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Niacin for primary and secondary prevention of cardiovascular events (Review)

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[Intervention Review]

Niacin for primary and secondary prevention of cardiovascular events

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ABSTRACT

Background

Nicotinic acid (niacin) is known to decrease LDL-cholesterol, and triglycerides, and increase HDL-cholesterol levels. The evidence of benefits with niacin monotherapy or add-on to statin-based therapy is controversial.

Objectives

To assess the effectiveness of niacin therapy versus placebo, administered as monotherapy or add-on to statin-based therapy in people with or at risk of cardiovascular disease (CVD) in terms of mortality, CVD events, and side effects.

Search methods

Two reviewers independently and in duplicate screened records and potentially eligible full texts identified through electronic searches of CENTRAL, MEDLINE, Embase, Web of Science, two trial registries, and reference lists of relevant articles (latest search in August 2016).

Selection criteria

We included all randomised controlled trials (RCTs) that either compared niacin monotherapy to placebo/usual care or niacin in combination with other component versus other component alone. We considered RCTs that administered niacin for at least six months, reported a clinical outcome, and included adults with or without established CVD.

Data collection and analysis

Two reviewers used pre-piloted forms to independently and in duplicate extract trials characteristics, risk of bias items, and outcomes data. Disagreements were resolved by consensus or third party arbitration. We conducted random-effects meta-analyses, sensitivity analyses based on risk of bias and different assumptions for missing data, and used meta-regression analyses to investigate potential relationships between treatment effects and duration of treatment, proportion of participants with established coronary heart disease and proportion of participants receiving background statin therapy. We used GRADE to assess the quality of evidence.

Main results

We included 23 RCTs that were published between 1968 and 2015 and included 39,195 participants in total. The mean age ranged from 33 to 71 years. The median duration of treatment was 11.5 months, and the median dose of niacin was 2 g/day. The proportion of participants with prior myocardial infarction ranged from 0% (4 trials) to 100% (2 trials, median proportion 48%); the proportion of participants taking statin ranged from 0% (4 trials) to 100% (12 trials, median proportion 100%).

Using available cases, niacin did not reduce overall mortality (risk ratio (RR) 1.05, 95% confidence interval (CI) 0.97 to 1.12; participants = 35,543; studies = 12; I^2 = 0%; high-quality evidence), cardiovascular mortality (RR 1.02, 95% CI 0.93 to 1.12; participants = 32,966; studies = 5; I^2 = 0%; moderate-quality evidence), non-cardiovascular mortality (RR 1.12, 95% CI 0.98 to 1.28; participants = 32,966; studies = 5; I^2 = 0%; high-quality evidence), the number of fatal or non-fatal myocardial infarctions (RR 0.93, 95% CI 0.87 to 1.00; participants = 34,829; studies = 9; I^2 = 0%; moderate-quality evidence), nor the number of fatal or non-fatal strokes (RR 0.95, 95% CI 0.74 to 1.22; participants = 33,661; studies = 7; I^2 = 42%; low-quality evidence). Participants randomised to niacin were more likely to discontinue treatment due to side effects than participants randomised to control group (RR 2.17, 95% CI 1.70 to 2.77; participants = 33,539; studies = 17; I^2 = 77%; moderate-quality evidence). The results were robust to sensitivity analyses using different assumptions for missing data.

Authors' conclusions

Moderate- to high-quality evidence suggests that niacin does not reduce mortality, cardiovascular mortality, non-cardiovascular mortality, the number of fatal or non-fatal myocardial infarctions, nor the number of fatal or non-fatal strokes but is associated with side effects. Benefits from niacin therapy in the prevention of cardiovascular disease events are unlikely.

PLAIN LANGUAGE SUMMARY

Niacin for people with or without established cardiovascular disease

Review question

We reviewed the evidence about the effects of niacin for the prevention of death and cardiovascular disease.

Background

Heart attack and stroke are the most common causes of death, illness, disability and reduced quality of life in industrialised countries.

Niacin (nicotinic acid, vitamin B3) was considered a promising candidate to prevent cardiovascular disease because it is known to lower cholesterol in the blood, which is one of the main risk factors. Therefore, long-term therapy with niacin was assumed to reduce the risk of heart attack, and stroke. We assessed whether clinical studies could show a benefit of taking niacin.

Study characteristics

We found 23 studies including 39,195 participants that compared niacin to placebo. The evidence is current up to August 2016. The majority of included participants were on average 65 years old and had already experienced a myocardial infarction. The participants took niacin or placebo for a period of between six months and five years. Seventeen out of 23 studies were fully or partially funded by the drug manufacturer with a commercial interest in the results of the studies.

Key results

Niacin did not reduce the number of deaths, heart attack or stroke. Many people (18%) had to stop taking niacin due to side effects. The results did not differ between participants who had or had not experienced a heart attack before taking niacin. The results did not differ between participants who were or were not taking a statin (another drug that prevents heart attack and stroke). The overall quality of evidence was moderate to high.

In summary, we found no evidence of benefits from niacin therapy.

Summary of findings for the main comparison. Niacin for primary and secondary prevention of cardiovascular events

Niacin for primary and secondary prevention of cardiovascular events

Patient or population: people with or at risk of cardiovascular disease
Setting: secondary care and tertiary care
Intervention: niacin monotherapy or add-on
Comparison: placebo or usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with niacin				
Overall mortality (follow-up: 0.5 years to 5 years)	Study population		RR 1.05 (0.97 to 1.12)	35,543 (12 RCTs)	⊕⊕⊕⊕ High	High-quality evidence that niacin does not reduce overall mortality (CI excludes clinically important benefit)
	86 per 1000	90 per 1000 (83 to 96)				
Cardiovascular mortality (follow-up: 1 year to 5 years)	Study population		RR 1.02 (0.93 to 1.12)	32,966 (5 RCTs)	⊕⊕⊕⊖ Moderate[1]	Moderate-quality evidence that niacin does not reduce cardiovascular mortality
	63 per 1000	64 per 1000 (58 to 70)				
Non-cardiovascular mortality (follow-up: 1 year to 5 years)	Study population		RR 1.12 (0.98 to 1.28)	32,966 (5 RCTs)	⊕⊕⊕⊕ High	High-quality evidence that niacin does not reduce non-cardiovascular mortality (CI excludes clinically important benefit)
	24 per 1000	27 per 1000 (24 to 31)				
Fatal or non-fatal myocardial infarction (follow up: 0.5 years to 5 years)	Study population		RR 0.93 (0.87 to 1.00)	34,829 (9 RCTs)	⊕⊕⊕⊖ Moderate[1]	Moderate-quality evidence that niacin does not reduce the number of fatal and non-fatal myocardial infarctions
	95 per 1000	90 per 1000 (83 to 95)				
Fatal and non-fatal stroke (follow-up: 0.5 years to 5 years)	Study population		RR 0.95 (0.74 to 1.22)	33,661 (7 RCTs)	⊕⊕⊖⊖ Low[1,2]	Low-quality evidence that niacin does not reduce the number of strokes
	47 per 1000	45 per 1000 (35 to 59)				

Discontinuation of treatment due to side effects (follow-up: 0.5 years to 4 years)	Study population		RR 2.17 (1.70 to 2.77)	33,539 (17 RCTs)	⊕⊕⊕⊖ Moderate[2]	Moderate-quality evidence that niacin does increase the number of participants discontinuing treatment due to side effects
	91 per 1000	210 per 1000 (162 to 273)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Confidence interval includes clinically relevant benefit and no benefit. We downgraded by one level due to imprecision.
[2]High heterogeneity in point estimates. We downgraded by one level due to inconsistency.

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is the most common cause of death, illness, disability and reduced quality of life in industrialised countries (Thom 2006). Mortality data for 2011 show that CVD accounted for one of three deaths in the USA (approximately 800,000) (Mozaffarian 2015). One of the major risk factors for CVD is elevated low-density lipoprotein cholesterol (LDL-C). In individuals with elevated LDL-C, statins (HMG CoA reductase inhibitors) are considered to be the first choice of pharmacological therapy, since they reduce CVD events and total mortality independently of baseline LDL-C levels (4S 1994; Baigent 2005; Graham 2007; HCSBG 2002; Hooper 2001; Lestra 2005; Mills 2010). However, despite significant risk reduction with statin therapy, many cardiac events are not prevented. Moreover, some people are unable to tolerate or have contraindications to statin therapy. Therefore, further investigation of additional or alternative lipid-lowering drug therapies is needed (Cannon 2008).

Description of the intervention

Nicotinic acid (niacin, vitamin B3) is a candidate to lower the remaining risk as it is known to decrease LDL-C, triglycerides and lipoprotein (a). In addition, it is the most effective currently available drug to increase high-density lipoprotein cholesterol (HDL-C) levels by up to 35% (Birjmohun 2005; McKenney 2004; Singh 2007). Common side effects of niacin therapy include skin flushing (up to 71%), headache (8%), pruritus (6%) and gastrointestinal symptoms (10%) (Ballantyne 2008a; Ballantyne 2008b; Insull 2009; Karas 2008; Zhao 2004). Skin flushing often leads to discontinuation of niacin treatment, although it is a tachyphylactic phenomenon, that is, once the body compensates, it is most likely that the frequency and intensity of such episodes will decrease within days or weeks and may even go away completely. Therefore, strategies to reduce flushing were developed, including modified release preparations, administration of aspirin, and formulation with laropiprant. Glucose intolerance with or without overt diabetes is another potential side effect of niacin therapy and may require adjustment of antihyperglycaemic therapy (Grundy 2002).

How the intervention might work

A meta-analysis published in 2006 and including 23 studies found that CVD event rates are reduced by nearly 1% for each 1% reduction in LDL-C and by at least 1% for each 1% increase in HDL-C, regardless of LDL-C reduction (Brown 2006). These findings imply a significant benefit of HDL-C-raising therapy independent of LDL-C reduction. However, a systematic review and meta-regression analysis including 108 studies found no additional effect of raised HDL-C levels on fatal or non-fatal myocardial infarction or overall mortality when the analysis was adjusted for changes in LDL-C levels (Briel 2009). A more recent meta-regression analysis also raised doubt as to the proposed relationship between HDL-C and risk of cardiac events (Hourcade-Potelleret 2015).

Decision analytic computer models have been used to estimate the economic value in terms of costs per life years gained for niacin therapy in addition to existing lipid-lowering therapy with statins. With incremental cost-effectiveness ratios (ICER) between EUR 10,000 and EUR 20,000, add-on niacin therapy was judged to be cost-effective (Michailov 2011; Roze 2007). However, these models rely on the assumption of an additional outcome benefit due to raised HDL-C levels, which is yet to be determined. Nevertheless, the cost of niacin treatment is generally considered to be low (Meyers 2003).

Why it is important to do this review

The evidence of CVD benefits with niacin therapy is controversial. Several randomised trials have investigated the efficacy and safety of niacin alone or in combination with other lipid-modifying drugs, focusing mostly on surrogate end points like changes in lipid profiles or carotid intima-media thickness as primary outcomes (e.g. Ballantyne 2008a; Canner 1986; JAMA 1975; Lee 2009; Maccubbin 2008; Moore 2007; Taylor 2004; Taylor 2009; Vaccari 2007). Several previous meta-analyses investigated the effects of lipid-modifying drugs and included niacin RCTs. However, these meta-analyses were either not based on systematic reviews (Goldberg 2004, Guyton 2009a, Bays 2012a, McKenney 2010, McKenney 2015) or they included niacin combination therapy (i.e. niacin plus another agent) or active control groups (e.g. niacin versus other lipid-modifying drugs) where it is impossible to discern any potentially incremental effects of niacin (Birjmohun 2005; Bruckert 2010; Charland 2010; Duggal 2010; Goldie 2015; Gould 2007; Keene 2014; Verdoia 2015). We identified only one previous systematic review and meta-analysis that addressed explicitly the incremental effect of niacin on patient-relevant outcomes: Ip 2015 assessed the effect of add-on lipid-modifying therapy on top of background statin treatment on major cardiovascular events. They included various comparisons but presented the subgroup of three RCTs that investigated the effect of niacin as add-on therapy (AIM-HIGH 2011; ARBITER-2 2004; HPS2-THRIVE 2014). None of the summary effects on clinical outcomes were significant. The risk ratio (RR) for all-cause mortality was 1.10 (95% confidence interval (CI) 1.00 to 1.20, I^2 = 0%), the RR for major cardiovascular events was 1.03 (95% CI 0.85 to 1.25, I^2 = 48%), the RR for death from coronary heart disease was 1.07 (95% CI 0.94 to 1.21, I^2 = 0%), the RR for myocardial infarction was 1.00 (95% CI 0.83 to 1.20, I^2 = 29%), and the RR for stroke was 1.52 (CI 0.57 to 4.06. I^2 = 11%) in favour of the placebo group. However, the meta-analysis was limited to high risk patients taking background statin therapy and failed to discuss methodological limitations of included trials. The 2013 American College of Cardiology/ American Heart Association guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults recommends considering re-emphasising adherence to lifestyle changes and to statin therapy before adding a non-statin drug (ACC/AHA guideline 2013). The expert panel could not find any data supporting the routine use of non-statin drugs combined with statin therapy to reduce cardiovascular events. In addition, no randomised controlled trials (RCTs) evaluating the effect of non-statin drugs on cardiovascular outcomes in statin-intolerant individuals were found.

OBJECTIVES

To assess the effectiveness of niacin therapy versus placebo administered as monotherapy or add-on to statin-based therapy in people with or at risk of cardiovascular (CVD) disease in terms of mortality, CDV events, and side effects.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs (published and unpublished) that documented an outcome of interest and had a treatment time (and thus follow-up) of at least six months.

Types of participants

Adults 18 years or older with or without established CVD disease.

Types of interventions

- Combination therapy including niacin plus other lipid-modifying drug(s) versus other lipid-modifying drug(s) alone for at least six months
- Niacin monotherapy versus placebo or usual care for at least six months

Types of outcome measures

Primary outcomes

- Overall mortality

Secondary outcomes

- Fatal myocardial infarction (including sudden death)
- Cardiovascular mortality (any death from cardiac or vascular cause)
- Non-cardiovascular mortality
- Non-fatal myocardial infarction
- Fatal or non-fatal myocardial infarction
- Fatal or non-fatal stroke
- Revascularisation procedures (bypass grafts, angioplasty)
- Patient-perceived quality of life (only measured using validated scales)
- Side effects, that is, skin flushing, pruritus, rash, headache, gastrointestinal symptoms, new onset of diabetes
- Discontinuation of treatment due to side effects
- Information on costs

Search methods for identification of studies

Electronic searches

We searched the following databases on 23 August 2016: Cochrane Central Register of Controlled Trials (CENTRAL, 2016, Issue 7) in the Cochrane Library, 'Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE' (Ovid, 1946 to 23 August 2016), 'Embase Classic and Embase' (Ovid, 1947 to 2016 August 22), and Web of Science (Thomson Reuters, 1970 to 23 August 2016).

When searching MEDLINE and Embase we used the Cochrane sensitivity-maximising filter for RCTs (Lefebvre 2011) and an adaptation of it for Web of Science. The search strategies used can be found in Appendix 1. No date or language restrictions were imposed.

Searching other resources

We further screened reference lists of included studies, published editorials, and previous systematic reviews or meta-analysis reviews on the topic (Bays 2012a; Birjmohun 2005; Bruckert 2010; Charland 2010; Duggal 2010; Goldberg 2004; Gould 2007; Guyton 2009a; Hourcade-Potelleret 2015; Ip 2015; Keene 2014; McKenney 2010; McKenney 2015; Robinson 2009a; Singh 2007; Verdoia 2015).

In addition, we searched clinical trials registries in August 2016, (ClinicalTrials.gov and www.isrctn.com) for additional eligible studies and additional publications of included RCTs. We searched registries using synonyms for niacin ("niacin", "nicotinic", "vitamin B").

Data collection and analysis

Selection of studies

Investigators, working in teams of two (SS, AN), independently reviewed potentially eligible titles and abstracts. If either reviewer believed the study to be eligible, we obtained the full report. After obtaining full reports of the candidate studies (either in full peer-reviewed publication or press article) the two reviewers independently assessed eligibility from full-text papers. Discrepancies were resolved by reviewers' consensus or, if needed, third party arbitration.

Data extraction and management

Two reviewers (SS and AN) used pre-piloted forms to independently extract all relevant data on baseline characteristics of trials, participant populations, and outcomes. Any disagreements between reviewers were resolved by consensus.

Assessment of risk of bias in included studies

Working in teams of two, we independently assessed the quality of each included trial with respect to random sequence generation, concealment of treatment allocation, blinding of participants, caregivers, or assessors of clinical outcomes, completeness of follow-up (Jüni 1999), and selective reporting of outcomes (Higgins 2011a). The results are presented as risk of bias tables as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Possible disagreement was resolved by consensus or third party arbitration if needed. We explored the influence of risk of bias on the primary outcome in a sensitivity analysis excluding RCTs with high or unclear risk of bias.

Measures of treatment effect

Ratio of risk for harmful events (risk ratio) and accompanying 95% confidence intervals.

Assessment of reporting biases

We checked for outcome reporting bias by comparing reported outcomes to outcomes mentioned in corresponding trial protocols (provided they were published prospectively) or trial registry records (provided the trial was registered prospectively). We investigated the presence of publication bias by means of funnel plots (Egger 1997; Sterne 2001).

Data synthesis

We used random-effects model meta-analyses to calculate a weighted average of risk ratios across studies for all outcomes.

We did not assume that all studies measure the same underlying true effect (that is, fixed-effect across studies) since we included primary and secondary prevention studies, and studies with and without background statin treatment. If a study reported more than one eligible comparison, we pooled the intervention arms and the control arms of the eligible comparisons. Whenever possible, we analysed participants as randomised irrespective of adherence to treatment. However, some studies excluded protocol violators from the follow-up or reported analysis. In that case, we also excluded them from our primary analysis, which was based on available cases. We considered available case analysis as our primary analysis because the underlying assumption is that missing data occurred at random. The commonly reported approach of using all randomised participants as a denominator for risks implicitly assumes no event for missing data which is less realistic than missing at random. We conducted all analyses using Review Manager 5 (RevMan 5) (RevMan 2014) and Stata 13 (stata.com).

In our analyses we made the following assumptions:

- If the denominator for available cases was not explicitly reported, we calculated the denominator by subtracting lost to follow-up from all randomised participants. For outcomes for which lost to follow-up was not reported, we assumed the available case denominator as reported or calculated for other outcomes. If the denominator differed by outcomes, we used the smallest.
- If a binary outcome was reported, both as a component of a composite endpoint (first occurrence) and as an independent outcome, we preferred the independent outcome in order to prevent bias due to competing risks.
- If myocardial infarction was not explicitly defined as fatal or non-fatal, we counted the events as 'fatal or non-fatal myocardial infarction' only. We used the same strategy for undefined stroke.
- If a specific side effect was reported both as 'discontinuation of treatment due to side effect' and 'experience of side effect', we preferred the latter in order to avoid assessment bias.
- If a specific side effect was only reported in combination with another side effect but not as an individual component (e.g. 'flushing or pruritus') we used the combined outcome in the meta-analysis of the individual component that occurred more frequently in other studies that reported both components. For example, if a study reported the outcome 'flushing or pruritus' we used 'flushing' in the meta-analysis because flushing occurred more frequently in other studies that reported both components separately.
- If several subcategories of an outcome (e.g. 'diarrhoea' as subcategory of 'gastrointestinal side effects') were reported but were not mutually exclusive, we assumed the outcome with the most events to represent the superordinate category. For instance, in a study that reported the outcomes 'diarrhoea' and 'vomiting', and 'diarrhoea' had more events than 'vomiting', we considered 'diarrhoea' to represent 'gastrointestinal side effects'.
- If a study reported that a participant was withdrawn from the study, but did not explicitly state whether the participant was withdrawn from the intervention (non-adherent) or from the follow-up (missing outcome data), we assumed withdrawal from follow-up.

Subgroup analysis and investigation of heterogeneity

We tested for heterogeneity with Cochrane's Q-test (Deeks 2011; Higgins 2002) and used I^2 (Higgins 2003) to measure inconsistency of treatment effects across primary and secondary outcomes. We conducted inverse variance-weighted meta-regression analysis (Thompson 1999) to investigate any association between the outcomes and duration of niacin therapy, proportion of participants with established coronary heart disease, and proportion of participants receiving background statin therapy.

Sensitivity analysis

We conducted sensitivity analyses for all outcomes by assuming three different relationships between outcomes of missing and observed participants (Higgins 2008; command "metamiss" in Stata, Table 1 (stata.com)). Therefore, we specified the informative missingness odds ratio (IMOR = odds of event in missing data/ odds of event in observed data) and specified a distribution of the assumed relationship of the standard deviation (logIMOR = 0.5) to account for the uncertainty of this assumption. For the first sensitivity analysis, we assumed missingness at random (IMOR 1.0 in each arm) that results in similar point estimates for the individual trials but may change the summary estimate by down-weighting studies with high proportions of missing data. In the second sensitivity analysis, we assumed a lower IMOR of 0.5 in the niacin arms and a higher IMOR of 2.0 in the control arms, thereby shifting the estimate in favour of niacin treatment. In a third sensitivity analysis, we assumed an IMOR of 2.0 in the intervention arms and an IMOR of 0.5 in the niacin arms thereby shifting the estimate in favour of the control treatment. We did draw forest plots given the minimal differences and large number of sensitivity analyses. For the primary outcome, we also conducted a sensitivity analysis restricting the analysis to trials with low risk of bias.

'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: overall mortality, cardiovascular mortality, non-cardiovascular mortality, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, and discontinuation of treatment due to side effects. We used the five GRADE considerations (risk of bias, inconsistency, imprecision, indirectness and publication bias) to assess the quality of a body of evidence. We used methods and recommendations described in Section 8.5 (Higgins 2011a) and Chapter 12 (Schünemann 2011) of the *Cochrane Handbook for Systematic Reviews of Interventions* using GRADEpro GDT 2014 software. We used footnotes to justify all decisions to downgrade the quality of evidence.

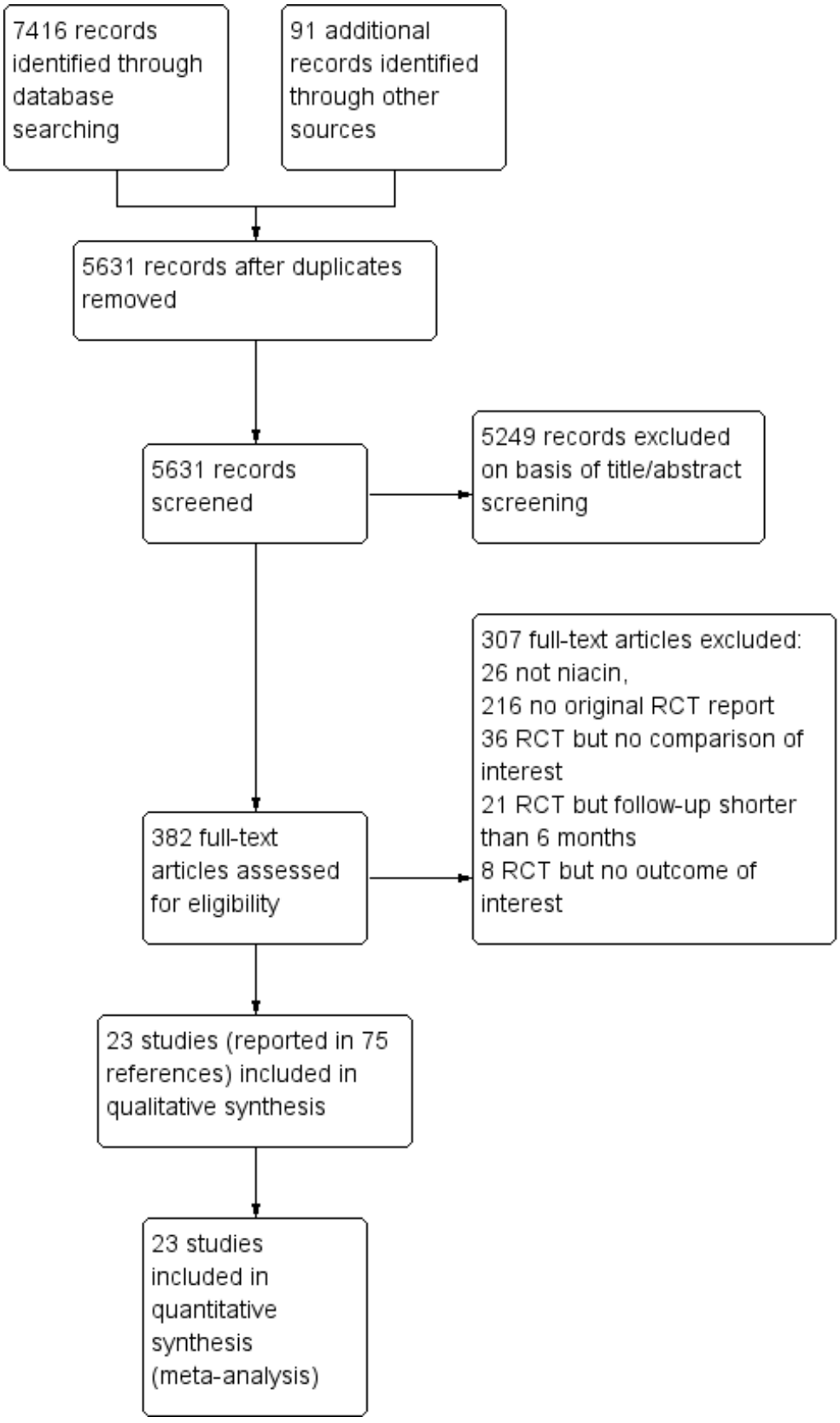
RESULTS

Description of studies

Results of the search

The search yielded 5631 unique records. We screened the full texts of 382 potentially eligible articles and finally included 23 RCTs (reported in 75 references) in our analysis (Figure 1; Characteristics of included studies). We excluded 307 articles including 65 RCTs involving niacin treatment that did not fulfil our eligibility criteria (Excluded studies).

