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## **Reassessing the Value of the Exercise Electrocardiogram in the Diagnosis of Stable Chest Pain**

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#### **1. Introduction**

 "Do not use exercise ECG to diagnose or exclude angina for people without known coronary artery disease" - a quote from the summary (Cooper et al, 2010) of the guidelines of the United Kingdom's National Institute for Health and Clinical Excellence (NICE) on the diagnosis of discomfort of suspected cardiac origin (NICE, 2010). Amongst other things, NICE recommends that the probability of coronary artery disease (pCAD) is determined from the person's symptoms and risk factors, and that the subsequent management depends on whether the pCAD is less than 10%, 10 to 30%, 30 to 60%, 60 to 90% or greater than 90%: if the pCAD is less than 10% or greater than 90% further testing is not required; if the pCAD is between 60 and 90%, the patient is a candidate for coronary arteriography; if the pCAD is between 10 and 60% non-invasive testing is indicated.

Ever since a meta-analysis (Gianrossi et al., 1989) of the exercise electrocardiogram (ECG), in which the sensitivity was assessed as being 68% and the specificity as 77%, the test's role in the diagnosis of coronary artery disease has been questioned. However, in 1979 Diamond & Forrester demonstrated that the greater the ST segment shift on exercise ECG, the greater the post-exercise probability of coronary artery disease (pCAD) whatever the pre-exercise pCAD. Furthermore, the Duke Treadmill Score (Mark et al., 1991) demonstrates that the greater the ST segment depression the worse the prognosis.

The purpose of this study is to show, using the data obtained from a West London population and NICE's methodology, the different impact the exercise ECG has on subsequent management, if Diamond & Forrester's method of analysing exercise ECG data is used instead of NICE's.

#### **2. Methods**

Patients with a history of chest pain referred direct from primary care to the rapid access chest pain clinic of the Hammersmith Hospital, London, between January 1999 and March 2010 were studied. Each person was asked to complete a questionnaire (Table 1) which combines questions from two previously published studies (Joswig et al., 1985; Pryor et al., 1993).



Table 1. The questionnaire each patient was asked to complete.

The questionnaire was translated into 5 languages commonly used in the local community, viz. Farsi, Hindi, Polish, Punjabi and Urdu. The raw data from the questionnaire were stored in a bespoke database. For a symptomatic diagnosis of Typical Angina (chest pain symptom score 3 points) the following criteria had to be met: a) 'Yes' to both question 10 and question 12 and b) 'Yes' to either question 14 or question 15 and c) 'between 30 seconds and 10 minutes' to question 16 or 'between 30 seconds and 10 minutes' to question 18 if the answer to question 17 was 'Yes'. Atypical Angina was diagnosed if any 2 of criteria a), b) and c) were met (chest pain symptom score 2 points); otherwise Non-Anginal Chest Pain was diagnosed (chest pain symptom score either 1 or 0 points).

From the questionnaire data, pCAD was calculated (Pryor et al., 1993) for routine clinical use (pCAD\_DUKE). To assess the impact of NICE's guidelines, NICE's modification of pCAD\_DUKE that omits the history of myocardial infarction and omits ECG data, was used to recalculate pCAD as pCAD\_NICE. The doctor or nurse assessing the patient had the pCAD\_DUKE available when deciding whether or not to exercise the patient.

Treadmill exercise ECGs were performed following the Bruce protocol (Bruce et al., 1949). The Mason-Likar electrode positions (Mason & Likar, 1966) were used. The maximum ST segment shift 60-80 ms after the end of the QRS was noted; it was considered less than 50  $\mu$ V if the ST segment was upsloping and the end of the QRS depressed. ST segment shifts due to rhythm disturbances were ignored. From the exercise ECG the post-exercise pCAD was calculated using Bayes' Theorem of conditional probability

post-exercise pCAD =  $[100 * pre-exercise pCAD * sensitivity]/[$  (pre-exercise pCAD  $*$ sensitivity) +  $(100 - \text{pre-exercise pCAD})$  \*  $(100 - \text{specificity})$ ]

and using the sensitivities and specificities in Table 2 for different levels of ST segment shift (Diamond & Forrester, 1979). Also calculated were

the positive likelihood ratio = sensitivity/ $(100 -$  specificity) and



the negative likelihood ratio =  $(100 -$  sensitivity)/ specificity

Table 2. The 6 combinations of sensitivity and specificity corresponding to the maximum ST segment shift on exercise (Diamond & Forrester, 1979). NICE's assumption of a sensitivity of 67% and a specificity of 69% for the single threshold point of 100  $\mu$ V has a positive likelihood ratio of 2.16 and a negative likelihood ratio of 0.48

