Review Article

Acute coronary syndrome

An Acute Inflammatory Syndrome

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ABSTRACT

Atherosclerosis begins with the accumulation of small lipoprotein particles within arterial intima. These particles coalesce together and are modified and then they induce localized endothelial inflammation, thereby attracting leukocytes. Scavenger receptors over the surface of monocytes bind to the modified low density lipoprotein particles, which transform into foam cells that become a source for further inflammatory cytokines. The level of inflammation is heightened in ruptured coronary plaques. In patients dying of an acute myocardial infarction, the level of inflammation is heightened in all lesions in the coronary tree. The inflammatory reaction in acute coronary syndrome is not confined to cellular immunity, but also encompasses humoral immunity. High sensitivity CRP (hs-CRP) measures systemic inflammation, and at low levels it has emerged as a strong predictor of adverse cardiovascular events. It is mainly used to further stratify the intermediate-risk patients. Many other molecules have shown promise as markers for increased inflammation and increased risk of adverse cardiac events. That risk may be additive in nature, and some studies suggest that inflammatory markers can also predict response to various treatment strategies during acute coronary syndromes.

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In order to fully appreciate the role, inflammation plays in acute coronary syndrome (ACS), it is vital initially to revise its role in the pathogenesis of atherosclerosis. Atherosclerosis begins with the accumulation of small lipoprotein particles within arterial intima.[1] These particles coalesce together, bind to proteoglycans, and are modified by oxidation and glycation.[2,3] Then they induce localized inflammation and enhance the expression of adhesion molecules over endothelial cells (vascular cell adhesion molecule, intracellular adhesion molecule,[4,5] and selectins[6,7]) thereby attracting leukocytes. Chemo-attractant molecules, such as monocyte chemoattractant particle -1, promote diapedesis of monocytes through arterial intima.[8] Monocyte colony stimulating factor promotes expression of scavenger receptors[9] over surface of monocytes, where modified LDL particles bind. The monocytes now form foam cells that becomes a source for inflammatory cytokines. T-lymphocytes accumulate in early atherosclerosis.[10,11] Helper-1 cells elaborate pro-inflammatory cytokines (interferon gamma, CD 40 ligand, tumor necrosis factor-alpha) leading to plaque destabilization and heightened thrombogenicity. T helper-2 cells, produce Interleukin-10, an anti-inflammatory cytokine.[12] Platelet derived growth factor (PDGF) from activated macrophages enhance smooth muscle cell migration into the forming plaque.[13] These cells divide and elaborate extracellular matrix, which forms most of the plaque volume. The production of extracellular matrix is a balance between its promoters (PDGF and tumor growth factor-beta [TGF-ß]), and enzymes that

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catalyze its breakdown (matrix metalloproteinase [MMP]). Over time there is progression from a fatty streak into a lipid-rich atheroma covered by an acellular fibrous cap. Inflammation affects plaque stability via cytokines and metalloproteinase that degrade the covering cap, aiding in plaque rupture.[15,17] The level of inflammation, is highest in ruptured coronary plaques, less so in lipid-rich plaques and least in stable, fibrous, calcified plaques.[14] Unstable plaques have increased leukocytic infiltrates, and T cells and macrophages predominate at rupture sites.[16] Autopsies of patients dying from an acute myocardial infarction[18] shows heightened levels of inflammation in all atherosclerotic lesions of their coronary arteries and not only the culprit lesions.

