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RESEARCH

Effect of fixed dose combination treatment on adherence and risk factor control among patients at high risk of cardiovascular disease: randomised controlled trial in primary care

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Abstract

Objective To evaluate whether provision of fixed dose combination treatment improves adherence and risk factor control compared with usual care of patients at high risk of cardiovascular disease in primary care.

Design Open label randomised control trial: IMPACT (IMProving Adherence using Combination Therapy).

Setting 54 general practices in the Auckland and Waikato regions of New Zealand, July 2010 to August 2013.

Participants 513 adults (including 257 indigenous Māori) at high risk of cardiovascular disease (established cardiovascular disease or five year risk ≥15%) who were recommended for treatment with antiplatelet, statin, and two or more blood pressure lowering drugs. 497 (97%) completed 12 months' follow-up.

Interventions Participants were randomised to continued usual care or to fixed dose combination treatment (with two versions available: aspirin 75 mg, simvastatin 40 mg, and lisinopril 10 mg with either atenolol 50 mg or hydrochlorothiazide 12.5 mg). All drugs in both treatment arms were prescribed by their usual general practitioners and dispensed by local community pharmacists.

Main outcome measures Primary outcomes were self reported adherence to recommended drugs (antiplatelet, statin, and two or more blood pressure lowering agents) and mean change in blood pressure and low density lipoprotein cholesterol at 12 months.

Results Adherence to all four recommended drugs was greater among fixed dose combination than usual care participants at 12 months (81% *v* 46%; relative risk 1.75, 95% confidence interval 1.52 to 2.03, P<0.001; number needed to treat 2.9, 95% confidence interval 2.3 to 3.7). Adherence for each drug type at 12 months was high in both groups but especially in the fixed dose combination group: for antiplatelet treatment it was 93% fixed dose combination *v* 83% usual care (P<0.001), for statin 94% *v* 89% (P=0.06), for combination blood pressure lowering 89% *v* 59% (P<0.001), and for any blood pressure lowering 96% *v* 91% (P=0.02). Self reported adherence was highly concordant with dispensing data (dispensing of all four recommended drugs 79% fixed dose combination *v* 47% usual care, relative risk 1.67, 95% confidence interval 1.44 to 1.93, P<0.001). There was no statistically significant improvement in risk factor control between the fixed dose combination and usual care groups over 12 months: the difference in systolic blood pressure was −2.2 mm Hg (−4.5 *v* −2.3, 95% confidence interval −5.6 to 1.2, P=0.21), in diastolic blood pressure −1.2 mm Hg (−2.1 *v* −0.9, −3.2 to 0.8, P=0.22) and in low density lipoprotein cholesterol −0.05 mmol/L (−0.20 *v* −0.15, −0.17 to 0.08, P=0.46). The number of participants with cardiovascular

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Appendix

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events or serious adverse events was similar in both treatment groups (fixed dose combination 16 *v* usual care 18 (P=0.73), 99 *v* 93 (P=0.56), respectively). Fixed dose combination treatment was discontinued in 94 participants (37%). The most commonly reported reason for discontinuation was a side effect (54/75, 72%). Overall, 89% (227/256) of fixed dose combination participants' general practitioners completed a post-trial survey, and the fixed dose combination strategy was rated as satisfactory or very satisfactory for starting treatment (206/227, 91%), blood pressure control (180/220, 82%), cholesterol control (170/218, 78%), tolerability (181/223, 81%), and prescribing according to local guidelines (185/219, 84%). When participants were asked at 12 months how easy they found taking their prescribed drugs, most responded very easy or easy (224/246, 91% fixed dose combination *v* 212/246, 86% usual care, P=0.09). At 12 months the change in other lipid fractions, difference in EuroQol-5D, and difference in barriers to adherence did not differ significantly between the treatment groups.

Conclusions Among this well treated primary care population, fixed dose combination treatment improved adherence to the combination of all recommended drugs but improvements in clinical risk factors were small and did not reach statistical significance. Acceptability was high for both general practitioners and patients, although the discontinuation rate was high.

Trial registration Australian New Zealand Clinical Trial Registry ACTRN12606000067572.

Introduction

International guidelines recommend antiplatelet, statin, and blood pressure lowering treatment for people with established cardiovascular disease.[1-3] In a recent survey, however, only 44% of people with established coronary or cerebrovascular disease in high income countries (13% in upper middle and 3% in lower middle and low income countries) reported taking at least three of four recommended preventive drugs for cardiovascular disease (aspirin, statin, angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and other blood pressure lowering drug).[4] In New Zealand, treatment rates are also suboptimal; in 2011, only 59% of people with established cardiovascular disease were dispensed an antiplatelet, a statin, and a blood pressure lowering agent in at least three out of four quarters of the year (75% were dispensed an antiplatelet, 70% a statin, and 77% a blood pressure lowering drug).[5] A single pill containing all three agents (fixed dose combination treatment) may help to reduce this treatment gap by simplifying the drug regimen for both prescribers and patients. The first recommended use for fixed dose combination treatment was among patients with established cardiovascular disease in initial publications.[6-8]

Several short term trials have assessed reductions in cardiovascular risk factors with fixed dose combinations and broadly found the same effects as those expected from the separate components.[9] However, despite recommendations dating back over a decade for research into fixed dose combination treatment in secondary prevention,[6] only two trials have been published in this patient group and only a minority of this evidence is from a primary care setting.[10 11]

Health professionals seem open to the theoretical possibility of prescribing fixed dose combination treatment for high risk patients,[12-14] and the concept of such a treatment seems generally acceptable to high risk patients taking three or more cardiovascular drugs.[15] However, no data are available on acceptability to both patients and primary care doctors who have had long term experience of fixed dose combination treatment.

The IMPACT (IMProving Adherence using Combination Therapy) trial[16] was designed to evaluate whether fixed dose combination treatment can improve adherence and control of risk factors in people with established cardiovascular disease or at similarly high risk treated in primary care, where the majority of care for patients with vascular disease occurs. The IMPACT trial is part of the SPACE (Single Pill to Avert Cardiovascular Events) Collaboration, which is undertaking a prospective meta-analysis on individual participant data.[17] All three contributing trials (IMPACT, UMPIRE (Use of a Multidrug Pill in Reducing Cardiovascular Events),[11] and Kanyini-GAP (Guidelines Adherence with the Polypill)[10]) tested the same fixed dose combination treatment compared with usual care in different settings, using a protocol based on that developed for the IMPACT trial.[18]

Methods

The protocol for the IMPACT trial has been previously described.[18] We conducted an open label, randomised controlled trial of fixed dose combination treatment compared with usual care for at least 12 months in people with a history of cardiovascular disease or at similarly high risk. Participants were recruited from 54 general practices in the Auckland and Waikato regions of New Zealand. Recruitment processes have been previously described.[19] Participants gave informed consent before taking part.

