



**HAL**  
open science

## Combination of indomethacin and statin compared with indomethacin and placebo in patients with first episode of acute pericarditis: preliminary findings

Pietro Di Pasquale, Sergio Cannizzaro, Sergio Fasullo, Filippo Ganci, Giorgio Marenghini, Sebastiano Scalzo, Francesco Giambanco, Giuseppe Vitale, Giovanni Polizzi, Salvatore Paterna

### ► To cite this version:

Pietro Di Pasquale, Sergio Cannizzaro, Sergio Fasullo, Filippo Ganci, Giorgio Marenghini, et al.. Combination of indomethacin and statin compared with indomethacin and placebo in patients with first episode of acute pericarditis: preliminary findings. *Clinical Science*, 2007, 113 (11), pp.443-448. 10.1042/CS20070092 . hal-00479374

**HAL Id: hal-00479374**

**<https://hal.science/hal-00479374>**

Submitted on 30 Apr 2010

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**THE COMBINATION OF INDOMETHACIN AND STATIN VERSUS INDOMETHACIN  
AND PLACEBO IN PATIENTS WITH A FIRST EPISODE OF ACUTE PERICARDITIS:  
PRELIMINARY FINDINGS.**

**Pietro Di Pasquale MD\*, Sergio Cannizzaro MD\*, Sergio Fasullo MD\*,Filippo Ganci MD\*,  
Giorgio Marenghini MD\*, Sebastiano Scalzo MD\*, Francesco Giambanco MD\*, Giuseppe  
Vitale MD\*, Giovanni Polizzi MD\*\*, Salvatore Paterna MD\*\*\*.**

**Running Title: Statin and NSAID in acute pericarditis**

**\* Division of Cardiology;G.F. Ingrassia Hospital,Palermo.**

**\*\* Division of Cardiology, Partinico Hospital,Palermo.**

**\*\*\*Department of Emergency Medicine; University of Palermo.**

**Correspondence to**

**Pietro Di Pasquale MD**

**Chief of Division “Paolo Borsellino”**

**G.F. Ingrassia Hospital,**

**Via Val Platani 3,90144, Palermo,Italy**

**Tel/Fax +39 091 7033742**

**E-Mail: Lehdi@tin.it**

### **Abstract**

The aim of the study was to evaluate the safety and efficacy of the combination of indomethacin and statin versus indomethacin plus placebo in patients with a first episode of pericarditis. Fifty five consecutive patients with acute pericarditis were randomized in double blind fashion into two groups: group 1 was treated with indomethacin 150 mg plus rosuvastatin 10 mg and group 2 was treated with indomethacin 150 mg plus placebo. Both groups received treatment up to the normalization of inflammation markers and for the following week. Clinical and laboratory assessments (WCC, ESR, CRP, TNI, CK/MB, BNP plasma levels) and ECG and echocardiogram were performed at baseline and daily up to discharge. All the patients were followed as outpatients for 3 months to evaluate a recurrence of pericarditis. The two groups were similar in age, sex and laboratory parameters. Group 1 (the statin group) included 28 patients, 18 M/10 F, age  $29.5 \pm 5.7$  years; group 2 (placebo group) comprised 27 patients 16 M/11 F, age  $29.2 \pm 4.8$  years. The statin group showed a significant faster reduction in CRP values ( $5.0 \pm 1$  vs  $6.0 \pm 2$  days,  $p=0.022$ ), in ST segment normalization ( $3.5 \pm 1$  vs  $4.5 \pm 1$  days,  $p=0.001$ ), pericardial effusion ( $4.5 \pm 1$  vs  $5.5 \pm 1$  days,  $p=0.001$ ) and ESR ( $5.0 \pm 1$  vs  $6.0 \pm 2$ ,  $p=0.022$ ). Our data show that the combination of statin and indomethacin in patients with acute pericarditis is feasible, showing a significant reduction in inflammatory markers and a favourable trend in hospitalization time ( $5.5 \pm 2$  vs  $6.5 \pm 2$ ,  $p=0.069$ ). These preliminary findings require further studies on a larger patient sample.

