Original Article

Framingham Risk Score Inadequately Predicts Cardiac Risk in Young Patients Presenting with a First Myocardial Infarction

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Abstract

Introduction: The Framingham Risk Score (FRS) is a well-validated epidemiologic tool used to assess the risk for a first cardiac event. Because young patients presenting with a first myocardial infarction (MI) tend to have less significant risk profiles compared with older patients, we hypothesized that FRS may underestimate cardiac risk in these patients. **Materials and Methods:** We studied 1267 patients between January 2002 and November 2007 presenting with a first MI. Patients with pre-existing diabetes mellitus and vascular disease were excluded. FRS was calculated for each patient. Patients were divided based on their age: group A (<40 years), group B (40 to 64 years) and group C (≥65 years). **Results:** The mean age was 54.7 ± 11 years, 88.4% of the patients were males. Younger patients were more likely to be assigned with lower scores. Based on FRS, 63.0%, 29.3% and 14.2% of group A, B and C patients were classified as low risk (10-year risk for cardiac events<10%) respectively, *P* <0.001. The sensitivity of FRS in identifying at least intermediate risk subjects (10-year risk for cardiac events >10%) was 37.0% in group A vs 85.8% in group C (*P* <0.001). The incidence of newly diagnosed diabetes mellitus was higher in younger patients (12.0% vs 13.2% vs 7.1 % in groups A, B and C respectively, *P* = 0.027). **Conclusions:** FRS inadequately predicts cardiac risk in young patients presenting with a first MI. This could be because a significant proportion of these young patients have undiagnosed diabetes mellitus, a coronary artery disease risk equivalent.

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Key words: Diabetes mellitus, Young myocardial infarction

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide. The Framingham Risk Score (FRS) was derived from the Framingham Heart Study (FHS) cohort and was designed to predict 10-year risk of hard coronary events, including mortality due to coronary heart disease and non-fatal myocardial infarction (MI) by considering the presence or absence of important risk factors. The FRS is calculated by taking into account age, sex, smoking status, total cholesterol, high-density lipoprotein cholesterol and systolic blood pressure.[1,2] The FRS is a widely adopted and well-validated tool to assess the risk for a first cardiac event, and focuses on absolute risk of disease rather than on modification of individual risk factors.[1,3-10] It is also useful in guiding the intensity of risk factor interventions.[2]

It has been shown that the vast majority of individuals with CVD carry at least one antecedent, traditional risk factor such as smoking, diabetes, hypertension and/or hypercholesterolaemia.[11] Exposure to high levels of these risk factors throughout life increases atherosclerotic burden,[12,13] resulting in an increased risk for future clinical CVD events.[14,15] Conversely, the absence of established risk factors is associated with very low lifetime risk for CVD and markedly longer survival.[12] The FHS cohort comprised primarily of middle-aged Caucasian men, and in middle-aged adults, measurement of traditional risk factors is a surrogate for atherosclerotic burden and hence, indicative of the risk of clinical CVD.

However, the same cannot be said for younger adults. Even though the atherosclerotic process begins at a young age in relation to traditional risk factor burden,[16] clinical CVD events do not occur until much later.[17,18] This means that while the majority of people of a relatively younger age are defined as low risk using existing risk algorithms, a low short-term risk in younger subjects may not reflect

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their true lifetime risk.

Additionally, diabetes mellitus is not traditionally considered when computing the FRS. Recently, diabetes mellitus is considered a coronary artery disease (CAD) equivalent because patients with diabetes without known CAD were found to have similar cardiac event rate as patients without diabetes who had a prior MI.[19] The Singapore National Health Survey 2004 reported that the proportion of Singapore residents with previously undiagnosed diabetes mellitus was 49.4%.[20] Thus, there is an underestimation of the prevalence of diabetes mellitus and therefore cardiac risk burden in the population.

We hypothesized that the FRS underestimates cardiovascular risk in young adults and this may in part be because of a higher incidence of newly diagnosed diabetes mellitus amongst the young.

Materials and Methods

Study Sample and Risk Factor Assessment

This is a retrospective medical casenote review. We investigated 1267 patients who were admitted to our institution between January 2002 and November 2007 with a first MI. Baseline demographics, smoking history, other co-morbidities (including hypertension, diabetes and hypercholesterolemia) and current treatments for them were obtained from review of casenotes. Other data collected included blood pressure on admission, fasting serum lipids and fasting blood glucose levels.

