

CARDIOVASCULAR MEDICINE

Changing the diagnostic criteria for myocardial infarction in patients with a suspected heart attack affects the measurement of 30 day mortality but not long term survival

C Packham, D Gray, C Weston, A Large, P Silcocks, J Hampton

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Objectives: To explore the effects of alternative methods of defining myocardial infarction on the numbers and survival patterns of patients identified as having sustained a confirmed myocardial infarct.

Design: An inclusive historical cohort of patients admitted with a suspected heart attack. Patients were recoded from raw clinical data (collected at the index admission) to the epidemiological definitions of myocardial infarction used by the Nottingham heart attack register (NHAR), the World Health Organization (MONICA), and the UK heart attack study.

Setting: Single health district.

Patients: The NHAR identified all patients admitted in 1992 with suspected myocardial infarction.

Outcome measures: Survival at 30 days and four year postdischarge.

Results: 2739 patients were identified, of whom 90% survived to discharge. Recoding increased the numbers of patients defined as having confirmed myocardial infarction from 26% under the original NHAR classification to 69%, depending on the classification system used. In confirmed myocardial infarction, subsequent 30 day survival from admission varied from 77–86% depending on the classification system; four year survival after discharge was not affected. The distribution of important prognostic variables differed significantly between groups of patients with confirmed myocardial infarction defined by different systems. Patients with suspected but unconfirmed myocardial infarction under all classification systems had a worse postdischarge mortality.

Conclusions: The classification system used had a substantial effect on the numbers of patients identified as having had a myocardial infarct, and on the 30 day survival. There were significant numbers of patients with more atypical presentations, not labelled as myocardial infarction, who did badly following discharge. More research is needed on these patients.

See end of article for authors' affiliations

Correspondence to:
Dr C Packham, Division of
Public Health Sciences,
Queens Medical Centre,
Nottingham NG7 2UH,
UK;
chris.packham@
nottingham.ac.uk

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Ensuring that a medical diagnosis is correct is fundamental to effective and appropriate health care. The emphasis in measuring the quality of care has moved towards improving clinical outcomes, such as rankings between hospitals of 30 day mortality after myocardial infarction (so called "league tables"). The criteria on which a diagnosis of acute myocardial infarction is based have not been universally agreed, and different coding systems continue to be employed in epidemiological and health services research programmes. Pleas for consistency of coding¹ have largely been ignored.

Rigorous definitions of non-fatal acute myocardial infarction were developed for the MONICA project (monitoring trends and determinants in cardiovascular disease),² based on Minnesota criteria which are "difficult, time consuming and subject to observer variation." Many clinicians prefer to use World Health Organization criteria,³ where the diagnosis relies on chest pain symptoms suggestive of myocardial infarction, supported by specific ECG changes, specific levels of cardiac enzymes, or both. A WHO diagnosis of "definite myocardial infarction" may miss some milder coronary events, but applying these criteria consistently does correlate with the subsequent use of thrombolysis.¹

Despite having typical ischaemic symptoms, some patients do not fulfil such strict criteria. Diagnostic criteria can also be used to "exclude" a cardiac event, so an agreed definition of what is *not* an infarct is at least as important. The fate of patients discharged after an initially suspected but later unconfirmed myocardial infarct⁴ varies according to subgrouping such as non-Q wave infarction or unstable angina.⁵

In current clinical practice, patients with typical angina-like symptoms are more likely to be considered to have an acute coronary syndrome, whereas previously the diagnosis would have been "unconfirmed myocardial infarction."⁶

Few studies have attempted to record outcome in patients with atypical chest pain or other symptoms; yet for an unselected cohort of such patients survival after discharge has been shown to be worse than after confirmed myocardial infarction.⁷ The Nottingham heart attack register (NHAR) provides a means of describing the long term survival of all patients admitted and managed as suspected myocardial infarction (which includes those with acute coronary syndromes). Our aim in the present study was to explore differences in survival resulting from the use of alternative definitions of myocardial infarction.

