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Long-term event rates, risk factors, and treatment pattern in 1.4 million individuals qualifying for dual blood pressure lowering therapy

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Objectives: We assessed rates of cardiovascular events, all-cause death, baseline risk factors, and treatment patterns in a population qualifying for initiation of dual combination blood pressure (BP)-lowering therapy. We also evaluated the association between dual versus monotherapy during follow-up and incidence of cardiovascular events.

Methods: This study utilized integrated databases in England: Clinical Practice Research Datalink, Hospital Episode Statistics, and Office for National Statistics. Individuals aged at least 18 years qualifying for dual therapy were identified during 15-year period (2005–2019). The primary endpoint was composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, and cardiovascular death. The secondary endpoint was all-cause death.

Results: Total 1 426 079 individuals met selection criteria. The 15-year event rates for the primary and secondary endpoints were 27.1 and 32.6%, respectively. Atherosclerotic cardiovascular disease, diabetes on insulin therapy, heart failure, atrial fibrillation, chronic kidney disease, and advanced age were associated with two to four-fold higher risk of primary and secondary endpoints. The estimated hazard ratio for dual versus monotherapy as a time-varying covariate was 0.82 (95% confidence interval 0.81–0.83) for the primary endpoint. At variance with guidelines, monotherapy was most common treatment pattern over 5-year follow-up.

Conclusion: Baseline characteristics conveying a multifold higher risk for cardiovascular events and all-cause death mostly represented nonmodifiable risk factors. Treatment with dual therapy as compared to monotherapy was associated with reduction in cardiovascular events. Monotherapy remained most common BP-lowering treatment indicating substantial opportunity for risk reduction by treatment intensification.

Graphical abstract: http://links.lww.com/HJH/C682

Keywords: atherosclerotic cardiovascular disease, blood pressure, cardiovascular risk, clinical practice guidelines, diabetes, dual combination therapy, hypertension

Abbreviations: ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin-receptor blocker; ASCVD, Atherosclerotic cardiovascular disease; BMI, Body mass index; BP, Blood pressure; CBVD, Cerebrovascular disease; CCB, Calcium channel blocker; CHD, Coronary heart disease; CI, Confidence interval; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; CV, Cardiovascular; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HES, Hospital Episode Statistics; ICD, International Classification of Diseases; IMD, Index of multiple deprivation; MI, Myocardial infarction; NCD-RisC, Non-Communicable Disease Risk Factor Collaboration; NICE, National Institute for Health and Care Excellence; ONS, Office for National Statistics; PAD, Peripheral arterial disease; SD, Standard deviation

INTRODUCTION

According to the WHO, the worldwide prevalence of hypertension is estimated at 1.3 billion [1]. Elevated blood pressure (BP) is a major modifiable risk factor for incident cardiovascular disease and recurrent cardiovascular events, including myocardial infarction (MI), stroke,

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hospitalization for heart failure, and cardiovascular death [2]. The relationship between BP and the risk of cardiovascular events is known to be continuous, extending to SBP level 115 mmHg or less [2,3]. For noncommunicable diseases, the WHO has set a target to reduce the prevalence of elevated BP by 33% between 2010 and 2030 [1]. A recent study from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC) based on 1201 population-representative studies with 104 million participants estimated that between 1990 and 2019, the worldwide rates of treatment and control were approximately 43 and 21%, respectively, in individuals with hypertension [4]. A similar study from the NCD-RisC summarizing data from 12 high-income countries from 2008 to 2017 reported the rates of treatment and control as 45–75% and 22–60%, respectively [5]. In the United Kingdom (UK), in 2016, the rates of treatment and control of BP were estimated at approximately 57 and 37%, respectively.

In hypertensive patients, diabetes and atherosclerotic cardiovascular disease (ASCVD) lead to a substantial risk of cardiovascular events. Approximately, 74% of patients with diabetes have SBP at least 140 mmHg or DBP at least 90 mmHg or receive antihypertensive medication [6]. According to the American Heart Association, 68% of diabetic individuals aged at least 65 years are suffering from cardiac issues and 16% had stroke [7]. Clinical practice guidelines recommend considering both BP and the risk of ASCVD while determining antihypertensive treatment for patients with diabetes. A recent study demonstrated that in individuals with type 2 diabetes who did not have significant cardiovascular comorbidities, the inclusion of ASCVD risk scores along with monitoring of SBP levels improved the ability to predict cardiovascular events. The coexistence of hypertension, diabetes, and ASCVD increases cardiovascular risks, necessitating therapeutic management in this population [8]. Evidence from randomized controlled trials (RCTs) demonstrates that each 5 mmHg decrease in SBP reduces the risk of major cardiovascular events by approximately 10%, establishing pharmacological BP-lowering to be a cornerstone of cardiovascular prevention [2].

