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Original Article

Comparison of traditional risk factors to clinical variables for the prediction of secondary cardiovascular events

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ABSTRACT:
Introduction: The purpose of this study was to prove the influence of combining cardiovascular risk factors and clinicalvariables to improve risk prediction in terms of secondary prevention in patients with known CAD. **Materials and Methods:** The patients were considered suffering from hypertension once the patient was on antihypertensive medications at the time of admission or the past medical history / record documented raised BP at multiple occasions or the BP was recorded higher (>140/90 mmHg) at separate occasions while remained admitted. **Results:** Diabetes mellitus increased the risk of secondary cardiovascular events and showed a hazard ratio (HR) of 1.8 in the overall cohort (HR = 1.8 in SAP patients) both with a significant result ($p<0.001$). Further predictive was the LDL/HDL ratio above 3.5 with HR = 1.6 in the overall cohort (HR = 1.8 in SAP patients) (both $p<0.001$) and ever smoking with HR = 1.3 in the overall cohort and HR = 1.4 in SAP patients (both $p<0.01$). **Conclusion:** Traditional risk factors have a high impact to identify patients at risk for a secondary event in a cohort with already proven coronary artery disease
Keywords: CVD, coronary artery disease, hypertension.

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INTRODUCTION:

The prevalence of classic cardiovascular risk factors such as hypertension, dyslipidemia, obesity and diabetes, varies widely between different countries, and shows some important secular trends. The conventional risk factors for CAD can be divided into non- modifiable and modifiable risk factors. The former include age, sex and family history, while the latter include diabetes mellitus (DM), smoking, dyslipidemia, hypertension and obesity. There is increasing incidence indicating that Asian Indians are at increased risk of CAD, which cannot be attributed tothe common risk factors. Recently, a number of newer cardiovascular risk factors have been identified, which are of great interest as more than 60% of CAD in native Indians remains unexplained by conventional risk factors. Comparative studies on newer risk factors show that Indians have higher C-reactive protein, plasminogen activator inhibitor (PAI-1) and homocysteine levels.[1]

Cardiovascular disease affects millions of people in both developed and developing countries. Although the rate of death attributable to the disease has declined in developed countries in the past several decades, it is still the leading cause of death and extorts a heavy social and economic toll globally. In low and middle income countries, the prevalence of cardiovascular disease has increased dramatically. The disease is forecasted to become the major cause of morbidity and mortality in most developing nations.2,3 CAD includes a spectrum of disease manifestations ranging from asymptomatic atherosclerotic disease to acute coronary syndrome, which includes ST elevation myocardial infarction (STEMI), Non-ST elevation myocardial infarction (NSTEMI) and unstable angina.

The prevalence of risk factors in a population determines the future burden on healthcare services and the loss of an individual's productive years. Risk factors constitute a health risk for the individual and impose an overall burden on the economy. There are no large scale studies of adequate sample size to evaluate the prevalence of risk factors, risk factor patterns and electrocardiographic changes in Indian populations. Coronary heart disease mortality is generally accepted as an indicator of socio-economic

conditions. In a changing social environment, early detection and treatment of youths at risk of premature IHD offers the greatest promise and an opportunity for age-specific interventions.4 Moreover, the potential gains from controlling major established risk factors could be substantial in South Asians and greater than that in Europeans.5 The purpose of this study was to prove the influence of combining cardiovascular risk factors and clinical variables to improve risk prediction in terms of secondary prevention in patients with known CAD.

METHODOLOGY:

All consecutive patients age below 45 years, having classical history of Ischemic heart disease and also having definite ECG changes consistent with coronary artery disease (recent / old) were enrolled. The patients were admitted in department of medicine, SVS medical college, Mahabubnagar, Andhra Pradesh. The data used for the study was collected from the patients and their previous medical records. Smoking was defined as use of bidis (small, thin hand-rolled cigarettes found primarily in India, consisting of tobacco, wrapped in leaves of tendu or temburni plants native to Asia) or cigarettes. Physical examination of patients included height, weight, abdominal circumference and two blood pressure measurements: at the time of admission and on the following day.

The patients were considered suffering from hypertension once the patient was on antihypertensive medications at the time of admission or the past medical history / record documented raised BP at multiple occasions or the BP was recorded higher (>140/90 mmHg) at separate occasions while remained admitted.

