What is the optimal blood pressure level for patients with atrial fibrillation treated with direct oral anticoagulants?

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Adjusted for sex, age, stroke/ischemic heart disease, dementia, liver disease, and current alcohol use. Events include first stroke, recurrent stroke, myocardial infarction, symptomatic intracranial bleed, and significant gastrointestinal bleed.

Figure 3. Adjusted Cox proportional hazard ratios (restricted cubic splines) of an event, all-cause mortality, and cardiovascular mortality in CPRD patients on DOACs (reference 160mmHg, 140mmHg and 120mmHg).
Adjusted for sex, age, stroke/ischemic heart disease, dementia, liver disease, and current alcohol use. Events include first stroke, recurrent stroke, myocardial infarction, symptomatic intracranial bleed, and significant gastrointestinal bleed.

Table 1: Cohort characteristics by post-DOACs initiation systolic blood pressure groups in CPRD patients on DOACs.

Table 2: Incidence rate for an event, and all-cause and cardiovascular mortality by post-DOACs initiation systolic blood pressure groups in CPRD patients on DOACs.

Key words: Anticoagulation, Blood Pressure, Stroke, Secondary Prevention, Atrial Fibrillation

Abstract

Objective: Limited data exist to inform blood pressure (BP) thresholds for patients with atrial fibrillation (AF) prescribed direct oral anticoagulants (DOAC) therapy in the real world setting.

Methods: Systolic blood pressure was measured in 9,051 primary care patients in England on DOACs for AF with post-initiation BP levels available within the Clinical Practice Research Datalink (CPRD). The incidence rate for the primary outcome of the first recorded event (defined as a diagnosis of first stroke, recurrent stroke, myocardial infarction, symptomatic intracranial bleed or significant gastrointestinal bleed) and of secondary outcomes all-cause mortality and cardiovascular mortality were calculated by post-initiation BP groups.

Results: The Cox proportional hazard ratio (HR) of an event (crude and adjusted HR 1.04 [95% CI 1.00-1.08], p=0.077 and 0.071, respectively) did not differ significantly with a 10mmHg increase in systolic BP. The hazard of all-cause mortality (crude HR 0.83 [95% CI 0.80-0.86], p=0.000; adjusted HR 0.84 [95% CI 0.81-0.87], p=0.000) and cardiovascular mortality (crude HR 0.92 [95% CI 0.85-0.99], p=0.021; adjusted HR 0.93 [95% CI 0.86-1.00], p=0.041) demonstrated a significant inverse relationship with a 10mmHg increase in systolic BP. Patients with a systolic BP within 161-210mmHg had the lowest all-cause death rate, while patients with systolic BP within 121-140mmHg had the lowest cardiovascular death rate.

Conclusion**:** Systolic BP values below 161mmHg are associated higher all-cause mortality, but lower event risk in patients with AF on DOAC therapy. This demonstrates a need for a prospective interventional study of BP control after initiation of anticoagulation.

INTRODUCTION

Increasing systemic blood pressure (BP) levels are associated with a linear increase in cardiovascular complications such as heart failure, atrial fibrillation (AF), myocardial infarction, stroke and death [1]. Furthermore, AF is considered the most prevalent co-morbidity in people with hypertension [2]. In recent years several randomized controlled trials (RCTs) have provided data on the non-inferiority of direct oral anticoagulant therapy (DOACs) compared to an established anticoagulation strategy with warfarin for prevention of stroke or systemic embolism, often with preferential side effect profiles to match [3-6]. These include a consistently lower intracranial hemorrhage rate, and a comparable gastrointestinal hemorrhage rate for some DOACs in comparison with standard dose-adjusted Warfarin. However, BP threshold values pertaining to an increased risk of symptomatic intracranial hemorrhage are not available from the DOACs studies. Furthermore, data comparing systolic BP at baseline between clinical trial populations (e.g. Apixaban and Warfarin) demonstrated SBP values of 130mmHg (25^{th} percentile of 120mmHg and 75^{th} percentile of 140mmHg) in both groups and no overall effect on bleeding risk, arguably as might be expected at these levels in a trial population [7]. Therefore, only very limited data exist to inform BP thresholds for widely used bleeding risk scores in people being prescribed DOACs in the real world setting.

Nonetheless, international guidelines on secondary prevention post-stroke advocate assessment of patients using bleeding risk scores when considering anticoagulation for atrial fibrillation [8]. Hypertension is included as a modifiable risk factor across the three widely accepted bleeding risk scores [9-11]. Importantly a threshold of 160mmHg systolic BP is provided as a guide for uncontrolled hypertension within these scoring matrices but optimal levels on treatment are not given and trial data that might inform are unavailable [9-11].

In addition, the National Institute for Health and Care Excellence (NICE) in the United Kingdom, advises assessment of stroke risk using the CHA_2DS_2-VASc score; anticoagulation

being offered to those with a CHA_2DS_2-VASc ≥2 or above with consideration for bleeding risk [12]. Overall, there is a paucity of evidence as to ideal BP levels when patients are on anticoagulant therapy and if higher levels within the normal range are associated with reduced hemorrhage risk. Therefore, we sought to investigate the incidence rate for the combined primary outcome of a diagnosis of first stroke, recurrent stroke, myocardial infarction, symptomatic intracranial bleed or significant gastrointestinal bleed by post-initiation BP for patients with AF commenced on DOACs therapy, using real world data.

