

Impact of single-pill combination therapy on adherence, blood pressure control, and clinical outcomes: a rapid evidence assessment of recent literature

Konstantinos Tsioufis^a, Reinhold Kreutz^b, Georgia Sykara^c, Joris van Vugt^d, and Tarek Hassan^e

Objective: The 2018 European Society of Cardiology/European Society of Hypertension Guidelines for the management of arterial hypertension raised the need for evidence to support the use of single-pill combination (SPC) therapy in preference to free-dosed therapy for hypertension. This systematic rapid evidence assessment sought to determine if initiating SPC therapy improves adherence, blood pressure (BP) control and/or cardiovascular outcomes vs. initiation of free-dose combination therapy.

Methods: Rapid evidence assessment conducted in MEDLINE, EMBASE, and Cochrane Library (1 January 2013–11 January 2019) to identify studies investigating SPC therapy for adults with hypertension. Information on adherence/persistence, BP lowering/goal attainment, and cardiovascular outcomes/events were extracted via two-phase screening process. Studies not focusing on adherence, persistence, or compliance with SPC therapy were excluded. Methodological quality was assessed using appropriate scales.

Results: Of 863 citations, 752 failed to meet inclusion or were duplicates. Twenty-nine studies remained following full-text screening. Just four studies (14%) were randomized controlled studies; 25 (86%) were observational. A range of SPC therapies were studied, with calcium channel blocker/angiotensin receptor blocker combinations most common (11/29 studies). Adherence and persistence were generally higher with SPC vs. free-dose combination therapy; 15 studies (54%) directly compared adherence and four (14%) compared persistence. Patients achieving BP targets ranged from 25 to 89%. Despite all studies investigating patients with hypertension only 16 (55%) reported change in BP. Few studies reported on cardiovascular outcomes. Methodological reporting was often suboptimal.

Conclusion: Adherence and/or persistence were generally higher in patients taking antihypertensives as SPC vs. free-dose combination; however, methodological reporting was suboptimal to facilitate comparison. Specifically designed, well reported studies are required to determine if the increased adherence/persistence seen in patients on SPC regimen leads to improved BP control and/or cardiovascular outcomes.

Keywords: adherence, blood pressure, cardiovascular outcomes, fixed-dose combination therapy, hypertension, persistence, single-pill combination therapy

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; AH, arterial hypertension; AHA, American Heart Association; aml, amlodipine; ARB, angiotensin 1 receptor blocker; AT1, angiotensin 1 receptor; BP, blood pressure; CCB, calcium channel blocker; CI, confidence interval; DALY, disability-adjusted life-years; ESC, European Society of Cardiology; ESH, European Society of Hypertension; FDC, fixed-dose combination; HCTZ, hydrochlorothiazide; ind, indapamide; MPR, medication possession ratio; PCI, percutaneous coronary intervention; PDC, proportion of days covered; per, perindopril; RCT, randomized controlled trial; REA, rapid evidence assessment; SAE, serious adverse event; SLR, systematic literature review; SPC, single-pill combination; val, valsartan

INTRODUCTION

The Global Burden of Disease Study (2017) suggests that high blood pressure (BP) was, and has been for at least the past decade, the world's leading risk

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factor for attributable disability-adjusted life-years (DALYs), accounting for ~10.4 million deaths, and attributed ~218 million DALYs [1]. Furthermore, the global prevalence of elevated BP of at least 140 mmHg continues to rise [2,3]. This prevalence of arterial hypertension (AH) is relatively consistent, irrespective of income status [4,5], and identification and management are suboptimal around the world [5–8]. Hypertension also becomes progressively more common with advancing age, with a prevalence higher than 60% in people aged 60 years and older [2,4]. Therefore, as the population ages, it is predicted that the impact of AH will rise even further, if management is not optimized.

According to most international guidelines, including the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) 2018 guidelines for the management of AH in adults, aged at least 18 years, AH is defined as a SBP at least 140 mmHg and/or a DBP at least 90 mmHg [9]. However, in 2017, joint societies in the USA, including the American Heart Association (AHA)/American College of Cardiology (ACC) lowered the level at which 'hypertension should be defined, to at least 130/80 mmHg [10]. This consequently raised the prevalence of patients with hypertension according to this updated definition [2]. The ESC/ESH noted during the release of their guidelines in 2018 that the majority of patients do not achieve BP less than 140/90 mmHg, and therefore their focus was to improve goal attainment, rather than to lower the definition of BP beyond the traditional AH definition of BP at least 140/90 mmHg [9]. 'Normal' BP in patients aged less than 65 years according to both guidelines is, however, defined at a similar level, either as BP 120–129/80–89 mmHg [9] or as BP less than 120/80 mmHg [10]. Studies have demonstrated that attainment of 'normal' BP reduces the risk of future cardiovascular events [9–11]. However, goal attainment remains suboptimal throughout the world, even using BP goal of less than 140/90 mmHg [2,5–8].

Five classes of antihypertensive drugs are first-line therapies for the management of AH: angiotensin-converting enzyme inhibitors (ACEis), angiotensin 1 receptor (AT1) blockers (ARBs), calcium channel blockers (CCBs), and diuretics, with beta-blockers being recommended for patients with compelling indications [9,10]. These can be given either individually as a monotherapy; in combination as multiple pills; as a single-pill combination (SPC) [or alternatively termed fixed-dose combination (FDC)] agent that combine two or more drugs in one pill; or as a combination of individual and combined therapies.

Despite some differences in definitions, both the 2018 ESC/ESH and the 2017 ACC/AHA guidelines recommend that most patients with BP at least 140/90 mmHg (or >20/10 mmHg above target) initiate two antihypertensive agents as initial therapy (if tolerated) to reduce BP towards goal [9,10]. ESC/ESH guidelines have recommended the use of initial SPC therapy for patients requiring more than one antihypertensive therapy since 2013 [12], and in 2018 the guidelines were updated to include recommendations for initial SPC therapy for most patients with uncomplicated AH, with the exception of very old (≥ 80 years) or frailer patients and/or patients with low-risk grade 1 hypertension [9]. The 2017 ACC/AHA guidelines also recommend initiation of two antihypertensive therapies for patients with BP more than 20/10 mmHg above target, but this can be given either as two pills in a free

combination or as an SPC therapy [10]. SPC therapy is recognized to significantly improve patient adherence [13,14] and through improved adherence, some evidence suggests SPC therapy can improve BP-lowering and cardiovascular outcomes [14]; conversely, some evidence suggests no difference in BP effects, as when patients are adherent with SPC therapy and free-dose combination therapy, BP reduction is similar [13,15]. Despite some clinical evidence for the use of SPCs in the treatment of AH, a lack of quality evidence and a lack of definitive conclusions have been reported, regarding whether SPC or free-dose combination therapy leads to better efficacy [15]. In addition, there are other considerations around prescribing SPC therapies, including risk of treatment duplication, and the ability to individually titrate different components of the single pill with the incidence of any adverse event [16]. As such, further clarification of the benefits is needed for healthcare professionals. Through a systematic review of the literature, we sought to investigate the impact of initiating patients with AH onto SPC therapy vs. a free combination of therapeutic agents (herein termed free-dose combination therapy) on medication adherence, BP control and cardiovascular outcomes. This comparison was identified as an unmet need during discussion of the ESC/ESH 2018 guidelines [9]. Through a rigorous analysis, we also sought to highlight gaps in the literature to inform future design and development of studies in this area, and to support international guideline recommendations.

METHODS

Study design and data source

A systematic rapid evidence assessment (REA) was conducted within MEDLINE, EMBASE and the Cochrane Library Database between 1 January 2013 and 11 January 2019 (Appendix I, <http://links.lww.com/HJH/B268>). This time-span covers the treatment period since release of the 2013 ESC/ESH guidelines [12], where use of SPC therapy for patients with markedly high baseline BP or at high cardiovascular risk who required more than one antihypertensive agent was made. We sought to reflect changing treatment practices following these recommendations, and to bring literature up-to-date following release of guidelines in late 2017, and 2018 [9,10]. An REA enables a systematic assessment of peer-reviewed literature, in a streamlined and efficient fashion, while adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol guidelines [17]. The REA differs from a traditional systematic literature review (SLR) as it does not include grey or non-English language sources, and provided us with a more focused methodological approach to answer the specific question raised by the ESC/ESH [9].

Search strategy: inclusion and exclusion criteria

The full search strategies for each of the databases are given in Appendix I, <http://links.lww.com/HJH/B268> (Table S1, <http://links.lww.com/HJH/B268>). The inclusion criteria confined the search to studies in adults with AH, where at least one treatment arm was given as SPC therapy (or termed FDC therapy, bi or dual or triple SPC/FDC therapy). Terms specifically included in the search strategy for adherence included: adherence, compliance, persistence; and for

cardiovascular outcomes included: venous thromboembolic events, peripheral arterial disease, myocardial infarction, heart failure (ischemic or congestive), chronic kidney disease, transient ischemic attack or stroke, aortic aneurysms, atrial fibrillation, atherogenic index, palpitations/tachycardia, chest pain/angina, percutaneous coronary intervention (PCI), or peripheral vascular intervention (Table S1, <http://links.lww.com/HJH/B268>). SPC therapies considered in the search were based on commonly approved therapeutic agents, according to the US Food and Drug Administration, and including a combination of any first-line antihypertensive agents (i.e. a CCB, ARB, ACEi, diuretic and/or beta-blocker). A full list of specific therapeutic agents added to the search strategy is given in Table S2, <http://links.lww.com/HJH/B268>.

