SIRIRAJ MEDICAL LIBRARY

Multimarker Approach in Acute Coronary Syndromes: A Review

Kosit Sribhen, M.D., Dr. Med, Nilrat Wannasilp, M.D.

Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Siriraj Med J 2007; 59: 206-209
E-journal: http://www.sirirajmedj.com

In the past decade, measurements of cardiac troponins have been proven to be useful tools in the diagnosis, risk stratification and therapy guidance in the management of patients with acute coronary syndromes. There are also accumulating evidences in recent years of the added values of inflammatory markers and markers of myocardial dysfunction in the evaluation and prognostication of patients with unstable coronary artery disease. Because of the underlying shared etiologies related to the process of atherosclerosis and the complexity of the pathologic thrombotic events, the use of a single marker that relates to each stage of the atherothrombotic process may not provide an optimal risk assessment of acute coronary syndromes. A multimarker approach in these clinical settings has been proposed. The present review has summarized recent data on the clinical usefulness of the combined utilization of novel cardiac markers, with special emphasis on cardiac troponins, C-reactive protein (CRP), and B-type natriuretic peptide (BNP) in acute coronary syndrome patients. The pathophysiologic role of these markers in the whole spectrum of the atherothrombotic process will also be addressed.

Cardiac troponins and C-reactive protein

Atherosclerosis is an inflammatory disease and inflammatory markers have been implicated in the initiation, progression and induction of the atherothrombotic process.[1] Although the prognostic significance of markers of inflammation, eg. CRP, fibrinogen and serum amyloid A protein (SAA), may lie primarily in the prevention of cardiovascular disease in healthy persons,[2] there are several reports of the prognostic role of these markers in acute coronary syndrome patients.[3] Table 1 summarizes recent data on the combined use of the troponins and CRP as diagnostic and prognostic markers in patients with chest pain suspected of having acute coronary syndromes. Results from these trials indicated that in multivariate analysis a high baseline CRP level determined early after acute coronary events is an independent predictor of major adverse cardiac events (cardiac death, non-fatal MI) in the short and long term follow-up.[4-8] More importantly, the predictive value of CRP provided additional information beyond that of cardiac troponins.[6,7] In addition, the presence of elevations in both CRP and troponin identifies the highest-risk group, thus indirectly confirming the importance of underlying pathophysiologic mechanisms of inflammation and thrombosis in the atherothrombotic process.[5] Based on these results, it is recommended that measurements of both troponin and CRP should be performed in all patients with acute coronary syndromes.[9]

The pathophysiological mechanism of CRP in the atherothrombotic process is at present to a certain extent

TABLE 1. Clinical trials of the combined use of cardiac troponins and markers of inflammation in acute coronary syndrome patients.

Author	Patient	n	Troponin	Inflammatory marker	Follow-up	Predictive value
Toss et al. (1997)[4]	Unstable angina, non-Q-wave MI	965	TnT	CRP, fibrinogen	5 months	CRP and fibrinogen were independent predictors of death from and additive to TnT
Morrow et al. (1998)[5]	Acute coronary syndromes	437	TnT	CRP	14 days	CRP was an independent predictor of mortality, and CRP and TnT provided complementary information of mortality risk.
De Winter et al. (1999)[6]	Unstable angina, non-Q-wave MI	150	TnI	CRP	6 months	CRP was an independent predictor of major cardiac events and had an additive predictive value to TnI
Lindahl et al. (2000)[7]	Unstable coronary artery disease	917	TnT	CRP, fibrinogen	37 months	CRP and TnT were independent predictors of death from cardiac cause and their effects were additive to each other and other clinical indicators of risk.
James et al. (2003)[8]	Acute coronary syndromes	7108	TnT	CRP	30 days	CRP and TnT were independent predictors of mortality, but only TnT was associated with an increased risk of subsequent MI.

TABLE 2. Clinical trials of the combined use of cardiac troponins and natriuretic peptides in acute coronary syndrome patients.

