

Dataset Integrity Check for the HALT-PKD Data Files

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1 Standard Disclaimer

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 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 NIDDK Repository staff 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.

2 Study Background

The HALT-PKD study was a large randomized clinical trial to determine the impact of intensive blockade of the renin-angiotensin-aldosterone system (RAAS) and the level of blood pressure control on progressive renal disease in individuals with early and more advanced stages of autosomal dominant polycystic kidney disease (ADPKD). In Study A, participants with a glomerular filtration rate (GFR) greater than 60 mL/min/1.73 m², will be randomized to one of four conditions in a 2-by-2 design: combination angiotensin -converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) therapy at two levels of blood pressure control (standard, systolic 120-130 and diastolic 70-80 mm Hg vs. low, systolic 95-110 and diastolic 60-75 mm Hg) or ACE-I monotherapy at the same two levels of blood pressure control. The primary outcome of Study A is the percent change in total kidney volume, as measured by magnetic resonance imaging (MR). Study B will assess the effects of intensive blockade of the RAAS through combination ACE-I/ARB therapy as compared with ACE-I monotherapy, with both groups treated to a standard level of blood pressure control (systolic 110-130 mm Hg and diastolic 80 mm Hg) . The primary outcome for Study B is a composite endpoint of time to the 50% reduction of baseline eGFR, ESRD or death.

3 Archived Datasets

All SAS data files, as provided by the Data Coordinating Center (DCC), are located in the “Data” folder in the data package. For this replication, variables were taken from those datasets only.

4 Statistical Methods

Analyses were performed to duplicate the results for the data published in 2 papers in The New England Journal of Medicine in November 2014: the first by Schrier, et al.; and the second by Torres, et al. To verify the integrity of the datasets, Tables 1 and 2 in both of the papers were checked.

5 Results

- Table A lists the variables that were used in the replication of Study A Table 1.
- Table B compares the results calculated from the provided data files to the results published in Study A Table 1.
- Table C lists the variables that were used in the replication of Study A Table 2.
- Table D compares the results calculated from the provided data files to the results published in Study A Table 2.
- Table E lists the variables that were used in the replication of Study B Table 1.
- Table F compares the results calculated from the provided data files to the results published in Study B Table 1.
- Table G lists the variables that were used in the replication of Study B Table 2.
- Table H compares the results calculated from the provided data files to the results published in Study B Table 2.
- Table I lists the variables that were used in the replication of Study B Figure 3.
- Figure A compares the results calculated from the provided data files to the results published in Study B Figure 3.
- Table J compares the results calculated from the provided data files to the results published in Study B Figure 3.

6 Conclusions

The NIDDK repository is confident that the HALT_PKD data files to be distributed are a copy of the manuscript data with only inconsequential discrepancies.

7 References

[1]Schrier, Robert, et al. "Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease." The New England Journal of Medicine. DOI: 10.1056/NEJMoa1402685

[2]Torres, Vincente E., et al. "Angiotensin Blockade in Late Autosomal Dominant Polycystic Kidney Disease." The New England Journal of Medicine. DOI: 10.1056/NEJMoa1402686.

Table A: Variables used to replicate Study A Table 1: Demographic, Clinical, and Laboratory Characteristics at Baseline, According to Study Group of the 2-by-2 Factorial Design Trial.

| Characteristic | Variable(s) |
|--|--|
| Grouping of Treatment: Lisinopril vs Placebo | Baseline.study |
| Grouping of Blood Pressure | Baseline.randtype |
| Age (years) | Baseline.age |
| Male sex | Baseline.sex |
| Race – White | Baseline.racee |
| Race - Black | Baseline.raced |
| Race – Other | Baseline.racea,raceb,racec,racef |
| Race- Data missing | Baseline.racea, raceb, racec, raced, racee, racef, raceg |
| PKD genotype | Genetype09022014.genotype |
| Body-mass index | Baseline.bmi |
| Estimated GFR – ml/min/1.73 m ² | Baseline.ckd_epi_egfr |
| Urinary aldosterone – ug/24 hr | Baseline.ualdos |
| Urinary albumin – mg/24 hr | Baseline.ualbum |
| Total kidney volume – ml | Baseline.tkv |
| Renal blood flow – ml/min/1.73 m ² | Baseline.rbf_modify |
| Left-ventricular-mass index – g/m ² | Baseline.lvmi |

Table B: Comparison of integrity check values to Study A reference article Table 1 values

| Characteristic | Manuscript Lisinopril- Telmisartan (N=273) | DSIC Lisinopril- Telmisartan (N=273) | Manuscript Lisinopril- Placebo (N=285) | DSIC Lisinopril- Placebo (N=285) | DIFF |
|---|---|---|---|---|------|
| Age – yr | 37.0±8.3 | 37.0±8.3 | 36.3±8.3 | 36.3±8.3 | 0 |
| Male sex – no. (%) | 141 (51.6) | 141 (51.6) | 142 (49.8) | 142 (49.8) | 0 |
| Race – no. (%) | | | | | 0 |
| White | 255 (93.4) | 255 (93.4) | 262 (91.9) | 262 (91.9) | 0 |
| Black | 6 (2.2) | 6 (2.2) | 8 (2.8) | 8 (2.8) | 0 |
| Other | 10 (3.7) | 10 (3.7) | 17 (6.0) | 17 (6.0) | 0 |
| Data missing | 2 (0.7) | 2 (0.7) | 0 | 0 | 0 |
| PKD genotype – no./total no. (%) | | | | | 0 |
| PKD1 | 190/252 (75.4) | 190/252 (75.4) | 192/260 (73.8) | 192/260 (73.8) | 0 |
| PKD2 | 42/252 (16.7) | 42/252 (16.7) | 42/260 (16.2) | 42/260 (16.2) | 0 |
| No mutation detected | 20/252 (7.9) | 20/252 (7.9) | 26/260 (10.0) | 26/260 (10.0) | 0 |
| Body-mass index | 27.4±5.2 | 27.4±5.2 | 27.1±5.1 | 27.1±5.1 | 0 |
| Estimated GFR – ml/min/1.73 m ² | 90.4±17.5 | 90.4±17.5 | 92.6±17.4 | 92.6±17.4 | 0 |
| Urinary aldosterone – ug/24 hr | 12.2±10.0 | 12.2±10.0 | 12.2±9.1 | 12.2±9.1 | 0 |
| Urinary albumin – mg/24 hr | | | | | 0 |
| Median | 19.3 | 19.3 | 17.6 | 17.6 | 0 |
| Interquartile range | 12.7–35.2 | 12.7–35.2 | 11.7–30.6 | 11.7–30.6 | 0 |
| Total kidney volume – ml | 1264.6±786.2 | 1264.6±786.2 | 1164.0±661.0 | 1164.0±661.0 | 0 |
| Renal blood flow – ml/min/1.73 m ² | 607.7±195.3 | 607.7±195.3 | 609.2±216.2 | 609.2±216.2 | 0 |
| Left-ventricular-mass index –g/m ² | 64.1±13.2 | 64.1±13.2 | 63.7±12.9 | 63.7±12.9 | 0 |

| Characteristic | Manuscript Standard Blood Pressure (N=284) | DSIC Standard Blood Pressure (N=284) | Manuscript Low Blood Pressure (N=274) | DSIC Low Blood Pressure (N=274) | DIFF |
|---|---|---|--|--|------|
| Age – yr | 36.3±8.4 | 36.3±8.4 | 36.9±8.2 | 36.9±8.2 | 0 |
| Male sex – no. (%) | 143 (50.4) | 143 (50.4) | 140 (51.1) | 140 (51.1) | 0 |
| Race – no. (%) | | | | | 0 |
| White | 258 (90.8) | 258 (90.8) | 259 (94.5) | 259 (94.5) | 0 |
| Black | 7 (2.5) | 7 (2.5) | 7 (2.6) | 7 (2.6) | 0 |
| Other | 18 (6.3) | 18 (6.3) | 9 (3.3) | 9 (3.3) | 0 |
| Data missing | 2 (0.7) | 2 (0.7) | 0 | 0 | 0 |
| PKD genotype – no./total no. (%) | | | | | 0 |
| PKD1 | 204/260 (78.5) | 204/260 (78.5) | 178/252 (70.6) | 178/252 (70.6) | 0 |
| PKD2 | 34/260 (13.1) | 34/260 (13.1) | 50/252 (19.8) | 50/252 (19.8) | 0 |
| No mutation detected | 22/260 (8.5) | 22/260 (8.5) | 24/252 (9.5) | 24/252 (9.5) | 0 |
| Body-mass index | 27.3±5.4 | 27.3±5.4 | 27.1±4.9 | 27.1±4.9 | 0 |
| Estimated GFR – ml/min/1.73 m ² | 91.7±17.8 | 91.7±17.8 | 91.4±17.2 | 91.4±17.2 | 0 |
| Urinary aldosterone – ug/24 hr | 13.0±10.6 | 13.0±10.6 | 11.4±8.2 | 11.4±8.2 | 0 |
| Urinary albumin – mg/24 hr | | | | | 0 |
| Median | 19.1 | 19.1 | 17.7 | 17.7 | 0 |
| Interquartile range | 12.8–31.8 | 12.8–31.8 | 11.7–33.3 | 11.7–33.3 | 0 |
| Total kidney volume – ml | 1240.6±747.1 | 1240.6±747.1 | 1185.2±704.0 | 1185.2±704.0 | 0 |
| Renal blood flow – ml/min/1.73 m ² | 592.4±206.1 | 592.4±206.1 | 624.7±205.3 | 624.7±205.3 | 0 |
| Left-ventricular-mass index –g/m ² | 63.8±13.8 | 63.8±13.8 | 63.9±12.2 | 63.9±12.2 | 0 |

