Availability and utilization of cardiovascular fixed-dose combination drugs in the United States

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Background Solid clinical evidence supports the effectiveness and safety of multiple drugs in treating diabetes, dyslipidemia, and hypertension, and numerous fixed-dose combination products (FDCs) containing such drugs have been developed for patients with more severe forms of these diseases. We sought to evaluate the extent to which utilization of treatment combinations for these conditions corresponded to the availability of FDCs.

Methods Using claims data from a large national commercial insurer, we identified 2 cohorts of patients: those who filled multiple single-agent drugs to treat diabetes, dyslipidemia, and hypertension in 2012, and those who used FDCs containing these products during the same period. We determined the fill rate of single-agent pairs and FDCs, availability of FDCs for the most frequently filled single-agent and drug class pairs, and the number of conditions treated by frequently filled single-agent pairs and FDCs.

Results During our study period, 848,082 patients filled prescriptions for 3,248 unique single-agent pairs (mean 4.7 per patient, standard deviation [SD] 5.0); and 568,923 patients received prescriptions for 43 unique FDCs (mean 1.1 per patient, SD 0.3). Three (15%) of the 20 most frequently filled single-agent pairs were available as FDCs, whereas 9 (45%) of the 20 most frequently filled drug class pairs were available as FDCs. Nearly all of the frequently filled FDCs had lower fill rates than the most frequently filled single-agent pairs.

Conclusions Utilization of drug combinations to treat cardiovascular conditions does not correspond well with availability of FDCs containing these agents. A concerted set of strategies should be implemented to streamline the development of useful combination products, including expedited approval pathways and increased investment in formulation studies. (Am Heart J 2015;169:379-386.e1.)

In HIV/AIDS, respiratory disease, and certain cardiovascular diseases, multidrug regimens have become the standard of care.[1–5] Fixed-dose combinations (FDCs), which are prescription drug products that include more than 1 active pharmaceutical ingredient, can increase convenience for patients by reducing pill burden and promoting prescription synchronization, which may improve medication adherence among patients who require multiple drugs.[6–8] Certain combinations can have other benefits, such as avoidance of adverse effects related to hypokalemia with the combination of hydrochlorothiazide and triamterene. Recognizing the importance of FDCs, the Food and Drug Administration (FDA) recently proposed allowing more FDCs to be eligible for a longer period of market exclusivity to encourage development of these products.[9]

Chronic conditions such as diabetes, dyslipidemia, and hypertension are common causes of coronary heart disease and frequently coexist. In fact, 45% of adults in the United States have at least one of these diseases, 13% have at least 2, and 3% suffer from all 3 conditions.[10] Many different drug classes are used to treat these conditions;[11,12] so FDCs containing commonly coprescribed components may be particularly useful in affected patients,[13] and in particular may help improve adherence in this population, which has been reported to be less than 50%.[14,15]

Although an increasing number of FDCs are becoming available for these diseases, little is known about the degree to which they meet patient demand for FDC products. We examined prescription fill rates of FDCs and single-agent drugs used in combination in a large national commercial insurer database to determine the

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degree to which FDC availability aligns with multidrug regimen patterns for the treatment of diabetes, dyslipidemia, and hypertension.

Methods

Design overview

We used the Optum Research Database, which contains medical and pharmacy insurance claims data for >14 million current beneficiaries of the UnitedHealth commercially insured population.[16] The covered population has demographics similar to the US census age distribution for sex and age groups <65 years. The Brigham and Women's Hospital Institutional Review Board approved the study.

We identified every single-agent prescription drug product approved by the FDA to treat hypertension, dyslipidemia, and diabetes (online Appendix Supplementary Table I) and subclassified these by pharmacologic mechanism of action (eg, β-adrenergic blocking agents). We included only regular-release oral tablet and capsule formulations of drugs, excluding other oral formulations and parenteral routes of administration.

