Unstable Angina /Non ST Elevation Myocardial Infarction: Frequency of Conventional Risk Factors; TIMI Risk Score, and Their Impact On Angiographic Data

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ABSTRACT

Background: Appreciation of the crucial role of risk factors in the development of coronary artery disease (CAD) is one of the most significant advances in the understanding of this important disease. Extensive epidemiological research has established cigarette smoking, diabetes, hyperlipidemia, and hypertension as independent risk factors for CAD

Objective: To determine the prevalence of the 4 conventional risk factors(cigarette smoking, diabetes, hyperlipidemia, and hypertension) among patients with CAD and to determine the correlation of Thrombolysis in Myocardial Infarction (TIMI) risk score with the extent of coronary artery disease (CAD) in patients with unstable angina /non ST elevation myocardial infarction (UA/NSTEMI).

Methods: We conducted a descriptive study among 100 patients admitted with UA/NSTEMI to three major cardiac centers in Iraq: Iraqi Centre for Heart Disease ,Ibn- Al-Bitar Hospital for cardiac surgery and Al -Nasyria Cardiac Centre from January 2010 to January 2o11.Frequency of each conventional risk factors and number of conventional risk factors present among patients with CAD, compared between men and women and by age are estimated at study entry. The TIMI risk score was stratified on seven standard variables. The extent of CAD was evaluated on angiography and significant CAD was defined as ≥ 70% stenosis in any one of the three major epicardial vessels and ≥50% in LMS.

Results : Among 100 patients with UA/NSTEMI , 82% of patients have one or more risk factors and only 18%of patients lacked any of 4 conventional risk factors. Smoking is the most common risk factor in male patients while diabetes mellitus and dyslipidemia are common among female patients, and all these results are statistically significant.There were 64 % patients with TIMI score < 4 (low and intermediate TIMI risk score) and 36% patients with TIMI score >4 (high TIMI risk score). Patients with TIMI score > 4 were more likely to have significant three vessel CAD and LMS versus those with TIMI risk score < 4 who have less severe disease (single and two vessel disease).

Conclusion: Antecedent major CAD risk factor exposures were very common among those who developed CAD emphasizing the importance of considering all major risk factors in determining CAD risk estimation . Patients with a high TIMI risk score were more likely to have severe multivessel CAD compared with those with low or intermediate TIMI risk score. Hence, patients with TIMI score >4 should be referred for early invasive coronary evaluation to derive clinical benefit.

Key words: unstable angina , Thrombolysis in Myocardial Infarction score, risk factors

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Each year some 1.3 million patients in US have unstable angina or non-ST elevation myocardial infarction (UA/NSTEMI), a condition also referred to as non-ST elevation acute coronary syndrome (NSTEACS). Acute total occlusion of a coronary artery usually causes STEMI whereas UA/NSTEMI usually results from severe obstruction, but not total occlusion, of the culprit coronary artery[1].

Unstable angina is defined as angina pectoris (or equivalent type of ischemic discomfort) with at least one of the three features[1]: occurring at rest (or minimal exertion) and usually lasting >20 minutes (if not interrupted by nitroglycerin administration) being sever and described as frank pain , and of new onset (i.e., within 1 month; and [(3)] occurring with a crescendo pattern (i.e., more severe, prolonged, or frequent than previously). Of this group, approximately one half will have evidence of myocardial necrosis on the basis of elevated cardiac serum markers, such as creatine kinase isoenzyme (CK)-MB, and/or troponin T or I, and thus have a diagnosis of NSTEMI[2]. Five pathophysiological processes may contribute to the development of UA/NSTEMI. These include [1] plaque rupture or erosion with superimposed non occlusive thrombus (by far the most common cause of UA/NSTEMI);[2] dynamic obstruction (i.e., coronary spasm of an epicardial artery, as in Prinzmetal angina or constriction of the small muscular coronary arteries), [3] progressive mechanical obstruction, [(4)] inflammation, and [5] secondary unstable angina, related to increased myocardial oxygen demand or decreased supply (e.g.,anemia). Individual patients may have several of these processes coexisting as the cause of their episode of UA/NSTEMI. As noted subsequently, several new serum markers can serve as

effective tools in identifying these pathophysiological processes, and in predicting outcome–forming the foundation of a "multimarker strategy" for evaluation and risk stratification [3].