Table C: Variables used to replicate Study A Table 2: Adverse Events in the 2-by-2 Factorial Design Trial.

| Characteristic | Variable(s) |
|--|--|
| Grouping of Treatment: Lisinopril vs Placebo | Baseline.study_t |
| Grouping of Blood Pressue | Baseline.randtype |
| Mean follow-up – yr | Safety.yrsInStudyModified |
| Acute kidney injury – No. of events, No. of participants | Safety.countAKI, Safety.indAKI |
| Hyperkalemia – No. of events, No. of participants | Safety.hprk_any, Safety.ind_hprk_any |
| Hospitalizations – No. of events, Incidence – no. of events/100 person-yr | Safety.no_hospitalizations, Safety.yrsInStudyModified |
| Cardiac-related hospitalization – No. of events, Incidence – no. of events/100 person-yr | Safety.no_cardiac_hospitalizations, , Safety.yrsInStudyModified |
| Cancer – No. of events, No. of participants (%) | Safety.count_nonmelskincancer, Safety.count-melanoma, Safety.count_othercancer, Safety.ind_nonmelskincancer, Safety.ind_melanoma, Safety.ind_othercancer |
| Death – no. of participants | Safety.died |
| Cardiac disorder – No. of events, No. of participants | Safety.count_cardiac, Safety.ind_cardiac |
| Gastrointestinal disorder – No. of events, No. of participants | Safety.count_gastro, Safety.ind_gastro |
| Abdominal pain – No. of events, No. of participants | Safety.count_abdominalPain, Safety.ind_abdominalPain |
| Nervous system disorder – No. of events, No. of participants | Safety.count_nervous, Safety.ind_nervous |
| Renal or urinary system disorder – No. of events, No. of participants | Safety.count_renal, Safety.ind_renal |
| Nephrolithiasis or renal colic – No. of events, No. of participants | Safety.count_renalColic, Safety.ind_renalColic |

Table D: Comparison of integrity check values to Study A reference article Table 2 values

| Event | Manuscript Lisinopril- Telmisartan (N=273) | DSIC Lisinopril- Telmisartan (N=273) | Manuscript Lisinopril- Placebo (N=285) | DSIC Lisinopril- Placebo (N=285) | DIFF |
|---|---|---|---|---|------|
| Mean follow-up – yr | 5.6 | 5.6 | 5.7 | 5.7 | 0 |
| Acute kidney injury | | | | | |
| No. of events | 15 | 15 | 19 | 19 | 0 |
| No. of participants - % | 13 (4.8) | 13 (4.8) | 16 (5.6) | 16 (5.6) | 0 |
| Hyperkalemia | | | | | |
| No. of events | 13 | 13 | 6 | 6 | 0 |
| No. of participants - % | 11 (4.0) | 11 (4.0) | 5 (1.8) | 5 (1.8) | 0 |
| Hospitalization | | | | | |
| No. of events | 85 | 85 | 128 | 128 | 0 |
| Incidence – no. of events/100 | 5.55 | 5.55 | 7.92 | 7.92 | 0 |
| Cardiac-related hospitalization | | | | | |
| No. of events | 13 | 13 | 9 | 9 | 0 |
| Incidence – no. of events/100 | 0.85 | 0.85 | 0.56 | 0.56 | 0 |
| Cancer | | | | | |
| No. of events | 4 | 4 | 4 | 4 | 0 |
| No. of participants - % | 4 (1.5) | 4 (1.5) | 4 (1.4) | 4 (1.4) | 0 |
| Serious adverse event | | | | | |
| Death - no. of participants - % | 1 (0.4) | 1 (0.4) | 1 (0.4) | 1 (0.4) | 0 |
| Cardiac disorder | | | | | |
| No. of events | 9 | 9 | 6 | 6 | 0 |
| No. of participants - % | 6 (2.2) | 6 (2.2) | 5 (1.8) | 5 (1.8) | 0 |
| Gastrointestinal disorder | | | | | |
| No. of events | 11 | 11 | 17 | 17 | 0 |
| No. of participants - % | 8 (2.9) | 8 (2.9) | 12 (4.2) | 12 (4.2) | 0 |
| Abdominal pain | | | | | |
| No. of events | 3 | 3 | 9 | 9 | 0 |
| No. of participants - % | 3 (1.1) | 3 (1.1) | 6 (2.1) | 6 (2.1) | 0 |
| Nervous system disorder | | | | | |
| No. of events | 10 | 10 | 12 | 12 | 0 |
| No. of participants - % | 8 (2.9) | 8 (2.9) | 10 (3.5) | 10 (3.5) | 0 |
| Renal or urinary system disorder | | | | | |
| No. of events | 14 | 14 | 15 | 15 | 0 |
| No. of participants - % | 12 (4.4) | 12 (4.4) | 14 (4.9) | 14 (4.9) | 0 |
| Nephrolithiasis or renal colic | | | | | |
| No. of events | 3 | 3 | 4 | 4 | 0 |
| No. of participants - % | 3 (1.1) | 3 (1.1) | 4 (1.4) | 4 (1.4) | 0 |

| Event | Manuscript Standard Blood Pressure (N=284) | DSIC Standard Blood Pressure (N=284) | Manuscript Low Blood Pressue (N=274) | DSIC Low Blood Pressue (N=274) | DIFF |
|---|--|--|---|---|------|
| Mean follow-up – yr | 5.7 | 5.7 | 5.6 | 5.6 | 0 |
| Acute kidney injury | | | | | |
| No. of events | 17 | 17 | 17 | 17 | 0 |
| No. of participants - % | 13 (4.6) | 13 (4.6) | 16 (5.8) | 16 (5.8) | 0 |
| Hyperkalemia | | | | | |
| No. of events | 11 | 11 | 8 | 8 | 0 |
| No. of participants - % | 9 (3.2) | 9 (3.2) | 7 (2.6) | 7 (2.6) | 0 |
| Hospitalization | | | | | |
| No. of events | 120 | 120 | 93 | 93 | 0 |
| Incidence – no. of events/100 person-yr | 7.43 | 7.43 | 6.07 | 6.07 | 0 |
| Cardiac-related hospitalization | | | | | |
| No. of events | 13 | 13 | 9 | 9 | 0 |
| Incidence – no. of events/100 person-yr | 0.80 | 0.80 | 0.59 | 0.59 | 0 |
| Cancer | | | | | |
| No. of events | 2 | 2 | 6 | 6 | 0 |
| No. of participants - % | 2 (0.7) | 2 (0.7) | 6 (2.2) | 6 (2.2) | 0 |
| Serious adverse event | | | | | |
| Death - no. of participants - % | 2 (0.7) | 2 (0.7) | 0 | 0 | 0 |
| Cardiac disorder | | | | | |
| No. of events | 12 | 12 | 3 | 3 | 0 |
| No. of participants - % | 8 (2.8) | 8 (2.8) | 3 (1.1) | 3 (1.1) | 0 |
| Gastrointestinal disorder | | | | | |
| No. of events | 21 | 21 | 7 | 7 | 0 |
| No. of participants - % | 16 (5.6) | 16 (5.6) | 4 (1.5) | 4 (1.5) | 0 |
| Abdominal pain | | | | | |
| No. of events | 7 | 7 | 5 | 5 | 0 |
| No. of participants - % | 6 (2.1) | 6 (2.1) | 3 (1.1) | 3 (1.1) | 0 |
| Nervous system disorder | | | | | |
| No. of events | 14 | 14 | 8 | 8 | 0 |
| No. of participants - % | 11 (3.9) | 11 (3.9) | 7 (2.6) | 7 (2.6) | 0 |
| Renal or urinary system disorder | | | | | |
| No. of events | 16 | 16 | 13 | 13 | 0 |
| No. of participants - % | 14 (4.9) | 14 (4.9) | 12 (4.4) | 12 (4.4) | 0 |
| Nephrolithiasis or renal colic | | | | | |
| No. of events | 7 | 7 | 0 | 0 | 0 |
| No. of participants - % | 7 (2.5) | 7 (2.5) | 0 | 0 | 0 |

Table E: Variables used to replicate Study B Table 1: Demographic, Clinical, and Laboratory Characteristics of the Participants at Baseline.

| Characteristic | Variable(s) |
|--|----------------------------------|
| Grouping of Treatment: Lisinopril vs Placebo | Baseline.study |
| Age (years) | Baseline.age |
| Male sex | Baseline.sex |
| Race - White | Baseline.racee |
| Race - Black | Baseline.raced |
| Race - Other | Baseline.racea,raceb,racec,racef |
| PKD genotype | Genetype09022014.genotype |
| Body-mass index: | Baseline.bmi |
| Serum creatinine – mg/dl | Baseline.serumCreat_avg |
| Estimated GFR – ml/min/1.73 m ² | Baseline.ckd_epi_egfr |
| Urinary sodium – mmol/24 hr | Baseline.usodium |
| Urinary aldosterone – ug/24 hr | Baseline.ualdos |
| Urinary albumin – mg/24 hr | Baseline.ualbum |

