Title

Reaching cardiovascular prevention guideline targets with a polypill-based approach: a meta-analysis of randomized clinical trials

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Abstract

Objective

The aim of this study was to determine the effect of polypill-based care on the achievement of 2016 European Society for Cardiology (ESC) guideline targets for blood pressure (BP), low density lipoprotein cholesterol (LDL) and antiplatelet therapy.

Methods

We conducted an individual participant data meta-analysis of three randomized clinical trials that compared a strategy using a polypill containing aspirin, statin and antihypertensive therapy with usual care in patients with a prior CVD event or who were at high risk of their first event. Overall the trials included 3140 patients from Australia, England, India, Ireland, the Netherlands and New Zealand (75% male, mean age 62 years and 76% with a prior CVD event). The primary outcome for this study was the proportion of people achieving ESC guideline targets for BP, LDL and antiplatelet therapy.

Results

Those randomised to polypill-based care were more likely than those receiving usual care to achieve recommended targets for BP (62% vs 58%, risk ratio (RR) 1.08, 95% CI 1.02-1.15), LDL (39% vs 34%, RR 1.13, 1.02-1.25) and all three targets for BP, LDL and adherence to antiplatelet therapy (the latter only applicable to those with a prior CVD event) simultaneously (24% vs 19%, RR 1.27, 1.10-1.47) at 12 months. There was no difference between groups in antiplatelet adherence (96% vs 96%, RR 1.00, 0.98-1.01). There was heterogeneity by baseline treatment intensity such that treatment effects increased with the fewer the number of treatments being taken at baseline: for patients taking 3, 2 and 0-1 treatment modalities the risk ratios for reaching all three guideline goals simultaneously were 1.10 (0.94-1.30, 22% vs 20%), 1.62 (1.09-2.42, 27% vs 17%) and 3.07 (1.77-5.33, 35% vs 11%), respectively.

Conclusions

Polypill-based therapy significantly improved the achievement of all three ESC targets for BP, LDL and antiplatelet therapy compared with usual care, particularly among those undertreated at baseline.

Key questions

What is already known about this subject?

Polypill-based care has been shown to improve adherence, systolic blood pressure (BP) and low density lipoprotein cholesterol (LDL) levels compared with usual care among patients with cardiovascular disease (CVD) or at high risk of their first event.

What does this study add?

This study demonstrates that polypill-based care also resulted in an increase in the proportion of patients achieving guideline treatment targets for blood pressure (BP), low density lipoprotein cholesterol (LDL) and antiplatelet therapy, particularly for patients undertreated at baseline, and despite the use of more potent statins in the usual care group.

How might this impact on clinical practice?

This study adds weight to the growing evidence base supporting polypill-based care as an additional strategy to improve the implementation of guidelines for the prevention of CVD, particularly for undertreated patients.

Introduction

European Society for Cardiology (ESC) guidelines on the prevention of cardiovascular disease (CVD) recommend achievement of target blood pressure (BP) and lipid levels for people who have had a prior CVD event or who are at high risk of their first CVD event, along with antiplatelet therapy for people who have had a prior CVD event.[1] A recent cross-sectional survey of European patients with established coronary heart disease (EUROASPIRE IV) concluded that "*therapeutic targets for risk factors are not being achieved in far too many patients*" with 43% not achieving BP and 81% not achieving lipid targets.[2] Similar challenges are evident in other countries.[3] The ESC guidelines recommend that all targets be met simultaneously, thus a single pill containing aspirin, statin and BP lowering agents (a 'polypill') may assist by treating risk factors concurrently and enhancing uptake and adherence to guideline-recommended care.[3] Polypill-based care has been shown to improve adherence, systolic BP and low density lipoprotein cholesterol (LDL) compared with usual care among patients with CVD or at high risk of their first event.[5] No safety concerns beyond what would be expected given the component medications have been identified .[5] ESC guidelines on the management of acute myocardial infarction in patients presenting with ST-segment elevation recommend considering the use of a polypill to increase adherence to drug therapy.[4] The ESC guidelines on the prevention of CVD note that one gap in the evidence regarding the use of polypills is in whom polypill-based care would be the most effective.[3] The aim of this study was to determine whether these effects increase the proportion of patients who achieve targets recommended by the 2016 ESC guidelines on the prevention of CVD and, if so, in whom they would be most effective.[1]

Methods

This study uses data from the SPACE (Single Pill to Avert Cardiovascular Events) Collaboration individual participant data meta-analysis.[6] The protocol and main results of this meta-analysis have been previously described.[5, 6]

Contributing trials

The SPACE Collaboration includes three trials conducted during 2010 to 2013: IMPACT (n=513) with participants from New Zealand,[7] Kanyini-GAP (n=623) with participants from Australia[8] and UMPIRE (n=2,004) with participants from India, Ireland, The Netherlands and the United Kingdom (UK).[9] The three trials were planned, conducted and analysed collaboratively, and were based on the same protocol[10] with minor regional adaptations.[11, 12] All three trials used a randomised, open label, blinded endpoint design, and compared polypill-based care with usual care in individuals with established CVD or at high risk thereof. Individual participant data meta-analysis of the three trials was planned prospectively, although this current analysis was not pre-specified.[6]

Participants

Key inclusion criteria were (1) established atherothrombotic CVD or calculated 5-year cardiovascular risk of at least 15%,[13] and (2) all four components of at least one polypill version were indicated according to the participant's physician. In the UMPIRE trial, half the participants were from India and in the IMPACT and Kanyini-GAP trials, approximately half were indigenous peoples. Recruitment was from primary care clinics (Australia, New Zealand), hospital clinics (India), or a mixture of these clinics (Europe).

Randomisation

Participants were randomised 1:1 by central computer-based randomisation to polypill-based care or to continued usual care. Randomisation was stratified by recruitment site (Kanyini-GAP and UMPIRE) or Primary Health Organisation (IMPACT), presence of CVD at baseline (all trials), indigenous status (IMPACT), and whether participants were taking full combination therapy (antiplatelet, statin and ≥2 BP lowering agents) at baseline (IMPACT and Kanyini-GAP).