The post-exercise pCAD was also calculated using NICE's assumption of sensitivity 67% and specificity 69% for a ST segment shift threshold of 100  $\mu$ V. NICE's sensitivity and specificity were obtained from table 14 of Mowatt et al., 2008, in which the sensitivities and specificities obtained from Kuntz et al., 1999, and from Mowatt et al., 2004, were averaged.

#### **3. Statistics**

Multivariate linear regression analysis (StatsDirect version 2.7.8; StatsDirect Ltd, Altrincham, WA14 4QA, UK) was used to perform analysis of variance (ANOVA) to determine the impact of age, sex and race on the likelihood of a patient being referred for an exercise ECG. Dummy variables were generated for sex and race. Multivariate linear regression analysis was also used to determine the impact of age, sex, race on chest pain

symptom score and on exercise workload. Chi-square analysis was used to compare the numbers of exercised patients in each pCAD category with the numbers not exercised.

#### **4. Results**

All 7739 patients referred to the rapid access chest pain clinic completed the questionnaire. Following clinical assessment 5157 of the 7739 (66.6%) were exercised. 359 of 2582 (13.9%) who were not exercised had either left ventricular hypertrophy or an intraventricular conduction defect on 12 lead ECG, while 513 of 5157 (9.9%) who were exercised had either left ventricular hypertrophy or an intraventricular conduction defect ( $\chi^2$  = 26.9 P < 0.0001).





Table 3. The average chest pain symptom score of females (above) and males (below) not exercised by race and decade of age. Typical angina = 3, atypical angina = 2, non-anginal chest pain = 1 or 0. The numbers in brackets are the numbers of patients.

Table 3 shows the distribution of age, sex and race of those not exercised, while table 4 shows the distribution of age, sex and race of those exercised. The distributions are similar. Black men had similar chest pain symptom scores to White men and Black men to Black women, but the South Asian, Miscellaneous and Oriental women had higher chest pain

Age	<b>Black</b>	South	Miscellan-	Oriental	White	<b>Females</b>
		Asian	eous			Total
$20 - 29$			1.16(6)		1.27(18)	1.33(36)
	$1.5(6)$ 9.83	1.5(6)10.3	10.3		12.8	11.5
$30 - 39$	1.52(17)	1.53(28)	1.54(11)	2(4)	1.47(76)	1.51(136)
	9.05	8.07	7.72	9.25	11.2	9.99
$40 - 49$	1.72(84)	1.81(103)	1.79(64)	1.41(17)	1.53(236)	1.65(504)
	8.10	8.14	8.18	10.0	9.48	8.83
$50 - 59$	1.41(87)		1.75(68)	1.89(19)	1.45(373)	1.52(682)
	7.90	$1.6(135)$ 7.8	8.07	8.73	8.49	8.24
$60 - 69$	1.44 (90)	1.70 (98)	1.56(41)	1.63(19)	1.46 (363)	1.50(611)
	6.86	6.71	7.48	7.52	7.69	7.39
$70 - 79$	1.46(43)	1.36(25)	1.73(15)	1(1)	1.35(234)	1.38 (318)
	6.16	5.84	6.73	4	6.43	6.35
$80 - 89$	2(2)	1(1)			1.42(42)	1.44(45)
	2.5	$\overline{4}$			4.85	4.73
$90 - 99$					1(1)7	1(1)7
	1.51 (329)	1.65(396)	1.69(205)	1.66(60)	1.45(1343)	1.52(2333)
Total	7.50	7.54	7.94	8.68	8.19	7.97
Age	<b>Black</b>	South	Miscellan-	Oriental	White	<b>Males</b>
		Asian	eous			Total
10-19					0(1)16	0(1)16
20-29		0.83(12)	1.12(8)		1(26)	1.01(54)
	1.25(8)14.6	13.0	13.6		13.2	13.4
30-39		1.22(84)	1.20(43)		1.17(173)	1.23 (336)
	1.6(30) 12.3	11.7	12.5	$1.5(6)$ 12.6	13.0	12.5
40-49	1.38(68)	1.13(143)	1.46 (84)	0.90(11)	1.22(396)	1.24 (702)
	11.3	10.9	11.0	11.2	11.6	11.4
50-59	1.37(43)	1.28(146)	1.32(92)	0.91(12)	1.19 (472)	1.23(765)
	9.62	9.60	10.0	11.3	10.0	9.94
60-69	1.28(53)	1.50(111)	1.30(43)	2(3)	1.21(419)	1.28 (629)
	8.05	7.54	8.93	10	8.65	8.43
70-79	1.38(42)	1.37(51)	1.53(13)	0.75(4)	1.36 (188)	1.36(298)
	6.42	7.09	8.07	8.75	6.96	6.98
80-89	1.5(4)	1(2)	2(2)		1.38(31)	1.41 (39)
	6.75	5.5	5.5		5.51	5.64
Total	1.38 (248)	1.27(549)	1.35(285)	1.08(36)	1.22(1706)	1.25(2824)
	9.66	9.69	10.5	11.1	10.0	9.98

