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Type 2 Myocardial Infarction – the Chimaera of cardiology?

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Type 2 Myocardial Infarction – the Chimaera of cardiology?

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The **Chimera** (Χίμαιρα, *Chímaira*) was a monstrous fire-breathing hybrid creature of Lycia in Asia Minor, composed of the parts of more than one animal. Usually depicted as a lion, with the head of a goat arising from its back, and a tail that might end with a snake's head. The term chimera has come to describe any mythical or fictional animal with parts taken from various animals, or to describe anything composed of very disparate parts, or perceived as wildly imaginative, implausible, or dazzling. Is Type 2 myocardial infarction the chimaera of cardiology?

It is worth reviewing how "type 2 myocardial infarction" evolved. The development of the concept of type 2 myocardial infarction parallels the evolution of cardiac troponin assays. The initial generation of cardiac troponin assays were relatively insensitive[1 2 3]. They were superior to the existing conventional "cardiac enzyme" measurements at detecting prognostically significant myocardial injury in patients with an underlying pathophysiology of acute plaque rupture[4 5]. It was this property, combined with absolute cardiospecificity that led to their initial adoption. At this point, decision limits were chosen to confer specificity on the assay and were optimised for equivalence with myocardial infarction as defined by existing WHO criteria[6 7]. The background level of cardiac troponin detectable in the normal healthy individual was considered to be zero. A reference interval did not exist, only a single decision threshold[6 7 8].

Cardiac troponin measurement offered the Emergency Department physician and, to a lesser extent the cardiologist, a dream test[9]. The presence or absence of detectable cardiac troponin said whether the patient had suffered a myocardial infarction or not. However, early

on it was found that many patients classified as unstable angina according to contemporary criteria had detectable troponin levels, although below the decision limit for myocardial infarction[4 6 10 11]. These patients had a similar prognosis to those diagnosed with myocardial infarction. A special term was suggested for this finding, "minor myocardial damage"[6 12]. However, the term was never adopted by cardiological societies and the original redefinition of myocardial infarction considered the role of the new cardiac specific biomarker, cardiac troponin and defines myocardial infarction in terms of the decision limit for normality, the 99th percentile[13]. It also recommends an analytical imprecision goal of $\leq$ 10%. Hence, all reliably detected troponin elevations in a clinical context of an acute coronary syndrome were considered indicative of an acute myocardial infarction. Notably, in the original redefinition of myocardial infarction there is no such thing as type 2 myocardial infarction.

At that time the majority of cardiac troponin methods were unable to define a true 99th percentile. The limit of detection of the assay was a long way above the 99th percentile as was the 10% CV[14]. The redefinition of myocardial infarction acted as a spur to the manufacturers. Progressive improvements in assay technology reduced the limit of detection of cardiac troponin measurements and improved assay (im)precision. In addition, there was widespread measurement of cardiac troponin in patients other than those with acute chest pain. A growing number of studies confirmed early reports[15 16] that troponin was measureable and often a prognostic marker outside of the chest pain population[17 18]. In parallel with this, the increasingly widespread use of coronary angiography led to the realization that many patients with troponin elevation do not have evidence of plaque rupture or erosion of the intima with overlying thrombus formation in the coronary vessel or not even angiographically detectable atherosclerosis at all[19 20]. It is in this context that the concept

of a different sort of ischaemia producing another type of myocardial infarction was suggested.

Type 1 MI has always been clearly understood as troponin elevation in the context of acute plaque rupture and the clinical scenario of a suspected acute coronary syndrome[21 22]. The pathophysiology of type 1 myocardial infarction is well-defined. The relationship between troponin elevation, histopathological findings and cardiac imaging is well understood[23 24 25]. The treatment strategies are well-defined and based on prospective randomised controlled trials[26]. The combination of cardiac troponin measurement and intervention with improved outcomes is one of the triumphs of modern cardiology. The advent of more sensitive troponin measurements has simply allowed earlier diagnosis and intervention[27 28 29] with only a small increase in the absolute numbers of type I MI[30]. In contrast, type 2 myocardial infarction has always been defined by what it is not rather than what it is. The definition of type 2 myocardial infarction is[21]

"myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension or hypotension."

Troponin elevation occurs in a large number of clinical situations not considered to be an acute myocardial infarction[21 31]. The troponin elevation is associated with severity of illness and an adverse prognosis in the condition described[31 32 33]. Type 2 MI has been used to describe a subset of these conditions where myocardial ischaemia and cardiac myocyte damage is considered to be the representative pathology in an overlap with classical (type 1) myocardial infarction. Does current evidence support this approach?