Diabetes Mellitus was considered to be present when either patient was taking any anti-diabetic agents or blood glucose was found to be > 126 mg/ dl fasting or > 200 mg/dl at random sample at more than 02 occasions. Cigarette smoking was labeled if the patient had smoked within last 03 years. Family history of ischemic heart disease was considered positive when any close relative <55 years of age in males or

<65 years in female had history of angina pectoris or myocardial infarction in past.

The acquired data were analyzed statistically using Microsoft Excel. In T-test analysis, P value<0.05 was considered as statistically significant.

RESULTS:

Baseline comparison of the patients with no event and those with cardiovascular death or non- fatal myocardial infarction during follow up is shown in Table 1. Patients with an event wereolder than patients presenting without event. Incidence of diabetes mellitus and patients with LDL/HDL ratio above 3.5 was higher in the event cohort, while hypertension and smoking was similar in both groups. In terms of medication, patients without an event had higher rates of statins and beta-blockers. Ejection fraction was lower in the event cohort, while incidence of multi vessel disease (3 vessel disease) was higher in the event group.

Table 1. Baseline Characteristics in the Athero *Gene* study N = 3249.

Variable	No Event (2807)	CV Event (442)	All (3249)	P-Value
Sex (male)	2164 (77.0%)	328 (74.2%)	2492 (76.7%)	0.14
Age (years)	62.4± 11.0	65.0±11.1	62.6±11.0	< 0.0001
BMI (kg/m²)	28.3±4.5	28.1±5.0	28.3±4.6	0.13
Creatinine (mg/dL)	0.99 (0.87/1.12)	1.09 (0.93/1.26)	0.98 (0.87/1.13)	< 0.0001
Traditional Risk Factors				
Diabetes mellitus (yes)	444 (15.8%)	115 (26.0%)	559 (17.2%)	< 0.0001
Hypertension (yes)	2094 (74.5%)	327 (73.9%)	2421 (74.5%)	0.90
LDL/HDL ratio (> 3.5)	639 (22.7%)	145 (32.8%)	784 (24.1%)	< 0.0001
Smoking	1762 (62.7%)	285 (64.4%)	2047 (63.0%)	0.33
Medication				
Beta-blocker treatment	1803 (64.2%)	243 (54.9%)	2046 (62.9%)	0.00083
ACE-inhibitor treatment	1405 (50.0%)	251 (56.7%)	1656 (50.9%)	0.0038
Statin treatment	1313 (46.7%)	156 (35.2%)	1469 (45.2%)	< 0.0001
Clinical Variables				
eGFR (Cockroft-Gault) Cockroft-Gault Equation	88.0 (70.4/108.5)	74.3 (56.5/94.2)	86.1 (69.0/107.1)	< 0.0001
Ejection Fraction (%)	64.6±15.5	57.1±19.1	63.4±16.3	< 0.0001

Number of diseased vessels				
0	32 (1.1%)	3 (0.6%)	34 (1.0%)	0.16
1	788 (28.0%)	81 (18.3%)	869 (26.7%)	< 0.0001
2	838 (29.8%)	134 (30.3%)	972 (29.9%)	0.83
3	1145 (40.7%)	222 (50.2%)	1367 (42.0%)	0.00011
CRP (mg/L)	4.40 (1.53/10.01)	6.32 (2.31/15.81)	4.62 (1.61/10.63)	< 0.0001

Cox proportional hazard regression analyses are shown in Table 2 for the overall cohort and in Table 3 for the SAP cohort. Diabetes mellitus increased the risk of secondary cardiovascular events and showed a hazard ratio (HR) of 1.8 in the overall cohort (HR = 1.8 in SAP patients) both with a significant result ($p<0.001$). Further predictive was the LDL/HDL ratio above 3.5 with HR = 1.6 in the overall cohort (HR = 1.8 in SAP patients) (both $p<0.001$) and ever smoking with HR = 1.3 in the overall cohort and HR = 1.4 in SAP patients (both $p<0.01$). For the clinical variables evaluated in this study, the highest HR with 3.3 was shown for ejection fraction below 40% in the overall cohort (HR = 3.3 in SAP) (p for both <0.001), followed by impaired creatinine clearence with a threshold of 60mL/min with a HR = 2.3 in the overall cohort and HR = 2.6 in SAP patients (both $p<0.001$) and CRP with HR 1.6 (SAP HR 1.6) as well as multi vessel disease with HR 1.6 (SAP HR 1.4). The hazard ratios for the different mod els are presented in Figs 1and 2. Arterial hypertension, a major CV risk factor, did not provide additional information regarding risk stratification in this study.