Intervention and control

Two polypills were available, both manufactured and supplied by Dr Reddy's Laboratories, Hyderabad, India. The choice of polypill was made by the participant's physician (within a primary care or hospital clinic), who indicated prior to randomisation the version they would use for that participant if they were randomised to the polypill group. The polypills were: *Polypill 1:* aspirin 75mg, simvastatin 40mg, lisinopril 10mg, atenolol 50mg; *Polypill 2:* aspirin 75mg, simvastatin 40mg, lisinopril 10mg, hydrochlorothiazide 12.5mg. Polypills were available from community pharmacies in IMPACT and Kanyini-GAP (with the usual co-payment of a subsidised medication) and were dispensed for free from trial clinics in UMPIRE (due to the requirements of the approving ethics committees). Both polypill and usual care groups were managed by the participant's physician (within primary care or hospital clinic) according to local clinical guidelines. Participants randomised to the polypill group could be prescribed additional antiplatelet, statin and BP lowering medication on top of the polypill, at the discretion of the treating physician.

Outcomes

The primary outcomes for this analysis were whether or not 2016 ESC guideline targets[1] for BP, LDL and antiplatelet therapy (separately or together) had been achieved for trial participants (Table 1). Outcomes were assessed at 12 months.

BP was measured using calibrated automated sphygmomanometers during study visits, and all recordings were printed and logged to ensure unbiased measurement. Two models of sphygmomanometer were used (Omron T9P in IMPACT and Omron 705CPII for Kanyini GAP and UMPIRE), both of which have been validated against protocols for both the European Society of Hypertension and the British Hypertension Society. Cholesterol was measured by community laboratories blind to participation in the trial and treatment allocation.

Participants in whom aspirin or an alternative antiplatelet drug are indicated according to 2016 ESC guidelines (i.e., those with established CVD) were regarded as having achieved the antiplatelet therapy treatment target if they self-reported adherence to an antiplatelet drug on at least four days in the preceding week. Direct measurement of antiplatelet adherence was not used in the trials because of its high cost and the intrusiveness and impracticality of this method of measurement in the primary care setting.[14] Indirect measurement of antiplatelet adherence can be obtained through self-report, which is a practical and valid way to measure adherence in clinical practice according to a review of measures of adherence.[15] Further, self-reported non-adherence has been associated with an increase in cardiovascular events in a cohort of patients with stable coronary heart disease.[16] The 2016 ESC guidelines do not recommend antiplatelet therapy in patients without established CVD. Therefore, participants at high risk but without established CVD were excluded from the analysis of the antiplatelet therapy treatment target, and for the analysis of the achievement of all three guideline targets for BP,

LDL and antiplatelet therapy simultaneously, only BP and LDL target achievement were considered.

Analyses

Analyses were performed on the combined SPACE Collaboration dataset using one-stage meta-analyses (i.e., individual participant data were pooled, then models run on the combined dataset).[17] Log-binomial regression with fixed treatment and random trial effects was used. This model was used to estimate the proportions of participants achieving targets and risk ratios (RRs) for the treatment. For comparison, we did the same analysis for the achievement of UK[18-22] and US[23, 24] guideline targets. We interpreted significance of the effect estimates after correction of p values for multiple comparisons of the targets within each guideline using the Holm-Bonferroni method, describing corrected $p < 0.05$ as statistically significant. Subgroup analyses were performed by adding a fixed effect for subgroup as well as a fixed interaction between the treatment effect and the subgroup of interest. Subgroups comprised the following at baseline: age group (≤62 years or >62 years, the mean age), sex, the number of medication modalities used (0, 1, 2 or 3 of antiplatelet, BP-lowering and statin therapy), use of all four indicated CVD medications (antiplatelet, statin and ≥2 BP-lowering medications; yes, no) and history of CVD (yes, no). Patients with missing data were excluded from analyses. For composite targets (i.e., those based on the achievement of more than one target), patients were classified as not having achieved the target if the target had not been met for any available target, even if data were not available for all targets contributing to the composite measure. All analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA), except for the Holm-Bonferroni correction procedure which was performed in Microsoft Excel 2016.

Results

Baseline characteristics

Data on 3140 participants, all those randomised in the three contributing trials, were available for analysis. Mean age was 62 years, 75% were male and 76% had established CVD.[5] Intervention and control groups were similar at baseline according to major characteristics (Table 2).[5]

Outcomes

Participants randomised to polypill-based care were more likely to achieve recommended ESC targets for BP (62% vs 58%, risk ratio, RR 1.08, 95% CI 1.02-1.15) and LDL (39% vs 34%, RR 1.13, 1.02-1.25) but not antiplatelet therapy (96% vs 96%, RR 1.00, 95% CI 0.98-1.01) when compared with those receiving usual care at 12 months follow-up (Table 3). The benefit of polypill-based care compared with usual care was more pronounced when considering simultaneous achievement of all three targets for BP, LDL and antiplatelet therapy at 12 months (24% vs 19%, RR 1.27, 1.10-1.47). The absolute achievement of all three targets simultaneously was modest in both groups. Similar relative benefits were observed for the effect of polypill-based care compared with usual care in the achievement of UK[18-22] and US[23, 24] guidelines (Appendix 1), as well as using a longer follow-up period (end of trial, median duration 15 months, Appendix 4).

Subgroup analyses

The effect of polypill-based care on the achievement of all recommended treatment targets simultaneously at 12 months was not significantly different according to age group, sex or history of CVD (Figure, Appendix 2). There was heterogeneity in the effect of polypill based

care compared with usual care on the proportion of participants achieving all recommended treatment targets at 12 months according to baseline treatment (either on the basis of the number of modalities of treatment (p=0.001), or whether or not all indicated medications were being used at baseline (p=0.002)). For patients taking 3, 2 and 0-1 treatment modalities the risk ratios for reaching all three guideline goals simultaneously were 1.10 (95% CI 0.94-1.30, 22% vs 20%), 1.62 (1.09-2.42, 27% vs 17%) and 3.07 (1.77-5.33, 35% vs 11%), respectively. Similar patterns were observed in subgroup analyses of the effect of polypill-based care compared with usual care on the achievement of UK (54% vs 47%, RR 1.13, 95% CI 1.05-1.22) and US (27% vs 22%, RR 1.20, 1.05-1.37) guideline targets (Appendix 3). While there was a wide range in the background rate of reaching all targets across the different guidelines, the absolute treatment effects from allocation to polypill-based care were broadly consistent, with NNTs of 20 for European and US, and 14 for US, guideline targets.

