Prevention of Coronary disease in the presence of other chronic disease: Blood Pressure monitoring.

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Summary. People at increased risk of coronary disease are often advised to monitor their health by regularly undergoing health check-ups in which various parameters including, and perhaps most importantly, blood pressure is measured. However, a person's mean blood pressure is very difficult to estimate both from a statistical and practical point of view and the interpretation of the results can leave the patient confused. This presentation describes some of these problems, and indicates how a time series of blood pressure measurements can be interpreted graphically and how the CUSUM can be used to reveal changes that may not be evident from a simple graph of the time series. However, blood pressure is only one of the factors that may be monitored in order to prevent coronary heart disease. If other measures are available from a comprehensive health check up a quantitative risk score can be evaluated. On the basis of this risk score, a decision has to made about whether treatment, for example with anti-hypertensive drugs should be started. This decision may be made easier by the consideration of the number of persons it is necessary to treat (NNT) in order to save one life. The techniques are illustrated using real data which relate to the author.

Time series analysis.

Observations made on an individual during an interval of time require special statistical techniques for their analysis and the collection of these techniques is generally known as “Time series analysis”. The reason why these special techniques are necessary is that almost all standard methods of statistical analysis assume that the observations are independent. In the case of observations collected serially in time there is almost certainly dependence between the successive values. For example, a particularly high value may tend to be followed by another high value; or indeed a high value may tend to be followed by a low value; there may be cycles in the time series, for example blood pressures measured at night may tend to be lower than those measured during the day; there may be weekly cycles, with perhaps lower values being observed at the weekends and so on. A graph of the time series and the CUSUM (cumulative sum) are simple techniques for the analysis of a time series. These methods were originally developed for use in the manufacturing industries for quality control. For example, suppose a machine is set to produce a component of a fixed length, say 5cm. Initially, the machine is set correctly, and every so often a sample of the components is taken and measured in order to determine if the machine is still producing components of mean length 5 cm. At some point, the mean may differ from 5cm in which case it may be necessary to stop the machine and make an adjustment to the settings. The length of the component will not always be exactly equal to 5cm even if the machine is set correctly, and the length may vary around a mean of 5 cm, and thus it may not be obvious whether the machine needs adjustment

or not. The same sort of problem also arises in clinical medicine and epidemiological monitoring. For example monitoring the number of new cases of a disease may be useful for identifying the start or progress of an epidemic; the daily number of road vehicle accidents may be monitored to discover weekly cycles, or to decide whether a preventive intervention is necessary. The author has monitored his blood pressure on and off for a period of more than eight years.

John Osborn's blood pressure.

The author has made a total of four complete health check-ups between 1997, when he was 54 years old and 2004. He has no clinical signs or symptoms of coronary heart disease. The median (of five observations) blood pressures obtained in the four visits are shown in table 1. Without applying any statistical techniques, (apart form the "eye ball" method, that is, just looking at the results), there is no evidence to suggest that the blood pressures are increasing or decreasing during the seven year interval. Even though the values are medians of five observations, and thus more precise than a single reading of the pressure, it is not obvious exactly what these values represent. They do not estimate the mean pressure during the year in which the measurements were taken nor even the mean value on the day; in any case, the daily mean pressures vary considerably even in a short period of time.

Traditionally, the values of blood pressure considered normal are systolic: 90 – 140 mmHg; diastolic 60 – 90 mmHg and a weighted average of these two known as the "mean arterial pressure" 70 – 100 mmHg. According to the results in table 1, John Osborn has never been "abnormal" and in particular, if a case of hypertension is

defined to be a person with systolic pressure greater 140 mmHg or diastolic pressure greater than 90 mmHg (or both), John Osborn has never been *a case* of hypertension. On the other hand, his pressures have always been "high normal" , particularly that of 2004, 138/85 mmHg; John Osborn is hypertensive but is not a case of hypertension!

During the last thirty years or so, doubts have expressed about the precision of traditional methods to measure blood pressure. In particular, "white coat" hypertension has been recognised; some patients, who in the clinical environment appear to have hypertension, really have normal levels when the pressure is measured outside the medical environment. For this reason, and maybe other reasons, nowadays the pressures may be measured frequently (every 15 or 30 minutes) for a period of about 24 hours using a small electronic machine which is carried by the patient. This is known as ambulatory blood pressure monitoring (ABPM) and has identified daily cycles in the pressures. Blood pressures tend to be higher during the day and lower at night.

