Hypertension

REVIEW

Starting Antihypertensive Drug Treatment With Combination Therapy

Controversies in Hypertension - Con Side of the Argument

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The 2018 European Society of Cardiology/European Society of Hypertension[1] and the 2020 International Society of Hypertension[2] guidelines for the management of hypertension proposed that initial combination therapy with 2 antihypertensive agents in a single-pill combination (SPC) is preferred in most patients in need of blood pressure (BP) lowering treatment and should replace the long-standing concept of starting treatment with a single agent, rotating through antihypertensive drug classes, and next moving towards combining drug classes. By moving SPCs forward as the initial BP-lowering strategy, the European[1] and International[2] Societies of Hypertension Guideline Committees overlooked several principles in hypertension management: (1) understanding the pathophysiology of hypertension; (2) prioritizing evidence from randomized clinical trials above observational studies and expert opinion; and (3) giving consideration to the cost-effectiveness of antihypertensive drug treatment and the sustainability of health care. This article addresses these points. Sources of information included (1) guidelines issued by European,[1,3,4] American,[5–7] International,[2,8,9] and British[10–12] Expert Committees, published between 1999[8] and 2020,[2] summarized in Table S1 in the Data Supplement; (2) a PubMed search ran on May 5, 2020, without limitations with as search terms in the abstract or title "hypertension" combined with "fixed combination" OR "hypertension" combined with "single" and "costs"; (3) the placebo-controlled trials of antihypertensive drug treatment, as identified from the reference lists of 5 systematic literature reviews,[13–17] of which 2 were published by the Blood Pressure Lowering Trialists' Collaboration[14,16]; (4) 3 randomized controlled trials of usual versus intensive BP control[18–20]; and (5) the retail costs of antihypertensive drugs on the Belgian market (https://www.bcfi.be).

TAILORING ANTIHYPERTENSIVE TREATMENT

In the early 1970s, Laragh's group coined the terms low-renin, normal-renin, and high-renin hypertension by relating plasma renin activity to the daily sodium excretion.[21] Under normal conditions, plasma renin activity increases with sodium restriction but decreases with higher BP.[21] Although an imperfect generalization, low-renin hypertension is characterized by volume expansion

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and its high-renin counterpart by increased peripheral resistance,[22,23] and are indications to start BP-lowering treatment with a diuretic as opposed to an inhibitor of the renin-angiotensin system or vasodilator.[24] The activity of the renin system decreases with advancing age[22] and is lower in Blacks compared with Whites.[25–27] These pathophysiological principles explain why guidelines, with the exception of the 2018 European[1] and the 2020 International[2] guidelines recommend to start antihypertensive drug treatment with ACE (angiotensin-converting enzyme) inhibitors or ARBs below age 55 and with thiazide diuretics (TDs) or dihydropyridine CCBs (calcium-channel blockers) in older patients and in Blacks across the adult age range. Isolated systolic hypertension, which in its initial course is not associated with increased peripheral resistance, but is caused by stiffening of the large arteries[28] is an indication for TDs[29] or CCBs.[30,31] The 2020 International Society of Hypertension guideline[2] supported the use of thiazide-like diuretics, that is, indapamide and chlorthalidone, rather than regular TDs (chlorothiazide and hydrochlorothiazide), based on a systematic review of 19 randomized clinical trials involving 112 113 patients.[32] The observed benefits were mainly confined to thiazide-like diuretics rather than TDs with reductions in the risk of cardiac events (odds ratio, 0.78; $P<0.001$), heart failure (odds ratio, 0.57; $P<0.001$), and stroke (odds ratio, 0.82; $P=0.016$).[32]

ACE inhibitors not only inhibit the generation of active angiotensin II, but also the inactivation of the vasodilator bradykinin, explaining their higher potency compared with ARBs and direct renin inhibitors and the recommendation to prescribe ARBs only in ACE inhibitor-intolerant patients.[33,34] The involvement of sympathetic drive and the renin-angiotensin system in the cardiovascular and renal complications of hypertension and its comorbidities clarifies why guidelines[1–12] unanimously recommend the use ACE inhibitors and ARBs in patients with diabetes or chronic kidney disease, and βBs (beta-blockers),[35,36] ACE inhibitors, and ARBs in secondary prevention.

CONTROL RATES ON MONOTHERAPY VERSUS COMBINATION THERAPY

With as objective to estimate the proportion of patients with hypertension who can be controlled on monotherapy, we reviewed the placebo-controlled randomized clinical trials listed in systematic reviews of BP-lowering therapies[13–17] as well as the trials of intensive versus usual BP control.[18–20] We extracted control rates on monotherapy from the trial reports.

Placebo-Controlled Trials

Table 1 lists the placebo-controlled trials from which the proportion of patients remaining on monotherapy could be extracted. These trials were published from 1985[37] until 2008.[38] The first Medical Research Council Trial (age range, 35–64 years)[37] and the Perindopril Protection Against Recurrent Stroke Study (age range, not reported)[39] enrolled adults, but all other recruited older patients,[30,31,38,40–43] including exclusively[38] or a substantial proportion of octogenarians.[41,42] Considering the patients randomized to active treatment, at 2 years, from 25.8%[38] to 90.0%[41,42] remained on a single drug and at 4 years from 48.0%[40] to 87.0%.[41,42] In the Hypertension in the Very Elderly Trial[38] and in the Systolic Hypertension in Europe Trial,[30] the study coordinating office emailed or faxed recommendations for intensification of treatment to the local investigators, whenever at a visit a patient was not at goal BP, resulting in a substantially smaller proportion of patients remaining on monotherapy in the placebo compared with the active treatment group (Table 1). In the first Medical Research Council Trial,[37] at 4 years of follow-up, 70.0% of patients had attained the target BP, defined as a diastolic BP of <90 mm Hg. Thus, a substantial proportion of patients remained on monotherapy or reached goal BP on a single drug in the placebo-controlled trials listed in Table 1.