The inflammatory reaction in acute coronary syndrome is by no means confined to cellular immunity. Calligiuri et al[19] showed that total IgM levels in serum were higher in patients with unstable angina at the time of presentation, compared to patients with chronic stable angina ($p<0.001$). Serum IgM levels then continued to rise at 7 to 15 days after the culprit event ($p<0.05$). The increment of IgM is significantly greater in the subgroup of patients with unstable angina patients who stabilized with initial medical therapy and went on have more favorable clinical outcomes ($p<0.05$). High sensitivity CRP (hs-CRP) measures systemic inflammation, and provides diagnostic and prognostic information in the setting of ACS. C-reactive protein (CRP) is an acute-phase protein produced by the liver in response to systemic cytokinemia (Interleukin-6, Interleukin-1, tumor necrosis factor-alpha) during tissue injury, infection and inflammation.[20] High sensitivity CRP assays (Hs-CRP) detects CRP levels within the normal range, which are associated with increased risk for cardiovascular events. In a nested case-controlled substudy of 245 patients;[21] Hs-CRP was significantly associated with higher cardiovascular risk (risk ratio for patients with high hs-CRP and TC:HDL was 5.0, risk ratio for high hs-CRP was 1.5, risk ratio for high total cholesterol was 2.3, $p=0.0001$). In another substudy of the TIMI 11A trial,[22] elevated CRP levels in unstable angina patients correlated significantly with 14-day-mortality. An early positive troponin assay (cTnT) and a high hs-CRP predicted the highest mortality (9.10% versus 4.65% for high hs-CRP or positive cTnT versus 0.36% for low hs-CRP and negative cTnT; $p=0.0003$). In a single-center registry of 727 patients who underwent early percutaneous coronary intervention for NSTEMI,[23] baseline of hs-CRP remained independently predictive of excess 30-day death or myocardial infarction (highest quartile of Hs-CRP: odds ratio: 3.68; 95% confidence interval: 1.51 - 8.99; $p=0.004$). In another prospective study of 1042 patients who underwent primary percutaneous intervention for NSTEMI,[24] followed up for 20 months; the Hs-CRP was >10mg/L portended a 4.18 times relative risk for all cause mortality (1.59-10.96; $p=0.004$). High sensitivity-CRP is similarly associated with heightened risk for carotid artery stenosis. In 124 hypertensive patients followed up for 35 months,[25] the Hs-CRP was a superior independent predictor of the progression of carotid atherosclerosis than pulse pressure or systolic blood pressure. Among 14,719 healthy women followed up for 8 years,[26] survival free of cardiovascular disease was highest amongst those with low hs-CRP (<3 mg/L) and no criteria for metabolic syndrome, and least in women with metabolic syndrome and high hs-CRP, indicating that Hs-CRP added relevant prognostic information for women with metabolic syndrome. High sensitivity-CRP maybe a stronger predictor of cardiovascular events than in LDL cholesterol.[27] In women, hs-CRP was the strongest univariate predictor for cardiovascular risk[28] In multivariate analyses, hs-CRP and total cholesterol: HDL cholesterol independently predicted cardiovascular risk (RR for hs-CRP in highest quartile 1.5; 1.1 - 2.1. RR for the ratio of total cholesterol to HDL: 1.4; 1.1 - 1.9). The Reykjavik study[29] followed healthy men and women for an average of 11 years. Participants with baseline hs-CRP in the highest third had an odds ratio for developing coronary heart disease of 1.45 (1.25 - 1.68). This risk associated with hs-CRP was stronger than the risk associated with baseline erythrocyte sedimentation rate and baseline von Willebrand factor level, but it was less than that associated with other established cardiac risk factors, such as high total cholesterol and cigarette smoking. From the CARE trial,[30] patients with highest baseline hs-CRP had a RR for recurrent cardiovascular events that is 75% higher than those with the lowest hs-CRP (RR=1.77, $p=0.02$). In another trial,[31] among patients with ACS randomized to pravastatin 40 mg or atorvastatin 80 mg; those in whom statin therapy resulted in LDL cholesterol levels <70 mg/dL (1.8 mmol/L) had lower cardiovascular event rates. An identical reduction in risk was observed among participants who had hs-CRP levels <2 mg/L after statin therapy (2.8 versus 3.9 events per 100 person/years, $p=0.006$). Low hs-CRP level after statin therapy translated into better cardiovascular outcomes, regardless of the resultant level of LDL cholesterol. The use of aspirin[32] is associated with significant reductions in the risk of future MI among patients with high Hs-CRP (55.7% reduction, $p=0.02$), but not among patients with low Hs-CRP (13.9%, $p=0.77$).