The 2018 European Society of Cardiology and European Society of Hypertension (ESC/ESH) guidelines [3] and the 2023 ESH guidelines [9] recommend initiating dual combination therapy in most individuals requiring BP-lowering treatment. A targeted literature search (Supplementary data file, http://links.lww.com/HJH/C681 "PubMed query for prior evidence") indicated a lack of data on the estimates of cardiovascular event rates, risk factors, treatment patterns, and BP control in a population qualifying for the initiation of dual combination therapy [3]. The quantification of cardiovascular event rates, risk factors, and treatment patterns is important for assessing the magnitude of clinical benefit, with improved guideline concordance in real-world populations, overall and in relevant high-risk subgroups. This real-world study aimed to assess the rates of cardiovascular events and all-cause death, associated risk factors, and patterns of BP-lowering therapies in population with hypertension qualifying for initiating dual combination therapy representing usual clinical practice setting in England with 15-year follow-up period.

Findings from this study were utilized in a companion study [10], which provided estimates of clinical benefit due to guidelines based antihypertensive treatment in this population and provide insights into subgroups and treatment strategies that result in a high clinical benefit.

MATERIALS AND METHODS

Study design and population

This was a longitudinal, retrospective, observational study with a population of interest identified between 2005 and 2019. The study end date was set as March 1, 2020. Supplementary Figure S1, http://links.lww.com/HJH/C681 provides an overview of the study design.

The study population was intended to represent individuals qualifying for dual BP-lowering therapy [3]. Individuals aged at least 18 years with a diagnosis of hypertension were initially identified during a 15-year period (2005–2019) in the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) databases. The population was restricted to those with SBP at least 140 mmHg while receiving BP-lowering monotherapy or at least 150 mmHg while untreated, which defined the index date (in case of multiple qualifying time points for an individual, the first was chosen). The index date thus corresponded to the first date when an individual became eligible for dual BP-lowering therapy. At least a 1-year period of continuous enrollment in the CPRD database prior to the index date was required. Patients with a diagnosis of secondary hypertension or hypertension during pregnancy were excluded. The main subgroups of interest were ASCVD and diabetes mellitus. Diabetes on insulin therapy was defined as diabetes with a prescription for insulin. Codes for identification of the study population are summarized in Supplementary Table S1, http://links.lww.com/HJH/C681. Supplementary Table S2, http://links.lww.com/HJH/C681 and Figure S2, http://links.lww.com/HJH/C681 provide details of operationalization of study variables and determination of treatment status at baseline. The study cohort was established by integrating data from the CPRD, HES, and Office for National Statistics (ONS) databases. The CPRD is an anonymized electronic health record database in the UK. In 2022, it represented approximately 41.7 million individuals from over 1491 primary care practices [11]. This database encompasses patient demographics, diagnoses, drug exposure, and laboratory and pathology tests as well as referrals to hospitals. The HES database comprises information on all admissions, including diagnoses and procedures, to the National Health Service hospitals in England. The ONS database records death registration data in the UK and provides complete and reliable details on the date and cause of death. The CPRD linked to the HES and ONS databases provides a longitudinal comprehensive view into the patients' medical experience as documented by general practitioner visits, inpatient visits, and detailed death information that includes cause of death [12,13].

An additional analysis was conducted to investigate patients' characteristics predictive of receiving monotherapy versus dual therapy in patients qualified for combination therapy (Supplementary file, http://links.lww.com/HJH/C681).

Outcomes

The primary endpoint was defined as a composite of nonfatal MI, nonfatal stroke (ischemic or hemorrhagic), hospitalization for heart failure, and cardiovascular death. The secondary endpoint was all-cause death. This study also evaluated associated risk factors and treatment patterns from the time when patients qualified for dual BP-lowering therapy. Only data on primary diagnoses from hospitalization (HES) were used to identify cardiovascular events. Nonfatal events were defined by exclusion of fatal ones. Death was defined as cardiovascular related if the International Classification of Diseases, 10th Revision diagnosis codes were between I00 and I99 for the cause of death (underlying cause and/or contributing causes). A nonfatal cardiovascular event was reclassified as fatal if death was recorded during subsequent 30 days. All-cause death was ascertained from any record of death in the ONS or CPRD database. Codes and algorithms for operationalizing the study endpoints are summarized in Supplementary Tables S1 and S3, http://links.lww.com/HJH/C681, which were obtained via prior investigations [14,15] and reviewed by the authors/experts to ensure specificity.

BP measurements and treatment status with BP-lowering therapies were based on information available on the CPRD database, representing records in a primary care setting.

Statistical analysis

Event rates over time for the primary and secondary endpoints were evaluated via the Kaplan–Meier method (1–KM rates are reported). A Cox regression model was used to evaluate baseline risk factors associated with the primary and secondary endpoints. The variable selection for the Cox model utilized backward selection with a *P*-value of 0.05 [14]. Variables selected in the Cox model for the primary endpoint were used as the final set of variables for other endpoints. Additionally, treatment status (number of antihypertensive therapies) over follow-up was included as a time-dependent covariate for the primary endpoint to estimate the effect of dual versus monotherapy after patients had qualified for dual therapy (see Supplementary file, http://links.lww.com/HJH/C681 for full details). For these analyses, patients were followed from the index date to the endpoints of interest and censored at death, deregistration, or study end date, whichever occurred first.

Treatment patterns of BP-lowering therapy within the first 5 years after index were summarized via the percentage of patient-time on a given therapy for overall population and main subgroups (ASCVD or diabetes). Patient-time was estimated as follows: for each patient during a given 1-year time interval, the percentage of time on a given therapy was calculated (more details in Supplementary file, http://links.lww.com/HJH/C681).