Participants

Adults aged 18-79 years at high risk of cardiovascular disease (based on either established disease (coronary, cerebrovascular, or peripheral vascular) or ≥15% five year risk of a cardiovascular event) were eligible for the trial. We estimated the five year risk using the Framingham equation for cardiovascular disease, adjusted for current preventive drugs (risk×1.15 for each of the drug classes being taken by participants: antiplatelet, blood pressure lowering, cholesterol lowering) and, consistent with New Zealand guidelines, adjusted upwards by 5% for patients with additional risk factors, such as a family history of premature cardiovascular disease.[20] In accordance with New Zealand guidelines, we assumed the five year risk to be more than 15% in patients with high blood pressure (>170/100 mm Hg), high cholesterol levels (total cholesterol >8 mmol/L or total cholesterol to high density lipoprotein cholesterol ratio >8), or a genetic lipid abnormality. Other inclusion criteria were that the patient's general practitioner considered all the drugs in at least one of the two versions of the fixed dose combination treatment available were recommended, and was uncertain if treatment was best provided as fixed dose combination based treatment or as usual care. Exclusion criteria were contraindications to any of the components of the fixed dose combination, congestive heart failure, haemorrhagic stroke, active stomach or duodenal ulcer, receipt of an oral anticoagulant, concerns by the general practitioner about the risk to a patient of changing his or her cardiovascular disease drugs, impending alteration of a drug regimen for an important length of time (for example, planned coronary bypass graft operation), or the participant was unlikely to complete the trial or the trial procedures (for example, terminal illness). The participant's general practitioner confirmed trial eligibility before activating randomisation.

Randomisation

A central randomisation service randomly assigned (1:1) participants to fixed dose combination based treatment or usual care. A minimisation algorithm included the stratification factors: primary health organisation (these provide business

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management and quality of care services to groups of general practices), history of cardiovascular disease (yes or no), self reported adherence to recommended drugs (antiplatelet, statin, and ≥2 blood pressure lowering drugs; yes or no), and ethnicity (indigenous Māori or non-Māori).

Intervention

After randomisation, the participant's cardiovascular drugs were reviewed by their usual general practitioner (who was encouraged to manage the participants irrespective of treatment allocation in accordance with New Zealand cardiovascular disease risk assessment and management guidelines).[20 21] Changes or additions to a cardiovascular drug regimen were at the discretion of the general practitioner, who remained the principal ongoing healthcare provider, including overseeing the use of fixed dose combination treatment where appropriate.

General practitioners had the choice of two fixed dose combinations. Both contained aspirin 75 mg, simvastatin 40 mg, and lisinopril 10 mg, with atenolol 50 mg additionally added to one combination and hydrochlorothiazide 12.5 mg to the other. General practitioners could select the combination to use, change combinations, or discontinue treatment at any stage during the trial. There were no limitations on the use of any concomitant (including cardiovascular) drugs the general practitioners considered appropriate. Fixed dose combination treatment was prescribed according to the general practitioner's usual method. They identified the community pharmacies most often used by their patients and we invited these pharmacies to stock fixed dose combination treatment; thus, both trial drugs and usual drugs were dispensed through community pharmacies. Participants were required to pay what they would normally pay to receive a single government subsidised drug, thus mimicking real practice were fixed dose combination treatment to be funded by New Zealand's Pharmaceutical Management Agency. Standard patient copayments of NZ$5 (£2.6; €3.1; $4.3) for each item every three months were required for the dispensing of both fixed dose combination treatment (a single copayment) and usual drugs (a single copayment for each drug).

Trial procedures

The minimum follow-up time was 12 months after the last participant was randomised. We estimated this would provide a median follow-up of 18 months. Participants attended their general practice at randomisation. Research nurses undertook follow-up either by phone (one month and six month assessments) or face to face (12 month and end of trial assessments), at the participant's home or at another location of the participant's choosing (such as their general practice or work).

We obtained blood pressure and fasting lipid levels at baseline, 12 months, and end of the trial. Paper printouts of blood pressure and heart rate obtained from electronic sphygmomanometers (Omron T9P) were logged and audited. Fasting blood samples were analysed by local accredited laboratories. Self reported adherence at each follow-up was assessed by asking participants for the names and dosages of all prescription and over the counter drugs currently being taken. If the drug the participants reported taking included an antiplatelet, statin, and two or more blood pressure lowering drugs, they were classed as "adherent"; otherwise they were classed as "non-adherent" to recommended treatment. Other data collected included barriers to adherence, reasons for stopping fixed dose combination treatment, serious adverse events, cardiovascular events, and quality of life (EuroQol EQ-5D).[22]

Using data linkage with the national pharmaceutical dispensing claims database, we obtained data on all publicly funded antiplatelet, statin, and blood pressure lowering drug dispensed to participants. We obtained dispensing data on fixed dose combination treatment from paper based trial dispensing logs on fixed dose combinations and by searching the electronic records of trial pharmacists.

We invited the general practitioners of each participant randomised to fixed dose combination treatment to complete a post-trial survey on the acceptability of the treatment. General practitioners with more than one participant randomised to fixed dose combination treatment completed a separate survey for each participant. The general practitioners were asked to rate different aspects of fixed dose combination based care and to indicate the most important advantage and disadvantage of such treatment for their patients.

At 12 months and end of the trial, we asked all participants: "During the study, how easy did you find it to take all of the medicines prescribed to you by your doctor? (including the polypill)." Participants were able to select one of the five options: very easy, easy, average, difficult, or very difficult.

A blinded and independent endpoint committee adjudicated several prespecified events: cardiovascular events (deaths, non-fatal stroke, transient ischaemic attack, subarachnoid haemorrhage, non-fatal myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, admission to hospital for unstable angina, admission to hospital for heart failure, new symptomatic claudication, amputation due to ischaemia, peripheral arterial revascularisation procedure), renal events (new onset of microalbuminuria, progression to macroalbuminuria, ≥50% loss of estimated glomerular filtration rate and start of renal replacement therapy for end stage renal disease), and major extracranial bleeding events (active bleeding that resulted in a reduction of haemoglobin of at least 20 g/L, or required transfusion of at least two units of blood, or symptomatic bleeding in a critical area or organ).