Table 2. Cox Proportional Hazard Regression in the overall cohort (N = 3249). Overall Cohort (N = 3249)

Variable	N	HR	Lower CI	Upper CI	p-value
LDL/HDL ratio (LDL/HDL Ratio >3.5 vs. <3.5)	3249	1.58	1.29	1.95	< 0.0001
Smoking (Smoker vs. Never-Smoker)	3249	1.35	1.08	1.68	0.0063
Diabetes Mellitus (Treated with oral medication or Insulin vs. No Diabetes)	3249	1.72	1.38	2.14	< 0.0001
Hypertension (Treated vs. not diagnosed)	3249	0.99	0.81	1.24	0.87
eGFR (eGFR >60ml/min vs. eGFR <60ml/min)	3249	2.28	1.79	2.91	< 0.0001
Ejection Fraction (EF >40% vs. EF <40%)	2314	3.33	2.54	4.35	< 0.0001
Number of dis. Vessels (One vs. Multivessel Disease)	3247	1.64	1.28	2.07	0.00016
CRP (CRP >3 mg/L vs. CRP < 3mg/L)	3206	1.65	1.35	3.00	< 0.0001

Table 3. Cox proportional hazard regression in the stable angina cohort (N = 2662). Stable Angina (N = 2662).

Variable	N	HR	Lower CI	Upper CI	p-value
LDL/HDL ratio (LDL/HDL Ratio >3.5 vs. <3.5)	2662	1.81	1.45	2.27	< 0.0001
Smoking (Ever-Smoker vs. Never-Smoker)	2662	1.40	1.08	1.77	0.0083
Diabetes Mellitus (Treated with oral medication or Insulin vs. No Diabetes)	2662	1.70	1.34	2.17	< 0.0001
Hypertension (Treated or diagnosed vs. Not diagnosed)	2662	0.97	0.76	1.25	0.70
eGFR (eGFR >60ml/min vs. eGFR <60ml/min)	2662	2.61	1.99	3.40	< 0.0001
Ejection Fraction (EF >40% vs. EF <40%)	1973	3.35	2.48	4.55	< 0.0001
Number of dis. Vessels (One vs. Multivessel Disease)	2661	1.45	1.08	1.90	0.0096
CRP (CRP >3 mg/L vs. CRP < 3mg/L)	2632	1.64	1.32	2.05	< 0.0001

On top of the traditional risk factors age and sex (C-index 0.58 and 0.59 in SAP), each risk factor alone improved the C-Index with exception of arterial hypertension (Table 4 for the overall cohort and Table 5 for the SAP cohort). The traditional risk factor with the highest influence was diabetes mellitus with a C-index of 0.6 (0.61 in SAP), showing the best improvement of all traditional risk factors in both the overall and SAP cohort. Combining all traditional risk factors with age and sex (C-index 0.62 and 0.63 in SAP), these clinical variables increased the C-index additionally. In the overall cohort C-index for renal function, CRP and ejection fraction were all 0.64 and 0.63 for multivessel disease. In the SAP cohort, the highest C-index was shown for renal function with 0.66, followed by CRP with 0.65 and equally ejection fraction and multivessel disease with 0.64.In all, the highest C-index was achieved upon adding the traditional risk factors and the

clincial variables to age and sex showing a C-index of 0.66 in the overall cohort and 0.67 in the stable angina cohort, thus allowing the most precise risk prediction.

Table 4. Comparison of the C-Index regarding cardiovascular events vs. no events during follow-up in the overall cohort. Overall Cohort(N = 3249).

Variable	N	C-Index	Lower 95% CI	Upper 95% CI	P-Value
Diabetes Mellitus (Treated with oral medication or Insulin vs. No Diabetes known)	3249	0.598	0.572	0.629	< 0.0001
LDL/HDL ratio (>3.5 vs. <3.5)	3249	0.595	0.567	0.624	< 0.0001
Smoking (Ever-Smoker vs. Never-Smoker)	3249	0.592	0.563	0.621	< 0.0001
Hypertension (Treated or Diagnosed by physican vs. Not Known)	3249	0.585	0.557	0.614	< 0.0001
Variable	N	C-Index	Lower 95% CI	Upper 95% CI	P-Value
eGFR (>60 mL/min vs. <60mL/min)	3249	0.644	0.617	0.672	< 0.0001
CRP (>3mg/L vs. <3 mg/L)	3206	0.641	0.614	0.668	< 0.0001
Ejection Fraction (>40% vs. <40%)	2314	0.639	0.606	0.672	< 0.0001
Number of dis. Vessels (Multivessel vs. 1-Vessel disease)	3237	0.630	0.602	0.657	< 0.0001

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Table 5. Comparison of the C-Index regarding cardiovascular events vs. no events during follow-up in the stable angina cohort. Stable Angina Pec-toris Cohort (N = 2662).