Discussion

This individual participant data meta-analysis of 3140 participants at high CVD risk found allocation to polypill-based care increased achievement of ESC targets for BP and LDL separately, and all three targets for BP, LDL and antiplatelet therapy simultaneously, when compared with usual care at 12 months. There was no difference between groups in antiplatelet adherence. The beneficial effect of polypill-based care compared with usual care on the proportion of participants achieving all three targets at the same time at 12 months was most pronounced among those receiving no treatment or only one treatment modality at baseline (34% vs 11%, RR 3.07, 1.77 to 5.33), which suggests this strategy is most likely to be best targeted to undertreated populations. Effects were similar when achievement of UK and US guidelines targets was assessed.

Despite the improvement in target achievement, only 24% of participants receiving polypill-based care (compared with 19% of those receiving usual care) achieved all three targets simultaneously at 12 months indicating large treatment gaps remained for guideline-recommended therapy. These low rates are primarily driven by low rates of achievement of the ESC LDL-based cholesterol target (39% vs 34%). It should be noted that in 2010, when the SPACE trials were initiated, target LDL levels were higher (e.g. 2.5 mmol/L for people with established CVD in the contemporaneous European guideline[25]). Absolute achievement of all three targets simultaneously at 12 months was much greater using the UK guidelines, which have a total cholesterol-based target (54% vs 47%).

A potential limitation of this study is the reliance on self-reported measurement of antiplatelet use, which risks bias due to inaccurate recall or social desirability[14] A post-hoc analysis of data from the IMPACT trial found a high level of agreement between self-reported aspirin use and dispensing data (kappa 0.75, 95% CIO 0.69 to 0.82).[26] Absolute estimates of aspirin adherence were higher from self-reported use than from dispensing data (77% vs 69%), although dispensing data may not have captured over-the-counter (non-dispensed) aspirin.[26]

This is the first study, to our knowledge, that has compared the effect of access to a polypill (containing statin, aspirin and blood pressure lowering medications) with usual care on the achievement of guideline-based treatment targets for CVD. A major strength of this study was that individual participant data from 3140 participants were available from three similar pragmatic clinical trials run in six countries. In addition, the large sample size enabled robust subgroup analyses. This study provides evidence directly relevant to clinical implementation, contrasting with trial designs in which participants are prescribed the same medications as separate pills in the usual care group. In addition, participants were recruited regardless of

baseline level or type of therapy, which again aids in assessment of treatment impact in real-life situations[27] and is of particular importance when assessing the potential role of a polypill in reducing treatment gaps.

The SPACE trials were designed to compare the efficacy of a polypill-based approach with usual care among patients with indications for treatment. Blinding of participants and their physicians to treatment allocation was not possible. However, a number of strategies reduced the risk of bias associated with the open-label design, such as automated sphygmomanometers with printed recordings and community laboratories blind to participation in the trial for cholesterol measurement.

The rate of achieving all three LDL, BP and antiplatelet therapy targets in the usual care group in this trial population was broadly similar to that seen in the EUROASPIRE[2] and Survey of Risk Factors (SURF)[28] surveys (6722, 66%, of participants from Europe). For individual BP, LDL and antiplatelet goal achievement among participants with CVD, we observed 63%, 27% and 96% respectively in the usual care group at 12 months, while EUROASPIRE[2] observed 57%, 20% and 94%,[2] and SURF[28] observed 60%, 30% and 90%. There are relatively few data on the rates of people reaching all three goals simultaneously elsewhere in the literature. Kerr et al reported that 59% of the New Zealand population with CVD were receiving BP-lowering therapy, statin and an antiplatelet.[29] This compares with 76% receiving all three modalities in the SPACE trial population at baseline. These results, together with the consistency of treatment effects in terms of improved adherence across diverse geographic regions[5] suggest these findings have important clinical relevance.

The improvements seen here were achieved with two polypill versions containing no dose options. They also contained simvastatin (which was off patent when the trials were designed); more potent statins such as atorvastatin and rosuvastatin were used more commonly in the usual care group. Future research in polypill-based care should use newer polypills encompassing more dose versions and/or more potent components, as this may lead to greater achievement of treatment targets,[30] particularly those of the most recent US cholesterol guideline, which are based on the intensity of statin therapy as opposed to cholesterol levels.[31]

Although this study assesses achievement of European guidelines, along with those from the UK and US, our findings are applicable to, and have implications for, low and middle income countries. Generally, guidelines from these countries propose similar targets with respect to blood pressure and lipid levels. For example, guidelines from India and Malaysia recommend a target LDL of less than 1.8 mmol/L and BP of less than 140/90 mmHg among people with established CVD.[32, 33]

In addition to supporting the achievement of treatment targets, there is evidence that polypill-based care is preferable to treatment with separate medications for other reasons. In the TEMPUS crossover trial, treatment with the polypill was preferred by 92% of participants compared to treatment with separate medications.[34] Given the increasing recognition of the importance of patient experience and preference to the delivery of high value cardiovascular care,[35] patient preference for polypill-based care needs to be considered alongside other benefits of polypill-based care such as improvements in adherence,[5] risk factor levels[5] and the achievement of treatment targets.

A systematic review and meta-analysis by Santo et al, assessing interventions to improve medication adherence in patients with coronary heart disease (CHD), found that simple interventions to improve adherence to multiple CVD medications, such as a polypill, significantly improved the odds of being adherent.[4] Further, there was no significant difference in the improvement in adherence whether the intervention was simple or complex (two or more components).[4] The reviewers concluded that "simple one-component interventions might be a promising way to improve medication adherence in a CHD population, as they would be easier to replicate in different settings and on a large scale".[4] However, recent trials that have assessed alternatives to polypill-based care (reminder devices either alone[36] or in combination with financial incentives and social support[37]) have found no statistically significant difference in adherence with usual care.