Outcomes

We prespecified the primary outcomes as adherence (self reported current use of antiplatelet, statin, and at least two blood pressure lowering drugs) at 12 months, and change in blood pressure and low density lipoprotein cholesterol between baseline and 12 months. The use of three primary outcome measures enabled assessment of the consistency of results between self reported and directly measured data. Healthcare resource consumption is the subject of a separate economic analysis.

Statistical analysis

We determined that a recruitment target of 600 provided 95% power at two sided P=0.05 to detect a 0.25 mmol/L difference in low density lipoprotein cholesterol and 4 mm Hg difference in systolic blood pressure between the intervention and usual care groups, assuming standard deviations around the change from baseline score of 0.8 mmol/L and 14 mm Hg, respectively.[18] This would also provide more than 95% power to detect a 30% improvement in adherence compared with baseline (for example, from 50% to 65% adherence). Given the available funding resources, the recruitment target was revised down to 500, which provided 89-93% power to detect the same differences between risk factors and 92% power to detect a 30% relative improvement in adherence. We aimed to recruit equal numbers of Māori and non-Māori participants to assess the consistency of effects across these groups.

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For continuous outcomes, we compared the change from baseline to follow-up between fixed dose combination treatment and usual care arms using two sample *t* tests. We compared binary outcomes using the χ^2 test. Primary outcomes were analysed by intention to treat: where 12 month adherence was missing, the participant was assumed to be non-adherent, and where change in blood pressure or low density lipoprotein cholesterol levels from baseline to 12 months was missing, we assumed the change to be zero. We carried out adjusted analyses for adherence at 12 months (logistic regression) and change in blood pressure and low density lipoprotein cholesterol levels from baseline to 12 months (linear regression) and included predefined covariates (treatment group, stratification factors, age, and sex). To assess whether the covariates in the adjusted model significantly improved goodness of fit of the model, we used the likelihood ratio χ^2 test between unadjusted and adjusted models. We performed prespecified subgroup analyses for the primary outcomes if the results were highly significant (P<0.005) using tests of heterogeneity for stratification factors, age, and sex.

Results

Trial flow and baseline characteristics

Between July 2010 and July 2012, we screened and randomised 513 (from 91 general practitioners) of 814 potentially eligible patients invited by their doctors to participate in the trial and who had provided written informed consent (fig 1⇓). The median duration of follow-up was 23 months in both arms. Follow-up concluded in August 2013, 12 months after the last participant was randomised, as planned. Primary outcome data were available for 95-97% of participants (fig 1).

Fixed dose combination treatment and usual care groups had similar characteristics at baseline (table 1⇓). Forty five per cent (n=233) of participants were included on the basis of a history of cardiovascular disease, and 43% of participants (n= 223) reported taking recommended treatment (antiplatelet, statin, and ≥2 blood pressure lowering agents) at baseline.

Primary outcomes

Table 2⇓ shows self reported adherence to recommended drugs (antiplatelet, statin, and ≥2 blood pressure lowering agents) at 12 months was greater in participants randomised to fixed dose combination treatment compared with usual care (81% *v* 46%, relative risk 1.75, 95% confidence interval 1.52 to 2.03, P<0.001). The absolute difference in adherence (35%) gave a number needed to treat (NNT) of 2.9 patients (95% confidence interval 2.3 to 3.7 patients). The reduction in systolic blood pressure between baseline and 12 months was 4.5 mm Hg (SD 21.0) in the fixed dose combination treatment group compared with 2.3 mm Hg (SD 18.1) in the usual care group. The unadjusted treatment difference was not significant (−2.2 mm Hg, 95% confidence interval −5.6 to 1.2, P=0.21). The result was unchanged after adjustment for prespecified explanatory variables (−2.2 mm Hg, −5.6 to 1.2, P=0.21) but was significant after adjustment for baseline systolic blood pressure in addition to the prespecified explanatory variables (−3.2 mm Hg, −6.1 to −0.3, P=0.03). Change of diastolic blood pressure did not differ significantly. The difference in low density lipoprotein cholesterol level was −0.20 (SD 0.73) mmol/L among participants in the fixed dose combination treatment group compared with −0.15 (SD 0.72) mmol/L among participants in the usual care group. The difference between the groups was not significant (−0.05 mmol/L, 95% confidence interval −0.17 to 0.08, P=0.46) and did not change in adjusted analyses.

Secondary outcomes

The change in other lipid fractions between baseline and 12 months did not differ significantly between treatment groups (table 2). Quality of life measures at 12 months (visual analogue scale, table 2, and EQ-5D domain scores, appendix on bmj.com) did not differ statistically between the groups, nor was there a difference in the proportion of participants who at 12 months reported missing prescribed drugs in the preceding month due to different possible barriers to adherence (see appendix on bmj.com).

The number of participants with a cardiovascular event that met predefined criteria by a blinded endpoint adjudication committee did not differ (fixed dose combination 16 *v* usual care 18, P=0.73). Ten participants died (fixed dose combination 4 *v* usual care 6, P=0.75). Several other outcomes were also reported, and adjudicated: coronary heart disease (fixed dose combination 12 *v* usual care 12, P=0.99), admission to hospital for heart failure (0 *v* 2, P=0.50), cerebrovascular disease (2 *v* 4, P=0.69), peripheral vascular disease (3 *v* 2, P=0.69), renal events (39 *v* 30, P=0.24), and major extracranial bleeding events (4 *v* 0, P=0.06). The appendix on bmj.com provides further information on adjudicated events.

Ninety nine participants in the fixed dose combination group (39%) and 93 in the usual care group (36%) experienced at least one serious adverse event during the trial (P=0.56, table 3⇓). Seventy two (28%) participants in the fixed dose combination group and 70 (27%) in the usual care group had a serious adverse event that led to hospital admission (P=0.82), whereas other serious adverse events (principally other medical events not further specified) were reported for 44 (17%) and 32 (12%) participants in the fixed dose combination and usual care groups, respectively (P=0.13).