Variable	N	C-Index	Lower 95% CI	Upper 95% CI	P-Value
Diabetes Mellitus (Treated with oral known) medication or Insulin vs. No Diabetes	2662	0.607	0.575	0.638	< 0.0001
LDL/HDL ratio (>3.5 vs. <3.5)	2662	0.606	0.575	0.638	< 0.0001
Smoking (Ever-Smoker vs. Never-Smoker)	2662	0.599	0.568	0.633	< 0.0001
Hypertension (Treated or Diagnosed by physican vs. Not Known)	2662	0.592	0.560	0.624	< 0.0001
Variable	N	C-Index	Lower 95% CI	Upper 95% CI	P-Value
eGFR (>60 mL/min vs. <60mL/min)	2662	0.660	0.629	0.689	< 0.0001
CRP (>3mg/L vs. <3 mg/L)	2622	0.653	0.623	0.683	< 0.0001
Ejection Fraction (>40% vs. <40%)	1973	0.642	0.606	0.678	< 0.0001
Number of dis. Vessels (Multivessel vs. 1-Vesseldisease)	2661	0.640	0.609	0.671	< 0.0001

DISCUSSION:

In this cohort, diabetes mellitus was the strongest traditional risk factor for prediction of future cardiovascular events. Further, patients with known CAD ever smoking or with an increased LDL/HDL-ratio had an elevated risk for cardiovascular death or non-fatal myocardial infarction. This was further enhanced when clinical variables were taken into account. Patients with stable angina and known CAD did show the same influence of traditional risk factors and clinical variables as the overall cohort regarding secondary.

Modifiable risk factors are important in the prevention setting; other studies could already show the high influence of these factors.[6-10] Overall the results of Cox proportional regression analysis and the integrated discrimination improvement IDI analysis showed that diabetes mellitus was the risk factor with the most impact on predicting outcome. This information was further improved after combination with ever smoking and a LDL/HDL ratio >3.5. The baseline model of age and sex was augmented by the traditional risk factors to a C-index of 0.62 in the overall cohort, improv- ing risk stratification in the AtheroGene Study. In the secondary prevention setting, some of the traditional risk factors like arterial hypertension and positive family history have not the same influence as reported from the primary prevention setting.[11-14]

The Framingham study shows the mechanism of this correlation; that cigarette smoking is strongly associated with “atherogenic” lipoprotein cholesterol profiles in young adults.[15] This signifies the fact that

cessation of smoking may be the most cost effective approach in primary and secondary prevention.

We have observed that hypertension was the second commonest risk factor (37%) and was equally distributed in both sexes. The exact mechanism through which systemic hypertension induces MI has not been studied in detail, but there is evidence that Hypertension causes LV Hypertrophy and progression of atherosclerosis resulting in CAD.[16]

Diabetes mellitus was noted in 17%. The disease is more prevalent in males (14%) compared to females (4%) and in older patients as compared to younger patients. This fact has been documented in a number of previous studies.[17-18]

Higher BMI was documented in 46% of patients. Sixteen were obese. There was no statistical difference comparing males with females. Asians have a higher body fat percentage for a given BMI than other ethnic groups. Prevalence of obesity and over- weight is low, while DM and HTN occur at a lower level of BMI compared to western population. It has been suggested that Asians have a different fat distribution pattern and are more prone to central obesity at low BMI levels.[19]

Prevention and control of the risk factors for CAD can reduce the rate of CAD. This requires changes in the individual as well as at the community level. Modifying risk factors such as smoking, increased levels of body fat, consuming too much fat and salt, and a sedentary life- style together with the use of accessible and affordable preventive medicines, can lower the risk of CAD. Television and other media can be utilised to create awareness among the general population. Local resident welfare associations and religious groups can also be encouraged to promote a healthy lifestyle and exercise among the community.

CONCLUSION

To conclude, traditional risk factors have a high impact to identify patients at risk for a secondary event in a cohort with already proven coronary artery disease. Nevertheless, occurrence of cardiovascular death and non-myocardial infarction were also influenced by clinical variables like ejection fraction and creatinine clearance as measure of renal function. Combining risk factors and clinical variables predicted outcome better than risk factors alone. Thus, this combined approach is superior.

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