Optimal Systolic Blood Pressure Target, Time-to-Intensification and Time-to-Follow-up in the Treatment of Hypertension

OPTIMAL SYSTOLIC BLOOD PRESSURE TARGET, TIME-TO-INTENSIFICATION AND TIME-TO-FOLLOW-UP IN THE TREATMENT OF HYPERTENSION

by

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I have reviewed this thesis. It represents work done by the author under my supervision and guidance.

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ABSTRACT

Background

Hypertension is the most common risk factor for cardiovascular disease worldwide. However, the optimal systolic intensification threshold, time to medication intensification after the first elevated blood pressure measurement, and time to blood pressure follow-up after medication intensification in the management of hypertension are not well established.

Objective

I sought to determine the systolic intensification threshold, time-to-intensification and time-to-follow-up associated with the lowest risk of cardiovascular events or death in a population of primary care patients with hypertension.

Methods

A retrospective cohort study of 88,756 patients with hypertension from The Health Improvement Network database was performed. The systolic intensification threshold, time-to-intensification and time-to-follow-up were established over a 10-year assessment period, and analyzed with respect to subsequent risk of acute cardiovascular event or death. The Cox survival model was adjusted for age, sex, smoking status, socioeconomic deprivation, history of diabetes, cardiovascular disease or chronic kidney disease, Charlson Comorbidity Index, body mass index, medication possession ratio, and baseline blood pressure elevation.

Results

During a median follow-up of 37.4 months after the treatment strategy assessment period, 9,985 participants experienced acute cardiovascular event or death (11.3%). Systolic intensification thresholds of 130-150 mmHg were associated with no difference in risk, while thresholds greater than 150 mmHg were associated with progressively greater risk. Outcome risk increased progressively from the lowest (0-1.4 months) to the highest quintile of time to medication

intensification. The highest quintile of time to-follow-up (>2.7 months) was also associated with increased outcome risk.

Conclusions

Systolic intensification threshold higher than 150 mmHg, delays of greater than 1.4 months before medication intensification following systolic blood pressure elevation, and delays of greater than 2.7 months before blood pressure follow-up following antihypertensive medication intensification were associated with increased risk for acute cardiovascular events or death.

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GLOSSARY OF ABBREVIATIONS

BMI	Body mass index
CCI	Charlson comorbidity index
CAD	Coronary artery disease
CHF	Congestive heart failure
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CVA	Cerebrovascular accident
DM	Diabetes mellitus
ESH/ESC	European Society of Hypertension / European Society of Cardiology
JNC	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
NICE	National Institute for Health and Care Excellence
PVD	Peripheral vascular disease
SBP	Systolic blood pressure
THIN	The Health Improvement Network
UK	United Kingdom

INTRODUCTION

Elevated blood pressure is the single most common risk factor for cardiovascular morbidity and mortality worldwide, and the lowering of blood pressure through medical treatment mitigates this risk. Hypertension is the most commonly diagnosed outpatient condition among non-pregnant adults in the United States and United Kingdom. Hypertension management is among the most common reasons for outpatient physician visits, and the medical treatment of hypertension is the most common reason for chronic medication prescriptions[2-5]. However, many key aspects of optimal medical management for hypertension remain unclear.

Definition of Hypertension

Higher blood pressure is correlated with increased risk of risk stroke, myocardial infarction, heart failure, renal disease, and mortality in a continuous manner well into the normotensive range, though very low blood pressures may also confer increased risk.[6-9] The definition of hypertension is therefore somewhat arbitrary, but is necessary to guide patient assessment and management. In actual practice, patients with systolic blood pressure above 140 mmHg are routinely diagnosed with hypertension based on several sets of recent guidelines, and the existence of this diagnosis encourages providers to treat patients until systolic blood pressure falls below 140 mmHg. Nonetheless, the original systolic threshold for hypertension was defined using observational data (rather than treatment data) associating higher blood pressure with cardiovascular risk, and the evidence that medically treating patients with stage 1 systolic hypertension improves outcomes is limited.[14]

Systolic Blood Pressure Treatment Threshold: Current Guidelines and State of the Literature

Major society guidelines differ substantially in their recommendations for the management of patients with stage 1 systolic hypertension. While the JNC 8 and ESH/ESC guidelines suggest a goal SBP of <140 mmHg for younger patients and <150 mmHg for older patients, they differ with regard to the age at which treatment may be liberalized. On the other hand, the NICE guidelines recommend treating patients with SBP <160 mmHg only when other cardiovascular risk factors or end-organ damage are present,[4] and a Cochrane review found no clear evidence of benefit in pharmacotherapy for mild hypertension without considering pre-existing diabetes or end organ damage.[17] These disagreements are also reflected in guidelines issued by other international societies, and reflect difficulties in weighing the available evidence in the absence of definitive data.[10]

There is no clinical trial that has adequately examined the question of whether medical treatment of grade 1 systolic hypertension (140-159 mmHg) leads to improved outcomes; the question of whether treating patients with systolic blood pressure between 140-149 mmHg confers clinical benefit is particularly controversial. Several large randomized trials including FEVER, MRC, and HDFP have shown cardiovascular benefit when reducing blood pressure below 140 mmHg, but all included patients with initial blood pressure above 150 mmHg. Other issues that limit the generalizability of available randomized clinical trials include the paucity of direct comparisons between blood pressure targets, incongruity of patient populations (differences in age, previous cardiovascular history, and other comorbidities), and the difficulty of achieving sufficient power to detect differences at various thresholds.

Time-to-intensification and Follow-up after Intensification

Among all patients there is little available evidence to guide the optimal time interval between measurement of elevated blood pressure and antihypertensive medication

intensification, or between medication intensification and follow-up measurement of blood pressure. This is particularly important because routine clinical practice differs from clinical trials in that substantial delays may exist between the observation of an elevated blood pressure and medication intensification or between medication intensification and follow-up measurement of blood pressure, but the impact of such delays on patient outcomes is not well understood.

The current ESH/ESC and previous JNC 7 management guidelines suggest follow-up after antihypertensive treatment intensification within 2-4 weeks or 1 month, respectively, but these recommendations are primarily based on expert opinion rather than clinical data. The recent JNC 8 guidelines do not suggest a particular interval for blood pressure assessment, but recommend—based on expert opinion—intensifying treatment within a month if goal blood pressure is not attained on the current treatment.[11]

Although direct clinical evidence in support of these recommendations is limited, previous studies have examined the relationship between visit frequency and hypertension management. Increased encounter frequency has been associated with improved intermediate outcomes such as increased incidence of blood pressure control and more rapid blood pressure control.[24-26] There is also evidence that providers often delay intensifying antihypertensive therapy when treatment goals are not met, and that more frequent intensification of antihypertensive therapy leads to better blood pressure control. In addition, several studies have suggested that delays in blood pressure control lead to increased outcome risk. The VALUE trial initially achieved greater blood pressure reductions in the amlodipine group compared to the valsartan group, and a transient difference in the incidence of stroke was observed while this difference persisted.[28] In an open-label extension of the Syst-Eur trial, patients who were immediately randomized to the treatment arm had lower risk for stroke and cardiovascular complication, compared to those who received delayed treatment in the extension phase.[29]

Study Objective

I conducted a retrospective cohort study to establish the systolic intensification threshold, time-to-intensification and time-to-follow-up that are associated with the lowest risk of cardiovascular events or death in a large population of primary care patients with hypertension.

METHODS

Data Source

The Health Improvement Network (THIN) is an electronic medical record database containing patient encounter data collected from primary care practices throughout the United Kingdom that choose to submit their electronic records for research purposes. Patient and practice characteristics within the THIN database are representative of those within the general UK primary care population.[30] General practitioners are required to document patient encounters via a process that is subject to audit, and the accuracy of patient records is linked with compensation via the UK Quality and Outcomes Framework. Patient mortality and death dates in THIN are assessed using information which is forwarded to the patient's general practitioner upon administration of the death certificate. The accuracy of diagnosis and death records in the THIN database have been previously validated.

Study Cohort

Adults registered in primary care practices in the THIN database between 1986 and 2010 were studied. I included all patients who were 18 years or older, had at least one diagnosis code associated with hypertension (Table S1), had at least one blood pressure measurement and at least one antihypertensive medication initiated or intensified, had at least 10 years of continuous

data (to allow adequate time to assess treatment strategy), and had at least one set of height and weight data. To permit adjustment for socioeconomic deprivation, patients with missing postal codes were excluded. I also excluded patients with BMI less than 15 or greater than 100 to minimize the effect of implausible values.

This study was approved by the Partners HealthCare System institutional review board. A waiver was obtained for the requirement of written informed consent.

Study Measurements

Baseline patient characteristics and pre-existing medical conditions were assessed during the run-in period.[33] The run-in period began on the clinic registration date and ended on the latter date of 1) twelve months after clinic registration or 2) the first documentation of a hypertension-related diagnosis code or systolic blood pressure (SBP) greater than or equal to 130 mmHg.

A treatment strategy assessment period was defined for each patient, which consisted of the first 10 years following the end of the run-in period. This approach allowed us to represent the patient's treatment as a single summary as is the standard approach in cohort studies.[34]

During the treatment strategy assessment period, the minimum intensification threshold was defined as the lowest SBP at which antihypertensive medication intensification occurred (over the set of all known intensification events), rounded down to the nearest 10 mmHg. Antihypertensive medication intensifications were defined as the initiation of a new antihypertensive (complete medication list in Table S2), or an increase in the daily dose of an existing antihypertensive, on a date on which blood pressure was measured.[35] Medication adjustments performed when SBP was already lower than 130 mmHg are unlikely to represent antihypertensive medication intensifications and were therefore excluded from the analysis.

Time-to-intensification was defined as the mean length of unintensified hypertensive periods; each hypertensive period started on the day when SBP was first measured to be above the minimum intensification threshold and ended on the first subsequent day when medications were intensified, or when the unintensified period was censored (e.g. SBP fell below the threshold). Transient hypertensive periods, defined by a single elevated blood pressure measurement above the intensification threshold that fell below the threshold at the next blood pressure reading in the absence of medication intensification, were excluded from the analysis.

Time-to-follow-up was defined as the mean time between each medication intensification and the next visit at which blood pressure was recorded.

Time to outcome was defined as the time elapsed between the end of the treatment strategy assessment period and the composite outcome, which was defined as first acute cardiovascular event (myocardial infarction, cerebrovascular accident, acute congestive heart failure episode or peripheral vascular disease) or death (Table S3). The overall relationship between the run-in, treatment strategy assessment and outcome assessment periods is illustrated in Figure 1.

Age was calculated at the conclusion of the run-in period. BMI was calculated using the first set of height and weight data available for each patient. Smoking history was defined as past or current tobacco use. Chronic kidney disease was defined as the presence of a diagnosis code associated with CKD (except stage 1 or 2 CKD) or an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Table S3).[36] Medication possession ratio (as a proxy for compliance) was calculated for each patient as a weighted average of the number of days' supply actually prescribed for each medication, divided by the total period of time over which that medication was prescribed.[37] The Charlson comorbidity index (CCI) was calculated from the Read code list

using a previously described and validated method while excluding conditions individually included in the multivariable analysis.[38]

Socioeconomic status was estimated using the Townsend socioeconomic deprivation score, which is calculated using economic and demographic data based on the patient's postal code.[39] Patients who had multiple addresses during the follow-up period had their Townsend deprivation score calculated as a weighted average based on time spent living at each address.

