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Dataset Integrity Check (DSIC) for the
Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C)
Main Results Analysis Dataset

Reference paper: Bisceglie AM, et.al. Prolonged Therapy of Advanced Chronic Hepatitis C with Low-Dose Peginterferon
The New England Journal of Medicine 359 [Dec 2008]: 2429-41.

The HALT-C trial is a large, prospective, randomized, controlled trial of long-term peginterferon therapy in adult patients with advanced hepatitis C with no sustained virologic response to a previous course of interferon-based therapy. The objective of the trial is to determine if long-term therapy with interferon results in improvements in histologic and clinical outcomes of hepatitis C. As a partial check of the integrity of the HALT-C main results analysis dataset archived in the NIDDK data repository, a dataset integrity check (DSIC) was performed to verify that selected published results from the HALT-C main results paper can be reproduced using the archived dataset. The DSIC consists of a small number of analyses performed to duplicate published results reported by HALT-C Trial Investigators in *The New England Journal of Medicine* in December, 2008[1]. Results of the DSIC are described below.

The intent of this DSIC is to provide confidence that the data distributed by the NIDDK repository is a true copy of the study data. Our intent is ***not*** to assess the integrity of the statistical analyses reported by study investigators. As with all statistical analyses of complex datasets, complete replication of a set of statistical results should not be expected on a first (or second) exercise in secondary analysis. This occurs for a number of reasons including differences in the handling of missing data, restrictions on cases included in samples for a particular analysis, software coding used to define complex variables, etc. Experience suggests that most discrepancies can ordinarily be resolved by consultation with the study data coordinating center (DCC), however this process is labor-intensive for both DCC and Repository staff. It is thus not our policy to resolve every discrepancy that is observed in an integrity check. Specifically, we do not attempt to resolve minor or inconsequential discrepancies with published results or discrepancies that involve complex analyses, *unless staff of the NIDDK Repository suspect that the observed discrepancy suggests that the dataset may have been corrupted in storage, transmission, or processing by repository staff*. We do, however, document in footnotes to the integrity check those instances in which our secondary analyses produced results that were not fully consistent with those reported in the target publication.

Archived Dataset Contents. The DCC submitted a single *SAS v9* analytical data file (RAND_FINAL.sas7bdat) representing the calculated variables used for the analysis in Bisceglie [2008][1]. In total, the file contained 1050 observations, corresponding to the 1050 randomized subjects in the analysis cohort, and 181 variables labeled with a detailed description. The indicator for diabetes history was not present in the analysis dataset. Instead, the DCC submitted the code for recreating the diabetes indicator from raw data files (see Attachment 2, "*SAS 9.1* log for programming code submitted in replication of the results in Table 1 and Figure 2b in Bisceglie, et.al [2008]").

As described in the publication, the primary outcome is progression of liver disease within 1400 days after randomization, as indicated by death, hepatic decompensation (variceal hemorrhage; ascites, which may include hepatic hydrothorax; spontaneous bacterial peritonitis; or hepatic

encephalopathy), hepatocellular carcinoma, or a Child-Turcotte-Pugh score of 7 or more on two consecutive study visits. For patients with noncirrhotic fibrosis at baseline (<*fibrosis*>=0), and who did not attain a clinical outcome, the primary outcome was defined as an increase in the Ishak hepatic fibrosis score of at least 2 points. The calculated summary indicator for attainment of the primary outcome (clinical outcome or two point increase in Ishak fibrosis score) is <*clin_tpi*>. The indicator for attainment of the primary clinical outcome is <*pri_outcome*>, and the variable identifying the first clinical outcome is <*first_out*>. The indicator for attainment of a two point increase in Ishak fibrosis score is <*tpi*>.

DSIC Analysis Methods. For purposes of this DSIC, a portion of published results was selected for replication to assure the quality of the archived dataset. As indicated in the publication, baseline demographic and clinical characteristics between treatment groups were compared using the χ^2 tests, the t-test, or the Wilcoxon rank-sum test. The primary analysis of the primary clinical end point involved the comparison of survival curves using the log-rank test, with patients stratified according to the presence of noncirrhotic fibrosis or of cirrhosis.

Baseline Comparisons. Baseline comparisons, as reported in Table 1 of the study publication[1], were replicated exactly by analyses of archived data for the 1050 patients. [DSIC Table 1]

Clinical and Histologic End Points. As reported in the publication, a primary clinical or histologic outcome had occurred in 157 patients in the treatment group and 157 patients in the control group, 3.5 years after randomization. Kaplan-Meier product-limit survival estimates of the proportion of patients with a clinical or histological outcome was 34.1% in the treatment group and 33.8% in the control group, exactly replicating publication estimates. The hazard ratio was 1.02 (95% CI, 0.82 to 1.28), which is close to the published hazard ratio of 1.01 (95% CI, 0.81 to 1.27).

Proportional hazards regression showed no significant interaction between treatment group and the presence of noncirrhotic fibrosis/cirrhosis (P=0.70), similar to published results (P=0.66). Among patients with cirrhosis, Kaplan-Meier product-limit survival estimates of the proportion of patients with an outcome at 1400 days were 30.2% for treated patients and 31.2% for control patients, exactly replicating published results. Among patients with noncirrhotic fibrosis, survival estimates were 36.7% for treated patients and 35.5% for control patients, again replicating published results.

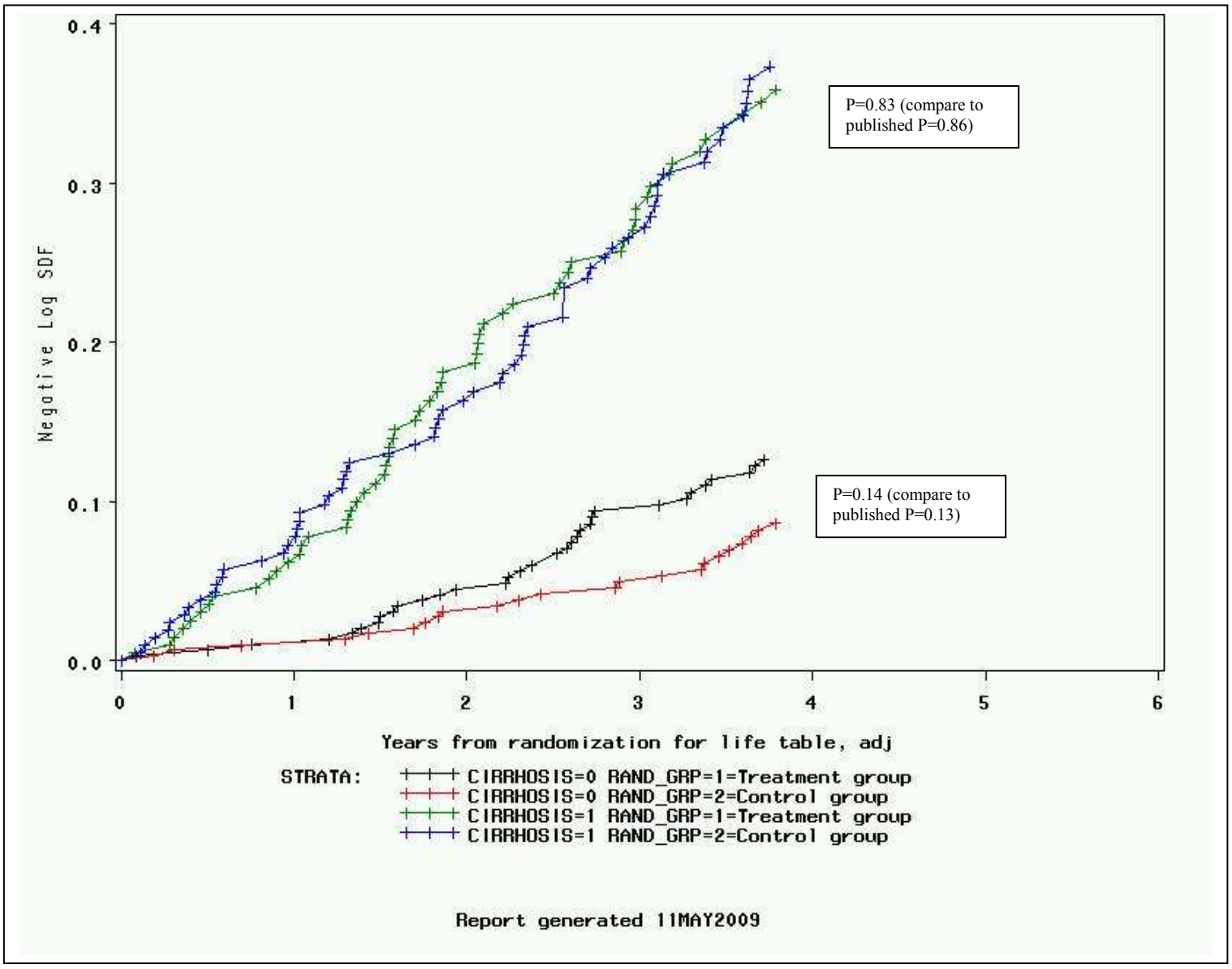
The percentage of patients with a clinical outcome, as assessed by Kaplan-Meier survival analysis for the DSIC, was similar to results reported in the publication[1] for treated and control patients with cirrhosis [DSIC Figure 1]. Likewise, among patients with noncirrhotic fibrosis, DSIC results were similar to reported results in that clinical outcomes were more frequent in treated patients than control patients, but the difference was not significant (P=0.14 using the log-rank test, similar to the reported P=0.13).

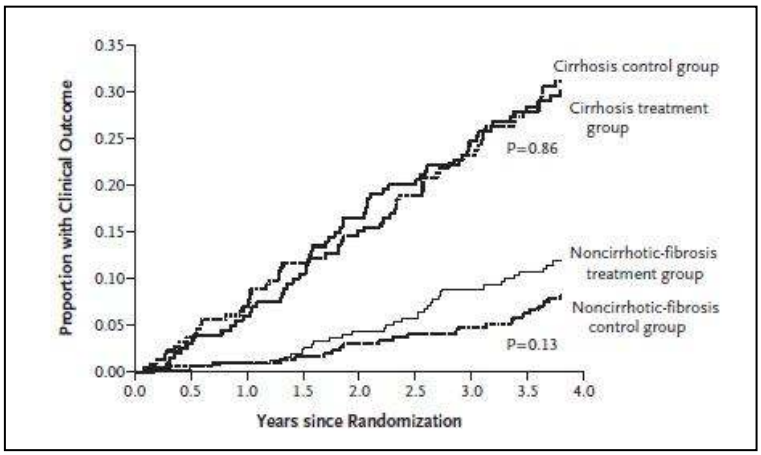
In conclusion, selected analysis of the HALT-C legacy main study analysis dataset closely replicates results reported by the HALT-C investigators in Bisceglie (2008). These results provide confidence that the analysis dataset distributed by the NIDDK Repository is a true copy of the HALT-C main study analysis dataset.

DSIC Table 1. Baseline Demographic, Biochemical, and Histologic Features of the Patients (with reference to Bisceglie [2008]: Table 1, p. 2434)

Variable	Treatment Group (N=517) Archived (n=196)	Treatment Group (N=517) Published (n=196)	Difference (0)	Control Group (N=533) Archived (n=205)	Control Group (N=533) Published (n=205)	Difference (0)	*P* value Archived	*P* value Published
Cohort (% of patients)							**0.90**	**0.90**
Lead-in (no response)	30.2	30.2	**0.0**	30.8	30.8	**0.0**		
Lead-in (partial response)	33.5	33.5	**0.0**	31.7	31.7	**0.0**		
Lead-in (breakthrough or relapse)	13.7	13.7	**0.0**	15.0	15.0	**0.0**		
Express	22.6	22.6	**0.0**	22.5	22.5	**0.0**		
Age (yr)	51.1 ± 7.3	51.1 ± 7.3	**0.0 ± 0.0**	50.1 ± 7.0	50.1 ± 7.0	**0.0 ± 0.0**	**0.02**	**0.02**
Duration of exposure to HCV (yr)	28.8 ± 7.9	28.8 ± 7.9	**0.0 ± 0.0**	27.4 ± 8.0	27.4 ± 8.0	**0.0 ± 0.0**	**0.004**	**0.004**
Female sex (% of patients)	30.0	30.0	**0.0**	28.1	28.1	**0.0**		
Race or ethnic group (% of patients)							**0.70**	**0.70**
White	72.0	72.0	**0.0**	71.3	71.3	**0.0**		
Black	18.8	18.8	**0.0**	17.6	17.6	**0.0**		
Hispanic	7.5	7.5	**0.0**	8.4	8.4	**0.0**		
Other	1.7	1.7	**0.0**	2.6	2.6	**0.0**		
Body mass index	29.7 ± 5.3	29.7 ± 5.3	**0.0 ± 0.0**	30 ± 5.6	30 ± 5.6	**0.0 ± 0.0**	**0.44**	**0.44**
Diabetes (% of patients)	24.4	24.4	**0.0**	24.0	24.0	**0.0**	**0.89**	**0.89**
Lifetime alcohol consumption (median of drinks)	7229	7229	**0**	7537	7537	**0**	**0.43**	**0.43**
HCV genotype -- % of patients							**0.02**	**0.02**
1	95.2	95.2	**0.0**	91.6	91.6	**0.0**		
2	1.2	1.2	**0.0**	2.8	2.8	**0.0**		
3	2.1	2.1	**0.0**	4.1	4.1	**0.0**		
4 or 6	1.6	1.6	**0.0**	1.5	1.5	**0.0**		
Baseline serum HCV RNA level (log_{10} IU/ml)	6.42 ± 0.54	6.42 ± 0.54	**0.00 ± 0.00**	6.44 ± 0.51	6.44 ± 0.51	**0.00 ± 0.00**	**0.62**	**0.62**
Serum alanine aminotransferase (U/liter)	104 ± 74	104 ± 74	**0 ± 0**	110 ± 80	110 ± 80	**0 ± 0**	**0.24**	**0.24**
Ratio of the patient's alanine aminotransferase level to the upper limit of normal	2.07 ± 1.53	2.07 ± 1.53	**0.00 ± 0.00**	2.18 ± 1.70	2.18 ± 1.70	**0.00 ± 0.00**	**0.27**	**0.27**
Total serum bilirubin (mg/dl)	0.79 ± 0.41	0.79 ± 0.41	**0.00 ± 0.00**	0.78 ± 0.39	0.78 ± 0.39	**0.00 ± 0.00**	**0.75**	**0.75**
Serum albumin (g/dl)	3.88 ± 0.38	3.88 ± 0.38	**0.00 ± 0.00**	3.86 ± 0.40	3.86 ± 0.40	**0.00 ± 0.00**	**0.44**	**0.44**
Prothrombin time (INR)	1.04 ± 0.12	1.04 ± 0.12	**0.00 ± 0.00**	1.04 ± 0.11	1.04 ± 0.11	**0.00 ± 0.00**	**0.99**	**0.99**
Cirrhosis on biopsy (% of patients)	40.2	40.2	**0.0**	41.3	41.3	**0.0**	**0.73**	**0.73**
Ishak fibrosis score	4.08 ± 1.25	4.08 ± 1.25	**0.00 ± 0.00**	4.13 ± 1.28	4.13 ± 1.28	**0.00 ± 0.00**	**0.55**	**0.55**
Ishak inflammation score	7.55 ± 2.10	7.55 ± 2.10	**0.00 ± 0.00**	7.54 ± 2.02	7.54 ± 2.02	**0.00 ± 0.00**	**0.91**	**0.91**
Mean length of biopsy specimen - cm	1.8 ± 1.0	1.8 ± 1.0	**0.0 ± 0.0**	1.8 ± 0.8	1.8 ± 0.8	**0.0 ± 0.0**	**0.24**	**0.24**
Esphageal varices (% of patients)	24.3	24.3	**0.0**	27.0	27.0	**0.0**	**0.32**	**0.32**

Above: DSIC Figure 1.
Below: Bisceglie [2008]: Figure 2B, p.2436 [1]





References

[1] Bisceglie AM, Mitchell LS, Everson GT, Linday KL, Everhard JE, Wright EC, Lee WM, Lok AS, Bonkovsky HL, Morgan TR, Ghany MG, Morishima C, Snow KK, and Kienstag JL for the HALT-C Trial Investigators. **Prolonged Therapy of Advanced Chronic Hepatitis C with Low-Dose Peginterferon.** *New England Journal of Medicine* 359(23): 2429-41 [December 2008].