Figure 1. Study flow diagram



Included studies

Methodology

We included 23 RCTs that were published between 1968 and 2015. In total, we included 39,195 participants. The median duration of treatment was 11.5 months. Of the 23 RCTs, there was one prospectively published protocol (Heart positive 2011) and five retrospectively published protocols (after end of recruitment) (ADMIT 2000; AIM-HIGH 2011; CDP 1975; HPS2-THRIVE 2014; Hunninghake 2003); 12 (52%) RCTs were registered in a clinical trials registry (all ClinicalTrials.gov). Pharmaceutical companies were mentioned as the only funding source in ten RCTs (ADMIT 2000; Capuzzi 2003; Carotid IMT 2008; Goldberg 2000; Guyton 2008; HPS2-THRIVE 2014; Hunninghake 2003; Lee 2009; Maccubbin 2008; MacLean 2011) and provided partial funding in another seven RCTs (ARBITER-2 2004; Harikrishnan 2008; Lee 2011; Linke 2009; Nash 2011; NIA Plaque 2013; Schoch 1968); four RCTs were explicitly not industry funded (AIM-HIGH 2011; ALPINE-SVG 2015; CDP 1975; Heart positive 2011) and funding was not disclosed in two RCTs (PAST 1995; Sang 2009).

Populations

Mean age ranged from 33 to 71 years across individual trials. Most trials included more men than women, two trials included as many women as men and only one trial (MacLean 2011) included more women than men. In two RCTs, all participants had experienced a prior myocardial infarction (CDP 1975; Schoch 1968) (secondary prevention trials). Four trials explicitly excluded people with prior myocardial infarction (Capuzzi 2003; Heart positive 2011; Linke 2009; Nash 2011) (primary prevention trials). In the remaining trials (mixed prevention trials), the proportion of individuals with prior myocardial infarction was in the range of 9% to 89% (ADMIT 2000; AIM-HIGH 2011; ALPINE-SVG 2015; ARBITER-2 2004; Guyton 2008; Harikrishnan 2008; HPS2-THRIVE 2014; Lee 2009; Lee 2011; NIA Plaque 2013; PAST 1995; Sang 2009) or was not reported in four trials (Carotid IMT 2008; Goldberg 2000; Hunninghake 2003; MacLean 2011).

Of the 23 included RCT populations, 16 (70%) received therapy with statin (ADMIT 2000; AIM-HIGH 2011; ALPINE-SVG 2015; ARBITER-2 2004; Capuzzi 2003; Carotid IMT 2008; Guyton 2008; Harikrishnan 2008; HPS2-THRIVE 2014; Hunninghake 2003; Lee 2009; Lee 2011; Maccubbin 2008; MacLean 2011; NIA Plaque 2013; Sang 2009). The proportions of individuals receiving statin therapy ranged from 67% to 100%. Statin therapy was part of the randomised interventions in eight RCTs, part of inclusion criteria in three RCTs, and part of allowed background therapy in five RCTs. The proportion of individuals receiving statins was 0% in four RCTs and not reported in three RCTs.

Most trials recruited participants in North America (ADMIT 2000; AIM-HIGH 2011; ARBITER-2 2004; Capuzzi 2003; CDP 1975; Goldberg 2000; Guyton 2008; Heart positive 2011; Hunninghake 2003; Nash 2011; NIA Plaque 2013; Schoch 1968), followed by Europe (Lee 2009; Linke 2009; PAST 1995), Asia (Harikrishnan 2008; Lee 2011; Sang 2009), or recruited world-wide (Carotid IMT 2008; HPS2-THRIVE 2014; Maccubbin 2008; MacLean 2011). Most studies did not report on the healthcare setting; four included participants in tertiary care (ALPINE-SVG 2015; ARBITER-2 2004; Capuzzi 2003; Harikrishnan 2008), one in secondary care (NIA Plaque 2013), and three from mixed healthcare settings (ADMIT 2000; Heart positive 2011; HPS2-THRIVE 2014).

Interventions

The included trials administered a median dose of niacin of 2 g/day (range 0.5 g/day to 4.0 g/day) and the duration of treatment ranged between six months and six years. Nineteen trials applied one or more methods to reduce skin flushing due to niacin intake: Ten trials used an extended-release formula (ALPINE-SVG 2015; Capuzzi 2003; Goldberg 2000; HPS2-THRIVE 2014; Linke 2009; Maccubbin 2008; MacLean 2011; Nash 2011; NIA Plaque 2013; Sang 2009), four trials combined niacin with laropiprant (Carotid IMT 2008; HPS2-THRIVE 2014; Maccubbin 2008; MacLean 2011), ten trials gave aspirin prior to intake of niacin (AIM-HIGH 2011; ARBITER-2 2004; Goldberg 2000; Harikrishnan 2008; Hunninghake 2003; Lee 2009; Linke 2009; Maccubbin 2008; MacLean 2011; Nash 2011) and nine trials recommended intake at bedtime to reduce flushing, some together with a snack (AIM-HIGH 2011; ARBITER-2 2004; Capuzzi 2003; Goldberg 2000; Guyton 2008; Hunninghake 2003; Lee 2009; Maccubbin 2008; Nash 2011). Four trials (ADMIT 2000; ALPINE-SVG 2015; AIM-HIGH 2011; Heart positive 2011) applied a placebo that contained a minimal dose of niacin, enough to trigger skin flushes but with no effect on lipid levels, in order to prevent unblinding due to flushing.

Table 2 provides an overview of the change in lipid parameters associated with niacin therapy for each included RCT. Niacin increased the concentration of HDL-C and decreased the concentration of triglycerides in all studies that reported these data. Niacin decreased the concentrations of LDL-C and total cholesterol in most studies.

Comparisons

Of the 23 RCTs, 14 had a placebo for niacin in the control group (ADMIT 2000; ALPINE-SVG 2015; AIM-HIGH 2011; ARBITER-2 2004; Carotid IMT 2008; CDP 1975; Goldberg 2000; HPS2-THRIVE 2014; Lee 2009; Maccubbin 2008; MacLean 2011; Nash 2011; NIA Plaque 2013; Schoch 1968). The remaining nine RCTs administered standard treatment without a specific placebo for niacin (Capuzzi 2003; Guyton 2008; Harikrishnan 2008; Heart positive 2011; Hunninghake 2003; Lee 2011; Linke 2009; PAST 1995; Sang 2009).

Outcomes

Ten trials specified a serum lipid parameter as their primary outcome (Capuzzi 2003; Goldberg 2000; Guyton 2008; Heart positive 2011; Hunninghake 2003; Maccubbin 2008; MacLean 2011; Nash 2011; Sang 2009; Schoch 1968), seven trials an angiographic outcome (AIM-HIGH 2011; ALPINE-SVG 2015; Carotid IMT 2008; Lee 2009; Lee 2011; NIA Plaque 2013; PAST 1995), two trials a composite of cardiovascular events (AIM-HIGH 2011; HPS2-THRIVE 2014), one trial feasibility (ADMIT 2000), and another trial overall mortality (CDP 1975). Two trials did not specify a primary outcome (Harikrishnan 2008; Linke 2009).

Of the 23 RCTs, 12 (52%) reported the outcome overall mortality, the primary outcome of the present systematic review. Of these, five specified overall mortality explicitly as an outcome (AIM-HIGH 2011; ARBITER-2 2004; CDP 1975; HPS2-THRIVE 2014; Schoch 1968) while the remaining seven studies reported overall mortality under safety/adverse events (Goldberg 2000; Hunninghake 2003; Maccubbin 2008; MacLean 2011; NIA Plaque 2013; PAST 1995; Sang 2009).

None of the included studies reported information about quality of life or costs.

Excluded studies

Overall, we excluded 65 RCT reports that involved niacin treatment but did not report a comparison of interest (36 RCT reports), had a follow-up shorter than six months (21 RCT reports), or reported no ocutome of interest (8 RCT reports) (see Characteristics of excluded studies).

Risk of bias in included studies

Figure 2 and Figure 2 provide an overview of the risk of bias in individual studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

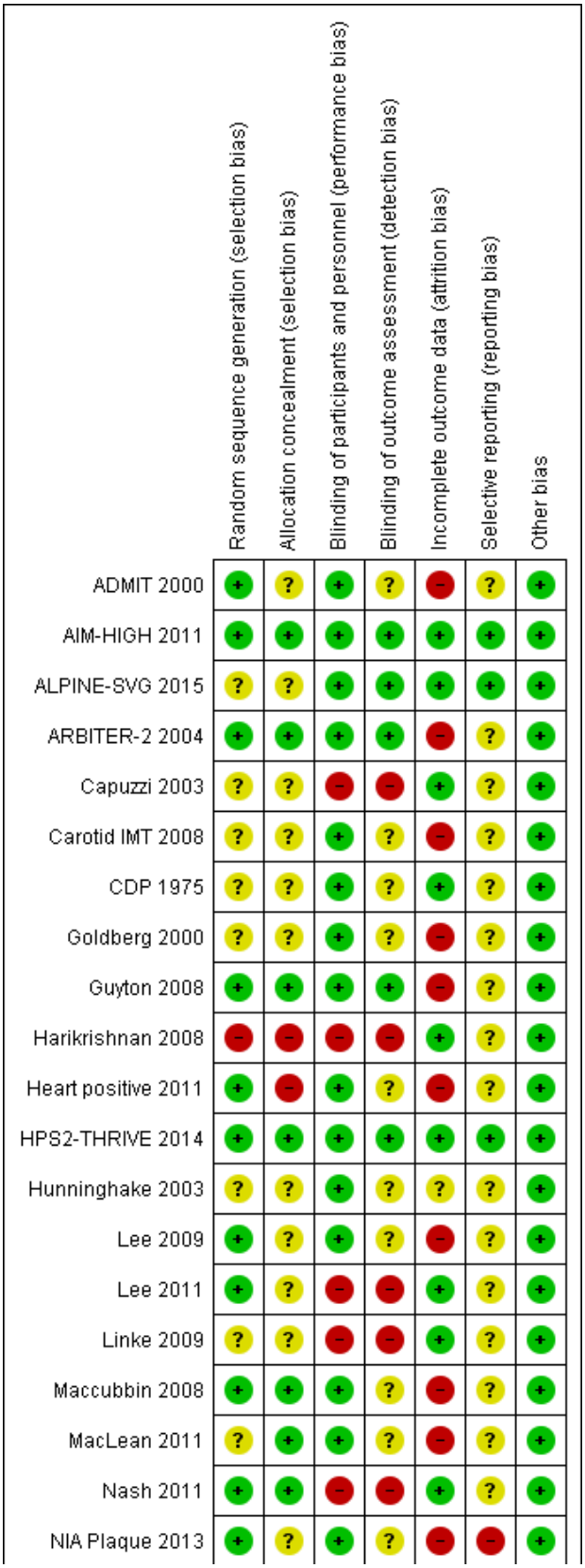
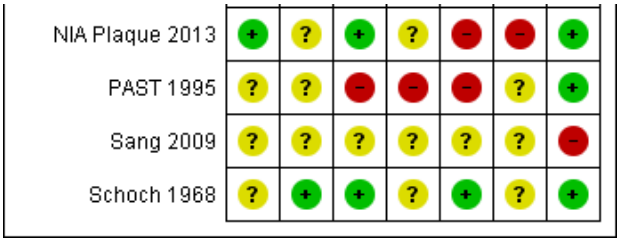


Figure 2. (Continued)



Allocation

Eleven trials reported a method to generate the random sequence (low risk of bias), 11 trials did not report the method of random sequence generation (unclear risk of bias), and one trial used quasi randomisation (high risk of bias) (Figure 2).

Eight trials reported an adequate method to conceal allocation (low risk of bias), 13 trials reported no method (unclear risk of bias), and two trials did clearly not conceal allocation (high risk of bias) (Figure 2)..

Blinding

Sixteen trials were reported as double-blind (low risk of performance bias), five as open-label and one as single-blind (high risk of performance bias), and the blinding status of participants and study personnel remained unclear in one trial (unclear risk of performance bias) (Figure 2).

Outcome assessment was blinded in five trials (low risk of detection bias), not mentioned in 12 trials (unclear risk of detection bias), and unblinded in six trials (high risk of detection bias) (Figure 2).

Incomplete outcome data

We judged the risk of attrition bias as high in 11 trials (proportion of missing data > 10%, or ratio events/missing < 1), unclear in two studies, and low in the remaining 10 studies (Figure 2). The median proportion of missing data in the 12 trials that reported overall mortality was 25% in the intervention arms and 19% in the control arm (Table 3). None of the included trials mentioned a sensitivity analysis for missing outcome data with respect to the clinical outcomes.

Selective reporting

We systematically compared planned and reported outcomes in ten studies that provided a prospectively published protocol (Heart positive 2011) or prospectively published registry record (ALPINE-SVG 2015; Carotid IMT 2008; Guyton 2008; Heart positive 2011; HPS2-THRIVE 2014; Lee 2009; Maccubbin 2008; MacLean 2011; NIA Plaque 2013). Of these, we judged the risk of outcome reporting bias as high for one study that failed to report pre-specified cardiovascular events (NIA Plaque 2013). The trials ALPINE-SVG 2015, AIM-HIGH 2011, and HPS2-THRIVE 2014 reported all pre-specified outcomes and were therefore judged as being at low risk of reporting bias. We judged the risk of reporting bias in the remaining five trials with a prospective protocol as unclear because the clinical outcomes that we extracted (e.g. death or flushing) were reported as side effects but not pre-specified as separate outcomes. The risk of reporting bias was unclear for the 13 trials without published protocol or registry record (Figure 2).

Other potential sources of bias

We considered Sang 2009 at high risk of bias because the reported information was insufficient to rate any item of the risk of bias tool. In addition, treatment groups were considerably unbalanced with respect to cardiovascular risk factors, prior myocardial infarction (control: 36%, intervention 10%) and diabetes (control: 16%, intervention 54%) which raises doubts whether the method of randomisation was appropriate.

One trial was stopped early for futility (AIM-HIGH 2011). It has been argued that stopping early for futility bears a potential risk for underestimation of potential treatment effects (Walter 2017). However, we considered a relevant bias extremely unlikely given the conservative stopping rules and point estimates consistently excluding any benefits.

Effects of interventions

See: **Summary of findings for the main comparison** Niacin for primary and secondary prevention of cardiovascular events

Primary outcome

Twelve RCTs reported the primary outcome of overall mortality. Using available cases, we found high-quality evidence that niacin did not reduce overall mortality (RR 1.05, 95% CI 0.97 to 1.12; participants = 35,543; studies = 12; I^2 = 0%; Analysis 1.1). The sensitivity analyses using relatively extreme assumptions for imputation of missing data did not change the primary outcome (Table 1). When we considered only the two trials at low risk of bias (AIM-HIGH 2011 and HPS2-THRIVE 2014) as a sensitivity analysis, the pooled results suggested that niacin may increase overall mortality (RR 1.10, 95% CI 1.00 to 1.20; participants = 28,840; studies = 2; I^2 = 0% Analysis 1.2).

Meta-regression analyses did not suggest a significant effect modification by duration of treatment (P = 0.15, Figure 3), proportion of participants with established coronary heart disease (P = 0.19, Figure 4), or proportion of participants receiving background statin therapy (P = 0.15, Figure 5).

Figure 3. Meta-regression by duration of treatment using the 'matreg' command in Stata version 13 (stata.com) (Number of observations: 12, P = 0.15)

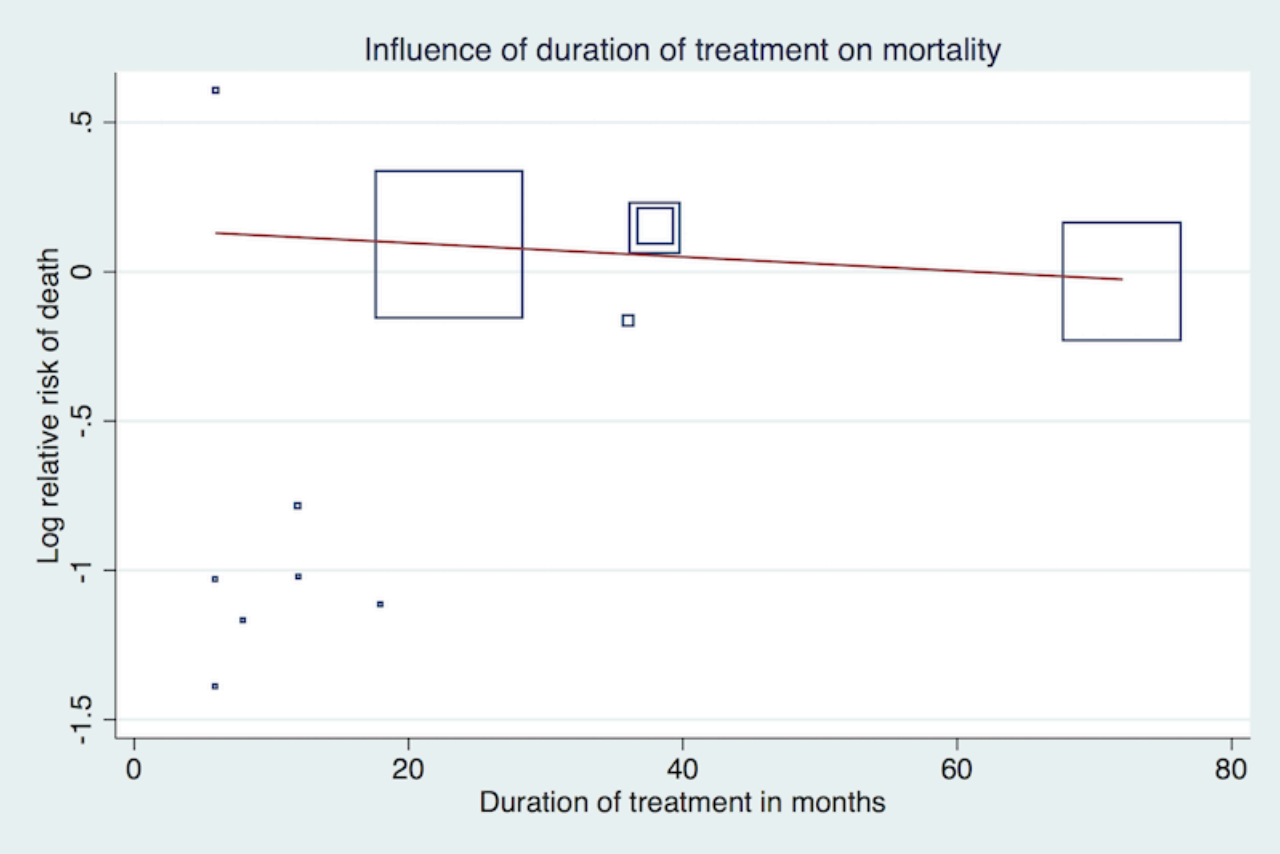


Figure 4. Meta-regression by proportion of participants with prior myocardial infarction using the 'matreg' command in Stata version 13 (stata.com) (Number of observations:8, P = 0.19)

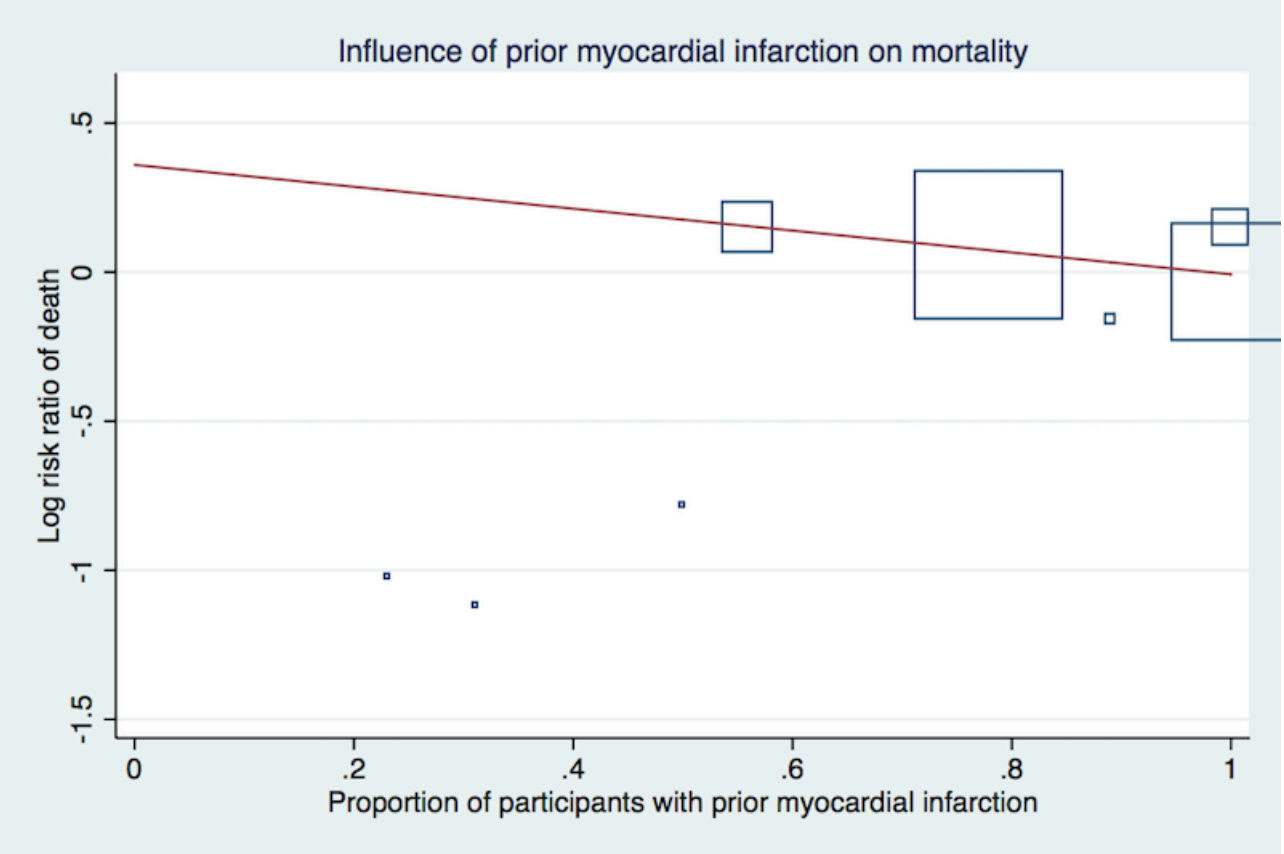
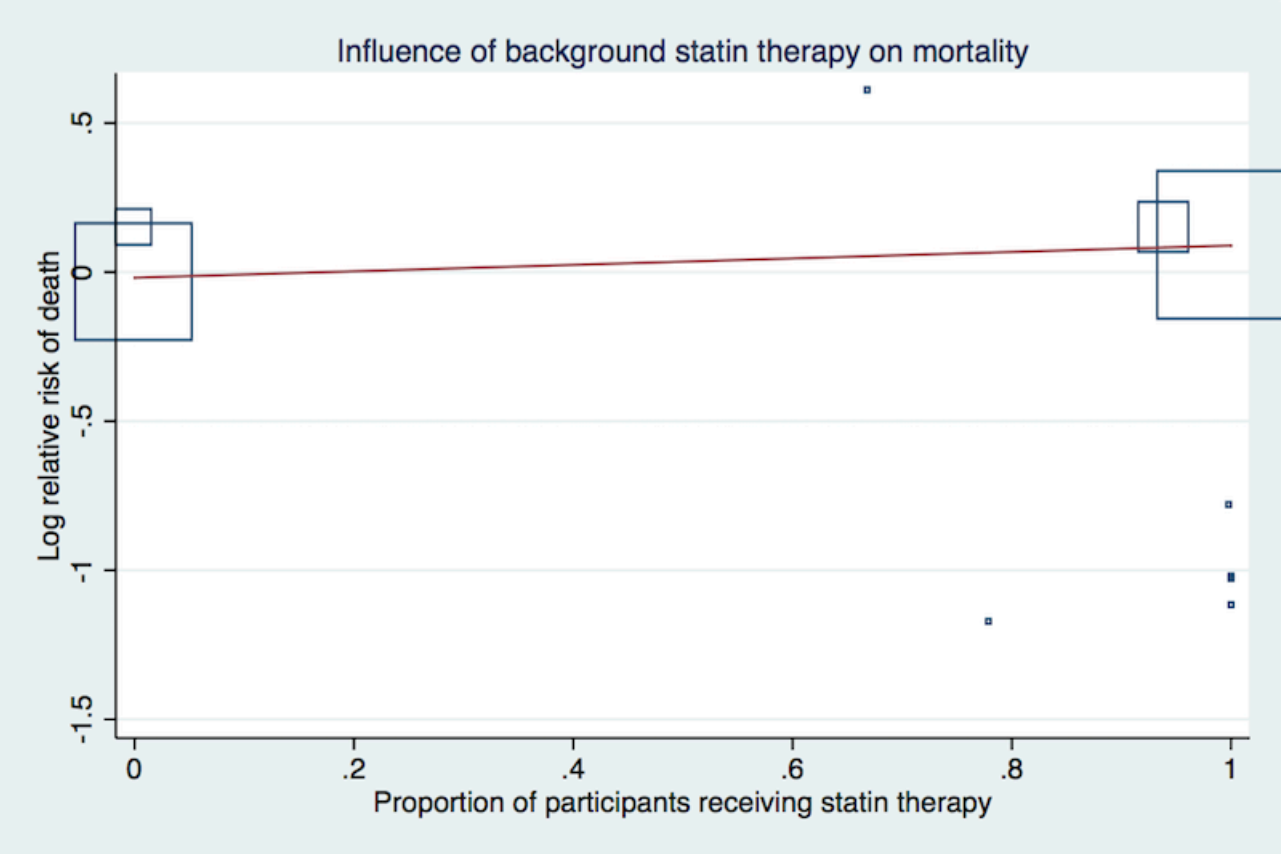


Figure 5. Meta-regression by proportion of participants receiving background statin therapy using the 'matreg' command in Stata version 13 (stata.com) (Number of observations: 10, P = 0.15)



Secondary outcomes

The effect of niacin was not significant in any cardiovascular outcome.