The 10-year FRS was calculated for each patient using their admission demographics and fasting lipid profiles. The risk predictors used were age, total serum cholesterol, serum high-density lipoprotein, systolic blood pressure, treatment for hypertension (if any), and smoking status.[21]

Exclusions

During the period of January 2002 and November 2007, 1744 patients were admitted for acute MI, of whom 1267 were recruited. The remaining 477 (27%) patients with pre-existing diabetes mellitus and vascular disease were excluded.

Statistical Analyses

Patients were divided into 3 groups based on their age: group A (<40 years), group B (40 to 64 years) and group C (≥65 years). For each group, based on the FRS, patients were divided into risk deciles – the first decile corresponding to a 10-year CVD risk of 3% or less, the tenth corresponding to a risk of more than 30%, and the remainder falling in between at approximately equal intervals apart.

The distribution of risk deciles and the sensitivity of the FRS in identifying at least intermediate risk subjects (10-year risk for cardiac events >10%) were computed for each age group. The one-way ANOVA test with post hoc multiple comparisons was used to compare between groups. $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 16.0 for Windows.

Institutional Review Board Approval

The study was approved by the National Health Group institutional review board.

Results

Baseline Characteristics

The mean age was 54.7 ± 11 years, and 88.4% were males. Table 1 shows baseline characteristics of the 3 different age groups. History of cigarette smoking and hyperlipidaemia were the predominant cardiovascular risk factors among the young. The incidence of newly diagnosed diabetes mellitus is higher in groups A and B as compared to group C (12.0%

Table 1. Baseline Characteristics of Study Cohort

Characteristics	Groups (age in years)		
	Group A (< 40)	Group B (40-64)	Group C (≥65)
N	92	921	254
Age, y	35.3 ± 4.0	52.2 ± 6.5	70.7 ± 4.1
Race, %			
Chinese	55.4	61.5	67.3
Malay	15.3	24.0	22.5
Indian	29.3	14.5	10.2
Gender, %			
Male	94.6	92.4	71.7
Female	5.4	7.6	28.3
Total cholesterol, mmol/L $P < 0.001$	5.79 ± 1.18	5.59 ± 1.15	5.30 ± 1.20
HDL-cholesterol, mmol/L $P < 0.001$	0.97 ± 0.25	1.03 ± 0.25	1.11 ± 0.31
LDL-cholesterol, mmol/L $P = 0.001$	3.98 ± 1.22	3.75 ± 1.00	3.54 ± 1.03
Triglyceride, mmol/L $P < 0.001$	2.24 ± 1.35	1.85 ± 1.15	1.53 ± 0.74
SBP, mmHg $P = 0.004$	131.2 ± 19.3	136.1 ± 23.1	140.2 ± 27.2
DBP, mmHg $P = 0.001$	78.9 ± 13.7	81.8 ± 16.2	77.8 ± 16.3
Smoker, % $P < 0.001$	73.9	57.8	38.6
Newly diagnosed DM, % $P = 0.027$	12.0	13.2	7.1