Fixed dose combination treatment was discontinued for over a third of participants during the trial (n=94, 37%), with similar numbers discontinuing each of the two fixed dose combinations (49 discontinued the combination treatment with atenolol 50 mg; 45 discontinued the combination treatment with hydrochlorothiazide 12.5 mg). The main reasons for discontinuing fixed dose combination treatment reported by participants were: medical practitioner decision; not further specified[15]; dizziness or hypotension[13]; cough[10]; patient choice[9]; deterioration in renal function[6]; fatigue[6]; inadequate risk factor control[5]; unknown reason[4]; bleed[3]; gastritis, dyspepsia, or ulcer[3]; other side effect[13]; and other reason.[7]

Other outcomes and prespecified subgroup analyses

National dispensing claims data for antiplatelet, statin, and two or more BP lowering drugs at 12 months (fixed dose combination 79% *v* usual care 47%, P<0.001, table 2) showed close concordance with the self reported adherence primary outcome (81% *v* 46%, P<0.001).

The improvement in adherence with fixed dose combination based care remained significant to the end of the trial (72 *v* 46%, relative risk 1.56 (95% confidence interval 1.34 to 1.82), P<0.001, Table 2 and web extra appendix on bmj.com). At the end of the trial the reduction in blood pressure (systolic or diastolic) or low density lipoprotein cholesterol in the fixed dose combination compared with usual care groups did not differ significantly, irrespective of whether analyses were or were not adjusted.

The effect of fixed dose combination based care on self reported adherence at 12 months by prespecified subgroups was significantly greater in participants not adherent to recommended

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drugs at baseline (P<0.001, fig 2⇓) and those aged <60 years (P=0.003), but there was no heterogeneity of treatment effect by sex, ethnicity, primary health organization, or history of cardiovascular disease. Self reported adherence to antiplatelet, statin, and one or more (as opposed to ≥2) blood pressure lowering agents, as well as individual components, at 12 months was greater in the fixed dose combination group than in the usual care group (table 2).

Acceptability for patients and prescribers

When participants were asked how easy they found taking all of their prescribed medicines at 12 months on a five point Likert scale (from "very easy" to "very difficult"), the most common response was very easy (53% *v* 46% for fixed dose combination and usual care, respectively). The overall P value for the comparison between treatment arms across all five categories was 0.06 (see web extra appendix on bmj.com).

Overall, 89% (227/256) of general practitioners who prescribed fixed dose combination treatment completed a survey after trial completion. Most respondents considered fixed dose combination treatment satisfactory or very satisfactory for starting treatment (206/227, 91%), blood pressure control (180/220, 82%), cholesterol control (170/218, 78%), tolerability (181/223, 81%), and prescribing according to New Zealand guidelines (185/219, 84%). Fifty seven per cent (127/221) of participants' general practitioners reported improved treatment adherence to be the most important advantage of fixed dose combination treatment, whereas for 37% (82/221) of participants' general practitioners lack of flexibility was cited as the most important disadvantage (see web extra appendix on bmj.com). Ninety per cent (203/225) of participants' general practitioners stated that if they had another patient like this they would start them on fixed dose combination treatment if it were available.

Discussion

This primary care based trial found that access to fixed dose combination treatment containing aspirin, statin, and two blood pressure lowering agents led to improved adherence to the recommended combination of drugs, with high acceptability to general practitioners and patients. The estimated improvement in adherence from self report was replicated almost exactly by dispensing data, and persisted although it was attenuated after a median follow-up of 23 months. Risk factor control showed no statistically significant improvement with fixed dose combination treatment. The apparent discrepancy between adherence and risk factor outcomes is likely to be because treatment rates with individual treatment modalities were already high in usual care, so there was little room for improvement. For example, table 4⇓ shows that since 91% of usual care patients received some blood pressure lowering drugs, even the 30% absolute increase in those receiving combination blood pressure lowering treatment and the 5% increase in those receiving any blood pressure lowering in the fixed dose combination treatment group, would only be expected to result in a 2.8 mm Hg difference in mean systolic blood pressure.[23] This expected effect is closely consistent with what was observed in the trial.

Discontinuation of fixed dose combination treatment averaged 20% per year, similar to that seen in two other long term trials.[10 11] Of the 94 participants who discontinued treatment, a main reason was available for 75 participants, and of these, the reason given for stopping was a possible side effect for 54 (72%) and requirement for better risk factor control for five (7%). Possible factors contributing to the discontinuation rate were lack of variety in the components and dosages of fixed dose combination treatment (such as a version with an angiotensin receptor blocker for patients who develop cough) and unfamiliarity with fixed dose combination treatment and the trial itself of doctors not part of the trial, such as those who treated participants during hospital or outpatient visits. Despite the level of discontinuation, the fixed dose combination treatment group had better overall adherence to drugs.

There was no clear difference in the number of participants with serious adverse events, overall or for specific organ systems. An excess of reported serious adverse events occurred in some categories: hypotension (fixed dose combination 6 *v* usual care 0, P=0.01), bleeding (4 *v* 0, P=0.06), and macroalbuminuria (12 *v* 4, P=0.04), but the absolute excesses were small. Presumably these findings were at least in part due to the higher use of blood pressure lowering drugs and aspirin in the fixed dose combination group.

Despite general practitioners indicating that their main concern with fixed dose combination treatment was the reduced ability to individualise treatment, the trial showed that this did not lead to a worsening in risk factor control when compared with a relatively high standard of usual care.

Strengths and limitations of this study

A major strength of this trial is that it tested the strategy of fixed dose combination treatment in a pragmatic primary care setting. Participants were recruited by their usual general practitioner who retained responsibility for the participant's medical care, including prescribing fixed dose combination treatment; the treatment was dispensed by community pharmacists, with copayments made exactly as if the product were available as a government subsidised agent on the market.

The trial had only moderate statistical power and hence could not rule out either small increases or moderate decreases in risk factor levels. In addition, only a small number of clinical events were observed. Furthermore, despite our efforts to evaluate typical usual care, treatment rates were much higher than national figures: at trial entry 82% (191/233) of participants with established cardiovascular disease were taking an antiplatelet, statin, and at least one blood pressure lowering agent, compared with 59% nationally.[5] Hence, there was limited ability to test this fixed dose combination treatment strategy among the significant number of patients currently taking little or no preventive drugs, who are most in need of strategies to improve adherence.[4 24]

The open label trial design was unavoidable but raises the possibility of differential intensity of treatment, diagnosis, or adverse event reporting between the groups. Pill counts or electronic pill bottles may have enabled a more objective assessment of adherence during the trial, but their cost and inconvenience for participants (which may in and of itself have affected adherence) ruled them out of the trial; besides, we found self reported adherence to be highly concordant with dispensing data. Conversely, the open label nature of the trial enabled assessment of whether knowledge of receiving the polypill reduced participation in lifestyle activities, which has been cited as a risk: we observed no differences in participation.