Attachment 1

Full Text of Article

Bisceglie AM, Mitchell LS, Everson GT, Linday KL, Everhard JE, Wright EC, Lee WM, Lok AS, Bonkovsky HL, Morgan TR, Ghany MG, Morishima C, Snow KK, and Kienstag JL for the HALT-C Trial Investigators.
Prolonged Therapy of Advanced Chronic Hepatitis C with Low-Dose Peginterferon.
New England Journal of Medicine 359(23): 2429-41 [December 2008]

ORIGINAL ARTICLE

Prolonged Therapy of Advanced Chronic Hepatitis C with Low-Dose Peginterferon

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ABSTRACT

BACKGROUND

In patients with chronic hepatitis C who do not have a response to antiviral treatment, the disease may progress to cirrhosis, liver failure, hepatocellular carcinoma, and death. Whether long-term antiviral therapy can prevent progressive liver disease in such patients remains uncertain.

METHODS

We conducted a randomized, controlled trial of peginterferon alfa-2a at a dosage of 90 μg per week for 3.5 years, as compared with no treatment, in 1050 patients with chronic hepatitis C and advanced fibrosis who had not had a response to previous therapy with peginterferon and ribavirin. The patients, who were stratified according to stage of fibrosis (622 with noncirrhotic fibrosis and 428 with cirrhosis), were seen at 3-month intervals and underwent liver biopsy at 1.5 and 3.5 years after randomization. The primary end point was progression of liver disease, as indicated by death, hepatocellular carcinoma, hepatic decompensation, or, for those with bridging fibrosis at baseline, an increase in the Ishak fibrosis score of 2 or more points.

RESULTS

We randomly assigned the patients to receive peginterferon (517 patients) or no therapy (533 patients) for 3.5 years. The level of serum aminotransferases, the level of serum hepatitis C virus RNA, and histologic necroinflammatory scores all decreased significantly ($P<0.001$) with treatment, but there was no significant difference between the groups in the rate of any primary outcome (34.1% in the treatment group and 33.8% in the control group; hazard ratio, 1.01; 95% confidence interval, 0.81 to 1.27; $P=0.90$). The percentage of patients with at least one serious adverse event was 38.6% in the treatment group and 31.8% in the control group ($P=0.07$).

CONCLUSIONS

Long-term therapy with peginterferon did not reduce the rate of disease progression in patients with chronic hepatitis C and advanced fibrosis, with or without cirrhosis, who had not had a response to initial treatment with peginterferon and ribavirin. (ClinicalTrials.gov number, NCT00006164.)

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*The other investigators participating in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial are listed in the Appendix.

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More than 3 million Americans and 170 million persons worldwide are chronically infected with hepatitis C virus (HCV),[1,2] which can result in progressive hepatic injury and fibrosis, culminating in cirrhosis and end-stage liver disease.[3] Among adults in the Western world, chronic hepatitis C is a major cause of cirrhosis and a major indication for liver transplantation. Chronic hepatitis C has contributed also to the increasing incidence of hepatocellular carcinoma, for which few satisfactory therapies exist.[4]

Therapy with peginterferon and ribavirin for 24 to 48 weeks leads to a sustained loss of serum HCV RNA (termed a sustained virologic response), with resolution of chronic hepatitis in approximately half of patients.[5,6] Unfortunately, treatment options are few for the half of treated patients who do not have a sustained virologic response. Several new, potent HCV protease and polymerase inhibitors have been described recently,[7,8] but none are currently available for therapeutic use.

An approach to management of chronic hepatitis C in patients who do not have a sustained virologic response to initial therapy is long-term, maintenance peginterferon therapy. The rationale is that treatment with interferon can lead to suppression of HCV RNA levels and decreases in serum aminotransferase levels and improvements in liver histologic findings, even without eradication of the virus.[9] In addition, several reports suggest that interferon therapy can reduce the frequency of hepatocellular carcinoma; however, most of these studies were retrospective and were confounded by lead-time bias.[10,11] Whether long-term therapy with interferon results in improvements in histologic and clinical outcomes of hepatitis C has yet to be shown. Therefore, we conducted a large, prospective, randomized, controlled trial of long-term peginterferon therapy in adult patients with advanced hepatitis C who had not had a sustained virologic response to a previous course of interferon-based therapy.[12]

METHODS

PATIENTS

The design of the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial has been described previously.[12] Briefly, patients meeting the following criteria were entered into this study from 10 study centers in the United States between August 2000 and August 2004: lack of a sustained virologic response to previous therapy, advanced hepatic fibrosis according to liver biopsy (an Ishak fibrosis score[13] of 3 or more; scores range from 0 to 6, with higher scores indicating greater degrees of fibrosis and scores of 5 or 6 indicating cirrhosis), no history of hepatic decompensation or hepatocellular carcinoma, and absence of exclusion criteria (e.g., liver disease other than hepatitis C, uncontrolled medical or psychiatric conditions, or contraindications to interferon treatment). The patients were stratified according to their Ishak fibrosis score. The noncirrhotic-fibrosis stratum consisted of 622 patients with a score of 3 or 4, and the cirrhosis stratum consisted of 428 patients with a score of 5 or 6. The patients provided written informed consent for participation in the trial.

During the lead-in phase of the trial, all patients underwent treatment with 180 μg of subcutaneous pegylated interferon alfa-2a weekly (Pegasys, Roche; the drug had not yet been approved by the Food and Drug Administration [FDA] when the trial began) and oral ribavirin (1000 to 1200 mg daily, according to body weight) for at least 24 weeks before undergoing randomization (Fig. 1). Randomization was stratified according to clinical center and the presence or absence of cirrhosis and was performed centrally by computer with the use of permuted blocks of random size. Patients with detectable serum HCV RNA levels at treatment week 20 were classified as having no response (<1 $\log_{10}$ IU per milliliter decrease in HCV RNA level from baseline) or a partial response (≥1 $\log_{10}$ IU per milliliter decrease in HCV RNA level from baseline) and were assigned for the next 3.5 years to either the maintenance-therapy group (90 μg of peginterferon alfa-2a weekly, without ribavirin) or the untreated control group. For treated patients who had unacceptable side effects, the weekly peginterferon dose was reduced to 45 μg or even lower, as needed.

Patients with undetectable serum HCV RNA at week 20 continued therapy for an additional 48 weeks, as reported previously.[14] If HCV RNA was detected in a patient again after week 20, either during treatment (breakthrough) or after cessation of treatment (relapse), the patient was

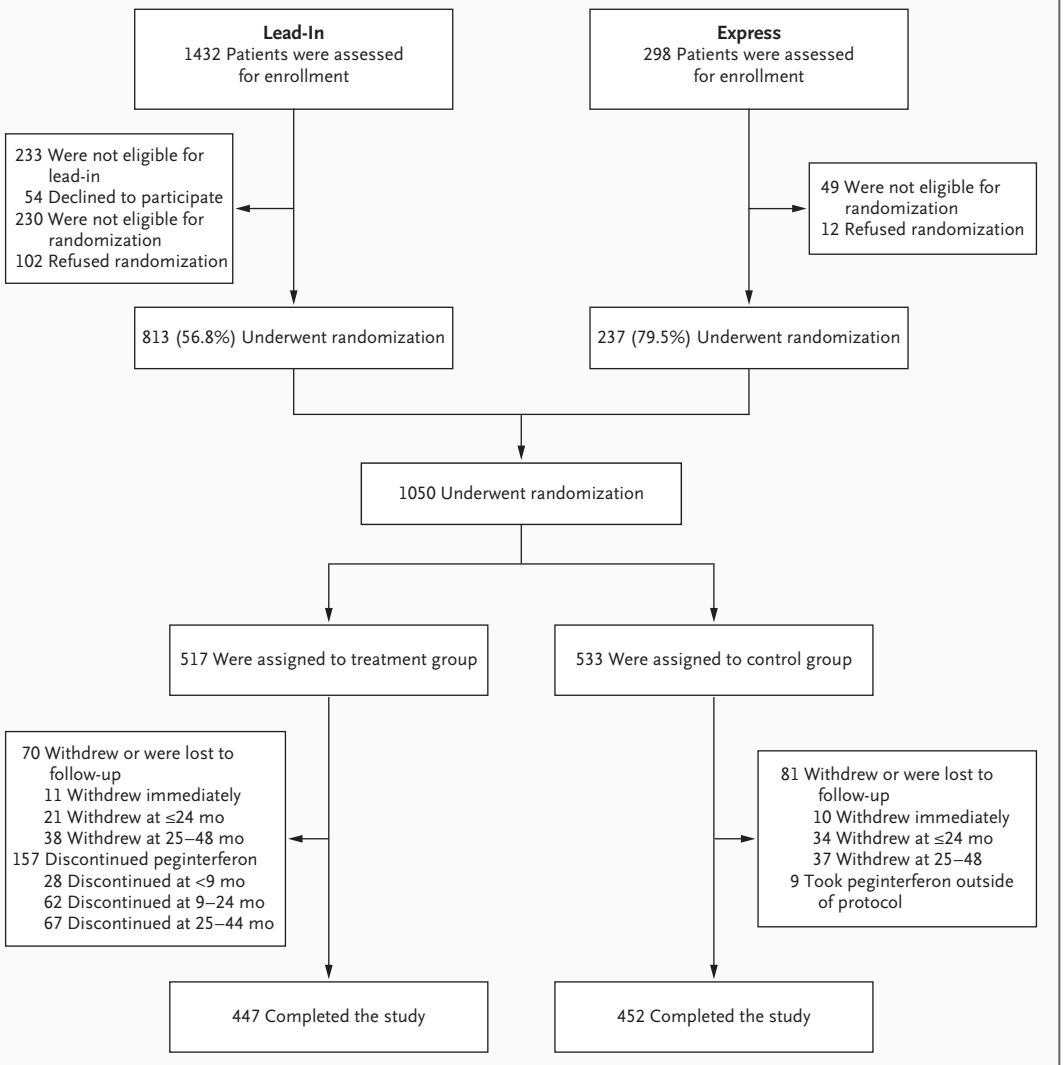

Figure 1. Enrollment, Randomization, and Follow-up of Study Participants.

Patients were enrolled either in the lead-in cohort of patients who underwent another course of antiviral treatment with peginterferon and ribavirin within the study or in the express cohort of patients who were initially treated outside the study. They were then randomly assigned to either the treatment or the control group and were followed up to monitor for clinical outcomes and histologic evidence of progression of liver disease.

offered the opportunity to undergo randomization in the controlled phase of the trial (the "breakthrough or relapse" cohort). During the trial, after pegylated interferons became available for treating hepatitis C, we amended the protocol to allow patients who had been treated with peginterferon plus ribavirin outside the study but had not had a sustained virologic response to treatment to undergo randomization to the treatment or control group (the "express" cohort).

OUTCOMES

The primary outcome variable was progression of liver disease within 1400 days (3.83 years) after randomization, as indicated by death, hepatic decompensation (variceal hemorrhage; ascites, which may include hepatic hydrothorax; spontaneous bacterial peritonitis; or hepatic encephalopathy), hepatocellular carcinoma,[15] a Child–Turcotte–Pugh score[16] of 7 or more on two consecutive study visits (the score measures hepatic decom-

pensation and ranges from 5 to 15, with higher numbers indicating greater decompensation), or for patients with noncirrhotic fibrosis at baseline, an increase in the Ishak hepatic fibrosis score of at least 2 points according to assessment of a liver-biopsy specimen obtained during the study. An outcome committee whose members were unaware of the treatment assignments reviewed and adjudicated the validity of each primary clinical outcome. The prespecified secondary end points were a change in quality of life, serious adverse events, events requiring dose reduction (a decrease in the platelet or neutrophil count or an increase in the serum alanine aminotransferase level), an increase in the Ishak fibrosis score from baseline to the follow-up biopsies, and the development of presumed hepatocellular carcinoma.

During the randomized phase of the trial, the patients were seen every 3 months for history taking, physical examination, and laboratory testing to monitor the effects of peginterferon therapy and to assess for clinical end points and adverse events. The patients underwent hepatic ultrasound examination every 12 months to screen for hepatocellular carcinoma, as well as liver biopsy at baseline and at 1.5 and 3.5 years after randomization. The stage of histologic fibrosis was interpreted according to the Ishak score[13] by consensus face-to-face vote of the 10 study-site pathologists and a coordinating pathologist from the Armed Forces Institute of Pathology. All reported clinical outcomes had to meet predetermined criteria and be certified by majority vote of a rotating committee of three investigators.

Routine blood chemical studies and hematologic tests were performed in local clinical laboratories at each of the 10 clinical sites. The serum HCV RNA level and HCV genotype were determined in a single central laboratory at the University of Washington, Seattle; the HCV RNA level was determined by the Roche Cobas Monitor assay, and samples with negative test results according to this assay were retested with the more sensitive Roche Cobas Amplicor assay. HCV genotyping was performed by line-probe assay (Inno-LiPA, Innogenetics).