The degree of data completeness and patterns of missingness were summarized for all covariates proposed for inclusion in the regression analysis of the primary objective using a pattern of missingness matrix. The number and proportion of missing data for each variable and the top five most frequent patterns of missingness were observed. Over 95% of the study participants had complete data for the variables considered in the Cox model and a complete case analysis was performed. Data analyses were performed using SAS (Statistical Analysis System) 9.4M8 version (SAS Institute Inc., Cary, NC, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

The study adhered to the Good Pharmacovigilance Practices, Good Pharmacoepidemiology Practices, and the Declaration of Helsinki and its amendments, as well as applicable national guidelines, laws, and regulations. The Medicines and Healthcare products Regulatory Agency and Independent Scientific Advisory Committee reviewed proposals based on the CPRD and linked databases and approved the study protocol and its amendment (Approval number: 21_000499).

RESULTS

Baseline patient characteristics

A total of 1 426 079 individuals met the selection criteria (Fig. 1). As shown in Table 1, the mean age (standard deviation [SD]) was 62.9 (14.1) years, and nearly 50% were men. Approximately 11.4% had coronary heart disease (CHD) and 4.5% had cerebrovascular disease at baseline. Among other comorbidities, diabetes (13.8%) was the most common, followed by chronic kidney disease (CKD, stages III–V; 10.6%), chronic obstructive pulmonary disease (COPD, 6.3%), atrial fibrillation (4.3%), heart failure (3.1%), and moderate/severe liver disease (2.6%). Nearly half of the participants did not receive BP-lowering therapy at baseline. Participants with ASCVD were older, more likely to have cardiovascular and non-cardiovascular related comorbidities, and more likely to receive BP-lowering therapy than those without ASCVD. The pattern was similar in participants with diabetes (Table 1). In individuals with diabetes at baseline, the association with the primary endpoint and all-cause death was higher in those on insulin therapy than in those without insulin therapy (Supplementary Table S4, http://links.lww.com/HJH/C681).

The median follow-up from the index date was 5.2 years, with interquartile range between 2.3 and 9.4 years. Overall, 51.8 and 22.2% of participants had at least 5 years and 10 years of follow-up, respectively.

Patients who initiated dual therapy early in follow-up/within 6 months were more likely to be obese, have ASCVD, elevated SBP level, and received treatment with diuretics, β-blockers, or lipid-lowering therapy at baseline than those who initiated or remained on monotherapy (Supplementary Table S5, http://links.lww.com/HJH/C681).

Study outcomes

The 15-year Kaplan–Meier event rate for the primary endpoint was 27.1% and was mainly driven by cardiovascular death (15-year event rate for cardiovascular death as an individual endpoint was 18.4%). The 15-year KM event rate for the secondary endpoint was 32.6%. Figure 2a and 2b and Supplementary Table S6, http://links.lww.com/HJH/C681 summarizes 15-year Kaplan–Meier event rates for the overall population as well as the ASCVD or diabetes