The ESC guidelines on the prevention of CVD have requested evidence regarding in whom polypill-based care would be most effective.[3] This study has demonstrated that polypill-based care resulted in an increase in the proportion of patients achieving treatment targets, especially those who are undertreated at baseline. Polypill-based care should therefore be prioritised in patients undertreated at baseline, particularly given the lack of alternative evidence-based and scalable solutions to address the global problem of suboptimal implementation of guidelines for the prevention of CVD**.**

Funding

RW is funded by an NHMRC early career fellowship. The authors have received grants from several research charities and national funding agencies for research on cardiovascular polypills, and from Dr Reddy's Ltd for co-ordination of the SPACE program (www.spacecollaboration.org). The polypills used in the SPACE trials were manufactured and supplied by Dr Reddy's Ltd free of charge. Some authors received funding from Dr Reddy's Laboratories Ltd to attend investigator meetings related to the polypill (VS, RW, AP, ST, CRE, NR, AW, AR). None of the funders or Dr Reddy's Laboratories Limited had any role in study design; the collection, analysis or interpretation of data; the writing of the article; or the decision to submit the article for publication. All authors are independent from trial funders. All authors accept full responsibility for the conduct of the study, had access to the data and controlled the decision to publish.

Acknowledgements

We acknowledge the contribution of the hundreds of collaborators and co-investigators who helped to undertake the IMPACT, Kanyini-GAP and UMPIRE trials, and the Steering Committees of each of these trials. We are indebted to the 3140 individuals who volunteered as participants in these trials.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare:

- Support for the submitted work: RW is funded by an NHMRC early career fellowship. The authors have received grants from several research charities and national funding agencies for research on cardiovascular polypills, and from Dr Reddys Ltd for co-ordination of the

SPACE program (www.spacecollaboration.org). The polypills used in the SPACE trials were manufactured and supplied by Dr Reddy's Ltd free of charge. Some authors received funding from Dr Reddy's Laboratories Ltd to attend investigator meetings related to the polypill (VS, RW, AP, ST, NR, AW, AR). George Health Enterprises, the social enterprise arm of The George Institute for Global Health (employer of some co-authors) has received investment for the development of fixed dose combination therapy containing statin, aspirin and blood pressure lowering medications.

- 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: CB has received fees from Te Arai Biofarma Ltd (speaker fees) and Boehringer Ingelheim NZ Ltd (speaker fees). BN has received funding from Janssen (grant and personal fees for trial conduct and reporting) and Actelion (for trial conduct). AT has received fees from Amgen (speaker fees, Advisory Board), Bayer (speaker fees, travel costs), Merck (Safety Monitoring Committee) and Sanofi (Advisory Board).

Declaration of Helsinki

Each SPACE trial complied with the Declaration of Helsinki. Local ethical and regulatory approval was obtained for each SPACE trial. Trial participants gave informed consent before taking part.

Authors' contributions

All authors are members of SPACE trial Steering Committees and as such made substantial contributions to the acquisition of the data for the work. R Webster is the co-ordinator, A Rodgers is the Chair and A Patel is the Deputy Chair of the SPACE Collaboration. Analyses were undertaken by S Stepien. The first draft of this paper was written by V Selak and all authors revised the article critically for important intellectual content. All authors provided final approval of the work to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Text tables

Table 1. 2016 European Society for Cardiology[1] targets for BP, LDL and antiplatelet therapy

Patient characteristics	BP target (mm Hg)	LDL target (mmol/L)	Antiplatelet recommended
CVD without DM	<140/90	<1.8	Yes
CVD with DM	<140/85	<1.8	Yes
No CVD but high risk & no DM	<140/90	<2.6	No
No CVD but high risk & DM	<140/85	<2.6	No

BP=blood pressure, LDL=low density lipoprotein cholesterol, CVD=cardiovascular disease, DM=diabetes mellitus

Table 2. Baseline characteristics of SPACE participants

Baseline characteristic	Polypill-based care N = 1569	Usual care N = 1571
Age, years (SD)	62.3 (10.6)	62.0 (10.9)
Female, n (%)	398 (25%)	381 (24%)
Blood pressure, mmHg (SD)		
Systolic	139.2 (20.8)	139.8 (21.0)
Diastolic	79.0 (12.1)	79.5 (11.9)
Lipid fractions, mmol/L (SD)		
Total cholesterol	4.2 (1.0)	4.3 (1.3)
High density lipoprotein cholesterol	1.1 (0.3)	1.1 (0.3)
Low density lipoprotein cholesterol (derived)	2.4 (0.9)	2.4 (0.9)
Triglycerides	1.6 (1.1)	1.6 (1.0)
History of symptomatic cardiovascular disease, n (%)	1192 (76%)	1204 (77%)
Coronary heart disease	1021 (65%)	1025 (65%)
Cerebrovascular disease	216 (14%)	231 (15%)
Peripheral vascular disease	92 (6%)	70 (5%)
Diabetes mellitus, n (%)	581 (37%)	542 (35%)
Treatment modalities, n (%)		
Statin	1339 (85%)	1333 (85%)
Antiplatelet	1359 (87%)	1360 (87%)
BP lowering	1423 (91%)	1429 (91%)
All three	1193 (76%)	1206 (77%)
Use of all indicated[a] medications, (%)	833 (53%)	880 (56%)

Achievement of European targets treatment targets		
Blood pressure	762 (49%)	729 (46%)
LDL	559 (36%)	493 (31%)
Antiplatelet[b]	1085 (91%)	1104 (92%)
Physician-intended polypill version prior to randomisation (if patient randomised to polypill)		
Polypill 1[c]	852 (54%)	866 (55%)
Polypill 2 [c]	717 (46%)	702 (45%)

BP=blood pressure, LDL=low density lipoprotein cholesterol, SD=standard deviation

[a]Statin, antiplatelet and ≥2 BP-lowering medications; all were indicated according to the participant's physician on trial entry

[b]Antiplatelet target only applicable to people with established cardiovascular disease

[c]Polypill 1: aspirin 75mg, simvastatin 40mg, lisinopril 10mg, atenolol 50mg; Polypill 2: aspirin 75mg, simvastatin 40mg, lisinopril 10mg, hydrochlorothiazide 12.5mg.

