Single-Pill vs Free-Equivalent Combination Therapies for Hypertension: A Meta-Analysis of Health Care Costs and Adherence

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This meta-analysis compares health care resource use costs, adherence, and persistence between groups of patients taking antihypertensives as single-pill combinations (SPCs) vs free-equivalent components (FEC) based on a structured review of published studies. The search yielded 12 retrospective database studies included in analyses. The mean difference in combined total annual all-cause and hypertension-related health care costs was $1357 (95% confidence interval [CI], $778–$1935) lower in favor of SPC than FEC groups. Adherence, measured as the mean difference in medication possession ratio, was estimated to be 8% higher for patients naive to prior antihypertensives and 14% higher for nonnaive SPC patients compared with corresponding FEC patients. Persistence in the SPC groups was twice as likely as the FEC groups (pooled risk ratio, 2.1; 95% CI, 1.1–4.1). Improved adherence and persistence may have contributed to the lower costs in the SPC groups via improved clinical outcomes. *J Clin Hypertens (Greenwich).* 2011;13:898–909. ©2011 Wiley Periodicals, Inc.

Hypertension is a chronic medical condition and recent estimates suggest that 76.4 million US adults 20 years or older have hypertension.[1] Total costs (direct plus indirect) for hypertension in the United States were estimated at $73.4 billion in 2009.[1]

Pharmaceutical treatment of hypertension can be very successful, with the potential to reduce blood pressure (BP) to recommended levels in almost all patients (<140/90 mm Hg or <130/80 mm Hg for patients with diabetes or chronic kidney disease). However, recent data show that only 50% of patients with hypertension achieved BP control.[2] Uncontrolled BP can result in significant morbidity and mortality, with increased risk of adverse cardiovascular (CV), cerebrovascular, and renal outcomes.[3–5] Furthermore, uncontrolled BP can result in increased medication costs compared with costs for hypertension patients with appropriately controlled BP.[6]

Two of the main reasons for a lack of adequate BP control are lack of adherence (missing doses of an antihypertensive medication in the context of ongoing treatment) and lack of persistence (discontinuation of an antihypertensive medication).[7,8] Adherence to antihypertensive therapy is often very low, ranging from 15% to 35%.[9] One major factor contributing to decreased adherence and persistence with antihypertensive medications is the complexity of treatment regimens. Many patients with hypertension require ≥2 medications to provide adequate BP control. Only one third of patients with hypertension require a single medication for BP control, one third require 2 medications, and the remaining one third require ≥3 medications.[10]

Strategies to improve adherence and persistence to prescribed antihypertensive medications are likely to improve BP control and thus can potentially have substantial medical and economic benefits. One such strategy is the use of fixed-dose single-pill combination (SPC) medications, which combine ≥2 active agents in a single pill. SPC medications simplify the treatment regimen and decrease the daily pill burden for patients, both of which are associated with improved adherence.[7] Two previous meta-analyses reported increased adherence with SPC products compared with multiple pills of the same active agents for patients with a combination of chronic conditions or for patients with hypertension.[11,12] However, we are unaware of previous systematic reviews and analyses evaluating the relationship between health care costs and the use of SPC products for hypertension. This report presents results of a meta-analysis performed to assess health care costs, adherence, and persistence among patients receiving SPC products vs free-equivalent components (FECs) (ie, the corresponding single-agent pills) for hypertension.

METHODS

Literature Search

A systematic literature search within PubMed, EMBASE, The Cochrane Library, and EconLit was conducted to identify publications comparing adherence, persistence, or costs and resource use associated with the use of SPC products vs FEC medications for hypertension. Comprehensive combinations of MeSH and free-text terms were used for the literature search. We searched English-language publications only, with no limit on publication dates.

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Abstracts of identified publications were first reviewed to determine relevancy based on the following inclusion criteria:

- The study was a clinical trial or observational study, such as a database or registry analysis.
- The study compared fixed-dose SPC products (double or triple combinations) with FEC as pharmaceutical interventions for CV disease. No single-arm studies were included.
- The study presented data on any of the following outcomes of interest:
  - o Compliance, adherence, persistence.
  - o Health care costs and/or resource use.

Eligible publications, along with articles identified from expert suggestions, were reviewed in full and references were checked for additional citations. Studies were excluded if the product was not marketed in the United States. For selected articles, information about study characteristics, treatment and baseline data, adherence or compliance, resource utilization costs, percentage resource utilization, and mean resource utilization was extracted from articles. Data extraction and validation and entry were conducted by different team members.

