

13350 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

6.1.1 Randomization by sex within clinics

In comparing mortality in the treatment groups in relation to background variables, the UGDP investigators presented data that showed that the excess of cardiovascular deaths in the tolbutamide group was particularly marked among the females. The mortality was 10.6% in the tolbutamide group as against 2.1% in the placebo group; the corresponding rates for males were 17.5% and 11.1% respectively. In the course of reviewing this finding in the individual clinics we discovered a puzzling anomaly concerning the distribution of the two sexes to the four treatment groups within clinics.

Table A.1 shows the numbers of patients of each sex allocated to each treatment group within each clinic. The proportion of males allocated to placebo was surprisingly high in Boston and in Seattle. The discrepancy in Seattle alone would represent an unusual event in random allocation ($\chi^2=11.31$ on 1 df; $P=0.001$) and the results taken as a whole are also anomalous ($\chi^2=33.33$ on 12 df; $P=0.001$).

These unexpected findings do not in themselves explain the cardiovascular mortality differences. In an analysis discussed later in this section, adjustments are made for sex and clinic as well as other covariables, and there is no substantial change in the apparent effect of tolbutamide treatment on cardiovascular mortality. A more important point is whether these findings provide evidence of a breakdown of the randomization procedure—a contingency that might have grave implications for the credibility of the whole study.

The randomization procedure used by the UGDP has already been described briefly in section 3.1.2. In an attempt to find an explanation for the peculiar allocation by sex within clinics, the committee reviewed the randomization in detail. We were given access to the log books in which the Coordinating Center maintained records of the allocation of each patient to a treatment group and were impressed by the quality of the documentation that the investigators provided. We were not able to find an assignable cause for the surprising allocation of the sexes to treatments but have no reason to think that the study has been compromised by a breakdown in the randomization of patients to the treatment groups. Because of the imbalance of sexes in the * * * however, allowance for this has been made in our analysis. In institutions such as Seattle, in which no cardiovascular deaths occurred in either the placebo or tolbutamide groups, there would, of course, be no effect due to the imbalance. In general, however, all analyses of the data should be adjusted simultaneously for sex and clinic.

6.1.2 Cardiovascular failure rates

Cardiovascular failure rates in the UGDP study are presented in Tables A.2 through A.4. The rate for the tolbutamide group is 5.4/1,000 quarter-years (Table A.2, top) and this is significantly higher than the rate for the placebo group. In the next two parts of Table A.2 the rates for the treatment groups are presented separately for the two sexes, and the differential between the placebo and tolbutamide groups is substantial and significant for females (4.4 vs 0.8) but less marked and nonsignificant for males (7.5 vs 5.0). The number of subjects at risk is smaller for the males than for the females, and the chance of detecting treatment differences is therefore greater for the latter group. The results are consistent with the view that the tolbutamide rate is higher for both sexes, but if the males were considered in isolation, the evidence in their case would not be strong. Further, it is the older women who in particular show substantially different rates for the two treatment groups. Among women over 53 years of age receiving tolbutamide, the rate is 8.6% and for those receiving placebo, 1.4%. For younger women the corresponding rates are 0.6% and 0.5%.

In Table A.3 the failure rates are presented by sex and treatment group at each clinic. These are the data that have already been referred to in section 5.3 to make the point that excess mortality in the tolbutamide group was not confined to a few clinics. In the case of the females it was observed at the clinics in Boston, Minneapolis, Williamson, Cincinnati, Cleveland, and Birmingham. Of the remaining six clinics, four had less than 200 quarter-years of patient exposure and showed no deaths from cardiovascular causes in either treatment group. In the part of the table showing data for both sexes combined it is seen that in seven clinics the failure rate in the tolbutamide group was higher and in two it was lower than in the placebo group and that in three there was no information.