Using available cases, niacin did not reduce:

- the number of fatal myocardial infarctions (RR 1.01, 95% CI 0.91 to 1.11; participants = 33,336; studies = 6; I^2 = 0%, moderate-quality evidence, downgraded due to imprecision, Analysis 1.3);
- cardiovascular mortality (RR 1.02, 95% CI 0.93 to 1.12; participants = 32,966; studies = 5; I^2 = 0%, moderate-quality evidence, downgraded due to imprecision, Analysis 1.4);
- non-cardiovascular mortality (RR 1.12, 95% CI 0.98 to 1.28; participants = 32,966; studies = 5; I^2 = 0%; high-quality evidence, Analysis 1.5);
- the number of non-fatal myocardial infarctions (RR 0.91, 95% CI 0.77 to 1.07; participants = 33,164; studies = 4; I^2 = 53%, low-quality evidence, downgraded due to imprecision and inconsistency, Analysis 1.6);
- the number of fatal or non-fatal myocardial infarctions (RR 0.93, 95% CI 0.87 to 1.00; participants = 34,829; studies = 9; I^2 = 0%, moderate-quality evidence, downgraded due to imprecision, Analysis 1.7);
- the number of fatal or non-fatal strokes (RR 0.95, 95% CI 0.74 to 1.22; participants = 33,661; studies = 7; I^2 = 42%, low-quality evidence, downgraded due to imprecision and inconsistency, Analysis 1.8); nor
- the number of revascularisation procedures (RR 0.85, 95% CI 0.68 to 1.06; participants = 33,130; studies = 8; I^2 = 45%, low-quality evidence, downgraded due to imprecision and inconsistency, Analysis 1.9).

Using available cases, niacin increased the number of side effects, specifically:

- flushing (RR 7.69, 95% CI 4.14 to 14.28; participants = 11,038; studies = 15; I^2 = 91%, moderate-quality evidence, downgraded due to inconsistency, Analysis 1.10);
- pruritus (RR 5.26, 95% CI 2.68 to 10.32; participants = 5800; studies = 6; I^2 = 66%, moderate-quality evidence, downgraded due to inconsistency, Analysis 1.11);
- rash (RR 3.15, 95% CI 1.94 to 5.13; participants = 31,485; studies = 9; I^2 = 52%, moderate-quality evidence, downgraded due to inconsistency, Analysis 1.12);
- headache (RR 1.40, 95% CI 0.86 to 2.28; participants = 300; studies = 3; I^2 = 0%, moderate-quality evidence, downgraded due to imprecision, Analysis 1.13);
- gastrointestinal symptoms (RR 1.69, 95% CI 1.37 to 2.07; participants = 35,353; studies = 12; I^2 = 60%, moderate-quality evidence, downgraded due to inconsistency, Analysis 1.14); and
- discontinuation of treatment due to side effects (RR 2.17, 95% CI 1.70 to 2.77; participants = 33,539; studies = 17; I^2 = 77%,

moderate-quality evidence, downgraded due to inconsistency, Analysis 1.15).

The statistical heterogeneity (I^2) was high for the outcomes flushing, pruritus, rash, gastrointestinal symptoms, and discontinuation of treatment due to side effects, and we could not explain the heterogeneity by dose, pharmacological measures to prevent side effects, use of run-in or enrichment period, or risk of bias. Therefore, we downgraded our judgement of the quality of evidence due to statistical inconsistency. However, the consistent directions of effects and the generally large effect sizes leave no doubt that niacin does substantially increases the number of side effects. Although the exact size of the estimate is compromised by the inconsistency, the clinical implication is clear and pooling seems appropriate.

Sensitivity analyses using different assumptions for missing data did not affect the conclusion for any secondary outcome (Table 1. We did not draw forest plots given the minimal differences and large number of sensitivity analyses.

For the outcome of new onset of diabetes, none of the three included studies reported available case analysis. Instead, we considered all randomised participants (which assumes no events for missing participants). The pooled results suggested that Niacin increased the number of participants developing diabetes (RR 1.32, 95% CI 1.16 to 1.51; participants = 27,982; studies = 3; I^2 = 0%, high-quality evidence, Analysis 1.16). We did not downgrade due to risk of attrition bias because the proportion of missing data was as low as 1% in the dominating trial (HPS2-THRIVE 2014). Therefore, we considered the risk of bias to be low for the body of evidence.

None of the studies reported information about quality of life or costs.

DISCUSSION

Summary of main results

We found high-quality evidence that niacin does not reduce the risk for overall mortality. A sensitivity analysis limited to the two RCTs at low risk of bias (28,840 participants), suggested that niacin may even increase the number of deaths. We found no significant effect modification by duration of treatment, prior myocardial infarction, or background statin therapy.

We found moderate- to high-quality evidence that niacin does not reduce any other cardiovascular outcomes such as cardiovascular mortality, non-cardiovascular mortality, fatal myocardial infarctions, non-fatal myocardial infarction, or fatal or non-fatal myocardial infarction. Low-quality evidence suggested that niacin does not reduce the number of fatal or non-fatal strokes, or revascularisation procedures.

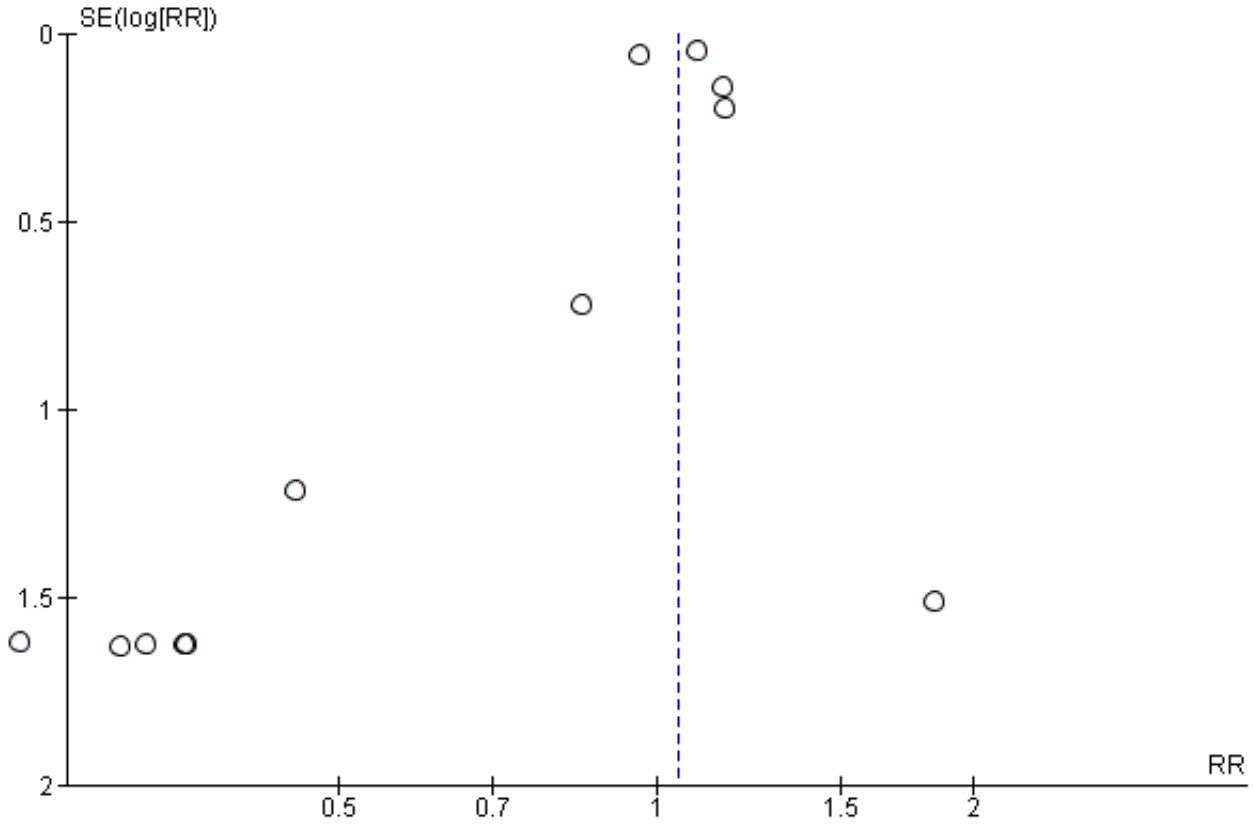
We found moderate-quality evidence that niacin does substantially increase the number of participants discontinuing treatment due to side effects and the number of selected side effects such as flushing, pruritus, rash, and gastrointestinal symptoms, but also the serious side effect of new onset diabetes.

Overall completeness and applicability of evidence

Completeness

We extensively searched the literature and carefully screened reference lists of relevant articles. Although we are confident that we did not miss any relevant study, potential selective outcome reporting might affect our results. First, the proportion of trials contributing to the meta-analysis for our primary outcome (overall mortality) was below 50% when we also consider the six excluded RTCs that failed to report any clinically relevant outcome (Furukawa 2007). In addition, the funnel plot of the primary outcome was asymmetrical and suggested that positive studies were more likely to be published (Figure 6). Since positive study bias would overestimate beneficial effects of niacin, it is unlikely that missing studies may have biased our conclusion that niacin is not beneficial.

Figure 6. Funnel plot of comparison: 1 niacin over placebo, maximum follow-up, available case analysis, outcome: 1.1 overall mortality



Applicability

Low heterogeneity despite considerable variety in populations suggests that the absence of beneficial effects of niacin treatment on mortality and cardiovascular outcomes are widely applicable. The generalisability is further supported by the fact that the meta-regression analyses did not show any significant association between effect estimate and duration of treatment, secondary or primary prevention, or background statin therapy. Although there was high statistical heterogeneity in side effects and discontinuation of treatment due to side effects, the clinical interpretation that niacin does substantially increase the number of side effects was consistent across studies and can be generalised.

Quality of the evidence

The meta-analyses were largely driven by one large trial at low risk of bias (HPS2-THRIVE 2014). Therefore, although we considered most trials to be at high risk of bias, mainly due to missing data, we did not downgrade any outcome for risk of bias. The results were robust in a sensitivity analysis where we made relatively extreme assumptions for missing outcome data (Table 1). Moreover, other potential sources of bias such as performance bias due to open-label medication or detection bias through unblinded outcome assessment were unlikely to affect our conclusions because the anticipated direction of these biases would favour niacin. Following the same logic, we did not downgrade for potential publications bias; the funnel plot for the main outcome was skewed in favour of positive studies (Figure 6).

We downgraded our certainty in effects due to imprecision when the confidence interval of the overall effect included both no effect and potential benefit. When the confidence interval excluded benefit but included no effect and potential harm, we did not downgrade. The rationale for the latter approach is that the distinction between no effect and harm is irrelevant for clinical decision-making; the clinical interest lies in potential benefits of niacin.

We downgraded two outcomes for inconsistency. Overall, the quality of evidence ranged between high and moderate; quality was low only for the stroke outcome.

Potential biases in the review process

We screened all potentially relevant abstracts and full texts in duplicate and extracted included studies in duplicate. A potential limitation is that we did not systematically search the grey literature and did not systematically contact authors of identified studies for additional unpublished data. However, given the lack of significant benefits of niacin therapy, the large number of participants in our meta-analysis, and the low heterogeneity, only a large trial demonstrating a clear benefit could affect the conclusions. It is unlikely that we missed such a trial.

We made a number of (conservative) assumptions when outcome details were not clearly reported, as specified under data synthesis. A survey of investigators would have been optimal. However, the reporting quality of the main trial (HPS2-THRIVE 2014) was high and

the potential risk of bias introduced by these assumptions therefore minimal.

Agreements and disagreements with other studies or reviews

Our conclusions are in line with the conclusions of related meta-analyses. Ip 2015 reported a potentially harmful effect of niacin on overall mortality when niacin is administered on top of background statin treatment in high-risk participants (RR 1.10, 95% CI 1.00 to 1.20, I^2 = 0%), which is identical to our estimate based on the two trials at low risk of bias. Regarding new onset of diabetes, a recent meta-analysis (Goldie 2015) found that "Niacin therapy was associated with an increase of new onset diabetes of RR 1.34 (95% CIs 1.21 to 1.49)". Although Goldie et at included RCTs evaluating niacin combination therapy, the estimate was very similar to our estimate (RR 1.32, 95% CI 1.16 to 1.51, I^2 = 0%).

AUTHORS' CONCLUSIONS

Implications for practice

In summary, moderate- to high-quality evidence suggests that niacin does not reduce mortality or cardiovascular events. Our confidence is increased by the fact that none of the outcomes showed a significant benefit, despite potential biases in favour of Niacin. Niacin cannot be recommended for primary or secondary prevention of cardiovascular events.

Implications for research

No further research is required to evaluate the role of niacin in the prevention of cardiovascular events. The body of evidence appears sufficient to conclude that niacin has no role in the primary or secondary prevention of cardiovascular events, not as mono nor as add-on therapy. Considering the potential increase in overall mortality, as suggested by two large trials at low risk of bias, additional randomised controlled trials in similar populations would be unethical.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ADMIT 2000

Methods	**Design:** parallel-group, factorial (niacin x antioxidant x warfarin), pilot trial **Recruitment:** 468 participants from 1993-1994 in 6 study centres in the USA **Setting:** primary, secondary, and tertiary care **Funding:** Bristol Myers Squibb supplied pravastatin, Hoffman LaRoche supplied antioxidants, Merck Dupont supplied warfarin, and Upsher Smith supplied niacin
Participants	**Inclusion criteria:** 30 years or older, ankle-brachial index < 0.85, documented surgery or angioplasty for peripheral arterial disease, average LDL-C level < 190 mg/dL. Able to tolerate niacin and warfarin (see run-in) **Exclusion criteria:** baseline fasting TG 500 mg/dL or averaged 400 mg/dL; overt complications of peripheral arterial disease, cardiovascular events within 6 months, unstable angina, history of congestive heart failure NYHA class III or IV, atrial fibrillation, poorly controlled diabetes, uncontrolled hypertension, active peptic ulcer, history of bleeding, history of repeated venous thromboembolic disease, cancer within last 10 years, renal insufficiency, liver disease, thrombocytopenia, anaemia, history of gout, history of myositis/rhabdomyolysis, hypothyroidism, therapy with warfarin, heparin or ticlopidine, lipid-lowering drug, cyclosporine, corticosteroids, alcohol consumption > 14 drinks/week, Women with child-bearing potential, contraindications to study medications, non-compliance during run-in **Run-in/enrichment:** 3-4 months, niacin 1 mg/day (eligibility criteria), warfarin 1 mg/day, and placebos **Baseline characteristics** Age: 65 years, SD 9 Men: 81% (379/468) Diabetes: 24% (110/468) Current smoker: 39% (183/468) Prior MI/established CHD: 40% (187) Hypertension: 61% (287/486) Statin therapy: 100%
Interventions	**Arm 1:** Niacin 3000 mg/day or maximally tolerated dosage (randomised = 237, complete cases = 213) **Arm 2:** Placebo (randomised = 231, complete cases = 209) **Duration of treatment:** 11 months, “follow-up at 48 weeks was approximately 85% in each treatment group.” **Measure to prevent flushing/unblinding due to flushing:** 15% of placebo tables contained low dose niacin (50 mg, no lipid effect expected). Participants therefore experienced intermittent flushing in order to minimise unmasking of niacin therapy **Background therapy:** All participants received open-label pravastatin titrated to achieve LDL-C < 130 mg/dL. Factorial trial: participants were randomly assigned either to active or placebo antioxidant (beta-carotene, vitamin E, and vitamin C antioxidants). Participants were randomly assigned to active or placebo warfarin. All participants were encouraged to stop smoking and/or maintain abstinence from smoking. All participants received aspirin
Outcomes	**Multiple primary outcomes:** (1) assessment of the ability to treat and follow symptomatic and asymptomatic participants with peripheral arterial disease in a multifactorial, doubly-masked trial; (2) deter-

ADMIT 2000 *(Continued)*

	mination of the feasibility of recruiting women and minorities, asymptomatic people with peripheral arterial disease, and people without overt coronary vascular disease; (3) assessment of the ability to maintain therapy masking; (4) success in treatment during follow-up measured in terms of the proportion of values within target range at the 3-month follow-up for biochemical parameters (LDL-C, 70 mg/dL-130 mg/dL; HDL-C, increased 20% to 25%; international normalised ratio, 1.5 to 2.0; additionally, antioxidant levels were obtained to measure the effect of the antioxidant therapy); (5) safety maintained by close monitoring of side effects, alanine aminotransferase, haemoglobin A1c, and international normalised ratio; and (6) adherence to therapy measured by pill count and proportion of scheduled follow-up visits completed and by dropout rate **Secondary outcomes:** Not reported
Notes	**Compliance:** based on pill count, 90% in the niacin group and 87% in the placebo group **Registration:** Not reported **Not completed as planned:** Original sample size was 600

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not explicitly reported but likely computer-generated. "Randomization assignments at each clinical centre were made in blocks of random size where the block size was a multiple of 8"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind", placebo-controlled, specific measures to blind investigators and prevent unblinding of participants, "assessment of the ability to maintain therapy masking" mentioned as outcome
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, low for participant-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcome mortality not reported. Outcome "discontinuation of treatment due to side effects": proportion of missing data 10% in both groups; events/missing: 19/43 in intervention, 9/31 in control
Selective reporting (reporting bias)	Unclear risk	Only retrospectively published protocol available
Other bias	Low risk	None

AIM-HIGH 2011

Methods	**Design:** 2 parallel-groups **Recruitment:** 3414 participants from 2006-2010 at 92 centres in USA and Canada **Setting:** Not reported **Funding:** National Heart, Lung, and Blood Institute, unrestricted grant from Abbott Laboratories. Abbott Laboratories donated the extended-release niacin, the matching placebo, and ezetimibe; Merck

AIM-HIGH 2011 *(Continued)*

	donated simvastatin. Neither of these companies had any role in the oversight or design of the study or in the analysis or interpretation of the data
Participants	**Inclusion criteria:** 45 years or older, established cardiovascular disease (documented stable CHD, cerebrovascular or carotid disease, or peripheral arterial disease), low baseline levels of HDL cholesterol (< 40 mg/dL for men; < 50 mg/dL for women), elevated triglyceride levels (150 mg/dL-400 mg/dL), LDL-C levels lower than 180 mg/dL. **Exclusion criteria:** hospitalised for an acute coronary syndrome or had undergone a planned revascularisation within 4 weeks, stroke within 8 weeks, fasting glucose > 180 mg/dL or haemoglobin A1C > 9.0%, BP > 200/100 mm Hg unresponsive to medical therapy, active peptic ulcer, active liver disease, recent history of acute gout, chronic renal insufficiency, risk of pregnancy, significant comorbidity likely to cause death in the 3- to 5-year follow-up, AIDS/active HIV infection, history of substance abuse within 5 years **Run-in/enrichment:** open-label simvastatin 40 mg/day + extended-release niacin increasing to 2000 mg/day. Run-in phase could be extended to 8 weeks to demonstrate tolerance of at least 1500 mg/day of niacin **Baseline characteristics** Age: Mean 63.7, SD 8.7 Men. 85% Diabetes: 33% Current smoker: not reported Prior MI/established CHD: 56% Hypertension: 71% Statin therapy: 94%
Interventions	**Arm 1:** niacin extended-release at a dose of 1500 mg/day-2000 mg/day plus simvastatin 40 mg/day. For those limited to a niacin dose of 1500 mg/day during the run-in, there was a subsequent attempt to increase dosage to 2000 mg/day over the first year (randomised = 1718, complete cases = 1693) **Arm 2:** simvastatin + a matching placebo (randomised = 1696, complete cases = 1672) **Duration of treatment:** mean 36 months **Measure to prevent flushing/unblinding due to flushing:** medication at bedtime with a low-fat snack and, if allowed by private physician, taking 325 mg aspirin up to 30 min before taking blinded study medication, avoid hot or spicy food/drink around the time of dosing. Each placebo tablet included a sub-therapeutic dose of immediate-release niacin 50 mg. **Background therapy:** simvastatin 40 mg/day titrated to LDL-C level in the range of 40 mg/dL-80 mg dL. Participants in both groups could receive ezetimibe, at a dose of 10 mg/day, to achieve the target LDL-C level
Outcomes	**Primary outcome:** composite, first occurrence of CHD death, non-fatal MI, ischaemic stroke, hospitalisation for acute coronary syndrome, or symptom-driven coronary or cerebral revascularisation **Secondary outcomes:** composite end points of (1) CHD death, non-fatal MI, ischaemic stroke, or high-risk acute coronary syndrome; or (2) CHD death, non-fatal MI, or ischaemic stroke; or (3) any cardiovascular death **Tertiary outcomes**: all-cause death, composite of all-cause death, admission for acute coronary syndrome, ischaemic stroke or any arterial revascularisation, and the individual components of the end points

AIM-HIGH 2011 *(Continued)*

Notes	**Compliance:** the study drug was discontinued in 25.4% of the participants in the niacin group and in 20.1% of the participants in the placebo group. The overall rate of adherence *among the participants who continued treatment* was at least 75% **Registration:** NCT00120289 **Not completed as planned:** “As a result of the much lower than expected overall event rate, the primary endpoint was redefined.” In addition, the follow-up was stopped for futility and harm: “the data and safety monitoring board recommended that the blinded intervention be stopped because the boundary for lack of efficacy had been crossed and an unexpected higher rate of ischaemic stroke had been observed among patients who were being treated with niacin”

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not explicitly reported but likely computer-generated: "Randomization was performed with the use of a secure Internet application"
Allocation concealment (selection bias)	Low risk	"Randomization was performed with the use of a secure Internet application"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Blinded treatment to patients and study personnel"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A clinical events committee reviewed suspected primary end points (including silent myocardial infarction) with supporting documentation that did not reveal the treatment assignments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Proportion of missing data: 1.5% in both groups; event/missing: 96/25 in intervention and 82/24 in control
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified in the prospectively published trial registry record were subsequently reported
Other bias	Low risk	None

ALPINE-SVG 2015

Methods	**Design:** parallel-group **Recruitment:** 38 participants from 2011-2012 in the USA, number of study centres not reported, veterans **Setting:** tertiary care **Funding:** North Texas Veterans Healthcare System
Participants	**Inclusion criteria:** ≥ 18 years, coronary saphenous vein graft, graft stenosis 30%-60% of angiographic diameter, undergoing clinically-indicated coronary angiography **Exclusion criteria:** known intolerance to niacin or statin, life expectancy less than 12 months, a history of liver disease, TG > 500 mg/dL, LDL-C > 200 mg/dL, HDL-C > 60 mg/dL, poorly controlled diabetes or hypertension, congestive heart failure NYHA class III or IV

