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Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review

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AIMS

While suboptimal adherence to statin medication has been quantified in real-world patient settings, a better understanding of its impact is needed, particularly with respect to distinct problems of medication taking. Our aim was to synthesize current evidence on the impacts of statin adherence, discontinuation and persistence on cardiovascular disease and mortality outcomes.

METHODS

We conducted a systematic review of peer-reviewed studies using a mapped search of Medline, Embase and International Pharmaceutical Abstracts databases. Observational studies that met the following criteria were included: defined patient population; statin adherence exposure; defined study outcome [i.e. cardiovascular disease (CVD), mortality]; and reporting of statin-specific results.

RESULTS

Overall, 28 studies were included, with 19 studies evaluating outcomes associated with statin adherence, six with statin discontinuation and three with statin persistence. Among adherence studies, the proportion of days covered was the most widely used measure, with the majority of studies reporting increased risk of CVD (statistically significant risk estimates ranging from 1.22 to 5.26) and mortality (statistically significant risk estimates ranging from 1.25 to 2.54) among non-adherent individuals. There was greater methodological variability in discontinuation and persistence studies. However, findings of increased CVD (statistically significant risk estimates ranging from 1.22 to 1.67) and mortality (statistically significant risk estimates ranging from 1.79 to 5.00) among nonpersistent individuals were also consistently reported.

CONCLUSIONS

Observational studies consistently report an increased risk of adverse outcomes associated with poor statin adherence. These findings have important implications for patients and physicians and emphasize the importance of monitoring and encouraging adherence to statin therapy.

Introduction

Statins are lipid-lowering agents that inhibit the rate-limiting step of cholesterol synthesis [1]. Their beneficial effects, including reduction of mortality and cardiovascular events, have been established in randomized clinical trials, including the West of Scotland Coronary Prevention Study in patients with hyperlipidaemia [2], the Scandinavian Simvastatin Survival Study of patients with angina pectoris or myocardial infarct [3] and the Heart Protection Study in coronary heart disease patients [4]. However, recent evidence has emerged that the effectiveness of statins in real-world settings is inferior to that seen in trials, and this has been attributed to poor medication adherence [5].

Medication adherence is a complex construct that encompasses the following distinct problems: (i) poor execution of the dosing regimen, such that doses are delayed or omitted, which may lead to transient interruptions in drug action; and (ii) discontinuation of the medication, which may lead to intermittent or permanent loss of drug effects [6, 7]. There is great need for consistency and use of standardized terminology in the medication adherence literature [8]. The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Special Interest Group has proposed standardization of terms, with 'adherence' referring to conforming to recommendations with respect to timing, dosage and frequency of medication taking and 'persistence' referring to conforming to recommendations of continuing treatment for the prescribed duration [9]. We propose that 'discontinuation' be included as a separate term when evaluating the problem of stopping therapy, and not the period of medication use.

Poor statin adherence in terms of execution of dosing regimen has been reported in up to 50% of patients [10]. Statin discontinuation rates have been reported ranging from 15 [5] to 75% [11], with most studies reporting rates of ≥50% [12–16]. Long-term persistence is also suboptimal as it has been reported in a study that only 52% of patients remain on statin therapy after 5 years [17]. A comprehensive understanding of statin adherence involves not only quantifying the extent of the problem but also evaluating its impact on relevant patient outcomes. While prior articles have synthesized [18–20] and pooled data [21] on the impact of statin adherence on adverse outcomes, including cardiovascular disease (CVD) events and mortality, they have not distinguished impacts of specific adherence problems. With growing recognition that dynamics and processes involved in problems of medication adherence are different, it is important to evaluate the burden and impacts of statin adherence, discontinuation and persistence separately [7]. Prior articles have also combined clinical trials along with observational studies, which may be problematic as adherence rates reported in clinical trials may not reflect rates observed in real-world settings [5]. To address these issues and update the evidence, we conducted a systematic review of observational studies among real-world patient settings evaluating adverse outcomes associated with distinct problems of statin adherence, discontinuation and persistence.

Methods

Literature search strategy

In August 2013, we searched the databases Medline (1966 onwards), Embase (1980 onwards) and International Pharmaceutical Abstracts (1970 onwards), using terms that mapped to Medical Subject Headings in combination with keywords for nonmapping concepts (e.g. 'discontinuation', 'persistence'; Table 1). We also conducted a hand search of bibliographies of articles retrieved from the electronic search.

Selection of studies

Titles and abstracts were reviewed for selection of publications meeting the following inclusion criteria: (i) prospective observational study design (e.g. cohort study, nested case–control study); (ii) population of adults (≥18 years of age); (iii) statin exposure as either execution of dosing ('adherence'), stopping of medication ('discontinuation') or duration of therapy ('persistence'); (iv) defined study outcome (e.g. CVD, mortality); and (v) reporting of statin-specific results. Two authors (MADeV and LCB) independently reviewed all titles, abstracts and articles for selection, quality assessment and data extraction. Discrepancies were resolved by consensus.

Data extraction and quality assessment

We extracted information on year of publication, country, study design, patient population and size, length of study follow-up and data source (e.g. administrative database, electronic pharmacy record). Of particular importance was

Table 1

Medical Subject Headings (MeSH) terms and keywords applied in electronic search strategy

Concept	MeSH terms	Keywords
Statins	Antilipaemic agents, anticholesterolaemic agents, hydroxymethylglutaryl-CoA reductase inhibitors, lovastatin, simvastatin, pravastatin	Statins
Adherence	Health behaviour, patient compliance, medication adherence, quality of healthcare, guideline adherence	Patient compliance, compliance, adherence, persistence, discontinuation
Cardiovascular diseases	Cardiovascular diseases, heart diseases, coronary artery disease, myocardial infarction, vascular diseases	Acute myocardial infarction, cardiovascular disease(s)
Mortality	Mortality, cause of death, fatal outcome, hospital mortality, survival rate, death	Mortality, death

information on the type of statin non-adherence, and we categorized studies as those evaluating the impact of the following: (i) poor execution of the dosing regimen ('adherence'); (ii) stopping of medication ('discontinuation'); or (iii) the duration of time patients remained on therapy ('persistence'). Equally important as how the problem was operationalized was how it was measured, and we extracted information on measurement of the following factors: (i) adherence [e.g. proportion of days covered (PDC), medication possession ratio]; (ii) discontinuation (e.g. time point at which discontinuation status was defined); and (iii) persistence (e.g. number of months on statin treatment). We also assessed whether adherence was treated as a fixed-in-time or time-dependent variable, cut-off values to categorize subjects who were adherent and non-adherent, and the reference category assigned for statistical models. We also extracted information on study outcomes (e.g. CVD, mortality) and reported measures of association [e.g. odds ratio (OR), relative risk (RR), hazard ratio (HR)]. We plotted reported risk estimates (and corresponding lower and upper limits) for mortality (Figure 2) and CVD outcomes (Figure 3), according to adherence, discontinuation and persistence studies, to show the association between statin non-adherence and adverse outcome. That is, for studies that modelled non-adherent subjects as the reference group, we plotted the reported risk estimate and for studies that modelled adherent subjects as the reference group, we calculated the inverse of the reported risk estimate (i.e. 1/OR) and lower and upper limits.