A rigorous, two-stage screening process was carried out: Stage 1 involved screening titles and abstracts of identified publications, and retaining relevant literature for full-text review. The second stage involved full-text screening and retaining literature that met full search criteria. Studies were retained for full text-review that included information on adherence and/or persistence and/or compliance measures. Information on BP measurement and control and/or cardiovascular outcomes (or cardiovascular events) and/or mortality or morbidity (including cardiovascular or non-cardiovascular-related death) were extracted alongside information on adherence and/or persistent measures.

Studies that did not focus on adherence, persistence, or compliance as an assessment, or that did not focus on combination/SPC treatment arms of interest were excluded. Studies that focused on pregnant patients or other nonarterial causes of hypertension were also excluded, as were studies that only discussed monotherapy or that focused on anti-hypertension combinations with statins (i.e. only one antihypertensive agent), anti-angina agents, or that focused on behavioral outcomes only (including patient education/reminder system/nutrition/exercise/herbal etc.). Studies that focused on clinical outcomes other than BP control, BP goal attainment, or cardiovascular outcomes were not eligible for inclusion, such as primary assessment of blood measures (e.g. lipid profiles or inflammatory markers), drug survival rates, retention rates, discontinuation, or dropout rates. Studies that were preclinical, Phase 1 studies, case reports, or studies of less than 30 patients; a letter to the editor, opinion piece, or review or meta-analysis, were excluded from this REA.

Data extraction

Full publications of retained records were examined in detail for information relating to study design, participants and population, intervention, treatment, and adherence, BP and cardiovascular outcomes, according to Population, Interventions, Comparator, Outcomes, and Study designs (PICOS) methodology. Information on adverse events was captured from retrieved studies, including information on serious adverse events (SAEs). Observational data were summarized using descriptive statistics.

Methodological reporting

Methodological quality assessment was conducted for all randomized controlled trials (RCTs) according to the National Institute of Health and Care Excellence (NICE)

Single Technology Appraisal (STA) recommendation [18]. NICE STA involves scoring studies as 'low', 'unclear', or 'high' across 11 domains [18]. Observational studies were assessed using the Newcastle-Ottawa Quality Assessment Scale [19]. The Newcastle-Ottawa scale involves rating elements of study selection, comparability and exposure. A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability [19]. A 'good' quality score required 3 or 4 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes. A 'fair' quality score required 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes. A 'poor' quality score reflected 0 or 1 star(s) in selection, or 0 stars in comparability, or 0 or 1 star(s) in outcomes.

RESULTS

Study selection

Of the 863 citations identified, 756 remained after duplicates were removed. A further 645 articles failed to meet inclusion criteria, based on title and abstract screening. Overall, 111 publications were screened in full, and 82 were excluded due to reasons outlined in Fig. 1. As a result, 29 articles were considered suitable for inclusion [14,20–47].

Study populations and antihypertensive therapy prescribed

All 29 studies reported on adherence and/or persistence in patients taking SPC therapy for hypertension. Four studies were RCTs (14%) [35,37,38,46]; the remainder ($n = 25$; 86%) were observational studies [14,20–34,36,39–45,47] (Table S3, <http://links.lww.com/HJH/B268>). Sample sizes varied considerably, from $n = 75$ to $n = 79\,958$ for SPC therapy and $n = 73$ to $n = 383\,269$ for free-dose combination therapy. Thirteen studies (45%) were carried out in Europe, seven in Asia (24%), with other studies carried out across different continents (Table S3, <http://links.lww.com/HJH/B268>). The mean age across studies ranged from 46.8 to 71.5 years. Follow-up also varied widely, from 0.5 to 60 months, depending on study. Within the studies, reporting of baseline demographics varied. Of note, only 17 studies (59%) reported baseline BP, although all focused on management of patients with 'hypertension' as defined by their inclusion criteria.

A range of SPC therapy combinations were reported in the identified publications (Fig. 2). CCB/ARB combinations were the most common type of SPC therapy used by 11 treatment arms, followed by CCB/ACEi SPC, by 10 treatment arms. Amlodipine (amlo) besylate was the most commonly identified, specific antihypertensive agent in the SPC therapies, regardless of drug class. In the studies identified, amlo was used in treatment combination with all classes of antihypertensive, that is, in dual-SPC with an ARB, ACEi, beta-blocker or diuretic, and in 3-SPC therapy in combination with ARB/hydrochlorothiazide (HCTZ) and ACEi/HCTZ. The most commonly used ACEi was perindopril (per), and valsartan (val) was the most commonly used ARB in an SPC therapy, although some observational studies did not specify the type of ARB or ACEi within the SPC therapy. No combination agent included amiloride or spironolactone.

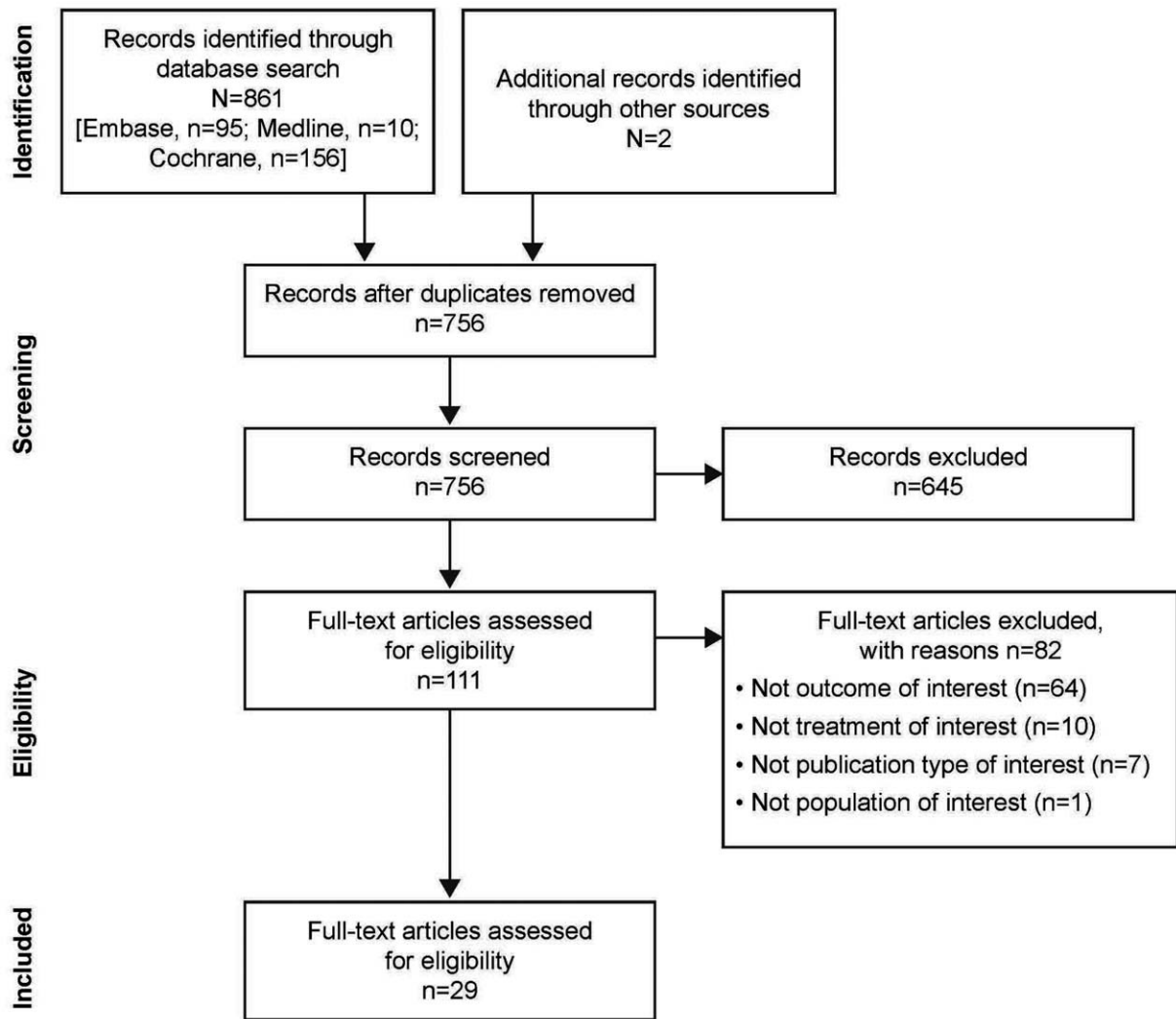


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Adherence and persistence

Twenty-eight studies reported data on adherence. One study reported data on persistence only (Table 1). All four RCTs reported adherence, although generally reported adherence for the whole study population rather than for each treatment arm separately, and specific comparison of adherence assessments was only reported by one of the RCT (Webster *et al.* [46]). Proportion of days covered (PDC) was the most commonly used measure of adherence, by nine of 28 studies (32%) (Table 1). Generally a definition of 'adherent' was PDC at least 80% in these studies (Table 1). Other measures for adherence included tablet count ($n = 3$), patient self-reported adherence ($n = 4$), medication possession ratio (MPR) ($n = 2$) and Morisky Medication Adherence Scale ($n = 2$). Medication discontinuation (>60 days), ingestion, physician-rated and Hill-Bone Compliance were used to measure adherence in one study each; four studies did not report the method used to measure adherence, but noted that adherence was assessed.

