Original Investigation

Effects of a Fixed-Dose Combination Strategy on Adherence and Risk Factors in Patients With or at High Risk of CVD
The UMPIRE Randomized Clinical Trial

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IMPORTANCE Most patients with cardiovascular disease (CVD) do not take recommended medications long-term. The use of fixed-dose combinations (FDCs) improves adherence in several clinical areas. Previous trials of cardiovascular FDCs have assessed short-term effects compared with placebo or no treatment.

OBJECTIVE To assess whether FDC delivery of aspirin, statin, and 2 blood pressure–lowering agents vs usual care improves long-term adherence to indicated therapy and 2 major CVD risk factors, systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C).

DESIGN, SETTING, AND PARTICIPANTS The UMPIRE trial, a randomized, open-label, blinded-end-point trial among 2004 participants with established CVD or at risk of CVD enrolled July 2010–July 2011 in India and Europe. The trial follow-up concluded in July 2012.

INTERVENTIONS Participants were randomly assigned (1:1) to an FDC-based strategy (n=1002) containing either (1) 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 50 mg atenolol or (2) 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 12.5 mg hydrochlorothiazide or to usual care (n=1002).

MAIN OUTCOMES AND MEASURES Adherence to medication (defined as self-reported use of antiplatelet, statin, and ≥2 BP-lowering medications) and changes in SBP and LDL-C from baseline.

RESULTS At baseline, mean BP was 137/78 mm Hg, LDL-C was 91.5 mg/dL, and 1233 (61.5%) of 2004 participants reported use of antiplatelet, statin, and 2 or more BP-lowering medications. Median follow-up was 15 months (interquartile range, 12-18 months). The FDC group had improved adherence vs usual care (86% vs 65%; relative risk [RR] of being adherent, 1.33; 95% CI, 1.26-1.41; $P < .001$) with concurrent reductions in SBP (−2.6 mm Hg; 95% CI, −4.0 to −1.1 mm Hg; $P < .001$) and LDL-C (−4.2 mg/dL; 95% CI, −6.6 to −1.9 mg/dL; $P < .001$) at the end of the study. Although there was consistency of effects across predefined subgroups, evidence existed of larger benefits in patients with lower adherence at baseline. In this subgroup of 727 participants (36%), adherence at the end of study was 77% vs 23% (RR, 3.35; 95% CI, 2.74-4.09; $P < .001$ for interaction), SBP was reduced by 4.9 mm Hg (95% CI 7.3-2.6 mm Hg; $P = .01$ for interaction), and LDL-C was reduced by 6.7 mg/dL (95% CI, 10.5-2.8 mg/dL; $P = .11$ for interaction). There were no significant differences in serious adverse events or cardiovascular events (50 [5%] in the FDC group and 35 [3.5%] in the usual care group; RR, 1.45; 95% CI, 0.94-2.24; $P=.09$) between the groups.

CONCLUSIONS AND RELEVANCE Among patients with or at high risk of CVD, use of an FDC strategy for blood pressure, cholesterol, and platelet control vs usual care resulted in significantly improved medication adherence at 15 months and statistically significant but small improvements in SBP and LDL-C.

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The long-term use of cardiovascular disease (CVD) preventive therapy is low among people with established disease.[1] This shortfall is greatest in low- and middle-income countries, but even in high-income countries treatment coverage in the community is only about 50% in those with coronary disease and 35% in those with stroke.[1] People who are at similar risk but have not reached the clinical threshold of experiencing a CVD event are even less likely to be adequately treated.[2] Fixed-dose combination (FDC) therapy may reduce these treatment gaps by reducing cost, complexity, therapeutic inertia, and low adherence. However, FDCs could lead to suboptimal risk factor control as a result of reduced tailoring of individual medications, and concerns have been expressed that lifestyle measures could be neglected or medications not restarted if the FDC is stopped. The balance of these potential benefits and risks remains uncertain.

Some trial data are available on antiplatelet, statin, and blood pressure (BP)-lowering FDCs, but these trials were mostly short-term and in populations with low to moderate CVD risk.[3-7] Despite recommendations,[8] no evidence has been generated on benefits or risks of an FDC-based strategy among individuals with established CVD, for whom there is no contention about the indications for use of all the medication components.[9-11] This patient population was the first suggested[8,12-14] for a treatment that has come to be known as the *polypill*.[12] In 2009, the European Commission called for research testing a treatment strategy "that combines existing safe and effective drugs for treating chronic diseases in a single daily pill," stipulating that "this fixed-dose-combination pill should be low-cost and suitable for production and widespread use in resource-poor countries" and that the work should "address two major challenges of effective secondary prevention and treatment of chronic diseases: adherence and access to treatment in developing countries." The UMPIRE (Use of a Multidrug Pill in Reducing Cardiovascular Events) trial was designed in response to this funding call.

CVD *cardiovascular disease*

FDC *fixed-dose combination*

HDL-C *high-density lipoprotein cholesterol*

LDL-C *low-density lipoprotein cholesterol*

SBP *systolic blood pressure*

Methods

Study Design and Conduct

The UMPIRE trial protocol has been previously described[15] and is available at www.spacecollaboration.org along with the protocols of related trials running in parallel.[16,17] Ethics approval was granted by the relevant committees in each participating country.

We conducted a randomized, open-label, blinded-endpoint clinical trial of an FDC-based treatment strategy compared with usual care in participants with established CVD or an estimated 5-year CVD risk of 15% or greater in India and in 3 European countries (England, Ireland, and the Netherlands). Participants gave written informed consent and were randomly assigned to continuation with usual care or to an FDC-based treatment strategy with follow-up planned between 12 and 24 months. The primary objective was to assess whether provision of an FDC compared with usual medications improves adherence to indicated therapy and 2 major cardiovascular risk factors: systolic BP (SBP) and low-density lipoprotein cholesterol (LDL-C).

Participants

Men and women aged 18 years or older with high cardiovascular risk, defined as either established CVD (history of coronary heart disease, ischemic cerebrovascular disease, or peripheral vascular disease) or an estimated 5-year CVD risk of 15% or greater,[18] were eligible; the risk score included age, sex, SBP, ratio of total to high-density lipoprotein cholesterol (HDL-C), diabetes, smoking, and a 5% adjustment for people from the Indian subcontinent. There had to be clear indications with no contraindications for the components of at least 1 of 2 FDC formulations (see below). Individuals were excluded if alteration of medications was clinically inappropriate or the patient was considered unlikely to follow the trial procedures, including attending scheduled visits. Participants in Europe were recruited via research databases, hospital clinics, and general practice registries at 3 trial centers in London, England; Dublin, Ireland; and Utrecht, the Netherlands. Indian participants were recruited via hospital specialist clinics in 28 centers across the country.

