACS. Recently the same team...
reported the results of a 2-year follow up of the ROMICAT 1 cohort for the development of major cardiac events. They showed that the rate of events was 0 in patients whose CT scan was normal 2 years before, 1.2% in those with a non-obstructive lesion and 8% in those with stenosis > 50% [28]. These results show the excellent prognostic value of a normal coronary CT angiography.

Recently two randomized studies assessed the pertinence of coronary CT angiography in the emergency room in patients with suspected ACS. In the study by Litt et al., [29] the primary judgment criteria was safety in relation to the evaluation of major cardiac events one month later in the CT group (908 patients), compared to the low risk group that received traditional management. A total of 141/908 patients (16%) who were randomized into the CT group did not receive contrast medium injection, mainly because of increased heart rate, a probably because it was felt that the quality of test would have been poor. None of the patients without stenosis > 50% (83% of the total) died or developed myocardial infarction after one-month follow-up. Fifty percent of the CT group were discharged directly from the emergency room compared to 22% in the group that was managed by the traditional protocol, resulting in a shorter overall hospital stay (18/24 hours).

The goal of the study by Hoffmann et al. [30] was to evaluate the efficacy of coronary CT angiography performed as early as possible after ECG and cardiac enzyme testing in low or intermediate risk patients with ACS (age between 40 and 75 years old, no history of heart disease, no initial ECG or troponin abnormality) compared to traditional management (including functional tests). This new scientific approach compared two strategies in a randomized manner in which patient management in both study arms was performed according to the rules of existing good medical practice and not determined by a strict protocol. The main difference with traditional randomized phase III studies was that there was no control of the way patients were "managed". The main hypothesis was that performing coronary CT angiography in the early assessment of ACS would reduce the length of the hospital stay (primary criteria). The statistical size of the study was determined with the goal of identifying a reduction of 8 h based on a model of data from ROMICAT 1. Two groups of 500 patients were therefore randomized including 85, or 7% of the total who presented with ACS, in the form of a myocardial infarction in 25% and unstable angina in 75% (52/85). Nearly 473/501 patients in the CT group (94%) actually underwent exploratory CT. The primary criteria was reached because the length of the hospital stay was reduced by 7 hours in the CT group compared to the standard management group, and 50% of the patients in the CT group were released after 8 hours, compared to only 10% in the other cohort. Among the secondary criteria, a diagnosis was reached in 6 hours compared to 21 hours and the rate of patients discharged directly was 47% versus 12% respectively. There was no statistically significant difference in the use of additional resources or in cost at one month, to reach a diagnosis or in the occurrence of major cardiac events. The authors concluded that including a CT in the triage strategy of patients presenting in the emergency room for chest pain improved the efficacy (the diagnostic cost-benefit/profitability) of the decision-making process. It is important to note that these two studies as well as all previously published studies were performed during the day, so that CT was performed during working hours and never at night. Their conclusions are therefore limited to low risk patients who could wait for the CT unit to open the next day, or patients admitted during the day when the CT was accessible in the hospital with no need to be transferred.

**Efficacy of coronary CT angiography**

Now that the diagnostic value of coronary CT angiography has been confirmed, in addition to the clinical assessment, it is necessary to obtain an economic assessment and take into account the organizational aspects of this approach in order develop diagnostic and follow-up strategies. Four cost-effective studies can be found in the medico-economic literature [31–34], all performed in American emergency rooms, comparing management strategies including coronary CT angiography to management strategies including scintigraphy (SPECT) or stress echocardiography in patients in the emergency room. Three of these studies presented separate results on efficacy (percentage of diagnoses, length of hospital stay) and the costs of coronary CT angiography versus stress echocardiography or SPECT based on a model that calculated the incremental cost-effectiveness ratios (costs by QALY earned) of different diagnostic strategies involving coronary CT angiography, echocardiography or SPECT. The results of the studies agreed. According to the authors, in patients consulting in the emergency room, 64-slice coronary CT angiography was as effective as SPECT (or stress echocardiography) and less expensive. Discharging patients based on a negative coronary CT angiography reduces the length of the stay in the emergency unit compared to conventional management (with SPECT or stress echocardiography) and reduces the cost of the hospital stay. Nevertheless, it seems difficult to extrapolate these results to France. At present there are no French data available on this topic, however, because of specificities in France in terms of cost and access to different imaging techniques, we can fairly confidently estimate that in case of suspected ACS, a strategy including coronary CT angiography as the first line test would be dominant, because it is less expensive with a better cost-effect relation ratio. Finally, in terms of safety, except in cases of kidney failure and allergic type hypersensitivity to iodated contrast agents, there is no confirmed significant risk associated with this technique. Radiation exposure, in particular, has been significantly reduced by using prospective ECG-gated CT, which is possible in 80% of the cases (possible by drug induced reduction of heart rate to below 65/min) and by iterative reconstruction. With these dose optimization protocols, the effective dose is around 2.5 milliSievert in the most recent studies [35,36]. Moreover, technical advances are still being made, in particular investigating the possibility of studying myocardial perfusion at rest and under pharmacological stress to improve the specificity of the method [37,38].