The clinical relevance of CRP measurements in the prediction of the risk of CHD remains under scrutiny, partly because there are no prospective randomized clinical trials to demonstrate that lowering CRP offsets CHD events beyond established lifestyle and pharmacological modalities. There is currently no agent that can reduce the inflammatory cascade (as measured by hs-CRP), without affecting other cardiac risk factors. High sensitivity-CRP is linked to these risk factors and treating them also lowers CRP. Control[33] states that hs-CRP is an independent risk factor for cardiovascular disease, "to be used at the discretion of the treating physician", and it would be "most useful when cardiovascular risk is intermediate". Metalloproteinase (MPO) is another inflammatory marker that participates in atherosclerosis. Metalloproteinase is a heme peroxidase that generates reactive oxidants and free radicals, as part of innate host defenses.[34,35] Metalloproteinase levels are elevated within human atheroma.[36] Metalloproteinase in leukocytes generates oxidants capable of initiating lipid peroxidation,[37] including the conversion of low density lipoprotein into its atherogenic form recognized by macrophage scavenger receptors.[38] Metalloproteinase promotes endothelial dysfunction, by consuming nitric oxide.[39] Recent clinical studies,[40] demonstrate that levels of MPO are independent predictors of CAD. Brennan[41] and Baldus et al[42] proved the utility of circulating MPO as a predictor of plaque vulnerability. Sugiyama et al[43] demonstrated that MPO-generated HOCl, provokes endothelial cell activation and tissue factor elaboration, as well as endothelial cell apoptosis, thereby contributing to increased plaque vulnerability. Another inflammatory marker is the CD 40 Ligand, expressed at the surface of platelets,[44] and released into serum upon platelet activation. CD 40 Ligand binds to endothelial cell receptors and upregulates tissue factor expression[45] and enhances expression of adhesion molecules. Among patients with chest pain;[46] elevated soluble CD40 ligand levels identified those at highest risk for death or nonfatal MI (adjusted HR: 6.65; 3.18 - 13.89; $p<0.001$). Last and not least, is IL-6; produced locally at the site of active plaque rupture.[47-49] Interleukin-6 travels through the blood to reach the liver and enhances CRP and fibrinogen production. In patients with AMI,[48] samples of blood collected from the coronary arteries at the sites surrounding ruptured plaques had significantly higher IL-6 levels than in the aorta ($p<0.0001$). In a nested substudy,[49] the risk of future MI was related to the increasing quartiles of baseline IL-6. Healthy men in the highest baseline IL-6 quartile had a relative risk of 2.3 times higher than those in the lowest quartile (1.3-4.3, $p=0.005$); for each quartile increase, there was a 38% increase in MI risk ($p=0.001$). In the FRISC trial,[50] baseline IL-6 levels ≥5 ng/L was associated with significantly increased mortality among NSTEMI patients treated non-invasively (7.9% versus 2.3%; relative risk [RR], 3.47; 1.94-6.21) and in the placebo-treated group (7.9% versus 2.5%; RR, 3.19; 1.77-5.74). The question which now arises naturally is which marker to use and when? There is evidence to suggest that the risk of a future cardiovascular event imparted by the elevation of inflammatory markers, is additive. Sabatine et al,[51] evaluated the results of 2 trials: TACTICS-TIMI 18 and OPUS-TIMI 16. Both trials had assessed levels of 3 key biomarkers in patients with NSTEMI: Troponin I, hs-CRP, and Brain Natriuretic Peptide. In OPUS-TIMI 16, each biomarker was an independent predictor of the composite endpoint of death, MI, or CHF followed through 10 months. The 30-day risk of death increased in proportion to the number of cardiac biomarkers elevated at baseline (p=0.014), with a doubling of mortality risk for each additional elevated biomarker. In a validation cohort of 1,635 patients in TACTICS-TIMI 18, the number of elevated biomarkers remained a significant predictor of the composite endpoint. Some treatment options work better when specific inflammatory markers are elevated. An early invasive treatment strategy strongly reduced 12-month mortality among patients with elevated IL-6 levels (5.1% absolute reduction; $p=0.004$);[48] the increased of cardiovascular risk in patients with elevated soluble CD40 ligand levels is significantly reduced by treatment with the GP IIb/IIIa inhibitor; abciximab (adjusted HR: 0.37; 0.20 - 0.68; $p=0.001$).[46] Among patients with baseline hs-CRP ≥90th percentile, the proportion of recurrent coronary events prevented by pravastatin was 54%, compared to only 25% among those with low hs-CRP levels, despite no difference in baseline lipid profile measurements.[30]

In conclusion, vascular inflammation is enhanced prior to plaque rupture. In ACS the inflammatory response is systemic. Mediators of vascular inflammation provide diagnostic and prognostic information in patients with ACS. Inflammatory markers may also be able to predict response to different treatment options.

References

1. Kruth HS. The fate of lipoprotein cholesterol entering the arterial wall. ***Curr Opin Lipidol*** 1997; 8: 246.
2. Camejo G, Hurt-Camejo E, Wiklund O. Association of ApoB Lipoproteins with Arterial Proteoglycans: Pathological Significance and Molecular Basis. ***Atherosclerosis*** 1998; 139: 205.