METHODS

At selected intervals since 1973, the NHAR has collected extensive information on clinical care and outcome on all patients (irrespective of age) referred acutely to Nottingham's two district general hospitals and presenting with symptoms

Abbreviations: MONICA, monitoring trends and determinants in cardiovascular disease study; NHAR, Nottingham heart attack register; NSTEMI, non-ST-elevation myocardial infarction; OXMIS, Oxford myocardial infarction study; STEMI, ST elevation myocardial infarction; UKHAS, UK heart attack study.

thought by the admitting medical team to be suggestive of acute myocardial infarction. Details of its operation have been reported.⁸ Patients in all acute settings are included in the NHAR.

Subjects and setting

For this exercise, a cohort of patients who were admitted in 1992 was identified from the register. We have previously reported on postdischarge management and on the survival of those with confirmed⁹ and unconfirmed⁷ myocardial infarction.

Case definitions used in the NHAR

Definite myocardial infarction—Symptoms compatible with acute myocardial infarction accompanied by both definite ECG changes of myocardial infarction and rises in both of two cardiac enzymes (lactate dehydrogenase and creatine phosphokinase) to above twice the upper limit of normal.

Probable myocardial infarction—Symptoms compatible with acute myocardial infarction and *either* definite ECG changes of myocardial infarction *or* rises in cardiac enzymes to above twice the upper limit of normal.

Possible myocardial infarction—Symptoms compatible with acute myocardial infarction and *either* an abnormal ECG (but not characteristic of myocardial infarction) *or* abnormal cardiac enzyme rises to less than twice the upper limit of normal.

Ischaemic heart disease—Symptoms compatible with acute myocardial infarction *and* only old ECG changes (old Q waves on ECG) with no new sustained ECG or cardiac enzyme changes.

In this study, *definite myocardial infarction* and *probable myocardial infarction* are jointly analysed as *confirmed myocardial infarction*.

Survival

The methods used to identify and subsequently trace the original cohort have been published.^{7,9} We report the complete survival history for a minimum of four years following discharge from the index event for patients in all the above categories.

Initial working diagnosis

The NHAR database records both the final case definition above, and also the initial working diagnosis of the admitting medical team.¹⁰ Although it is a primary requirement of registration that all patients are investigated for a suspected myocardial infarct, the initial working diagnosis reflects the clinical certainty of myocardial infarction based on the history and presenting ECG. The initial working diagnosis is based on the admitting doctor's differential diagnosis list:

- chest pain of uncertain cause
- definite myocardial infarction: the diagnosis is not in doubt
- chest pain—rule out myocardial infarction; differential diagnosis: cardiovascular system only
- other symptoms: tests requested, predominant symptom not chest pain
- heart failure: main symptom is breathlessness *or*, clinically, pulmonary oedema, and an underlying cardiac cause is sought.

Statistical methods

Kaplan–Meier and Cox proportional hazards analyses were used to explore survival. Alternative case definitions used in published series of acute cardiovascular events were applied to the NHAR clinical data. Reclassified cases were then analysed in a similar manner. The primary outcome was survival status at 30 days from admission and four year survival following discharge alive.

Final classifications were based on cardiac enzyme changes and ECG changes. Data were also available on the initial clinical working diagnosis at admission and other clinical variables. These were examined in a multivariate model that took account of age, sex, a past history of myocardial infarction, the presence of abnormal ECG or cardiac enzyme results, Killip score on admission, whether receiving a diuretic on discharge, and the classification into confirmed myocardial infarction or not. These factors were chosen on the basis of the previous demonstration of their prognostic value.¹¹ Agreement between the different classification systems was calculated using the κ statistic. Diabetes mellitus comorbidity was not accurately recorded in this dataset in 1992.

Reclassification of NHAR cases

Modification of the NHAR classification

Two approaches were used:

(1) The case definition of “confirmed myocardial infarction” was expanded to include patients with any of the following: a rise of a single enzyme to more than twice the upper limit of normal; sequential ST and T wave changes in the absence of Q wave development; new T wave inversion.

(2) To address more recent changes in clinical practice, a diagnosis of “acute coronary syndrome” was assigned to all confirmed cases of acute myocardial infarction, and those with an initial working diagnosis of “definite myocardial infarction” or “chest pain—rule out myocardial infarction” where either the ECG or cardiac enzymes were found to be abnormal.