Statistical Analysis

Summary statistics were produced using frequencies and proportions for categorical variables, and means, standard deviations, medians and ranges for continuous variables.

A Cox proportional hazards regression model was used to compare event-free survival for patients with various treatment strategies as defined by systolic intensification threshold, time-to-intensification and time-to-follow-up.[40] The analysis was stratified by entry age category (<60, 60-75, >75) and also adjusted for sex, smoking status, Townsend score, past history of diabetes/cardiovascular disease/chronic kidney disease, Charlson comorbidity index, body mass index, medication possession ratio, and the mean difference by which SBP exceeded the minimum intensification threshold at the beginning of each hypertensive period.[43]

I anticipated that time-to-intensification and time-to-follow-up may have a nonlinear relationship with respect to event risk, with an optimal range of values and increased hazards outside this range. On the other hand, thresholds defined by quintiles of each variable are somewhat arbitrary, with the boundaries determined by physician behavior in our particular sample. To provide an alternative view of the relationship between time-to-intensification, time-to-follow-up and event risk, I constructed Cox regression models which included time-to-intensification and time-to-follow-up as natural cubic splines to account for a continuous

nonlinear functional dependence between these treatment parameters and the log hazard rate.[44] Spline knots were placed at the 5th, 25th, 75th and 95th percentiles of the overall distribution for time to intensification and time to follow-up. These models were stratified by entry age and adjusted for smoking status, socioeconomic deprivation, history of cardiovascular disease/diabetes/chronic kidney disease, and Charlson comorbidity index.

P-values were obtained using the type III test, and significance thresholds were adjusted for multiple hypothesis testing using the Simes-Hochberg method. All analyses were performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

Patient Characteristics

I identified 148,930 patients from the THIN database with a hypertension diagnosis code and at least 10 years of subsequent primary care records between 1986 and 2010. I excluded patients who had no blood pressure measurements, were under 18 years, had fewer than 10 years of follow-up, had no medication intensifications during the 10 years following hypertension diagnosis, had missing demographic data, or implausible BMI values (Figure S1). The final study population therefore consisted of 88,756 adult patients.

Baseline patient characteristics are shown in Table 1. Following the treatment strategy assessment period, mean follow-up time was 37.4 months; 11.3% of patients experienced an acute cardiovascular event or death.

Treatment Strategy and Outcome Risk

In the multivariable analysis, male gender, older age, obesity, diabetes, previous cardiovascular disease, chronic kidney disease, history of smoking, increased Charlson

comorbidity index and socioeconomic deprivation were associated with greater risk for cardiovascular events or death (Table 3). SBP intensification thresholds of 160 mmHg or higher were also associated with progressively increased risk for the composite outcome (Table 2). Systolic intensification thresholds lower than 150 mmHg weakly trended towards further decreased composite outcome risk, but the difference did not reach statistical significance.

The lowest quintile of time to medication intensification (0-1.4 months) was associated with the lowest risk for the composite outcome, and higher quintiles were associated with progressively greater risk. Compared to patients who received blood pressure follow-up within 0-2.7 months (quintiles 1-4), patients who had time-to-follow-up greater than 2.7 months also had increased risk for the composite outcome.

To examine the relationship between prescribing behavior and event rate without dividing follow-up and intensification time into discrete categories, a natural cubic spline model was created (Figure 2). Shorter times to medication intensification were associated with decreased risk of cardiovascular event or death, with the greatest rate of risk increase occurring within the first 9 months. A J-shaped curve was noted for time-to-follow-up, as both very short and very long follow-up times were associated with increased risk of cardiovascular event or death.

A secondary analysis was performed using all-cause mortality as the endpoint. In this analysis a similar relationship was found between systolic intensification threshold, time-to-intensification, time-to-follow-up and all-cause mortality (Table S4). Higher quintiles of time-to-intensification were associated with progressively increased overall mortality risk, as were time-to-follow-up after intensification greater than 2.7 months and systolic intensification thresholds of greater than 150 mmHg.

Sensitivity Analysis

To investigate whether defining a shorter treatment strategy assessment period would lead to misclassification of prescribing strategies, we attempted to define a 5-year treatment strategy assessment period for the study population. With this approach, 33.5% of all patients in the highest quintile for time-to-intensification (when using the 10-year treatment strategy assessment period) were reclassified to lower quintiles. The fraction of unintensified periods in the highest quartile which were censored also decreased with increasing length of the treatment strategy assessment period (Figure S2).

Nonetheless, we examined the effect that alternative inclusion criteria would have on the optimal intensification threshold. To this end, we conducted an alternative analysis in which a 3-year period was used to assess the medication intensification strategy (instead of 10 years). Since 66.6% of these patients did not have any medication intensifications during the first 3 years, time-to-intensification and time-to-follow-up after intensification were not defined. For patients without intensifications, we assumed that the highest blood pressure attained remained below the intensification threshold. For such patients we therefore defined the estimated systolic intensification threshold as the highest attained non-transient blood pressure during the treatment strategy assessment period, rounded up to the nearest 10mmHg. Under these liberalized inclusion criteria, 329,491 patients were identified. In this analysis, intensification thresholds >150 mmHg remained associated with increased risk for cardiovascular events or death (Table S5). Notably, in this model intensification thresholds of 150 mmHg or lower were associated with progressively decreased risk, down to a minimum intensification threshold of 130 mmHg.

Strategy Changes after Acute Cardiovascular Events

To investigate whether physician prescribing behavior changes after an acute cardiovascular event, we calculated minimum systolic intensification thresholds for the 7,578 patients who had an acute cardiovascular event during the treatment strategy assessment period. Among these patients, treatment became more aggressive after an acute cardiovascular event (mean minimum systolic intensification threshold 161 mmHg vs 154 mmHg, $p < 0.0001$). This was true even among patients for whom this event was not their first acute cardiovascular event (mean minimum systolic intensification threshold 160 mmHg vs 154 mmHg, $p < 0.0001$).

In the event that physicians decide to alter their hypertension management strategy after the patient experiences an acute cardiovascular event, the current approach raises a risk of misrepresenting treatment strategies when there are risk factors present (e.g. acute cardiovascular events) that are at the same time determined by previous exposure (e.g. hypertension control) and themselves alter the subsequent treatment strategy.[47] To estimate the effect that acute cardiovascular events during the treatment strategy assessment period may have on our model, I included a variable corresponding to the presence of such an event during this period. Although any acute cardiovascular event during the treatment strategy assessment period was strongly correlated with risk for subsequent events (HR 1.918, 95% CI 1.821-2.021), the inclusion or exclusion of this variable did not alter either the direction or significance of hazard differences between treatment strategies.

Visit Frequency

To investigate whether time-to-intensification and time-to-follow-up have an effect on outcomes independent of visit frequency, I introduced a variable corresponding to the total number of blood pressure measurements over the 10-year treatment strategy assessment period. The inclusion of this variable did not qualitatively change the significance or direction of the

previously observed interquintile risk differences in time-to-intensification or time-to-follow-up. Increased visit frequency was associated with increased composite outcome risk after adjustment for time-to-intensification and time-to-follow-up (HR 1.003 per visit, 95% CI 1.001-1.004, $p < 0.0001$), but not before (HR 1.001, 95% CI 1.000-1.003, $p = 0.065$).

DISCUSSION

In this large retrospective study, I examined the relationship between several process measures of treatment of elevated blood pressure and risk of cardiovascular events or death. I found that systolic intensification thresholds higher than 150 mmHg and delays of greater than 1.4 months before medication intensification following SBP elevation above the intensification threshold were associated with increased risk for acute cardiovascular event or death. After each antihypertensive medication intensification, lack of blood pressure follow-up within 2.7 months was also associated with increased risk for the composite outcome.

I observed that a systolic treatment target greater than 150 mmHg was associated with greater risk for acute cardiovascular event or death, when compared to SBP targets of 150 mmHg or lower. These results are broadly consistent with the extant evidence from available clinical trials. In the main model, there was a weak trend towards improved outcomes at even lower intensification thresholds. When the inclusion criteria were liberalized in a sensitivity analysis to include all patients with three or more years of data whether or not their treatment was intensified, significant progressive decrease in risk was seen down to the lowest threshold of 130 mmHg. This raises the possibility that more aggressive intensification thresholds have a small added benefit that could be better characterized with an even larger dataset.

A “J-curve” corresponding to increased outcome risk at low blood pressure has previously been reported in observational studies for diastolic and occasionally systolic[7-9] blood

pressure, but I did not detect this phenomenon. Notably in our study I examined SBP targets, whereas previous studies that noted the systolic J-curve analyzed mean blood pressures without regard for treatment which may be more vulnerable to confounding from baseline patient illness. On the other hand, it remains possible that systolic treatment thresholds even lower than 130 mmHg, which was the lowest treatment target I examined, may be associated with increased cardiovascular risk.

In this study, I demonstrate that two process measures of blood pressure management that are directly related to encounter frequency - the time to medication intensification and the time to follow-up after intensification - are independent predictors of risk for cardiovascular mortality or death. This is, to our knowledge, the first study that has directly examined the effect of these variables on patient outcomes. In our study population, the majority of patients had blood pressure follow-up within 2.7 months after each medication intensification, which was the time period associated with lowest risk for the composite outcome. However, the majority of patients did not receive medication intensification within 1.4 months. Further investigation is needed to determine whether interventions to reduce the time to medication intensification would improve outcomes.

Limitations

There are several significant limitations to this study. I assumed that providers intensify antihypertensive treatment until the goal blood pressure is reached, and therefore used the minimum intensification threshold as a proxy for goal blood pressure. Patients with hypertension resistant to treatment may never reach the provider's intended treatment goal, leading to potential overestimation of the systolic treatment threshold. However this would be expected to bias the results towards the null hypothesis, e.g. if some treatment thresholds are overestimated, then the

optimal systolic interpretation threshold may be even lower than 150 mmHg. As aforementioned, this possibility is supported by the small improvements in outcome observed at lower intensification thresholds under some sensitivity analyses (Table S5).

There is controversy surrounding the optimum systolic treatment threshold for patients with diabetes, chronic kidney disease, atherosclerosis, or advanced age, but our sample size was insufficiently large to permit stratification by these subgroups. Although I examined the effects of treatment on outcome, and our treatment strategy assessment period chronologically preceded the outcome assessment period, the retrospective nature of our data limits our ability to make causal inferences. Our study was limited to patients who had regular access to primary care, and who had hypertension diagnosed by a general practitioner. However, approximately 99% of residents of the United Kingdom are registered with a general practitioner, so the potential for patient selection bias is less than it would be in many other countries.[49]

The use of certain anti-hypertensive medications (for instance angiotensin converting enzyme inhibitors and beta blockers) may have effects on cardiovascular outcome that are independent of their effect on blood pressure. In this study I assumed that all new antihypertensive medications prescribed for a patient with elevated blood pressure represented hypertension treatment intensifications, and was not able to account for dual indications which might compel a physician to select one class of anti-hypertensive instead of another.

