Terminal digit preference and single-number preference in the Syst-Eur trial: influence of quality control

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Background Terminal digit and single-number preference may produce inaccuracy and biased results when measuring blood pressure. We describe these preferences in the Syst-Eur randomized placebo-controlled trial of the treatment of isolated systolic hypertension and describe how we sought to eliminate these problems.

Methods The Data Monitoring Committee of the trial conducted yearly quality control meetings in Belgium and visited the participating centres to check their adherence to the protocol. These meetings involved identifying terminal digit preference, improving blood pressure control and boosting recruitment.

Results The prevalence of use of terminal digit zero when measuring sitting systolic blood pressure (first readings) reduced from an average of 42.4% in the year prior to the date when a centre first randomized a patient to 31.5, 25, 22.3, 26.3, 23.2 and 22% in the subsequent 6 years. This trend was independent of the calendar year during which a centre entered the trial and supports the hypothesis that data-quality monitoring, including the feedback of digit preference to centres, led to a reduction in terminal digit zero preference. In addition, a higher than expected prevalence of the systolic blood pressure value of 148 mmHg was found in the active treatment groups in the double-blind phase. Selection for 148 mmHg persisted over time and constituted a single-number preference bias. This arose from the instruction to investigators to reduce systolic blood pressure to below 150 mmHg.

Conclusion Monitoring and feedback of data quality should be undertaken to minimize digit and number preference. Automatic devices should ideally be employed to help to avoid these problems as long as the devices are fully validated and regularly serviced, and providing that readings are not rejected and repeated. *Blood Press Monit* **7**: 169–177 © 2002 Lippincott Williams & Wilkins.

Blood Pressure Monitoring 2002, 7:169–177

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Keywords: blood pressure, digit preference, number preference, bias, education, data quality

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Previous presentations: This work has been published as an abstract in the Journal of Human Hypertension as part of the proceedings of the British Hypertension Society. *J Hum Hypertens* 1998; 12:793–794.

Conflicts of interest: None.

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Received 12 December 2001 Revised 02 April 2002
Accepted 04 April 2002

Introduction

Terminal digit preference is a common source of inaccuracy when taking blood pressure readings and in the case of zero digit preference constitutes an error up to ±5 mm mercury [1]. This error is large in proportion to the accuracy required for the estimation of cardiovascular risk [2] and may be expected to lead to individual patients being misclassified in terms of their risk in clinical practice and inclusion in clinical trials. Single-number preference could presumably lead to bias when reporting the populations with pressures above or below a given end-point.

It was a stated objective of the data monitoring committee in the Syst-Eur trial that terminal digit preference should be identified in all centres and reduced by annually feeding back to investigators charts of their digit preference. We describe the quality control programme in the Syst-Eur trial that was relevant to digit preference. We also report the terminal digit preference in the blood pressure readings over the course of the Syst-Eur investigation and the distribution of blood pressure and single-number preference over time.

Methods

The Syst-Eur trial was a multi-centre international trial involving 198 centres in 23 countries, which randomized

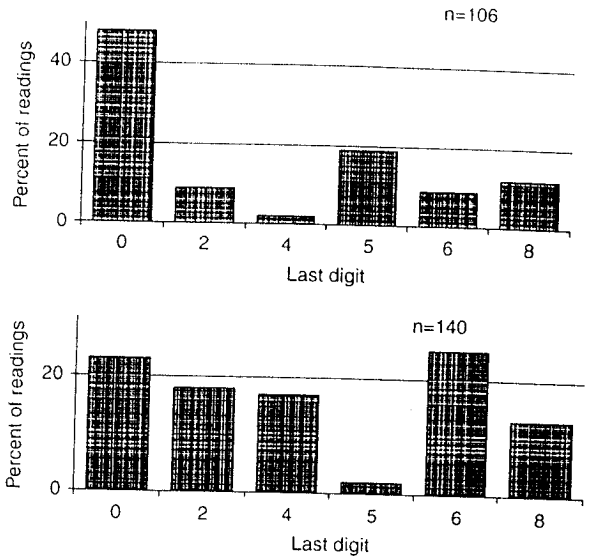
4695 patients from 1989 up to January 1997. The methodology [3] and principal results [4] have already been reported. Hypertensive patients were identified and subjected to three screening visits to their centres where blood pressure and other data were collected (the 'run-in phase'). In a given Syst-Eur assessment, two sets of blood pressure readings (systolic and diastolic phase V), taken in the lying, sitting and standing positions in that order (12 blood pressure readings per visit), were recorded for each patient. Diastolic phase IV blood pressure was recorded when phase V was not measurable; these results are not presented in this paper. To enter the double-blind phase, a patient was required to have a mean sitting systolic blood pressure over the three run-in visits of 160 mmHg or above and a diastolic phase V pressure of less than 95 mmHg. Further data have been collected in an open follow-up phase since the double-blind phase ended. Centres were instructed to measure blood pressure using mercury sphygmomanometers according to guidelines [5] and to record to the nearest 2 mmHg.

