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Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences

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Aims The aim of this study was to determine the extent to which adherence to individual vascular medications, assessed by different methods, influences the absolute and relative risks (RRs) of cardiovascular disease (CVD) and all-cause mortality.

Methods and results We performed a systematic review and meta-analysis of prospective epidemiological studies (cohort, nested case–control, or clinical trial) identified through electronic searches using MEDLINE, Web of Science, EMBASE, and Cochrane databases, involving adult populations (≥18 years old) and reporting risk estimates of cardiovascular medication adherence with any CVD (defined as any fatal or non-fatal coronary heart disease, stroke or sudden cardiac death) and/or all-cause mortality (defined as mortality from any cause) outcomes. Relative risks were combined using random-effects models.

Forty-four unique prospective studies comprising 1 978 919 non-overlapping participants, with 135 627 CVD events and 94 126 cases of all-cause mortality. Overall, 60% (95% CI: 52–68%) of included participants had good adherence (adherence ≥80%) to cardiovascular medications. The RRs (95% CI) of development of CVD in those with good vs. poor (<80%) adherence were 0.85 (0.81–0.89) and 0.81 (0.76–0.86) for statins and antihypertensive medications, respectively. Corresponding RRs of all-cause mortality were 0.55 (0.46–0.67) and 0.71 (0.64–0.78) for good adherence to statins and antihypertensive agents. These associations remained consistent across subgroups representing different study characteristics. Estimated absolute risk differences for any CVD associated with poor medication adherence were 13 cases for any vascular medication, 9 cases for statins and 13 cases for antihypertensive agents, per 100 000 individuals per year.

Conclusion A substantial proportion of people do not adhere adequately to cardiovascular medications, and the prevalence of suboptimal adherence is similar across all individual CVD medications. Absolute and relative risk assessments demonstrate that a considerable proportion of all CVD events (~9% in Europe) could be attributed to poor adherence to vascular medications alone, and that the level of optimal adherence confers a significant inverse association with subsequent adverse outcomes. Measures to enhance adherence to help maximize the potentials of effective cardiac therapies in the clinical setting are urgently required.

Keywords Medication adherence • Cardiovascular disease

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Introduction

Medication adherence is defined as the extent to which a patient takes medications as prescribed by their healthcare providers.[1] Suboptimal adherence reduces the effectiveness of essential medications and has been highlighted as a significant obstacle in achieving better patient outcomes.[1–3] An earlier World Health Organization report described poor adherence as 'a worldwide problem of striking magnitude'.[4] Poor adherence itself though is a problem that should be viewed as 'diagnosable and treatable'.[5] The issue has a global relevance particularly in wealthier nations, where access and use of healthcare systems are high, and further increasing the effectiveness of a medication could rely largely on improving adherence levels.[6] For example, one in every two patients in developed nations do not adequately adhere to long-term therapies,[7] and 33–69% of all adverse medication reaction-related hospital admissions in the USA are due to poor medication adherence, with a resultant estimated annual cost of $100 billion.[8,9] Cardiovascular medications (such as statins,[10] antihypertensive,[11] and antithrombotic agents[12,13]) remain the most common medical interventions worldwide for both primary and secondary prevention of cardiovascular diseases (CVD), through modification of intermediate determinants of CVD. Suboptimal adherence to these commonly prescribed agents may contribute significantly to worsening of diseases and deaths at the population level.[14] One US study estimated that these medications alone might be responsible for half of the overall 50% reduction in mortality from coronary heart disease (CHD) observed over the past 20 years.[15] Although cumulative evidence from RCTs have established the efficacy of cardiovascular medications, adherence in patients taking these medications for both primary and secondary prevention of CVD was estimated at only 57% in a recent meta-analysis of almost 400 000 patients.[16] The relative and absolute risks of future adverse events associated with suboptimal adherence to these medications remain unclear. Such assessments are crucial as a better understanding of whether the levels of adherence and the associated risks vary importantly by subgroups (e.g. patient characteristics, adherence assessment approach, or medication types) may help shape clinical and public health strategies.

We report a systematic review and meta-analysis of available prospective studies to: (i) estimate the absolute risk differences for CVD for suboptimum adherence to cardiovascular medication and (ii) quantify future risks of CVD and all-cause mortality outcomes associated with good adherence to cardiovascular medication, separately by medication type, adherence assessment approach and other clinically relevant study characteristics.

Methods

Search strategy

This review was conducted using a predefined protocol and in accordance with the *PRISMA* and *MOOSE* guidelines[17,18] (Supplementary material online, *Appendices S1* and *S2*). We systematically identified studies published between January 1960 and 31 August 2012 (date last searched), without any language restriction, through electronic searches using MEDLINE, Web of Science, EMBASE, and Cochrane databases (*Figure 1* and Supplementary material online, *Appendix S3*). We used combinations of medical subject headings and free text words that included search terms related to the exposure (e.g. medication adherence, medication compliance, medication persistence) and medication groups (e.g. hydroxymethylglutaryl-CoA reductase inhibitors, antihypertensive agents, aspirin, adrenergic beta-antagonists, hypoglycaemic agents), which were combined with search terms related to the outcomes (e.g. cardiovascular diseases coronary artery disease, stroke, cerebrovascular, mortality). We identified articles eligible for further review by performing an initial screen of identified titles or abstracts, followed by a full-text review. Authors of the retrieved papers were contacted directly for additional tabular data when required. In the case of multiple publications, the most recent and complete report was included.

