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EDITORIAL

Single-pill combinations, hypertension control and clinical outcomes: potential, pitfalls and solutions

Hypertension is the most prevalent cardiovascular risk factor and carries the greatest population attributable risk for cardiovascular disease [1]. Better hypertension control is among the most effective public health and population healthcare levers for reducing years of life lost and disability adjusted life years [2]. Unfortunately, the global burden of hypertension and related cardiovascular and renal diseases continues to grow. Hypertension control rates remain low globally [3]. One relatively simple and potentially scalable approach to improving hypertension control is greater use of single-pill combinations (SPC) containing two or more different classes of antihypertensive medications as initial and add-in therapy [4–12].

In this editorial, the literature is selectively reviewed and summarised on SPC, especially as initial therapy, compared with monotherapy and multiple pill regimens on adherence, hypertension control, clinical outcomes, population impact and adverse effects. An attempt is made to quantify the relative use of SPC versus monotherapy and free-dose combinations in hypertension management. Barriers and potential pathways to greater use of SPC in managing hypertension are explored.

Adherence

In a recent systematic review and meta-analysis, which included >370,000 individuals on SPC, adherence was significantly greater with SPC than free-equivalent combinations (FEC) in 18 of 23 studies, which included >250,000 individuals on SPC [11]. Most reports were from retrospective studies. Four studies showed non-statistically significant numerical advantages for SPC. In one cited report, SPC were associated with significantly greater adherence than FEC among both statin adherence and statin non-adherent subgroups, but adherence was significantly lower with SPC among statin naïve individuals. The studies cited in the report, which provided data on adherence as the proportion of days covered or medication possession ratio, are summarised in Table 1. In general, SPC was associated with approximately a 10-percentage point (absolute 10%) higher adherence rate than FEC.

BP reduction and hypertension control

Analyses of multiple randomised trials indicated that half-standard doses (one-quarter maximum recommended dose) of the major classes of antihypertensive medications lowered systolic (S)BP ~7 mmHg, standard doses ~9 mmHg and twice standard doses ~11 mmHg [12]. Consistent with these findings, a subsequent systematic review and meta-analysis [8] reported that two antihypertensive medication classes at $^1/_2$-standard dose (one-quarter the maximum recommended dose) lowered SBP ~2.8 mmHg more than a single medication at standard dose. Two antihypertensive medications at standard dose lowered SBP ~7.5 mmHg more than a single medication at standard dose and increased the probability of controlling BP 42% (Risk Ratio 1.42 [95% confidence interval 1.27–1.58]) [8].

Therapeutic inertia

A key challenge in clinical practice, unlike protocol-driven clinical trials conducted by trained investigative teams, is that individuals begun on monotherapy are more likely to remain on monotherapy than those begun on combination therapy, even after three years [6]. In the United States, available evidence indicate that the interval between follow-up visits for adults with uncontrolled hypertension occurs at an average interval of 14 weeks or nearly 3-1/2 months [13]. An antihypertensive medication class is added or the dose of an existing medication raised on roughly one in eight visits. Thus, it often takes two years or more of uncontrolled hypertension before antihypertensive medication is added or the dose increased for an existing medication. Similarly, in a report from Italy, 64% of individuals beginning with antihypertensive monotherapy remained on monotherapy three years later [7]. In contrast, 78% of adults initiated on combination therapy remained on combination therapy after three years. These observations align with evidence from clinical practice and clinical trials that initial treatment with SPC leads to greater reduction in BP and better hypertension control than initial monotherapy [4,5,8–10,14].

Time to hypertension control

Not surprisingly, time to control is also more prompt with initial single-pill combination therapy than initial

Table 1. Adherence with single-pill combinations compared to free-equivalent combinations.