Treatment and Randomization

Randomization to FDC or usual care was conducted in a 1:1 ratio and allocation was stratified by site and by the presence or absence of established CVD using a web-based clinical data management system (InForm; PhaseForward Inc). Participants randomized to usual care continued to be treated at the discretion of their usual physician. Participants randomized to the FDC strategy were prescribed 1 of 2 FDC formulations chosen by the trial physician: version 1 (aspirin, 75 mg; simvastatin, 40 mg; lisinopril, 10 mg; and atenolol, 50 mg) or version 2 (aspirin, 75 mg; simvastatin, 40 mg; lisinopril, 10 mg; and hydrochlorothiazide, 12.5 mg). The FDC was taken once daily, with timing suggested by the physician. Physicians could, at their discretion, add additional medications, stop the FDC and begin treatment with separate medications, or switch FDCs. Because of requirements of local ethics committees, participants in the FDC group were dispensed study FDC treatment from their trial center free of charge as 6-monthly supplies. Participants in the usual care group acquired their medications subject to local payments or exemptions and according to usual dispensing schedules (typically 3-monthly). Eligibility for exemption from prescription or medication charges was assessed at randomization.

Trial Procedures

The minimum planned follow-up time was 1 year. The end-of-study visit for all participants was scheduled to take place about 12 months after the randomization of the last participant into the trial, and all participants were followed up for as long as possible within that interval, with a range of follow-up

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of 12 to 24 months. Participants attended clinic visits for randomization, at 12 months, and at the end of the study. Telephone or clinic visits were conducted at 1 month, 6 months, and 18 months (if applicable). Blood pressure and fasting lipid levels were measured at baseline, at 12 months, and at the end of the study. Blood pressure and heart rate measurements were made with electronic devices (Omron 705CP II) and paper printouts were logged. Fasting blood samples were analyzed by local laboratories. Self-reported adherence to all medications was recorded as the number of days medication was taken in the week prior to the visit (value between 0-7 days). During trial contacts, the research team asked about barriers to adherence, quality of life (measured using the self-administered EQ-5D questionnaire[19]), cardiovascular and other serious adverse events, and reasons for stopping cardiovascular medications.

Outcomes

Primary outcomes included adherence to indicated medications (self-reported current use of antiplatelet, statin, and ≥2 BP-lowering therapies, defined as taking the medication for at least 4 days during the week preceding the visit) at baseline and at the end of the trial and changes in SBP and LDL-C from baseline to the end of the trial.

Secondary outcomes included adherence at 12 months, reasons for stopping cardiovascular medications, quality of life, serious adverse events, and changes in total cholesterol, HDL-C, triglycerides, and creatinine from baseline to 12 months and end of study and cardiovascular events (including coronary heart disease, heart failure leading to death or hospital admission, and cerebrovascular or peripheral arterial disease events).[15]

Statistical Analysis

The sample size of 1000 participants in Europe and 1000 participants in India provided 90% power (α = .05) within each region (Europe and India) to detect absolute differences of 3 mm Hg in SBP, 7.7 mg/dL in LDL-C (to convert LDL-C to mmol/L, multiply by 0.0259), and 10 percentage points in rates of adherence to indicated medication (either as FDC or separate antiplatelet, statin, and ≥2 BP-lowering medicines) between the intervention and control groups at the end of the trial. The prespecified primary analysis was to evaluate the effects across both Europe and India combined, and the trial had 90% power overall to detect differences of 2.2 mm Hg in SBP, 4.7 mg/dL in LDL-C, and 8 percentage points in adherence. These estimates all assumed SDs of 14 mm Hg and 30.9 mg/dL in SBP and LDL-C, respectively, a 50% adherence rate in the usual care group, and up to 10% of patients having died or been lost to follow-up.

The primary analysis of mean differences in changes in SBP and LDL-C at the end of study between the FDC and usual care groups was conducted using analysis of covariance including the randomized treatment and either baseline SBP or baseline LDL-C. Relative risks (RRs) of self-reported adherence to indicated medications at the end of the study were calculated using log-binomial regression including randomized treatment. Adjusted analyses included randomized treatment, baseline value (either SBP, LDL-C, or baseline adherence) plus age, sex, country, and established disease as covariates.

Longitudinal analyses using generalized linear models with a compound-symmetry covariance structure were used as sensitivity analyses for the 3 primary end points. The models included all values collected during follow-up. Because the end-of-study visit could happen at any time from month 12 onward, data collected at the end-of-study visit were reallocated to 1 of the possible scheduled visits (months 12, 18, or 24). Models included randomized treatment, visit, treatment × visit interaction, and for SBP and LDL-C, the corresponding baseline value. Region, baseline adherence to indicated medications, established CVD, age, sex, diabetes mellitus, smoking, and economic stratum were used to predefine subgroup analyses. For each subgroup, we repeated the primary analysis with the addition of the subgroup variable along with its interaction with treatment. Heterogeneity was assessed based on the significance of the interaction term. Continuous secondary end points including diastolic BP, HDL-C, total cholesterol, triglycerides, creatinine, quality-of-life scores, anthropometric measurements, and lifestyle factors were assessed using analysis of covariance. Differences in incidence of cardiovascular outcomes were analyzed using Cox models after checking the proportional hazard assumption.

All analyses were conducted on an intention-to-treat basis with no imputation of missing data. A 2-sided P<.05 was used to indicate statistical significance for all tests. Although formal adjustments for multiple tests were not made, findings are interpreted in light of the number of comparisons made and the level of significance of the result.

Results

Baseline Characteristics of Trial Participants and Trial Structure

A total of 2138 potential participants were screened, 134 were ineligible and 2004 were randomized (1000 in India and 1004 in Europe) between July 2010 and July 2011 (**Figure 1**). Among the 1002 participants randomized to the FDC group, physicians started therapy with FDC version 1 for 589 (58.8%) and FDC version 2 for 413 (41.2%). Baseline characteristics of the FDC and usual care groups were similar (**Table 1**), with no major baseline imbalances. The majority of participants (n=1771 [88%]) were included on the basis of established CVD. Table 1 also describes the use of prerandomization antiplatelet, statin, and BP-lowering medications, showing that the entire group had a high level of adherence to the indicated medications (n=1233 [61.5%] at the outset). At baseline, reported use of antiplatelet therapy (n=1832 [91.4%]), statins (n=1760 [87.8%]), and BP-lowering therapy (n=1862 [92%]) was high, although levels were lower for those reporting 2 or more BP-lowering drugs 1371 (68.4%). The median duration of follow-up was 15 months (interquartile range, 12-18 months) for both groups, and follow-up concluded in July 2012. One hundred sixty-three participants missed at least 1 visit and of these, 68 came to a subsequent visit. At the end of the study, data on self-reported adherence, systolic BP, and LDL-C were available for 1921 (96%),

