HYPERTENSION

Data Supplement

Starting Antihypertensive Treatment with Combination Therapy — Con Side of the Argument

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References

Table S1.

Hypertension Guidelines

Guideline	Ref	Guideline
JNC7, 2003	1	TDs should be used as initial therapy for most patients, either alone (stage-1 hypertension [140-159/90-99 mm Hg]) or in combination (≥160/≥100 mm Hg) with an ACEI, ARB, bB, or CCB. Selection of one of these other agents as initial therapy is recommended when a TD cannot be used or when a compelling indication is present that requires a specific drug class. If the initial drug selected is not tolerated or is contraindicated, then a drug from one of the other classes should be substituted. Since most hypertensive patients will require ≥2 antihypertensive medications to achieve their BP goals, addition of a second drug from a different class should be initiated when use of a single agent in adequate doses fails to achieve the goal. When BP is ≥20 mm Hg above systolic goal (≤140 mm Hg; ≤130 mm Hg in patients with DM or CKD) or ≥10 mm Hg above diastolic goal (≤90 mm Hg and ≤80 mm Hg, respectively), consideration should be given to initiate therapy with 2 drugs, either as separate prescriptions or in fixed-dose combinations.
JNC8, 2014	2	The goal BP is <150/<90 mm Hg in patients ≥60 years, <140/<90 mm Hg in patients aged <60 years, and <140/<90 mm Hg in DM and CKD patients. In nonblacks, including those with DM, initial antihypertensive treatment should include a TD, CCB, ACEI or ARB. In blacks, including those with DM, initial antihypertensive treatment should include a TD or CCB. In patients with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB. If goal BP is not reached, increase the dose of the initial drug or add a second drug from another class. Maximize first medication before adding second or add second medication before reaching maximum dose of first medication or start with 2 medication classes separately or as fixed-dose combination. If goal BP cannot be reached with 2 drugs, add and titrate a 3th drug.

Table S1.

Hypertension Guidelines (Continued from Page 7)

Guideline	Ref	Guideline
ACC/AHA, 2017	3	Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage-1 hypertension (130-139/80-89 mm Hg) and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension (≥140/≥90 mm Hg) and an average BP >20/>10 mm Hg above their BP target.
ESC/ESH, 2007	4	The goal BP is <140/<90 mm Hg and <130/<80 mm Hg in diabetic and high-risk patients. The main benefits of antihypertensive therapy are due to lowering of BP per se. Five major classes of antihypertensive agents – TDs, CCBs, ACEIs, ARBs and bBs – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. Although the fixed dose of the combination components limits the flexibility of upward and downward treatment strategies, fixed combinations reduce the number of tablets to be taken by the patient, and this has some advantage for the adherence to treatment.
ESC/ESH, 2013	5	The goal BP is <140/<90 mm Hg, 140-150 mm Hg systolic in elderly hypertensive patients and <85 mm Hg diastolic in DM patients. Monotherapy can effectively reduce BP in only a limited number of hypertensive patients and most patients require the combination of at least 2 drug classes to achieve BP control. The obvious advantage of initiating treatment with monotherapy is that of using a single agent, thus being able to ascribe effectiveness and adverse effects to that agent. The disadvantages are that, when monotherapy with one agent is ineffective or insufficiently effective, finding an alternative monotherapy that is more effective or better tolerated may be a painstaking process and discourage adherence. Combinations of 2 antihypertensive drugs at fixed doses in a single tablet may be recommended and favoured, because reducing the number of daily pills improves adherence, which is low in patients with hypertension.

Table S1.

Hypertension Guidelines (Continued from Page 8)