Selection criteria and data extraction

Two investigators independently assessed literature eligibility; discrepancies were resolved by consensus with a third investigator. Articles were considered for inclusion if the study (i) was a prospective study (cohort, nested case–control or clinical trial); (ii) involved an adult population ($\geq$18 years old); and (iii) reported risk estimates of cardiovascular medication adherence with any CVD (defined as any fatal or non-fatal CHD, stroke, or sudden cardiac death) and/or all-cause mortality (defined as mortality from any cause) outcomes. Two independent reviewers used a pre-designed structured database to collect relevant information from the selected studies. Collected information included the qualitative aspects of identified studies (e.g. publication date, design, geographic location, and population sources); participant profile (e.g. characteristics of the population at entry, total number, average age, gender, ethnicity, recruitment procedures, socioeconomic status, co-morbid conditions, and treatment regimens); characteristics of the exposure/intervention evaluated (definition of medication adherence, methods used to assess adherence and overall level of adherence); outcomes (e.g. measures of disease association, outcome type, and disease definition used); and statistical estimates (e.g. type of statistical analysis, measure of association, and adjustment variables employed).

Exposure assessment and statistical methods

Epidemiological studies have used a wide range of tools to assess medication adherence, which can be broadly classified as indirect or direct. Indirect assessments typically include patient questionnaires, self-reports, pill counts, rates of prescription refill etc., whereas direct methods include directly observed therapy and measurement of the levels of medicine/metabolite or a biological marker in the blood. To classify, where possible, the indirect assessments of adherence in a consistent way [e.g. medication possession ratio (MPR) and proportion of days covered (PDC)], all individual study methods were assessed systematically using standard definitions reported previously.[19] The majority of studies tend to employ indirect measures of adherence and categorize the medication use during the course of therapy into either 'good' or 'poor' levels of adherence. To allow consistent comparisons, we have harmonized these estimates using established methods,[20] to good (defined as $\sim \geq$ 80% adherence to CVD medications) and poor (less than 80%) medication adherence. This proportion, although somewhat arbitrary, has been accepted as the most conventional and widely reported cut-off for optimum adherence.[14]

We calculated absolute risk differences associated with poor adherence to cardiovascular medications by multiplying the background incidence rate of cardiovascular outcomes (CVD, CHD, or stroke) in the general European Union (EU) population[21] with (estimated RR−1). The RR was derived from this meta-analysis. Population attributable risk (PAR) was calculated based on the following equation: $PAR\% = 100 \times Pe(HR - 1)/(Pe[HR - 1] + 1)$,[22] for which the Pe, the prevalence of the exposure (poor adherence) in the population, and the hazard

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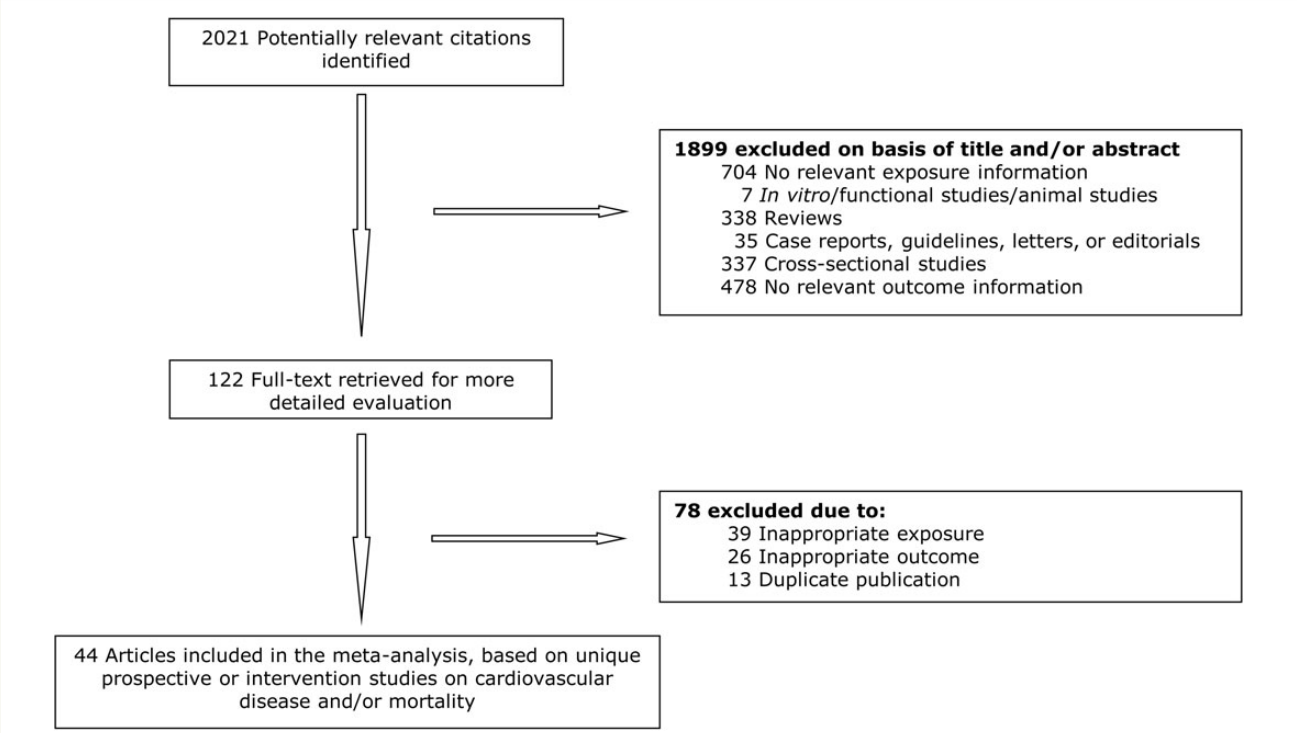