DBP: diastolic blood pressure; DM: diabetes mellitus; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure
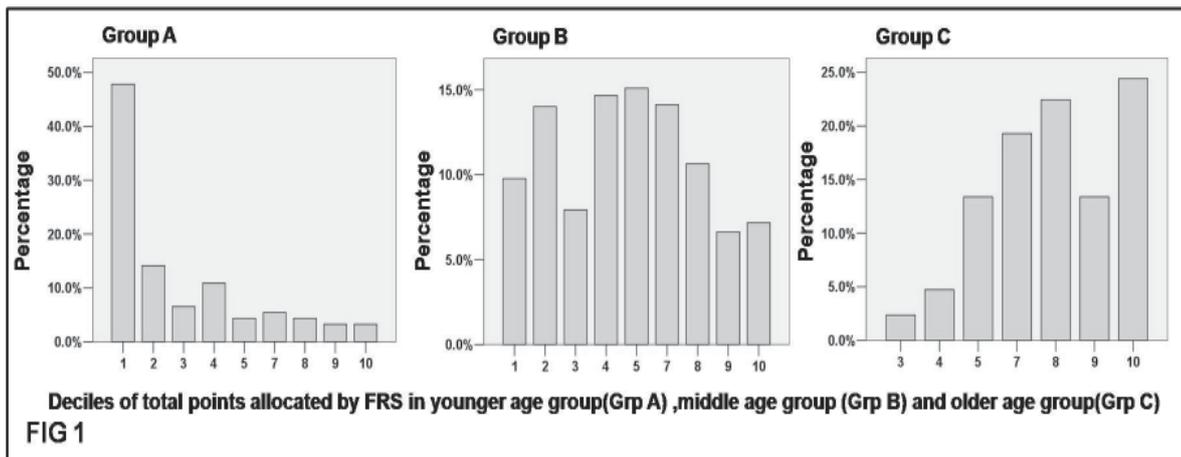
Fig. 1. Deciles of total points allocated by FRS in younger age group (group A), middle-age group (group B) and older age group (group C).

vs 13.2% vs 7.1 % in groups A, B and C respectively, $P = 0.027$). On the other hand, both systolic and diastolic blood pressure positively correlated with increasing age.

Prediction of CVD risk

The participants were stratified into deciles of predicted risk for chronic heart disease (CHD) death based on the FRS, with decile 1 being the lowest and decile 10 the highest predicted risk. Figure 1 shows the distribution of deciles for each group.

Table 2 shows that younger patients were more likely to be assigned with lower FRS scores. Based on FRS, 63.0%, 29.3% and 14.2% of groups A, B and C patients were classified as low risk (10-year risk for cardiac events <10%) respectively, $P < 0.001$. The sensitivity of the FRS in identifying subjects of at least intermediate risk (10-year risk for cardiac events >10%) was significantly lower in group A compared with group C (37.0% vs 85.8%).

Table 2. FRS-predicted 10-year CVD Risk for each Group

Characteristics	Groups (age in years)		
	Group A (<40)	Group B (40-64)	Group C (≥65)
Low (<10%)	63.0	29.3	14.2
Intermediate (10%-20%)	27.2	50.3	49.6
High (>20%)	9.8	20.4	36.2

$P < 0.001$

Discussion

This study highlighted several important findings. The majority of young patients who presented with a first MI were classified by the FRS as low risk (10-year risk for cardiac events <10%). Yet risk factor burden within this group was remarkably high, due in part to the higher prevalence of smokers and higher incidence of newly diagnosed diabetes mellitus, which constitutes a coronary artery disease risk equivalent. Similar finding was noted by Zarich et al.[22]

This has important public health implications. In order to develop a targeted approach, where persons who are truly high risk are identified and receive individualised intervention, an effective and accurate risk algorithm must be in place. This might be so for older patients, but as yet no such risk-stratifying strategy exists for younger patients. The accuracy of the currently available methods for risk estimation in this age range is yet to be elucidated, and our results are among the first to examine systematically their performance when applied to young adults.

The propensity for these methods to classify young individuals inappropriately as "low risk" underscores some important limitations to these models and their current application in clinical practice.[6] While the Framingham risk algorithm reflects the importance of age in predicting absolute risk,[6] the result is that typically only older patients exceed thresholds for treatment. Younger patients, on the other hand, may be missed even though they carry significant risk factor burden. This, and the false sense of security such an age-weighted risk algorithm generates, denies treatment to a large proportion of those that need it.

In order to minimise the bias of weighting by age, some authors have proposed using relative risk estimates in place of age-dependent absolute risk estimates for individuals with low short-term risk, where comparisons are made only to age-similar individuals.[23,24] Others have argued for estimation of absolute lifetime risks.[25,26] While the FRS may not identify subjects with low short-term but high lifetime risk for CVD (probably due to changes in risk factor status over time), lifetime risk estimates avoid this problem of age-dependency. This allows the identification of younger individuals who are truly at high risk, providing the window

for intensive lifestyle modification or early initiation of medical therapy. Finally, another strategy would be to use similar 10-year risk estimates for this patient population, but with lower, age-specific, limits for the definition of "high-risk". However, the drawback is that even then those individuals in the highest quartile of risk by FRS may not be the same individuals at highest lifetime risk; the FRS is shown to be a poor indicator of lifetime risk amongst younger men.[26]

Future research is needed to clarify if any of these strategies are effective in the identification of "high-risk" young individuals. Once identified, these strategies must then be evaluated further in clinical and public health settings to determine their efficacy.