We also extracted information on confounders included in multivariable analyses. We applied the World Health Organization's five dimensions (factors) of medication adherence as a framework and categorized confounders according to the following factors: (i) patient factors; (ii) condition factors; (iii) therapy factors; (iv) social/economic factors; and (v) healthcare system factors [22]. We further assigned subcategories; for example, demographic characteristics (e.g. age, sex) comprise a subcategory within patient factor, while comorbidities and medications are subcategories within condition factors.

We assessed studies by applying guidelines by ISPOR's Medication Compliance and Persistence Special Interest Group, which were developed to meet the need for improved consistency and quality among studies evaluating problems of medication taking, by establishing standards for data sources, operational definitions, measurement of medication adherence and reporting of results [23]. We condensed the guidelines into a 20-item checklist, which included items on appropriate description of data sources, explicit definition and calculation of adherence exposures, and explicit definition of outcome, to yield a score (0–20) based on the sum of items. Due to the heterogeneity in patient populations and exposure definitions of statin adherence across studies, a meta-analysis was not conducted.

Results

Literature search

The electronic search strategy identified 2615 articles, with 31 articles included after hand searching references (Figure 1). Abstract review led to the exclusion of 142 articles due to lack of outcome (n = 33), exposure (n = 22) or both (n = 28), irrelevant study type (n = 56) and lack of assessment of impact of exposure on outcome (n = 3). After review of 36 studies, failure to report statin-specific results led to further exclusion of eight studies. Overall, 28 studies were included; 19 studies evaluated outcomes associated with statin adherence, six with statin discontinuation and three with statin persistence. As described earlier in the Introduction, while discontinuation and persistence represent opposite concepts and could be classified together, we separated studies into respective types to distinguish between those that evaluated the problem of stopping therapy and those that evaluated the period of continuous use.

Study characteristics, including design, patient population, sample size, follow-up period and assessment score, are summarized in Table 2. Scores ranged from 15 to 19, suggesting that most articles included key recommended items. Table 3 summarizes definition and measurement of statin adherence, outcomes evaluated and main results. In addition, the final column in Table 3 shows confounders included in reported multivariable models grouped according to the World Health Organization's five dimensions of medication adherence, i.e. patient (P), condition (C), therapy (T), social/economic (S) and healthcare system (H) factors. Table S1 provides detailed, item-by-item information on these confounders. Figures 2 and 3 summarize the main results by showing risk estimates for the association between non-adherence and mortality and CVD outcomes, respectively.

Statin adherence studies

Most of the studies included (n = 19; study IDs A1–A19) evaluated outcomes associated with statin adherence. Eight studies investigated statin adherence for primary prevention in general populations (A6, A9, A12, A13, A15, A17–A19), eight for secondary prevention among patients with prior CVD conditions [A1, A3, A5, A7, A8, A10, A11, A16], and three studies investigated both primary and secondary prevention [A2, A4, A14].

Primary prevention

Five Canadian studies evaluated the impact of statin adherence in the general population on various CVD outcomes using administrative data from Quebec. Bouchard *et al*. [24] [A6] used a cohort design and defined a population of individuals aged 50–64 years without CVD and newly treated with statins. They calculated PDC as the number of days of statin medication dispensed divided by

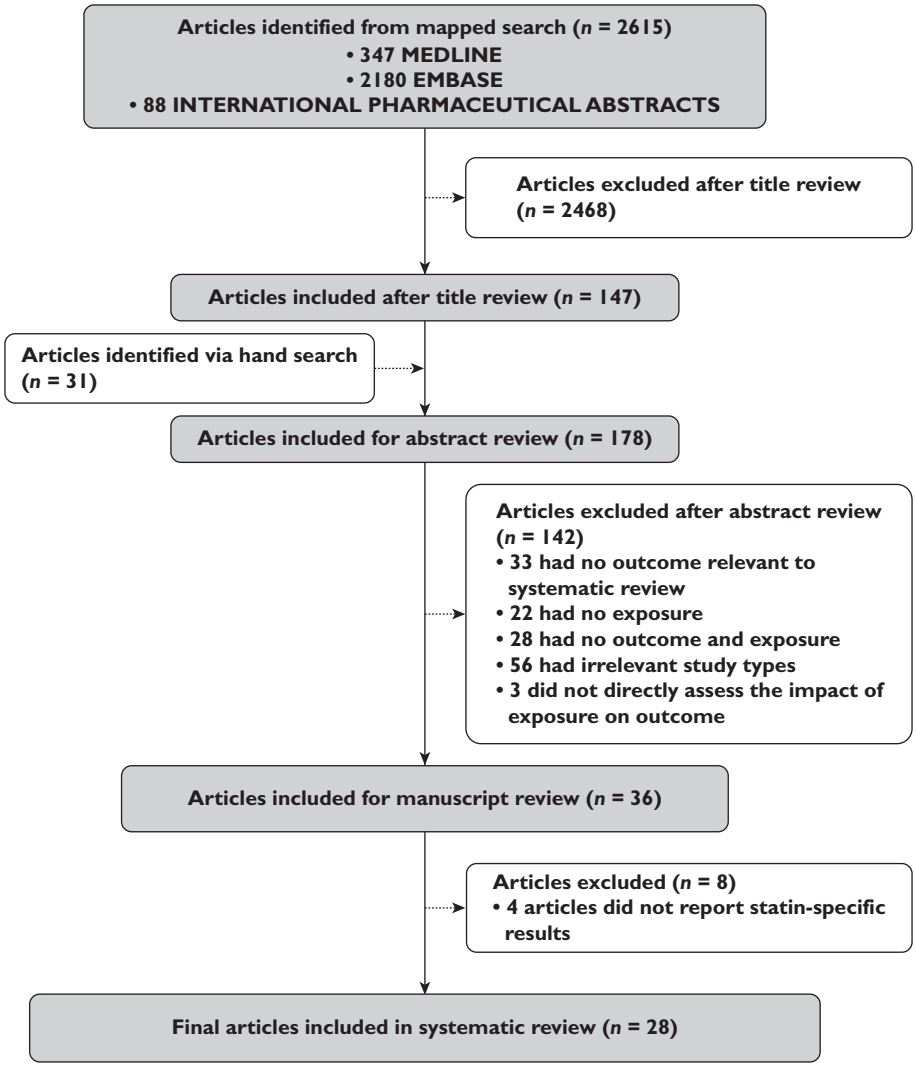

Figure 1
Systematic review study flow diagram

the number of days over which the prescriptions were used and applied a cut-off of ≥0.90 to define good adherence. Altogether, authors reported a significant association between good adherence and lower risk of coronary artery disease [CAD; OR, 0.81; 95% confidence interval (CI), 0.67–0.97] after the first year of follow-up [24]. Applying a nested case–control design, three subsequent studies by Perreault *et al*. used the same cohort of individuals aged 45–85 years without CVD and newly treated with statins to evaluate the following unique outcomes of: (i) chronic heart failure [25] [A9]; (ii) CAD [26] [A12]; and (iii) cerebrovascular accidents (CVA) [27] [A13]. Across all studies, the medication possession ratio, representing the percentage of days exposed to statins in a given follow-up period, was calculated from the start of statin prescription until the date of the outcome for cases and date of selection for controls and categorized as ≥80, 60–79, 40–59, 20–39 and 1–19% (reference group) [25–27]. Authors reported similar associations with the highest adherence category and chronic heart failure occurring in the first year of follow-up (OR, 0.72; 95% CI, 0.53–0.98) and after 1 year of follow-up (OR, 081; 95% CI, 0.71–0.91) [25] [A9] and significant associations for CAD (OR, 0.82; 95% CI, 0.77–0.87) [26] [A12] and CVA (OR, 0.74; 95% CI, 0.65–0.84) [27] [A13] after 1 year of follow-up. Of note, while the same base cohort was applied, each study yielded unique samples of cases representing each outcome and corresponding controls {coronary heart disease (n = 4309 cases; n = 45 707 controls) [A9]; CAD (n = 15 268 cases; n = 227 646 controls) [A12]; and CVA (n = 3959 cases; n = 58 972 controls) [A13]} suggesting minimal to no overlap across. Finally, Dragomir *et al*. [28] [A17] also used a cohort of new statin users and