Table F: Comparison of integrity check values to Study B reference article Table 1 values

| Characteristic | Manuscript Lisinopril- Telmisartan (N=244) | DSIC Lisinopril- Telmisartan (N=244) | Manuscript Lisinopril- Placebo (N=242) | DSIC Lisinopril- Placebo (N=242) | DIFF |
|--|---|---|---|---|------|
| Age – yr | 48.6±8.5 | 48.6±8.5 | 48.9±8.1 | 48.9±8.1 | 0 |
| Male sex – no. (%) | 115 (47.1) | 115 (47.1) | 120 (49.6) | 120 (49.6) | 0 |
| Race – no. (%) | | | | | 0 |
| White | 230 (94.3) | 230 (94.3) | 224 (92.6) | 224 (92.6) | 0 |
| Black | 5 (2.0) | 5 (2.0) | 7 (2.9) | 7 (2.9) | 0 |
| Other | 9 (3.7) | 8 (3.3) | 11 (4.5) | 11 (4.5) | -1 |
| PKD genotype – no./total no. (%) | | | | | 0 |
| PKD1 | 179/223 (80.3) | 179/223 | 183/224 (81.7) | 183/224 (81.7) | 0 |
| PKD2 | 30/223 (13.5) | 30/223 | 30/224 (13.4) | 30/224 (13.4) | 0 |
| No mutation detected | 14/223 (6.3) | 14/223 (6.3) | 11/224 (4.9) | 11/224 (4.9) | 0 |
| Body-mass index | 28.0±4.9 | 28.0±4.9 | 28.0±5.5 | 28.0±5.5 | 0 |
| Serum creatinine – mg/dl | 1.5±0.4 | 1.5±0.4 | 1.6±0.4 | 1.6±0.4 | |
| Estimated GFR – ml/min/1.73 m ² | 48.5±11.5 | 48.5±11.5 | 47.9±12.2 | 47.9±12.2 | 0 |
| Urinary sodium – mmol/24 hr | 177.4±78.2 | 177.4±78.2 | 178.2±84.0 | 178.2±84.0 | |
| Urinary aldosterone – ug/24 hr | 10.2±8.4 | 10.2±8.4 | 9.1±5.8 | 9.1±5.8 | 0 |
| Urinary albumin – mg/24 hr | | | | | 0 |
| Median | 29.7 | 29.7 | 28.1 | 28.1 | 0 |
| Interquartile range | 16.6–71.8 | 16.6–71.8 | 17.3–78.0 | 17.3–78.0 | 0 |

Table G: Variables used to replicate Study B Table 2: Serious Adverse Events.

| Characteristic | Variable(s) |
|---|--|
| Grouping of Treatment: Lisinopril vs Placebo | Baseline.study_t |
| Mean duration of follow-up – yr | Safety.yrsInStudyModified |
| Death – no. of participants | Safety.died |
| Cardiac disorder – No. of events, No. of participants | Safety.count_cardiac, Safety.ind_cardiac |
| Coronary artery disease – No. of events, No. of participants | Safety.count_coronaryArteryDisease, Safety.ind_coronaryArteryDisease |
| Arrhythmia - No. of events, No. of participants | Safety.count_arrhythmias, Safety.ind_arrhythmias |
| Other - No. of events, No. of participants | Safety.count_otherCardiacDisorder, Safety.ind_otherCardiacDisorder |
| Gastrointestinal disorder – No. of events, No. of participants | Safety.count_gastro, Safety.ind_gastro |
| Nervous system disorder – No. of events, No. of participants | Safety.count_nervous, Safety.ind_nervous |
| Cerebrovascular event – No. of events, No. of participants | Safety.count_cerebrovascular, Safety.ind_cerebrovascular |
| Headache – No. of events, No. of participants | Safety.count_headache, Safety.ind_headache |
| Other – No. of events, No. of participants | Safety.count_otherNervousSystemDisorder + Safety.count_syncope, Safety.ind_otherNervousSystemDisorder + Safety.ind_syncope |
| Renal or urinary system disorder – No. of events, No. of participants | Safety.count_renal, Safety.ind_renal |
| Renal hemorrhage or hematuria – No. of events, No. of participants | Safety.count_renalHemorrhage, Safety.ind_renalHemorrhage |
| Nephrolithiasis or renal colic – No. of events, No. of participants | Safety.count_renalColic, Safety.ind_renalColic |
| Acute kidney injury – No. of events, No. of participants | Safety.count_acuteKidneyInjury, Safety.ind_acuteKidneyInjury |
| Other – No. of events, No. of participants | Safety.count_otherRenalSystemDisorder + Safety.count_urinaryTractObstruct, Safety.ind_otherRenalSystemDisorder + Safety.urinaryTractObstruct |

Table H: Comparison of integrity check values to Study B reference article Table 2 values

| Event | Manuscript Lisinopril- Telmisartan (N=244) | DSIC Lisinopril- Telmisartan (N=244) | Manuscript Lisinopril- Placebo (N=242) | DSIC Lisinopril- Placebo (N=242) | DIFF |
|---|---|---|---|---|------|
| Mean duration of follow-up – yr | 5.2 | 5.2 | 5.2 | 5.2 | 0 |
| Death - no. of participants - % | 4 (1.6) | 4 (1.6) | 5 (2.1) | 5 (2.1) | 0 |
| Cardiac disorder | | | | | |
| No. of events | 12 | 12 | 18 | 18 | 0 |
| No. of participants - % | 11 (4.5) | 11 (4.5) | 13 (5.4) | 13 (5.4) | 0 |
| Coronary artery disease | | | | | |
| No. of events | 3 | 3 | 9 | 9 | 0 |
| No. of participants - % | 3 (1.2) | 3 (1.2) | 9 (3.7) | 9 (3.7) | 0 |
| Arrhythmia | | | | | |
| No. of events | 5 | 5 | 6 | 6 | 0 |
| No. of participants - % | 4 (1.6) | 4 (1.6) | 3 (1.2) | 3 (1.2) | 0 |
| Other | | | | | |
| No. of events | 4 | 4 | 3 | 3 | 0 |
| No. of participants - % | 4 (1.6) | 4 (1.6) | 3 (1.2) | 3 (1.2) | 0 |
| Gastrointestinal disorder | | | | | |
| No. of events | 18 | 18 | 33 | 33 | 0 |
| No. of participants - % | 15 (6.1) | 15 (6.1) | 25 (10.3) | 25 (10.3) | 0 |
| Nervous system disorder | | | | | |
| No. of events | 9 | 9 | 10 | 10 | 0 |
| No. of participants - % | 8 (3.3) | 8 (3.3) | 9 (3.7) | 9 (3.7) | 0 |
| Cerebrovascular event | | | | | |
| No. of events | 4 | 4 | 3 | 3 | 0 |
| No. of participants - % | 4 (1.6) | 4 (1.6) | 3 (1.2) | 3 (1.2) | 0 |
| Headache | | | | | |
| No. of events | 2 | 2 | 2 | 2 | 0 |
| No. of participants - % | 2 (0.8) | 2 (0.8) | 2 (0.8) | 2 (0.8) | 0 |
| Other | | | | | |
| No. of events | 3 | 3 | 5 | 5 | 0 |
| No. of participants - % | 3 (1.2) | 3 (1.2) | 4 (1.7) | 4 (1.7) | 0 |
| Renal or urinary system disorder | | | | | |
| No. of events | 14 | 14 | 34 | 34 | 0 |
| No. of participants - % | 14 (5.7) | 14 (5.7) | 19 (7.9) | 19 (7.9) | 0 |
| Renal hemorrhage or hematuria | | | | | |
| No. of events | 5 | 5 | 2 | 2 | 0 |
| No. of participants - % | 5 (2.0) | 5 (2.0) | 2 (0.8) | 2 (0.8) | 0 |
| Nephrolithiasis or renal colic | | | | | |
| No. of events | 1 | 1 | 12 | 12 | 0 |
| No. of participants - % | 1 (0.4) | 1 (0.4) | 4 (1.7) | 4 (1.7) | 0 |