ALPINE-SVG 2015 *(Continued)*

	Run-in/enrichment: 4 weeks **Baseline characteristics** Age: 65 years, SD 6 Men: not reported Diabetes: 63% Current smoker: not reported Prior MI/established CHD: 67% Hypertension: 95% Statin therapy: 100%
Interventions	**Arm 1:** extended-release niacin (Niaspan), 1500 mg/day-2000 mg/day (randomised = 19, complete cases = 19) **Arm 2:** placebo (randomised = 19, complete cases = 19) **Duration of treatment:** 12 months **Measure to prevent flushing/unblinding due to flushing:** 4 week run-in, matching placebo contained 50 mg of crystalline niacin that causes flushing but has no effect on lipid levels **Background therapy:** all participants received statin drugs
Outcomes	**Primary outcome:** change in percent atheroma volume at intravascular ultrasonography **Secondary outcomes:** a number of radiographic measures for Intermediate saphenous vein graft lesions, exercise capacity and ischaemia assessed by exercise stress testing, carotid intima-media thickness, reactive hyperemia index, endothelial progenitor cells-colony forming units/mL of peripheral blood, major adverse cardiac events
Notes	**Compliance**: 89% in the intervention, and 95% in the control arm **Registration:** NCT01221402 ALPINE-SVG was stopped early after publication of AIM-HIGH 2011 and HPS2-THRIVE 2014 (planned: 138 participants, enrolled: 38 participants)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)"

ALPINE-SVG 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	"All patients entering the trial prior to early termination of enrolment completed the trial"
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified in the prospectively published trial protocol were subsequently reported
Other bias	Low risk	None

ARBITER-2 2004

Methods	**Design:** Parallel-group **Recruitment:** 167 participants from 2001-2003 at 1 study centre in the USA **Setting:** tertiary care military medical centre **Funding:** partial funding for this study was provided by Kos Pharmaceuticals in the form of an unrestricted research grant administered by the Henry M. Jackson Foundation for the Advancement of Military Medicine
Participants	**Inclusion criteria:** 30 years or older, coronary vascular disease, currently treated with a statin, LDL-C < 130 mg/dL and HDL-C < 45 mg/dL **Exclusion criteria:** known intolerance to niacin, a history of liver disease, or abnormal liver associated enzymes **Run-in/enrichment:** not reported **Baseline characteristics** Age: 67 years, SD 10 Men: 91% Diabetes: 28% Current smoker: 10% Prior MI/established CHD: 50% Hypertension: 75% Statin therapy: 100%
Interventions	**Arm 1:** extended-release niacin (Niaspan), dose increased from 500 mg-1000 mg within 30 days (randomised = 87, complete cases = 78) **Arm 2:** placebo (randomised = 80, complete cases = 71) **Duration of treatment:** maximum 12 months **Measure to prevent flushing/unblinding due to flushing:** medication taken at night, taken with the participant's usual daily dose of aspirin **Background therapy:** all participants received statin drugs
Outcomes	**Primary outcome:** common carotid intima-media thickness

ARBITER-2 2004 *(Continued)*

	Secondary outcomes: changes in serum lipid concentrations, liver-associated enzyme elevations, composite of clinical cardiovascular events including any hospitalisation for an acute coronary syndrome, stroke, an arterial revascularisation procedure, or sudden cardiac death
Notes	**Compliance:** adherence to study medication based on pill counts at 90, 180, 270, and 365 days ranged from 90.3% to 94.5% and was not statistically different between the placebo and niacin groups. **Registration:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated sequence"
Allocation concealment (selection bias)	Low risk	"Central research pharmacy to dispense the study medication"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind", "Only the research pharmacist was aware of the study drug assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Only the research pharmacist was aware of the study drug assignment."
Incomplete outcome data (attrition bias) All outcomes	High risk	Proportion of missing data: 10% in intervention and 11% in control; event/missing: 1/9 in intervention and 2/9 in control
Selective reporting (reporting bias)	Unclear risk	No protocol published, not registered
Other bias	Low risk	None

Capuzzi 2003

Methods	**Design:** parallel-group **Recruitment:** 270 participants in 39 centres in the USA (time not reported) **Setting:** tertiary care **Funding:** AstraZeneca Pharmaceuticals, LP, Wilmington, DE. The primary study site at Thomas Jefferson University also received support from the Sidney Kimmel Laboratory for Preventive Cardiology
Participants	**Inclusion criteria:** aged ≥ 18 years, combined dyslipidaemia, fasting levels of cholesterol ≥ 200 mg/dL, TG ≥ 200 mg/dL and ≤ 800 mg/dL, apolipoprotein B ≥ 110 mg/dL, and HDL-C < 45 mg/dL **Exclusion criteria:** active arterial disease within 3 months, major organ dysfunction, taking other medications that posed potential study concerns, women at risk of pregnancy, uncontrolled hypertension, hypothyroidism; creatine kinase > 3 times the upper limit of normal; serum creatinine concentrations > 1.8 mg/dL, use of concomitant medications known to affect serum lipid levels or present safety concerns

Capuzzi 2003 *(Continued)*

	Run-in/enrichment: 6-week, instruction to discontinue all lipid-modifying medications, dietary supplements, and food additives, and to adhere to the American Heart Association Step I diet **Baseline characteristics** Age: 56.8, SD 10.5 Men: 74% Diabetes: 15% Current smoker: not reported Prior MI/established CHD: 0% Hypertension: not reported (uncontrolled hypertension was an exclusion criterion) Statin therapy: 100% (part of interventions)
Interventions	**Arm 1:** rosuvastatin 40 mg monotherapy: rosuvastatin 10 mg for 12 weeks, 20 mg for 6 weeks, and 40 mg for 6 weeks (randomised = 72, complete cases = 60) **Arm 2:** niacin extended-release 0.5 g for 4 weeks, 1.0 g for 8 weeks, 1.5 g for 6 weeks, and 2.0 g for 6 weeks **Arm 3:** rosuvastatin 40 mg/niacin extended-release 1 g: niacin 0.5 g for 4 weeks, 1.0 g for 2 weeks, 1.0 g plus rosuvastatin 10 mg for 6 weeks, 1.0 g plus rosuvastatin 20 mg for 6 weeks, and 1.0 g plus rosuvastatin 40 mg for 6 weeks (randomised = 46, complete cases = 43) **Arm 4:** rosuvastatin 10-mg/niacin extended-release 2-g group: niacin 0.5 g for 4 weeks, 1.0 g for 2 weeks, 1.0 g plus rosuvastatin 10 mg for 6 weeks, 1.5 g plus rosuvastatin We included the comparison arm 1 vs. arm 3 **Duration of treatment:** maximum 12 months **Measure to prevent flushing/unblinding due to flushing:** extended-release, niacin taken with water at bedtime after a low-fat snack **Background therapy:** not reported
Outcomes	**Primary outcome:** fasting plasma LDL-C levels **Secondary outcomes:** Fasting plasma levels of TC, non-HDL cholesterol, TG, VLDL cholesterol, apolipoprotein B, HDL cholesterol, apolipoprotein A-1, and lipoprotein(a) (Lp[a])
Notes	**Compliance:** intervention: 67%, control: 47% **Registration:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	"Open-label"; low risk of bias for mortality, high for subjective outcomes

Capuzzi 2003 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome overall mortality not reported. Outcome discontinuation of treatment due to side effects: proportion of missing data: 7% in intervention and 4% in control; events/missing: 7/5 in intervention, 1/2 in control
Selective reporting (reporting bias)	Unclear risk	No protocol published, not registered
Other bias	Low risk	None

Carotid IMT 2008

Methods	**Design:** parallel **Recruitment:** 432 participants from 2006-2008 worldwide (countries not reported) **Setting:** not reported **Funding:** Merck Sharp & Dohme Corp
Participants	**Inclusion criteria:** 18-70 years, heterozygous familial hypercholesterolaemia, LDL-C > 100 mg/dL, TG < 400 mg/dL, stable dose of intensive LDL-C-lowering therapy **Exclusion criteria: <** 80% drug study compliance, medical conditions known to influence serum lipids, lipoproteins, or ultrasound acoustic window, medication at unstable dose, premenopausal women, poorly controlled or new onset diabetes mellitus, stenosis of the carotid artery, chronic heart failure, uncontrolled cardiac arrhythmias, unstable hypertension, active or chronic hepatobiliary or hepatic disease, HIV positive, episode of gout **Run-in/enrichment:** niacin for 8 weeks. **Baseline characteristics** Age: 54 years, SD 9 Men: 63% Diabetes: not reported Current smoker: bot reported Prior MI/established CHD: not reported Hypertension: not reported Statin therapy: 100% (inclusion criterion)
Interventions	**Arm 1:** niacin 2000 mg/day + laropiprant (dose not reported) (randomised = 214, complete cases = 180) **Arm 2:** placebo (randomised = 218, complete cases = 204) **Duration of treatment:** maximum 96 weeks **Measure to prevent flushing/unblinding due to flushing:** laropiprant

Carotid IMT 2008 *(Continued)*

	Background therapy: not reported
Outcomes	**Primary outcome:** carotid intima media thickness **Secondary outcomes:** lipid profile
Notes	**Compliance:** not reported **Registration:** NCT00384293 **Not completed as planned:** no reason provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, low risk of bias for participant-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcome overall mortality not reported. Outcome fatal or non-fatal MI: proportion of missing data: 16% in intervention and 6% in control; events/missing ratio: 0/34 in intervention, 1/14 control
Selective reporting (reporting bias)	Unclear risk	No protocol published, clinical outcomes not specified in registry
Other bias	Low risk	None

CDP 1975

Methods	**Design:** parallel-group **Recruitment:** 8341 participants from 1966-1969 in 53 study centres in the USA **Setting:** not reported **Funding:** National Heart and Lung Institute
Participants	**Inclusion criteria:** men; aged 30-64 years; proved previous MI (class I or II of the functional classification of the NYHA and free from a specified list of diseases and conditions), at least 3 months beyond their most recent MI, free of evidence of recent worsening of their coronary disease or of other major illnesses **Exclusion criteria:** not reported **Run-in/enrichment:** 2-month control period

CDP 1975 *(Continued)*

	Baseline characteristics Age: ≥ 55 years Men: 44% Diabetes: 5% oral hypoglycaemic drug Current smoker: 38% Prior MI/established CHD: 100% Hypertension: 52% Statin therapy: 0% (not available at the time)
Interventions	**Arm 1:** conjugated estrogens, 2.5 mg/day **Arm 2:** conjugated estrogens, 5.0 mg/day **Arm 3:** clofibrate, 1.8 g/day **Arm 4:** dextrothyroxine sodium, 6.0 mg/day **Arm 5:** niacin, 3.0 g/day (randomised = 1119, complete cases = 1116) **Arm 6:** placebo (randomised = 2798, complete cases = 2797) We included the comparison arm 5 vs arm 6 **Duration of treatment:** maximum 96 weeks **Measure to prevent flushing/unblinding due to flushing:** not reported **Background therapy:** not reported
Outcomes	**Primary outcome:** overall mortality **Secondary outcomes:** other major end points included cause-specific mortality, particularly coronary mortality and sudden death, and non-fatal cardiovascular events such as recurrent MI, acute coronary insufficiency, development of angina pectoris, congestive heart failure, stroke, pulmonary embolism, and arrhythmias
Notes	**Compliance:** median compliance 85% over 5 years **Registration:** NCT00000482

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the participant nor the clinic staff was informed of participant drug allocation

CDP 1975 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Only four dropout patients (three in niacin, and one in placebo) have been lost to follow-up such that their vital status at the five year follow-up was not known." Events/missing: 237/3 in intervention and 583/1 in control
Selective reporting (reporting bias)	Unclear risk	Protocol published after end of recruitment, registered retrospectively
Other bias	Low risk	None

Goldberg 2000

Methods	**Design:** parallel-group **Recruitment:** 131 participants in 8 study centres in the USA (time period not reported) **Setting:** not reported **Funding:** this study was supported by Kos Pharmaceuticals, Inc., Miami, Florida
Participants	**Inclusion criteria:** either average LDL-C ≥ 190 mg/dL and no CHD risk factors, or average LDL > 160 and < 190 mg/dL and a minimum of 2 CHD risk factors **Exclusion criteria:** secondary hyperlipoproteinaemia, type I or uncontrolled type II diabetes mellitus, baseline alanine aminotransferase levels > 1.3 times the upper limit of normal, active peptic ulcer disease, gout, and hyperuricaemia. **Run-in/enrichment:** 6-week, diet run-in followed by a 2-week phase to determine LDL-C stability **Baseline characteristics:** Age: mean 54 years, range 21-75 Men: 59% Diabetes: not reported (but part of exclusion criteria) Current smoker: not reported Prior MI/established CHD: not reported Hypertension: not reported Statin therapy: not reported
Interventions	**Arm 1:** niacin extended-release 3000 mg/day 1 dose at bedtime. Initial dosing with extended-release placebo was 375 mg/day, raised to 500 mg/day, and further increased in 500-mg increments at 4-week intervals to a maximum of 3000 mg/day (randomised = 87, complete cases = 46) **Arm 2:** placebo (randomised = 44, complete cases = 34) **Duration of treatment:** 25 weeks maximum **Measure to prevent flushing/unblinding due to flushing:** extended-release, medication at bedtime, 325 mg aspirin 30 min before medication

Goldberg 2000 *(Continued)*

	Background therapy: not reported
Outcomes	**Primary outcome:** LDL-C and apolipoprotein B levels **Secondary outcome:** TC, HDL-C, VLDL, plasma TG, HDL subfractions, apolipoprotein A-1, and lipoprotein(a)
Notes	**Compliance:** not reported **Registration:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, low for participant-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Proportion of missing data: 47% in intervention and 23% in control; events/missing: 0/41 in intervention and 1/10 in control
Selective reporting (reporting bias)	Unclear risk	No protocol published, not registered
Other bias	Low risk	None

Guyton 2008

Methods	**Design:** parallel-group **Recruitment:** 1220 participants from 2005-2008 in 106 study centres in the USA **Setting:** not reported **Funding:** Merck/Schering-Plough Pharmaceuticals
Participants	**Inclusion criteria:** aged 18-79 years, LDL-C levels (130 mg/dL-190 mg/dL), triglyceride levels (≤ 500 mg/dL), and metabolic and clinical stability (e.g. euthyroid, creatinine < 2 mg/dL, creatinine kinase ≤ 2 x ULN, transaminases ≤ 1.5 x ULN) were eligible for inclusion in the study **Exclusion criteria:** not reported **Run-in/enrichment:** 4-week washout period **Baseline characteristics**

Guyton 2008 *(Continued)*

	Age: mean 57 years, SD 10.5 Men: 50% Diabetes: 16% Current smoker: not reported Prior MI/established CHD: 9% Hypertension: 65% Statin therapy: 100% (part of interventions)
Interventions	**Arm 1:** ezetimibe/simvastatin (10/20 mg/day) + niacin (titrated to 2 g/day) (randomised = 676, complete cases = 391) **Arm 2:** niacin (titrated to 2 g/day) **Arm 3:** ezetimibe/simvastatin (10/20 mg/day) (randomised = 272, complete cases = 213) We included the comparison arm 1 vs arm 3 **Duration of treatment:** maximum 24 weeks (first part of a 64-week study) **Measure to prevent flushing/unblinding due to flushing:** participants were consulted to take niacin at bedtime with a low–fat snack, aspirin (325 mg), or ibuprofen (200 mg) 30 min before taking niacin, and to avoid alcoholic and hot beverages near the time of taking niacin **Background therapy:** not reported
Outcomes	**Primary outcome:** LDL-C **Secondary outcomes:** non–HDL-C, HDL-C, TG, LDL-C, non–HDL-C, TC, apolipoprotein B, ApoA-I, lipid/lipoprotein ratio, and high- sensitivity C-reactive protein
Notes	**Compliance:** not reported **Registration:** NCT00271817

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, probably low risk of bias
Allocation concealment (selection bias)	Low risk	"Central allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All study personnel remained blinded to treatment allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All study personnel remained blinded to treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	High risk	Proportion of missing data: 42% in intervention and 22% in control; events/missing: 0/285 in intervention and 0/59 in control

Guyton 2008 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol published, prospectively registered but clinical outcomes not pre-specified
Other bias	Low risk	None

Harikrishnan 2008

Methods	**Design:** parallel-group **Recruitment:** 210 from 1 centre in India **Setting:** tertiary care **Funding:** Reagent kits sponsored by Reddys laboratories, a Pharma company
Participants	**Inclusion criteria:** aged 30-70 years, at least 6 months on statin therapy, at least 2 months on atorvastatin therapy, HDL ≤ 35 mg/dL, adhering to NYHA step II diet **Exclusion criteria:** triglyceride > 300 mg/dL, hepatobiliary and renal disease, type I diabetes or poorly-controlled diabetes, secondary forms of hyperlipidaemia, acute MI or unstable angina, hypothyroidism, gout and hyperuricaemia, left ventricular dysfunction **Run-in/enrichment:** 8 weeks of atorvastatin if participants were taking an other statin **Baseline characteristics (based on comparison of interest)** Age: mean 52.5 years, range 22-70 Men: 97% Diabetes: not reported Current smoker: not reported Prior MI/established CHD: 65% Hypertension: not reported Statin therapy: 100% (part of intervention)
Interventions	**Arm 1:** niacin 1.5 g/day + atorvastatin (randomised = 104, complete cases = 102) **Arm 2:** atorvastatin (randomised = 106, complete cases = 102) **Duration of treatment:** 9 months, SD 1.8 months **Measure to prevent flushing/unblinding due to flushing:** aspirin along with niaci (dose not reported) **Background therapy:** for uniformity in interpreting data, only participants on atorvastatin were included. Those participants who were taking a statin other than atorvastatin entered the trial after a run-in period of 8 weeks of atorvastatin after stopping the other statin. Atorvastatin was used in conventional dosages as would be required for target LDL-C levels
Outcomes	**Primary outcome:** not defined **Outcomes:** completion 8 months' follow-up, intolerance attributable to study drug which participant feels unable to continue, rise in liver enzymes, rise in creatin kinase asymptomatic, generalised muscle pain/tenderness, worsening glucose intolerance/diabetes
Notes	**Compliance:** not reported

Harikrishnan 2008 *(Continued)*

Registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi randomised, alternating weekly according to authors
Allocation concealment (selection bias)	High risk	Quasi randomised, alternating weekly according to authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome mortality not reported. Outcome "discontinuation of treatment due to side effects": proportion of missing data, 2% in intervention and 4% in control; events/missing: 4/2 in intervention, 1/4 in control
Selective reporting (reporting bias)	Unclear risk	No protocol published, not registered
Other bias	Low risk	None

Heart positive 2011

Methods	**Design:** parallel-group **Recruitment:** 221 from > 3 centres in the USA (time span and exact number of centres not reported) **Setting:** primary and secondary care **Funding:** National Institutes of Health, Baylor College of Medicine General Clinical Research Center. Study drugs provided by Abbott Laboratories, Neither the NIH nor Abbott had any role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. Abbott asked to read a draft of the manuscript before its submission for publication
Participants	**Inclusion criteria:** HIV, 21-65 years, stable highly active antiretroviral therapy (HAART) regimen for a minimum of 6 months, fasting serum triglyceride level 1.7 mmol/L, body mass index ≥ 18.5 and ≤ 30 **Exclusion criteria:** fasting serum triglyceride level ≥ 11.3 mmol/L, diabetes, use of any medications known to affect lipid or lipoprotein metabolism including, nutritional supplements (including but not limited to fish oils, creatine), steroidal compounds or anabolic agents, inability to perform the prescribed graded exercise regimen, CD4 cell count less than 200 x 106 cells/L, or presence of an opportunistic infection or conditions likely to prevent the subject from completing the required exercise regimen through the course of the study, history of symptomatic coronary artery disease (MI, angina) or peripheral vascular disease (claudication). Conditions that could affect drug safety including known adverse reactions to niacin or fibrates, serum alanine or aspartate aminotransferase level greater than two-fold the ULN adult range, renal insufficiency, treatment with warfarin anticoagulants, pregnancy, history of myositis or rhabdomyolysis, past or present alcohol abuse, peptic ulcer disease, cholelithiasis, and gout or hyperuricaemia

Heart positive 2011 *(Continued)*

	Run-in/enrichment**:** not reported **Baseline characteristics (based on comparison of interest)** Age: mean 43 years, SD 1.4 Men: 88% Diabetes: 0% Current smoker: not reported (58% had history of smoking) Prior MI/established CHD: 0% (exclusion criterion) Hypertension: not reported Statin therapy: 0% (exclusion criterion)
Interventions	**Arm 1:** usual care + guideline for nutrition and health **Arm 2:** low-saturated-fat diet and exercise **Arm 3:** low-saturated-fat diet and exercise + fenofibrate 145 **Arm 4:** low-saturated-fat diet and exercise + niacin 2 g /day **Arm 5:** low-saturated-fat diet and exercise + fenofibrate 145 mg + niacin 2 g/day We included the comparison pooled arms 4 + 5 (randomised = 92, complete cases = 49) vs pooled arms 2 + 3 (randomised = 88, complete cases = 53) **Duration of treatment:** 6 months maximum **Diet:** education in weight-maintaining diet with 50% of calories from carbohydrates, 30% of calories from fat, cholesterol no greater than 200 mg/d, and fibre 20–30 g/d **Exercise:** exercise programme at a study gymnasium, following guidelines of the American College of Sports Medicine. The sessions were supervised by certified trainers 3/weekly for 75–90 min, with aerobic and resistance components We compared pooled arms 4 + 5 vs pooled arms 2 + 3 **Measure to prevent flushing/unblinding due to flushing:** placebo contained 50 mg niacin **Background therapy:** not reported
Outcomes	**Primary outcomes:** fasting triglyceride levels, HDL-C, and non-HDL-C **Secondary outcomes:** insulin sensitivity, glycaemia, adiponectin, C-reactive protein, energy expenditure, body composition
Notes	**Compliance:** not reported **Registration:** NCT00246376

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random number table"

Heart positive 2011 *(Continued)*

Allocation concealment (selection bias)	High risk	"Study personnel were blinded to group allocations except for the person who performed the randomisation and acted as liaison between the pharmacy and the clinical coordinator"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind", "placebo-controlled"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, low risk of bias for participant-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcome 'mortality' not reported. Outcome 'flushing': proportion of missing data, 47% in intervention and 40% in control; events/missing: 16/26 in intervention, 2/19 in control
Selective reporting (reporting bias)	Unclear risk	Protocol published and registered, clinical outcomes not pre-specified
Other bias	Low risk	None

HPS2-THRIVE 2014

Methods	**Design:** parallel-group **Recruitment:** 25,673 participants from 2007-2010 in 245 centres in China, UK, Denmark, Finland, Norway, and Sweden **Setting:** secondary and tertiary care **Funding:** Merck
Participants	**Inclusion criteria:** history of MI, cerebrovascular atherosclerotic disease; or peripheral arterial disease, diabetes mellitus with any of the above or with other evidence of symptomatic CHD **Exclusion criteria**: < 50 or > 80 years, acute MI, coronary syndrome or stroke within 3 months; planned revascularisation procedure, history of chronic liver disease, or abnormal liver function, breathlessness at rest for any reason, renal insufficiency, active inflammatory muscle disease, adverse reaction to a statin, ezetimibe, niacin or laropiprant, active peptic ulcer, concurrent treatment with fibrate, niacin, ezetimibe, statin, potent CYP3A4 inhibitor, ciclosporin, amiodarone, verapamil, danazol, known to be poorly compliant with clinic visits or prescribed medication; medical history that might limit the individual's ability to take trial treatments for the duration of the study **Run-in/enrichment:** 4 weeks to standardised simvastatin 40 mg daily or, if not sufficient to achieve a TC < 3.5 mmol/L when measured after 4 weeks, simvastatin 40 mg plus ezetimibe 10 mg daily **Baseline characteristics** Age: mean 64.9 years, SD 7.5 Men: 83% Diabetes: 32% Current smoker: 18% Prior MI/established CHD: 78%

HPS2-THRIVE 2014 *(Continued)*

	Hypertension: 62% (treated hypertension) Statin therapy: 100% (background therapy)
Interventions	**Arm 1:** niacin extended-release 2 g plus laropiprant 40 mg daily (randomised = 12,838, complete cases = 12,730) **Arm 2:** matching placebo (randomised = 12,835, complete cases = 12,745) **Duration of treatment:** median of 3.9 years **Measure to prevent flushing/unblinding due to flushing:** extended-release **Background therapy:** statin-based LDL-C–lowering therapy
Outcomes	**Primary outcome:** composite of first non-fatal MI, coronary death, stroke, or arterial revascularisation **Secondary outcome:** major coronary events, non-fatal MI or coronary death
Notes	**Compliance:** 75% in intervention, 83% in control **Registration:** NCT00461630 and ISRCTN29503772

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization... was provided by the study clinic computer which was synchronized frequently with the study database at the coordinating centre in the Clinical Trial Service Unit, Oxford via secure Internet connection."
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Blind to treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Proportion of missing data: 1% in both arms; events/missing: 798/108 in intervention and 732/90 in control
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified in the prospectively published trial registry record were subsequently reported
Other bias	Low risk	None

Hunninghake 2003

Methods	**Design:** parallel-group **Recruitment:** 237 in 1999 from 23 centres in the USA **Setting:** not reported