Outcome Measures

Three outcome measures were of primary interest: health care costs, adherence, and persistence. Cost outcomes identified from the literature were: all-cause health care costs, CV- or hypertension-related costs, and pharmacy costs. In all studies eligible for analysis, health care cost data (total or CV-related) were provided in 2002 to 2009 US dollars as unadjusted annual mean costs for SPC vs FEC groups. Unless specifically identified, we assumed that costs were based on the year prior to study publication. Costs were converted to 2009 US dollars using the medical care component of the consumer price index for all urban consumers.[16] In one article, where 6-month costs were provided, the values were doubled to correspond to a 12-month period.[14] For pharmacy costs, total costs spent on prescription medications were assessed; data on prices or copayments of specific products projected annually were not considered. Few articles gave variance measures for cost data. Since cost data generally have a positively skewed distribution, a constant variance coefficient was assumed across studies. An average coefficient of variation was calculated from studies that provided adequate information[14,17,18]; this derived estimate was then used to impute an average standard deviation for studies without such data.

Most hypertension studies that presented adherence or compliance outcomes provided the average medication possession ratio (MPR), defined as the total days' supply of medication during the study follow-up period divided by the length of the follow-up period. Studies provided the MPR at 12 months for each group, with the exception of Shaya and colleagues (2009)[19] and Yang and colleagues (2010).[15] These studies were not included in the meta-analysis. Few studies provided a variance measure for this end point. An average value for the standard deviation using data from the two studies that provided a variance measure[13,20] was imputed for the other studies. With the exception of one article,[15] all hypertension studies reported persistence as the percentage of patients meeting a predefined threshold during a 12-month follow-up period. Although persistence was measured over similar duration across the remaining studies, the permissible gap between the end of the days' supply and the end of observation used to define persistence varied from 6 days to 6 months across studies, which exacerbated the variance in this measure. Despite these differences in the definitions for persistence, we considered the persistence data suitable for meta-analyses since groups were compared within each study.

Statistical Analysis

In order to conduct the meta-analysis, effect sizes for comparing single-pill and free-equivalent groups within each study were generated as mean differences for continuous end points (costs and adherence) and risk ratios for categorical end points (persistence). Meta-analyses were performed on the difference in mean total health care resource costs and pharmacy costs between the single-pill cohort and free-equivalent cohort. All-cause total costs and costs specific to hypertension or CV-related care were determined separately. Due to unexplained heterogeneity for all outcomes, we present CIs generated with a random effects method. Clinical and methodologic differences across studies were examined to investigate sources of heterogeneity and inform possible stratification, but these efforts were limited by the small number of studies. Analyses were performed using RevMan software version 5 (http://ims.cochrane.org/revman; accessed December 1, 2010).

RESULTS

After screening 260 abstracts, 40 articles were reviewed in full. Of 22 studies that met inclusion criteria, 7 addressed indications other than hypertension (5 in diabetes, 1 in hyperlipidemia, and 1 in mixed hyperlipidemia/hypertension) and 15 were in hypertension. The hypertension studies shown in the Table are the subject of this paper. Three articles were not included in meta-analyses: Asplund and colleagues[21] did not provide a clear definition of adherence, Schweizer and colleagues[27] had a very short follow-up period (1 month), and Yang and colleagues[15] adjusted for covariates in the analysis and these results could not be combined with other studies that presented unadjusted outcomes. The remaining 12 studies were all retrospective studies published in the past 10 years. Five studies either used a matched cohort design[14,18] or presented similarities in group baseline characteristics.[13,23,26] Of 5 studies that noted more comorbidities in the patient groups taking free combination

TABLE. Characteristics of Studies in Hypertension (N=15)

First Author, Y	Study Design and Data Source	Population	Drug Classes and Extracted Outcomes	Findings of SPC vs FEC Therapies on Adherence, Compliance, Persistence, and Health Care Costs
Asplund, 1984[21a]	Randomized, multicenter, crossover study (N=160) Follow-up: 4 months + crossover 25 physicians from 18 hospitals in Sweden	Patients with HTN taking treatment with a β-adrenoceptor blocker and a thiazide diuretic	BETA + DIUR Adherence	Approximately 90% of patients took >90% of prescribed doses throughout the study. Approximately 75% of patients preferred 1 tablet daily, but combining 2 drugs in 1 tablet had no effect on compliance
Barron, 2008[17]	Retrospective database study (N=5625) Follow-up: 12 months Five commercial health plans in southeastern, mid-Atlantic, central, and western regions of the US	Patients aged ≥18 y diagnosed with HTN; enrolled ≥12 months preindex and postindex; ≥1 claim of SPC or FEC filled within 15 days of each other. Required at least 1 refill within a period <2× ''days supply''; excluded if ≥1 claim for antihypertensive medication during 6 months prior to index date or ≥1 claim for any other drugs within 15 days[c]	ACEI + CCB HTN-related costs	Patients in the SPC group had significantly lower unadjusted medical, pharmacy, and total HTN-related health care costs than the FEC cohort Patients in the FEC cohort were older than those in the SPC cohort and had a significantly higher comorbidity score Adjusting for covariates, HTN-related costs were 44.8% higher for patients in the FEC cohort than the SPC, with a difference in predicted mean costs of $562 per y (*P*=.001)
Brixner, 2008[20]	Retrospective database study (N=8711) Follow-up: 12 months Integrated Healthcare Information Services National Managed Care Benchmark Database	Patients continuously eligible for Rx benefit from January 1997–June 2004. Absence of anti-HTN claim in the 110 days prior to study medications; dual therapy initiated within 180 days of index ARB or diuretic[c]	ARB + DIUR Adherence, persistence, total costs[d]	The SPC group had a larger portion of men and fewer concomitant cardiovascular medications and diseases Based on adjusted linear regression analyses, SPC patients had improved values for medication adherence compared with the FEC group (62.1% vs 53.0%, *P*<.001) and persistence values were improved at both 180 days (73% vs 28%, *P*<.001) and 365 days (54% vs 19%, *P*<.001). Both prescription drug ($1587 vs $2050, *P*<.001) and medical ($3343 vs $3817, *P*<.001) costs were lower in the SPC cohorts
Dezii, 2000[22]	Retrospective database study (N=2268 and 1674) Follow-up: 12 months National commercial pharmacy benefits manager	Patients with HTN who received the agents of interest from the second quarter of 1995 through the fourth quarter of 1999 but no such agents in the preceding 6 months[c]	ACEI + DIUR Persistence[d]	Persistence rates at 12 months were 69% in the lisinopril/HCTZ SPC group, 70% in the enalapril maleate/HCTZ SPC group, and 58% in each of the FEC groups (*P*<.05).