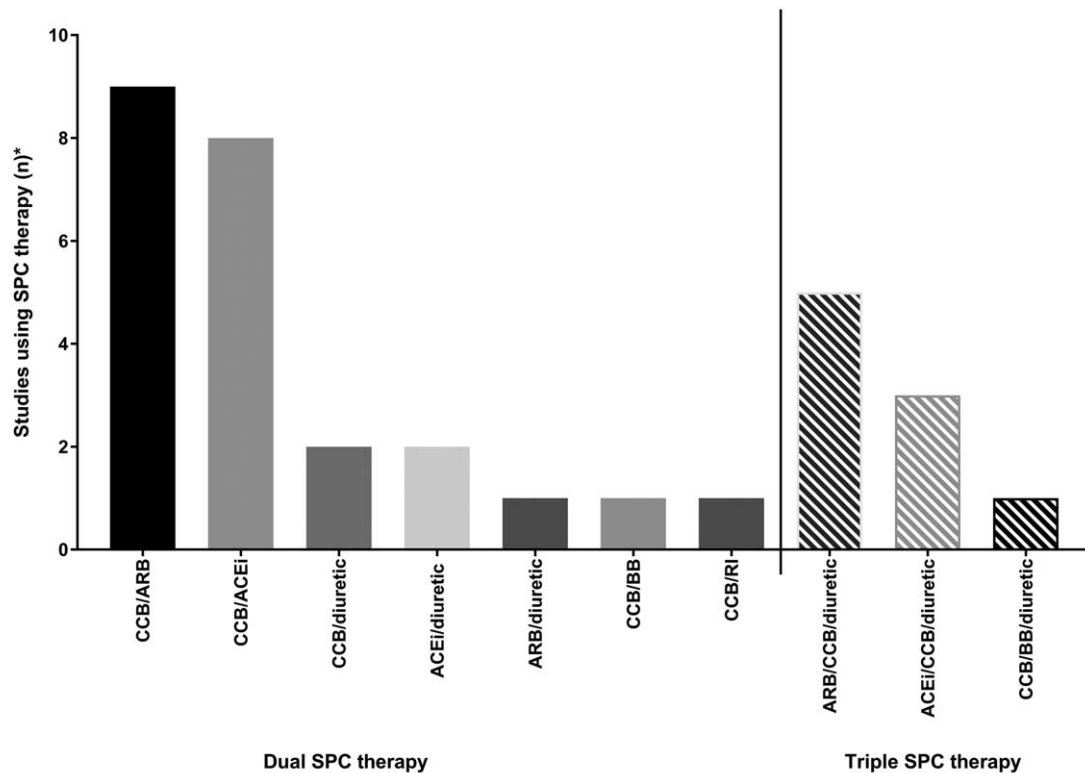
For the 15 studies (54%) that directly compared adherence with SPC therapy vs. free-dose combination therapy, adherence was generally higher with SPC therapy than with

free-dose combination therapy (Table 1). Only six of 15 studies included statistical comparison of treatment arms. Of these six studies, only Webster *et al.* [46] did not see a difference in adherence between SPC and free-dose combination therapy ($P = 0.82$), although this study did use ingestion as a measure of adherence, whereas the other studies used PDC or MPR.

Seven studies (24%) discussed persistence assessments, of which only four studies directly compared SPC vs. free-dose combination therapy (Table 1). All four of these studies demonstrated a significant improvement in persistence with SPC vs. free-dose combination therapy (Table 1).

Change in blood pressure and blood pressure control

Only 14 studies (48%) reported the number of patients reaching their target BP, although none reported the time to achieve BP control (Fig. 3). BP was consistently assessed as less than 140/90 mmHg in studies that defined BP targets. The percentage of patients who achieved target BP ranged from 25% (reported at 1 month) [37] to 89% (reported at 4 months) [45]. All four RCTs reported on BP goal



*categories are not mutually exclusive as some studies had more than 1 SPC therapy arm.
BB, beta-blocker; RI, renin-inhibitor.

FIGURE 2 Single-pill combination therapies utilized in studies identified by the rapid evidence assessment of recent literature.

attainment following randomization to treatment [21,37,38,46]. However, of these, just two studies provided statistical comparison of treatment arms, both of which demonstrated a significant improvement in BP goal attainment with SPC vs. free-dose combination therapy (Fig. 3).

Despite all studies investigating antihypertensive treatments, only half of the studies [16/29 studies (55%)] clearly reported change in BP during the study. All of these 16 studies, which included all four RCTs, noted BP reduction following antihypertensive treatment, although the time-to-follow-up varied. The majority of these 16 studies reported a significant change in BP from baseline. Three studies (19%) compared change in BP between SPC and free-dose combination regimens [22,38,46]. Of these three studies, Webster *et al.* [46] reported a significant difference in BP with SPC vs. free-dose combination therapy (reduction in SBP -29.3 vs. -20.6 mmHg; $P < 0.001$), whereas Bramlage *et al.* [22] reported no significant difference in change in BP with SPC vs. free-dose combination (change in SBP -9.1 vs. -8.7 mmHg; $P = 0.964$) and Nedogoda *et al.* [38] reported change in BP was similar between triple SPC [per/indapamide (ind)/amlo] and two-pill therapy (dual SPC per/ind + amlo; change in SBP -21.5 vs. -20.0 mmHg).

Cardiovascular morbidity and mortality

There were no RCTs that investigated cardiovascular outcomes (Table 2); however, some studies provided information regarding cardiovascular outcomes with SPC therapy. For example, Simons *et al.* [42] specifically discussed cardiovascular mortality over 48-month follow-up, and the

adjusted hazard ratio for risk of death over 48 months for single-pill vs. two-pill therapy (any CCB/ACEi therapy vs. amlo + per therapy) was 1.83 [95% confidence interval (CI) 1.55–2.16]. In addition, hazard ratio for discontinuation with SPC vs. two-pill therapy was 1.86 (95% CI 1.74–1.99) [42]. The authors noted that the mortality outcome may be an overestimate due to residual confounding [42]. Verma *et al.* [14] reported on the hazard ratio of death for patients taking any SPC vs. free-dose combination therapy in Canada, and found (in an intention-to-treat analysis) a significantly lower rate of composite primary outcome, respectively (3.4 events/100 persons vs. 3.9 events/100 persons; hazard ratio = 0.89; 95% CI, 0.81–0.97; $P < 0.01$) [14]. However, for an on-treatment analysis (only patients who remained adherent with medication), there was no significant difference between treatment arms, demonstrating the importance of adherence in the treated population (hazard ratio = 1.06; 95% CI, 0.86–1.31; $P = 0.60$) [14]. Tung *et al.* [44] reported event rates with SPC of amlo/val vs. free-dose combination therapy (any CCB + any ARB) after a median follow-up of 15.2 months in a data set from Taiwan. This study also reported a reduction in major adverse cardiovascular events (hazard ratio = 0.83; 95% CI, 0.73–0.94; $P < 0.001$), and a reduction in the rates of heart failure, PCI, and malignant dysrhythmia with SPC vs. free-dose combination therapy [44].

Summary of adverse events

In general, study medication was well tolerated in the 15 studies (52%) that reported on drug-related adverse events.