Coronary Arteriographic Findings.

The extent of coronary disease among patients with UA/NSTEMI enrolled in the invasive arm of TACTICS-TIMI 18, who systematically underwent angiography, was: 34 percent had significant obstruction (>50 percent luminal diameter stenosis) of three vessels; 28 percent had two vessel disease; 26 percent had single vessel disease; and 13 percent had no coronary stenosis >50 percent[3]. Approximately 5 to 10 percent had left main stem stenosis >50 percent Registries of unselected UA/NSTEMI patients have reported similar findings. Women and non-whites with UA/NSTEMI have less extensive coronary disease than their counterparts, whereas patients with NSTEMI have more extensive disease than those who present with unstable angina[4,-7]. Approximately one third of patients with UA/NSTEMI without a critical epicardial obstruction have impaired coronary flow assessed angiographically–suggesting a pathophysiological role for coronary microvascular dysfunction. The short-term prognosis is excellent in this group of patients.[8] The culprit lesion in UA/NSTEMI typically exhibits an eccentric stenosis with scalloped or overhanging edges and a narrow neck These angiographic findings may represent disrupted atherosclerotic plaque, thrombus, or a combination. Features suggesting thrombus include globular intra luminal masses with a rounded or polypoid shape "Haziness" of a lesion has been used as an angiographic marker of possible thrombus, but this finding is less specific. Patients with angiographically visualized thrombus has impaired coronary flow and worse clinical outcomes, compared to those without thrombus. Patients with UA/NSTEMI have impaired coronary flow as measured by the TIMI flow grade or frame count, and TIMI myocardial perfusion grade– especially those with an elevated troponin level which is independently associated with adverse outcomes.[9,10]

Integrating all of the above factors, several groups have developed comprehensive risk scores that use clinical variables and findings from the ECG and/or from serum cardiac markers]. The TIMI Risk score identified seven independent risk factors: age >65 years, >3 risk factors for CAD, documented coronary artery disease at catheterization, ST deviation >0.5 mm, >2 episodes of angina in last 24 hours, ASA use within prior week, and elevated cardiac markers. Use of this scoring system was able to risk-stratify patients across a 10-fold gradient of risk, from 4.7 percent to 40.9 percent ($p<0.001$) .] More importantly, this risk score predicts the response to several of the therapies in UA/NSTEMI: patients with higher TIMI risk scores had significant reductions in events when treated with enoxaparin as compared with unfractionated heparin with a GP IIb/IIIa inhibitor as compared with placebo and with an invasive versus conservative strategy [11-14]

Natural HistoryPatients with UA have lower short-term mortality (1.7 percent at 30 days) than those with NSTEMI or STEMI, whereas the mortality risk of the two types of MI is similar (5.1 percent for each type) The early mortality risk in ACS is related to the extent of myocardial damage and resulting hemodynamic compromise.In contrast, long-term outcomes– both for mortality and nonfatal events, is actually worse for patients with either UA or NSTEMI compared with STEMI. This finding likely results from the older age, greater extent of coronary disease, and prior MI and comorbidities–such as diabetes and impaired renal function–in patients with UA/NSTEMI versus STEMI[15].

