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Idiopathic Membranous Nephropathy and Treatment Related Complications

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ABSTRACT

Introduction: Idiopathic Idiopathic membranous nephropathy (iMN) is an immune-complex mediated renal disease which is usually associated with the nephrotic syndrome (NS). The course of the disease is variable. Some patients maintain normal kidney function with or without a spontaneous remission of proteinuria, while others progress to end-stage renal failure or die from complications related to the nephrotic syndrome. Whether or not to treat a patient with idiopathic membranous nephropathy is still controversial. The controversy is mainly related to the toxicity of the therapy and the variable natural course of the disease-spontaneous remission occurs in 40–50% of patients. **Aim:** The aim of this study was to describe our experience of treatment of an idiopathic membranous nephropathy (iMN), efficacy and complications rate. **Case report:** Our patient was older, mail gender, in high-risk group with persistent proteinuria 10,68 g/day and stable renal function. We have taken these factors into consideration, along with age and other comorbidities, that may significantly elevate the risk of treatment. We chose to start with early treatment, following the Ponticelli's group protocol based on high dose corticosteroids (odd months) alternating with clorambucil (even months) for six months. This treatment was accompanied by the steroid side effects, including hyperglycaemia dependance on insulin therapy and pulmonary thromboembolism despite administered prophylactically low molecular weight heparin. The six-month treatment was successfully completed with the reduction of proteinuria to nephritic values 2,86 g/day, despite many complications. Complete remission of the disease with non-significant proteinuria and with stable renal function was achieved in 14 months which has been maintained for 2 years. **Conclusion:** We suggest that decisions on the timing of start of therapy, whom to treat, best sequence of the use of the various immunosuppressive drugs must be based on an individualized assessment of risks and benefits.

Keywords: Membranous nephropathy, Ponticelli's protocol, pulmonary thromboembolism.

1. INTRODUCTION

Membraneous nephropathy (MN) is the most common cause of the nephrotic syndrome in adults in Europe countries (1). Although MN can occur secondary to infections, systemic diseases, use of drugs, or malignancies. Awareness of malignacy is particularly important in the elderly. The prevalence of malignancy was 4,1 % in patients < 60 years, and 19,4% in patients > 60 years of age (2). In most patients no underlying cause is identified idiopathic membranous nephropathy (iMN). The clinical course of patients with iMN and nephrotic proteinuria is quite variable. One-third exibit spontaneous remission of disease, usually in the first 2 years after diagnosis, although remission can occur at any time. One-third exibit chronic persistent proteinuria with preservation of renal function, and one-third progress slowly to end stage renal disease (ESRD). Untreated 40-50% of patients with iMN and nephrotic proteinuria will develop end stage renal disease (3,4). The treatment of iMN is heavily debated (5-7). Although several studies have claimed success of immunosuppressive therapy (8-12). A meta analysis and Cochrane review concluded that there is insufficient evidence of the efficacy of immunosuppressive therapy (13), and many studies have reported a relatively good outcome in untreated patients (14, 15). The perception that immunosuppressive is of limited benefits may lead to therapeutic nihilism. Guidelines for all common histologic variants of iMN have recently been published under the auspices of the KDIGO (Kidney Disease: Improving Global Outcomes) initiative (16). These guidelines, graded by the quality of evidence, were established to help the clinician's, but not to replace physician. Cyclophosphamide is preferred over chlorambucil (13, 14).

The optimal duration of therapy is debated. The use of alkylating agents is complicated by serious side effects, like as infertility and risk of late malignancies.

Additionally, the risk of complications from cyclophosphamide may be higher in older individuals and/or in those with a reduced glomerular filtrate rate (GFR). On the other hand, cyclosporine is often difficult to manage and not as well tolerated in patients with reduced GFR and/or in those with severe underlying vascular damage on kidney biopsy, which tends to accentuate the calcineurin inhibitor (CNI) nephrotoxicity (17, 18). Recently, there has been evidence suggesting that treatment with rituximab (19-21) and synthetic adrenocorticotropic hormone (ACTH) can be an effective alternative to these agents (22, 23). One of the first immunosuppressive regimens proven to be effective against iMN was the combination of chlorambucil and prednisone (8). Ponticelli et al. (8) showed a significant increase in complete and partial remissions compared to symptomatic management. In our clinic, we usually prescribe these regimens with some modification.