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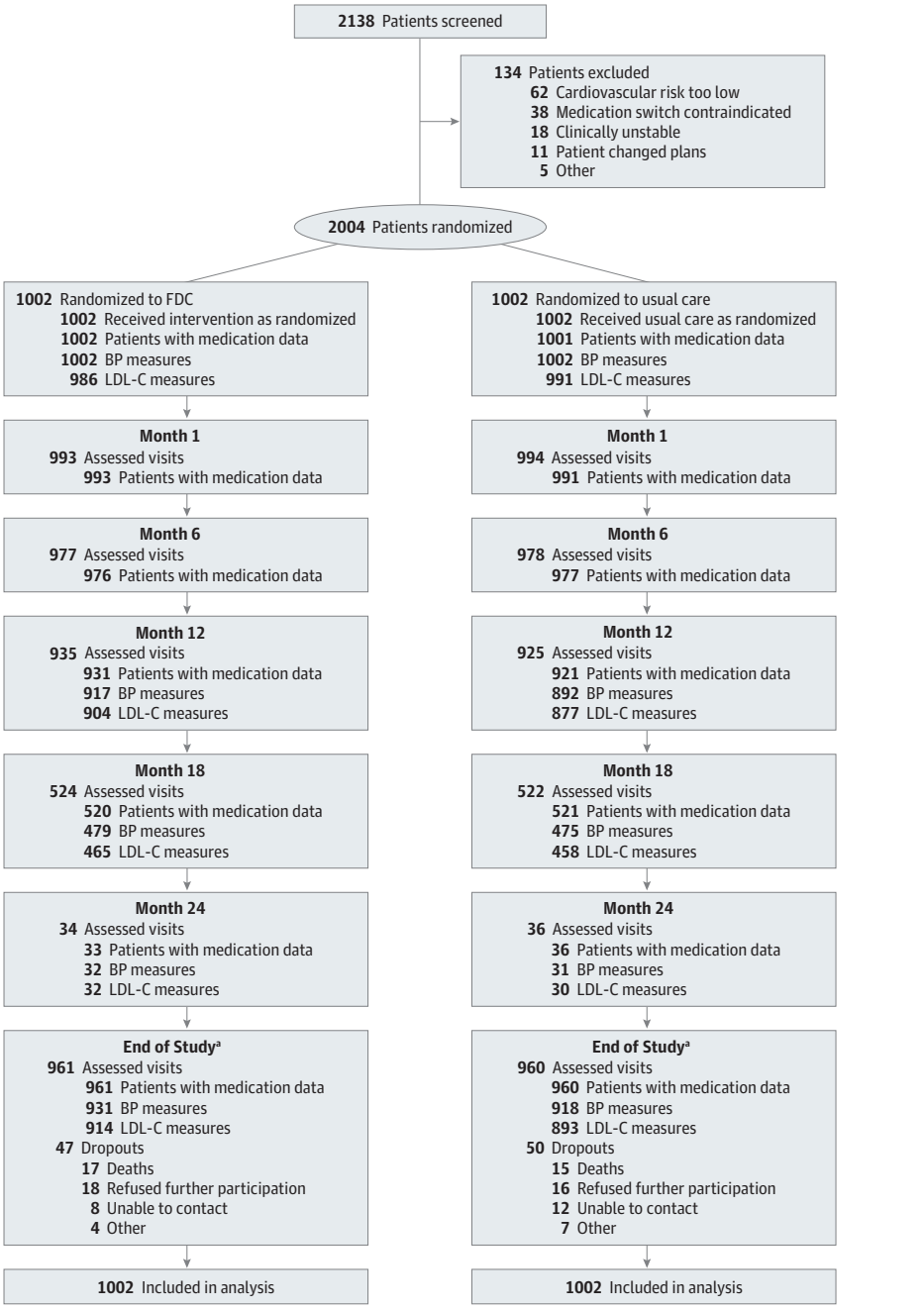
Figure 1. Study Flow



FDC indicates fixed-dose combination; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol.
[a]Median time to end of study was 15 months (range, 12-24 months; n=454 median follow-up days in both groups).

1849 (92%), and 1807 (90%) randomized participants, respectively (Figure 1). Nine hundred sixty-six participants (48%) reported exemption from prescription or medication charges (Table 1).

Overall Effects on Primary Outcomes of Adherence, SBP, and LDL-C

At the end of the study, 829 (86.3%) of 961 participants in the FDC group were continuing with indicated medications compared with 621 (64.7%) of 960 in the usual care group (unadjusted RR, 1.33; 95% CI, 1.26-1.41; $P < .001$) (**Table 2** and **Figure 2**A). In absolute terms, this amounted to a 21.6% difference (95% CI, 17.8%-25.3%; $P < .001$) in treatment rates and a number needed to treat of 4.6 patients (95% CI, 4.0-5.6 patients). For each treatment mode, there was an increase in treatment rates after randomization of about 5% in participants in the usual care group who were prescribed additional individual medications and a larger absolute increase in the FDC group as a result of FDC initiation. In the usual care group, adherence to each treatment mode decreased slightly over time but remained higher than baseline at 18 months. At 1 month, use of indicated medications in the FDC group was 97.3% compared with 68.3% in the usual care group. The absolute difference between groups decreased slightly by 6 months and

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Table 1. Baseline Characteristics[a]

Characteristics	Fixed-Dose Combination (n = 1002)	Usual Care (n = 1002)
Continent, No. of patients		
India	501	499
Europe	501	503
Age	62.1 (10.4)	61.6 (10.8)
Male, No. (%)	817 (81.5)	825 (82.3)
Systolic blood pressure, mm Hg	137.0 (21.3)	137.7 (21.1)
Diastolic blood pressure, mm Hg	77.4 (12.0)	78.1 (11.5)
Heart rate, /min	71.0 (15.1)	70.8 (14.6)
Total cholesterol, mg/dL	160.5 (39.8)	162.8 (41.6)
High-density lipoprotein cholesterol, mg/dL	43.5 (10.7)	43.4 (10.5)
Low-density lipoprotein cholesterol, mg/dL	90.5 (32.5)	92.5 (36.0)
Triglycerides, mg/dL	133.3 (77.5)	136.1 (77.8)
Glucose, mg/dL	112.9 (42.4)	114.0 (41.2)
Creatinine, mg/dL	1.01 (0.25)	1.01 (0.25)
Current smokers, No. (%)	131 (13.1)	144 (14.4)
Ever smokers, No. (%)	541 (54.0)	504 (50.3)
Weight, kg	76.1 (17.8)	76.3 (17.7)
Waist circumference, cm	97.5 (12.4)	97.6 (11.9)
Body mass index[b]	27.0 (4.6)	26.9 (4.7)
Moderate physical activity, min/wk	163.2 (178.8)	158.3 (180.3)
Vigorous physical activity, min/wk	22.7 (75.0)	25.2 (78.5)
EQ-5D score	0.8 (0.2)	0.8 (0.2)
Medical history, No. (%)		
Coronary heart disease	769 (76.7)	759 (75.7)
Cerebrovascular disease	154 (15.4)	157 (15.7)
Peripheral vascular disease	56 (5.6)	43 (4.3)
Diabetes mellitus	283 (28.2)	281 (28.0)
Current drug treatment, No. (%)		
Antihypertensive treatment		
None	76 (7.6)	66 (6.6)
1 Blood pressure-lowering drug	266 (26.5)	225 (22.5)
≥2 Blood pressure-lowering drugs	660 (65.9)	711 (71.0)
Statin	882 (88.0)	878 (87.6)
Antiplatelet drug	920 (91.8)	912 (91.0)
Indicated medications[c]	598 (59.7)	635 (63.4)
Exempt from medication charges, No. (%)	505 (50)	461 (46)

