Combined Effect of Income and Medication Adherence on Mortality in Newly Treated Hypertension: Nationwide Study of 16 Million Person-Years

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Background—Low socioeconomic status and poor medication adherence are known to be associated with increased morbidity and mortality among patients with hypertension, but their combined effects have not been studied. We therefore evaluated the joint association of household income and medication adherence with death and cardiovascular disease in patients newly treated for hypertension.

Methods and Results—This was a nationwide cohort study using the Korean National Health Insurance database. We included 1 651 564 individuals, aged 30 to 80 years, with newly treated hypertension and no prior cardiovascular disease and followed them for 10 years. Main exposures were household income in quintiles and adherence to antihypertensive medication, estimated by medication possession ratio: good (≥0.8), moderate (0.5 to <0.8), or poor (<0.5). The primary outcomes were all-cause and cardiovascular deaths. Higher mortality risk was observed in patients with low income (adjusted hazard ratio = 1.50, 99% CI = 1.46-1.53; lowest versus highest quintile) and poor medication adherence (adjusted hazard ratio = 1.66, 99% CI = 1.63-1.68; poor versus good adherence). When compared with the highest-income and good-adherence group, adjusted hazard ratio (99% CI) of death was 1.56 (1.52-1.61) for highest-income poor-adherers, 1.46 (1.41-1.51) for lowest-income good-adherers, and 2.46 (2.38-2.54) for lowest-income poor-adherers (P for interaction <0.001).

Conclusions—Low socioeconomic status and poor adherence to antihypertensive medication are associated with increased mortality and cardiovascular disease risks, but patients with low income are subject to larger excess risks by nonadherence. This highlights the potential importance of promoting medication adherence for risk reduction, especially in low-income patients with hypertension. (J Am Heart Assoc. 2019;8:e013148. DOI: 10.1161/JAHA.119.013148.)

Key Words: health disparities • hypertension • income • medication adherence • mortality • real-world data

High blood pressure is the leading risk factor for death and cardiovascular disease (CVD) globally.1 Despite effective blood pressure-lowering treatments available, populations of low socioeconomic status often have poor awareness and control.2-4 Accruing evidence suggests that socioeconomic deprivation is associated with increased risk for death and CVD.5 However, among patients newly treated for hypertension, there are scarce data on mortality according to income gradient or on which factors can be improved to lower poverty-related death in these patients.

Previous studies have reported an association between adherence to antihypertensive medication and cardiovascular events.6,7 Medication adherence is an important clinical and public health issue, given that nonadherence is a major risk factor for adverse outcome and increased medical cost.8 Although nonadherence is prevalent among low-income patients, it is unclear whether its effect on clinical outcome varies according to socioeconomic gradient because the combined effect of income and medication adherence has not been fully studied. Therefore, in a large primary prevention population, we investigated the risks for death and CVD hospitalizations according to combination of household...
Clinical Perspective

What Is New?

• Both low income and poor medication adherence are associated with higher mortality, but their joint association is more potent than each risk factor individually.
• The excess risk by poor medication adherence is greater in individuals with low socioeconomic status, but even with good medication adherence, low-income patients are still at increased mortality risk.

What Are the Clinical Implications?

• Measures to improve medication adherence should be sought to reduce mortality in low-income patients with hypertension, and management of poverty-driven cardiovascular risk factors should accompany these measures.
• Because socioeconomic information is readily available from existing data, future research may identify uniquely vulnerable patients for evidence-based interventions to optimize pharmacologic therapy and improve medication adherence.

income and medication adherence in patients who started hypertension treatment.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers may be sent to the National Health Insurance Service (NHIS) at https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do

Data Source

We used a nationwide electronic database provided by the NHIS, which includes deidentified claim records of the entire Korean population. The NHIS is the single provider of universal healthcare coverage in South Korea. The NHIS database encompasses both insurance programs: health insurance program covering 97% of the population, and medical aid program covering the remaining 3% with financial needs or under special provisions (eg, national meritorious individuals). The database contains sociodemographic details, reimbursement claims with International Classification of Disease, Tenth Edition (ICD-10) coding, general health checkup results, and death information.9 Description of the data source has been done in previous studies.10 The study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System, Seoul, Korea (Approval No. 4-2017-0322). Informed consent was not required, as this is a retrospective study of deidentified administrative data.

Study Population

We identified 1 977 432 individuals, aged 30 to 80, newly treated for primary hypertension (ICD-10 code I10 with antihypertensive medication; Table S1) from January 1, 2004 to December 31, 2007. Identification of treated hypertension followed the protocol developed by the Korean Society of Hypertension.10,11 We excluded patients with prior diagnosis or medication for any hypertensive disease, prior myocardial infarction (MI), heart failure, or stroke (Table S2), or fewer than 2 prescriptions during the first year of treatment (Figure S1). To minimize the effect of reverse causality, we also excluded individuals who died or had a CVD event within 2 years following the index date (N=88 830). Those with incomplete income information, including medical aid beneficiaries, were also omitted from the analysis (N=237 038). The final 1 651 564 individuals were followed until death, migration from the database, or censoring date (10 years from the index date), whichever came first.

Sociodemographic Information and Covariates

As a proxy for household income we used insurance premium, determined by government assessment of salary and assets, rather than self-report. Household insurance premiums were grouped into quintiles among all households in Korea at the index year. Medical aid beneficiaries do not pay insurance premiums; their economic statuses are heterogeneous and are not included in the income quintiles. We therefore excluded medical aid from the study. Working status was categorized into either employed or self-/unemployed. The Charlson Comorbidity Index was calculated using ICD-10 codes12,13 claimed during the 2 years before the index date.

Assessment of Medication Adherence

Antihypertensive adherence was determined by medication possession ratio, which is the number of days’ medication supplied divided by the number of days in a time period.14 The medication possession ratio is among the best available methods using retrospective data15 and correlates well with other adherence measures.16 We calculated the medication possession ratio for the first 2 years after index date and classified it into 3 levels: good (≥0.8), moderate (≥0.5 and <0.8), or poor (<0.5) adherence, as done in previous studies.7,17,18 We capped the medication possession ratio at 1.0 to discard days oversupplied.
Outcomes
The primary outcomes were all-cause and cardiovascular deaths. All deaths and their causes were ascertained by linkage to the Statistics Korea database via resident registration numbers. Cardiovascular death was defined as death due to CVD (ICD-10, I00-I99) by certificate. The secondary outcomes were atherosclerotic CVD, a composite of MI and/or stroke, MI, stroke, and heart failure, defined as the first hospitalization with the corresponding condition as the main diagnosis (Table S2).

Statistical Analyses
Baseline characteristics were reported as frequency and percentage or median and interquartile range. We used a Cox proportional hazards model to calculate hazard ratio (HR) and 99% CI for each outcome according to household income, medication adherence, and the combination of the 2 (15 levels: 5 levels of income by 3 levels of adherence). Multivariable Cox regression was adjusted for age, sex, employment status, household income, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, antihypertensive drug class, and medication adherence. We further stratified our analyses by sex, given that health-related behaviors, medication adherence, and mortality may differ by sex. Interactions of sex with income and adherence and interaction between the income and adherence interaction within each sex were tested as continuous terms in the full model. The proportionality of hazards was checked graphically by log-minus-log plot and by Schoenfeld residuals. The assumption of proportional hazards was not violated.

Several additional analyses were done on different subsets or inclusion of data. First, monotherapy initiators (N=923 664, excluding first-line β-blockers) and combination therapy initiators (N=572 445) were analyzed separately. Second, given our operational definition excluding individuals with only 1 prescribing visit for stricter identification of treated hypertension, we performed sensitivity analyses including those without further visits (total N=2 163 335) to ensure that excluding these individuals did not alter the association between adherence and mortality. Finally, because our main analysis did not account for lifestyle or clinical parameters, we performed additional analyses on 643 026 individuals with health checkup results closest to, and within the past 2 years from, the index date (median 7.3 months). We added cigarette smoking (never, past, or current), alcohol consumption (none, 1–2 times/wk, ≥3 times/wk), physical exercise (none, 1–2 times/wk, ≥3 times/wk), body mass index, systolic blood pressure, fasting glucose, and total cholesterol in this model. Details of health screening variables are described elsewhere. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) with survival package.

Results
Baseline Characteristics
A total of 1 651 564 individuals were followed for 15 956 805 person-years. Baseline characteristics by income levels are summarized in Table 1. Median age was 53 (interquartile range 46-63) years, and 47.5% were women. Age was comparable across income levels, and female sex and employed status were more prevalent in the lowest income group. Individuals with lower income were more likely to be on multiple antihypertensive agents. For the initial regimen, diuretics, beta-blockers, or calcium channel blockers were more common in lower income groups, whereas angiotensin II receptor blockers were more frequently used in higher income groups. Distribution of Charlson Comorbidity Index was comparable across the groups, but patients with lower income had marginally fewer documented comorbidities.