Figure 1 Search strategy for the studies included in current review.

ratios were both derived from the current meta-analysis. For these analyses, it is assumed that all participants within each study who were at high risk of CVD, either without pre-existing vascular disease (primary prevention) or with pre-existing vascular disease (secondary prevention), were offered preventive therapy. Hazard ratios and odds ratios were assumed to approximate the same measure of relative risk (RR, principal summary measure). Summary RRs were calculated by pooling the study-specific estimates for various vascular medication types (including statins, antihypertensive, aspirin, and antidiabetic agents) using a random-effects model that included between-study heterogeneity (parallel analyses used fixed-effect models). Heterogeneity of RR estimates across studies was evaluated by the I^2 statistic.[23] The possibility of publication bias was evaluated using the Begg test[24] and visual inspection of funnel plots. Heterogeneity at the level of individual studies was assessed by comparing results from studies grouped according to pre-specified study-level characteristics using the meta-regression technique. These subsidiary analyses included study characteristics (e.g. baseline population, location, study design, method employed to measure adherence, adherence threshold used and follow-up duration), analytical strategy (e.g. adjustment for socioeconomic variables, co-morbidities and use of multiple medications, i.e. 'poly pharmacy') and outcome types. All statistical tests were two-sided and used a significance level of $P < 0.05$. All analyses were performed using Stata release 11 (StataCorp, College Station, TX, USA).

Results

Literature search

A total of 2021 citations were retrieved from the electronic search (*Figure 1*). After initial screening based on titles and abstracts, 122 articles remained for further evaluation. In the full-text assessment, 44 of these articles (Supplementary material online, *Appendix S4*) met our inclusion criteria. Of the 78 excluded articles following full text evaluation, 39 were based on unrelated exposures, 26 reported on outcomes other than CVD or all-cause mortality, and 13 were duplicate publications.

Study characteristics

The characteristics of the studies included are summarized in *Table 1* and Supplementary material online, *Table S1*. Overall, data were available on 1 978 919 unique participants with 135 627 CVD and 94 126 all-cause mortality events collected over an average follow-up between 1 and 10 years. The average age of the participants was 63.1 years and 55% of the participants were male. Seventeen studies were based in Europe, 21 in North America, 3 in Asia-Pacific, and 3 were conducted in multiple countries. Overall, 25 studies recruited patients from healthcare registers, 9 from insurance databases, while 10 involved participants from clinical trial registers. Of these, 26 studies assessed adherence by pharmacy refill data based on the MPR(14 studies) or PDC (12 studies); 16 by other indirect measures including self-reports (6 studies); and 2 by direct measures (e.g. electronic monitoring systems or blood tests). The majority of the studies provided RRs for more than one medication (e.g. separate RRs for CVD for good adherence to statins and antihypertensives). Approximately half of these studies reported RRs of good adherence to individual medications, which were adjusted for other concomitant medications. Among the studies identified, 21 reported solely on CVD outcomes, 11 reported only on all-cause mortality and 12 reported on both outcomes.

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Table 1 Summary characteristics of the unique studies included in this review

	Studies		Participants	
	n[a]	%	*n*[a]	%
Eligible studies				
Total unique studies	44	100.0	1 978 919	100.0
Cohort	33	75.0	1 721 351	87.0
Nested case–control	8	18.2	222 160	11.2
Clinical trial	3	6.8	35 408	1.8
Average follow-up (years), (range)	3.2	(1.0–10.0)		
Participants				
Male (%), (range)	55.2	(0–100)		
Average age (years), (range)	63.1	(53.0–76.3)		
Location				
Europe	17	38.6	1 002 095	50.6
North America	21	47.7	920 373	46.5
Asia-Pacific	3	6.8	42 916	2.2
Multiple countries	3	6.8	13 535	0.7
Baseline population				
Healthy	2	4.5	95 266	4.8
Hypertensive	8	18.2	448 156	22.6
Hypercholesterolaemic	8	18.2	899 587	45.5
Diabetic	3	6.8	24 715	1.2
Known prior CVD	23	52.3	511 195	25.8
Population source				
Healthcare register	25	56.8	1 070 878	54.1
Insurance register	9	20.5	868 660	43.9
Clinical trial register	10	22.7	39 381	2.0
Medication group(s)				
Statins	15	34.1	1 253 748	63.4
Antihypertensives	14	31.8	470 452	23.8
Antiplatelet agents	2	4.5	11 068	0.6
Antidiabetic agents	2	4.5	1 112	0.1
Multiple vascular agents	11	25.0	242 539	12.2
Adherence measure				
Indirect measures	42	95.5	1 978 794	>99.9
MPR	14	31.8	1 018 802	51.5
PDC	12	27.3	661 668	33.4
Others	16	36.4	298 324	15.1
Direct measures	2	4.5	125	<0.1
Prevalence of good adherence				
To any CVD medication	34	77.3	1 230 382	62.2
Per cent (95% CI)	60	(52–68)		
Outcome events				
CVD events	33	75.0	135 627	6.9
Coronary heart disease	13	29.5	50 023	2.5
Stroke	7	15.9	6305	0.3
All-cause mortality events	23	52.3	94 126	4.8