STATISTICAL ANALYSIS

Statistical analyses were performed at the data coordinating center with the use of SAS software, release 9.1. We estimated that 900 patients would need to be followed for 3.5 years[12] on the basis of a power of 90%, a two-sided significance level of 5%, annual estimated rates of progression of 6% in the control group and 3% in the treatment group, and an anticipated 10% loss to follow-up. After adjustments for nonadherence to the study protocol, we estimated the outcome rates would be 18.7% in the control group and 10.6% in the treatment group at the end of 3.5 years. The decision to include patients who had a relapse after the end of the lead-in phase resulted in 1050 patients who underwent randomization.

Baseline variables in the two treatment groups were compared with the use of chi-square tests, the t-test, or the Wilcoxon rank-sum test. The primary analysis of the primary outcome involved comparison of the survival curves with the use of the log-rank test (SAS Proc Lifetest) with patients stratified according to the presence of noncirrhotic fibrosis or of cirrhosis. Secondary analyses of the primary outcome included Cox proportional-hazards regression with patients stratified according to the presence of noncirrhotic fibrosis or of cirrhosis and according to clinical center and Kaplan–Meier estimates of the event rates 1400 days after randomization. Data were censored at the patient's last follow-up visit or at 1400 days (3.83 years) after randomization, whichever occurred first. The progress of the trial was reviewed every 6 months by a data and safety monitoring board. Three interim analyses for efficacy were planned with the use of O'Brien–Fleming boundaries (East, version 4, Cytel) when approximately 25%, 50%, and 75% of events had occurred. The data and safety monitoring board decided that the third interim analysis was not necessary. Data from patients who dropped out were censored at the time of withdrawal from the trial, and these patients were not considered to have reached an end point. Patients classified as having noncirrhotic fibrosis who did not undergo any follow-up biopsies and for whom no clinical outcome was recorded were not included in the analyses. All reported P values are two-sided. We performed a post hoc exploratory analysis to examine the heterogeneity of treatment effect according to the guidelines of the *Journal*.[17]

The study was designed by a steering committee composed of one representative from each of the participating institutions. Data were entered by the site coordinators into a central database

maintained by the New England Research Institutes, which also performed the statistical analyses. All investigators vouch for the accuracy and completeness of the reported findings. The study was approved by the ethics committee of each participating institution.

RESULTS

PATIENTS

We randomly assigned 1050 patients to receive peginterferon (517 patients) or no therapy (533 patients) for 3.5 years. Patients were enrolled in three cohorts consisting of 662 patients with no response or a partial response to lead-in therapy (63.0%); 151 patients who had a breakthrough or relapse and in whom HCV RNA became detectable again after week 20, during the lead-in phase of treatment (14.4%); and 237 "express" patients who were treated outside the study but did not have a sustained virologic response to treatment (22.6%).

The treatment and control groups were well matched with regard to clinical, biochemical, virologic, and histologic characteristics (Table 1). The mean age of the patients was 51 years; 71.0% were men; 71.6% were non-Hispanic whites, 8.0% were Hispanic whites, 18.2% were blacks, and 2.2% were Asian Americans or members of other racial or ethnic groups. Among 984 patients for whom the time of infection could be estimated, the mean duration of infection was 28 years. Serum alanine aminotransferase levels were elevated in 83.0% of the patients, and the mean alanine aminotransferase level was 2.1 times the upper limit of normal. The mean serum HCV RNA level at baseline was 6.4 $\log_{10}$ IU per milliliter. Approximately 40% of the patients in each group had cirrhosis, according to the liver biopsy (Ishak fibrosis score, 5 or 6), and the remainder had bridging hepatic fibrosis (Ishak fibrosis score, 3 or 4).

SERUM LEVELS OF ALANINE AMINOTRANSFERASE AND HCV RNA DURING TREATMENT

Serum alanine aminotransferase levels declined between baseline and 1.5 years by 0.45 times the upper limit of the normal range among treated patients, as compared with only 0.21 times the upper limit of normal among control patients, a difference of 0.24 times the upper limit of the normal range (95% confidence interval [CI], 0.09 to 0.39; P=0.002). At 3.5 years after baseline, the decline among treated patients was 0.47 times the upper limit of the normal range, as compared with 0.19 times among control patients, a difference of 0.28 times the upper limit of the normal range (95% CI, 0.12 to 0.44; P<0.001). At the time of randomization, 17.0% of all patients had normal serum alanine aminotransferase levels; 3.5 years after randomization, 35.1% of treated patients and 22.6% of control patients had normal alanine aminotransferase levels (P<0.001).

Serum HCV RNA levels fell by 0.81 $\log_{10}$ IU per milliliter in the treatment group at 1.5 years, as compared with 0.07 $\log_{10}$ IU per milliliter in the control group, a difference of 0.74 $\log_{10}$ IU per milliliter (95% CI, 0.61 to 0.87; P<0.001). Similar changes were seen at 3.5 years: the decrease was 0.71 $\log_{10}$ IU per milliliter in the treatment group and 0.12 $\log_{10}$ IU per milliliter in the control group, a difference of 0.59 $\log_{10}$ IU per milliliter (95% CI, 0.45 to 0.72; P<0.001). A sustained virologic response occurred in 18 treated patients (3.5%) but in only 1 control patient (who was enrolled on the basis of an isolated positive sample at week 20 but in whom HCV RNA was actually undetectable at randomization).

CLINICAL AND HISTOLOGIC END POINTS

At 3.5 years after randomization, a primary clinical or histologic outcome had occurred in 157 patients in the treatment group and 157 patients in the control group (Table 2 and Fig. 2A). The Kaplan–Meier survival estimates of the proportion of patients with an outcome at 1400 days were 34.1% (95% CI, 29.8 to 38.5) in the treatment group and 33.8% (95% CI, 29.4 to 38.1) in the control group; the hazard ratio was 1.01 (95% CI, 0.81 to 1.27; P=0.90). There was no significant interaction between treatment group and the presence of noncirrhotic fibrosis or of cirrhosis (P=0.66). Among patients with cirrhosis, the Kaplan–Meier estimates of the proportion of patients with an outcome at 1400 days were 30.2% for treated patients and 31.2% for control patients (hazard ratio, 0.97; 95% CI, 0.68 to 1.38); among those with noncirrhotic fibrosis, the estimates were 36.7% for treated patients and 35.5% for control patients (hazard ratio, 1.05; 95% CI, 0.78 to 1.39).

The percentage of patients with a clinical outcome, as assessed by Kaplan–Meier survival analysis, was similar in treated and control patients with cirrhosis (Fig. 2B). Among patients with noncirrhotic fibrosis, clinical outcomes were more frequent in treated patients than in control pa-

Table 1. Baseline Demographic, Biochemical, and Histologic Features of the Patients.*

Variable	Treatment Group (N=517)	Control Group (N=533)	P Value†
Cohort (% of patients)‡			0.90
Lead-in (no response)	30.2	30.8	
Lead-in (partial response)	33.5	31.7	
Lead-in (breakthrough or relapse)	13.7	15.0	
Express	22.6	22.5	
Age (yr)	51.1±7.3	50.1±7.0	0.02
Duration of exposure to HCV (yr)	28.8±7.9	27.4±8.0	0.004
Female sex (% of patients)	30.0	28.1	0.51
Race or ethnic group (% of patients)§			0.70
White	72.0	71.3	
Black	18.8	17.6	
Hispanic	7.5	8.4	
Other	1.7	2.6	
Body-mass index¶	29.7±5.3	30.0±5.6	0.44
Diabetes (% of patients)	24.4	24.0	0.89
Lifetime alcohol consumption (median no. of drinks)	7229	7537	0.43
HCV genotype — % of patients			0.02‖
1	95.2	91.6	
2	1.2	2.8	
3	2.1	4.1	
4 or 6	1.6	1.5	
Baseline serum HCV RNA ($\log_{10}$ IU/ml)	6.42±0.54	6.44±0.51	0.62
Serum alanine aminotransferase (U/liter)	104±74	110±80	0.24
Ratio of the patient's alanine aminotransferase level to the upper limit of normal	2.07±1.53	2.18±1.70	0.27
Total serum bilirubin (mg/dl)**	0.79±0.41	0.78±0.39	0.75
Serum albumin (g/dl)	3.88±0.38	3.86±0.40	0.44
Prothrombin time (INR)	1.04±0.12	1.04±0.11	0.99
Cirrhosis on biopsy (% of patients)	40.2	41.3	0.73
Ishak fibrosis score††	4.08±1.25	4.13±1.28	0.55
Ishak inflammation score‡‡	7.55±2.10	7.54±2.02	0.91
Mean length of biopsy specimen — cm	1.8±1.0	1.8±0.8	0.24
Esophageal varices (% of patients)	24.3	27.0	0.32

* Percentages may not total 100 because of rounding. Plus–minus values are means ±SD. HCV denotes hepatitis C virus, and INR international normalized ratio.

† The P values were determined with the use of the t-test or the chi-square test, except for the P value for lifetime alcohol consumption, which was determined with the use of the Wilcoxon rank-sum test.

‡ The 813 lead-in patients were classified as having had no response to lead-in therapy if they had a decrease in the serum HCV RNA level of less than 1 $\log_{10}$ IU per milliliter from baseline to lead-in week 20, as having had a partial response if they had a decrease in HCV RNA of at least 1 $\log_{10}$ IU per milliliter from baseline to week 20 and detectable HCV RNA at week 20, and as having had a breakthrough or relapse if they had undetectable HCV RNA at week 20 and then had detectable HCV RNA either during or after treatment. The 237 "express" patients underwent randomization after having received treatment with peginterferon plus ribavirin outside the study but without having had a sustained virologic response.

§ Race or ethnic group was self-reported.

¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.

‖ The P value is given for the comparison of the frequency of genotype 1 with the frequencies of genotypes 2, 3, and 4.

** To convert values for bilirubin to micromoles per liter, multiply by 17.1.

†† The Ishak fibrosis score measures structural changes associated with fibrosis and cirrhosis and ranges from 0 to 6, where 0 indicates no fibrosis and 6 indicates cirrhosis.

‡‡ The Ishak inflammation score measures several components of necroinflammatory changes in the liver-biopsy specimen and ranges from 0 to 18, with 18 being the worst score.[18]

Table 2. First Primary Outcome in Treated and Control Patients with Noncirrhotic Fibrosis or Cirrhosis at Baseline.*

Outcome	Noncirrhotic Fibrosis		Cirrhosis		Total	
	Treatment Group (N=309)	Control Group (N=313)	Treatment Group (N=208)	Control Group (N=220)	Treatment Group (N=517)	Control Group (N=533)
Death — no.	8	2	5	6	13	8
Hepatocellular carcinoma — no.	8	5	4	10	12	15
Ascites — no.	6	0	7	8	13	8
Hepatic encephalopathy — no.	1	4	4	3	5	7
Variceal hemorrhage — no.	1	2	2	4	3	6
Spontaneous bacterial peritonitis — no.	0	0	0	1	0	1
Child–Turcotte–Pugh score ≥7 on 2 consecutive visits — no.†	10	10	37	32	47	42
Progression of fibrosis — no.	64	70	NA	NA	64	70
Patients with primary outcome — no. (%)	98 (31.7)	93 (29.7)	59 (28.4)	64 (29.1)	157 (30.4)	157 (29.5)
Kaplan–Meier estimate of rate — %	36.7	35.5	30.2	31.2	34.1	33.8

* NA denotes not applicable.

† The Child–Turcotte–Pugh score assesses the presence and degree of hepatic decompensation, with scores for hypoalbuminemia, hyperbilirubinemia, hypoprothrombinemia, ascites, and hepatic encephalopathy. The score ranges from 5 to 15, with 15 being the worst. Patients with scores of 7 or less are classified as having class A liver disease, those with scores of 8 to 11 as having class B disease, and those with scores of 12 or more as having class C disease. Class A disease is compensated, and class B and class C disease are associated with worsening degrees of hepatic decompensation.[16]

tients (11.9% vs. 8.3%), but the difference was not significant (P=0.13).

The most common clinical outcome was an increase of 2 or more points in the Child–Turcotte–Pugh score (documented on two consecutive visits), which occurred in 109 patients (10.4%). Other hepatic-decompensation outcomes included ascites in 59 patients (5.6%), hepatic encephalopathy in 37 patients (3.5%), variceal hemorrhage in 16 patients (1.5%), and spontaneous bacterial peritonitis in 6 patients (0.6%). Hepatocellular carcinoma occurred in 29 patients (2.8%), 13 in the noncirrhotic-fibrosis stratum (2.1%) and 16 in the cirrhosis stratum (3.7%). Fifty-three patients (5.0%) died, 31 in the treatment group (15 of liver-related causes) and 22 in the control group (12 of liver-related causes) (P=0.18). At 3.8 years, the overall death rate was 6.6% among patients who received peginterferon and 4.6% among control patients (P=0.18). There was a significant difference in mortality between the treatment and control groups among patients with noncirrhotic fibrosis (5.0% and 1.9%, respectively; P=0.04), but not among patients with cirrhosis (9.1% and 8.4%, respectively; P=0.93).

Among patients with noncirrhotic fibrosis, 86.4% had either undergone a biopsy or had a clinical outcome by the 1.5-year time point, and 80.0% had either undergone a biopsy or had a clinical outcome by the 3.5-year time point. The rate of progression to cirrhosis (defined as an increase of at least 2 points in the Ishak fibrosis score) among patients with noncirrhotic fibrosis was similar in the treatment and control groups (28.2% [95% CI, 22.8 to 33.9] and 31.9% [95% CI, 26.0 to 37.8], respectively; P=0.46). Among patients with noncirrhotic fibrosis, the mean Ishak fibrosis score increased by 0.38 and 0.42 points at year 3.5 in the treatment and control groups, respectively, a difference of 0.04 (95% CI, −0.27 to 0.20; P=0.77), despite a significant mean reduction in the necroinflammatory score in the treatment group as compared with the control group (−1.03 vs. −0.03; difference, −1.00; 95% CI, −1.46 to −0.55; P<0.001). Among patients with cirrhosis, a similar, significant decrease in the necroinflammatory score occurred in treated patients as compared with control patients (−1.38 vs. −0.33; difference, −1.05; 95% CI, −1.66 to −0.44; P<0.001). In a post hoc exploratory analysis, we did not observe heterogeneity of treatment effect according to baseline characteristics (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org).