Table 3. Achievement of European treatment targets at 12 months

Target[a]	Polypill-based care		Usual care		RR[b] (95% CI)
	n/N (crude %)	Estimated[b] % (95% CI)	n/N (crude %)	Estimated[b] % (95% CI)	
BP	865/1393 (62%)	54% (44-67%)	776/1347 (58%)	50% (41 to 62%)	1.08 (1.02-1.15)*
SBP	919/1393 (66%)	60% (52-70%)	831/1347 (62%)	56% (48-66%)	1.07 (1.01-1.13)*
DBP	1183/1393 (85%)	80% (71-90%)	1092/1347 (81%)	75% (67-85%)	1.05 (1.02-1.09)*
LDL	524/1343 (39%)	43% (35-51%)	443/1294 (34%)	38% (31 to 46%)	1.13 (1.02-1.25)*
Antiplatelet[c]	1038/1086 (96%)	93% (88-98%)	1031/1078 (96%)	93% (89 to 98%)	1.00 (0.98-1.01)
BP and LDL and antiplatelet[c]	331/1377 (24%)	24% (22-26%)	252/1336 (19%)	19% (17 to 21%)	1.27 (1.10-1.47)*

BP=blood pressure, CI=confidence interval, DBP=diastolic BP, LDL=low density lipoprotein cholesterol, SBP=systolic BP, TC=total cholesterol

*$p<0.05$ after Holm-Bonferroni correction for multiple testing of targets within the same guideline

[a]see Table 1 for criteria

[b]Estimated proportions and risk ratios were obtained from a log-binomial regression model as described in the methods section

[c]Antiplatelet target only applicable to people with established cardiovascular disease

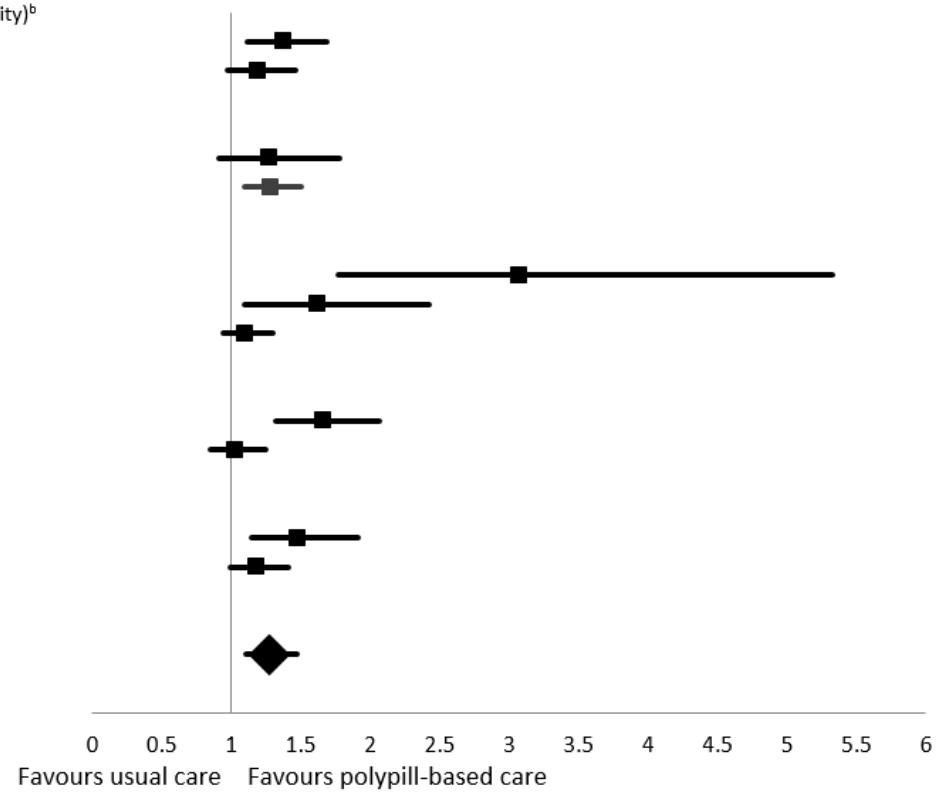
Figure legend

Figure. Achievement of all three treatment targets simultaneously at 12 months by subgroup

Figure

Figure. Achievement of all three[a] European treatment targets simultaneously at 12 months by subgroup

	Polypill-based care		Usual care			
	All 3 targets	Total	All 3 targets	Total	RR[a] (95% CI)	p value (heterogeneity)[b]
Age						
</= 62 years	167	691	117	663	1.37 (1.11-1.69)	
> 62 years	164	686	135	673	1.19 (0.97-1.46)	0.350
Sex						
Female	66	330	49	311	1.27 (0.91-1.78)	
Male	265	1047	203	1025	1.28 (1.09-1.50)	0.971
Number of treatment modalities at baseline						
0-1	42	121	14	124	3.07 (1.77-5.33)	
2	54	201	30	181	1.62 (1.09-2.42)	
3	235	1055	208	1031	1.10 (0.94-1.30)	0.001
Use all indicated[c] medications at at baseline						
No	172	635	95	581	1.66 (1.32-2.07)	0.002
Yes	159	724	157	755	1.03 (0.85-1.25)	
CVD history						
No	112	322	70	298	1.48 (1.15-1.91)	
Yes	219	1055	182	1038	1.18 (0.99-1.41)	0.151
Overall	331	1377	252	1336	1.27 (1.10- 1.47)	



CI=confidence interval, RR=risk ratio

[a]Statin, antiplatelet and ≥2 BP-lowering medications; all were indicated according to the participant's physician on trial entry

[b]RR and p value (heterogeneity) estimated from log-binomial regression model

[c]Antiplatelet target only applicable to people with established cardiovascular disease

Appendix 1- US and UK cardiovascular prevention guideline targets

Methods

Achievement of targets for US and UK guidelines for BP, cholesterol and antiplatelet therapy for trial participants at 12 months was assessed in the same way as for the European guidelines. For the US, targets were obtained from the eighth Joint National Committee (JNC8) for BP (<140/90 mm Hg, or <150/90 mm Hg for those aged >60 years)[1] and from the American Heart Association (AHA) / American College of Cardiology Foundation (ACCF) for low density lipoprotein cholesterol (<70 mg/dL [1.8 mmol/L; or non-high density lipoprotein cholesterol of <100 mg/dL [2.6 mmol/L]] for those with a prior event, otherwise <100 mg/dL [2.6 mmol/L]; or non-high density lipoprotein cholesterol of <130 mg/dL [3.4 mmol/L]) and antiplatelet therapy for secondary prevention.[2] The most recent US guideline for the treatment of cholesterol focuses on the appropriate intensity of statin therapy as opposed to target cholesterol levels.[3] UK targets were obtained from National Institute for Health and Care Excellence (NICE) guidelines (BP <140/90 mm Hg,[4] total cholesterol <5 mmol/L,[5] and antiplatelet therapy for secondary prevention.[6-8]