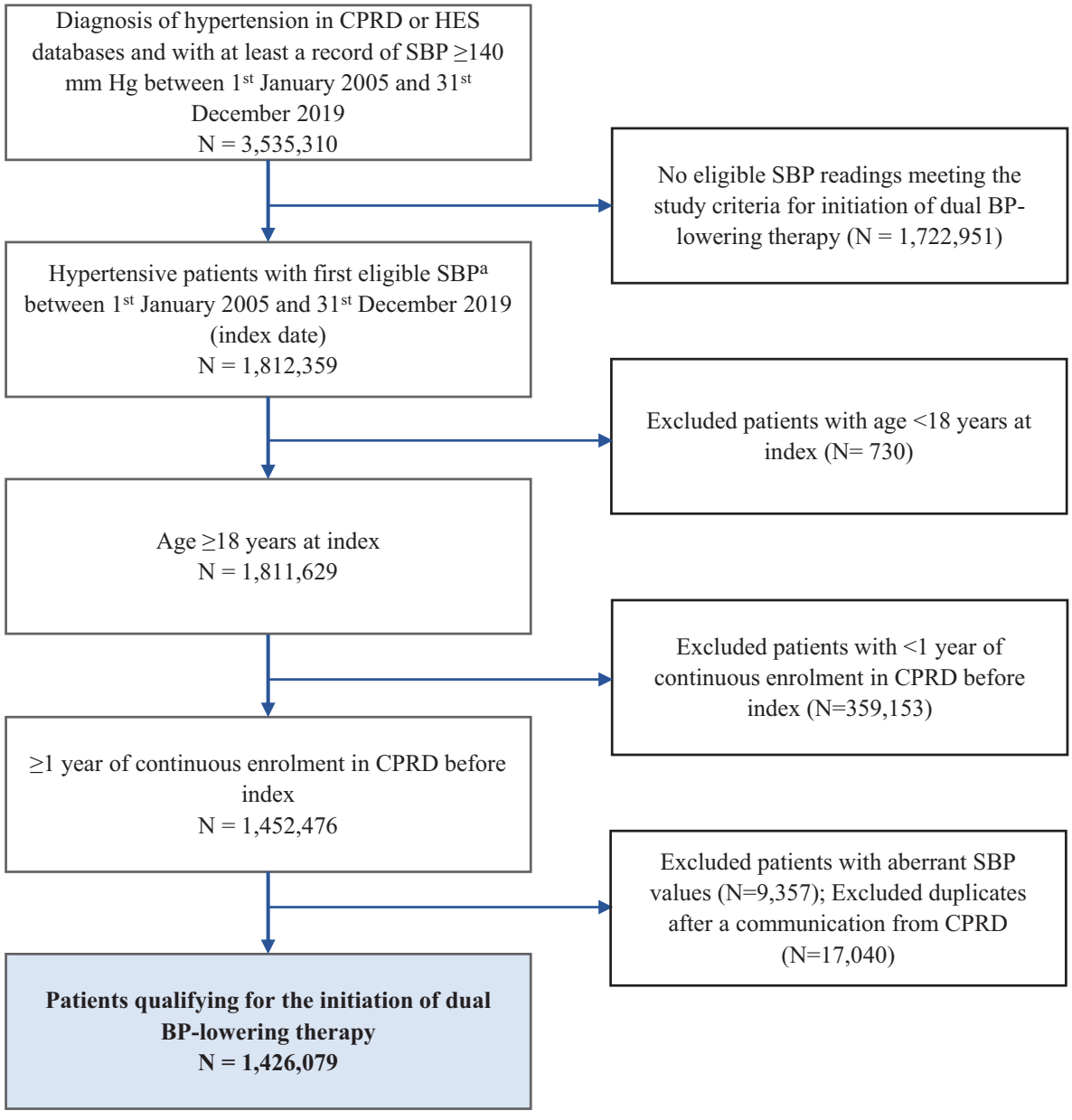

FIGURE 1 Consort diagram for patient selection. [a]At least one record of SBP ≥140 mmHg while under BP-lowering monotherapy or one record of SBP ≥150 mmHg after the hypertension diagnosis. BP, blood pressure; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics.

subgroups. Hazard ratios for baseline risk factors and time-varying antihypertensive treatment status are summarized in Table 2 for the primary endpoint. The estimated hazard ratio for dual versus mono therapy was 0.82 (95% confidence interval 0.81–0.83; $P < 0.0001$), indicating an 18% relative risk reduction for cardiovascular events at any given time during follow-up. Baseline risk factors most strongly associated with the risk of experiencing the primary endpoint (defined as hazard ratio >1.50 with $P < 0.0001$) were age at least 65 years, heart failure, atrial fibrillation, diabetes on insulin therapy, CKD stage IV/V, history of MI or other CHD or stroke, and peripheral arterial disease (PAD). Risk factors associated with the secondary endpoint and individual events included in the composite primary endpoint, as assessed in a Cox regression model considering only baseline risk factors, are summarized in Supplementary Table S7, http://links.lww.com/HJH/C681.

The proportion of patient-time on monotherapy decreased from 56.7% in Year 1 to 42.6% in Year 5, while that on dual combination therapy increased from 14.9% in Year 1 to 25.5% in Year 5 (Table 3). Similar pattern was observed in the ASCVD and diabetes subgroups (Supplementary Tables S8 and S9, http://links.lww.com/HJH/C681, respectively). The mean SBP for the overall population decreased from 147.8 mmHg in Year 1 to 138.0 mmHg in Year 5 (Supplementary Table S10–S11, http://links.lww.com/HJH/C681).

TABLE 1. Baseline characteristics: overall and by subgroups atherosclerotic cardiovascular disease or diabetes status

