Online Appendices

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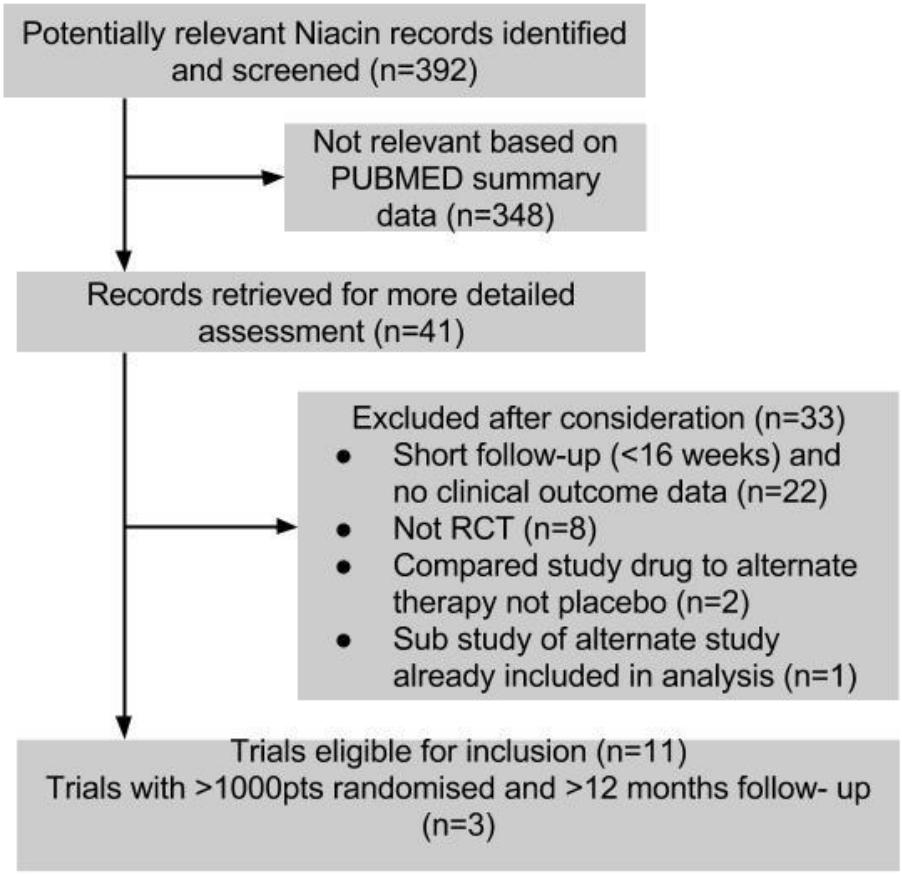
Online Appendix 1 – Search terms used to identify studies

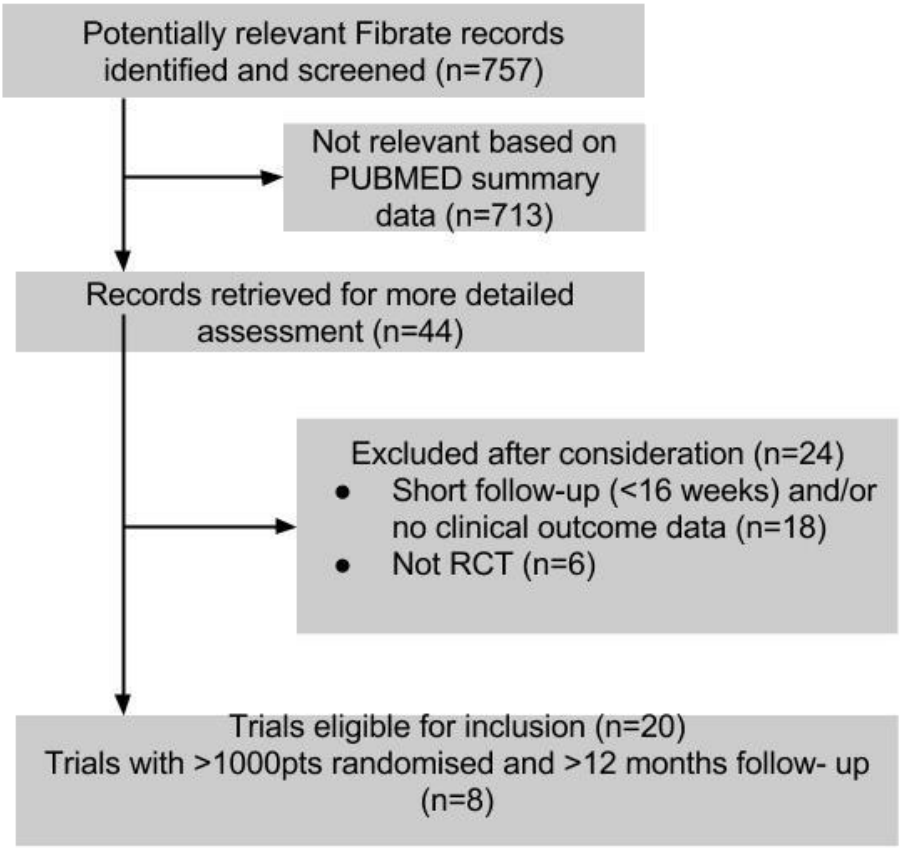
(((HDL OR high-density lipoprotein[Title/Abstract]) AND (niacin OR nicotinic acid OR acipimox[Title/Abstract])) AND (randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo clinical trial OR randomly OR trial[Title/Abstract])) NOT animals[Title/Abstract]

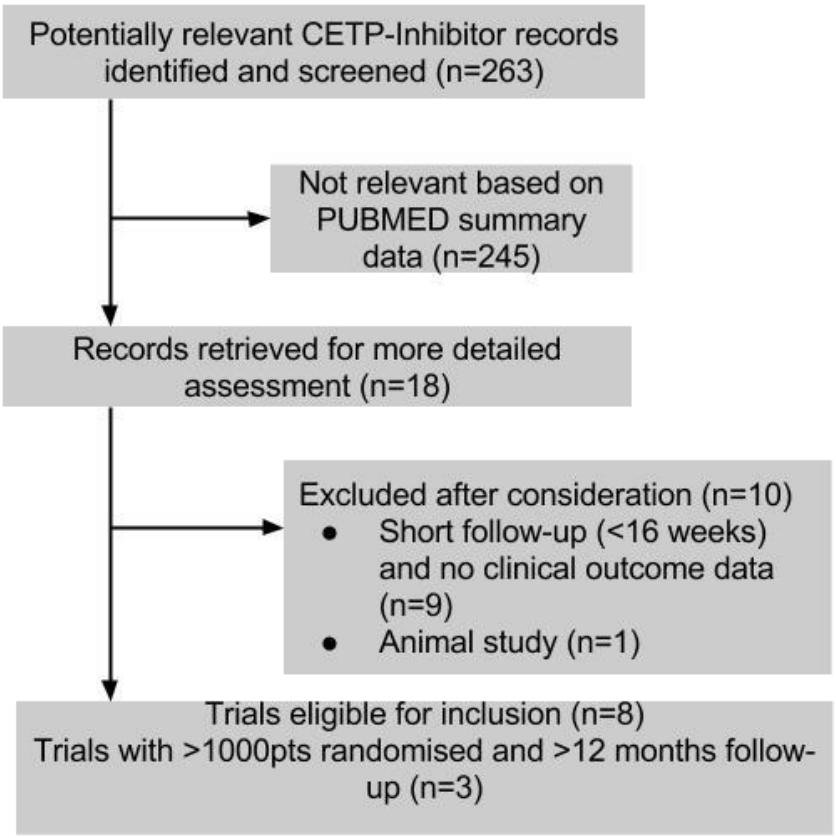
(((HDL OR high-density lipoprotein[Title/Abstract]) AND (cholesteryl ester transfer protein OR torcetrapib OR dalcetrapib OR Evacetrapib OR anacetrapib[Title/Abstract])) AND ((randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo clinical trial OR randomly OR trial[Title/Abstract]))) NOT animals[Title/Abstract]

(((HDL OR high-density lipoprotein[Title/Abstract]) AND (fibrate OR clofibrate OR bezafibrate OR gemfibrozil OR fenofibrate[Title/Abstract])) AND ((randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo clinical trial OR randomly OR trial[Title/Abstract]))) NOT animals[Title/Abstract]

Online Appendix 2 The identification process for eligible studies




Potentially relevant Fibrate records identified and screened (n=757)
Not relevant based on PUBMED summary data (n=713)
Records retrieved for more detailed assessment (n=44)
Excluded after consideration (n=24)
Short follow-up (<16 weeks) and/or no clinical outcome data (n=18)
Not RCT (n=6)
Trials eligible for inclusion (n=20)
Trials with >1000pts randomised and >12 months follow- up (n=8)


Potentially relevant CETP-Inhibitor records identified and screened (n=263)
Not relevant based on PUBMED summary data (n=245)
Records retrieved for more detailed assessment (n=18)
Excluded after consideration (n=10)
Short follow-up (<16 weeks) and no clinical outcome data (n=9)
Animal study (n=1)
Trials eligible for inclusion (n=8)
Trials with >1000pts randomised and >12 months follow-up (n=3)