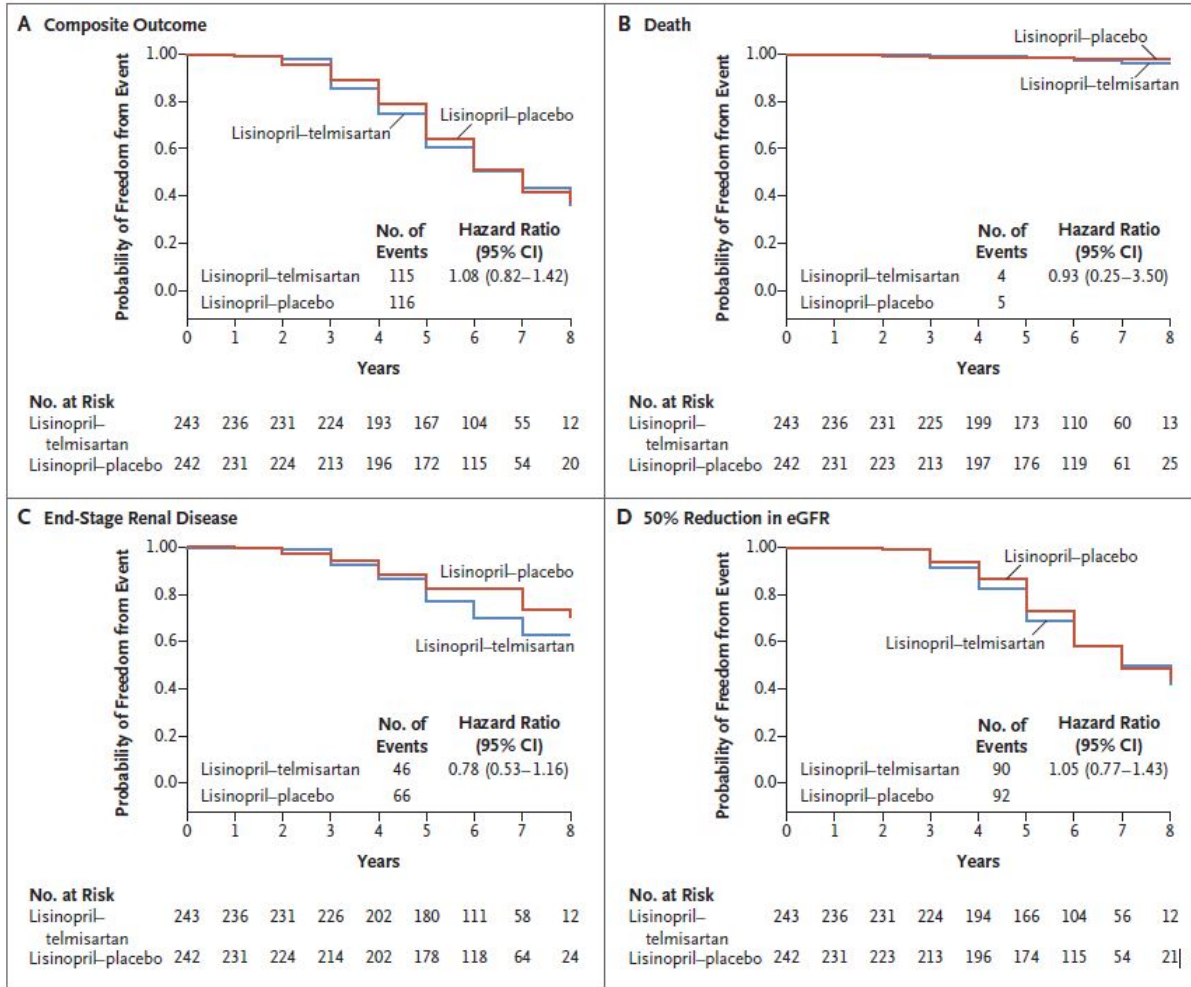
| Event | Manuscript Lisinopril- Telmisartan (N=244) | DSIC Lisinopril- Telmisartan (N=244) | Manuscript Lisinopril- Placebo (N=242) | DSIC Lisinopril- Placebo (N=242) | DIFF |
|----------------------------|---|---|---|---|------|
| Acute kidney injury | | | | | |
| No. of events | 3 | 3 | 5 | 5 | 0 |
| No. of participants - % | 3 (1.2) | 3 (1.2) | 5 (2.1) | 5 (2.1) | 0 |
| Other | | | | | |
| No. of events | 5 | 5 | 15 | 15 | 0 |
| No. of participants - % | 5 (2.0) | 5 (2.0) | 12 (5.0) | 12 (5.0) | 0 |

Table I: Variables Used to Replicate Study B Figure 3: Effect of Lisinopril-Telmisartan, as Compared with Lisinopril-Placebo, on the Time to Primary-Outcome Events and on the Estimated Glomerular Filtration Rate (eGFR)

| Characteristic | Variable(s) |
|-------------------------------------|--|
| Composite Outcome | endpoints_sep2014.death, endpoints_sep2014.esrd, endpoints_sep2014.egfr_50 |
| Death | endpoints_sep2014.death |
| End-Stage Renal Disease | endpoints_sep2014.esrd |
| 50% Reduction in eGFR | endpoints_sep2014.egfr_50 |
| No. at Risk – Composite Outcome | endpoints_sep2014.any_endpoint_date, endpoints_sep2014.b2date, endpoints_sep2014.lastVisit_rev, endpoints_sep2014.death, endpoints_sep2014.esrd, endpoints_sep2014.egfr_50 |
| No. at Risk - Death | endpoints_sep2014.dthdate, endpoints_sep2014.b2date, endpoints_sep2014.lastVisit_rev, endpoints_sep2014.death |
| No. at Risk – ESRD | endpoints_sep2014.tosdate, endpoints_sep2014.b2date, endpoints_sep2014.lastVisit_rev, endpoints_sep2014.esrd |
| No. at Risk – 50% Reduction in eGFR | endpoints_sep2014.confdate, endpoints_sep2014.b2date, endpoints_sep2014.lastVisit_rev, endpoints_sep2014.egfr_50 |

Figure A: Comparison of Values Computed in Integrity Check to Reference Article Figure 3 Values

Manuscript



DSIC

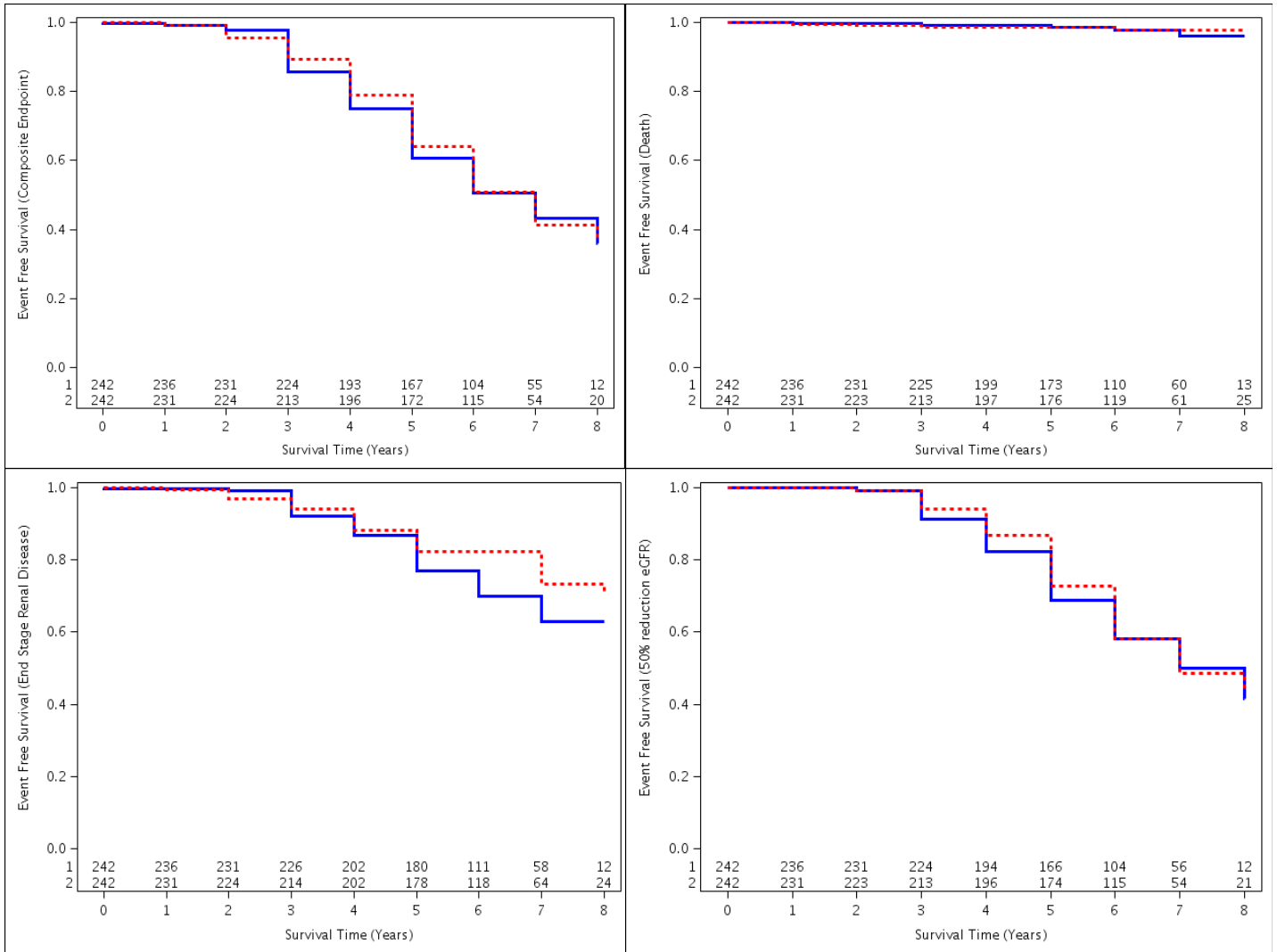


Table J: Comparison of Values Computed in Integrity Check to Reference Article Figure 3 Values

No. of Events:

| Event | Manuscript Lisinopril- telmisartan | DSIC Lisinopril- telmisartan | Difference | Manuscript Lisinopril- placebo | DSIC Lisinopril- placebo | Difference |
|----------------------------|--|------------------------------------|------------|--------------------------------------|--------------------------------|------------|
| Composite Outcome | 115 | 115 | 0 | 116 | 116 | 0 |
| Death | 4 | 4 | 0 | 5 | 5 | 0 |
| End-Stage Renal Disease | 46 | 46 | 0 | 66 | 66 | 0 |
| 50% Reduction in eGFR | 90 | 90 | 0 | 92 | 92 | 0 |