Intensive Versus Usual BP Control

Of the 3 trials[18–20] comparing intensive with usual BP control, 2[19,20] reported on treatment status by randomization group. In the ACCORD Trial (Action to Control Cardiovascular Risk in Diabetes)[19] and in SPRINT (Systolic Blood Pressure Intervention Trial),[20] patients with a systolic BP of 130 mm Hg or higher and an increased cardiovascular risk were randomly assigned to a systolic BP target of <120 mm Hg (intensive treatment) or a systolic target of <140 mm Hg (usual treatment). In the type-2 diabetic patients randomized to intensive (N=2174) and usual (N=2208) BP control in ACCORD,[19] after 1 year, the achieved systolic BP averaged 119.3 mm Hg on intensive treatment and 133.5 mm Hg in the control group; in SPRINT,[20] these levels were 121.4 mm Hg (N=4683) and 136.2 mm Hg (N=4683), respectively. In ACCORD (median follow-up, 4.7 years),[19] at 1 year, 174 (8.0%) and 265 (28.0%) of patients randomized to intensive and standard treatment were on monotherapy and at the last visit 184 (8.0%) and 553 (24.0%); in SPRINT (median follow-up, 3.3 years),[20] these numbers at last follow-up were 493 (10.5%) and 1455 (31.1%), respectively.

EVIDENCE SUPPORTING SPCS

The literature on SPCs focuses on efficiency, adherence (also known as compliance),[44] persistence, and safety. Over time, these notions permeated to several,[1–9] but not all,[10–12] guidelines. What is the evidence?

Table 1. Patients Remaining on First-Line Drug Treatment in Placebo-Controlled Randomized Clinical Trials

Trial, publication year	Ref	Age, y	Blood pressure, mm Hg		Y	Drugs	N	Follow-up, number of patients (%)			
			Entry	Goal				Year 1	Year 2	Year 3	Year ≥4
HYVET, 2008	38	83.6, ≥80	173.0/90.8 (≥160/<100)	<150/<80	1.8	PLAC	1912		100 (14.2)		
						IND	1933		196 (25.8)		
MRC1, 1985	37	52.0, 35–64	161.3/98.2 (<200/90–109)	NA/<90	4.9	PLAC	8654	… (…)†	… (…)	… (…)	… (…)‡
								… (≈39.9)	… (≈41.9)	… (≈43.9)	… (≈45.9)§
				↓13.5/6.5*		BDF	4927	… (≈81.9)	… (≈77.4)	… (≈74.3)	… (≈72.3)‡
								… (≈63.1)	… (≈67.1)	… (≈68.1)	… (≈70.1)§
				↓9.5/5.5*		PROP	4403	… (≈89.9)	… (84.9)	… (≈82.4)	… (≈79.9)‡
								… (≈61.9)	… (66.4)	… (≈67.8)	… (70.4)§
MRC2, 1992	40	65.7, 65–74	184.7/90.7 (160–209/<115)	150–160/NA†	5.8	PLAC	2213				… (…)‡
											… (…)§
				↓13.6/7.0*		HCTZ/AM	1081				… (62.0)‡
											… (…)§
				↓13.6/7.0*		AT	1102				… (48.0)‡
											… (…)§
PROGRESS, 2001	39	65.0, NA	144.0/84.0 (NA)	↓4.9/2.8	3.9	PLAC	1280				… (≈87.0)§
						PER	1281				… (≈86.0)§
SCOPE, 2004	41,42	76.4, 70–89	164.7/90.4 (160–179/90–99)	>160/>85	3.6	PLAC	845		≈634 (88.0)		≈150 (80.0)§
				↓10/NA		PER	1235		≈998 (90.0)		≈271 (87.0)§
STONE, 1996	43	66.4, 60–79	168.5/97.7 (160–219/96–124)	<160/<90	2.5	PLAC	815		… (…)		
						NIF	817		≈531 (65.0)		
Syst-China, 1998	31	66.4, ≥60	170.5/86.0 (160–219/<95)	>150/NA	3.0	PLAC	1141	578 (60.4)	348 (42.9)	203 (30.9)	58 (36.0)§
				↓20/NA		NIT	1253	832 (72.3)	584 (62.7)	374 (51.5)	110 (53.7)§
Syst-Eur, 1997	30	70.3, ≥60	173.8/85.5 (160–219/<95)	>150/NA	2.0	PLAC	2297	693 (41.2)	343 (27.8)	178 (19.2)	95 (13.9)§
				↓20/NA		NIT	2398	1037 (59.0)	597 (46.5)	385 (39.3)	216 (30.6)§