Results

Appendix 1 Table 1. Achievement of treatment targets by guideline at 12 months

Target	Polypill n/N (crude %)	Usual care n/N (crude %)	RR[a] (95% CI)
UK guidelines			
BP	887/1393 (64%)	794/1347 (59%)	1.08 (1.02-1.14)*
TC	1154/1371 (84%)	1062/1333 (80%)	1.06 (1.02-1.10)*
Antiplatelet	1038/1086 (96%)	1031/1078 (96%)	1.00 (0.98-1.01)
BP and TC and antiplatelet[b]	746/1393 (54%)	642/1352 (47%)	1.13 (1.05-1.22)*
US guidelines			
BP	1011/1393 (73%)	915/1347 (68%)	1.07 (1.03-1.13)*
LDL	513/1343 (38%)	430/1294 (33%)	1.14 (1.03-1.26)*
Antiplatelet	1038/1086 (96%)	1031/1078 (96%)	1.00 (0.98-1.01)
BP and LDL and antiplatelet[b]	370/1373 (27%)	298/1327 (22%)	1.20 (1.05-1.37)*
Non-HDL cholesterol	608/1364 (45%)	560/1323 (42%)	1.05 (0.96-1.14)

BP=blood pressure, CI=confidence interval, HDL=high density lipoprotein, LDL=low density lipoprotein cholesterol, RR=risk ratio, TC=total cholesterol

*$p<0.05$ after Holm-Bonferroni correction for multiple testing of targets within the same guideline

[a]RRs were obtained from a log-binomial regression model as described in the methods section

[b]Antiplatelet target only applicable to people with established cardiovascular disease

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Appendix 2- Subgroup analyses – European guideline targets

Appendix 2 Table. Achievement of all three[a] European treatment targets simultaneously by subgroup at 12 months

Subgroup		Polypill-based care		Usual care		RR[b] (95% CI)	p het[b]
		n/N (crude %)	Estimated[b] % (95% CI)	n/N (crude %)	Estimated[b] % (95% CI)		
Age (years)	</=62	167/ 691 (24%)	24% (21-28%)	117/ 663 (18%)	18% (15-21%)	1.37 (1.11-1.69)	0.350
	>62	164/ 686 (24%)	24% (21-27%)	135/ 673 (20%)	20% (17-23%)	1.19 (0.97-1.46)	
Sex	Female	66/ 330 (20%)	20% (16-25%)	49/ 311 (16%)	15% (12-20%)	1.27 (0.91-1.78)	0.971
	Male	265/ 1047 (25%)	25% (23-28%)	203/ 1025 (20%)	20% (18-22%)	1.28 (1.09-1.50)	
Baseline treatment modalities	0-1	42/ 121 (35%)	34% (27-44%)	14/ 124 (11%)	11% (7-18%)	3.07 (1.77-5.33)	0.001
	2	54/ 201 (27%)	27% (21-34%)	30/ 181 (17%)	17% (12-23%)	1.62 (1.09-2.42)	
	3	235/1055 (22%)	22% (20-25%)	208/1031 (20%)	20% (18-23%)	1.10 (0.94-1.30)	
Baseline use of all indicated[c] medications	No	172/ 635 (27%)	27% (24-31%)	95/ 581 (16%)	16% (14-20%)	1.66 (1.32-2.07)	0.002
	Yes	159/ 724 (21%)	21% (19-25%)	157/ 755 (21%)	21% (18-24%)	1.03 (0.85-1.25)	
CVD	No	112/ 322 (35%)	35% (28-43%)	70/ 298 (24%)	23% (18-30%)	1.48 (1.15-1.91)	0.151
	Yes	219/1055 (21%)	18% (15-23%)	182/1038 (18%)	16% (12-19%)	1.18 (0.99-1.41)	

CI=confidence interval, CVD=cardiovascular disease, het=heterogeneity (between subgroups), RR=risk ratio

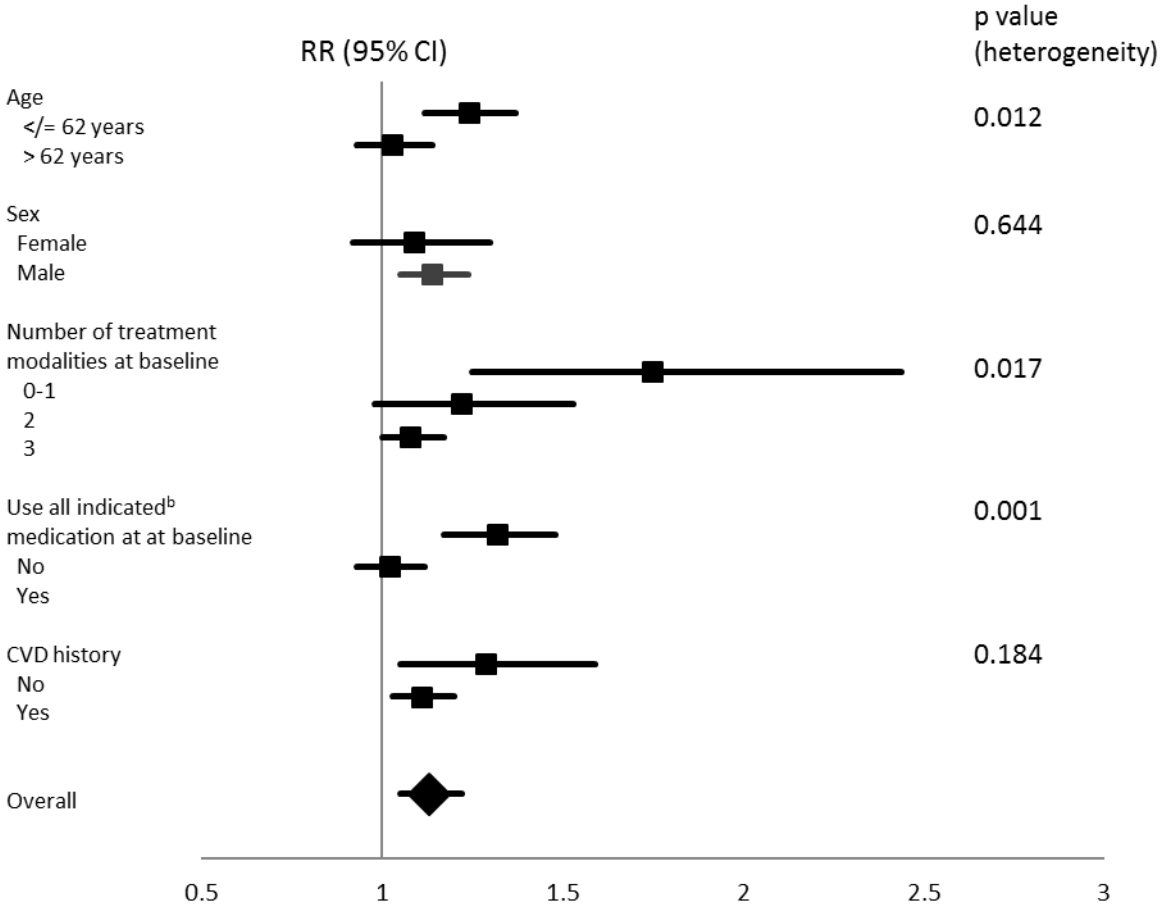
[a]Antiplatelet target only applicable to people with established cardiovascular disease