SI conversions: To convert total, high-density lipoprotein, and low-density lipoprotein cholesterol to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113; to convert glucose to mmol/L, multiply by 0.0555; and to convert creatinine to μmol/L, multiply by 88.4.

[a] Data are expressed as mean (SD) unless otherwise indicated.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Indicated medications = antiplatelet + statin + ≥2 blood pressure-lowering drugs (as the measure of baseline adherence).

remained approximately constant thereafter. The decrease between 1 and 6 months in the FDC group largely occurred among patients who were not adherent at baseline; of the 56 who stopped FDC during this period, 40 (71.4%) were not adherent at baseline. At the end of the study, FDC use was reported in 747 (77.7%) of 961 participants in the FDC group, with a further 82 (8.5%) adhering to their indicated medications by taking separate tablets.

An alternate definition of adherence involving taking antiplatelet, statin, and at least 1 BP-lowering drug also showed benefit (873/961 [90.8%] in the FDC group vs 808/960 [84.2%] in the usual care group; $P < .001$) owing to improved adherence to antiplatelet and statin therapy (there was no difference in the proportion taking at least 1 BP-lowering drug at the end of the study [95.2% vs 95.9%]). A sensitivity analysis of the adherence definition was performed using 2 alternative definitions at the end of the study, one based on taking indicated medications on 1 day or more in the last week and another based on taking medications every day of the last week. The RR for adherence associated with the FDC group using 1 day or more was 1.33 (95% CI, 1.26-1.40) and the RR using 7 days was 1.41 (95% CI, 1.33-1.49). These did not differ from the RR using the definition of 4 or more days (RR, 1.33; 95% CI, 1.26-1.41).

Table 2 shows mean differences in the changes in SBP and LDL-C using the primary analysis of covariance method. Overall, SBP (−2.6 mm Hg; 95% CI, −4.0 to −1.1 mm Hg) and LDL-C (−4.2 mg/dL; 95% CI, −6.6 to −1.9 mg/dL) levels were modest but significantly lower in the FDC group compared with the usual care group at the end of the study. **Figure 3** shows changes over time and overall differences using a longitudinal generalized linear model. For this analysis, overall mean differences over time were −3.3 mm Hg (95% CI, −4.6 to −1.9 mm Hg; $P < .001$) for SBP and −5.3 mg/dL (95% CI, −7.5 to −3.2 mg/dL; $P < .001$) for LDL-C.

Adjusted models including randomized treatment, baseline value, country, history of CVD, age, and sex are shown in eTable 1 in the Supplement. Adjusted and unadjusted effects were similar for treatment effect estimates of SBP and LDL-C reduction. However, the adjusted effect for adherence was somewhat lower (RR, 1.13; 95% CI, 1.08-1.18; $P < .001$) than for unadjusted analyses as a result of a small baseline imbalance in use of antiplatelet, statin, and 2 or more BP-lowering agents and the effect modification for this variable (see below).

The effects of the FDC strategy on adherence, SBP, and LDL-C in prespecified subgroups defined by baseline characteristics are shown in **Figure 4** and **Figure 5**. The number of subgroups should be taken into consideration, and across the 3 coprimary end points, the only consistent effect modifier was whether patients were taking antiplatelet, statin, and 2 or more BP-lowering drugs at baseline. This was most marked for the adherence outcome, as it shared the same definition as the effect modifier. For the adherence outcome, effects were statistically significant in every subgroup but were quantitatively larger in patients at high estimated CVD risk (RR, 1.93; 95% CI, 1.51-2.47; $P < .001$), those with low baseline adherence (RR, 3.35; 95% CI, 2.74-4.09; $P < .001$), smokers (RR, 1.69; 95% CI, 1.42-2.02; $P = .002$), and those for whom their physician intended to use FDC version 2 (RR, 1.45; 95% CI, 1.32-1.59; $P = .02$). In terms of SBP reduction, treatment effects were larger in those without baseline adherence to indicated medications (reduced by 4.9 mm Hg; 95% CI, 7.3-2.6 mm Hg; $P = .01$) and in

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Table 2. Effect of Treatment on Adherence to Primary and Secondary End Points

Outcomes	Fixed-Dose Combination (n = 1002)	Usual Care (n = 1002)	Treatment Effect (95% CI)[a]	P Value
Primary end points				
Adherence, No./total (%)[b]	829/961 (86)	621/960 (65)	1.33 (1.26 to 1.41)	<.001
Systolic blood pressure, mm Hg	129.2 (128.1-130.2)	131.7 (130.7-132.8)	−2.6 (−4.0 to −1.1)	<.001
Low-density lipoprotein cholesterol, mg/dL	84.2 (82.5-85.8)	88.4 (86.7-90.0)	−4.2 (−6.6 to −1.9)	<.001
Secondary end points				
Adherence at 12 mo, No./total (%)	827/935 (88)	602/925 (65)	1.36 (1.29 to 1.43)	<.001
Diastolic blood pressure, mm Hg	72.8 (72.2-73.5)	75.2 (74.7-75.8)	−2.5 (−3.3 to −1.6)	<.001
Total cholesterol, mg/dL	156.6 (154.6-158.5)	159.1 (157.1-161.1)	−2.5 (−3.3 to 0.3)	.08
High density lipoprotein cholesterol, mg/dL	44.2 (43.7-44.6)	43.7 (43.2-44.2)	0.5 (−0.2 to 1.1)	.14
Triglycerides, mg/dL	142.3 (137.8-146.9)	138.8 (134.2-143.4)	3.6 (−2.9 to 10.0)	.28
Plasma creatinine, mg/dL	1.07 (1.06-1.08)	1.04 (1.03-1.05)	0.03 (0.01 to 0.05)	.002

SI conversions: To convert total, high-density lipoprotein, and low-density lipoprotein cholesterol to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113; and to convert creatinine to μmol/L, multiply by 88.4.

[a] Treatment effect: relative risk for adherence and mean difference for blood pressure, cholesterol measures, and creatinine.