Hunninghake 2003 *(Continued)*

	Funding: Kos Pharmaceuticals, Inc
Participants	**Inclusion criteria: ≥** 18 years, elevated LDL-C levels or elevated LDL-C and TG levels. **Exclusion criteria:** TG > 800 mg/dL, hepatic dysfunction, renal disease, biliary disease, severe hypertension, recent major vascular event, peptic ulcer, gout, type 1 or uncontrolled type 2 diabetes mellitus, cancer, risk of pregnancy, statin within 4 weeks **Run-in/enrichment:** 6 weeks' wash out and baseline evaluation **Baseline characteristics (based on comparison of interest)** Age: mean 59 years, SD 12 Men: 51% Diabetes: not reported Current smoker: not reported Prior MI/established CHD: not reported Hypertension: not reported Statin therapy: 100% (part of the intervention)
Interventions	**Arm 1:** niacin extended-release 1000 mg/day + lovastatin 20 mg/day **Arm 2:** niacin extended-release 2000 mg/day + lovastatin 40 mg/day (randomised = 57, complete cases = 57) **Arm 3:** niacin extended-release 2000 mg/day **Arm 4:** lovastatin 40 mg/day (randomised = 61, complete cases = 61) We included comparison arm 2 vs arm 4 **Duration of treatment:** maximum 28 weeks **Measure to prevent flushing/unblinding due to flushing:** medication at bedtime along with a low-fat snack and were allowed to take aspirin 325 mg **Background therapy:** not reported
Outcomes	**Primary outcome:** LDL-C **Secondary outcomes:** TC, HDL-C, TG, lipoprotein(a), and apolipoprotein B, non-HDL-C
Notes	**Compliance:** not reported for each arm **Registration:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Hunninghake 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind", "Several measures were undertaken to ensure blinding. First, all study medications were identical in shape, size, and colour. Second, equal numbers of active treatment and matched placebo tablets were administered to all four treatment groups during each phase of the study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, low risk of bias for participant-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up per group not reported
Selective reporting (reporting bias)	Unclear risk	Protocol published retrospectively, not registered
Other bias	Low risk	None

Lee 2009

Methods	**Design:** parallel groups **Recruitment:** 71 participants from a single centre in the UK (time period not reported) **Setting:** not reported **Funding:** investigator-initiated study funded by Merck KGaA
Participants	**Inclusion criteria:** HDL-C < 40 mg/dL in previous 12 months and carotid atherosclerosis or peripheral arterial disease **Exclusion criteria:** contraindications to MRI or to niacin; severe carotid stenosis (> 70%); treatment with fibrates, nicorandil, or oral nitrates, recent acute coronary syndrome; uncontrolled diabetes; fasting triglyceride level > 500 mg/dL; peptic ulcer; cardiac failure requiring diuretic treatment **Run-in/enrichment:** not reported **Baseline characteristics** Total randomised: 71 Age: mean 65, SD 9 Men: 94% Diabetes: 65% Current smoker: 83% Prior MI/established CHD: 48% Hypertension: 78% Statin therapy: 100%
Interventions	**Arm 1:** nicotinic acid was increased on a weekly basis from 375 mg to 500 mg, and then to 750 mg daily. Participants subsequently received 1000 mg for 4 weeks, 1500 mg for a further 4 weeks, and then 2000 mg daily for the remainder of the study (randomised = 35, complete cases = 25) **Arm 2:** placebo (randomised = 36, complete cases = 30)

Lee 2009 *(Continued)*

	Duration of treatment: maximum 12 months **Measure to prevent flushing/unblinding due to flushing:** medication at night, together with aspirin **Background therapy:** not reported
Outcomes	**Primary outcome:** carotid artery wall area **Secondary outcomes:** other MRI outcomes
Notes	**Compliance:** niacin (93%) and placebo (92%) based on pill count **Registration:** NCT00232531

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, low risk of bias for participant-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcome "mortality" not reported. Outcome "discontinuation of treatment due to side effects": proportion of missing data, 17% in intervention and 14% in control; events/missing: 7/6 in intervention, 2/5 in control
Selective reporting (reporting bias)	Unclear risk	No protocol published, clinical outcomes not specified in registry
Other bias	Low risk	None

Lee 2011

Methods	**Design:** pilot, parallel **Recruitment:** 28 participants from 1987-1989 in 6 centres in Korea **Setting:** not reported **Funding:** Korean Society of Circulation (Industrial-Educational Cooperation 2006)
Participants	**Inclusion criteria:** 20-70 years, coronary stenosis in angiogram, and who had not been taking, hormone therapy or anti-oxidant vitamins within the previous 2 months. **Exclusion criteria:** cholesterol lowering, anti-oxidants, or hormones within 2 months, premenopausal women, hypercholesterolaemia, cyclosporine or antifungal agents (azole), severe left ventricular dysfunction, liver disease, renal dysfunction, hypothyroidism, ileal bypass.

Lee 2011 *(Continued)*

	Run-in/enrichment**:** not reported **Baseline characteristics** Age: mean 60, SD 7 Men: 50% Diabetes: 46% Current smoker: 29% Prior MI/established CHD: 57% Hypertension: 32% Statin therapy: 100% (part of intervention)
Interventions	**Arm 1:** niacin 1,000 mg + simvastatin 40 mg (randomised = 14, complete cases = 14) **Arm 2:** simvastatin 40 mg (randomised = 14, complete cases = 14) **Duration of treatment:** maximum 9 months **Measure to prevent flushing/unblinding due to flushing:** medication at night **Background therapy:** not reported
Outcomes	**Primary outcomes:** normalised total atheroma volume, percent atheroma volume, C-reactive protein, matrix metalloproteinase-9, soluble CD40 ligand **Secondary outcome:** secondary end points were changes in high sensitivity C-reactive protein, matrix metalloproteinase-9 and soluble CD40 ligand
Notes	**Compliance:** not reported **Registration:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer-generated"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data reported

Lee 2011 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol published, not registered
Other bias	Low risk	None

Linke 2009

Methods	**Design:** parallel-group **Recruitment:** 60 participants in 6 centres in Germany (timeframe not reported) **Setting:** not reported **Funding:** Merck (not involved in either the study design or the data analysis) and Leipzig University, Germany
Participants	**Inclusion criteria:** between 35 and 65 years HDL-C < 1.0 mmol/L. Impaired glucose tolerance, absence inflammatory disease, undetectable antiGAD antibodies, (3) systolic BP < 140 mmHg, diastolic BP < 90 mmHg **Exclusion:** cardiovascular or peripheral artery disease, thyroid dysfunction, concomitant medication intake, alcohol or drug abuse, pregnancy, impaired liver function, impaired renal function **Run-in**/enrichment**:** not reported **Baseline characteristics** Age: mean 45 years, SD 4 Men: 70% Diabetes: 0% (exclusion criterion) Current smoker: not reported Prior MI/established CHD: 0% (exclusion criterion) Hypertension: 0% (exclusion criterion) Statin therapy: 0% (exclusion criterion)
Interventions	**Arm 1:** extended-release niacin 1000 mg /day (randomised = 30, complete cases = 30) **Arm 2:** Usual care, any medication or lifestyle intervention (randomised = 30, complete cases = 30) **Duration of treatment:** maximum 6 months **Measure to prevent flushing/unblinding due to flushing:** extended-release, aspirin 300 mg **Background therapy:** not reported
Outcomes	**Primary outcome:** not reported **Secondary outcome:** not reported
Notes	**Compliance:** 100% **Registration**: not reported
Risk of bias	

Linke 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data reported
Selective reporting (reporting bias)	Unclear risk	No protocol published, not registered
Other bias	Low risk	None

Maccubbin 2008

Methods	**Design:** parallel **Recruitment:** 1613 participants multiple centres worldwide (countries and timeframe not reported) **Setting:** not reported **Funding:** Merck
Participants	**Inclusion criteria:** age 18–85, primary hypercholesterolaemia or mixed dyslipidaemia, ongoing statin, be at or below their National Cholesterol Education Program, LDL-C < 100 mg⁄dL for high-risk participants, < 130 mg⁄dL (3.37 mmol⁄L) for participants with multiple risk factors. 130-190 mg/dL for low-risk participants, TG < 350 mg⁄dL **Exclusion criteria:** impaired renal function, impaired liver function, creatine kinase > 2 x ULN or thyroid stimulating hormone outside the central laboratory's normal reference range. Experiencing menopausal flashes, poorly controlled, unstable, or new onset diabetes, various concomitant drugs **Run-in**/enrichment**:** 4 weeks' placebo **Baseline characteristics (based on all randomised participants)** Total randomised: 1613 (813 in comparison of interest. Other arms: 800 in arm 1) Age: mean 58, SD 11 Men: 61% Diabetes: 16% Current smoker: not reported

Maccubbin 2008 *(Continued)*

	Prior MI/established CHD: not reported Hypertension: not reported Statin therapy: 67%
Interventions	**Arm 1:** niacin extended-release 2000 mg/day + laropiprant 40 mg/day **Arm 2:** niacin extended-release 2000 mg/day **Arm 3:** placebo We included the comparison combined arms 1 and 2 (randomised = 1343, complete cases = 917) vs arm 3 (randomised = 270, complete cases = 239) **Duration of treatment:** Max 26 weeks **Measure to prevent flushing/unblinding due to flushing:** extended-release, laropiprant, medication at bedtime after snack, aspirin 100 mg permitted **Background therapy:** Not reported
Outcomes	**Primary outcome:** LDL-C levels, flushing **Secondary outcomes:** additional lipid end-points, additional flushing end-points including discontinuation of treatment due to flushing
Notes	**Compliance:** not reported **Registration:** NCT00269204

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, but probably low
Allocation concealment (selection bias)	Low risk	"Randomisation of study drug was achieved via an Interactive Voice Response System"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, low risk of bias for participant-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Proportion of missing data: 32% in intervention group, 12% in control group; event/missing: 2/230 in intervention and 0/31 in control
Selective reporting (reporting bias)	Unclear risk	No protocol published, clinical outcomes not specified in registry
Other bias	Low risk	None

MacLean 2011

Methods	**Design:** parallel **Recruitment:** 796 from 2007-2008 in 32 centres in the USA and 62 international centres **Setting:** not reported **Funding:** Merck
Participants	**Inclusion criteria:** 18-80 years, type 2 diabetes mellitus, stable dose of anti-diabetes mellitus medication, LDL-C between 1.55 and 2.97 mmol/L, TG ≤ 5.65 mmol/L **Exclusion criteria:** type 1 diabetes mellitus, renal dysfunction, liver dysfunction, elevated thyroid-stimulating hormones, poorly-controlled type 2 diabetes mellitus (within 3 months of randomisation), various concomitant drugs **Run-in/enrichment:** 4 weeks lipid-modifying run-in period to attain LDL-C < 2.97 mmol/L if necessary **Baseline characteristics (based on all randomised participants)** Age: 62 years, SD 9.4 Men: 314/796, 39% Diabetes: 796/796, 100% Current smoker: not reported Prior MI/established CHD: not reported Hypertension: not reported Statin therapy: 78%
Interventions	**Arm 1:** extended-release niacin + laropiprant. Starting dose 1 g/20 mg, doubled after 4 weeks of double-blind treatment to 2 g/40 mg (randomised = 454, complete cases = 298) **Arm 2:** placebo (randomised = 342, complete cases = 277) **Duration of treatment:** maximum 36 weeks **Measure to prevent flushing/unblinding due to flushing:** extended-release, laropiprant **Background therapy:** permitted lipid-altering therapies included fish oils, statins, fibrates, ezetimibe, ezetimibe/simvastatin combination tablet, and bile acid sequestrants
Outcomes	**Primary outcome:** LDL-C levels **Secondary outcomes:** other lipid endpoints and C-reactive protein
Notes	**Compliance:** not reported **Registration:** NCT00485758

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Interactive voice-response system

MacLean 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, low risk of bias for participant-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Proportion of missing data: 34% in intervention and 19% in control; events/missing ratio: 0/156 for intervention and 1/65 for control
Selective reporting (reporting bias)	Unclear risk	No protocol published, clinical outcomes not specified in registry
Other bias	Low risk	None

Nash 2011

Methods	**Design:** parallel **Recruitment:** 97 participants in 3 centres in the USA **Setting:** not reported **Funding:** National Institute on Disability and Rehabilitation Research, US Department of Education; and Kos Pharmaceuticals, Inc
Participants	**Inclusion criteria:** 18-65 years, chronic tetraplegia for longer than 1 year, in good health and without evidence of acute illness **Exclusion criteria:** recurrent acute infection or illness, trauma, or surgery within 6 months; pregnancy; previous MI or cardiac surgery; lipid-lowering therapy within 6 months; daily alcohol consumption; abnormal menstruation; lifestyle modifications within 6 months of study enrolment; various concomitant medication **Run-in/enrichment:** none **Baseline characteristics (based on all randomised participants)** Age: Mean 33.0, SD 8.7 Men: not reported Diabetes: mot reported Current smoker: 0% Prior MI/established CHD: 0% (exclusion criterion) Hypertension: not reported Statin therapy: not reported
Interventions	**Arm 1:** placebo (randomised = 23, complete cases = 23) **Arm 2:** extended-release niacin 2000 mg/day (randomised = 31, complete cases = 31) **Duration of treatment:** maximum 48 weeks

Nash 2011 *(Continued)*

	Measure to prevent flushing/unblinding due to flushing: extended-release, 325-mg aspirin, niacin before bedtime after snack, avoidance of alcohol and hot drinks **Background therapy:** not reported
Outcomes	**Primary outcome:** fasting HDL-C level and plasma TC/HDL-C ratio **Secondary outcomes:** other lipid outcomes
Notes	**Compliance:** not reported **Registration:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported but likely computer-generated, "permuted block design"
Allocation concealment (selection bias)	Low risk	Central allocation, "Study drug and placebo were dispensed, at the beginning of each study month, by the research pharmacies located at each study site."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Single-blind design", "Subjects were masked from their group assignment until after the study was completed or they withdrew from the trial"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Single-blind design", "Subjects were masked from their group assignment until after the study was completed or they withdrew from the trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data reported
Selective reporting (reporting bias)	Unclear risk	No protocol published, not registered
Other bias	Low risk	None

NIA Plaque 2013

Methods	**Design:** parallel **Recruitment:** 145 participants in a single centre in the USA (timeframe not reported) **Setting:** secondary care **Funding:** National Institute on Aging. Kos Pharmaceuticals, later acquired by Abbott Pharmaceuticals, provided study drug at no cost and funding to complete data analysis
Participants	**Inclusion criteria:** ≥ 65 years, history of cardio- vascular events or evidence of atherosclerosis, with baseline LDL < 3.24 mmol/L if already on statin therapy and < 3.89 mmol/L if untreated. **Exclusion criteria:** current use or intolerance of niacin, contraindication to MRI or gadolinium contrast, liver dysfunction, renal failure

NIA Plaque 2013 *(Continued)*

	Run-in/enrichment: none **Baseline characteristics (based on all randomised participants)** Age: 73, interquartile range 69–77 Men: 81% Diabetes: 26% Current smoker: 39% Prior MI/established CHD: 31% Hypertension: 78% Statin therapy: 100%
Interventions	**Arm 1:** placebo (randomised = 73, complete cases = 58) **Arm 2:** extended-release niacin 1500 mg/day (randomised = 72, complete cases = 59) **Duration of treatment:** maximum 18 months **Measure to prevent flushing/unblinding due to flushing:** extended-release **Background therapy:** not reported
Outcomes	**Primary outcome:** internal carotid artery wall volume **Secondary outcomes:** HDL, LDL, volumes of internal carotid artery lumen, internal carotid artery lipid core, common carotid artery wall, common carotid artery lumen and common carotid artery lipid core **Specified in trial registry but not reported**: cardiovascular events
Notes	**Compliance:** "A minimum pill count compliance of 80% was required to maintain enrolment" **Registration:** NCT00127218

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Likely computer-generated, "using a random number schema stratified to ensure equal numbers"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded to treatment group assignments
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, low risk of bias for participant-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Proportion of missing data: 18% in intervention and 21% in control; events/missing 0/13 in intervention and 1/15 in control

NIA Plaque 2013 *(Continued)*

Selective reporting (reporting bias)	High risk	Cardiovascular events specified in registry record but subsequently not reported
Other bias	Low risk	None

PAST 1995

Methods	**Design:** parallel **Recruitment:** 85 participants from 1986-1987 in Italy (number of centres not reported) **Setting:** not reported **Funding:** not reported
Participants	**Inclusion criteria:** 45-55 years, ischaemic heart disease **Exclusion criteria:** presence of symptoms of carotid and/or femoral artery disease **Run-in /** enrichment**:** not reported **Baseline characteristics** Age: 51 years, SD 3 Men: 95% Diabetes: 24% Current smoker: 31% Prior MI/established CHD: 89% Hypertension: 62% Statin therapy: not reported
Interventions	**Arm 1:** hypolipidaemic diet (randomised = 45, complete cases = 34) **Arm 2:** hypolipidaemic diet + acipimox 500 mg/day-750 mg/day (nicotinic compound) (randomised = 40, complete cases = 30) **Duration of treatment:** maximum 3 years **Measure to prevent flushing/unblinding due to flushing:** not reported **Background therapy:** not reported
Outcomes	**Primary outcome:** stenosis level of carotid and femoral artery **Secondary outcome:** not reported
Notes	**Compliance:** "The compliance with drug treatment was good" **Registration:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

PAST 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Randomization was performed by utilizing a table of casual numbers; its sequence was applied to the patients' list."
Allocation concealment (selection bias)	Unclear risk	"Randomization was performed by utilizing a table of casual numbers; its sequence was applied to the patients' list."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Cardiologists and patients were aware of the distribution into groups"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Cardiologists and patients were aware of the distribution into groups"
Incomplete outcome data (attrition bias) All outcomes	High risk	Proportion of missing data: 25% in intervention and 24% in control; events/missing ratio: 3/10 in intervention, 4/11 in control
Selective reporting (reporting bias)	Unclear risk	No protocol published, not registered
Other bias	Low risk	None

Sang 2009

Methods	**Design:** parallel **Recruitment:** 108 participants from 2006-2007 in a single centre in China **Setting:** not reported **Funding:** not reported
Participants	**Inclusion criteria:** at least 50% stenosis of one coronary artery **Exclusion criteria:** serious hepatic or kidney diseases; haemodynamic instability; cancer with expected survival < 1 year; administration of lipid-lowering drugs within the month before inclusion **Run-in/enrichment**: not reported **Baseline characteristics:** Age: 71 years, SD 9 Men: 61% Diabetes: 65% Current smoker: not reported Prior MI/established CHD: imbalance between groups: 36% control, 10% intervention Hypertension: 67% Statin therapy: 100% (part of intervention)
Interventions	**Arm 1:** atorvastatin 10 mg/day (randomised = 56, complete cases = 56)

Sang 2009 *(Continued)*

	Arm 2: atorvastatin 10 mg/day + extended-release niacin 1 g/day (randomised = 52, complete cases = 52) **Duration of treatment:** maximum 12 months **Measure to prevent flushing/unblinding due to flushing:** extended-release **Background therapy:** all participants were given advice on lifestyle modification and smoking cessation as well as professional training in moderate exercise. They were permitted no lipid-modifying therapy other than the study drug
Outcomes	**Primary outcome:** not defined Outcomes: LDL-C, HDL-C, TC, TG, apolipoprotein A, apolipoprotein B, lipoprotein a, and fasting glucose, haemoglobin A1c, creatine kinase, creatine kinase MB isoenzyme, aspartate aminotransferase, alanine aminotransferase, adverse events, death from any cause, MI, rehospitalisation, revascularisation
Notes	**Compliance:** not reported **Registration:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	No protocol published, not registered
Other bias	High risk	High risk of bias due to insufficient reporting of methods and substantial imbalance of prognostic factors between groups

Schoch 1968

Methods	**Design:** parallel-groups; modified factorial (niacin x estrogen x thyroxin) **Recruitment:** 570 US veterans between February 1963 and August 1966, number of centres not reported **Setting:** not reported

Schoch 1968 *(Continued)*

	Funding: drugs supplied by the Ayerst Laboratories, the National Drug Company and Travenol Laboratories, Inc
Participants	**Inclusion criteria:** only men; documented evidence of a transmural MI within 12 months prior to randomisation **Exclusion criteria:** major medical diseases (other than atherosclerosis) which might lead to death in < 5 years; presence of any medical condition in which the use of 1 of the 3 active therapeutic agents might be contraindicated **Run-in/enrichment**: 1 month prior to randomisation; all participants received placebo. **Baseline characteristics (based on all randomised participants)** Age: ≤ 45 years: 35%; 46-65 years: 47%; ≥ 66 years: 18% Men: 100% (570/570) Diabetes: 9% (54/570) Current smoker: not reported Prior MI/established CHD: 100% (inclusion criterion) Hypertension: 19% (106/570) Statin therapy: 0% (not available at the time)
Interventions	Each participant received 3 medications: estrogen (1.25 mg daily), dextrothyroxine (increasing from 1.0 mg to 4.0 mg daily over 4 months), and nicotinic acid (increasing from 1.0 to 4.0 mg daily over 1 month) – or identical placebo: **Arm 1:** placebo/placebo/placebo, n = 143 **Arm 2:** estrogen/placebo/placebo, n = 141 **Arm 3:** placebo/niacin/placebo, n = 77 **Arm 4:** estrogen/niacin/placebo, n = 68 **Arm 5:** placebo/placebo/thyroxin, n = 74 **Arm 6:** estrogen/placebo/thyroxin, n = 67 **Duration of treatment:** median 36 months We compared pooled arms 3 + 4 (niacin, randomised = 141, complete cases = 140) to pooled arms 1 + 2 (control, randomised = 284, complete cases = 283) **Measure to prevent flushing/unblinding due to flushing: n**one **Background therapy:** 50% received estrogen (due to factorial design)
Outcomes	**Primary outcome:** serum cholesterol Outcomes 'flushing' and 'diarrhoea' were only reported for all groups receiving niacin vs. and groups without niacin. Therefore, 33% (141/425) of participants in the placebo group received thyroxin but no participants in the niacin group **Secondary outcome:** not reported
Notes	**Compliance: "**Nicotinic acid caused the most troublesome side-effects, leading to frequent reduction in dosage. Some 28% of participants were maintained at full dose, another 32% had the drug discontinued altogether and the remaining 40% were at intermediate doses."