3. Witztum JL, Berliner JA. Oxidized Phospholipids and isoprostanes in atherosclerosis. ***Curr Opini Lipidol*** 1998; 9: 441.
4. Ley K, Huo Y. VCAM-1 is critical in Atherosclerosis. ***J Clin Invest*** 2001; 107: 1209.
5. Nakashima Y, Raines EW, Plump AS. Upregulation of VCAM-1 and ICAM-1 at atherosclerosis prone sites on the Endothelium in the APO-E deficient mouse. ***Arterioscler Thromb Vasc Biol*** 1998; 18: 842.
6. Vora DK, Fang ZT, Liva SM. Induction of P-selectin by oxidized lipoproteins: separate effects on synthesis and surface expression. ***Circ Res*** 1997; 80: 810.
7. Luster AD. Chemokines: chemotactic cytokines that mediate inflammation. ***N Engl J Med*** 1998; 338: 436.
8. Gu L, Okaida Y, Clinton S. Absence of Monocyte Chemoattractant protein-1 reduces atherosclerosis in low-density lipoprotein-deficient mice. ***Moll Cell*** 1998; 2: 275.
9. Miller YI, Chang MK, Binder CJ: Oxidized low density lipoprotein and innate immune receptors. ***Curr Opin Lipidol*** 2003; 14: 437.
10. Stemme S, Faber B, Holm J, Wiklund O, Witztum JL, Hansson GK et al. T lymphocytes from human atherosclerotic plaques recognize oxidized low density lipoprotein. ***Proc Natl Acad Sci U S A*** 1995; 92: 3893-3897.
11. Zhou X, Robertson AK, Rudling M, Parini P, Hansson GK. Lesion development and response to immunization reveals a complex role for CD4 in atherosclerosis. ***Circ Res*** 2005; 96: 427-434.
12. Pinderski LJ, Fischbein MP, Subbanagounder G, Fishbein MC, Kubo N, Cheroutre H et al. Overexpression of interleukin-10 by activated inhibits atherosclerosis in LDL receptor-deficient Mice by altering lymphocyte and macrophage phenotypes. ***Circ Res*** 2002; 90: 1064-1071.
13. Manabe I, Nagai R. Regulation of smooth muscle phenotype. ***Curr Atheroroscler Rep*** 2003; 5: 214.
14. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. ***J Am Coll Cardiol*** 2005; 46: 937-954.
15. Falk E, Shah PK, Fuster V. Coronary plaque disruption. ***Circulation*** 1995; 92: 657-671.
16. Libby P. Inflammation in atherosclerosis. ***Nature*** 2002; 420: 868-874.
17. Piek JJ, Van Der Wal AC, Meuwissen M, Koch KT, Chamuleau SA, Teeling RT, et al. Plaque inflammation in restenotic coronary lesions of patients with stable or unstable angina. ***Journal of the American College of Cardiology*** 2000; 35: 963-967.
18. Mauriello A, Sangiorgi G, Fratoni S, Palmieri, G, Bonanno E, Anemona L, et al. Diffuse and Active Inflammation Occurs in Both Vulnerable and Stable Plaques of the Entire Coronary Tree. A Histopathologic Study of Patients Dying of Acute Myocardial Infarction. ***J Am Coll Cardiol*** 2005; 45: 1585-1593.
19. ≠–Caligiuri G, Liuzzo G, Biasucci LM, Maseri A. Immune System Activation Follows Inflammation in Unstable Angina: Pathogenetic Implications. ***J Am Coll Cardiol*** 1998; 32: 1295-304.
20. Rader DJ. Inflammatory markers of coronary risk. ***N Engl J Med*** 2000; 343: 1179-1182.
21. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. ***Circulation*** 1998; 97: 2007-2011.
22. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. ***J Am Coll Cardiol*** 1998; 31: 1460-1465.
23. Chew DP, Bhatt DL, Robbins MA, Penn MS, Schneider JP, Lauer MS et al. Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention. ***Circulation*** 2001; 104: 992-997.
24. Müller C, Buettner HJ, Hodgson JM, Marsch S, Perruchoud AP, Roskamm H et al. Inflammation and long-term mortality after non-ST elevation acute coronary syndrome treated with a very early invasive strategy in 1042 consecutive patients. ***Circulation*** 2002; 105: 1412-1415.
25. Hashimoto H, Kitagawa K, Hougaku H, Etani H, Hori M. Relationship between C-reactive protein and progression of early carotid atherosclerosis in hypertensive subjects. ***Stroke*** 2004; 35: 1625-1630.
26. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. ***Circulation*** 2003; 107: 391-397.
27. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. ***N Engl J Med*** 2002; 347: 1557-1565.
28. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. ***N Engl J Med*** 2000; 342: 836-843.
29. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. ***N Engl J Med*** 2004; 350: 1387-1397.
30. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. ***Circulation*** 1998; 98: 839-844.
31. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. ***N Engl J Med*** 2005; 352: 20-28.
32. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. ***N Engl J Med*** 1997; 336: 973-979.
33. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon, III RO, Criqui M, et al. Markers of Inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. ***Circulation*** 2003; 107: 499-511.
34. Klebanoff SJ. Oxygen metabolism and the toxic properties of phagocytes. ***Ann Intern Med*** 1980; 93: 480-489.
35. Hazen SL, Heinecke JW. 3-Chlorotyrosine, a specific marker of myeloperoxidase-catalyzed oxidation, is markedly elevated in low-density lipoprotein isolated from human atherosclerotic intima. ***J Clin Invest*** 1997; 99: 2075-2081.
36. Sugiyama S, Okada Y, Sukhova GK, Virmani R, Heinecke JW, Libby P Macrophage myeloperoxidase regulation by granulocyte macrophage colony-stimulating factor in human atherosclerosis and implications in acute coronary syndromes. ***Am J Pathol*** 2001; 158: 879-891.
37. Zhang R, Brennan ML, Shen Z, MacPherson JC, Schmitt D, Molenda CE, et al. Myeloperoxidase functions as a major enzymatic catalyst for initiation of lipid peroxidation at sites of inflammation. ***J Biol Chem*** 2002; 277: 46116-46122.