MATERIALS AND METHODS

Study design and data source

This observational retrospective cohort study included a sample of primary care patients in England who were registered with practices contributing to the Clinical Practice Research Datalink (CPRD). The CPRD includes anonymised primary care electronic health records for over 11.3 million patients from 674 UK practices dating back to 1987 [13]. The CPRD includes data on approximately 6.9% of the UK population [13]. The data are broadly representative of the age, sex and ethnicity of the UK general population [13].

The study included all patients with a diagnosis of AF registered at practices contributing to the CPRD (Table I in the Supplementary Files). All patients were aged 18 years or older and initiated treatment with DOACs (Dabigatran, Apixaban, Rivaroxaban, Edoxaban) from 1 February, 2010 (earliest record) to 31 December, 2017. The index date was the first BP measurement following the first recorded prescription for a DOAC (Table II in the Supplementary Files). Patients were only included if linkage to Hospital Episode Statistics (HES) Admitted Patient Care database and Office of National Statistics (ONS) for mortality were available. Since linkage is only available for England, patients in Scotland and Ireland were automatically excluded from the sample. Follow-up began at the index date until the first event defined as a diagnosis of stroke, recurrent stroke, myocardial infarction, symptomatic

intracranial bleed, significant gastrointestinal bleed, death, or censoring (transferring out of practice, last collection of data from practice, or end of study on 31 December, 2017, whichever came first). Patients without at least one BP measurement within one year after DOAC initiation and whose first post-DOAC initiation BP was taken after experiencing an event were excluded. BP measurements that were not within a biologically plausible range (90-210mmHg) were excluded.

Exposure

Exposure was defined using "post-initiation" systolic BP; that is the systolic BP recorded in CPRD, closest to the date of DOACs initiation, and limited to a maximum of 365 days after DOACs initiation. Post-initiation BP was treated as a continuous variable for some analyses and divided into four clinically relevant groups (90-120, 121-140, 141-160, 161-210) for others.

Outcome

The primary outcome was the time until the first event after starting DOAC, defined as the first recorded diagnosis of stroke, recurrent stroke, myocardial infarction, symptomatic intracranial bleed, or significant gastrointestinal bleed occurring during the study period (Table III in the Supplementary Files). Diagnoses were obtained from either primary (CPRD) or secondary care (Hospital Episode Statistics (HES), first diagnosis position). All-cause mortality and cardiovascular-related mortality were investigated as secondary outcomes and were obtained from ONS. Cardiovascular mortality was a death with an underlying cause including ischemic heart disease (ICD-10 codes I20–I25), cardiac failure (I11, I13, I50), cerebrovascular disease (I60–I69), or peripheral artery disease (I70–I79).

Covariates

Demographic information, age and sex, and current alcohol use were obtained from CPRD. Current alcohol use was defined as one or more CPRD records indicating current alcohol use within 365 days before the index date. All other patients were considered non-current alcohol users. Pre-existing conditions including history of stroke or ischemic heart disease, dementia (as a surrogate for presence of small vessel disease), and liver disease were obtained from either primary (CPRD) or secondary care (HES, any diagnosis position) and were dated on or before the index date (Table IV in the Supplementary Files).

Statistical analyses

The incidence rate was calculated for the primary outcome and secondary outcomes by post-initiation BP. Cox regression modelling was used to investigate the association between post-initiation BP and the primary and secondary outcomes. Crude and adjusted hazard ratios (HR) were calculated for 10mmHg increases in systolic BP. HRs were adjusted for age, sex, current alcohol use, and comorbid stroke/ischemic heart disease, dementia, and liver disease. All analyses were performed in STATA 15 and SAS v9.4.

RESULTS

13,200 patients were initially extracted from the CPRD database, however following exclusions due to absence of post initiation BP measurement, index date after 31/12/17, date of death before index date and event before index date, 9,051 patients were included in the study (Figure 1). Post-DOACs initiation systolic BPs are also shown in Figure 1; these ranging from 90mmHg to 210mmHg. The cohort characteristics are well matched across all BP groups (Table 1). Within the study cohort, 832 events occurred and 1,013 all-cause deaths of which 249 were attributed to cardiovascular causes during 14,147 person-years of follow-up (mean 1.6 years (SD 1.2), maximum 6.9 years). The most common event was GI bleeding (n=285, 34.3% of events), while the least common was intracerebral hemorrhage (n= 75, 9.0% of

events). The distribution of post-initiation systolic BP in CPRD patients on DOACs is shown in Figure I in the Supplementary Files. The 90% of BPs fell between 110-152mmHg. The distribution of days between DOACs initiation and post-DOACs initiation systolic BP measurements demonstrated highest densities during the first 50 days. The mean number of days between initiation and BP measurement was 89.6 (SD 85.7) for patients with BP 90-120mmHg, 95.9 (SD 87.4) for patients with BP 121-140mmHg, 93.4 (SD 87.4) for patients with BP 141-160mmHg, and 87.4 (SD 85.7) for patients with BP 161-210mmHg (Figure II in the Supplementary Files). Figure III in the Supplementary Files demonstrates the highest density of initiation occurred between 2016-2017 for Apixaban, Edoxaban, and Rivaroxaban. On the other hand, the highest density of Dabigatran initiation was between 2013-2014.