Online Appendix 3a: Niacin. Risk of Bias Table

Trial Name	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias
	Random Sequence Generation	Allocation Concealment	Blinding of participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
AFREGS[5]	Randomly assigned 1:1 ratio	Assigned by a computer generated randomisation schedule	Matching placebos, Double blind trial, Central pharmacy held the code and the information was not shared with physicians or patients until the completion of the protocol, Unclear who had access to lipid measurements during study protocol, Flushing was almost universally seen in the drug group	Events were assessed for by a standardised questionnaire and an independent blinded end point committee adjudicated all serious events	7% treatment group withdrew from the study and 10% in the placebo group.	Industry funded the study but the sponsor had no role in the collection, analysis or interpretation of the data or in the decision to submit the study for publication. States that reported secondary outcomes will include NSTEMI and STEMI but in results only comments about STEMI data
Aim High[6]	Randomly assigned 1:1 ratio. Stratified by history of diabetes and clinical site	Assignment was performed with the use of a secure internet connection which provided a randomisation assignment as a numbered drug kit blinded to treatment/placebo	Matching placebos. Double blind trial. Placebo contained a small amount of trial drug with the aim of masking the identity of the blinded treatment to patients and study personnel. Only LDL results were reported to clinical sites personnel.	A clinical events committee reviewed suspected events with supporting documentation that did not reveal the treatment assignments	Trial terminated early due to increased endpoints in the treatment group. 25.4% of treatment group discontinued allocated therapy and 20.1% of placebo group discontinued allocated therapy. 6.1% discontinued in treatment group due to flushing and 2.5% in placebo group because of flushing	Industry funded the study but had no role in the oversight or design of the study or in the analysis or interpretation of the data
Arbiter 2[7]	Randomly assigned 1:1 ratio	Randomisation performed with a computer generated sequence of random numbers, participants were assigned a unique study identification that was used by a central research pharmacy to dispense the study medicine	Matching placebo, Double blind trial, Only the research pharmacist was aware of drug assignment. Measurements of lipid levels were made at the start and end of the trial only. 69.2% of treatment group reported flushing and only 12.7% in the placebo group	Unclear how events were adjudicated	10.3% of treatment group discontinued allocated therapy and 11.25% of placebo group discontinued allocated therapy	Single centre study. Sponsorship was utilised from industry but the study was investigator initiated and the trial database and analysis was performed by investigating institution

CDP Niacin 5 year[8]	Randomly assigned 2:5 (treatment : placebo). Stratified by disease severity	A separate random allocation schedule was utilised by the coordinating centre for each group within each participating clinic	Matching placebo. Double blind. Unclear who had access to cholesterol measurements during the trial	A central adjudication panel reviewed all events	10.7% treatment group dropped out of trial and 8% of placebo group dropped out	Multicentre collaborative study. We have reported the 5 year outcome data
CLAS[9]	Randomly assigned 1:1 ratio, stratified according to age and location	Unclear how randomisation was performed	Matching placebo. Study subjects were blinded to treatment assignment. Subjects and clinic staff were not blinded to on-trial lipid values. Blinding was affected due to the effects of niacin causing flushing (97% of treatment group compared to 6% of placebo group). All patients prior to randomisation were exposed to niacin therapy this meant that were better able to distinguish between placebo and active treatment later	Unclear how events were adjudicated – no comments made	15% of treatment group dropped out of trial and 13% of placebo group dropped out	Single centre study. No reported industry involvement
FATS[10]	Randomly assigned 1:1 ratio, stratified by age, smoking status and lipid pattern	Unclear how randomisation was performed	Matching placebo, Double blind study. Both patient and treating physician were blinded to changes in lipid levels	All clinical decisions were made by physicians who were reportedly independent of the study and were independent of the study and blinded to the patients; treatment assignments and to the changes in their lipid levels	33% of treatment group dropped out of the trial and 13% of placebo group dropped out	Single Centre study. Medication used in trial sponsored by industry. No reported industry involvement in trial design or data analysis
Guyton[11]	Randomly assigned 5:2 ratio in favour of treatment group, Stratified by lipid levels.	Unclear how randomisation was performed	Double blind study. Advised to take aspirin to reduce incidence of flushing	Unclear how events were adjudicated	23.3% of treatment group discontinued involvement with the trial and 9.6% of control arm discontinued. 9.9% of treatment group discontinued due to flushing and 0.4% discontinued due to flushing in the placebo group	No mention of industry sponsorship in manuscript

HPS 2 Thrive[12]	Randomly assigned 1:1 ratio. Stratified by age, gender, history of prior disease, smoking status, lipid levels, blood pressure, ethnic origin and history of prior statin use	Randomised using a minimised randomization program on the clinic IT system	Matching placebo. Laropiprant used to reduce flushing effects of niacin	A central blinded adjudication panel reviewed all events	25.4% of treatment group stopped the study medication and 16.6% stopped study medication in placebo group	Study sponsored by industry but study devised and data analysed independently
Sang[13]	Randomly assigned 1:1 ratio	Unclear how randomisation was performed	No mention of placebo. Unclear if blinded. Cholesterol levels measured during trial period but unclear who had access to results	Unclear how events were adjudicated	2% withdrew in treatment group and 4% withdrew in control group	Single centre study No mention of industry sponsorship in manuscript
Stockholm[14]	Randomly assigned 1:1. Stratified based on cholesterol, symptoms and age	Unclear how randomisation was performed	Non blinded study, Treatment was prescribed openly to all involved	Unclear how events were adjudicated	27% of treatment group withdrew from study and 12% of control group withdrew from the study	Single centre study. No mention of industry sponsorship in manuscript
UCSF-SCOR[15]	Randomly assigned 1:1 ratio. Stratified by sex and age and patients were grouped into blocks of four	Randomisation was performed by random selection of one of six possible sequences using tables of random numbers	The data manager maintained the randomisation schedule and made patient assignment. Due to SEs of niacin it was not considered possible to blind patients or physicians to treatment group assignment (therefore no placebo)	Unclear how events were adjudicated	8% discontinued therapy in treatment group and 19% of controls withdrew under advice from private physicians so as to intensify lipid therapy	Single centre study. No mention of industry sponsorship in manuscript

Online Appendix 3b: Fibrate. Risk of Bias Table

Trial Name	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias
	Random Sequence Generation	**Allocation Concealment**	**Blinding of participants and Personnel**	**Blinding of Outcome Assessment**	**Incomplete Outcome Data**	**Selective Reporting**
Becait[16]	Randomly assigned 1:1 ratio by a block design	Unclear how randomisation was performed	Matching Placebo. Double blind trial	Unclear how events were adjudicated	11% of treatment group withdrew from study and 13% of placebo group withdrew	Single centre study. Study supported by industry
SENDCAP[19]	Randomly assigned 1:1 ratio	A randomised list was prepared by the statistician in advance so that numbers assigned to each treatment would be approximately equal after every 10 subjects, subjects were allocated the next consecutive number in a double blind fashion	Matching Placebo, Double blind trial. Lipid measurements were concealed from those involved in the study	A safety committee reviewed all adverse events annually	33.3% of treatment group withdrew from the study and 36.1% of placebo group withdrew from the study	Study supported by industry. There was no extractable data from this trial
Leader[18]	Randomly assigned 1:1 ratio. Balanced between active and placebo treatment within each practice or hospital clinic	Unclear how randomisation was performed	Matching Placebo. Double blind trial. Unclear who had access to lipid measurement results during the trial	All possible endpoint episodes notified were documented and assessed independently and without knowledge of trial treatment allocation	47.1% of treatment group withdrew from the study and 51.3% of placebo group withdrew from the study. 5.4% of treatment group withdrew because they started a drug incompatible with trial drug(statin) and 13.9% of placebo withdrew because they started an incompatible drug (statin).	One study sites data was discarded as reported to be of poor quality and unreliable
BIP[17]	Randomly assigned 1:1 ratio	Patients were assigned consecutive randomisation numbers within each recruiting centre	Matching placebo. Double blind trial. Lipids measured at central laboratory during trial	An independent critical event committee whose members were blinded to treatment assignment reviewed end points	9% discontinued assigned drug in the treatment group due to receiving an open label lipid modifying therapy and 15% withdrew for the same reason in the placebo group	The trial reports it was conducted independently of the industry sponsor

Newcastle[22]	Randomly assigned 1:1 ratio	Patients were randomised through means of a randomisation scheme and allocation envelopes prepared by one individual and supervised by the pharmacists of the hospitals taking part in the trial	Matching placebo, Double blind trial. Unclear who had access to lipid measurement results during the trial	Cause of death was determined by the organising secretary while blinded to treatment allocation utilising the information available. Where possible necropsy was arranged. Similarly the organising secretary reviewed the details of all reported MIs	18% of the treatment group withdrew from the study and 11% withdrew from the placebo group	Funded by industry sponsor who also assisted with the analysis of the results
Scottish[23]	Randomly assigned 1:1 ratio	Unclear how randomisation was performed	Matching Placebo. Double blind trial except for those patients on OAC where the doctor knew the treatment allocation due to difficulties in dosing medication	Blinded review of patient details by one observer to determine clinical events	17% withdrew from the treatment group and 16% withdrew from the placebo group.	Independent statistical advice was obtained. There was industry support provided
WHO Clofibrate[25]	Randomly assigned 1:1 ratio	Unclear how randomisation was performed	Matching placebo. Double blind trial. Unclear who had access to cholesterol measurements during the trial	A panel of 2 centrally located physicians not concerned with the day-to-day running of the trial reviewed all events that the participating physicians in the centres considered might be due to IHD. Unclear if these individuals were blinded.	67% of treatment group completed 5 years of the trial and 68% of the placebo group completed 5 years of the trial	Medication supplied by industry
Diabetes Intervention Study (Hanefeld)[21]	Randomly assigned 1:1 ratio	Unclear how randomisation was performed	Matching placebo. Double blind trial. Unclear who had access to blood results for lipid levels	No central adjudication of events. Events were reported from hospital records. Most causes of deaths were confirmed by autopsy.	12% of treatment group did not complete the study and 14% of placebo group did not complete the study. Study only reported fatal stroke outcomes	Independent statistical advice was obtained