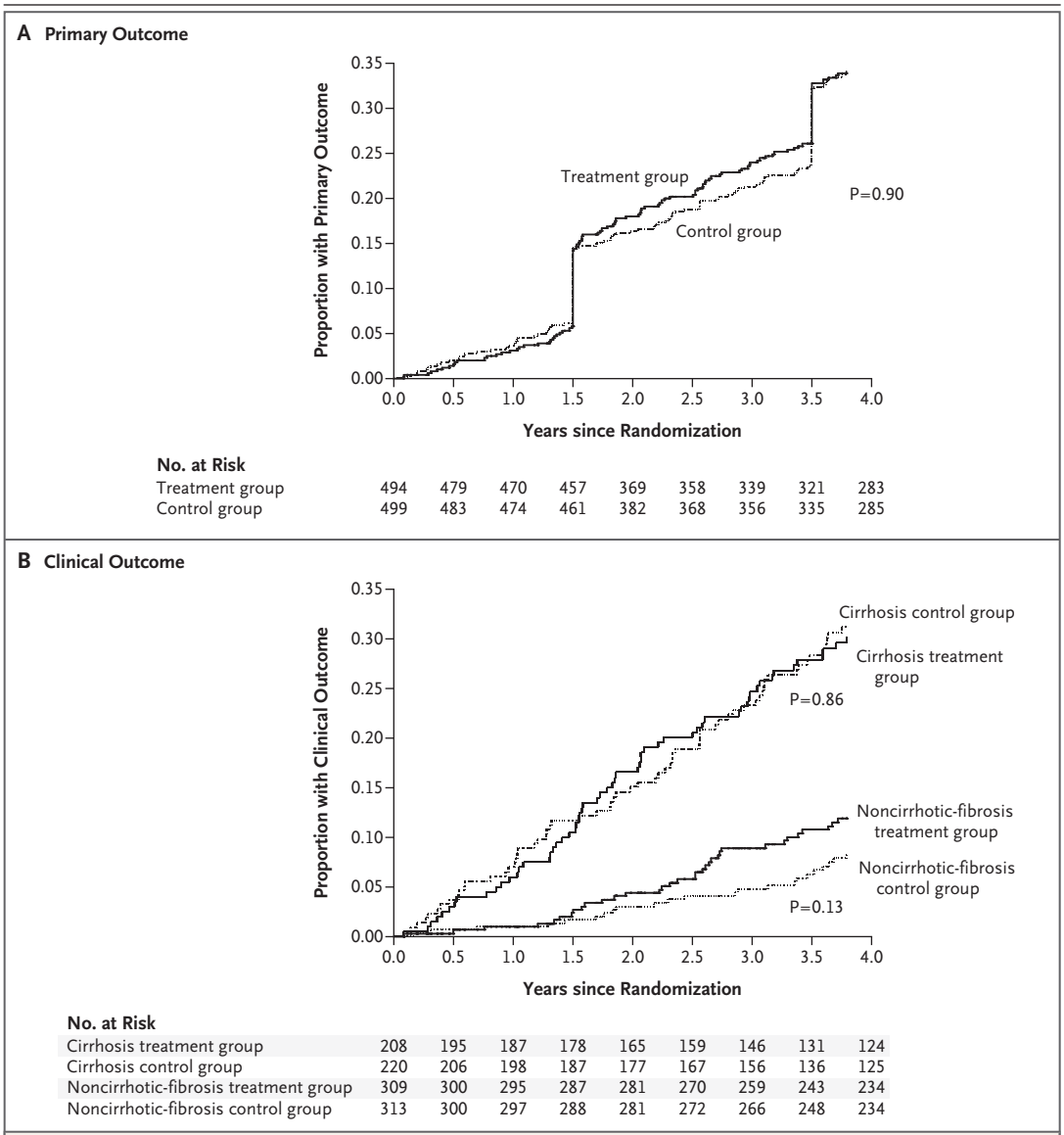

Figure 2. Kaplan–Meier Analysis of Time to the Primary Outcome and the First Clinical Outcome.

Panel A shows the time to the first primary outcome (death, hepatic decompensation, hepatocellular carcinoma, or histologic progression) according to group assignment (treatment or control). The large steps in the plot reflect liver biopsies performed for the study. Panel B shows the time to the first clinical outcome (death, hepatic decompensation, or hepatocellular carcinoma) according to group assignment and with patients stratified according to the presence or absence of cirrhosis.

ADVERSE EVENTS AND DRUG DISCONTINUATION

In the treatment group, 3991 adverse events occurred among 486 patients, as compared with 3129 adverse events among 492 patients in the control group; 330 patients had at least one serious adverse event (Table 3). A higher proportion of patients in the treatment group than in the control group had at least one serious adverse event (38.6% [95% CI, 33.8 to 43.3] vs. 31.8% [95% CI, 27.6 to 36.1] by Kaplan–Meier analysis), but this difference was not significant (P=0.07). Infectious complications, predominantly bacterial infections, were the most frequent adverse events.

During the trial, 157 treated patients discontinued therapy, including 43 who dropped out of the study and 114 who stopped therapy but agreed

to follow-up monitoring. The reasons for stopping therapy included anemia, neutropenia, or thrombocytopenia (25 patients); depression (22 patients); other adverse events (65 patients); and patient refusal (72 patients). Some patients had more than one reason for discontinuing treatment. Dose modifications for adverse events were frequent; by year 3.5, only 58.9% of patients who were still in the study and had not had a clinical outcome were receiving the full 90-μg prescribed weekly dose of peginterferon (Fig. 3). Nine patients assigned to the control group sought and received antiviral therapy with peginterferon, with or without ribavirin, outside the study for some period during the randomized phase.

DISCUSSION

The HALT-C trial assessed whether patients with chronic hepatitis C who had not had a sustained virologic response after optimal therapy with peginterferon and ribavirin would benefit from peginterferon maintenance therapy at a lower and perhaps better-tolerated dose.[12] The outcome measure in most trials of antiviral therapy for chronic hepatitis C has been a sustained virologic response (i.e., undetectable HCV RNA in the serum 6 months after the cessation of therapy[5]), which has been shown to be associated with long-term improvement in disease.[6] In this trial, among patients who had not had a sustained virologic response after previous therapy, the criteria for efficacy of therapy were the prevention of progression to cirrhosis (among patients with noncirrhotic fibrosis at baseline) and the prevention of clinical progression of disease. To test the efficacy of long-term maintenance therapy, we randomly assigned 1050 patients with advanced fibrosis who had not had a response to peginterferon and ribavirin to several years of treatment or no treatment.

When the trial began, peginterferon was not approved by the FDA, and many patients who had been treated with standard interferon had not received concomitant ribavirin. Therefore, to ensure that we were assessing maintenance therapy in a cohort of patients who had not had a sustained virologic response to optimal therapy, we required a lead-in phase of retreatment with a regimen of peginterferon and ribavirin that had been shown to be superior to standard interferon with ribavirin.[19] This lead-in phase provided not only a well-pedigreed cohort of uniformly documented patients who had not had a response to treatment but also a thoroughly evaluated group of patients highly motivated for such a demanding, long-term trial.

Maintenance peginterferon therapy was associated with significant decreases in serum HCV RNA levels, serum alanine aminotransferase levels, and histologic necroinflammatory scores. Nevertheless, therapy was not associated with a reduction in clinical outcomes or in the progression of fibrosis. Progression of liver disease (the primary study outcome) occurred in 34.1% of the treatment group and 33.8% of the control group. Among patients with bridging fibrosis at baseline, cirrhosis developed by year 3.5 in similar percentages of treated and control patients (28.2% and 31.9%, respectively). The high rate of clinical outcomes among patients with noncirrhotic fibrosis at baseline was not predicted and is worthy of note. A possible explanation for this finding is that liver biopsy underestimates the presence of cirrhosis, as evidenced by the presence of varices in some patients classified as having noncirrhotic fibrosis. Nonetheless, it is clear that patients with chronic hepatitis C and bridging fibrosis detected on biopsy appear to be at substantial risk for clinical outcomes, including hepatocellular carcinoma. The finding of excess deaths at 3.5 years among treated patients with noncirrhotic fibrosis at baseline was unexpected and is not well explained by other findings (i.e., changes in laboratory-test results and the rate of development of cirrhosis). All patients in this study continue to be followed prospectively, and it is important to assess whether this difference in mortality between treated patients and control patients will persist.

Our findings contradict the results of several previous studies, but those studies either were not prospective, randomized trials or relied on end points other than clinical outcomes.[9-11] Several reports have suggested that interferon-based therapy in patients with chronic hepatitis C, even with a course as brief as 6 months and even with no sustained virologic response, can reduce the frequency of hepatocellular carcinoma; however, these nonrandomized studies were based on retrospective analyses.[10,11] In contrast, a recent small study involving 102 patients with hepatitis C and cirrhosis who had not had a response to previous therapy with peginterferon and ribavirin and

Table 3. Serious Adverse Events in Treated and Control Patients with Noncirrhotic Fibrosis or Cirrhosis at Baseline.*

Event	Noncirrhotic Fibrosis		Cirrhosis		Total	
	Treatment Group (N=309)	Control Group (N=313)	Treatment Group (N=208)	Control Group (N=220)	Treatment Group (N=517)	Control Group (N=533)
	number of patients					
Any serious adverse event†	96	83	79	72	175	155
Blood and lymphatic	1	3	6	2	7	5
Anemia	0	3	3	2	3	5
Thrombocytopenia or pancytopenia	1	0	3	0	4	0
Cardiovascular and circulatory	12	10	6	9	18	19
Atherosclerotic disease	9	5	7	4	16	9
Arrhythmia	2	5	1	3	3	8
Other cardiovascular or circulatory event	2	1	2	4	4	5
Digestive system	12	13	6	13	18	26
Nonvariceal gastrointestinal bleeding	2	3	2	6	4	9
Hernia or intestinal obstruction	4	1	1	2	5	3
Other digestive system event	6	10	5	5	11	15
Endocrine and metabolic	7	5	2	5	9	10
Electrolyte, mineral, or water imbalance	4	2	2	5	6	7
Diabetes and its complications	1	1	0	1	1	2
Thyroid disease	2	2	0	0	2	2
Genitourinary and reproductive	8	4	4	6	12	10
Renal or urinary diseases	8	5	3	3	11	8
Gynecologic, menstrual, or sexual disorders	1	1	1	4	2	5
Hepatobiliary	14	6	6	12	20	18
Gallbladder disease	9	6	4	9	13	15
Other pancreatic or biliary disorders	5	1	2	4	7	5
Liver-disease events other than primary or secondary outcomes	1	0	0	1	1	1
Infection and infectious diseases	18	17	26	27	44	44
Mucocutaneous	2	6	7	10	9	16
Respiratory tract	9	2	10	9	19	11
Systemic	3	1	7	3	10	4
Other infections or infectious-disease events	5	10	10	9	15	19
Injury or poisoning	3	5	5	6	8	11
Injury	3	4	1	6	4	10
Drug reaction	0	2	4	0	4	2
Liver-biopsy complication	4	6	4	5	8	11
Musculoskeletal	16	14	11	10	27	24
Musculoskeletal surgery	18	13	7	8	25	21
Arthritis or back pain	5	3	4	3	9	6
Neoplasm	6	8	3	3	9	11
Malignant	5	7	3	3	8	10
Benign	1	3	0	0	1	3
Neurologic	1	5	5	1	6	6
Cerebral aneurysm, infarct, or stroke	1	4	2	0	3	4
Other neurologic event	0	1	3	1	3	2
Psychiatric	8	4	5	4	13	8
Affective disorders or delirium	7	2	1	2	8	4
Suicidal ideation or attempt	0	2	4	2	4	4
Substance abuse	2	1	1	0	3	1

Table 3. (Continued.)

Event	Noncirrhotic Fibrosis		Cirrhosis		Total	
	Treatment Group (N=309)	Control Group (N=313)	Treatment Group (N=208)	Control Group (N=220)	Treatment Group (N=517)	Control Group (N=533)
	number of patients					
Respiratory	1	4	1	3	2	7
Benign skin and nail disorders	0	1	0	1	0	2
Signs or symptoms‡	16	13	12	13	28	26
Cardiovascular	5	3	5	3	10	6
Hepatobiliary	6	3	2	3	8	6
Neurologic	5	2	2	4	7	6
Digestive	3	3	1	0	4	3
Other	1	4	3	4	4	8

* Patients are counted only once in each row of the table but may appear in more than one row.
† The percentage of patients with at least one serious adverse event, as estimated by Kaplan–Meier analysis, was 38.6% (95% CI, 33.8 to 43.3) in the treatment group and 31.8% (95% CI, 27.6 to 36.1) in the control group. The hazard ratio, adjusted for the presence or absence of cirrhosis, was 1.22 (95% CI, 0.99 to 1.52; P=0.07 by Cox regression).
‡ These clinical signs and symptoms are not associated with a specific diagnosis but are still classified as a serious adverse event. After serious adverse events related to death or other study-related clinical outcomes were excluded, 284 serious adverse events were recorded among 175 patients in the treatment group and 283 serious adverse events were recorded among 155 patients in the control group.

who were randomly assigned to receive either standard interferon or no treatment for 24 months yielded results similar to those of our trial.[20]

Several reports have suggested that interferon-based therapy in patients with chronic hepatitis C may reduce the risk of hepatocellular carcinoma among those patients with a sustained virologic response.[10,11] The HALT-C trial was a large-scale, randomized, controlled assessment of the effect of interferon on the incidence of hepatocellular carcinoma, and our findings show definitively that, even when maintained for several years, peginterferon therapy does not reduce the incidence of hepatocellular carcinoma in patients with advanced fibrosis and persistent viremia.

In the HALT-C trial, we used half the recommended dose of peginterferon alfa-2a (90 μg rather than 180 μg per week) because of concern about adverse events that may be associated with full-dose, long-term peginterferon therapy. Indeed, in this study, which was conducted among highly motivated patients, the starting peginterferon dose was maintained for the full 3.5 years in only 59% of patients. Higher doses of peginterferon might have been more effective in suppressing HCV replication and might have prevented disease progression. In addition, patients in the HALT-C trial did not receive long-term ribavirin with peginterferon, which might have been more potent than monotherapy in suppressing HCV RNA levels and improving clinical outcomes; however, the preliminary data suggesting that long-term antiviral therapy improves histologic results were generated in trials of interferon monotherapy. Furthermore, the rate of adverse events associated with maintenance therapy would almost certainly have been higher had ribavirin or full-dose peginterferon been included in the maintenance regimen.