In the natural cubic spline model (Figure 2), there is a visual trend towards higher hazards when patients had very quick blood pressure follow-up, though this did not reach statistical significance in the multivariable model. This is likely due to confounding by indication, since I was unable to distinguish scheduled appointments from urgent care visits. Patients with a blood pressure check immediately following a previous appointment may have been seen for other urgent indications, which may itself be associated with an apparent increase in outcome risk. If

urgent care visits were eliminated, it is possible that further benefits may be seen at follow-up intervals shorter than 2.7 months.

In this study, outcomes after hypertension treatment were evaluated by defining separate time periods for the assessment of treatment strategy and outcomes. This was done to reduce the time-dependent confounding caused by variations in blood pressure level, which predicts antihypertensive treatment, is itself influenced by treatment, and also affects outcome risk[52]. A concurrent treatment strategy assessment and outcome assessment period would also introduce an undesirable bias towards systematically shorter treatment strategy assessment periods for patients who have outcomes early in the study, resulting in systematic overestimation of treatment thresholds for patients with early cardiovascular events. I chose a 10-year treatment strategy assessment period because I found that shorter treatment strategy assessment periods are vulnerable to misclassification of time-to-intensification, since the assessment period may end before intensification occurs. Strategies corresponding to longer time-to-intensification and longer follow-up times would be disproportionally affected, which would lead to systematic censoring bias. This study design necessarily limits our analysis to patients who had 10 years of treatment data available past the hypertension diagnosis date (e.g. the length of the strategy assessment period). However, considering that mean life expectancy at age 65 in the United Kingdom is now over 17 years for men and 20 years for women, this may be a good initial approximation for patients in industrialized societies with routine access to medical care.[53]

Future Investigations

Marginal structural models are statistical constructs designed to address biases which are introduced when studying time-varying exposures (such as hypertension) which predict both

outcome risk and subsequent treatment. The use of a marginal structural model to confirm this analysis would have several potential benefits.

A marginal structural model would allow variations in blood pressure treatment for a given patient could be better taken into account, instead of the current approach which assumes a static blood pressure goal over the duration of the study period. This would reduce the need to define chronologically separate periods for the assessment of treatment and outcome, and would better reflect reality since blood pressure treatment is generally continuous until an acute event occurs (and also continues past the time of an acute cardiovascular event). When adjusting for an intermediate variable that is also a confounder—e.g. the degree of blood pressure elevation during the treatment period—standard regression models (such as the one used in this study) tend to block the indirect effect that previous hypertension treatment has on subsequent cardiovascular risk, whereas marginal structural models are less vulnerable to this bias.[55] Finally, my current model is potentially vulnerable to non-random censoring, in which patients who are lost to follow-up (e.g. censored) may also be more likely to have uncontrolled hypertension and/or have adverse outcomes. Although I mitigate this bias by adjusting for measures of compliance (medication possession ratio and visit frequency in the sensitivity analysis), inverse probability weighting as applied through a marginal structural model can simulate a pseudo-population in which all participants complete follow-up, and thereby attain a more accurate estimate of the treatment effect.[56]

Notably, each of the aforementioned biases would be expected to bias the results towards the null hypothesis by decreasing the apparent difference in hazard between treatment strategies. Therefore these limitations are somewhat mitigated by the large sample size, though it remains possible that the actual effect size is stronger than what I observed.

Although I considered implementing a marginal structural model for the current analysis, the approach is limited by the computational complexity of having multiple treatment parameters: intensification threshold, time-to-intensification, and time-to-follow-up, if implemented simultaneously, would generate a potential total of 6 x 5 x 5 = 150 treatment arms. In a future investigation, a marginal structural model that asks a more limited clinical question (e.g. short vs long follow-up time) may be helpful in verifying the results of the current study.

The strongest level of clinical evidence is a randomized controlled trial, which inherently balances treatment arms along both known and unknown variables and avoids the risk for allocation bias inherent in retrospective studies.[57] While there are inherent challenges to studying compliance-related variables in a clinical trial, one possible design would be to perform a randomized intervention study to measure differences in cardiovascular risk in a patient population known to have poor prior rates of timely blood pressure treatment and follow-up.[58]

SUMMARY

The optimal medical management of hypertension remains highly controversial. Despite the high prevalence of stage 1 hypertension, the JNC 8, ESH/ESC and NICE guidelines (among others) differ substantially in their recommendations for systolic treatment targets, how quickly patients with elevated blood pressure should be intensified, and how quickly patients should be followed up after antihypertensive treatment intensification.

In this retrospective cohort study, I find that systolic blood pressure target, time-to-intensification and time-to-follow-up are predictors of increased risk for acute cardiovascular events or death. I observe an increase in risk of cardiovascular events or death associated with systolic targets greater than 150 mmHg, delays of greater than 1.4 months before medication intensification or delays of greater than 2.7 months before blood pressure follow-up after

medication intensification. This is, to my knowledge, the first large study that specifically examines the effect of antihypertensive medication time-to-intensification and time-to-follow-up on patient outcomes. In patients with hypertension and regular access to primary care, timely achievement of blood pressure targets and regular follow-up may be an important factor in minimizing overall risk of cardiovascular events or death.

REFERENCES

1. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA. 2003; **290**(7): 891-7.
2. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. JAMA. 2010; **303**(20): 2043-50.
3. Hsiao CJ, Cherry DK, Beatty PC, Rechtsteiner EA. National Ambulatory Medical Care Survey: 2007 summary. Natl Health Stat Report. 2010; **2010 Nov 3**(27): 1-32.
4. National Institute for Health and Clinical Excellence. Hypertension: clinical management of primary hypertension in adults: CG127. NICE. 2011.
5. IMS Institute for Healthcare Informatics. The Use of Medicines in the United States: Review of 2011. 2012.
6. JA. C. High blood pressure and end-organ damage. J Hypertens. 1996; **14(suppl 6)**: S3–S6.
7. Vokó Z, Bots ML, Hofman A, Koudstaal PJ, Witteman JC, Breteler MM. J-shaped relation between blood pressure and stroke in treated hypertensives. Hypertension. 1999; **34**(6): 1181-5.
8. Shorr RI, Somes GW. Can Diastolic Blood Pressure be Excessively Lowered in the Treatment of Isolated Systolic Hypertension? J Clin Hypertens (Greenwich). 2000; **2**(2): 134-7.
9. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP, Committee. IPS, et al. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. Ann Intern Med. 2002; **136**(6): 438-48.
10. Al-Ansary LA, Tricco AC, Adi Y, Bawazeer G, Perrier L, Al-Ghonaim M, et al. A systematic review of recent clinical practice guidelines on the diagnosis, assessment and management of hypertension. PLoS One. 2013; **8**(1).
11. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2013.
12. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med. 1997; **157**(21): 2413-46.
13. Members. ATF, Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013; **34**(28): 2159-219.
14. Carretero OA, Oparil S. Essential Hypertension Part I: Definition and Etiology. Circulation. 2000; **101**: 329-35.
15. Zhang Y, Zhang X, Liu L, Zanchetti A. Is a systolic blood pressure target <140 mmHg indicated in all hypertensives? Subgroup analyses of findings from the randomized FEVER trial. Eur Heart J. 2011; **32**: 1500-8.
16. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JLJ, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. Hypertension. 2003; **42**: 1206-52.
17. Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. Cochrane Database Syst Rev. 2012; **8**.

18. Hypertension Detection and Follow-up Program Cooperative Group. The effect of treatment on mortality in "mild" hypertension: results of the hypertension detection and follow-up program. N Engl J Med. 1982; **307**(16): 976-80.
19. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. Br Med J (Clin Res Ed). 1985; **291**(6488): 97-104.
20. Peterson ED, Gaziano JM, Greenland P. Recommendations for Treating Hypertension: What Are the Right Goals and Purposes? JAMA. 2013.
21. Group. AS, Cushman WC, Evans GW, Byington RP, Goff DCJ, Grimm RHJ, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010; **362**(17): 1575-85.
22. Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension. 2006; **47**: 345-51.
23. Egan BM, Basile JN. Controlling blood pressure in 50% of all hypertensive patients: an achievable goal in the Healthy People 2010 Report? J Investig Med. 2003; **51**: 373-85.
24. Lichtenstein MJ, Steele MA, Hoehn TP, Bulpitt CJ, Coles EC. Visit frequency for essential hypertension: observed associations. J Fam Pract. 1989; **28**(6): 667-72.
25. Guthmann R, Davis N, Brown M, Elizondo J. Visit Frequency and Hypertension. The Journal of Clinical Hypertension. 2005; **7**(6): 327-32.
26. Turchin A, Goldberg SI, Shubina M, Einbinder JS, Conlin PR. Encounter frequency and blood pressure in hypertensive patients with diabetes mellitus. Hypertension. 2010; **56**(1): 68-74.
27. Berlowitz DR, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B, et al. Inadequate management of blood pressure in a hypertensive population. N Eng J Med. 1998; **339**(27): 1957-63.
28. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004; **363**(9426): 2022-31.
29. Staessen JA, Thijisq L, Fagard R, Celis H, Birkenhäger WH, Bulpitt CJ, et al. Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. J Hypertens. 2004 Apr;22(4):847-57.; **2004 Apr 22**(4): 847-87.
30. Lewis JD, Schninnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf. 2007; **16**(Journal Article): 393-401.
31. Hall GC. Validation of death and suicide recording on the THIN UK primary care database. Pharmacoepidemiol Drug Saf. 2009; **18**(2): 120-31.
32. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ. 1991; (302): 766-8.
33. Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the general practice research database. Pharmacoepidemiol Drug Saf. 2005; **14**(Journal Article): 443-51.
34. Rothman KJ, Greenland S, Lash TL. Cohort Studies. Modern Epidemiology, 3rd edition.
35. Turchin A, Shubina M, Chodos A, Einbinder J, Pendergrass M. Effect of board certification on antihypertensive treatment intensification in patients with diabetes mellitus. Circulation. 2008; **117**: 623-8.
36. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AFr, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; **150**(9): 604-12.
37. Schulz RM, Gagnon JP. Patient behavior patterns regarding prescription refills. Contemp Pharm Pract. 1982; **5**(3): 150-5.