The definition of type 1 MI includes a troponin above the 99th percentile and a significant change in troponin value, the delta troponin. It would seem attractive to use delta troponin to distinguish between type 1 and type 2 MI. It is our experience and the experience of others[33 34] that although delta troponin can be used to distinguish between acute and chronic myocardial injury from any cause, it cannot be used to distinguish between type 1 and type 2 MI. To date there have been no histopathological studies that have examined the pattern of tissue injury in type 2 myocardial infarction or a good animal model of pathophysiology. That myocardial injury occurs is not in doubt but the mechanism by which it occurs remains speculative. Therefore, there is considerable disagreement among researchers and clinicians how type 2 myocardial infarction should be defined[35 36]; and even worse how type 2 myocardial infarction should be diagnosed in clinical practice[37]. This uncertainty is reflected in the current clinical literature that has examined type 2 myocardial infarction (table 1). The populations examined have varied from clinical trial populations with suspected acute coronary syndrome [38] to more clinically representative patients presenting with chest pain[34 39 39]. Studies have included multicentre randomised controlled trials of therapeutic agents [38], single centre [34 36] or multicentre prospective observational studies[35 39 40], retrospective case record reviews [41] and registry studies[37 42]. The incidence of type 2 myocardial infarction has varied significantly across the studies from 1.6% [41]to 29.6%[36]. The criteria used are similarly disparate although all studies claim to use the universal definition. There are a range of different conditions associated with a diagnosis of type 2 MI (Table 2)[35 37 42] including some well described associations such as heart failure[43]. This, in itself, reflects the inherent confusion in the term type 2 MI. Type 2 MI is described in different series as being associated with [35 40], caused by [42] or with a secondary diagnosis considered to be the trigger of the type 2 M I[37]. In reality, the diagnosis of type 2 MI as defined by troponin elevation can only be

associated with another clinical condition as a pathophysiology is not defined. In two studies in the literature evidence of significant coronary artery disease has been required for making the diagnosis of type 2 myocardial infarction[36 44], although that is not an obligatory part of the definition that was proposed in the Universal definition of myocardial infarction[21 31]. There has been no study to date where all patients had their coronary anatomy defined prior to classification into type 1 or type 2 MI. Hence, type 2 myocardial infarction as defined according to the Universal definition [21](and third Universal definition)[22] of myocardial infarction is a mixed bag of patients, in whom the pathophysiology is different and, in fact in many cases, is unknown.

Table 1 Type 2 myocardial infarction in different studies – populations, incidence and outcomes

Reference	Population	Criteria	n	MI	Type 1 MI	Type 2 MI	Troponin assay	Mortality compared with no MI	Mortality type 1 vs type 2	Mortality predictors
Morrow, Bonaca [38 45]	Prospective trial patients with ACS undergoing PCI randomized to clopidogrel or prasugrel	Adjudicated end point committee using the universal definition	13608	1218	397 (32.6%)	43 (3.5%) 778 (63.9%) Type 3-5	Local laboratory assay and decision limit	180 days No MI 0.49% Type 2 MI 6.2% HR 5.4 (1.3-22.9)	180 days Unadjusted No MI 1.0% Type 1 6.4% HR 3.7 (1.9-7.0) Type 2 7.4% HR 2.7 (0.7-11.4). Adjusted Type 1 HR 4.1; 95% CI, 2.7– 6.3, *P*<0.001 Type 2 HR 2.8; 95% CI, 0.9–8.8; *P* = 0.085	
Javed [36]	Prospective enrolment of consecutive admissions over a 3 month period from the emergency department or inpatient beds and found to have an abnormal troponin	2 Reviewers Clinical ischaemia documented, No angiographic lesion or documented supply/demand mismatch	2942	216	143 (66.2%)	64(29.6%) 9 (4.1%) unclassified (type 3 and 4)	Siemens ultra (contemporary sensitive) 99th percentile 40 ng/L	No data	In hospital mortality Type 1 11%, Type 2 14% ns.	Peak cTnI Hyperlipidaemia Recreational drugs Angiogram result
Melberg [41]	Retrospective identification over 1 year of patients with an ACS diagnosis, admissions with a troponin measurement, all patients admitted	Adjudicated diagnosis (2 reviewers plus 1 adjudicator) Universal definition	1093	1093	967 (88.5%)	17 (1.6%) 109 (10%) Type 3-5	Roche 4th generation 99th percentile 30 ng/L	No data	No data	