**Key Words: Indomethacin, Acute Pericarditis, Rosuvastatine.**

## INTRODUCTION

Acute pericarditis is a common and frequent disease to be considered in the differential diagnosis of chest pain. Most patients with acute pericarditis have either viral or idiopathic pericarditis. In many cases, acute pericarditis has a brief and benign course after empirical treatment with non-steroidal anti-inflammatory drugs (NSAIDs). A viral aetiology is often presumed but evidence for this is not often sought due to the expense involved and the time required before the results of laboratory tests are available. The aims of treatment are to relieve symptoms, and most patients are hospitalized for complete diagnosis and observation of complications, particularly pericardial effusion and cardiac tamponade [1,2]. Although as many as 90% of isolated cases of acute pericarditis are idiopathic or viral, the list of other potential causes is extensive. The mainstay of therapy is NSAIDs and, recently, colchicine has also shown promise in the treatment of recurrent pericarditis [3]. Indomethacin and other NSAIDs can inhibit the activity of COX, a property which accounts for their shared therapeutic effects [4]. Recent studies have shown that it is possible to modulate C-reactive protein (CRP) levels with pharmacological intervention, including HMG-CoA reductase inhibitor drugs like statins [5-7]). The latter reduce cardiovascular risk also by diminishing arterial inflammation, as suggested by a reduction in serum CRP levels; this appears to be independent of a reduction in LDL cholesterol levels [8,9]. On the basis of these data a pilot study was carried out to evaluate the safety and feasibility of the indomethacin/statin combination, and if this should prove to be more effective than indomethacin plus placebo in patients with a first episode of acute pericarditis. Our endpoints were: 1) feasibility and safety; and 2) effects on clinical inflammation markers, pericardial effusion and ST-segment evolution.

## MATERIALS AND METHODS

The present study was performed in accordance with the declaration of Helsinki, and written informed consent was obtained from each patient before starting the study. The protocol was approved by the local ethical committee.

**Population.** 55 consecutive patients, hospitalized for a first episode of acute pericarditis at G.F. Ingrassia Hospital, Palermo, Italy, were studied prospectively between January 2005 and December 2006.

**Inclusion criteria:** age > 18 years, prodrome of fever, malaise, and myalgia, retrosternal or left precordial chest pain and shortness of breath, rapid and regular heart rate, pericardial friction rub, elevated white-cell count > 10,0 x 10<sup>9</sup> L, elevated erythrocyte sedimentation rate (ESR) >35 mm/h, high values of serum CRP (normal value <05 mg/dl), plasma troponin I (TNI) > 1.0 pg/ml, serum creatin kinase (CK) > 80 IU/l and its MB fraction concentration [1,2,10,11], classic ECG alterations (widespread upward concave ST-segment elevation and PR-segment depression), and echocardiographic evidence of a small pericardial effusion on admission (an echo-free space, anterior plus posterior, of <10 mm during diastole) [12]. As this was a pilot study, only patients with small pericardial effusion were included. Acute pericarditis was diagnosed when at least 4 of the following criteria were present: pericarditic chest pain, pericardial friction rub, widespread ST-

segment elevation on the electrocardiogram (ECG), echocardiographic evidence of a small pericardial effusion, elevated white-cell count (WCC), elevated erythrocyte sedimentation rate (ESR), high values of serum CRP, and increased values of TNI and CK and its MB fraction concentration.

**Exclusion criteria:** patients with infections, kidney failure, metastatic disease, those receiving medications, and radiation therapy, history of recent heart attack (myocardial infarction), rheumatoid arthritis and lupus, tuberculosis and AIDS, recent chest trauma, and receiving anti-inflammatory drugs before hospitalization, statin etc. Considering that most cases probably had a viral or idiopathic aetiology, with a possible brief and benign course after NSAIDs, we intentionally avoided performing an initial full diagnostic evaluation in all cases.

**Study protocol and follow up:** Just after admission, the suitable patients were double-blind randomized into two groups: one group received indomethacin 150 mg daily plus rosuvastatin 10 mg daily; the other group received indomethacin 150 mg daily plus placebo. Both groups received the treatments (rosuvastatin plus indomethacin or placebo plus indomethacin) up to the normalization of inflammation markers (CRP <0.5 pg/ml, WC <7.0 x 10<sup>9</sup> L, ESR < 20 mm/h) and for the whole following week. After baseline clinical and laboratory assessments, the patients were evaluated daily with a complete physical examination, a careful symptom check, blood pressure (BP) and heart rate (HR); blood samples were drawn daily to determine WCC, ESR, CRP, TNI, CK/MB (Dade Behring Diagnostics), pro-NT-BNP plasma levels (Roche), serum urea and creatinine. All laboratory measurements were made in a core laboratory and a validated assay for high-sensitive CRP was used (Dade Behring Co., Marburg, Germany). Chest-x ray was performed on admission and at discharge, while ECG and echocardiogram were performed daily up to discharge in order to control pericardial effusion. After discharge, the patients were followed as outpatients every week for the 1st month and every two weeks for the subsequent two months to evaluate a recurrence of pericarditis. Clinical evaluation, ECG, echocardiographic and laboratory assessments were performed at every follow up by two blinded physicians to evaluate if recurrence of pericarditis had occurred. No other anti-inflammatory drug was added or used during the study period. The side effects of indomethacin were recorded and gastroprotection with omeprazole (20 mg/day) was also administered..