Schoch 1968 *(Continued)*

Registration: not available at the time

Conflicting information about number of participants lost to follow-up proportions; proportions range between 8% and 50% for outcome 'overall mortality'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Medications were dispensed in the hospital pharmacy from bottles bearing coded numbers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, low risk of bias for participant-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Proportion of missing data: 0.5% in both groups; events/missing for overall mortality: 31/1 in intervention, 54/1 in control
Selective reporting (reporting bias)	Unclear risk	No protocol published, not registered
Other bias	Low risk	None

BP: blood pressure
CHD: coronary heart disease
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
MI: myocardial infarction
MRI: magnetic resonance imaging
NYHA: New York Heart Association
TC: total cholesterol
TG: triglycerides
ULN: upper limit of normal
VLDL: very low-density lipoprotein

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
AFREGS 2005	No comparison of interest
Airan-Javia 2009	No outcome of interest
ARBITER-6 2009	No comparison of interest
Arntz 2000	No comparison of interest

Study	Reason for exclusion
Aronov 2001	No outcome of interest
Bays 2003	Follow-up shorter than 6 months
Blankenhorn 1987	No comparison of interest
Brown 1990a	No comparison of interest
Cefali 2006	Follow-up shorter than 6 months
Cheung 2001a	No comparison of interest
Cheung 2001b	No comparison of interest
Dishy 2009	Follow-up shorter than 6 months
Dunbar 2009	No comparison of interest
FATS 2001	No comparison of interest
Guyton 2000	No comparison of interest
HDL-Artherosclerosis Treatment Study 2004	No comparison of interest
Hiatt 2010	No comparison of interest
Hoeg 1984	Follow-up shorter than 6 months
Hubacek 2010	Follow-up shorter than 6 months
Illingworth 1994	No comparison of interest
Insull 2004	Follow-up shorter than 6 months
Jungnickel 1997	Follow-up shorter than 6 months
Kane 1990	No comparison of interest
Keenan 1990	Follow-up shorter than 6 months
Klimov 1995	No comparison of interest
Knopp 1985	No comparison of interest
Knopp 1998	Follow-up shorter than 6 months
Lamon-Fava 2008	Follow-up shorter than 6 months
Low 2007	No outcome of interest
Morgan 1998	Follow-up shorter than 6 months
OCEANS 2008	No comparison of interest

Study	Reason for exclusion
Oster 1995	No comparison of interest
Pontiroli 1992	Follow-up shorter than 6 months
Pradhan 2005	Follow-up shorter than 6 months
Sacks 1994	No comparison of interest
Safarova 2011	No outcome of interest
Sakai 2001	No comparison of interest
SEACOAST I 2008c	No clinical outcome
SEACOAST II 2008	No comparison of interest
Shah 2010	No comparison of interest
Smith 1963	No comparison of interest
Sorrentino 2010	Follow-up shorter than 6 months
Sposito 1999	No comparison of interest
Superko 2009	No comparison of interest
Thoenes 2007	No outcome of interest
Tsalamandris 1994	No comparison of interest
Zema 2000	Follow-up shorter than 6 months

Characteristics of ongoing studies *[ordered by study ID]*

NCT00715273

Trial name or title	Carotid plaque composition study
Methods	Randomised parallel groups , double-blind, follow-up: 5 years
Participants	**Inclusion criteria:** Aged 21-70, clinically established coronary artery disease or carotid artery disease, family history of cardiovascular disease, apolipoprotein B level ≥ 120 mg/dL, LDL 100 mgdL-190 mg/dL without medication, lipid therapy for no more than 12 months before study entry, medically stable, able to undergo MRI procedure **Exclusion criteria:** immediate plans for carotid endarterectomy, alcohol or drug abuse, liver disease, elevated serum creatine kinase, elevated serum creatinine, diabetes, uncontrolled high BP **Run-in**/enrichment**:** not reported
Interventions	**Arm 1:** atorvastatin, placebo niacin, and placebo colesevelam. Target for LDL: ≤ 80 mg/dL **Arm 2:** atorvastatin, niacin, and placebo colesevelam. Target for LDL: ≤ 80 mg/dL **Arm 3:** atorvastatin, niacin, and colesevelam. Target for LDL-C: ≤ 60 mg/dL

NCT00715273 *(Continued)*

	Measure to prevent flushing/unblinding due to flushing: not reported
Outcomes	**Primary outcome:** carotid plaque composition, as assessed by MRI **Secondary outcomes:** composite of cardiovascular disease death, non-fatal heart attack, stroke, and worsening ischaemia requiring medical interventions
Starting date	June 2001
Contact information	See NCT00715273
Notes	NCT00715273

NCT02109614

Trial name or title	Early aortic valve lipoprotein(a) lowering trial (EAVaLL)
Methods	Randomised parallel groups, double-blind, pilot trial, follow-up: 2 years
Participants	**Inclusion criteria:** aged > 50 and < 85 years, aortic sclerosis, elevated lipoprotein A **Exclusion criteria:** current use or documented indication for niacin therapy, niacin intolerance, bicuspid valve, unicuspid valve or other congenital cardiac anomaly, renal disease, comorbidity limiting life expectancy to < 2 years, liver disease, newly diagnosed or poorly controlled diabetes, gout or use of anti-hyperuricaemic medications **Run-in/enrichment:** low-dose niacin (500 mg/d) for 6 weeks to randomisation to assess tolerability and compliance to the intervention. The niacin dose will be increased by 500 mg increments weekly, as tolerated, to a maximum of 1500 mg/day
Interventions	**Arm 1:** extended-release niacin 1500 mg/day-2000 mg/day **Arm 2:** placebo **Measure to prevent flushing/unblinding due to flushing:** extended-release
Outcomes	**Primary outcome:** calcium score by cardiac CT **Secondary outcome:** lipoprotein A, disease progression by echocardiography, peak velocity, mean gradient, aortic valve area, drug compliance, side effects and adverse events
Starting date	May 2014
Contact information	See NCT02109614
Notes	NCT02109614

NCT02258074

Trial name or title	The CKD optimal management with bInders and nicotinamide (COMBINE) study
Methods	Randomised parallel groups, double-blind, pilot study
Participants	**Inclusion criteria:** eGFR between 20 and 45 mL/min/1.73 m^2, aged 18-85 years, serum phosphate ≥ 2.8 mg/dL, platelet count ≥ 125,000/mm^3

NCT02258074 *(Continued)*

	Exclusion criteria: intolerance to study drugs, liver disease, elevated creatine kinase, major haemorrhagic event within the past 6 months, blood transfusion within the past 6 months, secondary hyperparathyroidism, malabsorption, anaemia, decreased serum albumin, dialysis or kidney transplantation, immunosuppressive medications, abuse of alcohol or drugs, vitamin D, phosphate binder, niacin/nicotinamide > 100 mg/day, malignancy **Run-in/enrichment: n**ot reported
Interventions	**Arm 1:** lanthanum carbonate 3000 mg/day + nicotinamide 1500 mg/day **Arm 2:** lanthanum carbonate 3000 mg/day + nicotinamide placebo **Arm 3:** lanthanum carbonate placebo and nicotinamide 1500 mg/day **Arm 4:** lanthanum carbonate placebo and nicotinamide placebo **Measure to prevent flushing/unblinding due to flushing:** not reported
Outcomes	**Primary outcome:** feasibility, serum phosphate, FGF23 **Secondary outcomes:** cardiovascular disease, left ventricular mass index, left ventricular end diastolic volume, and left atrial volume, intra-renal oxygenation and fibrosis, brain natriuretic peptide, troponin T, cholesterol, asymmetric dimethylarginine, parathyroid hormone, calcitriol, klotho, N terminal propeptide of type 1 procollagen, tartrate-resistant acid phosphatase, glomerular filtration, albuminuria, C reactive protein, interleukin 6
Starting date	March 2015
Contact information	See NCT02258074
Notes	NCT02258074

NCT02416739

Trial name or title	Anticancer activity of nicotinamide on lung cancer
Methods	Randomised, parallel, double-blind, 2 years' follow-up
Participants	**Inclusion criteria:** Aged 19-80 years, non-small-cell lung carcinoma, EGFR mutated, life expectation > 3 months, > 1 measurable lesion by RECIST 1.1 which were not exposed to radiation previously, Eastern Cooperative Oncology Group performance status grade 0˜2 **Exclusion criteria:** metastasised brain lesion needing operation or radiation, above grade 2 Common Toxicity Criteria for Adverse Effects criteria for blood, liver and kidney, no contraception, allergy to nicotinamide **Run-in/enrichment:** not reported
Interventions	**Arm 1:** nicotinamide 1000 mg/day + gefitinib 250 mg/day or erlotinib 150 mg/day **Arm 2:** placebo + gefitinib 250 mg/day or erlotinib 150 mg/day **Measure to prevent flushing/unblinding due to flushing:** not reported
Outcomes	**Primary:** progression-free survival **Secondary:** response rate, quality of life, overall survival
Starting date	March 2015

NCT02416739 *(Continued)*

Contact information	See NCT02416739
Notes	NCT02416739

NCT02558595

Trial name or title	NIAC-PKD2
Methods	Randomised, parallel, double-blind, pilot study, 12 months' follow-up
Participants	**Inclusion criteria:** aged 18-60 years, confirmed diagnosis of autosomal dominant polycystic kidney disease, EGFR > 50 mL/min/1.73 m^2 **Exclusion criteria:** liver disease, alcohol intake, malabsorption, thrombocytopenia, hypophosphataemia, pregnancy or lactation, anti-epileptic drugs, tolvaptan, not able to undergo MRI **Run-in/enrichment:** not reported
Interventions	**Arm 1:** niacinamide 30 mg/kg/day **Arm 2:** placebo
Outcomes	**Primary outcome:** acetylated/total p53 ratio **Secondary:** kidney volume, pain, MCP-1, EGFR
Starting date	September 2015
Contact information	See NCT02558595
Notes	NCT02558595

BP: blood pressure
CT: computed tomography
EGFR: estimated glomerular filtration rate
MRI: magnetic resonance imaging
RECIST: response evaluation criteria in solid tumours

DATA AND ANALYSES

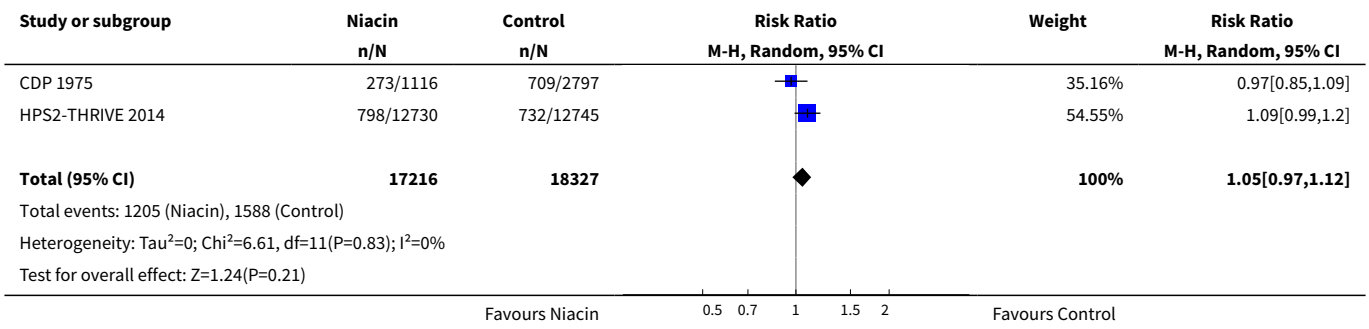
Comparison 1. Niacin versus control, maximum follow-up, available case analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall mortality	12	35543	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.97, 1.12]
2 Overall mortality, sensitivity analysis with stratification by risk of bias trials only	12	35543	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.97, 1.12]
2.1 High risk of bias	10	6703	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.09]

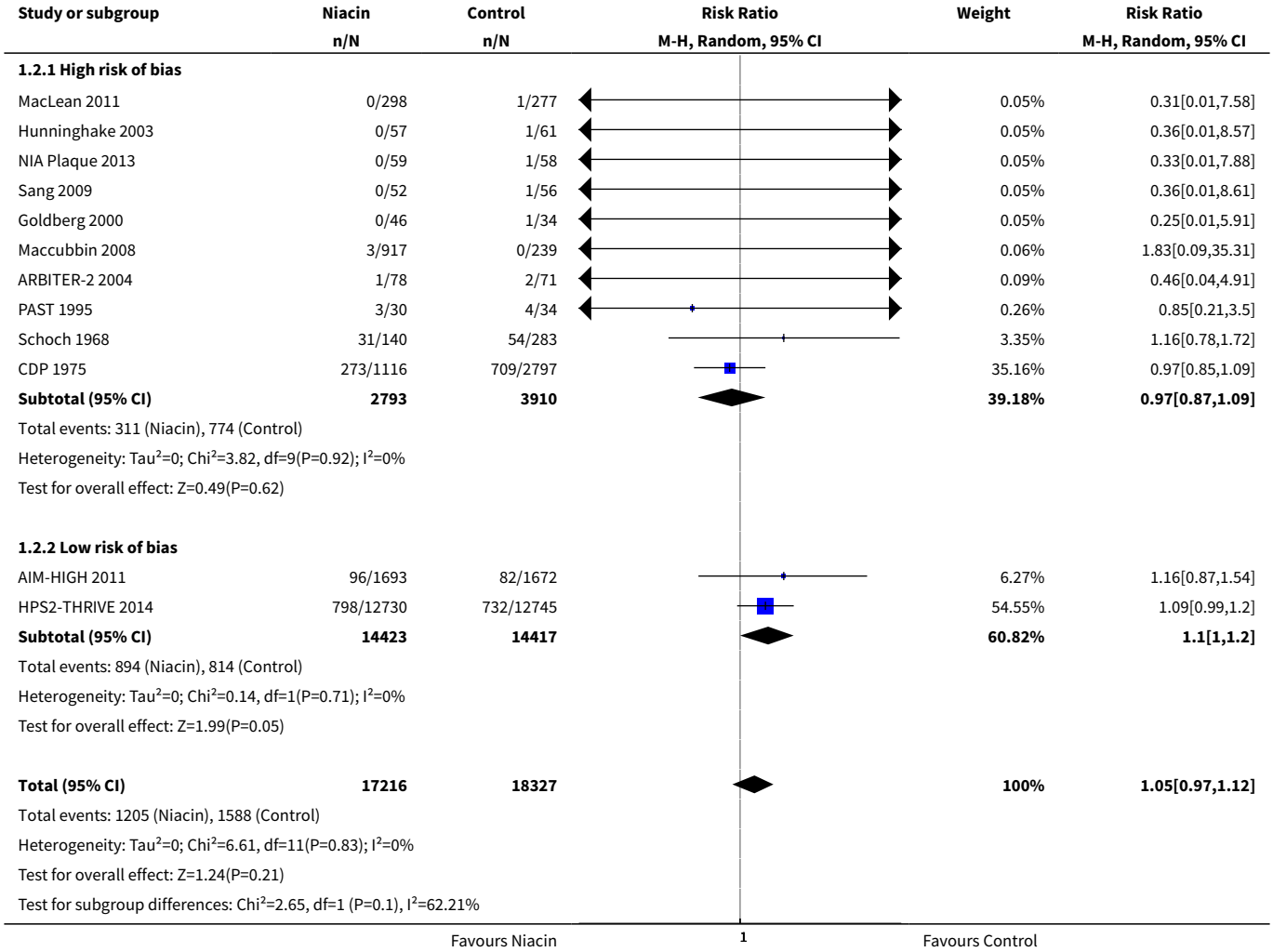
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Low risk of bias	2	28840	Risk Ratio (M-H, Random, 95% CI)	1.10 [1.00, 1.20]
3 Fatal myocardial infarction	6	33336	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.91, 1.11]
4 Cardiovascular mortality	5	32966	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.93, 1.12]
5 Non-cardiovascular mortality	5	32966	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.98, 1.28]
6 Non-fatal myocardial infarction	4	33164	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.77, 1.07]
7 Fatal or non-fatal myocardial infarction	9	34829	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.87, 1.00]
8 Fatal and non-fatal stroke	7	33661	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.74, 1.22]
9 Revascularisation procedures	8	33130	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.68, 1.06]
10 Flushing	15	11038	Risk Ratio (M-H, Random, 95% CI)	7.69 [4.14, 14.28]
11 Pruritus	6	5800	Risk Ratio (M-H, Random, 95% CI)	5.26 [2.68, 10.32]
12 Rash	9	31485	Risk Ratio (M-H, Random, 95% CI)	3.15 [1.94, 5.13]
13 Headache	3	300	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.86, 2.28]
14 Gastrointestinal symptoms	12	35353	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.37, 2.07]
15 Discontinuation of treatment due to side effects	17	33539	Risk Ratio (M-H, Random, 95% CI)	2.17 [1.70, 2.77]
16 New onset diabetes)	3	27982	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.16, 1.51]

Analysis 1.1. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 1 Overall mortality.

Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
MacLean 2011	0/298	1/277		0.05%	0.31[0.01,7.58]
Hunninghake 2003	0/57	1/61		0.05%	0.36[0.01,8.57]
NIA Plaque 2013	0/59	1/58		0.05%	0.33[0.01,7.88]
Sang 2009	0/52	1/56		0.05%	0.36[0.01,8.61]
Goldberg 2000	0/46	1/34		0.05%	0.25[0.01,5.91]
Maccubbin 2008	3/917	0/239		0.06%	1.83[0.09,35.31]
ARBITER-2 2004	1/78	2/71		0.09%	0.46[0.04,4.91]
PAST 1995	3/30	4/34		0.26%	0.85[0.21,3.5]
Schoch 1968	31/140	54/283		3.35%	1.16[0.78,1.72]
AIM-HIGH 2011	96/1693	82/1672		6.27%	1.16[0.87,1.54]
		Favours Niacin	0.5 0.7 1 1.5 2	Favours Control	

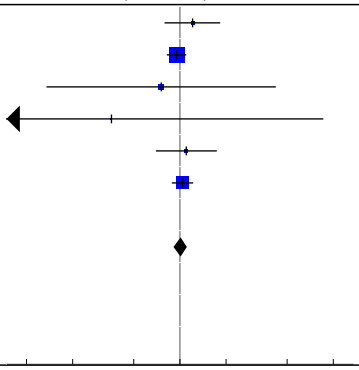


Analysis 1.2. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 2 Overall mortality, sensitivity analysis with stratification by risk of bias trials only.



Analysis 1.3. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 3 Fatal myocardial infarction.

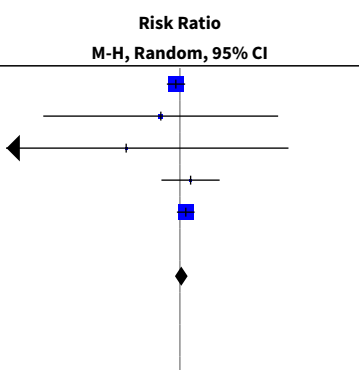
Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Schoch 1968	28/134	48/277		5.88%	1.21[0.79,1.83]
CDP 1975	203/1116	535/2797		48.23%	0.95[0.82,1.1]
PAST 1995	2/30	3/34		0.35%	0.76[0.14,4.22]
Sang 2009	0/52	1/56		0.1%	0.36[0.01,8.61]
AIM-HIGH 2011	38/1693	34/1672		4.9%	1.1[0.7,1.74]
HPS2-THRIVE 2014	302/12730	291/12745		40.55%	1.04[0.89,1.22]
Total (95% CI)	**15755**	**17581**		**100%**	**1.01[0.91,1.11]**
Total events: 573 (Niacin), 912 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.12, df=5(P=0.83); I^2=0%					
Test for overall effect: Z=0.1(P=0.92)					



Favours niacin — Favours placebo

Analysis 1.4. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 4 Cardiovascular mortality.

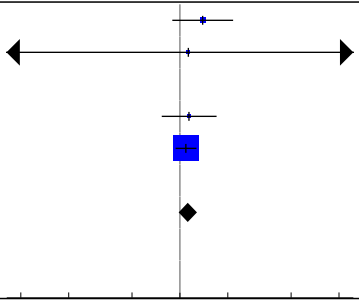
Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
CDP 1975	238/1116	633/2797		47.42%	0.94[0.83,1.08]
PAST 1995	2/30	3/34		0.28%	0.76[0.14,4.22]
ARBITER-2 2004	1/78	2/71		0.15%	0.46[0.04,4.91]
AIM-HIGH 2011	45/1693	38/1672		4.53%	1.17[0.76,1.79]
HPS2-THRIVE 2014	448/12730	411/12745		47.62%	1.09[0.96,1.24]
Total (95% CI)	**15647**	**17319**		**100%**	**1.02[0.93,1.12]**
Total events: 734 (Niacin), 1087 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.38, df=4(P=0.5); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					



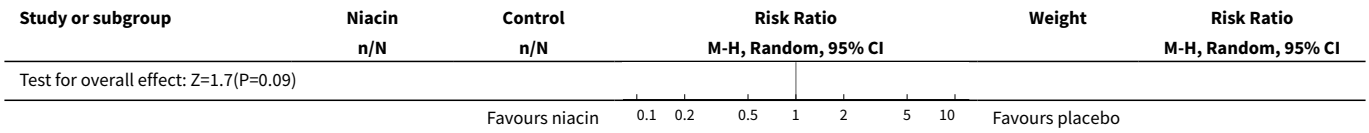
Favours niacin — Favours placebo

Analysis 1.5. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 5 Non-cardiovascular mortality.

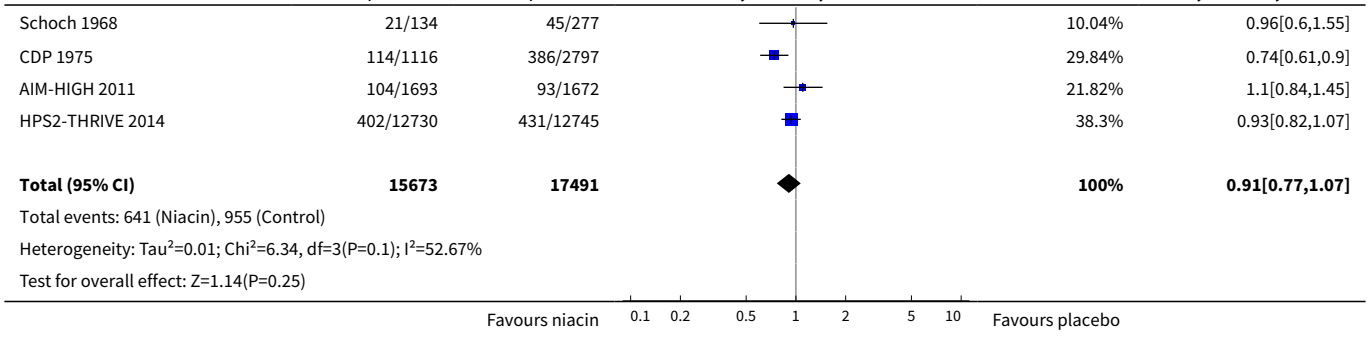
Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
CDP 1975	30/1116	54/2797		9.13%	1.39[0.9,2.16]
PAST 1995	1/30	1/34		0.24%	1.13[0.07,17.34]
ARBITER-2 2004	0/78	0/71			Not estimable
AIM-HIGH 2011	51/1693	44/1672		11.22%	1.14[0.77,1.7]
HPS2-THRIVE 2014	350/12730	321/12745		79.41%	1.09[0.94,1.27]
Total (95% CI)	**15647**	**17319**		**100%**	**1.12[0.98,1.28]**
Total events: 432 (Niacin), 420 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.06, df=3(P=0.79); I^2=0%					



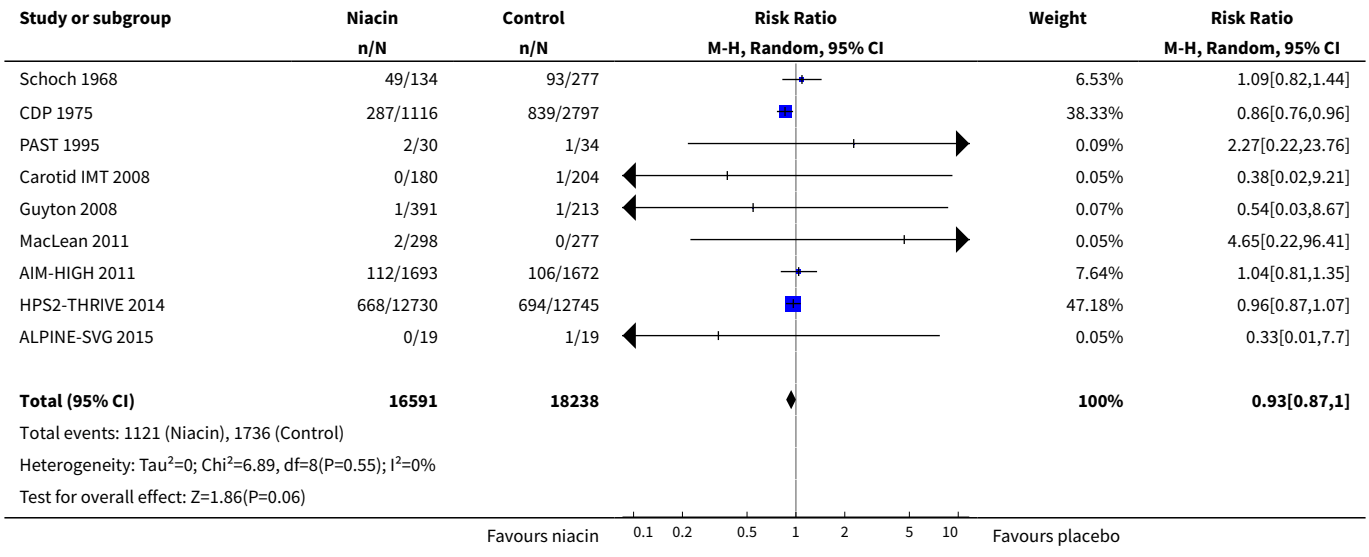
Favours niacin — Favours placebo



Analysis 1.6. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 6 Non-fatal myocardial infarction.

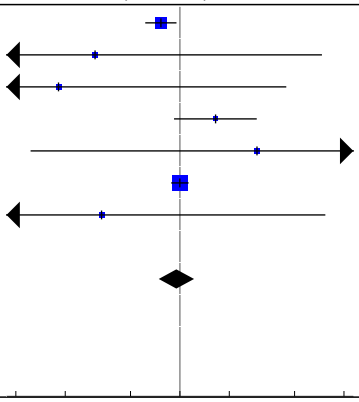


Analysis 1.7. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 7 Fatal or non-fatal myocardial infarction.



Analysis 1.8. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 8 Fatal and non-fatal stroke.

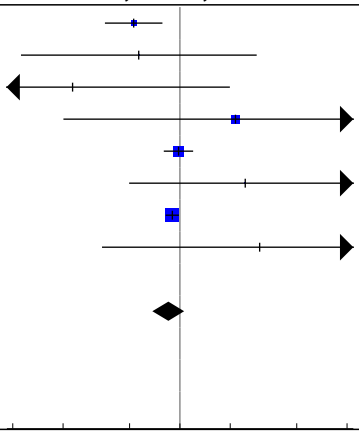
Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
CDP 1975	95/1116	311/2797		37.31%	0.77[0.61,0.95]
ARBITER-2 2004	0/78	1/71		0.59%	0.3[0.01,7.34]
Guyton 2008	0/391	1/213		0.59%	0.18[0.01,4.45]
AIM-HIGH 2011	30/1693	18/1672		13.44%	1.65[0.92,2.94]
NIA Plaque 2013	1/59	0/58		0.59%	2.95[0.12,70.96]
HPS2-THRIVE 2014	498/12730	499/12745		46.87%	1[0.88,1.13]
ALPINE-SVG 2015	0/19	1/19		0.61%	0.33[0.01,7.7]
Total (95% CI)	**16086**	**17575**		**100%**	**0.95[0.74,1.22]**
Total events: 624 (Niacin), 831 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=10.27, df=6(P=0.11); I^2=41.56%					
Test for overall effect: Z=0.4(P=0.69)					



Favours niacin — Favours placebo

Analysis 1.9. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 9 Revascularisation procedures.