38. Khan NF, Perer R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. BMC Family Practice. 2010; **11**(1).
39. Townsend P. Deprivation. J Soc Pol. 1987; (16): 125-46.
40. Cox DR. Regression models and life-tables. J R Stat Soc [B]. 1972; **34**(Journal Article): 187-220.
41. Pencina MJ, Larson MG, D'Agostino RB. Choice of time scale and its effect on significance of predictors in longitudinal studies. Stat Med. 2007; **26**(6): 1343-59.
42. Gail MH, Graubard B, Williamson DF, Flegal KM. Comments on 'Choice of time scale and its effect on signi cance of predictors in longitudinal studies'. Stat Med. 2009; **28**(8): 1315-7.
43. Morrison F, Shubina M, Turchin A. Encounter frequency and serum glucose level, blood pressure, and cholesterol level control in patients with diabetes mellitus. Arch Intern Med. 2011; **171**(17): 1542-50.
44. Harrell FJ, Jr. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. Springer Series in Statistics. New York: Springer-Verlag; 2001.
45. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988; **75**(Journal Article): 800-2.
46. Simes RJ. An improved Bonferroni procedure for multiple tests of significance. Biometrika. 1986; **73**(Journal Article): 751-4.
47. Robins JM. A graphical approach to the identification and estimation of causal parameters in mortality studies with sustained exposure periods. J Chronic Dis. 1987; **40 (supp 2)**: 139S-61S.
48. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A, et al. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. J Hypertens. 2005; **23**(12): 2157-72.
49. Boreham R, Airey C, Erens B, Tobin R. National surveys of NHS patients: General practice. 2002.
50. Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet. 2000; **355**(9215).
51. Lechat P, Escolano S, Golmard JL, Lardoux H, Witchitz S, Henneman JA, et al. Prognostic value of bisoprolol-induced hemodynamic effects in heart failure during the Cardiac Insufficiency BIsoprolol Study (CIBIS). Circulation. 1997; **96**(7).
52. Platt RW, Schisterman EF, Cole SR. Time-modified confounding. Am J Epidemiol. 2009; **170**(6): 687-94.
53. Mortality Statistics: Deaths registered in England and Wales (Series DR). 2012 Nov. 6, 2012 [cited Feb. 6, 2013]; Available from: http://www.ons.gov.uk/ons/rel/vsob1/mortality-statistics--deaths-registered-in-england-and-wales--series-dr-/index.html
54. Robins JM. Association, causation, and marginal structural models. Synthese. 1999; (121): 151-79.
55. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000; **11**(5): 550-60.
56. Danaei G, Rodríguez LA, Cantero OF, Logan R, Hernán MA. Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. Stat Methods Med Res. 2013; **22**(1): 70-96.

57. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010; **340:c869.**
58. Yang Y. State of the Science: The Efficacy of a Multicomponent Intervention for ART Adherence Among People Living With HIV. J Assoc Nurses AIDS Care. 2014.

FIGURES

Figure 1:

Design of study periods for evaluation of treatment strategy and outcome.

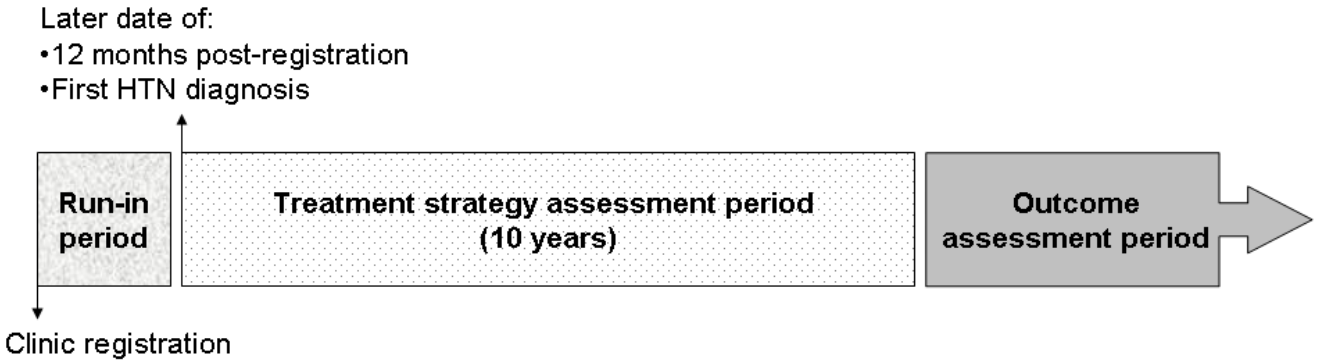


Figure 2:

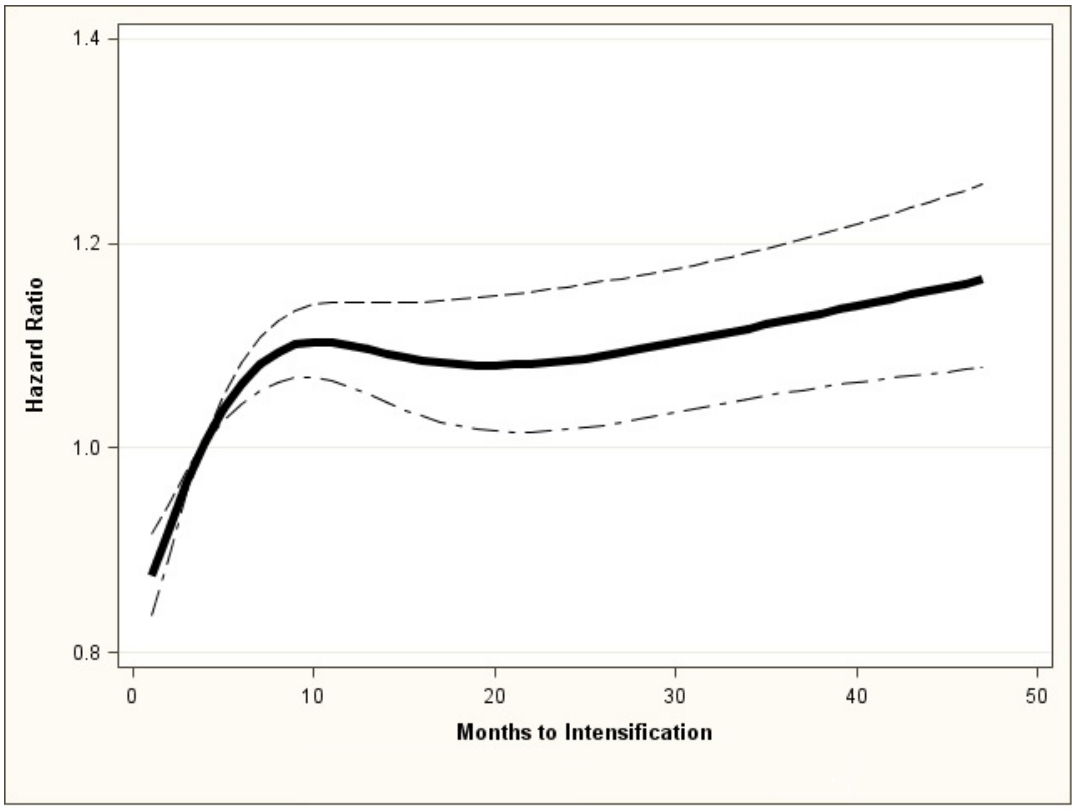
Effects of time to antihypertensive intensification and time-to-follow-up after intensification on risk of acute cardiovascular event or death.

In panel **A)**, the hazard ratio for acute cardiovascular event or death is shown in relation to the mean months elapsed between systolic blood pressure elevation above the minimum intensification threshold, and either antihypertensive medication intensification or censoring of the unintensified period (via spontaneous normalization of blood pressure).

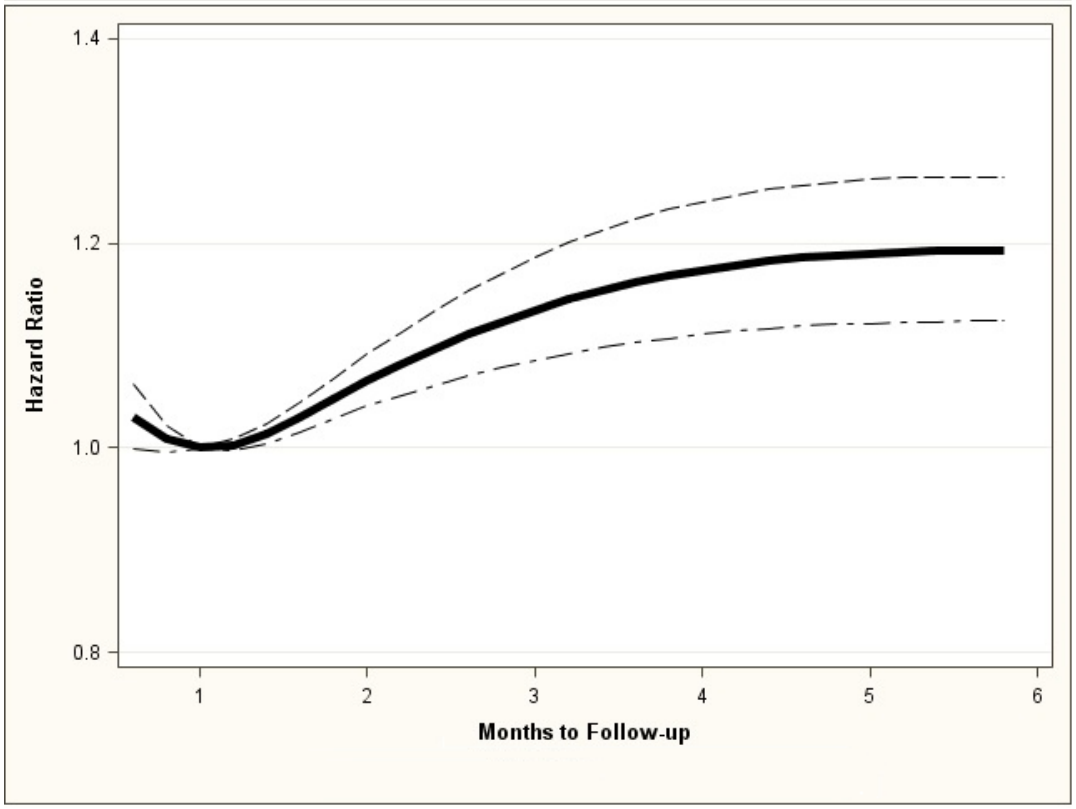
In panel **B)**, the hazard ratio for acute cardiovascular event or death is shown in relation to the mean months elapsed between each antihypertensive medication intensification, and the next blood pressure measurement.

Solid lines indicate hazard ratios, and dashed lines indicate 95% confidence intervals calculated using natural cubic spline regression. Reference points are placed at the means of the respective distributions for time-to-intensification and time-to-follow-up. Knots are placed at the 5th, 25th, 75th and 95th percentiles of each variable. The multivariable model is adjusted for age, sex, body mass index, smoking status, socioeconomic deprivation, history of cardiovascular disease, chronic kidney disease or diabetes, other chronic medical conditions as represented by the Charlson comorbidity index, minimum systolic intensification threshold, mean initial blood pressure elevation above the intensification threshold, and medication possession ratio.

A)


1.4
1.2
1.0
0.8
Hazard Ratio
0
10
20
30
40
50
Months to Intensification

B)


1.4
1.2
1.0
0.8
Hazard Ratio
1
2
3
4
5
6
Months to Follow-up

TABLES

Table 1:

Baseline characteristics of study patients.