Patient cohorts

We identified patients who filled FDA-approved FDC products containing 2 drugs from the single-agent drug list between January 1, 2012, and December 31, 2012. We identified a separate cohort of patients who used 2 single-agent products in combination during this period. We considered patients to be exposed to single-agent combination pairs when they filled the 2 single drugs on the same day or when they demonstrated concomitant use through multiple prescription dispensings.[17] In the latter scenario, patients were considered exposed to single-agent combination pairs when they filled a prescription for one drug (eg, drug A) followed by a prescription for another (eg, drug B) before the end of drug A's days' supply and then filled a prescription for drug A within 14 days of the elapsed days supplied of its previous fill (Figure). The refill requirement for drug A was included to ensure that patients were not switching from drug A to drug B. If a patient filled prescriptions for additional medications (drug C, drug D, etc) before both drug A's and drug B's days' supplies ran out, then drug A/drug C and drug B/drug C were also counted as single-agent combination pairs as long as the refill requirement for the earlier-filled prescription was met. Patients could be exposed to multiple single-agent combination pairs, but we counted exposure to each unique pair only once.

Outcomes and descriptive analyses

We determined the number of patients who used the 20 most frequently filled single-agent combination pairs and how many of these pairs were available as FDCs. We then repeated this analysis at the drug class level (eg, single-agent pair containing a β-blocker and thiazide diuretic). We also enumerated the 20 most frequently filled FDCs and determined the number of patients who filled corresponding single-agent combination pairs instead of the FDC products.

We used the publicly accessible Drugs@FDA database[18] to determine whether generic versions of each FDC and each component in the single-agent combination pairs were available during the study period. We also used this database to identify the number of marketed doses for each of the 20 most frequently filled FDCs and the number of possible dose combinations of their corresponding single-agent pairs.

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Results

Single-agent combination pairs

In 2012, 848,082 patients filled prescriptions for 3,248 unique single-agent combination pairs (mean 4.7 per patient, SD 5.0). The most commonly used single-agent pairs were lisinopril and simvastatin (491.4 users per 100,000 active enrollees), lisinopril and metformin (484.9 users per 100,000 active enrollees), and metformin and simvastatin (416.5 users per 100,000 active enrollees) (Table I).

Of the 20 most frequently filled single-agent pairs, all component drugs were available as generics. Three (15%) of these 20 pairs were available as FDCs: lisinopril and hydrochlorothiazide, amlodipine and atorvastatin, and glipizide and metformin. Generic versions were available for all 3 of these FDCs during the study period.

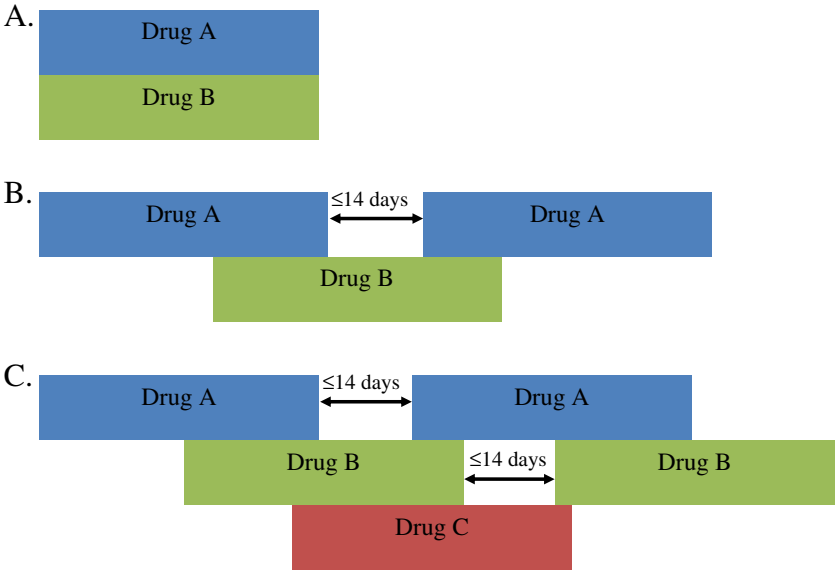
The 4 most frequently filled single-agent pairs and 13 (65%) of the top 20 treated 2 different conditions (eg, lisinopril and simvastatin treat hypertension and dyslipidemia, respectively). The remaining 7 (35%) of the top 20 pairs comprised single-agent products treating the same condition (eg, amlodipine and lisinopril both treat hypertension).