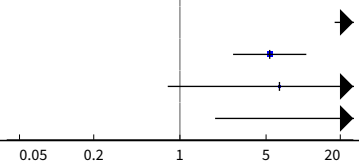
Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
CDP 1975	29/1119	132/2695		18.5%	0.53[0.36,0.79]
PAST 1995	2/30	4/34		1.78%	0.57[0.11,2.88]
ARBITER-2 2004	1/78	4/71		1.02%	0.23[0.03,1.99]
Sang 2009	2/52	1/56		0.85%	2.15[0.2,23.05]
AIM-HIGH 2011	167/1693	168/1672		32.85%	0.98[0.8,1.2]
NIA Plaque 2013	5/59	2/58		1.83%	2.46[0.5,12.16]
HPS2-THRIVE 2014	807/12730	897/12745		42.16%	0.9[0.82,0.99]
ALPINE-SVG 2015	3/19	1/19		1.01%	3[0.34,26.33]
Total (95% CI)	**15780**	**17350**		**100%**	**0.85[0.68,1.06]**
Total events: 1016 (Niacin), 1209 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=12.69, df=7(P=0.08); I^2=44.86%					
Test for overall effect: Z=1.41(P=0.16)					



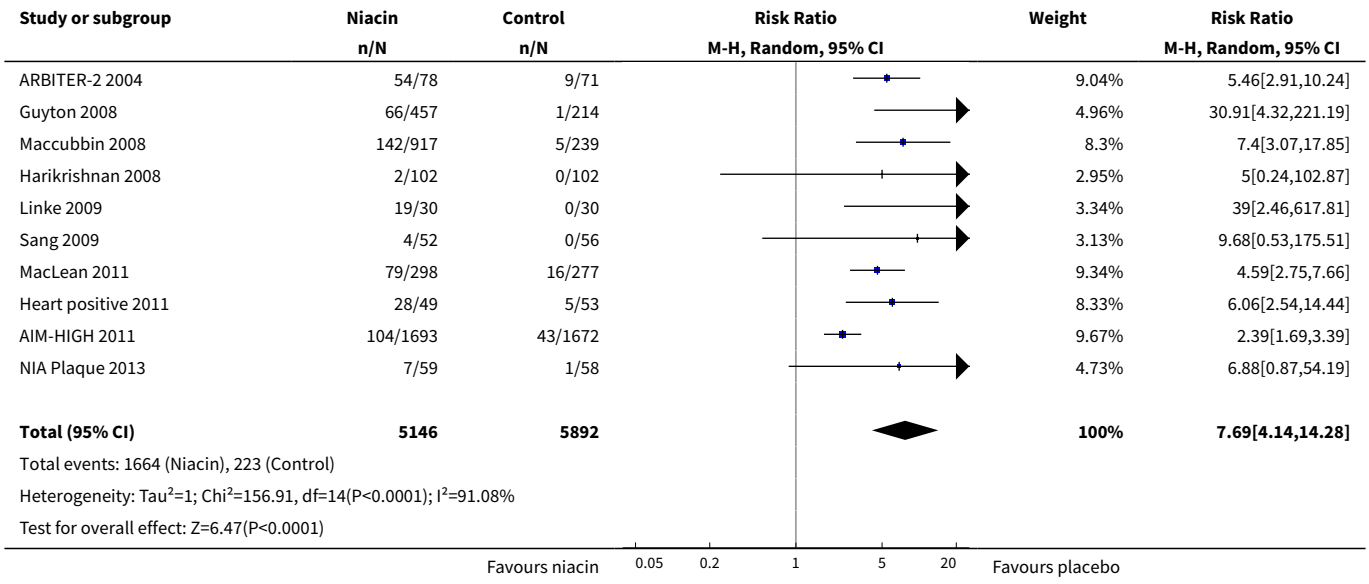
Favours niacin — Favours placebo

Analysis 1.10. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 10 Flushing.

Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Schoch 1968	71/134	20/277		9.47%	7.34[4.67,11.52]
CDP 1975	987/1073	115/2695		9.89%	21.56[18.01,25.8]
Goldberg 2000	74/87	7/44		8.89%	5.35[2.7,10.61]
Hunninghake 2003	6/57	1/61		4.67%	6.42[0.8,51.71]
Capuzzi 2003	21/60	0/43		3.31%	31.02[1.93,498.42]

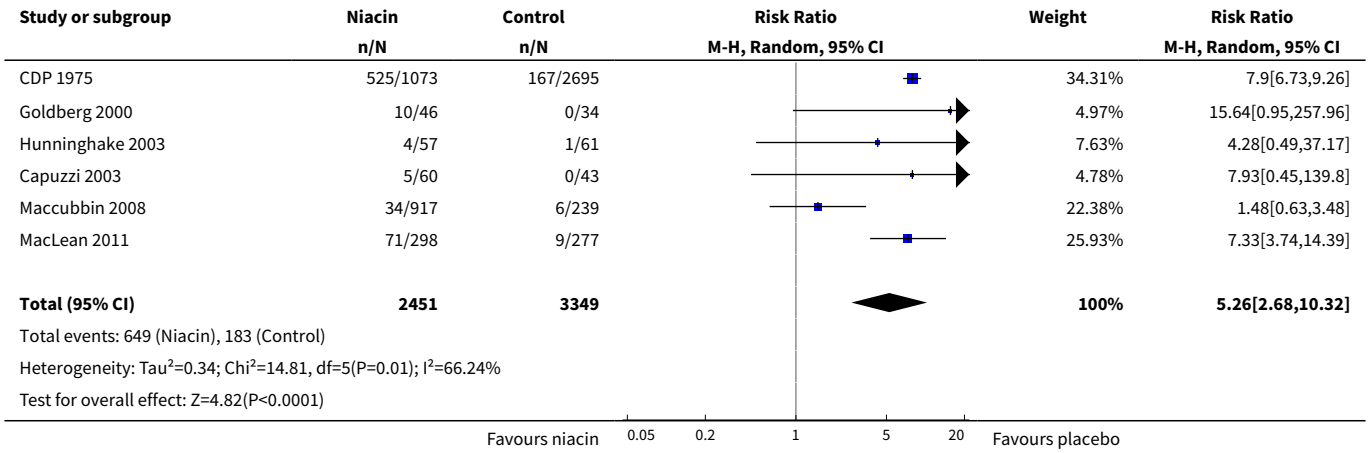


Favours niacin — Favours placebo



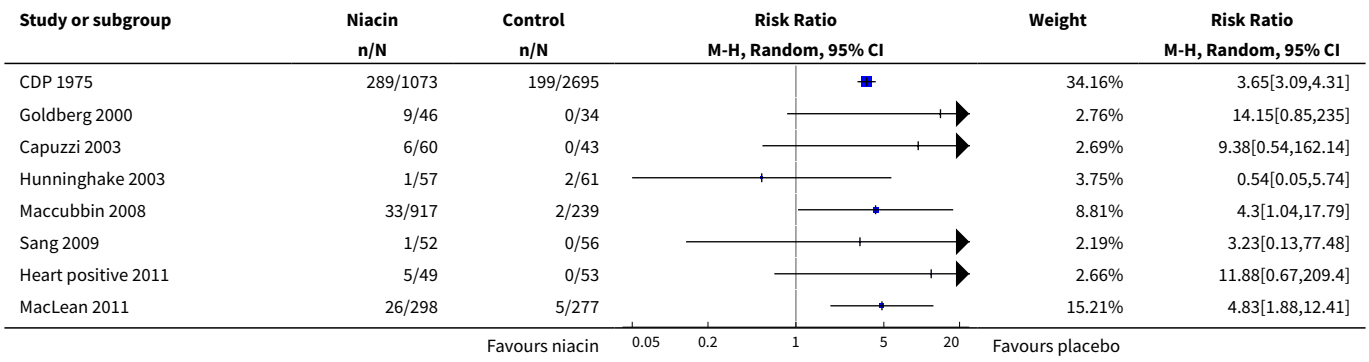
Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ARBITER-2 2004	54/78	9/71		9.04%	5.46[2.91,10.24]
Guyton 2008	66/457	1/214		4.96%	30.91[4.32,221.19]
Maccubbin 2008	142/917	5/239		8.3%	7.4[3.07,17.85]
Harikrishnan 2008	2/102	0/102		2.95%	5[0.24,102.87]
Linke 2009	19/30	0/30		3.34%	39[2.46,617.81]
Sang 2009	4/52	0/56		3.13%	9.68[0.53,175.51]
MacLean 2011	79/298	16/277		9.34%	4.59[2.75,7.66]
Heart positive 2011	28/49	5/53		8.33%	6.06[2.54,14.44]
AIM-HIGH 2011	104/1693	43/1672		9.67%	2.39[1.69,3.39]
NIA Plaque 2013	7/59	1/58		4.73%	6.88[0.87,54.19]
Total (95% CI)	**5146**	**5892**		**100%**	**7.69[4.14,14.28]**
Total events: 1664 (Niacin), 223 (Control)					
Heterogeneity: Tau²=1; Chi²=156.91, df=14(P<0.0001); I²=91.08%					
Test for overall effect: Z=6.47(P<0.0001)					

Analysis 1.11. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 11 Pruritus.

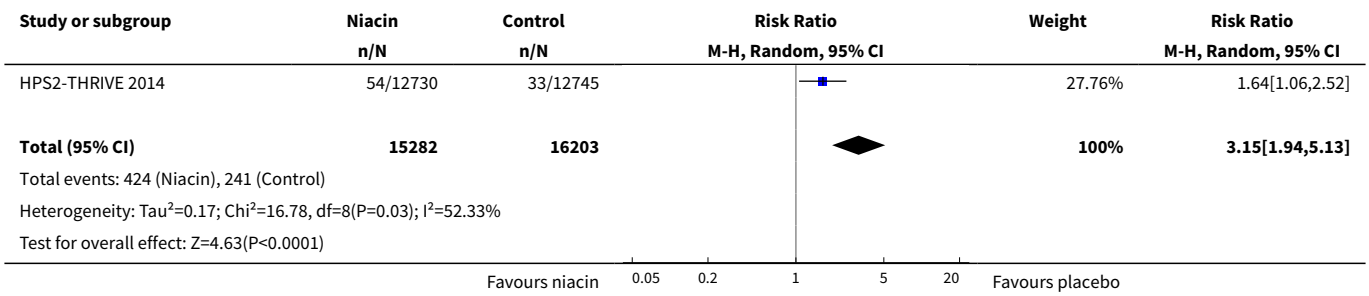


Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
CDP 1975	525/1073	167/2695		34.31%	7.9[6.73,9.26]
Goldberg 2000	10/46	0/34		4.97%	15.64[0.95,257.96]
Hunninghake 2003	4/57	1/61		7.63%	4.28[0.49,37.17]
Capuzzi 2003	5/60	0/43		4.78%	7.93[0.45,139.8]
Maccubbin 2008	34/917	6/239		22.38%	1.48[0.63,3.48]
MacLean 2011	71/298	9/277		25.93%	7.33[3.74,14.39]
Total (95% CI)	**2451**	**3349**		**100%**	**5.26[2.68,10.32]**
Total events: 649 (Niacin), 183 (Control)					
Heterogeneity: Tau²=0.34; Chi²=14.81, df=5(P=0.01); I²=66.24%					
Test for overall effect: Z=4.82(P<0.0001)					

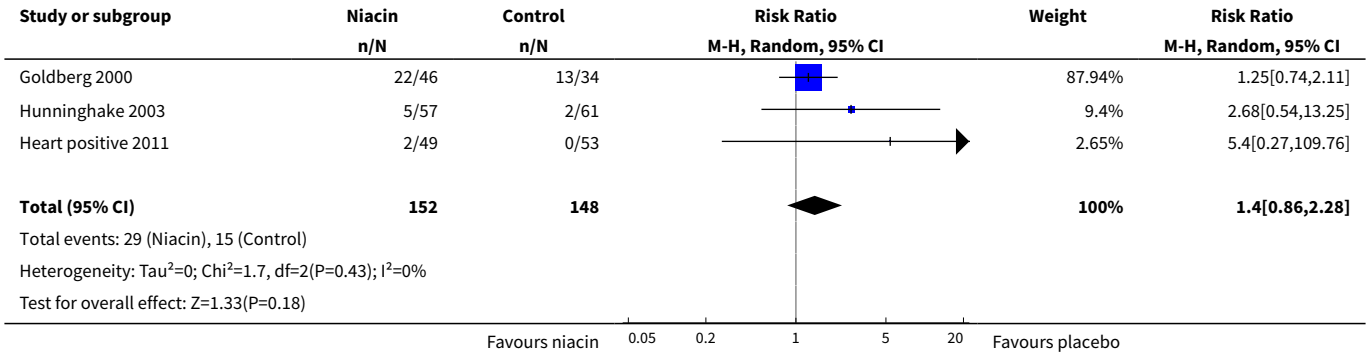
Analysis 1.12. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 12 Rash.



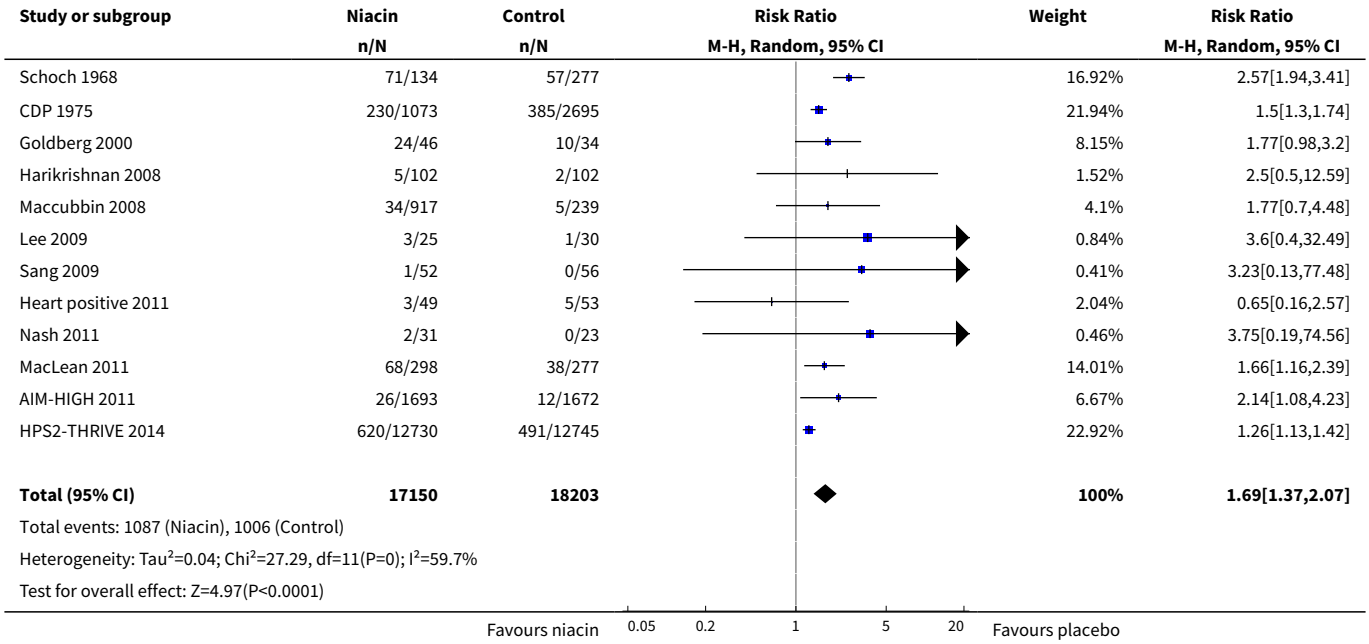
Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
CDP 1975	289/1073	199/2695		34.16%	3.65[3.09,4.31]
Goldberg 2000	9/46	0/34		2.76%	14.15[0.85,235]
Capuzzi 2003	6/60	0/43		2.69%	9.38[0.54,162.14]
Hunninghake 2003	1/57	2/61		3.75%	0.54[0.05,5.74]
Maccubbin 2008	33/917	2/239		8.81%	4.3[1.04,17.79]
Sang 2009	1/52	0/56		2.19%	3.23[0.13,77.48]
Heart positive 2011	5/49	0/53		2.66%	11.88[0.67,209.4]
MacLean 2011	26/298	5/277		15.21%	4.83[1.88,12.41]



Analysis 1.13. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 13 Headache.

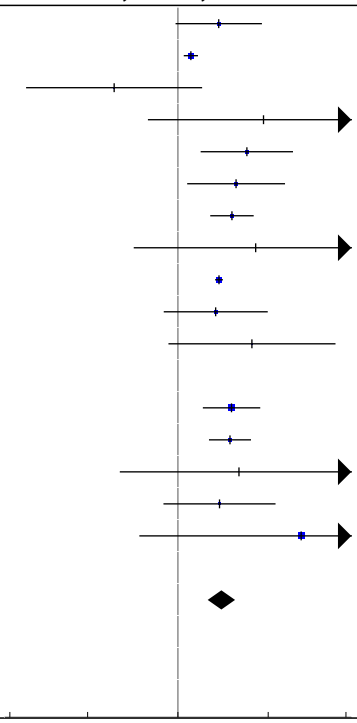


Analysis 1.14. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 14 Gastrointestinal symptoms.



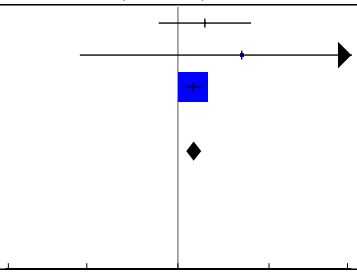
Analysis 1.15. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 15 Discontinuation of treatment due to side effects.

Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ADMIT 2000	19/213	9/209		6.23%	2.07[0.96,4.47]
AIM-HIGH 2011	436/1693	341/1672		15.67%	1.26[1.11,1.43]
ARBITER-2 2004	2/80	6/77		2.11%	0.32[0.07,1.54]
Capuzzi 2003	7/67	1/44		1.29%	4.6[0.59,36.09]
Carotid IMT 2008	23/203	7/211		5.71%	3.42[1.5,7.78]
Goldberg 2000	26/72	5/39		5.28%	2.82[1.18,6.75]
Guyton 2008	156/547	26/239		11.6%	2.62[1.78,3.86]
Harikrishnan 2008	4/102	1/102		1.17%	4[0.45,35.18]
HPS2-THRIVE 2014	2105/12730	1014/12740		16.12%	2.08[1.94,2.23]
Hunninghake 2003	11/57	6/61		4.87%	1.96[0.78,4.96]
Lee 2009	7/29	2/31		2.31%	3.74[0.85,16.56]
Lee 2011	0/14	0/14			Not estimable
Maccubbin 2008	166/1080	15/254		9.53%	2.6[1.56,4.34]
MacLean 2011	102/400	31/308		11.82%	2.53[1.74,3.68]
Nash 2011	4/31	1/23		1.22%	2.97[0.35,24.82]
NIA Plaque 2013	11/66	5/63		4.37%	2.1[0.77,5.7]
PAST 1995	4/34	0/34		0.69%	9[0.5,160.96]
Total (95% CI)	**17418**	**16121**		**100%**	**2.17[1.7,2.77]**
Total events: 3083 (Niacin), 1470 (Control)					
Heterogeneity: Tau^2=0.1; Chi^2=65.36, df=15(P<0.0001); I^2=77.05%					
Test for overall effect: Z=6.21(P<0.0001)					



Analysis 1.16. Comparison 1 Niacin versus control, maximum follow-up, available case analysis, Outcome 16 New onset diabetes).

Study or subgroup	Niacin n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Guyton 2008	28/676	7/272		2.54%	1.61[0.71,3.64]
Maccubbin 2008	7/1129	0/232		0.21%	3.09[0.18,53.97]
HPS2-THRIVE 2014	494/12838	376/12835		97.25%	1.31[1.15,1.5]
Total (95% CI)	**14643**	**13339**		**100%**	**1.32[1.16,1.51]**
Total events: 529 (Niacin), 383 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.57, df=2(P=0.75); I^2=0%					
Test for overall effect: Z=4.21(P<0.0001)					



ADDITIONAL TABLES

Table 1. Sensitivity analysis assuming different relationship between the outcomes from observed and missing participants

Outcome	Available case analysis		IMOR 1.0, 1.0*		IMOR 0.5, 2.0*		IMOR 2.0, 0.5*	
	RR (95% CI)	I^2	RR (95% CI)	I^2	RR (95% CI)	I^2	RR (95% CI)	I^2
Overall mortality	1.05 (0.97 to 1.12)	0%	1.05 (0.97 to 1.12)	0%	1.04 (0.96 to 1.11)	0%	1.06 (0.98 to 1.14)	0%
Cardiovascular mortality	1.02 (0.93 to 1.12)	0%	1.02 (0.93 to 1.12)	0%	1.01 (0.92 to 1.11)	0%	1.03 (0.94 to 1.13)	0%
Non-cardiovascular mortality	1.12 (0.98 to 1.28)	0%	1.12 (0.98 to 1.28)	0%	1.11 (0.97 to 1.27)	0%	1.14 (1.00 to 1.30)	0%
Fatal or non-fatal myocardial infarction	0.93 (0.87 to 1.00)	0%	0.93 (0.87 to 1.00)	0%	0.92 (0.86 to 0.99)	0%	0.96 (0.87 to 1.05)	14%
Fatal myocardial infarction	1.01 (0.91 to 1.11)	0%	1.01 (0.91 to 1.11)	0%	1.00 (0.90 to 1.10)	0%	1.02 (0.92 to 1.12)	0%
Non-fatal myocardial infarction	0.91 (0.77 to 1.07)	53%	0.91 (0.77 to 1.07)	53%	0.89 (0.76 to 1.05)	47%	0.92 (0.77 to 1.10)	57%
Fatal or non-fatal stroke	0.95 (0.74 to 1.22)	42%	0.95 (0.74 to 1.22)	42%	0.94 (0.73 to 1.21)	42%	0.97 (0.75 to 1.26)	42%
Revascularisation	0.85 (0.68 to 1.06)	45%	0.85 (0.68 to 1.06)	45%	0.83 (0.66 to 1.04)	48%	0.88 (0.69 to 1.09)	47%
Discontinuation of treatment due to side effects	2.16 (1.70 to 2.76)	77%	2.15 (1.68 to 2.74)	75%	1.96 (1.55 to 2.49)	73%	2.35 (1.82 to 3.03)	77%
Flushing	7.69 (4.15 to 14.26)	91%	7.66 (4.11 to 14.29)	91%	6.68 (3.54 to 12.58)	91%	8.61 (4.67 to 15.87)	90%
Rash	3.16 (1.96 to 5.12)	52%	3.14 (1.93 to 5.10)	51%	2.74 (1.80 to 4.19)	40%	3.69 (2.13 to 6.40)	60%
Pruritus	5.15 (2.62 to 10.13)	67%	5.21 (2.68 to 10.13)	62%	4.23 (1.94 to 9.23)	72%	6.48 (3.78 to 11.10)	46%
Gastrointestinal symptoms	1.69 (1.37 to 2.09)	62%	1.69 (1.36 to 2.11)	60%	1.53 (1.23 to 1.91)	59%	1.88 (1.48 to 2.39)	66%
Headache	1.41 (0.86 to 2.30)	0%	1.43 (0.83 to 2.46)	0%	1.14 (0.64 to 2.03)	0%	1.76 (1.05 to 2.97)	0%

CI: confidence interval; **IMOR**: informative missingness odds ratio; **RR**: risk ratio

Sensitivity analysis for random-effects meta-analysis assuming different relationship between the outcomes from observed and missing participants and accounting for the uncertainty introduced by the proportion of missing data and assumed relationship (informative missingness odds ratio, IMOR = odds of event in missing data/odds of event in observed data, SD(logIMOR) = 0.5). We used the “metamiss”-command in Stata (version 13) (stata.com).

*The two numbers represent the assumed IMORs for the niacin and the control arm, respectively: 1.0, 1.0: missing at random; 0.5, 2.0: assumption favours niacin, 2.0, 0.5: assumption favours control.

We could not conduct sensitivity analysis for the outcome 'new onset diabetes' because the proportion of missing data was not reported.