Study*	Design	SPC, N	FEC, N	†PDC SPC vs. FEC, *p*-value
Ah, *et al*	RetroDB	20,175	20,175	80% vs. 70%, $p < 0.01$
Breitscheidel, *et al*	RertroDB	45,511	26,172	78.1% vs. 71.5%, $p < 0.0001$
Degli Esposti, *et al*	RetroCoh	302	791	79.8% vs. 70.9%, $p < 0.01$
Dickson, *et al*	RetroCoh	2336	3368	63.4% vs. 49%, $p < 0.0001$
Hess, *et al*	RetroCoh	7225	7224	76.9% vs. 54.4%, $p < 0.001$
Ho, *et al*	RetroDB	13,176	4392	58% vs 47%, $p < 0.001$
Hsu, *et al*	RetroDB	5725	1623	42.1% vs 32.4%, $p < 0.001$
Jin-Young, *et al*	RetroOB	757	707	MP*R* $\geq$ 80%: 91.9% vs. 88.9%, NS
Koval, *et al*	RandPG	39	36	87% vs. 61%, $p < 0.05$
Machniki, *et al*	RetroDB	1884	1884	70.0% vs. 60.6%, $p < 0.0001$
Marazzi, *et al*	RanPro	154	152	94% vs. 85%, $p = 0.034$
Schweizer, *et al*	NRPro	197	138	100% vs. 92%, *p*=NS
Tung, *et al*	RetroDB	1136	4544	PDC $\geq$ 80%: 65.0% vs. 56.9%, $p < 0.001$
Yang, *et al*	RetroDB	382,476	197,375	72.8% vs. 61.3% (11.6% [11.4–11.7])

*All studies in the table are from Parati, *et al.* [11].
†When only medication possess ratio (MPR) provided, MPR multiplied × 100 and expressed as percent to approximate proportion of days covered (PDC).
SPC: single-pill combinations; FEC: free equivalent combinations; RetroDB: retrospective database design; RetroCor: retrospective cohort; RetroOb: retrospective observational; RanPro: randomised, prospective; NRPro: non-randomised prospective; P = NS: not significant or not provided.

Table 2. Clinical outcomes with single-pill combinations versus comparators.

	*Initial CombRx vs. MonoRx[6]	†Initial CombRx vs. MonoRx[7]	†SPC vs. FEC[18]
Primary Outcome	0.84 (0.79–0.90), $p < 0.001$	0.85 (0.74–0.97), $p = 0.02$	0.89 (0.81–0.97), $p < 0.01$
Stroke/cerebrovascular disease	0.85 (9.51–0.98), $p = 0.027$	0.83 (0.61–1.14), $p = 0.26$	1.08 (0.86 − 1.36), $p = 0.51$
AMI/Ischaemic heart disease	0.80 (0.71–0.91), $p < 0.001$	0.73 (0.56–0.95), $p = 0.02$	0.89 (0.71 − 1.12), $p = 0.33$
Heart Failure	0.65 (0.51–0.82), $p < 0.001$	0.90 (0.54–1.51), $p = 0.69$	0.93 (0.71 − 1.12), $p = 0.62$
Death	0.80 (0.72–0.89), $p < 0.001$	Not reported	0.85 (0.77–0.94), $p < 0.01$

*Proportional Ratios and 95% confidence intervals adjusted for baseline covariates.
†Incidence Risk ratios [7] and Hazard Ratios [18] with 95% confidence intervals performed on high-density propensity score-matched groups.[7,18].
ComboRx: combination treatment with two anti-hypertensive medication either as a single-pill or separate pill; SPC: single-pill combination antihypertensive therapy; FEC: free equivalent combination single antihypertensive medication, two antihypertensive medications as two separate pills with same medications comparator SPC.

monotherapy [4,5]. Time to control is an important variable as clinical outcomes are better when hypertension is controlled within the first three to six months of treatment than after longer periods of time [15].