	for revascularization and all with sudden death?MI									
Saaby [35]	Prospective enrolment over 1 year of all patients who had cTnI measured	3 adjudicators. Strict criteria for supply or demand mismatch. Angiographic classification not used.	4499, 1961 with elevated cTnI (43.5%)	553	397 (71.7%)	144 (26.0%) 12 (2.2%) Type 4-5	Architect contemporary assay. Cut off 30 mg /L (10% CV 32 ng/L, 99th percentile 28 ng/L)			
Saaby [40]	Prospective enrolment over 1 year of all patients who had cTnI measured	3 adjudicators. Strict criteria for supply or demand mismatch. Angiographic classification not used.	3762, 1577 with elevate d cTnI (41.9%)	488	360 (73.7%)	119 (24.4%) 9 (1.8%) Type 4/5	Architect contemporary assay. Cut off 30 ng/L (10% CV 32 ng/L, 99th percentile 28 ng/L)	No data	Mortality type 1 vs type 2 In hospital 6.9% vs 19.3% 30 day 9.2% vs 23.6% 1 year 16.7% vs 43.7% P <0.0001	Age Type 2 MI Smoking Hyperchol esterolaem ia Prior MI Ejection fraction Creatinine
Sandoval [34]	Prospective unselected consecutive ED admissions over 6 months	2 separate reviewers, consensus resolution of disagreement. Universal definition	1144, 32 ST elevation MI (exclude d) 856 no MI	256	66 (6%)	190 (17%)	Ortho diagnostics (contemporary sensitive) 10% CV 34 ng/L, 99th percentile 34 ng/L	180 day No MI 3.2%, type 2 MI 11.4% p<0.001	180 day Type 1 7.6%, type 2 11.4% ns	
Smith [39]	Multicentre study of prospective ED admissions with ?ACS over 9 months	Central adjudication(3 reviewers) Universal definition	1096 962 no MI	134	127 (94.7%)	7 (5.2%)	13 different assays, 99th percentile.	No data	No data	
Stein [42]	Registry study of ACS patients CCU and	Local clinician Universal definition		2818	2691 (95.5%)	127 (4.5%)	Local assays	No data	In hospital type 1 4.2% type 2 11.8% p = 0.0005	

	cardiology wards plus 37 Internal medicine wards								30 day type 1 4.9% type 2 13.6% One year type 1 4.4% type 2 12.2% p <0.0001	
Baron[37]	Registry study of consecutive admissions with MI admitted to cardiac or medical intensive care	Local clinician Universal definition		1976 3	17488 (88.5%)	1403 (7.1%) 872 (4.4%) Type 3-5 or unclassifie d	Local assays	No data	I year Unadjusted Type 1 13.5% type 2 24.7% p <0.001(HR type 2 1.86 (1.66-2.08) Adjusted 1.03 (0.86-1.23)	

Table 2 Conditions associated with Type 2 Myocardial infarction in different series.

	Saaby[35]	Stein[42]	Baron[37]
n	144	127	1403
Anaemia	30 (20.8%)	39 (31%)	186 (13.3%)
Shock	9 (6.2%)	18 (14%)	
Bradyarrthymia	4 (2.8%)	22 (17%)	
VT	14 (9.7%)		331 (23.6%)
SVT	28(19.4%)		
Respiratory failure	30 (20.8%)		19 (1.4%)
COPD/Asthma			78 (5.6%)
Pulmonary oedema	13 (9.0%)		
Heart failure			260 (18.5%)
Sepsis		30(24%)	246 (17.5%)
Post-operative		18 (14%)	
Heart failure		14 (11%)	
Valve disease		13(10%)	
Stress		4(3%)	
Drugs		2(2%)	
Other		5(4%)	
Renal insufficiency			82 (5.8%)
Hypertension/Hypertensive crisis	1 (0.7%)		30 (2.4%)
Stroke/TIA			24 (1.7%)
Multifactorial	15 (10.4%)		

In addition to type 2 MI troponin release occurs in a range of conditions where myocardial injury may be ischaemic or non-ischaemic or both[32 46]. This has been christened non-ischaemic myocardial injury with necrosis but there is significant overlap with what might be regarded as type 2 MI. In patients with traumatic myocardial injury such as a penetrating chest wound involving the heart or a road traffic accident when the patient is young troponin elevation is clearly non-ischaemic. In the patient on the intensive care unit with hypotension and probable underlying myocardial ischaemia the distinction is rather more difficult. In patients with myocarditis imaging clearly shows diffuse myocardial involvement but it is impossible to exclude microvascular injury as part of the pathophysiology[47]. In patients with rheumatological conditions vascular injury in addition to atherosclerosis may be present.