CDP Fibrate 5 year[8]	Randomly assigned 2:5 (treatment : placebo). Stratified by disease severity	A separate random allocation schedule was utilised by the coordinating centre for each group within each participating clinic	Matching placebo. Double blind. Unclear who had access to cholesterol measurements during the trial	A central adjudication panel reviewed all events	At 5 years 7.4% treatment group dropped out of trial and 8% of placebo group dropped out	Multicentre collaborative study
Stockholm[14]	Randomly assigned 1:1 ratio. Stratified based on cholesterol, symptoms and age	Unclear how randomisation was performed	Non blinded study, Treatment was prescribed openly to all involved	Unclear how events were adjudicated	27% of treatment group withdrew from study and 12% of control group withdrew from the study	Single centre study. No mention of industry sponsorship in manuscript
Acheson[20]	Randomly assigned 1:1 ratio	Patients matched in pairs according to clinical status, duration of disease, cholesterol level, age and sex and then randomised	Matching placebo. Not documented as blinded. The observers had no knowledge of cholesterol levels when patients were reviewed	Unclear how events were adjudicated	8 patients refused to cooperate in follow up and were thus excluded from the trial and 1 patient discontinued clofibrate in the treatment arm	Industry supplied the drugs used
VA Neuro[24]	Randomly assigned 1:1 ratio	Unclear how randomisation was performed	Matching placebo. Double blind. Unclear who had access to cholesterol measurements during the trial	A central adjudication panel reviewed all mortality and vascular events	26% of treatment group were lost to follow up and 22% of placebo group were lost to follow up. A cohort of patients was excluded immediately after randomisation this was due to concern raised over a particular trial centre.	Medication used in the study were supplied by industry
Accord[26]	Randomly assigned in a 2 by 2 factorial design	Randomisation was performed centrally via an online system and used a permuted block randomisation procedure	Matching placebo. Double blind. Unclear who had access to cholesterol measurements during the trial	A central blinded adjudication committee reviewed all events	All enrolled patients followed up for a mean duration of 4.7 years for the primary outcome and 5 years for total rates of death. At final visit 77.3% of treatment group were taking assigned medication and 81.3% in the treatment group were taking their assigned medication. 80% of patients in each group remained compliant with statin therapy at the end of the trial. For CHD death included only fatal MI	Drugs were donated by industry who had no role in the design or analysis of the study

Field[28]	Randomly assigned 1:1 ratio. Stratified by age, sex and clinical details	Randomisation was completed by a central computer using a dynamic allocation method	Matching placebo. Double blind. Unclear who had access to cholesterol measurements during the trial	A central blinded adjudication committee reviewed all events	20% of the treatment group discontinued therapy and 19% of placebo group discontinued therapy	Addition of additional lipid lowering therapy was at the discretion of the treating physician. The industry sponsor of the study had no role in data collection or data analysis
Dais[27]	Randomly assigned 1:1 ratio. Stratified by gender, prior coronary intervention and clinical centre	A permuted blocks randomisation procedure was used. The randomisation sequence was generated at the statistical coordinating centre by means of the pseudo random number generating routine in SAS	Matching placebo. Double blind. Unclear who had access to cholesterol measurements during the trial	A central blinded adjudication committee reviewed all events	Follow up data was allowed for all subjects. 13 patients could not have a final angiogram as per trial design but that was because they died during the trial period	Supported by industry
VA-HIT[32]	Randomly assigned 1:1 ratio. Stratified by centre	Telephone randomisation via the coordinating centre and used a permuted blocks randomisation procedure.	Matching placebo. Double blind. Unclear who had access to cholesterol measurements during the trial	A central blinded adjudication committee reviewed all primary end points	<1% of patients were lost to follow up	Supported by industry
LOCAT[31]	Randomly assigned 1:1 ratio	Unclear how randomisation was performed	Matching placebo. Double blind. Unclear who had access to cholesterol measurements during the trial	Unclear how events were adjudicated	94% of trial participants completed the trial. No data for non-fatal MI included as grouped MI with revascularisation and unable to determine between the two	Supported by sponsorship from industry
HHS[29]	Randomly assigned 1:1 ratio	Block design for each clinic, no further details	Matching placebo. Double blind. Unclear who had access to cholesterol measurements during the trial	A review committee evaluated the classification of all end points. When the reported end point differed from that of the review committee a four member safety committee reviewed the data	No patients were lost to follow up although only 70% continued to the end in the trial following their assigned treatment. 14.7% of the treatment group discontinued therapy by the end of year one and 12.6% of placebo group discontinued therapy by the end of year one	Supported by sponsorship from industry, statistical analysis was performed at the sponsor. Stroke data reported includes only fatal stroke data

HHS Exclusions[30]	Randomly assigned 1:1 ratio. Stratified by age, smoking status and history/evidence of prior MI	Unclear how randomisation was performed	Matching placebo. Double blind. Unclear who had access to cholesterol measurements during the trial	All endpoints were analysed blindly without knowledge of the treatment group, unclear who and when performed this analysis	38.3% of treatment group withdrew from the trial and 31.5% withdrew from the placebo group.	Trial conducted to ensure support of companies providing the study population for another trial
AFREGS[5]	Randomly assigned 1:1 ratio	Assigned by a computer generated randomisation schedule	Matching placebo. Double blind trial. Central pharmacy held the code and the information was not shared with physicians or patients until the completion of the protocol. Unclear who had access to lipid measurements during study protocol. Flushing was almost universally seen in the drug group	Events were assessed for by a standardised questionnaire and an independent blinded end point committee adjudicated all serious events	7% treatment group withdrew from the study and 10% in the placebo group.	Industry funded the study but the sponsor had no role in the collection, analysis or interpretation of the data or in the decision to submit the study for publication. States that reported secondary outcomes will include NSTEMI and STEMI but in results only comments about STEMI data

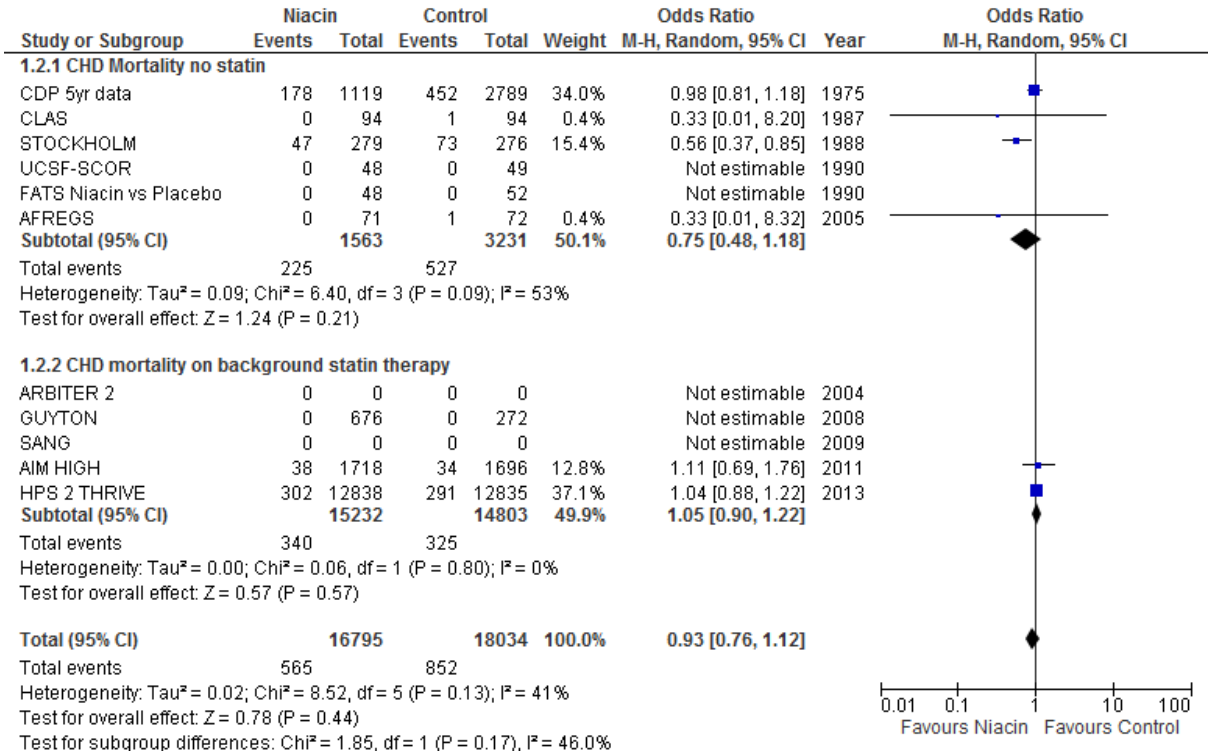
Online Appendix 3c: CETP-I. Risk of Bias Table

Trial Name	Selection Bias Random Sequence Generation	 Allocation Concealment	Performance Bias Blinding of participants and Personnel	Detection Bias Blinding of Outcome Assessment	Attrition Bias Incomplete Outcome Data	Reporting Bias Selective Reporting
Dal-Outcomes[33]	Randomly assigned 1:1 ratio, stratified according to country and cardiac biomarker levels	Interactive voice response system/interactive web response system	Identical matching placebo Double blind trial. Interim HDL measurements blinded from investigators and patients	Independent data and safety monitoring board monitored the trial and performed analyses of un-blinded data	Study terminated early due to futility. Study drug discontinued in 21% of treatment group and 19% of placebo group. 1.6% treatment group and 1.3% placebo group were lost to follow-up	Sponsored by industry who helped design the study. Analyses reported performed by two of the authors who are employees of the sponsor, data was confirmed by an academic statistician. Stroke data reported only ischaemic strokes.
Dal-Plaque[34]	Randomly assigned 1:1 ratio, stratified by centre	Randomised by a computer generated global randomisation code	Identical matching placebo. Double blind trial. Interim HDL measurements blinded from investigators and patients	Independent clinical endpoint committee adjudicated on safety and clinical endpoints	22% placebo withdrew and 10% treatment group withdrew. 2% treatment group withdrew due to clinical adverse event and 3% placebo group withdrew due to clinical adverse event	Final study protocol designed in collaboration with industry sponsor. Predefined end point extended from 12 to 24 months during trial
Dal-Vessel[35]	Randomly assigned 1:1 ratio	Randomised by a computer generated global randomisation code	Identical matching placebo. Double blind trial. Interim HDL measurements blinded from investigators and patients. One patient crossed over groups unclear why	Cardiovascular events were recorded and adjudicated by the clinical events committee	11% treatment group did not complete treatment and 10% of placebo group did not complete treatment. 5% treatment group discontinued trial drug due to clinical adverse event and 4% placebo group discontinued due to clinical adverse events. <1% in both treatment and placebo groups failed to return to follow up	Sponsor participated in discussions regarding the design and conduct of the study with the steering committee.
Define[36]	Randomly assigned 1:1 ratio	Unclear how randomisation was performed	Identical matching placebo, Double blind trial. Investigators and sponsor were unaware of the results of the lipid measurements	Cardiovascular events were adjudicated by an external independent adjudication committee whose members were unaware of the patients' group assignments	5.4% of treatment group had a clinical adverse event leading to discontinuation of study drug and 5.7% of placebo group discontinued due to a clinical adverse event. 2.7% of treatment group discontinued study drug due to a drug related adverse event and 2.2% of placebo group discontinued due to drug related adverse event.	Study was sponsored by industry