[a]Results presented are for number of studies or number of participants unless otherwise specified.

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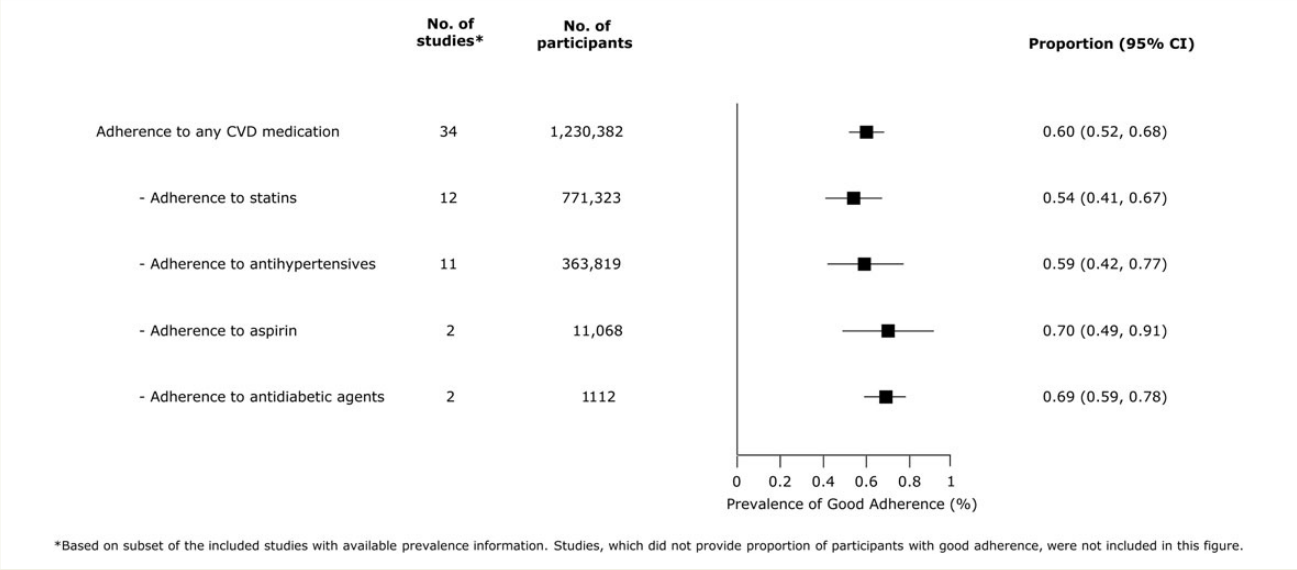

Figure 2 Prevalence (95% CI) of good adherence to cardiovascular medications among participants in prospective studies with available information.

Prevalence and determinants of good adherence

Data on the prevalence of good adherence were available in 34 studies (1 230 382 participants). In these studies, the overall prevalence of good adherence to CVD medications was 60% (95% 52–68) (*Figure 2*, Supplementary material online, *Figure S1*). The reported proportions of good adherence ranged from 4.9 to 93.3%, across studies and differed by medication type. Prevalence of good adherence was 54% (95% CI: 41–67) for statins (12 studies), 59% (95% CI 42–77) for antihypertensives (11 studies), 70% (95% CI 49–91) for aspirin (2 studies), and 69% (95% CI 59–78) for antidiabetic medications (2 studies) (Supplementary material online, *Figures S1* and *S2*). The key factors that predicted adherence rates in these studies were age, gender, comorbidity, and polypharmacy (Supplementary material online, *Table S2*).