TABLE. Characteristics of Studies in Hypertension (N=15) (Continued)

First Author, Y	Study Design and Data Source	Population	Drug Classes and Extracted Outcomes	Findings of SPC vs FEC Therapies on Adherence, Compliance, Persistence, and Health Care Costs
Dickson, 2008[13]	Retrospective database study (N=5704) Follow-up: 12 months South Carolina Medicaid database	Patients aged 65–99 y (elderly) continuously eligible for Medicaid for 12 months following index date; received at least 2 prescriptions for components during 1997–2001; excluded if hospitalized for >180 days, <30 days of study drug supply, or nursing home claims during follow-up	ACEI + CCB Compliance, total costs[d]	Demographics of the 2 groups were similar Compliance with antihypertensive therapy was significantly higher for patients in the SPC group (63.4%) vs the FEC group (49.0%; $P<.005$). The average total cost of care (in 2002 dollars) for the SPC group was $3179, compared with $5236 in the FEC group ($P<.0001$). In multivariate logistic regression analyses with propensity scores, average total costs were reduced by 12.5% for patients using SPC vs FEC therapy ($P<.003$).
Dickson, 2008[23]	Retrospective database study (N=4076) Follow-up: 12 months South Carolina Medicaid database	Patients aged 18–99 y continuously eligible for Medicaid for 12 months following index date; received ≥2 prescriptions for components 1997–2001; excluded if hospitalized for >180 d/<30 d of study drug supply, or nursing home claims during follow-up	ACEI + CCB Compliance, total costs[d]	The demographics in groups were similar Compliance with antihypertensive therapy was significantly greater in patients who received SPC (58.6%) vs patients who received FEC (48.1%; $P<.05$), independent of race The average total cost of care for the SPC group was $4605, compared with $8531 in the FEC group. Each category of expenditure was lower with SPC vs FEC therapy (hospital costs were 70% lower, drug costs 27% lower, and ambulatory costs 38% lower). In adjusted regression analyses, use of SPC was associated with 24% lower total cost of care
Gerbino, 2007[24]	Retrospective database study (N=6206) Follow-up: 12 months Managed care organization in northeastern US	Patients on antihypertensive therapy continuously eligible for 12 months with ≥2 prescriptions for SPC or components; excluded if prescribed SPC ACEI-diuretic	ACEI + CCB Adherence[d]	Demographic information was not available Adherence rates were among patients receiving SPC (87.9%) vs FEC (69.2%) were ($P<.0001$). The average number of concomitant drug classes in the SPC group was 4.0, compared with 5.2 in the FEC group. As the number of concomitant drugs increased, the difference in MPR increased in favor of SPC
Hasford, 2007[25]	Retrospective database study (N=13,763) Follow-up: 12 months IMS Disease Analyzer database	Patients with hypertension newly diagnosed and prescribed initial treatment with either monotherapy or a specified FEC or SPC of 2 antihypertensive drugs[b,c]	ARBs or ACEI + other Persistence	Persistence with the initially prescribed antihypertensive treatment was longest for the ARB SPC group compared with the other drug classes ($P<.001$) One y after initiation, 87.1% of patients taking FEC (ACEI and other) and 64.4% taking ARB SPCs discontinued initial treatment for at least 6 mo In the third year, persistence with the initially prescribed drug class varied between 3.2% (FEC of ACEI and other) and 17.7% (ARB SPCs).

