**Time-dependent influences of cardioprotective antihypertensive medication exposure on outcomes of maintenance dialysis patients**

**Running Title**: Time-dependent medication exposure and outcomes in dialysis

**Supplementary Tables**

Table S1. Baseline patient factors associated with all-cause mortality across individual antihypertensive classes, time-dependent modeling of exposures

| | ACEI/ARBs | | β-Blockers | | CCBs | |
|---|---|---|---|---|---|---|
| | AHRs and 99% CIs for individual antihypertensive classes | | | | | |
| | AHR | 99% CI | AHR | 99% CI | AHR | 99% CI |
| Drug class effect | 0.590 | 0.553-0.628 | See interaction table S2 below | | See interaction table S3 below | |
| Age, per year | 1.024 | 1.022-1.025 | 1.024 | 1.022-1.025 | 1.023 | 1.022-1.025 |
| Female sex | 0.946 | 0.913-0.980 | 0.928 | 0.897-0.961 | 1.002 | 0.967-1.039 |
| Race/Ethnicity | | | | | | |
| Caucasian | 1.0 | - | 1.0 | - | 1.0 | - |
| African-American | 0.755 | 0.725-0.786 | 0.748 | 0.719-0.778 | 0.845 | 0.809-0.883 |
| Hispanic | 0.651 | 0.619-0.685 | 0.618 | 0.589-0.649 | 0.725 | 0.688-0.764 |
| Other | 0.588 | 0.545-0.635 | 0.555 | 0.515-0.598 | 0.633 | 0.587-0.683 |
| BMI category | | | | | | |
| < 20 kg/m$^2$ | 1.244 | 1.178-1.313 | 1.212 | 1.147-1.280 | 1.243 | 1.178-1.312 |
| 20-24.9 kg/m$^2$ | 1.0 | - | 1.0 | - | 1.0 | - |
| 25-29.9 kg/.m$^2$ | 0.865 | 0.829-0.903 | 0.871 | 0.835-0.909 | 0.860 | 0.824-0.898 |
| 30+ kg/m$^2$ | 0.779 | 0.746-0.813 | 0.780 | 0.748-0.814 | 0.757 | 0.725-0.790 |
| Smoker | 1.177 | 1.102-1.257 | 1.146 | 1.073-1.223 | 1.207 | 1.130-1.289 |
| Substance abuser | 1.209 | 1.092-1.340 | 1.188 | 1.072-1.316 | 1.187 | 1.072-1.316 |
| Employed | 0.751 | 0.637-0.885 | 0.736 | 0.624-0.867 | 0.767 | 0.651-0.904 |
| Inability to ambulate | 1.266 | 1.174-1.364 | 1.212 | 1.123-1.308 | 1.202 | 1.116-1.296 |
| Inability to transfer | 1.217 | 1.081-1.371 | 1.215 | 1.078-1.368 | 1.220 | 1.084-1.374 |
| Comorbidities | | | | | | |
| Diabetes | 1.237 | 1.189-1.286 | 1.185 | 1.142-1.229 | 1.190 | 1.148-1.234 |
| Congestive heart failure | 1.205 | 1.163-1.248 | 1.229 | 1.186-1.273 | 1.123 | 1.083-1.165 |
| Coronary artery disease | 1.066 | 1.026-1.107 | 1.149 | 1.104-1.198 | 1.020 | 0.982-1.060 |
| Cerebrovascular accident | 1.141 | 1.088-1.197 | 1.142 | 1.089-1.198 | 1.165 | 1.111-1.222 |
| Peripheral vascular disease | 1.086 | 1.039-1.135 | 1.078 | 1.031-1.127 | 1.049 | 1.003-1.096 |
| Propensity score | 0.879 | 0.840-0.919 | 0.844 | 0.808-0.881 | 0.764 | 0.730-0.800 |
| Self-care dialysis | 1.045 | 0.965-1.131 | 1.010 | 0.933-1.093 | 0.992 | 0.917-1.074 |

AHR, adjusted hazards ratio; CI, confidence interval; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BMI, body mass index

Table S2. Adjusted hazard ratios (AHR)* for all-cause mortality using time-dependent drug exposure measures comparing active ß-Blocker use to non-use accounting for number of switches and percentage of prior weeks with medication