			ASCVD		Diabetes	
		Overall (*N* = 1 426 079)	Yes (*N* = 226 106)	No (*N* = 1 199 973)	Yes (*N* = 197 492)	No (*N* = 1 228 587)
Year of inclusion in study (%)	2005–2009	36.2	34.4	36.5	30.1	37.2
	2010–2014	30.1	30.9	30.0	30.9	30.0
	2015–2019	33.7	34.7	33.5	39.0	32.9
Age (years)	Mean (SD)	62.9 (14.1)	72.2 (12.2)	61.2 (13.7)	64.8 (13.7)	62.6 (14.1)
	Min, max	18.0, 109.7	18.2, 109.7	18.0, 108.2	18.1, 108.8	18.0, 109.7
Sex, %	Male	49.8	56.7	48.5	55.4	48.9
Race, %	Black	4.0	1.9	4.5	5.5	3.7
	Nonblack	96.0	98.1	95.5	94.5	96.3
BMI, %[c]	Underweight[a]	1.1	2.2	0.9	0.7	1.3
	Healthy weight[a]	20.9	27.1	19.6	15.9	22.2
	Overweight[a]	37.0	38.9	36.6	33.9	37.8
	Obese[a]	41.0	31.8	42.9	49.5	38.7
Smoking status (%)	Current smoker[a]	27.6	29.3	27.2	27.8	27.5
	Ex-smoker[a]	37.4	45.5	35.8	43.5	36.3
	Nonsmoker[a]	35.1	25.1	37.0	28.7	36.1
IMD[b] (%)	Quintile 1	21.7	19.6	22.1	17.2	22.4
	Quintile 2	20.5	19.8	20.6	17.9	20.9
	Quintile 3	20.0	20.2	20.0	19.6	20.1
	Quintile 4	18.9	19.8	18.7	21.1	18.6
	Quintile 5	18.9	20.6	18.6	24.2	18.0
ASCVD (%)	Yes	15.9	100	–	26.6	14.1
CHD (%)	Prior MI	3.9	24.7	–	7.6	3.3
	No prior MI	7.5	47.5	–	12.7	6.7
CBVD (%)	Prior stroke	3.9	22.4	0.4	5.8	3.6
	No prior stroke	0.6	3.2	0.1	0.9	0.5
PAD (%)	Yes	3.1	19.7	–	6.3	2.6
HF (%)	Yes	3.1	12.9	1.2	6.4	2.5
Atrial fibrillation (%)	Yes	4.3	13.1	2.6	5.9	4.0
CKD (%)	Stage ≤II	89.4	75.2	92.1	79.9	91.0
	Stage III	8.7	19.0	6.7	15.1	7.6
	Stage IV	0.5	1.4	0.4	1.4	0.4
	Stage V	1.4	4.3	0.8	3.6	1.0
Liver disease (%)	Moderate/severe	2.6	3.4	2.4	5.7	2.1
COPD (%)	Yes	6.3	15.3	4.6	8.8	5.9
Diabetes (%)	Not on insulin	11.0	17.3	9.9	79.8	-
	On insulin	2.8	5.9	2.2	20.2	-
SBP (mmHg), %	≥140 to <150	26.9	39.2	24.6	38.3	25.1
	≥150 to <160	27.8	27.1	28.0	29.3	27.6
	≥160 to <170	20.8	17.0	21.5	17.6	21.3
	≥170	24.5	16.8	25.9	14.7	26.0
Number of BP-lowering therapies (%)	0	49.8	30.3	53.5	33.3	52.5
	1	50.2	69.7	46.5	66.7	47.5
BP-lowering therapies (%)	ACEi	17.5	19.3	17.2	32.4	15.1
	ARB	4.4	5.7	4.1	8.1	3.8
	CCB	13.3	13.8	13.2	10.5	13.7
	Diuretics	6.6	8.7	6.2	6.1	6.7
	β-blockers	7.7	21.0	5.2	8.5	7.5
Lipid-lowering therapy (%)		25.1	56.9	20.0	58.6	18.8

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CBVD, cerebrovascular disease; CCB, calcium channel blocker; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; IMD, index of multiple deprivation; MI, myocardial infarction; PAD, peripheral arterial disease; SD, standard deviation.
[a]These proportions are based on individuals with nonmissing data. The missing datum for smoker is 2.4% of the overall population.
[b]IMD classifies areas into five quintiles based on relative disadvantage, quintile 1 being the least deprived and quintile 5 being the most deprived (0.1% missing data).
[c]BMI (kg/m^2), underweight: <18.5; healthy weight: 18.5–25; overweight: 25–30; obese: ≥30.

DISCUSSION

In this large, integrated, retrospective, observational study with well characterized population of more than 1.4 million individuals qualifying for the initiation of dual BP-lowering therapy, representing usual clinical practice in England, 27.1% experienced the primary endpoint (a composite of nonfatal MI, nonfatal stroke, heart failure hospitalization, and cardiovascular death) and ≈32.6% experienced the secondary endpoint (all-cause death) over 15 years. These risks were substantially higher in individuals with ASCVD or diabetes at baseline. The ASCVD subgroup had a 15-year risk of 57.5% for the primary endpoint, ≈2.5-fold higher than those without ASCVD (22.1%). Similarly, the diabetes