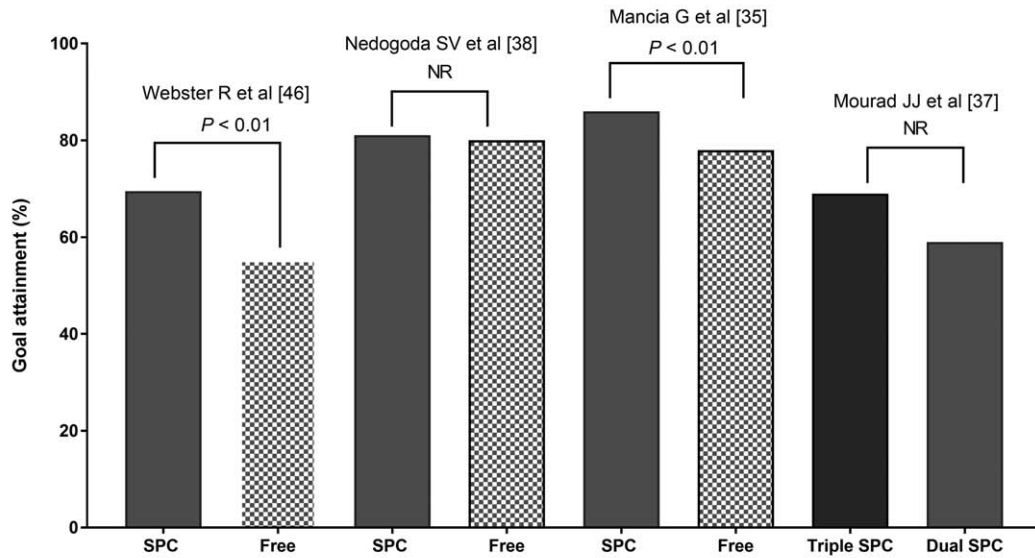
TABLE 1. Studies reporting assessments of adherence or persistence with single-pill combination therapy or with free-dose combination therapy

1st Author (year) [REF], study type	Sample size	Treatment (SPC/free)	Treatment details	Follow-up (months)	Measure of adherence/persistence ^a	P value	
(a) Measures of adherence ^b Bramlage (2018) [22] – Obs	10938	SPC	ram/amlo	12	MPR ≥ 80%	5699 (52.1)	
	60525	Free	ram + amlo	12	MPR ≥ 80%	19913 (32.9)	
	1413	SPC	cand/amlo	12	MPR ≥ 80%	1195 (84.6)	
	9082	Free	cand + amlo	12	MPR ≥ 80%	5286 (58.2)	
	349 (321, adherence calculation)	SPC	tel/amlo/chlo	6	Ingestion ≥ 4 of last 7 days	305 (95.0)	
	351 (336, adherence calculation)	Free	Not specified	6	Ingestion ≥ 4 of last 7 days	318 (94.6)	
	3597	SPC	per/amlo	12	PDC ≥ 80%	2597 (72.2)	
	20423	Free	Not specified	12	PDC ≥ 80%	12969 (63.5)	
	79958	SPC	Not specified	12	PDC ≥ 80%	40505 (51.3)	
	383 269	Mono	Not specified	12	PDC ≥ 80%	161 356 (42.1)	
Levi (2016) [32] – Obs	4522	SPC	olim/amlo	6	PDC ≥ 80%	1684 (55.1)	
	2090	Free	olim + amlo	6	PDC ≥ 80%	291 (15.9)	
	1884	SPC	amlo/val/HCTZ	12	PDC ≥ 80%	1040 (55.2)	
	1884	Free	amlo + val + HCTZ	12	PDC ≥ 80%	629 (33.4)	
	5725	SPC	ARB/thiazide diuretic	24	MPR ≥ 80%	1747 (30.5)	
	1623	Free	ARB + thiazide diuretic	24	MPR ≥ 80%	371 (22.9)	
	239	SPC	olim/amlo	6	PDC ≥ 80%	188 (78.7)	
	20769	Free	Not specified	6	PDC ≥ 80%	13084 (63)	
	8516	SPC (triple-pill)	olim/amlo/HCTZ or val/amlo/HCTZ	12	PDC ≥ 80%	4710 (55.3)	
	7842	Mix (2 pills)	olim/amlo + HCTZ or val/amlo + HCTZ, or olim/HCTZ + amlo, or val/HCTZ + amlo	12	PDC ≥ 80%	3171 (40.4)	
Panjabi (2013) [39] – Obs	1107	Free (3 pills)	olim + alm + HCTZ or val + alm + HCTZ	12	PDC ≥ 80%	361 (32.6)	
	4005	Mix (2 pills)	amlo/HCTZ + ARB	34.2	PDC ≥ 80%	1033 (25.8)	
	1335	Free (3 pills)	amlo + HCTZ + ARB	34.6	PDC ≥ 80%	184 (13.8)	
	6082	Mix (2 pills)	amlo/HCTZ + ACEi	33.6	PDC ≥ 80%	1448 (23.8)	
	3041	Free (3 pills)	amlo + HCTZ + ACEi	33.3	PDC ≥ 80%	487 (16.0)	
	609	Mix (2 pills)	amlo/HCTZ + BB	34.7	PDC ≥ 80%	173 (28.4)	
	1218	Free (3 pills)	amlo + HCTZ + BB	35.6	PDC ≥ 80%	166 (13.6)	
	(b) Measures of persistence ^c Bramlage (2018) [22] – Obs	10938	SPC	ram/amlo	12	Prescription fill	7186 (65.7)
		60525	Free	ram + amlo	12	Prescription fill	29415 (48.6)
		1413	SPC	cand/amlo	12	Prescription fill	784 (55.5)
9082		Free	cand + amlo	12	Prescription fill	3914 (43.1)	
79958		SPC	Not specified	12	Prescription refill	40938 (51.2)	
383 269		Monotherapy	Not specified	12	Prescription refill	164806 (43)	
9340 (700 for persistence calculation)		SPC	amlo/per	42	Prescription refill	350 (50)	
3093 (78 for persistence calculation)		Free	amlo + per	42	Prescription refill	21 (27)	
5725		SPC	ARB/thiazide diuretic	24	Prescription refill	1494 (26.1)	
1623		Free	ARB + thiazide diuretic	24	Prescription refill	317 (19.5)	
Machnicki (2015) [34] – Obs	1884	SPC	amlo/val/HCTZ	12	30-day Tx gap	882 (46.8)	
	1884	Free	amlo + val + HCTZ	12	30-day Tx gap	445 (23.6)	
	8516	SPC (triple-pill)	olim/amlo/HCTZ or val/amlo/HCTZ	12	Prescription refill	7541 (88.55)	
	7842	Mix (2 pills)	olim/amlo + HCTZ or val/amlo + HCTZ, or olim/HCTZ + amlo, or val/HCTZ + amlo	12	Prescription refill	6363 (81.14)	
	1107	Free (3 pills)	olim + alm + HCTZ or val + alm + HCTZ	12	Prescription refill	869 (78.5)	
	Xie (2014) [47] – Obs	10938	SPC	ram/amlo	12	Prescription fill	7186 (65.7)
		60525	Free	ram + amlo	12	Prescription fill	29415 (48.6)
		1413	SPC	cand/amlo	12	Prescription fill	784 (55.5)
		9082	Free	cand + amlo	12	Prescription fill	3914 (43.1)
		79958	SPC	Not specified	12	Prescription refill	40938 (51.2)
383 269		Monotherapy	Not specified	12	Prescription refill	164806 (43)	
9340 (700 for persistence calculation)		SPC	amlo/per	42	Prescription refill	350 (50)	
3093 (78 for persistence calculation)		Free	amlo + per	42	Prescription refill	21 (27)	
5725		SPC	ARB/thiazide diuretic	24	Prescription refill	1494 (26.1)	
1623		Free	ARB + thiazide diuretic	24	Prescription refill	317 (19.5)	

^aN (%) adherent or persistent based on study criteria.
^bACEi, angiotensin-converting enzyme inhibitor; amlo, amlodipine; ARB, angiotensin 1 receptor (AT1); BB, beta-blocker; cand, candesartan; CCB, calcium channel blocker; chlo, chlorthalidone; HCTZ, hydrochlorothiazide; medox, medoximil; MPR, medication possession ratio; NR, not reported; Obs, observational; olm, olmesartan; per, perindopril; ram, ramipril; RCT, randomized-controlled trial; SPC, single-pill combination; tel, telmisartan; val, valsartan.

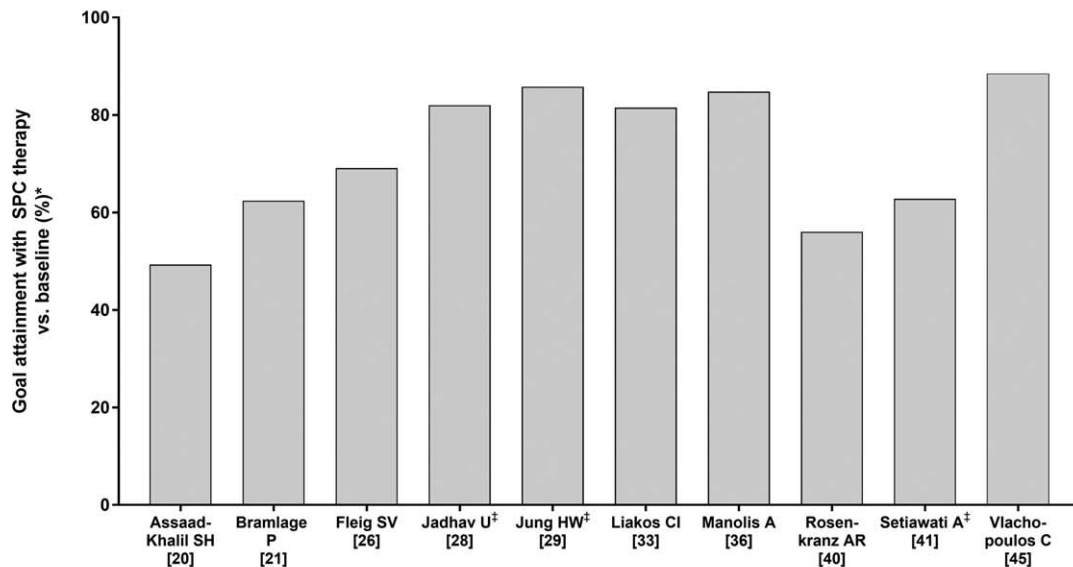
^cAdherence at 97.6 ± 6.4% (undefined measure) across the whole study population but did not differentiate between SPC and free-combination therapy [38]. Tung *et al.* (2015) reported mean PDC and is not included in the table [44]. Verma *et al.* (2017) (Obs) reported median PDC and is not included in the table [14]. Kumagia *et al.* (2013) (Obs) adherence was self-reported ingestion and is not included in the table [30]. Simonyi *et al.* (2016) (Obs) compared SPC of two different drug combinations and is not included in the table (no coadministered therapy comparator) [43].
^dTung *et al.* (2015) (Obs) reported data as mean persistence days and is not included in table [44].