While the absolute event rates in younger patients are low, individual risk factors already present at this age are significant and strong predictors of future clinical events. In a cohort of male medical students, serum total cholesterol was a strong and independent predictor of future CVD events over the course of 27 to 42 years of follow-up.[18] Forty years of follow-up of young adults (aged 30 to 39) in the FHS found similar associations between total cholesterol and both cardiovascular and all-cause mortality.[27] The Chicago Heart Association Detection Project in Industry showed that major coronary disease risk factors such as age, serum total cholesterol, blood pressure, and cigarette smoking were observed to be strong and independent risk factors for CHD death in younger adults (aged 18 to 39) in long-term follow-up.[17]

These risk factors promote subclinical asymptomatic atherosclerosis from a young age if present. The earliest evidence of this emerged from autopsy studies from the Korean[28] and Vietnam[29] wars, in which significant subclinical coronary atherosclerosis was present among young individuals who died of non-CVD-related causes. It has been shown that premature atherosclerosis does not affect all young adults equally and is associated with the presence of major cardiovascular risk factors.[30] More recently, the Bogalusa Heart Study has shown that these traditional risk factors are significantly associated with the accumulation of aortic and coronary atherosclerosis in a population aged 2 to 39 years.[16] As noted above, these risk factors increase the risk for future clinical CVD events through an increase in atherosclerotic burden.[12-15]

On the other hand, despite its inadequacy in predict in predicting cardiovascular risk in young individuals, a recent local study by Lee et al[31] showed that FRS is still a better predictor for cardiovascular death than metabolic syndrome as set out by the American Heart Association (AHA)/National Heart, Lung and Blood Institute (NHLBI) in individuals with an average age of 38.5 years.

Cost-effectiveness of interventions is an important consideration from a public health standpoint. Accurately identifying individuals at the highest risk using a global risk assessment tool like the FRS provides a framework within which clinical decisions may be made. Given the example of cholesterol-lowering drug therapy, prior studies have shown that from a societal standpoint, the greatest benefit is achieved when the highest risk individuals are treated with statin drugs.[32] Applying this to the younger population, while it may not be cost-effective to treat the majority of young adults with intermediate risk factor burden with statins, it would likely be cost-effective to treat only the very highest risk young adults. Primary prevention with therapeutic lifestyle changes, however, may be implemented more ubiquitously: prior estimates suggest that in men with a variety of risk factor levels, primary prevention with diet can be a very cost-effective strategy.[32] Without more accurate risk estimates, large proportions of the younger population may be incorrectly classified as "low risk" and the message of therapeutic lifestyle change may not be effectively communicated to them.

Limitations

Our study has some limitations. Firstly, the study sample is predominantly male (88.4%). Prior studies have shown that there are clear gender differences in coronary heart disease, and that established risk factors have a varied impact on disease risk for both sexes.[33,34] Secondly, while FHS cohort is predominantly Caucasian, the ethnic make-up of the present study cohort is Asians. It has been shown that the ability of the FRS to accurately predict CVD risk in cohorts of different ethnic make-ups varies considerably, and that recalibration of the FRS is necessary for local application.[35,36] That being said, the FRS tends to overestimate CVD risk in Asians.[34] Finally, the present study did not take into consideration other known cardiovascular risk factors such as family history, obesity (BMI), hyperhomocysteinaemia, and inflammatory markers. Indeed, elevated C-reactive protein blood levels has been shown to predict the risk of MI.[37]

Conclusion

The movement towards global risk assessment has certainly served us well. However, while the FRS has been useful in predicting 10-year coronary risks accurately amongst older patients, it inadequately predicts cardiac risk in young patients despite substantial risk factor burden. This could be in part due to a higher proportion of young patients having undiagnosed diabetes mellitus, a coronary artery disease risk equivalent. Future clinical guidelines should consider alternative strategies to better estimate and communicate CVD risk to the young adult population. Perhaps these alternatives may overcome the inherent bias of age-weighted risk algorithms, and incorporate certain recently discovered cardiovascular risk factors.