For type 2 MI to be a useful diagnostic label then it should contribute to prognostic assessment and have treatment implications. Studies of the prognostic value of the diagnosis of type 2 MI have been contradictory, as shown in Table 1, probably dependant on the differing criteria used for defining type 2 myocardial infarction and on different study populations. In a large study of 3762 consecutive patients of whom 480 had a myocardial infarction, type 1 MI was diagnosed in 360 and type 2 MI in 119[40]. The authors used strict criteria for type 2 MI. these included anaemia, hypotension and respiratory failure (on the supply side) and tachydysrhythmia and hypertension (on the demand side)[35]. They demonstrated that the mortality in those with a final diagnosis of type 2 MI was high and higher than that than those patients diagnosed with type 1 MI, with a hazard ratio of 2. However, the criteria used would equally apply to patients in the intensive care unit where such co-morbidities are common and elevation of troponin is both common and prognostic[15 48]. A second large registry study analysed 19,763 patients from the SWEDEHEART registry with diagnosis of type 2 MI based on local application of the

universal definition of myocardial infarction[37]. Arguably the diagnostic classification was less rigorous but the numbers were very large and results from angiography were frequently available. The incidence of type 2 myocardial infarction was overall 7.1% but varied from 0.2%% to 13.0 % (10^{th}-90^{th} percentiles). Here, the one year mortality was significantly higher in those who had type 2 MI (42.4%) than those with type 1 MI. However, after adjustment background characteristics, treatments and clustering by treating hospitals the difference in one year mortality was attenuated and did not reach statistical significance of the hazard ratio 1.03[37]. 180 day mortality has similarly been reported as similar between patients with type 1 MI and type 2 MI although greater than that of patients having no MI and a normal cardiac troponin I at baseline[34]. A survey of 2818 patients from the National acute coronary syndrome Israel surveys identified only 127 (4.5%) of patients with type 2 MI but this was associated with a significantly higher rate of in-hospital (11.8% versus 4.2%) and one year mortality (23.9% versus 8.6%) than type I MI[42]. This study excluded patients admitted to medical intensive care units no non-cardiac units. There is some consistency between Type 2 patients however as shown in table 3. Patients with type 2 MI are older[37 40 42], female [34 37 40 42]usually have a history of pre-existing vascular disease[37 40], heart failure[35 37 42], stroke[37 40 42] and other comorbidities and have creatinine elevation[37 40].

Table 3 Comparison of comorbid conditions and previous therapy between individual studies. A significantly higher incidence in type 2 myocardial infarction patients is indicated by Y. N indicates significantly lower incidence. Levels of significance are stated in parentheses, ns = not significantly different. Blank entries indicate where data was not available. Shaded cells indicate where there is consistency across all studies.

	Saaby [40]	Sandoval [34]	Stein [42]	Baron [37]
Age	Y (<0.0001)	ns	Y (<0.0001)	Y (<0.001)
Female gender	Y (0.03)	Y (0.01)	Y (<0.0001)	Y (<0.001)
Smoking	ns		N (<0.0001)	N (0.006)
Hypertension	ns	ns	Y (<0.0001)	Y (0.011)
Diabetes	Y(0.005)	ns	Y (0.003)	Y (<0.001)
Hyperlipidaemia	ns	N (0.002)	ns	
Previous PCI	ns		Y (0.03)	NS
Previous CABG	ns		Y (0.02)	Y (<0.001)
Previous AMI	ns		Y (0.0001)	Y (<0.001)
Previous CHF	Y (<0.0001)		Y (<0.0001)	Y (<0.001)
Previous CVA	Y (0.03)		Y (0.0002)	Y (<0.001)
ACE	ns			Y (0.009)
ARB				Y (0.001)
B blockers	ns			Y (0.001)
Digitalis				Y (0.001)
Aspirin/Antiplatelet	ns			Y (0.001)