Both primary and secondary prevention of coronary artery disease (CAD) have indisputable public health importance. Given the prevalence of

CAD, preventing even a small proportion of events would save thousands of lives, avoid inestimable suffering, and save billions of health care dollars. Because cardiovascular disease (CVD) has become the number one killer worldwide, widespread deployment of affordable preventive strategies should have high priority in developed and developing countries. Most people with cardiovascular disease have small, concurrent adverse changes in multiple risk factors rather than extreme deviations in any single risk factor.[(16)]1-Risk factors for which interventions have proved to lower risk of CAD.a-Cigarette smoking by the middle of the 20th century, seminal studies linking smoking and heart disease had been published. The Surgeon General's report in 1964 confirmed the epidemiological relationship between the two and, by 1983, the Surgeon General firmly established cigarette smoking as the leading avoidable cause of cardiovascular disease. The Surgeon General's 1989 report presented definitive data from observational case-control and cohort studies, largely among men, that demonstrated that smoking doubles the incidence of CAD and increases CAD mortality by 50 percent, and that these risks increase with age and the number of cigarettes smoked. Similar increases in the relative risk for CAD have been observed among women. Men are slightly more current smoker than women ; approximately 23 percent of men aged 18 and older are smokers, as compared with 18 percent of women[17]. Smoking rates tend to be higher among those with lower socioeconomic status and those with a high school education or less. [18] Smokers who quit reduce their excess risk of a coronary event by 50 percent in the first year or two after cessation, with much of this gain in the first few months. This period is followed by a more gradual decline, with the risk of former smokers approaching that of never-smokers after 3 to 5 years[18]. b-Lipid disorder several cholesterol parameters are causally associated with an increased risk of CAD. One mg/dl increase in the serum LDL cholesterol level is associated with a 2 to 3 percent increase in risk for CAD, and elevations earlier in life may be associated with higher increases in risk. HDL cholesterol has emerged as an important independent predictor of CAD; every one mg/dl decrease in HDL cholesterol causes a 3

to 4 percent increase in coronary artery disease. Furthermore, the ratio of total LDL cholesterol to HDL cholesterol may predict CAD risk better than LDL alone. A one unit decrease in this ratio (which is easily achievable with statin drugs) reduces the risk of myocardial infarction by more than 50 percent.[19] Imprecise measurements of triglyceride , interindividual variability, diet dependence, and complex interactions between triglycerides and other lipid parameters may obscure the impact of triglycerides in the development of CAD. However, fasting triglyceride levels do correlate with CAD risk, particularly when HDL levels are considered. This interdependence suggests that some triglyceride-rich lipoproteins are atherogenic. A number of studies have suggested that elevated triglycerides independently predict CAD risk. The clinical usefulness of non fasting triglyceride levels remains unclear.Clear benefits have been demonstrated for dietary and pharmacological treatments that lower serum cholesterol . A number of completed large scale primary and secondary prevention trials using 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have demonstrated significant reductions in CAD and stroke in various populations[20]. C-AtherogenicdietAnatherogenic diet and lack of ohysicalativity are considered leading preventable causes of death,second to tobacco use.considerable epidemiological data indicate that populations with diet high in saturated and transfatty acids have higher rate of CAD,conversely,those populations that consume large amount of calories as vegetables,cereals, and fish have lower ratesofCAD.[(21)]d-HypertensionStudies have consistently demonstrated that elevated systolic or diastolic blood pressure is associated with an increased risk of CVD[22]. Hypertension is also associated with increased risk of heart failure, stroke, and kidney disease. The shape of the cardiovascular disease risk curve is linear. For individuals aged 40 to 70 years, each increment of 20 mm Hg in systolic blood pressure or 10 mm Hg in diastolic blood pressure doubles the risk of cardiovascular disease across a blood pressure range from 115/75 to 185/115 mm Hg. Systolic blood pressure remains the most useful clinical predictor of risk. High blood pressure is more common in blacks than whites and in men than women. The prevalence of hypertension increases with age, from 7 percent of those aged 18 to 39 years to 66 percent of those older than 60 years. Data from the Framingham Heart Study have suggested that normotensive individuals at age 55 have a 90 percent lifetime risk for developing hypertension[23]. Detection and management of hypertension are highly cost-effective in both primary and secondary prevention. The JNC-7 has set a blood pressure goal of <140/90 mm Hg for lower risk patients and of <130/80 mm Hg for those with cardiovascular disease, diabetes, or chronic kidney disease[24]. 2-Risk factors for witch interventions are likely to lower riskofCAD.a-Diabetes mellitusIn the United States, nearly 21 million people, 7 percent of the U.S. population, have diabetes mellitus; approximately 90 percent of cases are type 2 diabetes. One third of people with diabetes are not aware that they have the disease. The prevalence of diabetes appears to have increased over the last decade, which may be a reflection of increasing body mass index (BM)[25] .Diabetes is a powerful risk factor for atherosclerotic disease, its complications, and cardiovascular disease–related mortality. By age 40, CAD is the leading cause of death in both diabetic men andwomen[26] . Diabetes has a stronger effect on the risk of CAD in women compared with men, with diabetic women facing a greater risk of CAD mortality.[27] .Evidence has indicated that individuals with diabetes but without established CAD have as high a risk for fatal CAD as those with established CAD but without diabetes[28] .Individuals with diabetes must be considered at high risk for CAD, regardless of the presence or absence of other risk factors and, furthermore, diabetic patients with well-controlled levels of hemoglobin A1c (HbA1c) appear to be at lower vascular risk than those with poor control[29] .b-Physical inactivity c-Obesity d-Metabolic syndrome. 3-Risk factor for witch interventions have not been shown to lower risk of CAD. a-Lipoprotein LP(a) b-Hyperhomocysteinemia. Unmodifiable risk factors. a-Age and sex, b-Family history of early onset CAD