The most frequently filled drug class pairs were angiotensin-converting enzyme (ACE) inhibitors and statins (1607.2 users per 100,000 active enrollees), β-blockers and statins (1465.4 users per 100,000 active enrollees), and biguanides and statins (1086.1 users per 100,000 active enrollees) (Table II). No FDCs containing these drug class pairs were available, whereas 6 (30%) of the top 20 most frequently filled drug class pairs were available as FDCs. The 5 most frequent filled drug class pairs and 11 (55%) of the top 20 treated 2 different conditions.

Fixed-dose combinations

We identified 568,923 patients who received prescriptions for 43 unique FDCs (mean 1.1 per patient, SD 0.3)

Figure Illustration of concomitant use of single-agent combination pairs.



a, Scenario 1: patient fills prescriptions for 2 different drugs on the same day. Drug A/drug B counts as a single-agent pair for this patient.**b**, Scenario 2 with 2 drugs: patient fills prescription for drug A, followed by a prescription for drug B before drug A's days' supply runs out, and then refills drug A within 14 days of the elapsed days supplied of its previous fill. Drug A/drug B counts as a single-agent pair for this patient.**c**, Scenario 2 with more than 2 drugs: patient fills prescriptions for drug A, drug B, and drug C. Using the approach described in **b** for designating close-in-time prescription fills, drug A/drug B, drug A/drug C, and drug B/drug C all count as unique single-agent pairs for this patient.

during 2012 (Table III). Patients most frequently filled prescriptions for hydrochlorothiazide/lisinopril (1224.5 users per 100,000 active enrollees), hydrochlorothiazide/triamterene (646.9 users per 100,000 active enrollees), and hydrochlorothiazide/losartan (593.9 users per 100,000 active enrollees). With the exception of the 3 most frequently filled FDCs in 2012, prescription fill rates of the remaining combination products were lower than those of most of the frequently filled single-agent pairs. Three-quarters of the combination products (32/43, 74%) had <100 users per 100,000 active enrollees, and 40% (17/43) had <10 users per 100,000 active enrollees.

All of the 20 most frequently filled FDCs treated a single condition. Fourteen (70%) were available as generics during the study period, including 3 that lost exclusivity in 2012 (valsartan/hydrochlorothiazide, metformin/pioglitazone, and irbesartan/hydrochlorothiazide). Amlodipine/atorvastatin (14.9 users per 100,000 active enrollees) and simvastatin/sitagliptin (1.0 users per 100,000 active enrollees) were the only dual-disease combination products in our study (treating hypertension/dyslipidemia and dyslipidemia/diabetes, respectively). Twelve (60%) of the 20 most frequently filled FDCs were marketed in one-quarter or fewer of the dose combinations available for their component single-agent pairs.

Discussion

Our study revealed a large discrepancy between the utilization of single-agent drugs in combination for the treatment of common cardiovascular diseases and the availability of FDC products containing these agents. Fixed-dose combinations were available for only 3 of the 20 most frequently filled cardiovascular single-agent pairs and 6 of the 20 most frequently filled drug class pairs in 2012. There were also lower fill rates for the majority of FDC products compared to frequently filled single-agent pairs.

Several factors may explain the market discordance that we observed. Fixed-dose combinations are not always straightforward to manufacture, and creating stable FDC tablets and capsules can require substantial technical expertise and resources.[19] In addition, FDA approval of FDCs sometimes requires additional Phase 3 clinical trials to demonstrate the FDC's efficacy and safety.[20–22] According to the FDA, whether new trials are needed is determined on an individual basis for each proposed product. Moreover, when FDCs containing generic components are approved by the FDA, they receive only 3 years of FDA-imposed exclusivity and must compete with the lower-cost component agents. Obtaining additional market exclusivity-extending patents on FDCs containing generic

Table I. Top 20 most frequently filled cardiovascular single-agent combination pairs among patients in the Optum database, 2012