Hazard Ratio (95% CI):

| Event | Manuscript | DSIC | Difference |
|----------------------------|------------------|--------------------|------------------|
| Composite Outcome | 1.08 (0.82-1.42) | 1.08 (0.83-1.4) | 0 (0.01-0.02) |
| Death | 0.93 (0.25-3.50) | 0.94 (0.25 – 3.56) | 0.01 (0 – 0.06) |
| End-Stage Renal Disease | 0.78 (0.53-1.16) | 0.77 (0.53 – 1.14) | 0.01 (0-0.02) |
| 50% Reduction in eGFR | 1.05 (0.77-1.43) | 1.06 (0.79 – 1.42) | 0.01 (0.02-0.01) |

No. at Risk – Composite Outcome

| Treatment Group | Year 0 Manuscript | Year 0 DSIC | Year 1 Manuscript | Year 1 DSIC | Year 2 Manuscript | Year 2 DSIC | Year 3 Manuscript | Year 3 DSIC | Year 4 Manuscript | Year 4 DSIC |
|------------------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|
| Lisinopril-telmisartan | 243 | 242 | 236 | 236 | 231 | 231 | 224 | 224 | 193 | 193 |
| Lisinopril-placebo | 242 | 242 | 231 | 231 | 224 | 224 | 213 | 213 | 196 | 196 |

| Treatment Group | Year 5 Manuscript | Year 5 DSIC | Year 6 Manuscript | Year 6 DSIC | Year 7 Manuscript | Year 7 DSIC | Year 8 Manuscript | Year 8 DSIC |
|------------------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|
| Lisinopril-telmisartan | 167 | 167 | 104 | 104 | 55 | 55 | 12 | 12 |
| Lisinopril-placebo | 172 | 172 | 115 | 115 | 54 | 54 | 20 | 20 |

No. at Risk – Death

| Treatment Group | Year 0 Manuscript | Year 0 DSIC | Year 1 Manuscript | Year 1 DSIC | Year 2 Manuscript | Year 2 DSIC | Year 3 Manuscript | Year 3 DSIC | Year 4 Manuscript | Year 4 DSIC |
|------------------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|
| Lisinopril-telmisartan | 243 | 242 | 236 | 236 | 231 | 231 | 225 | 225 | 199 | 199 |
| Lisinopril-placebo | 242 | 242 | 231 | 231 | 223 | 223 | 213 | 213 | 197 | 197 |

| Treatment Group | Year 5 Manuscript | Year 5 DSIC | Year 6 Manuscript | Year 6 DSIC | Year 7 Manuscript | Year 7 DSIC | Year 8 Manuscript | Year 8 DSIC |
|------------------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|
| Lisinopril-telmisartan | 173 | 173 | 110 | 110 | 60 | 60 | 13 | 13 |
| Lisinopril-placebo | 176 | 176 | 119 | 119 | 61 | 61 | 25 | 25 |

No. at Risk – End-Stage Renal Disease

| Treatment Group | Year 0 Manuscript | Year 0 DSIC | Year 1 Manuscript | Year 1 DSIC | Year 2 Manuscript | Year 2 DSIC | Year 3 Manuscript | Year 3 DSIC | Year 4 Manuscript | Year 4 DSIC |
|------------------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|
| Lisinopril-telmisartan | 243 | 242 | 236 | 236 | 231 | 231 | 226 | 226 | 202 | 202 |
| Lisinopril-placebo | 242 | 242 | 231 | 231 | 224 | 224 | 214 | 214 | 202 | 202 |

| Treatment Group | Year 5 Manuscript | Year 5 DSIC | Year 6 Manuscript | Year 6 DSIC | Year 7 Manuscript | Year 7 DSIC | Year 8 Manuscript | Year 8 DSIC |
|------------------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|
| Lisinopril-telmisartan | 180 | 180 | 111 | 111 | 58 | 58 | 12 | 12 |
| Lisinopril-placebo | 178 | 178 | 118 | 118 | 64 | 64 | 24 | 24 |

No. at Risk – 50% Reduction in eGFR

| Treatment Group | Year 0 Manuscript | Year 0 DSIC | Year 1 Manuscript | Year 1 DSIC | Year 2 Manuscript | Year 2 DSIC | Year 3 Manuscript | Year 3 DSIC | Year 4 Manuscript | Year 4 DSIC |
|------------------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|
| Lisinopril-telmisartan | 243 | 242 | 236 | 236 | 231 | 231 | 224 | 224 | 194 | 194 |
| Lisinopril-placebo | 242 | 242 | 231 | 231 | 223 | 223 | 213 | 213 | 196 | 196 |

| Treatment Group | Year 5 Manuscript | Year 5 DSIC | Year 6 Manuscript | Year 6 DSIC | Year 7 Manuscript | Year 7 DSIC | Year 8 Manuscript | Year 8 DSIC |
|------------------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|-------------------|-------------|
| Lisinopril-telmisartan | 166 | 166 | 104 | 104 | 56 | 56 | 12 | 12 |
| Lisinopril-placebo | 174 | 174 | 115 | 115 | 54 | 54 | 21 | 21 |

Appendix A – SAS code for Study A Integrity Check

```
%let flnm = %sysfunc(getoption(sysin));
title "Program saved as: &FLNM.";
title2 "Check HALT_PKD Study A input files for DSIC";

/*****
*****
Programmer: Patty Griffin
Date: March 24, 2015

Function/Notes: Check HALT_PKD Study A input files for DSIC

Run with SAS v9.3 or later.

*****
*****/
* Input file *;
*****;
libname inlib "/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Primary
Paper Analysis Data/Final SAS datasets/";
libname informs "/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Non-CRF
Data/";
options nofmterr;

*****;
* Formats *;
*****;
proc format;

*****;
* Macro *;
*****;

%global caser;

*** Macro ***;
%macro freqdatal(order=, invar=, level=, levelname= );

data data0 datal;
  set _null_;

  proc freq data=table1 noprint;
    tables &invar*&caser/out=data0 outpct missing;
    format _all_;
  run;

data datal;
  set data0;
  length LEVEL $100 LEVELNAME $100;
  LEVEL=strip(&invar);
  LEVELNAME=strip(&levelname);

  data datal(keep=&caser name LEVEL LEVELNAME CHARALL ORDERER);
    set datal;
    length name $100 CHARALL $100;
    name=upcase("&invar");
    PCT_DISP=round(PCT_COL,.1);
    CHARALL=compress(put(COUNT,8.)||" ("||compress(put(PCT_DISP,8.1))||")");
    ORDERER=&order;
    if level in &level then output datal;

data accumfreq1;
  set accumfreq1 datal;

%mend freqdatal;
```

```

%macro meandatal(order=, invar=, roundvar=, digit=);
proc means data=table1 mean stddev noprint;
    var &invar;
    class &caser;
    output out=datal mean=mean stddev=stddev ;
run;

data datal(drop=_TYPE_ _FREQ_ mean stddev );
    set datal;
    length name CHARALL $100;
    name=upcase("&invar");
    mean=round(mean,&roundvar);
    stddev=round(stddev,&roundvar);
    CHARALL=compress(put(mean,8.&digit)||" ± "||compress(put(stddev,8.&digit)));
    ORDERER=&order;
    output;

data accummean1;
    set accummean1 datal;

%mend meandatal;

%macro mediandatal(order=, invar=, roundvar=, digit=);
proc means data=table1 median p25 p75 min max noprint;
    var &invar;
    class &caser;
    output out=datal median=median p25=p25 p75=p75 min=min max=max;
run;

data datal(drop=_TYPE_ _FREQ_ median p25 p75 min max);
    set datal;
    length name CHARALL $100;
    name=upcase("&invar");
    median=round(median,&roundvar);
    min=round(min,&roundvar);
    max=round(max,&roundvar);
    ORDERER=&order;
    CHARALL=compress(put(median,8.&digit));
    output;
    ORDERER=ORDERER+.01;
    *CHARALL=compress(put(min,8.&digit)||"-"||put(max,8.&digit));
    CHARALL=compress(put(p25,8.&digit)||","||put(p75,8.&digit));
    output;

data accummedian1;
    set accummedian1 datal;

%mend mediandatal;

%macro sumdatal(order=, invar=);
proc means data=table1 sum noprint;
    var &invar;
    class &caser;
    output out=datal sum=sum ;
run;

data datal(drop=_TYPE_ _FREQ_ sum );
    set datal;
    length name CHARALL $100;
    name=upcase("&invar");
    CHARALL=compress(put(sum, 8.));
    ORDERER=&order;
    output;

data accumsum1;
    set accumsum1 datal;

%mend sumdatal;