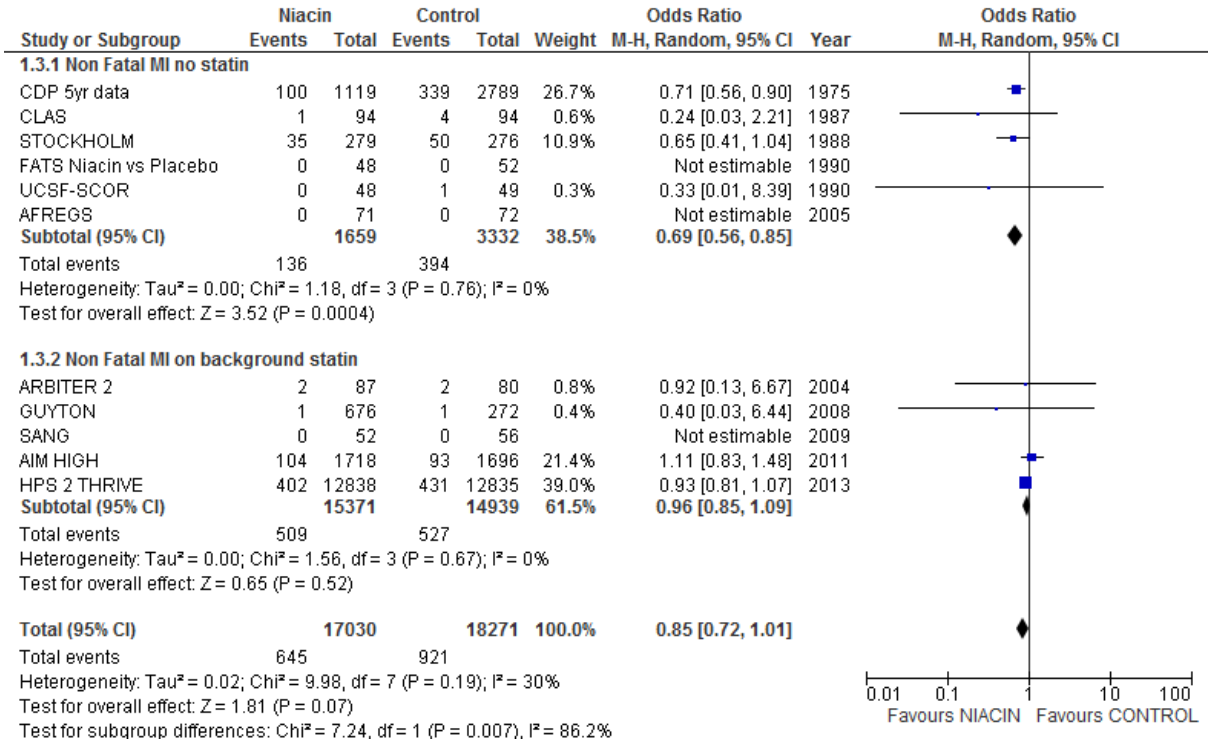
Illuminate[37]	Randomly assigned 1:1 ratio	Used a central randomisation strategy with a block size of four	Matching placebo, Double blind trial. Unclear who had access to Cholesterol measurements during trial	A central committee who were unaware of study-group assignments adjudicated potential outcomes as reported by investigators	13.4% of treatment group discontinued therapy early and 11.0% discontinued therapy early in the placebo group. <1% in both groups lost to follow up. 9.3% of treatment group discontinued therapy due to a non fatal adverse event and 5.7% of placebo group discontinued due to a non fatal adverse event	Trial designed in collaboration with industry sponsor. Data was analysed independently. Original protocol amended at the time of trial termination to include additional primary endpoints to increase the number of events and thus increase the statistical power to reject the null hypothesis.
Illustrate[38]	Randomly assigned 1:1 ratio. Stratified according to geographic region and dose of statin Used a permuted block size of 4	Unclear how randomisation was performed	Matching placebo, Double blind trial. Unclear who had access to cholesterol measurements during trial	A committee whose members were unaware of treatment assignment centrally adjudicated major cardiovascular adverse events.	23.8% of treatment group discontinued involvement in the trial and 23.5% discontinued from the placebo group. 11.2% discontinued in the treatment group because of adverse events and 10.7% discontinued in the placebo group	Trial designed in collaboration with the sponsor. Study database was independently analysed but was initially held by the sponsor
Radiance 1[39]	Randomly assigned 1:1 ratio	Unclear how randomisation was performed	Matching placebo, Double blind trial. Patients and study personnel were unaware of study group assignment, laboratory measurements and carotid imaging findings	Investigator reported clinical events were not centrally adjudicated	6% of treatment group and 6% of placebo group did not complete the trial	Trial was designed by academic investigators in collaboration with the industry sponsor. Study database was independently analysed but was initially held by the sponsor
Radiance 2[40]	Randomly assigned 1:1 ratio. Blocks were stratified by geographic region and statin dose	Randomised by use of a central scheme with a computer generated permuted block design and a block size of four	Identical matching placebo Double blind trial. Participants and study personnel were unaware of treatment assignment, laboratory measurements and carotid imaging findings	Investigator reported clinical events were not centrally adjudicated	Study terminated early as another torcetrapib trial reported an increase in death in the treatment arm	Trial was designed by academic investigators in collaboration with the industry sponsor

Online Appendix 4: Forest Plots showing the effects of Niacin, Fibrate and CETP-I on the risk of CHD Mortality, Non Fatal MI and Stroke

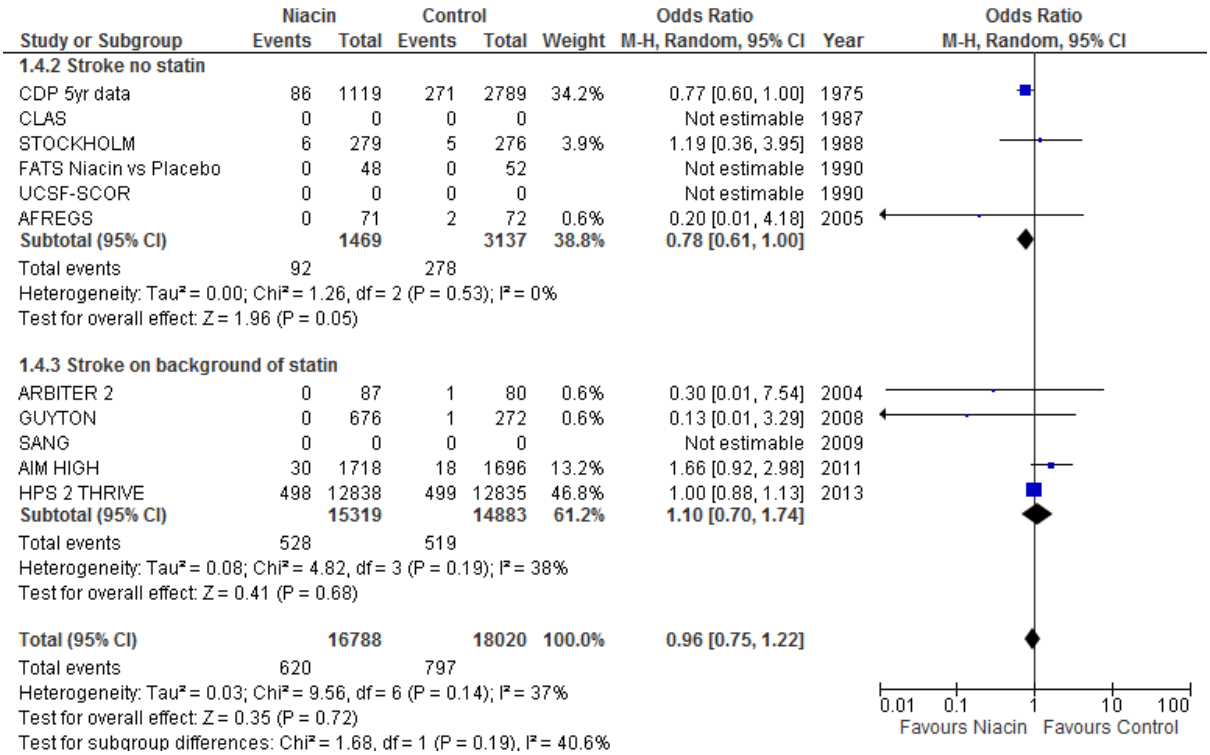
Effect of Niacin on the risk of CHD Mortality