TABLE. Characteristics of Studies in Hypertension (N=15) (Continued)

First Author, Y	Study Design and Data Source	Population	Drug Classes and Extracted Outcomes	Findings of SPC vs FEC Therapies on Adherence, Compliance, Persistence, and Health Care Costs
Hess, 2008[18]	Matched cohort retrospective database study (N=14,449) Follow-up: 12 months Thomson Medstat MarketScan database	Patients with HTN with coverage for 12 months before and ≥12 months after index date from January 2004. Cases required filled prescriptions for SPC for ≥3 months before switch to FEC regimen (index date). Comparable cohorts were identified using propensity scores with patients matched for age, sex, payer type, comorbidities, and risk factors[b]	ARB + DIUR; or ACEI + DIUR; or ACEI + CCB Compliance, persistence, costs	Based on multivariate adjusted regression, patients continuing with SPC therapy had better persistence (42.5% higher; $P<.002$) and compliance (22.1% higher; $P<.001$), compared with patients who were switched to FEC therapy The higher compliance rate for patients continuing SPC was associated with significantly lower expenditures for hypertension-related health care ($P<.001$) and an estimated 5% reduction in hypertension-related expenditures
Jackson, 2008[26]	Retrospective database study (N=908) Follow-up: 12 months Integrated Health Care Information Solutions National Benchmark Database	Aged ≥18 y diagnosed with hypertension and naive to antihypertensives prior to index date January 1997 through June 2004. Excluded if <1 refill, did not continuously have refills, or were switched from 1 medication to another without a time overlap[b,c]	ARB + DIUR + CCB[d] Adherence	The mean MPRs were 75.4% (2-pill valsartan + amlodipine), 73.1% (2-pill valsartan/HCTZ + amlodipine), and 60.5% (3-pill valsartan + HCTZ + amlodipine), $P=.005$. Based on adjusted analyses of variance, adherence decreased with the increase in tablets per regimen, and improved adherence was correlated with increasing age
Malesker, 2010[14]	Matched cohort retrospective study (N=200) Follow-up: 6 months Electronic medical records from outpatient clinics affiliated with universities in eastern Nebraska and western Iowa	Patients aged ≥19 y with hypertension who did not respond to an ARB or a DHP-CCB from July 1, 2007, through June 30, 2008. Patients who were switched to an SPC were considered cases; controls who were not switched were propensity-matched for age, sex, race, baseline BP, and comorbidities[b]	ARB + CCB Costs[d]	Although the acquisition cost of SPC was greater than that of the individual drugs, this difference was not statistically significant SPC combination therapy resulted in fewer clinic visits ($P=.005$), laboratory tests, and ECGs. As a result, the total cost of SPC therapy was significantly less than that associated with the use of the individual drug components ($P=.024$).
Schweizer, 2007[27a]	Prospective, nonrandomized, 2-stage study (N=197) Follow-up: 1 month Patients attending general or internal medicine clinics in Germany between July and December 2006	Patients aged ≥18 y with uncomplicated moderate essential hypertension. Exclusions for controlled BP on current medication; severe hypertension; heart failure; secondary hypertension; and other comorbidities; contraindications for study medication or use of concomitant medications known to significantly affect BP; pregnant, nursing, or childbearing potential; not using contraception	ARB + DIUR Compliance	Adequate compliance was noted in 92.9% of patients receiving FEC and 100% of patients receiving SPC

TABLE. Characteristics of Studies in Hypertension (N=15) (Continued)

First Author, Y	Study Design and Data Source	Population	Drug Classes and Extracted Outcomes	Findings of SPC vs FEC Therapies on Adherence, Compliance, Persistence, and Health Care Costs
Shaya, 2009[19]	Retrospective database study (N=568) Follow-up: 12 months Maryland Medicaid Database	Patients taking antihypertensive therapy as active Medicaid recipients January 2002–December 2004 with ≥1 y follow-up after initiating combination therapy, but no prior antihypertensive use during first 6 months[c]	ACEI + DIUR Compliance	Multivariate-adjusted logistic regression analysis showed that patients receiving SPC therapy were 60% more likely to comply with their assigned treatment than those receiving free-combination therapy (P=.02). Older age, Caucasian race, fewer severe comorbidities and simplified antihypertensive regimens were significant predictors of compliance Patients with less severe comorbidities were more likely to be prescribed SPC therapy than those with more severe comorbidities; the authors suggested that this may be related to findings from other studies showing that cardiologists and other specialists are more reluctant to prescribe SPC therapies to sicker patients because SPC therapy may not offer the same flexibility to adjust and titer doses as free-combination regimens
Taylor, 2003[28]	Retrospective database study (N=5732) Follow-up: 12 months Managed care organization	Patients aged 18–64 y with hypertension who were continuously eligible at least 12 months after first prescription for either of the 2 regimens and had at least 2 prescriptions during the study period[b]	ACEI + CCB Adherence, costs[d]	The overall MPR was significantly higher for patients prescribed SPC than that for patients prescribed a regimen as separate drugs (80.8% vs 73.8%; P<.001). The average annual cost of cardiovascular-related care per patient was significantly lower in the SPC group ($427 vs $574; P<.001). The authors acknowledged that the 2 groups were not completely comparable because comorbidity status was significantly higher in the FEC cohort and no adjustments were made for confounding factors