Characteristic	
Number of participants	88756
Age, mean (SD)	58.5 (11.9)
Men (%)	36800 (41.5)
BMI, mean (SD)	27.6 (5.0)
Past/current smoker (%)	50176 (56.5)
History of any cardiovascular disease (%)	9907 (11.2)
History of coronary artery disease (%)	6827 (7.7)
History of congestive heart disease (%)	601 (0.7)
History of stroke (%)	2450 (2.8)
History of peripheral vascular disease (%)	981 (1.2)
History of diabetes (%)	5863 (6.6)
History of chronic kidney disease (%)	2420 (2.7)
Modified Charlson index, mean (SD)	0.27 (0.6)
Townsend deprivation score, mean (SD)	2.66 (1.3)

Table 2:

Characteristics of the Treatment Strategy Assessment Period.

P-values in *italics* are not significant after Simes-Hochberg adjustment for multiple hypothesis testing. Mean SBP elevation over intensification threshold denotes mean difference between actual blood pressure and systolic intensification threshold at the beginning of each hypertensive period.

Characteristic	n (%) or mean (SD)	Hazard Ratio	p-value	95% CI
Minimum systolic intensification threshold, mmHg				
130-139	12229 (13.8)	0.984	*0.69*	0.908-1.066
140-149	20458 (23.0)	1.000	--	--
150-159	21329 (24.0)	1.033	*0.34*	0.966-1.103
160-169	17513 (19.7)	1.211	<0.0001	1.127-1.300
170-179	8978 (10.1)	1.424	<0.0001	1.306-1.554
180+	8249 (9.3)	1.688	<0.0001	1.549-1.839
Mean time to intensification, quintiles, months				
0-1.439	17752 (20.0)	1.000	--	--
1.440-4.681	17751 (20.0)	1.119	0.0009	1.047-1.196
4.682-8.689	17749 (20.0)	1.229	<0.0001	1.148-1.315
8.690-15.320	17753 (20.0)	1.193	<0.0001	1.111-1.281
15.321+	17751 (20.0)	1.254	<0.0001	1.166-1.349
Mean time to follow-up after intensification, quintiles, months				
0-0.723	18283 (20.6)	1.058	*0.085*	0.992-1.128
0.724-1.018	17524 (19.7)	1.000	--	--
1.019-1.544	17887 (20.2)	1.013	*0.71*	0.949-1.079
1.545-2.727	17537 (19.8)	1.066	*0.050*	1.000-1.137
2.727+	17525 (19.7)	1.178	<0.0001	1.108-1.253
Mean SBP elevation over intensification threshold, mmHg (%)				
1-9	47173 (53.1)	1.000	--	--
10-19	31376 (35.4)	1.128	<0.0001	1.068-1.191
20-29	8514 (9.6)	1.375	<0.0001	1.271-1.488
30-39	1508 (1.7)	1.505	<0.0001	1.308-1.731
40-49	185 (0.2)	1.777	0.0010	1.263-2.501
Medication possession ratio	0.859 (0.19)	0.798	<0.0001	0.728-0.876

Table 3:

Effects of baseline patient characteristics on the risk of acute cardiovascular event or death. Age categories are calculated at the beginning of the outcome assessment period. History of cardiovascular disease and diabetes were omitted from the calculation of the modified Charlson index. Hazard ratio for Townsend deprivation score is per quintile increase in socioeconomic deprivation. Hazard ratio for the modified Charlson comorbidity index is per one point increase in the Charlson score.

Variable	Hazard ratio	95% CI	p-value
Female gender	0.736	0.705-0.767	<0.0001
Age			
<60	1.000	--	--
60-74	2.369	2.188-2.565	<0.0001
75+	5.993	2.537-6.486	<0.0001
Townsend deprivation score	1.094	1.079-1.111	<0.0001
Past or current smoker	1.212	1.162-1.265	<0.0001
Modified Charlson comorbidity index	1.138	1.108-1.167	<0.0001
BMI			
<20	1.949	1.659-2.289	<0.0001
20-24.9	1	--	--
25-29.9	0.974	0.930-1.020	*0.27*
30+	1.079	1.022-1.139	0.0058
Preexisting medical conditions			
Diabetes	1.616	1.511-1.729	<0.0001
CAD	1.481	1.398-1.570	<0.0001
CHF	1.607	1.379-1.871	<0.0001
CVA	1.445	1.322-1.774	<0.0001
PVD	1.596	1.435-1.729	<0.0001
Chronic kidney disease	1.151	1.021-1.298	0.021

SUPPLEMENTAL FIGURES

Figure S1:

Study patients and exclusion criteria.

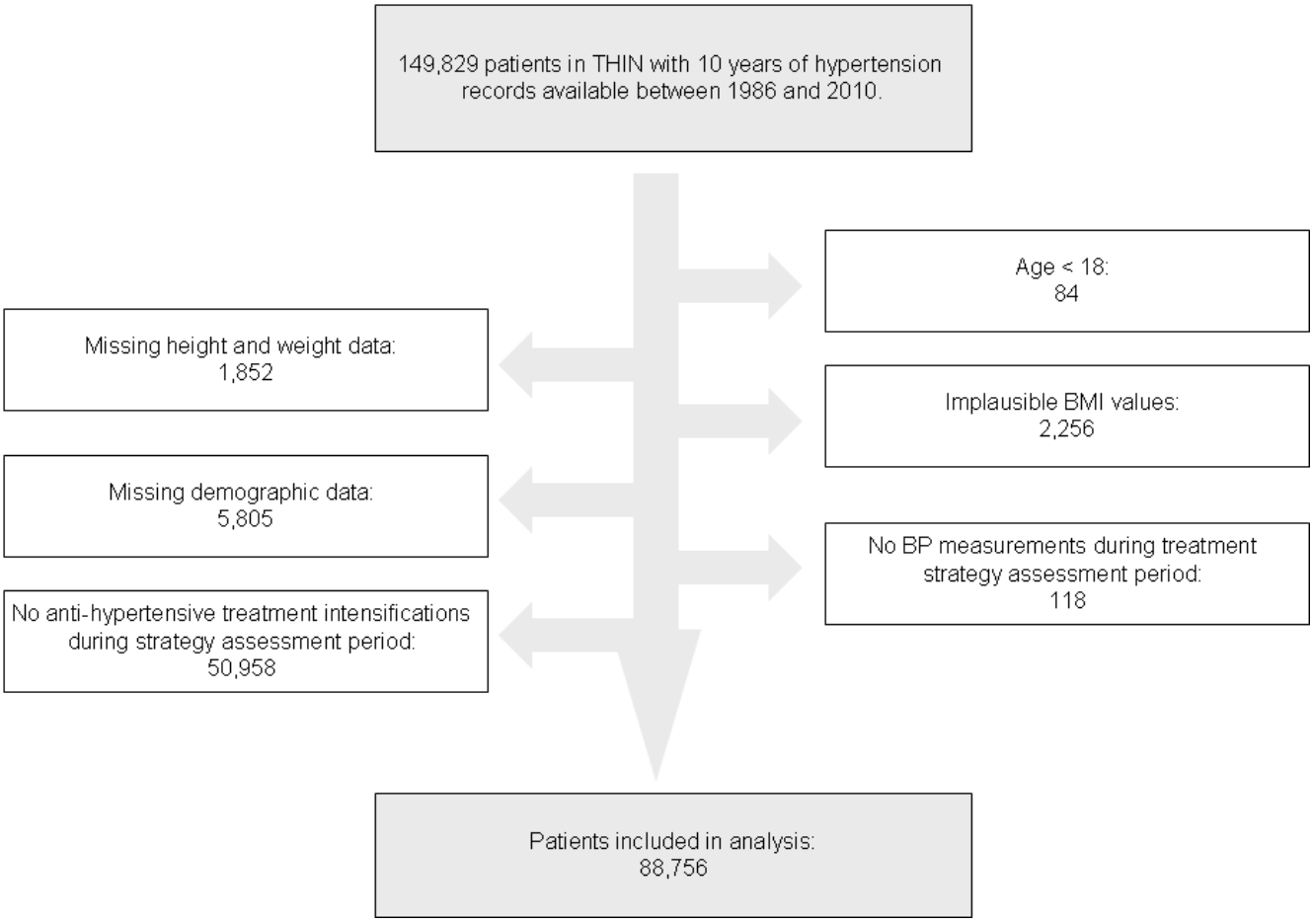
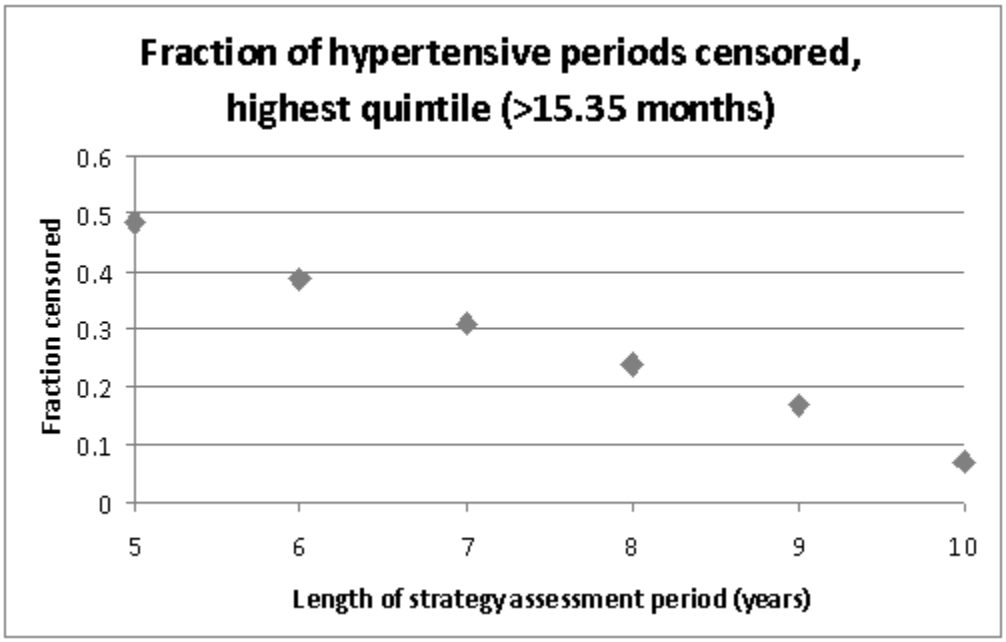


Figure S2:

Censoring of time-to-intensification vs. length of the treatment strategy assessment period.



SUPPLEMENTAL TABLES

Table S1:

List of Read codes used to identify patients with hypertension in the THIN database.

Descriptions are as provided by the NHS Read code dictionary, version 2.