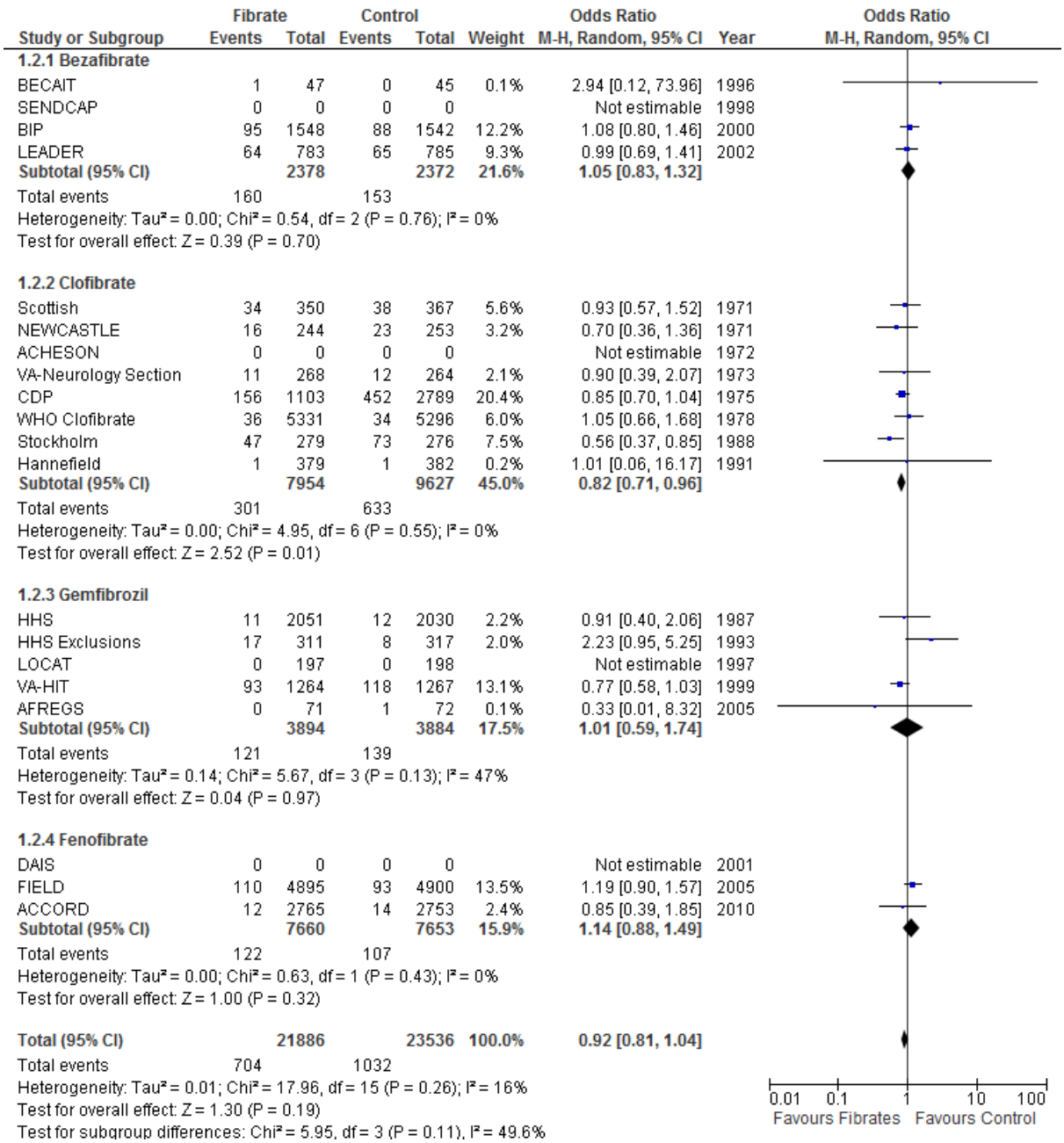
Effect of Niacin on the risk of Non-Fatal MI



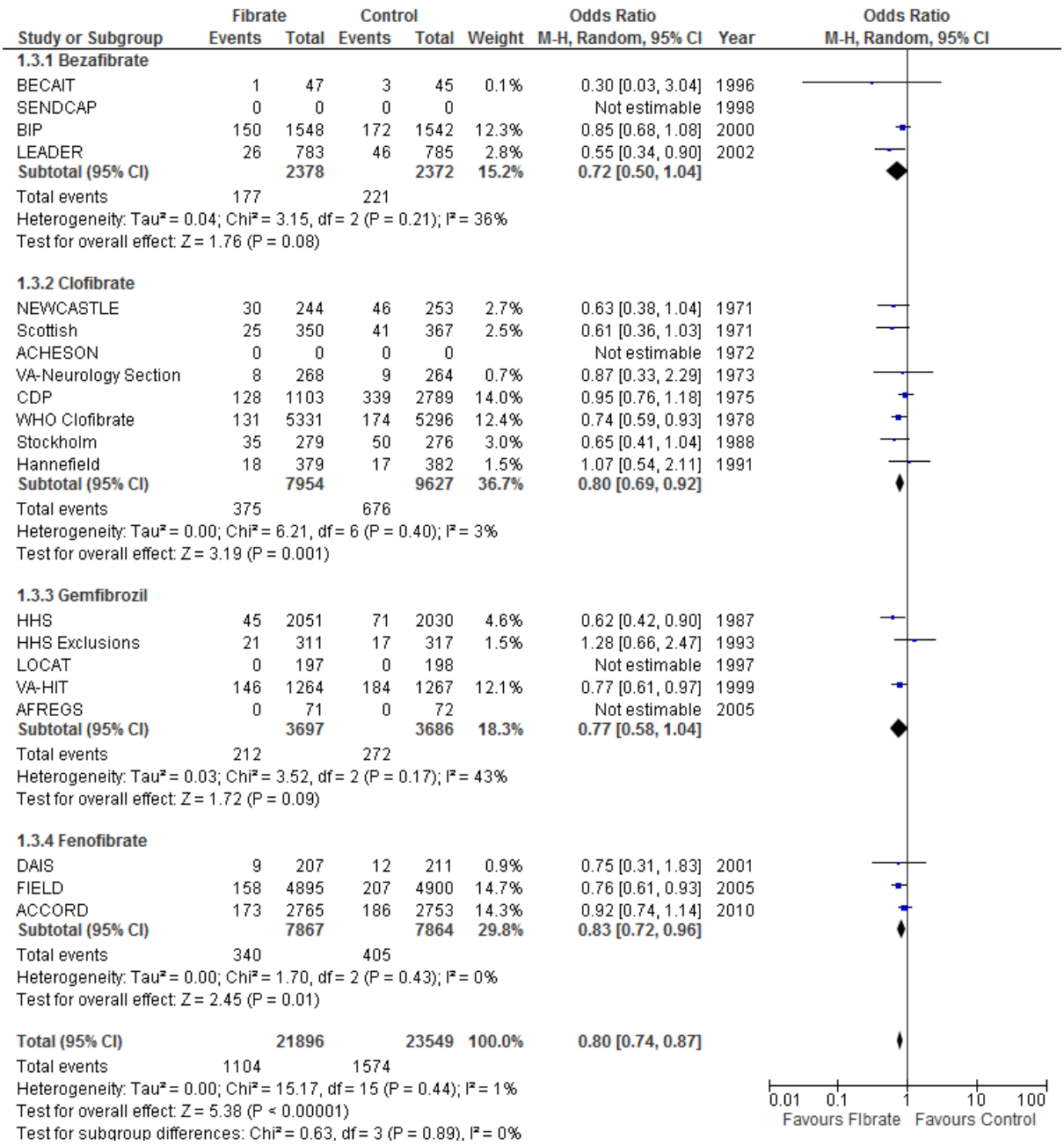
Effect of Niacin on the risk of Stroke



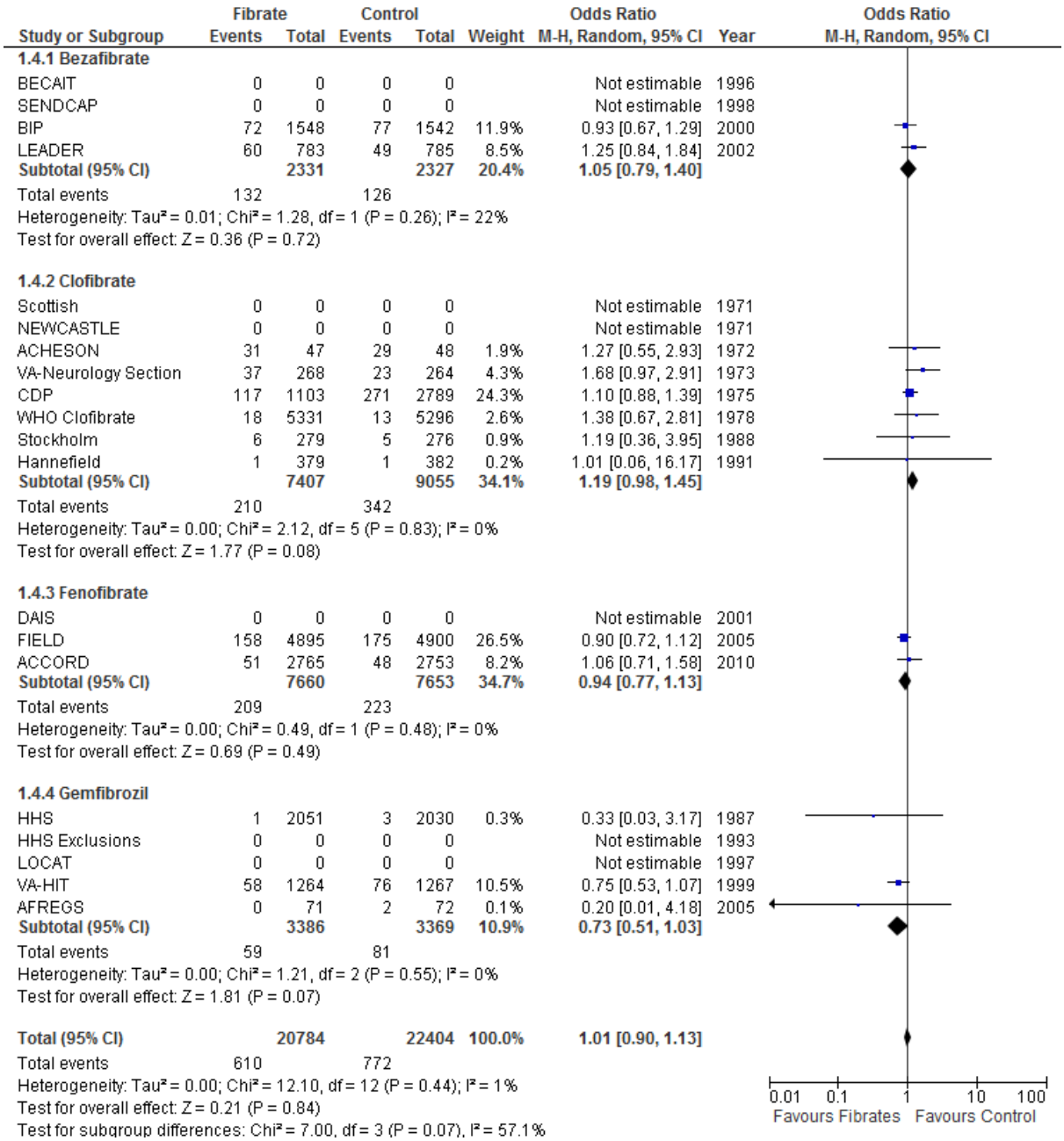
Effect of Fibrate on the risk of CHD Mortality