REFERENCES

1. D'Agostino RB Sr., Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180-7.
2. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
3. Kannel WB, Dawber TR, Friedman GD, Glennon WE, McNamara PM. Risk factors in coronary heart disease. An evaluation of several serum lipids as predictors of coronary heart disease; the Framingham Study. Ann Intern Med 1964;61:888-99.
4. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1991;121(1 Pt 2):293-8.
5. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation 1991;83: 356-62.
6. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47.
7. Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, et al. Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. American Heart Association. Circulation 1998;97:1876-87.
8. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyörälä K. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on coronary prevention. Eur Heart J 1998;19:1434-503.
9. Jackson R. Guidelines on preventing cardiovascular disease in clinical practice. BMJ 2000;320:659-61.
10. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106:388-91.
11. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA 2003;290:891-7.
12. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113:791-8.
13. Smith SC, Jr., Greenland P, Grundy SM. AHA Conference Proceedings. Prevention conference V: Beyond secondary prevention: Identifying the high-risk patient for primary prevention: executive summary. American Heart Association. Circulation 2000;101:111-6.
14. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210-5.
15. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340:14-22.
16. Berenson GS, Srinivasan SR, Bao W, Newman WP, 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998;338:1650-6.
17. Navas-Nacher EL, Colangelo L, Beam C, Greenland P. Risk factors for coronary heart disease in men 18 to 39 years of age. Ann Intern Med 2001;134:433-9.
18. Klag MJ, Ford DE, Mead LA, He J, Whelton PK, Liang KY, et al. Serum cholesterol in young men and subsequent cardiovascular disease. N Engl J Med 1993;328:313-8.
19. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.
20. National Health Survey 2004. Singapore: Epidemiology & Disease Control Division, Ministry of Health, 2005.
21. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
22. Zarich S, Luciano C, Hulford J, Abdullah A. Prevalence of metabolic syndrome in young patients with acute MI: does the Framingham Risk Score underestimate cardiovascular risk in this population? Diab Vasc Dis Res 2006;3:103-7.
23. Ridker PM, Cook N. Should age and time be eliminated from cardiovascular risk prediction models? Rationale for the creation of a new national risk detection program. Circulation 2005;111:657-8.
24. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil 2007;14Suppl2:S1-113.
25. Lloyd-Jones DM, Wilson PW, Larson MG, Beiser A, Leip EP, D'Agostino RB, et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. Am J Cardiol 2004;94:20-4.
26. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. Lancet 1999;353:89-92.
27. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. JAMA 1987;257:2176-80.
28. Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea; preliminary report. J Am Med Assoc 1953;152:1090-3.
29. McNamara JJ, Molot MA, Stremple JF, Cutting RT. Coronary artery disease in combat casualties in Vietnam. JAMA 1971;216:1185-7.
30. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. A preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. JAMA 1990;264:3018-24.
31. Lee J, Heng D, Ma S, Chew SK, Hughes K, Tai ES. The metabolic syndrome and mortality: the Singapore Cardiovascular Cohort Study. Clin Endocrinol 2008;69:225-30.
32. Prosser LA, Stinnett AA, Goldman PA, Williams LW, Hunink MG, Goldman L, et al. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. Ann Intern Med 2000;132:769-79.
33. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. Diabetes, blood lipids, and the role of obesity in coronary heart disease risk for women. The Framingham Study. Ann Intern Med 1977;87:393-7.
34. Rich-Edwards JW, Manson JE, Hennekens CH, Buring JE. The primary prevention of coronary heart disease in women. N Engl J Med 1995;332:1758-66.
35. Brindle P, Emberson J, Lampe F, Walker M, Whincup P, Fahey T, et al. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. BMJ 2003;327:1267.
36. Liu J, Hong Y, D'Agostino RB Sr, Wu Z, Wang W, Sun J, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA 2004;291:2591-9.
37. Wilson AM, Ryan MC, Boyle AJ. The novel role of C-reactive protein in cardiovascular disease: risk marker or pathogen? Int J Cardiol 2006;106:291-7.