Patients found to have this reduction in pressure at are known as "dippers". The magnitude of the "dip" may have prognostic implications; a dip of 10% - 20% is considered normal; patients with less dip are known as "non dippers" and may have an increase in the risk of cardiovascular disease, whereas a dip between 20% and 30% may imply for these "super dippers" neurological consequences.

The "Blood Pressure Load", BPL, is a summary measure for the 24 hours and is the proportion of blood pressure values which exceed the limits 140/90 during the day

and 120/80 during the night. The BPL may be useful for the diagnosis of hypertension.

Given that John Osborn had been found to be hypertensive during a period of seven years, even though the blood pressure has not reached the conventional threshold for the definition of a case of hypertension, it was decided that his pressure should be monitored for a period of 24 hours. The summary results of this monitoring are shown in table 2. A graph of the results for the systolic blood pressure is shown in figure 1 this clearly shows the peaks and troughs which occurred during the period and these can be usefully correlated with activities performed during the day. In particular there are high peaks which coincide with his driving a car in the city of Rome. There is a dip during the night, but this is partially obscured by the big fluctuations.

The CUSUM is a technique which is particularly useful for identifying changes in the mean level of a response, y, for example blood pressure, in a time series. To calculate the CUSUM, it is necessary to specify a target value for the response; in the case that y is systolic blood pressure, a target value could be 140 mmHg. The CUSUM at time t is the sum of the differences between y and the target value, 140. That is CUSUM at time $t = \sum(y_i - 140)$ for all values of i from time zero to time t. The graph of the CUSUM against t will have positive slope when the systolic pressure is more than 140 mmHg; it will be horizontal when the pressure is 140 mmHg and negative when it is less than 140 mmHg. Rapid fluctuations in the pressure will not be evident in the graph of the CUSUM. In figure 2 it can be seen that the graph of the CUSUM of the

systolic blood pressures generally has negative slope, that is the systolic pressure is less than 140 mmHg; the slope is positive only between 11.00 and 12.00, from 14.30 to15.30 and between 19.30 and 21.00 when the systolic pressure is more than 140 mmHg. Angles in the CUSUM graph indicate the times when the mean systolic blood pressure changes.

As a result of this monitoring, the blood pressure was judged to be “high normal” and it was suggested that it might be useful to start taking an anti-hypertensive drug with the aim of reducing the pressure by about 10 mmHg. If this suggestion were followed, what would be the likely advantage in terms of health, and in particular, survival? There have been several attempts to estimate the risk of fatal cardiovascular disease according to the presence and level of coronary risk factors. One such study (1) refers specifically to European populations and enables the 10 year risk of fatal cardiovascular disease to be estimated taking account of:

1. Country of residence “low risk” or “high risk”
2. Gender
3. Smoking
4. Systolic blood pressure
5. Age
6. Total cholesterol.

For John Osborn, assuming the value of systolic blood pressure is about 140 mmHg and this should be reduced to 130 mmHg, the reduction in the estimated 10 year risk would be from 3% to about 2.5%. That is, if 200 men like John Osborn were to

follow the suggestion to reduce their systolic blood pressure by 10 mmHg, 5 men would die in a 10 year period instead of 6. This number, 200, is known as the NNT, the number of patients that it is necessary to treat in order to save one life. It can be calculated as the reciprocal of the difference between the two risks; in this example, the risks are 3% and 2.5%, or 0.03 and 0.025 and the difference between them is 0.005. The reciprocal of 0.005 is 200, implying that it would be necessary to treat 200 men for ten years in order to save one life – a total of 2000 person-years of pharmacological treatment!

Reference

1. Conroy RM, Pyorala K, Fitzgerald AP et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. European Heart Journal 2003; 24:987-1003.

Table 1. Blood pressures (median of five measurements) recorded in medical check-ups, 1997 – 2004.

Year	1997	1999	2001	2004
Age (years)	54	56	58	61
Blood pressure mmHg				
Systolic/diastolic	135/85	128/81	130/83	138/85

Table 2 Summary of the results of ABPM: Total time 22 hours 44 minutes. Total number of measurements 85

All observations	minimum	mean	maximum	standard deviation
Systolic mmHg	109	132	159	10.86
Diastolic mmHg	60	85	101	8.23
MAP mmHg	76	102	124	9.74
Heart rate /minute	53	66	95	6.39

23.5% of the systolic values >140 mmHg
35.3% of the diastolic values >90 mmHg

Time 08.00 to 01.00	minimum	mean	maximum	standard deviation
Systolic mmHg	109	136	159	10.27
Diastolic mmHg	74	89	101	5.73
MAP mmHg	88	106	124	7.76
Heart rate /minute	53	66	95	6.94