38. Podrez EA, Febbraio M, Sheibani N, Schmitt D, Silverstein RL, Hajjar DP et al. Macrophage scavenger receptor CD36 is the major receptor for LDL modified by monocyte-generated reactive nitrogen species. ***J Clin Invest*** 2000; 105: 1095-1108.
39. Eiserich JP, Baldus S, Brennan ML, Ma W, Zhang C, Tousson A et al. Myeloperoxidase, a leukocyte-derived vascular NO oxidase. ***Science*** 2002; 296: 2391-2394.
40. Zhang R, Brennan ML, Fu X, Aviles RJ, Pearce GL, Penn MS et al. Association between myeloperoxidase levels and risk of coronary artery disease. ***JAMA*** 2001; 286: 2136-2142.
41. Brennan ML, Penn MS, Van Lente F, Nambi V, Shishehbor MH, Aviles RJ et al. Prognostic value of myeloperoxidase in patients with chest pain. ***N Engl J Med*** 2003; 349: 1595-1604.
42. Baldus S, Heeschen C, Meinertz T, Zeiher AM, Eiserich JP, Munzel T et al. CAPTURE Investigators. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. ***Circulation*** 2003; 108: 1440-1445.
43. Sugiyama S, Kugiyama K, Aikawa M, Nakamura S, Ogawa H, Libby P. Hypochlorous acid, a macrophage product, induces endothelial apoptosis and tissue factor expression: involvement of myeloperoxidase-mediated oxidant in plaque erosion and thrombogenesis. ***Arterioscler Thromb Vasc Biol*** 2004; 24: 1309-1314.
44. Andre P, Nannizzi-Alaimo L, Prasad SK, Phillips DR. Platelet-derived CD40L: the switch-hitting player of cardiovascular disease. ***Circulation*** 2002; 106: 896-869.
45. Mach F, Schonbeck U, Bonnefoy JY, Pober JS, Libby P. Activation of monocyte/macrophage functions related to acute atheroma complication by ligation of CD40: induction of collagenase, stromelysin, and tissue factor. ***Circulation*** 1997; 96: 396-369.
46. Heeschen C, Dimmeler S, Hamm CW, van den Brand MJ, Boersma E, Zeiher AM et al. CAPTURE Study Investigators. Soluble CD40 ligand in acute coronary syndromes. ***N Engl J Med*** 2003; 348: 1104-1111.
47. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. ***N Engl J Med*** 1999; 340: 448-454.
48. Maier W, Altwegg LA, Corti R, Gay S, Hersberger M, Maly FE et al. Inflammatory markers at the site of ruptured plaque in acute myocardial infarction: locally increased interleukin-6 and serum amyloid A but decreased C-reactive protein. ***Circulation*** 2005; 111: 1355-1361.
49. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. ***Circulation*** 2000; 101: 1767-1772.
50. Lindmark E, Diderholm E, Wallentin L, Siegbahn A. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. ***JAMA*** 2001; 286: 2107-2113.
51. Sabatine MS, Morrow DA, de Lemos JA, Gibson CM, MurphySA, et al. Multimarker Approach to Risk Stratification in Non-ST Elevation Acute Coronary Syndromes. ***Circulation*** 2002; 105: 1760.