Use of a Multidrug Pill In Reducing cv Events

Final Report Summary - UMPIRE (Use of a multidrug pill in reducing cv events)

Executive Summary:

Background

The vast majority of cardiovascular disease (CVD) patients do not receive recommended medications long-term. Even in high income countries, one third to a half do not take all recommended medications a year or more after an acute event. In low income countries, where most cardiovascular deaths now occur, treatment gaps frequently exceed 90%. The ‘Use of a multidrug pill in reducing cardiovascular events’ (UMPIRE) trial tested the hypothesis: that a fixed dose combination (FDC) based CVD prevention strategy for delivery of indicated medications, e.g. aspirin, statin and higher than two blood pressure (BP) lowering agents, compared to usual care might improve adherence to guideline-indicated therapy and induce favourable changes in systolic BP (SBP) and low density lipoprotein (LDL) cholesterol in people with or at high risk of CVD.

Methods

We conducted a prospective, randomised, open label, blinded endpoint (PROBE) clinical trial involving 2 004 participants with established CVD or an estimated five year CVD risk of higher than 15% in India and Europe. Two thousand four comparatively well treated participants were randomised to a FDC based strategy or usual care. The FDC version one contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10mg and atenolol 50 mg; version two contained hydrochlorothiazide 12.5 mg instead of atenolol. Primary outcomes were adherence to indicated medication (self-reported use of antiplatelet, statin and higher than two BP lowering therapy) and changes in SBP and LDL cholesterol from baseline.

Findings
The FDC improved adherence by 33% (13% after adjustment). This increase was reflected by improvements in SBP (-2.6 mmHg [95% confidence interval (CI) -4.0 -1.1] p=0.0005) and LDL cholesterol (-0.11 mmol out of L [95% Cl -0.17 -0.05] p=0.0005) which were sustained throughout the average follow-up interval of 15 months.

Interpretation

Among this population of patients with CVD or similarly high risk, provision of indicated cardiovascular preventive medications as a FDC led to improvements in adherence, SBP and LDL cholesterol.

Project Context and Objectives:

Background

The long-term use of recommended CVD preventive therapy is remarkably low among people with established disease. This shortfall is greatest in low and middle income countries (LMIC) 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. People who are at similar risk but have not reached the clinical threshold of suffering a CVD event are even less likely to be adequately treated. FDC therapy may reduce these treatment gaps, by reducing cost, complexity, therapeutic inertia and low adherence. On the other hand, 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 data are available on antiplatelet, statin and BP lowering FDCs, but these trials were mostly short-term and in low-to-moderate CVD risk populations. Despite high-level recommendations for over a decade, so far 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. This patient population was the first suggested for a treatment that has come to be widely known as the 'polypill'. In 2009 the European Commission (EC) 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 FDC 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 trial was designed in response to this funding call.

The trial assessed the effects of a FDC cardiovascular prevention strategy on adherence to indicated medication and clinical outcomes as well as the safety and efficacy of this strategy in Europe and India. The protocol and analysis plan are available at [http://www.spacecollaboration.org](http://www.spacecollaboration.org). The trial was sponsored by Imperial College London and is registered with the European Clinical Trials database (see https://eudract.ema.europa.eu out of index.html): EudraCT number 2009-016278-34 and with the Clinical Trials Registry, India (see http: out of out of [www.ctri.in](http://www.ctri.in) out of Clinicaltrials out of index.jsp): number CTRI out of 2010 out of 091 out of 000250. Ethics approval was granted by the relevant committees in each participating country.

Main objectives of the Seventh Framework Programme (FP7) project and the UMPIRE trial:

1. to conduct a clinical trial comparing a FDC cardiovascular prevention strategy with usual care in a setting of secondary CVD prevention; thereby confirming or refuting the hypothesis that a FDC will improve adherence to indicated medications and consequently improve clinical outcomes in high risk patients.
2. to measure barriers to adherence, quality of life, safety and cardiovascular events;
3. to disseminate results through national and international publications and scientific journals, the media and web-based communications.
4. to formulate internationally applicable recommendations for health policy relevant to developing and developed countries.
5. to engage the pharmaceutical industry (innovative and generic) in further development that will improve distribution and enhance wide individual low cost access to appropriate drugs.