Guideline	Ref	Guideline
ESC/ESH, 2018	6	The goal BP is <140/<90 mm Hg in all patients and, provided that treatment is well tolerated, treated BP values should ≤130/≤80 mmHg or lower in most patients. Systolic BP should be lowered to 120–129 mm Hg in most patients aged <65 years, and to 130-139 mm Hg in the elderly. A diastolic BP of <80 mm Hg should be targeted in all hypertensive patients, independent of the level of risk and comorbidities. Antihypertensive treatment should be initiated with a 2-drug combination, preferably in a SPC. The exceptions are frail older patients and those at low risk and with grade 1 hypertension (140-159/90-99 mm Hg), particularly if systolic BP is <150 mm Hg.
WHO/ISH, 1999	7	The goal BP is <150/<95 mm Hg and <140/<90 mm Hg in low- and high-rist patients, respectively. In patients with grade 1 hypertension (140-159/90-99 mm Hg), monotherapy with most agents (TDs, bBs, CCBs, ACEIs or ARBs) will produce reductions in systolic/diastolic BP of about 10/5 mm Hg. In patients with higher grades of hypertension, it is possible to achieve sustained blood pressure reductions of ≥20/≥10 mm Hg, particularly if combination drug therapy is used. The use of appropriate drug combinations maximizes the BP lowering effect, while minimizing side effects. Changing to a different drug class is recommended, if there is very little response or poor tolerability to the 1st drug used, before increasing the dose of the 1st drug or adding a 2nd drug. It is often preferable to add a small dose of a 2nd drug rather than increasing the dose of the original drug. This allows both the 1st and 2nd drugs to be used in the low-dose range that is more likely to be free of side effects.
WHO/ISH, 2003	8	Based on clinical trial evidence and also on extrapolation of epidemiological studies, a BP target pf <130/<80 mm Hg seems appropriate, with a systolic target of <150 mm Hg in low-resource settings. For most patients without a compelling indication, a low dose of a TD as the first choice of therapy on the basis of comparative trial evidence, availability and cost. A TD is often available in single tablets combined with other classes of drugs. Where they are no more expensive, such combined formulations may be preferable, since they have advantages in terms of adherence and BP-lowering efficacy.

Table S1.

Hypertension Guidelines (Continued from Page 9)

Guideline	Ref	Guideline
WHO/ISH, 2020	9	The BP is a reduction by ≥20/≥10 mm Hg, ideally, to <130/<80 mm Hg and <140/<90 mm Hg in patients age <65 and ≥65 years, respectively, but with individualized thresholds in the context of frailty, independence and likely tolerability. Use whatever drugs are available with ideal characteristics (proven benefit in terms of outcome, long-acting, affordability and cost-effectiveness). Start with dual low-dose combination, consisting of an ACEI or ARB combined with a TD; in Blacks, consider starting with a dual combination of an ACEI or ARB with either a CCB or TD; add a 3rd drug to control BP, if required; in treat-ment resisatnt patients, add spironolactone, an a-blocker or another drug class. Use free combinations, if SPCs are not available or unaffordable. Use of thiazide-like diuretics rather than TD.
NICE, 2006	10	To achieve a goal BP of <140/<90 mm Hg, in hypertensive patients aged ≥55 and in black patients of any age, the first-choice initial therapy should be either a CCB or a TD; in hypertensive patients aged >55 years, the first-choice initial therapy should be ACEI (or ARB in ACEI intoelrant patients). If a second drug is required, add an ACEI (or ARB) to initial therapy with a CCB or TD or a CCB or TD to initil therapy with an ACEI (or ARB). If triple therapy is required, combine an ACEI (or ARB), a CCB and a TD. If triple therapy is not sufficient, consider a higher dose of a TD, a bB or a selective a-blocker. No recommendation to use SPCs.
NICE, 2011	11	Similar to the 2006 guideline; spironoloactone added to step 4; bBs not retained as first-line antihypertensive agents. No recommendation to use SPCs.
NICE, 2019	12	Similar to the 2011 guideline; experts ruled that there was not enough evidence to determine confidently the benefits or harms of starting treatment with dual therapy.

Drug classes: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type-1 receptor blocker; bB, b-blocker; CCB, dihydropyridine calcium-channel blocker; TDs, thiazide diuretics; SPCs, single-pill combination; SD, single drug.
Compelling indications of antihypertensive drugs to address comorbidities and secondary prevention are beyond the scope of this debate article, which primarily deals with the initiation and titration of antihypertensive drug treatment in primary care.

Table S2.