Quality control

The Data Monitoring Committee established a detailed protocol of quality control from the start of the Syst-Eur study. This aimed to find missing data that had not been forwarded to the Coordinating Office in Leuven, Belgium, to increase recruitment to the trial and to maximize protocol adhesion and data quality. From 1992, all principal investigators at the centres were invited to an annual meeting in Belgium at which feedback was given on their recruitment rate, blood pressure control and digit preference charts (Fig. 1). Centres not represented at these meetings were sent these charts and correspondence covered any problems. In addition, if digit preference was a major persisting problem, centres were sent a reminder of the trial target of 20% for each of the even terminal digits. Many centres also received a visit to the centre from one or more members of the organizing committees of Syst-Eur. These occurred for large centres, for randomly selected small centres and when there were doubts about data quality. At these visits, semi-structured assessment sheets were used to explore other matters, such as whether consent forms were signed, the supply of and compliance with medication, whether the sealed envelopes determining randomization group were properly handled and whether the follow-up visits were correctly scheduled every 3 months.

One hundred and eighty assessment sheets were identified for analysis, including those from 106 visits to centres and from 74 assessments at the meetings in Belgium. Some visits involved a combined meeting of several centres in a given country, for example Poland, Bulgaria, Israel and Russia. Assessment sheets were available for 114 centres, and quality control checks on the remaining 84 centres did not reveal any major problems. Centres were not usually

Fig. 1



Terminal digit preference charts used to feed back performance to two of the centres in the Syst-Eur trial. The upper figure provides the results for a centre with considerable zero preference and the lower figure those for a centre with little zero preference.

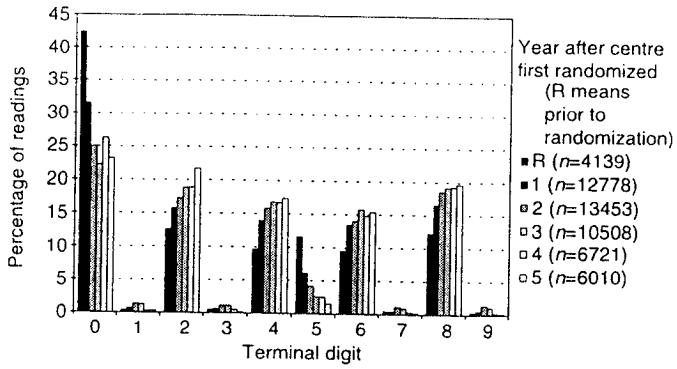
assessed more than twice, but exceptionally up to seven assessments were recorded. The quality control visits to centres took place throughout the trial, although 70% were conducted during the 4 years after the individual centres had first been randomized.

Statistical methods

Blood pressure measurements were pooled across all centres and analysed according to the date that the first patient was randomized in the respective centre. The time difference between a given measurement and that of the centre's first randomization of a patient was rounded to the nearest year (e.g. the first 12 months after randomization were designated year 1). Initially, the first and second readings on one occasion were analysed for both systolic and diastolic pressure and in terms of lying, sitting and standing postures. Thereafter, the analysis was made using the first sitting systolic blood pressure reading unless otherwise stated ($n = 61\,320$). A total of 4174 readings predated the date on which the particular centre first randomized a patient; these represent those patients participating in the run-in phase during the first months of a centre's recruitment. These have been included as year R (Fig. 2).