2. CASE REPORT

A 60 years old man with a history of newly diagnosed proteinuria was admitted to our hospital with a two months history of fatigue, with trace lower extremity edema. The patient had arthralgias of both knees and hands that had not changed in intensity. There was no hystory of rash, cough, sinus symptoms, chest pain or gastrointestinal complaints. He had long standing nocturia, and increased urinary frequency, but no dysuria. He had undergone routine cholecystectomy 4 months prior to current presentation. On admission, physical exam revealed man in good condition, with trace lower extremity edema, and normal cardiac, pulmonary and abdominal exam, no ascites or hepatosplenomegaly was detected. There was no rash, livedo reticularis, joint effusions or synovitis. He was afebrile, with blood pressure of 110/60 mmHg, heart rate 80 beat /min. Laboratory exam revealed a white blood count (WBC) of 6,15 x109/L (4-109/L), red blood count (RBC) was 5,32 1012/L (4,30-5,70 x 10 12/L), normal hemoglobin 170 g/L (135-175 g/L), platelet count 254 x109/L (150-400 x 109/L, APTT 32,5 sec (27,4-37,7 sec), and INR 0,85 (0,80-1,20). Erytrocyte sedimentation rate was mild elevated 48 mm/hr, as was the value of iron 37,2 μmol/L (9-31,3 μmol/L). Urinalysis revealed 3+ proteine, no nitrites or glucose. Evaluation of urine sediment revealed several granulated casts, with 20-25/μl RBC, 8-10 /μl WBC. Renal function was normal with serum creatinine 86 μmol/L (63 -109 μmol/L). Urine protein was quantified at 10,68 gr/24h (<150 mg/24 hours), Bence-Jones proteins were not detected in urine specimen. Serum total protein and albumin were respectively of 46,0 g/L (62,0-82,0 g/L) and 17,0 g/L (35,0-50,0 g/L). The total cholesterol was 7,6 mmol/L (<5,3 mmol/L), and triglyceride of 1,82 mmol/L (0,4-0,9 mmol/L). A diagnosis of nephrotic syndrome was confirmed. Our patient received no drugs; no features of acute or chronic infections were found. The investigating for secundary causes of this membranous glomerulonephritis included: anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibodies and antinuclear antibodies (ANA), titers for antineutrophil cytoplasmic antibodies (ANCA), complement levels and tests for cryoglobulins and rheumatoid factor, thyroid hormone, were negative or normal. Serologies for hepatitis A, B, C and HIV, were nonreactive. Measurement of tumor markers Ca -125 showed mild elevated 37,7 U/ml (0-35 U/ml). Thoracoabdominal tomography, stool for fecal occult blood, prostate – specific tumor markers (PSA) were normal or negative. Chest x ray showed no evidence of infiltrate, vascular congestion or cardiac enlargment (the chest radiography was normal). By ultrasound the right kidney's longitudinal diameter was 13,8 cm and left kidney 14,2 cm, with no pelviectasis, but mild increases parenhimal echogenicity. No renal venous thrombosis was faund on the Doppler sonography. Renal biopsy showed that this was caused by membranous nephropathy. It showed glomeruli with thickening of the capillary walls and capillary loops. There was no mesangial hypercellularity and 40% of interstitium was fibrous. Imunofluorescence showed strong granular IgG along the capillary wall. No IgA deposition and complement were seen.