Good adherence to individual cardiovascular therapy and adverse outcomes

Among 33 studies reporting on cardiovascular outcomes (1 615 126 participants and 135 627 CVD events), the combined RR (95% CI) for good adherence compared with poor adherence for any CVD medication was 0.80 (95% CI: 0.77–0.84) (*Figure 3*), with an I^2 estimate of 96.2% (Supplementary material online, *Figure S3*). Corresponding RRs were 0.85 (0.81–0.89), 0.81 (0.76–0.86), and 0.60 (0.31–1.16) for good adherence to statins, antihypertensive agents, and aspirin, respectively (*Figure 3* and Supplementary material online, *Figures S4* and *S5*). Only one study was identified in the literature search that assessed the association of clopidogrel with CVD independently of aspirin. The risk of CVD events was non-significant for both clopidogrel and aspirin in this study, but insufficient information was available to include the results in this meta-analysis.[25] In subsidiary assessments involving cause-specific CVD events, RRs were broadly similar for CHD and stroke outcomes for good adherence to statins and antihypertensive agents (Supplementary material online, *Figure S6*). In 23 studies with available data on all-cause mortality outcome (533 381 participants and 94 126 mortality events), the combined RR (95% CI) for good vs. poor adherence to any CVD medication was 0.62 (0.57–0.67) (*Figure 4*), with an I^2 estimate of 96.1% (Supplementary material online, *Figure S7*). Corresponding RRs (95% CIs) for all-cause mortality were 0.55 (0.46–0.67), 0.71 (0.64–0.78), and 0.45 (0.16–1.29) for good adherence to statins, antihypertensive agents, and aspirin, respectively (*Figure 4* and Supplementary material online, *Figures S8* and *S9*). There was no association between good adherence to antidiabetic medications and all-cause mortality (two studies, data not shown). Findings were broadly similar when using a fixed-effects model as subsidiary analyses.

Absolute risk difference associated with poor adherence

Using CVD estimates from the studies based on EU nations,[21] the corresponding absolute risk differences in the number of cases per 100 000 individuals per year associated with poor adherence were 13 cardiovascular cases for any CVD medication, 9 cardiovascular cases for statins, and 13 cardiovascular cases for antihypertensive agents. Similar calculations for the US population are presented in Supplementary material online, *Appendix S5*. Assuming the population prevalence of poor adherence to be 40% among patients who were prescribed CVD medications, 9.1% of all CVD events were attributable to poor adherence.

Assessment of heterogeneity and publication bias

The pooled estimates associated with good adherence to statin and antihypertensive medications remained largely unchanged when all

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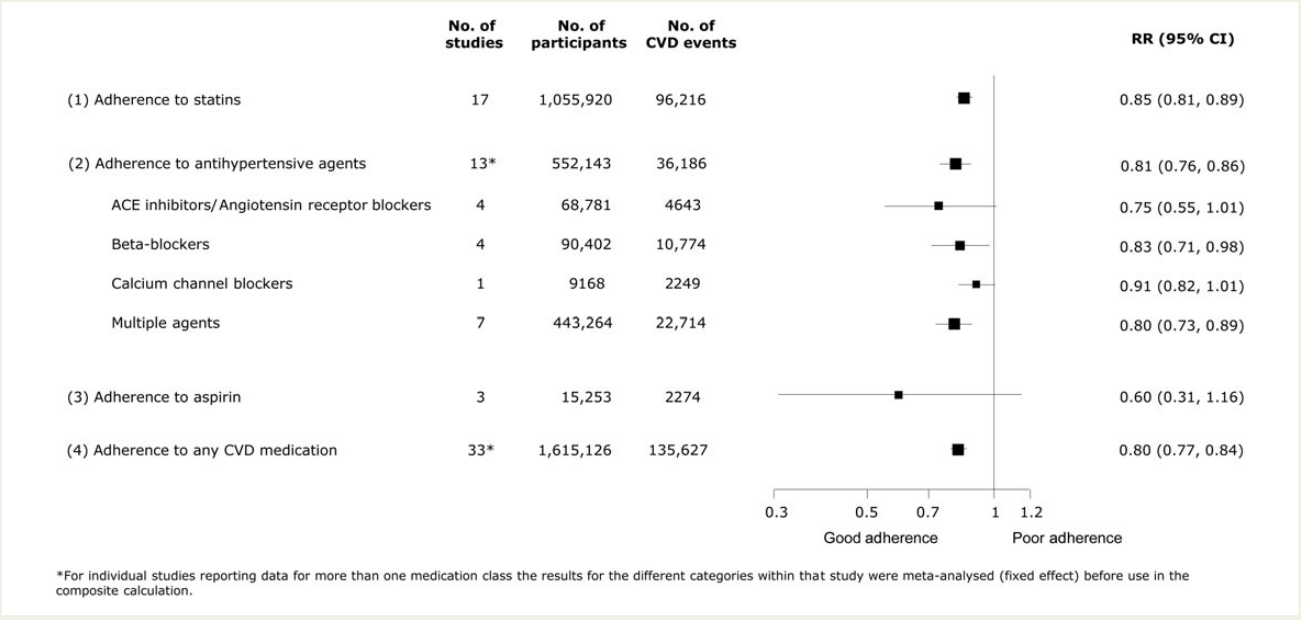

Figure 3 Relative risks for any cardiovascular disease in good vs. poor adherence to major cardiovascular disease medications.