Single-agent pairs	No. of users per 100000 active enrollees	No. of corresponding FDC patients per 100000 active enrollees (if FDC is available)	Regulatory status in 2012
1. Lisinopril, simvastatin*	491.4	N/A	Generic, generic
2. Lisinopril, metformin*	484.9	N/A	Generic, generic
3. Metformin, simvastatin*	416.5	N/A	Generic, generic
4. Atorvastatin, lisinopril*	343.8	N/A	Generic, generic
5. HCTZ, lisinopril	310.3	1224.5	Generic, generic
6. Amlodipine, lisinopril	299.2	N/A	Generic, generic
7. Atorvastatin, metformin*	298.2	N/A	Generic, generic
8. Amlodipine, atorvastatin*	251.5	14.9	Generic, generic
9. Amlodipine, HCTZ	245.2	N/A	Generic, generic
10. Amlodipine, simvastatin*	244.9	N/A	Generic, generic
11. Glipizide, metformin	217.6	14.6	Generic, generic
12. Amlodipine, metformin*	216.6	N/A	Generic, generic
13. HCTZ, simvastatin*	215.7	N/A	Generic, generic
14. Atorvastatin, metoprolol succinate*	203.5	N/A	Generic, generic
15. Lisinopril, metoprolol succinate	186.6	N/A	Generic, generic
16. Glimepiride, metformin	184.0	N/A	Generic, generic
17. Metoprolol succinate, simvastatin*	184.0	N/A	Generic, generic
18. HCTZ, metformin*	178.6	N/A	Generic, generic
19. Lisinopril, metoprolol tartrate	169.6	N/A	Generic, generic
20. Lisinopril, pravastatin*	164.7	N/A	Generic, generic

HCTZ = hydrochlorothiazide; FDC = fixed-dose combination.
*Single-agent pair that treats 2 diseases (eg, hypertension and diabetes).

components may not be possible because the patents on the underlying products have expired. By contrast, new brand-name drugs receive 5 years of FDA-imposed exclusivity and are often protected by patents that may provide over 12 years of exclusivity, which can also apply to FDCs containing brand-name agents.[23] Thus, there is more incentive to create combination products containing brand-name agents than lower-cost generics even if the individual components are not frequently filled together. Despite the FDA's recent effort to incentivize development of FDCs by making more combination products eligible for 5 years of FDA-imposed exclusivity, the expanded eligibility criteria still require at least one component of the FDC to be a new molecular entity;[9] thus, this incentive does not apply to new FDCs containing only generic components.

Encouraging the development of cardiovascular combination products to address the utilization gap that we identified (ie, FDCs of frequently filled single-agent pairs) requires a multipronged approach. The FDA could streamline the review and approval of FDCs if both components have been well studied in clinical and postmarketing studies and a substantial number of patients are already taking them concurrently. The FDA has previously stated that the clinical benefits and safety of combination products do not need to be demonstrated via new clinical trials in some cases and can instead be supported though meta-analyses and subgroups of clinical trials.[24] For example, the FDA did not require new Phase 3 trials for approval of the dual-disease FDC simvastatin/sitagliptin, which instead was based on subanalyses of previously conducted trials for sitagliptin.[25] The single-agent components of simvastatin/sitagliptin were less commonly used concomitantly when the FDC was approved in 2011 (62.4 users per 100,000 active enrollees in our database). By contrast, the FDA did not apply this expedited approval pathway in the case of amlodipine/atorvastatin, instead requiring the sponsor to conduct additional Phase 3 clinical trials even though both components were marketed for over 7 years before the FDC was approved and even though the single-agent components were commonly used together (217.6 users per 100,000 active enrollees in our database in 2004, the year that the FDC was approved).[26]

The government can also work with manufacturers to streamline the engineering and formulation of combination products. Most companies that manufacture FDCs currently rely on trial and error to formulate new combination pills and do not allocate substantial resources to this area because of a perceived lack of return on investment.[19] Just as the National Institutes of Health funds the discovery of potential new medical products, it can support formulations research, a complex and crucial step in FDC development, to facilitate faster and more efficient technical development of FDCs. In addition, regulatory incentives such as the partial or full waiver of user fees—which for new products can exceed $2.3 million[27]—could be offered to encourage development of combination products with the potential for a large public health impact.