```

```

%macro incidencel00(order=, invar=, timevar=);
proc means data=table1 sum noprint;
    var &invar &timevar;
    class &caser;
    output out=data1 sum=sum_events sum_time ;
run;

data data1(drop=_TYPE_ _FREQ_ sum sum_events sum_time incidence);
    set data1;
    length name CHARALL $100;
    LEVELNAME = "Incidence";
    name=upcase("&invar");
    incidence=(sum_events/sum_time)*100;
    CHARALL=compress(put(incidence,4.2));
    ORDERER=&order;
    output;

data accumincidl;
    set accumincidl data1;

%mend incidencel00;

%macro inertdatal(order=);

data inert1;
    length orderer &caser 8.;
    orderer=&order.;
    &caser=-1;
    output;
    orderer=&order.;
    &caser=0;
    output;
    orderer=&order.;
    &caser=1;
    output;

data accuminert1;
    set accuminert1 inert1;

%mend inertdatal;

%macro datachunk();

%meandatal(order=1, invar=age, roundvar=.1, digit=1);
%freqdatal(order=2, invar=sex, level=(1), levelname="Male");
%freqdatal(order=3, invar=race, level=(1), levelname="Race - White");
%freqdatal(order=4, invar=raced, level=(1), levelname="Race - Black");
%freqdatal(order=5, invar=race_other, level=(1), levelname="Race - Other");
%freqdatal(order=6, invar=race_missing, level=(1), levelname="Race - Data missing");
%meandatal(order=10, invar=bmi, roundvar=.1, digit=1);
%meandatal(order=11, invar=ckd_epi_egfr, roundvar=.1, digit=1);
%meandatal(order=12, invar=ualdos, roundvar=.1, digit=1);
%mediandatal(order=13, invar=ualbum, roundvar=.1, digit=1);
%meandatal(order=14, invar=TKV, roundvar=.1, digit=1);
%meandatal(order=15, invar=rbf_modify, roundvar=.1, digit=1);
%meandatal(order=16, invar=lvmi, roundvar=.1, digit=1);

%mend datachunk;

%macro datachunk2();

%meandatal(order=1, invar=yrsInStudyModified, roundvar=.1, digit=1);
%sumdatal(order=2, invar=countAKI);
%freqdatal(order=3, invar=indAKI, level=(1), levelname="AKI - No. of participants");
%sumdatal(order=4, invar=hprk_any);
%freqdatal(order=5, invar=ind_hprk_any, level=(1), levelname="Hyperkalemia - No. of
participants");

```



```

%sumdatal(order=6, invar=no_hospitalizations);
%incidencel00(order=7, invar=no_hospitalizations, timevar=yrsInStudyModified);
%sumdatal(order=8, invar=no_cardiac_hospitalizations);
%incidencel00(order=9, invar=no_cardiac_hospitalizations, timevar=yrsInStudyModified);
%sumdatal(order=10, invar=count_cancer);
%freqdatal(order=11, invar=ind_cancer, level=(1), levelname="Cancer - No. of participants");
%freqdatal(order=12, invar=died, level=(1), levelname="Death - No. of participants");
%sumdatal(order=13, invar=count_cardiac);
%freqdatal(order=14, invar=ind_cardiac, level=(1), levelname="Cardiac disorder - No. of
participants");
%sumdatal(order=15, invar=count_gastro);
%freqdatal(order=16, invar=ind_gastro, level=(1), levelname="Gastrointestinal disorder - No. of
participants");
%sumdatal(order=17, invar=count_abdominalPain);
%freqdatal(order=18, invar=ind_abdominalPain, level=(1), levelname="Abdominal pain - No. of
participants");
%sumdatal(order=19, invar=count_nervous);
%freqdatal(order=20, invar=ind_nervous, level=(1), levelname="Nervous system disorder - No. of
participants");
%sumdatal(order=21, invar=count_renal);
%freqdatal(order=22, invar=ind_renal, level=(1), levelname="Renal or urinary system disorder -
No. of participants");
%sumdatal(order=23, invar=count_renalColic);
%freqdatal(order=24, invar=ind_renalColic, level=(1), levelname="Nephrolithiasis or renal colic
- No. of participants");

%mend datachunk2;

*****;
* Create dataset with all necessary data fields for Study A tables 1 and 2 *;
*****;
data baseline;
  set inlib.halt_baseline;
  if study_t = 1;          *study A;

  if (racea=1 or raceb=1 or racec=1 or racef=1) then race_other=1;
  else race_other=0;

  if (racea=0 and raceb=0 and racec=0 and raced=0 and racee=0 and racef=0 and raceg=0) then
race_missing=1;
  else race_missing=0;

  format _all_;
run;

proc freq data = baseline;
  table study randtype / list missing;
run;

proc sort data = baseline;
  by haltid;
run;

*****;
* This file needs v9.3 or later *;
*****;
data genotype(keep=haltid genotype);
  set informs.genotype09022014;
run;

proc sort data=genotype;
  by haltid;
run;

data safety;
  set informs.safety;
  count_cancer = count_nonmelskincancer + count_melanoma + count_othercancer;
  ind_cancer = ind_nonmelskincancer + ind_melanoma + ind_othercancer;

```

```

run;

data table1;
  merge baseline(in=inbase) genotype(in=ing) safety(in=ins);
  by haltid;
  if inbase;
  rename genotype=genotype;
run;

proc freq data = table1(where=(genotype ne .));
  table study*genotype randtype*genotype ;
run;

*****;
*   Create Study A Table 1                               *;
*****;
%let caser=randtype;
*** Column processing;

data accumfreq1 accummean1 accummedian1 accumsum1 accumincidl accuminert1;
  set _null_;

%datachunk();

data accumtabl;
  set accumfreq1 accummean1 accummedian1 accumsum1 accumincidl accuminert1;
  if &caser=. then delete;

proc sort data=accumtabl;
  by &caser orderer;

proc print data=accumtabl noobs;
  by &caser;
  pageby &caser;
  title3 'Table 1 stats for Study Grouping (Treatment vs Control)';
  where &caser in (1 2);

*****;
%let caser=study;
*** Column processing;

data accumfreq1 accummean1 accummedian1 accumsum1 accumincidl accuminert1;
  set _null_;

%datachunk();

data accumtabl;
  set accumfreq1 accummean1 accummedian1 accumsum1 accumincidl accuminert1;
  if &caser=. then delete;

proc sort data=accumtabl;
  by &caser orderer;

proc print data=accumtabl noobs;
  by &caser;
  pageby &caser;
  title3 'Table 1 stats for Study Grouping (Blood Pressure)';
  where &caser in (1 2);

*****;
*   Create Study A Table 2                               *;
*****;
%let caser=randtype;
*** Column processing;

data accumfreq1 accummean1 accummedian1 accumsum1 accumincidl accuminert1;
  set _null_;

%datachunk2();

```

```

data accumtab1;
  set accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  if &caser=. then delete;

proc sort data=accumtab1;
  by &caser orderer;

proc print data=accumtab1 noobs;
  by &caser;
  pageby &caser;
  title3 'Table 2 stats for Study Grouping (Treatment vs Control)';
  where &caser in (1 2);

*****;
%let caser=study;
*** Column processing;

data accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  set _null_;

%datachunk2();

data accumtab1;
  set accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  if &caser=. then delete;

proc sort data=accumtab1;
  by &caser orderer;

proc print data=accumtab1 noobs;
  by &caser;
  pageby &caser;
  title3 'Table 2 stats for Study Grouping (Blood Pressure)';
  where &caser in (1 2);

```

Appendix B – SAS code for Study B Integrity Check

```
%let flnm = %sysfunc(getoption(sysin));
title "Program saved as: &FLNM.";
title2 "Check HALT_PKD Study B input files for DSIC";

/*****
*****
Programmer: Patty Griffin
Date: March 26, 2015

Function/Notes: Check HALT_PKD Study B input files for DSIC

Run with SAS v9.3 or later.

*****
*****/
* Input file *;
*****;
libname inlib "/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Primary
Paper Analysis Data/Final SAS datasets/";
libname informs "/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Non-CRF
Data/";
options nofmterr;

*****;
* Formats *;
*****;
proc format;

*****;
* Macro *;
*****;

%global caser;

*** Macro ***;
%macro freqdata1(order=, invar=, level=, levelname= );

data data0 data1;
  set _null_;

  proc freq data=table1 noprint;
    tables &invar*&caser/out=data0 outpct missing;
    format _all_;
  run;

data data1;
  set data0;
  length LEVEL $100 LEVELNAME $100;
  LEVEL=strip(&invar);
  LEVELNAME=strip(&levelname);

  data data1(keep=&caser name LEVEL LEVELNAME CHARALL ORDERER);
    set data1;
    length name $100 CHARALL $100;
    name=upcase("&invar");
    PCT_DISP=round(PCT_COL,.1);
    CHARALL=compress(put(COUNT,8.)||" ("||compress(put(PCT_DISP,8.1))||")");
    ORDERER=&order;
    if level in &level then output data1;

data accumfreq1;
  set accumfreq1 data1;

%mend freqdata1;
```

```

%macro meandatal(order=, invar=, roundvar=, digit=);
proc means data=table1 mean stddev noprint;
    var &invar;
    class &caser;
    output out=datal mean=mean stddev=stddev ;
run;

data datal(drop=_TYPE_ _FREQ_ mean stddev );
    set datal;
    length name CHARALL $100;
    name=upcase("&invar");
    mean=round(mean,&roundvar);
    stddev=round(stddev,&roundvar);
    CHARALL=compress(put(mean,8.&digit)||" ± "||compress(put(stddev,8.&digit)));
    ORDERER=&order;
    output;

data accummean1;
    set accummean1 datal;

%mend meandatal;

%macro mediandatal(order=, invar=, roundvar=, digit=);
proc means data=table1 median p25 p75 min max noprint;
    var &invar;
    class &caser;
    output out=datal median=median p25=p25 p75=p75 min=min max=max;
run;

data datal(drop=_TYPE_ _FREQ_ median p25 p75 min max);
    set datal;
    length name CHARALL $100;
    name=upcase("&invar");
    median=round(median,&roundvar);
    min=round(min,&roundvar);
    max=round(max,&roundvar);
    ORDERER=&order;
    CHARALL=compress(put(median,8.&digit));
    output;
    ORDERER=ORDERER+.01;
    *CHARALL=compress(put(min,8.&digit)||"-"||put(max,8.&digit));
    CHARALL=compress(put(p25,8.&digit)||","||put(p75,8.&digit));
    output;

data accummedian1;
    set accummedian1 datal;

%mend mediandatal;

%macro sumdatal(order=, invar=);
proc means data=table1 sum noprint;
    var &invar;
    class &caser;
    output out=datal sum=sum ;
run;

data datal(drop=_TYPE_ _FREQ_ sum );
    set datal;
    length name CHARALL $100;
    name=upcase("&invar");
    CHARALL=compress(put(sum, 8.));
    ORDERER=&order;
    output;

data accumsum1;
    set accumsum1 datal;

%mend sumdatal;