UMPIRE trial design

Participants, randomisation, treatment and follow-up
Two thousand four participants were recruited from 28 government and private hospital clinics in India and from three large, established research centres in London (United Kingdom), Dublin (Ireland) and Utrecht (the Netherlands). Participants were included on the basis of a history of atherothrombotic CVD or an estimated five year CVD risk of higher than 15% (calculated using the Framingham risk equation as adjusted by the New Zealand Guidelines Group. Eligibility criteria were as follows:

1. Inclusion: age higher than 18 years and high cardiovascular risk, defined as either established CVD (a history of coronary heart disease out of ischaemic cerebrovascular disease out of peripheral vascular disease) or an estimated five year CVD risk of higher than 15% and FDC components all indicated.

2. Exclusion: one or more of the following: contraindication to or known intolerance of any FDC component, alteration of medications clinically inappropriate, anticipated medication adjustments, unlikely to follow the trial procedures.

Randomisation was conducted one to one, FDC: usual care and the allocation sequence was stratified by site and by the presence or absence of established CVD using a web-based clinical data management system (InForm). Participants randomised to usual care continued to be treated at the discretion of their routine doctor consistent with current guidelines and no attempt was made to influence usual care. Participants randomised to the FDC strategy were prescribed one of two FDC formulations at the discretion of the trial investigator: red heart pill (RHP) version one (containing aspirin 75mg, simvastatin 40mg, lisinopril 10mg, atenolol 50mg) or RHP version two (containing aspirin 75mg, simvastatin 40mg, lisinopril 10mg, hydrochlorothiazide 12.5mg). The FDC was taken once daily and timing was left to the discretion of the doctor and the participant. The FDC was regarded as 'background treatment' to which additional medications could be added according to individual requirements to achieve target BP or cholesterol or to treat concomitant conditions. Participants in the FDC group were dispensed the RHP free of charge from their trial centre. Participants in the usual care group acquired their medications subject to prevailing local payments or exemptions.

Trial recruitment took place over 13 months (June 2010 to July 2011) with planned for 12 months after the last patient first visit and therefore trial follow was between 12 to 24 months with a median in trial duration of 15 months. Participants attended clinic visits for randomisation, at 12 months and at the end of the study. Prior to randomisation the doctor answered the question: ‘if this participant is allocated to the FDC group, which version should be chosen?’ Telephone or clinic visits were conducted at one month, six months and 18 months (if applicable). BP and fasting lipids were measured at baseline, 12 months and at the end of the study. BP and heart rate measurement were standardised using automated electronic devices (Omron 705CP II). Fasting blood samples were analysed by local laboratories. Self-reported adherence to all medications was assessed at all trial visits and recorded as the number of days medication was taken in the week prior to trial visit (value between none to seven days). During trial contacts, the research team asked about barriers to adherence, quality of life, cardiovascular and other serious adverse events and reasons for stopping cardiovascular medications. The primary objective was to assess whether provision of a FDC compared to usual medications improves adherence to indicated therapy and, as a consequence, whether it improves two major cardiovascular risk factors systolic SBP and LDL cholesterol. Secondary objectives were assessing barriers to adherence, quality of life, safety, cardiovascular events and comparison of the results from India with those from Europe.

Outcomes and analysis

Primary outcomes were:

1. adherence to indicated medications (defined as self-reported current use of antiplatelet, statin and higher than two BP lowering therapy) at the end of the trial; current use of a medication was defined as taking the medication for at least four days during the week preceding the visit.

2. changes in SBP and LDL cholesterol from baseline to end of the trial.

Secondary outcomes included:

1. adherence to indicated medications at 12 months.

2. reasons for stopping cardiovascular medications.

3. serious adverse events.

4. change in total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides and creatinine from baseline to 12 months and end of study.

5. cardiovascular events (including coronary heart disease, heart failure leading to death or hospital admission, cerebrovascular and peripheral arterial disease).
Sample size calculations and the statistical analysis plan are available at http://www.spacecollaboration.org.