Age: average age at randomization (age eligibility criterion). Blood pressure: the blood pressure data given are the average systolic/diastolic blood pressure at randomization (blood pressure eligibility criteria) and the goal blood pressure (required decrease in blood pressure). In MRC1, nurses doing screening did 2 sets of BP measurements on separate occasions, but to ensure their diagnostic categorization, the third entry BP was done by a physician. As a result, it took nearly 9 months for the entry BP to reach its lowest approximately stable level. Mean diastolic BP in women randomized to placebo continued to fall for 5 years. As reported in reference 37, only a third (N=2285) had no measurements of diastolic BP below 90 mm Hg at any follow-up visit. Follow-up: Data are the number of patients (percentage) remaining on first-line monotherapy. AT indicates atenolol (50–100 mg/d); BDF, bendrofluazide (10 mg/d); CAND, candesartan (8–16 mg/d); HTCZ/AM, hydrochlorothiazide/amiloride (25/2.5 mg/d); HYVET, Hypertension in the Very Elderly Trial; IND, indapamide (1.5 mg/d); MRC1, Medical Research Council Trial in Young Adults; MRC2, Medical Research Council Trial in Older Adults; N, number of patients randomized; NA, not applicable; NIF, nifedipine (20–60 mg/d); NIT, nitrendipine (10–40 mg/d); PER, perindopril (4 mg/d); PLAC, matching placebo; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; PROP, propranolol (up to 240 mg/d); SCOPE, Study on Cognition and Prognosis in the Elderly; STONE, Shanghai Trial of Nifedipine in the Elderly; Syst-China, Systolic Hypertension in China Trial; Syst-Eur, Systolic Hypertension in Europe Trial.; and Y, median or average follow-up on randomized treatment.

*The average placebo-corrected decrease in blood pressure on active treatment.

†An ellipsis indicates that the data could not be extracted from the trial report.

‡Number of patients (percentage) remaining on monotherapy.

§Number of patients (percentage) reaching goal blood pressure.

Randomized Clinical Trials

Our extensive literature review revealed only one randomized clinical trial comparing the efficacy and safety of a SPC with its components.[45,46] The COACH Study (Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure) was a double-blind trial, conducted at 172 clinical sites in the United States.[45,46] Patients aged 18 years or older with a diastolic BP ranging from 95 to 120 mm Hg were randomized in equal proportions to combination therapy with olmesartan/amlodipine (daily doses, 10/5, 20/5, 40/5, 10/10, 20/10, or 40/10 mg) or monotherapy with olmesartan (10, 20, or 40 mg) or amlodipine (5 or 10 mg). Of 4234 patients, who entered the 2-week washout phase, 1940 (45.8%) were randomized (women, 45.7%; mean age, 54.0 years; mean entry BP, 164/102 mm Hg) and 1689 (87.1%) completed the 8-week trial. Predictably, each treatment modality, compared with placebo, produced dose-dependent decreases in systolic and diastolic BP and at each dose, combination therapy reduced BP more and achieved BP control more frequently (<140/<90 and <130/<90 mm Hg in diabetic patients)

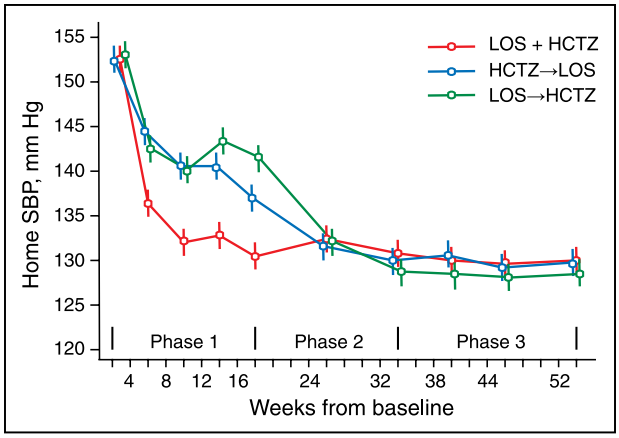

Figure 1. Systolic home blood pressure (BP) by randomization group and follow-up duration.
Data points are means. Vertical bars indicate 95% CI. Patients were randomized to initial monotherapy with losartan (LOS) 50–100 mg (N=151) or hydrochlorothiazide (HCTZ) 12.5–25 mg (N=150), crossing over at 8 weeks (switching to the alternative monotherapy), or initial combination treatment with losartan 50–100 mg plus hydrochlorothiazide 12.5–25 mg (N=304). In phase 2 (weeks 17–32), all patients received losartan 100 mg and hydrochlorothiazide 12.5 to 25 mg. In phase 3 (weeks 33–52), amlodipine with or without doxazosin could be added to achieve target BP. SBP indicates systolic BP. Reproduced from MacDonald et al[24] with permission. Copyright ©2017, Wiley.

than the equivalent dose of the single-component drug. Limitations of the COACH trial were selection of patients (45.8% of those screened were randomized), the short washout (2 weeks) and follow-up (8 weeks), the highly predictable BP results,[47] and the post hoc analysis of patients with isolated systolic hypertension.[46]

The Simplified Treatment Intervention to Control Hypertension Study was a cluster-randomized trial, involving 45 family practices in Ontario, Canada and compared control rates of hypertension as achieved by a simplified treatment algorithm (experimental group) or following the Canadian Hypertension Program guideline (control group).[48] The systolic/diastolic target BP was <140/<90 mm Hg and <130/<90 mm Hg in diabetic patients. The simplified treatment algorithm consisted of the following: (1) initial therapy with a low-dose ACE inhibitor/TD or ARB/TD SPC; (2) uptitration of the combination therapy to the highest dose; (3) addition and subsequent uptitration of a CCB; and (4) addition of a βB, α-blocker, or spironolactone. The proportion of patients achieving target BP at 6 months was higher in the experimental (N=802) than the control (N=1246) group (64.7% versus 52.7%; P=0.026). At 6 months, 82.8% of patients in the experimental group were on SPCs and 16.4% in the control group. However, no information on BP control beyond 6 months was provided.[48]