31.7% of the systolic values >140 mmHg
46.0% of the diastolic values >90 mmHg

Time 01.00 to 08.00	minimum	mean	maximum	standard deviation
Systolic mmHg	110	124	132	5.99
Diastolic mmHg	60	78	93	8.09
MAP mmHg	76	93	106	7.40
Heart rate /minute	56	64	72	4.15

0.0% of the systolic values >140 mmHg
4.5% of the diastolic values >90 mmHg

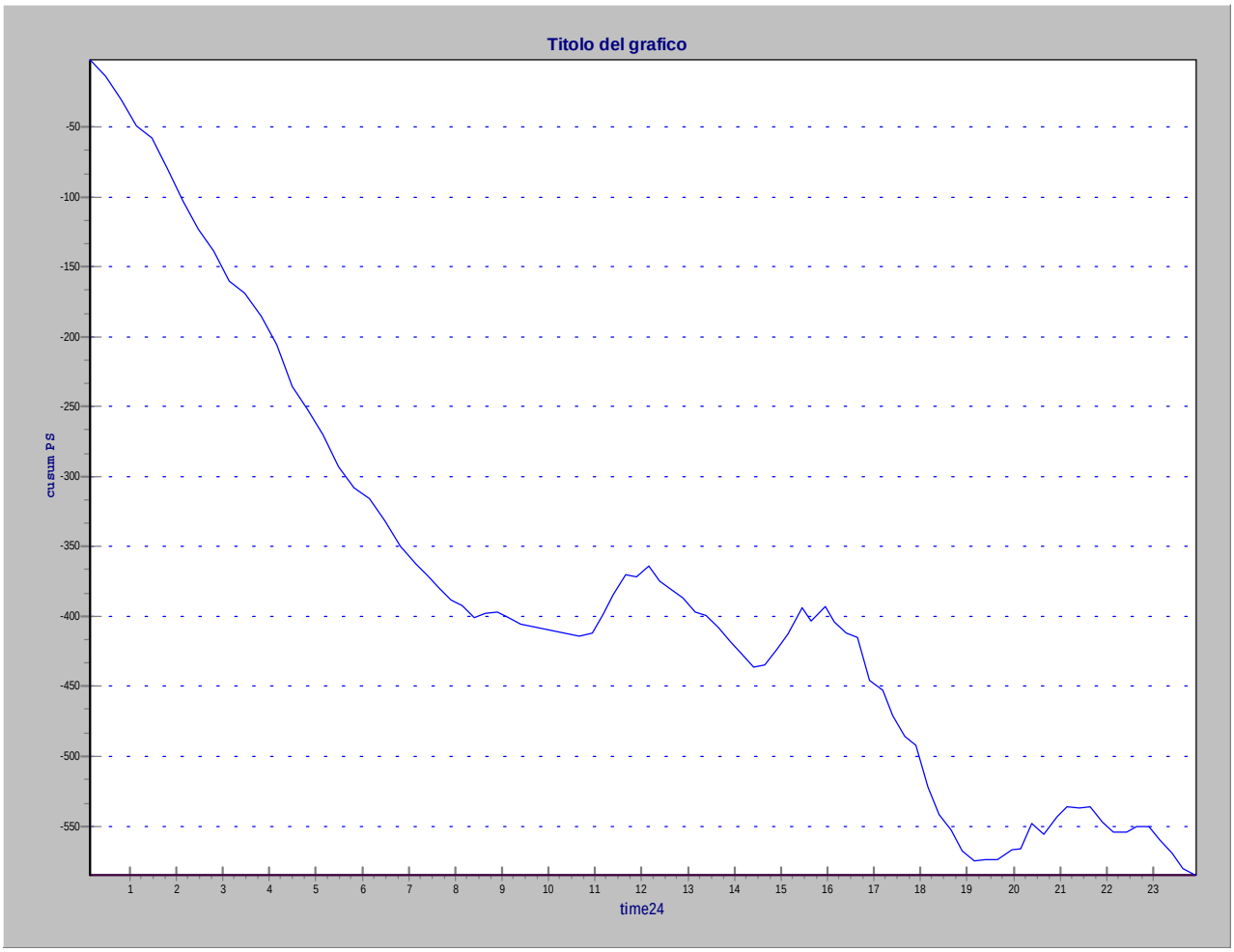

Figure 2. CUSUM of systolic blood pressure relative to a target value 140 mmHg.