### Statistical Analysis

Continuous data are reported as the mean value  $\pm$  SD and compared, using the unpaired *t* test and variance analysis (ANOVA) for repeated measures with Bonferroni correction for intragroup data. Categorical variables are expressed as proportions or percentages and compared using chi-square analysis. A value of *p* < 0.05 was considered to show statistical significance.

### RESULTS

All the 55 enrolled patients (mean age  $29.3 \pm 5.2$  years, range 20-38 years, 34 men and 21 women) showed an acute onset, pericardial chest pain and ECG ST-segment elevation with a typical ECG evolution at entry.

Pericardial friction rub was present in 45 cases and small pericardial effusion was present in 47 patients. The treatment was effective in all the 55 cases and no patient displayed initial treatment failure. The treatment was well tolerated without serious drug side effects. We recorded only one minor side effect, including dyspepsia, abdominal pain, and gastritis (from the statin group). After a mean follow-up of 3 months, no recurrence of pericarditis and any rebound effect after discontinuing the statin therapy was observed. The two groups were similar by clinical characteristics, age, sex and laboratory parameters (**Table 1**). The statin group showed a significant faster reduction/normalization in CRP values ( $5.0 \pm 1$  vs  $6.0 \pm 2$  days,  $p=0.022$ ); in ST segment normalization ( $3.5 \pm 1$  vs  $4.5 \pm 1$  days,  $p=0.001$ ); pericardial effusion ( $4.5 \pm 1$  vs  $5.5 \pm 1$  days,  $p=0.001$ ); ESR ( $5 \pm 1$  vs  $6 \pm 2$  days;  $p=0.022$ ), while WCC ( $3.0 \pm 2$  vs  $4.0 \pm 2$  days) and hospitalization time ( $5.5 \pm 2$  versus  $6.5 \pm 2$  days) showed a not significant but favourable trend,  $p=0.069$  (**Table 2**). These data were calculated when the patients were completely free of symptoms and, in the same time period ESR, WCC fell in the normal range ( $<20$  mm/h and  $<7.0 \times 10^9$  L respectively). This moment was also chosen to analyze the CRP values. TNI and CK/MB in patients presenting with increased levels at entry did not show any differences in normalization time and plasma levels during the study period (**Table 2**). The absence of effects of the combined treatment on TNI and CK/MB was probably due to the kinetic of myocardial enzymes, which usually depends on baseline values and which represents myocardial damage already present at entry. Pro-BNP (Roche) values showed normal values ( $< 125$  pg/ml) either on admission or during the study period. **Table 3** shows the daily variations in plasma inflammation markers (WCC, ESR, CRP) during hospitalization. The statin group displayed earlier changes in CRP, WCC and ESR in comparison with the placebo group. These results are in agreement with the faster favourable clinical evolution, as reported by an analysis of the ST-segment and pericardial effusion resolution.

## DISCUSSION

This study points to the safety of a combined indomethacin/statin therapy. Moreover, this combination, determining an earlier normalization of clinical and laboratory inflammatory markers in patients with a first episode of acute pericarditis, was also observed. To date, this is the first time that a combination of NSAID and statin has been used in the setting of such patients. This treatment took into consideration the results of recent reports, in which the important anti-inflammatory effects of statins were discussed [13-15]. Statins can interfere with the proinflammatory pathway of adhesion and migration at the level of protein expression and function. For example, statins diminish the expression of the integrin dimer CD11b (Mac-1, the cognate ligand of ICAM-1 on the endothelium and other cells) on monocytes and they also inhibit the adhesion of leukocytes to endothelial cells [16-18]. Statins can selectively inhibit leukocyte adhesion by direct interaction with the leukocyte-function antigen-1 (LFA-1), thereby providing definitive evidence for functions which are independent of lipid lowering. [19] By binding to a new allosteric site within this  $\beta_2$  integrin, rather than targeting HMG-CoA reductase, statins block the adhesion of lymphocytes to the endothelium to such a degree so as to suppress the inflammatory response in peritonitis in mice. [19]. Statins are also reported to ameliorate inflammatory diseases in murine autoimmune models, by inhibiting Th1 responses [20], and to influence cell activation through the inhibition of NF $\kappa$ B [21,22] and diminished T-cell proliferation, probably

