

# The incremental value of combination copeptin and troponin T for early diagnosis of acute myocardial infarction

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**Background:** Copeptin is a protein that is released when the body experiences endogenic stress. The level of copeptin elevated very early and slowly decreases in myocardial infarction.

**Aim:** to determine the incremental value of combination copeptin and troponin T for early diagnosis of Acute Myocardial Infarction.

**Methods:** A search was conducted on PubMed and Cochrane. After screening title and abstract using inclusion and exclusion criteria, three articles were available as full text, but only 2 articles were considered useful by authors and were appraised based on its validity, importance and applicability. The other one article was excluded because the outcome of the study basically differentiates ACS and cardiomyopathy.

**Results:** Both articles show that the diagnostic value results are not so different. From the first article, a combination of copeptin and troponin T gives the results of sensitivity 87.4%, specificity 66.2%, PPV 46.9%, NPV 93.9%, pre-test probability 21.5%, post-test probability 40.8%, and AUC 0.91. The second article showed a combination of both gave sensitivity values of 98.8%, specificity 77.1%, PPV 46.2%, NPV 99.7%, pre-test probability 16.67%, and post-test probability 46.29%, and AUC 0.97.

**Conclusion:** the combination of troponin T increase the sensitivity of diagnosis of AMI among patients suspected with acute coronary syndrome compared to troponin T alone. The combination of both can be considered as a test to diagnose AMI at early hours.

(J Kardiol Indones. 2011;32:113-7)

**Keywords:** EBCR, copeptin, troponin T, acute myocardial infarction

## Clinical Scenario

Fifty eight years old man was admitted to the hospital with chest pain since 3 hours before admission. He also had symptoms of shortness of breath, weakness, dizziness, palpitations, cold perspiration.

From the physical examination, BP: 150/90, temperature 36°C, HR: 110x, RR: 34x. Chest examination revealed no abnormality. ECG showed ST depression at lead II, III, aVF.

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To confirm the diagnosis, the doctor needed to check the cardiac enzyme, but he was unsure whether the level of Troponin T was sufficient to be detected. One of his co-worker, suggest him to try to check for the Copeptin instead.

## Introduction

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentation ranging from unstable angina pectoris (UAP), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI). Diagnosis of acute myocardial infarction (AMI) confirmed by a finding of the typical rise and fall of biochemical markers of myocardial necrosis coupled with one of the following findings: ischemic symptoms, development of pathologic Q waves, ischemic ST-segment changes on electrocardiogram (ECG) or in the setting of a coronary intervention.<sup>1</sup> Troponin is the biomarker of choice for the detection of cardiac injury. Cardiac troponin level begins to rise at 4–6 hours after the onset of symptoms and the peak value occur at 18–24 hours after the onset of the symptom.<sup>2</sup> Considering the necessity to conduct an early diagnosis in patient with ACS, several studies have been developed to find the role of copeptin in diagnosing ACS. Copeptin is the C-terminal part of pro-Agrinin Vasopressin and is released together with Agrinin Vasopressin (AVP) and it is released when body experiences endogenic stress such as myocardial infarction. Copeptin elevated very early (0 to 4 hours) after the onset of AMI symptom and slowly decrease after that.<sup>3</sup> However, researches are still needed to study the diagnostic value of copeptin in diagnosing AMI.

## Clinical Question

In adult patient with suspected Acute Coronary Syndrome, can Copeptin combined with Troponin T establish early diagnosis of AMI?

## Methods

### Search Strategy

Pubmed and Cochrane search was performed on 30<sup>th</sup> May 2011. We used term “copeptin” and in refining order we used terms “troponin T” and “myocardial infarction” (Table 1).

### Selection Criteria

After filtering using Boolean operator and MESH Terms, the first selection was based on title and abstract using inclusion and exclusion criteria. All diagnostic studies were included, while the studies using high-sensitive troponin T and prognostic study are excluded. After reading the full text, one article was excluded because the outcome of the study basically differentiates ACS and cardiomyopathy.

## Result

All appraised articles are cohort prospective studies conducted in Germany. Till Keller *et al* studied 1386 consecutive patients came with chest pain symptom, 806 of which were admitted to the hospital within 6 hours onset. Of the 806 patients, 175 were diagnosed AMI, while the remainder were diagnosed UAP and non-coronary chest pain. All patients underwent copeptin and troponin T examination. Level of troponin T was considered significant if >0.03 ng/ml and for copeptin if > 9.8 pmol/l. Examination of troponin T alone gave sensitivity values of 50%, specificity 97.7%, PPV 87.9%, NPV 85.3%, pre-test probability 21.5%, post-test probability 85.4%, and AUC 0.8. Copeptin examination alone gave sensitivity value of 74.9%, specificity 7.6%, PPV 44%, NPV 88.8%, pre-test probability 21.5%, post-test probability of 38.2%, and AUC 0.78, meanwhile, a combination of both gives the results of sensitivity 87.4%, specificity 66.2%, PPV 46.9%, NPV 93.9%, pre-test probability 21.5%,