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Table 4. The average chest pain symptom score of females (above) and males (below) exercised and average exercise workload achieved (metabolic equivalents) by race and decade of age. Typical angina = 3, atypical angina = 2, non-anginal chest pain = 1 or 0. The numbers in brackets are the numbers of patients and the third number in a cell is the average exercise workload

symptom scores than the Black and White women. Analysis of Variance (ANOVA) showed that a higher chest pain symptom score was found in females and in those who were South Asians or in those having a Miscellaneous race (compared to being White). However, the descriptors explained only 2.4% of the variance in chest pain symptom score. ANOVA also showed that the younger the age, being male and a higher symptom score all made being exercised more likely. The descriptors explained 1.6% of the variance in the likelihood of being exercised. Table 4 also shows the workload achieved on exercise. For the 5157 patients who were exercised, younger males with low symptom scores were those who achieved the highest workload. Whites and Orientals were the races that achieved the highest workload and South Asians the lowest. The descriptors explained 36.4% of the variance.

Table 5 shows a comparison of the pre-test pCADs of the patients who were not exercised with those who were exercised. Chi-square analysis showed a significant difference in the proportions exercised and the proportions not exercised  $(\chi^2=120.4$  with 4 degrees of freedom;  $P < 0.0001$ ). Those with a pCAD below 10% were less likely to be exercised than those with pCAD between 10 and 90%.



pCAD = probability of coronary artery disease

Table 5. The pre-test pCAD of the patients according to whether or not they were exercised. The "exercised" column includes the percentage (in brackets) of the patients for a given pretest pCAD who were exercised. Patients with a pre-test pCAD of less than 10% were less likely to be exercised than those with pCAD between 10 and 90%

Table 6 shows the change in pCAD categories following exercise. In the top part of Table 6 the numbers in each cell show how the pCAD changes when 6 combinations of sensitivity and specificity are used to calculate the post-exercise pCAD. 3296 of 5157 (63.9%) changed category: 535 of the 3296 increased pCAD while 2761 reduced pCAD. Had only the 2910 patients with pre-test pCAD between 10 and 60% been exercised, 1383 (47.5%) would have had CAD ruled out and 48 (1.6%) CAD ruled in. Another 170 (5.8%) would have become candidates for coronary arteriography. Figure 1 illustrates the change in pCAD. The bottom part of Table 6 shows the change in pCAD categories following exercise when NICE's assumption of one combination of sensitivity (67%) and specificity (69%) is used to calculate the post-exercise pCAD. 2271 of 5157 (44.0%) changed category. Of those with a pre-exercise pCAD of between 10% and 60%, 793 of 2910 (27.3%) had CAD ruled out and 128 (4.4%) became candidates for coronary arteriography. Figure 2 illustrates the change in pCAD.