[b] Self-reported use of antiplatelet, statin, and ≥2 blood pressure–lowering drugs.

men (reduced by 3.3 mm Hg; 95% CI, 4.9-1.7 mm Hg; $P = .03$), whereas in terms of LDL-C reduction, the effects were larger in participants from India (reduced by 10.8 mg/dL; 95% CI, 14.1-7.41; $P < .001$). Although it was not a predefined analysis, adherence was assessed by whether or not patients were exempt from medication charges, and the RRs for adherence were 1.33 (95% CI, 1.23-1.44) and 1.34 (95% CI, 1.25-1.44), respectively.

Effects on Secondary Outcomes

Creatinine, Glucose, and Other Laboratory Measures

Creatinine increased in both the FDC and usual care groups between baseline and the end of the study (FDC, from 1.01 to 1.07 mg/dL; usual care, from 1.01 to 1.04 mg/dL) and the difference in this increase between the 2 groups was statistically significant (FDC − usual care, 0.03 mg/dL; 95% CI, 0.01-0.05; $P = .002$) (Table 2). There was also an increase in uric acid in the FDC group (FDC, from 5.6 to 5.9 mg/dL; usual care, from 5.7 to 5.8 mg/dL) and the difference in this increase between the 2 groups was also significant (FDC − usual care, 0.2 mg/dL; 95% CI, 0.1-0.3; $P < .001$). There were no significant differences between groups in the levels of sodium, potassium, alanine transaminase, aspartate aminotransferase, or glucose at the end of the study (eTable 2 in the Supplement).

Weight, Lifestyle Factors, and Quality-of-Life Scores

Weight, waist circumference, and body mass index did not change during follow-up and did not differ between groups at the end of the study. Self-reported time engaged in vigorous physical activity, participation in exercise programs, attendance at dietetic clinics, and participation in smoking cessation programs were also similar in both groups at the end of follow-up (eTable 3 in the Supplement). Reported time engaged in moderate physical activity was similar in the 2 groups at baseline (FDC, 163 [SD, 179] min/wk vs usual care, 158 [SD, 180] min/wk) but significantly higher in the FDC group than in the usual care group at the end of the study (157 [SD, 178] min/wk vs 141 [SD, 157] min/wk, respectively; $P = .03$). Quality of life did not differ between the 2 groups at the end of the study, although the EQ-5D visual analog scale score was significantly higher in the FDC group (2.43; 95% CI, 0.87-3.99; $P = .002$) (eTable 4 in the Supplement).

Reasons for Stopping CVD Medications

Among the 219 participants in the FDC group who discontinued the FDC, the main stated reasons were patient choice (61/219 [28%]), medical advice without specified reason or adverse effect (26/219 [26%]), cough (46/219 [21%]), dizziness (20/219 [9%]), serious adverse events (18/219 [8%]), other adverse events (35/219 [16%]), and other reasons (eg, increased creatinine level, fatigue; 18/219 [8%]). A total of 9 participants switched to the alternative FDC version. Among participants who stopped the FDC during the course of follow-up, 73 (58%) of 126 assessed at month 18 had switched to antiplatelet, statin, and BP-lowering therapy via separate medications whereas 26 (21%) of 126 participants were not taking any cardiovascular medications. The medications provided to those who stopped the FDC are described in eTable 5 in the Supplement.

Cardiovascular End Points, Serious Adverse Events, and Mortality

In total, 85 participants had a cardiovascular end point as a first event (50 [5.0%] in the FDC group and 35 [3.5%] in the usual care group; RR, 1.45; 95% CI, 0.94-2.24; $P = .09$) (eTable 6 in the Supplement). Overall, there were 118 patients (11.8%) with at least 1 serious adverse event in the FDC group compared with 102 (10.2%) in the usual care group, with no significant differences in any major subcategory (eTable 7 in the Supplement). A similar number of deaths occurred in each group (17 in the FDC group vs 15 in the usual care group; RR, 1.13; 95% CI, 0.57-2.26; $P = .72$). Vascular deaths were reported as 14 vs 8 in FDC vs usual care ($P = .20$) and nonvascular deaths were reported as 3 vs 7, respectively ($P = .20$).

Discussion

To the best of our knowledge, this was the first randomized trial to assess the long-term use of an FDC containing anti-

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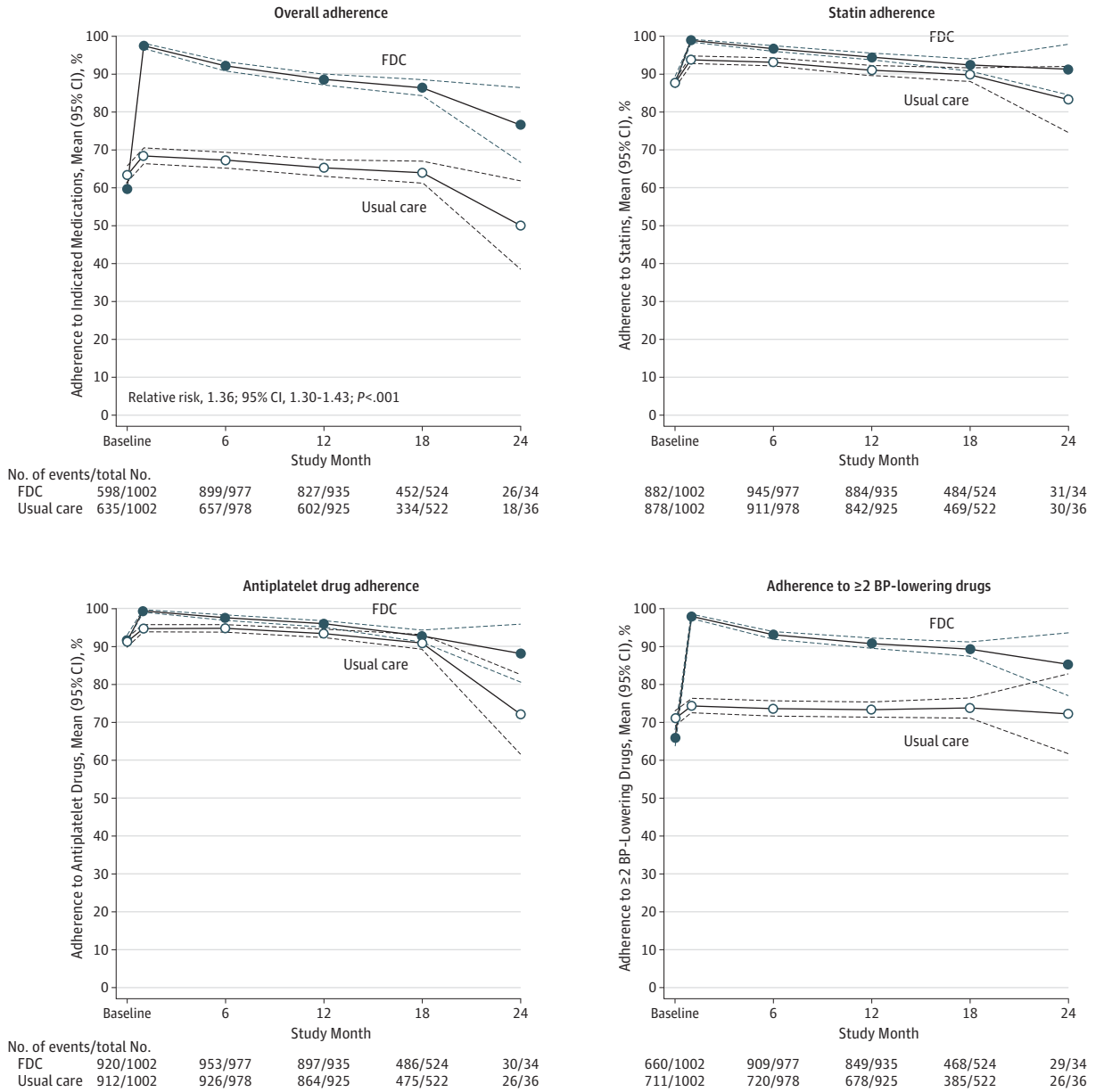
Figure 2. Adherence to Indicated Medications by Treatment Group During Follow-up