```

```

%macro inertdatal(order=);
data inert1;
  length orderer &caser 8.;
  orderer=&order.;
  &caser=-1;
  output;
  orderer=&order.;
  &caser=0;
  output;
  orderer=&order.;
  &caser=1;
  output;

data accuminert1;
  set accuminert1 inert1;

%mend inertdatal;

%macro datachunk();

%meandatal(order=1, invar=age, roundvar=.1, digit=1);
%freqdatal(order=2, invar=sex, level=(1), levelname="Male");
%freqdatal(order=3, invar=racee, level=(1), levelname="Race - White");
%freqdatal(order=4, invar=raced, level=(1), levelname="Race - Black");
%freqdatal(order=5, invar=race_other, level=(1), levelname="Race - Other");
%meandatal(order=10, invar=bmi, roundvar=.1, digit=1);
%meandatal(order=11, invar=serumCreat_avg, roundvar=.1, digit=1);
%meandatal(order=12, invar=ckd_epi_egfr, roundvar=.1, digit=1);
%meandatal(order=13, invar=usodium, roundvar=.1, digit=1);
%meandatal(order=14, invar=ualdos, roundvar=.1, digit=1);
%mediandatal(order=15, invar=ualbum, roundvar=.1, digit=1);

%mend datachunk;

%macro datachunk2();

%meandatal(order=1, invar=yrsInStudyModified, roundvar=.1, digit=1);
%freqdatal(order=2, invar=died, level=(1), levelname="Death - No. of participants");
%sumdatal(order=3, invar=count_cardiac);
%freqdatal(order=4, invar=ind_cardiac, level=(1), levelname="Cardiac disorder - No. of participants");
%sumdatal(order=5, invar=count_coronaryArteryDisease);
%freqdatal(order=6, invar=ind_coronaryArteryDisease, level=(1), levelname="Coronary artery disease - No. of participants");
%sumdatal(order=7, invar=count_arrhythmias);
%freqdatal(order=8, invar=ind_arrhythmias, level=(1), levelname="Arrhythmia - No. of participants");
%sumdatal(order=9, invar=count_otherCardiacDisorder);
%freqdatal(order=10, invar=ind_otherCardiacDisorder, level=(1), levelname="Other - No. of participants");
%sumdatal(order=11, invar=count_gastro);
%freqdatal(order=12, invar=ind_gastro, level=(1), levelname="Gastrointestinal disorder - No. of participants");
%sumdatal(order=13, invar=count_nervous);
%freqdatal(order=14, invar=ind_nervous, level=(1), levelname="Nervous system disorder - No. of participants");
%sumdatal(order=15, invar=count_cerebrovascular);
%freqdatal(order=16, invar=ind_cerebrovascular, level=(1), levelname="Cerebrovascular event - No. of participants");
%sumdatal(order=18, invar=count_headache);
%freqdatal(order=19, invar=ind_headache, level=(1), levelname="Headache - No. of participants");
%sumdatal(order=20, invar=count_otherNervous);
%freqdatal(order=21, invar=ind_otherNervous, level=(1), levelname="Other - No. of participants");
%sumdatal(order=22, invar=count_renal);
%freqdatal(order=23, invar=ind_renal, level=(1), levelname="Renal or urinary system disorder - No. of participants");
%sumdatal(order=24, invar=count_renalHemorrhage);

```

```

%freqdatal(order=25, invar=ind_renalHemorrhage, level=(1), levelname="Renal hemorrhage or
hematuria - No. of participants");
%sumdatal(order=26, invar=count_renalColic);
%freqdatal(order=27, invar=ind_renalColic, level=(1), levelname="Nephrolithiasis or renal colic
- No. of participants");
%sumdatal(order=28, invar=count_acuteKidneyInjury);
%freqdatal(order=29, invar=ind_acuteKidneyInjury, level=(1), levelname="Acute kidney injury -
No. of participants");
%sumdatal(order=30, invar=count_otherRenal);
%freqdatal(order=31, invar=ind_otherRenal, level=(1), levelname="Other - No. of participants");

%mend datachunk2;

*****;
* Create the report for all of the datasets in inlib *;
*****;
data baseline;
  set inlib.halt_baseline;
  if study_t = 2;          *study B;

  if (racea=1 or raceb=1 or racec=1 or racef=1) then race_other=1;
  else race_other=0;

  format _all_;
run;

proc freq data = baseline;
  table study randtype / list missing;
run;

proc sort data = baseline;
  by haltid;
run;

*****;
* This file needs v9.3 or later *;
*****;
data genotype(keep=haltid genotype);
  set informs.genotype09022014;
run;

proc sort data=genotype;
  by haltid;
run;

data safety;
  set informs.safety;
  count_otherNervous = count_otherNervousSystemDisorder + count_syncope ; *defined in
PrimaryPaper_StudyB.sas program;
  ind_otherNervous = ind_otherNervousSystemDisorder + ind_syncope ;
  count_otherRenal = count_otherRenalSystemDisorder + count_urinaryTractObstruct; *defined in
PrimaryPaper_StudyB.sas program;
  ind_otherRenal = ind_otherRenalSystemDisorder + ind_urinaryTractObstruct;
run;

data table1;
  merge baseline(in=inbase) genotype(in=ing) safety(in=ins);
  by haltid;
  if inbase;
  rename genotype=genotype;
run;

proc freq data = table1(where=(genotype ne .));
  table study*genotype randtype*genotype ;
run;

proc freq data = table1;
  table randtype*racea*raceb*racec*raced*racee*racef*raceg / list missing;
run;

```

```

*****;
*   Create Study B Table 1                                     *;
*****;
%let caser=randtype;
*** Column processing;

data accumfreq1 accummean1 accummedian1 accumsum1 accuminert1;
  set _null_;

%datachunk();

data accumtab1;
  set accumfreq1 accummean1 accummedian1 accumsum1 accuminert1;
  if &caser=. then delete;

proc sort data=accumtab1;
  by &caser orderer;

proc print data=accumtab1 noobs;
  by &caser;
  pageby &caser;
  title3 'Table 1 stats for Study Grouping (Treatment vs Control)';
  where &caser in (1 2);
run;

*****;
*   Create Study B Table 2                                     *;
*****;
data accumfreq1 accummean1 accummedian1 accumsum1 accumincidl accuminert1;
  set _null_;

%datachunk2();

data accumtab1;
  set accumfreq1 accummean1 accummedian1 accumsum1 accumincidl accuminert1;
  if &caser=. then delete;

proc sort data=accumtab1;
  by &caser orderer;

proc print data=accumtab1 noobs;
  by &caser;
  pageby &caser;
  title3 'Table 2 stats for Study Grouping (Treatment vs Control)';
  where &caser in (1 2);

**** Endpoints DSIC;
title 'HALT-PKD Endpoints DSIC';

title2 ' ';

libname haltpkd '/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/';

libname analysis '/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Primary
Paper Analysis Data/Final SAS datasets/';

libname out
'/prj/niddk/dataset_files/HALT_PKD_V3/Data/Primary_Paper_Analysis_Data/Final_SAS_datasets/';

%include '/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Primary Paper
Analysis Data/Final SAS programs/HALT_format.sas';

```



```

options nofmterr;

data endpoints;

    set haltpkd.endpoints_sep2014;

data out.endpoints_sep2014;

    set endpoints;

proc contents data = endpoints;

data studyb;

    set endpoints;

    by haltid;

if study_t=2;

if esrd = 1 or egfr_50 = 1 or death = 1 then composite_outcome = 1;

else composite_outcome = 0;

if b2date='09SEP1900'd then b2date=.;

*DAYS from b2Date;

**any endpoint;

if any_endpoint_date ne . then days_anyEnd = (any_endpoint_date-b2Date);

    else days_anyEnd = (lastVisit_rev-b2Date);

**death;

if dthdate ne . then days_death = (dthdate-b2Date);

    else days_death = (lastVisit_rev-b2Date);

**ESRD;

if tosdate ne . then days_esrd = (tosdate-b2Date);

    else days_esrd = (lastVisit_rev-b2Date);

**50% reduction eGFR;

**note: confsdate is confirmation sample date;

if confsdate ne . then days_egfr50 = (confsdate-b2Date);

    else days_egfr50 = (lastVisit_rev-b2Date);

*YEARS from b2Date;

yrsToAnyEnd = round(days_anyEnd/365.25);