Table 1. Search strategy used in Pubmed and Cochrane, conducted on 30<sup>th</sup> May 2011

Engine	Search Terms	Result
Pubmed	copeptin[All Fields] AND (“troponin T”[MeSH Terms] OR “troponin T”[All Fields]) AND (“myocardial infarction”[MeSH Terms] OR (“myocardial”[All Fields] AND “infarction”[All Fields]) OR “myocardial infarction”[All Fields])	5
Cochrane	“copeptin” AND “troponin T” AND “myocardial infarction”	1

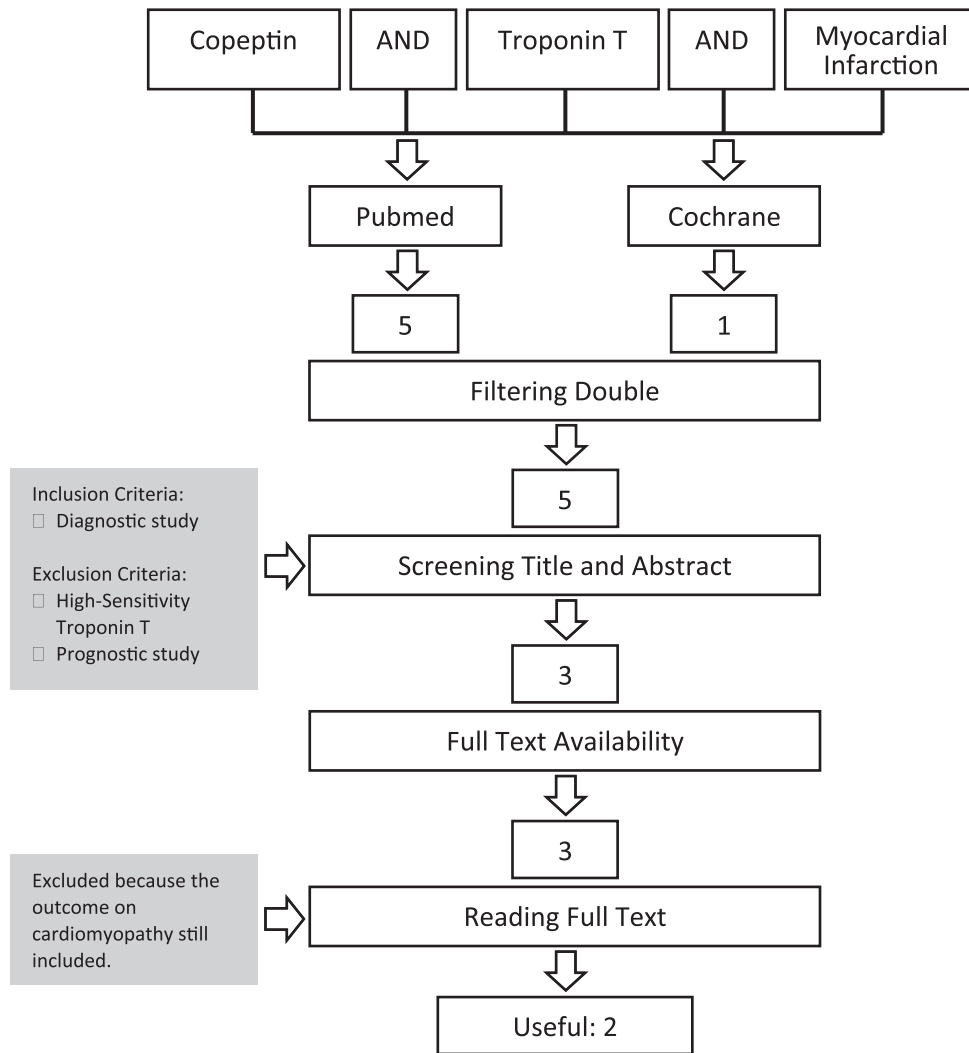


Figure 1. Flow chart of conducted search

Table 2. Critical appraisal of useful articles based on its validity, importance, relevance and applicability

		Articles	
		Copeptin Improves Early Diagnosis of Acute Myocardial Infarction Till Keller, et al.	Incremental Value of Copeptin for Rapid Rule Out of Acute Myocardial Infarction Tobias Reclin, et al.
Validity	Was there an Independent, blind comparison with a reference standard of diagnosis?	Yes	Yes
	Was the diagnostic test evaluated in an appropriate spectrum of patients?	Yes	Yes
	Was the reference standard applied regardless of the diagnostic test result?	Yes	Yes