Table 2

Characteristics of studies included in the systematic review

Study ID	Author	Country	Setting	Study design	Patient population	Sample size	Follow-up (years)	Quality score
Statin adherence studies								
A1	Wei *et al.* (2002) [32]	Scotland	Population based	Cohort	AMI	5590	2.4	17
A2	Howell *et al.* (2004) [40]	UK	General practitioner practice	Cohort	Primary care	1010	2.6	15
A3	Blackburn *et al.* (2005) [34]	Canada	Population based	Cohort	CAD	1221	3.2	18
A4	Ho *et al.* (2006) [42]	USA	Health maintenance organization	Cohort	Diabetes	11 532	1.3	17
A5	Ho *et al.* (2006) [36]	USA	Health maintenance organization	Cohort	Diabetes with IHD	3696	1	19
A6	Bouchard *et al.* (2007) [24]	Canada	Population based	Nested case–control	General population	20 543	1.6	18
A7	Rasmussen *et al.* (2007) [35]	Canada	Population based	Cohort	AMI	31 455	2.4	18
A8	Ho *et al.* (2008) [37]	USA	Health maintenance organization	Cohort	CAD	13 596	4.1	19
A9	Perreault *et al.* (2008) [25]	Canada	Population based	Nested case–control	General population	111 481	–	19
A10	Wei *et al.* (2008) [33]	Scotland	Population based	Cohort	CVD	3472	–	17
A11	McGinnis *et al.* (2009) [38]	USA	Health maintenance organization	Cohort	AMI	2201	–	15
A12	Perreault *et al.* (2009) [26]	Canada	Population based	Nested case–control	General population	115 290	–	19
A13	Perreault *et al.* (2009) [27]	Canada	Population based	Nested case–control	General population	112 092	2.95	19
A14	Shalev *et al.* (2009) [41]	Israel	Health maintenance organization	Cohort	(i) General population (ii) CHD	229 918	(i) 4 (ii) 5	18
A15	Corrao *et al.* (2010) [29]	Italy	Population based	Cohort	General population	90 832	4.25	19
A16	Tuppin *et al.* (2010) [39]	France	National health insurance (~70%)	Cohort	AMI	11 604	2.5	17
A17	Dragomir *et al.* (2010) [28]	Canada	Population based	Cohort	General population	55 134	3	18
A18	Degli Esposti *et al.* (2012) [30]	Italy	Local health unit	Cohort	General population	19 232	1.9	17
A19	Rabinowich *et al.* (2012) [31]	Israel	Health maintenance organization	Cohort	General population	127 822	4.65	18
Statin discontinuation studies								
D20	Ho *et al.* (2006) [43]	USA	Hospital	Cohort	AMI	1521	1	16
D21	Colivicchi *et al.* (2007) [44]	Italy	Hospital	Cohort	CVA	631	1	16
D22	Penning-van Beest *et al.* (2007) [46]	The Netherlands	Population based	Cohort	(i) General population (ii) CVD	(i) 46 332 (ii) 12 762	–	17
D23	Daskalopoulou *et al.* (2008) [45]	UK	Population based	Cohort	AMI	9939	1	18
D24	De Vera *et al.* (2011) [47]	Canada	Population based	Cohort	Rheumatoid arthritis	4102	3.5	19
D25	De Vera *et al.* (2012) [48]	Canada	Population based	Cohort	Rheumatoid arthritis	4102	3.6	20
Statin persistence studies								
P26	Hippisley-Cox & Coupland (2006) [49]	UK	Population based	Nested case–control	IHD	13 029	1.6	19
P27	Haukka *et al.* (2012) [50]	Finland	Population based	Cohort	General population	336 618	4.4	18
P28	Rublee *et al.* (2012) [51]	USA	Commercial insurance members	Cohort	(i) General population (ii) CHD	(i) 79 010 (ii) 15 277	1	16

Abbreviations are as follows: AMI, acute myocardial infarction; CAD, coronary artery disease; CHD, coronary heart disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; IHD, ischaemic heart disease.

Table 3

Statin adherence exposure definitions, outcomes, results and confounders considered in multivariable models of studies included in the systematic review