Use of alternative classification systems

MONICA classification

The NHAR dataset was recoded to fulfil as nearly as possible the MONICA criteria.² Patients over 64 years of age were excluded in MONICA. The hospital admitted cases included in the NHAR were equivalent to the *Definite non-fatal myocardial infarction* cases identified in MONICA.

Oxford myocardial infarction study (OXMIS)

This study closely followed the MONICA coding scheme but included patients under 80 years of age.¹²

UK heart attack study (UKHAS)

The classification system used in this study was clinical and based on at least two of the following criteria: a typical chest pain history, a doubling of creatinine kinase, and an abnormal ECG (sequential ECG changes compatible with myocardial infarction—either new Q wave development, or ST and T wave changes, or left bundle branch block (Gaylani E, personal communication). Cases in this study were restricted to patients aged 75 years or less.¹³

Clinical classification

The data were reclassified to reflect more familiar clinical definitions of ST elevation myocardial infarction, non-ST elevation myocardial infarction, unstable angina, classical angina, and “other presentations” (which were generally more atypical, but still conformed to presentation with suspected myocardial infarction and having ECG and/or cardiac enzyme abnormalities). These categories were compared with the cases of confirmed myocardial infarction defined by the epidemiological methods discussed above.

RESULTS

Nottingham patient population

In 1992, 4571 patients were admitted to the two Nottingham hospitals with suspected myocardial infarction. Of these, 81% fell into the four NHAR categories outlined above. A further 850 patients were classified as “chest pain of unknown cause”

Table 1 In-hospital mortality of patients in the Nottingham heart attack register.

NHAR diagnosis	% Died in hospital (95% CI and number in group)	Discharged alive	Total in group
Confirmed MI	22 (19 to 25)	564	723
Definite MI	17 (14 to 20)	440	531
Probable MI	35 (29 to 42)	124	192
Possible MI	7 (5 to 8)	1659	1776
Ischaemic heart disease	4 (2 to 7)	230	240
Totals		2453	2739

Proportion dying in hospital dependent on NHAR category.

χ^2 (on categories in bold) = 14.1, dF = 2, $p < 0.0001$.

CI, confidence interval; NHAR, Nottingham heart attack register; MI, myocardial infarction

as ECG and cardiac enzymes were normal. Patients from outside Nottingham were excluded (owing to a lack of follow up data), as were recurrent admissions. The remaining 2739 patients fell into the diagnostic categories outlined above (table 1). Of these, 286 died during admission (in-hospital survival of 90%), leaving 2453 patients for the survival analysis following hospital discharge. Survival of all those admitted was 87% by 30 days and 58% after four years (1130 deaths). Of those discharged alive, 844 (34%) subsequently died during the four year follow up period.

Patients classified as having "confirmed myocardial infarction" were slightly younger and had a substantially lower prevalence of reported previous myocardial infarction than patients classified as not having had myocardial infarction, whichever classification system was used (NHAR, MONICA, or UKHAS).

Survival according to original NHAR diagnosis

The crude (unadjusted) in-hospital mortality of the different diagnostic groups was substantially different (table 1). The 30 day mortality (table 2) was worse in patients of all ages with confirmed myocardial infarction; even after adjustment, the NHAR category was a highly significant predictor of 30 day survival, with confirmed myocardial infarction remaining the group with the worst prognosis.

Survival after discharge from hospital showed a pattern that was distinct from that observed in hospital, patients with confirmed myocardial infarction having a significantly better

four year prognosis during this time than patients not classified as having confirmed myocardial infarction, before and after adjustment for available prognostic variables (adjusted hazard ratio range 0.78–0.87).

Reclassification of NHAR cases

The results of the reclassification of NHAR cases are given in table 2.

Modified NHAR classification

Recoding the cases to encompass single cardiac enzyme or ECG changes as defined increased the number of patients classified as having sustained a myocardial infarct by 69% in hospital (from 723 to 1224), and by 89% in those who were discharged alive (from 564 to 1065).

In all, 1661 patients fulfilled the recoding criteria for an "acute coronary syndrome" (an increase of some 1.3-fold compared with the original NHAR confirmed number of myocardial infarcts).