(a) **RCT studies**



BP goal was <140/90 mmHg.
 Webster R et al [46] and Mancía G et al [35] reported after 6-months' follow-up. Nedogoda SV et al [38] and Mourad JJ et al [37] reported after 3-months' follow-up.
 NR = not reported.

(b) **Observational studies**



BP goal was <140/90 mmHg
 †Previously uncontrolled on monotherapy, switched to SPC therapy.
 ‡No studies reported significance in goal attainment with SPC therapy vs. either baseline or vs. comparator therapy.
 Follow-up was 3-6 months in all studies, with the exception of Jadhav U et al. [28] (at 1.5 months).

FIGURE 3 Studies reporting patients achieving blood pressure goal on single-pill combination therapy vs. free-dose combination therapy.

Depending on the study, adverse events were captured by clinical report or from information included in clinical records. Although of note, none of the studies were designed to be safety studies, and furthermore many of these studies were observational and allowed concomitant medications as required. Therefore, adverse event observations should be considered in light of these points. Of the

15 studies that included information on adverse events, eight (53%) reported SAEs, of which five studies (33%) specifically compared treatment with SPC vs. free-dose combination therapy. In these studies, the proportion of patients reporting SAEs on SPC therapy was generally 1% or less (Table S4, <http://links.lww.com/HJH/B268>). Only one study reported SAEs in free vs. SPC therapy, where SAEs

TABLE 2. Reported cardiovascular-related outcomes in studies comparing single-pill combination and free-dose combination regimens

1st Author (year) [REF], study type	Treatment (SPC/free)	Treatment details	n/N [%]							
			Hypotension	Oedema	Syncope	Angina	MI	HF	Stroke	
Verma (2018) [14] – Obs	SPC	NR	NR	NR	NR	NR	NR	46/8258 (0.6)	19/8261 (0.2)	39/8243 (0.5)
	Free	NR	NR	NR	NR	NR	NR	34/6322 (0.5)	11/6330 (0.2)	26/6320 (0.4)
Webster (2018) [46] – RCT	SPC	tel/amlo/chlo	2 (0.6)	6 (1.7)	18 (5.2)	11 (3.2)	NR	NR	NR	NR
	Free	NR	2 (0.6)	5 (1.4)	10 (2.8)	10 (2.8)	NR	NR	NR	NR
Nedogoda (2017) [38] – RCT	SPC	per/ind/amlo	NR	NR	NR	NR	NR	NR	NR	NR
	Free (2 pills)	(per/ind) + amlo	1 (1.3)	NR	NR	NR	NR	NR	NR	NR
Tung (2015) [44] – Obs	SPC	amlo/val	NR	NR	NR	NR	NR	19 (0.58)	70 (2.12)	197 (5.97)
	Free	ARB + CCB	NR	NR	NR	NR	NR	122 (0.92)	431 (3.26)	864 (6.54)
Panjabi (2013) [39] – Obs	Mix (2 pills)	amlo/HCTZ + ARB	NR	NR	NR	NR	NR	55 (1.37)	242 (6.04)	66 (1.65)
	Free (3 pills)	amlo + HCTZ + ARB	NR	NR	NR	NR	NR	17 (1.27)	90 (6.74)	27 (2.02)
	Mix (2 pills)	amlo/HCTZ + ACEi	NR	NR	NR	NR	NR	68 (1.12)	282 (4.64)	96 (1.58)
	Free (3 pills)	amlo + HCTZ + ACEi	NR	NR	NR	NR	NR	40 (1.32)	147 (4.83)	56 (1.84)
	Mix (2 pills)	amlo/HCTZ + BB	NR	NR	NR	NR	NR	30 (0.49)	33 (5.42)	11 (1.81)
	Free (3 pills)	amlo + HCTZ + BB	NR	NR	NR	NR	NR	20 (1.64)	101 (8.29)	26 (2.13)

ACEi, angiotensin-converting enzyme inhibitor; amlo, amlodipine; ARB, angiotensin 1 receptor (AT1) blocker; BB, beta blockers; BP, blood pressure; CCB, calcium channel blocker; chlo, chlorthalidone; HCTZ, hydrochlorothiazide; HF, heart failure; ind, indapamide; MI, myocardial infarction; per, perindopril; tel, telmisartan; val, valsartan.

were similar (7.7% with SPC vs. 6.0% with free). No deaths were reported to be directly related to study treatment. Discontinuation from study medication due to adverse events was not widely reported.

The most commonly reported adverse events in the 15 studies that reported on individual adverse events were oedema (10 publications) and hypotension (seven publications).

Methodological reporting practices

Four studies were RCTs and assessed according to the NICE STA checklist. Of these four studies, most had low or unclear ratings across the methodological assessment scales (Table S5A, <http://links.lww.com/HJH/B268>). Twenty-five observational studies were assessed according to the Newcastle-Ottawa Quality assessment [19]. Aspects of methodological reporting varied, with a median score of 8 seen across the 25 studies (Table S5B, <http://links.lww.com/HJH/B268>); the maximum score possible on the Newcastle-Ottawa scale was 9 which was scored by nine studies [14,27,29,31,32,34,42,44,47].

DISCUSSION

This systematic REA found that adherence and persistence are generally higher in patients initiating antihypertensive medication as SPC therapy rather than taking their antihypertensive therapy as multiple tablets, in free-dose combinations. However, we also found a paucity in data comparing BP lowering, BP control and/or cardiovascular outcomes in patients taking SPC therapy vs. free-dose combination therapy, with just four of 29 studies (14%) conducted as RCTs and, of these RCTs, only one reported a direct comparison of adherence for SPC vs. free-dose combination therapy. Within the studies identified, clear comparison of BP lowering or goal attainment for the SPC vs. free-dose combination therapy was presented in a

minority of studies, and links to improved adherence were unclear. As such, more high-quality evidence is required to determine if the increases in adherence seen in patients on SPC therapy translate into better BP control and ultimately improve long-term cardiovascular outcomes.

Since the development of SPC therapies in the hypertension arena and their recommendation for clinical use, debate has been rife on the benefits and drawbacks of prescribing therapies as a single pill to patients requiring more than one antihypertensive therapy, rather than in free-dose combinations that may be more easily and individually titrated, especially should an adverse event occur [16,48,49]. Data suggest that the majority of patients with AH will require more than one antihypertensive therapy to achieve BP goals [9,10], with complementary combinations of therapeutics providing, in some cases, improved tolerability alongside additional BP lowering towards therapeutic targets [50,51]. However, evidence is limited beyond the BP-lowering benefits of SPC therapies, and longer-term benefits on morbidity and/or mortality outcomes is largely assumed from efficacy data from RCTs involving the parent drugs. Recent guidelines from the ESC/ESH recommend that the majority of patients with AH initiate two antihypertensive agents and preferably as an SPC, to reduce BP quickly towards target [9]. Individual evidence suggests more frequent BP control after 1 year for patients initiating SPC therapy compared with monotherapy, in addition to a steeper dose–BP response curve [52]. However, in presenting their guidelines, the ESC/ESH committees sought further evidence on the impact of single pill vs. multiple-drug treatment strategies on adherence to treatment, BP control and clinical outcomes [9]. In addition to investigating these points, our study sought to highlight the gaps in literature to guide future study design and development to fully answer the unmet need highlighted by the ESC/ESH in 2018.