Study ID	Author	Patient population	Exposure definition	Type of variable	Variable categories and reference group	Outcomes	Main results	Confounders according to WHO dimensions				
Statin adherence studies												
A1	Wei *et al.* (2002) [32]	AMI	PDC statin initiation to outcome/end of study	Fixed in time	≥0.80 0.40–070 <0.39 0* (NA)	(i) AMI (ii) Mortality	(i) RR 0.19 (0.08–0.47) (ii) RR 0.47 (0.22–0.99)	P	C	T	S	H
A2	Howell *et al.* (2004) [40]	Primary care	PDC statin from first to last statin prescription	Fixed in time	≥0.80* <0.80	(i) AMI (ii) Mortality	(i) Not reported (ii) HR 2.54 (1.31–4.93)	P	C	–	–	–
A3	Blackburn *et al.* (2005) [34]	CAD	Statin fill frequency	Fixed in time	≥80% ≤60%* (NA)	(i) AMI (ii) Mortality	HR 0.45 (0.20–0.99) HR 0.68 (0.14–3.26)	P	C	T	–	H
A4	Ho *et al.* (2006) [42]	Diabetes	1 year PDC from statin initiation	Fixed in time	≥0.80* (A) <0.80	Mortality	OR 1.39 (1.18–1.63)	P	C	–	–	–
A5	Ho *et al.* (2006) [36]	Diabetes with IHD	1 year PDC from statin initiation	Fixed in time	≥0.80 <0.80* (NA)	Mortality	OR 0.59 (0.41–0.87)	P	C	–	–	–
A6	Bouchard *et al.* (2007) [24]	General population	PDC statin initiation to outcome/end of study	Fixed in time	≥0.90 <0.90* (NA)	(i) CAD <1 year (ii) CAD >1 year	(i) OR 1.02 (0.87–1.18) (ii) OR 0.81 (0.67–0.97)	P	C	T	S	–
A7	Rasmussen *et al.* (2007) [35]	AMI	1 year PDC from statin initiation	Fixed in time	≥0.80* (A) 0.40–0.80 <0.40	Mortality	RR 1.25 (1.09–1.42)	P	C	–	S	H
A8	Ho *et al.* (2008) [37]	CAD	PDC over 180 day time intervals	Time dependent	≥0.80* (A) <0.80	(i) Mortality (ii) CVD mortality (iii) CVD	(i) HR 1.85 (1.63–2.09) (ii) HR 1.62 (1.24–2.13) (iii) HR 1.35 (1.21–1.50)	P	C	–	–	–
A9	Perreault *et al.* (2008) [25]	General population	MPR statin initiation to outcome/end of study	Fixed in time	≥80% 60–79% 40–59% 20–39% 1–19%* (NA)	(i) CHF <1 year (ii) CHF >1 year	(i) OR 0.72 (0.53–0.98) (ii) OR 0.81 (0.71–0.91)	P	C	T	S	–
A10	Wei *et al.* (2008) [33]	CVD	PDC statin initiation to outcome/end of study	Fixed in time	≥0.80 <0.80* (NA)	CVD	HR 0.66 (0.47–0.91)	P	C	–	S	–
A11	McGinnis *et al.* (2009) [38]	AMI	PDC statin initiation to outcome/end of study	Fixed in time	≥0.80 <0.80* (NA)	–	(i) HR 0.44 (0.30–0.64) (ii) HR 0.99 (0.76–1.30)	P	C	–	–	–
A12	Perreault *et al.* (2009) [26]	General population	MPR statin initiation to outcome/end of study	Fixed in time	≥80% 60–79% 40–59% 20–39% 1–19%* (NA)	(i) CAD <1 year (ii) CAD >1 year	(i) OR 0.88 (0.77–1.01) (ii) OR 0.82 (0.77–0.87)	P	C	T	S	–
A13	Perreault *et al.* (2009) [27]	General population	MPR statin initiation to outcome/end of study	Fixed in time	≥80% 60–79% 40–59% 20–39% 1–19%* (NA)	(i) CVA <1 year (ii) CVA >1 year	(i) OR 1.03 (0.76–1.38) (ii) OR 0.74 (0.65–0.84)	P	C	T	S	–
A14	Shalev *et al.* (2009) [41]	(i) General population (ii) CHD	PDC statin initiation to outcome/end of study	Fixed in time	PDC ≥ 0.90 PDC < 0.90* (NA)	Mortality	(i) HR 0.55 (0.49–0.61) (ii) HR 0.49 (0.46–0.53)	P	C	T	S	H
A15	Corrao *et al.* (2010) [29]	General population	PDC statin initiation to outcome/end of study	Time dependent	>75% 51–75% 26–50% ≤25%* (NA)	IHD	HR 0.81 (0.71–0.94)	P	C	T	–	–
A16	Tuppin *et al.* (2010) [39]	AMI	PDC statin initiation to outcome/end of study	Fixed in time	>0.80* (A) ≤0.80	Mortality or ACS	HR 1.58 (1.37–1.81)	P	C	–	S	H
A17	Dragomir *et al.* (2010) [28]	General population	MPR statin initiation to outcome/end of study	Fixed in time	≥0.80* (A) <0.80	(i) CAD (ii) CVA (iii) CHF	(i) HR 1.07 (1.01–1.13) (ii) HR 1.13 (1.01–1.25) (iii) HR 1.13 (1.01–1.15)	P	C	–	S	H
A18	Degli Esposti *et al.* (2012) [30]	General population	PDC statin initiation to outcome/end of study	Fixed in time	>80% 61–80% 41–60% 21–40%* (NA)	(i) Mortality (ii) AMI (iii) CVA	(i) HR 0.46 (0.38–0.55) (ii) HR 0.79 (0.56–1.10) (iii) HR 0.73 (0.58–0.90)	P	C	–	–	–
A19	Rabinowich *et al.* (2012) [31]	General population	PDC statin initiation to outcome/end of study	Fixed in time	≥66% 33–66% <33%* (NA)	VTE	HR 0.78 (0.69–0.89)	P	C	–	–	–

Table 3
Continued

Study ID	Author	Patient population	Exposure definition	Type of variable	Variable categories and reference group	Outcomes	Main results	Confounders according to WHO dimensions				
Statin discontinuation studies												
D20	Ho *et al*. (2006) [43]	AMI	Statin discontinuation at 1 month postdischarge	Fixed in time	Nondiscontinuer* (A) Discontinuer	Mortality	HR 2.86 (1.47–5.55)	P	C	–	S	H
D21	Colivicchi *et al*. (2007) [44]	CVA	Statin discontinuation at 1, 6 and 12 months after discharge	Time dependent	Nondiscontinuer* (A) Discontinuer	Mortality	HR 2.78 (1.96–3.72)	P	C	–	–	–
D22	Penning-van Beest *et al*. (2007) [46]	(i) General population (ii) CVD	Continuous statin use in the first 2 years of treatment	Fixed in time	2 years continous use 18 months–2 years continuous use <18 months continous use* (NA)	AMI	(i) RR 0.70 (0.60–0.81) (ii) RR 0.70 (0.54–0.91)	P	C	S	–	–
D23	Daskalopoulou *et al*. (2008) [45]	AMI	Statin discontinuation in the first 90 days post-AMI	Fixed in time	Non-user* (NU) Users Starters Stoppers	Mortality	RR 1.88 (1.13–3.07)	P	C	–	–	H
D24	De Vera *et al*. (2011) [47]	Rheumatoid arthritis	Statin discontinuation status in month before outcome	Time dependent	Nondiscontinuer* (A) Discontinuer	AMI	HR 1.67 (1.24–2.25)	P	C	T	–	H
D25	De Vera *et al*. (2012) [48]	Rheumatoid arthritis	Statin discontinuation status in month before outcome	Time dependent	Nondiscontinuer* (A) Discontinuer	(i) CVD mortality (ii) Mortality	(i) HR 1.60 (1.15–2.23) (ii) HR 1.79 (1.46–2.20)	P	C	T	–	H
Statin persistence studies												
P26	Hippisley-Cox & Coupland (2006) [49]	IHD	Persistence of statin use (months)	Time dependent	>60 months No statin use* (NU)	Mortality	HR 0.20 (0.08–0.47)	P	C	–	S	–
P27	Haukka *et al*. (2012) [50]	General population	Statin use as function of time	Time dependent	Persistent Nonpersistent* (NA)	Mortality	HR 0.39 (0.37–0.40)	P	C	–	—	–
P28	Rublee *et al*. (2012) [51]	(i) General population (ii) CHD	Persistence of statin use using anniversary method	Time dependent	Persistent Nonpersistent* (NA)	(i) CVD (ii) CVD	(i) HR 0.82 (0.74–0.91) (ii) HR 0.74 (0.66–0.82)	P	C	–	S	H

Abbreviations are as follows: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CHF, chronic heart failure; CVA, cerebrovascular accident; CVD, cardiovascular disease; HR, hazard ratio; MPR, medication possession ratio; OR, odds ratio; PDC, proportion of days covered; RR, relative risk; VTE, venous thromboembolism. Abbreviations for confounders considered according to the World Health Organization's five dimensions (factors) of medication non-adherence are as follows: C, condition factors; H, healthcare system factors; P, patient factors; S, social/economic factors; T, therapy factors. *Abbreviations for referent categories are as follows: A, adherent group is referent category; NA, non-adherent group is referent category; NU, non-user group is referent category.

the medication possession ratio with a cut-off of 80% to evaluate the impact of adherence on healthcare services and costs. While not the primary outcomes, they additionally reported significant associations with CAD (OR, 1.07; 95% CI, 1.01–1.13), CVA (OR, 1.13; 95% CI, 1.01–1.25) and chronic heart failure (OR, 1.13; 95% CI, 1.01–1.15) [28] [A17].