Survival at 30 days was worse in the recoded confirmed myocardial infarction group and correspondingly better in the remainder of the cohort.

MONICA and OXMIS classifications

Recoding of the NHAR cases applying MONICA criteria increased the number of patients classified as having a confirmed myocardial infarct by 69% (from 723 to 1051), and by a similar amount if the analysis was restricted to patients

Table 2 30 day survival following admission with suspected myocardial infarction by system of classification

Classification system (No. with confirmed MI/No. in group)	Survival (%) for "confirmed MI" (No. of events)	Survival (%) for the remainder of the cohort	Unadjusted hazard ratio for "confirmed MI" v remainder (95% CI)	Adjusted hazard ratio* for "confirmed MI" v remainder (95% CI)
<i>NHAR original classification</i>				
All: n=723/2739	77% (167)	91%	2.77* (2.24 to 3.41)	12.0* (9.0 to 16.0)
Under 65 (289/991)	87% (37)	97%	3.95* (2.36 to 6.61)	
Under 76 (547/1959)	82% (98)	93%	2.87* (2.13 to 3.75)	
Under 80 (628/2250)	78% (135)	93%	3.28* (2.56 to 4.20)	
<i>NHAR amended classifications</i>				
Extended ECG and single cardiac enzyme (1224/2739)	85% (184)	89%	1.40* (1.13 to 1.72)	3.73* (2.86 to 4.86)
All likely "acute coronary syndromes" (1825/2739)	89% (199)	83%	0.62* (0.50 to 0.76)	0.86 (0.77 to 1.25)
<i>MONICA classification</i>				
All: n=1051/2739	84% (171)	89%	1.57* (1.28 to 1.94)	6.84* (5.10 to 9.20)
Under 65: n=404/991	91% (38)	96%	2.47* (1.48 to 4.16)	
Under 80: n=904/2250 (OXMIS)	85% (135)	91%	1.80* (1.40 to 2.30)	
<i>UKHAS classification</i>				
All: n=807/2739	86% (117)	89%	1.20 (0.91 to 1.49)	4.54* (3.10 to 6.64)
Under 76: n=621/1959	88% (72)	95%	1.27 (0.95 to 1.70)	

Hazard ratio and 95% confidence interval: adjusted for age, sex, past history of myocardial infarction, Killip score on admission, receiving a diuretic on discharge, abnormal ECG, or cardiac enzymes during admission.

* $p < 0.01$.

Total number of events for all ages, n=357.

CI, confidence interval; MI, myocardial infarction; MONICA, monitoring trends and determinants in cardiovascular disease study; NHAR, Nottingham heart attack register; OXMIS, Oxford myocardial infarction study; UKHAS, United Kingdom heart attack study.

Table 3 Comparison between epidemiological and clinical classifications

Clinical classification	Confirmed MI by classification system			
	Original NHAR (N=723)	Amended NHAR (N=1224)	MONICA (N=1051)	UKHAS (N=807)
STEMI (n=583)	583	583	583	465
NSTEMI (n=344)	123	344	290	305
UA (n=153)	0	0	0	0
Classical angina (n=726)	0	137	102	0
Other presentations (n=931)	18	160	76	37

Number of cases common to both classifications shown.

MI, myocardial infarction; MONICA, monitoring trends and determinants in cardiovascular disease study; NHAR, Nottingham heart attack register; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST elevation myocardial infarction; UA, unstable angina; UKHAS, United Kingdom heart attack study.

Table 4 Differences between classification systems in 30 day survival following a confirmed myocardial infarct

Age range (years)	Survival (95% CI) by classification system†				
	NHAR	NHAR extended	MONICA	UKHAS	OXMIS
<65 (n=941)	87% (83 to 91)	–	91% (88 to 96)	–	–
<76 (n=1959)	82% (79 to 85)	–	–	*88% (85 to 91)	–
<80 (n=2250)	78% (75 to 81)	–	–	–	*84% (82 to 87)
All (n=2753)	77% (74 to 80)	*85% (83 to 87)	–	–	–

*Significant differences in survival between NHAR and alternative classification systems.