Chi-square analysis was used to compare the observed terminal digit distributions with those expected (an equal distribution of the even terminal digits). No account was

Fig. 2



Terminal digits of the first sitting systolic blood pressure by time of measurement in years from the first randomization in each centre.

taken of the fact that the readings were repeated measurements on individual patients as, after entry to the trial, the vast majority of patients made four visits per year and thus contributed equally during a given year. Distributions of systolic blood pressure were compared with a distribution based on the normal distribution with the same mean and standard deviation but with data at even numbers only (consistent with the measurement guidelines). Blood pressure readings that were odd numbers were rounded down to the nearest even number. This is an approximation because it is known that systolic pressure is skewed towards higher blood pressure values, although in this trial the distribution of treated blood pressure was near normal (Fig. 3). For the analysis comparing the centres, we considered only the 36 largest, each providing over 500 readings, in order to avoid the high statistical variability associated with small samples.

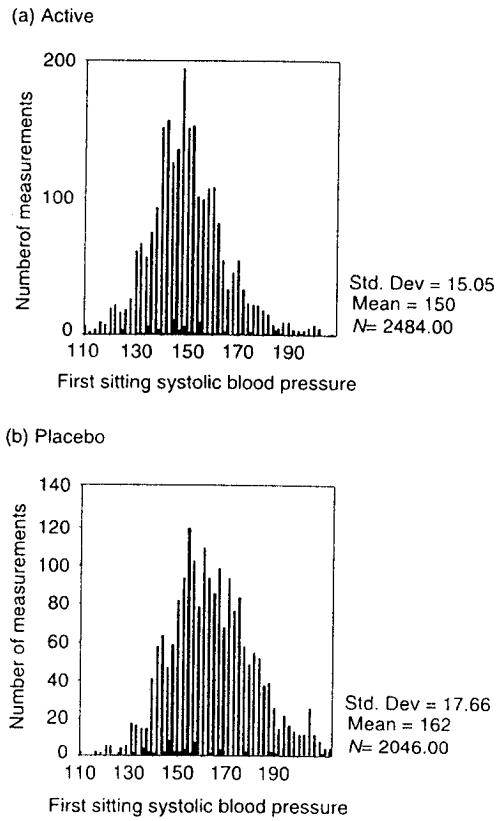
Results

Data were available for analysis from 61 320 patient visits covering the three run-in phase visits ($n = 16\,729$), the double-blind phase ($n = 39\,708$) and the open follow-up ($n = 4883$).

Terminal digit preference of the systolic and diastolic readings at each visit

The percentages of terminal digit zero for the first set (diastolic blood pressure and systolic blood pressure, respectively) were lying, 33 and 30%; sitting, 31 and 27%; and standing, 31 and 28%. For the second set on the same occasion, they were 1–3% lower ($P < 0.001$, chi-square) for lying (30, 27%), sitting (29, 26%) and standing (29, 27%). The proportion of terminal digit zero occurrences was consistently about 3% less for systolic than for diastolic blood pressure ($P = 0.001$, chi-square). Because of these

Fig. 3



First sitting systolic blood pressure in the fifth year following first randomization for (a) active treatment group and (b) placebo group. Note that the most common result for the active treatment mode is 148 mmHg and that the distribution is near normal.