Two studies [A15, A18] from Italy evaluated statin adherence in the general population. Corrao *et al*. [29] [A15] used population-based data from Italy's National Health Service to identify individuals with first statin prescriptions. Statin adherence was assessed using PDC (the number of days for which medication was dispensed divided by the number of follow-up days) categorized as very low (≤25%), low (26–50%), intermediate (51–75%) and high (>75%) coverage. Compared with individuals in the very low coverage group, those with high coverage had lower risk of ischaemic heart disease (HR, 0.81; 95% CI, 0.71–0.94) [29]. Degli Esposti *et al*. [30] [A18] used local health unit databases from Florence in their study of incident statin users, with PDC from the first prescription to the study outcome calculated, and categorized as low (21–40%), intermediate-low (41–60%), intermediate-high (61–80%) and high (>80%; individuals with PDC ≤20% were excluded). Compared with individuals with low adherence, those with high (HR, 0.46; 95% CI, 0.37–0.55), intermediate-high (HR, 0.53; 95% CI, 0.43–0.66) and intermediate-low adherence (HR, 0.81; 95% CI, 0.66–0.99) had reduced mortality [30].

Finally, the study by Rabinowich *et al*. [31] [A19] using health maintenance organization data in Israel was the only one evaluating venous thromboembolism outcomes. The PDC was calculated from the first prescription to the end of the study and divided into three groups (<33, 33–66 and ≥66%). Individuals with intermediate (HR, 0.81; 95% CI, 0.70–0.93) and high adherence (HR, 0.78; 95% CI,

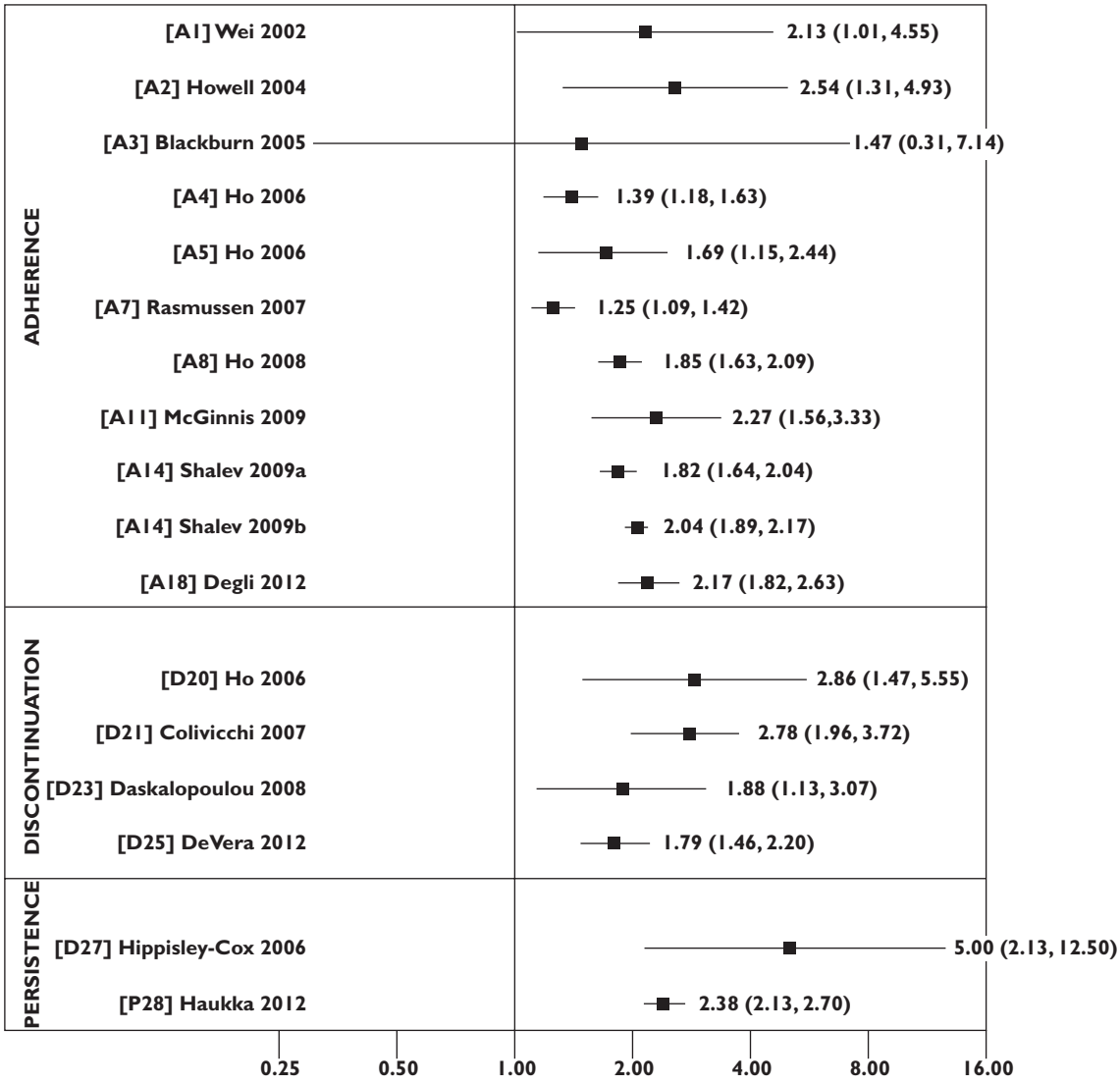

Figure 2

Risk estimates for the association between statin non-adherence and mortality outcomes according to adherence, discontinuation and persistence studies

0.69–0.89) had lower risk of venous thromboembolism compared with those who had low adherence [31].

Secondary prevention

The majority of studies of statin adherence were conducted among patients with prior CVD [A1, A3, A5, A7, A8, A10, A11, A16]. Using population-based data from the Medicine Monitoring Unit's database in Tayside, UK, the study by Wei *et al*. [32] [A1] in post-acute myocardial infarction (AMI) patients used PDC calculated as the number of days of statin supply divided by the number of days from the first prescription to the end of the study, grouped into four categories (0, <0.39, 0.40–0.70 and ≥0.80). Compared with the zero adherence group, those in the highest adherence category had a lower risk of AMI recurrence (HR, 0.19; 95% CI, 0.08–0.47) and mortality (HR, 0.47; 95% CI, 0.22–0.99) [32]. Using the same database, Wei *et al*. [33] [A10] focused on individuals with prior CVD, defined as hospitalization due to angina, AMI, heart failure, CVA or peripheral vascular disease. The PDC was calculated in a similar manner but dichotomized using a cut-off value of ≥0.80 to define good adherence. A protective effect of good adherence on recurrent CVD outcomes was reported (HR, 0.66; 95% CI, 0.47–0.91) [33].