Author	Patient	n	Troponin	Natriuretic peptide	Follow-up	Predictive value
De Lemos et al. (2001)[15]	Acute coronary syndromes	2525	TnI	BNP	10 months	BNP was an independent predictor of death and new or worsening heart failure across the entire spectrum of ACS
Jernberg et al. (2002)[16]	Non-ST-segment elevation ACS	755	TnT	NT-pro BNP	40 months	NT-pro BNP was an independent predictor of death
Omland et al. (2002)[17]	Acute coronary syndromes	609	TnT	NT-pro BNP	51 months	NT-pro BNP was an independent predictor of long-term mortality and provided complementary prognostic information to TnT
Morrow et al. (2003)[18]	Non-ST-segment elevation ACS	1676	TnI	BNP	6 months	BNP provided independent prognostic information of mortality and congestive heart failure and added incremental information to TnI
Galvani et al. (2004)[19]	Acute coronary syndromes	1756	TnT	NT-pro BNP	30 days	NT-proBNP was independently associated with death and severe heart failure across the entire spectrum of ACS.

elucidated. It has been demonstrated that CRP may promote cardiovascular disease by increasing the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1), thereby promoting leukocyte adhesion to the intima, the initial step in atherosclerosis.[10] Since CRP has been shown to influence the production of reactive oxygen species by macrophages and smooth muscle cells, it can also facilitate low density lipoprotein (LDL) oxidation, leading to an increased uptake of oxidized LDL by intimal macrophages and formation of foam cells.[11] In addition, high levels of CRP suppress the production of nitric oxide (NO) by reducing endogenous NO synthase (eNOS) mRNA expression, protein levels and enzyme activity.[10,11] Furthermore, colocalization of CRP and complement have been observed in atherosclerotic vessels and CRP may constitute a cardiovascular risk factor by promoting local complement activation which, in turn, enhances the induction of tissue factor expression.[12] Thus, these results indicate that CRP is not only a biomarker, but also represents an active mediator in the pathogenesis of the atherothrombotic process.

Cardiac troponins and B-type natriuretic peptide

Myocardial dysfunction is a common complication observed after acute coronary events, and plasma markers of ventricular dysfunction, eg. BNP and other natriuretic peptides, are being increasingly used as prognostic indicators in the management of acute coronary syndrome patients.[13,14] Table 2 demonstrates recent major clinical trials utilizing BNP or N-terminal probrain natriuretic peptide (NT-pro BNP) with the troponins in the risk assessment of patients with unstable coronary artery disease. All of these studies uniformly reported that elevated BNP or NT-pro BNP were independently associated with mortality in the short and long term follow-up.[15-19] In addition, measurements of natriuretic peptides were able to provide predictive information for the occurrence of new or worsening heart failure across the entire spectrum of acute

TABLE 3. Clinical trials of the triple-marker strategy in acute coronary syndrome patients.

Author	Patient	n	Troponin	Inflammatory marker	Natriuretic peptide	Follow-up	Prognostic value
Sabatine et al. (2002)[21]	Non-ST-elevation ACS	450	TnI	CRP	BNP	10 months	Each marker was an independent predictor of death, MI and CHF and the combination of markers had additive predictive value.
		1635	TnI	CRP	BNP	6 months	TnI, CRP and BNP each provided independent and incremental prognostic information of major cardiac events.
Mega et al. (2004)[22]	ST-segment elevation MI	438	TnI	CRP	BNP	30 days	BNP was a strong and independent indicator of mortality risk. TnI did not offer prognostic information independent of BNP, and CRP was not associated with mortality or recurrent MI.
Bazzino et al. (2004)[23]	Non-ST-elevation ACS	1483	TnT	CRP	NT-pro BNP	6 months	NT-pro BNP was the strongest independent predictor of mortality and added significant prognostic information to the TIMI risk score, but was not associated with risk of new MI.
Heeschen et al. (2004)[24]	Non-ST-elevation ACS	1791	TnT	CRP	NT-pro BNP	30 days	NT-pro BNP was an independent predictor of death and MI, and identified a subgroup of high risk persons in TnT-negative patients. CRP was not an independent predictor of outcome.

coronary syndromes.[15,18,19] Furthermore, both BNP and NT-proBNP provided complementary prognostic information to that obtained from the troponins.[17,18] Taken together, these results indicate that, along with a careful history and physical examination, the evaluation of a panel of biomarkers like the troponins and natriuretic peptides will provide an optimal risk assessment in acute coronary syndrome patients.