Comparison with other studies

Our findings are consistent with those of the UMPIRE[11] and Kanyini-GAP[10] trials, which used a similar protocol and tested the same fixed dose combination treatment. The trials had similar point estimates and overlapping confidence intervals

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for primary outcomes despite differences in setting (UMPIRE recruited from secondary care), geography (in UMPIRE, half of the participants were from Western Europe and half from India), and access to fixed dose combination treatment (dispensed by trial centre free of charge in UMPIRE). This suggests the main findings have broad generalisability. In all trials, treatment effects were greatest among patients not taking all recommended treatments at baseline.

No other long term data are yet available from other randomised controlled trials of fixed dose combinations containing aspirin, statin, and blood pressure lowering agents,[9] although the FOCUS trial[25] will report soon. Long term data are available for statin-blood pressure lowering agent combinations: the CRUCIAL trial compared access to Caduet (amlodipine 5-10 mg with atorvastatin 10-20 mg) with usual care in patients at high risk of cardiovascular disease with no history of coronary heart disease in a mixture of primary and secondary care settings. The results indicated improved blood pressure and low density lipoprotein cholesterol levels in patients with the combination,[26] but the size of these benefits is uncertain owing to baseline imbalance in the cluster randomised design. Another cluster randomised trial, STITCH-2, compared usual care with a simplified regimen, including increased access to Caduet and several blood pressure lowering drug combinations.[27] Overall, blood pressure decreased but not low density lipoprotein cholesterol levels.

Implications of findings and future research

Our results support the potential usefulness of fixed dose combination based care in people at high risk of cardiovascular disease, particularly in the large group currently receiving few recommended cardiovascular preventive drugs. Current guidelines recommend concomitant use of aspirin, statin, and blood pressure lowering agents in several high risk patient groups. For example, guidelines from the National Institute for Health and Care Excellence recommend that all patients with coronary heart disease receive aspirin, statin, angiotensin converting enzyme inhibitor, and β blocker.[28] Yet many patients in high income countries, and most in low income countries, do not receive such treatment long term.[4]

Given that the trial results show that fixed dose combination based care is approximately the same as usual care in a high income country such as New Zealand, acceptability and cost effectiveness are particularly important for the implications in such settings. This trial showed high levels of acceptability to patients, the importance of which is increasingly recognised.[29] There was also high acceptability for prescribers. A full economic analysis is required, but in terms of expenditure on drugs, cost savings can be expected in these settings. Reimbursers typically set the price of such combinations at or just under the sum of the costs of the separate drugs, which are now all available at low cost. Hence cost savings can be expected as a result of the higher average costs of usual care drugs (which included on-patent and more expensive drugs) and additional dispensing costs.

A prospective individual participant meta-analysis of three sister trials will be conducted to assess the consistency of effects on primary outcomes across different populations, and to measure the effects on cardiovascular outcomes.[17] Beyond this, implementation research to identify cost effective, acceptable options for increasing the use of fixed dose combination treatment in patients currently receiving little or no treatment is a research priority. Further pragmatic trials, such as IMPACT, are needed that are set in primary care and emulate local cardiovascular disease risk management, prescribing, and dispensing practices.

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What is already known on this topic

Fixed dose combinations containing aspirin, statin, and blood pressure (BP) lowering drugs confer broadly the same short term risk factor reductions to be expected from separate components

Two recent long term trials indicate large improvements in self reported adherence to recommended drugs and modest improvements in risk factor control in high risk patients

What this study adds

Fixed dose combination treatment improved adherence to all the recommended drugs, but improvements in clinical risk factors were small and did not reach statistical significance

With usual care treatment rates for antiplatelet, statin, and blood pressure lowering drugs each over 80%, there was relatively little room for improvement with fixed dose combination treatment

There were high levels of acceptability for fixed dose combination treatment among general practitioners and patients alike, although the discontinuation rate was high

Pharmacy 44 Ltd Rotorua, Ranui Pharmacy, Roberts Ngaruawahia Pharmacy, Seddon Street Pharmacy Pukekohe, Southmall Pharmacy Manurewa, Te Kohao Health Nga Hua Pharmacy Hamilton, Thorntons Pharmacy Avondale, Tuakau Amcal Pharmacy, Turuki Pharmacy Mangere, Unichem Guys Pharmacy Papakura, Unichem Pharmacy Manurewa, Waiuku Medical Pharmacy, and Westview Care Chemist Glen Eden.

Contributors: AR and NR had the initial idea for the trial. The trial was initially designed by AR, NR, BA, DB, Jennie Connor, Robert Cook, SC, RND, Valery Feigin, RJ, Tim Maling, RM, Bruce Neal, Anushka Patel, David Simmons, and Stephen Vander Hoorn. Additional contributions to trial design were made by VS, CRE, AW, and MH. The statistical analysis plan was written by Stephen Vander Hoorn, AR, and CRE. The trial was implemented by AW, VS, CRE, SC, MH, CB, Avinesh Pillai, and NR. Data collection tools were initially designed by VS, NR, AR, SC, Valery Feigin, Stephen Vander Hoorn, and Andrew Jull. Additional contributions to the design of data collection tools were made by CRE, MH, and AW. AW, VS, CRE, Avinesh Pillai, and CB monitored data collection. VP and VS analysed the data. VS wrote the first draft of the paper. AR and CRE made substantial contributions to revisions. All coauthors reviewed and provided feedback on the paper. CB is guarantor for the paper.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Support for the submitted work: project grants from the New Zealand Health Research Council, the National Heart Foundation of New Zealand, the New Zealand Lotteries Grants Board, the Elsie Shrimpton Fund (University of Auckland), PHARMAC (New Zealand's Pharmaceutical Management Agency), Te Kupenga Hauora Māori (University of Auckland), Auckland regional district health boards (Auckland, Counties Manukau, and Waitemata), the Faculty Research Development Fund (University of Auckland), and the Auckland Medical Research Foundation. The Health Research Council was the trial sponsor. VS is, and NR was, a National Heart Foundation of New Zealand research fellow. AR was a National Heart Foundation of New Zealand senior fellow during the course of the trial. The George Institute for Global Health (employer of AR) has received a grant from Dr Reddy's Laboratories Limited (DRL), Hyderabad, India for the SPACE collaboration coordinating centre (www.spacecollaboration.org), which provides academic and administrative support to achieve collaboration between this and two other clinical trials involving fixed dose combination treatment provided by DRL free of charge. RND holds the New Zealand Heart Foundation chair of heart health. No financial relationships with any organisations that might have an interest in the submitted work in the previous three years. Other relationships or activities that could appear to have influenced the submitted work: The George Institute for Global Health (employer of AR) recently secured an exclusive global license for the fixed dose combination treatment used in this trial after a decision by DRL not to proceed with taking the products to market because of existing regulatory requirements. VS, CRE, AW, NR, and AR received reimbursements for travel and accommodation from DRL to attend international collaborative meetings on fixed dose combination treatment, but have no financial interest in this product. VS received reimbursement for travel from the George Institute for Global Health to attend an international collaborative meeting on fixed dose combination treatment. NR received reimbursement for travel from the George Institute for Global Health. MH is on the board of directors for the Health Research Council of New Zealand. BA is on the educational committee for PHARMAC (New Zealand's Pharmaceutical Management Agency) and its anti-infective agent advisory board. BA was on the primary care advisory board for the Future Forum from 2003 to 2008. This forum is funded by Astra-Zeneca (UK). DB is employed by the Waitemata District Health Board, which, along with other district health boards, contributed funding.