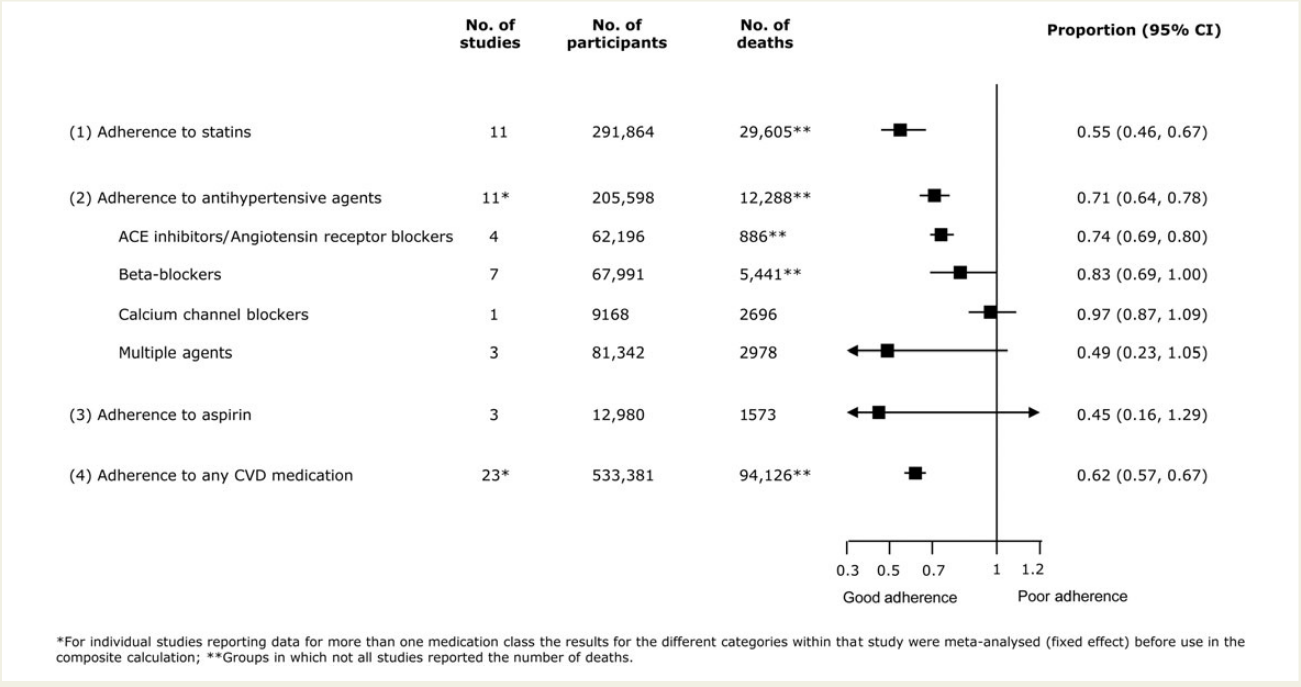

Figure 4 Relative risks for all-cause mortality in good vs. poor adherence to major cardiovascular medications.

included studies were grouped by various adherence measurement methods ($P_{heterogeneity}$ >0.05 for statins and antihypertensives, *Figure 5*). There was no material difference in the overall RRs among the studies according to the analytical approaches (i.e. studies that included socioeconomic status, polypharmacy, or co-morbid conditions in the multivariate models, vs. the ones that did not) and the clinical cut-offs used to define adherence ($P_{heterogeneity}$ >0.05, Supplementary material online, *Figures S10* and *S11*). Additionally, estimates were generally similar for study characteristics such as age, location, source of participants (trial vs. healthcare vs. insurance databases) and type of cohort (e.g. primary vs. secondary vs. mixed, see Supplementary material online, *Table S2*). There was no evidence of publication bias except for the studies reporting on adherence to statins and any CVD