†Comparisons only reported for the age ranges used in major publications.

CI, confidence interval; NHAR, Nottingham heart attack register; MONICA, monitoring trends and determinants in cardiovascular disease study; OXMIS, Oxford myocardial infarction study; UKHAS, United Kingdom heart attack study.

under 65 (as in the original MONICA study) or under 80 (OXMIS).

UKHAS

The number of patients coded as having confirmed myocardial infarction increased by 12% (from 723 to 807). Patients under 76 (the UKHAS study age group) showed the same patterns of 30 day and four year survival as the original NHAR and the MONICA coded groupings (table 2).

Clinical classification

These results are shown in table 3. The numbers of patients classified as ST elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI) were 583 and 344, respectively. This gave a total of 927 cases with a clinically defined myocardial infarct, an increase of 28% on the

originally defined NHAR confirmed number. The 30 day survival from admission of patients with STEMI and NSTEMI was 75% and 94%, respectively; the difference between these two groups remained highly significant following adjustment (hazard ratio 3.1, 95% confidence interval 1.9 to 4.9). Patients classified as STEMI were almost all identified by the epidemiological classifications of confirmed myocardial infarction, but there was less agreement for NSTEMI.

Differences in survival of confirmed myocardial infarction cases identified by different coding schemes

The unadjusted 30 day survival in confirmed cases was significantly different between the different classification systems (table 4). This effect was less evident under the age of 65, but this may have reflected smaller numbers and wider confidence intervals. There were no corresponding significant

Table 5 Distribution of major prognostic variables in patients by classification system of confirmed myocardial infarction

Prognostic variables	Frequency of prognostic variable by classification system for confirmed MI (%)			
	Original NHAR group (n=723)	Amended NHAR group (n=1224)	MONICA (n=1051)	UKHAS (n=807)
Median age (years)	67	68	68	67
Past history of MI	19.9*	24.5*	24.3*	22.2
Heart failure on presentation	10.7*	10.3*	9.8	8.3*
Male sex	61.0*	62.3*	62.4*	65.7*
Abnormal ECG	98.6*	95.3*	96.6*	95.5*
Abnormal cardiac enzymes	89.6*	83.6*	91.8*	100*
Diuretic use at discharge	26.1*	31.5*	29.9*	28.0*
Aspirin use at discharge	65.0*	65.2*	67.9	69.8*
β Blocker use at discharge	30.8*	31.9	33.1	34.7*

*p < 0.05 between frequency of variable in that classification and frequency in at least one alternative classification.

CI, confidence interval; NHAR, Nottingham heart attack register; MI, myocardial infarction; MONICA, monitoring trends and determinants in cardiovascular disease study; OXMIS, Oxford myocardial infarction study; UKHAS, United Kingdom heart attack study.

differences in postdischarge four year survival. The κ statistics for comparison between the MONICA and amended NHAR and between the UKHAS and NHAR systems were 0.78 and 0.68, respectively, indicating "substantial" or "very high" levels of agreement in both comparisons.

Distribution of major prognostic variables between epidemiological classification systems

The distribution of available major prognostic variables in confirmed cases of myocardial infarction between the different classification systems was significantly different (table 5). Although median age was similar between classification systems, there were differences in the frequency of other important prognostic variables.

DISCUSSION

Clinical outcomes of 30 day mortality following myocardial infarction are now being used as measures of hospital performance. The potential for variations in 30 day survival shown here, which are simply due to the way confirmed myocardial infarction cases are defined, reinforces the need for a consistent and robust national classification system before league tables using this outcome should be compared. Other audit activity that relies on establishing a denominator of confirmed cases of myocardial infarction—such as the current Royal College of Physicians myocardial infarction audit work including examination of thrombolysis times, or standards for cardiac rehabilitation after myocardial infarction—may be subject to similar variation unless case definitions are clear and unambiguous. Adjusting for significantly different distributions of prognostic variables appears to be necessary if different classification systems are used. However, this is difficult and reinforces the need for robust and agreed case definitions.