The pathophysiological mechanism of the association between natriuretic peptide levels and mortality in acute coronary syndromes is at present not fully understood but may involve several co-operating factors. One possible mechanism may be that the levels of BNP and other natriuretic peptides are indicators of several co-morbidities including advanced age, hypertension, diabetes mellitus and renal impairment, all of which are proven to be associated with a worse outcome in acute coronary syndrome patients.[13,17] Another possible explanation lies in the fact that elevated BNP or NT-pro BNP may reflect left ventricular dysfunction established prior to or during the current episodes of instability, a known important predictor of mortality in these patients.[13,16] Furthermore, the release of natriuretic peptides into the circulation may also reflect the temporary left ventricular dysfunction secondary to the acute ischemic event.[13,15,17] In this context, it has been reported that the level of BNP is correlated to the size of the ischemic territory induced by dynamic exercise in patients with angina pectoris.[20] However, whereas cardiac troponin was shown to be predictive of death and recurrent ischemic events, BNP exhibited a strong relationship with mortality and congestive heart failure, but not with recurrent infarction. Nevertheless, when used together in a combined strategy, the two markers provide an optimal and effective tool for identifying patients at increased risk for recurrent cardiac events related both to ischemia and heart failure.[18]

Triple-marker strategy

Limited information concerning the use of triple-marker strategy in acute coronary syndrome patients is currently available in the literature, and the data are heterogenous with respect to the prognostic value of these markers. Although a previous study reported the usefulness of the combination of TnI, CRP and BNP in the risk assessment of non-ST-elevation acute coronary syndrome patients, the result could not be confirmed by several subsequent trials (Table 3). Nevertheless, when combined with other markers, B-type natriuretic peptides seem to provide the most valuable prognostic information of future outcome in the short and long term follow-up. In contrast, measurements of CRP did not have the same prognostic ability and did not provide additive prognostic information to other cardiac markers in the short-term risk assessment of patients with acute coronary syndromes.

Future direction

In the past decade, sophisticated methods in laboratory medicine have been developed which have a consolidated role in identification of early stage disease, risk prediction and assessment through simultaneous measurements of several biochemical protein markers at a certain point in time.[25] In this context, the term 'proteome' was introduced nearly 10 years ago by Wilkins et al.,[26] and investigations into the proteome have been named 'proteomics'. In contrast to the conventional protein chemistry which measures individual proteins, the proteomic analyses are directed at a complex mixture of proteins in a larger system or network. In this regards, the mass spectrometry-based method has assumed a key role in most of the proteomic studies. Although at present the most promising area in proteomic research lies in cancer diagnostics, the important role of proteomics in cardiovascular medicine is now being increasingly recognized.[27] It is to be anticipated that this new technique will significantly improve the role of clinical laboratory investigations in the near feature.

CONCLUSION

The combined utilization of the novel cardiac markers, cardiac troponins with CRP or with natriuretic peptides, have been proven to be useful tools in the risk assessment of patients with acute coronary syndromes. Elevated levels of CRP were shown to be independently associated with future cardiac death, and increased CRP together with elevated troponin levels identify a subset of patients at the highest risk of mortality in the long term follow-up. Similarly, elevated natriuretic peptide levels were found to be an independent predictor of mortality and heart failure, and the combination of BNP or NT-proBNP with cardiac troponins provide an optimal risk assessment in acute coronary syndrome patients. At present, results from the triple-marker strategy are heterogenous, and more information is needed from future investigations. It remains to be determined; whether the multimarker approach utilizing a panel of cardiac markers will provide a cost-effective strategy in the management of patients with acute coronary syndromes. In the future, measurements of proteomic pattern by mass spectrometry may become an essential tool in clinical research involving coronary heart disease.

ACKNOWLEDGEMENTS

We would like to thank Miss Apisara Chotipaporn for her contribution to preparation of the manuscript.