Two Canadian studies [A3, A7] used population-based provincial administrative health databases. Blackburn *et al*. [34] [A3] studied individuals with prior CAD in Saskatchewan, defining adherence using statin fill frequency or the number of prescription fills divided by the months of observation [34]. Cut-off values were ≤60% (non-adherent)

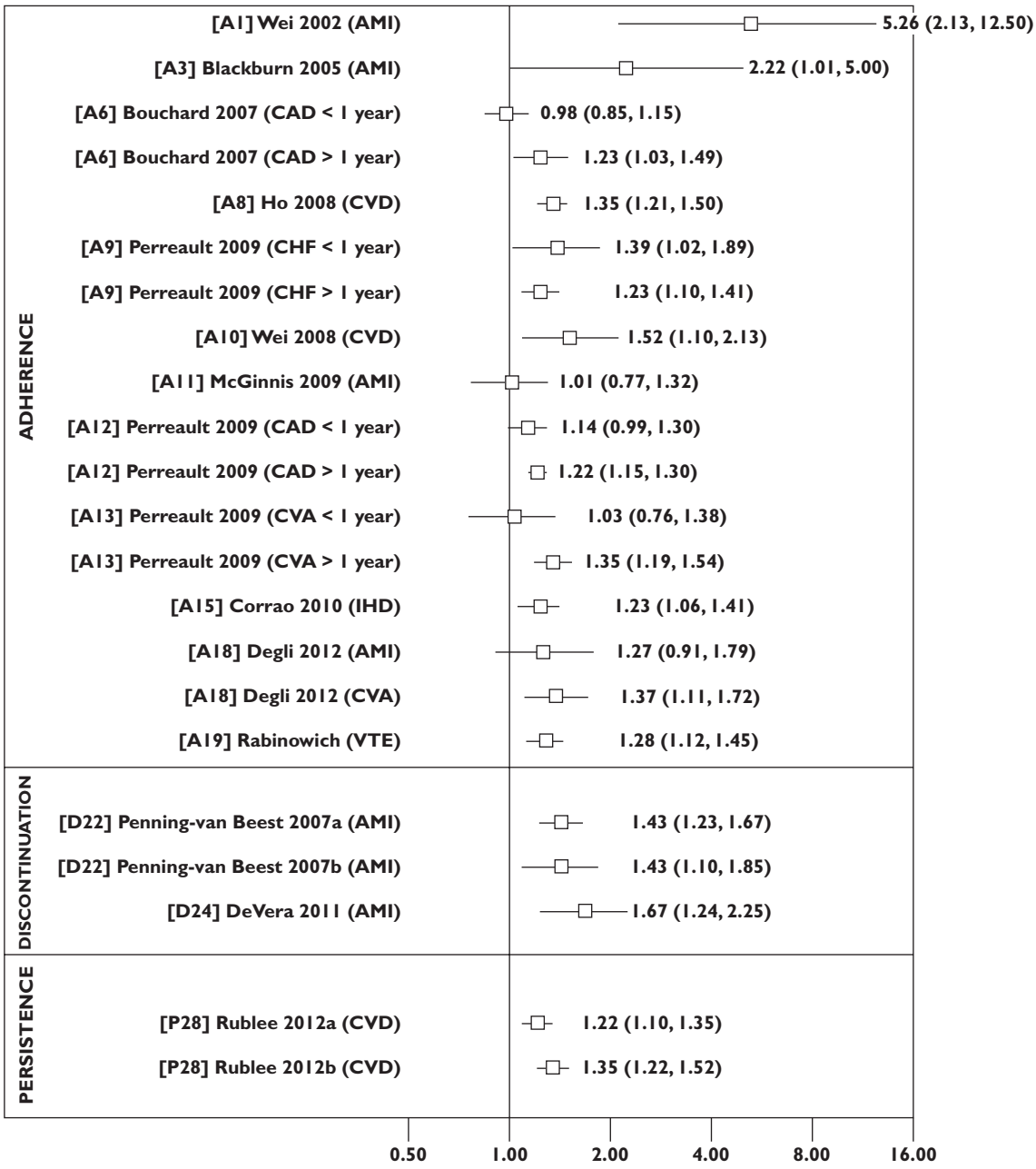

Figure 3

Risk estimates for the association between statin non-adherence and cardiovascular disease outcomes according to adherence, discontinuation and persistence studies. Abbreviations are as follows: AMI, acute myocardial infarction; CAD, coronary artery disease; CHF, chronic heart failure; CVA, cerebrovascular accident; CVD, cardiovascular disease; IHD, ischaemic heart disease; VTE, venous thromboembolism

and ≥80% (adherent). Compared with the non-adherent group, those in the adherent group had significantly lower risk of AMI (HR, 0.45; 95% CI, 0.20–0.99) [34]. In Ontario, Rasmussen *et al*. [35] [A7] evaluated the impact of adherence to cardioprotective medications, including statins, in AMI patients. One year PDC was calculated and categorized as high (≥0.80), intermediate (0.40–0.79) and low adherence (<0.40). Compared with patients in the high adherence group, those in the low adherence group had a higher risk of mortality (HR, 1.25; 95% CI, 1.09–1.42) [35].

Three secondary prevention studies of statin adherence were based on data from a health maintenance organization in the USA [A5, A8, A11]. Ho *et al*. [36] [A5] evaluated diabetes patients with ischaemic heart disease, using 1 year PDC, calculated as the number of days of prescription divided by 365 [36]. Compared with patients

in the non-adherent group (<0.80), patients in the adherent group had a lower risk of mortality (OR, 0.59; 95% CI, 0.41–0.87) [36]. Another study by Ho *et al*. [37] [A8] evaluated the impact of adherence to cardioprotective medications among individuals with prior CAD. The PDC was calculated over 180 day intervals from initiation of medication until the end of follow-up, and modelled as a time-dependent variable. The authors reported that statin non-adherence (<0.80) was associated with increased overall mortality (HR, 1.85; 95% CI, 1.63–2.09), CVD mortality (HR, 1.62; 95% CI 1.24–2.13) and CVD (HR, 1.35; 95% CI 1.21–1.50) [37]. McGinnis *et al*. [38] [A11] evaluated the impact of statin adherence on mortality and AMI recurrence in patients with prior AMI, using PDC categorized at the cut-off value of ≥0.80. Good statin adherence was significantly associated with a decreased mortality (HR, 0.44; 95% CI, 0.30–0.64), but not AMI (HR, 0.99; 95% CI, 0.76–1.30) [38].

Finally, using national health insurance data covering ~70% of the population of France, Tuppin *et al*. [39] [A16] evaluated statin adherence following hospital admission for AMI. Adherence was defined using PDC calculated from statin initiation until the end of the study and a cut-off value of 0.80. Non-adherence was significantly associated with higher risk of the combined study outcome of mortality or hospitalization for acute coronary syndrome (HR 1.58; 95% CI, 1.37–1.81); however, separate risk estimates for each outcome were not reported [39].