The incidence rate for an event, all-cause, and cardiovascular mortality by post-DOAC initiation is shown in Table 2. Patients with BP 161-210mmHg had the highest event rate, 78.8 (95% CI 61.3-101.3) per 1,000 person-years. Patients with BP 121-140 mmHg had the lowest event rate, 55.0 (49.7-60.9) per 1,000 person-years. Patients with BP 90-120 had the highest all-cause and cardiovascular mortality rates, 105.3 (95% CI 95.7-115.8) and 23.7 (95% CI 19.4-29.0) per 1,000 person-years, respectively. On the other hand, patients with BP 161-210mmHg had the lowest all-cause mortality rate and patients with BP 121-140 had the lowest cardiovascular mortality rate, 50.4 (95% CI 36.8-69.0) and 14.3 (95% CI 11.8-17.5) per 1,000 person-years, respectively.

First, we confirmed that the relationship between systolic BP and log relative risk of an event was linear so splines were not required. The Cox proportional HR of all-cause mortality (crude HR 0.83 [95% CI 0.80-0.86], p=0.000; adjusted HR 0.84 [95% CI 0.81-0.87], p=0.000) and cardiovascular mortality (crude HR 0.92 [95% CI 0.85-0.99], p=0.021; adjusted HR 0.93 [95% CI 0.86-1.00], p=0.041) demonstrated a significant inverse relationship with each 10mmHg

increase in systolic BP. On the other hand, the hazard of an event (crude HR 1.04 [95% CI 1.00-1.08], p=0.077; adjusted HR 1.04 [95% CI 1.00-1.08], p=0.071) was not significantly associated with 10mmHg increases in systolic BP. We also examined the hazard of a significant bleeding event (intracranial hemorrhage and GI bleeding), which did not differ significantly with each 10mmHg increase in systolic BP (crude and adjusted HR 1.01 [95% CI 0.95-1.07], p=0.769 and 0.745, respectively).

Events

Adjusted event data with the 140mmHg and 120mmHg reference levels demonstrated a trend towards lower BP levels (<90mmHg) being associated with lower event rates as compared to systolic BP levels >200mmHg (Figure 2). The 140mmHg level pertains to a threshold perceived to describe a clinically important reduction in BP as part of a secondary prevention strategy [14]. The 160mmHg reference level demonstrates a similar relationship with systolic BP values with 150mmHg demonstrating increased risk of an event and 170mmHg demonstrating a trend towards lower risk (Figure 2). The nadir at 120mmHg is noted across all BP reference values and associates with a lower event rate (Figure 3).

All-cause mortality

All-cause mortality with the 140mmHg and 120mmHg reference levels demonstrated a significant linear trend towards higher mortality with lower systolic BP (<120mmHg) and lower mortality with higher systolic BP (>140mmHg) (Figure 2). This linear relationship was also demonstrated with the 160mmHg reference level (Figure 2). The nadir is 160mmHg and associates with lower all-cause mortality (Figure 3).

Cardiovascular mortality

Cardiovascular mortality with the 140mmHg and 120mmHg reference levels demonstrated a significant linear trend towards higher cardiovascular mortality with lower systolic BP

(<120mmHg) and lower cardiovascular mortality with higher systolic BP (>120mmHg) (Figure 2). The nadir is at 130mmHg and associates with a trend towards lower cardiovascular mortality (Figure 3).

Bleeding events

Bleeding related events demonstrated little variation based on systolic BP change from the 140mmHg and 160mmHg reference ranges (Figure IV in the Supplementary Files).

Prior ischemic heart disease or stroke

Higher systolic BP >160mmHg conferred an all-cause and cardiovascular mortality benefit in those with and without prior IHD/stroke disease (Figure V in the Supplementary Files). In addition, in those without a history of IHD/stroke there was a significant benefit up to the reference point of 140mmHg. This negative linear relationship for systolic BP and all-cause and cardiovascular mortality was comparable in those without a history of IHD/stroke. However, in those with a history of IHD/stroke, there was a much flatter relationship albeit with a paradoxical demonstration of the lowest systolic BP levels of 60mmHg conferring a lower event risk though also conferring a higher all-cause and cardiovascular mortality.

DISCUSSION

Main findings

This is the first study to our knowledge to provide data on the relationship between systolic BP post-DOAC initiation in patients with AF and clinical outcomes. The main finding of this study is that BP values below 161mmHg were associated with higher all-cause mortality risk but lower event risk.

Low systolic BP (121-140) confers no benefit in minimising events compared to the highest BP group (within 161-210mmHg), but confers a significantly greater risk of death (all-cause crude and adjusted). Therefore, increasing hypotension (<100mmHg) could be considered a prognostic marker of adverse outcomes, possibly driven by cardiac failure as recent work in AF patients has shown [15], or overall poor cardiac performance mediated by cardiovascular morbidity. The mortality risk is not reflected in patients with systolic BP values between 120-200mmHg and cardiovascular mortality is not significantly affected by significant hypertension (180-200mmHg).