	Post-exercise pCAD% 6 Sensitivities and Specificities									
Pre-exercise pCAD%	< 10	$10 - 30$	$30 - 60$	$60 - 90$	> 90	Total				
$\leq 10$	1146	73	21	3		1243				
$10 - 30$	1287	225	119	38	7	1676				
$30 - 60$	96	795	170	132	41	1234				
$60 - 90$		113	393	207	121	834				
> 90				77	93	170				
Total	2529	1206	703	457	262	5157				
Post-exercise pCAD% Sensitivity 67% Specificity 69%										
Pre-exercise pCAD%	< 10	$10 - 30$	$30 - 60$	$60 - 90$	> 90	Total				
< 10	1162	81				1243				
$10 - 30$	793	760	123			1676				
$30 - 60$		664	442	128		1234				
$60 - 90$			371	417	46	834				
> 90				65	105	170				
Total	1955	1505	936	610	151	5157				

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pCAD = probability of coronary artery disease

Table 6. The top part of the table shows how the numbers of patients in each category changed following exercise using the 6 combinations of sensitivity and specificity as in table 2. The bottom part of the table shows how the numbers of patients in each category changed following exercise using a single combination of sensitivity (67%) and specificity (69%).



Fig. 1. The probability (%) of CAD after exercise plotted against the probability of CAD before exercise when 6 combinations (5 thresholds of ST shift) of sensitivity and specificity were used. The graph shows the discrimination that can be obtained by using several thresholds of ST shift and how CAD can be ruled out if the ST shift is less than 50  $\mu$ V. The units of the thresholds in the legend are  $\mu$ V.



Fig. 2. The probability (%) of CAD after exercise plotted against the probability of CAD before exercise using a single threshold of 100  $\mu$ V.

#### **5. Discussion**

The purpose of this study has been to try and demonstrate the superior diagnostic value of taking the amount of ST segment shift into account compared with using a single threshold point when interpreting the exercise ECG. The publication of the method used by NICE to obtain the pre-exercise probability of CAD (pCAD) made this comparison and the testing of NICE's recommendations feasible. NICE recommends firstly, that symptoms and risk factors should be used to derive pCAD and secondly, that the subsequent management depends on whether the pCAD is less than 10%, between 10 and 30%, between 30 and 60%, between 60 and 90%, or greater than 90%. Those with a pCAD of less than 10% have CAD ruled out and need no further investigation for CAD. Those with a pCAD of more than 90% have CAD ruled in. Those with a pCAD between 60 and 90% should be considered for coronary arteriography. NICE recommends that those with a pCAD between 10 and 60% need further investigation, but not exercise ECG.

In this study 5157 of 7739 consecutive patients referred to the rapid access chest pain clinic had an exercise ECG. Table 6 shows that using NICE's methodology and a sensitivity of 67% and a specificity of 69% for an ST segment shift of 100  $\mu$ V, the exercise ECG rules out CAD in 793 (27.3%) of the 2910 patients with a pre-exercise pCAD between 10 and 60%, while another 128 (4.4%) become candidates for coronary arteriography. However, modifying the calculation of the post-exercise pCAD to account for increasing ST segment shift during exercise has a dramatic effect: of the 2910 patients who had a pre-test pCAD between 10 and 60% and who were exercised, 1383 (47.5%) would have had CAD ruled out and 48 (1.6%) CAD ruled in. Another 170 (5.8%) would have become candidates for coronary arteriography. The exercise ECG would therefore have defined the subsequent management of more than half the patients that had a pre-test pCAD between 10 and 60%.

The distributions by age, sex and race of patients referred for exercise ECG were similar to those of the whole cohort. Women were more likely to have angina than men. As recommended by NICE, patients referred for exercise testing were less likely to have a

pCAD below 10% than those with a pCAD between 10 and 30%. The workload achieved during exercise was greater in men than in women and declined with age.

Table 2 reproduces part of table 4 of Diamond & Forrester, 1979 and adds corresponding positive and negative likelihood ratios. Diamond & Forrester reviewed 31 published papers to derive the table. From these papers they were able to derive a sensitivity and a specificity for each of the 5 thresholds. The assumption is that these are mutually exclusive events, each having their own receiver operating characteristic curve. Table 2 shows that increasing the ST segment shift above 100 µV steadily increases the likelihood of CAD, while an ST segment shift of less than 50  $\mu$ V reduces the likelihood of CAD.