Ethical approval: The trial was conducted in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Ethical approval of the trial protocol and participant information documents was obtained from the New Zealand Northern X Regional Ethics Committee (NTX/06/06/072). Trial participants gave informed consent before taking part.

Data sharing: The IMPACT Steering Committee supports the policy of making relevant anonymised patient level data available on reasonable request. Requests should be directed via the principal investigator, CB (c.bullen@auckland.ac.nz).

Transparency: CB affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies

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Tables

Table 1| Baseline characteristics of study participants in fixed dose combination treatment and usual care groups. Numbers are means (standard deviations) unless stated otherwise

Characteristics	Fixed dose combination (n=256)	Usual care (n=257)
Age (years)	62 (8)	62 (8)
No (%) of Māori ethnicity	129 (50)	128 (50)
No (%) women	99 (39)	88 (34)
Systolic blood pressure (mm Hg)	143 (20)	145 (20)
Diastolic blood pressure (mm Hg)	83 (12)	83 (11)
Total cholesterol (mmol/L)	4.5 (1.0)	4.4 (1.0)
Low density lipoprotein cholesterol (mmol/L)	2.6 (0.8)	2.5 (0.8)
High density lipoprotein cholesterol (mmol/L)	1.2 (0.3)	1.1 (03)
Triglycerides (mmol/L)	1.6 (0.7)	1.6 (0.7)
Fasting glucose (mmol/L)	6.8 (2.4)	6.7 (2.3)
Glycated haemoglobin (%)	7.0 (1.5)	6.9 (1.5)
Median (interquartile range) urine albumin:creatinine ratio	1.2 (1-5.1)	1 (1-3.2)
Creatinine (μmol/L)	85 (45)	84 (23)
No (%) current tobacco smokers	73 (29)	81 (32)
Body mass index (weight (kg)/height (m)^2)	33 (7)	33 (7)
Median (interquartile range) moderate physical activity (mins in past week)	180 (1-420)	210 (20-420)
Median (interquartile range) vigorous physical activity (mins in past week)	0 (0-0)	0 (0-0)
Median (interquartile range) alcohol (standard units/wk)	0 (0-5)	0 (0-6)
Visual analogue scale for health state (EQ-5D)	80 (17)	78 (17)
No (%) with medical history:		
Coronary artery disease	89 (35)	97 (38)
Cerebrovascular disease	27 (11)	27 (11)
Peripheral vascular disease	11 (4)	8 (3)
Cardiovascular disease*	116 (45)	117 (46)
High cardiovascular risk†	135 (53)	136 (53)
Other high cardiovascular risk‡	4 (2)	4 (2)
Diabetes mellitus	113 (44)	105 (41)
No (%) with self reported adherence at baseline:		
≥1 blood pressure lowering drug	229 (89)	232 (90)
≥2 blood pressure lowering drugs	145 (57)	146 (57)
Statin	208 (81)	214 (83)
Antiplatelet	195 (76)	199 (77)
Recommended drugs§	107 (42)	116 (45)
Antiplatelet+statin+≥1 blood pressure lowering drug	167 (65)	174 (68)
No (%) in paid employment	117 (46)	112 (44)

*One or more of coronary, cerebrovascular, or peripheral vascular disease.

†Over 15% five year adjusted Framingham risk for cardiovascular disease, without previous cardiovascular disease.

‡Over 15% based on high blood pressure (>170/100 mm Hg) or genetic lipid abnormality as per New Zealand guidelines.

§Antiplatelet+statin+≥2 blood pressure lowering drugs.

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Table 2| **Differences in primary, secondary, and post hoc outcomes between fixed dose combination treatment and usual care groups**