Read code	Description
G2...00	Hypertensive disease
G2...11	BP - hypertensive disease
G20..00	Essential hypertension
G20..11	High blood pressure
G200.00	Malignant essential hypertension
G201.00	Benign essential hypertension
G202.00	Systolic hypertension
G20z.00	Essential hypertension NOS
G20z.11	Hypertension NOS
G24..00	Secondary hypertension
G240.00	Secondary malignant hypertension
G240000	Secondary malignant renovascular hypertension
G240z00	Secondary malignant hypertension NOS
G241.00	Secondary benign hypertension
G241000	Secondary benign renovascular hypertension
G241z00	Secondary benign hypertension NOS
G244.00	Hypertension secondary to endocrine disorders
G24z.00	Secondary hypertension NOS
G24z000	Secondary renovascular hypertension NOS
G24z100	Hypertension secondary to drug
G24zz00	Secondary hypertension NOS
G2y..00	Other specified hypertensive disease
G2z..00	Hypertensive disease NOS

Table S2:

List of anti-hypertensive medications

MEDICATION
ACEBUTOLOL
ALISKIREN
AMILORIDE
AMLODIPINE
ATENOLOL
BAMETHAN
BENDROFLUMETHIAZIDE
BENZTHIAZIDE
BETAXOLOL
BETHANIDINE
BISOPROLOL
BUMETANIDE
CANDESARTAN
CAPTOPRIL
CARTEOLOL
CARVEDILOL
CELIPROLOL
CHLOROTHIAZIDE
CHLORTALIDONE
CILAZAPRIL
CLONIDINE
CLOPAMIDE
CYCLOPENTHIAZIDE
DEBRISOQUINE
DILTIAZEM
DOXAZOSIN
ENALAPRIL
EPLERENONE
EPROSARTAN
ESMOLOL
ETACRYNIC
FELODIPINE
FOSINOPRIL
FUROSEMIDE
GUANETHIDINE
HARMONYL
HYDRALAZINE
HYDROCHLOROTHIAZIDE
HYDROFLUMETHIAZIDE
IMIDAPRIL
INDAPAMIDE
INDORAMIN
INOSITOL
IRBESARTAN
ISOSORBIDE

ISRADIPINE
LABETALOL
LACIDIPINE
LERCANIDIPINE
LISINOPRIL
LOSARTAN
MEFRUSIDE
METHOSERPIDINE
METHYLDOPA
METOLAZONE
METOPROLOL
MIBEFRADIL
MINOXIDIL
MOEXIPRIL
MOXONIDINE
NADOLOL
NEBIVOLOL
NICARDIPINE
NIFEDIPINE
NIMODIPINE
NISOLDIPINE
OLMESARTAN
OXPRENOLOL
PENBUTOLOL
PERINDOPRIL
PHENOXYBENZAMINE
PINDOLOL
PIRETANIDE
POLYTHIAZIDE
PRAZOSIN
PROPRANOLOL
QUINAPRIL
RAMIPRIL
RESERPINE
SOTALOL
SPIRONOLACTONE
TELMISARTAN
TERAZOSIN
TIMOLOL
TORASEMIDE
TRANDOLAPRIL
TRIAMTERENE
VALSARTAN
VERAPAMIL
XIPAMIDE

Table S3:

List of Read codes associated with baseline medical conditions or acute cardiovascular events.

Descriptions are as provided by the NHS Read code dictionary, version 2.

Condition	Read Code	Description
CAD	G3...00	Ischaemic heart disease
CAD	G3...12	Atherosclerotic heart disease
CAD	G3...13	IHD - Ischaemic heart disease
CAD	G30..00	Acute myocardial infarction
CAD	G30..11	Attack - heart
CAD	G30..12	Coronary thrombosis
CAD	G30..13	Cardiac rupture following myocardial infarction (MI)
CAD	G30..14	Heart attack
CAD	G30..15	MI - acute myocardial infarction
CAD	G30..16	Thrombosis - coronary
CAD	G300.00	Acute anterolateral infarction
CAD	G301.00	Other specified anterior myocardial infarction
CAD	G301000	Acute anteroapical infarction
CAD	G301100	Acute anteroseptal infarction
CAD	G301z00	Anterior myocardial infarction NOS
CAD	G302.00	Acute inferolateral infarction
CAD	G303.00	Acute inferoposterior infarction
CAD	G304.00	Posterior myocardial infarction NOS
CAD	G305.00	Lateral myocardial infarction NOS
CAD	G306.00	True posterior myocardial infarction
CAD	G307.00	Acute subendocardial infarction
CAD	G307000	Acute non-Q wave infarction
CAD	G307100	Acute non-ST segment elevation myocardial infarction
CAD	G308.00	Inferior myocardial infarction NOS
CAD	G309.00	Acute Q-wave infarct
CAD	G30A.00	Mural thrombosis
CAD	G30B.00	Acute posterolateral myocardial infarction
CAD	G30X.00	Acute transmural myocardial infarction of unspecif site
CAD	G30X000	Acute ST segment elevation myocardial infarction
CAD	G30y.00	Other acute myocardial infarction
CAD	G30y000	Acute atrial infarction
CAD	G30y200	Acute septal infarction
CAD	G30yz00	Other acute myocardial infarction NOS
CAD	G30z.00	Acute myocardial infarction NOS
CAD	G311.11	Crescendo angina
CAD	G311.13	Unstable angina
CAD	G311.14	Angina at rest
CAD	G311100	Unstable angina
CAD	G311200	Angina at rest
CAD	G311300	Refractory angina
CAD	G311400	Worsening angina

Condition	Read Code	Description
CAD	G311500	Acute coronary syndrome
CAD	G312.00	Coronary thrombosis not resulting in myocardial infarction
CAD	G31y.00	Other acute and subacute ischaemic heart disease
CAD	G31y000	Acute coronary insufficiency
CAD	G32..00	Old myocardial infarction
CAD	G33..00	Angina pectoris
CAD	G33z.00	Angina pectoris NOS
CAD	G33z300	Angina on effort
CAD	G33z400	Ischaemic chest pain
CAD	G33z700	Stable angina
CAD	G33zz00	Angina pectoris NOS
CAD	G340.00	Coronary atherosclerosis
CAD	G340.11	Triple vessel disease of the heart
CAD	G340.12	Coronary artery disease
CAD	G340000	Single coronary vessel disease
CAD	G340100	Double coronary vessel disease
CAD	G343.00	Ischaemic cardiomyopathy
CAD	G34z000	Asymptomatic coronary heart disease
CAD	G3z..00	Ischaemic heart disease NOS
CAD	G70y011	Carotid artery disease
CAD	G30..17	Silent myocardial infarction
CAD	G32..11	Healed myocardial infarction
CAD	G32..12	Personal history of myocardial infarction
CHF	G211100	Benign hypertensive heart disease with CCF
CHF	G21z100	Hypertensive heart disease NOS with CCF
CHF	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
CHF	G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
CHF	G58..00	Heart failure
CHF	G58..11	Cardiac failure
CHF	G580.00	Congestive heart failure
CHF	G580.11	Congestive cardiac failure
CHF	G580.14	Biventricular failure
CHF	G580000	Acute congestive heart failure
CHF	G580100	Chronic congestive heart failure
CHF	G580200	Decompensated cardiac failure
CHF	G580300	Compensated cardiac failure
CHF	G581.00	Left ventricular failure
CHF	G581.12	Pulmonary oedema - acute
CHF	G581.13	Impaired left ventricular function
CHF	G581000	Acute left ventricular failure
CHF	G582.00	Acute heart failure
CHF	G58z.00	Heart failure NOS
CHF	G58z.12	Cardiac failure NOS
CHF	1O1..00	Heart failure confirmed
CHF	8B29.00	Cardiac failure therapy
CHF	8CL3.00	Heart failure care plan discussed with patient
CHF	8H2S.00	Admit heart failure emergency
CHF	G554000	Congestive cardiomyopathy
CVA	G6...00	Cerebrovascular disease
CVA	G60..00	Subarachnoid haemorrhage

Condition	Read Code	Description
CVA	G61..00	Intracerebral haemorrhage
CVA	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
CVA	G61..12	Stroke due to intracerebral haemorrhage
CVA	G610.00	Cortical haemorrhage
CVA	G611.00	Internal capsule haemorrhage
CVA	G612.00	Basal nucleus haemorrhage
CVA	G613.00	Cerebellar haemorrhage
CVA	G614.00	Pontine haemorrhage
CVA	G615.00	Bulbar haemorrhage
CVA	G616.00	External capsule haemorrhage
CVA	G617.00	Intracerebral haemorrhage, intraventricular
CVA	G618.00	Intracerebral haemorrhage, multiple localized
CVA	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
CVA	G61X000	Left sided intracerebral haemorrhage, unspecified
CVA	G61X100	Right sided intracerebral haemorrhage, unspecified
CVA	G61z.00	Intracerebral haemorrhage NOS
CVA	G63..00	Precerebral arterial occlusion
CVA	G63..11	Infarction - precerebral
CVA	G630.00	Basilar artery occlusion
CVA	G631.00	Carotid artery occlusion
CVA	G631.12	Thrombosis, carotid artery
CVA	G632.00	Vertebral artery occlusion
CVA	G63y.00	Other precerebral artery occlusion
CVA	G63y000	Cerebral infarct due to thrombosis of precerebral arteries
CVA	G63y100	Cerebral infarction due to embolism of precerebral arteries
CVA	G64..00	Cerebral arterial occlusion
CVA	G64..11	CVA - cerebral artery occlusion
CVA	G64..12	Infarction - cerebral
CVA	G64..13	Stroke due to cerebral arterial occlusion
CVA	G640.00	Cerebral thrombosis
CVA	G640000	Cerebral infarction due to thrombosis of cerebral arteries
CVA	G64z.00	Cerebral infarction NOS
CVA	G64z.11	Brainstem infarction NOS
CVA	G64z.12	Cerebellar infarction
CVA	G64z000	Brainstem infarction
CVA	G64z100	Wallenberg syndrome
CVA	G64z111	Lateral medullary syndrome
CVA	G64z200	Left sided cerebral infarction
CVA	G64z300	Right sided cerebral infarction
CVA	G64z400	Infarction of basal ganglia
CVA	G65..00	Transient cerebral ischaemia
CVA	G65..12	Transient ischaemic attack
CVA	G65zz00	Transient cerebral ischaemia NOS
CVA	G66..00	Stroke and cerebrovascular accident unspecified
CVA	G66..11	CVA unspecified
CVA	G66..12	Stroke unspecified
CVA	G66..13	CVA - Cerebrovascular accident unspecified
CVA	G660.00	Middle cerebral artery syndrome
CVA	G661.00	Anterior cerebral artery syndrome