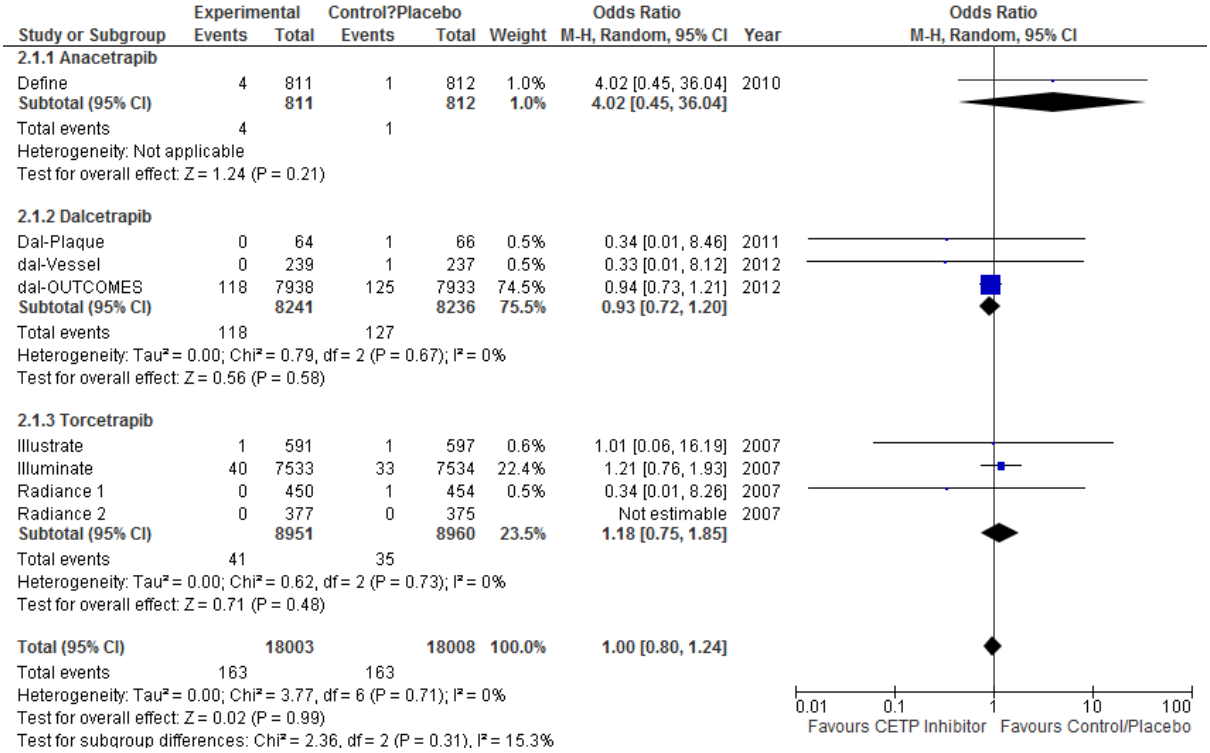
Effect of Fibrate on the risk of Non-Fatal MI



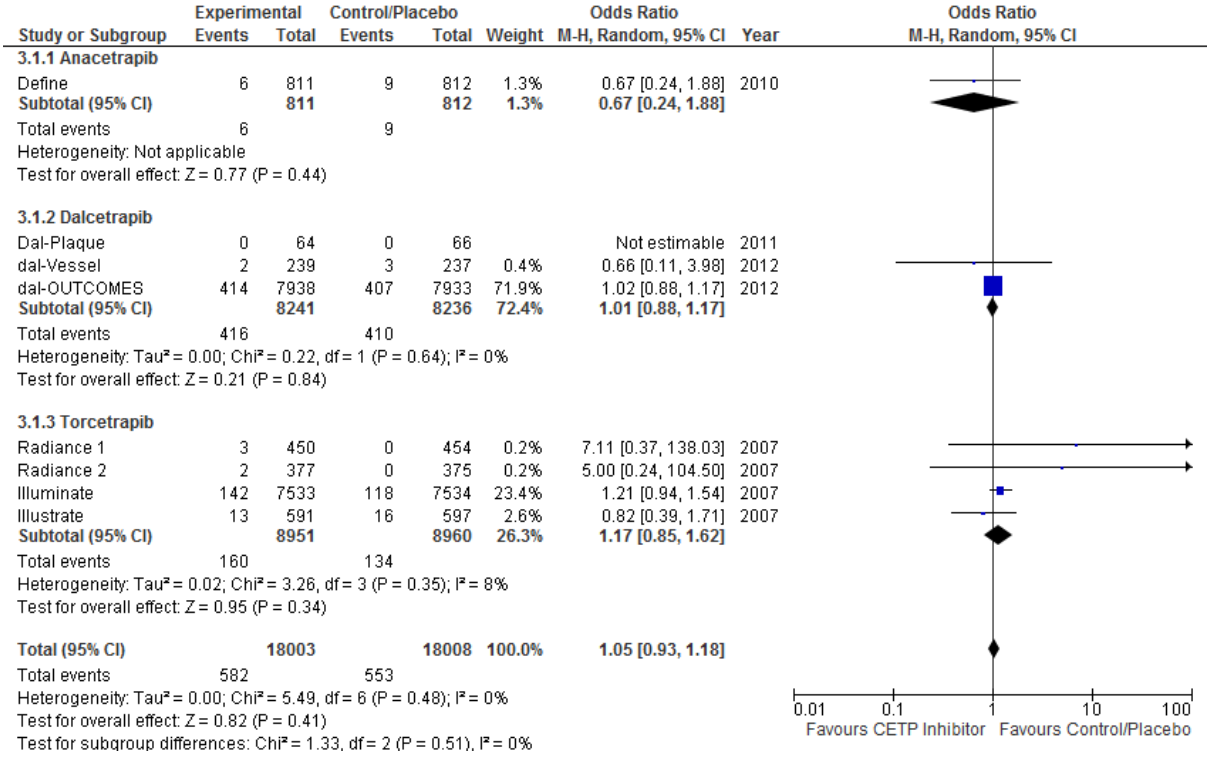
Effect of Fibrate on the risk of Stroke



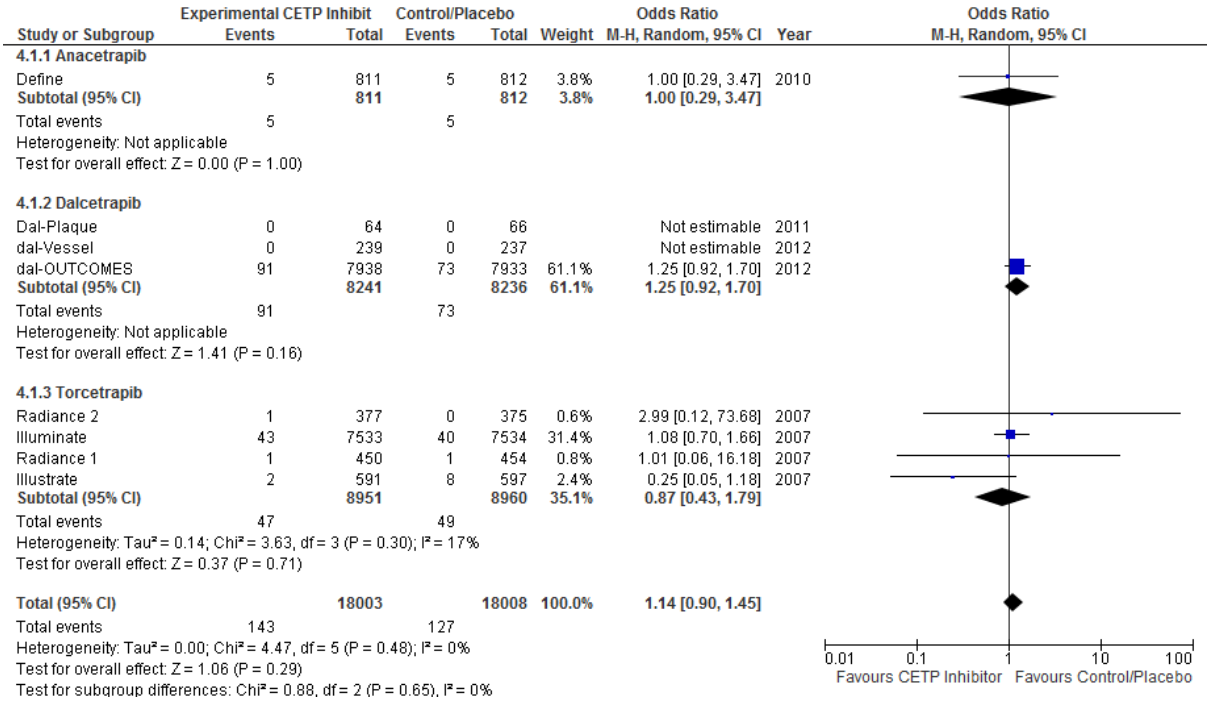
Effect of CETP-I on the risk of CHD Mortality



Effect of CETP-I on the risk of Non-Fatal MI



Effect of CETP-I on the risk of Stroke



Online Appendix 5: Selected Sensitivity Analyses

Requested by reviewers

Niacin trials excluding HPS 2 Thrive

All-Cause Mortality	0.97 (0.83 to 1.1.3)	p=0.69
CHD Mortality	0.85 (0.62 to 1.16)	p=0.30
Non-fatal MI	0.80 (0.61 to 1.03)	p=0.09
Stroke	0.94 (0.56 to 1.58)	p=0.82