A third randomized double-blind study evaluated the efficacy and safety of triple therapy with amlodipine/valsartan/hydrochlorothiazide for moderate or severe hypertension (systolic/diastolic BP, 145/100 mm Hg or higher).[49] After a 1-week single-blind placebo run-in, patients were randomly assigned to valsartan/amlodipine/hydrochlorothiazide 320/10/25 mg, valsartan/hydrochlorothiazide 320/25 mg, valsartan/amlodipine 320/10 mg, or amlodipine/hydrochlorothiazide 10/25 mg with uptitration of these once daily SPCs from week 1 to week 3. Of the 4285 patients screened, 2271 (53.0%) were randomized (women, 44.7%; mean age, 53.2 years; mean entry BP, 169.9/106.5 mm Hg) and 2060 (90.7%) completed the 8-week trial. Triple therapy was significantly superior to all of the dual therapies in reducing BP (P<0.0001).[49] Results were similar across sex, age, and ethnicity strata. The limitations of this study were like those of the COACH trial.[45,46]

In the double-blind PATHWAY-1 study (Prevention and Treatment of Hypertension With Algorithm-Based Therapy Trial),[24] of 796 screened patients, 605 (76.0%) were randomized and 432 (71.4%) completed the 1-year follow-up period. Eligible patients were untreated, aged 18 to 79 years, and had a self-measured home systolic/diastolic BP of ≥150/≥95 mm Hg. They were randomized to initial monotherapy with losartan 50 to 100 mg/d (N=151) or hydrochlorothiazide 12.5 to 25 mg/d (N=150), crossing over at 8 weeks (switching to the alternative monotherapy), or initial combination treatment with losartan 50 to 100 mg/d plus hydrochlorothiazide 12.5 to 25 mg/d (N=304). In phase 2 (weeks 17–32), all patients received losartan 100 mg and hydrochlorothiazide 12.5 to 25 mg. In phase 3 (weeks 33–52), amlodipine with or without doxazosin could be added to achieve target BP. The primary end point was the change in the systolic home BP (target systolic/diastolic home BP >140/>90 mm Hg). The original protocol prespecified the time of the primary end point at the end of phase 2, namely, 32 weeks after randomization, at which time all patients were receiving the same therapy. The statistical analysis plan, published before the data lock and unblinding, introduced 2 hierarchical co-primary end points.[50] The first was the reduction in the systolic home BP averaged over phases 1 and 2, testing for the superiority of initial combination therapy over monotherapy. The co-primary end point, to be tested only if the first hypothesis was confirmed, was the reduction in systolic home BP at week 32, a time point, when all participants were receiving the same treatment. Comparing initial monotherapy with initial combination therapy (Figure 1), the systolic/diastolic reductions in the home BP were 13.3/6.5 versus 21.9/12.1 mm Hg (end of phase 1), 20.1/10.7 versus 19.5/10.6 mm Hg at week 24 (midpoint of phase 2), 23.6/12.7 versus 22.0/11.9 mm Hg at week 32 (end of phase 2), and 24.5/13.9 versus 23.6/13.4 mm Hg at week 52 (end of study). By the end of phase 3, over 75% of participants in the initial monotherapy and combination therapy groups had attained the target home BP with no difference between groups at the end of either phase 2 or 3.[24] Based on the redefinition of the primary end points,[50] the PATHWAY-1 researchers reported the average BP results combining phases 2 and 3 and all

study periods.[24] They concluded that initial combination therapy achieved target BP in twice as many participants as initial monotherapy,[24] whereas in fact starting from week 24 (Figure 1), home BP was similar irrespective of whether antihypertensive treatment was started with SPC or free SD combination therapy. In the context of the current debate, a relevant finding of the PATHWAY-1 trial was that the BP reductions induced by losartan and hydrochlorothiazide were greatest in the top and bottom plasma renin activity tertiles, respectively,[24] an argument supporting an insightful rather than a simplistic initiation of antihypertensive drug therapy.

Observational Studies

A common denominator of all observational studies was that they had a retrospective design. A meta-analysis published in 2011[51] summarized 12 studies published from 2000[52] until 2010.[53] It compared health care costs, adherence, and persistence between groups of patients taking antihypertensive agents as SPCs versus free-equivalent SDs. The mean difference in the annual all-cause and hypertension-related health care costs was $1357 (CI, $778–$1935) lower in favor of SPCs than free SD combinations. Adherence, measured as the mean difference in medication possession ratio, was 8% higher in patients naive to prior antihypertensive drugs and 14% higher in non-naive SPC patients compared with their counterparts on free SD combinations. Persistence in the SPC groups was twice as likely as in the free SD combination groups (pooled risk ratio, 2.1 [CI, 1.1–4.1]). The authors hypothesized that improved adherence and persistence likely contributed to the lower health care costs in the SPCs groups via improved clinical outcomes. Of the 12 studies included in the meta-analysis,[52–63] 2 did not include a conflict of interest statement,[54,56] 10 were directly funded by the pharmaceutical industry,[52,53,55,57–63] and 7[52,56–59,61,63] had one or more co-authors employed by drug companies having a commercial interest in SPCs.