During the first 2 years of treatment, 742 387 (45.0%) patients showed good adherence, 348 236 (21.1%) moderate adherence, and 560 941 (34.0%) poor adherence to antihypertensive agents. For the initial regimen, diuretics, beta-blockers, or calcium channel blockers were more common in lower income groups, whereas angiotensin II receptor blockers were more frequently used in higher income groups. Distribution of Charlson Comorbidity Index was comparable across the groups, but patients with lower income had marginally fewer documented comorbidities.

Death and CVD Hospitalizations According to Income and Medication Adherence
During 15 956 805 person-years, 136 287 deaths were observed. Mortality rates were higher in individuals with lower household income (1010.9 versus 779.1 per 100 000 person-years; lowest versus highest income). Lower household income was independently associated with increased mortality, even after adjustment for age, sex, employment, comorbidities, antihypertensive medications, and adherence. The HR (99% CI) for all-cause and cardiovascular death were 1.64 (1.59-1.68) and 1.75 (1.64-1.87) in men and 1.31 (1.27-1.36) and 1.38 (1.29-1.47) in women, when lowest-income group was compared with highest-income group (Table 2). Poor medication adherence was also associated with greater risk for all-cause and cardiovascular death—HR (99% CI), 1.70 (1.66-1.73) and 1.95 (1.86-2.05) in men and 1.56 (1.52-1.60) and 1.74 (1.64-1.83) in women—when compared with good adherence and adjusted for covariates (Table 2). There were significant
interactions of sex with both income and adherence in association with all outcomes ($P<0.005$) except for myocardial infarction ($P>0.1$).

When stratified by the combination of income and adherence, poor medication adherence was associated with higher risk for all-cause and cardiovascular death across all income groups. However, the absolute risks and their difference by adherence gradually increased toward lower household income, especially in men. In lowest-income men, cumulative death rates were 1714.7 versus 1064.8 per 100 000 person-years for poor versus good adherers, whereas in highest-income men, rates were 1110.1 versus 694.9 per 100 000 person-years for poor versus good adherers. After adjustment for covariates, excess risk for all-cause death associated with poor medication adherence was 117% in lowest-income men and 59% in highest-income

### Table 1. Baseline Characteristics by Household Income

| Household Income, Quintile | Q5, Highest | Q4 | Q3 | Q2 | Q1, Lowest |
|-----------------------------|-------------|----|----|----|------------|
| (N=470 609)                 | (N=371 434) | (N=297 474) | (N=240 613) | (N=271 434) |
| Age, y                      | 54 [46-64]  | 53 [45-63]  | 53 [46-61]  | 53 [46-61]  | 55 [47-63]  |
| Sex                         |             |     |    |    |            |
| Female                      | 212 709 (45.2%) | 170 661 (45.9%) | 137 849 (46.3%) | 117 620 (48.9%) | 145 660 (53.7%) |
| Male                        | 257 900 (54.8%) | 200 773 (51.4%) | 159 625 (53.7%) | 122 993 (51.1%) | 125 774 (46.3%) |
| Employment status           |             |     |    |    |            |
| Employed workers            | 107 543 (22.9%) | 69 086 (18.6%) | 56 082 (18.9%) | 49 733 (20.7%) | 93 535 (34.5%) |
| Self- or unemployed         | 363 066 (77.1%) | 302 348 (81.4%) | 241 392 (81.1%) | 190 880 (79.3%) | 177 899 (65.5%) |
| Initial antihypertensive agent* |         |    |    |    |            |
| Diuretics                   | 123 885 (26.3%) | 102 736 (27.7%) | 84 339 (28.4%) | 69 269 (28.8%) | 78 558 (28.9%) |
| β-blockers                  | 99 990 (21.2%) | 81 707 (22.0%) | 66 773 (22.4%) | 54 863 (22.8%) | 61 236 (22.6%) |
| Calcium channel blockers    | 262 915 (55.9%) | 215 554 (58.0%) | 175 943 (59.1%) | 144 130 (59.9%) | 163 669 (60.3%) |
| ACE inhibitors              | 58 650 (12.5%) | 47 909 (12.9%) | 38 161 (12.8%) | 30 340 (12.6%) | 34 068 (12.6%) |
| Angiotensin II receptor blockers | 112 559 (23.9%) | 78 138 (21.0%) | 60 241 (20.3%) | 46 758 (19.4%) | 51 299 (18.9%) |
| Others                      | 3643 (0.8%) | 2589 (0.7%) | 2004 (0.7%) | 1610 (0.7%) | 1818 (0.7%) |
| Number of antihypertensive class |         |    |    |    |            |
| 1                           | 314 312 (66.8%) | 243 264 (65.5%) | 192 307 (64.6%) | 154 550 (64.2%) | 174 688 (64.4%) |
| 2                           | 125 283 (26.6%) | 102 261 (27.5%) | 83 115 (27.9%) | 68 000 (28.3%) | 76 719 (28.3%) |
| ≥3                          | 31 014 (6.6%) | 25 909 (7.0%) | 22 052 (7.4%) | 18 063 (7.5%) | 20 029 (7.4%) |
| Use of glucose-lowering drugs | 79 180 (16.8%) | 64 529 (17.4%) | 52 405 (17.6%) | 42 794 (17.8%) | 48 045 (17.7%) |
| Use of lipid-lowering drugs  | 66 642 (14.2%) | 47 198 (12.7%) | 35 768 (12.0%) | 27 490 (11.4%) | 30 420 (11.2%) |
| Charlson Comorbidity Index  |             |     |    |    |            |
| 0                           | 231 950 (49.3%) | 185 006 (48.9%) | 151 885 (51.1%) | 124 890 (51.9%) | 142 041 (52.3%) |
| 1                           | 89 736 (19.1%) | 71 188 (19.2%) | 55 936 (18.8%) | 45 156 (18.8%) | 53 196 (19.6%) |
| 2                           | 81 841 (17.4%) | 63 871 (17.2%) | 50 237 (16.9%) | 39 405 (16.4%) | 42 729 (15.7%) |
| ≥3                          | 67 082 (14.3%) | 51 369 (13.8%) | 39 416 (13.3%) | 31 162 (13.0%) | 33 468 (12.3%) |
| Medication possession ratio | 0.78 [0.37-0.95] | 0.75 [0.32-0.94] | 0.72 [0.29-0.93] | 0.71 [0.27-0.92] | 0.73 [0.30-0.93] |
| Medication adherence         |             |     |    |    |            |
| Good                        | 225 169 (47.8%) | 167 883 (45.2%) | 128 731 (43.3%) | 101 928 (42.4%) | 118 676 (43.7%) |
| Moderate                    | 97 682 (20.8%) | 78 119 (21.0%) | 63 202 (21.2%) | 51 511 (21.4%) | 57 722 (21.3%) |
| Poor                        | 147 758 (31.4%) | 125 432 (33.8%) | 105 541 (35.5%) | 87 174 (36.2%) | 95 036 (35.0%) |

Data are presented as median [interquartile range] or frequency (percent). ACE indicates angiotensin-converting-enzyme.

*Counted with duplicates for combination therapy.
men (Figure 1). Similarly, excess risks for cardiovascular death associated with poor adherence were 178% versus 84% in lowest- versus highest-income men, respectively (Figure 1). There were significant interactions between income and adherence in association with all-cause and cardiovascular death ($P<0.001$ and $0.020$). In women, the difference in mortality risk by income was also present but was not as prominent as in men. Excess risks associated with poor adherence in women were 142% versus 78% in lowest- versus highest-income women, respectively (Figure 1).