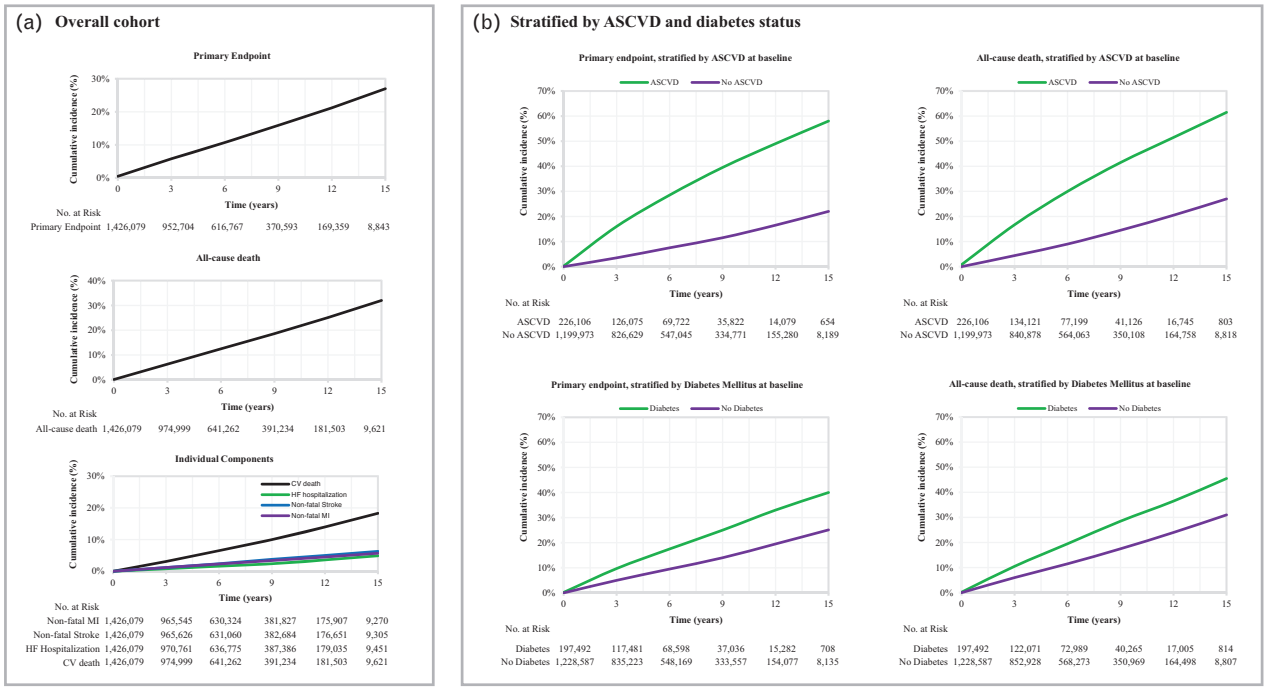

FIGURE 2 Event rate over time for the primary and secondary endpoints (all-cause death) and individual components; (a) Overall cohort, (b) Stratified by ASCVD and diabetes status. Primary endpoint: A composite of nonfatal MI, nonfatal stroke (ischemic or hemorrhagic), hospitalization for HF, and CV death. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

subgroup had a 15-year risk of 40.1% for the primary endpoint, ≈1.5-fold higher than those without diabetes (25.4%) (unadjusted analyses). The adjusted Cox model indicated that specific baseline conditions translate to a ≈2- to 4-fold high risk of experiencing the primary endpoint, more pertinent with ASCVD (e.g., prior MI, prior stroke, and PAD), diabetes on insulin therapy, heart failure, atrial fibrillation, CKD, and advanced age. The pattern was consistent for the all-cause death.

Findings for the primary endpoint with patient baseline characteristics in the confounder set, demonstrated an 18% relative risk reduction for cardiovascular events for treatment with dual therapy as compared with monotherapy at any given time after patients had qualified for dual therapy. Evidence [16–19] had shown the association between treatment with dual antihypertensive therapy and better cardiovascular outcomes. The treatment with dual therapy can increase the effectiveness of antihypertensive treatment-related cardiovascular prevention.

In the UK, up to 50% of medicines are reported not taken as intended [20]. In those receiving medications for chronic conditions in the UK, suboptimal intensification has been reported [21]. In this study, 25% of patient-time represented not receiving any BP-lowering therapy each year during follow-up (e.g., due to factors such as suboptimal initiation, adherence, or persistence), and among those receiving BP-lowering therapy, ≈60 to 75% were receiving monotherapy. This provides an opportunity for a substantial risk reduction in this population, especially in those representing high-risk conditions, by ensuring appropriate initiation, adherence, and persistence to BP-lowering therapy in those already receiving BP-lowering therapy, ensuring a higher adoption of guidelines-recommended dual combination therapy.

The findings of this study on the event rates in ASCVD or diabetes subgroups revealed further insights. Patients with diabetes on insulin typically represent longstanding diabetes, following years of treatment with oral agents that lose effectiveness over time. Longstanding diabetes is known to, and thus be associated with organ damage [22]. In an adjusted analysis, these patients were more likely to have concomitant CKD stage III–V, heart failure, or ASCVD (Supplementary Table S4, http://links.lww.com/HJH/C681). Diabetes on insulin was a statistically significant risk factor; it can be considered an independent risk factor beyond the comorbidities accounted in the analyses, possibly serving as a proxy for additional unmeasured factors representing compromised patient health status and higher risk. In addition, ASCVD at baseline (e.g., prior MI, prior stroke, and PAD) conferred a higher risk for the primary endpoint and all-cause death than that for diabetes on insulin therapy. A study by Ke *et al.* [23] representing a large population from Canada demonstrated that the cardiovascular risk is lower in individuals with diabetes (without ASCVD) than those with ASCVD (with or without diabetes). Before Year 2000, the risk levels for diabetes patients without ASCVD and those with ASCVD were similar. However, the risk for diabetes without ASCVD group has been decreasing due to better diabetes management. This suggest that while diabetes is significant cardiovascular risk factor, it may not be considered "CV disease risk equivalent" [23]. The study represented different population, geography, and healthcare system, lends an

TABLE 2. Association of baseline characteristics and time-varying antihypertensive treatment status with the primary composite endpoint