via the direct engagement of the T-cell receptor.[23,24]. The type of immune response supported may also depend on the ability of statins to induce the release of the  $T_H2$ -promoting cytokines (eg, IL-4, IL-5, IL-10, or transforming growth factor- $\beta$ ), and diminish the secretion of the  $T_H1$  subtype (eg, IL-2, IL-12, or interferon. [25]. Statins may also repress the activation of T lymphocytes by inhibiting major histocompatibility complex class II antigen expression. [26]. Notably, HMG-CoA reductase inhibitors also regulate the expression and function of these mediators. In addition, statins determined the prevention of atrial fibrillation (AF) in an experimental model of pericarditis with elevated CRP, and prevented the promotion of atrial electrophysiological and structural changes resulting from inflammation. [27]. Similarly, a recent clinical study has shown that the use of statins in patients with lone AF was associated with a decrease in the recurrence of AF after successful cardioversion [28]. These data show that statins can mediate modest but clinically apparent anti-inflammatory effects by modifying vascular risk factors in the context of high-grade autoimmune inflammation [29]. Indomethacin is a widely used NSAID and it is generally known to exhibit multiple biological functions by inhibiting cyclooxygenases. Indomethacin inhibits the activity of the enzyme cyclooxygenase by decreasing the formation of the precursors of prostaglandins and thromboxanes from arachidonic acid or by activating peroxisome proliferator-activated receptors [30] However, recent studies have revealed that a number of the actions of indomethacin are independent of COXs.[31]. In addition, it was shown that the novel  $PGD_2$  receptor chemoattractant receptor-homologous molecule, expressed on Th2 cells (CRTH2), is another functional target for indomethacin [32,33].In addition, indomethacin was able to reduce virus infection at a postbinding step early in the infection cycle, thereby inhibiting virus protein synthesis, but it did not seem to affect viral RNA synthesis [34]. We hypothesized that the combination of both drugs, which displays different actions in the inflammatory process, could determine an enhancing of anti-inflammatory effects and it could also explain the observed effects on CRP plasma levels from day 1 of treatment. We studied patients with acute pericarditis because these patients are young and with no other diseases which could interfere with the inflammatory state determined by pericarditis. The randomized patient sample comprised patients exclusively at low risk because this was the first time that this combination had been used. Indeed, the primary endpoint was safety and feasibility. The effects observed on clinical and laboratory inflammatory markers were of great interest but the low number of patients and brief observation period were insufficient in permitting definitive conclusions. We believe that the favourable trend in reducing hospitalization time (not significant), the significant earlier normalization in ST-segment elevation and pericardial effusion were obtained due to a more rapid cessation of the inflammatory process. Our data are insufficient to suggest additive or synergistic effects of the indomethacin/statin combination and should, therefore, be considered as a preliminary stage and to be interpreted with caution; further investigation, however, is warranted.

**Table 1: Clinical characteristics and baseline values of the enrolled patients. Data are expressed as mean $\pm$  SD.**