Studies Comparing Single-Pill Combinations with Single Drugs or Free Combinations of Single Drugs

Study	Ref	Endpoints	Data sources and methods	Study limitations
Yang W, 2010*†‡	13	Adherence all-cause hospitalizations all-cause medical costs	Thompson-Reuters Market Scan Commercial and Medicare Supplemental Databases 2006-2008 Comparison of SPC (ARB plus CCB, ARB plus HCTZ, ACEI plus HCTZ)	Representative for the continental US; unbalanced information for patients on SPC (N=382,476) and SD (N=197,375) combination groups; the observational window for patients on SPC and SD combinations including an ARB plus CCB was shortened to the 07/2007-06/2008 interval; residual confounding from factors not observable in claims.
Baser O, 2011*†‡	14	Adherence persistence health-care costs	Proprietary US health plan database associated with i3 Global (01/2007 →04/2008) Comparison of the SPC of valsartan plus amlodipine (N=3259) with SD combinations of an ARB with CCB (N=9369)	Retrospective analysis of filled prescriptions; significant differences in the observed baseline characteristics of the two groups; starting blood pressure level unknown; extrapolation of the clinical baseline characterictics (Deyo adaptation of the Charlson Comorbidity Index); concomittant medications accounted for, but HCTZ was excluded from the diuretics class;
Sherrill, 2011*†‡	15	Adherence peristence use of health care resources	Meta-analysis of 12 retrospective studies	No adjustment for patient characteristics; imputation of variance for estimates of costs and adherence; heterogeneity across reviewed studies

Table S2.

Studies Comparing Single-Pill Combinations with Free Combinations of Single Drugs (Continued from Page 11)

Study	Ref	Endpoints	Data sources and methods	Study limitations
Belsey JD, 2012*†	16	Cardiovascular events hospital admission and drug costs annual management costs	The Health Improvement Network – a primary care database Comparison of SPC with SD combinations in UK general practices in a retrospective cohort of cases (SPC; N=9929) matched with two controls (SDs; N=18,665)) over a follow-up of ≥5 years. SPCs included b-blockerACEI/ARB plus thiazide and b-blockerACEI/ARB plus CCB.	Retrospective analysis; matching for sex, age and general practice only; more patients in the SD compared with the SPC group had no record of the baseline blood pressure (36 *vs* 18%); risk factors not adjusted for; justification of the choice of the drug classes not documented, e.g., to address comorbidities; diagnostic fluidity in the ascertainment of cardiovascular events, such as heart failure.
Breitscheidel 2012*†‡	17	Adherence peristence drug costs	IMS® Disease Analyzed Database (09/2008→08/2009) SPC of ARBs with HCTZ or amlodipine yielded greater adherence, persistence and lower drug costs (retail prizes at the pharmacy) than SD combinations or semi-fixed combinations associated or not with other antihypertensive drugs	Retrospective analysis, representative of general practice; starting blood pressure level unknown; analyses centered around hypertensive patients, who received an ARB prescription; adherence and persistence were assessed from filled prescriptions in 17,310 patients, excluding 74.9% of patients, because no follow-up of 1 year was available; incomplete adjustment of the adherence data; triple SPC not analyzed, because of low number (N=85); drug costs (2010) assessed in 45,254 of 69,060 hypertensive recipients of an ARB prescription.

Table S2.

Studies Comparing Single-Pill Combinations with Free Combinations of Single Drugs (Continued from Page 12)

Study	Ref	Endpoints	Data sources and methods	Study limitations
Hong SH, 2013	18	Drug costs	2009 Medical Expenditure Survey FDA National Drug Directory	SPC more expensive than SDs, if SDs were available as generics, but indications justifying choice of drug class unavailable
Stafylas P, 2015*‡	19	Cost-utility of antihypertensive drug treatment	Markov modeling of eight health states Comparison of triple vs dual SPC: valsartan plus amlodipine and HCTZ *vs* valsartan plus amlopine or HCTZ.	Blood pressure decrease not measured, but extrapolated from a randomized clinical trial (20); transition states extrapolated from the SCORE and Framnigham risk scores, the NICE guideline or noncardiovacular mortality rates in Greece; treatment costs of adverse effects was disregarded; hospitalisation costs extrapolated from the Diagnostic Related Groups (DRG).
Tamblyn R, 2018	21	Out-of-pocket costs of antihypertensive drugs	Single-blind cluster randomized clinical trial Test a difference in the prescription of antihypertensive drugs by giving physicians of the intervention group ready access to the the out-of-pocket costs incurred by patients.	Generalizability limited to primary care, health care in the Province of Quebec, Canada and uncomplicated hypertension; spill-over effects not excluded, because the unit of randomization was the physician, not the practice.

Table S2.