Table II. Top 20 most frequently filled cardiovascular single-agent drug class pairs among patients in the Optum Database, 2012

Single-agent drug class pairs	No. of users per 100000 active enrollees	FDCs containing drug class agents
1. ACE inhibitor, statin	1607.2	None
2. β-Blocker, statin	1465.4	None
3. Biguanide, statin	1086.1	None
4. Calcium-channel blocker (DHP), statin	860.9	Amlodipine/atorvastatin
5. ARB, statin	750.9	None
6. ACE inhibitor, β-blocker	674.1	None
7. Statin, thiazide	627.5	None
8. ACE inhibitor, biguanide	611.7	None
9. Statin, sulfonylurea	521.1	None
10. Biguanide, sulfonylurea	503.4	Glyburide/metformin, glipizide/metformin
11. β-Blocker, calcium-channel blocker (DHP)	463.2	None
12. ACE inhibitor, thiazide	453.5	Lisinopril/HCTZ, benazepril/HCTZ, enalapril/HCTZ, quinapril/HCTZ, captopril/HCTZ, moexipril/HCTZ, fosinopril/HCTZ
13. Fibrate, statin	441.9	None
14. ACE inhibitor, calcium-channel blocker (DHP)	439.3	Amlodipine/benazepril
15. β-Blocker, thiazide	388.5	Propranolol/HCTZ, metoprolol succinate/HCTZ, metoprolol tartrate/HCTZ, atenolol/chlorthalidone, bisoprolol/HCTZ, nadolol/bendroflumethiazide
16. ARB, calcium-channel blocker (DHP)	375.2	Telmisartan/amlodipine, olmesartan/amlodipine, valsartan/amlodipine
17. ARB, β-blocker	360.1	None
18. β-Blocker, biguanide	346.6	None
19. Loop diuretic, statin	344.7	None
20. ACE inhibitor, sulfonylurea	312.2	None

Statin = HMG CoA reductase inhibitors; β-blocker = β-adrenergic blocking agent; calcium-channel blocker (DHP) = dihydropyridine calcium channel blocking agent; ARB = angiotensin receptor blocker; FDC = fixed-dose combination; HCTZ = hydrochlorothiazide.

A multifaceted approach is also needed to promote the uptake of FDCs after their approval. Prescribers may not always be aware of all of the drugs that their patients take, and patients and prescribers alike may not be aware of the availability of FDCs. In addition, prescribers who are aware of the combination therapy options may choose to initiate patients on single-agent products to retain the increased flexibility to titrate the medication to treatment goal as well as to identify a drug causing an adverse event through dechallenge and rechallenge. Electronic medical records can assist in coordinating medication records among patients' multiple providers and in alerting prescribers to the availability of FDCs when their patients are prescribed both components. Pharmacy benefit managers can identify patients filling both components of an approved combination product and alert the patient, provider, and/or pharmacist of the FDC's availability. Although providers may still choose to initiate therapy using single-agent products, these notification pathways bolster the likelihood that patients will be transitioned to a lower pill burden via FDCs after being stabilized on single-agent drugs. Furthermore, although it would be impractical to expect FDCs to be available in every dose combination of its component agents, the marketed doses should reflect the most frequently filled single-agent combination pair doses. In the case of metformin and simvastatin, only 4 doses of a theoretical FDC would cover more than three-quarters of patients who filled this pair in 2012, despite 25 different possible combinations of the single-agent pair components.

Limited dosing flexibility may play a role in a clinician's decision not to prescribe an FDC, but it does not always appear to be a major barrier to FDC use. The most frequently filled FDC in our study, lisinopril/hydrochlorothiazide, was marketed in only 3 doses, compared with 24 possible dose combinations for its component pair. By contrast, although it is available in 11 of 12 possible doses, amlodipine/atorvastatin experienced a low relative fill rate in 2012 (14.9 users per 100,000 active enrollees for the FDC versus 251.5 for the single-agent pair). For the policy and practice interventions that we have proposed to work, clinicians must be willing to adopt FDCs as a routine aspect of patient care. This is especially the case for dual-disease FDCs, the scenario in which we observed the most discordance between availability of FDCs and utilization of single-agent pair combinations.