By assessing the existing literature, we highlight a number of areas where improvements could be made to study

TABLE 3. Gap in evidence for assessing efficacy of single-pill combination therapy vs. free-dose combination therapy

Topic	Evidence gap	Recommendations
Study design	RCTs [only 14% (4/29 in past 5 years)] Long-term prospective studies Outcome studies	Well-designed studies providing a direct comparison between adherence and BP control and/or CV outcomes for studies comparing SPC and free-dose combination therapies Longer-term follow-up to analyze efficacy Consistent recording and reporting of BP
Length of follow-up	Variation in follow-up length and time points made comparisons between studies difficult Few studies reported results beyond six months to one year of follow-up	Multiple and standardized time points should be included in future studies Longer follow-up periods will provide useful information on the long-term adherence benefits of SPC therapy
Assessment of efficacy	Approx. half of studies reported BP measurement or patients reaching BP goals Time to reach BP control not reported How BP was measured was rarely reported	Standard inclusion of BP efficacy measurement(s) Clear definition of time to reach BP control Follow standardized techniques for accurate BP measurement according to up-to-date guidelines Employ ABPM/HPBM/app technology (or similar) to improve assessment of BP out-of-office
Adherence/persistence measure	No standardized reporting of adherence or persistence measurements	Clear and consistent reporting measures for adherence (PDC and MPR are most commonly used) to facilitate comparison between studies Standardized and recommended reporting methodology for persistence Use of validated scales to confirm adherence in specific patient populations
Adverse events	AEs were rarely reported in studies comparing patients receiving SPC and free-combination therapies Few studies reported the grade of AE	Specific studies to determine if increased adherence on SPC therapy is associated with a different safety profile, rather than physicians having to extrapolate information from the safety profile of individual components of the SPC
Patient/physician preferences	Few studies reported patient or physician preferences for SPC or free-combination therapies, or types of antihypertensive medications being prescribed	Evaluate patient preferences for medication type and other factors affecting adherence to aid understanding of preferences around SPC therapy Educate physicians' treatment decisions as increased importance is being placed on patient preferences across all aspects of health care

ABPM, ambulatory blood pressure monitoring; AE, adverse event; BP, blood pressure; CV, cardiovascular; HBPM, home blood pressure monitoring; MPR, medication possession ratio; PDC, proportion of days covered; RCT, randomized controlled trial; SPC, single-pill combination.

reporting, design, or conduct (Table 3). First, specifically designed and powered RCTs are lacking, as just 10% supported evidence for SPC therapy, with just three RCTs providing statistical evidence for adherence and/or efficacy. In addition, well-designed, longer-term observational studies that support the efficacy observations from the RCTs are also required (Table 3). The majority of studies conducted in the past 5 years were observational (86%), which are inherently limited by the data they are using. As such, well-designed studies around international recommendations are still needed. Our assessment of methodological reporting highlighted that many studies were considered 'low' on basic aspects of reporting RCT design (on the NICE STA methodological scoring). Just nine of the 25 observational studies (36%) scored full 'points' on the Newcastle-Ottawa Quality assessment, indicating better reporting of fundamental aspects of observational study methodology, but still only in the minority of studies. Gaps in evidence will only be answered by ensuring full reporting of these, and other, fundamental points of methodology (Table 3).

One of the key driving forces behind the benefits for using SPC therapies is evidence that higher patient pill burden negatively affects adherence [47,53,54], and in turn lower adherence leads to poorer efficacy outcomes [55–57]. Although patients with hypertension and other cardiovascular risk factors may have comorbidities and be taking other medications [9,10], reducing pill count from three or two separate pills to one SPC would still impact their overall pill burden [53,58]. In line with our conclusion, previous literature analyses have demonstrated higher adherence for patients treated with SPC vs. free-dose combination therapy [15,59]. However, we found that direct comparisons were in the minority of studies; indeed from the four RCTs identified, only one directly compared adherence with SPC and

comparator therapy [46]. Similarly, only four studies (14%) included a direct comparison of persistence between SPC and free-dose combination therapy, none of which were RCTs [22,27,34,47]. Adherence is typically defined as an MPR or PDC above 80% [60], and 11 studies that used PDC or MPR in the current analysis did use this definition within their reporting. However, many studies simply included the statement that 'adherence was good...', or similar, limiting accurate representation of medication-taking behavior.

Another limitation to qualitative assessment of adherence with SPC vs. free-dose combination therapy was the use of many different types of assessment for adherence and persistence, each with their own intricacies. There are limitations associated with any self-reported measures [60], and scales should be validated in the patient population of interest [61–64], to ensure they can be relied upon [65]. Of note, monitoring ingestion by returned tablets was the only study that did not demonstrate a difference in adherence [46]. Regardless, more standardized assessment would facilitate comparison among studies, and a better fundamental understanding of medication-taking behavior. Therefore, we suggest there are evidence gaps in methodological design regarding the assessment of adherence/persistence, with a need to standardize definitions of 'adherent/persistent' (Table 3). There are many aspects that affect adherence beyond those directly related to the treatment, including patient-related and physician-related factors or socioeconomic reasons. Patient preference was assessed in only two studies [23,41], and no study reported on physician preference. As such, there is a lack of information available on all aspects of adherence, which is needed to fully understand why patients become non-adherent to their medications (Table 3). International guidelines may consider promoting methods to improve adherence, such

as those issued by the WHO based around the five dimensions of adherence [66].

Assessment of effectiveness in observational studies depends on the data available within the healthcare records; however, to confirm effectiveness of an antihypertensive, and that patients are taking their medication, BP needs to be routinely and accurately measured. For example, it is very surprising and a major shortcoming that only half of studies clearly reported BP reduction over time, and only approximately half of studies reported information on BP goal attainment. Guidelines clearly outline target BP for patients of different ages, risk levels and with different comorbidities [9,10]. These goals are developed through rigorous assessment of clinical evidence and academic debate, and although United States and European Union guidelines differ in their definition of 'hypertension', 'normal' BP is similarly defined (BP < 120 mmHg or BP 120–129 mmHg for the United States and European Union, respectively [9,10]). The importance of consistency and accuracy in measuring BP is something that has been commented on for decades [67–69] but still remains a major drawback when comparing clinical studies or real-world data [67]. To assess efficacy or effectiveness of any antihypertensive therapy, BP should be accurately recorded as standard medical practice after therapy initiation. Just three studies (10%) included ambulatory BP monitoring (ABPM) [26,35,37] and methodology of BP monitoring was generally insufficiently reported. Many studies have debated the need for more standardized and careful methodology for BP monitoring [67–69] and/or the use of ABPM/home BP monitoring, where costs and equipment allow [9,10]. Some investigations are ongoing in this area to confirm if out-of-office BP can improve cardiovascular outcomes [70–72], in an attempt to more accurately monitor BP away from the in-office setting. This includes investigating how cell phone apps, such as those developed by the ESC/ESH, may assist with BP monitoring [73,74]; but recent studies highlight that only the minority of existing apps meet quality and accuracy standards [75]. With the acceleration of technological interventions in recent times, improvements in monitoring apps is inevitable. But, improving study reporting and consistency in BP monitoring will aid interpretation of BP recording, and how the number reflects 'real' BP (Table 3).

In addition, there are gaps in the literature for studies assessing BP goal attainment with SPC therapy vs. free-dosed combination therapy, ideally in an RCT alongside other efficacy outcomes and/or retrospective observational studies that allow assessment of information on cardiovascular outcomes (Table 3). Moreover, studies are needed that not only demonstrate the continued efficacy of SPC therapies, but that allow loss of efficacy to be investigated. For example, highlighting the need to up-titrate by dose, or to add additional medications (e.g., two-pill SPC to three-pill SPC), and/or to address loss of adherence. Few studies provided statistical evidence for both improved adherence and improved efficacy or effectiveness of SPC therapy vs. free-dose combination therapy. In the longer term, evidence is needed to support a meta-analysis or similar, to determine if SPC

therapies lower cardiovascular mortality, as indicated by some individual observational studies. Of interest, very recently the WHO added, for the very first time, a SPC comprising two antihypertensive medications to the WHO Essential Medicines List [76], thereby acknowledging that the use of SPC is the emerging best practice for safe, effective, rapid, and convenient hypertension control worldwide [77].

Our study should be considered in light of its limitations. We conducted a systematic rapid-evidence assessment to focus our methodology within databases known to publish high-quality evidence, but this methodology is less exhaustive than a full SLR. It is possible that by conducting an SLR, information published outside of EMBASE, MEDLINE, and COCHRANE may have been captured, and the number of studies included changed as a result. Our assessments are naturally limited by the information available in the publications. Therefore, further information on BP measurement, for example, may not have been included due to word constraints or similar. The use of concomitant medications in all patient groups should be considered when efficacy observations are compared. The aim of each study would have varied, depending on if any specific patient type was being investigated. Higher risk patients would have been managed differently, and the selection of medications would have been made in light of any comorbidities or existing medications. For example, no SPC included the combination of a thiazide diuretic + potassium-sparing diuretic, which can be prescribed in SPC in specific patient groups [78]. Finally, we summarize information published from RCT trials (14%) alongside observational studies of healthcare records, and the difference in these approaches should be considered when interpreting our observations. These observational studies reflect real-world clinical practice, and by selecting both types of study conducted in the past 5 years, we have been able not only to support adherence observations for selecting SPC therapy, but also to acknowledge the gaps in literature, by study type.