Parameter	Modalities	Primary endpoint[a] HR	95% CI	P
Characteristics at index date				
Age (years)	(45–65)	Ref		
	(18–45)	0.50	0.48–0.52	< 0.0001
	65+	2.97	2.92–3.02	< 0.0001
Gender	Female	0.82	0.81–0.83	< 0.0001
Smoking status	Nonsmoker	Ref		
	Ex-smoker	1.00	0.99–1.02	0.620
	Current smoker	1.32	1.30–1.34	< 0.0001
Year of inclusion	2005–2009	Ref		
	2010–2014	0.90	0.89–0.92	< 0.0001
	2015–2019	0.80	0.79–0.81	< 0.0001
Comorbidities				
CKD	No CKD or stage I/II	Ref		
	Stage III	1.44	1.42–1.47	< 0.0001
	Stage IV	2.17	2.07–2.29	< 0.0001
	Stage V	1.98	1.92–2.04	< 0.0001
Chronic obstructive pulmonary disease	Yes	1.43	1.40–1.45	< 0.0001
Moderate/severe liver disease	Yes	1.12	1.08–1.17	< 0.0001
HF	Yes	1.83	1.79–1.87	< 0.0001
Atrial fibrillation	Yes	1.63	1.59–1.67	< 0.0001
Diabetes mellitus	No diabetes	Ref		
	Diabetes mellitus without insulin	1.31	1.29–1.34	< 0.0001
	Diabetes mellitus with insulin	1.74	1.69–1.79	< 0.0001
Baseline atherosclerotic cardiovascular disease				
History of CHD	No history of CHD	Ref		
	MI prior to index	1.87	1.83–0.92	< 0.0001
	Other CHD without MI prior to index	1.46	1.43–1.49	< 0.0001
History of CBVD	No CBVD	Ref		
	Stroke prior to index	2.20	2.16–2.25	< 0.0001
	Other CBVD without stroke prior to index	1.49	1.42–1.57	< 0.0001
PAD	Yes	1.50	1.46–1.53	< 0.0001
Laboratory and vital measurements				
SBP	≥ 140 to < 150 mmHg	Ref		
	≥ 150 to < 160 mmHg	1.09	1.07–1.11	< 0.0001
	≥ 160 to < 170 mmHg	1.15	1.13–1.18	< 0.0001
	≥ 170 mmHg	1.37	1.34–1.40	< 0.0001
DBP	< 70 mmHg	Ref		
	≥ 70 to < 80 mmHg	0.87	0.85–0.89	< 0.0001
	≥ 80 to < 90 mmHg	0.81	0.79–0.83	< 0.0001
	≥ 90 to < 100 mmHg	0.75	0.73–0.77	< 0.0001
	≥ 100 to < 110 mmHg	0.75	0.73–0.78	< 0.0001
	≥ 110 mmHg	0.91	0.87–0.94	< 0.0001
Concurrent cardiovascular medications				
ACEi	Yes	1.09	1.06–1.11	< 0.0001
ARBs	Yes	1.02	0.99–1.06	0.1561
CCB	Yes	1.19	1.16–1.21	< 0.0001
Diuretics	Yes	1.48	1.45–1.51	< 0.0001
β-blockers	Yes	1.24	1.22–1.27	< 0.0001
Other diuretics[b]	Yes	1.56	1.40–1.73	< 0.0001
α-blockers	Yes	1.22	1.14–1.31	< 0.0001
LLT	Yes	0.76	0.74–0.77	< 0.0001
Anticoagulants	Yes	1.13	1.09–1.16	< 0.0001
Antiplatelets	Yes	1.33	1.31–1.35	< 0.0001
Time-varying antihypertensive treatment status				
Number of drugs	Monotherapy	Ref		
	Untreated	1.38	1.36–1.40	< 0.0001
	Dual therapy	0.82	0.81–0.83	< 0.0001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CBVD, cerebrovascular disease; CCB, calcium channel blocker; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; PAD, peripheral arterial disease.
[a]Nonfatal MI, nonfatal stroke, HF hospitalization, and CV death.
[b]Other diuretic include spironolactone, eplerenone, amiloride and triamterene.

TABLE 3. Percentage of patient-time on blood pressure lowering regimens during follow-up for the overall population

Sr. no.	BP-lowering regimen	Percentage of patient-time by years since follow-up initiation				
		0–1 year	1–2 years	2–3 years	3–4 years	4–5 years
1	No treatment for 31–90 days	3.7	3.5	3.4	3.3	3.3
2	No treatment for >90 days	12.9	14.2	13.8	13.2	12.6
3	Monotherapy	56.7	49.7	46.7	44.5	42.6
4	Combination with two agents	14.9	19.3	21.9	23.9	25.5
5	Combination with ≥3 agents	2.6	4.1	5.2	6.1	6.9

BP, blood pressure.

independent support to this finding with an added implication that diabetes on insulin therapy may still be considered closer to being "CV disease risk equivalent."

In this study, there was a decrease in monotherapy from 56.7 to 42.6% in the overall population as well as in high-risk ASCVD (52.9 to 38.3%) and diabetes (57.7 to 42.3%) subgroups during 5-year follow-up, providing further opportunity to optimize guidelines recommended dual BP-lowering therapy. A higher use of monotherapy than dual combination therapy has also been reported [24–27]. A potential reason could be that the index dates for patient identification ranged from 2005 to 2019, suggesting that the majority of patients received standard treatment in clinical practice prior to the 2018 ESC/ESH guideline recommending dual therapy. Another reason could be adoption of the National Institute for Health and Care Excellence (NICE) guidelines recommending an initial monotherapy in most patients with hypertension [28]. Conversely, the population in this study is from England, where the prevalence of treatment with appropriate guideline-based therapies for chronic conditions can be higher than in other countries [21].