Shiffman et al.[9] found that among patients who did not have a viral response to interferon therapy but who had a histologic response after 6 months, extended treatment suppressed HCV RNA levels, with reductions in necroinflammation and fibrosis. Unfortunately, the degree of virologic suppression in the HALT-C trial did not result in a diminished rate of disease progression, although theoretically, maintenance therapy that is associated with more marked suppression of serum HCV RNA levels might be more effective. We conclude that long-term maintenance therapy with half-dose peginterferon is ineffective in preventing clinical and histologic disease progression and is not indicated in patients with hepatitis C–associated advanced fibrosis, with or without cirrhosis, who have not had a response to a

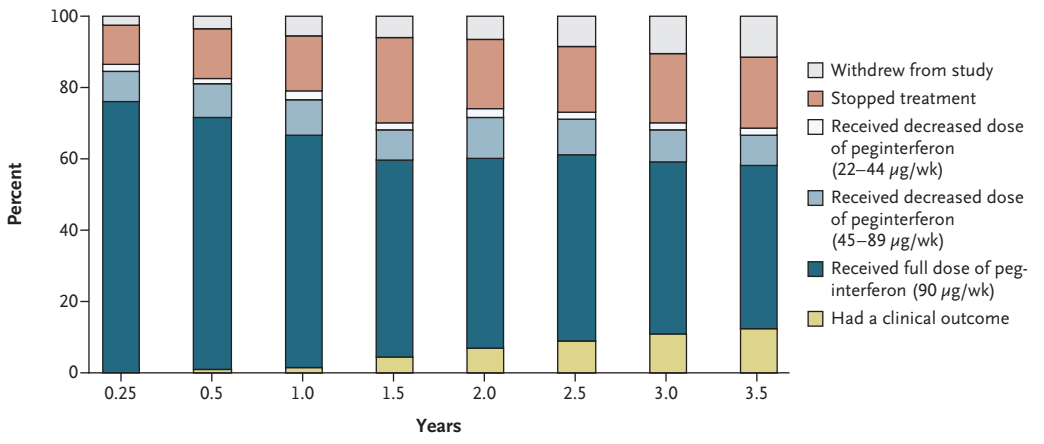

Figure 3. Changes in Dose or Discontinuation of Peginterferon among Patients in the Treatment Group.

The figure shows the proportion of patients who had a clinical outcome and stopped treatment, received a full dose of peginterferon (90 μg per week), decreased their dose of peginterferon (to either 45 to 89 μg or 22 to 44 μg per week), withdrew from the study, or stopped treatment but continued to be followed for assessment of outcomes.

standard course of peginterferon and ribavirin therapy.

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APPENDIX

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Dallas (NIDDK N01-DK-9-2321, GCRC M01-RR-00633) — T.E. Rogers, P.F. Malet, J. Shelton, N. Crowder, R. Elbein; *University of Southern California, Los Angeles* (NIDDK N01-DK-9-2325, GCRC M01-RR-00043) — S. Govindarajan, C.B. Jones, S.L. Milstein; *University of Michigan Medical Center, Ann Arbor* (NIDDK N01-DK-9-2323, GCRC M01-RR-00042) — R.J. Fontana, J.K. Greenson, P.A. Richtmyer; *Virginia Commonwealth University Health System, Richmond* (NIDDK N01-DK-9-2322, GCRC M01-RR-00065) — R.K. Sterling, M.J. Contos, A.S. Mills, C. Hofmann, P. Smith; *Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD* — T.J. Liang, D. Kleiner, Y. Park, E. Rivera, V. Haynes-Williams; *Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD* — L.B. Seeff, P.R. Robuck, J.H. Hoofnagle; *University of Washington, Seattle* (NIDDK N01-DK-9-2318) — D.R. Gretch, M. Chung, R. Shankar; *New England Research Institutes, Watertown, MA* (NIDDK N01-DK-9-2328) — M.C. Bell, A.M. Stoddard, T.M. Curto, L.J. Massey, M.S. Mihova, D. Naishadham, L. Padmanabhan, D. Tran, F.Y. Chen; *Armed Forces Institute of Pathology, Washington, DC* — Z.D. Goodman; *Data and Safety Monitoring Board* — G.L. Davis (chair), G. Garcia-Tsao, M. Kutner, S.M. Lemon, R.P. Perrillo.

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CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most clinical trials for publication only if they have been registered (see N Engl J Med 2004;351:1250-1). Current information on requirements and appropriate registries is available at www.icmje.org/faq.pdf.

Attachment 2

SAS 9.1 Log
for programming code submitted
for the replication of results
in Table 1 and Figure 2b in
Bisceglie AM, et.al. [Dec 2008]

```
NOTE: Copyright (c) 2002-2003 by SAS Institute Inc., Cary, NC, USA.
NOTE: SAS (r) 9.1 (TS1M3)
      Licensed to RTI INTERNATIONAL, Site 0047670001.
NOTE: This session is executing on the XP_PRO  platform.



NOTE: SAS 9.1.3 Service Pack 4

NOTE: SAS initialization used:
      real time           2.07 seconds
      cpu time            0.67 seconds

1    options ps=65 ls=78 nonumber formchar='|----|+\---+=|-^<>*' mprint
orientation=portrait;
2
3    * SAS program for data integrity check of: Halt-C Main Study Paper *;
4    * Prolonged Therapy of Advanced Chronic Hepatitis C with Low-Dose Peginterferon
*;
5    * NEJM 2008 359: 2429-41 *;
6    * Program by:  S.Tan, NIDDK Central Repository, June 30 2009 (update 10/15/09);
7
8    libname leadin 'Z:\03_Data_And_Tools\Studies\HALT-C\official-archive\HALT-C
Data\LEADIN
8  ! phase';
NOTE: Libref LEADIN was successfully assigned as follows:
      Engine:        V9
      Physical Name: Z:\03_Data_And_Tools\Studies\HALT-C\official-archive\HALT-C
Data\LEADIN phase
9    libname haltc_rx 'Z:\03_Data_And_Tools\Studies\HALT-C\official-archive\HALT-C
Data\Randomized
9  !  phase';
NOTE: Libref HALTC_RX was successfully assigned as follows:
      Engine:        V9
      Physical Name: Z:\03_Data_And_Tools\Studies\HALT-C\official-archive\HALT-C
Data\Randomized
      phase
10
11   libname halt_pap 'Z:\05_Users\Sylvia\Halt-C\analysis data';
NOTE: Libref HALT_PAP was successfully assigned as follows:
      Engine:        V9
      Physical Name: Z:\05_Users\Sylvia\Halt-C\analysis data
12
13   OPTIONS  FMTSEARCH=(leadin.formats0 leadin.formats1 haltc_rx.formats0
haltc_rx.formats1) ;
14
15   data haltrand; set halt_pap.rand_final;
16     if geno_grp2=1 then geno_1=1; else if geno_grp2 in (2,3,4) then geno_1=0;
17     * geno_grp2 is HCV genotype: 1,2,3,4&6 *;
18     * combine 2,3,4&6 together due to small s.s. *;
19     * note: this variable has already been created as geno1s *;
20
21
**************************************************************************
***;
22     * 10/15/2009: Diabetes indicator in table 1 is not in analysis dataset ;
23     * per email Halt-C DCC:  recreate Diabetes Indicator from datasets Form003 &
Form030 *;
24
25   * obtain existing diabetes indicator from Form 003 *;

NOTE: There were 1050 observations read from the data set HALT_PAP.RAND_FINAL.
NOTE: The data set WORK.HALTRAND has 1050 observations and 182 variables.
```

```
NOTE: DATA statement used (Total process time):
      real time           2.92 seconds
      cpu time            0.03 seconds


26   data diabetes; set leadin.form003; keep diabetes subj_id;
27     if diabetes = 2 then diabetes = 0;

NOTE: There were 1382 observations read from the data set LEADIN.FORM003.
NOTE: The data set WORK.DIABETES has 1382 observations and 2 variables.
NOTE: DATA statement used (Total process time):
      real time           1.73 seconds
      cpu time            0.01 seconds


28   proc sort data=diabetes; by subj_id;
29
30   * obtain fasting glucose values from Form 030*;

NOTE: There were 1382 observations read from the data set WORK.DIABETES.
NOTE: The data set WORK.DIABETES has 1382 observations and 2 variables.
NOTE: PROCEDURE SORT used (Total process time):
      real time           0.01 seconds
      cpu time            0.01 seconds


31   data Pt_type; set haltrand(keep=subj_id newstat);
32     if newstat=5 then express=1; * per DCC email 10/27/09:
33                                    patients randomized via the Express mechanism *;
34       else if newstat in (3,4) then express=0;
35         * 3: patients randomized after lead-in,
36           4: after breakthrough/relapse *;

NOTE: There were 1050 observations read from the data set WORK.HALTRAND.
NOTE: The data set WORK.PT_TYPE has 1050 observations and 3 variables.
NOTE: DATA statement used (Total process time):
      real time           0.00 seconds
      cpu time            0.00 seconds


37   proc sort; by subj_id;
38

NOTE: There were 1050 observations read from the data set WORK.PT_TYPE.
NOTE: The data set WORK.PT_TYPE has 1050 observations and 3 variables.
NOTE: PROCEDURE SORT used (Total process time):
      real time           0.00 seconds
      cpu time            0.00 seconds


39   data FORM30_R00 (keep=subj_id glucose_r00)
40        FORM30_W00 (keep=subj_id glucose_w00);
41     set haltc_rx.Form030_34_35 (keep=subj_id visit_num glucose);
42     visit_num=upcase(visit_num);
43     if visit_num='W00' then do;
44          glucose_w00 = glucose;
45          output form30_w00;
46          end;
47     if visit_num='R00' then do;
48            glucose_r00 = glucose;
49            output form30_r00;
50            end;
51      run;
```

```
NOTE: There were 27274 observations read from the data set HALTC_RX.FORM030_34_35.
NOTE: The data set WORK.FORM30_R00 has 385 observations and 2 variables.
NOTE: The data set WORK.FORM30_W00 has 1145 observations and 2 variables.
NOTE: DATA statement used (Total process time):
      real time           12.93 seconds
      cpu time            0.06 seconds


52   proc sort data=form30_w00;
53   by subj_id;

NOTE: There were 1145 observations read from the data set WORK.FORM30_W00.
NOTE: The data set WORK.FORM30_W00 has 1145 observations and 2 variables.
NOTE: PROCEDURE SORT used (Total process time):
      real time           0.01 seconds
      cpu time            0.01 seconds


54   proc sort data=form30_r00;
55   by subj_id; run;

NOTE: There were 385 observations read from the data set WORK.FORM30_R00.
NOTE: The data set WORK.FORM30_R00 has 385 observations and 2 variables.
NOTE: PROCEDURE SORT used (Total process time):
      real time           0.00 seconds
      cpu time            0.00 seconds


56
57   data alldiab;
58     merge pt_type (in=in1) diabetes form30_w00 form30_r00;
59     by subj_id; if in1;
60
61   * Express use R00 *;
62   if express=1 then  glucose = glucose_r00;
63     *Others use W00*;
64   else if express=0 then glucose = glucose_w00;
65
66     if glucose ne . then highglucose=(glucose>126);
67     diabhighglu=max(of diabetes,highglucose);
68     label
69       diabhighglu='Glucose >= 126 OR diabetes' /* used in Table 1  */
70       diabetes='History of diabetes'
71       glucose='Glucose, mg/dL';

NOTE: There were 1050 observations read from the data set WORK.PT_TYPE.
NOTE: There were 1382 observations read from the data set WORK.DIABETES.
NOTE: There were 1145 observations read from the data set WORK.FORM30_W00.
NOTE: There were 385 observations read from the data set WORK.FORM30_R00.
NOTE: The data set WORK.ALLDIAB has 1050 observations and 9 variables.
NOTE: DATA statement used (Total process time):
      real time           0.01 seconds
      cpu time            0.01 seconds


72   proc sort data=haltrand; by subj_id;

NOTE: There were 1050 observations read from the data set WORK.HALTRAND.
NOTE: The data set WORK.HALTRAND has 1050 observations and 182 variables.
NOTE: PROCEDURE SORT used (Total process time):
      real time           0.01 seconds
      cpu time            0.01 seconds
```

```
73   data haltrand; merge haltrand(in=in1) alldiab(keep=subj_id diabhighglu); by
subj_id; if in1;
73 ! run;

NOTE: There were 1050 observations read from the data set WORK.HALTRAND.
NOTE: There were 1050 observations read from the data set WORK.ALLDIAB.
NOTE: The data set WORK.HALTRAND has 1050 observations and 183 variables.
NOTE: DATA statement used (Total process time):
      real time           0.01 seconds
      cpu time            0.01 seconds


74   ************************************************************;
75
76     title Table 1:  freqs/chisq tests for nominal/categorical variables ;
77   proc freq; tables (basevr female race4 diabhighglu geno_grp2 geno1s cirrhosis
77 ! esoph_var)*rand_grp/chisq ; format rand_grp randgrp.; run;

NOTE: There were 1050 observations read from the data set WORK.HALTRAND.
NOTE: PROCEDURE FREQ used (Total process time):
      real time           0.46 seconds
      cpu time            0.03 seconds


78
79     title Table 1:  means for continuous variables ;
80   proc means maxdec=2; class rand_grp; format rand_grp randgrp.;
81     var age_rand durinf bmi logcount alt alt_ratio tot_bilirubi albumin
82     prothrombin fibro_ishak_s00 infla_ishak_s00 spec_length_s00; run;

NOTE: There were 1050 observations read from the data set WORK.HALTRAND.
NOTE: PROCEDURE MEANS used (Total process time):
      real time           0.67 seconds
      cpu time            0.01 seconds


83
84     title Table 1:  ttests for continuous variables ;
85   proc ttest; class rand_grp; format rand_grp randgrp.;
86     var age_rand durinf bmi logcount alt alt_ratio tot_bilirubi albumin
87     prothrombin fibro_ishak_s00 infla_ishak_s00 spec_length_s00; run;

NOTE: There were 1050 observations read from the data set WORK.HALTRAND.
NOTE: PROCEDURE TTEST used (Total process time):
      real time           0.28 seconds
      cpu time            0.00 seconds


88
89     title Table 1:  median number of drinks ;
90   proc univariate; class rand_grp; var life_drinks; format rand_grp randgrp.; run;

NOTE: PROCEDURE UNIVARIATE used (Total process time):
      real time           0.32 seconds
      cpu time            0.00 seconds


91
92     title Table 1:  wilcoxon rank-sum test for number of drinks ;
93   proc npar1way wilcoxon; class rand_grp; var life_drinks; format rand_grp
randgrp.; run;
```

```
NOTE: There were 1050 observations read from the data set WORK.HALTRAND.
NOTE: PROCEDURE NPAR1WAY used (Total process time):
      real time           0.32 seconds
      cpu time            0.00 seconds


94   /*
95     * Table 2. First primary outcome in Treated and Control Patients with
Noncirrhotic Fibrosis
95 !  or Cirrhosis at Baseline. ;
96     * Results not reported in DSIC *;
97     * 100% match *;
98   data haltrand; set haltrand;
99     if rand_grp=1 then treatment=1; else if rand_grp=2 then treatment=0;
100  proc sort; by cirrhosis;
101  proc freq; by cirrhosis; tables (first_out clin_tpi)*rand_grp/missing; run;
102  proc freq; by cirrhosis; tables tpi*rand_grp; where first_out=.; run;
103  proc freq; tables (first_out clin_tpi)*rand_grp/missing; run;
104  proc lifetest data=haltrand interval=(0 to 3.85 by 0.01) outsurv=all_clintpi;
105    time clin_tpi_yeara*clin_tpi(0);  by cirrhosis;
106    strata rand_grp; format rand_grp randgrp.;run;
107  proc lifetest data=haltrand interval=(0 to 3.85 by 0.01) outsurv=all_clintpi;
108    time clin_tpi_yeara*clin_tpi(0);
109    strata rand_grp; format rand_grp randgrp.;run; */
110  /*
111    * Figure 2. Kaplan Meier analysis of time to primary outcome and the first
clinical
111! outcome. *;
112    * figure A: time to first primary outcome (not reported in DSIC) *;
113  proc sort data=haltrand; by rand_grp;
114  proc lifetest data=haltrand plots=(s,h,ls,lls) interval=(0 to 3.85 by 0.01);
115    time clin_tpi_yeara*clin_tpi(0);
116    strata rand_grp; format rand_grp randgrp.; run;
117    * (clin_tpi_yeara: Years for TPI or clinical outcome) *; */
118
119  Title figure B: time to first clinical outcome ;
120    * Reported in DSIC *;
121  proc sort data=haltrand; by cirrhosis rand_grp;

NOTE: There were 1050 observations read from the data set WORK.HALTRAND.
NOTE: The data set WORK.HALTRAND has 1050 observations and 183 variables.
NOTE: PROCEDURE SORT used (Total process time):
      real time           0.01 seconds
      cpu time            0.01 seconds


122  proc lifetest data=haltrand plots=(s,h,ls,lls) interval=(0 to 3.85 by 0.01);
123    time outc_yeara*pri_outcome(0);
124    strata cirrhosis rand_grp; format rand_grp randgrp.; run;

NOTE: HAZARD estimates are not computed with the product-limit method.
NOTE: Graph's name, LIFETEST, changed to LIFETES1. LIFETEST is already used or not a
valid SAS
      name.
NOTE: Graph's name, LIFETEST, changed to LIFETES2. LIFETEST is already used or not a
valid SAS
      name.
NOTE: PROCEDURE LIFETEST used (Total process time):
      real time           0.76 seconds
      cpu time            0.12 seconds
```