Mixed primary and secondary prevention

In the UK, the study by Howell *et al*. [40] [A2] of individuals in primary care with and without a history of coronary heart disease used electronic medical record data from a group of general practitioners in Liverpool. The PDC was calculated as the number of days of statin prescription dispensed divided by the number of days between the first and last prescriptions, and dichotomized using a cut-off value of 0.80. A 2.5-fold increased risk of mortality was reported in the non-adherent group compared with the adherent group (HR, 2.54; 95% CI, 1.31–4.93) [40]. A study by Shalev *et al*. [41] [A14] used health maintenance organization data from Israel to evaluate the impact of statin adherence on mortality in adults from the general population prescribed statins and in coronary heart disease patients. The PDC was calculated from the date of first statin prescription to the end of follow-up, and subjects were categorized as adherent or non-adherent based on a cut-off value of 0.90. Authors reported similar protective effects of statin adherence on mortality in both the general (HR, 0.55; 95% CI, 0.49–0.61) and coronary heart disease patient populations (HR, 0.49; 95% CI, 0.46–0.53) [41]. Finally, a study by Ho *et al*. [42] [A4] evaluated the impact of medication adherence on mortality in a community cohort of patients with diabetes, regardless of baseline CVD risk, using US health maintenance organization data. Medications evaluated included oral hypoglycaemic agents, antihypertensives and statins, and for each medication category the PDC in the first year of therapy was calculated as the number of days of prescription dispensed divided by 365, and dichotomized using a 0.80 cut-off value. The authors reported an increased risk of mortality with non-adherence to statins (OR, 1.39; 95% CI, 1.18–1.63) and cardioprotective medications overall (HR, 1.77; 95% CI, 1.45–2.15) [42].

Statin discontinuation studies

A smaller number of statin discontinuation studies were identified ($n = 6$; study IDs D20–D25). Three studies investigated statin use for secondary prevention [D20, D21, D23] and three studies investigated both primary and secondary prevention [D22, D24, D25].

Secondary prevention Using data from the registry data from 19 US hospitals, Ho *et al*. [43] [D20] evaluated mortality associated with discontinuation of statins among patients following AMI hospitalization. Discontinuation of medication was based on patient reports during telephone interviews 1 month after discharge. Statin discontinuation was associated with a 2.86-fold increased risk of mortality (HR, 2.86; 95% CI, 1.47–5.55) over the 1 year study follow-up [43]. In Italy, Colivicchi *et al*. [44] [D21] assessed the impact of statin discontinuation on mortality among patients discharged from hospital following an acute ischaemic stroke. Discontinuation was assessed by telephone interview at 1, 6 and 12 months, and a time-dependent explanatory variable was used in Cox proportional hazards models to account for changes in statin use status over follow-up. Authors reported a 2.78-fold increased risk of death associated with statin discontinuation (HR, 2.78; 95% CI, 1.96–3.72) [44]. Finally, using data from the UK General Research Practice Database (GPRD), Daskalopoulou *et al*. [45] [D23] evaluated the extent to which different patterns of statin use before and after an index AMI event were associated with mortality. Patients were classified into the following four groups based on statin use before the index AMI and during the 90 days following the AMI: non-users (never on statins); users (statins before and post-AMI); starters (no statin before and started statins post-AMI); and stoppers (statins before and stopped statins post-AMI). Authors used 'non-users' as the reference group and reported an 88% increased risk of mortality in statin stoppers relative to individuals who never used a statin [45]. Authors did not report results comparing statin stoppers *vs.* continuous users.

Mixed primary and secondary prevention In The Netherlands, Penning-van Beest *et al*. [46] [D22] used administrative pharmacy records to evaluate the impact of statin discontinuation on AMI outcomes in low-risk (general population) and high-risk (prior CVD) populations. The definition of statin exposure was based on the number of days of continuous statin use in the first 2 years of

treatment, and patients were categorized as follows: (i) 2 years of continuous use; (ii) 18 months of continuous use; and (iii) <18 months of continuous use (noncontinuous). Authors reported that compared with noncontinuous users, 2 years continuous statin users had a lower risk of AMI in both the primary (HR, 0.70; 95% CI, 0.60–0.81) and secondary (HR, 0.70; 95% CI, 0.54–0.91) prevention groups [46].

Using administrative databases in British Columbia, Canada, De Vera *et al*. studied incident statin users from a population-based cohort of rheumatoid arthritis patients, with and without prior CVD, to evaluate risk of AMI [47] [D24] and mortality [48] [D25]. Statin discontinuation was defined as no statin prescription for 3 months or more at any time during therapy course, and Cox proportional hazards models were used to model statin discontinuation as a time-dependent variable over the follow-up. Statin discontinuation was associated with an increased risk of AMI in patients with no prior AMI (HR, 1.61; 95% CI, 1.16–2.22) as well as in patients with prior AMI (HR, 1.55; 95% CI, 1.07–3.36) [47]. In the latter study, statin discontinuation was also associated with an increased risk of CVD mortality (HR, 1.79; 95% CI, 1.46–2.20) and of all-cause mortality (HR, 1.60; 95% CI, 1.15–2.23) [48].

Statin persistence studies

Three studies evaluated statin persistence; one for primary prevention [P26], one for secondary prevention [P27] and one for both [P28]. Hippisley-Cox & Coupland [49] [P26] studied individuals with ischaemic heart disease using the UK QRESEARCH database. Persistence of statin use was measured in months of use, and the authors found that compared with nonstatin users, those with the longest persistence (>60 months duration of use) had the lowest risk of mortality (OR, 0.20; 95% CI, 0.08–0.47) [49]. Using nationwide healthcare databases in Finland, Haukka *et al*. [50] [P27] assessed statin persistence as a function of time remaining on statin therapy since the beginning of the first statin prescription. When using a cut-off value of ≥80%, high persistence was associated with reduced mortality (HR, 0.39; 95% CI, 0.37–0.40) [50]. Using US databases for commercially insured individuals, Rublee *et al*. [51] [P28] applied an anniversary model [52] of a 90 day period to define atorvastatin persistence in individuals without and with prior coronary heart disease. Compared with nonpersistent users, those with persistent use had lower risk of cardiovascular events in both primary (HR, 0.82; 95% CI, 0.74–0.91) and secondary (HR, 0.74; 95% CI, 0.66–0.82) prevention groups [51].

Discussion

The objective of this systematic review was to synthesize evidence on the adverse outcomes associated with distinct problems of statin adherence, discontinuation and persistence in real-world patient settings. Altogether, the included studies consistently reported increased risks of CVD and mortality associated with poor adherence with respect to both execution of regimen and stopping of therapy. It is important to note that the majority of included studies were published in the last 5 years (17 of 28; study IDs A9–A19, D23–D25, P27–P28), suggesting an increased recognition of the importance of assessing statin adherence and its adverse impact.

Of interest in this systematic review were methodological considerations, particularly operationalization and measurement of medication adherence, which lacked consistency across studies. All studies evaluating statin adherence used electronic data sources (e.g. administrative data, pharmacy records) [A1–A19] and applied measures of medication availability, such as the PDC or medication possession ratio. Yet despite use of PDC in 14 of 19 studies, there was variability in the method to calculate values, with some studies using an interval-based PDC calculated over 1 year, others using a prescription-based PDC calculated between first and last statin prescriptions and still others using a combination of interval and prescription-based PDC calculated from the first statin prescription to the study outcome or end of follow-up. Each approach provides advantages, and it is unclear which is preferable to use. Calculating PDC over 1 year allows a fixed interval, which may facilitate comparison across studies. However, an interval-based measure using the first and last statin prescriptions may better reflect 'true' adherence by eliminating aspects of persistence that may be incorporated into the measure. Calculating PDC from the first statin prescription to study outcome, as done in some studies, has the advantage of evaluating longer-term effects of adherence, but also poses the problem of capturing both persistence and adherence in a single variable, especially if the outcome occurs long after the last prescription. Aside from differences in calculation of the adherence measure, cut-off values used to define good adherence also varied across studies. While the majority of studies used a cut-off value of ≥0.80 to dichotomize adherence, there were studies that divided their adherence measure into more than two categories, again with varying cut-off values.