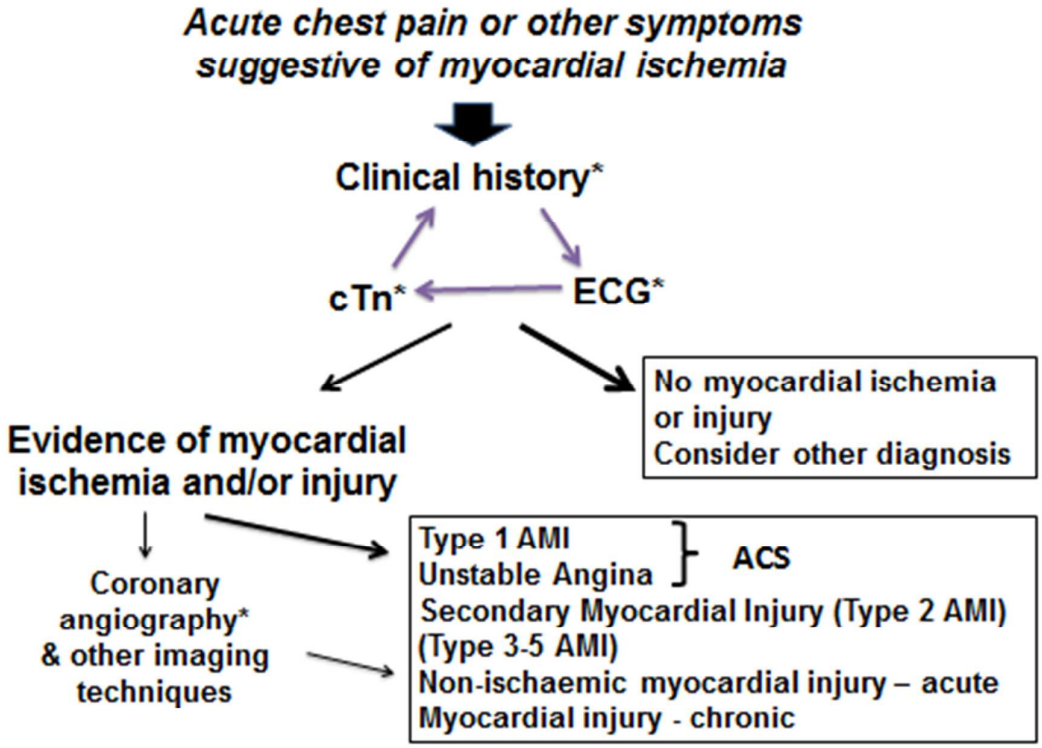
agents				
Anticoagulants	ns			Y (0.001)
Statins	ns			Y (0.001)
Diuretics				Y (0.001)
Max troponin	N (<0.0001)	N (0.007)		N (0.001)
Creatinine elevation	Y (<0.0001)			Y (0.001)
CRF		Y (<0.0001)		

When it comes to treatment there is even less evidence. There are no recommendations in current guidelines or standardised protocols of type 2 MI. Comparison of series reveals that patients with type 2 MI receive less invasive assessment in the form of angiography and receive less of the accepted secondary prevention treatments normally associated with type I [34 36 37 40 42]. Arguably, the optimal treatment will be dependent on the underlying cause of the supply-demand mismatch.

Type 2 MI could therefore be considered not to be useful term as it is currently defined. It might be more appropriate to consider it as secondary myocardial injury which occurs in association with a particular clinical condition and whether it occurs in a patient with or without coexisting coronary artery disease. Whether ischaemic related injury can be realistically distinguished from non-ischaemic cardiac injury or not is a matter of debate. In a large international prospective cohort study of myocardial injury after non-cardiac surgery 15065 patients were enrolled. 1200 patients had an elevated troponin but only 58.2% would have been classified as type 1 AMI and only 15.8% had ischaemic symptoms. An elevated troponin after non-cardiac surgery independently predicted 30 day mortality irrespective of the presence of an ischaemic feature[49].

When assessing patients presenting with suspected acute coronary syndromes that have troponin measured it is important to consider the totality of the clinical features and investigations. An example of this approach is illustrated in figure 1.

Figure 1 Holistic assessment of patients with suspected myocardial injury.