REFERENCES

1. Ross R. Atherosclerosis - an inflammatory disease. N Engl J Med 1999; 340: 115-26.
2. Liuzzo G, Rizzello V. C-reactive protein and primary prevention of ischemic heart disease. Clin Chim Acta 2001; 311: 45-48.
3. Biasucci LM. C-reactive protein and secondary prevention of coronary events. Clin Chim Acta 2001; 311: 49-52.
4. Toss H, Lindahl B, Siegbahn A, Wallentin L, for the FRISC study group. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. Circulation 1997; 96: 4204-10.
5. Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin I in acute coronary syndromes : a TIMI IIA substudy. J Am Coll Cardiol 1998; 31: 1460-5.
6. De Winter RJ, Bholasingh R, Lijmer JG, et al. Independent prognostic value of C-reactive protein and troponin I in patients with unstable angina or non-Q-wave myocardial infarction. Cardiovasc Res 1999; 42: 240-5.
7. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L, for the FRISC study group. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. N Engl J Med 2000; 343: 1139-47.
8. James SK, Armstrong P, Barnathan E, et al., and the GUSTO-IV-ACS investigators. Troponin and C-reactive protein have different relations to subsequent mortality and myocardial infarction after acute coronary syndrome. A GUSTO-IV substudy. J Am Coll Cardiol 2003; 41: 916-24.
9. Topol EJ. A guide to therapeutic decision-making in patients with non-ST-segment elevation acute coronary syndromes. J Am Coll Cardiol 2003; 41: 123S-129S.
10. Kluft C. Identifying patients at risk of coronary vascular disease: the potential role of inflammatory markers. Eur Heart J 2004; 6 (Suppl C): C21-C27.
11. Labarrere CA, Zaloga GP. C-reactive protein : from innocent bystander to pivotal mediator of atherosclerosis. Am J Med 2004; 117: 499-507.
12. Lagrand WK, Visser CA, Hermens WT, et al. C-reactive protein as a cardiovascular risk factor. More than an epiphenomenon? Circulation 1999; 100: 96-102.

13. Jernberg T, James S, Lindahl B, et al. Natriuretic peptides in unstable coronary artery disease. Eur Heart J 2004; 25: 1486-93.
14. De Lemos JA, Morrow DA. Brain natriuretic peptide measurement in acute coronary syndromes. Ready for clinical application? Circulation 2002; 106: 2868-70.
15. De Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 2001; 345: 1014-21.
16. Jernberg T, Stridberg M, Venge P, Lindahl B. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. J Am Coll Cardiol 2002; 40: 437-45.
17. Omland T, Persson A, Ng L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. Circulation 2002; 106: 2913-18.
18. Morrow DA, de Lemos JA, Sabatine MS, et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST-elevation myocardial infarction. B-type natriuretic peptide and prognosis in TACTICS-TIMI 18. J Am Coll Cardiol 2003; 41: 1264-72.
19. Galvani M, Ottani F, Oltrona L, et al., on behalf of the Italian Working Group on Atherosclerosis, thrombosis, and Vascular Biology and the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO). N-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. Circulation 2004; 110: 128-34.
20. Marumoto K, Hamada M, Hiwada K. Increased secretion of atrial and brain natriuretic peptides during acute myocardial ischemia induced by dynamic exercise in patients with angina pectoris. Clin Sci (Lond) 1995; 88: 551-6.
21. Sabatine MS, Morrow DA, de Lemos JA, et al. Multimarker approach to risk stratification in non-ST-elevation acute coronary syndromes. Simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation 2002; 105: 1760-63.
22. Mega JL, Morrow DA, de Lemos JA, et al. B-type natriuretic peptide at presentation and prognosis in patients with ST-segment elevation myocardial infarction. An ENTIRE-TIMI-23 substudy. J Am Coll Cardiol 2004; 44: 335-9.
23. Bazzino O, Fuselli JJ, Botto F, de Arenaza DP, Bahit C, Dadone J, for the PACS group of investigators. Relative value of N-terminal probrain natriuretic peptide, TIMI risk score, ACC/AHA prognostic classification and other risk markers in patients with non-ST-elevation acute coronary syndromes. Eur Heart J 2004; 25: 859-66.
24. Heeschen C, Hamm CW, Mitrovic V, Lantelme NH, White HD, for the Platelet Receptor Inhibition in Ischemic syndrome Management (PRISM) investigators. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. Circulation 2004; 110: 3206-12.
25. Plebani M. Proteomics: The next revolution in laboratory medicine? Clin Chim Acta 2005; 357: 113-22.
26. Wilkins MR, Williams KL, Appel RD, Hochstrasser DF, editors. Proteome research: new frontiers in functional genomics. Berlin: Springer; 1997: 243.
27. Zerkowski HR, Grussenmeyer T, Matt P, Grapow M, Engelhardt S, Lefkovits I. Proteomics strategies in cardiovascular research. J Proteome Res 2004; 3: 200-8.