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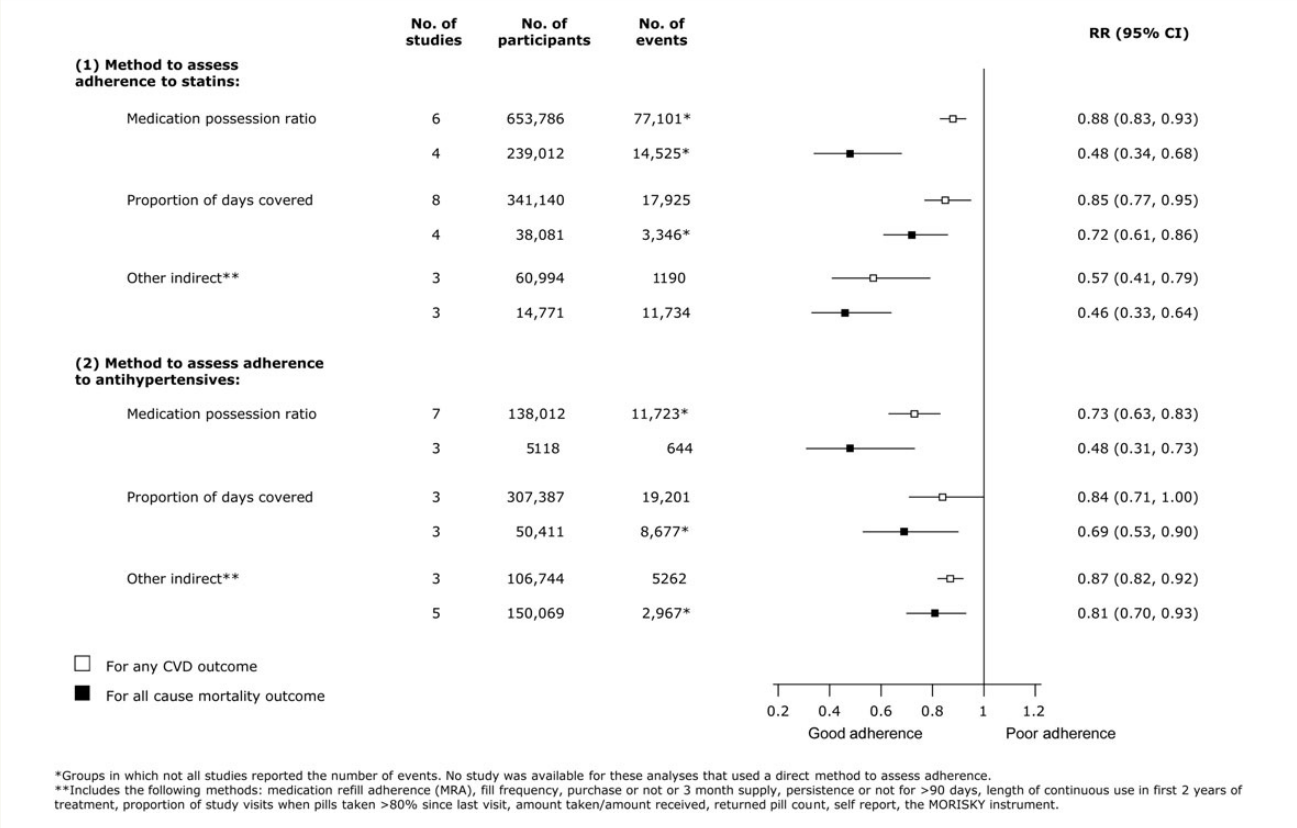

Figure 5 Relative risks of cardiovascular disease and all-cause mortality for good vs. poor adherence in prospective cohort studies, assessed by various indirect methods.

outcomes (P_{Begg} <0.05), which indicated a possible lack of publication of smaller studies reporting null or negative associations between statin adherence and CVD outcomes (Supplementary material online, *Figure S12*).

Discussion

Overall, based on available prospective cohort studies, we found that a substantial proportion of participants do not adequately adhere to cardiovascular medications, and the prevalence of such suboptimal adherence was high across all types of CVD medications. Using incidence rates from the general EU population,[21] the absolute risk difference associated with poor medication adherence to CVD medication was 13 per 100 000 CVD deaths per year, and ~9% of all CVD cases in the EU could be attributable to poor adherence. Furthermore, combining data from ~2 million participants indicates that good adherence to cardiac therapies could be associated with a 20% lower risk of CVD and a 35% reduced risk of all-cause mortality, irrespective of most clinically relevant patient and study characteristics.

Several factors may contribute to the low levels of good adherence to cardiovascular medications observed among the participants of the studies that we reviewed. Factors which significantly influenced adherence levels (in a subset of studies with relevant information) were low social status, low health literacy, existence of co-morbid conditions, and polypharmacy (Supplementary material online, *Table S3*). Other potential evidence-based promoters of non-adherence have been reported as no-fill of first prescription, irregular refills obtained, uncertainty about the effectiveness, prohibitive costs, and serious adverse events.[2] The proportion of study participants with good adherence to cardiovascular medications in this review (based on prospective studies from affluent settings) was very similar to a previous review,[26] which involved principally cross-sectional studies in resource-poor settings and reported this proportion as 57%. This perhaps reinforces the fact that suboptimal adherence is a problem of global dimensions. The most common predictors of poor adherence in this earlier report included poor knowledge, negative perceptions about medication, side effects, and cost.[26]

Favourable clinical consequences in those with good adherence levels to cardiovascular medications observed in our review may have several explanations. First, it is possible that adherence in these studies may simply be a surrogate marker of unmeasured confounders in these participants, with good adherence reflecting healthy behaviours or, conversely, co-morbidities such as depression contributing to poor adherence in participants.[27–29] This 'healthy adherer effect' has been examined in a number of studies; however, their results remain inconclusive. Rasmussen *et al.*[30] reported that outcome benefits were mediated principally by cardiovascular medication effects, whereas Curtis *et al.* [31] found that high adherence in the placebo arm of the Women's Health Initiative trial was associated with some favourable clinical outcomes including MI and all-cause mortality, yet not CHD death. Our subgroup