At the end of the study (median, 15 months), there was a 21% ($P < .001$) difference in reported adherence for indicated medications (fixed-dose combination [FDC; 86%] − usual care [65%]; all 4 medication types). The end-of-study differences (FDC − usual care) were smaller for each class: statins, 2% (93% − 91%; $P = .08$); antiplatelet drugs, 1% (94% − 93%; $P = .41$), and 2 or more blood pressure (BP)–lowering drugs, 15% (89% − 74%; $P < .001$). Overall relative risk was obtained via repeated log-binomial regression using a covariance matrix with a compound-symmetry structure (panel A only). Estimates combine all nonmissing values collected at months 1, 6, 12, 18, and 24. Model terms include treatment, month, and treatment × month interaction. Dashed lines indicate 95% confidence bands.

platelet, statin, and BP-lowering drugs compared with usual care in patients with CVD. The results show that access to FDCs in patients with CVD or similarly high risk improved adherence, BP, and cholesterol levels. The reductions in BP and cholesterol level were small overall in this comparatively well-treated population but were larger in the subgroup not receiving all recommended treatments at baseline.

The trial had several strengths in terms of sample size, duration of follow-up, and completeness of data collection. However, there are several issues to be considered when interpreting results from adherence trials in general and this study in particular. The generalizability of these findings is limited. Participants were selected on the basis of being willing and able to attend study visits, so the recruited population is not nec-

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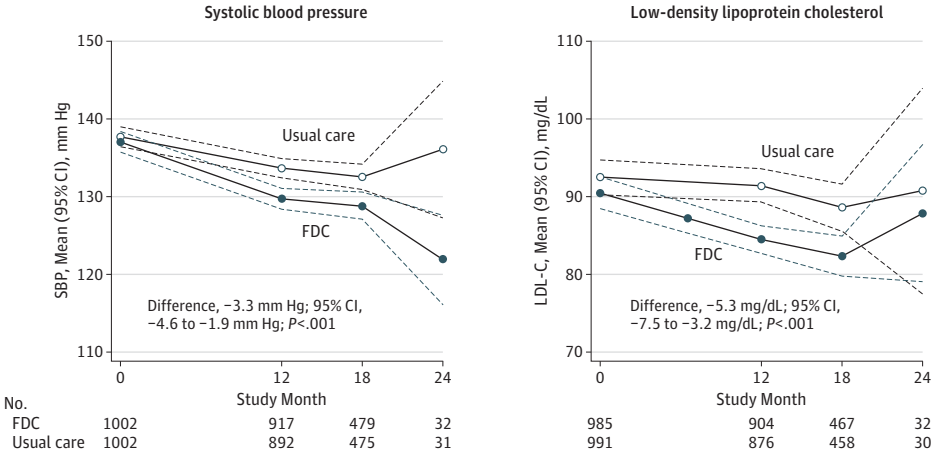
Figure 3. SBP and LDL-C Levels by Treatment Group During Follow-up



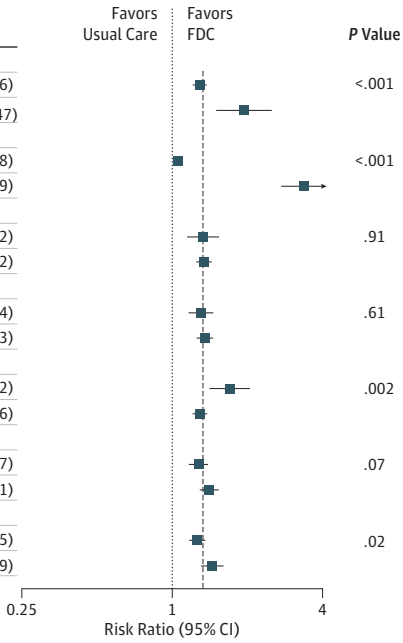
No.				
FDC	1002	917	479	32
Usual care	1002	892	475	31

985	904	467	32
991	876	458	30

At the end of the study (median, 15 months; see Table 2), there was a 2.6-mm Hg difference ($P < .001$) in systolic blood pressure (SBP) (fixed-dose combination [FDC] – usual care) and a 4.2-mg/dL difference ($P < .001$) in low-density lipoprotein cholesterol (LDL-C) (FDC – usual care). Overall mean differences were obtained via repeated linear regression using a covariance matrix with a compound-symmetry structure. Estimates combine all nonmissing values collected at months 12, 18, and 24. Model terms include treatment, month, treatment × month interaction, and baseline SBP or LDL-C level. Dashed lines indicate 95% confidence bands.