3. CLINICAL FOLLOW UP

Treatment was based on the alternating pulse of methylprednisolone, oral corticosteroid and chlorambucil. Treatment consisted of 1 g intravenous methylprednisolone given every 24 hours for three consecutive days, followed by oral prednisone at a dose of 0,5 mg/kg/day in a single morning administration for 27 days. After the first month prednisone was stopped and the patient was given chlorambucil, 0,2 mg/kg/day for one month. The whole treatment lasted six months, three with corticosteroids and three with chlorambucil. Before start treatment with high dose prednisone, which might predispose to thrombosis, and low serum albumin which was <20 g/L, the patient was initially treated with prophylactic anticoagulation (low molecular weight heparin), angiotenzin converting enzyme inhibitors (ACEi), statins and dietary sodium restrictio. After the first month of treatment, the proteinuria decreased at 6,97 g/24h, the patient felt well, had no difficulty. At the end of the second month, after cycle with chlorambucil, proteinuria was in a slight decline 6,21 g/24h, and the patient was admitted to the hospital, where he continued terapy with methylprednisolone 1,0 g intravenous for 3 days. On the third day, a few hours after methilprednisolone bolus, he presented with chest pain, cough, and dyspnoea. He had smoked 40 cigarettes every day for years. On physical examination, his body temperature was 37,5 degrees Celsius, with a respiratory rate of 30 breaths per minute, a heart rate of 120 beats per minute, and arterial pressure of 100/80 mmHg. The heart sounds were regular, with no added murmurs. His breathing sounds were reduced bilaterally at the lower lung fields with a few crackeles. The electrocardiogram showed sinus tachycardia and no other abnormalities. The arterial blood gases were normal, with a pH of 7,446 (7,35-7,45), partial pressure of

oxygen (PaO2) 8,58 (11.1-14.4 kPa), partial pressure of carbon dioxide (PaCO2) 5,14 (4,7-6,4 kPa), and bicarbonate of 26,1 (22-26 mmol/L). D -Dimers were high 1314 (0-0,55 mg/L FEU). A spiral CT angiogram was then performed, which showed a large thrombus in the right pulmonary artery and an infarct of the lower lobe. Acute pulmonary embolism was diagnosed and the dose of anticoagulant therapy was increased to heparin in bolus 80 IU/kg TT + continue infusion at 18 IU/kg TT for 24h after very careful evaluation and monitoring the risk of bleeding. On the fifth day of terapy, oral anticoagulant (acenocoumarol) was included in addition to heparin, and heparin was discontinued after seven days. Oral prednisone was continued in the divided daily dose in two separate dose twice daily.

At the end of the cycle with prednisone and at beginning of the fourth month of tretament there was no swelling in his legs. The proteinuria decresed at 4,08 g/24h, but lipids increased as did glycemia. Glucose rate was elevated at 15,9 mmol/l, total cholesterol 13,5 mmol/L and triglyceride of 2,79 mmol/L. There was no significant variaton in other laboratory findings. Insulin therapy was also initiated at the time of diagnosis of diabetes mellitus iatrogenes. The next dose of chlorambucil, the forth month of treatment, was reduced to 0,15 mg/kg day, because the average protein excretion in urine was slightly descreased in the months of chlorambucil, while in the months of prednisolone, it decreased significantly. On the fifth month of tretament, in the third cycle of methilprednisolone, we reduced the pulse dose to 500mg/day for 3 days, followed by oral prednisolone divided daily dose in two separate dose twice daily. At the end of the sixth month of tretament, proteinuria decresed at 2,86 g/24h. In continuation of treatment, steroid therapy and cyclophosphamide were exluded. In therapy, the patient continues to use angiotenzin converting enzyme inhibitors (ACEi), statins and prophylactic oral anticoagulation for the next six months, dietary sodium restriction with monthly monitoring of proteinuria and renal function and waiting for a reasonable period of time (about 8 months) to see whether or not spontaneous remission (complete or partial) occurs. Each month proteinuria gradually declined and renal function remained maintained. After fourteen months of follow-up, complete remission of the disease with non-significant proteinuria was achieved. The patient did not have a recurrence of the disease within two years after the end of treatment.