Addressing the utilization discordance identified in our study can help unlock the clinical benefits of combination therapeutics (eg, decreased adverse effects, as in the case of triamterene/hydrochlorothiazide, and the potential for increased medication adherence) and also reduce cost for both patients and institutions. Patient out-of-pocket costs

Table III. Top 20 most frequently filled FDCs among patients in the Optum Database, 2012

FDCs	No. of users per 100000 active enrollees	No. of users of FDC components as single-agent pair per 100000 active enrollees	No. of FDC doses (no. of component dose combinations)	Regulatory status in 2012
1. Lisinopril/HCTZ	1224.5	310.3	3 (24)	Generic
2. Triamterene/HCTZ	646.9	0.2	3 (8)	Generic
3. Losartan/HCTZ	593.9	112.5	3 (12)	Generic
4. Valsartan/HCTZ	331.6	34.4	5 (16)	Generic (9/2012)
5. Amlodipine/benazepril	326.7	83.3	6 (12)	Generic
6. Olmesartan/HCTZ	324.4	24.9	3 (12)	Brand
7. Ezetimibe/simvastatin	237.4	20.5	4 (5)	Brand
8. Sitagliptin/metformin	192.9	133.5	5 (24)*	Brand
9. Bisoprolol/HCTZ	140.6	3.7	3 (8)†	Generic
10. Glyburide/metformin	117.0	101.6	3 (30)	Generic
11. Amlodipine/olmesartan	103.5	35.1	4 (9)	Brand
12. Atenolol/chlorthalidone	96.4	6.9	2 (6)	Generic
13. Amlodipine/valsartan	89.3	43.4	4 (12)	Brand
14. Benazepril/HCTZ	83.9	35.5	4 (16)	Generic
15. Telmisartan/HCTZ	79.5	7.3	3 (12)	Brand
16. Metformin/pioglitazone	66.7	116.4	4 (24)‡	Generic (8/2012)
17. HCTZ/reserpine	41.7	0.8	2 (8)	Generic
18. Enalapril/HCTZ	30.5	31.3	2 (16)	Generic
19. Spironolactone/HCTZ	29.7	13.7	2 (12)	Generic
20. Irbesartan/HCTZ	25.6	20.0	3 (12)	Generic (3/2012)

* There are 2 doses available for the original FDC formulation and 3 doses available for the extended-release FDC formulation; 15 dose combinations are available for the component pair sitagliptin and metformin regular-release formulation, and 9 dose combinations are available for the component pair sitagliptin and metformin extended-release formulation.
† The HCTZ component of the FDC is available only in the 6.25-mg dose, although it is available as 4 different doses as a single-agent drug (12.5, 25, 50, and 100 mg).
‡ There are 2 doses available for the original FDC formulation and 2 doses available for the extended-release FDC formulation; 15 dose combinations are available for the component pair with metformin regular-release formulation, and 9 dose combinations are available for the component pair with metformin extended-release formulation.

would be reduced via a decreased number of copayments required to fill an FDC compared to its components as single-agent pairs. However, because copayments for brand-name drugs may be substantially higher than those for generic agents, such cost-saving would not be realized for brand-name-only FDCs containing otherwise generically available components. Fixed-dose combinations can also reduce institutional costs by streamlining logistical, administrative, and inventory processes. As such, savings achieved from increased utilization of FDCs may outweigh the investments necessary to enhance their prevalence.

Our study has several limitations. First, our data source covers only patients with commercial insurance and Medicare Advantage plans and therefore may not be representative of cardiovascular combination product use of the overall US population, which has a higher proportion of elderly patients and may differ socioeconomically from our study population. Second, our method of counting single-agent pairs as fills even if a patient fills the pair only once may not accurately reflect long-term use of these products. However, because we also required patients to fill only a single FDC prescription, the results should reflect whether currently available FDCs meet the clinical need for cardiovascular combination products. Third, we restricted our list of cardiovascular drugs to agents that treated diabetes, dyslipidemia, and hypertension; in doing so, we chose to exclude such classes as antiplatelet agents, anticoagulants, and antiarrhythmics, all of which may have a significant rate of concomitant use with one another or with the drugs in our study. Indeed, a recent study showed that antiplatelet drugs were the nonlipid agent most frequently incorporated into combination products with statins in India.[28] Fourth, although we restricted our focus to oral tablets and capsules, we did not consider other potential incompatibilities between the single-agent pair combinations in FDC form. For example, certain medications require different dosing schedules (eg, once daily vs twice daily) that would complicate or preclude the development of a corresponding FDC. Finally, we focused only on single-agent pairs and 2-drug cardiovascular FDCs. Many patients take more than 2 cardiovascular drugs, and a limited number of combination products are available that contain 3 agents (eg, valsartan/amlodipine/hydrochlorothiazide and olmesartan/amlodipine/hydrochlorothiazide). There have been calls in recent years for the formulation and widespread use of "polypills," which contain up to 5 therapies in a single product for preventing or treating cardiovascular disease [29]; and recent large-scale clinical studies have shown their benefits.[30,31] Developers of polypills should take combination utilization rates, such as the ones we have documented in our analysis, into consideration when deciding on the components and dosages to include in

the combination products. Future studies on efficiency and value in the field of combination therapy could also consider other more complicated combinations, such as 3-drug combinations and polypills.