Studies Comparing Single-Pill Combinations with Free Combinations of Single Drugs (Continued from Page 13)

Study	Ref	Endpoints	Data sources and methods	Study limitations
Ren M, 2019*	22	Cost-effectiveness from the payer perspective	Markov modeling of five health states of hypertensive patients aged 35-84 years Comparison of olmesartan plus amlodipine with valsartan plus amlodipine	Comparison based on a network meta-analysis, because direct head-to-head RCTs were unavailable Prevalence and transition probabilities extrapolated from the literature; costs of antihypertensive drugs estimated from the IMS database; once daily administration assumed; adherence not measured, but extrapolated from the literature.
Park C, 2020	23	Drug costs as covered by payers	2014–2015 Medical Expenditure Panel Survey Data Comparison of the annual costs of antihypertensive drugs, used as SD compared with multiple drugs (SPC and SDs combinations) with adjustment for the complex sample frame and covarables, including ethnicity/race, sex, age, body mass index, current smoking, insurance type, (private *vs* public only), educational attainment, family income, the Charlson Comorbidity Index, and a weight variable accounting for the number of years of follow-up.	No data available on the baseline and attained blood pressure level; the possibility of recall bias; no information on annual drug costs by specific comorbidities, such as diabetes or chronic kidney disease; no information on out-of-pocket expenses.

Drug classes: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type-1 receptor blocker; bB, b-blocker; CCB, dihydropyridine calcium-channel blocker; TDs, thiazide diuretics; SPCs, single-pill combination; SD, single drug.
Abbreviations: IMS, Intercontinental Medical Statistics (the largest vendor of US physician prescribing data [https://https://en.wikipedia.org/wiki/IMS_Health]);

SD, single drug or free single-drug combinations; SPC, fixed single-pill combination.
Conflict of interest: *direct industry support; †involvement of subcontractor to the pharmaceutical industry; one or more co-authors are industry employees.

Table S3.

Retail Prizes of Antihypertensive Drugs in Belgium

Drugs	Low Dose		High Dose	
	Drug Doses (mg)	Cost per Day (€)	Drug Doses (mg)	Cost per Day (€)
O/A/H-b	20/5/12.5	0.385	40/10/25	0.515
O/A/H-g	NA	NA	NA	NA
V/A/H-b	160/5/12.5	0.657	320/10/25	0.508
V/A/H-g	160/5/12.5	0.456	320/10/25	0.497
O/A-b	20/5	0.385	20/5 (×2)	0.777
O/A-g	20/5	0.385	40/10	0.515
V/A-b	160/5	0.350	160/5 (×2)*	0.700
V/A-g	160/5	0.385	160/5 (×2)*	0.700
O/H-b	20/12.5	0.292	40/25	0.334
O/H-g	20/12.5	0.316	40/25	0.316
V/H-b	160/12.5	0.271	160/12.5 (×2)*	0.355
V/H-g	160/12.5	0.239	160/12.5 (×2)*	0.355
O-b	20	0.292	40	0.326
O-g	20	0.304	40	0.304
V-b	160	0.255	320	0.267
V-g	160	0.239	320	0.240
A-b	5	0.125	10	0.240
A-g	5	0.120	10	0.231
P-b	4	0.248	8	0.422
P-g	4	0.197	8	0.326
B-b	5	0.138	10	0.187
B-g	5	0.103	10	0.146
C-b	12.5	0.052	25	0.103
I-b	1.25	0.080	2.5	0.159
I-g	1.25	0.072	2.5	0.144

Abbreviations: A, amlodipine; C, chlorthalidone; H, hydrochlorothiazide; I, indapamide; O, olmesartan; P perindopril; V, valsartan. “-b” and “-c” denote branded and generic, respectively. NA indicates not marketed in Belgium. An asterisk indicates a regimen of two tablets per day to match a high-dose regimen. Cost are expressed in Euro’s for the greatest package available on the Belgian market. The data source is available at https:\\www.bcfi.be. In Belgium, health insurance covers ~75% of the costs of antihypertensive drugs for most people and ~85% for patients with a preferential status (e.g., incapacitated patients (https://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-

ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/specialiteiten/Paginas/farmaceutische-specialiteiten-vergoedingscategorieen.aspx). Multiply by 1.14 to convert Euro to US dollar.