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analyses comparing studies that adjusted for socioeconomic variables and co-morbidities with studies that did not, also yielded no material difference in estimates. Nonetheless, despite the argued role of behavioural (or other unmeasured) attributes—the potential clinical benefits of good adherence to efficacious vascular medications are likely to be substantial and should not be underestimated. For example, it has been estimated that over a period of 4 years of statin use, a reduction of 1 mmol/L (39 mg/dL) in the level of low-density lipoprotein cholesterol translates into a 13% reduction in death from all causes.[32] This is of particular importance as the current widespread use of CVD medications (e.g. ~24 million statin[33] and 40 million antihypertensive users[34] in the USA alone) is expected to increase even further in the coming years as the world's population ages.[35] Secondly, a significant number of studies in this review were based on medication databases that used a wide range of definitions of adherence, based on which the level of adherence may vary substantially within the same population.[36] However, estimates from our subgroup analyses based on different measurement methods or cut-offs employed across studies were largely similar to the overall findings. Finally, an inability to adequately identify and address poor adherence to medications (e.g. antihypertensive agents) may result in intensified clinical measures with higher doses of medication—thereby increasing the risk of adverse effects,[37] misdiagnoses, unnecessary treatment and further worsening of pre-existing illnesses.[2]

Strengths and limitations of our review merit careful considerations. We have reported a comprehensive meta-analysis, based on 44 long-term prospective studies with aggregate adherence data on a wide array of CVD medications and >220 000 incident CVD and all-cause mortality events. We have conducted detailed assessments of risk according to different types of medications, cause-specific CVD outcomes, and by multiple patient and study-level characteristics. However, we were limited by the moderate amount of available data on medication subtypes (e.g. for statins or antidiabetic agents) and medication doses. Without appropriate data on medication doses it is difficult to estimate what proportion of the risk of development of CVD and/or all-cause mortality that has been attributed in this review to poor adherence is in fact explained by prescription of suboptimal medication doses. There was heterogeneity among the studies, which was only partially explained by differences in location, study design, and sample size. Most included studies used indirect methods to assess adherence and were limited by the premise that medication acquisition and perception of 'good' adherence are reasonable proxies for correct consumption. Most studies incorporated arbitrary thresholds to define 'good' and 'poor' adherence and were, therefore, unable to describe any dose–response relationship.[7] The majority of studies were of secondary prevention or a mixture of primary and secondary prevention participants and, therefore, the scope for analysis according to prevention type was restricted. As there was no significant heterogeneity between the studies when stratified by prevention type for the main analyses results for both CVD and mortality outcomes were pooled to increase the power to estimate differences in risk. Absolute risk differences were primarily presented for the EU population as absolute risk differences calculated using standardized death rates for the general US population would be likely to over-estimate the differences associated with poor adherence. This is due to the majority of US participants in the component studies being identified from insurance registers, therefore, excluding those uninsured in the population who are expected to receive less timely management of medical conditions. As the current review combined only summary level data from published studies, we were not able to assess trends in levels of adherence over time. Additionally, as the current review is based on published reports, our results may have been affected by selective underreporting of adherence, publication bias or inability to control for all relevant covariates in a consistent way. Testing for publication bias indicated a potential lack of smaller studies that may have identified a null or negative association between statin adherence and CVD outcomes, which could have resulted in a slight overestimation of the risk reduction credited here to 'good' adherence to statins.

Nonetheless, our findings reinforce the overall importance of optimal adherence to cardiovascular medications in achieving better health outcomes, considering the widespread use of these medications and potentially high level of non-adherence worldwide. These results are likely to complement findings from ongoing intervention studies (behavioural and device based) to improve medication adherence in patients (Supplementary material online, *Table S3*) and large-scale surveys to influence clinical management of non-compliance (e.g. Pan-European *ABC study*).[38] Finally, they reinforce the need for further detailed research to reliably quantify effects of medication dose on adherence levels, and the effects on adherence of specific combinations of medications common to cardiovascular management, in various populations and socioeconomic groups. Studies included in this review were based on affluent settings and/or individuals from insurance or trial registers, therefore, the observed levels of good adherence in these studies might be higher than average proportions globally. About three-quarters of global deaths due to CVD occur in low and middle-income countries where very high out-of-pocket expenditure for medicines, low affordability and availability of medicines, and fragile health systems with weak follow-up mechanisms contribute to much lower adherence levels.[39] The contribution worldwide of suboptimal adherence levels to CVD outcomes is, therefore, likely to be even higher than what has been demonstrated in our review.

Conclusions

A substantial proportion of people do not adhere adequately to cardiovascular medications, and the prevalence of such suboptimal adherence is similar across all individual CVD medications. Absolute and relative risk assessments indicate that a large proportion of all CVD events (~9% in Europe) may be attributed to poor adherence to vascular medications alone, and that the level of optimal adherence may confer a significant inverse association with subsequent adverse outcomes. As poor adherence remains a major barrier in achieving the full potentials of efficacious vascular medications, developing cost-effective measures to increase adherence should be considered a priority.

Supplementary material

Supplementary Material is available at *European Heart Journal* online.

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Authors' contributions

O.H.F., H.K., and R.C. conceived the study. R.C., H.K., E.H., A.S., S.F., and O.H.F. did the literature searches. H.K. and E.H. did the data extraction and analyses. R.C., H.K., E.H., and O.H.F. wrote the manuscript. R.C., O.H.F., E.H., H.K., A.S., S.F., C.M., S.M., J.M., B.S., and A.H. contributed to the critical revision of the manuscript before publication. R.C., H.K., and E.H. contributed equally to the study. O.H.F. is the guarantor.

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Conflict of interest: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work. Ethical approval: not required. Data sharing: no additional data available.

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