Table 2. Lipid data

Study	Niacin dose g/day	Follow-up in months	Total cholesterol	LDL-cholesterol	HDL-cholesterol	Triglycerides
			Baseline mean, (treatment effect: difference between niacin and control group in mean change from baseline) in mg/dL			
ADMIT 2000	3	11	214 (-4)	138 (-6)	41 (+11)	176 (-34)
AIM-HIGH 2011	2	38	NA (NA)	74 (-3)	35 (+10)	165 (-21)
ALPINE-SVG 2015	2	12	136 (+1)	69 (+2)	38 (+3)	158 (-19)
ARBITER-2 2004	1	12	158 (+6)	89 (+3)	40 (+8)	163 (-12)
Capuzzi 2003	2	6	262 (+3)	146 (+6)	36 (+6)	377 (-6)
Carotid IMT 2008	2	18	237 (-6)	154 (-9)	42 (+6)	201 (-16)
CDP 1975	3	72	249 (-20)	NA (NA)	NA (NA)	NA (NA)
Goldberg 2000	3	6	300 (-31)	216 (-48)	45 (+8)	191 (NA)
Guyton 2008	2	6	241 (-4)	156 (-9)	51 (+11)	159 (-30)
Harikrishnan 2008	1.5	9	178 (-9)	112 (-11)	35 (+5)	157 (-5)
Heart positive 2011	2	6	211 (-7)	NA (NA)	39 (+5)	306 (-25)
HPS2-THRIVE 2014	2	23	128 (-5)	63 (-10)	43 (+6)	124 (-33)
Hunninghake 2003	2	6	NA (NA)	188 (-10)	44 (+24)	197 (-23)
Lee 2009	2	12	157 (+1)	85 (-15)	38 (+22)	180 (-7)
Lee 2011	1	9	198 (NA)	122 (NA)	49 (NA)	160 (NA)
Linke 2009	1	6	218 (+4)	133 (-9)	33 (+5)	154 (-29)
Maccubbin 2008	2	6	192 (-9)	223 (-20)	52 (+22)	122 (-57)
MacLean 2011	2	8	127 (NA)	164 (-33)	86 (+21)	50 (-15)
Nash 2011	2	12	178 (-15)	118 (-22)	33 (+8)	141 (-21)
NIA Plaque 2013	1.5	18	172 (0)	90 (-4)	60 (+8)	130 (-26)
PAST 1995	0.5	36	243 (-8)	169 (-13)	42 (+1)	162 (-25)
Sang 2009	1	12	183 (NA)	105 (NA)	50 (NA)	147 (NA)
Schoch 1968	4	38	242 (-34)	NA (NA)	NA (NA)	NA (NA)

NA: not available

Table 3. Number randomised, complete, missing, and events

Study	Outcome	Niacin group				Control group			
		Randomised	Complete	Missing	Events	Randomised	Complete	Missing	Events
ADMIT 2000	Discontinuation of treatment due to side effects	237	213	24	19	231	209	22	9
AIM-HIGH 2011	Fatal myocardial infarction	1718	1693	25	38	1696	1672	24	34
	Non-cardiovascular mortality	1718	1693	25	51	1696	1672	24	44
	Fatal or non-fatal myocardial infarction	1718	1693	25	112	1696	1672	24	106
	Cardiovascular mortality	1718	1693	25	45	1696	1672	24	38
	Overall mortality	1718	1693	25	96	1696	1672	24	82
	Non-fatal myocardial infarction	1718	1693	25	104	1696	1672	24	93
	Revascularisation procedures	1718	1693	25	167	1696	1672	24	168
	Fatal or non-fatal stroke	1718	1693	25	30	1696	1672	24	18
	Flushing	1718	1693	25	104	1696	1672	24	43
	Gastrointestinal symptoms	1718	1693	25	26	1696	1672	24	12
	Discontinuation of treatment due to side effects	1718	1693	25	436	1696	1672	24	341
ARBITER-2 2004	Flushing	87	78	9	54	80	71	9	9
	Overall mortality	87	78	9	1	80	71	9	2
	Cardiovascular mortality	87	78	9	1	80	71	9	2
	Non-cardiovascular mortality	87	78	9	0	80	71	9	0
	Revascularisation procedures	87	78	9	1	80	71	9	4
	Fatal or non-fatal stroke	87	78	9	0	80	71	9	1

Table 3. Number randomised, complete, missing, and events *(Continued)*

	Discontinuation of treatment due to side effects	87	80	7	2	80	77	3	6
ALPINE-SVG 2015	Fatal or non-fatal myocardial infarction	19	19	0	0	19	19	0	1
	Fatal and non-fatal stroke	19	19	0	0	19	19	0	1
	Revascularisation procedures	19	19	0	3	19	19	0	1
Capuzzi 2003	Flushing	72	60	12	21	46	43	3	0
	Pruritus	72	60	12	5	46	43	3	0
	Rash	72	60	12	6	46	43	3	0
	Discontinuation of treatment due to side effects	72	67	5	7	46	44	2	1
Carotid IMT 2008	Fatal or non-fatal myocardial infarction	214	180	34	0	218	204	14	1
	Discontinuation of treatment due to side effects	214	203	11	23	218	211	7	7
CDP 1975	Overall mortality	1119	1116	3	273	2798	2797	1	709
	Cardiovascular mortality	1119	1116	3	238	2798	2797	1	633
	Non-cardiovascular mortality	1119	1116	3	30	2798	2797	1	54
	Fatal myocardial infarction	1119	1116	3	203	2798	2797	1	535
	Non-fatal myocardial infarction	1119	1116	3	114	2798	2797	1	386
	Fatal or non-fatal myocardial infarction	1119	1116	3	287	2798	2797	1	839
	Fatal or non-fatal stroke	1119	1116	3	95	2798	2797	1	311
	Revascularisation procedures	1119	1116	3	29	2798	2695	103	132
	Gastrointestinal symptoms	1119	1073	46	230	2798	2695	103	385
	Flushing	1119	1073	46	987	2798	2695	103	115

Table 3. Number randomised, complete, missing, and events *(Continued)*

	Pruritus	1119	1073	46	525	2798	2695	103	167
	Rash	1119	1073	46	289	2798	2695	103	199
Goldberg 2000	Flushing	87	87	0	74	44	44	0	7
	Headache	87	46	41	22	44	34	10	13
	Gastrointestinal symptoms	87	46	41	24	44	34	10	10
	Pruritus	87	46	41	10	44	34	10	0
	Rash	87	46	41	9	44	34	10	0
	Overall mortality	87	46	41	0	44	34	10	1
	Discontinuation of treatment due to side effects	87	72	15	26	44	39	5	5
Guyton 2008	Overall mortality	676	391	285	0	272	213	59	0
	Fatal or non-fatal myocardial infarction	676	391	285	1	272	213	59	1
	Fatal or non-fatal stroke	676	391	285	0	272	213	59	1
	Flushing	676	457	219	66	272	214	58	1
	New onset diabetes	569	NR	NR	25	229	NR	NR	2
	Discontinuation of treatment due to side effects	676	547	129	156	272	NR	33	26
Harikrishnan 2008	Flushing	104	102	2	2	106	NR	4	0
	Gastrointestinal symptoms	104	102	2	5	106	102	4	2
	Discontinuation of treatment due to side effects	104	102	2	4	106	102	4	1
Heart positive 2011	Gastrointestinal symptoms	92	49	43	1	88	53	35	2
	Rash	723	412	311	1	315	237	78	2

Table 3. Number randomised, complete, missing, and events *(Continued)*

	Headache	780	493	287	2	378	315	63	0
	Flushing	92	49	43	28	88	53	35	5
HPS2-THRIVE 2014	Fatal or non-fatal myocardial infarction	12838	12730	108	668	12835	12745	90	694
	Non-fatal myocardial infarction	12838	12730	108	402	12835	12745	90	431
	Non-cardiovascular mortality	12838	12730	108	350	12835	12745	90	321
	Fatal myocardial infarction	12838	12730	108	302	12835	12745	90	291
	Cardiovascular mortality	12838	12730	108	448	12835	12745	90	411
	Fatal or non-fatal stroke	12838	12730	108	498	12835	12745	90	499
	Revascularisation procedures	12838	12730	108	807	12835	12745	90	897
	Overall mortality	12838	12730	108	798	12835	12745	90	732
	New onset diabetes	8704	NR	NR	494	8670	NR	NR	376
	Gastrointestinal symptoms	12838	12730	108	620	12835	12745	90	491
	Rash	12838	12730	108	54	12835	12745	90	33
	Discontinuation of treatment due to side effects	12838	12730	108	2105	12835	12740	95	1014
Hunninghake 2003	Flushing	57	57	0	6	61	61	0	1
	Overall mortality	57	57	0	0	61	61	0	1
	Headache	57	57	0	5	61	61	0	2
	Pruritus	57	57	0	4	61	61	0	1
	rash	57	57	0	1	61	61	0	2
	Discontinuation of treatment due to side effects	57	57	0	11	61	61	0	6

Table 3. Number randomised, complete, missing, and events *(Continued)*

Lee 2009	Gastrointestinal symptoms	35	25	10	3	36	30	6	1
	Discontinuation of treatment due to side effects	35	29	6	7	36	31	5	2
Lee 2011	Discontinuation of treatment due to side effects	14	14	0	0	14	14	0	0
Linke 2009	flushing	30	30	0	19	30	30	0	0
	Overall mortality	30	30	0	0	30	30	0	0
Maccubbin 2008	Rash	1343	917	426	33	270	239	31	2
	Discontinuation of treatment due to side effects	1339	1080	259	166	270	254	16	15
	Overall mortality	1343	917	426	3	270	239	31	0
	Pruritus	1343	917	426	34	270	239	31	6
	Flushing	1343	917	426	142	270	239	31	5
	Gastrointestinal symptoms	1343	917	426	34	270	239	31	5
	New onset diabetes	1129	NR	NR	7	232	NR	NR	2
MacLean 2011	Discontinuation of treatment due to side effects	454	400	54	102	342	308	34	31
	Overall mortality	454	298	156	0	342	277	65	1
	Fatal or non-fatal myocardial infarction	454	298	156	2	342	277	65	0
	Gastrointestinal symptoms	454	298	156	68	342	277	65	38
	Pruritus	454	298	156	71	342	277	65	9
	Rash	454	298	156	26	342	277	65	5
	Flushing	454	298	156	79	342	277	65	16

Table 3. Number randomised, complete, missing, and events *(Continued)*

Nash 2011	Gastrointestinal symptoms	31	31	0	2	23	23	0	0
	Discontinuation of treatment due to side effects	31	31	0	4	23	23	0	1
NIA Plaque 2013	Revascularisation procedures	72	59	13	5	73	58	15	2
	Fatal or non-fatal stroke	72	59	13	1	73	58	15	0
	Overall mortality	72	59	13	0	73	58	15	1
	Flushing	72	59	13	7	73	58	15	1
	Discontinuation of treatment due to side effects	72	66	6	11	73	63	10	5
PAST 1995	Overall mortality	40	30	10	3	45	34	11	4
	Fatal myocardial infarction	40	30	10	2	45	34	11	3
	Cardiovascular mortality	40	30	10	2	45	34	11	3
	Non-cardiovascular mortality	40	30	10	1	45	34	11	1
	Fatal or non-fatal myocardial infarction	40	30	10	2	45	34	11	1
	Revascularisation procedures	40	30	10	2	45	34	11	4
	Discontinuation of treatment due to side effects	40	34	6	4	45	34	11	0
Sang 2009	Rash	52	52	0	1	56	56	0	0
	Flushing	52	52	0	4	56	56	0	0
	Gastrointestinal symptoms	52	52	0	1	56	56	0	0
	Revascularisation procedures	52	52	0	2	56	56	0	1
	Overall mortality	52	52	0	0	56	56	0	1
	Fatal myocardial infarction	52	52	0	0	56	56	0	1

Table 3. Number randomised, complete, missing, and events *(Continued)*

Schoch 1968	Gastrointestinal symptoms	141	134	7	71	284	277	7	57
	Flushing	141	134	7	71	284	277	7	20
	Overall mortality	141	140	1	31	284	283	1	54
	Fatal myocardial infarction	141	134	7	28	284	277	7	48
	Non-fatal myocardial infarction	141	134	7	21	284	277	7	45
	Fatal or non-fatal myocardial infarction	141	134	7	49	284	277	7	93

APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MeSH descriptor Niacin, this term only

#2 MeSH descriptor Niacinamide, this term only

#3 (niacin):ti,ab,kw

#4 (nicotinic acid):ti,ab,kw

#5 (nicamin):ti,ab,kw

#6 nicotinate:ti,ab,kw

#7 (nico 400):ti,ab,kw

#8 (nico-400):ti,ab,kw

#9 (nico400):ti,ab,kw

#10 induracin:ti,ab,kw

#11 (nicolar):ti,ab,kw

#12 (nicocap):ti,ab,kw

#13 wampocap:ti,ab,kw

#14 (nicobid):ti,ab,kw

#15 (3 pyridinecarboxylic acid):ti,ab,kw

#16 3-pyridinecarboxylic acid:ti,ab,kw

#17 (enduracin):ti,ab,kw

#18 (niacinamide):ti,ab,kw

#19 papulex:ti,ab,kw

#20 vitamin b3:ti,ab,kw

#21 (vitamin b 3):ti,ab,kw

#22 (vitamin pp):ti,ab,kw

#23 nicotinamide:ti,ab,kw

#24 enduramide:ti,ab,kw

#25 (nicobion):ti,ab,kw

#26 (3 pyridinecarboxamide)

#27 (3-pyridinecarboxamide):ti,ab,kw

#28 (nicotinsaureamid):ti,ab,kw

#29 (Niaspan):ti,ab,kw

#30 (Tredaptive):ti,ab,kw

#31 (antipellagra factor):ti,ab,kw

#32 (b-3-50*.):ti,ab,kw

#33 niacor:ti,ab,kw

#34 (nicotinex):ti,ab,kw

#35 (vitb3):ti,ab,kw

#36 nicamid:ti,ab,kw

#37 (nicomide-t):ti,ab,kw

#38 nicosedine:ti,ab,kw

#39 (pellagra* near/2 factor).:ti,ab,kw

#40 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)

#41 MeSH descriptor Cardiovascular Diseases explode all trees

#42 (cardio*):ti,ab,kw

#43 (cardia*):ti,ab,kw

#44 (heart*):ti,ab,kw

#45 (coronary*):ti,ab,kw

#46 (angina*):ti,ab,kw

#47 (ventric*):ti,ab,kw

#48 (myocard*):ti,ab,kw

#49 (pericard*):ti,ab,kw

#50 (isch?em*):ti,ab,kw

#51 MeSH descriptor Stroke explode all trees

#52 (stroke or stokes):ti,ab,kw

#53 (cerebrovasc*):ti,ab,kw

#54 (apoplexy):ti,ab,kw

#55 (brain near/2 accident*):ti,ab,kw

#56 ((brain* or cerebral or lacunar) near/2 infarct*):ti,ab,kw

#57 MeSH descriptor Hypertension explode all trees

#58 (hypertensi*):ti,ab,kw

#59 (peripheral arter* disease*):ti,ab,kw

#60 ((high or increased or elevated) near/2 blood pressure):ti,ab,kw

#61 MeSH descriptor Hyperlipidemias explode all trees

#62 (hyperlipid*):ti,ab,kw

#63 (hyperlip?emia*):ti,ab,kw

#64 (hypercholesterol*):ti,ab,kw

#65 (hypercholester?emia*):ti,ab,kw

#66 (hyperlipoprotein?emia*):ti,ab,kw

#67 (hypertriglycerid?emia*):ti,ab,kw

#68 (#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67)

#69 (#40 AND #68)

MEDLINE O vid

1 Niacin/

2 Niacinamide/

3 niacin.tw.

4 nicotinic acid.tw.

5 nicamin.tw.

6 nicotinate.tw.

7 nico 400.tw.

8 nico-400.tw.

9 nico400.tw.

10 induracin.tw.

11 nicolar.tw.

12 nicocap.tw.

13 wampocap.tw.

14 nicobid.tw.

15 3 pyridinecarboxylic acid.tw.

16 3-pyridinecarboxylic acid.tw.

17 enduracin.tw.

18 niacinamide.tw.

19 papulex.tw.

20 vitamin b3.tw.

21 vitamin b 3.tw.

22 vitamin pp.tw.

23 nicotinamide.tw.

24 enduramide.tw.

25 nicobion.tw.

26 3 pyridinecarboxamide.tw.

27 3-pyridinecarboxamide.tw.

28 nicotinsaureamid.tw.

29 Niaspan.tw.

30 Tredaptive.tw.

31 antipellagra factor.tw.

32 b-3-50*.tw.

33 niacor.tw.

34 nicotinex.tw.

35 vitb3.tw.

36 nicamid.tw.

37 nicomide-t.tw.

38 nicosedine.tw.

39 (pellagra* adj2 factor).tw.

40 or/1-39

41 exp Cardiovascular Diseases/

42 cardio*.tw.

43 cardia*.tw.

44 heart*.tw.

45 coronary*.tw.

46 angina*.tw.

47 ventric*.tw.

48 myocard*.tw.

49 pericard*.tw.

50 isch?em*.tw.

51 exp Stroke/

52 (stroke or stokes).tw.

53 cerebrovasc*.tw.

54 apoplexy.tw.

55 (brain adj2 accident*).tw.

56 ((brain* or cerebral or lacunar) adj2 infarct*).tw.

57 exp Hypertension/

58 hypertensi*.tw.

59 peripheral arter* disease*.tw.

60 ((high or increased or elevated) adj2 blood pressure).tw.

61 exp Hyperlipidemias/

62 hyperlipid*.tw.

63 hyperlip?emia*.tw.

64 hypercholesterol*.tw.

65 hypercholester?emia*.tw.

66 hyperlipoprotein?emia*.tw.

67 hypertriglycerid?emia*.tw.

68 or/41-67

69 40 and 68

70 randomized controlled trial.pt.

71 controlled clinical trial.pt.

72 randomized.ab.

73 placebo.ab.

74 drug therapy.fs.

75 randomly.ab.

76 trial.ab.

77 groups.ab.

78 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77

79 exp animals/ not humans.sh.

80 78 not 79

81 69 and 80

Em base Ovid

1 Niacin/

2 Niacinamide/

3 niacin.tw.

4 nicotinic acid.tw.

5 nicamin.tw.

6 nicotinate.tw.

7 nico 400.tw.

8 nico-400.tw.

9 nico400.tw.

10 induracin.tw.

11 nicolar.tw.

12 nicocap.tw.

13 wampocap.tw.

14 nicobid.tw.

15 3 pyridinecarboxylic acid.tw.

16 3-pyridinecarboxylic acid.tw.

17 enduracin.tw.

18 niacinamide.tw.

19 papulex.tw.

20 vitamin b3.tw.

21 vitamin b 3.tw.

22 vitamin pp.tw.

23 nicotinamide.tw.

24 enduramide.tw.

25 nicobion.tw.

26 3 pyridinecarboxamide.tw.

27 3-pyridinecarboxamide.tw.

28 nicotinsaureamid.tw.

29 Niaspan.tw.

30 Tredaptive.tw.

31 antipellagra factor.tw.

32 b-3-50*.tw.

33 niacor.tw.

34 nicotinex.tw.

35 vitb3.tw.

36 nicamid.tw.

37 nicomide-t.tw.

38 nicosedine.tw.

39 (pellagra* adj2 factor).tw.

40 or/1-39

41 exp Cardiovascular Diseases/

42 cardio*.tw.

43 cardia*.tw.

44 heart*.tw.

45 coronary*.tw.

46 angina*.tw.

47 ventric*.tw.

48 myocard*.tw.

49 pericard*.tw.

50 isch?em*.tw.

51 exp Stroke/

52 (stroke or stokes).tw.

53 cerebrovasc*.tw.

54 apoplexy.tw.

55 (brain adj2 accident*).tw.

56 ((brain* or cerebral or lacunar) adj2 infarct*).tw.

57 exp Hypertension/

58 hypertensi*.tw.

59 peripheral arter* disease*.tw.

60 ((high or increased or elevated) adj2 blood pressure).tw.

61 exp Hyperlipidemias/

62 hyperlipid*.tw.

63 hyperlip?emia*.tw.

64 hypercholesterol*.tw.

65 hypercholester?emia*.tw. (

66 hyperlipoprotein?emia*.tw.

67 hypertriglycerid?emia*.tw.

68 or/41-67

69 40 and 68

70 random$.tw.

71 factorial$.tw.

72 crossover$.tw.

73 cross over$.tw.

74 cross-over$.tw.

75 placebo$.tw.

76 (doubl$ adj blind$).tw.

77 (singl$ adj blind$).tw.

78 assign$.tw.

79 allocat$.tw.

80 volunteer$.tw.

81 crossover procedure/

82 double blind procedure/

83 randomized controlled trial/

84 single blind procedure/

85 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84

86 (animal/ or nonhuman/) not human/

87 85 not 86

88 69 and 87

ISI Web of Science

#14 #13 AND #12

#13 TS=((random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*))

#12 #11 AND #7

#11 #10 OR #9 OR #8

#10 TS=(hypertensi* or peripheral arter* disease* or ((high or increased or elevated) near/2 ("blood pressure")) or hyperlipid* or hyperlip?emia* or hypercholesterol* or hypercholester?emia* or hyperlipoprotein?emia* or hypertriglycerid?emia*)

#9 TS=((stroke or stokes) or cerebrovasc* or apoplexy or (brain near/2 accident*) or ((brain* or cerebral or lacunar) near/2 infarct*))

#8 TS=(cardio* or cardia* or heart* or coronary* or angina* or ventric* or myocard* or pericard* or isch?em*)

#7 #6 OR #5 OR #4 OR #3 OR #2 OR #1

#6 TS=(antipellagra factor or b-3-50* or niacor or nicotinex or vitb3 or nicamid or nicomide-t or nicosedine or (pellagra* near/2 factor))

#5 TS=(nicobion or 3 pyridinecarboxamide or 3-pyridinecarboxamide or nicotinsaureamid or Niaspan or Tredaptive)

#4 TS=(vitamin b3 or vitamin b 3 or vitamin pp or nicotinamide or enduramide)

#3 TS=(3 pyridinecarboxylic acid or 3-pyridinecarboxylic acid or enduracin or niacinamide or papulex)

#2 TS=(induracin or nicolar or nicocap or wampocap or nicobid)

#1 TS=(niacin or nicotinic acid or nicamin or nicotinate or nico 400 or nico-400 or nico400)

CONTRIBUTIONS OF AUTHORS

SS screened titles and abstracts, retrieved potentially eligible full texts, assessed full texts for eligibility, screened reference lists and trials registries, extracted relevant data, assessed risk of bias, conducted the statistical analyses, contributed to interpretation of the results and writing of the final review. SS is the guarantor.

MB conceived the review, wrote the protocol, contributed to data extraction, risk of bias assessment, the statistical analysis, the interpretation of results and writing of the final review.

RS wrote the protocol, contributed to screening of titles and abstracts, retrieval of potentially eligible full texts, assessment of full texts for eligibility, data extraction, risk of bias assessment and critical revision of the final review.

KKO contributed to screening of titles and abstracts, retrieval of potentially eligible full texts, assessment of full texts for eligibility, data extraction, risk of bias assessment and critical revision of the final review.

AA contributed to retrieval of potentially eligible full texts, data extraction, risk of bias assessment and critical revision of the final review.

LH contributed to assessment of full texts for eligibility, data extraction, reviewed the manuscript and approved the final version.

AJN conceived the review, wrote the protocol, screened titles and abstracts, assessed full texts for eligibility, extracted relevant data, assessed risk of bias, contributed to the interpretation of results and writing of the final review.

DECLARATIONS OF INTEREST

SS: none known
MB: none known
RS: none known
KKO: none known
AA: none known
LH: none known
AJN: none known

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Internal sources

- No sources of support., Other.

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not search the database CINAHL which is of little relevance for cardiovascular trials.

We did not conduct the pre-specified meta-regression analyses for participant age and gender, since mean age and proportion of men did not vary substantially across trials. We did not conduct the pre-specified meta-regression analysis for items about trial quality. Instead, we stratified the primary analysis by trials with low, unclear, or high risk of bias and considered the trials at low risk of bias in a sensitivity analysis.

We planned to calculate the percentage of change in lipid levels for each trial as the difference in the mean change from baseline to end of follow-up. Instead we have presented the data in Table 2 in mg/dL.

Since niacin did not effectively improve any of our pre-specified clinical outcomes (seriously limiting the variability of the dependent variable) and because our group had already conducted a large meta-regression analysis including any lipid-modifying agents and diets that showed a strong association of change of LDL-cholesterol with clinical outcomes but no independent association of change of HDL-cholesterol with clinical outcomes (Briel 2009), we refrained from conducting the pre-specified meta-regression analysis of niacin trials investigating the association between clinical outcomes and change in HDL-cholesterol.

We did not contact experts in the field and authors of included studies about incomplete data, ongoing and unpublished studies.

We refined our strategy to conduct sensitivity analysis. Instead of stratifying treatment effects by individual items of the risk of bias instrument, we stratified the primary meta-analysis by trials with low, unclear, and high risk of bias. Instead of stratifying by trials using niacin on top of other lipid-modifying drugs versus trials using niacin monotherapy, we conducted a meta-regression analysis investigating the association between outcome and percentage of participants receiving background statin therapy.

We changed our strategy to handle missing data from assuming that no clinical events occurred for participants with missing outcomes data. Instead, we considered available case analysis as our primary analysis and conducted sensitivity analyses using three different assumptions about the relationship between missing and observed outcome data.

We could not assess the risk of reporting bias by comparing protocols to publications because the available protocols were either published retrospectively or did not specify any outcome relevant for the present systematic review.

Given the results, we did not calculate numbers needed to treat per year to prevent one event.

We added the outcome new onset diabetes motivated by the meta-analysis Goldie 2015, which found a significantly increased risk for new onset diabetes.

We used the GRADE approach to assess the quality of evidence and included a 'Summary of findings' table.

INDEX TERMS

Medical Subject Headings (MeSH)

*Primary Prevention; *Secondary Prevention; Cardiovascular Diseases [mortality] [*prevention & control]; Myocardial Infarction [mortality] [prevention & control]; Niacin [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic [statistics & numerical data]; Stroke [mortality] [prevention & control]; Vasodilator Agents [*administration & dosage] [adverse effects]

MeSH check words

Adult; Aged; Humans; Middle Aged