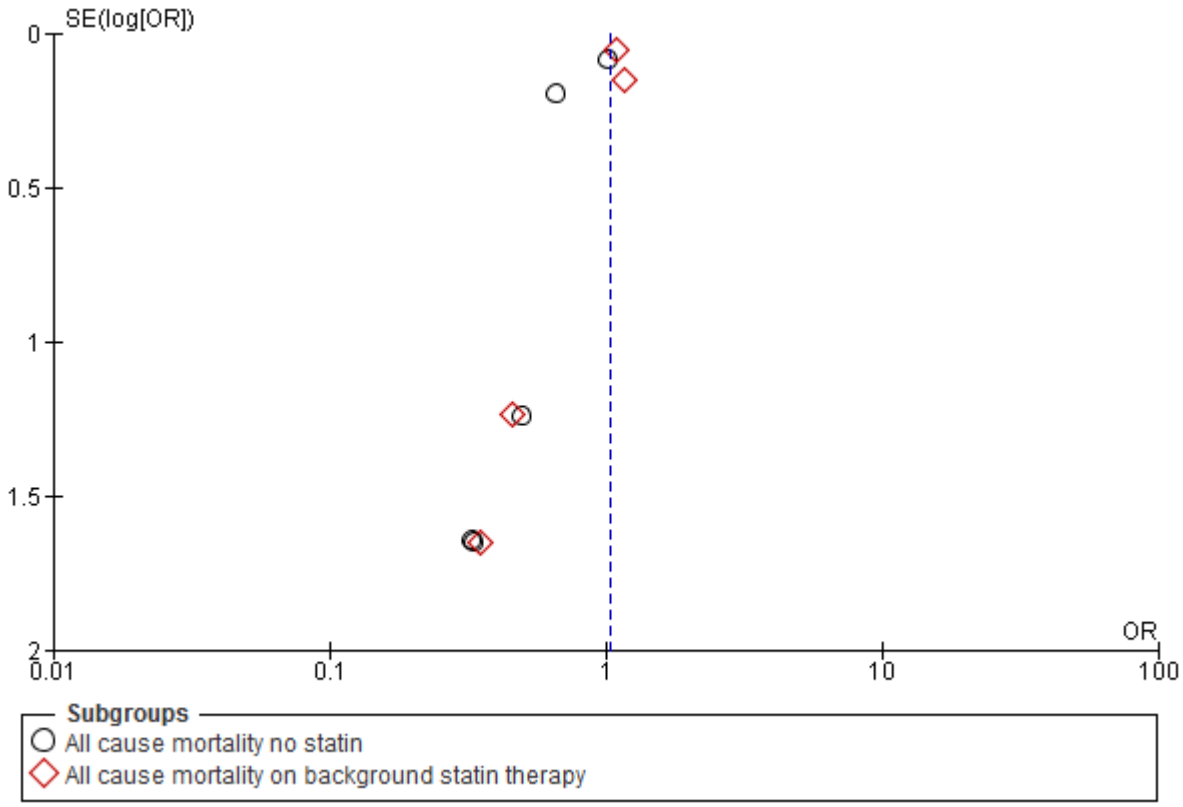
Sensitivity analysis for trials where Fibrate and Niacin where used in combination against control:

Niacin:
All-cause mortality including AFREGS and Stockholm OR 1.03 (95% CI 0.92 to 1.15) p=0.59
All-cause mortality excluding AFREGS and Stockholm OR 1.08 (95% CI 0.99 to 1.17) p= 0.09
CHD mortality including AFREGS and Stockholm OR 0.93 (95% CI 0.76 to 1.12) p=0.44
CHD mortality excluding AFREGS and Stockholm OR 1.02 (95% CI 0.90 to 1.15) p= 0.79
Non-fatal MI including AFREGS and Stockholm OR 0.85 (95% CI 0.72 to 1.01) p = 0.07
Non-fatal MI excluding AFREGS and Stockholm OR 0.88 (95% CI 0.74 to 1.05) p = 0.16
Stroke including AFREGS and Stockholm OR 0.96 (95% CI 0.75 to 1.22) p= 0.72
Stroke excluding AFREGS and Stockholm OR 0.96 (95% CI 0.73 to 1.27) p=0.78

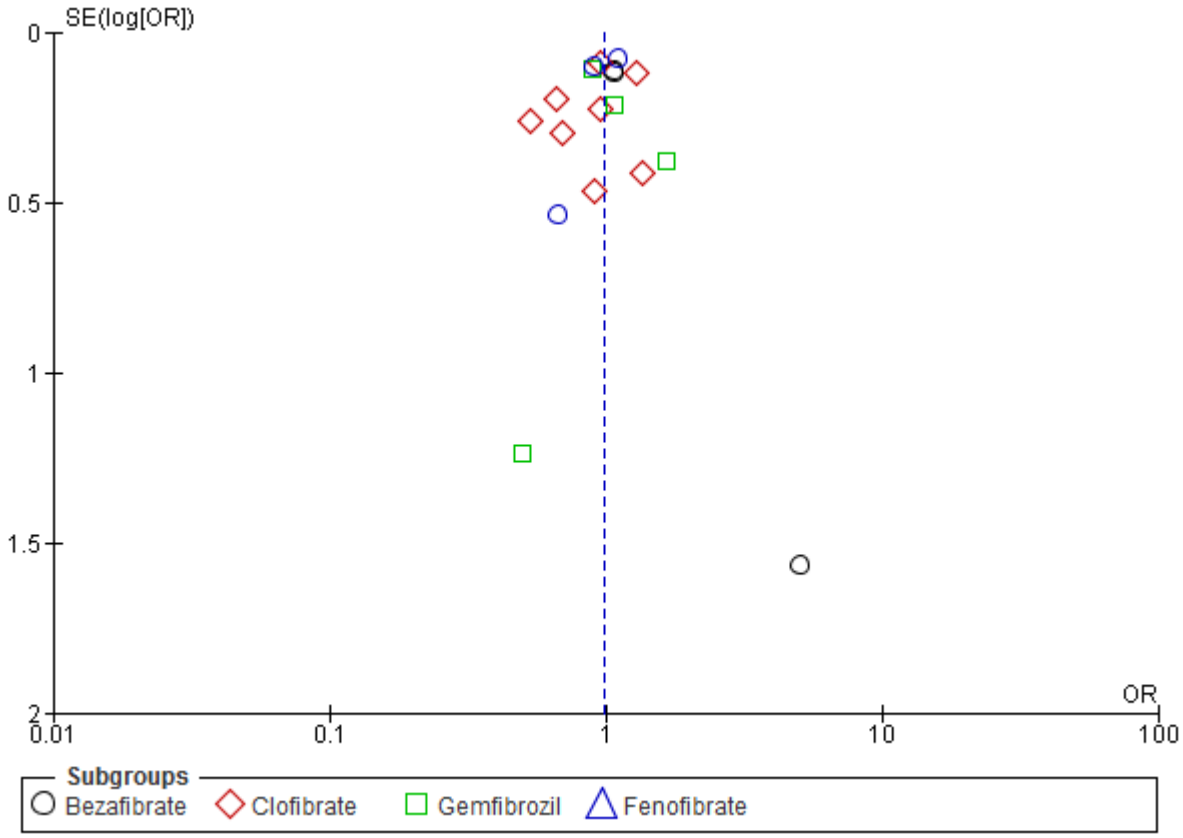
Fibrate:
All-cause mortality including AFREGS and Stockholm OR 0.98 (95% CI 0.89 to 1.08) p=0.66
All-cause mortality excluding AFREGS and Stockholm OR 1.00 (95% CI 0.91 to 1.10) p= 0.97
CHD mortality including AFREGS and Stockholm OR 0.92 (95% CI 0.81 to 1.04) p=0.19
CHD mortality excluding AFREGS and Stockholm OR 0.95 (95% CI 0.85 to 1.06) p= 0.34
Non-fatal MI including AFREGS and Stockholm OR 0.80 (95% CI 0.74 to 0.87) p <0.00001
Non-fatal MI excluding AFREGS and Stockholm OR 0.80 (95% CI 0.74 to 0.87) p <0.00001
Stroke including AFREGS and Stockholm OR 1.01 (95% CI 0.90 to 1.13) p= 0.84
Stroke excluding AFREGS and Stockholm OR 0.96 (95% CI 0.90 to 1.15) p=0.78

Online Appendix 6: Funnel Plots

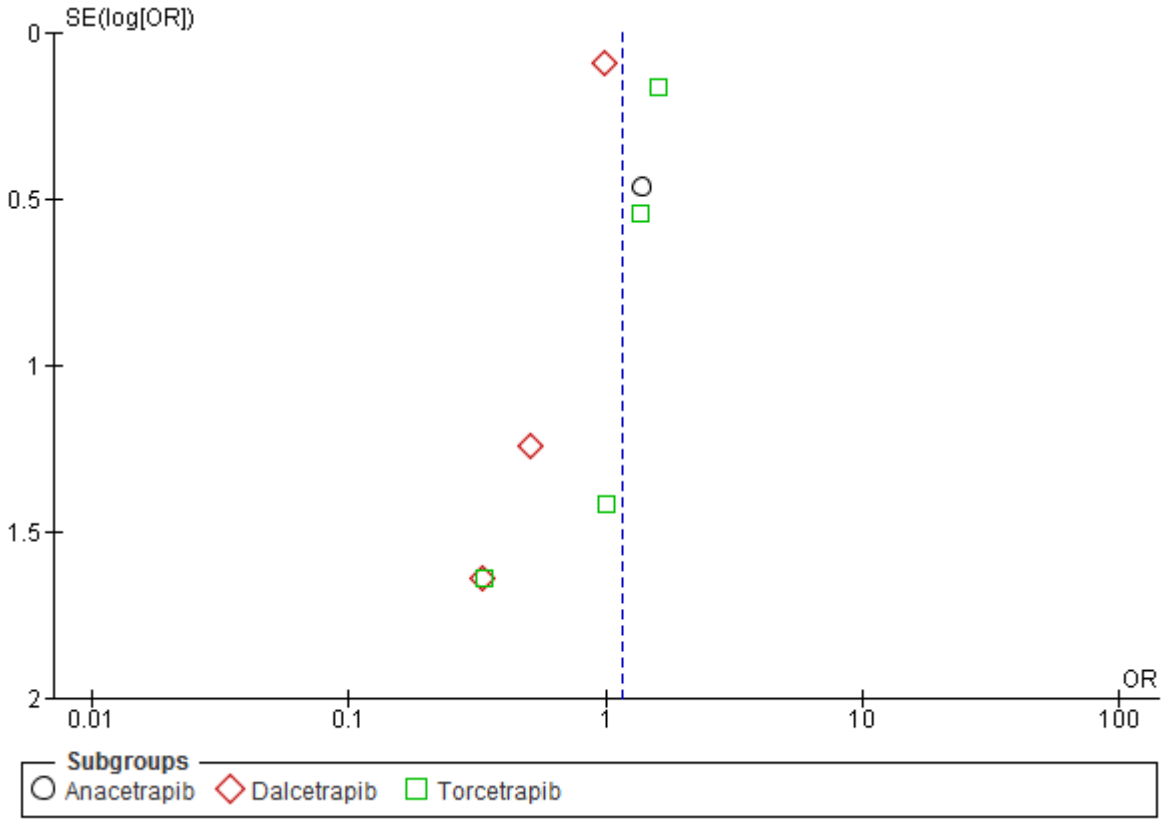
Niacin Funnel Plots for All-Cause Mortality