TABLE. Characteristics of Studies in Hypertension (N=15) (Continued)

First Author, Y	Study Design and Data Source	Population	Drug Classes and Extracted Outcomes	Findings of SPC vs FEC Therapies on Adherence, Compliance, Persistence, and Health Care Costs
Yang, 2010[15a]	Retrospective database study (N=579,851) Follow-up: 6 months Thomson Reuters MarketScan Commercial and Medicare Supplemental Databases	Adult patients with hypertension were eligible if ≥18 y old on the index date, continuous eligibility in the database for 6 months before and 6 months after the index date and valid 3-digit zip code data in the database	ARB + CCB; or ARB + DIUR; or ACEI + DIUR Compliance, costs	Adjusting for baseline characteristics, SPC patients demonstrated significantly higher MPR than free-combination patients (difference, 11.6%; 95% CI, 11.4%–11.7%). SPC patients had fewer all-cause hospitalizations (adjusted IRR, 0.77; 95% CI, 0.75–0.79) and ED visits (adjusted IRR ¼ 0.87; 95% CI, 0.86–0.89) than FEC patients. Results for cardiovascular-related utilization were similar to all-cause results Compared with FEC, SPC patients showed significantly greater reductions post-therapy initiation in all-cause medical costs by –$208 (95% CI, –$302 to –$114), but larger increases in hypertension-related prescription costs by $53 (95% CI, $51–$55). SPC use was associated with significantly better compliance/persistence and fewer hospitalization and ED visits than FEC in hypertensive patients at the national level and in almost all states. Larger reductions in medical costs with SPC use more than offset higher drug costs within most states

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BETA, β-blocker; BP, blood pressure; CCB, calcium channel blocker; CI, confidence interval; DHP, dihydropyridine; DIUR, diuretic; ECG, electrocardiography; ED, emergency department; HCTZ, hydrochlorothiazide; IRR, incidence rate ratio; FEC, free-equivalent component; MPR, medication possession ratio; Rx, prescription; SPC, single-pill combination; US, United States. [a]Study was excluded from meta-analyses. See text for rationale. [b]Diagnosed = yes if study identified patients using diagnosis codes, rather than based on medication usage. [c]Patients were considered naive if the study required a period prior to the index date with no antihypertensive medications. [d]Indicates that specific drug products were specified in the fixed-dose, single-pill regimen, or in both single-pill and free-equivalent dose regimens.

regimens, 3 provided adjusted results[17,19,20] and 2 did not.[25,28] Two studies did not provide information on group characteristics.[22,24]

The following drug class combinations/classes were represented:

- Angiotensin-receptor blocker (ARB) + diuretic.
- ARB + calcium channel blocker (CCB).
- Angiotensin-converting enzyme (ACE) inhibitor + diuretic.
- ACE inhibitor + CCB.
- β-Blocker + diuretic.

Only one study examined patients taking triple treatment for hypertension.[26] Differentiation among class combinations was not made in the meta-analyses presented here due to the limited number of studies.

Annual Health Care Costs

Figure 1 shows the meta-analysis of annual health care costs from 44,336 patients in 7 observational studies comparing SPC products for hypertension with FEC regimens. In all studies, the annual health care costs in the SPC groups were lower than costs in the free-equivalent groups, and comparisons were statistically significant except in one study.[20]

The overall pooled summary includes both all-cause total costs and hypertension-related costs, depending on what was available in the studies. Subtotals are presented separately for studies that reported all-cause total costs (n=4) or only costs related to hypertension, CV disease, or both (n=3). The pooled analyses for each of these strata indicate significantly lower annual costs for patients in the SPC groups than for those in the FEC groups. All-cause total costs in the SPC group were estimated to be lower by $2039 (95% CI, $1030–$3047) and hypertension/CV-related costs were estimated to be lower by $709 (95% CI, $117–$1302).

Significant heterogeneity was present within each cost type, and efforts were made to identify the source of the heterogeneity. Removal of individual studies one by one did not resolve the issue. We examined characteristics of the studies for possible explanations including the use of all-cause or hypertension- or CV-related costs, inclusion of Medicare/Medicaid patients, use of diagnosis codes for patient identification, prior use of antihypertensives, and class of drugs. However, specific subgroups could not be analyzed due to the small number of studies. The possibility remains that heterogeneity could be due to data imputation. The average of the variance measures from the Barron and colleagues[17] and Hess[18] studies were imputed for the other studies.