Figure 4. Primary Outcome of Adherence by Prespecified Subgroups

	Adherence, No./Total (%)		Risk Ratio (95% CI)	P Value
	Usual Care	FDC		
CVD risk				
Established CVD	576/848 (67.9)	743/850 (87.4)	1.29 (1.22-1.36)	<.001
≥15% 5-y CVD risk	45/112 (40.2)	86/111 (77.5)	1.93 (1.51-2.47)	
Adherence to indicated medication at baseline				
Yes	541/614 (88.1)	534/580 (92.1)	1.04 (1.01-1.08)	<.001
No	80/346 (23.1)	295/381 (77.4)	3.35 (2.74-4.09)	
Sex				
Female	105/168 (62.5)	144/174 (82.8)	1.32 (1.16-1.52)	.91
Male	516/792 (65.2)	685/787 (87.0)	1.34 (1.26-1.42)	
Diabetes				
Yes	175/267 (65.5)	230/269 (85.5)	1.30 (1.18-1.44)	.61
No	446/693 (64.4)	599/692 (86.6)	1.34 (1.26-1.43)	
Smoking				
Yes	70/134 (52.2)	108/122 (88.5)	1.69 (1.42-2.02)	.002
No	551/826 (66.7)	721/839 (85.9)	1.29 (1.22-1.36)	
Continent				
Europe	319/485 (65.8)	413/494 (83.6)	1.27 (1.18-1.37)	.07
India	302/475 (63.6)	416/467 (89.1)	1.40 (1.30-1.51)	
FDC choice				
Version 1	391/562 (69.6)	497/565 (88.0)	1.26 (1.19-1.35)	.02
Version 2	230/398 (57.8)	332/396 (83.8)	1.45 (1.32-1.59)	



The primary outcome of adherence (defined as taking statin, antiplatelet, and ≥2 blood pressure–lowering drugs at end of study) is shown by prespecified baseline subgroups. Error bars indicate 95% CIs, boxes are placed at the relative risk for and sized proportional to the amount of information per subgroup, and vertical dashed lines show the overall effect for each outcome. *P* values are for the test of homogeneity for each subgroup. FDC indicates fixed-dose combination; CVD, cardiovascular disease. See Methods for descriptions of versions 1 and 2 of FDC.

essarily representative,[20] and there was a high level of reported adherence at baseline compared with the general population.[1] In a population with lower use of indicated medications, the effect of the FDC strategy might be greater, as suggested by results from the minority of individuals who were not taking indicated medications at baseline. In this group, randomization to FDC resulted in a 3-fold increase in adherence levels (77% vs 23%) and larger reductions in SBP and LDL-C. Effects were observed in a trial population of whom 82% initially reported use of antiplatelet, statin, and BP-lowering drug (s), whereas comparable combination treatment rates are around 50% in high-income countries and 5% to 20% in low- and middle-income countries.[1] Furthermore, improvements were observed compared with a usual care group in whom treatment rates increased initially and remained higher than baseline throughout the study, whereas adherence typically reduces over time.[21,22]

Limitations of the findings relate to constraints on the trial design. Regulations in India and in Europe mandate distribution of a trial treatment by the approved trial teams and also prohibit charging for prescription of trial treatments. Consequently, the FDC group received their treatment free of charge from the trial centers and other medications from their routine clinic or general practitioner attendances, whereas the usual care group received all of their medications via their routine clinic or general practitioner attendances. However, post hoc analysis comparing adherence between patients exempt from medication charges and those who were not exempt showed

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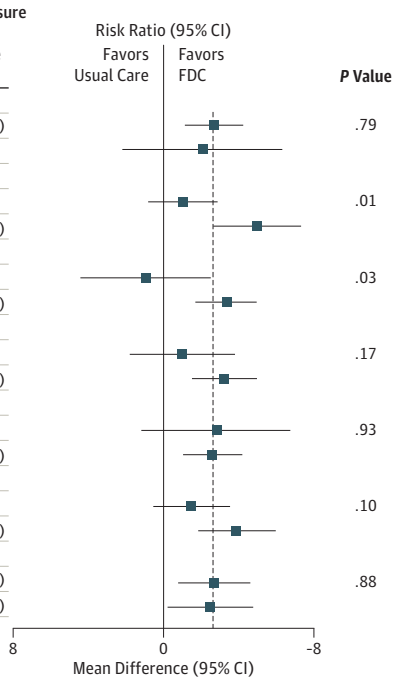
Figure 5. Primary Outcomes of SBP and LDL-C by Prespecified Subgroups

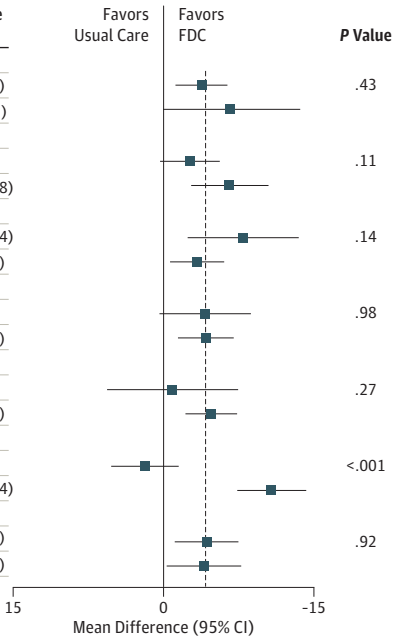
Systolic Blood Pressure

	SBP, Mean (SE), mm Hg		Mean Difference (95% CI)	P Value
	Usual Care	FDC		
CVD risk				
Established CVD	131.3 (0.6)	128.6 (0.6)	-2.7 (-4.2 to -1.1)	.79
≥15% 5-y CVD risk	135.4 (1.5)	133.3 (1.5)	-2.0 (-6.3 to 2.2)	
Adherence to indicated medication at baseline				
Yes	131.7 (0.7)	130.7 (0.7)	-1.0 (-2.9 to 0.8)	.01
No	131.8 (0.9)	126.8 (0.8)	-4.9 (-7.3 to -2.6)	
Sex				
Female	129.9 (1.3)	130.9 (1.2)	1.0 (-2.5 to 4.4)	.03
Male	132.1 (0.6)	128.8 (0.6)	-3.3 (-4.9 to -1.7)	
Diabetes				
Yes	132.3 (1.0)	131.4 (1.0)	-1.0 (-3.7 to 1.8)	.17
No	131.5 (0.6)	128.3 (0.6)	-3.2 (-4.9 to -1.5)	
Smoking				
Yes	130.5 (1.4)	127.7 (1.5)	-2.8 (-6.7 to 1.2)	.93
No	131.9 (0.6)	129.4 (0.6)	-2.6 (-4.1 to -1.0)	
Continent				
Europe	133.9 (0.7)	132.4 (0.7)	-1.5 (-3.4 to 0.5)	.10
India	129.5 (0.7)	125.7 (0.7)	-3.8 (-5.9 to -1.8)	
FDC choice				
Version 1	130.8 (0.7)	128.1 (0.7)	-2.7 (-4.5 to -0.8)	.88
Version 2	133.1 (0.8)	130.6 (0.8)	-2.4 (-4.7 to -0.2)	