Condition	Read Code	Description
CVA	G662.00	Posterior cerebral artery syndrome
CVA	G663.00	Brain stem stroke syndrome
CVA	G664.00	Cerebellar stroke syndrome
CVA	G665.00	Pure motor lacunar syndrome
CVA	G666.00	Pure sensory lacunar syndrome
CVA	G667.00	Left sided CVA
CVA	G668.00	Right sided CVA
CVA	G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
CVA	G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
CVA	G6z..00	Cerebrovascular disease NOS
CVA	F11x200	Cerebral degeneration due to cerebrovascular disease
CVA	G600.00	Ruptured berry aneurysm
CVA	G63..12	Stenosis of precerebral arteries
CVA	G633.00	Multiple and bilateral precerebral arterial occlusion
CVA	G63z.00	Precerebral artery occlusion NOS
CVA	G641000	Cerebral infarction due to embolism of cerebral arteries
CVA	G65y.00	Other transient cerebral ischaemia
CVA	G67..00	Other cerebrovascular disease
CVA	G671.00	Generalised ischaemic cerebrovascular disease NOS
CVA	G671z00	Generalised ischaemic cerebrovascular disease NOS
CVA	G677400	Occlusion??? of multiple and bilat cerebral arteries
CVA	G67y.00	Other cerebrovascular disease OS
CVA	G67z.00	Other cerebrovascular disease NOS
CVA	G68..00	Late effects of cerebrovascular disease
CVA	G6y..00	Other specified cerebrovascular disease
CVA	Gyu6.00	Cerebrovascular diseases
CVA	Gyu6500	Occlusion and stenosis of other precerebral arteries
CVA	Gyu6600	Occlusion and stenosis of other cerebral arteries
CVA	Gyu6700	Other specified cerebrovascular diseases
CVA	Gyu6D00	Sequelae/other unspecified cerebrovascular diseases
CVA	G68W.00	Sequelae/other unspecified cerebrovascular diseases
PVD	G631.11	Stenosis, carotid artery
PVD	G634.00	Carotid artery stenosis
PVD	G650.11	Insufficiency - basilar artery
PVD	G651000	Vertebro-basilar artery syndrome
PVD	G656.00	Vertebrobasilar insufficiency
PVD	G65z.00	Transient cerebral ischaemia NOS
PVD	G70z.00	Arteriosclerotic vascular disease NOS
PVD	G73..00	Other peripheral vascular disease
PVD	G73..11	Peripheral ischaemic vascular disease
PVD	G73..12	Ischaemia of legs
PVD	G73..13	Peripheral ischaemia
PVD	G732.00	Peripheral gangrene
PVD	G732000	Gangrene of toe
PVD	G732100	Gangrene of foot
PVD	G73yz00	Other specified peripheral vascular disease NOS
PVD	G73z.00	Peripheral vascular disease NOS
PVD	G73z000	Intermittent claudication
PVD	G73z011	Claudication
PVD	G73zz00	Peripheral vascular disease NOS

Condition	Read Code	Description
Diabetes	1434	H/O: diabetes mellitus
Diabetes	2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
Diabetes	2BBL.00	O/E - diabetic maculopathy present both eyes
Diabetes	2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy
Diabetes	2BBP.00	O/E - right eye background diabetic retinopathy
Diabetes	2BBQ.00	O/E - left eye background diabetic retinopathy
Diabetes	2BBR.00	O/E - right eye preproliferative diabetic retinopathy
Diabetes	2BBS.00	O/E - left eye preproliferative diabetic retinopathy
Diabetes	2BBV.00	O/E - left eye proliferative diabetic retinopathy
Diabetes	66A5.00	Diabetic on insulin
Diabetes	66AI.00	Diabetic - good control
Diabetes	66AJ.00	Diabetic - poor control
Diabetes	66AJ.11	Unstable diabetes
Diabetes	66AJz00	Diabetic - poor control NOS
Diabetes	66AK.00	Diabetic - cooperative patient
Diabetes	66AS.00	Diabetic annual review
Diabetes	66AV.00	Diabetic on insulin and oral treatment
Diabetes	8A13.00	Diabetic stabilisation
Diabetes	8BL2.00	Patient on maximal tolerated therapy for diabetes
Diabetes	8H2J.00	Admit diabetic emergency
Diabetes	C10..00	Diabetes mellitus
Diabetes	C100.00	Diabetes mellitus with no mention of complication
Diabetes	C100000	Diabetes mellitus, juvenile type, no mention of complication
Diabetes	C100011	Insulin dependent diabetes mellitus
Diabetes	C100100	Diabetes mellitus, adult onset, no mention of complication
Diabetes	C100111	Maturity onset diabetes
Diabetes	C100112	Non-insulin dependent diabetes mellitus
Diabetes	C100z00	Diabetes mellitus NOS with no mention of complication
Diabetes	C101.00	Diabetes mellitus with ketoacidosis
Diabetes	C101100	Diabetes mellitus, adult onset, with ketoacidosis
Diabetes	C101z00	Diabetes mellitus NOS with ketoacidosis
Diabetes	C102.00	Diabetes mellitus with hyperosmolar coma
Diabetes	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
Diabetes	C102z00	Diabetes mellitus NOS with hyperosmolar coma
Diabetes	C103.00	Diabetes mellitus with ketoacidotic coma
Diabetes	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
Diabetes	C103z00	Diabetes mellitus NOS with ketoacidotic coma
Diabetes	C104.11	Diabetic nephropathy
Diabetes	C104000	Diabetes mellitus, juvenile type, with renal manifestation
Diabetes	C104y00	Other specified diabetes mellitus with renal complications
Diabetes	C104z00	Diabetes mellitis with nephropathy NOS
Diabetes	C105.00	Diabetes mellitus with ophthalmic manifestation
Diabetes	C105100	Diabetes mellitus, adult onset, ophthalmic manifestation
Diabetes	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
Diabetes	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
Diabetes	C106.00	Diabetes mellitus with neurological manifestation
Diabetes	C106.11	Diabetic amyotrophy
Diabetes	C106.12	Diabetes mellitus with neuropathy
Diabetes	C106100	Diabetes mellitus, adult onset, neurological manifestation

Condition	Read Code	Description
Diabetes	C106y00	Other specified diabetes mellitus with neurological comps
Diabetes	C106z00	Diabetes mellitus NOS with neurological manifestation
Diabetes	C107.00	Diabetes mellitus with peripheral circulatory disorder
Diabetes	C107.11	Diabetes mellitus with gangrene
Diabetes	C107.12	Diabetes with gangrene
Diabetes	C107000	Diabetes mellitus, juvenile ??? circulatory disorder
Diabetes	C107200	Diabetes mellitus, adult with gangrene
Diabetes	C107300	IDDM with peripheral circulatory disorder
Diabetes	C107400	NIDDM with peripheral circulatory disorder
Diabetes	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
Diabetes	C108.00	Insulin dependent diabetes mellitus
Diabetes	C108.11	IDDM-Insulin dependent diabetes mellitus
Diabetes	C108.12	Type 1 diabetes mellitus
Diabetes	C108.13	Type I diabetes mellitus
Diabetes	C108000	Insulin-dependent diabetes mellitus with renal complications
Diabetes	C108011	Type I diabetes mellitus with renal complications
Diabetes	C108012	Type 1 diabetes mellitus with renal complications
Diabetes	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
Diabetes	C108212	Type 1 diabetes mellitus with neurological complications
Diabetes	C108400	Unstable insulin dependent diabetes mellitus
Diabetes	C108500	Insulin dependent diabetes mellitus with ulcer
Diabetes	C108511	Type I diabetes mellitus with ulcer
Diabetes	C108700	Insulin dependent diabetes mellitus with retinopathy
Diabetes	C108711	Type I diabetes mellitus with retinopathy
Diabetes	C108712	Type 1 diabetes mellitus with retinopathy
Diabetes	C108800	Insulin dependent diabetes mellitus - poor control
Diabetes	C108811	Type I diabetes mellitus - poor control
Diabetes	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
Diabetes	C108B11	Type I diabetes mellitus with mononeuropathy
Diabetes	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
Diabetes	C108D00	Insulin dependent diabetes mellitus with nephropathy
Diabetes	C108D11	Type I diabetes mellitus with nephropathy
Diabetes	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
Diabetes	C108E11	Type I diabetes mellitus with hypoglycaemic coma
Diabetes	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
Diabetes	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
Diabetes	C108F11	Type I diabetes mellitus with diabetic cataract
Diabetes	C108G00	Insulin dependent diab mell with peripheral angiopathy
Diabetes	C108H00	Insulin dependent diabetes mellitus with arthropathy
Diabetes	C109.00	Non-insulin-dependent diabetes mellitus
Diabetes	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
Diabetes	C109.12	Type 2 diabetes mellitus
Diabetes	C109.13	Type II diabetes mellitus
Diabetes	C109000	Non-insulin-dependent diabetes mellitus with renal comps
Diabetes	C109011	Type II diabetes mellitus with renal complications
Diabetes	C109012	Type 2 diabetes mellitus with renal complications
Diabetes	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
Diabetes	C109212	Type 2 diabetes mellitus with neurological complications
Diabetes	C109400	Non-insulin dependent diabetes mellitus with ulcer
Diabetes	C109411	Type II diabetes mellitus with ulcer

Condition	Read Code	Description
Diabetes	C109500	Non-insulin dependent diabetes mellitus with gangrene
Diabetes	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
Diabetes	C109611	Type II diabetes mellitus with retinopathy
Diabetes	C109612	Type 2 diabetes mellitus with retinopathy
Diabetes	C109700	Non-insulin dependant diabetes mellitus - poor control
Diabetes	C109711	Type II diabetes mellitus - poor control
Diabetes	C109712	Type 2 diabetes mellitus - poor control
Diabetes	C109900	Non-insulin-dependent diabetes mellitus without complication
Diabetes	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
Diabetes	C109B11	Type II diabetes mellitus with polyneuropathy
Diabetes	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
Diabetes	C109C11	Type II diabetes mellitus with nephropathy
Diabetes	C109C12	Type 2 diabetes mellitus with nephropathy
Diabetes	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
Diabetes	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
Diabetes	C109E11	Type II diabetes mellitus with diabetic cataract
Diabetes	C109E12	Type 2 diabetes mellitus with diabetic cataract
Diabetes	C109F11	Type II diabetes mellitus with peripheral angiopathy
Diabetes	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
Diabetes	C109H00	Non-insulin dependent d m with neuropathic arthropathy
Diabetes	C109H11	Type II diabetes mellitus with neuropathic arthropathy
Diabetes	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
Diabetes	C109J00	Insulin treated Type 2 diabetes mellitus
Diabetes	C109J11	Insulin treated non-insulin dependent diabetes mellitus
Diabetes	C109J12	Insulin treated Type II diabetes mellitus
Diabetes	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
Diabetes	C10A.00	Malnutrition-related diabetes mellitus
Diabetes	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
Diabetes	C10B000	Steroid induced diabetes mellitus without complication
Diabetes	C10D.00	Diabetes mellitus autosomal dominant type 2
Diabetes	C10E.00	Type 1 diabetes mellitus
Diabetes	C10E.11	Type I diabetes mellitus
Diabetes	C10E.12	Insulin dependent diabetes mellitus
Diabetes	C10E000	Type 1 diabetes mellitus with renal complications
Diabetes	C10E100	Type 1 diabetes mellitus with ophthalmic complications
Diabetes	C10E200	Type 1 diabetes mellitus with neurological complications
Diabetes	C10E400	Unstable type 1 diabetes mellitus
Diabetes	C10E412	Unstable insulin dependent diabetes mellitus
Diabetes	C10E500	Type 1 diabetes mellitus with ulcer
Diabetes	C10E600	Type 1 diabetes mellitus with gangrene
Diabetes	C10E800	Type 1 diabetes mellitus - poor control
Diabetes	C10E900	Type 1 diabetes mellitus maturity onset
Diabetes	C10EA00	Type 1 diabetes mellitus without complication
Diabetes	C10ED00	Type 1 diabetes mellitus with nephropathy
Diabetes	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
Diabetes	C10EF00	Type 1 diabetes mellitus with diabetic cataract
Diabetes	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
Diabetes	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
Diabetes	C10EM00	Type 1 diabetes mellitus with ketoacidosis
Diabetes	C10EM11	Type I diabetes mellitus with ketoacidosis