**Table 2. All-Cause and Cardiovascular Death According to Household Income and Medication Adherence**

| Variables          | People | All-Cause Death | Cardiovascular Death |
|--------------------|--------|-----------------|----------------------|
|                    |        | Events | Rate* | HR (95% CI) | Events | Rate* | HR (95% CI) |
|                    |        |        |       | Model 1  |        |       | Model 1  | Model 2  |        |       | Model 2  |
| Total              | 1 651 564 | 136 287 | 854.1 | 1.00 (reference) | 27 195 | 170.4 |
| Income, quintile   |        |        |       |          |        |       |          |          |        |       |          |
| 5, highest         | 470 609 | 35 544 | 779.1 | 1.00 (reference) | 6974 | 152.9 |
| 4                  | 371 434 | 29 156 | 810.5 | 1.16 (1.13-1.18) | 5838 | 162.3 |
| 3                  | 297 474 | 23 888 | 831.0 | 1.29 (1.26-1.32) | 4681 | 162.8 |
| 2                  | 240 613 | 21 365 | 921.7 | 1.46 (1.42-1.49) | 4274 | 184.4 |
| 1, lowest          | 271 434 | 26 334 | 1010.9 | 1.54 (1.51-1.58) | 5428 | 208.4 |
| Adherence          |        |        |       |          |        |       |          |          |        |       |          |
| Good               | 742 387 | 49 451 | 683.6 | 1.00 (reference) | 9374 | 129.6 |
| Moderate           | 348 236 | 29 140 | 866.5 | 1.35 (1.32-1.37) | 5883 | 174.9 |
| Poor               | 560 941 | 57 964 | 1076.4 | 1.70 (1.67-1.73) | 11 938 | 222.7 |
| Men                | 867 065 | 85 811 | 1032.1 | 1.00 (reference) | 15 198 | 182.8 |
| Income, quintile   |        |        |       |          |        |       |          |          |        |       |          |
| 5, highest         | 257 900 | 21 290 | 854.9 | 1.00 (reference) | 3589 | 144.1 |
| 4                  | 200 773 | 18 669 | 966.7 | 1.20 (1.17-1.23) | 3353 | 173.6 |
| 3                  | 159 625 | 15 624 | 1020.7 | 1.35 (1.31-1.38) | 2743 | 179.2 |
| 2                  | 122 993 | 14 139 | 1207.0 | 1.58 (1.54-1.63) | 2589 | 221.0 |
| 1, lowest          | 125 774 | 16 089 | 1351.4 | 1.70 (1.66-1.75) | 2924 | 245.6 |
| Adherence          |        |        |       |          |        |       |          |          |        |       |          |
| Good               | 389 003 | 30 735 | 815.2 | 1.00 (reference) | 5191 | 137.7 |
| Moderate           | 180 554 | 17 823 | 1029.5 | 1.36 (1.33-1.40) | 3139 | 181.3 |
| Poor               | 297 508 | 37 253 | 1324.4 | 1.77 (1.73-1.80) | 6868 | 244.2 |
| Women              | 784 499 | 50 476 | 660.5 | 1.00 (reference) | 11 997 | 157.0 |
| Income, quintile   |        |        |       |          |        |       |          |          |        |       |          |
| 5, highest         | 212 709 | 14 254 | 688.0 | 1.00 (reference) | 3385 | 163.4 |
| 4                  | 170 661 | 10 487 | 629.5 | 1.10 (1.07-1.14) | 2485 | 149.2 |
| 3                  | 137 849 | 8264 | 615.0 | 1.21 (1.17-1.25) | 1938 | 144.2 |
| 2                  | 117 620 | 7226 | 630.2 | 1.27 (1.22-1.32) | 1685 | 147.0 |
| 1, lowest          | 145 660 | 10 245 | 724.3 | 1.34 (1.30-1.39) | 2504 | 177.0 |
| Adherence          |        |        |       |          |        |       |          |          |        |       |          |
| Good               | 353 384 | 18 716 | 540.3 | 1.00 (reference) | 4183 | 120.8 |
| Moderate           | 167 682 | 11 317 | 693.6 | 1.30 (1.26-1.34) | 2744 | 168.2 |
| Poor               | 263 433 | 20 443 | 802.6 | 1.57 (1.53-1.61) | 5070 | 199.1 |

Model 1 included either income or adherence as the primary independent variable and was adjusted for age, sex, and employment status. Model 2 included both income and adherence as independent variables and was adjusted for age, sex, employment status, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, and antihypertensive drug class. HR indicates hazard ratio.

*Per 100 000 person-years.

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adherence in lowest- versus highest-income women were 73% versus 52% for all-cause death and 102% versus 58% for cardiovascular death (Figure 1). Income-adherence interaction did not reach statistical significance in women (P>0.1). Kaplan-Meier curves for all-cause and cardiovascular death showed that both income and adherence were individually associated with survival, but the impact of low income on survival was much less in women than in men (Figure 2). Associations with CVD hospitalizations showed similar joint effects of income and adherence, but interactions between income and adherence did not reach statistical significance for nonfatal outcomes (P>0.1) except for stroke in women (Figures S2, S3, and Tables S4, S5).

**Additional Analyses**

We performed several additional analyses on different subsets or inclusion criteria. First, when monotherapy and combination therapy initiators were analyzed separately, the income-adherence joint associations with mortality and its sex difference were consistently observed in both groups (Figures S4 and S5). Second, when patients with fewer than 2 visits were added as sensitivity analyses, the HRs were marginally attenuated, but the joint income-adherence associations with mortality and sex difference remained (Figure S6). Finally, we performed an additional analysis on 643 026 individuals with health examination results. Overall mortality rates in health examinees were lower than in the entire study patients (685.3 per 100 000 person-years). We observed consistent joint associations of income and adherence with death and CVD, as described in the main analysis, but with attenuated HRs when further adjustment was made for cigarette smoking, alcohol consumption, physical exercise, body mass index, systolic blood pressure, fasting glucose, and total cholesterol (Figure 3 and Tables S6 and S7). Income-adherence interaction did not reach...
A fraction of these participants underwent a repeated examination within 2 to 4 years after index date (median 2.8 years, N = 466,103).

On follow-up, individuals with poor medication adherence had smaller blood pressure reduction than those with good adherence (Figure S7). This trend was comparable across all income groups and after adjustment for baseline systolic blood pressure and other risk factors.

**Figure 2.** Kaplan-Meier curves for all-cause and cardiovascular death stratified by income and adherence in men and women. *Income was dichotomized into high (upper 50%) and low (lower 50%).

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nonadherence and mortality. Of note, Koreans have a high
in the lowest income group, assuming causality between
adherence and mortality. Therefore, the finding of a signi-
cant differential income effect under such a highly accessible healthcare system is unexpected and noteworthy.

Socioeconomic status has long been implicated as a major
risk factor for death and CVD. Low-income countries as well
as low-income subpopulations within developed countries
have higher CVD prevalence and mortality rates. However,
there is limited evidence of which modi-

Discussion

In this nationwide study of newly treated hypertension, we
found that low income and poor adherence to antihyperten-
sive medication were associated with increased mortality, and
the excess risk by poor adherence was greater in individuals
with low socioeconomic status. People with lower household
income were not only more likely to be nonadherent but were
also at higher risk for death when they were not adherent to
antihypertensive medication. From this excess risk from poor
versus good medication adherence in our study, we project an
absolute risk reduction over 500 per 100 000 person-years
for an intervention that would promote medication adherence
in the lowest income group, assuming causality between
nonadherence and mortality. Of note, Koreans have a high
rate of healthcare utilization due to universal health insurance
coverage, as evident by the largest number of doctor visits per
capita among Organisation for Economic Cooperation and
Development countries, and a high participation rate in the
national general health screening program (eg, 77.7% in
2016). Therefore, the finding of a significant differential
income effect under such a highly accessible healthcare
system is unexpected and noteworthy.

Socioeconomic status has long been implicated as a major
risk factor for death and CVD. Low-income countries as well
as low-income subpopulations within developed countries
have higher CVD prevalence and mortality rates. However,
there is limited evidence of which modifiable risk factor
should be targeted for intervention in low-income patients
with hypertension. Previous studies have reported that poor

Figure 3. Combined effect of income and adherence on all-cause and cardiovascular death in health examinees. Multivariate Cox regression with model 1 adjusted for age, sex, employment status, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, and antihypertensive drug class; model 2 further adjusted for cigarette smoking, alcohol consumption, physical exercise, body mass index, systolic blood pressure, fasting glucose, and total cholesterol. P for interaction between income and adherence in model 1 and model 2 was 0.173 and 0.385 for all-cause death and 0.144 and 0.192 for cardiovascular death, respectively. HR indicates hazard ratio. *Per 100 000 person-years.
medication adherence is associated with morbidity and mortality in individuals with hypertension. Our findings suggest that low income and medication nonadherence are important risk factors for mortality and CVD among initiators of hypertension treatment, and the joint association of income and adherence appears to be even more potent than each risk factor individually. Because these measures are readily available from existing data, it may be possible to identify uniquely vulnerable patients for evidence-based interventions that seek to optimize pharmacologic therapy and to improve medication adherence.

Determinants of medication adherence may be multifactorial, including demographics, comorbidities, and socioeconomic status. In our study good medication adherence was associated with older age, female sex, higher income, employed status, concurrent uses of glucose-lowering and lipid-lowering drugs, and single-pill combination antihypertensive therapy, although further study is needed because only a limited number of predictors could be assessed. Use of single-pill combinations may promote adherence and reduce cost simultaneously. Optimal visit schedules or follow-up strategies to maximize adherence in low-income patients should be further studied, and policies should tackle socioeconomic barriers to healthcare access in patients with low income or other social deprivations.