Attachment 3

SAS 9.1 Output
for programming code submitted
for the replication of results
in Table 1 and Figure 2b in
Bisceglie AM, et.al. [Dec 2008]

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Table of BASEVR by RAND_GRP

BASEVR(HCV at base:Null L-I,Other L-I,Bt/rel,Express)
RAND_GRP(Randomization group)

Frequency Percent Row Pct Col Pct	1=Treatment group	2=Control group	Total
1	156 14.86 48.75 30.17	164 15.62 51.25 30.77	320 30.48
2	173 16.48 50.58 33.46	169 16.10 49.42 31.71	342 32.57
3	71 6.76 47.02 13.73	80 7.62 52.98 15.01	151 14.38
4	117 11.14 49.37 22.63	120 11.43 50.63 22.51	237 22.57
Total	517 49.24	533 50.76	1050 100.00

Statistics for Table of BASEVR by RAND_GRP

Statistic	DF	Value	Prob
Chi-Square	3	0.5775	0.9016
Likelihood Ratio Chi-Square	3	0.5777	0.9015
Mantel-Haenszel Chi-Square	1	0.0042	0.9486
Phi Coefficient		0.0235	
Contingency Coefficient		0.0234	
Cramer's V		0.0235	

Sample Size = 1050

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Table of FEMALE by RAND_GRP

FEMALE(Female) RAND_GRP(Randomization group)

Frequency Percent Row Pct Col Pct	1=Treatment group	2=Control group	Total
0	362 34.48 48.59 70.02	383 36.48 51.41 71.86	745 70.95
1	155 14.76 50.82 29.98	150 14.29 49.18 28.14	305 29.05
Total	517 49.24	533 50.76	1050 100.00

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Statistics for Table of FEMALE by RAND_GRP

Statistic	DF	Value	Prob
Chi-Square	1	0.4302	0.5119
Likelihood Ratio Chi-Square	1	0.4302	0.5119
Continuity Adj. Chi-Square	1	0.3456	0.5566
Mantel-Haenszel Chi-Square	1	0.4298	0.5121
Phi Coefficient		-0.0202	
Contingency Coefficient		0.0202	
Cramer's V		-0.0202	

Fisher's Exact Test

Cell (1,1) Frequency (F)	362
Left-sided Pr <= F	0.2783
Right-sided Pr >= F	0.7654
Table Probability (P)	0.0437
Two-sided Pr <= P	0.5408

Sample Size = 1050

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Table of RACE4 by RAND_GRP

RACE4(Race (White, Black, Hispanic, Other))
RAND_GRP(Randomization group)

Frequency Percent Row Pct Col Pct	1=Treatment group	2=Control group	Total
1	372 35.43 49.47 71.95	380 36.19 50.53 71.29	752 71.62
2	97 9.24 50.79 18.76	94 8.95 49.21 17.64	191 18.19
3	39 3.71 46.43 7.54	45 4.29 53.57 8.44	84 8.00
4	9 0.86 39.13 1.74	14 1.33 60.87 2.63	23 2.19
Total	517 49.24	533 50.76	1050 100.00

Statistics for Table of RACE4 by RAND_GRP

Statistic	DF	Value	Prob
Chi-Square	3	1.4043	0.7045
Likelihood Ratio Chi-Square	3	1.4130	0.7025
Mantel-Haenszel Chi-Square	1	0.5456	0.4601
Phi Coefficient		0.0366	
Contingency Coefficient		0.0365	
Cramer's V		0.0366	

Sample Size = 1050

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Table of diabhighglu by RAND_GRP

diabhighglu(Glucose >= 126 OR diabetes)
RAND_GRP(Randomization group)

Frequency Percent Row Pct Col Pct	1=Treatment group	2=Control group	Total
0	391 37.24 49.12 75.63	405 38.57 50.88 75.98	796 75.81
1	126 12.00 49.61 24.37	128 12.19 50.39 24.02	254 24.19
Total	517 49.24	533 50.76	1050 100.00

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Statistics for Table of diabhighglu by RAND_GRP

Statistic	DF	Value	Prob
Chi-Square	1	0.0182	0.8928
Likelihood Ratio Chi-Square	1	0.0182	0.8928
Continuity Adj. Chi-Square	1	0.0039	0.9500
Mantel-Haenszel Chi-Square	1	0.0182	0.8928
Phi Coefficient		-0.0042	
Contingency Coefficient		0.0042	
Cramer's V		-0.0042	

Fisher's Exact Test

Cell (1,1) Frequency (F)	391
Left-sided Pr <= F	0.4749
Right-sided Pr >= F	0.5820
Table Probability (P)	0.0569
Two-sided Pr <= P	0.9426

Sample Size = 1050

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Table of GENO_GRP2 by RAND_GRP

GENO_GRP2(HCV genotype: 1,2,3,4&6)
RAND_GRP(Randomization group)

Frequency Percent Row Pct Col Pct	1=Treatment group	2=Control group	Total
1	492 46.86 50.20 95.16	488 46.48 49.80 91.56	980 93.33
2	6 0.57 28.57 1.16	15 1.43 71.43 2.81	21 2.00
3	11 1.05 33.33 2.13	22 2.10 66.67 4.13	33 3.14
4	8 0.76 50.00 1.55	8 0.76 50.00 1.50	16 1.52
Total	517 49.24	533 50.76	1050 100.00

Statistics for Table of GENO_GRP2 by RAND_GRP

Statistic	DF	Value	Prob
Chi-Square	3	7.2980	0.0630
Likelihood Ratio Chi-Square	3	7.4951	0.0577
Mantel-Haenszel Chi-Square	1	2.9934	0.0836
Phi Coefficient		0.0834	
Contingency Coefficient		0.0831	
Cramer's V		0.0834	

Sample Size = 1050

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Table of geno1s by RAND_GRP

geno1s(Genotype 1 No/Yes by any method)
RAND_GRP(Randomization group)

Frequency Percent Row Pct Col Pct	1=Treatment group	2=Control group	Total
0	25 2.38 35.71 4.84	45 4.29 64.29 8.44	70 6.67
1	492 46.86 50.20 95.16	488 46.48 49.80 91.56	980 93.33
Total	517 49.24	533 50.76	1050 100.00

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Statistics for Table of geno1s by RAND_GRP

Statistic	DF	Value	Prob
Chi-Square	1	5.4881	0.0191
Likelihood Ratio Chi-Square	1	5.5672	0.0183
Continuity Adj. Chi-Square	1	4.9237	0.0265
Mantel-Haenszel Chi-Square	1	5.4829	0.0192
Phi Coefficient		-0.0723	
Contingency Coefficient		0.0721	
Cramer's V		-0.0723	

Fisher's Exact Test

Cell (1,1) Frequency (F)	25
Left-sided Pr <= F	0.0129
Right-sided Pr >= F	0.9935
Table Probability (P)	0.0063
Two-sided Pr <= P	0.0253

Sample Size = 1050

Table of CIRRHOSIS by RAND_GRP

CIRRHOSIS(Cirrhosis on biopsy (Ishak 5-6)) RAND_GRP(Randomization group)

Frequency / Percent / Row Pct / Col Pct	1=Treatment group	2=Control group	Total
0	309	313	622
	29.43	29.81	59.24
	49.68	50.32	
	59.77	58.72	
1	208	220	428
	19.81	20.95	40.76
	48.60	51.40	
	40.23	41.28	
Total	517	533	1050
	49.24	50.76	100.00

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Statistics for Table of CIRRHOSIS by RAND_GRP

Statistic	DF	Value	Prob
Chi-Square	1	0.1184	0.7308
Likelihood Ratio Chi-Square	1	0.1184	0.7308
Continuity Adj. Chi-Square	1	0.0791	0.7785
Mantel-Haenszel Chi-Square	1	0.1183	0.7309
Phi Coefficient		0.0106	
Contingency Coefficient		0.0106	
Cramer's V		0.0106	

Fisher's Exact Test

Cell (1,1) Frequency (F)	309
Left-sided Pr <= F	0.6579
Right-sided Pr >= F	0.3893
Table Probability (P)	0.0472
Two-sided Pr <= P	0.7536

Sample Size = 1050

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Table of ESOPH_VAR by RAND_GRP

ESOPH_VAR(F023: Esophogeal varices (0/1))
RAND_GRP(Randomization group)

Frequency Percent Row Pct Col Pct	1=Treatment group	2=Control group	Total
0	377 37.11 49.93 75.70	378 37.20 50.07 72.97	755 74.31
1	121 11.91 46.36 24.30	140 13.78 53.64 27.03	261 25.69
Total	498 49.02	518 50.98	1016 100.00

Frequency Missing = 34

Table 1: freqs/chisq tests for nominal/categorical variables
16:59 Tuesday, October 27, 2009

The FREQ Procedure

Statistics for Table of ESOPH_VAR by RAND_GRP

Statistic	DF	Value	Prob
Chi-Square	1	0.9911	0.3195
Likelihood Ratio Chi-Square	1	0.9920	0.3193
Continuity Adj. Chi-Square	1	0.8533	0.3556
Mantel-Haenszel Chi-Square	1	0.9902	0.3197
Phi Coefficient		0.0312	
Contingency Coefficient		0.0312	
Cramer's V		0.0312	

Fisher's Exact Test

Cell (1,1) Frequency (F)	377
Left-sided Pr <= F	0.8571
Right-sided Pr >= F	0.1778
Table Probability (P)	0.0349
Two-sided Pr <= P	0.3505

Effective Sample Size = 1016
Frequency Missing = 34

Table 1: means for continuous variables

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The MEANS Procedure

Randomization group	N Obs	Variable	Label	N	Mean
1=Treatment group	517	AGE_RAND	Age at Randomization	517	51.15
		DURINF	Duration of infection - MD	485	28.84
		BMI	Body Mass Index	517	29.73
		logcount	Log HCV RNA (IU/mL)	517	6.42
		alt	ALT, U/L	517	104.03
		ALT_RATIO	ALT ratio to ULN	517	2.07
		tot_bilirubi	Total bilirubin, mg/dL	517	0.79
		albumin	Albumin, g/dL	517	3.88
		prothrombin	Prothrombin time,INR	517	1.04
		FIBRO_ISHAK_S00	Ishak Fibrosis S00 biopsy	517	4.08
		INFLA_ISHAK_S00	Ishak inflammation S00	517	7.55
		SPEC_LENGTH_S00	Specimen length S00	517	1.84
2=Control group	533	AGE_RAND	Age at Randomization	533	50.08
		DURINF	Duration of infection - MD	499	27.38
		BMI	Body Mass Index	533	29.99
		logcount	Log HCV RNA (IU/mL)	533	6.44
		alt	ALT, U/L	533	109.64
		ALT_RATIO	ALT ratio to ULN	533	2.18
		tot_bilirubi	Total bilirubin, mg/dL	533	0.78
		albumin	Albumin, g/dL	533	3.86
		prothrombin	Prothrombin time,INR	533	1.04
		FIBRO_ISHAK_S00	Ishak Fibrosis S00 biopsy	533	4.13
		INFLA_ISHAK_S00	Ishak inflammation S00	533	7.54
		SPEC_LENGTH_S00	Specimen length S00	533	1.77

Randomization group	N Obs	Variable	Label	Std Dev	Minimum
1=Treatment group	517	AGE_RAND	Age at Randomization	7.32	19.00
		DURINF	Duration of infection - MD	7.92	5.00
		BMI	Body Mass Index	5.34	18.38
		logcount	Log HCV RNA (IU/mL)	0.54	3.12
		alt	ALT, U/L	73.95	15.00
		ALT_RATIO	ALT ratio to ULN	1.53	0.30
		tot_bilirubi	Total bilirubin, mg/dL	0.41	0.20
		albumin	Albumin, g/dL	0.38	2.70
		prothrombin	Prothrombin time,INR	0.12	0.80
		FIBRO_ISHAK_S00	Ishak Fibrosis S00 biopsy	1.25	2.00
		INFLA_ISHAK_S00	Ishak inflammation S00	2.10	1.00
		SPEC_LENGTH_S00	Specimen length S00	0.97	0.20
2=Control group	533	AGE_RAND	Age at Randomization	6.99	19.00
		DURINF	Duration of infection - MD	8.01	9.00
		BMI	Body Mass Index	5.59	17.54