Table 1 **The proportions of terminal digit zero in first sitting systolic blood pressure readings, by calendar year and time in years after the centre first randomized a patient**

Year after randomization		Calendar year									
		1989	1990	1991	1992	1993	1994	1995	1996	1997	Zeros by year after randomisation
	n	478	1362	3952	5451	6964	8880	11838	16346	6008	
R	4174	32.3%	39.6%	42.9%	56.3%	39.3%	41.2%	44.3%	39.5%		42.4%
1	12888	28.6%	34.1%	38.8%	36.5%	44.6%	34.9%	26.4%	23.4%	21.9%	31.5%
2	13650		29.6%	25.8%	28.4%	33.4%	38.4%	21.7%	17.9%	28.1%	25.0%
3	10762			24.0%	23.5%	25.3%	26.1%	27.9%	17.7%	16.8%	22.3%
4	6986				34.0%	28.7%	24.2%	28.9%	25.1%	17.8%	26.3%
5	6253					29.9%	22.0%	23.4%	21.7%	23.1%	23.2%
6	4410						25.0%	23.8%	20.0%	23.4%	22.0%
7	1459							27.2%	23.5%	21.1%	23.9%
Zeros by calendar year		29.7%	34.7%	36.2%	32.6%	31.7%	29.3%	26.6%	20.9%	21.0%	

n, number of readings; R, readings taken before randomization.

differences, all the subsequent analyses presented are based on the first sitting systolic blood pressure reading.

Terminal digit preference in systolic blood pressure readings

In the Syst-Eur trial, 26.9% of the sitting systolic blood pressure readings ended with terminal digit zero. The values for terminal digits 2, 4, 5, 6 and 8 were 17.8, 15.6, 4.1, 14.3 and 18.3%, respectively, and those for other odd terminal digits less than 1%. The proportion of zeros reduced over the course of the trial (Fig. 2 and Table 1), the largest fall occurring between year R and year 1. The use of terminal digit 5 became less prevalent, and that of all the other odd digits remained at a level of 1% or less throughout the study.

Table 1 shows that the initial zero preference was high in all the years up until 1995. In any given calendar year, the zero preference in the centre concerned became lower with time from the first randomization of a patient. The chi-square statistic was calculated for goodness of fit to a uniform even digit distribution and improved over time for each year after randomization. The largest contribution to this statistic in the years R, 1, 2, 3, 4 was for digit zero (over-represented) and in the years 5, 6 and 7 for digit 6 (under-represented).

Terminal digit zero preference in systolic blood pressure, first reading: differences between Syst-Eur centres

Centres varied considerably in their zero preference behaviour over time, most improving, some dropping below the 20% zero target and others behaving erratically. Many, however, recorded too few readings for these time trends to be statistically significant. We therefore analysed the 36 centres that contributed over 500 patient visits in the trial (total 37 185 patient visits, with data from the run-in, double-blind and open follow-up phases). They were examined according to their zero preference in the first year after their centre had been randomized (Table 2). Although most of the centres in the highest initial zero 'unacceptable' preference band 4 (40% or more) improved to 'acceptable', band 2 (10–29%), or 'marked digit preference', band 3 (30–39%), one centre remained 'unacceptable' at year 3. It is also evident that, of the group initially considered to fall within acceptable limits, four centres by year 2, and three in year 3, showed a markedly low zero preference. One centre had, however, deteriorated to band 3 by year 3.

Number preference in first sitting systolic blood pressure readings

This analysis was performed separately for the active and placebo groups for the double-blind phase data only, when the target blood pressure was 'less than 150 mmHg and a decrease [of] at least 20 mmHg'. In the double-blind phase, the series of blood pressure distributions indicated an over-representation of the value 148 mmHg for the active treatment group (Fig. 3). Figure 4 demonstrates that, over time from randomization, the recording of 148 mmHg increased in frequency relative to the theoretical normal distribution (based on even digits only) from 117 to 150% and was the modal value from year 3 to year 7. This was not the case for the placebo group (Fig. 4). The second series of sitting systolic measurements and both series of supine and standing systolic measurements similarly did not show a preference for 148 mmHg (data not shown). Figure 4 also shows a high proportion of readings at 150 mmHg in the early years, reducing over time consistent with the general reduction in terminal digit preference.