4. DISCUSSION

Optimum treatment of idiopathic membranous nephropaty is controversial and challenging because there are very few randomized trials in patients with iMN, the natural hystory of iMN is quite variable, and many studies have reported a relatively good outcome in untreated patients (13-15). Without immunosuppresive therapy, >50% of patients would have developed a spontaneous remission. Moreover, 38% of patients needed a second course of therapy because of initial treatment failure or relapse. The immunosuppressive agents have serious side effects, and it is quite difficult to balance the risk and benefits (13,14). The most extensively studied and frequently used immunosuppressive regimens for this disease comprise alkylating agents plus corticosteroids or cyclosporin. All of these treatment options have inherent problems. The optimal timing of start of therapy is uncetain. In the study of Hofstra JM et all., early treatment resulted in a more rapid onset of remission and there fore shortened the duration of the nephrotic phase, it did not result in a better presevation of renal function at the end of follow-up (7). It therefore seems that treatment can safely be postponed until renal function deteriorates. Hower, when postponing treatment, there might be a larger risk of both nephrotic syndrome - related and treatment-related side effects. Finally, elderly patients are more prone to develop treatment-related comlications. Membranous nephropathy is the most cause of nephrotic syndrome in patients over age of 60 years (24, 25). This age group accounts for 23% of patients diagnosed with iMN (25). Older patients will require attention given their lower reserve of kidney function at baseline, but age alone should not preclude therapy. Several works, especially those from Cattran's group, have shown that male gender, age older than 50 years, and the presence of sustained proteinuria >8 g/day for longer than 6 months are criteria for a poor prognosis, and thus lower possibility of spontaneous remission (26). When risk asessment leads to the decision not to start treatment in an individual patient, re-evaluation should take place after 6 months or earlier if the clinical condition of the patients changes. Treatment with alkylating agents is usually combined with high dose steroid treatment. The dose and duration of steroid tretamnet varies and clinical trials are lacking. The most popular immunosuppressive regimen for MGN is from Ponticelli 's group, based on high dose steroids alternating with chlorambucil (8). Our patient was older, mail gender, in high-risk group with persistent proteinuria 10,68 g/day and stable renal function. We have taken these factors into consideration, along with age and other comorbidities, that may significantly elevate the risk of treatment, we chose to start therapy earlier than the 6 months of observation. He received supportive therapy and six month therapy with methylprednisolone and chlorambucil alternated every other month. After three months of treatment, due to complications (pulmonary thromboembolism and iatrogenic diabetes), we had to reduce the doses of the medication chlorambucil and the pulse dose methylprednisolone, oral prednisolone divided daily dose in two separate dose twice daily. He was initially treated with prophylactic anticoagulation, but when a large thrombus in the right pulmonary artery and an infarct of the lower lobe were diagnosed, prophylactic low molecular weight heparin was changed to high dose heparin in bolus end continued infusion for 24h after very careful evaluation and monitoring the risk of bleeding. Nephrotic syndrome is also associated with increased arterial as well as venous thromboembolism (27, 28). The majority of thromboembolic events occur within 6 months of the diagnosis of nephrotic syndrome

(28, 29). Patients with nephrotic syndrome demonstrate urinary loss of anticoagulants (antithrombin III) with increased liver procoagulant synthesis (fibrinogen, factor V, factor VIII), increased platelet activation and aggregability, decreased fibrinolytic activity and localized clotting activation in the kidney (27). Despite the urinary loss of hemostatic proteins levels, some proteins, including fibrinogen, are increased and correlate with the hypoalbuminemia (30). It is believed that hypoalbuminemia stimulates the hepatic synthesis of hemostatic proteins to make up for the urinary loss (31). Hypoalbuminemia increased risk of venous thromboembolic events when serum albumin was below 25g/L (32). In some studies, massive proteinuria has been found to be a more significant predictor of venous thromboembolic events than serum albumin (33). Dehydration, diuretic use, trauma, steroid use as well as immobility (28,29) are other frequently quoted, non hematologic reasons for thrombotic tendecies in this population of patients. Established risk factors for arterial TE in NS include age, sex, hypertension, smoking, diabetes and low estimated glomerular filtration rate (eGFR) (32). Alkylating agents in combination with steroids are the preferred therapy because of their proven efficacy in preventing end-stage renal disease. Calcineurin inhibitors can be used as an alternative although efficacy data are limited (17,18). Relapses of the nephrotic syndrome after cessation of treatment are a common problem in iMN. Experience with the use of rituximab in iMN is growing, but this drug is still considered an experimental therapy (19-21). Adrenocorticotropic hormones and mycophenolate mofetil may play a role in iMN, but research is still too limited to make formal recommendations regarding the routine use of these treatments.