Hypotension as a marker of poor prognosis

A terminal decline of systolic BP in the final two years of life has been demonstrated in a large registry study [16]. The relative odds of systolic BP <120mmHg were higher in the last 3 months of life as compared to 5 years previously. With a mean age of 77.2 years across all systolic BP quintile groups, it is highly possible that some individuals within this study will be on this systolic BP trajectory [16]. Furthermore, previous data support hypotension in patients with cardiovascular disease, being at higher risk of further cardiovascular events [17]. In those with AF, post hoc analysis of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial demonstrated convergent findings to our study in AF patients on Warfarin (i.e. in the pre DOAC era). Similarly, the authors proposed a greater BP target than the general population as adverse events were seen if systolic BP was reduced to <110 mmHg [19]. In an oral anticoagulant-naïve population, BP of <120/80mmHg was associated with higher risk of a major cardiovascular event in patients with AF undergoing hypertension treatment [19]. However, recent conflicting findings from the ORBIT-AF registry demonstrated higher SBP was associated with increasing adverse events [20]. Our study findings are novel as they address BP targets after taking DOAC therapy and assess prognosis

in AF patients, providing convergent results to BP data in an anticoagulant naïve AF population.

140mmHg and 120mmHg threshold

In recent work by Douros and colleagues [21], using 140mmHg as a reference point, systolic BP of 125mmHg was associated with significantly increased risk of death, which was not the case with higher values of systolic BP (reversed J-shaped curve). This 'real-world' study highlighted those >80 years of age being particularly susceptible to increased mortality risk with BP values <140mmHg. To further support the 140mmHg threshold, analysis of pooled data from the Stroke Prevention using an Oral Thrombin Inhibitor in AF III and V trials demonstrated those with a mean systolic BP >140mmHg had an increased risk of stroke and systemic embolic events [21]. This study supports the findings of this prior work highlighting the paradoxical behaviour of event risk and mortality risk around a probable threshold systolic BP of 140mmHg [22]. The 'Bleeding with Antithrombotic Therapy (BAT) study demonstrated increasing BP levels positively associate with development of ICH and highlight the importance of adequate BP control [23]. This study provided an estimated cut off BP (using ROC curve analyses) to predict impending risk of ICH as ≥130/81mmHg [23]. The BAT study enrolled a majority of patients solely on antiplatelet therapy, however, 32.4% were receiving anticoagulants [23]. This was significantly more than the preceding PROGRESS study (Perindopril Protection Against Recurrent Stroke Study), which only included 10% of patients on anticoagulants yet still demonstrated a 50% ICH reduction after mean BP lowering of just 9/4mmHg [24]. The 120mmHg threshold provides a greater understanding of the nadir across events, all-cause and cardiovascular mortality. In particular, the lower event rate (120mmHg) and lower cardiovascular mortality (130mmHg) at the respective nadirs provides support for current guideline-recommended values.

160mmHg threshold and HAS-BLED

Despite the HAS-BLED score demonstrating better discrimination for all-cause mortality, as compared to HEMORR$_2$HAGES and ATRIA [25], there remain questions over ensuring systolic BP is below the 160mmHg threshold advocated during initiation of DOACs [9]. Prior work has shown the HAS-BLED score is not only useful in the assessment of bleeding risk, but also shows some predictive value for cardiovascular events and mortality in anticoagulated patients with AF [26]. However, the previously assumed close relationship between bleeding and mortality end-points in anti-coagulation studies is debatable considering the data presented within this study. Bleeding demonstrated a less pronounced relationship with systolic BP as compared to event and mortality risk.

Previous cohort study data have shown tachycardia, lower BMI, history of chronic renal disease and malignant disease were all strongly associated with early death after AF diagnosis (<4 months). Cardiovascular co-morbidities, as well as chronic illness, were important predictors for late death (>4 months) [27].

Patients with hypertension and AF are three to five times more likely to have a stroke or thromboembolic event compared with normotensive individuals with AF [28, 29]. Interestingly, our data support BP >200mmHg being preferable to BP <120mmHg in those without a stroke/IHD history as compared to those with a stroke/IHD history (Figure V in the Supplementary Files). The key findings of the analyses of those with and without a prior history of stroke/IHD are the lower event rate at the lowest BP values and higher all-cause mortality for those with prior stroke/IHD. This paradoxical behaviour is not in keeping with those without prior IHD/stroke or indeed the entire cohort studied. This is an interesting finding as hypertension is known to increase the risk of recurrent stroke, but extremes of hypotension in the context of presumed chronic stroke and IHD were not previously considered to be protective. The presence of heart failure in those with stroke/IHD could explain the potential benefit of lower BP values on event risk and cardiovascular mortality risk [15]. This

corresponds with prior AFFIRM trial data suggesting that using rhythm control for AF with SBP >160mmHg has no significant increase in all-cause mortality [18]. Although we do not have data to support higher usage of rhythm control medications in those AF patients without a prior history of stroke/IHD, this is a potential confounder to explain these findings. In only those with a history of stroke, the demonstration that systolic BP levels >180mmHg appear to confer a protective effect on mortality with no significant reduction in events demonstrates higher proportion of chronic stroke disease patients included. Additionally, although not significant, the more convincing positive linear trend relationship between events and higher systolic BP in those with stroke demonstrates once more the trade-off between events and mortality. However, once more the hypotension and mortality risk is convincing in those with and without a history of stroke, suggesting the AFFIRM trial data are also applicable to this patient population. The 2016 ESC guideline recommendation (Class IIa, Level B evidence) provides the only current guidance on BP management in AF [8]. Importantly, our study demonstrates the need for a prospective study of BP control after anticoagulation to both strengthen and refine current guideline recommendations.