Discussion

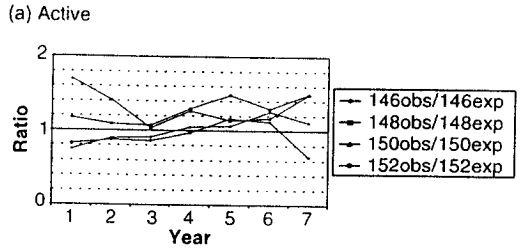
A substantial starting terminal digit preference in centres recruiting for the Syst-Eur trial diminished toward the 20% target level by 3 years after the centres randomized their first patient, this improvement being sustained. The reduction in zero preference over time was independent of calendar year and consistent with the effect of quality

Table 2 Comparison of zero preference for the 36 largest centres in the year that they were first randomized with their results in the second and third years

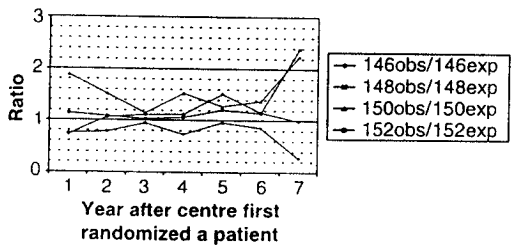
		Number of centres			
		Markedly low zero preference (< 10%)	Acceptable zero preference* (10–29%)	Marked zero preference (30–39%)	Unacceptable zero preference (≥ 40%)
Year 1		1	19	7	9
Year 2	< 10%	1	4	0	0
	10–29%	0	13	5	4
	30–39%	0	2	2	1
	≥ 40%	0	0	0	4
Year 3	< 10%	1	3	0	0
	10–29%	0	14	5	5
	30–39%	0	1	2	3
	≥ 40%	0	0	0	1

*One centre in initial zero preference band 2 had fewer than 100 measurements in year 3 and is not represented in this table.

Fig. 4



Year	1	2	3	4	5	6	7
N=	3107	5008	4611	2900	2484	1771	576
Mode	150	150	148	148	148	148	148
Median	154	152	150	150	148	148	148
Mean	155.4	153	151.4	150.6	150.0	149.1	149.6



	1	2	3	4	5	6	7
N=	2840	4709	4208	2521	2046	1362	383
Mode	160	160	160	160	152	168	148
Median	162	162	160	160	160	160	160
Mean	163.9	163.1	161.6	162	162.2	161.5	162.0

Ratios of observed (obs) first sitting systolic blood pressures of 146, 148, 150 and 152 mmHg to predicted values (exp) from the normal distribution for (a) the active treatment group and (b) the placebo group. Mode, median and mean are included for each year. For active treatment, the mode of 148 mmHg is over-represented from 4 years onwards, as it is for the seventh year with placebo treatment.

control. We do not have digit preference data over time from other trials, but it would be worth considering whether or not similar effects occurred and whether or not they changed over the course of the trial.

In the Syst-Eur investigation, the quality control of blood pressure accuracy was included as part of a wider approach to check on adherence to trial protocols. Other trials such as the APTH [6] trial also provide digit preference data on readings from mercury sphygmomanometers to all centres. The HYVET trial [7] requires the use of either mercury or validated automatic machines with a programme of quality control site visits. Bias has been reduced by the use of automatic sphygmomanometers in some other studies, such as the ASCOT [8] and HOT [9] trials.

The zero preference in the run-in phase of the trial was 42.4%; this fell to 22.3% in the third year of the double-blind phase, equating to a greater uncertainty over the systolic blood pressure readings at the start of the trial. In the context of Syst-Eur, the effect of these errors on the estimate of the reduction in systolic blood pressure between the treatment and placebo groups (10.1 mmHg) was removed by a simultaneous comparison of the active and placebo groups. The errors caused by an excess zero digit preference would, however, have an important effect on managing an individual patient: a doctor who had a 42% zero preference would be rather less certain that he or she had successfully achieved the blood pressure reduction required. The production of terminal digit preference charts for use by individual primary and secondary care practitioners deserves consideration.