The aims of the study were to study the frequency of conventional risk factors for CAD among patient with UA/NSTEMI, to determine the coronary angiographic finding in patient with UA/NSTEMI and to Identify the association between TIMI risk score and coronary angiographic finding in patient with UA/NSTEMI.

Methods. A descriptive study was conducted on 100 patients who presented with UA/NSTEMI to CCU of three major cardiac centres in Iraq; Iraqi Centre for Heart Disease , Ibn Al- Bitar Hospital for Cardiac Surgery and Al -Nasyria Cardiac Centre from January 2010 to January 2011. Patients who had chest pain suggestive of angina or angina equivalent symptoms and a diagnosis as UA/NSTEMI based on ECG criteria or cardiac enzymes were included in the study. we excluded those patients who had ST segment elevation MI(STEMI), new LBBB on ECG , prior revascularization either surgical or percutaneous and those with less than 70% stenosis of epicardial CA on coronary angiography and less than 50% stenosis of LMS. A proforma was designed inquiring about age, gender, presence of major cardiac risk factors(diabetes, hypertension, dyslipidemia, and cigarette smoking), chest pain episode during last 24 hours, use of aspirin during last 7 days and prior CAD. Blood samples for cardiac troponin I were immediately drawn upon presentation to the CCU. Patients with UA/NSTEMI were further risk stratified with TIMI risk scores.the seven predictor variables for this score are(1) age≥65 years, (2)three or more cardiovascular risk factors (family history of premature CAD, diabetes mellitus, hypertention, dyslipidemia or current smoker), (3) previous CAD(≥50% stenosis at angiography) (4) severe angina symptoms (2 episodes in the last 24 hours), (5) use of aspirin in the last 7 days (6) ST

segment deviation ≥0.5mm and (7)elevated serum troponin level[10].

All Patients with UA/NSTEMI were underwent coronary angiograms to assess the extent of CAD .The coronary angiography was performed by the physician who had experience of performing coronary angiography.The extent of CAD evaluated on angiography was classified as follows: significant CAD was defined as ≥75% stenosis in any of the three major epicardial coronary arteries or a left main coronary artery stenosis ≥50%, Angiograms revealing coronary artery stenosis of less than 75% in major epicardial coronary arteries were termed non obstructive CAD[1]. Extent of CAD was defined as significant one ,two or three vessel CAD. Diabetes Association, 2007, define DM as a fasting blood glucose ≥7.0 mmol/L (126 mg/dl) or random blood glucose ≥ 11.1 mmol/L (200 mg/dL)with symptoms or being on treatment (25)Hypertension was defined as systolic blood pressure≥140 mm Hg or diastolic blood pressure ≥90 mm Hg with or without antihypertensive treatment(22) Patients were considered to have dyslipidemia if they have any of the followings: total serum cholesterol ≥ 200mg/ dl (≥5.18mmol /l), LDL cholesterol >100mg/dl2.58mmol/l) , and HDL cholesterol of <40mg/dl in male(1.18mmol/l) and <50mg/(<1.51mmol/l) in female.(19) The patients were considered smokers if they were current smokers or had quit smoking less than two years before[29] , those patients who are X smokers are ignored because they are statistically insignificant.