Pharmacy Costs

Five studies presented data on pharmacy costs of drugs for patients taking SPC or FEC products (Figure 2). We provide separate findings for all-cause drug costs and hypertension-/CV-related drug costs, since results are not consistent across these two strata. One study provided data for both all-cause annual medication costs and medication costs specifically related to CV disease.[28]

Annual all-cause medication costs averaged $605 (95% CI, $376–$835) lower for patients taking SPC antihypertensive regimens than for those taking FEC

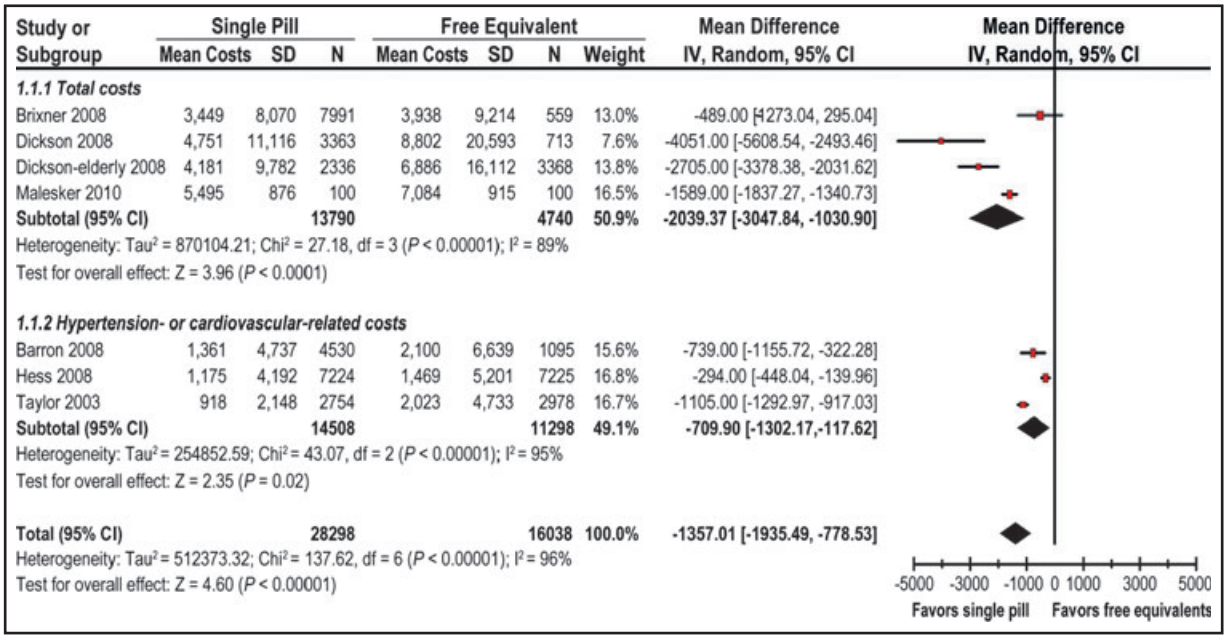

FIGURE 1. Meta-analysis of annual health care costs (2009 US dollars). CI indicates confidence interval; IV, inverse variance; SD, standard deviation.

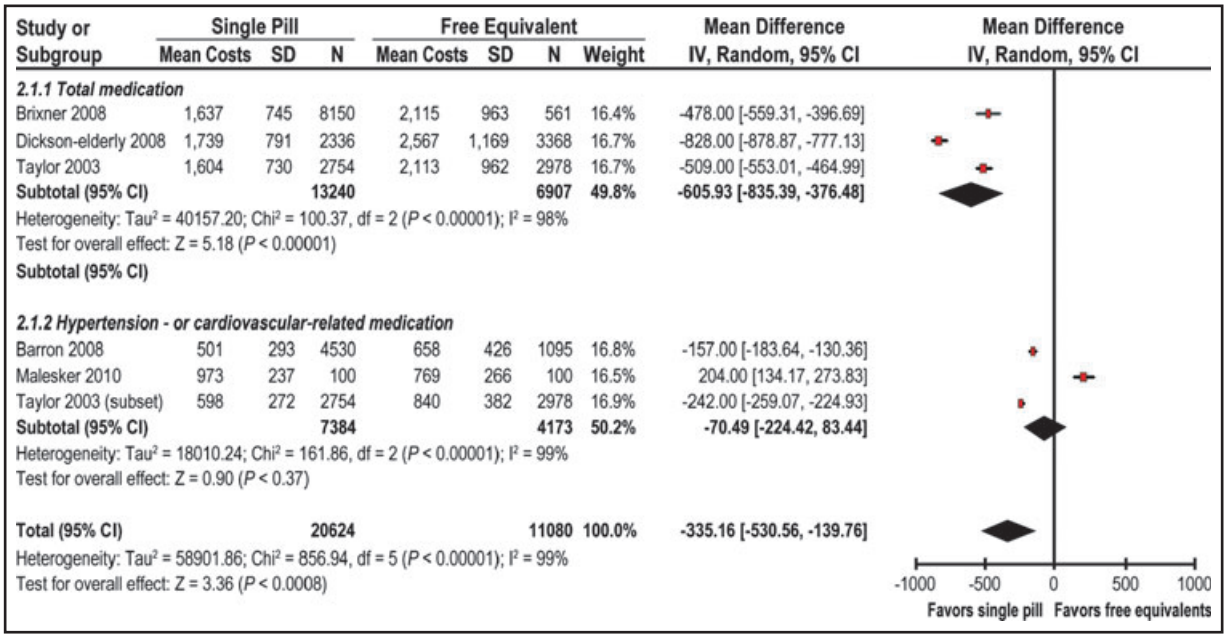

FIGURE 2. Meta-analysis of annual pharmacy costs (2009 US dollars). CI indicates confidence interval; IV, inverse variance; SD, standard deviation.

medications. However, mixed results were found in analyses of medication costs related to hypertension. Two studies[17,28] showed significantly lower costs for SPC regimens while one study[14] showed significantly lower costs for FEC medications. The latter results were based on a shorter timeframe (6 months) than other studies and groups were matched by age, sex, race, baseline BP, and comorbidities.