There are several explanations how nonadherence-related adverse outcome could be affected by income gradient. Despite universal health insurance coverage in Korea, relative poverty and its implication in health disparity require attention. In the KNHANES (Korean National Health and Nutrition Examination Survey), patients with low income were more likely to experience unmet healthcare needs and to have uncontrolled hypertension or comorbidities. Limited access to healthcare services in a low-income population may lead to more masked or undocumented comorbidities. Clinical severity and unhealthy lifestyle are also associated with low socioeconomic status and, in turn, with adverse outcome. A high proportion of low-income patients in our study were prescribed 3 or more antihypertensive agents, reflecting greater likelihood of their having severe or uncontrolled hypertension. Furthermore, prevalence of other metabolic abnormalities may also be higher in low-income individuals. In our additional analysis with adjustments for smoking, drinking, exercise, body mass index, systolic blood pressure, fasting glucose, and total cholesterol, the joint association of income and adherence with mortality was attenuated but still remained. Moreover, residual risk by low income in good medication adherers is still unexplained after full adjustments. Therefore, further study is needed on some other contributing factors. Notably, Koreans have higher sodium consumption (4.5 g/d) than global average or WHO recommendations, and sodium intake is even higher in individuals with low socioeconomic status or with other poor health behaviors. Job strain is another important risk factor for higher prevalence and worse control of hypertension associated with low socioeconomic status. Although we did not specify job types, we observed higher proportions of employed workers in lower income groups, where job strain may have contributed to difficult blood pressure control and worse cardiovascular outcome.

The reason for sex difference in poverty-related mortality in our study is not clear. Because overall mortality rate and cardiovascular risk are much lower in women, the impact of socioeconomic status may not be as conspicuous as in men. In our study, medication adherence was marginally higher, and the difference by income was smaller, in women than in men. This is in line with another study reporting higher health literacy in women and smaller gradient of health literacy by income in women compared with men. Differences in social and occupational positions by sex may also provide some explanations. Fewer than 10% of women in our study were employed workers, and conversely, the vast majority of women were dependant family members who may have had less exposure to work-related risk factors and better access to healthcare services, compared with employed workers. Moreover, household income may have a weaker association with health-related behaviors in family dependents, whose individual economic status are not directly represented. Further study is needed to investigate these matters.

Our study has several strengths. We utilized a nationwide longitudinal database that covers the entire Korean population. Hence, we captured nearly all patients who started antihypertensive treatment, allowing a large sample size and long follow-up despite strict identification criteria. Because of this large inception cohort design, detailed stratified analyses by sociodemographic factors were also possible. Furthermore, main exposure variables were derived from objective data rather than from self-report. Especially, NHIS premium is levied according to comprehensive assessment of income and assets and is thus a reliable measure of household socioeconomic status. However, we acknowledge that our study also has some limitations. First, the NHIS cohort is based on secondary administrative data in which all medical information had been collected by healthcare professionals but not strictly controlled for research purposes. In this regard the operational definitions of hypertension and CVD may be prone to misdiagnoses and require further validations in future studies. Nonetheless, diagnosis of hypertension using claims has been well reviewed, and its agreement with medical records has been reported. Generally accepted identification criteria include case exclusion for the previous ≥6 months and availability of data for ≥12 months following index date with ≥2 prescriptions. We used similar standards...
but a longer window period—24 months before and 24 months following index date—to allow stricter case definition and assessment of comorbidity. However, individuals with high blood pressure but with no records of healthcare utilization would not have been identified. Because people with low income have lower rates of awareness and treatment for hypertension,2-4 excess risk for mortality with low income may have been underestimated in our study. Second, the household income quintile may not equate to an individual family member’s income or a sex-specific or within-study income quintile. However, it is unlikely that this measurement error would distort the income-mortality association observed in our study. Third, we arbitrarily chose the first 2 years of treatment for calculating medication adherence. Although considering a longer period of time could provide a more inclusive measure of medication adherence, it may also be more prone to reverse causality or overestimation of adherence.36 In a clinical setting, attainment of early treatment compliance is often challenging. An Italian population-based study reported almost 50% cumulative incidence of discontinuation of antihypertensive medication at 2 years after initiation.37 Association of early discontinuation with cardiovascular events was also reported.38 Therefore, early-treatment nonadherence would be a reasonable representation of high-risk behaviors associated with adverse outcome. Fourth, lifestyle and some risk factors were not universally available in our data. Thus, we performed additional analyses on a subgroup with health examination results and found similar results. However, information on sodium intake, education level, or a distinction between self- and unemployed individuals was not available. Therefore, some residual and unmeasured confounding may exist. Finally, our study was based on Korean adults under universal health insurance and should be interpreted with caution when applied to different populations or different healthcare systems.

In conclusion, both low household income and poor medication adherence are associated with higher risk for death and CVD hospitalization in individuals newly treated for hypertension, but those with low income are subject to greater increase of risk attributable to poor adherence. Therefore, monitoring adherence is crucial when treating hypertension in low-income patients, and policies should focus on promoting medication adherence in populations of low socioeconomic status.

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Author Contributions
Lee and Kim conceived and designed the study. Lee performed statistical analyses; Lee and Kim interpreted the findings. Lee drafted the manuscript. J. H. Park, Floyd, S. Park, and Kim made critical revision of the manuscript for key intellectual content. All authors approved the final manuscript. Kim is the guarantor of this work and, as such, had full access to the data and takes responsibility for their integrity and accuracy.

Disclosures
Dr Floyd has consulted for Shionogi Inc. The remaining authors have no disclosures to report.

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Supplemental Material
| Drug class                      | ATC code*                              |
|--------------------------------|----------------------------------------|
| Diuretics                      | C03A, C03B, C03C, C03D, C03E           |
| Beta-blockers                  | C07                                    |
| Calcium channel blockers       | C08                                    |
| ACE inhibitors                 | C09A, C09B                             |
| Angiotensin II receptor blockers| C09C, C09D                             |
| Others                         | C02A, C02C, C02D, C02L                 |

*Including subcodes.
ACE, angiotensin-converting-enzyme; ATC, Anatomical Therapeutic Chemical classification.
**Table S2. Hospital diagnosis codes.**

| Diagnosis                              | ICD-10 code*                      |
|----------------------------------------|-----------------------------------|
| Primary hypertension                   | I10 and antihypertensive medication |
| Any hypertensive disease (for exclusion)| I10-I13, I15 or antihypertensive medication |
| Myocardial infarction                  | I21-I23                           |
| Heart failure                          | I50                               |
| Stroke                                 | I60-I64                           |
| Cardiovascular death                   | I00-I99                           |

*Including subcodes.

ICD-10, International Classification of Disease, 10th edition.
| Variables                                      | Good (N=742,387) | Moderate (N=348,236) | Poor (N=560,941) |
|-----------------------------------------------|------------------|----------------------|------------------|
| Age, yr                                       | 55 [47-63]       | 53 [46-63]           | 52 [44-62]       |
| Sex                                           |                  |                      |                  |
| Female                                        | 353,384 (47.6%)  | 167,682 (48.2%)      | 263,433 (47.0%)  |
| Male                                          | 389,003 (52.4%)  | 180,554 (51.8%)      | 297,508 (53.0%)  |
| Household income, quintile                    |                  |                      |                  |
| 5, highest                                    | 225,169 (30.3%)  | 97,682 (28.1%)       | 147,758 (26.3%)  |
| 4                                             | 167,883 (22.6%)  | 78,119 (22.4%)       | 125,432 (22.4%)  |
| 3                                             | 128,731 (17.3%)  | 63,202 (18.1%)       | 105,541 (18.8%)  |
| 2                                             | 101,928 (13.7%)  | 51,511 (14.8%)       | 87,174 (15.5%)   |
| 1, lowest                                     | 118,676 (16.0%)  | 57,722 (16.6%)       | 95,036 (16.9%)   |
| Employment status                             |                  |                      |                  |
| Employed workers                              | 178,942 (24.1%)  | 77,744 (22.3%)       | 119,293 (21.3%)  |
| Self- or non-employed                         | 563,445 (75.9%)  | 270,492 (77.7%)      | 441,648 (78.7%)  |
| Initial antihypertensive agent*               |                  |                      |                  |
| Diuretics                                     | 201,016 (27.1%)  | 96,758 (27.8%)       | 161,013 (28.7%)  |
| Beta-blockers                                 | 152,823 (20.6%)  | 75,183 (21.6%)       | 136,563 (24.3%)  |
| Calcium channel blockers                      | 459,464 (61.9%)  | 205,924 (59.1%)      | 296,823 (52.9%)  |
| ACE inhibitors                                | 95,696 (12.9%)   | 46,386 (13.3%)       | 67,046 (12.0%)   |
| ARBs                                          | 173,857 (23.4%)  | 74,762 (21.5%)       | 100,376 (17.9%)  |
| Others                                        | 3,104 (0.4%)     | 2,093 (0.6%)         | 6,467 (1.2%)     |
| Number of drug classes                        |                  |                      |                  |
| 1                                             | 465,491 (62.7%)  | 224,131 (64.4%)      | 389,497 (69.4%)  |
| 2                                             | 217,481 (29.3%)  | 98,464 (28.3%)       | 139,433 (24.9%)  |
| ≥3                                            | 59,415 (8.0%)    | 25,641 (7.4%)        | 32,011 (5.7%)    |
| Use of glucose-lowering drugs                  | 130,753 (17.6%)  | 67,687 (19.4%)       | 88,513 (15.8%)   |
| Use of lipid-lowering drugs                    | 97,451 (13.1%)   | 43,893 (12.6%)       | 66,174 (11.8%)   |
| Charlson Comorbidity Index                    |                  |                      |                  |
| 0                                             | 394,445 (53.1%)  | 175,640 (50.4%)      | 265,687 (47.4%)  |
| 1                                             | 139,405 (18.8%)  | 67,814 (19.5%)       | 107,993 (19.3%)  |
| 2                                             | 119,432 (16.1%)  | 57,726 (16.6%)       | 100,925 (18.0%)  |
| ≥3                                            | 89,105 (12.0%)   | 47,056 (13.5%)       | 86,336 (15.4%)   |
| Medication possession ratio                    | 0.95 [0.89-1.00] | 0.67 [0.59-0.74]     | 0.16 [0.06-0.33] |