This review should be conducted not in a linear way but as a circular review process. Each of the three factors in the diagnostic triad, the clinical features, the electrocardiogram and troponin values are considered in relation to each other. It is the relative weight of each feature that contributes to the final diagnosis. Hence, the electrocardiogram (ECG) is considered in relation to the clinical features and troponin. For example, if the ECG shows non-specific changes with atypical clinical features and a significantly very elevated troponin, the clinical picture is unlikely to be acute myocardial infarction and more likely to be myocarditis. Similarly, the troponin values should be considered in relation to the clinical features and electrocardiogram. This is particularly where delta values are useful in distinguishing between an acute and chronic cause of myocardial injury. Similarly, the

clinical features must be considered in relation to the ECG and troponin. A history of acute chest trauma even with ECG changes is compatible with acute myocardial injury which is non-ischaemic in origin. The diagnosis must take into account the relative contribution of each of the diagnostic triad. Examples of the types of factors to be considered are shown below.

Clinical history

- Sudden typical ischemic chest pain – *favors type 1 AMI*
- Triggering factor causing increased oxygen demand or decreased supply – *favors secondary myocardial injury (type 2 AMI)*
- Symptoms and signs indicating "non-AMI", e.g. myocarditis, pulmonary embolism) – *favors secondary injury or non-ischemic myocardial injury*

Cardiac Troponin

- High levels – *favors type 1 AMI*
- No elevation – *excludes myocardial injury*
- No delta changes – *favors chronic myocardial injury*

ECG

- ST-elevation – *favors type 1 AMI*
- ST-depression – *favors ischemic injury; type 1 or secondary myocardial injury (type 2 AMI) UA if no cTn elevation.*
- New Q-waves – *favors type 1 AMI*
- Rhythm disturbance - *favours secondary myocardial injury (type 2 AMI)*

Coronary angiography

- Culprit lesion with thrombus – *favors type 1 AMI*
- Significant CAD without clear culprit lesion – *favors secondary myocardial injury (type 2 AMI).*
- No significant CAD – *favors secondary myocardial injury (type 2 AMI) or non-ischemic myocardial injury*

In conclusion, we feel that the term type 2 myocardial infarction should be abandoned and replaced with secondary myocardial injury, possibly subdivided into acute and chronic. Whether this should include pathophysiology where there is a clear non-ischaemic aetiology can be debated but given the considerable overlap between ischaemic and non-ischaemic aetiology, it is probably not clinically useful.

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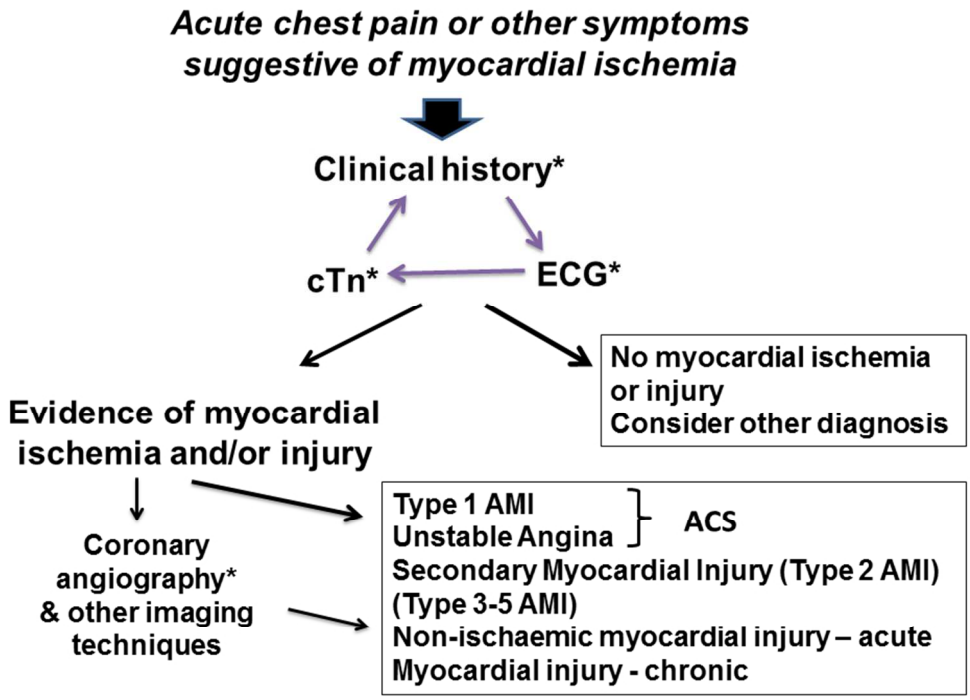

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