Significant heterogeneity was present within each cost type, and efforts were made to identify the source of the heterogeneity. Removal of individual studies one by one did not resolve the issue. As in the meta-analysis of total costs, variance measures were imputed for most studies.

Adherence

All studies that reported MPR (n=7) found significantly higher adherence in groups taking SPC medications than in groups taking FEC medications, with the biggest difference found in a study by Hess[18] that matched groups by age, sex, payer type, comorbidities, and risk factors (Figure 3). In the stratified meta-analysis, studies in patients naive or experienced with hypertension medication both showed significantly higher adherence in groups taking SPC than in FEC groups. The average MPR was 8% higher in naive patient groups taking SPC and 14% higher in experienced patients.

Persistence

The pooled risk ratio from meta-analysis of 4 studies shows the SPC groups to be twice as likely as the FEC groups to meet criteria for persistence (relative risk, 2.13; 95% CI, 1.11–4.09) (Figure 4). Again, the largest difference between groups was seen in the study by Hess,[18] in which groups were matched on baseline characteristics.

DISCUSSION

Results from meta-analyses of data extracted from 12 observational studies corroborate and expand on 2 previous meta-analyses that demonstrated improved adherence to antihypertensive treatment regimens that combine ≥2 active agents in a single pill.[11,12] Compared with the earlier papers, we detected larger, statistically significant effects on both adherence/compliance and persistence for SPC products compared with FEC products for hypertension. The adherence difference of 13% from the meta-analysis shown here compares with that estimated by Yang and colleagues[15] based on multivariate modeling from a large cohort in a claims database. Similarly, this meta-analysis confirms results from Yang that treatment continuation or persistence is twice as likely in a single-pill cohort. The strength of evidence provided here rests on the rigor of the literature search and the careful delineation of definitions used for adherence/compliance and persistence.

Previously, Rose and colleagues[29] reported that patients with 100% adherence to hypertension therapy experienced a decrease in systolic BP of 12 mm Hg to 15 mm Hg and a decrease in diastolic BP of 7 mm Hg to 8 mm Hg compared with those having <60% adherence. Multiple studies have reported lower rates

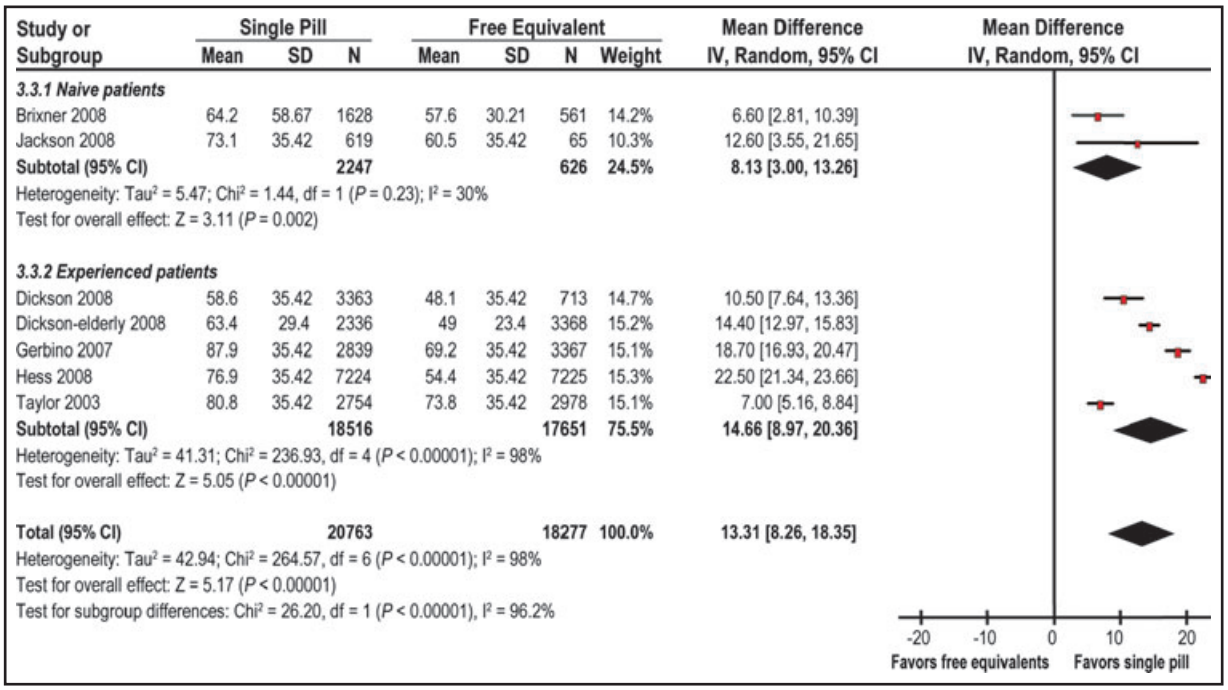

FIGURE 3. Stratified meta-analysis of adherence (mean medication possession ratio [MPR]). CI indicates confidence interval; IV, inverse variance; SD, standard deviation.