Project Results:

UMPIRE Trial results

Baseline characteristics of trial participants and trial structure

A total of 2,138 potential participants were screened, 134 were ineligible and 2,004 were randomised (1,000 in India, 1,004 in Europe) between July 2010 and July 2011. Amongst the 1,002 participants randomised to the FDC group, physicians started therapy on FDC version one (simvastatin, aspirin, lisinopril and atenolol) for 589 of 1,002 (58.8%) and the remainder on FDC version two (simvastatin, aspirin, lisinopril, hydrochlorothiazide). The median duration of follow-up was 15 months (interquartile range, 12 to 18 months) for both groups. Baseline characteristics of the FDC and usual care groups were well matched; randomisation resulted in no major baselines imbalances. Minor imbalances are expected by chance and their impact is assessed in the adjusted analyses reported below. The majority (1,771 out of 2,004 - 88%) of participants were included on the basis of established CVD. The whole group had a high level of adherence to the indicated medications 1,233 of 2,004 (61.5%) at the outset. Baseline reported use was high for statins 1,760 of 2,004 (87.8%), anti-platelet therapy 1,832 of 2,004 (91.4%) and BP lowering therapy 1,862 of 2,004 (92%), although levels were somewhat lower for those reporting higher than two BP lowering drugs 1,371 out of 2,004 (68.4%).

Overall effects on primary outcomes of adherence, systolic BP and LDL-cholesterol

At the end of study 829 out of 961 (86.3%) of participants in the FDC group were continuing with indicated medications compared with 621 out of 960 (64.7%) of the usual care group (unadjusted RR 1.33 [95% CI 1.26 - 1.41] P<0.0001. In absolute terms, this amounted to a 21.6% difference in treatment rates (95% CI 17.8% - 25.3%, p<0.001) and a number needed to treat of 4.6 patients (95% CI 4.0 - 5.6). For each treatment modality there was an increase in treatment rates after randomisation; this amounted to an absolute increase of about 5% for each modality 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 modality decreased slightly over time, but remained higher than baseline at 18 months. At one month use of indicated medications in the FDC group was 966 out of 993 (97.3%) whereas in the usual care group 672 out of 994 (67.6 %) of patients were taking all indicated medications as separate pills. The absolute difference between groups decreased slightly by six months and then remained approximately constant thereafter. The decrease between one and six months in the FDC group largely occurred among people 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 study FDC use was reported in 747 out of 961 (77.7 %) of participants in the FDC group, with a further 82 out of 961 (8.5 %) adhering to indicated medication by taking separate tablets. An alternate definition of adherence involving taking statin, antiplatelet and at least one BP lowering drug also showed benefits [873 out of 961 (90.8 %) in FDC versus 808 out of 960 (84.2 %) in usual care, p<0.0001] which was due to improved adherence to antiplatelet and statin therapy as there was no difference in the proportion taking at least one BP lowering drug at the end of study (95.2 % versus 95.9 %).

The mean difference in the changes in SBP and LDL cholesterol is described using the primary analysis-of-covariance method. Overall, SBP (-2.6 mmHg [95% CI -4.0 -1.1]) and LDL cholesterol (-0.11 mmol out of L [95% CI -0.17 -0.05]) were significantly lower in the FDC group compared to the usual care group at the end of study. The secondary analysis method of repeated linear regression was also used. For this analysis, overall average differences over time were 3.3 mmHg (-4.6 -1.9 p<0.001) for SBP and 0.14 mmol out of L (-0.19 -0.08 p<0.001) for LDL-cholesterol.

Adjusted models included the following variables: randomised treatment, baseline value, country, history of CVD, age and sex. Adjusted and unadjusted effects were essentially identical for treatment effect estimates of SBP and LDL cholesterol reduction. However, the adjusted effect for adherence was somewhat lower (RR 1.13 [1.08 -1.18] p<0.0001) than for unadjusted analyses, as a result of a small baseline imbalance in use of antiplatelet, statins and higher than 2 BP lowering agents and the effect modification for this variable.

Treatment effects on primary outcomes in pre-defined participant sub-groups

The effects of the FDC strategy on adherence, SBP and LDL cholesterol in pre-specified subgroups were also defined by baseline characteristics. Across the three co-primary endpoints, the only consistent effect modifier was whether or not patients were taking
statin, aspirin and two BP lowering drugs at baseline. This was most marked for the adherence outcome, given that the two shared the same definition. For the adherence outcome, effects were statistically significant in every subgroup but were quantitatively larger in those at high estimated CVD risk, those with low baseline adherence, smokers and those for whom the physician intended to use FDC version two. In terms of SBP reduction, treatment effects appeared larger in those without baseline adherence to indicated medications and in men; whereas in terms of LDL cholesterol reduction the effects appeared to be larger in participants from India.

