VARIABILITY OF ANGINA SOME IMPLICATIONS FOR EPIDEMIOLOGY

BY

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In laboratory studies it is generally accepted that the significance of a particular measurement can only be understood in the light of proper numerical estimates of its variability; but in clinical studies the need for such information is less widely appreciated. This is particularly unfortunate since such inquiries as have been made have shown that the variability of clinical measures is generally far greater than has been supposed.

This study deals with angina as assessed by a standard questionnaire. Very similar considerations apply to any qualitative attribute of disease whose presence or absence may be assessed differently on different occasions.

MATERIAL AND METHODS

In 1961 Dr Charles Fletcher initiated a follow-up study of bronchitis in an industrial population in London, and generously agreed to a cardiovascular extension of the examinations. The initial study population comprised 1,136 men aged 35 to 59 years, of whom 800 were engineers and the rest clerks. Subsequent attrition has averaged about 5 per cent. per year.

The assessment of angina was based on defined criteria embodied in a standard interviewer-administered questionnaire; the method has been validated and widely used (Rose, 1962, 1965). Tape-recordings of interviews showed only very slight observer variation in the administration of questions and the coding of answers. Analysis is based on the results of interviews in each of four summers: 1961, 1962, 1964, and 1965. (Unfortunately interviews had to be omitted in 1963 through lack of available examination time.)

RESULTS

At the initial examination 43 men were assessed by the questionnaire as "angina-positive", a prevalence of 3.8 per cent. In each subsequent year about 40 per cent. of these individuals were positive

again, this figure showing little change over the whole of the follow-up period (Table I).

TABLE I
PROBABILITY OF PERSISTENCE OF "ANGINA" IN
SUBSEQUENT YEARS IN MEN POSITIVE IN 1961
(*n* = 43)

Year of Examination	No. Positive as Percentage of those originally Positive and still in Study
1961	100
1962	39
1964	45
1965	46

The probability in each year of a man becoming positive for the first time is shown in Table II. The value does not decline except between the first and second examinations. In each year the total "angina-positive" group is composed of those former members who remain positive, together with the new recruits. Over the period of the study the size of the group showed little proportionate change, apart from a small tendency to increase, possibly because of ageing of the population.

TABLE II
PROBABILITY OF BEING CLASSED "ANGINA-POSITIVE"
FOR THE FIRST TIME IN EACH SUCCESSIVE YEAR

Year	No. of Men in Study and not previously "Angina-positive"	Percentage becoming Positive for First Time
1961	1,136	3.8
1962	946	2.5
1964	837	2.9
1965	758	3.6

Of the 818 men who remained in the study up to 1965, 77 had been assessed as "angina-positive" at one or more of the four examinations. Table III (opposite) shows the frequency of positive diagnoses in these men. Clearly persistence of "angina"

throughout the period is very exceptional, the large majority of positive classifications being confined to a single occasion.

TABLE III
NUMBER OF "ANGINA-POSITIVE" CLASSIFICATIONS
OF THE 1965 EXAMINEES

No. of Times "Angina-positive"	No. of Men
0	741
1	$\left. \begin{array}{c} 53 \\ 12 \\ 7 \\ 5 \end{array} \right\} 77$
2	
3	
4	
Total	818

Such a situation might result either from frequent true changes in disease status, or from a misleading variability in subjects' answers to the questionnaire, or from a combination of both these factors. The true explanation has little direct bearing on the particular implications that are to be considered here: all the same it is of much general interest. Unfortunately there is no objective direct measure of the accuracy of a diagnosis of "angina", but association with ECG changes may be used as an index by which to compare different symptomatic groups. 12-lead resting electrocardiograms were recorded on these men in 1961 and 1963. Subjects have been arbitrarily assessed as "ECG-positive" if they showed any codable Q/QS item, S-T depression, or T-wave flattening or inversion, using Minnesota Code criteria (Blackburn, Keys, Simonson, Rautaharju, and Punsar, 1960). The association between the assessments by questionnaire and by ECGs is set out in Table IV. Clearly the persistence of angina is strongly related to the probability of these ischaemic-type changes in the ECG, and to the probability of their persistence. In individuals, however, there was no obvious coincidence in time between the appearance of symptoms and of ECG changes: the two manifestations appeared to come and go independently of one another.

TABLE IV
ASSOCIATION BETWEEN ECG FINDINGS AND
PERSISTENCE OF "ANGINA" IN THE 1965 EXAMINEES
($n=818$)

No. of Times "Angina-positive"	No. of Men	Percentage "ECG-positive"	
		Either 1961 or 1963	Both 1961 and 1963
0	741	19	5
1-2	65	34	13
3-4	12	92	42

DISCUSSION

The observed variability in the natural history of angina carries some important implications for epidemiological studies of ischaemic heart disease, whether of prevalence or of incidence. These, however, are no more than particular examples of problems that must be faced in any study of a chronic disease, the assessment of whose attributes is subject to variation.