Statin discontinuation studies reflected even greater variability across data sources and measures used. Electronic data sources were used in four studies, while self-reported data on medication use were used in two studies. With these data sources, a challenge in evaluating outcomes associated with statin discontinuation is that subjects must first be followed for a sufficient time to allow discontinuation and then be followed for a sufficient time to develop the outcome of interest. An additional complexity is that use may vary over time, including intermittently stopping and then resuming statins. Therefore, the use of a fixed time point to define statin discontinuation employed in some studies may potentially lead to inaccurate assessment of true exposure status. For example, Ho

et al. [43] [D20] defined statin discontinuation exposure based on patient self-reports of medication use 1 month after hospital discharge. Subjects reporting 'discontinuation' may have filled their statin prescription after 1 month and remained continuous users for the duration of follow-up or, conversely, subjects reporting continuous use at 1 month may have subsequently discontinued. Penning-van Beest *et al*. [46] [D22] used a similar approach of defining statin discontinuation over a fixed period of 2 years, which may be less problematic as stabilization of drug use patterns would be more likely to have occurred over this period. Three studies [D21, D24–25] modelled statin discontinuation as a time-dependent variable in their analyses. By modelling 'actual' statin discontinuation exposure over the entire duration of follow-up and efficiently using both exposed and non-exposed periods for all subjects, time-dependent approaches provide the ability to capture real-life patterns of drug use, where people might stop and resume drugs over time, and to evaluate their long-term effects.

Given our focus on observational studies, confounders included in multivariable models or biases accounted for are also important methodological considerations, because many of the electronic databases used in included studies may not capture important clinical and lifestyle factors associated with statin adherence and outcomes of interest. Applying the World Health Organization's five dimensions of medication adherence [22] as a framework provided a systematic assessment of whether studies considered patient, condition, therapy, social/economic and healthcare system factors. As shown in Table 3 (and Table S1), only patient factors (particularly age and sex) and condition factors (particularly comorbidities and use of other medications) were considered across all studies, probably because the databases used are comprised of coded healthcare visits that allow for assignment of comorbid diagnoses as well as prescription events that allow capture of comedications. Only two studies considered all five dimensions (A2, A14), 13 studies considered four (A3, A6, A7, A9, A12, A13, A16, A17, D20, D23–D25, P28), four studies considered three dimensions (A10, A15, D22, P26) and nine studies considered only patient and condition factors (A2, A4, A5, A8, A11, A18, A19, D21, D27). Along with these dimensions, also important are variables that may be associated with statin adherence and outcomes of interest that are often not captured in these databases, including smoking and lifestyle factors. Along with being confounders, lifestyle factors may also contribute to a potential 'healthy adherer' effect, whereby individuals who tend to follow prescribed medication regimens closely are also those who exhibit healthier behaviours, such as better diet, more physical activity and less smoking. The majority of studies included in our systematic review address the possibility that this 'healthy adherer' bias may limit their findings, including 13 adherence studies (A4–A7, A9, A10, A12–19), three discontinuation studies (D21, D24, D25) and one persistence study (P28). Only one study by Wei *et al*. (A10) directly evaluated the 'healthy adherer' effect by studying patients with CVD and comparing the impact of statin adherence and aspirin adherence [33]. The authors reported that in patients taking both drugs, adherence to statins but not aspirin was associated with a lower risk of CVD recurrence, but the same was not observed with adherence to aspirin but not statins, suggesting that healthy behaviour alone may not fully explain adverse outcomes in poorly adherent patients [33].

Our systematic review highlights the need for consistency in the medication adherence literature, which has been advocated in recent papers, including those by ISPOR's Medication Compliance and Persistence Special Interest Group for adherence studies in general [9] and by Hess *et al*. for studies using pharmacy administrative databases [8]. We observed inconsistencies in our systematic review, including the interchangeable use of terminology; for example, among the articles that evaluated statin adherence, some used the term 'compliance' in their title and one article used the term 'continuation'. Of note, the three studies that evaluated statin persistence did not indicate the term in the title, such that it was only at the data abstraction stage that the persistence exposure was confirmed. Overall, this emphasizes the importance of using standard terminology in future studies evaluating medication adherence and also highlights the importance of applying a comprehensive search strategy in systematic reviews of medication adherence, because some articles might not have been found had our search strategy not accounted for inconsistent terminology use.

Our systematic review builds on recent literature that has synthesized the impact of poor statin adherence, including previous review articles by Liberopoulous *et al*. [18] and Simpson *et al*. [19]. However, as these were based on single PUBMED searches, the inclusion of EMBASE and International Pharmaceutical Abstracts database searches as well as a more recent search (conducted in 2013) in our systematic review provides a more comprehensive and updated capture of studies. Our systematic review also builds on a previous systematic review by Gomez Sandoval *et al*. [20] and a recent meta-analysis Chowdhury *et al*. [21]. However, unlike prior works, we evaluated the impacts of distinct adherence problems, in line with recognition that differences in dynamics and economics of adherence problems warrant separate assessments [7]. Previous articles have allowed the inclusion of clinical trials in which the impact of adherence was assessed as a secondary objective, whereas our systematic review focused solely on observational studies, better to reflect statin use in real-world patient populations [5]. As described in the Methods, because patient populations, follow-up periods and, in particular, exposure definitions for the different types of adherence were heterogeneous across included studies, we did not conduct meta-analysis. For example, of

19 studies evaluating the impact of execution of dosing ('adherence'), 14 were based on PDC calculated across various time periods (e.g. 1 year PDC from statin initiation to 365 days, PDC over 180 day intervals, PDC from initiation to end of study/outcome, PDC from statin initiation to last statin prescription) and using varying adherence categories (e.g. binary cut-off at 0.80, at least two categories with varying cut-offs). Although it may be possible to pool studies across exposures that could be harmonized (for example, PDCs or medication possession ratios that were calculated across similar time periods), this would have been possible for only a small subset of included studies (e.g. three studies used 1 year PDCs which may be pooled), and this would not have been possible for discontinuation and persistence studies.

Overall, our systematic review identified a number of studies that consistently reported the association between statin adherence, across problems of execution and discontinuation, and the risk of CVD and mortality. These data expand upon previous reports quantifying the magnitude of statin adherence in real-world patient settings, by focusing on impacts on adverse outcomes. The findings have important implications for people taking statins, healthcare providers who prescribe them and other healthcare professionals involved in pharmacological care by emphasizing the importance of monitoring and discussing adherence to therapy.

Competing Interests

All authors have completed the Unified Competing Interest form at http://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 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1
Confounders evaluated in multivariable models for included studies according to the World Health Organization's five dimensions of medication adherence