Effects on secondary outcomes

Creatinine, glucose and other laboratory parameters

Creatinine rose in both FDC and usual care groups between baseline and end of study (89.0 to 94.3 µmol out of L, FDC; 89.7 to 92.2 µmol out of L, usual care) and the difference in this rise between the 2 groups was statistically significant (FDC - usual care, +2.7 µmol out of L, [95% CI 1.0 4.4] P=0.002). There was also an increase in uric acid in the FDC group (330.0 to 355.7 µmol out of L, FDC; 330.0 to 344.1 µmol out of L, usual care) and the difference in this rise between the 2 groups was significant (FDC - usual care, +11.6 µmol out of L [95% CI 4.8 18.4] p=0.0008). There were no significant changes between groups in the levels of sodium, potassium, alanine transaminase, aspartate aminotransferase (data not shown) or glucose. Glucose levels at the end of study were 6.2 ± 2.2 mmol out of L (FDC) and 6.2 ± 2.0 mmol out of L (usual care).

Weight, lifestyle factors and quality of life scores

Weight, waist circumference and body mass index did not change during follow-up and were virtually identical in both groups at the end of 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 (data not shown). Reported time engaged in moderate physical activity (minutes out of week) was similar in the two groups at baseline 163 (± 179) versus 158 (± 180) but significantly higher in the FDC group than in the usual care group at the end of study 157 (± 178) versus 141 (± 157), p=0.0334. Quality of life as measured by the visual analogue scale within EQ5D was significantly higher in the FDC group at the end of study (+2.43 [95% CI 0.87 3.99] p=0.0023). There were no differences in the other EQ5D indices.

Reasons for stopping cardiovascular medications

Among the 219 participants in the FDC group who discontinued the FDC, the following were the main stated reasons: patient choice 61 out of 219 (28%), medical advice without specified reason or side effect 26 out of 219 (26%), cough 46 out of 219 (21%), dizziness 20 out of 219 (9%), serious adverse events (SAEs) 18 out of 219 (8%), other adverse events (AEs) 35 out of 219 (16%) and other reasons (e.g. raised creatinine, fatigue, etc.) 18 out of 219 (8%). A total of 9 participants switched to the alternative FDC version. Amongst those participants who stopped the FDC during the course of follow-up, 58-74% were switched to antiplatelet, statin and BP lowering therapy with separate medications whereas 7-20% of participants were not taking any cardiovascular medications.

Cardiovascular endpoints, SAEs and mortality

In total, 85 participants had a cardiovascular endpoint as a first event: 50 (5.0%) in the FDC group and 35 out of 1002 (3.5%) in the usual care group (RR=1.45 [95% CI 0.94 2.24] p=0.0908). Overall, there were 118 out of 1002 (11.8%) patients with at least one SAE in the FDC group, compared to 102 out of 1002 (10.2%) in the usual care group, with no significant differences in any major subcategory. A similar number of deaths occurred in each group (17 in the FDC group versus 15 in the usual care group, RR 1.13 [95% CI 0.57 2.26] p=0.7216). Vascular deaths were reported as 14 versus 8 in FDC versus usual care (p=0.1983) and nonvascular deaths were reported as 3 versus 7 (p=0.2048).

Potential Impact:

This was the first randomised trial to assess the long-term use of a fixed dose combination containing antiplatelet, statin and BP lowering drugs compared to usual care in people with cardiovascular disease. The results show that access to FDCs in people with CVD or similarly high risk improves adherence, BP and cholesterol levels.

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. Most importantly,
the trial likely under-estimated benefits in a general population setting with typical adherence levels, since volunteers for clinical trials tend to be relatively motivated and clinical management in a trial setting tends to be more intensive than usual care. The size of this under-estimation is suggested in the minority of individuals who were not taking indicated medications at baseline, in whom randomisation to FDC resulted in a three-fold increase in adherence levels (77% versus 23%) and larger reductions in SBP and LDL-cholesterol. Effects were nonetheless observed in a trial population of whom 82% initially reported use of statin, antiplatelet and BP lowering drug(s), whereas comparable combination treatment rates are around 50% in high income countries and 5-20% in LMIC. Furthermore, improvements were observed compared to a usual care group in whom treatment rates rose initially and remained higher than baseline throughout the study, whereas adherence typically reduces over time.

