

half simply to reduce their intake of table sugar. The dose of tolbutamide was two thirds of that used by the UGDP. The subjects were allocated to the treatment groups by a method of randomization that was based on the use of numbers read from a telephone book. There was no stratification according to risk factors prior to the randomization.

At the time of entry to the trial, information was obtained on age, sex, weight, clinical history of arterial disease, blood pressure, and blood glucose level. Follow-up examinations were conducted at intervals of every six months except on three occasions when the interval was one year. The cardiovascular component of the follow-up examination included the administration of the Rose questionnaire and the taking of an electrocardiogram.

Two types of outcome have been considered in the analyses: (1) death, either from cardiovascular causes, as identified on the death certificate, or from all causes; or (2) cardiovascular events, which, in addition to death from cardiovascular causes, include cardiac infarction, angina, worsening of the ECG, onset of claudication, and stroke. The trial was planned as a double-blind study. A list of treatment assignments was available to the principal investigator and was occasionally consulted by him when it was thought that the welfare of the patient required it. The principal investigator is confident that the decoded information was promptly forgotten by him and did not influence his assessment of the patient's outcome.

The findings reported by Keen and Jarrett (6) on cardiovascular events at the end of the seven years of study are given in Table 2.

The authors noted that in each treatment group, the frequency of cardiovascular events was, as expected, higher in the subjects who were thought a priori to be at higher risk. They found no evidence of a treatment difference in the high risk group but "in the low risk individuals, the rate of events in the tolbutamide-treated group is about half that in the placebo group, a difference significant at the 2% level." (6) They further conclude, "a significant degree of primary protection against cardiovascular events can be conferred by tolbutamide in mildly and moderately hyperglycemic people."

Mortality data from the same study are presented in a report by Keen. (5) At the end of eight years from the beginning of the trial, 25 deaths had been observed in the placebo group and 24 in the tolbutamide group, 14 of the former and 12 of the latter being due to cardiovascular causes. Both total death rate and that from cardiovascular causes were at approximately the same level in the two treatment groups. The total death rate of 19.8% was approximately double that observed in the UGDP study. One important factor in this difference is the relatively high proportion of subjects over 70 years of age in the Bedford study, as shown in Table 3. Another might be that in the Bedford study there was no selection based on the likelihood of a five-year survival, as was employed by the UGDP.

The data of Table 3 show the higher mean age of the Bedford subjects as compared with those in the UGDP. The percent over 70 years of age is as high as 23.8 in the former and only 5.9 in the latter.

Table 3 also provides an instance of a difference in the distribution of base-line variables between the two treatment groups of the Bedford study. Of the placebo group, 29.6% are over 70 years of age as compared with 17.9% of the tolbutamide group. The difference is statistically significant at the 5% level. In section 6 of this report, an analysis will be given to take such differences in base-line variables into account.

4.2 Paasikivi (18)

This is a study of hypoglycemic treatment in 178 survivors from a first myocardial infarction. A further 92 patients who had been treated for an infarction during the same period were excluded for various reasons. The antihypoglycemic agent was tolbutamide, which was tested against a placebo.

Even or odd birth date determined whether the patient received placebo or tolbutamide. The maximal dose of tolbutamide given was 1 gm; this was also the usual dose since it was given to all but 28% of the patients, who mostly received 0.75 gm/day. The period of follow-up ranged from 1 to 5.5 years, the average being 2.9 years for the tolbutamide group and 3.0 years for the placebo group.

Sixteen patients of 83 (19%) died in the control group, and 13 of 95 (14%) died in the tolbutamide group. All deaths were considered to have been due to