The early literature was almost unanimous in stating that SPCs, in comparison with SDs or free combinations of SDs, were more efficacious in lowering BP, increasing adherence and persistence, and lowering health care costs. In view of this exceptional consistency, we searched PubMed for publications with discordant results. We identified 10 studies,[51,64–72] published between 2010[64] until 2020,[73] of which the principal outcome measures, data sources consulted, the methods applied, and principal limitations are summarized in Table S2. Of the 10 studies,[51,64–72] 7[51,64–67,69,70] were directly supported by SPCs producers, 5[51,64–67] involved a subcontractor to these manufacturers, and 5[51,64,65,67,69] were co-authored by one or more industry employees. The study by Hong et al[68] stands out, because it was a publication not supported by industry, in which none of the authors reported a conflict of interest. In this article, free SD combinations had average monthly drug costs similar to the respective SPCs, when SPCs were not generically available.[68] However, free SD combinations were more expensive compared with generic SPCs.[68]

A study published in 2020 without industry support,[72] applied the 2014 to 2015 Medical Expenditure Panel Survey data, to assess the uses and expenses of antihypertensive drugs among American men and nonpregnant women, aged 18 or older, who had a diagnosis of hypertension. Multiple medications users were patients who used 2 or more antihypertensive medications each year, including SPCs or multiple free SD combinations, or who switched BP-lowering agents within or between classes. Among 10 971 hypertensive adults, 4759 (44.1%) were SD users and 6212 (55.9%) were multiple medication users. The average annual total cost for antihypertensive medications was $336 per person: $199 for SD users and $436 for multiple medication users. The average annual costs for each medication class were estimated at $438 for ARBs and $49 for TDs. Thus, users of multiple medications, including SPCs, incurred more than twice the expense than single medication users.[72] When comparing classes of medications, the costs for ARBs were highest, whereas those for TDs were lowest (Figure 2), a trend still visible in the 2020 retail prizes of antihypertensive drugs on the Belgian market (Table S3).[72]

Several studies addressed the health-economic aspects of the use of SPCs versus SDs or free combinations of SDs,[65–67,70,73] or triple versus dual SPCs.[69] Data from the MarketScan Database 2006 to 2008 in the United States showed that SPC patients (N=382 476) fared better over a 6-month period than their counterparts on free SD combinations (N=197 375).[73] The analyses were adjusted for the baseline characteristics of the selected patients, a reason why this article[73] was excluded from the 2011 meta-analysis.[51] SPC patients had higher medication possession rates (+11.6%), fewer all-cause hospitalizations (−23.0%), and emergency room visits (−13.0%). SPC patients showed greater reductions in post-therapy initiation in all-cause medical costs ($208 [CI, −$302 to −$114]), but larger increases in hypertension-related prescription costs (+$53 [CI, +$51 to +$55]).[73] Similarly, in a study conducted in UK general-practice, hospitalization costs validated up to 2011 were lower in SPC patients compared with free SD users (N=9929 versus 18 665; £62 versus £112; $P<0.001$), whereas drug costs were higher (£126 versus £78; $P<0.001$), resulting in similar mean annual management costs in the 2 groups (£192 versus £192).[66]

All observational reviewed above (Table S2) had a retrospective design and were, therefore, vulnerable to overt and hidden sources of bias, for which analyses did not account. Particularly, most studies had no information on the severity of hypertension at the time of initiation or adjustment of BP-lowering treatment, higher BP being an indication for SPCs or multiple

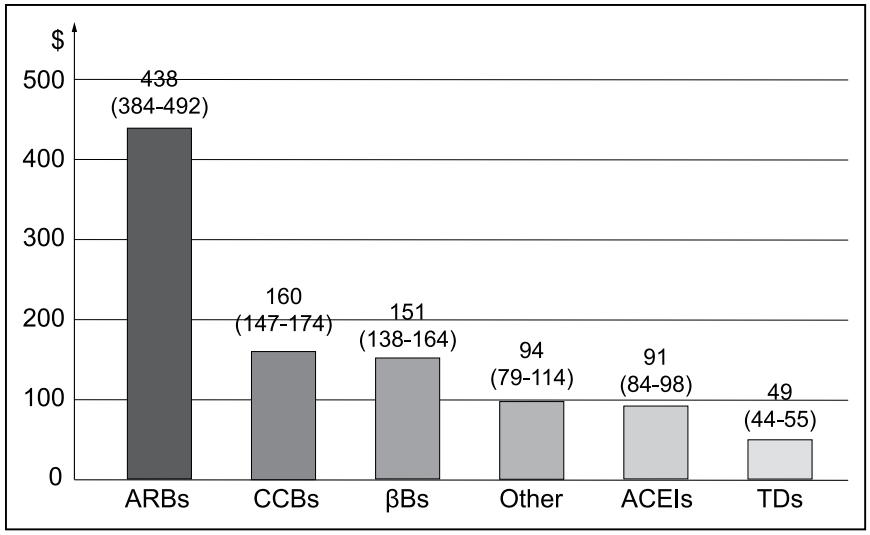

Figure 2. Estimated average annual per capita expenses of each medication class (95% CI), expressed in US dollars based on the 2014–2015 Medical Expenditure Panel Survey Notes.
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; and TD, thiazide diuretics. Reproduced from Park et al[72] with permission. Copyright ©2020, Elsevier.