| Percent of preceding weeks with drug | AHRs (99% CI) | | | |
|---|---|---|---|---|
| | # Switches between On and Off status | | | |
| | 1 | 2 | 5 | 10 |
| 10% | 0.734 (0.670 – 0.813) | 0.756 (0.690 – 0.828) | 0.812 (0.738 – 0.895) | - |
| 25% | 0.712 (0.657 – 0.773) | 0.726 (0.672 – 0.783) | 0.767 (0.711 – 0.828) | 0.842 (0.746 – 0.949) |
| 40% | 0.687 (0.641 – 0.738) | 0.696 (0.652 – 0.744) | 0.724 (0.682 – 0.770) | 0.774 (0.711 – 0.842) |
| 50% | 0.671 ÿ0.628 – 0.718) | 0.677 (0.637 – 0.722) | 0.697 (0.660 – 0.737) | 0.731 (0.684 – 0.782) |
| 60% | 0.656 (0.613 – 0.702) | 0.660 (0.619 – 0.703) | 0.671 (0.636 – 0.709) | 0.691 (0.651 – 0.733) |
| 75% | 0.633 (0.587 - 0.683) | 0.633 (0.590 - 0.680) | 0.634 (0.595 - 0.675) | 0.635 (0.591 – 0.683) |
| 90% | 0.611 (0.558 - 0.668) | 0.608 (0.558 - 0.662) | 0.599 (0.553 - 0.648) | 0.584 (0.526 – 0.648) |

*Model adjusted for factors listed in Table S1
AHR, adjusted hazards ratio; CI, confidence interval

Table S3. Adjusted hazard ratios (AHR)* for all-cause mortality using time-dependent drug exposure measures comparing active calcium channel blocker use to non-use accounting for percentage of prior weeks with medication

| Percent of preceding weeks with drug | AHRs (99% CI) |
|---|---|
| 10% | 0.676 (0.612 – 0.746) |
| 25% | 0.655 (0.605 – 0.709) |
| 40% | 0.635 (0.595 – 0.676) |
| 50% | 0.621 (0.587 – 0.658) |
| 60% | 0.608 (0.577 – 0.642) |
| 75% | 0.590 (0.556 - 0.625) |
| 90% | 0.571 (0.532 - 0.613) |

*Model adjusted for factors listed in Table S1
AHR, adjusted hazards ratio; CI, confidence interval

Table S4. Adjusted hazard ratios (AHR)* for combined CVD-endpoint using time-dependent drug exposure measures comparing active use of any of the selected antihypertensive agents to non-use accounting for percentage of prior weeks with medication

| Percent of preceding weeks with drug | AHRs (99% CI) |
|---|---|
| 10% | 1.178 (1.072-1.294) |
| 25% | 1.120 (1.038-1.209) |
| 40% | 1.066 (1.002-1.133) |
| 50% | 1.031 (0.975-1.089) |
| 60% | 0.997 (0.946-1.051) |
| 75% | 0.948 (0.896-1.003) |
| 90% | 0.902 (0.843-0.966) |

*Model adjusted for factors listed in Table 2
AHR, adjusted hazards ratio; CVD, cardiovascular disease; CI, confidence interval; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker

Table S5. Baseline patient factors associated with combined CVD-endpoint for individual antihypertensive classes, time-dependent modeling of exposures

| Drug class effect | AHRs and 99% CIs for individual antihypertensive classes | | | | | |
|---|---|---|---|---|---|---|
| | ACEI/ARBs | | β-Blockers | | CCBs | |
| | AHR | 99% CI | AHR | 99% CI | AHR | 99% CI |
| Drug class effect | See interaction table S5 below | | See interaction table S6 below | | See interaction table S6 below | |
| Age, per year | 1.013 | 1.011-1.014 | 1.013 | 1.012-1.015 | 1.012 | 1.011-1.013 |
| Female sex | 1.032 | 0.996-1.068 | 1.019 | 0.985-1.055 | 1.062 | 1.026-1.100 |
| Race/Ethnicity | | | | | | |
|   Caucasian | 1.0 | - | 1.0 | - | 1.0 | - |
|   African-American | 0.871 | 0.835-0.909 | 0.853 | 0.816-0.891 | 0.948 | 0.906-0.992 |
|   Hispanic | 0.861 | 0.818-0.905 | 0.826 | 0.788-0.866 | 0.921 | 0.875-0.970 |
|   Other | 0.751 | 0.696-0.809 | 0.724 | 0.673-0.779 | 0.791 | 0.734-0.853 |
| BMI category | | | | | | |
|   < 20 kg/m$^2$ | 1.042 | 0.983-1.105 | 1.046 | 0.985-1.110 | 1.037 | 0.979-1.100 |
|   20-24.9 kg/m$^2$ | 1.0 | | 1.0 | | 1.0 | |
|   25-29.9 kg/.m$^2$ | 0.945 | 0.906-0.986 | 0.948 | 0.908-0.989 | 0.945 | 0.906-0.986 |
|   30+ kg/m$^2$ | 0.887 | 0.851-0.926 | 0.897 | 0.860-0.935 | 1.195 | 1.149-1.242 |
| Smoker | 1.168 | 1.094-1.247 | 1.147 | 1.075-1.224 | 1.176 | 1.102-1.256 |
| Substance abuser | 1.070 | 0.964-1.186 | 1.075 | 0.970-1.192 | 1.066 | 0.961-1.182 |
| Employed | 0.921 | 0.806-1.052 | 0.925 | 0.810-1.057 | 0.930 | 0.815-1.063 |
| Inability to ambulate | 0.966 | 0.890-1.050 | 0.978 | 0.899-1.063 | 0.931 | 0.857-1.011 |
| Inability to transfer | 1.060 | 0.924-1.216 | 1.067 | 0.930-1.224 | 1.042 | 0.909-1.196 |
| Comorbidities | | | | | | |
|   Diabetes | 1.270 | 1.219-1.324 | 1.223 | 1.179-1.268 | 1.255 | 1.210-1.301 |
|   Congestive heart failure | 1.289 | 1.244-1.335 | 1.293 | 1.248-1.339 | 1.219 | 1.175-1.265 |
|   Coronary artery disease | 1.245 | 1.199-1.294 | 1.267 | 1.210-1.328 | 1.020 | 0.982-1.060 |
|   Cerebrovascular accident | 1.059 | 1.008-1.113 | 1.066 | 1.015-1.120 | 1.081 | 1.029-1.136 |
|   Peripheral vascular disease | 1.093 | 1.045-1.143 | 1.096 | 1.048-1.146 | 1.067 | 1.019-1.116 |
| Propensity score | 0.907 | 0.866-0.951 | 0.954 | 0.908-1.002 | 0.800 | 0.763-0.839 |
| Self-care dialysis | 0.940 | 0.870-1.016 | 0.931 | 0.862-1.006 | 0.925 | 0.856-0.999 |