[b]Estimated proportions, RR and p het were obtained from a log-binomial regression model as described in the methods section of the main paper

[c]Statin, antiplatelet and ≥2 BP-lowering medications; all were indicated according to the participant's physician on trial entry

Appendix 3

Appendix 3 Figure 1. Achievement of all three[a] UK treatment targets simultaneously at 12 months by subgroup

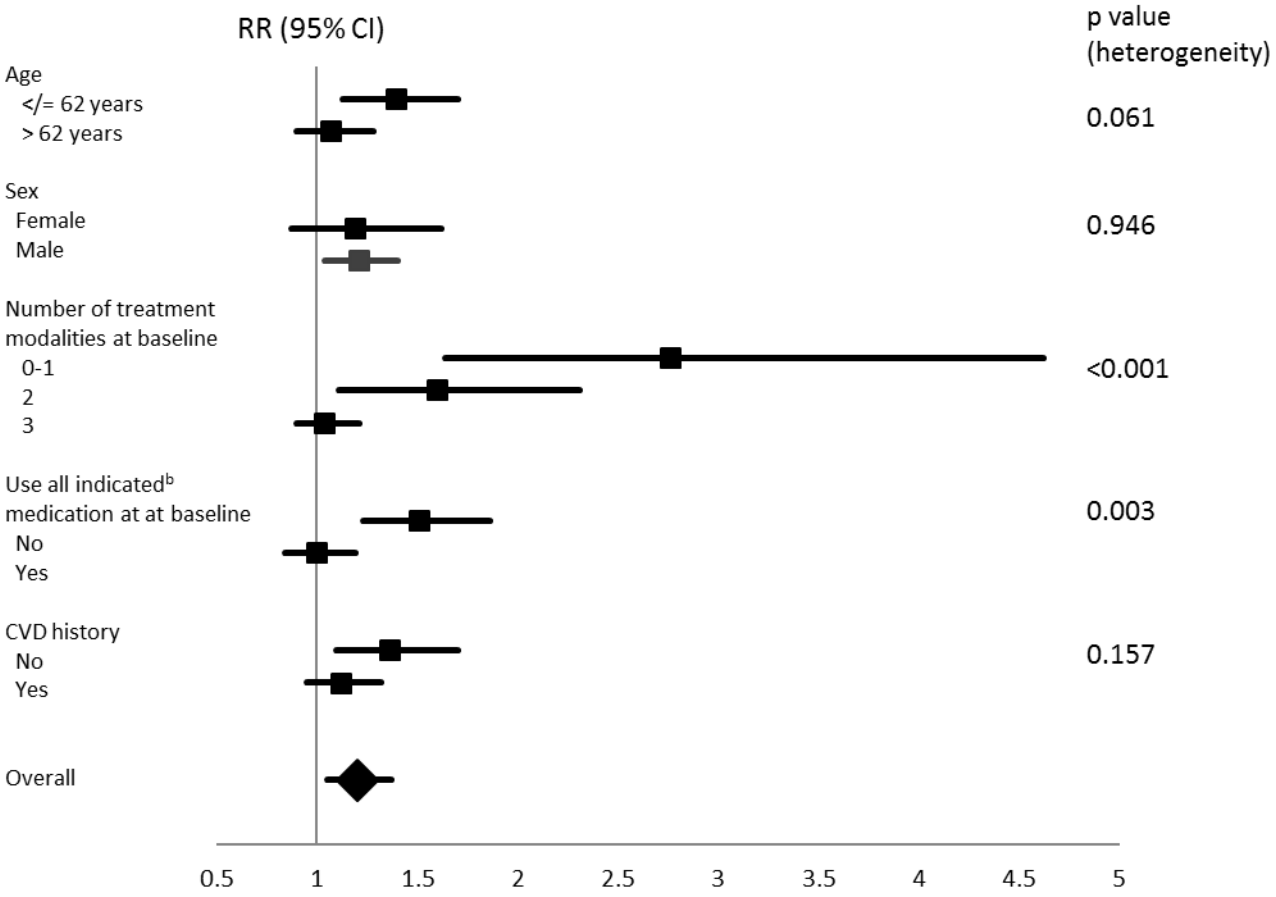


CI=confidence interval, RR=risk ratio

[a]Antiplatelet target only applicable to people with established cardiovascular disease

[b]Statin, antiplatelet and ≥2 BP-lowering medications; all were indicated according to the participant's physician on trial entry

*Appendix 3 Figure 2***.** Achievement of all three[a] US treatment targets simultaneously at 12 months by subgroup



CI=confidence interval, RR=risk ratio

[a]Antiplatelet target only applicable to people with established cardiovascular disease

[b]Statin, antiplatelet and ≥2 BP-lowering medications; all were indicated according to the participant's physician on trial entry

Appendix 3 Table 1. Achievement of all three[a] UK treatment targets simultaneously by subgroup at 12 months