```

```

yrsToDeath = round(days_death/365.25);
yrsToESRD = round(days_esrd/365.25);
yrsToEGFR50 = round(days_egfr50/365.25);

format randtype randtype2f.;

run;

proc freq data = studyb;

    tables death*randtype esrd*randtype egfr_50*randtype composite_outcome*randtype /list
missing;

    format randtype randtype2f.;

proc phreg data = studyb;

    class randtype (ref = 'Lisinopril/Telmisartan');

    model yrsToAnyEnd*composite_outcome(0) = randtype age sex /risklimits ties=efron;

    strata siteid;

proc phreg data = studyb;

    class randtype (ref = 'Lisinopril/Placebo') ;

    model yrsToDeath * death(0) = randtype age sex ckd_epi_eGFR0 /risklimits ties=efron;

    strata siteid;

    baseline out=survs survival=s;

proc phreg data = studyb;

    class randtype (ref = 'Lisinopril/Placebo') ;

    model yrsToESRD*esrd(0)= randtype age sex ckd_epi_eGFR0 /risklimits ties=efron;

    strata siteid;

    baseline out=survs survival=s;

proc phreg data = studyb;

    class randtype (ref = 'Lisinopril/Telmisartan');

    model yrsToEGFR50*egfr_50(0) = randtype age sex ckd_epi_eGFR0 /risklimits ties=efron;

    strata siteid;

    baseline out=survs survival=s;

```

```

ods graphics on;

ods path show;

ods path(prepend) work.templat(update);

proc template;
define style MYSTYLE4;
parent=STYLES.MYSTYLE;

style GraphFonts from GraphFonts

"Fonts used in graph styles" /

'GraphDataFont' = ("

```

```

if (EXISTS(STRATUMID))
    entrytitle " " " for " STRATUMID;
else
    entrytitle " " " ";
endif;

if (PLOTATRISK)
    entrytitle " " / textattrs=
        GRAPHVALUETEXT;
endif;

*/

layout overlay / xaxisopts=(label="Survival Time (Years)" shortlabel=XNAME
offsetmin=.05

linearopts=(viewmax=MAXTIME tickvaluelist=XTICKVALS
tickvaluefitpolicy=XTICKVALFITPOL)) yaxisopts=(label=
"&title" shortlabel="Survival" linearopts=(
viewmin=0 viewmax=1 tickvaluelist=(0 .2 .4 .6 .8 1.0)));
if (PLOTBW=1 AND PLOTEP=0)
    bandplot LimitUpper=HW_UCL LimitLower=HW_LCL x=TIME /
        modelname="Survival" fillattrs=GRAPHCONFIDENCE name="HW"
        legendlabel=LABELHW;
endif;
if (PLOTBW=0 AND PLOTEP=1)
    bandplot LimitUpper=EP_UCL LimitLower=EP_LCL x=TIME /
        modelname="Survival" fillattrs=GRAPHCONFIDENCE name="EP"
        legendlabel=LABELEP;
endif;
if (PLOTBW=1 AND PLOTEP=1)
    bandplot LimitUpper=HW_UCL LimitLower=HW_LCL x=TIME /
        modelname="Survival" fillattrs=GRAPHDATA1
        /*datatransparency=.55*/ name="HW" legendlabel=LABELHW;
    bandplot LimitUpper=EP_UCL LimitLower=EP_LCL x=TIME /
        modelname="Survival" fillattrs=GRAPHDATA2
        /*datatransparency=.55*/ name="EP" legendlabel=LABELEP;

```

```

endif;

if (PLOTCL=1)
    if (PLOTHW=1 OR PLOTEP=1)
        bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL x=TIME /
            modelname="Survival" display=(outline) outlineattrs=
            GRAPHPREDICTIONLIMITS name="CL" legendlabel=LABELCL;
    else
        bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL x=TIME /
            modelname="Survival" fillattrs=GRAPHCONFIDENCE name=
            "CL" legendlabel=LABELCL;
    endif;
endif;

stepplot y=SURVIVAL x=TIME / name="Survival" rolename=( _tip1=
    ATRISK _tip2=EVENT) tip=(y x Time _tip1 _tip2) legendlabel=
    "Survival" lineattrs=(thickness=2.5);

if (PLOTCEASURED=1)
    scatterplot y=CENSORED x=TIME / markerattrs=(symbol=plus)
        name="Survival" legendlabel="Censored";
endif;

if (PLOTCL=1 OR PLOTHW=1 OR PLOTEP=1)
    discretelegend "Censored" "CL" "HW" "EP" / location=outside
        halign=center;
/* else
    if (PLOTCEASURED=1)
        discretelegend "Censored" / location=inside valign=bottom halign=center
*autoalign=(bottom
        topright bottomleft)*;
    endif;*/
endif;

if (PLOTATRISK=1)
    innermargin / align=bottom;
    blockplot x=TATRISK block=ATRISK / repeatedvalues=true
        display=(values) valuehalign=start valuefitpolicy=
        truncate labelposition=left /*labelattrs=GRAPHVALUETEXT

```

```

        valueattrs=GRAPHDATATEXT (size=9pt)*/
        includemissingclass=false;
        endinnermargin;
    endif;
endlayout;
else
/*
    entrytitle METHOD " " " ";
    if (EXISTS(SECONDTITLE))
        entrytitle SECONDTITLE / textattrs=GRAPHVALUETEXT;
    endif;
*/
    layout overlay / xaxisopts=(label="Survival Time (Years)" shortlabel=XNAME
offsetmin=.05
        linearopts=(viewmax=MAXTIME tickvaluelist=(0 1 2 3 4 5 6 7 8)
        tickvaluefitpolicy=XTICKVALFITPOL)) yaxisopts=(label=
"&title" shortlabel="Survival" linearopts=(
viewmin=0 viewmax=1 tickvaluelist=(0 .2 .4 .6 .8 1.0)));
    if (PLOTBW)
        bandplot LimitUpper=HW_UCL LimitLower=HW_LCL x=TIME / group=
            STRATUM index=STRATUMNUM modelname="Survival"
            /*datatransparency=Transparency*/;
    endif;
    if (PLOTTP)
        bandplot LimitUpper=EP_UCL LimitLower=EP_LCL x=TIME / group=
            STRATUM index=STRATUMNUM modelname="Survival"
            /*datatransparency=Transparency*/;
    endif;
    if (PLOTCL)
        if (PLOTBAND)
            bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL x=TIME /
                group=STRATUM index=STRATUMNUM modelname="Survival"
                display=(outline);
        else

```

```

bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL x=TIME /
    group=STRATUM index=STRATUMNUM modelname="Survival"
    /*datatransparency=Transparency*/;
endif;
endif;
stepplot y=SURVIVAL x=TIME / group=STRATUM index=STRATUMNUM
    name="Survival" rolename=( _tip1=ATRISK _tip2=EVENT) tip=(y x
    Time _tip1 _tip2) lineattrs=(thickness=3px);
if (PLOTCEASURED)
    scatterplot y=CENSORED x=TIME / group=STRATUM index=
        STRATUMNUM markerattrs=(symbol=plus);
endif;
if (PLOTATRISK)
    innermargin / align=bottom;
    blockplot x=TATRISK block=ATRISK / class=CLASSATRISK
        repeatedvalues=true display=(label values) valuehalgn
        =start valuefitpolicy=truncate labelposition=left
        /*labelattrs=GRAPHVALUETEXT /*valueattrs=GRAPHDATATEXT (
        size=9pt)*/ includemissingclass=false;
    endinnermargin;
endif;
/*DiscreteLegend "Survival" / title="" location=inside valign=bottom
halign=center;*/
if (PLOTCEASURED)
    if (PLOTTEST)
        layout gridded / rows=2 /*autoalign=(BOTTOM TOPRIGHT BOTTOMLEFT
        TOP)*/ border=false BackgroundColor=
        GraphWalls:Color Opaque=true;
        entry "";
        if (PVALUE < .0001)
            entry TESTNAME " p " eval (PUT(PVALUE, PVALUE6.4));
        else
            entry TESTNAME " p=" eval (PUT(PVALUE, PVALUE6.4));
        endif;
    endif;
endif;

```

```

        endlayout;
    else
        layout gridded / rows=1 /*autoalign=(BOTTOM TOPRIGHT BOTTOMLEFT
        TOP)*/ border=false BackgroundColor=
        GraphWalls:Color Opaque=true;
        entry "";
        endlayout;
    endif;
else
    if (PLOTTEST)
        layout gridded / rows=1 /*autoalign=(BOTTOM TOPRIGHT BOTTOMLEFT
        TOP)*/ border=true BackgroundColor=
        GraphWalls:Color Opaque=true;
        if (PVALUE < .0001)
            entry TESTNAME " p " eval (PUT(PVALUE, PVALUE6.4));
        else
            entry TESTNAME " p=" eval (PUT(PVALUE, PVALUE6.4));
        endif;
        endlayout;
    endif;
endif;
endlayout;
endif;
EndGraph;
end;
run;

proc lifetest data = studyb notable plots = survival(atrisk=0 to 8 by 1 nocensor);
time &var1 * &var2(0);
strata randtype;
test randtype;
run;

```



```
%mend;
```

```
%life(title=Event Free Survival (Composite Endpoint),var1=yrsToAnyEnd,var2=any_endpoint);
```

```
%life(title=Event Free Survival (Death),var1=yrsToDeath,var2=death);
```

```
%life(title=Event Free Survival (End Stage Renal Disease),var1=yrsToESRD,var2=esrd);
```

```
%life(title=Event Free Survival (50% reduction eGFR),var1=yrsToEGFR50,var2=egfr_50);
```