Condition	Read Code	Description
Diabetes	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
Diabetes	C10EQ00	Type 1 diabetes mellitus with gastroparesis
Diabetes	C10F.00	Type 2 diabetes mellitus
Diabetes	C10F.11	Type II diabetes mellitus
Diabetes	C10F000	Type 2 diabetes mellitus with renal complications
Diabetes	C10F011	Type II diabetes mellitus with renal complications
Diabetes	C10F100	Type 2 diabetes mellitus with ophthalmic complications
Diabetes	C10F200	Type 2 diabetes mellitus with neurological complications
Diabetes	C10F400	Type 2 diabetes mellitus with ulcer
Diabetes	C10F500	Type 2 diabetes mellitus with gangrene
Diabetes	C10F600	Type 2 diabetes mellitus with retinopathy
Diabetes	C10F611	Type II diabetes mellitus with retinopathy
Diabetes	C10F700	Type 2 diabetes mellitus - poor control
Diabetes	C10F711	Type II diabetes mellitus - poor control
Diabetes	C10F900	Type 2 diabetes mellitus without complication
Diabetes	C10FA00	Type 2 diabetes mellitus with mononeuropathy
Diabetes	C10FB00	Type 2 diabetes mellitus with polyneuropathy
Diabetes	C10FC00	Type 2 diabetes mellitus with nephropathy
Diabetes	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
Diabetes	C10FE00	Type 2 diabetes mellitus with diabetic cataract
Diabetes	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
Diabetes	C10FG00	Type 2 diabetes mellitus with arthropathy
Diabetes	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
Diabetes	C10FJ00	Insulin treated Type 2 diabetes mellitus
Diabetes	C10FJ11	Insulin treated Type II diabetes mellitus
Diabetes	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
Diabetes	C10FL11	Type II diabetes mellitus with persistent proteinuria
Diabetes	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
Diabetes	C10FN00	Type 2 diabetes mellitus with ketoacidosis
Diabetes	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
Diabetes	C10FR00	Type 2 diabetes mellitus with gastroparesis
Diabetes	C10G.00	Secondary pancreatic diabetes mellitus
Diabetes	C10H.00	Diabetes mellitus induced by non-steroid drugs
Diabetes	C10M.00	Lipoatrophic diabetes mellitus
Diabetes	C10N.00	Secondary diabetes mellitus
Diabetes	C10y.00	Diabetes mellitus with other specified manifestation
Diabetes	C10y100	Diabetes mellitus, adult, other specified manifestation
Diabetes	C10yy00	Other specified diabetes mellitus with other spec comps
Diabetes	C10z.00	Diabetes mellitus with unspecified complication
Diabetes	C10z100	Diabetes mellitus, adult onset, unspecified complication
Diabetes	C10zz00	Diabetes mellitus NOS with unspecified complication
Diabetes	Cyu2.00	[X]Diabetes mellitus
Diabetes	F372.11	Diabetic polyneuropathy
Diabetes	F372.12	Diabetic neuropathy
Diabetes	F374z00	Polyneuropathy in disease NOS
Diabetes	F381300	Myasthenic syndrome due to diabetic amyotrophy
Diabetes	F381311	Diabetic amyotrophy
Diabetes	F3y0.00	Diabetic mononeuropathy
Diabetes	F420.00	Diabetic retinopathy
Diabetes	F420100	Proliferative diabetic retinopathy

Condition	Read Code	Description
Diabetes	F420200	Preproliferative diabetic retinopathy
Diabetes	F420300	Advanced diabetic maculopathy
Diabetes	F420400	Diabetic maculopathy
Diabetes	F420600	Non proliferative diabetic retinopathy
Diabetes	F420700	High risk proliferative diabetic retinopathy
Diabetes	F420800	High risk non proliferative diabetic retinopathy
Diabetes	F420z00	Diabetic retinopathy NOS
Diabetes	F464000	Diabetic cataract
Diabetes	G73y000	Diabetic peripheral angiopathy
Diabetes	L180500	Pre-existing diabetes mellitus, insulin-dependent
Diabetes	L180600	Pre-existing diabetes mellitus, non-insulin-dependent
Diabetes	L180X00	Pre-existing diabetes mellitus, unspecified
Chronic kidney disease	14V2.00	H/O: renal dialysis
Chronic kidney disease	14V2.11	H/O: kidney dialysis
Chronic kidney disease	1Z12.00	Chronic kidney disease stage 3
Chronic kidney disease	1Z13.00	Chronic kidney disease stage 4
Chronic kidney disease	1Z14.00	Chronic kidney disease stage 5
Chronic kidney disease	1Z15.00	Chronic kidney disease stage 3A
Chronic kidney disease	1Z16.00	Chronic kidney disease stage 3B
Chronic kidney disease	1Z1B.00	Chronic kidney disease stage 3 with proteinuria
Chronic kidney disease	1Z1C.00	Chronic kidney disease stage 3 without proteinuria
Chronic kidney disease	1Z1D.00	Chronic kidney disease stage 3A with proteinuria
Chronic kidney disease	1Z1E.00	Chronic kidney disease stage 3A without proteinuria
Chronic kidney disease	1Z1F.00	Chronic kidney disease stage 3B with proteinuria
Chronic kidney disease	1Z1G.00	Chronic kidney disease stage 3B without proteinuria
Chronic kidney disease	1Z1H.00	Chronic kidney disease stage 4 with proteinuria
Chronic kidney disease	1Z1J.00	Chronic kidney disease stage 4 without proteinuria
Chronic kidney disease	1Z1K.00	Chronic kidney disease stage 5 with proteinuria
Chronic kidney disease	1Z1L.00	Chronic kidney disease stage 5 without proteinuria
Chronic kidney disease	7A60600	Creation of graft fistula for dialysis
Chronic kidney disease	7A61900	Ligation of arteriovenous dialysis fistula
Chronic kidney disease	7L1A.11	Dialysis for renal failure
Chronic kidney disease	7L1A000	Renal dialysis
Chronic kidney disease	7L1A100	Peritoneal dialysis
Chronic kidney disease	7L1A200	Haemodialysis NEC
Chronic kidney disease	7L1A400	Automated peritoneal dialysis
Chronic kidney disease	7L1A500	Continuous ambulatory peritoneal dialysis
Chronic kidney disease	7L1A600	Peritoneal dialysis NEC
Chronic kidney disease	7L1B.11	Placement ambulatory dialysis apparatus - compens renal fail
Chronic kidney disease	7L1B000	Insertion of ambulatory peritoneal dialysis catheter
Chronic kidney disease	7L1B100	Removal of ambulatory peritoneal dialysis catheter
Chronic kidney disease	7L1C000	Insertion of temporary peritoneal dialysis catheter
Chronic kidney disease	8882	Intestinal dialysis
Chronic kidney disease	K05..12	End stage renal failure
Chronic kidney disease	K050.00	End stage renal failure
Chronic kidney disease	K0D..00	End-stage renal disease
Chronic kidney disease	SP01500	Mechanical complication of dialysis catheter
Chronic kidney disease	SP05613	[X] Peritoneal dialysis associated peritonitis
Chronic kidney disease	SP07G00	Stenosis of arteriovenous dialysis fistula

Condition	Read Code	Description
Chronic kidney disease	TB11.00	Kidney dialysis with complication, without blame
Chronic kidney disease	Z919100	Priming haemodialysis lines
Chronic kidney disease	Z919300	Reversing haemodialysis lines
Chronic kidney disease	Z91A.00	Peritoneal dialysis bag procedure
Chronic kidney disease	ZV45100	[V]Renal dialysis status
Chronic kidney disease	ZV56.00	[V]Aftercare involving intermittent dialysis
Chronic kidney disease	ZV56011	[V]Aftercare involving renal dialysis NOS
Chronic kidney disease	ZV56100	[V]Preparatory care for dialysis
Chronic kidney disease	ZV56y11	[V]Aftercare involving peritoneal dialysis
Chronic kidney disease	ZVu3G00	[X]Other dialysis

Table S4:

Antihypertensive treatment strategy and overall mortality risk.

Characteristic	n (%) or mean (SD)	Hazard Ratio	p-value	95% CI
Minimum systolic intensification threshold, mmHg				
130-139	10853 (13.4)	0.987	*0.80*	0.895-1.089
140-149	18646 (23.0)	1.000	--	--
150-159	19724 (24.3)	1.052	*0.22*	0.970-1.140
160-169	16177 (19.9)	1.256	<0.0001	1.153-1.368
170-179	8253 (10.2)	1.424	<0.0001	1.283-1.581
180+	7525 (9.3)	1.690	<0.0001	1.526-1.872
Mean time to intensification, quintiles, months				
0-1.406	16233 (20.0)	1.000	--	--
1.407-4.646	16238 (20.0)	1.112	0.0088	1.027-1.203
4.647-8.684	16236 (20.0)	1.235	<0.0001	1.139-1.339
8.685-15.350	16238 (20.0)	1.196	<0.0001	1.099-1.302
15.351+	16233 (20.0)	1.297	<0.0001	1.190-1.415
Mean time to follow-up after intensification, quintiles, months				
0-0.723	16652 (20.5)	1.023	*0.55*	0.948-1.104
0.724-1.018	14747 (18.2)	1.000	--	--
1.019-1.544	17110 (21.1)	1.005	*0.90*	0.931-1.085
1.545-2.694	16577 (20.4)	1.053	*0.18*	0.976-1.137
2.695+	16092 (19.8)	1.210	<0.0001	1.125-1.301
Mean SBP elevation over intensification thresold, mmHg (%)*				
1-9	43576 (53.7)	1.000	--	--
10-19	28627 (35.3)	1.119	0.0008	1.048-1.195
20-29	7521 (9.3)	1.311	<0.0001	1.192-1.443
30-39	1301 (1.6)	1.576	<0.0001	1.339-1.854
40-49	153 (0.2)	1.975	0.0006	1.336-2.920
Medication possession ratio	0.861 (0.192)	0.919	*0.14*	0.822-1.028

Table S5:

Intensification Thresholds and Composite Outcome Risk under Liberalized Inclusion Criteria.

	Minimum systolic intensification threshold, mmHg					
	130-139	**140-149**	**150-159**	**160-169**	**170-179**	**180+**
Number of patients (%)	42343 (12.9)	71820 (21.8)	79630 (24.2)	66204 (20.1)	36926 (11.2)	32568 (9.9)
Hazard ratio	0.923	1.000	1.073	1.202	1.327	1.678
p-value	<0.0001	--	<0.0001	<0.0001	<0.0001	<0.0001
95% CI	0.888-0.959	--	1.041-1.106	1.166-1.240	1.283-1.373	1.624-1.734