Subgroup		Polypill-based care		Usual care		RR[b] (95% CI)	p het[b]
		n/N (crude %)	Estimated[b] % (95% CI)	n/N (crude %)	Estimated[b] % (95% CI)		
Age (years)	</=62	397/ 705 (56%)	49% (40-62%)	311/ 673 (46%)	40% (31-50%)	1.24 (1.12-1.37)	0.012
	>62	349/ 688 (51%)	44% (35-55%)	331/ 679 (49%)	43% (34-53%)	1.03 (0.93-1.14)	
Sex	Female	150/ 337 (45%)	41% (33-52%)	130/ 316 (41%)	38% (30-48%)	1.09 (0.92-1.30)	0.644
	Male	596/1056 (56%)	49% (40-60%)	512/1036 (49%)	43% (35-53%)	1.14 (1.05-1.24)	
Baseline treatment modalities	0-1	59/ 125 (47%)	44% (35-59%)	35/ 129 (27%)	26% (18-36%)	1.75 (1.25-2.44)	0.017
	2	100/ 202 (50%)	45% (36-57%)	74/ 184 (40%)	37% (28-48%)	1.22 (0.98-1.53)	
	3	587/1066 (55%)	48% (39-59%)	533/1039 (51%)	44% (36-54%)	1.08 (1.00-1.17)	
Baseline use of all indicated[c] medications	No	349/ 644 (54%)	49% (39-61%)	243/ 590 (41%)	37% (30-47%)	1.32 (1.17-1.48)	0.001
	Yes	397/ 749 (53%)	45% (36-56%)	399/ 762 (52%)	44% (36-55%)	1.02 (0.93-1.12)	
CVD	No	133/ 329 (40%)	40% (33-49%)	96/ 304 (32%)	31% (25-39%)	1.29 (1.05-1.59)	0.184
	Yes	613/1064 (58%)	51% (43-61%)	546/1048 (52%)	46% (39-55%)	1.11 (1.03-1.20)	

CI=confidence interval, CVD=cardiovascular disease, het=heterogeneity (between subgroups), RR=risk ratio

[a]Antiplatelet target only applicable to people with established cardiovascular disease

[b]Estimated proportions, RR and p het were obtained from a log-binomial regression model as described in the methods section of the main paper

[c]Statin, antiplatelet and ≥2 BP-lowering medications; all were indicated according to the participant's physician on trial entry

Appendix 3 Table 2 Achievement of all three[a] US treatment targets simultaneously by subgroup at 12 months

Subgroup		Polypill-based care		Usual care		RR[b] (95% CI)	p het[b]
		n/N (crude %)	Estimated[b] % (95% CI)	n/N (crude %)	Estimated[b] % (95% CI)		
Age (years)	</=62	177/ 691 (26%)	26% (23-29%)	122/ 660 (19%)	18% (16-22%)	1.39 (1.13-1.70)	0.061
	>62	193/ 682 (28%)	28% (25-32%)	176/ 667 (26%)	26% (23-30%)	1.07 (0.90-1.28)	
Sex	Female	73/ 329 (22%)	22% (18-27%)	57/ 306 (19%)	19% (15-24%)	1.19 (0.87-1.62)	0.946
	Male	297/1044 (28%)	28% (26-31%)	241/1021 (24%)	24% (21-26%)	1.21 (1.04-1.40)	
Baseline treatment modalities	0-1	43/ 121 (36%)	36% (28-45%)	16/ 124 (13%)	13% (8-20%)	2.76 (1.64-4.62)	<0.001
	2	61/ 201 (30%)	30% (25-37%)	34/ 179 (19%)	19% (14-26%)	1.60 (1.11-2.31)	
	3	266/1051 (25%)	25% (23-28%)	248/1024 (24%)	24% (22-27%)	1.04 (0.90-1.21)	
Baseline use of all indicated[c] medications	No	188/ 635 (30%)	30% (26-33%)	113/ 578 (20%)	20% (17-23%)	1.51 (1.23-1.86)	0.003
	Yes	182/ 738 (25%)	25% (22-28%)	185/ 749 (25%)	25% (22-28%)	1.00 (0.84-1.19)	
CVD	No	130/ 321 (41%)	41% (35-48%)	87/ 293 (30%)	30% (24-36%)	1.36 (1.09-1.70)	0.157
	Yes	240/1052 (23%)	22% (18-25%)	211/1034 (20%)	19% (16-23%)	1.12 (0.95-1.32)	

CI=confidence interval, CVD=cardiovascular disease, het=heterogeneity (between subgroups), RR=risk ratio

[a]Antiplatelet target only applicable to people with established cardiovascular disease

[b]Estimated proportions, RR and p het were obtained from a log-binomial regression model as described in the methods section of the main paper

[c]Statin, antiplatelet and ≥2 BP-lowering medications; all were indicated according to the participant's physician on trial entry

Appendix 4. Achievement of European treatment targets at end of study (median duration 15 months)

Target[a]	Polypill-based care		Usual care		RR[b] (95% CI)
	n/N (crude %)	Estimated[b] % (95% CI)	n/N (crude %)	Estimated[b] % (95% CI)	
BP	935/1460 (64%)	56% (46-69%)	848/1449 (59%)	52% (42 to 64%)	1.09 (1.03-1.15)*
SBP	975/1460 (67%)	60% (51-71%)	903/1449 (62%)	57% (48-67%)	1.06 (1.01-1.12)
DBP	1264/1460 (87%)	81% (71-91%)	1176/1449 (81%)	76% (67-86%)	1.06 (1.03-1.09)*
LDL	551/1388 (40%)	43% (36-50%)	510/1368 (37%)	40% (34 to 48%)	1.06 (0.96-1.16)
Antiplatelet[c]	1062/1139 (93%)	90% (84-95%)	1083/1151 (94%)	91% (86 to 97%)	0.98 (0.97-1.00)
BP and LDL and antiplatelet[c]	340/1437 (24%)	23% (20-26%)	297/1426 (21%)	20% (17-23%)	1.13 (0.99-1.30)

BP=blood pressure, CI=confidence interval, DBP=diastolic BP, LDL=low density lipoprotein cholesterol, SBP=systolic BP, TC=total cholesterol

*p<0.05 after Holm-Bonferroni correction for multiple testing of targets within the same guideline [a]see Table 1 for criteria

[b]Estimated proportions and risk ratios were obtained from a log-binomial regression model as described in the methods section

[c]Antiplatelet target only applicable to people with established cardiovascular disease