AHR, adjusted hazards ratio; CVD, cardiovascular disease; CI, confidence interval; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BMI, body mass index

Table S6. Adjusted hazard ratios (AHR)* for combined CVD-endpoint using time-dependent drug exposure measures comparing active ACEI/ARB use to non-use accounting for number of switches and percentage of prior weeks with medication

| | AHRs (99% CI) | | | |
|---|---|---|---|---|
| | # Switches between On and Off status | | | |
| Percent of preceding weeks with drug | 1 | 2 | 5 | 10 |
| 10% | 1.327 (1.215 - 1.450) | 1.288 (1.184 - 1.400) | 1.176 (1.048 - 1.319) | - |
| 25% | 1.212 (1.125 - 1.306) | 1.185 (1.105 - 1.271) | 1.107 (1.014 - 1.208) | 0.988 (0.833 - 1.171) |
| 40% | 1.107 (1.034 - 1.184) | 1.090 (1.025 - 1.160) | 1.041 (0.975 - 1.113) | 0.966 (0.857 - 1.088) |
| 50% | 1.042 (0.974 - 1.114) | 1.031 (0.970 - 1.096) | 1.000 (0.944 - 1.060) | 0.951 (0.865 - 1.046) |
| 60% | 0.980 (0.914 - 1.051) | 0.975 (0.915 - 1.040) | 0.961 (0.907 - 1.017) | 0.937 (0.860 - 1.020) |
| 75% | 0.895 (0.827 - 0.969) | 0.897 (0.834 - 0.966) | 0.904 (0.843 - 0.970) | 0.916 (0.824 - 1.018) |
| 90% | 0.817 (0.744 - 0.899) | 0.826 (0.755 - 0.903) | 0.851 (0.775 - 0.935) | 0.895 (0.769 - 1.043) |

*Model adjusted for factors listed in Table S4

AHR, adjusted hazards ratio; CVD, cardiovascular disease; CI, confidence interval; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker

Table S7. Adjusted hazard ratios (AHR)* for combined CVD-endpoint using time-dependent drug exposure measures comparing active ß-Blocker and calcium channel blocker use to non-use accounting for number of switches and percentage of prior weeks with medication

| Percent of preceding weeks with drug | ß-Blockers AHR (99% CI) | Calcium channel blockers AHR (99% CI) |
|---|---|---|
| 10% | 1.527 (1.415 – 1.649) | 1.107 (1.009 – 1.215) |
| 25% | 1.354 (1.270 – 1.443) | 1.035 (0.960 – 1.116) |
| 40% | 1.200 (1.135 – 1.269) | 0.968 (0.910 – 1.030) |
| 50% | 1.070 (1.049 – 1.169) | 0.926 (0.875 – 0.980) |
| 60% | 1.022 (0.966 – 1.081) | 0.886 (0.838 – 0.936) |
| 75% | 0.960 (0.850 - 0.866) | 0.828 (0.779 - 0.880) |
| 90% | 0.803 (0.744 - 0.867) | 0.775 (0.719 - 0.834) |

*Models adjusted for factors listed in Table S4

AHR, adjusted hazards ratio; CVD, cardiovascular disease; CI, confidence interval