Anti-hypertensive efficacy of single-pill and free combinations that are not always equivalent classes

Most SPC approved for clinical use have approximately additive antihypertensive effects [16]. By definition, SPC and FEC are equivalent medication classes. In clinical practice, a significant proportion of free combinations do not reflect any marketed SPC [5]. Moreover, a significant proportion of individuals on two antihypertensive medications, despite absence of compelling indications, report taking a combination of a renin-angiotensin system blocker and β-blocker [17], which have less than additive antihypertensive effects.

Clinical outcomes

As noted, adults with hypertension begun on a single antihypertensive medication often remain on a single medication for extended periods of time. Unfortunately, the majority of adults with hypertension are not controlled on monotherapy, even when maximally recommended doses are given [16]. Observational studies indicate that adults with hypertension who are initiated on a combination of two antihypertensive medication classes have fewer composite cardiovascular events than individuals initiated on monotherapy (Tables 2 and 3). Of interest, evidence also suggests that hard clinical outcomes including death are reduced when equivalent two-drug combination therapy is prescribed as a single-pill rather than as separate pills [18]. The difference appears to be driven by greater adherence as an on-treatment analysis did not show any significant difference in outcomes.

Projected benefits of SPC vs. alternative therapeutic approaches

The available data on SPC therapy and alternative treatment approaches to SPC including current treatment practices and free choice combinations were examined in a microsimulation model. The results suggested that the composite outcome of ischaemic heart disease, stroke and chronic kidney disease could be reduced across five countries ranging from a low of 4.9% to a high of 11.5% [19].

Table 3. Antihypertensive medications prescribed individually and as SPC among the top 300 prescription medications in the U.S. [21].

Top 300#	Med	Scripts	Pts	Top 300#	Med	Scripts	Pts	Top 300#	Med	Scripts	Pts
3	Lisinopril	91.9	20	82	Propranolol	9.3	2.4	191	Nebivolol	3.1	0.7
5	Metoprolol	74.6	15.2	99	Hydralazine	6.7	1.7	198	Labetalol	2.8	0.7
6	Amlodipine	73.5	16.4	115	HCTZ/Triamterene	5.8	1.3	203	Terazosin	2.7	0.6
9	Losartan	51.8	11.8	118	Nifedipine	5.6	1.2	210	Doxazosin	2.5	0.6
11	HCTZ	38.6	9.4	130	Benazepril	5.2	1.3	213	Amlodipine/benazepril	2.3	0.6
17	Furosemide	28.4	6.6	135	Chlorthalidone	5.0	1.2	238	Valsartan/HCTZ	2.0	0.5
33	Carvedilol	20.6	4.6	140	Guanfacine	4.6	0.7	241	Bumetanide	2.0	0.4
39	Atenolol	18.1	3.8	141	Verapamil	4.6	0.9	249	Bisoprolol	1.9	0.3
44	HCTZ/Lisinopril	16.0	3.3	154	Valsartan	4.2	1.1	270	Telmisartan	1.6	0.4
63	Spironolactone	11.4	3.0	164	Olmesartan	3.7	1.0	280	Bisoprolol/HCTZ	1.4	0.3
64	Clonidine	11.4	2.2	170	Prazosin	3.6	0.6	294	Quinapril	1.3	0.3
72	Diltiazem	10.6	2.2	178	Ramipril	3.3	0.9				
73	HCTZ/Losartan	10.3	2.3	181	Irbesartan	3.2	0.9				

[#]Ranking number
Number of prescription (Scripts) and patients (Pts) in millions.