Study limitations

There are several limitations to consider. The large number of exclusions may have biased the results. In addition, concerns exist over BP measurement in patients with AF due to limited evidence and significant heterogeneity in the studies that validated automated BP monitors in AF. Given the observational nature of the study, the methodology for BP measurement was not standardised, however BP measurement guidelines exist within the UK [30]. Additionally, meta-analyses have shown that these monitors appear to be accurate in measuring systolic, but not diastolic, BP. In the context of clinic measured BP, there is potential for a degree of measurement error, though this is unquantifiable and likely to exist for all individuals [31]. Furthermore, although BP measurement processes within CPRD have the potential to

incorporate “white coat effect” and variations in fidelity to international guidelines for BP measurement, they represent actual data from a ‘real world’ primary care setting reflecting current clinical practice. Association was also based on a BP measure taken at a single time-point and without acknowledgement for those on existing anti-hypertensive treatment, the effect specific BP agents can have or indeed the effect of different DOAC dosages. Therefore, the effect of changes in BP over time were not analysed. DOAC initiation was determined based on prescriptions recorded in CPRD. There is potential for misclassification as patients may not have filled, initiated, or adhered to the medication regimen. There may be additional measured or unmeasured factors that were not accounted for within the analysis that could confound the association between systolic blood pressure and the primary and secondary outcomes. Further, this study was observational in nature, therefore causality cannot be determined. However, there are significant strengths including the large cohort size, multi variables available within CPRD and robust analyses and adjustments.

In conclusion, this study demonstrated that systolic BP values below 161mmHg are associated with higher all-cause and cardiovascular mortality risk, but lower event risk in patients with AF on DOAC therapy. This demonstrates a need for a prospective interventional study of BP control after initiation of anticoagulation.

REFERENCES

1. Bohm M, Schumacher H, Teo KK, et al. Cardiovascular outcomes and achieved blood pressure in patients with and without diabetes at high cardiovascular risk. *Eur Heart J*. 2019. doi: ehz149 [pii].

2. Savoia C, Sada L, Volpe M. Blood pressure control versus atrial fibrillation management in stroke prevention. *Curr Hypertens Rep*. 2015;17(6):55-1.

3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.

4. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.

5. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.

6. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104.

7. Hylek EM, Held C, Alexander JH, et al. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes. *J Am Coll Cardiol*. 2014;63(20):2141-2147.

8. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Kardiol Pol*. 2016;74(12):1359-1469.

9. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093-1100.

10. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151(3):713-719.

11. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol*. 2011;58(4):395-401.

12. National Institute for Health and Care Excellence. Atrial fibrillation: management. Clinical Guideline [CG180]. 2014.

13. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836.

14. Mant J, McManus RJ, Roalfe A, et al. Different systolic blood pressure targets for people with history of stroke or transient ischaemic attack: PAST-BP (Prevention After Stroke--Blood Pressure) randomised controlled trial. *BMJ*. 2016;352:i708.

15. Pana TA, McLernon DJ, Mamas MA, et al. Individual and Combined Impact of Heart Failure and Atrial Fibrillation on Ischemic Stroke Outcomes. *Stroke*. 2019:STROKEAHA119025481.

16. Ravindrarajah R, Dregan A, Hazra NC, Hamada S, Jackson SHD, Gulliford MC. Declining blood pressure and intensification of blood pressure management among people over 80 years: cohort study using electronic health records. *J Hypertens*. 2017;35(6):1276-1282.

17. Owens P, O'Brien E. Hypotension in patients with coronary disease: can profound hypotensive events cause myocardial ischaemic events?. *Heart*. 1999;82(4):477-481.

18. Badheka AO, Patel NJ, Grover PM, et al. Optimal blood pressure in patients with atrial fibrillation (from the AFFIRM Trial). *Am J Cardiol*. 2014;114(5):727-736.

19. Kim D, Yang PS, Kim TH, et al. Ideal Blood Pressure in Patients With Atrial Fibrillation. *J Am Coll Cardiol*. 2018;72(11):1233-1245.

20. Vemulapalli S, Inohara T, Kim S, et al. Blood Pressure Control and Cardiovascular Outcomes in Patients With Atrial Fibrillation (From the ORBIT-AF Registry). *Am J Cardiol*. 2019;123(10):1628-1636.

21. Douros A, Tolle M, Ebert N, et al. Control of blood pressure and risk of mortality in a cohort of older adults: the Berlin Initiative Study. *Eur Heart J*. 2019. doi: ehz071 [pii].

22. Lip GY, Frison L, Grind M, SPORTIF Invetigators. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J*. 2007;28(6):752-759. doi: ehl504 [pii].

23. Toyoda K, Yasaka M, Uchiyama S, et al. Blood pressure levels and bleeding events during antithrombotic therapy: the Bleeding with Antithrombotic Therapy (BAT) Study. *Stroke*. 2010;41(7):1440-1444.

24. Chapman N, Huxley R, Anderson C, et al. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. *Stroke*. 2004;35(1):116-121.

25. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. *J Am Coll Cardiol*. 2012;60(9):861-867.

26. Gallego P, Roldan V, Torregrosa JM, et al. Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortality in anticoagulated patients with atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2012;5(2):312-318.

27. Miyasaka Y, Barnes ME, Gersh BJ, et al. Coronary ischemic events after first atrial fibrillation: risk and survival. *Am J Med*. 2007;120(4):357-363.

28. Lip GY. Atrial fibrillation in hypertension: under recognised or over diagnosed?. *J Hum Hypertens*. 1997;11(11):691-693.

29. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154(13):1449-1457.

30. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. Clinical Guideline [NG136]. 2019.

31. Stergiou GS, Kollias A, Destounis A, Tzamouranis D. Automated blood pressure measurement in atrial fibrillation: a systematic review and meta-analysis. *J Hypertens.* 2012;30(11):2074-2082.

Itemised list of tables and figures:

Figure 1. Participant flow diagram.

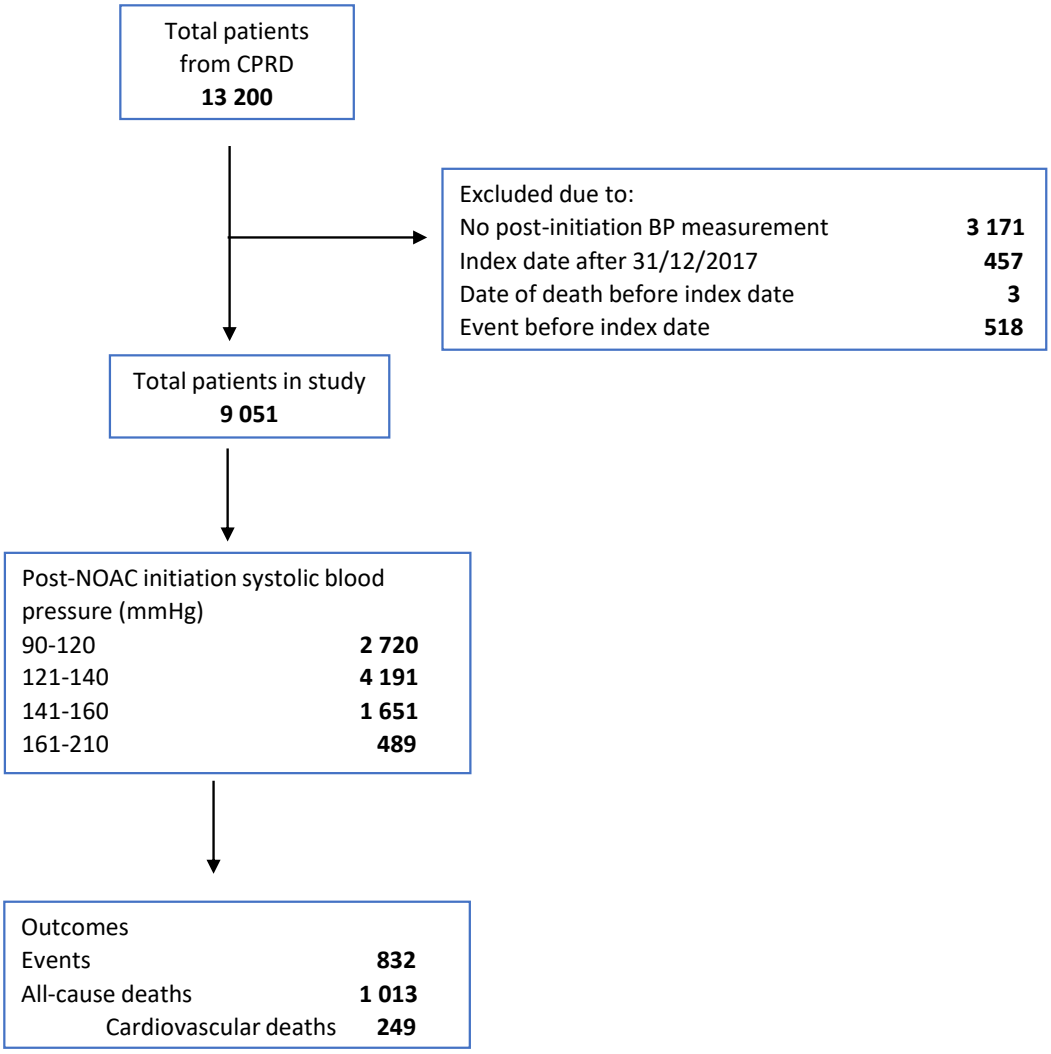

Figure 2. Adjusted Cox proportional hazard ratios of an event, all-cause mortality, and cardiovascular mortality in CPRD patients on DOACs (reference 160mmHg, 140mmHg and 120mmHg).