5. CONCLUSION

We believe that a general conservative therapy for nephrotic syndrome should be prescribed in every patient with iMGN, including ACEIs or ARA and statins, and wait for a reasonable time period to see whether or not spontaneous remission (complete or partial) occurs. In those cases with massive proteinuria not showing a decreasing trend, and especially in male patients aged > 50 years, it is reasonable to shorten the observation period. We prefer to start with early treatmen, with steroids plus an alkylating agents, as this may allow a good chance of remission and may protect renal function in the long-term, with relatively few side-effects. We suggest that decisions on the timing of start of therapy, whom to treat, best sequence of the use of the various immunosuppressive drugs must be based on an individualized assessment of risks and benefits. Treatment should be restricted to high-risk patients who can be identified by the level and /or the composition of urinary proteins.

REFERENCES

1. McQuarrie EP, Mackinnon B, Stewart GA, Geddes CC. Membranous nephropathy remains the commonest primary cause of nephrotic syndrome in a northern European Caucasian population. Nephrol Dial Transplant. 2010; 25: 1009-1010.

2. Lefaucheur C, Stengel B, Nochy D, Martel P, Hill GS, Jacquot C et al. Membranous nephropathy and cancer: Epidemiologic evidence and determinants of high-risk cancer association. Kidney Int. 2006; 70: 1510-1517.

3. Mazuecos AM, Praga M, Araque A, Hernández E, Sánchez R, Andrés A et al. Evolución a largo plazo de las glomerulonefritis membranosas idiopáticas no tratadas. Nefrología. 1993; 13: 299-305.

4. Fulladosa X, Praga M, Segarra A, Martínez Ara J. Glomerulonefritis membranosa. Nefrología. 2007; 27 (Supl. 2): 70-86.

5. du Buf-Vereijken PW, Feith GW, Hollander D, Gerlag PGG, Wirtz JJJM, Noordzij TC et al. Restrictive use of immunosuppressive treatment in patients with idiopathic membranous nephropathy: high renal survival in a large patient cohort. QJM. 2004; 97: 353-360.

6. du Buf-Vereijken PW, Branten AJ, Wetzels JF. Cytotoxic therapy for membranous nephropathy and renal insufficiency: improved renal survival but high relapse rate. Nephrol Dial Transplant. 2004; 19: 1142-1148.

7. Hofstra JM, Wetzels JF. Alkylating agents in membranous nephropathy: efficacy proven beyond doubt. Nephrol Dial Transplant. 2010; 25: 1760-1766.

8. Ponticelli C, Zucchelli P, Passerini P, Cesana B, Locatelli F, Pasquali S et al. A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. Kidney Int. 1995; 45: 1600-1604.

9. Jha V, Ganguli A, Saha TK, Kohli HS, Sud K, Gupta KL et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. J Am Soc Nephrol. 2007; 18: 1899-1904.

10. Aaltonen S, Honkanen E. Outcome of idiopathic membranous nephropathy using targeted stepwise immunosuppressive treatment strategy. Nephrol Dial Transplant. 2011; 26(9): 2871-7.

11. Kalliakmani P, Koutroulia E, Sotsiou F, Vlachojannis JG, Goumenos DS. Benefit and cost from the long-term use of cyclosporine-A in idiopathic membranous nephropathy. Nephrology (Carlton). 2010; 15: 762-767.

12. Branten AJW, du Buf-Vereijken PWG, Vervloet M, Wetzels JF. Mycophenolate mofetil in idiopathic membranous nephropathy: a clinical trial with comparison to a historic control group treated with cyclophosphamide. Am J Kidney Dis. 2007; 50: 248-256.

13. Chen Y, Schieppati A, Cai G, Chen X, Zamora J, Giuliano GA and al. Immunosuppression for Membranous Nephropathy: A Systematic Review and Meta-Analysis of 36 Clinical Trials. Clin J Am Soc Nephrol. 2013; 8: 787-796.