drugs, or on the patients' health insurance status as determinant of the out-of-pocket costs and adherence (Table S2). Data on health behaviors, patients' lifestyle, and use of over-the-counter drugs were unavailable. In several analyses, there was a remarkable imbalance between SPC and free SD combination users,[65–67,73] indicating selection bias in the patients being prescribed SPCs versus free SD combinations or in data extraction from the claims databases by researchers. Medication possession rate, although an objective measure, but only in settings with a closed pharmacy system,[44] is an ambiguous concept. Although there is moderate association between claims for filled prescriptions and measured drug levels[44] or prevention of adverse health outcomes,[74] claims databases do not ensure that the medication was taken as prescribed. Moreover, information from claims databases disfavors free SD drug combinations, because in their publications investigators selected the SD with the worse adherence,[73] or when 2 or more SDs were prescribed, probabilities of nonadherence were multiplicative, not additive. Furthermore, the claims data used for the health-economic analyses were collected for payment purposes rather than for research. A diagnostic code on a medical claim is no proof for the presence of disease, because diagnoses might be incorrectly coded or included as a rule-out criterion rather than as an actual disease. All reviewed health-economic studies only accounted for direct health care costs, disregarding patient values,[75] and out-of-pocket costs.[71] A follow-up duration ranging from 6 months[64] to 5 years[66] is not representative of the life course of hypertension. No study measured adverse health outcomes in a prospective manner (Table S2). Transitions between health states applied in Markov modeling were not directly measured, but extrapolated,[69,70] introducing arbitrariness in selecting data sources best fitting the hypothesis to be proven.

Narrative Reviews

Of 7 reviews on the use of SPCs,[76–82] published from 2009[76] until 2019,[82] 6 were written with direct financial support from SPC manufacturers,[77–82] 3 included co-authors employed by these manufacturers,[77,79,82] 2 involved a for-profit company running the literature search[77] or providing assistance in writing the text,[78] and 1 article's co-author received research support from a company marketing SPCs.[76]

TAKE HOME MESSAGES

Table 2 lists the major limitations of the recommended policy to initiate antihypertensive treatment using SPCs in most patients.[1,2]

Weaknesses of Current Guidelines

Lengthy guidelines comprehensible only by hypertension specialists, lead to therapeutic inertia in primary care and fall short of their very reason of existence. The 98-page 2018 European recommendations[1] go as far as stating that initial combination therapy is invariably more effective in lowering BP than monotherapy and is, therefore, indicated in most patients. The reference cited to substantiate this claim was a meta-analysis, not of SPCs versus SD free combinations, but comparing treatment strategies consisting of increasing the dose of the first-line antihypertensive agent or adding a second drug class.[47] Two of its authors held patents for a combination pill (polypill) for the prevention of cardiovascular disease.[47] To permeate clinical practice, recommendations must excel in simplicity, allowing summarizing key issues in a simple mnemonic rule, such as the AB/CD algorithm in the 2006 British guideline (Figure 3).[10] Admittedly, the position of βBs as first-line treatment remains a matter of debate, albeit not in the last author's interpretation of the literature.[36,83] One might argue that SPCs combining

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Table 2. Take Home Messages

Issue	Summary of the literature
RCTs	Lack of RCTs comparing the long-term efficiency, adverse effects, and cost-effectiveness of initiating antihypertensive drug treatment with SPCs as compared with free combinations of SDs. The scarce RCT evidence currently available shows that 3 months after initiation of treatment BP is not better controlled by SPCs than free combinations of SDs. The literature does not support the notion that early BP control leads to long-term benefit in the prevention of cardiovascular end points.
Observational studies	Short-term observational studies, most with retrospective design and short duration (<6 months), are the main source of information supporting European and International recommendations to start antihypertensive treatment with SPCs. In retrospective observational studies of SPCs, adverse effects cannot be associated with a drug class, but are vaguer and more difficult to pick up, such as fatigue or hypotension, are under-reported.
Sponsors	Manufacturers of SPCs sponsored almost all studies, explaining bias in choosing data sources informing health-economic analyses, definitions of nonadherence to SDs, and the complete absence of dissonant results in the literature.
Health care costs	Use of SPCs increase drug costs, mainly due to the high retail price of sartans; SPCs do not reduce overall health care costs.
Components of SPCs	The diuretic in SPCs is overwhelmingly the short-acting hydrochlorothiazide, whereas preference should be given to the long-acting chlorthalidone. SPCs combining a βB and an ACEI are not guideline-endorsed.
Ease of use	SPCs lack flexibility in combining and dosing individual drug classes and in spreading dosing of drugs over the day. Patients with chronic disease value minimizing side-effects and long-term toxicities over frequency of dosing and other administration characteristics.

βB indicates β-blockers; ACEI, angiotensin-converting enzyme inhibitors; BP, blood pressure; RCT, randomized clinical trial; SDs, single drugs; and SPCs, single-pill combinations.

a βB and an ACE inhibitor, as for instance marketed in Belgium (www.bcfi.be) might allow initiating treatment in high-renin hypertensive patients in line with pathophysiologic insights, but in line with the older literature[84] no guideline[1–12] supports this combination for BP lowering. Nevertheless, guidelines do support such combination in secondary prevention.