The collected data was entered and analyzed by the statistical package for social sciences(SPSS).Frequencies and percentages were computed for gender ,risk factors and Chi -square test was applied to determine the proportions difference between groups. A p value <0.05 was considered as significant.

Results. The study sample consisted of 100 patients with UA/NSTEMI documented by coronary angiography(CA), their mean age was 56.23 ± 9.69, (68%) were males and (32%) were females. 3.1:Frequency of conventional CAD risk factors.It is shown in table 1 that current smoking is the most common observed risk factor, which represents(54% ,54 patients) of the total number of the patients followed by, in order of frequency; hypertension (52% , 52 patients), DM (50% , 50% patients) and dyslipidemia (20% ,20% patients). Regarding the gender distribution of CAD risk factors: Current smoking was the most common risk factor among male patient, which represent (44%) followed by HT (32%) and DM (28%), while among female patients,

DM is the most common risk factor (22%) followed by HT (20%) and dyslipidemia (12%). The frequency of smoking was higher in male, while the frequency of DM and dyslipidemia were higher in female and these differences are statistically significant as shown in table (1)3.2:Distribution of patient according to number of risk factor and gender. From the total patients; (38%, 38 patients) of them have multiple risk factors, and (14% ,14 patients) of them have double risk factors and (30% ,30 patients) have single risk factor, and only (18%, 18 patients) have no risk factor. The gender difference is of no statistical significance as shown in table2. 3.3:Association between number of risk factors and number of diseased coronary vessels.

Table 3 reveals that ; patient with multiple risk factors has tendency for advance CAD and LMS and Patient with no risk factor has a tendency to have single vessel disease.3.4:Extent of CAD in the study population based on TIMI risk score.

Table 4 reveals that patient with high TIMI risk score (TIMI risk score>4) has tendency for advance CAD (3VD and LMS) on one hand and patient with low TIMI risk score (TIMI risk score ≤4) has tendency for single or two vessel disease. These findings were statistically significant.

Discussion. Appreciation of the crucial role of risk factors in the development of coronary artery disease (CAD) is one of the most significant advances in the understanding of this important disease. Extensive epidemiological research has established cigarette smoking, diabetes, hyperlipidemia, and hypertension as independent risk factors for CAD. In addition, treatment of these risk factors has been convincingly shown to reduce the risk of future cardiac events[30]. Because of the strength of evidence supporting their role in the pathogenesis of CAD, these 4 risk factors have often been labeled as “conventional” risk factors The Fraction of female patient was low in agreement with other studies which report that CAD rates are certainly lower in women than in men Al-Farhan, Al-Safar study(31) and Jason et al(32)4.1:Conventional CAD risk factors frequency

Our study identified that smoking is the most common risk factor in male patient which represented (44%) and this is compatible with that of Jason et al; who reported that smokers represent (65%) of patients with CAD, and this fact could be explained by; cigarette smoking increase the risk of thrombosis, Zimmerman FH et al.(33)While smoking is not common in female patients (10%) and this is because smoking is very infrequent in Iraqi women for social reason. DM and dyslipidemia were more prevalent in female patients than male in our study and this finding was in agreement with Knopp et al who reported that the prevalence of these risk factors (DM and dyslipidemia) was greater in women than men[34]. Because CAD typically presents 10 years later in women than men, higher risk factor prevalence in women is necessary to lead to the development of CAD at the same age as in men[34].