(1) POINT-PREVALENCE ESTIMATES MAY BE MISLEADING

It has been seen (Table III) that, of the total number of men judged "angina-positive" at some time within the follow-up period, only a minority were likely to be positive at any particular instant. The greater the number of examinations in a follow-up study, and the longer the period over which they are spread, the more completely will the total number of affected persons be ascertained. The extent of this effect can be seen in Table V, which shows for the present study the rise in estimates of angina prevalence for the same cohort of men as the number of examinations is increased. The prevalence estimate for the 4-year period is more than three times the initial point-prevalence estimate, and would presumably have been higher still if the 1963 interviews had not been omitted. In general it may be said that *point-prevalence rates underestimate true prevalence to an extent that is proportional to the variability of the characteristic.*

TABLE V
ESTIMATES OF POINT- AND PERIOD-PREVALENCE
OF "ANGINA", BASED RESPECTIVELY ON 1, 2, 3,
AND 4 EXAMINATIONS

Period	Total No. of Examinations	Total Prevalence per cent. of "Angina" for the Period
1961	1	3.8
1961-62	2	5.9
1961-64	3	8.0
1961-65	4	10.4

(2) DEFINITIONS OF "INCIDENCE" TEND TO BE ARBITRARY

In estimating incidence, "a new case" (for example of angina or infarction) would generally be taken to be one occurring in a person not previously known to be affected. Unfortunately the concept is complicated by variability of the manifestation:

- (a) The greater the variability, the greater the risk that a supposedly "new case" may

merely represent the re-appearance of disease in someone who temporarily appeared negative at the initial examination. Because of this tendency to mistake recurrence of old disease for a new case, *incidence estimates tend to be exaggerated to an extent proportional to the variability of the manifestation.*

- (b) Consider two incidence studies, in one of which the investigator excludes "old cases" on the basis of a single examination, whereas in the other the investigator has access to information from a number of previous medical examinations. Clearly, the second investigator will tend to exclude more "old cases", and consequently to reach a lower incidence estimate based on the subsequent appearances of "new cases". Thus, *incidence estimates tend to be reduced in proportion to the number of initial examinations at which "old cases" are excluded.*
- (c) Conversely, frequent follow-up examinations enhance the probability of recognizing new instances of an inconstant manifestation, as compared with studies in which examinations are undertaken only, for example, at the start and end of the follow-up period. Thus, *more frequent follow-up examinations tend to produce higher estimates of incidence.*

The study reported here was based on four examinations (covering a 4-year period, but with one annual examination omitted). In calculating incidence there is a choice between using the first 1, 2, or 3 of these to exclude "old cases", leaving 3, 2, or 1 for ascertaining "new cases". Depending on this arbitrary decision, the estimate of excluded cases of "old angina" would in fact range from 43 to 91, with a corresponding range of "new cases" contributing to "incidence". These figures yield estimates of incidence ranging from 1.0 to 3.6 per cent. per year.

These problems indicate the need for caution in comparing different incidence studies unless the nature and frequency of examinations is standardized; and incidence estimates clearly cannot be interpreted unless the variability of the manifestation is known. In fact, if variability is large, incidence may cease altogether to be a useful measure.

(3) INFARCTION AND SUDDEN DEATH IN PREVIOUSLY "FIT" PERSONS MAY BE LESS FREQUENT THAN HAS BEEN SUPPOSED

A syndrome of angina may be reported at one examination, yet all memory of it is often denied on a later occasion. Similarly an ECG abnormality is commonly evanescent.

In the present study there were 49 "clinical coronary events" during the follow-up period, 26 of them fatal. The records showed that no fewer than 59 per cent. of these events had been preceded by a positive response to the questionnaire ("angina" or "possible infarction"), and 80 per cent. by either a positive questionnaire or a positive ECG (Q/QS, S-T, or T item), or both. Relatively few of these earlier manifestations would have been recognized apart from the survey examinations, and the physician in charge would then have concluded that a major illness had occurred without prior warning.

After 4 years of annual examinations, a total of 40 per cent. of men had on one or more occasions been classed as positive to questionnaire, ECG, or both. This figure approaches the proportion of men who at this age might be expected to have major pathological changes in their coronary arteries. Many of the symptoms and ECG changes may be false positives; yet equally it is possible that major changes in the coronary arteries are rarely "silent".

(4) REPEATED EXAMINATIONS PERMIT A USEFUL CLASSIFICATION OF DISEASE SEVERITY ACCORDING TO ITS PERSISTENCE

When subjects are classified as "healthy" or "affected" by a single examination, the supposedly healthy group tends to be contaminated by persons in whom disease manifestations are only temporarily unrecognizable. This contamination may obscure an association with some aetiological factor. But the use of repeated examinations permits a semi-quantitative classification, according to the number of positive and negative assessments. Important associations may then be more clearly shown. This was seen, for example, for the association between angina and ECG changes (Table III).

Measures of the persistence of disease may provide a means of characterizing groups as well as individuals. In the present study there were two groups: clerks and engineers. Among persons affected by "angina", the symptom tended to be more persistent in the engineers than in the clerks: thus, 19 per cent. of all "angina-positive" engineers were classed as positive on more than two occasions, as compared with 0 per cent. of "angina-positive"

clerks. By the criterion of "persistence" it seems, therefore, that the engineers were the more severely-affected group. This fits in with other measures of disease severity in the same groups: among engineers and clerks the respective initial prevalence rates for "angina" were 4.2 and 2.8 per cent. and the 5-year coronary mortality rates were 3.0 and 0.6 per cent.

SUMMARY

The presence or absence of "angina" has been assessed by standard criteria and questionnaire on four occasions, between 1961 and 1965, in an industrial sample comprising initially 1,136 men aged 35 to 59. Point-prevalence in the sample remained relatively constant at around 4 per cent., but there was a great deal of flux among the "angina-positive" group: the large majority were positive on only a single occasion. The 4-year period-prevalence was 10.4 per cent.

The results contain various implications of general importance in chronic disease studies:

- (1) Point-prevalence may grossly underestimate the total burden of disease.
- (2) In relation to a variable attribute of disease, definitions of incidence tend to be arbitrary because of difficulties in defining what is meant by "old" and "new" cases. The present results may yield estimates ranging from 1.0 to 3.6 per cent. per year.
- (3) Evidence is produced of the value of repeated examinations in permitting a semi-quantitative grading of subjects, based on the number of times that each has been classified as positive.

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