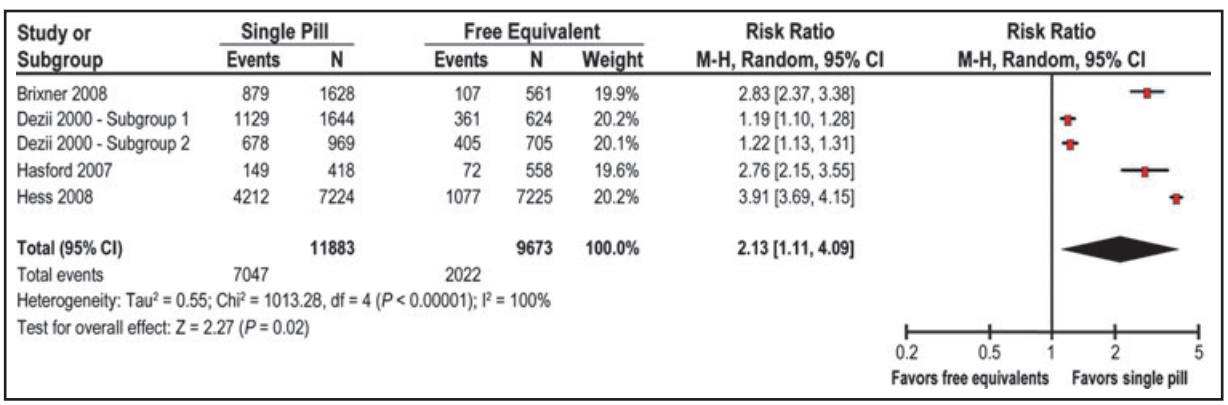

FIGURE 4. Meta-analysis of persistence. Events represent the number of patients meeting the definition of persistence. CI indicates confidence interval; IV, inverse variance; SD, standard deviation.

of hypertension-related complications and decreased medical care costs among individuals with improved adherence to antihypertensive medications.[7,8] The meta-analyses presented here are consistent with those individual studies, demonstrating better adherence and significantly lower annual health care resource use costs for patients taking SPC treatments for hypertension than for patients taking FEC regimens. The magnitude of this cost reduction is variable, possibly due to heterogeneity across study groups. Stratification of results was limited by the small number of studies that varied on other characteristics such as whether a hypertension diagnosis was required, whether patients were naive to antihypertensive treatment, which drug classes were considered, and whether the data source was a public or private health plan.

Overall, all-cause pharmacy costs were also shown to be reduced for SPCs. The results from Maleskar[14] showing higher hypertension- or CV-related medication costs in the SPC group differed from other study results but may be more reliable given the use of matched cohorts.

LIMITATIONS

The use of unadjusted costs is a limitation of the meta-analysis, as underlying patient characteristics could have contributed to differences in adherence and costs across SPC and FEC medications. However, we note that the unadjusted values used in meta-analyses were generally consistent with author findings based on adjusted regression analyses (where available). Also, effects from matched cohorts were in the same direction as other studies except for pharmacy costs. The limited number of available studies restricted our ability to perform subgroup analysis. Previous studies have reported that adherence to antihypertensive therapy can vary substantially among patient subgroups, and not always in directions assumed a priori. Another clear limitation of the meta-analyses is that variance measures were unavailable from most studies and had to be imputed for costs and adherence measures. Data on use of specific health care resources were sparse and not analyzed. Heterogeneity was present in the analyses of each outcome, and attempts to explain it by stratification were limited by the small number of studies that varied on other characteristics such as whether a hypertension diagnosis was required, whether patients were naive to antihypertensive treatment, which drug classes were considered, and whether the data source was a public or private health plan.

CONCLUSIONS

These meta-analyses compile the evidence showing improved medication adherence and lower all-cause health care costs for patients taking SPC products for hypertension compared with patients taking free-equivalent products. Other patient, physician, health care system, and societal factors also influence selection for and adherence to antihypertensive therapy. However, our findings suggest that interventions to improve adherence to and persistence with antihypertensive therapy should incorporate the use of SPC medications among patients not adequately controlled on a single agent. By minimizing the complexity of treatment regimens and thus improving adherence and persistence, strategies involving SPC therapy in this population may both improve clinical outcomes and reduce costs.

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