Table 1: means for continuous variables

16:59 Tuesday, October 27, 2009

The MEANS Procedure

Randomization group	N Obs	Variable	Label	Std Dev	Minimum
2=Control group	533	logcount	Log HCV RNA (IU/mL)	0.51	4.37
		alt	ALT, U/L	80.18	19.00
		ALT_RATIO	ALT ratio to ULN	1.70	0.38
		tot_bilirubi	Total bilirubin, mg/dL	0.39	0.10
		albumin	Albumin, g/dL	0.40	2.70
		prothrombin	Prothrombin time,INR	0.11	0.80
		FIBRO_ISHAK_S00	Ishak Fibrosis S00 biopsy	1.28	2.00
		INFLA_ISHAK_S00	Ishak inflammation S00	2.02	2.00
		SPEC_LENGTH_S00	Specimen length S00	0.76	0.20

Randomization group	N Obs	Variable	Label	Maximum
1=Treatment group	517	AGE_RAND	Age at Randomization	80.00
		DURINF	Duration of infection - MD	71.00
		BMI	Body Mass Index	58.36
		logcount	Log HCV RNA (IU/mL)	7.63
		alt	ALT, U/L	647.00
		ALT_RATIO	ALT ratio to ULN	13.55
		tot_bilirubi	Total bilirubin, mg/dL	3.80
		albumin	Albumin, g/dL	4.90
		prothrombin	Prothrombin time,INR	2.00
		FIBRO_ISHAK_S00	Ishak Fibrosis S00 biopsy	6.00
		INFLA_ISHAK_S00	Ishak inflammation S00	12.00
		SPEC_LENGTH_S00	Specimen length S00	15.00
2=Control group	533	AGE_RAND	Age at Randomization	72.00
		DURINF	Duration of infection - MD	58.00
		BMI	Body Mass Index	56.91
		logcount	Log HCV RNA (IU/mL)	7.52
		alt	ALT, U/L	772.00
		ALT_RATIO	ALT ratio to ULN	17.16
		tot_bilirubi	Total bilirubin, mg/dL	2.90
		albumin	Albumin, g/dL	4.90
		prothrombin	Prothrombin time,INR	1.60
		FIBRO_ISHAK_S00	Ishak Fibrosis S00 biopsy	6.00
		INFLA_ISHAK_S00	Ishak inflammation S00	12.00
		SPEC_LENGTH_S00	Specimen length S00	5.80

Table 1: ttests for continuous variables

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The TTEST Procedure

Statistics

Variable	RAND_GRP	N	Lower CL Mean	Mean	Upper CL Mean	Lower CL Std Dev	Std Dev	Upper CL Std Dev	Std Err
AGE_RAND	1=Treatment group	517	50.513	51.145	51.777	6.8958	7.3162	7.7917	0.3218
AGE_RAND	2=Control group	533	49.484	50.079	50.674	6.5957	6.9918	7.4388	0.3028
AGE_RAND	Diff (1-2)		0.1998	1.0663	1.9327	6.8598	7.1534	7.4733	0.4416
DURINF	1=Treatment group	485	28.132	28.839	29.546	7.4529	7.9221	8.4547	0.3597
DURINF	2=Control group	499	26.672	27.377	28.081	7.5393	8.0072	8.5374	0.3585
DURINF	Diff (1-2)		0.4657	1.4624	2.4591	7.6281	7.9653	8.334	0.5079
BMI	1=Treatment group	517	29.264	29.725	30.186	5.0289	5.3355	5.6822	0.2347
BMI	2=Control group	533	29.511	29.987	30.462	5.2739	5.5906	5.9481	0.2422
BMI	Diff (1-2)		-0.923	-0.261	0.4008	5.2422	5.4665	5.711	0.3374
logcount	1=Treatment group	517	6.3766	6.4233	6.47	0.5094	0.5405	0.5756	0.0238
logcount	2=Control group	533	6.3965	6.4395	6.4826	0.4771	0.5057	0.538	0.0219
logcount	Diff (1-2)		-0.08	-0.016	0.0471	0.5016	0.5231	0.5465	0.0323
alt	1=Treatment group	517	97.643	104.03	110.42	69.704	73.953	78.759	3.2525
alt	2=Control group	533	102.82	109.64	116.47	75.638	80.18	85.306	3.473
alt	Diff (1-2)		-14.96	-5.611	3.7375	74.01	77.177	80.629	4.764
ALT_RATIO	1=Treatment group	517	1.9419	2.0741	2.2063	1.4424	1.5304	1.6298	0.0673
ALT_RATIO	2=Control group	533	2.0396	2.184	2.3284	1.6008	1.6969	1.8054	0.0735
ALT_RATIO	Diff (1-2)		-0.306	-0.11	0.0859	1.5507	1.6171	1.6894	0.0998
tot_bilirubi	1=Treatment group	517	0.7567	0.7923	0.8278	0.3879	0.4115	0.4383	0.0181
tot_bilirubi	2=Control group	533	0.7513	0.7844	0.8176	0.3677	0.3898	0.4147	0.0169
tot_bilirubi	Diff (1-2)		-0.041	0.0078	0.0564	0.3842	0.4007	0.4186	0.0247
albumin	1=Treatment group	517	3.8476	3.8807	3.9137	0.3605	0.3825	0.4073	0.0168
albumin	2=Control group	533	3.8276	3.8619	3.8962	0.3804	0.4032	0.429	0.0175
albumin	Diff (1-2)		-0.029	0.0187	0.0664	0.377	0.3931	0.4107	0.0243
prothrombin	1=Treatment group	517	1.0303	1.0404	1.0505	0.1101	0.1168	0.1244	0.0051
prothrombin	2=Control group	533	1.0314	1.0405	1.0496	0.1009	0.1069	0.1138	0.0046

Table 1: ttests for continuous variables

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The TTEST Procedure

Statistics

Variable	RAND_GRP	N	Lower CL Mean	Mean	Upper CL Mean	Lower CL Std Dev	Std Dev	Upper CL Std Dev	Std Err
prothrombin	Diff (1-2)		-0.014	-1E-4	0.0135	0.1073	0.1119	0.1169	0.0069
FIBRO_ISHAK_S00	1=Treatment group	517	3.9748	4.0832	4.1915	1.1819	1.254	1.3355	0.0552
FIBRO_ISHAK_S00	2=Control group	533	4.0209	4.1295	4.238	1.2036	1.2759	1.3575	0.0553
FIBRO_ISHAK_S00	Diff (1-2)		-0.2	-0.046	0.107	1.2133	1.2652	1.3218	0.0781
INFLA_ISHAK_S00	1=Treatment group	517	7.3695	7.5513	7.733	1.9829	2.1038	2.2406	0.0925
INFLA_ISHAK_S00	2=Control group	533	7.3651	7.5366	7.7081	1.9011	2.0152	2.1441	0.0873
INFLA_ISHAK_S00	Diff (1-2)		-0.235	0.0147	0.2641	1.9748	2.0593	2.1515	0.1271
SPEC_LENGTH_S00	1=Treatment group	517	1.7511	1.8352	1.9193	0.9172	0.9731	1.0364	0.0428
SPEC_LENGTH_S00	2=Control group	533	1.7061	1.7711	1.8361	0.7208	0.764	0.8129	0.0331
SPEC_LENGTH_S00	Diff (1-2)		-0.042	0.0641	0.1699	0.8374	0.8733	0.9123	0.0539

T-Tests

Variable	Method	Variances	DF	t Value	Pr > |t|
AGE_RAND	Pooled	Equal	1048	2.41	0.0159
AGE_RAND	Satterthwaite	Unequal	1042	2.41	0.0160
DURINF	Pooled	Equal	982	2.88	0.0041
DURINF	Satterthwaite	Unequal	982	2.88	0.0041
BMI	Pooled	Equal	1048	-0.77	0.4389
BMI	Satterthwaite	Unequal	1048	-0.77	0.4386
logcount	Pooled	Equal	1048	-0.50	0.6155
logcount	Satterthwaite	Unequal	1038	-0.50	0.6158
alt	Pooled	Equal	1048	-1.18	0.2392
alt	Satterthwaite	Unequal	1045	-1.18	0.2386
ALT_RATIO	Pooled	Equal	1048	-1.10	0.2709
ALT_RATIO	Satterthwaite	Unequal	1043	-1.10	0.2702
tot_bilirubi	Pooled	Equal	1048	0.32	0.7515
tot_bilirubi	Satterthwaite	Unequal	1041	0.32	0.7517
albumin	Pooled	Equal	1048	0.77	0.4401
albumin	Satterthwaite	Unequal	1047	0.77	0.4397

Table 1: ttests for continuous variables

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The TTEST Procedure

T-Tests

Variable	Method	Variances	DF	t Value	Pr > |t|
prothrombin	Pooled	Equal	1048	-0.01	0.9885
prothrombin	Satterthwaite	Unequal	1033	-0.01	0.9885
FIBRO_ISHAK_S00	Pooled	Equal	1048	-0.59	0.5535
FIBRO_ISHAK_S00	Satterthwaite	Unequal	1048	-0.59	0.5534
INFLA_ISHAK_S00	Pooled	Equal	1048	0.12	0.9081
INFLA_ISHAK_S00	Satterthwaite	Unequal	1042	0.12	0.9082
SPEC_LENGTH_S00	Pooled	Equal	1048	1.19	0.2347
SPEC_LENGTH_S00	Satterthwaite	Unequal	978	1.18	0.2364

Equality of Variances

Variable	Method	Num DF	Den DF	F Value	Pr > F
AGE_RAND	Folded F	516	532	1.09	0.2991
DURINF	Folded F	498	484	1.02	0.8133
BMI	Folded F	532	516	1.10	0.2857
logcount	Folded F	516	532	1.14	0.1284
alt	Folded F	532	516	1.18	0.0647
ALT_RATIO	Folded F	532	516	1.23	0.0183
tot_bilirubi	Folded F	516	532	1.11	0.2147
albumin	Folded F	532	516	1.11	0.2274
prothrombin	Folded F	516	532	1.19	0.0428
FIBRO_ISHAK_S00	Folded F	532	516	1.04	0.6923
INFLA_ISHAK_S00	Folded F	516	532	1.09	0.3247
SPEC_LENGTH_S00	Folded F	516	532	1.62	<.0001

Table 1: median number of drinks 16:59 Tuesday, October 27, 2009

The UNIVARIATE Procedure
Variable: LIFE_DRINKS (Total number of drinks lifetime)
RAND_GRP = 1=Treatment group

Moments

N	516	Sum Weights	516
Mean	15799.507	Sum Observations	8152545.6
Std Deviation	23759.9465	Variance	564535056
Skewness	3.67462679	Kurtosis	22.59515
Uncorrected SS	4.19542E11	Corrected SS	2.90736E11
Coeff Variation	150.384101	Std Error Mean	1045.97332

Basic Statistical Measures

Location		Variability	
Mean	15799.51	Std Deviation	23760
Median	7228.80	Variance	564535056
Mode	0.00	Range	249480
		Interquartile Range	18864

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	15.10508	Pr > |t|	<.0001
Sign	M	214.5	Pr >= |M|	<.0001
Signed Rank	S	46117.5	Pr >= |S|	<.0001

Quantiles (Definition 5)

Quantile	Estimate
100% Max	249480.0
99%	109576.8
95%	58284.0
90%	42624.0
75% Q3	20125.2
50% Median	7228.8
25% Q1	1261.2
10%	0.0
5%	0.0
1%	0.0
0% Min	0.0

Table 1: median number of drinks 16:59 Tuesday, October 27, 2009

The UNIVARIATE Procedure
Variable: LIFE_DRINKS (Total number of drinks lifetime)
RAND_GRP = 1=Treatment group

Extreme Observations

----Lowest----		-----Highest----	
Value	Obs	Value	Obs
0	1041	111456	965
0	1031	116640	355
0	1027	117000	432
0	1002	149520	467
0	989	249480	913

Missing Values

Missing Value	Count	-----Percent Of----- All Obs	Missing Obs
.	1	0.19	100.00

Table 1: median number of drinks 16:59 Tuesday, October 27, 2009

The UNIVARIATE Procedure
Variable: LIFE_DRINKS (Total number of drinks lifetime)
RAND_GRP = 2=Control group

Moments

N	532	Sum Weights	532
Mean	20420.082	Sum Observations	10863483.6
Std Deviation	36344.587	Variance	1320929006
Skewness	4.76476932	Kurtosis	33.0259099
Uncorrected SS	9.23247E11	Corrected SS	7.01413E11
Coeff Variation	177.984531	Std Error Mean	1575.73769

Basic Statistical Measures

Location		Variability	
Mean	20420.08	Std Deviation	36345
Median	7537.20	Variance	1320929006
Mode	0.00	Range	357314
		Interquartile Range	24859

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	12.95906	Pr > |t|	<.0001
Sign	M	221	Pr >= |M|	<.0001
Signed Rank	S	48951.5	Pr >= |S|	<.0001

Quantiles (Definition 5)

Quantile	Estimate
100% Max	357314.4
99%	162432.0
95%	77703.6
90%	56160.0
75% Q3	26109.6
50% Median	7537.2
25% Q1	1250.4
10%	0.0
5%	0.0
1%	0.0
0% Min	0.0

Table 1: median number of drinks 16:59 Tuesday, October 27, 2009

The UNIVARIATE Procedure
Variable: LIFE_DRINKS (Total number of drinks lifetime)
RAND_GRP = 2=Control group

Extreme Observations

----Lowest----		-----Highest----	
Value	Obs	Value	Obs
0	1028	185256	955
0	1026	235914	588
0	1020	289188	42
0	996	338580	817
0	991	357314	438

Missing Values

Missing Value	Count	-----Percent Of----- All Obs	Missing Obs
.	1	0.19	100.00

Table 1: wilcoxon rank-sum test for number of drinks
16:59 Tuesday, October 27, 2009

The NPAR1WAY Procedure

Wilcoxon Scores (Rank Sums) for Variable LIFE_DRINKS
Classified by Variable RAND_GRP

RAND_GRP	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
2=Control group	532	282880.0	279034.0	4886.85122	531.729323
1=Treatment group	516	266796.0	270642.0	4886.85122	517.046512

Average scores were used for ties.

Wilcoxon Two-Sample Test

Statistic	266796.0000
Normal Approximation	
Z	-0.7869
One-Sided Pr < Z	0.2157
Two-Sided Pr > |Z|	0.4313
t Approximation	
One-Sided Pr < Z	0.2158
Two-Sided Pr > |Z|	0.4315

Z includes a continuity correction of 0.5.