*Counted with duplicates for combination therapy.
Data are presented as median [interquartile range] or frequency (percent). ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker.
Table S4. Hospitalizations for ASCVD and heart failure according to household income and medication adherence.

| Variables | Persons | Events | Rate* | ASCVD (MI and/or stroke) | Heart failure | Events | Rate* |
|-----------|---------|--------|-------|-------------------------|--------------|--------|-------|
|           |         |        |       |                         | Model 1      |         |       |
|           |         |        |       |                         | HR (99% CI)  |         |       |
|           |         |        |       |                         | Model 2      |         |       |
|           |         |        |       |                         | HR (99% CI)  |         |       |
| Total     | 1,651,564 | 78,701 | 501.0 |                         |              | 8,736 | 54.8  |
| Income, quintile |        |        |       |                         |              |         |       |
| 5, highest | 470,609 | 20,760 | 461.7 | 1.00 (reference)       | 1.00 (reference) | 2,335 | 51.2 |
|           |         |        |       |                         |              |         |       |
| 4         | 371,434 | 17,152 | 484.1 | 1.11 (1.08-1.14)       | 1.09 (1.07-1.12) | 1,871 | 52.1 |
|           |         |        |       |                         |              |         |       |
| 3         | 297,474 | 14,184 | 501.3 | 1.21 (1.17-1.24)       | 1.17 (1.14-1.20) | 1,483 | 51.7 |
|           |         |        |       |                         |              |         |       |
| 2         | 240,613 | 12,158 | 533.3 | 1.30 (1.26-1.34)       | 1.25 (1.21-1.28) | 1,331 | 57.5 |
|           |         |        |       |                         |              |         |       |
| 1, lowest  | 271,434 | 14,447 | 564.5 | 1.36 (1.32-1.40)       | 1.30 (1.26-1.33) | 1,716 | 66.0 |
| Adherence |          |        |       |                         |              |         |       |
| Good      | 742,387 | 28,519 | 399.2 | 1.00 (reference)       | 1.00 (reference) | 3,171 | 43.9 |
|           |         |        |       |                         |              |         |       |
| Moderate  | 348,236 | 17,158 | 518.6 | 1.37 (1.33-1.40)       | 1.35 (1.32-1.39) | 1,944 | 57.9 |
|           |         |        |       |                         |              |         |       |
| Poor      | 560,941 | 33,024 | 628.4 | 1.71 (1.67-1.74)       | 1.75 (1.71-1.79) | 3,621 | 67.7 |
| Men       | 867,065 | 46,456 | 568.9 |                         |              | 3,767 | 45.4 |
| Income, quintile |        |        |       |                         |              |         |       |
| 5, highest | 257,900 | 12,030 | 490.6 | 1.00 (reference)       | 1.00 (reference) | 972  | 39.1 |
|           |         |        |       |                         |              |         |       |
| 4         | 200,773 | 10,281 | 541.5 | 1.14 (1.10-1.18)       | 1.11 (1.08-1.15) | 816  | 42.3 |
|           |         |        |       |                         |              |         |       |
| 3         | 159,625 | 8,710  | 579.5 | 1.25 (1.20-1.29)       | 1.20 (1.16-1.25) | 667  | 44.9 |
|           |         |        |       |                         |              |         |       |
| 2         | 122,993 | 7,398  | 644.4 | 1.37 (1.32-1.42)       | 1.30 (1.26-1.36) | 589  | 50.3 |
|           |         |        |       |                         |              |         |       |
| 1, lowest  | 125,774 | 8,037  | 689.9 | 1.43 (1.36-1.49)       | 1.35 (1.30-1.41) | 703  | 59.1 |
| Adherence |          |        |       |                         |              |         |       |
| Good      | 389,003 | 16,776 | 451.3 | 1.00 (reference)       | 1.00 (reference) | 1,327 | 35.2 |
|           |         |        |       |                         |              |         |       |
| Moderate  | 180,554 | 9,863  | 580.2 | 1.36 (1.32-1.41)       | 1.34 (1.30-1.39) | 800  | 46.3 |
|           |         |        |       |                         |              |         |       |
| Poor      | 297,508 | 19,817 | 720.7 | 1.73 (1.68-1.77)       | 1.77 (1.72-1.81) | 1,640 | 58.4 |
| Women     | 784,499 | 32,245 | 427.6 |                         |              | 4,969 | 65.1 |
| Income, quintile |        |        |       |                         |              |         |       |
| 5, highest | 212,709 | 8,730  | 427.0 | 1.00 (reference)       | 1.00 (reference) | 1,363 | 65.9 |
|           |         |        |       |                         |              |         |       |
| 4         | 170,661 | 6,871  | 417.9 | 1.09 (1.05-1.14)       | 1.08 (1.03-1.12) | 1,055 | 63.4 |
|           |         |        |       |                         |              |         |       |
| 3         | 137,849 | 5,474  | 412.7 | 1.17 (1.12-1.22)       | 1.14 (1.09-1.19) | 796  | 59.3 |
|           |         |        |       |                         |              |         |       |
| 2         | 117,620 | 4,760  | 420.6 | 1.23 (1.17-1.29)       | 1.18 (1.13-1.24) | 742  | 64.8 |
|           |         |        |       |                         |              |         |       |
| 1, lowest  | 145,660 | 6,410  | 459.7 | 1.31 (1.25-1.37)       | 1.26 (1.20-1.31) | 1,013 | 71.7 |
| Adherence |          |        |       |                         |              |         |       |
| Good      | 353,384 | 11,743 | 342.7 | 1.00 (reference)       | 1.00 (reference) | 1,844 | 53.3 |
|           |         |        |       |                         |              |         |       |
| Moderate  | 167,682 | 7,295  | 453.4 | 1.36 (1.31-1.41)       | 1.35 (1.30-1.40) | 1,144 | 70.2 |
|           |         |        |       |                         |              |         |       |
| Poor      | 263,433 | 13,207 | 527.2 | 1.66 (1.60-1.71)       | 1.70 (1.65-1.76) | 1,981 | 77.9 |

Model 1 was adjusted for age, sex, and employment status.
Model 2 was further adjusted for household income, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, antihypertensive drug class, and medication adherence.

*Rate per 100,000 person-years. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.
## Table S5. Hospitalizations for myocardial infarction and stroke according to household income and medication adherence.