According to the ESTEBAN Survey in France, 62.1% of patients received a single antihypertensive class, while 37.9% received antihypertensives of two or more classes [29]. A nationwide German survey found that BP control remains below 50%, with around one-third of patients receiving monotherapy, contrary to current guideline recommendations [30]. The recent HYPEDIA study evaluated the implementation of the 2018 ESC/ESH guidelines for treating hypertension in primary care. In nearly 50% of the treated uncontrolled patients with hypertension, treatment was not intensified, indicating poor implementation of 2018 ESC/ESH guidelines recommendation in the primary care [31]. Therefore, effective health promotion and digital tools are thus crucial for communication of evidence and guideline adoption among healthcare professionals.

Key strengths of this study include a large, well characterized, contemporary population, representing usual clinical practice, with a long-term follow-up of 15 years. The linked nature of databases (CPRD, HES, and ONS) covered primary care and hospitalization settings as well as the death status and is expected to result in a substantial increase in the reliability of patient characterization and follow-up for the study endpoints [32]. Study showed significant risk reduction in cardiovascular events rates in patients receiving treatment with dual therapy compared to monotherapy. The study has few limitations from observational data-based investigations, such as ascertainment of treatment status from prescription records, coding accuracy, and potentially missing data. Even if it is acknowledged that 20–60% of nonfatal MI remained undiagnosed, the rates for nonfatal MI in this study appear to be underestimated compared with other reports (Supplementary Table S6, http://links.lww.com/HJH/C681). Transient ischemic attack and minor ischemic stroke have manifestations overlapping with major ischemic stroke (except for neuroimaging findings) and the approach to clinical management is similar [33]. However, these events may not be consistently categorized under rigorous stroke codes in the HES database, resulting in an underestimation of nonfatal stroke events.

For the primary endpoint, ascertainment of nonfatal events was based on the primary diagnosis during hospitalizations, which might explain the observed underestimation. However, the data used for ascertaining all-cause death and cardiovascular death were derived from the ONS database. As cardiovascular death is a major component of the primary endpoint, this likely mitigated the underestimation of nonfatal events and also likely resulted in the findings on the rates of primary endpoints being on the conservative side. Finally, the study population represented England, which may not be representative of the entire UK or international populations. We attempted backward selection for achieving reduction in number of predictor variables in the Cox models. However, it retained all the variables as they were highly significant.

In conclusion, this real-world study represents a large population reflecting a usual clinical practice setting in England, qualifying for initiating dual BP-lowering therapy as per most recent European and international guidelines. Patients with hypertension qualifying for dual BP-lowering therapy are at a high risk of cardiovascular events and death over a 15-year follow-up period, with the risk being substantially elevated in subgroups. Treatment with dual therapy as compared to monotherapy is associated with reduction in cardiovascular events. Conditions representing substantial increase in risk were mainly non-modifiable factors, such as established ASCVD, diabetes on insulin therapy, heart failure, atrial fibrillation, CKD, and advanced age. Monotherapy remained the most common BP-lowering treatment indicating that there is a substantial opportunity for risk reduction by treatment intensification.

The overarching aim of this study was to offer insights on populations with a high imperative for timely initiation of

dual BP-lowering antihypertensive therapy. The study outcomes and the analytic dataset served as inputs for a subsequent simulation-based study intended to inform the implications of guidelines based antihypertensive therapy intensification on clinical outcomes [10]. Future research is required to assess the association between achieved BP levels and cardiovascular event rates in clinical setting.

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Conflicts of interest

Antonio Coca has received consulting fees from Sanofi and Menarini and honorarium and fees for speakers' bureaus from Berlin-Chemie, Biolab, Ferrer, Menarini, and Sanofi and is a part of the advisory boards of Ferrer and Sanofi. Claudio Borghi has received consulting fees from Alfasigma, Sanofi, AstraZeneca, Gilead, and Menarini and honorarium and fees for speakers' bureaus from Alfasigma, Berlin-Chemie, Servier, Recordati, and Novo Nordisk. George S. Stergiou has received consulting fees from AstraZeneca, Menarini, Sanofi, Servier, and Viatris; lecture honoraria from AstraZeneca, Menarini, Sanofi, Servier, and Viatris; and travel support from Menarini. Nelly Francoise Ly, Christopher Lee, Aurore Tricotel, and Anna Castelo-Branco are employees of IQVIA and have received consulting fees from Sanofi for conducting the analyses reported in this manuscript. Jacques Blacher has received consulting fees from Sanofi and Quantum Genomics; honorarium and fees for speakers' bureaus from Hikma, El Kendi, Vivactis, Servier, and Mylan; and travel support from Servier. Irfan Khan and Mohamed Abdel-Moneim are employees of Sanofi and may hold shares and/or stock options in the company.

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