Centres differed importantly in how their results changed over the course of this trial. Although 13 (36%) of the largest centres improved, four (11%) remained unacceptable and four (11%) became worse. The written quality reports sometimes indicated that there were staff changes or other organizational difficulties that might have contributed to poor performance in the trial. We can speculate that the variability in performance would have been greater in the absence of quality control. Indeed, there is a suggestion of a rebound worsening in zero preference after 3–4 years after entry into the double-blind phase. This occurred several years after the main effort of visiting had been completed, reinforcing the message that

ongoing quality control is necessary. In addition, the data include several examples of zero being uncommon as a terminal digit over time. This constitutes a new form of bias, the significance of which is unknown and worthy of further investigation. Future trials should consider efforts to correct digit preference prior to randomization, with a continuous monitoring of centres to ensure that neither a recurrence of zero preference nor any new bias is introduced.

With regard to the double-blind phase, the preference for a systolic blood pressure reading of 148 mmHg suggests that the number of patients who achieved the target blood pressure was exaggerated. If so, there are patients within this group whose true blood pressure is higher, and who are therefore predisposed to greater risk, than is apparent. This may imply an overestimation of the blood pressure reduction achieved by active treatment in the Syst-Eur investigation, but the effect is likely to be small since 150 mmHg and higher values were also frequently represented. Our data suggest that there was more '148 mmHg' preference for the active treatment group than for the placebo group. Since the actively treated patients had a lower mean systolic blood pressure and hence were closer to the target, it was easier for those measuring to record the desired figure and confirm that target had been achieved.

The absence of a preference for 148 mmHg in the standing and supine systolic blood pressure readings would tend to support the hypothesis of number preference since these readings were not used to determine blood pressure control. The effect was, however, less obvious in the second series of blood pressure readings, made at the same visit, and it may therefore be that the first series was given greater importance by the researchers in spite of the fact that the mean of the first and second readings was used to determine treatment. It is interesting to note that the American Heart Association recommends that clinicians ignore the first blood pressure reading and average the second and third [10]. According to our results, this practice would reduce single-number preference.

The preference for a systolic value of 148 mmHg in the double-blind phase led us to speculate that a similar preference might occur in other situations in which a target blood pressure is introduced into a clinical or research protocol. For example, since entry into the Syst-Eur trial required a mean sitting systolic pressure of 160 mmHg or more (six readings), there might be preference for 160 mmHg and perhaps higher readings. A process of selection into the trial would be consistent with the large drop in blood pressure (13 mmHg) of the placebo group in the Syst-Eur study. Our analysis has proved inconclusive on this point owing to the absence of data from patients who were found not to meet the trial entry criteria. A similar process has previously been described related to the office blood pressure of patients referred to a hypertension clinic, which showed a preference for values indicating severe hypertension when compared with that patient's clinic ambulatory blood pressure [11]. We recommend that number preference around the threshold and target values in clinical trials is monitored for the potential bias it introduces into results.

The benefits of treatment in the Syst-Eur trial are known to relate to a lower ambulatory pressure [12] and may well relate to a lower clinic pressure if this is recorded by an automatic device. This fact, taken in conjunction with the number preference demonstrated here and the known risks of mercury [13], suggests that automatic devices are the instruments of choice when they are fully validated and serviced regularly, and provided readings are not rejected and repeated.

Acknowledgements

The Syst-Eur trial, initiated by the late Professor A. Amery, was a concerted action of the BIOMED Research Programme sponsored by the European Union. The trial was carried out in consultation with the World Health Organization, the International Society of Hypertension, the European Society of Hypertension and the World Hypertension League. The trial was sponsored by Bayer A.G. (Wuppertal, Germany). The National Fund for Scientific Research (Brussels, Belgium) provided additional support. Study medication was donated by Bayer A.G. and Merck Sharpe and Dohme Inc. (West Point, Pennsylvania, USA). Statistical support has been received from the Department of Statistics of Imperial College School of Medicine, London, UK.

D.W. was funded for the current study by the NHS Executive London (NHSE-LRO), Research & Development, Responsive Funding Programme. The views and opinions expressed do not necessarily reflect those of the NHSE (LRO) or the UK Department of Health.

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Croatia: N. Pivac, Z. Rumboldt.

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