Epidemiological and familiar pragmatic clinical definitions of ST elevation myocardial infarction, non-ST elevation myocardial infarction, and angina may not include or identify the same patients (table 3), particularly for less "typical" presentations. For instance, of the 344 patients defined as having non-ST elevation myocardial infarction in this cohort, many were not identified as confirmed cases of infarction by the rigorously defined original NHAR classification (35%), with greater proportions being identified using MONICA (84%) or UKHAS (89%).

The method used to define myocardial infarction has significant implications for epidemiological monitoring, for those whose work requires a commercial driving licence, and for insurance purposes. Clinically, inappropriate underdiagnosis may deny some patients access to monitoring and interventions of proven benefit. Uncertainty of diagnosis may also be associated with additional psychological morbidity.¹⁴ Numbers of patients defined as confirmed myocardial infarction and survival at 30 days varied considerably, and this study suggests that for these variables rigour in case definition is necessary. Postdischarge four year survival patterns were similar whichever system was used.

The case definition of acute coronary syndrome focused on the identification of patients with "typical" chest pain.⁶ However, NHAR data suggest that significant numbers of suspected cases of myocardial infarction might be excluded because symptoms were "atypical". Across all classification systems, patients with more atypical presentations not only showed greater variability in the classification accorded to them, but those not classified as "confirmed acute myocardial infarcts" had similar postdischarge mortality to confirmed cases.¹¹

The NHAR eligibility criteria might be considered overinclusive, but if that were the case, the finding of a high postdischarge mortality in unconfirmed cases of myocardial infarction is even more unexpected and a cause for concern. However, all the patients in this study had abnormal ECGs or

cardiac enzymes during the index admission, and have been shown to have predominantly cardiovascular causes of death.⁷ It is therefore likely that as a cohort they were generally suffering from coronary heart disease, an observation made in other settings.⁴

The recoding of NHAR data was at best an approximation. The method we adopted to identify patients with acute coronary syndrome was deliberately overinclusive, and troponin measurements were not available to refine the selection. It was unlikely that patients misclassified as "acute coronary syndrome" would have had systematically higher mortality, so the finding that the remaining patients with "suspected myocardial infarction" not in the acute coronary syndrome group had comparable mortality is significant. If the use of troponin measurements in such patients were patchy in clinical practice, risk stratification relying on this measure may miss some with a high subsequent mortality.

The NHAR recoding system identified a group with at least as bad a prognosis when compared with the direct measurement of patients with acute coronary syndromes in other populations, and this appeared to be valid. Postdischarge survival of patients recoded as acute coronary syndrome in this study was 87%, 83%, 78%, and 69% at 6, 12, 24, and 48 months, respectively. In other studies of postdischarge survival in patients with acute coronary syndrome, survival has been reported to be 85% at six months,¹⁵ 89% at 12 months,¹⁶ and 74% at 60 months.¹⁷

Although different diagnostic criteria generated different numbers of infarct events, there was much similarity in survival outcome following hospital discharge over a four year period. The recent Joint European Society of Cardiology redefinition of myocardial infarction (2000), based on the use of troponins as markers of myocardial infarction, may improve both diagnostic precision and risk stratification.¹⁸ Our study suggests that this is very important if short term outcomes that compare performance in different settings are to be credible. It remains to be seen what impact these may have on the numbers of patients diagnosed as having sustained a myocardial infarct, and the characteristics of excluded patients, and some doubts remain.¹⁹ Further work is under way to describe in more detail the patients with non-confirmed myocardial infarction in recent cohorts.

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Authors' affiliations

C Packham, University Division of Public Health Sciences, Queens Medical Centre, Nottingham, UK

D Gray, A Large, J Hampton, University Division of Cardiovascular Medicine, Queens Medical Centre

P Silcocks, Trent Institute of Health Services Research, Queens Medical Centre

C Weston, Department of Medicine, Singleton Hospital, Swansea, UK

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IMAGES IN CARDIOLOGY.....