	<b>Statin</b>	<b>Placebo</b>	<b>P&lt;</b>
<b>Patients No</b>	<b>28</b>	<b>27</b>	<b>ns</b>
<b>Age (years)</b>	<b>29.5<math>\pm</math>5.7</b>	<b>29.2<math>\pm</math>4.8</b>	<b>ns</b>
<b>Sex (M/F)</b>	<b>18/10</b>	<b>16/11</b>	<b>ns</b>
<b>Systolic Blood Pressure (mmHg)</b>	<b>118<math>\pm</math>8.1</b>	<b>117.7<math>\pm</math>7.3</b>	<b>ns</b>
<b>Diastolic Blood Pressure (mmHg)</b>	<b>72.8<math>\pm</math>6.4</b>	<b>73.3<math>\pm</math>7.0</b>	<b>ns</b>
<b>Heart Rate (b/min)</b>	<b>101<math>\pm</math>2<math>\pm</math>8.2</b>	<b>100.8<math>\pm</math>7.7</b>	<b>ns</b>
<b>BUN (mg/dl)</b>	<b>29.56<math>\pm</math>5.4</b>	<b>28.7<math>\pm</math>5.2</b>	<b>ns</b>
<b>Creatinine (mg/dl)</b>	<b>0.82<math>\pm</math>0.22</b>	<b>0.84<math>\pm</math>0.24</b>	<b>ns</b>
<b>Ejection Fraction%</b>	<b>60.1<math>\pm</math>3.7</b>	<b>59.8<math>\pm</math>3.9</b>	<b>ns</b>
<b>C-Reactive Protein (mg/dl)</b>	<b>9.36<math>\pm</math>3.3</b>	<b>9.25<math>\pm</math>3.0</b>	<b>ns</b>
<b>Erythrocyte sediment. rate (mm/h)</b>	<b>40.1<math>\pm</math>6.41</b>	<b>39.96<math>\pm</math>6.74</b>	<b>ns</b>
<b>Troponin I (pg/ml)</b>	<b>1.21<math>\pm</math>0.7</b>	<b>1.18<math>\pm</math>0.6</b>	<b>ns</b>
<b>White Cell count (x 10 L)</b>	<b>11,21<math>\pm</math>2.3</b>	<b>11,11<math>\pm</math>2.6</b>	<b>ns</b>
<b>Creatin Kinase (IU/l)</b>	<b>193.8<math>\pm</math>50.43</b>	<b>189.5<math>\pm</math>45.35</b>	<b>ns</b>

White cell count values are x10/L.



**Table: 2: Effects of the combination of statin and indomethacin versus indomethacin and placebo on the normalization time of inflammatory markers, ST-segment normalization and pericardial effusion disappearance (days). The time (days) was calculated from admission (baseline values) to normalization of inflammation markers and when the patients were symptom-free and in the same time ESR, WCC resulted in normal range (<20 mm/h and <7.0 X 10<sup>9</sup> L respectively). This moment was also chosen to analyze the CRP values. Data are expressed as mean±SD.**

	<b>Statin</b>	<b>Placebo</b>	<b>p&lt;</b>
<b>Time of hospitalization (days)</b>	<b>5.5±2</b>	<b>6.5±2</b>	<b>0.069</b>
<b>ST segment normalization (days)</b>	<b>3.5±1</b>	<b>4.5±1</b>	<b>0.001</b>
<b>Pericardial effusion (days)</b>	<b>4.5±1</b>	<b>5.5±1</b>	<b>0.001</b>
<b>ESR (mm/h &lt;20) (days)</b>	<b>5.0±1</b>	<b>6.0±2.</b>	<b>0.022</b>
<b>WCC (&lt;7.0 X 10<sup>9</sup> L)(days)</b>	<b>3.0±2</b>	<b>4.0±2</b>	<b>0.069</b>
<b>CRP (≤ 0.5 mg/dl)(days)</b>	<b>5.0±1</b>	<b>6.0±2</b>	<b>0.022</b>
<b>TNI (&lt;0.5 pg/ml)(days)</b>	<b>4.5±1</b>	<b>4.5±1</b>	<b>ns</b>
<b>CK (&lt;80 IU/L)(days)</b>	<b>3.5±1</b>	<b>3.5±1</b>	<b>ns</b>

**WCC=White Cells count; ESR= Erythrocyte sedimentation rate; CRP= C-reactive protein; TNI= Troponin I; CK=creatin Kinase.**

**Table 3: Changes in C-reactive protein, erythrocyte sedimentation rate, and white cell count during hospitalization period. Data are expressed as mean  $\pm$  SD**