In conclusion, adherence and persistence were generally higher for patients taking antihypertensive medication as a SPC rather than as free-dose combination therapy, although a number of different ways of measuring adherence and persistence limited the ability to directly compare studies. In addition, few studies compared BP control and/or fewer still reported cardiovascular outcomes in patients prescribed SPC vs. free-dose combination therapy. Most surprisingly, only half of studies clearly reported change in BP during the study, and fewer still included detail on the methodology used to measure BP, limiting our ability to effectively compare the BP-lowering outcomes of these hypertension management approaches. As a result, future studies need to work on filling these gaps in the literature (Table 3), with specifically designed and reported studies aiming to determine if an increase in adherence with SPC regimen leads to better efficacy outcomes. Furthermore, better methodological reporting and recommendations from international bodies on standardizing assessments would also aid fuller comparison of medication-taking behavior and allow the benefits of SPC therapy to be more fully explored.

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Conflicts of interest

K.T. has received research grants or honoraria for advisory boards and lectures from Medtronic, Servier, Bayer, Menarini, Novartis, AstraZeneca, Boehringer Ingelheim, Pfizer, Chiesi, Sanofi, Amgen, ELPEN, Recordati and Winmedica. He was a member of the Task Force of the 2018 ESC/ESH Hypertension Guidelines. R.K. has received honoraria for consultancy, lectures, and support for research from Bayer Pharma, Berlin-Chemi Menarini, Daiichi Sankyo, Ferrer, Sanofi and Servier. He was a member of the Task Force of the 2018 ESC/ESH Hypertension Guidelines. G.S., J.V.V., and T.H. are full-time employees of Upjohn a division of Pfizer Inc.

REFERENCES

- GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392:1923–1994.
- Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. *JAMA* 2017; 317:165–182.
- NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017; 389:37–55.
- Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013; 310:959–968.
- Raal FJ, Alsheikh-Ali AA, Omar MI, Rashed W, Hamoui O, Kane A, et al. Cardiovascular risk factor burden in Africa and the Middle East across country income categories: a post hoc analysis of the cross-sectional Africa Middle East Cardiovascular Epidemiological (ACE) study. *Arch Public Health* 2018; 76:15.
- Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation* 2016; 134:441–450.
- Geldsetzer P, Manne-Goehler J, Marcus ME, Ebert C, Zhumadilov Z, Wesseh CS, et al. The state of hypertension care in 44 low-income and middle-income countries: a cross-sectional study of nationally representative individual-level data from 1.1 million adults. *Lancet* 2019; 394:652–662.
- NCD Risk Factor Collaboration (NCD-RisC). Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. *Lancet* 2019; 394:639–651.
- Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018; 36:1953–2041.
- Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; 71:e13–e115.
- Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373:2103–2116.
- Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, 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). *J Hypertens* 2013; 31:1281–1357.
- Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension* 2010; 55:399–407.
- Verma AA, Khuu W, Tadrous M, Gomes T, Mamdani MM. Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: a population-based retrospective cohort study. *PLoS Med* 2018; 15:e1002584.
- Mallat SG, Tanios BY, Itani HS, Lotfi T, Akl EA. Free versus fixed combination antihypertensive therapy for essential arterial hypertension: a systematic review and meta-analysis. *PLoS One* 2016; 11:e0161285.
- Angeli F, Reboldi G, Mazzotta G, Garofoli M, Ramundo E, Poltronieri C, et al. Fixed-dose combination therapy in hypertension: cons. *High Blood Press Cardiovasc Prev* 2012; 19:51–54.
- Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015; 350:g7647.
- National Institute for Health and Care Excellence (NICE). Guide to the single technology appraisal HBPM, home blood pressure monitoring. Available at: <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Guide-to-the-single-technology-appraisal-process.pdf>. [Accessed 25 June 2019].
- Wells G, Shea B, O'Connell D, Robertson J, Peterson J, Welch V, et al. The Newcastle–Ottawa scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. 2019. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Accessed 18 April 2019].
- Assaad-Khalil SH, Nashaat N. Real-life effectiveness and safety of amlodipine/valsartan single-pill combination in patients with hypertension in Egypt: results from the EXCITE study. *Drugs Real World Outcomes* 2016; 3:307–315.
- Bramlage P, Ketelhut R, Fronk EM, Wolf WP, Smolnik R, Zemmrich C, et al. Clinical impact of patient adherence to a fixed-dose combination of olmesartan, amlodipine and hydrochlorothiazide. *Clin Drug Investig* 2014; 34:403–411.
- Bramlage P, Schmidt S, Sims H. Fixed-dose vs free-dose combinations for the management of hypertension – an analysis of 81 958 patients. *J Clin Hypertens (Greenwich)* 2018; 20:705–715.
- Czarnecka D, Koch EM, Gottwald-Hostalek U. Benefits of a fixed-dose combination of bisoprolol and amlodipine in the treatment of hypertension in daily practice: results of more than 4000 patients. *Curr Med Res Opin* 2015; 31:875–881.
- Degli Esposti L, Perrone V, Veronesi C, Gambera M, Nati G, Perone F, et al. Modifications in drug adherence after switch to fixed-dose combination of perindopril/amlodipine in clinical practice. Results of a large-scale Italian experience. The amlodipine-perindopril in real settings (AMPERES) study. *Curr Med Res Opin* 2018; 34:1571–1577.
- Degli Esposti L, Saragoni S, Buda S, Degli Esposti E. Drug adherence to olmesartan/amlodipine fixed combination in an Italian clinical practice setting. *Clinicoecon Outcomes Res* 2014; 6:209–216.
- Fleig SV, Weger B, Haller H, Limbourg FP. Effectiveness of a fixed-dose, single-pill combination of perindopril and amlodipine in patients with hypertension: a non-interventional study. *Adv Ther* 2018; 35:353–366.
- Hsu CI, Hsiao FY, Wu FL, Shen LJ. Adherence and medication utilisation patterns of fixed-dose and free combination of angiotensin receptor blocker/thiazide diuretics among newly diagnosed hypertensive patients: a population-based cohort study. *Int J Clin Pract* 2015; 69:729–737.