Table 7 shows the effect of varying the combination of sensitivity and specificity on a single ST segment shift with a threshold of 100  $\mu$ V. NICE assumed for calcium scoring a sensitivity



Table 7. Three parts of the table show the effect on the data of using different combinations of sensitivity and specificity. At the top is that for a sensitivity of 89% and a specificity of 43% (NICE's combination for Calcium Scoring). In the middle is that for a sensitivity of 86% and a specificity of 64% (NICE's combination for Myocardial Perfusion Scanning). Below is that for a sensitivity of 68% and a specificity of 77% (the combination from the meta-analysis of Gianrossi et al., 1989).

of 89% and a specificity of 43%; this is the combination in the top part. NICE assumed for myocardial perfusion scanning with single photon emission computed tomography a sensitivity of 86% and a specificity of 64%; this is the combination in the middle part. From their meta-analysis Gianrossi et al., 1989 obtained a sensitivity of 68% and a specificity of 77%; this is the combination in the bottom part. For ruling out CAD when the pre-exercise pCAD is between 10 and 60%, table 7 and the bottom part of table 6 indicate that NICE's combinations of sensitivity and specificity used with calcium scoring (51.3% ruled out) and with myocardial perfusion scanning (55.8% ruled out) are both superior to NICE's combination used with exercise ECG (27.3% ruled out) and to the combination used by Gianrossi et al (33.9% ruled out). However, NICE recommends using myocardial perfusion scanning only if the preexercise pCAD is between 30 and 60%. Consequently, only 151 of 1234 (12.2%) would have had CAD ruled out. Only the combination of 6 sensitivities and specificities resulted in any of those with a pre-test pCAD between 10 and 60% having CAD ruled in.

As NICE, 2010, assumed costs of \$100 (£66), \$450 (£293) and \$160 (£103) for exercise ECG, for myocardial perfusion scanning and for calcium scoring respectively, the explanation for the recommendation not to use the exercise ECG may be partly due to the assumptions about the proportions of indeterminate tests. NICE assumed 24% of exercise ECGs were indeterminate, 6% of myocardial perfusion scans were indeterminate and 2% of calcium scores were indeterminate. The 24% was NICE's modification of the unsubstantiated 30% in Kuntz et al., 1999. In the present study no exercise ECG was indeterminate, although it is accepted that interpretation of ST shift in the presence of left ventricular hypertrophy or of intraventricular conduction defect is unreliable. Ten per cent of the ECGs of the patients exercised showed either left ventricular hypertrophy or an intraventricular conduction defect.

### **6. Study limitations**

Firstly, the sensitivities and specificities of each of the 5 thresholds of ST shift used were obtained by a review of the literature (Diamond & Forrester, 1979) rather than by a formal meta-analysis. Secondly, the patients were not asked about their race. The members of the ECG team assessed a person's race. Even though there were only 5 different races from which to choose, it is likely that misclassification occurred. Thirdly, being in paper format, the answers to the questionnaire were subject to transcription errors when entered into the database. Fourthly, measurement of the maximum ST segment shift on exercise was made by the member of the ECG team supervising the test. Until June 2006 all exercise tests were checked by the author. After June 2006 a weekly tutorial session with the author enabled the ECG team to discuss ST segment shifts that were difficult to assess.

### **7. Conclusions**

It is concluded firstly, that the exercise ECG does indeed have limited diagnostic value if a single threshold is used for the diagnosis of CAD; secondly, that the exercise ECG has considerable diagnostic value if several thresholds are used; and thirdly, that NICE's recommendation "Do not use exercise ECG to diagnose or exclude angina for people without known coronary artery disease" seems to be partly the result of an unjustified assumption about the proportion of indeterminate exercise ECGs.

#### **8. Acknowledgements**

I thank the members of the ECG Team who entered the data into the bespoke database.

Some of the data presented has previously been published as a letter (Bourdillon, 2010).

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**Coronary Artery Disease - Current Concepts in Epidemiology, Pathophysiology, Diagnostics and Treatment** Edited by Dr. David Gaze

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Cardiovascular disease is ranked as the leading cause of death world wide, responsible for 17.1 million deaths globally each year. Such numbers are often difficult to comprehend. Heart disease kills one person every 34 seconds in the USA alone. Although the leading killer, the incidence of cardiovascular disease has declined in recent years due to a better understanding of the pathology, implementation of lipid lowering therapy new drug regimens including low molecular weight heparin and antiplatelet drugs such as glycoprotein IIb/IIIa receptor inhibitors and acute surgical intervention. The disease burden has a great financial impact on global healthcare systems and major economic consequences for world economies. This text aims to deliver the current understanding of coronary artery disease and is split into three main sections: 1. Epidemiology and pathophysiology of coronary artery disease 2. Coronary artery disease diagnostics and 3. Treatment regimens for coronary artery disease

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