Kruskal-Wallis Test

Chi-Square	0.6194
DF	1
Pr > Chi-Square	0.4313

figure B: time to first clinical outcome

16:59 Tuesday, October 27, 2009

The LIFETEST Procedure

Stratum 1: CIRRHOSIS = 0 RAND_GRP = 1=Treatment group

Product-Limit Survival Estimates

OUTC_ YEARA	Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.00000	1.0000	0	0	0	309
0.08487	0.9967	0.00329	0.00328	1	303
0.49829	0.9934	0.00660	0.00465	2	300
0.75838	0.9900	0.00996	0.00572	3	295
1.20465	0.9867	0.0133	0.00663	4	291
1.34155	0.9833	0.0167	0.00743	5	289
1.38809	0.9798	0.0202	0.00814	6	288
1.48939	0.9764	0.0236	0.00880	7	287
1.50034	0.9730	0.0270	0.00940	8	286
1.57153	0.9696	0.0304	0.00997	9	285
1.59890	0.9662	0.0338	0.0105	10	284
1.74127	0.9628	0.0372	0.0110	11	283
1.84531	0.9594	0.0406	0.0115	12	282
1.94114	0.9560	0.0440	0.0119	13	281
2.22313	0.9526	0.0474	0.0124	14	274
2.24230	0.9491	0.0509	0.0128	15	272
2.30801	0.9456	0.0544	0.0132	16	271
2.37372	0.9421	0.0579	0.0136	17	270
2.52430	0.9351	0.0649	0.0144	19	267
2.58179	0.9316	0.0684	0.0148	20	266
2.60917	0.9281	0.0719	0.0151	21	265
2.63655	0.9246	0.0754	0.0155	22	264
2.65572	0.9211	0.0789	0.0158	23	263
2.71321	0.9176	0.0824	0.0161	24	261
2.72690	0.9140	0.0860	0.0164	25	260
2.74059	0.9105	0.0895	0.0168	26	259
3.11020	0.9069	0.0931	0.0171	27	252
3.26899	0.9033	0.0967	0.0174	28	249
3.29363	0.8997	0.1003	0.0177	29	248
3.38398	0.8960	0.1040	0.0180	30	244
3.41958	0.8923	0.1077	0.0183	31	243
3.63587	0.8886	0.1114	0.0186	32	239
3.66872	0.8849	0.1151	0.0189	33	236
3.71800	0.8811	0.1189	0.0192	34	234
5.56057*	.	.	.	34	0

NOTE: The marked survival times are censored observations.

figure B: time to first clinical outcome

16:59 Tuesday, October 27, 2009

The LIFETEST Procedure

Summary Statistics for Time Variable OUTC_YEARA

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
75	.	.	.
50	.	.	.
25	.	.	.

Mean	Standard Error
3.54983	0.03282

NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

figure B: time to first clinical outcome

16:59 Tuesday, October 27, 2009

The LIFETEST Procedure

Stratum 2: CIRRHOSIS = 0 RAND_GRP = 2=Control group

Product-Limit Survival Estimates

OUTC_ YEARA	Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.00000	1.0000	0	0	0	313
0.18891	0.9968	0.00325	0.00324	1	307
0.30938	0.9934	0.00656	0.00462	2	300
0.69815	0.9901	0.00989	0.00568	3	297
1.29500	0.9867	0.0133	0.00660	4	291
1.42916	0.9833	0.0167	0.00741	5	288
1.68925	0.9799	0.0201	0.00814	6	284
1.76044	0.9764	0.0236	0.00882	7	283
1.83436	0.9730	0.0270	0.00944	8	282
1.86174	0.9695	0.0305	0.0100	9	281
2.17659	0.9660	0.0340	0.0106	10	275
2.29979	0.9625	0.0375	0.0111	11	274
2.43121	0.9590	0.0410	0.0116	12	272
2.86105	0.9554	0.0446	0.0121	13	267
2.88022	0.9518	0.0482	0.0126	14	266
3.12936	0.9481	0.0519	0.0131	15	256
3.35387	0.9443	0.0557	0.0135	16	252
3.37029	0.9406	0.0594	0.0140	17	251
3.46064	0.9368	0.0632	0.0144	18	248
3.51540	0.9330	0.0670	0.0149	19	244
3.59480	0.9291	0.0709	0.0153	20	240
3.64134	0.9252	0.0748	0.0157	21	238
3.68241	0.9213	0.0787	0.0161	22	235
3.78919	0.9174	0.0826	0.0165	23	234
4.74743*	.	.	.	23	0

NOTE: The marked survival times are censored observations.

Summary Statistics for Time Variable OUTC_YEARA

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
75	.	.	.
50	.	.	.
25	.	.	.

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Mean	Standard Error
3.67958	0.02859

NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

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The LIFETEST Procedure

Stratum 3: CIRRHOSIS = 1 RAND_GRP = 1=Treatment group

Product-Limit Survival Estimates

OUTC_ YEARA	Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.00000	1.0000	0	0	0	208
0.08214	0.9951	0.00488	0.00487	1	204
0.28474	0.9902	0.00983	0.00692	2	200
0.30938	0.9852	0.0148	0.00847	3	199
0.36140	0.9803	0.0197	0.00977	4	198
0.40520	0.9753	0.0247	0.0109	5	196
0.46270	0.9703	0.0297	0.0119	6	195
0.50924	0.9653	0.0347	0.0129	7	194
0.52841	0.9603	0.0397	0.0137	8	192
0.77755	0.9553	0.0447	0.0146	9	190
0.85695	0.9503	0.0497	0.0153	10	189
0.90075	0.9453	0.0547	0.0161	11	188
0.96920	0.9402	0.0598	0.0167	12	187
1.03217	0.9352	0.0648	0.0174	13	186
1.04586	0.9302	0.0698	0.0180	14	185
1.08693	0.9251	0.0749	0.0186	15	184
1.30322	0.9201	0.0799	0.0192	16	183
1.31143	0.9151	0.0849	0.0197	17	182
1.33060	0.9101	0.0899	0.0202	18	181
1.36071	0.9050	0.0950	0.0207	19	180
1.40999	0.9000	0.1000	0.0212	20	179
1.47023	0.8950	0.1050	0.0217	21	178
1.52498	0.8899	0.1101	0.0221	22	177
1.53046	0.8849	0.1151	0.0226	23	176
1.54689	0.8799	0.1201	0.0230	24	175
1.55236	0.8749	0.1251	0.0234	25	174
1.57426	0.8698	0.1302	0.0238	26	173
1.70568	0.8598	0.1402	0.0246	28	170
1.72485	0.8547	0.1453	0.0250	29	169
1.78508	0.8496	0.1504	0.0253	30	168
1.83162	0.8446	0.1554	0.0257	31	167
1.85079	0.8395	0.1605	0.0260	32	166
2.04517	0.8294	0.1706	0.0267	34	164
2.05886	0.8243	0.1757	0.0270	35	163
2.06708	0.8193	0.1807	0.0273	36	162
2.09719	0.8092	0.1908	0.0279	38	160
2.21218	0.8041	0.1959	0.0281	39	159
2.26420	0.7990	0.2010	0.0284	40	157
2.50240	0.7939	0.2061	0.0287	41	155
2.54073	0.7888	0.2112	0.0290	42	154
2.58727	0.7836	0.2164	0.0292	43	152
2.60370	0.7785	0.2215	0.0295	44	151

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Stratum 3: CIRRHOSIS = 1 RAND_GRP = 1=Treatment group

Product-Limit Survival Estimates

OUTC_ YEARA	Survival	Failure	Survival Standard Error	Number Failed	Number Left
2.89117	0.7733	0.2267	0.0297	45	150
2.91034	0.7682	0.2318	0.0300	46	149
2.96235	0.7630	0.2370	0.0302	47	148
2.97604	0.7579	0.2421	0.0305	48	147
3.04175	0.7475	0.2525	0.0309	50	143
3.06366	0.7422	0.2578	0.0311	51	141
3.16769	0.7369	0.2631	0.0314	52	138
3.18412	0.7315	0.2685	0.0316	53	137
3.34839	0.7260	0.2740	0.0318	54	132
3.38125	0.7205	0.2795	0.0321	55	131
3.59480	0.7095	0.2905	0.0325	57	129
3.70157	0.7040	0.2960	0.0327	58	128
3.78919	0.6984	0.3016	0.0329	59	124
4.66804*	.	.	.	59	0

NOTE: The marked survival times are censored observations.

Summary Statistics for Time Variable OUTC_YEARA

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
75	.	.	.
50	.	.	.
25	3.04175	2.21218	.

Mean	Standard Error
3.22455	0.07287

NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

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Stratum 4: CIRRHOSIS = 1 RAND_GRP = 2=Control group

Product-Limit Survival Estimates

OUTC_ YEARA	Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.00000	1.0000	0	0	0	220
0.11225	0.9953	0.00465	0.00464	1	214
0.13963	0.9907	0.00930	0.00655	2	213
0.19713	0.9860	0.0140	0.00800	3	212
0.27105	0.9814	0.0186	0.00922	4	211
0.28474	0.9767	0.0233	0.0103	5	210
0.36413	0.9721	0.0279	0.0112	6	208
0.39425	0.9674	0.0326	0.0121	7	207
0.46270	0.9627	0.0373	0.0129	8	206
0.54483	0.9581	0.0419	0.0137	9	205
0.55031	0.9534	0.0466	0.0144	10	204
0.58864	0.9487	0.0513	0.0151	11	203
0.59411	0.9440	0.0560	0.0157	12	202
0.81314	0.9393	0.0607	0.0163	13	200
0.93908	0.9346	0.0654	0.0169	14	199
0.96372	0.9299	0.0701	0.0174	15	198
1.01027	0.9252	0.0748	0.0180	16	197
1.02122	0.9205	0.0795	0.0185	17	196
1.03217	0.9159	0.0841	0.0190	18	195
1.17454	0.9065	0.0935	0.0199	20	193
1.20465	0.9018	0.0982	0.0204	21	192
1.27858	0.8970	0.1030	0.0208	22	190
1.28405	0.8923	0.1077	0.0212	23	189
1.30595	0.8876	0.1124	0.0216	24	188
1.31964	0.8829	0.1171	0.0220	25	187
1.54962	0.8781	0.1219	0.0224	26	185
1.69747	0.8733	0.1267	0.0228	27	182
1.81246	0.8685	0.1315	0.0232	28	181
1.82067	0.8637	0.1363	0.0235	29	180
1.83984	0.8589	0.1411	0.0239	30	179
1.86174	0.8541	0.1459	0.0242	31	178
1.98220	0.8493	0.1507	0.0246	32	177
2.03970	0.8445	0.1555	0.0249	33	176
2.19302	0.8397	0.1603	0.0252	34	174
2.21218	0.8349	0.1651	0.0255	35	173
2.27515	0.8301	0.1699	0.0258	36	172
2.31896	0.8252	0.1748	0.0261	37	170
2.32991	0.8204	0.1796	0.0264	38	169
2.33265	0.8155	0.1845	0.0267	39	168
2.35455	0.8106	0.1894	0.0270	40	167
2.55715	0.8058	0.1942	0.0273	41	165
2.56537	0.7911	0.2089	0.0280	44	162

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Stratum 4: CIRRHOSIS = 1 RAND_GRP = 2=Control group

Product-Limit Survival Estimates

OUTC_ YEARA	Survival	Failure	Survival Standard Error	Number Failed	Number Left
2.69405	0.7862	0.2138	0.0283	45	161
2.71869	0.7813	0.2187	0.0285	46	160
2.79808	0.7764	0.2236	0.0288	47	158
2.84189	0.7715	0.2285	0.0290	48	157
2.93498	0.7666	0.2334	0.0292	49	156
3.03080	0.7616	0.2384	0.0295	50	153
3.06366	0.7566	0.2434	0.0297	51	151
3.08830	0.7516	0.2484	0.0299	52	149
3.09925	0.7465	0.2535	0.0301	53	148
3.10198	0.7414	0.2586	0.0304	54	146
3.13484	0.7364	0.2636	0.0306	55	145
3.37577	0.7313	0.2687	0.0308	56	143
3.38946	0.7261	0.2739	0.0310	57	141
3.46338	0.7209	0.2791	0.0312	58	138
3.48255	0.7156	0.2844	0.0314	59	136
3.59754	0.7102	0.2898	0.0317	60	132
3.61944	0.7048	0.2952	0.0319	61	130
3.62491	0.6994	0.3006	0.0321	62	129
3.63587	0.6940	0.3060	0.0323	63	128
3.75086	0.6885	0.3115	0.0325	64	125
4.32854*	.	.	.	64	0

NOTE: The marked survival times are censored observations.

Summary Statistics for Time Variable OUTC_YEARA

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
75	.	.	.
50	.	.	.
25	3.09925	2.56537	.

Mean	Standard Error
3.20069	0.07082

NOTE: The mean survival time and its standard error were underestimated because the largest

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observation was censored and the estimation was restricted to the largest event time.

Summary of the Number of Censored and Uncensored Values

Stratum	CIRRHOSIS	RAND_GRP	Total	Failed	Censored	Percent Censored
1	0	1=Treatment group	309	34	275	89.00
2	0	2=Control group	313	23	290	92.65
3	1	1=Treatment group	208	59	149	71.63
4	1	2=Control group	220	64	156	70.91
Total			1050	180	870	82.86

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Testing Homogeneity of Survival Curves for OUTC_YEARA over Strata

Rank Statistics

Stratum	Log-Rank	Wilcoxon
1	-21.707	-19715
2	-33.170	-30014
3	25.880	23644
4	28.997	26085

Covariance Matrix for the Log-Rank Statistics

Stratum	1	2	3	4
1	38.4475	-17.3913	-10.2377	-10.8185
2	-17.3913	38.6188	-10.3208	-10.9068
3	-10.2377	-10.3208	27.0088	-6.4503
4	-10.8185	-10.9068	-6.4503	28.1755

Covariance Matrix for the Wilcoxon Statistics

Stratum	1	2	3	4
1	30449264	-1.367E7	-8154253	-8624170
2	-1.367E7	30572053	-8213774	-8687439
3	-8154253	-8213774	21572700	-5204672
4	-8624170	-8687439	-5204672	22516282

Legend for Strata

Stratum	CIRRHOSIS	RAND_GRP
1	0	1=Treatment group
2	0	2=Control group
3	1	1=Treatment group
4	1	2=Control group

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Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	72.3888	3	<.0001
Wilcoxon	74.6050	3	<.0001
-2Log(LR)	69.7060	3	<.0001