Articles		Copeptin Improves Early Diagnosis of Acute Myocardial Infarction	Incremental Value of Copeptin for Rapid Rule Out of Acute Myocardial Infarction
		Till Keller, et al.	Tobias Reclin, et al.
Criterion			
Importance		Combination of Copeptin <sup>a</sup> and Troponin T <sup>b</sup>	Combination of Copeptin <sup>c</sup> and Troponin T <sup>d</sup>
	Sensitivity	87,4%	98,8%
	Specificity	66,2%	77,1%
	Positive Predictive Value	46,9%	46,2%
	Negative Predictive Value	93,9%	99,7%
	Likelihood ratio (positive result)	2,57	4,31
	Likelihood ratio (negative result)	0,19	0,02
	Pre-test probability	21,5%	16,67%
	Post-test probability	40,8%	46,29%
	AUC	0,91	0,97
Relevance	Domain	Patients 48-75 years old with chest pain onset <6 hours	Patients 45-79 years old with chest pain onset <12 hours
	Determinant	Troponin T, Copeptin, Myoglobin, CKMB, NT-ProBNP, and combination	Troponin T, Copeptin, and Combination
	Comparison	Criteria for acute myocardial infarction: <ul style="list-style-type: none"> <li>• Typical chest pain</li> <li>• ECG changes</li> <li>• Elevated serial biomarker</li> </ul>	Criteria for acute myocardial infarction: <ul style="list-style-type: none"> <li>• Symptom of myocardial ischemia</li> <li>• Rising/falling pattern of serial Troponin T</li> </ul>
	Outcome	Added value of copeptin in early evaluation of patients with suspected AMI	Incremental value of copeptin for rapid rule out of AMI
Applicability	Is the diagnostic test available, affordable, accurate, and precise in your setting?	No	No
	Can you generate a clinically sensible estimate of your patient's pre-test probability?	Yes	Yes
	Will the resulting post-test probabilities affect your management and help your patient?	Yes	Yes
	Would the consequences of the test help your patient?	Yes	Yes

<sup>a</sup>Copeptin level >9,8 pmol/l, <sup>b</sup>Troponin T level >0,03ng/ml, <sup>c</sup>Copeptin level >14 pmol/l, <sup>d</sup>Troponin T level >0,04ng/ml

post-test probability 40.8%, and AUC 0.91. From these results, it can be concluded that the combination of troponin T and copeptin can increase the sensitivity up to 87.4% and NPV to 93.9%, with AUC 0.91.<sup>4</sup>

In the study conducted Tobias Rechlin et al, 487 patients with chest pain onset less than 12 hours were included in this study and 81 of them were diagnosed as AMI. All patients were going through copeptin and troponin T examination, and in this study, level of copeptin was considered significant if  $>0.04$  ng/ml and for troponin T if  $>14$  pmol/l. This study did not give numbers of sensitivity and specificity of troponin T and copeptin examination separately, but a combination of both gave sensitivity values of 98.8%, specificity 77.1%, PPV 46.2%, NPV 99.7%, pre-test probability 16.67%, and post-test probability 46.29%. Nevertheless, Tobias et al compared the AUC of each examination. AUC for the examination of troponin T alone is 0.86, copeptin alone 0.75, and a combination of both increased the AUC to 0.97.<sup>5</sup>

## Commentary

The appraisals of the articles above show that they have similar value in validity and results. However, they also have some points of strengths and weaknesses in each other.

Till Keller et al conducted a study with 1386 patients enrolled consecutively from January 2007 until July 2008. The researcher used such a large number of subjects that the results can determine the added value of copeptin in early diagnosis of AMI precisely. Furthermore, the characteristic of the patients in this study was similar to our patient. In this study, the patients' mean age in this study was  $61,5 \pm 13,4$  and most of them are man (920 subjects), while our patient was included in, too. The chest pain onset (CPO) less than 6 hours in this study was also similar to our clinical setting: 3 hours after onset of symptoms.

Tobias Reichlin et al conducted a study with 487 consecutive patients presenting to the Emergency Department. The characteristic of the patients in this study (mean age  $62 \pm 17$  and 321 male) was similar to our patient. However, the CPO studied in this article

was less than 12 hours, which was quite different with our patient's clinical setting. Compared with Till Keller et al, this study shows the Negative Predictive Value and Area under the ROC curves for the diagnosis of AMI higher.

Overall, study by Till Keller convincingly concluded that the combination of copeptin and troponin T improves early diagnosis of AMI in a large number of patients suspected with Acute Coronary Syndrome.

## Conclusions and Recommendations

From all of researches, it can be concluded that the combination of troponin T and copeptin significantly improve early diagnosis of AMI. That combination increase the sensitivity of diagnosis of AMI among patients suspected with acute coronary syndrome compared to troponin T or copeptin alone. Although copeptin examination not yet available in Indonesia, we recommend the provision of copeptin examination and we also suggest the utilization of this combination in everyday practice for patients with early onset chest pain because based on researches, combination of copeptin and troponin T are very beneficial for diagnosing AMI at early hours. Early diagnosis is hopefully lead to a more appropriate patient management for AMI so that the mortality rates can be reduced.

## References

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