| Variables       | Persons | Events | Rate* | Myocardial infarction | HR (99% CI) | Stroke | Events | Rate* | HR (99% CI) |
|-----------------|---------|--------|-------|-----------------------|-------------|--------|--------|-------|-------------|
|                 |         |        |       |                       | Model 1     | Model 2 |        |       |             |
| **Total**       | 1,651,564 | 15,811 | 99.4  |                       | 64,098      | 406.8  |        |       |             |
| Income, quintile|         |        |       |                       |             |        |        |       |             |
| 5, highest      | 470,609 | 4,260  | 93.7  | 1.00 (reference)      | 16,810      | 372.8  | 1.00   | 1.00  |             |
| 4               | 371,434 | 3,494  | 97.4  | 1.09 (1.03-1.16)      | 13,911      | 395.1  | 1.12   | 1.09-1.15 | 1.10 (1.06-1.13) |
| 3               | 297,474 | 2,935  | 102.4 | 1.19 (1.11-1.26)      | 11,479      | 404.5  | 1.22   | 1.18-1.25 | 1.17 (1.14-1.21) |
| 2               | 240,613 | 2,394  | 103.6 | 1.22 (1.14-1.30)      | 9,942       | 434.8  | 1.32   | 1.28-1.37 | 1.26 (1.22-1.30) |
| 1, lowest       | 271,434 | 2,728  | 105.1 | 1.24 (1.16-1.32)      | 11,956      | 465.7  | 1.40   | 1.35-1.44 | 1.32 (1.28-1.37) |
| Adherence       |         |        |       |                       |             |        |        |       |             |
| Good            | 742,387 | 6,363  | 88.2  | 1.00 (reference)      | 22,583      | 315.2  | 1.00   | 1.00  |             |
| Moderate        | 348,236 | 3,528  | 105.3 | 1.25 (1.19-1.32)      | 13,880      | 418.2  | 1.39   | (1.35-1.43 | 1.38 (1.34-1.42) |
| Poor            | 560,941 | 5,920  | 110.8 | 1.35 (1.29-1.41)      | 27,635      | 524.2  | 1.80   | 1.76-1.84 | 1.84 (1.80-1.89) |
| **Men**         | 867,065 | 11,171 | 134.9 |                       | 36,092      | 440.1  |        |       |             |
| Income, quintile|         |        |       |                       |             |        |        |       |             |
| 5, highest      | 257,900 | 3,055  | 123.2 | 1.00 (reference)      | 9,191       | 373.4  | 1.00   | 1.00  |             |
| 4               | 200,773 | 2,478  | 128.8 | 1.07 (0.99-1.14)      | 7,967       | 417.9  | 1.15   | 1.11-1.20 | 1.13 (1.08-1.17) |
| 3               | 159,625 | 2,124  | 139.4 | 1.17 (1.08-1.25)      | 6,749       | 447.1  | 1.27   | 1.22-1.33 | 1.22 (1.17-1.27) |
| 2               | 122,993 | 1,675  | 143.6 | 1.19 (1.10-1.29)      | 5,835       | 508.0  | 1.43   | 1.37-1.49 | 1.35 (1.29-1.41) |
| 1, lowest       | 125,774 | 1,839  | 155.3 | 1.26 (1.17-1.36)      | 6,350       | 542.4  | 1.50   | 1.43-1.56 | 1.40 (1.34-1.46) |
| Adherence       |         |        |       |                       |             |        |        |       |             |
| Good            | 389,003 | 4,545  | 121.0 | 1.00 (reference)      | 12,500      | 335.0  | 1.00   | 1.00  |             |
| Moderate        | 180,554 | 2,446  | 141.9 | 1.22 (1.14-1.30)      | 7,596       | 444.9  | 1.41   | 1.36-1.47 | 1.39 (1.34-1.45) |
| Poor            | 297,508 | 4,180  | 149.3 | 1.31 (1.24-1.38)      | 15,996      | 579.1  | 1.87   | 1.82-1.93 | 1.91 (1.85-1.97) |
| **Women**       | 784,499 | 4,640  | 60.8  |                       | 28,006      | 370.8  |        |       |             |
| Income, quintile|         |        |       |                       |             |        |        |       |             |
| 5, highest      | 212,709 | 1,205  | 58.3  | 1.00 (reference)      | 7,619       | 372.0  | 1.00   | 1.00  |             |
| 4               | 170,661 | 1,016  | 61.1  | 1.19 (1.07-1.33)      | 5,944       | 360.9  | 1.08   | 1.03-1.13 | 1.16 (1.02-1.11) |
| 3               | 137,849 | 811    | 60.5  | 1.28 (1.14-1.45)      | 4,730       | 356.0  | 1.15   | 1.10-1.21 | 1.12 (1.07-1.18) |
| 2               | 117,620 | 719    | 62.8  | 1.38 (1.22-1.56)      | 4,167       | 362.3  | 1.21   | 1.15-1.27 | 1.16 (1.11-1.22) |
| 1, lowest       | 145,660 | 889    | 63.0  | 1.33 (1.19-1.49)      | 5,066       | 401.3  | 1.31   | 1.25-1.37 | 1.25 (1.20-1.31) |
| Adherence       |         |        |       |                       |             |        |        |       |             |
| Good            | 353,384 | 1,818  | 52.6  | 1.00 (reference)      | 10,083      | 293.8  | 1.00   | 1.00  |             |
| Moderate        | 167,682 | 1,082  | 66.4  | 1.29 (1.17-1.43)      | 6,284       | 389.9  | 1.36   | 1.30-1.42 | 1.35 (1.29-1.41) |
| Poor            | 263,433 | 1,740  | 68.4  | 1.40 (1.28-1.52)      | 11,639      | 463.7  | 1.70   | 1.64-1.76 | 1.74 (1.68-1.80) |

Model 1 was adjusted for age, sex, and employment status.
Model 2 was further adjusted for household income, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, antihypertensive drug class, and medication adherence.

*Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.
Table S6. All-cause and cardiovascular death according to household income and medication adherence in health examinees.

| Variables                        | Persons  | Events | Rate* (HR (99% CI)) | Cardiovascular death | Rate* (HR (99% CI)) |
|----------------------------------|----------|--------|---------------------|----------------------|---------------------|
|                                  |          |        | Model 1 Model 2     | Model 1 Model 2      |
| **Total**                        | 643,026  | 42,918 | 685.3 1.00 (reference) 1.00 (reference) | 7,825 124.9 |
| **Income, quintile**             |          |        |                     |                      |
| 5, highest                       | 197,745  | 11,301 | 584.7 1.00 (reference) 1.00 (reference) | 2,023 104.6 1.00 (reference) 1.00 (reference) |
| 4                                | 146,368  | 9,108  | 637.6 1.18 (1.14-1.22) 1.14 (1.10-1.18) | 1,661 116.3 1.22 (1.12-1.33) 1.17 (1.07-1.27) |
| 3                                | 109,060  | 7,401  | 697.3 1.30 (1.25-1.35) 1.23 (1.18-1.27) | 1,343 126.5 1.33 (1.22-1.46) 1.25 (1.14-1.37) |
| 2                                | 85,692   | 6,698  | 806.5 1.43 (1.38-1.49) 1.33 (1.27-1.38) | 1,227 147.7 1.46 (1.33-1.60) 1.34 (1.22-1.48) |
| 1, lowest                        | 104,161  | 8,410  | 833.6 1.47 (1.41-1.52) 1.36 (1.31-1.41) | 1,571 155.7 1.50 (1.37-1.64) 1.37 (1.26-1.50) |
| **Adherence**                    |          |        |                     |                      |
| Good                             | 308,232  | 16,835 | 557.4 1.00 (reference) 1.00 (reference) | 2,877 95.2 1.00 (reference) 1.00 (reference) |
| Moderate                         | 132,247  | 9,010  | 700.1 1.29 (1.24-1.33) 1.25 (1.21-1.29) | 1,703 132.3 1.44 (1.33-1.56) 1.40 (1.30-1.52) |
| Poor                             | 202,547  | 17,073 | 873.1 1.57 (1.53-1.62) 1.50 (1.45-1.54) | 3,245 165.9 1.81 (1.70-1.94) 1.75 (1.64-1.88) |
| **Income and Adherence**         |          |        |                     |                      |
| Good, highest                    | 99,188   | 4,747  | 487.2 1.00 (reference) 1.00 (reference) | 820 84.2 1.00 (reference) 1.00 (reference) |
| Moderate, highest                | 40,270   | 2,392  | 608.5 1.31 (1.23-1.40) 1.27 (1.19-1.36) | 427 108.6 1.38 (1.18-1.61) 1.34 (1.15-1.56) |
| Poor, highest                    | 58,287   | 4,162  | 735.3 1.51 (1.43-1.60) 1.45 (1.37-1.53) | 776 137.1 1.69 (1.48-1.92) 1.64 (1.44-1.87) |
| Good, 4                          | 69,541   | 3,643  | 534.1 1.18 (1.11-1.25) 1.14 (1.08-1.21) | 622 91.2 1.18 (1.03-1.16) 1.14 (0.99-1.31) |
| Moderate, 4                      | 29,922   | 1,863  | 638.3 1.48 (1.38-1.59) 1.40 (1.30-1.50) | 364 124.7 1.73 (1.47-2.03) 1.63 (1.38-1.91) |
| Poor, 4                          | 46,905   | 3,602  | 792.4 1.82 (1.72-1.93) 1.67 (1.58-1.77) | 675 148.5 2.09 (1.82-2.39) 1.94 (1.69-2.22) |
| Good, 3                          | 49,969   | 2,692  | 549.7 1.22 (1.15-1.30) 1.16 (1.09-1.23) | 459 93.7 1.22 (1.05-1.42) 1.15 (0.99-1.34) |
| Moderate, 3                      | 22,631   | 1,571  | 714.0 1.66 (1.54-1.78) 1.52 (1.41-1.64) | 301 136.8 1.90 (1.59-2.26) 1.73 (1.45-2.06) |
| Poor, 3                          | 36,460   | 3,138  | 892.4 2.10 (1.98-2.23) 1.90 (1.78-2.01) | 583 165.8 2.39 (2.08-2.76) 2.17 (1.89-2.50) |
| Good, 2                          | 39,344   | 2,445  | 636.1 1.41 (1.33-1.51) 1.31 (1.23-1.40) | 401 104.3 1.35 (1.15-1.58) 1.24 (1.06-1.45) |
| Moderate, 2                      | 17,886   | 1,474  | 851.4 1.87 (1.73-2.02) 1.70 (1.57-1.83) | 281 162.3 2.08 (1.74-2.49) 1.88 (1.57-2.25) |
| Poor, 2                          | 28,462   | 2,779  | 1017.9 2.20 (2.07-2.34) 1.94 (1.82-2.06) | 545 199.6 2.60 (2.25-3.00) 2.31 (2.00-2.67) |
| Good, 1, lowest                  | 21,538   | 1,710  | 819.1 1.78 (1.65-1.91) 1.60 (1.49-1.72) | 330 158.1 1.96 (1.65-2.32) 1.75 (1.48-2.08) |
| Moderate, 1, lowest              | 32,433   | 3,392  | 1093.6 2.31 (2.18-2.45) 2.04 (1.92-2.16) | 666 214.7 2.68 (2.34-3.07) 2.38 (2.07-2.72) |

Model 1 was adjusted for age, sex, employment status, household income, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, antihypertensive drug class, and medication adherence.
Model 2 was further adjusted for cigarette smoking, alcohol consumption, physical exercise, body mass index, systolic blood pressure, fasting glucose, and total cholesterol.

*Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.
Table S7. Hospitalizations for ASCVD and heart failure according to household income and medication adherence in health examinees.

| Variables               | Persons | ASCVD (MI and/or stroke) | Heart failure |
|-------------------------|---------|--------------------------|---------------|
|                         |         | Events                  | Rate*         | Events                  | Rate*         |
|                         |         | Model 1                 | HR (99% CI)   | Model 2                 | HR (99% CI)   |
| **Total**               | 643,026 | 26,934                  | 436.1         | 2,696                   | 43.1          |
| Income, quintile        |         |                         |               |                         |               |
| 5, highest              | 197,745 | 7,604                   | 398.4         | 1.00 (reference)        | 1.00 (reference) |
| 4                       | 146,368 | 5,922                   | 420.2         | 1.10 (1.05-1.15)        | 1.06 (1.02-1.11) |
| 3                       | 109,060 | 4,651                   | 444.5         | 1.15 (1.10-1.21)        | 1.10 (1.05-1.15) |
| 2                       | 85,692  | 3,916                   | 478.7         | 1.21 (1.15-1.27)        | 1.14 (1.08-1.20) |
| 1, lowest               | 104,161 | 4,841                   | 487.4         | 1.22 (1.16-1.28)        | 1.15 (1.09-1.20) |
| Adherence               |         |                         |               |                         |               |
| Good                    | 308,232 | 10,675                  | 357.5         | 1.00 (reference)        | 1.00 (reference) |
| Moderate                | 132,247 | 5,792                   | 456.8         | 1.33 (1.27-1.38)        | 1.31 (1.25-1.37) |
| Poor                    | 202,547 | 10,467                  | 544.7         | 1.64 (1.58-1.70)        | 1.63 (1.57-1.69) |
| Income and Adherence    |         |                         |               |                         |               |
| 5, highest              | Good    | 99,188                  | 3,214         | 333.4                   | 1.00 (reference) |
|                         | Moderate| 40,270                  | 1,621         | 418.0                   | 1.32 (1.22-1.43) |
|                         | Poor    | 58,287                  | 2,769         | 497.2                   | 1.59 (1.49-1.70) |
| 4                       | Good    | 69,541                  | 2,362         | 350.2                   | 1.09 (1.02-1.17) |
|                         | Moderate| 29,922                  | 1,240         | 430.9                   | 1.42 (1.30-1.55) |
|                         | Poor    | 46,905                  | 2,320         | 518.9                   | 1.79 (1.66-1.92) |
| 3                       | Good    | 49,969                  | 1,720         | 355.2                   | 1.10 (1.02-1.19) |
|                         | Moderate| 22,631                  | 1,006         | 464.2                   | 1.52 (1.38-1.67) |
|                         | Poor    | 36,460                  | 1,925         | 557.2                   | 1.93 (1.79-2.08) |
| 2                       | Good    | 39,344                  | 1,465         | 385.8                   | 1.20 (1.11-1.30) |
|                         | Moderate| 17,886                  | 872           | 512.0                   | 1.61 (1.46-1.77) |
|                         | Poor    | 28,462                  | 1,579         | 589.1                   | 1.93 (1.79-2.09) |
| 1, lowest               | Good    | 50,190                  | 1,914         | 395.7                   | 1.21 (1.12-1.31) |
|                         | Moderate| 21,538                  | 1,053         | 512.6                   | 1.59 (1.45-1.75) |
|                         | Poor    | 32,433                  | 1,874         | 616.4                   | 1.98 (1.83-2.13) |

Model 1 was adjusted for age, sex, employment status, household income, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, antihypertensive drug class, and medication adherence.
Model 2 was further adjusted for cigarette smoking, alcohol consumption, physical exercise, body mass index, systolic blood pressure, fasting glucose, and total cholesterol.

*Rate per 100,000 person-years. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.
Figure S1. Flowchart of inclusion and exclusion criteria.

Age 30 to 80 claimed for I10 and antihypertensive medication 2004.1.1 - 2007.12.31 N=6,467,000

- Claimed for I10-13, I15 or antihypertensive medication in 2002 or 2003 N=3,628,834
- Claimed for MI, HF, or stroke before index date N=285,035
- Less than 2 prescriptions during the first year N=575,699

Newly treated hypertension 2004.1.1 - 2007.12.31 N=1,977,432

- Died or had CVD event within 2 years after index date N=88,830
- Household income unavailable or enrolled in Medical Aid N=237,038

Final study population N=1,651,564
Figure S2. Combined effect of household income and medication adherence on hospitalizations for ASCVD and heart failure in men and women.

| Men | Adherence | Persons | ASCVD (M or and/or stroke) | Heart failure |
|-----|-----------|---------|---------------------------|---------------|
|     |           | Events  | Rate*                     | HR (99% CI)   |
|     |           | Rate*   | HR (99% CI)               | Rate*         | HR (99% CI)   |
|     | Low risk  | High risk |                           |                | Low risk  | High risk |
| 5, highest | Good | 126,148 | 4,797 | 395.7 | 1.00 (reference) | 383 | 31.2 | 1.00 (reference) |
|     | Moderate | 53,094 | 2,592 | 514.2 | 1.36 (1.29-1.45) | 211 | 41.2 | 1.40 (1.12-1.74) |
|     | Poor     | 78,658 | 4,641 | 631.0 | 1.71 (1.62-1.81) | 378 | 50.4 | 1.69 (1.40-2.04) |

| Women | Adherence | Persons | ASCVD (M or and/or stroke) | Heart failure |
|-------|-----------|---------|---------------------------|---------------|
|       |           | Events  | Rate*                     | HR (99% CI)   |
|       |           | Rate*   | HR (99% CI)               | Rate*         | HR (99% CI)   |
|       | Low risk  | High risk |                           |                | Low risk  | High risk |
| 5, highest | Good | 99,021 | 3,422 | 356.8 | 1.00 (reference) | 570 | 58.9 | 1.00 (reference) |
|       | Moderate | 44,588 | 1,972 | 461.1 | 1.33 (1.24-1.43) | 286 | 66.0 | 1.13 (0.94-1.37) |
|       | Poor     | 69,100 | 3,336 | 507.0 | 1.59 (1.49-1.69) | 507 | 76.0 | 1.39 (1.18-1.62) |

P for interaction between income and adherence in men and women were 0.305 and 0.002 for ASCVD and 0.100 and 0.520 for heart failure. *Rate per 100,000 person-years. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HR, hazard ratio.
Figure S3. Combined effect of household income and medication adherence on hospitalizations for myocardial infarction and stroke in men and women.