Days	Statin	Placebo	P<	Statin	Placebo	P<	Statin	Placebo	P<
	C-Reactive--Protein			erythrocyte sedimentation rate			White Cells count		
Entry	9.36 $\pm$ 3.3	9.25 $\pm$ 3.0	0.89	40,1 $\pm$ 5,5	39,9 $\pm$ 5,7	ns	11210 $\pm$ 2590	1110 $\pm$ 2355	ns
Days 1	6.3 $\pm$ 2.3	8.5 $\pm$ 2.5	0.001	35 $\pm$ 4,5	37 $\pm$ 5,4	0.141	10125 $\pm$ 1855	10.600 $\pm$ 1950	0.359
Days 2	3.1 $\pm$ 1.1	4.9 $\pm$ 1.5	0.0001	30,5 $\pm$ 4,1	34 $\pm$ 4,7	0.005	9185 $\pm$ 1445	9850 $\pm$ 1650	0.117
Days 3	1.2 $\pm$ 0.5	2.5 $\pm$ 0.8	0.0001	30,1 $\pm$ 3,8	32 $\pm$ 3,8	0.069	8750 $\pm$ 1235	9.200 $\pm$ 1475	0.225
Days 4	0.82 $\pm$ 0.4	1.5 $\pm$ 0.7	0.0001	26,5 $\pm$ 3,4	26 $\pm$ 3,7	ns	7350 $\pm$ 1110	8250 $\pm$ 1325	0.008
Days 5	0.71 $\pm$ 0.2	0.92 $\pm$ 0.3	0.003	19,9 $\pm$ 2,8	26 $\pm$ 3,2	0.0001	6150 $\pm$ 855	7500 $\pm$ 650	0.0001
Days 6	0.5 $\pm$ 0.2	0.65 $\pm$ 0.2	0.007	18,1 $\pm$ 2,1	20.1 $\pm$ 1,9	0.0001	5965 $\pm$ 525	6285 $\pm$ 755	0.073
*P<	0.0001	0.0001		0.0001	0.0001		0.0001	0.0001	

\*p= intragroup differences (ANOVA).

**References:**

- 1) Spodick DH. Pericardial disease. Braunwald E, Zipes D, Libby P, editors. (2001).Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia, PA: W.B. Saunders.
- 2) Spodick DH. Acute pericarditis: current concepts and practice.(2003). *JAMA*;289:1150–1153
- 3) Adler Y, Finkelstein Y, Guindo J, et al. (1998) Colchicine treatment for recurrent pericarditis: a decade of experience. *Circulation* ;97 (21):2183-5
- 4) Vane, J. R. (1971). Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat. New Biol.* 231:232.
- 5) Ridker PM,Rifai N, Pfeffer MA *et al.* (1999). Long-term effects of pravastatin on plasma concentration of C-reactive protein: the Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* ;100;230–235.
- 6) Ridker PM, Rifai N,Lowenthal SP. (2001).Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. *Circulation* 103 ;1191–1193
- 7)Strandberg TE,Vanhanen H,Tikkanen MJ.(1999). Effect of statins on C-reactive protein in patients with coronary artery disease. *Lancet* 353 ;118–119.
- 8) Ridker PM, Rifai N,Clearfield M *et al.*, (2001), Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N. Engl. J. Med.* 344;1959–1965.
- 9) Jialal I, Stein D,Balis D *et al.*, (2001), Effect of hydroxymethyl glutaryl CoA reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation* 103 1933–1935.
- 10) Permanyer-Miralda G, Sagrista-Sauleda J, Soler-Soler J.(1985). Primary acute pericardial disease: a prospective series of 231 consecutive patients. *Am J Cardiol.*;56:623–630.
- 11) Imazio M, Demichelis B, Cecchi E, et al. (2003).Cardiac troponin I in acute pericarditis. *J Am Coll Cardiol* ;42:2144–2148
- 12) Weitzman LB, Tinker WP, Kronzon I, et al. (1984). The incidence and natural history of pericardial effusion after cardiac surgery: an echocardiographic study. *Circulation.*;69:506–511
- 13) Wæhre T, Damås JK, Gullestad L, et al. (2003).Hydroxymethylglutaryl coenzyme a reductase inhibitors down-regulate chemokines and chemokine receptors in patients with coronary artery disease. *J Am Coll Cardiol*;41(9); 1460-1467
- 14) Nissen SE, Murat Tuzcu E,Schoenhagen P,et al, for the Reversal of Atherosclerosis with Aggressive

Lipid Lowering (REVERSAL) Investigators (2005). Statin Therapy, LDL Cholesterol, C-Reactive Protein, and Coronary Artery Disease. *N Engl J Med*;352 (6);29-38.

15) Kinlay S, Schwartz,GG, Olsson AG, et al: for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators (2003).High-Dose Atorvastatin Enhances the Decline in Inflammatory Markers in Patients With Acute Coronary Syndromes in the MIRACL Study *Circulation.*;108:1560.