28. Jadhav U, Hiremath J, Namjoshi DJ, Gujral VK, Tripathi KK, Siraj M, *et al.* Blood pressure control with a single-pill combination of indapamide sustained-release and amlodipine in patients with hypertension: the EFFICIENT study. *PLoS One* 2014; 9:e92955.
29. Jung HW, Kim KI, Park CG, Kang DH, Ahn Y, Bae JH, *et al.* A multicenter, non-comparative study to evaluate the efficacy and safety of fixed-dose olmesartan/amlodipine in Korean patients with hypertension who are naive or non-responders to anti-hypertensive monotherapy (ACE-HY study). *Clin Exp Hypertens* 2015; 37:482–489.
30. Kumagai N, Onishi K, Hoshino K, Nakamori S, Kitai T, Yazu T, *et al.* Improving drug adherence using fixed combinations caused beneficial treatment outcomes and decreased health-care costs in patients with hypertension. *Clin Exp Hypertens* 2013; 35:355–360.
31. Lauffenburger JC, Landon JE, Fischer MA. Effect of combination therapy on adherence among US patients initiating therapy for hypertension: a cohort study. *J Gen Intern Med* 2017; 32:619–625.
32. Levi M, Pasqua A, Cricelli I, Cricelli C, Piccinni C, Parretti D, *et al.* Patient adherence to olmesartan/amlodipine combinations: fixed versus extemporaneous combinations. *J Manag Care Spec Pharm* 2016; 22:255–262.
33. Liakos CI, Papadopoulos DP, Kotsis VT. Adherence to treatment, safety, tolerance, and effectiveness of perindopril/amlodipine fixed-dose combination in Greek patients with hypertension and stable coronary artery disease: a pan-Hellenic prospective observational study of daily clinical practice. *Am J Cardiovasc Drugs* 2017; 17:391–398.
34. Machnicki G, Ong SH, Chen W, Wei ZJ, Kahler KH. Comparison of amlodipine/valsartan/hydrochlorothiazide single pill combination and free combination: adherence, persistence, healthcare utilization and costs. *Curr Med Res Opin* 2015; 31:2287–2296.
35. Mancía G, Asmar R, Amodeo C, Mourad JJ, Taddei S, Gamba MA, *et al.* Comparison of single-pill strategies first line in hypertension: perindopril/amlodipine versus valsartan/amlodipine. *J Hypertens* 2015; 33:401–411.
36. Manolis A, Grammatikou V, Kallistratos M, Zarifis J, Tsioufis K. Blood pressure reduction and control with fixed-dose combination perindopril/amlodipine: a Pan-Hellenic prospective observational study. *J Renin Angiotensin Aldosterone Syst* 2015; 16:930–935.
37. Mourad JJ, Amodeo C, de Champvallins M, Brzozowska-Villatte R, Asmar R, Study Coordinators. Blood pressure-lowering efficacy and safety of perindopril/indapamide/amlodipine single-pill combination in patients with uncontrolled essential hypertension: a multicenter, randomized, double-blind, controlled trial. *J Hypertens* 2017; 35:1481–1495.
38. Nedogoda SV, Stojanov VJ. Single-pill combination of perindopril/indapamide/amlodipine in patients with uncontrolled hypertension: a randomized controlled trial. *Cardiol Ther* 2017; 6:91–104.
39. Panjabi S, Lacey M, Bancroft T, Cao F. Treatment adherence, clinical outcomes, and economics of triple-drug therapy in hypertensive patients. *J Am Soc Hypertens* 2013; 7:46–60.
40. Rosenkranz AR, Ratzinger M. Efficacy, safety, and tolerability of anti-hypertensive therapy with aliskiren/amlodipine in clinical practice in Austria. The RALLY (Rasilamlo long lasting efficacy) study. *Wien Klin Wochenschr* 2015; 127:203–209.
41. Setiawati A, Kalim H, Abdillah A. Clinical effectiveness, safety and tolerability of amlodipine/valsartan in hypertensive patients: the Indonesian subset of the EXCITE study. *Acta Med Indones* 2015; 47:223–233.
42. Simons LA, Chung E, Ortiz M. Long-term persistence with single-pill, fixed-dose combination therapy versus two pills of amlodipine and perindopril for hypertension: Australian experience. *Curr Med Res Opin* 2017; 33:1783–1787.
43. Simonyi G, Ferenci T, Alföldi S, Farsang C. Ramipril + amlodipine and ramipril + hydrochlorothiazide fixed-dose combinations in relation to patient adherence. *J Int Med Res* 2016; 44:1087–1091.
44. Tung YC, Lin YS, Wu LS, Chang CJ, Chu PH. Clinical outcomes and healthcare costs in hypertensive patients treated with a fixed-dose combination of amlodipine/valsartan. *J Clin Hypertens (Greenwich)* 2015; 17:51–58.
45. Vlachopoulos C, Grammatikou V, Kallistratos M, Karagiannis A. Effectiveness of perindopril/amlodipine fixed dose combination in everyday clinical practice: results from the EMERALD study. *Curr Med Res Opin* 2016; 32:1605–1610.
46. Webster R, Salam A, de Silva HA, Selak V, Stepien S, Rajapakse S, *et al.* Fixed low-dose triple combination antihypertensive medication vs usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka: a randomized clinical trial. *JAMA* 2018; 320:566–579.
47. Xie L, Frech-Tamas F, Marrett E, Baser O. A medication adherence and persistence comparison of hypertensive patients treated with single-, double- and triple-pill combination therapy. *Curr Med Res Opin* 2014; 30:2415–2422.
48. Moriarty F, Bennett K, Fahey T. Fixed-dose combination antihypertensives and risk of medication errors. *Heart* 2019; 105:204–209.
49. Taddei S. Fixed-dose combination therapy in hypertension: pros. *High Blood Press Cardiovasc Prev* 2012; 19:55–57.
50. Talbert RL. Role of antihypertensive therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in combination with calcium channel blockers for stroke prevention. *J Am Pharm Assoc (2003)* 2010; 50:e116–e125.
51. Taddei S. Combination therapy in hypertension: what are the best options according to clinical pharmacology principles and controlled clinical trial evidence? *Am J Cardiovasc Drugs* 2015; 15:185–194.
52. MacDonald TM, Williams B, Webb DJ, Morant S, Caulfield M, Cruickshank JK, *et al.* Combination therapy is superior to sequential monotherapy for the initial treatment of hypertension: a double-blind randomized controlled trial. *J Am Heart Assoc* 2017; 6:e006986.
53. Benner JS, Chapman RH, Petrilla AA, Tang SSK, Rosenberg N, Schwartz JS. Association between prescription burden and medication adherence in patients initiating antihypertensive and lipid-lowering therapy. *Am J Health Syst Pharm* 2009; 66:1471–1477.
54. Vrijens B, Antoniou S, Burnier M, de la Sierra A, Volpe M. Current situation of medication adherence in hypertension. *Front Pharmacol* 2017; 8:100.
55. Leslie KH, McCowan C, Pell JP. Adherence to cardiovascular medication: a review of systematic reviews. *J Public Health (Oxf)* 2019; 41:e84–e94.
56. Bansilal S, Castellano JM, Garrido E, Wei HG, Freeman A, Spettell C, *et al.* Assessing the impact of medication adherence on long-term cardiovascular outcomes. *J Am Coll Cardiol* 2016; 68:789–801.
57. Faridi KF, Peterson ED, McCoy LA, Thomas L, Enriquez J, Wang TY. Timing of first postdischarge follow-up and medication adherence after acute myocardial infarction. *JAMA Cardiol* 2016; 1:147–155.
58. Truelove M, Patel A, Bompont S, Brown A, Cass A, Hillis GS, *et al.* The effect of a cardiovascular polypill strategy on pill burden. *Cardiovasc Ther* 2015; 33:347–352.
59. Salam A, Kanukula R, Atkins E, Wang X, Islam S, Kishore SP, *et al.* Efficacy and safety of dual combination therapy of blood pressure-lowering drugs as initial treatment for hypertension: a systematic review and meta-analysis of randomized controlled trials. *J Hypertens* 2019; 37:1768–1774.
60. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, *et al.* Medication compliance and persistence: terminology and definitions. *Value Health* 2008; 11:44–47.
61. Dehghan M, Dehghan-Nayeri N, Iranmanesh S. Translation and validation of the Persian version of the treatment adherence questionnaire for patients with hypertension. *ARYA Atheroscler* 2016; 12:76–86.
62. Moharamzad Y, Saadat H, Nakhjavan Shahraki B, Rai A, Saadat Z, Aerab-Sheibani H, *et al.* Validation of the Persian version of the 8-Item Morisky Medication Adherence Scale (MMAS-8) in Iranian hypertensive patients. *Glob J Health Sci* 2015; 7:173–183.
63. de Oliveira-Filho AD, Morisky DE, Neves SJ, Costa FA, de Lyra DP Jr. The 8-Item Morisky Medication Adherence Scale: validation of a Brazilian-Portuguese version in hypertensive adults. *Res Social Adm Pharm* 2014; 10:554–561.
64. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Curr Med Res Opin* 2009; 25:2303–2310.
65. van de Steeg N, Sielk M, Pentzek M, Bakx C, Altiner A. Drug-adherence questionnaires not valid for patients taking blood-pressure-lowering drugs in a primary health care setting. *J Eval Clin Pract* 2009; 15:468–472.
66. World Health Organization. Adherence to long-term therapies: evidence for action. 2003. Available at: http://www.who.int/chp/knowledge/publications/adherence_report/en/. [Accessed 25 June 2019].

67. Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S, *et al.* Measurement of blood pressure in humans: a scientific statement from the American Heart Association. *Hypertension* 2019; 73:e35–e66.
68. Target BP. BP guideline. 2016. Available at: <https://targetbp.org/guidelines17/>. [Accessed 12 August 2019].
69. Handler J. The importance of accurate blood pressure measurement. *Perm J* 2009; 13:51–54.
70. Agarwal R, Bills JE, Hecht TJ, Light RP. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: a systematic review and meta-analysis. *Hypertension* 2011; 57:29–38.
71. Niiranen TJ, Hanninen MR, Johansson J, Reunanen A, Jula AM. Home-measured blood pressure is a stronger predictor of cardiovascular risk than office blood pressure: the Finn-Home study. *Hypertension* 2010; 55:1346–1351.
72. Bliziotis IA, Destounis A, Stergiou GS. Home versus ambulatory and office blood pressure in predicting target organ damage in hypertension: a systematic review and meta-analysis. *J Hypertens* 2012; 30:1289–1299.
73. Parati G, Torlasco C, Omboni S, Pellegrini D. Smartphone applications for hypertension management: a potential game-changer that needs more control. *Curr Hypertens Rep* 2017; 19:48.
74. Parati G, Agabiti-Rosei E, Bakris GL, Bilo G, Branzi G, Cecchi F, *et al.* MASked-unconTrolled hypERTension management based on office BP or on ambulatory blood pressure measurement (MASTER) Study: a randomised controlled trial protocol. *BMJ Open* 2018; 8:e021038.
75. Leong AY, Makowsky MJ. Quality of blood pressure tracking apps for the iPhone: content analysis and evaluation of adherence with home blood pressure measurement best practices. *JMIR Mhealth Uhealth* 2019; 7:e10809.
76. Salam A, Kanukula R, Esam H, Bahiru E, Sharma A, Heller D, *et al.* An application to include blood pressure lowering drug fixed dose combinations to the model list of essential medicines lists for the treatment of essential hypertension in adults. 2018. Available at: https://www.who.int/selection_medicines/committees/expert/22/s12_FDC-antihypertensives.pdf?ua=1. [Accessed 14 October 2019].
77. Benjamin IJ, Kreutz R, Olsen MH, Schutte AE, Lopez-Jaramillo P, Frieden TR, *et al.* Fixed-dose combination antihypertensive medications. *Lancet* 2019; 394:637–638.
78. Roush GC, Sica DA. Diuretics for hypertension: a review and update. *Am J Hypertens* 2016; 29:1130–1137.