The pharmaceutical industry is an important motor in creating therapeutic innovation. To remain profitable, there is nothing wrong in SPC manufacturers highlighting the potential benefits of their products. However, a problem arises when retrospective observational studies[52–72] (Table S2) or systematic[51] or narrative[76–82] reviews of such studies become the source of information in evidence-based recommendations. Guidelines should be incremental over time, meaning that evidence published between successive versions should lead to removing or adjusting previous recommendation or introducing new ones. The British guidelines[10–12] are exemplary in this respect, giving great weight to new evidence as justification for any change in treatment advice (Table S1). The 2019 National Institute for Health and Care Excellence recommendation[11] stated that there was some limited evidence from a single study[85] that initial dual therapy, compared with placebo, might reduce cardiovascular complications in people with hypertension and type-2 diabetes, but the Committee Members were disappointed that more comprehensive data were unavailable.[11] The Committee discussed the benefits of optimizing treatment for hypertension early and agreed that this could substantially improve quality of life. However, they found that there was not enough evidence to determine confidently the benefits or harms of starting antihypertensive treatment with dual therapy.[11]

The 2018 European guideline[1] went on proposing that the combination of medications targeting multiple mechanisms, such as blocking the renin-angiotensin system and inducing vasodilatation and diuresis, reduces the heterogeneity of the BP responses to initial treatment and provides a steeper dose response than is observed with escalating doses of monotherapy.[1] Whereas this might be true during first 6 months after starting BP-lowering treatment,[50,86] this certainly does not apply to the long-term life course treatment of hypertension (Figure 1). A post hoc analysis of the

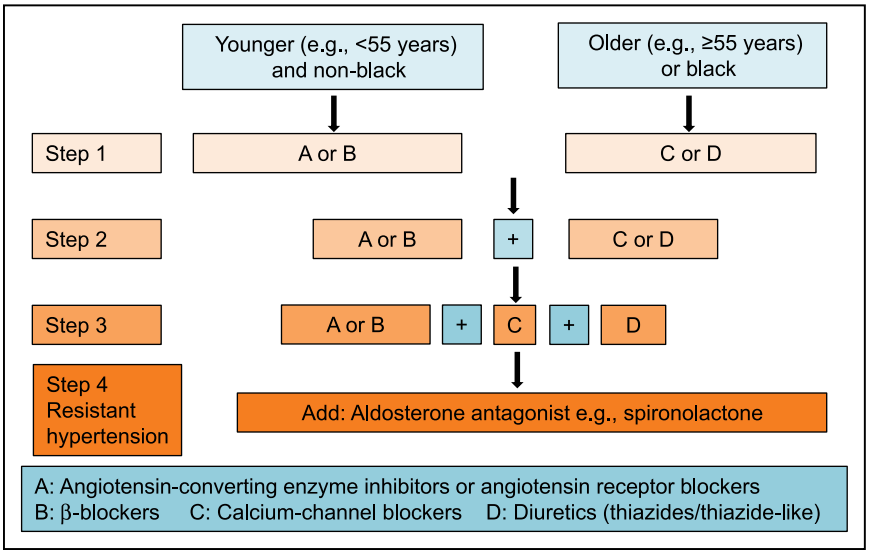

Figure 3. Recommendation for combining blood pressure-lowering drugs.
First-line drugs with different modes of action should be combined according to the AB/CD rule. Reproduced from British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, The Stroke Association[10] with permission. Copyright ©2020, BMJ Publishing Group Ltd.

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Valsartan Antihypertensive Long-Term Use Evaluation Trial did not confirm the widely promoted notion in SPC publications that earlier short-term differences in BP lowering over the long run would reduce cardiovascular end points.[87] Furthermore, the European[1] and International[2] Societies of Hypertension instructions ignored that the association of multiple drugs in a single pharmaceutical formulation may have effects on the pharmacokinetic and pharmacodynamic properties of each and every individual component and may lead to undesired interactions between components.[88,89] The trials[45,46,48–50] and observational studies[51–72] reviewed in this debate article were generally not powered or had a duration not long enough to highlight serious adverse effects. As demonstrated by an observational study of patients aged 50 years or more and reflecting a real-world setting, use of SPCs was associated with a greater risk of hypotension than titrated SD free combinations.[90] Moreover, abstraction made of commonly attributable adverse effects, for example, leg edema or cough respectively on treatment with CCBs or ACE inhibitors, many drug-induced complaints are vaguer and more difficult to be picked up, such as for instance fatigue or dizziness and in theory require rechallenge with the SD components of an SPC to identify the culprit drug. Fewer pills to be taken daily is a central concept in the promotion of SPCs,[91] but a literature review with as search terms "preference" AND "patient" AND "pills" or "SPC", ran on October 20, 2020, with no limitations, did not yield any article among the 46 hits that directly translated patient convenience into preference for SPCs in primary or secondary cardiovascular prevention. As a corollary, treatment-experienced persons living with HIV valued minimizing side-effects and long-term toxicities over dosing and administration characteristics.[92] Preferences varied widely,[92] highlighting the need to elicit individual patient preferences, when decisions about dosing schemes of medications are made, certainly in the light of the potential adverse events of SPCs as mentioned before. Finally, the advice to initiate antihypertensive drug therapy with SPCs also goes against pathophysiological principles supporting the use of TDs in low-renin hypertension, Blacks and older patients and the use vasodilators (ACE inhibitors, ARBs, or CCBs) in high-renin patients or younger individuals (Figure 3).