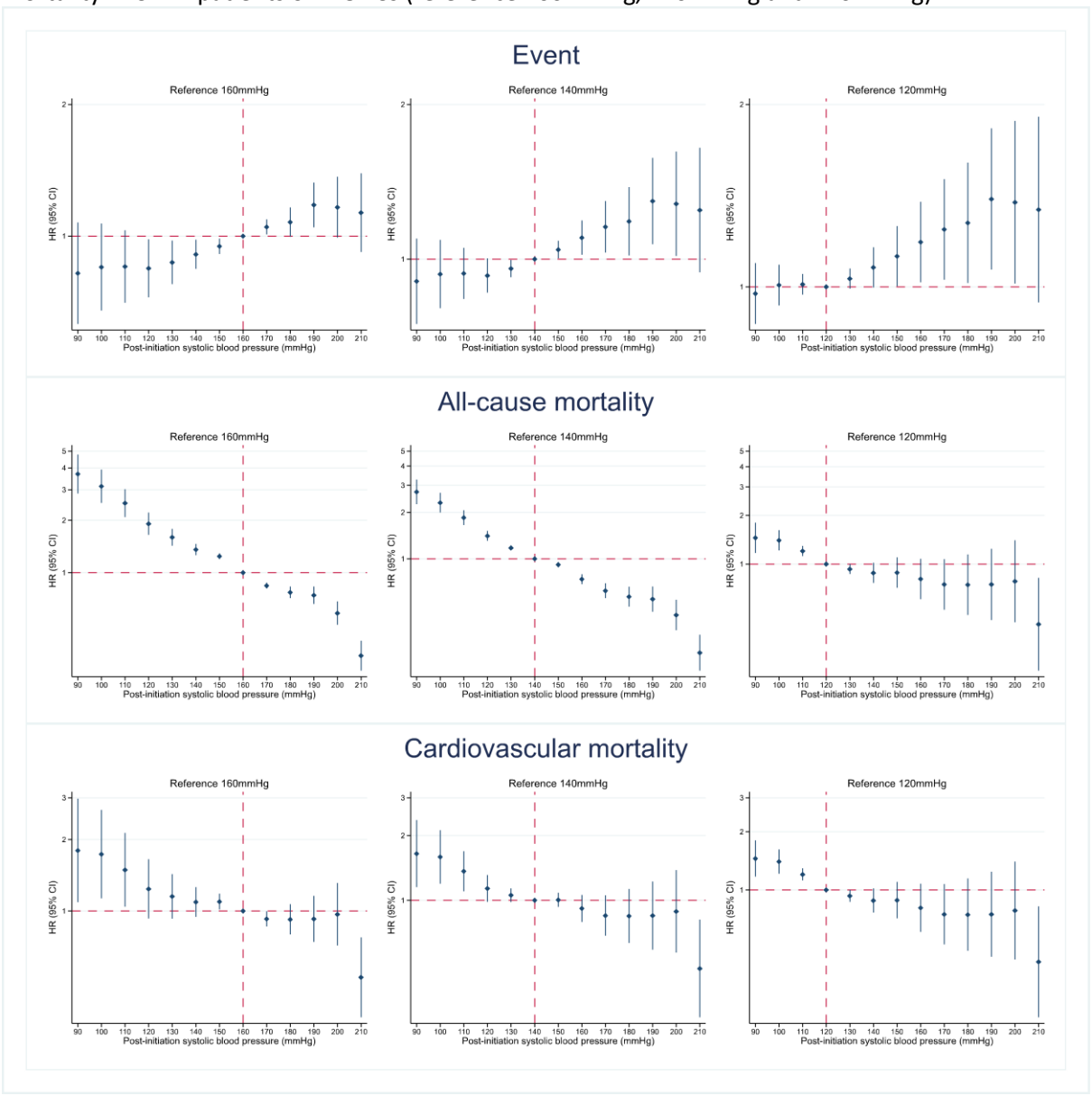

Figure 3. Adjusted Cox proportional hazard ratios (restricted cubic splines) of an event, all-cause mortality, and cardiovascular mortality in CPRD patients on DOACs (reference 160mmHg, 140mmHg and 120mmHg).
Adjusted for sex, age, stroke/ischemic heart disease, dementia, liver disease, and current alcohol use. Events include first stroke, recurrent stroke, myocardial infarction, symptomatic intracranial bleed, and significant gastrointestinal bleed.