| Men | Income | Adherence | Persons | Events  | Rate* | HR (99% CI) | Low risk | High risk | Myocardial infarction | Events  | Rate* | HR (99% CI) | Low risk | High risk | Stroke  |
|-----|--------|-----------|---------|---------|-------|------------|---------|----------|----------------------|---------|-------|------------|---------|----------|---------|
| 4, highest | Good | 126,148 | 1,357 | 110.9 | 1.00 (reference) | 3,513 | 288.7 | 1.00 (reference) | 80,474 | 980 | 112.0 | 1.02 (0.91-1.13) | 2,946 | 327.3 | 1.13 (1.06-1.21) |
| Moderate | 78,658 | 1,027 | 137.5 | 1.32 (1.18-1.47) | 3,708 | 502.0 | 1.87 (1.76-1.98) | 78,658 | 1,027 | 137.5 | 1.32 (1.18-1.47) | 3,708 | 502.0 | 1.87 (1.76-1.98) |
| Poor | 68,566 | 997 | 153.7 | 1.54 (1.38-1.72) | 3,443 | 537.2 | 2.12 (1.99-2.25) | 68,566 | 997 | 153.7 | 1.54 (1.38-1.72) | 3,443 | 537.2 | 2.12 (1.99-2.25) |
| 3, highest | Good | 67,773 | 825 | 126.1 | 1.15 (1.03-1.29) | 2,201 | 338.5 | 1.11 (1.21) | 33,791 | 501 | 125.4 | 1.18 (1.03-1.35) | 1,970 | 383.2 | 1.42 (1.32-1.53) |
| Moderate | 33,791 | 501 | 125.4 | 1.18 (1.03-1.35) | 1,970 | 383.2 | 1.42 (1.32-1.53) | 33,791 | 501 | 125.4 | 1.18 (1.03-1.35) | 1,970 | 383.2 | 1.42 (1.32-1.53) |
| Poor | 26,825 | 407 | 154.6 | 1.43 (1.23-1.66) | 1,426 | 466.4 | 1.69 (1.58-1.83) | 26,825 | 407 | 154.6 | 1.43 (1.23-1.66) | 1,426 | 466.4 | 1.69 (1.58-1.83) |
| 2, highest | Good | 6,183 | 872 | 126.1 | 1.15 (1.03-1.29) | 2,201 | 338.5 | 1.11 (1.21) | 19,086 | 520 | 112.0 | 1.02 (0.91-1.13) | 3,708 | 502.0 | 1.87 (1.76-1.98) |
| Moderate | 19,086 | 520 | 112.0 | 1.02 (0.91-1.13) | 3,708 | 502.0 | 1.87 (1.76-1.98) | 19,086 | 520 | 112.0 | 1.02 (0.91-1.13) | 3,708 | 502.0 | 1.87 (1.76-1.98) |
| Poor | 13,111 | 221 | 153.7 | 1.54 (1.38-1.72) | 3,443 | 537.2 | 2.12 (1.99-2.25) | 13,111 | 221 | 153.7 | 1.54 (1.38-1.72) | 3,443 | 537.2 | 2.12 (1.99-2.25) |
| 1, highest | Good | 53,775 | 739 | 143.7 | 1.26 (1.12-1.42) | 2,090 | 409.7 | 1.39 (1.29-1.49) | 26,111 | 407 | 165.4 | 1.48 (1.28-1.72) | 1,314 | 283.6 | 1.13 (1.06-1.21) |
| Moderate | 26,111 | 407 | 165.4 | 1.48 (1.28-1.72) | 1,314 | 283.6 | 1.13 (1.06-1.21) | 26,111 | 407 | 165.4 | 1.48 (1.28-1.72) | 1,314 | 283.6 | 1.13 (1.06-1.21) |
| Poor | 20,500 | 374 | 163.4 | 1.51 (1.34-1.71) | 2,445 | 449.8 | 1.62 (1.52-1.73) | 20,500 | 374 | 163.4 | 1.51 (1.34-1.71) | 2,445 | 449.8 | 1.62 (1.52-1.73) |

P for interaction between income and adherence in men and women were 0.093 and 0.459 for myocardial infarction and 0.116 and 0.001 for stroke. *Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.
P for interaction between income and adherence in men and women were 0.045 and 0.207 for all-cause death and 0.086 and 0.972 for cardiovascular death. *Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.
Figure S5. Combined effect of household income and medication adherence on all-cause and cardiovascular death in men and women who initiated combination therapy.

### Men

| Income | Adherence | Persons | Events | Rate* | HR (99% CI) |
|--------|-----------|---------|--------|-------|-------------|
| 5, highest | Good | 46,574 | 3,299 | 729.1 | 1.00 (1.00-1.00) |
| Moderate | 18,031 | 1,639 | 944.4 | 1.31 (1.21-1.42) |
| Poor | 23,222 | 2,743 | 1244.8 | 1.60 (1.50-1.71) |
| 4 | Good | 34,462 | 2,764 | 827.8 | 1.16 (1.06-1.24) |
| Moderate | 14,938 | 1,457 | 1071.3 | 1.49 (1.37-1.61) |
| Poor | 21,563 | 2,833 | 1391.1 | 1.99 (1.86-2.13) |
| 3 | Good | 26,802 | 2,169 | 836.6 | 1.23 (1.14-1.32) |
| Moderate | 12,414 | 1,277 | 1075.0 | 1.65 (1.52-1.80) |
| Poor | 18,754 | 2,428 | 1373.0 | 2.13 (1.99-2.29) |
| 2 | Good | 20,120 | 1,903 | 981.8 | 1.44 (1.35-1.55) |
| Moderate | 9,803 | 1,174 | 1251.1 | 1.90 (1.74-2.07) |
| Poor | 15,527 | 2,364 | 1630.4 | 2.51 (2.35-2.70) |
| 1, lowest | Good | 20,852 | 2,191 | 1094.9 | 1.55 (1.44-1.66) |
| Moderate | 9,848 | 1,353 | 1457.8 | 2.09 (1.92-2.27) |
| Poor | 15,504 | 2,655 | 1852.3 | 2.75 (2.57-2.95) |

### All-cause death

- **Low risk**
- **High risk**

### Cardiovascular death

- **Low risk**
- **High risk**

**P** for interaction between income and adherence in men and women were 0.009 and 0.463 for all-cause death and 0.012 and 0.694 for cardiovascular death. *Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.
### Men

| Income     | Adherence | Persons | Events | Rate* | HR (99% CI) | Low risk | High risk |
|------------|-----------|---------|--------|-------|-------------|----------|-----------|
| 5, highest | Good      | 126,153 | 8,530  | 694.8 | 1.00 (reference) | | |
|            | Moderate  | 53,621  | 4,467  | 863.1 | 1.29 (1.23-1.35) | | |
|            | Poor      | 150,452 | 14,951 | 1037.9 | 1.54 (1.54-1.59) | | |
| 4          | Good      | 90,481  | 6,830  | 777.6 | 1.14 (1.09-1.19) | | |
|            | Moderate  | 34,069  | 3,341  | 1022.9 | 1.68 (1.59-1.77) | | |
|            | Poor      | 42,086  | 3,906  | 965.4 | 1.50 (1.43-1.57) | | |
| 3          | Good      | 67,777  | 5,261  | 800.9 | 1.23 (1.18-1.29) | | |
|            | Moderate  | 34,069  | 3,341  | 1022.9 | 1.68 (1.59-1.77) | | |
|            | Poor      | 110,889 | 12,750 | 1200.4 | 2.15 (2.07-2.23) | | |
| 2          | Good      | 59,840  | 4,014  | 940.0 | 1.45 (1.38-1.52) | | |
|            | Moderate  | 26,045  | 2,959  | 1191.8 | 1.92 (1.81-2.03) | | |
|            | Poor      | 88,194  | 11,650 | 1402.2 | 2.47 (2.38-2.58) | | |
| 1, lowest  | Good      | 53,779  | 5,503  | 1065.2 | 1.59 (1.52-1.66) | | |
|            | Moderate  | 26,335  | 3,307  | 1234.9 | 2.03 (1.92-2.14) | | |
|            | Poor      | 86,108  | 12,900 | 1604.6 | 2.88 (2.59-2.78) | | |

### Women

| Income     | Adherence | Persons | Events | Rate* | HR (99% CI) | Low risk | High risk |
|------------|-----------|---------|--------|-------|-------------|----------|-----------|
| 5, highest | Good      | 99,023  | 5,997  | 577.3 | 1.00 (reference) | | |
|            | Moderate  | 45,001  | 3,198  | 730.6 | 1.28 (1.21-1.36) | | |
|            | Poor      | 134,438 | 9,750  | 747.1 | 1.47 (1.41-1.54) | | |
| 4          | Good      | 77,411  | 3,900  | 513.1 | 1.07 (1.02-1.13) | | |
|            | Moderate  | 36,671  | 2,402  | 672.3 | 1.41 (1.33-1.50) | | |
|            | Poor      | 110,213 | 7,376  | 688.3 | 1.61 (1.58-1.65) | | |
| 3          | Good      | 50,964  | 3,040  | 528.6 | 1.15 (1.11-1.21) | | |
|            | Moderate  | 29,635  | 1,763  | 610.4 | 1.43 (1.34-1.54) | | |
|            | Poor      | 89,586  | 5,674  | 875.0 | 1.78 (1.69-1.87) | | |
| 2          | Good      | 51,096  | 2,552  | 509.2 | 1.23 (1.16-1.31) | | |
|            | Moderate  | 25,842  | 1,707  | 678.6 | 1.59 (1.48-1.71) | | |
|            | Poor      | 76,878  | 5,253  | 704.1 | 1.87 (1.78-1.96) | | |
| 1, lowest  | Good      | 31,827  | 2,316  | 749.9 | 1.63 (1.53-1.74) | | |
|            | Moderate  | 91,883  | 7,410  | 836.3 | 1.95 (1.89-2.08) | | |
|            | Poor      | 34,902  | 3,027  | 570.8 | 1.31 (1.24-1.38) | | |

### P for interaction between income and adherence in men and women were <0.001 and 0.194 for all-cause death and 0.030 and 0.110 for cardiovascular death. *Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.
**Figure S7.** Blood pressure change from baseline on follow-up according to medication adherence. Error bars represent 99% confidence intervals.

| Medication adherence | SBP change, mmHg | DBP change, mmHg |
|----------------------|------------------|------------------|
| Good                 | 0                | 0                |
| Moderate             | -3               | -2               |
| Poor                 | -6               | -4               |

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