We were required by ethics committees to provide the FDC free of charge, whereas the usual care group continued to receive their medications with attendant costs or subsidies. In one sense, this reflects the real impact if the FDC were to be made available at low or zero cost to the patient, for example as part of a universal health care program. Among this trial population, the economic advantage for the FDC group would likely have been modest, both in India given the generally low cost of medicines and relative affluence of participants from tertiary care settings and in Europe given the prevalence of medication and prescription subsidies. A large United States of America (USA) trial recently showed that elimination of copayments for core cardiovascular medicines improved adherence by about 5% in absolute terms, which is smaller than the treatment effect seen here.

Adherence to medication is determined by a complex set of interactions between healthcare systems and patients. It may be defined as the extent to which a person's behaviour (taking medication) corresponds with agreed recommendations from a health care provider. There are several mechanisms whereby a 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 doctors 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 parallel changes in SBP and LDL-cholesterol.

In terms of assessing potential risks, the trial was not designed to assess side effects of component medicines (such as effects on cough, uric acid and creatinine) which have been fully established already, but rather the potential for an FDC strategy to lead to suboptimal care. One potential concern is that reduced choice of medications and doses and out of or unfamiliarity with use of FDC as background treatment will lead to suboptimal risk factor control; however, this trial showed that these issues were not sufficient to offset improvements in risk factor control brought about by improved adherence. The trial also demonstrated this FDC strategy does not lead to deterioration in other key measures relevant to CVD control, such as smoking, weight control and exercise, even when patients know they are receiving an FDC. The rate per month of stopping the FDC was about one-fifth of that seen in a previous placebo-controlled trial of treatment initiation with one of these FDCs, four partly 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 for side effects from one component, but this trial showed that other medicines can be re-instituted. Of the 829 out of 961 (86%) in the FDC-allocated group who were adherent at end of study, this was achieved with separate medicines for 82 out of 961 (8.5%).

The trial did not identify an effect on cardiovascular events, but with only 85 events it provided little power to detect meaningful differences between groups. Based on observed differences in SBP, LDL cholesterol and aspirin use, relative risk reductions of around 15% in coronary disease and stroke are anticipated after a few years. However, a clinical trial would need to observe over 1 000 events to reliably detect a relative risk reduction of 15%. The World Health Organisation (WHO) and Wellcome joint report in 2002 recommended that evaluation of these products in the secondary prevention setting be principally based on bioequivalence (i.e. studies showing the FDC is bioequivalent to the separate components) and evidence of improved adherence (such as improved risk factor control), 8 given the extensive evidence of clinical event reduction with the component medicines and drug classes, which has become even greater in the ensuing decade.

These results should be considered in the context of previous trials showing that FDCs improve adherence. The results should also be considered in the light of other trials of antiplatelet, statin and BP lowering FDCs. These trials had comparison groups of placebo or no treatment mostly with 12 weeks or less follow-up and generally showed risk factor reductions of the size expected from individual medications, once drop-in and drop-out are accounted for. This is the first trial evaluating FDC based care over a prolonged interval in participants with established CVD or at similarly high levels of risk. Approximately 40% of all cardiovascular events occur among people with a previous symptomatic event, such as myocardial infarction, stroke, angina or transient ischemic attack (TIA).

The Government of India has recently renewed undertakings to make medicines more widely available as part of its commitment to universal health care coverage. For the group targeted in this trial the 'essential vascular package' of statin, aspirin and combination BP
lowering is widely recommended by national and international guidelines and provides the highest absolute benefits. It addresses three quarters of the ‘A-B-C-S’ (appropriate aspirin therapy, BP control, cholesterol management and smoking cessation) task set by the USA Million Hearts initiative. In Europe a key objective of the WHO European ‘Health 2020’ policy is the reduction of health inequalities through measures to prevent major diseases including CVD. Development and testing of a cardiovascular FDC was one of the recommendations of the ‘Priority medicines for Europe and the world’ initiative. The WHO estimates that CVD costs European economies EUR 192 billion per year, that much of the associated mortality is preventable and recommends an FDC as part of a workable solution. Multiple economic analyses have demonstrated that improving access to this essential vascular package among those at highest risk can be highly cost-effective. Indeed scaled up access to core cardiovascular medicines could alone achieve most of the WHO goal for reducing the impact of non-communicable diseases.

List of Websites:

http://www.spacecollaboration.org

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