Despite the observed gap in utilization and availability of cardiovascular combination products, the progress of FDC development in another therapeutic area provides reason for optimism. In the early 2000s, few combination products were available for the treatment of HIV/AIDS in the United States, despite the availability of >20 unique antiretroviral drugs.[32] Starting in 2003, with the financial and political backing of the newly announced President's Emergency Plan for AIDS Relief, the FDA used such incentives as relaxed clinical trial requirements and waived user fees to encourage development of combination products for this disease. Within a decade, the field of antiretroviral drugs grew to include numerous FDCs, which contributed to their resounding clinical success both domestically and internationally.[33] A comprehensive and coordinated strategy could lead therapy for cardiovascular disease, the most common cause of death in the United States, down a similar path.

Disclosures

No conflict of interest disclosures reported.

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Appendix

Supplementary Table I. Pharmacologic agents treating the main predisposing conditions to coronary heart disease

Pharmacologic class	Drug
Hypertension	
α-Adrenergic agents: peripheral	Reserpine
	Prazosin
	Doxazosin
	Terazosin
	Alfuzosin
	Guanadrel
	Guanethidine
	Mecamylamine
α-Adrenergic agents: central	Clonidine
	Guanfacine
	Methyldopa
	Guanabenz
β-Adrenergic blocking agents	Acebutolol
	Atenolol
	Betaxolol
	Bisoprolol
	Metoprolol succinate
	Metoprolol tartrate
	Nadolol
	Penbutolol
	Pindolol
	Propranolol
	Timolol
α-β-Adrenergic blocking agents	Carvedilol
	Labetalol
Calcium channel blocking agents: DHP	Nimodipine
	Nifedipine
	Amlodipine
	Felodipine
	Isradipine
	Nicardipine
	Nisoldipine
Calcium channel blocking agents: NDHP	Diltiazem
	Verapamil
Loop diuretics	Torsemide
	Furosemide
	Bumetanide
	Ethacrynic acid
Thiazide diuretics	Bendroflumethiazide
	Chlorothiazide
	Chlorthalidone
	Indapamide
	Metolazone
	Hydrochlorothiazide
	Methyclothiazide
Potassium sparing diuretics	Spironolactone
	Eplerenone
	Triamterene
	Amiloride
ACE inhibitors	Captopril
	Enalapril
	Fosinopril
	Lisinopril
	Moexipril
	Perindopril
	Quinapril
	Ramipril
	Trandolapril
Angiotensin receptor blockers	Losartan
	Olmesartan
	Azilsartan
	Candesartan
	Eprosartan
	Irbesartan
	Telmisartan
	Valsartan
Vasodilators	Hydralazine
	Minoxidil
Dyslipidemia	
Bile acid sequestrants	Cholestyramine
	Colesevelam
	Colestipol
Cholesterol absorption inhibitors	Ezetimibe
Fibrates	Fenofibrate
	Fenofibric acid
	Gemfibrozil
HMG-CoA reductase inhibitors	Lovastatin
	Pravastatin
	Simvastatin
	Atorvastatin
	Fluvastatin
	Rosuvastatin
	Pitavastatin
Nicotinic acids	Niacin
Omega-3 fatty acids	Omega-3-acid ethyl esters
	Icosapent
Miscellaneous	Lomitapide
Diabetes	
Biguanides	Metformin
Sulfonylureas	Chlorpropamide
	Glimepiride
	Glipizide
	Glyburide
	Acetohexamide
	Tolbutamide
Thiazolidinediones	Rosiglitazone
	Pioglitazone
Bile acid sequestrants	Colesevelam
α-Glucosidase inhibitors	Miglitol
	Acarbose
DPP-4 inhibitors	Sitagliptin
	Saxagliptin
	Linagliptin
Meglitinides	Nateglinide
	Repaglinide