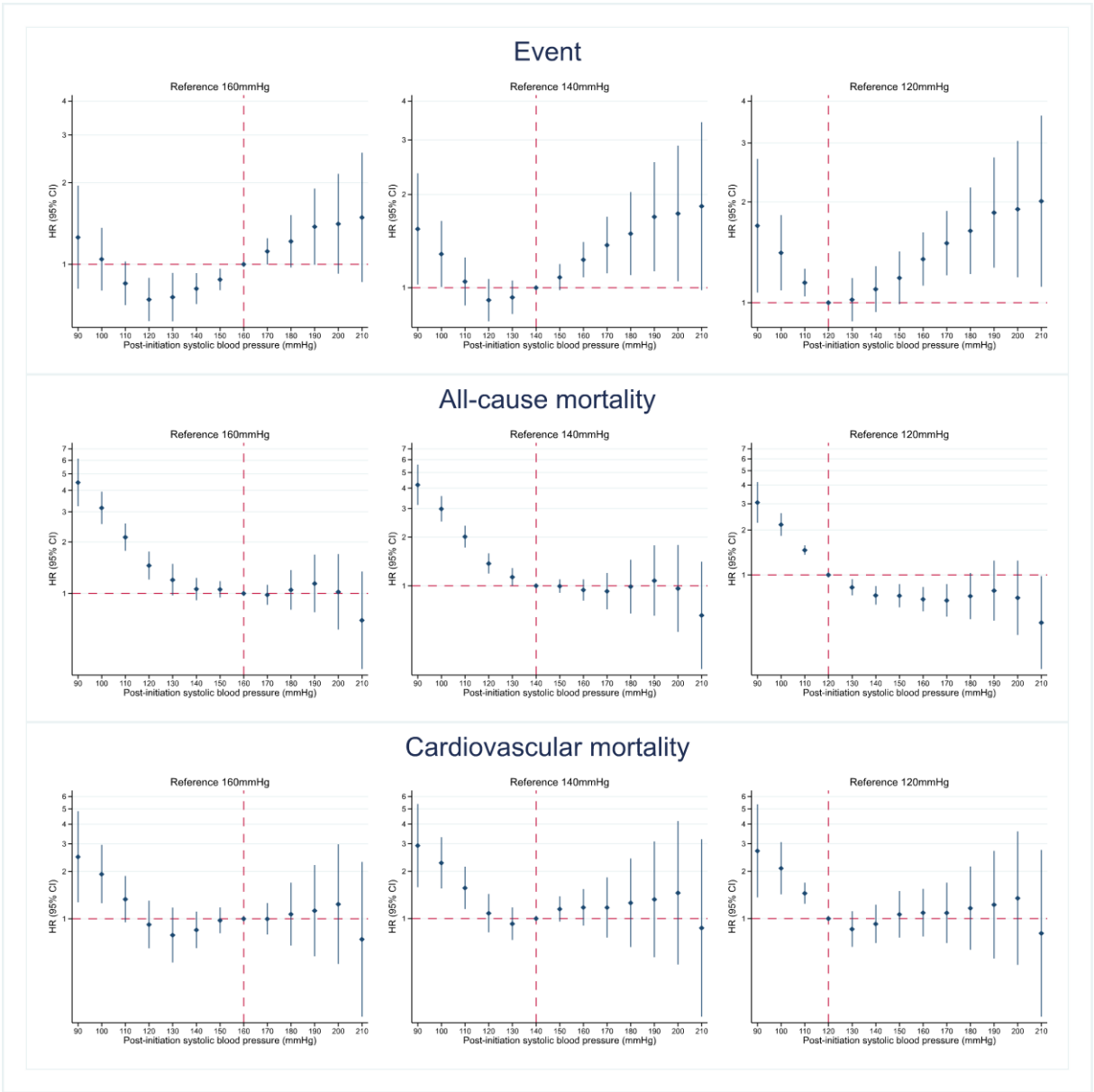

Table 1. Cohort characteristics by post-DOACs initiation systolic blood pressure groups in CPRD patients on DOACs.

	Post-initiation systolic blood pressure (mmHg)				
	90-120	**121-140**	**141-160**	**161-210**	**Total**
Total	N=2,720	N=4,191	N=1,651	N=489	N=9,051
Sex					
Male	1,540 (56.6%)	2,245 (53.6%)	858 (52.0%)	210 (42.9%)	4,853 (53.6%)
Female	1,180 (43.4%)	1,946 (46.4%)	793 (48.0%)	279 (57.1%)	4,198 (46.4%)
DOACs Initiated					
Apixaban	853 (31.4%)	1,278 (30.5%)	526 (31.9%)	165 (33.7%)	2,822 (31.2%)
Dabigatran	414 (15.2%)	709 (16.9%)	262 (15.9%)	87 (17.8%)	1,472 (16.3%)
Edoxaban	17 (0.6%)	29 (0.7%)	8 (0.5%)	0 (0.0%)	54 (0.6%)
Rivaroxaban	1,436 (52.8%)	2,175 (51.9%)	855 (51.8%)	237 (48.5%)	4,703 (52.0%)
Medical history					
Stroke/IHD	1,241 (45.6%)	1,775 (42.4%)	692 (41.9%)	216 (44.2%)	3,924 (43.4%)
Dementia	320 (11.8%)	327 (7.8%)	109 (6.6%)	32 (6.5%)	788 (8.7%)
Liver disease	74 (2.7%)	85 (2.0%)	33 (2.0%)	11 (2.2%)	203 (2.2%)
Current alcohol use*	590 (21.7%)	942 (22.5%)	348 (21.1%)	99 (20.2%)	1,979 (21.9%)
Age	77.2 (11.1)	76.9 (10.5)	77.5 (10.3)	78.6 (9.3)	77.2 (10.6)
AF duration (years)	4.3 (5.5)	4.5 (5.6)	4.4 (5.4)	4.7 (5.7)	4.4 (5.5)
Post-initiation BP time (days)	89.6 (85.7)	95.9 (87.4)	93.4 (87.4)	87.4 (85.7)	93.1 (86.8)

IHD=ischemic heart disease.
Age, AF duration, and post-initiation BP time are shown as mean (standard deviation).
AF duration (years)=years between first atrial fibrillation diagnosis and post-initiation BP measurement.
Post-initiation BP time (days)=days between DOACs initiation and post-initiation BP measurement.
Age range=27 to 104 years.

Table 2. Incidence rate for an event, and all-cause and cardiovascular mortality by post-DOAC initiation systolic blood pressure groups in CPRD patients on DOACs.

Blood pressure (mmHg)	Person-years	Event	Death				
			All-cause			Cardiovascular	
		n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)
90-120	4,007	227	56.6 (49.7-64.5)	422	105.3 (95.7-115.8)	95	23.7 (19.4-29.0)
121-140	6,763	372	55.0 (49.7-60.9)	409	60.5 (54.9-66.6)	97	14.3 (11.8-17.5)
141-160	2,604	172	66.1 (56.9-76.7)	143	54.9 (46.6-64.7)	44	16.9 (12.6-22.7)
161-210	774	61	78.8 (61.3-101.3)	39	50.4 (36.8-69.0)	13	16.8 (9.8-28.9)
Total	14,147	832	58.8 (54.9-62.9)	1,013	71.6 (67.3-76.2)	249	17.6 (15.5-19.9)

Rate=per 1,000 person-years