Low-Density Lipoprotein Cholesterol

	LDL-C, Mean (SE), mg/dL		Mean Difference (95% CI)	P Value
	Usual Care	FDC		
CVD risk				
Established CVD	88.6 (0.9)	84.7 (0.9)	-3.9 (-6.4 to -1.4)	.43
≥15% 5-y CVD risk	86.9 (2.5)	80.1 (2.5)	-6.8 (-13.7 to 0.1)	
Adherence to indicated medication at baseline				
Yes	88.0 (1.1)	85.4 (1.1)	-2.7 (-5.6 to 0.3)	.11
No	89.0 (1.4)	82.3 (1.3)	-6.7 (-10.5 to -2.8)	
Sex				
Female	91.9 (2.0)	83.9 (2.0)	-8.0 (-13.5 to -2.4)	.14
Male	87.6 (0.9)	84.2 (0.9)	-3.4 (-6.0 to -0.8)	
Diabetes				
Yes	86.0 (1.6)	81.9 (1.6)	-4.1 (-8.6 to 0.3)	.98
No	89.3 (1.0)	85.1 (1.0)	-4.2 (-7.0 to -1.5)	
Smoking				
Yes	84.8 (2.3)	84.0 (2.4)	-0.8 (-7.3 to 5.7)	.27
No	88.9 (0.9)	84.2 (0.9)	-4.8 (-7.3 to -2.2)	
Continent				
Europe	86.7 (1.2)	88.6 (1.2)	1.9 (-1.3 to 5.1)	<.001
India	90.2 (1.2)	79.4 (1.2)	-10.8 (-14.1 to -7.4)	
FDC choice				
Version 1	87.6 (1.1)	83.3 (1.1)	-4.3 (-7.3 to -1.2)	.92
Version 2	89.5 (1.3)	85.4 (1.3)	-4.0 (-7.7 to -0.4)	



The primary outcomes of systolic blood pressure (SBP), and low-density lipoprotein cholesterol (LDL-C) are shown by prespecified baseline subgroups. Error bars indicate 95% CIs, boxes are placed at the relative risk for and sized proportional to the amount of information per subgroup, and vertical dashed lines show the overall effect for each outcome. *P* values are for the test of homogeneity for each subgroup. FDC indicates fixed-dose combination; CVD, cardiovascular disease. See Methods for descriptions of versions 1 and 2 of FDC.

similar effects of the FDC strategy. Dispensing of medication also differed between the groups. The trial centers were advised to dispense the FDC as a 6-month supply, although in some circumstances in India, where cool storage temperature was a concern, 3-month supplies were issued. Routine prescribing and dispensing practices are varied in both India and Europe, with 3 months being the usual interval of supply. The net effect of the longer dispensing interval for FDC is uncertain, however, because the extended duration of supply was offset by the inconvenience of collection from the distant trial center as opposed to the neighborhood pharmacy. A large US trial recently showed that elimination of co-payments for core cardiovascular medicines improved adherence by about 5% in absolute terms, which is smaller than the treatment effect seen here.[23] This presents a potential bias favoring the FDC strategy.

Adherence to medication is determined by complex interactions between health care systems and patients. Adherence may be defined as the extent to which a person's behav-

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ior (taking medication) corresponds with agreed recommendations from a clinician, and it is best assessed by a complementary approach using a questionnaire in tandem with objective measures.[24] There are several mechanisms whereby an FDC strategy may enhance adherence. These encompass ease of prescription, overcoming physician inertia, patient acceptability, packaged delivery, and ease of taking. This trial has shown that physicians are willing to prescribe an FDC to this group of patients by involving them in the trial, and at the end of the study more patients were taking the combination treatment. The self-reported assessment of adherence is substantiated by the changes in SBP and LDL-C.

In terms of assessing potential risks, the trial was not designed to assess adverse effects of component medicines (such as effects on cough, uric acid, and creatinine), which have been established already, but rather assessed the potential risk of an FDC strategy to lead to suboptimal care. One expressed concern is that reduced choice of medications and doses and/or unfamiliarity with use of FDCs as background treatment leads to suboptimal risk factor control; however, this trial suggests that these issues were not sufficient to offset improvements in risk factor control brought about by improved adherence. The trial also demonstrated that this FDC strategy did not lead to deterioration in other key measures relevant to CVD control, such as smoking, weight control, and exercise, even when patients knew they were receiving an FDC. The rate per month of stopping the FDC was about one-fifth that seen in a previous placebo-controlled trial of treatment initiation with one of these FDCs,[4] in part because the current trial population had mostly been receiving the component medicines already. One potential concern is the stopping of all medicines if an FDC is stopped because of the adverse effects of 1 component, but this trial showed that separate medicines are routinely started instead.

The trial did not identify an effect on cardiovascular events, but with only 85 events it had insufficient power to detect meaningful differences between groups. If beneficial changes in SBP, LDL-C, and aspirin use of the magnitude observed in this trial were realized in a similar population, it has been estimated that RR reductions of about 15% in coronary artery disease and stroke might be expected after a few years.[4] However, a clinical trial would need to observe more than 1000 events to reliably detect an RR reduction of 15%.[25] A 2002 joint report by the World Health Organization and Wellcome[8] recommended that evaluation of these products in the secondary prevention setting be principally based on bioequivalence (ie, studies showing that the FDC is bioequivalent to the separate components) and evidence of improved adherence (such as improved risk factor control, as seen in this trial), given the extensive evidence of clinical event reduction with the component medicines and drug classes, which has increased in the ensuing decade.[26-30]

These results should be considered in the context of previous trials showing that FDCs improve adherence.[31-33]The results should also be considered in the light of other trials of antiplatelet, statin, and BP-lowering FDCs.[3-5,34,35] These trials had comparison groups of placebo or no treatment mostly with 12 weeks or less of follow-up and generally showed risk factor reductions of the size expected from individual medications, once dropins and dropouts are accounted for.[4,34] This is the first trial to our knowledge evaluating FDC-based care over a prolonged interval in participants with established CVD or at similarly high levels of risk, among whom more than 40% of all cardiovascular events occur.[36] This targeted approach to a high-risk population contrasts with the population-wide treatment approach that some have advocated for the polypill.[12] These data suggest that FDCs could play a role in increasing uptake of statins, aspirin, and combination blood pressure-lowering drugs in patients with CVD not currently receiving such treatment. Scaled-up access to core cardiovascular medicines is in keeping with national CVD prevention goals in India, Europe, and the United States[37-39] and could contribute importantly to World Health Organization goals for noncommunicable disease control.[40]

Conclusion

In summary, among patients with or at high risk of CVD, the use of an FDC strategy for BP, cholesterol, and platelet control compared with usual care resulted in significantly improved medication adherence at 15 months.

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fixed-dose combinations used in the UMPIRE trial following a decision by Dr Reddy's Laboratories not to proceed with taking the products to market because of uncertainty in regulatory requirements. No other disclosures were reported.

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Role of the Sponsor: The UMPIRE trial was designed and conducted by an investigator-led independent steering committee. Dr Reddy's Laboratories had a nonvoting member (Cidambi) on the trial steering committee who had a management role in the design and conduct of the study and reviewed the final manuscript. Neither the European Commission nor Dr Reddy's had any role in the collection, management, analysis and interpretation of the data; they had no role in approval of the manuscript or decision to submit the manuscript for publication. The European Commission had no role in preparation or review of the manuscript.

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