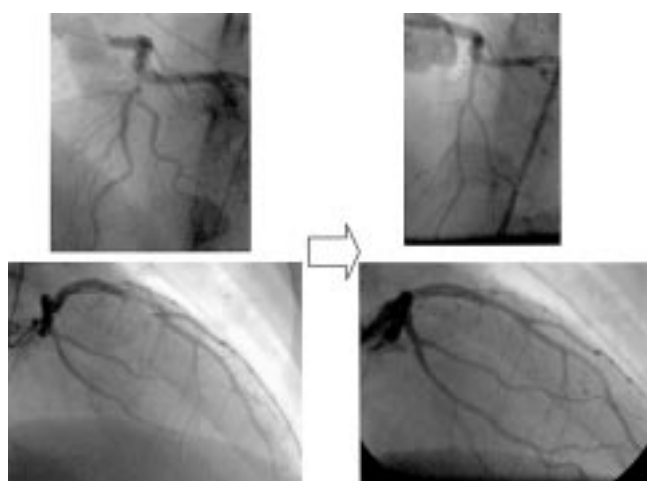
Coronary thrombus in a 23 year old anabolic steroid user

A 23 year old male body builder presented with a recent onset of central chest pain. He was a smoker with cholesterol concentration of 7.1 mmol/l on admission. He had been taking anabolic steroids (methandrostenolone 20 mg daily) for three months. Anteroseptal T wave inversion on a 12 lead ECG along with elevated troponin T prompted early coronary angiography. This revealed multiple filling defects in the mid left anterior descending (LAD) artery consistent with the presence of thrombus (below left). His LAD filled by collaterals from the right coronary artery. The rest of his coronary arteries were smooth and unobstructed. Repeat angiography was performed 48 hours later after treatment with abciximab, aspirin, and low molecular weight heparin and revealed complete dissolution of all thrombus. Intravascular ultrasound (IVUS) examination performed at this time revealed a segment of eccentric atheroma at the site of the previous filling defects (below right); the echogenicity was uniform with no focal echo lucent regions. The remainder of the LAD was normal at IVUS examination. The patient made an uneventful recovery and was discharged well to follow up.

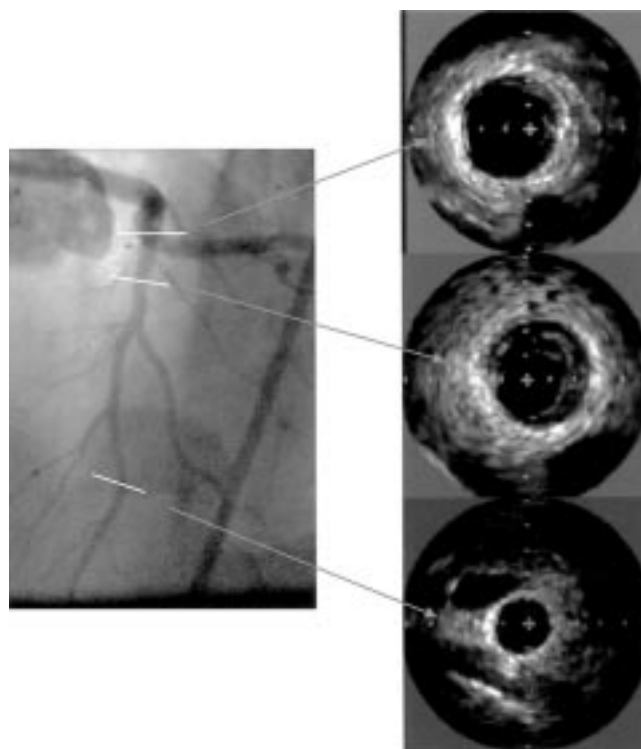
There have been several case reports of acute myocardial infarction in young male athletes using anabolic steroids. The mechanism is unclear but may involve the adverse effects on thrombosis and lipid profile. Some reports suggest thrombosis in "normal" coronary arteries, but underlying atheroma cannot be excluded without IVUS. This case supports the concept that both atheroma and the thrombogenic effects of anabolic steroids may be necessary for vessel occlusion.

J Ment
P F Ludman

p.f.ludman@bham.ac.uk



Top and bottom left: left anterior oblique and right anterior oblique views of left coronary artery with filling defect. Top and bottom right: same views after 48 hours of antithrombotic treatment (heparin, aspirin, and abciximab).



Intravascular ultrasound images at designated sites of the left anterior descending artery after 48 hours of antithrombotic treatment