European and North American expert societies have included an analysis of the results of all these clinical and medico-economic studies in their regularly updated guidelines on the role of coronary CT angiography in the diagnostic strategy of ACS and/or ACS. Thus, after the original guidelines in 2006 a second version of criteria for the use of CT in
the assessment of ACP was proposed in 2010 by the American College of Cardiology Foundation [39] and presented the following indications in the following situations: the use of CT was recommended for ACP in patients with a low and intermediate pre-test risk of heart disease with unchanged ECG and cardiac enzymes, inconclusive or non-diagnostic ECG and troponin values.

The most recent document, dated 2012 (it is updated every 2 years by the same multidisciplinary group) evaluating the different roles of various imaging techniques used in the management of ACP in subjects at low risk of developing ACS, confirms the increasing importance and central role of coronary CT angiography in this setting and concludes that it must be included in the decisional tree [40].

Finally in the European "guidelines" on the management of NSTEMI, published in 2011 [14], one grade IIA recommendation should be mentioned which states that when this technique is available it should be considered as an alternative to coronaryography to exclude the diagnosis of ACS in patients with low or intermediate risk of heart disease associated with inconclusive ECG and biochemical tests.

A new algorithm including coronary CT angiography in the management strategy of ACP

CT has already modified existing practices in the management of acute chest pain suggesting myocardial ischemia and associated with inconclusive ECG. CT is indicated when other obvious diagnoses have been excluded and when the US troponin assay is negative or if the dynamic changes are modest, slow and/or inconclusive [14,40–42]. The latter situation is increasingly frequent (the number of "positive troponins" has been multiplied by 4 with the US troponin test!) because the increased sensitivity of the US troponin assay has been obtained at the cost of a loss of "coronary" specificity of positive results.

When the known causes of elevated troponin have been eliminated (see above), a coronary CT angiography is justified as the first step in excluding ACS (Fig. 4). If the coronary CT angiography is normal or shows a non-severe lesion, the diagnosis of ACS can be excluded. In case of discovery of severe stenosis, coronaryography is indicated. In the presence of moderate stenosis or an inconclusive test, a test of myocardial ischemia (stress test, stress imaging) should then be performed followed by a diagnostic coronaryography depending on the results. A new protocol is needed with optimal communication between the healthcare team and the patient and that takes into account cost-effectiveness, the real burden of organizational constraints as well as optimization of the triage process. Ideally, coronary CT angiography should be performed within 3 to 48 hours after the initial consultation, thus avoiding overbooking the Emergency Unit or Cardiology Intensive Care Unit and imaging units.

The most important factor for the success of coronary CT angiography for this application will depend upon the capacity of emergency room specialists to properly select the target population. This population, we must again emphasize, will include patients with ACP in whom unstable angina must be excluded after 3 hours of observation as long as no other obvious causes have been discovered (pleuropericardiac, musculoskeletal, digestive, pulmonary) during the clinical work-up that is generally performed within the first 48 hours. Between these two limits (0 and 3 hours) repeated ECG and 2 US troponin assays are enough and the most cost-effective way to confirm the presence of myocardial infarction, STEMI or NSTEMI. No other imaging tests,
except for a possible coronary angiography, are needed during this first period in these patients.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