Variables impacting uptake of SPC across low- and middle-income countries

The burden of uncontrolled hypertension is very high, especially in low- and middle-income countries [1]. Scalable, low-complexity interventions including greater use of SPC emerge as important options for addressing the burden of preventable cardiovascular disease. A recently published analysis identified three key factors that impact the national uptake of SPC therapy for hypertension [20]. These items include: (i) inclusion of antihypertensive SPC on the national essential medications list (ii) recommended use of SPC in national or regional hypertension guidelines (iii) availability of SPC on the marketplace. The latter is unfortunately still a significant barrier for implementation, since there are significant regional differences regarding the availability of SPC. Indeed, although SPCs are widely available in some countries in Europe, North America (Canada and United States), and in Asia (China, Japan, India, and South Korea), fewer SPCs are available in countries in the Middle East and Australia, particularly those including a renin angiotensin system-blocker and a calcium channel blocker, while the corresponding information for Africa is in fact difficult to retrieve [10].

Concerns and limitations

In this editorial we have attempted to efficiently convey the advantages of SPC therapy as initial therapy for hypertension. Moreover, when patients require a third or occasionally a fourth medication to control hypertension, the use of SPC to reduce pill count appears advantageous. Nevertheless, a limited proportion of adults with hypertension can be controlled on standard or lower doses of a single antihypertensive medication class, which are often well tolerated. Many individuals controlled on monotherapy will be within 10 mmHg of their SBP goal before treatment. For these individuals, initiating treatment with a single medication class is appropriate [7,16]. Individuals who are older and frail also appear to be at greater risk for excessive reductions in BP [7]. For these individuals, initial monotherapy is appropriate. Another valid concern is that when adverse effects occur, it may be difficult to determine the responsible drug when starting with a SPC. Yet, evidence suggests that SPC therapy, especially at standard doses or lower, is well-tolerated with adverse effect and discontinuation rates that are not significantly different from those with standard or twice standard dose monotherapy and can be easily recognised [8].

Summary and recommendations

Potential, Pitfalls and Solutions.

Potential

Hypertension control is suboptimal globally and contributes to a devastatingly high health and economic burden of preventable cardiovascular and renal disease. Addressing the deficiency in hypertension control will require a multi-component approach. The extant literature indicates that greater use of SPC, especially as initial therapy, could substantially improve rates of hypertension control and decrease rates of cardiovascular disease and death.

Pitfalls

The majority of individuals with hypertension begins treatment with monotherapy, and unfortunately remain on monotherapy for an extended period of time, despite uncontrolled blood pressure. Several antihypertensive medications were among the top 300 medications prescribed in the U.S. during 2019. SPC accounted for 6.3% of antihypertensive medication prescriptions and 12.3% of antihypertensive medications within the top 300 (Table 3) [21]. In Europe, looking at the sales of antihypertensive drugs in 2020 (IQVIA^{TM} Analytics Link), the first SPC associating an ACE inhibitor and a diuretic is

ranking Nr 16 and the first SPC associating an ACE inhibitor and a calcium channel blocker ranked Nr 24. Changing prescribing behaviour has proven difficult. Therapeutic inertia, or the failure to add or intensity antihypertensive medication when blood pressure is uncontrolled, has remained at very high levels, despite clear identification of the problem more than two decades ago [13,22]. Another potential pitfall is the valid but impractical position that initial monotherapy with additional antihypertensive classes would be as effective as initial SPC if adults with uncontrolled hypertension are seen more frequently, intensification occurs promptly, and patients are as adherent with multiple pills as fewer pills. Few would disagree with this premise, yet the likelihood is low that this ideal scenario for initial monotherapy will occur at scale.

Solutions

Evidence suggests that inclusion of antihypertensive SPCs on national formularies, recommendations for use of SPC in national hypertension guidelines, and ready availability and affordability of SPC in the marketplace improve uptake of this treatment option. Implementation of treatment algorithms based on initial use of SPC combined with ongoing audit and feedback on adherence to the algorithm and hypertension control can lead to hypertension control rates consistently exceeding 80%. Fortunately, change is non-linear. Given the tension between poor hypertension control rates and the burden of preventable disability on one hand and the benefits of greater hypertension control on the other, SPC emerges as a scalable component of the solution. The tipping point for adoption could well be decades ahead of the slow rate of linear change to date.

Disclaimer

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