16) Weber C, Erl W, Weber KSC, et al. (1997). HMG-CoA reductase inhibitors decrease CD11b expression and CD11b-dependent adhesion of monocytes to endothelium and reduce increased adhesiveness of monocytes isolated from patients with hypercholesterolemia. *J Am Coll Cardiol*; 30: 1212–1217.

17) Kimura M, Kurose I, Russell J, et al.(1997). Effects of fluvastatin on leukocyte–endothelial cell adhesion in hypercholesterolemic rats. *Arterioscler Thromb Vasc Biol*; 17: 1521–1526.

18) Rasmussen LM, Hansen PR, Nabipour MT, et al. (2001).Diverse effects of inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase on the expression of VCAM-1 and E-selectin in endothelial cells.*Biochem J*; 360: 363–370.

19) Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. (2001).Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. *Nat Med*; 7: 687–692.

20) Leung BP, Sattar N, Crilly A, *et al.*, (2003). A novel anti-inflammatory role for simvastatin in inflammatory arthritis, *J. Immunol.* 170, 1524–1530.

21) Hilgendorff A, Muth H, Parviz B, *et al.* (2003). Statins differ in their ability to block NF-kappaB activation in human blood monocytes, *Int. J. Clin. Pharmacol. Ther*; 41, 397–401.

22) Dechend R, Fiebler A, Lindschau C, *et al* (2001).Modulating angiotensin II-induced inflammation by HMG Co-A reductase inhibition, *Am J Hypertens.* 14;. 55S–61S.

23) Li WM, Liu W, Gao C, Zhou BG. (2006). Immunoregulatory effects of atorvastatin on experimental autoimmune myocarditis in lewis rats. *Immunol Cell Biol.*;84(3):274-80.

24) Aktas O, Waiczies S, Smorodchenko A, et al.(2003). Treatment of relapsing paralysis in experimental encephalomyelitis by targeting Th1 cells through atorvastatin. *J Exp Med.*; 197: 725–733.

25) Youssef S, Stüve O, Patarroyo JC, et al.(2002).The HMG-CoA reductase inhibitor,atorvastatin, promotes

a Th2 bias and reverses paralysis in central nervous system autoimmune disease. *Nature*;420:78–84.

26) kwak B, Mulhaupt F, Myit S, et al.(2000). Statins as a newly recognized type of immunomodulator. *Nat Med.*; 6: 1399–1402.

27) Kumagai K, Nakashima H,Saku K. (2004).The HMG-CoA reductase inhibitor atorvastatin prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model *Cardiovasc Res* ;62:105-111

28) Siu CW,Lau CP, Tse HF. (2003).Prevention of atrial fibrillation recurrence by statin therapy in patients with lone atrial fibrillation after successful cardioversion. *Am J Cardiol.* 92 ,1343–1345

29) McCarey DW, McInnes PB, Madhok R,et al.(2004) Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial . *Lancet* ; 363; 2015-2021

30) Brooks G, Yu X.M., Wang Y, Crabbe M.J., Shattock M.J, Harper J.V.(2003). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit vascular smooth muscle cell proliferation via differential effects on the cell cycle. *J. harm. Pharmacol.*; 55,519–526.

31) Zhang X, Morham SG, Langenbach R, Young DA.(1999). Malignant transformation and antineoplastic actions of nonsteroidal anti-inflammatory drugs (NSAIDs) on cyclooxygenase–null embryo fibroblasts. *J Exp Med*; 190;451.

32) Lehmann JM.,Lenhard JM,Oliver BB,Ringold GM,Kliwer SA.(1997) Peroxisome proliferator-activated receptors and are activated by indomethacin and other non-steroidal anti-inflammatory drugs. *Biol. Chem.*; 272:3406.

33) Hirai H, Tanaka K, Takano S, Ichimasa M,Nakamura M, Nagata K.(2002). Cutting Edge: Agonistic Effect of Indomethacin on a Prostaglandin D<sub>2</sub> Receptor,CRTH2. *The Journal of Immunology*: 168;981-985.

34) Rossen JW,Bouma J,Raatgeep RH,Buller HA,Einerhand AW.(2004). Inhibition of cyclooxygenase activity reduces rotavirus infection at a postbinding step. *J Virol*;78(18):9721-30.