Outcomes	Fixed dose combination (n=256)	Usual care (n=257)	Treatment effect* (95% CI)	P value
Primary outcomes†				
No (%) with self reported current use of antiplatelet, statin, and ≥2 BP lowering drugs at 12 months	208 (81)	119 (46)	1.75 (1.52 to 2.03)	<0.001
Mean (SD) change in BP over 12 months (mm Hg):				
Systolic BP	−4.5 (21.0)	−2.3 (18.1)	−2.2 (−5.6 to 1.2)	0.21
Diastolic BP	−2.1 (11.8)	−0.9 (11.2)	−1.2 (−3.2 to 0.8)	0.22
Mean (SD) change in LDL-C over 12 months (mmol/L)	−0.20 (0.73)	−0.15 (0.72)	−0.05 (−0.17 to 0.08)	0.46
Secondary outcomes‡				
Median (IQR) visual analogue scale for health state (EQ-5D) at 12 months	80 (65-90) (n=249)	80 (70-90) (n=248)	NA	0.23§
Median (IQR) visual analogue scale for health state (EQ-5D) at trial end	80 (60-90) (n=238)	80 (65-90) (n=241)	NA	0.96§
Mean (SD) change in total cholesterol over 12 months (mmol/L)	−0.16 (0.88) (n=246)	−0.09 (0.85) (n=247)	−0.07 (−0.22 to 0.08)	0.37
Mean (SD) change in high density lipoprotein cholesterol over 12 months (mmol/L)	0.04 (0.16) (n=246)	0.05 (0.17) (n=247)	−0.01 (−0.04 to 0.02)	0.52
Median (IQR) change in triglycerides over 12 months (mmol/L)	0.00 (−0.3 to 0.3) (n=246)	0.00 (−0.3 to 0.4) (n=247)	NA	0.66§
No (%) with self reported current use of antiplatelet, statin, and ≥2 BP lowering drugs at trial end	185 (72)	119 (46)	1.56 (1.34 to 1.82)	<0.001
Mean (SD) change in BP over trial duration (mm Hg):				
Systolic BP†	−5.9 (20.6)	−4.6 (20.9)	−1.3 (−4.9 to 2.3)	0.48
Diastolic BP†	−2.5 (11.9)	−1.9 (12.2)	−0.7 (−2.7 to 1.4)	0.54
Mean (SD) change in LDL-C over trial duration (mmol/L)†	−0.21 (0.68)	−0.16 (0.64)	−0.05 (−0.17 to 0.06)	0.35
Mean (SD) change in total cholesterol over trial duration (mmol/L)	−0.18 (0.80) (n=242)	−0.11 (0.79) (n=239)	−0.07 (−0.21 to 0.07)	0.35
Mean (SD) change in HDL cholesterol over trial duration (mmol/L)	0.04 (0.18) (n=242)	0.04 (0.16) (n=239)	0.00 (−0.03 to 0.04)	0.79
Median (IQR) change in triglycerides over trial duration (mmol/L)	0.00 (−0.3 to 0.4) (n=242)	0.01 (−0.3 to 0.4) (n=239)	NA	0.46§
Other (post hoc) outcomes				
No (%) dispensed antiplatelet, statin, and ≥2 BP lowering drugs at 12 months	196/249 (79)	117/248 (47)	1.67 (1.44 to 1.93)	<0.001
No (%) with self reported use of antiplatelet, statin, and ≥1 BP lowering drugs at 12 months	219/249 (88)	187/248 (73)	1.20 (1.10 to 1.31)	<0.001
No (%) with self reported use of individual components of combination treatment at 12 months:				
≥1 BP lowering drugs	240/249 (96)	226/248 (91)	1.06 (1.01 to 1.11)	0.02
≥2 BP lowering drugs	222/249 (89)	147/248 (59)	1.50 (1.34 to 1.68)	<0.001
Statin	233/249 (94)	220/248 (89)	1.05 (1.00 to 1.11)	0.06
Antiplatelet	231/249 (93)	205/248 (83)	1.12 (1.05 to 1.20)	0.0006
No (%) with self reported use of individual components of combination treatment at trial end:				
≥1 BP lowering drugs	227/242 (94)	221/242 (91)	1.03 (0.98 to 1.08)	0.30
≥2 BP lowering drugs	202/242 (83)	148/242 (61)	1.36 (1.22 to 1.53)	<0.001
Statin	222/242 (92)	213/242 (88)	1.04 (0.98 to 1.11)	0.18
Antiplatelet	218/242 (90)	196/242 (81)	1.11 (1.03 to 1.20)	0.005

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Table 2 (continued)

Outcomes	Fixed dose combination (n=256)	Usual care (n=257)	Treatment effect* (95% CI)	P value

BP=blood pressure; IQR=interquartile range; LDL-C=low density lipoprotein cholesterol; EQ-5D=quality of life; NA=not applicable.
Complete case analysis (missing data excluded) unless otherwise specified. N=256 (fixed dose combination) and n=257 (usual care) unless otherwise stated. Mean (or median) change are change between baseline and 12 months or end of follow-up. All continuous data are normal unless otherwise specified. Trial end was 12 months after the last participant was randomised.
*Relative risks for binary outcomes or difference in change between baseline and 12 months or end of follow-up for continuous outcomes; all results unadjusted.
†Intention to treat analysis.
‡Other prespecified secondary outcomes were adjudicated cardiovascular events (see web extra appendix on bmj.com), serious adverse events (table 3), and consumption of healthcare resources and cost effectiveness over one year (not reported here).
§Non-normal continuous data, therefore Mann-Whitney test used.

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Table 3| Serious adverse events (SAEs) reported in fixed dose combination and usual care groups during the trial

Event type	Fixed dose combination (n=256)	Usual care (n=257)	P value*
SAEs, by severity:			
Participants with at least one serious adverse event	99	93	0.56
Death	4	6	0.75
Admission to hospital	72	70	0.82
Other	44	32	0.13
Total No of SAE	158	127	0.07†
SAEs, by system organ class‡:			
Blood and lymphatic system disorders	1	0	0.50
Cardiac disorders	13	18	0.36
Ear and labyrinth disorders	1	0	0.50
Endocrine disorders	1	0	0.50
Gastrointestinal disorders	12	9	0.50
General disorders and administration site conditions	1	3	0.62
Hepatobiliary disorders	3	3	1.00
Infections and infestations	22	21	0.86
Injury, poisoning, and procedural complications	7	2	0.11
Metabolism and nutrition disorders§	6	1	0.07
Musculoskeletal and connective tissue disorders	14	10	0.40
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	14	7	0.12
Nervous system disorders	8	4	0.26
Psychiatric disorders	0	1	1.00
Renal and urinary disorders	40	32	0.30
Reproductive system and breast disorders	2	5	0.45
Respiratory, thoracic, and mediastinal disorders	4	6	0.75
Skin and subcutaneous tissue disorders	1	0	0.50
Vascular disorders¶	9	2	0.04

SAEs were any event that resulted in death, was life threatening, required admission to hospital or prolongation of existing hospital stay, resulted in persistent or major disability or incapacity, was a malignancy, was an overdose, or was any other important medical event (such as those that were to be adjudicated).

*χ^2 test (or Fisher's exact test when any cell counts <5), except where indicated.

†Incidence rate ratio 1.24 (95% confidence interval 0.98 to 1.57).

‡All diagnoses for each SAE were coded using the *Medical Dictionary for Regulatory Activities*. Diagnoses are presented at level of system organ class. Numbers represent number of participants with at least one SAE during the trial with a diagnosis in that system organ class.

§Metabolism and nutrition disorders among fixed dose combination participants: poorly controlled diabetes (n=3), hypoglycaemia (n=1), hyperkalaemia (n=1), post-stomal dehydration (n=1); metabolism and nutrition disorders among usual care participants: poorly controlled diabetes (n=1).

¶Vascular disorders among fixed dose combination participants: hypotension(n=6), aortic aneurysm(n=1), arterial insufficiency(n=1), arteriosclersosis(n=1); vascular disorders among usual care participants: intermittent claudication (n=1), hypertension(n=1).