The higher prevalence of diabetes in women than in men is consistent with other studies that have shown that diabetes is powerful risk factor in women[34] , and Al-Farhan ,Al-Safar study[31]. Current study have identified that (52%) of total patients have multiple risk factors and this result comparable with other studies which have established that ,CAD is commonly characterized by multiple risk factors, Berenson et al[35] and Al-Farhan, Al-Safar study[31]4.2:Association between CAD risk factor and

Table1: Frequency of CAD risk factors according to gender.

CAD R,F	Male No.(%)	Female No.(%)	Total No.(%)	P value
Hypertension	32(32%)	20(20%)	52(52%)	0.149
Diabetes mellitus	28(28%)	22(22%)	50(50%)	0.010*
Dyslipidemia	6(6%)	12(12%)	20(20%)	0.0005*
Smoking	44(44%)	10(10%)	54(54%)	0.002*

*Highly significant

Table 2: Distribution of patients according to number of risk factors and gender.

CAD R.F	Male No.(%)	Female No.(%)	Total NO.(%)
NO R.F	14(14%)	4(4%)	18(18%)
Single R,F	20(20%)	10(10%)	30(30%)
Double R,F	10(10%)	4(4%)	14(14%)
Multiple R,F	24(24%)	14(14%)	38(38%)
Total	68(68%)	32(32%)	100(100%)

P=0.729 (Not significant)

Table 3: Association between number of risk factors and number of diseased Vessel.

Risk factors		Diseased coronary vessel		
	LMS No. (%)	Single vessel No.(%)	Double vessel No.(%)	Triple vessel (%)
No R.F	-	12(12%)	2(2%)	4(4%)
Single R.F	-	12(12%)	16(16%)	6(6%)
Double R.F	-	8(8%)	2(2%)	-
Multiple RF	6(6)*	2(2%)	10(10%)	20(20%)*
Total	6(6%)	34(34%)	30(30%)	30(30%)

*P=0.0001 (Highly significant)

Table 4: Extent of CAD in the studied groups based on TIMI risk score.

Extent of CAD	TIMI risk score ≤4 No.(%)	TIMI risk score>4 No.(%)	P value
One vessel diseas	32(32%)	2(2%)	<0.0002*
Two vessel disease	26(26%)	2(2%)	<0.0004
Three vessel disease	6(6%)	26(26%)	<0.0001*
LMS disease	0	6(6%)	<0.0001*

*Highly significant

angiographic data .Analysis of the correlation between number of risk factor and number of diseased vessel reveals that ;patients with multiple risk factors tend to have advanced CHD as epidemiological studies have established that multiple risk factors increase the probability of cardiovascular events because cardiovascular risk factors tend to be additive influencing morbidity and mortality rate(34)4.3:Extent of CAD in the study population based on the TIMI score. The study revealed that patient with higher TIMI score were associated with greater extent of significance CAD including 3VD and LMS and patient with low TIMI score were associated single vessel and two vessel disease. The result of our study compare well with the finding of Mega et al [36] A significant association between single vessel disease and low TIMI score were found .Zheng and colleagues in their study found that TIMI score correlated well with severity of CAD (37) Garcia and coworkers also showed that the extent and severity of CAD increases as the TIMI risk score increases[38].

In conclusion, current smoking is the most common CAD risk factor among patients (54%) while hypertension (52%) and DM (50%) are the second most common risk factors and dyslipidemia is the least common. Compared with male who have higher prevalence of smoking, female patient is more likely to have dyslipidemia and DM as more prevalent risk factors. Hypertension is prevalent in both male and female patients but it is statistically there is insignificant difference between male and female patient. Patients with high TIMI risk score were more likely to have severe multi vessel CAD compared with those with low or intermediate TIMI risk score.

The TIMI risk score was developed and adapted for patients with UA and NSTEMI. We suggest to use the TIMI risk score an effective protocol for predicting the risk of death and ischemic events. The TIMI risk score is used for objective risk stratification of patients into one of three groups: low score, intermediate and high score. The risk corresponds to future cardiac events including death, myocardial infarction or urgent revascularization within 14 days. It also identifies those who are likely to benefit most from an early invasive strategy.

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