14. Howman A, Chapman TL, Langdon MM, Ferguson C, Adu D, Feehally J et al. Immunosuppression for progressive membranous nephropathy: a UK randomised controlled trial. Lancet. 2013; 381 (9868): 744-51.

15. Polanco N, Gutierrez E, Covarsi A, Ariza F, Carreño A, Vigil A et al. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. J Am Soc Nephrol. 2010; 21: 697-704.

16. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int. 2012; Suppl. 2: 186-197.

17. Alexopoulos E, Papagianni A, Tsamelashvili M, Leontsini M, Memmos D. Induction and long-term treatment with cyclosporine in membranous nephropathy with the nephrotic syndrome. Nephrol Dial Transplant. 2006; 21: 3127-3132.

18. Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA, Hoy WE et al. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. Kidney Int. 2001; 59: 1484–1490.

19. Fervenza FC, Abraham RS, Erickson SB, Irazabal MV, Eirin A, Specks U et al. Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. Clin J Am Soc Nephrol. 2010; 5: 2188-2198.

20. Bomback AS, , Derebail VK, Mc Gregor JG, Kshirsagar AV, Falk RJ, Nachman PH. Rituximab therapy for membranous nephropathy: a systematic review. Clin J Am Soc Nephrol. 2009; 4: 734-744.

21. Ruggenenti P, Cravedi P, Chianca A, Perna A, Ruggiero B, Gaspari F et al. Rituximab in idiopathic membranous nephropathy. J Am Soc Nephrol. 2012; 23: 1416-1425.

22. Ponticelli C, Passerini P, Salvadori M, Manno C, Viola BF, Pasquali S et al. A randomized pilot trial comparing methylprednisolone plus a cytotoxic agent versus synthetic adrenocorticotropic hormone in idiopathic membranous nephropathy. Am J Kidney Dis. 2006; 47: 233-240.

23. Hladunewich MA, Cattran D, Beck LH, Odutayo A, Sethi S, Ayalon R et al. A pilot study to determine the dose and effectiveness of adrenocorticotrophic hormone (H.P. Acthar °Gel) in nephrotic syndrome due to idiopathic membranous nephropathy. Nephrol Dial Transplant. 2014; 29: 1570-1577.

24. Cameron JS. Nephrotic syndrome in the elderly. Semin Nephrol. 1996; 16: 319-329.

25. Zent R, Nagai R, Cattran DC. Idiopathic membranous nephropathy in the elderly: a comparative study. Am J Kidney Dis. 1997; 29: 200-206.

26. Cattran D, Pei Y, Greenwood C, Ponticelli C, Passerini P, Honkanen E. Validation of a predictive model of idiopathic membranous nephropathy: its clinical and researh implications. Kidney Int. 1997; 51: 901-907.

27. Christiansen CF, Schmidt M, Lamberg AL, Horvath-Puho E, Baron JA, Jespersen B et al. Kidney disease and risk of venous thromboembolism: a nation wide population-based case-control study. J Thromb Haemost. 2014; 12: 1449-54.

28. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. Clin J Am Soc Nephrol .2012; 7: 513–20.

29. Pincus KJ, Hynicka LM. Prophylaxis of thromboembolic events in patients with nephrotic syndrome. Ann Pharmacother. 2013; 47: 725-34.

30. Lee T, Biddle AK, Lionaki S, Derebail VK, Barbour SJ, Tannous S et al. Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. Kidney Int. 2014; 85: 1412-1420.

31. Hofstra JM, Wetzels JFM. Should aspirin be used for primary prevention of thrombotic events in patients with membranous nephropathy? Kidney Int. 2016; 89: 981-983.

32. Lee T, Derebail VK, Kshirsagar AV, Chung Y, Fine JP, Mahoney S et al. Patients with primary membranous nephropathy are at high risk of cardiovascular events. Kidney Int. 2016; 89: 1111-1118.

33. Mahmoodi BK, ten Kate MK, Waanders F, Veeger NJ, Brouwer JL, Vogt L et al. High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: Results from a large retrospective cohort study. Circulation. 2008; 15(2): 224-230.