In an era of epidemiological transition,[93] payers, doctors, and patients should join forces to keep health care sustainable in aging populations. In the placebo-controlled outcome trials (Table 1),[30,31,37–43] a substantial proportion of hypertensive patients could be controlled on a single drug. Arguably, the entry and target BPs in these trials were higher than those currently proposed. However, mutatis mutandis, lower BP levels, at which antihypertensive drug treatment should be initiated,[7] would increase the control rates on monotherapy. BP lowering to <140/90 mm Hg was achieved by monotherapy in about one-third of patients randomized to standard treatment in ACCORD[19] and SPRINT.[20] In needy patients, out-of-pocket costs are a major hurdle in long-term adherence.[71] In a Canadian cluster-randomized trial involving 76 primary care practices,[71] 3592 patients with uncomplicated hypertension were followed up for 5 years. Physicians were randomized to an out-of-pocket expenditure software module that provided alerts for out-of-reimbursement costs and recommended TDs as first-line therapy and control. In the intervention group, there was a significant increase in the prescription of TDs in newly treated patients (26.6% versus 19.8%). For patients already treated, older patients were less likely to be switched to a TD. Translating these findings to the Belgian context (Table S3), starting a patient on monotherapy with low-dose treatment with chlorthalidone, bisoprolol, amlodipine, perindopril, valsartan, or olmesartan entails an annual cost of €19, €38, €44, €72, €87, and €107, respectively, if the drug with the lowest retail prize would be prescribed; the corresponding annual expense for the lowest-cost SPC with valsartan/hydrochlorothiazide, olmesartan/hydrochlorothiazide, valsartan/amlodipine, and olmesartan/amlodipine amounts to €85, €107, €128, and €141. Giving that one-third of the patients started on antihypertensive therapy can be controlled by a SD, the potential savings for the Belgian health insurance are huge, if patients would no longer be started on dual SPCs.

Rational Use of SPCs

We proposed that starting antihypertensive therapy in treatment-naive hypertensive patients might be based on a few simple principles. First, use antihypertensive drugs with different modes of action in line with the AB/CD algorithm (Figure 3). Second, use antihypertensive agents with a long duration of action based on their molecular structure, so-called forgiving drugs, rather than extended-release dosage formulations.[94,95] Third, titrate each drug to the highest dose that does not produce adverse effects. Fourth, include a thiazide in the drug combination. Finally, once the right combination has been found by rotating through and combining drug classes as well as the timing of dosing, stimulate adherence by reducing the pill load by prescribing SPCs including 2 or 3 antihypertensive agents in adjustable doses. Initiating antihypertensive drug treatment with SDs overcomes the inflexibility of SPCs in titrating the doses of the SD components and the timing of their administration, for instance to prevent nocturnal diuresis or hypotension. In line with the above proposal, in Japan, only one triple-drug SPC is being marketed (telmisartan/amlodipine/hydrochlorothiazide 80/5/12.5 mg). It can only be prescribed after 8 weeks of successful treatment with its components given as dual SPCs plus one SD or as free 3-drug SD combinations

None of the trials of SPCs had a cardiovascular end point. In line with the 2019 National Institute for Health and Care Excellence guideline,[11] an important research issue is to mount outcome-driven randomized clinical trials to delineate particular subgroups of hypertensive patients who might benefit from starting dual therapy. Furthermore, compared

with hydrochlorothiazide, chlorthalidone is 1.5 to 2.0 × more potent, has a substantially longer duration of action (plasma half-life, 8 versus >24 hours), and is not metabolized but excreted unchanged in urine, thereby preventing drug-drug interactions.[32,95] Unfortunately, the diuretic in SPCs currently marketed is overwhelmingly hydrochlorothiazide, an issue to be addressed by manufacturers (Table 2). Finally, payers should better inform physicians and patients on the costs of antihypertensive drugs to reduce health care costs, decrease out-of-pocket costs as a factor limiting adherence,[71] and to support the sustainability of health care by lower drug costs and better prevention of the cardiovascular-renal hypertension-associated complications.

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Disclosures

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Response to Starting Antihypertensive Drug Treatment With Combination Therapy: Controversies in Hypertension - Con Side of the Argument

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Jan Staessen is an internationally recognized expert known for his independent and integer positions. He and his coauthors have produced a highly informative, original document against the extensive use of first-line single-pill combinations.

Still, we feel that it does not detract from our plea in favor of the use of combination therapy as first-line treatment in most patients with hypertension. Although studies supporting the benefit of this compared to other strategies have limitations, this is also the case for other treatment strategies used in daily practice. For example, the arguments in favor of the National Institute for Health and Care Excellence algorithm supported by Staessen and colleagues rest more on clinical expertise and general principles of pharmacology than on rigorously designed randomized controlled trials.

The recommendation to use dual antihypertensive therapy in most patients with hypertension is more a public health than a trialist's perspective.

As indicated by Prof. Staessen, two-thirds of patients with hypertension eventually need ≥2 antihypertensive drugs to achieve blood pressure control.

We simply think that using single-pill combinations as first-line therapy in those patients is the most effective way to overcome poor drug adherence and inertia, currently the main barriers to improve blood pressure control worldwide.

Admittedly, this recommendation may benefit the pharma industry. However, it is the responsibility of public health authorities to negotiate properly the price of single-pill combinations while supporting less expensive, generic alternatives.

Finally, the gap between Prof. Staessen's and our conception is less wide than it may appear.

While he focuses on cases in which monotherapy is the preferred approach—basically the same as us, patients with mild hypertension, particularly older patients with isolated systolic hypertension—we emphasize the big picture in favor of first-line dual antihypertensive therapy in most patients with hypertension, while mentioning the exceptions.