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Table 4| Expected reductions in systolic blood pressure (SBP), by treatment group, and number of blood pressure (BP) lowering drugs being taken

	Fixed dose combination		Usual care		Difference between groups	
No of BP lowering drugs	No (%) of participants	Expected average reduction in SBP (mm Hg)*	No (%) of participants	Expected average reduction in SBP (mm Hg)*	Difference in % of participants	Expected average reduction in SBP (mm Hg)*
0	9 (4)	0	22 (9)	0	–5	0
1	18 (7)	8.7	79 (32)	8.7	–25	0
≥2	222 (89)	16.5	147 (59)	16.5	30	0
Overall	249 (100)	15.3	248 (100)	12.5	0	2.8

*Compared with no treatment, assuming average pretreatment SBP 150 mm Hg.[23] Value for participants receiving ≥2 BP lowering drugs taken as that for those receiving two drugs. Equal numbers of participants took ≥3 BP lowering drugs in each group.

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Figures

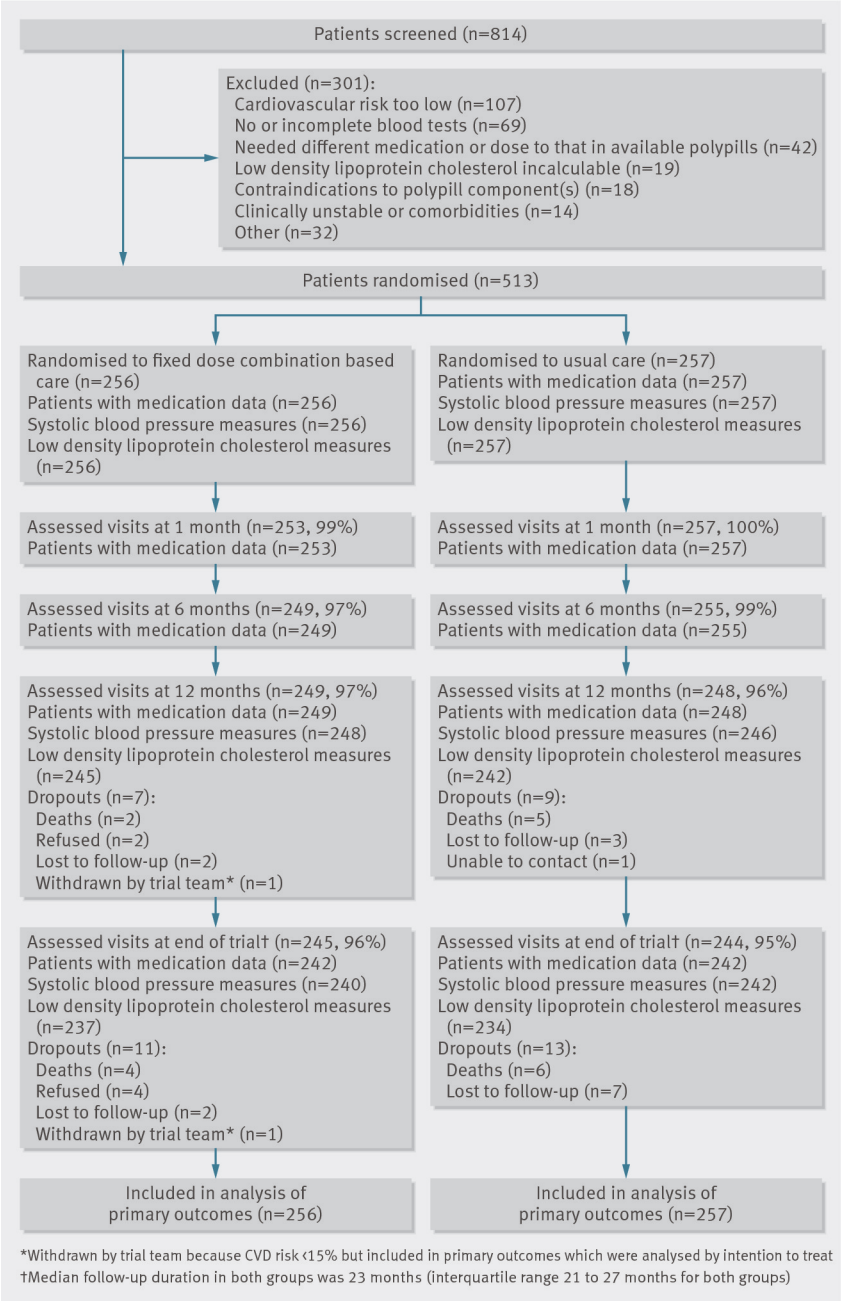

Fig 1 Flow of participants through trial. CVD=cardiovascular disease

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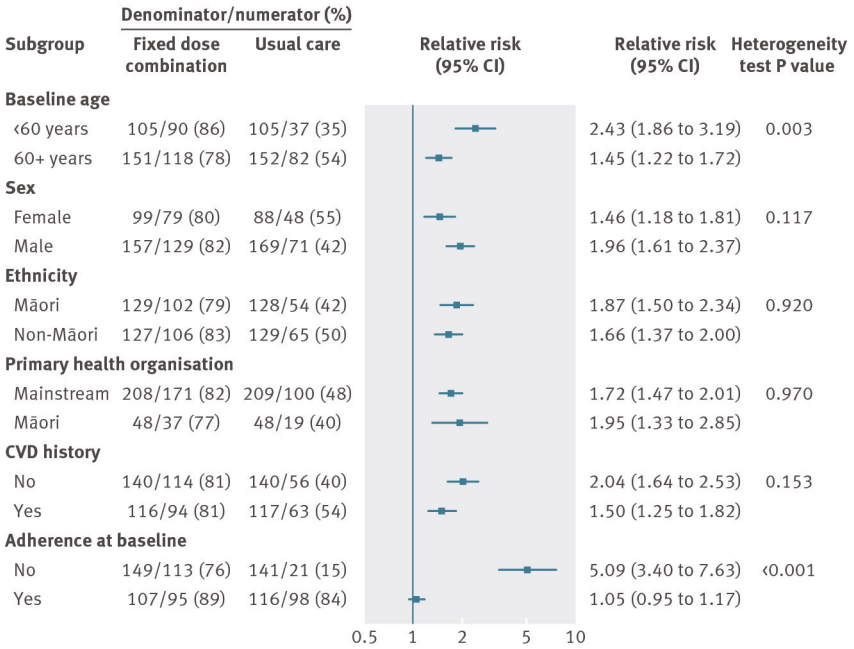

Fig 2 Self reported current use of antiplatelet, statin, and two or more blood pressure lowering drugs at 12 months by prespecified subgroups. CVD=cardiovascular disease

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