Fibrate Funnel Plot for All-Cause Mortality



CETP Inhibitor Funnel Plot for All-Cause Mortality



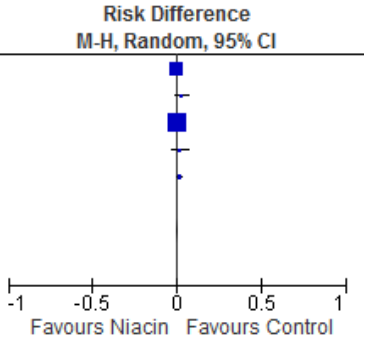
Online Appendix 7: Adverse Event Forest Plots

Niacin

Adverse Liver Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
AIM HIGH	5	1718	5	1696	38.9%	-0.00 [-0.00, 0.00]
CLAS	3	94	0	94	0.9%	0.03 [-0.01, 0.07]
HPS 2 THRIVE	39	12838	39	12835	54.8%	-0.00 [-0.00, 0.00]
SANG	1	52	0	56	0.6%	0.02 [-0.03, 0.07]
STOCKHOLM	5	279	0	276	4.8%	0.02 [0.00, 0.03]
Total (95% CI)		**14981**		**14957**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	53		44			

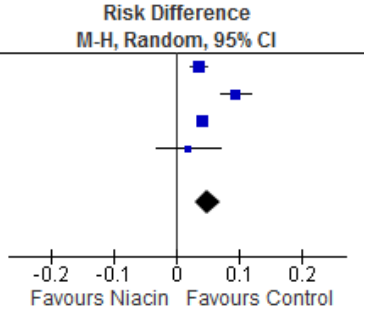
Heterogeneity: Tau² = 0.00; Chi² = 7.67, df = 4 (P = 0.10); I² = 48%
Test for overall effect: Z = 0.63 (P = 0.53)



Adverse Skin Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
AIM HIGH	104	1718	43	1696	30.3%	0.04 [0.02, 0.05]
GUYTON	66	670	1	272	24.1%	0.09 [0.07, 0.12]
HPS 2 THRIVE	693	12838	154	12835	34.1%	0.04 [0.04, 0.05]
SANG	1	52	0	56	11.5%	0.02 [-0.03, 0.07]
Total (95% CI)		**15278**		**14859**	**100.0%**	**0.05 [0.03, 0.07]**
Total events	864		198			

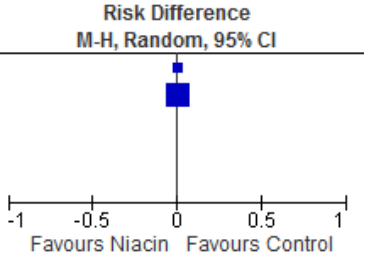
Heterogeneity: Tau² = 0.00; Chi² = 20.74, df = 3 (P = 0.0001); I² = 86%
Test for overall effect: Z = 4.64 (P < 0.00001)



Adverse Diabetic Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
AIM HIGH	29	1718	14	1696	23.8%	0.01 [0.00, 0.02]
HPS 2 THRIVE	460	12838	311	12835	76.2%	0.01 [0.01, 0.02]
Total (95% CI)		**14556**		**14531**	**100.0%**	**0.01 [0.01, 0.01]**
Total events	489		325			

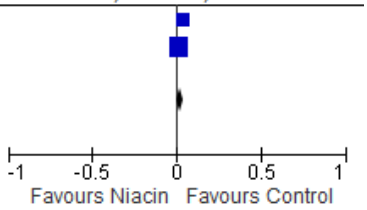
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 5.86 (P < 0.00001)



New Diabetes Mellitus Diagnosis Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
GUYTON	25	569	2	229	40.3%	0.04 [0.01, 0.06]
HPS 2 THRIVE	792	12838	632	12835	59.7%	0.01 [0.01, 0.02]
Total (95% CI)		**13407**		**13064**	**100.0%**	**0.02 [-0.00, 0.04]**
Total events	817		634			

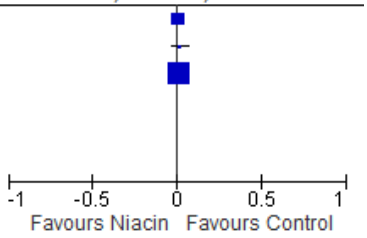
Heterogeneity: Tau² = 0.00; Chi² = 4.45, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 1.91 (P = 0.06)



Adverse Gastro-intestinal Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
AIM HIGH	26	1718	12	1696	33.2%	0.01 [0.00, 0.02]
CLAS	4	94	2	94	0.7%	0.02 [-0.03, 0.07]
HPS 2 THRIVE	620	12838	491	12835	66.1%	0.01 [0.01, 0.02]
Total (95% CI)		**14650**		**14625**	**100.0%**	**0.01 [0.01, 0.01]**
Total events	650		505			

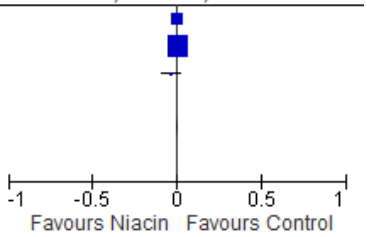
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 4.58 (P < 0.00001)



Adverse Musculoskeletal Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
GUYTON	4	605	1	260	30.7%	0.00 [-0.01, 0.01]
HPS 2 THRIVE	481	12838	385	12835	68.1%	0.01 [0.00, 0.01]
SANG	0	52	2	56	1.2%	-0.04 [-0.09, 0.02]
Total (95% CI)		**13495**		**13151**	**100.0%**	**0.01 [-0.00, 0.01]**
Total events	485		388			

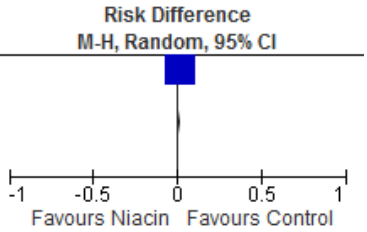
Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 2 (P = 0.25); I² = 28%
Test for overall effect: Z = 1.62 (P = 0.11)



Infection Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
HPS 2 THRIVE	1031	12838	853	12835	100.0%	0.01 [0.01, 0.02]
Total (95% CI)		**12838**		**12835**	**100.0%**	**0.01 [0.01, 0.02]**
Total events	1031		853			

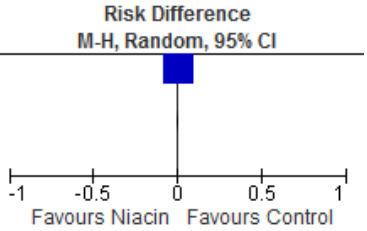
Heterogeneity: Not applicable
Test for overall effect: Z = 4.26 (P < 0.0001)



Adverse Bleeding Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
HPS 2 THRIVE	326	12838	238	12835	100.0%	0.01 [0.00, 0.01]
Total (95% CI)		**12838**		**12835**	**100.0%**	**0.01 [0.00, 0.01]**
Total events	326		238			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.75 (P = 0.0002)

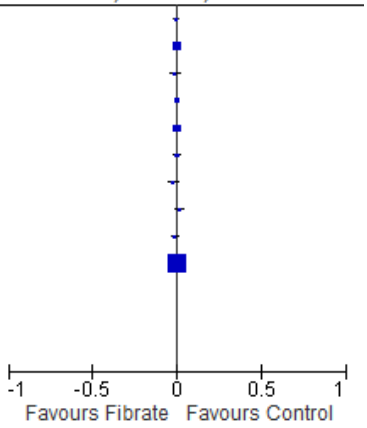


Fibrate

New Cancer Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
BIP	85	1548	91	1542	2.7%	-0.00 [-0.02, 0.01]
CDP	10	1103	24	2789	16.9%	0.00 [-0.01, 0.01]
DAIS	5	207	7	211	0.7%	-0.01 [-0.04, 0.02]
FIELD	393	4895	373	4900	6.4%	0.00 [-0.01, 0.01]
HHS	31	2051	26	2030	14.0%	0.00 [-0.00, 0.01]
HHS Exclusions	5	311	4	317	2.1%	0.00 [-0.02, 0.02]
LOCAT	3	197	7	198	0.8%	-0.02 [-0.05, 0.01]
Stockholm	10	279	6	276	0.9%	0.01 [-0.01, 0.04]
VA-HIT	125	1264	138	1267	1.3%	-0.01 [-0.03, 0.01]
WHO Clofibrate	58	5331	42	5296	54.1%	0.00 [-0.00, 0.01]
Total (95% CI)		**17186**		**18826**	**100.0%**	**0.00 [-0.00, 0.00]**
Total events	725		718			

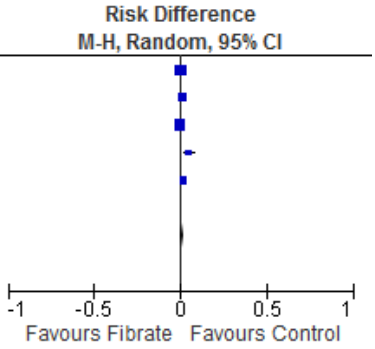
Heterogeneity: Tau² = 0.00; Chi² = 5.66, df = 9 (P = 0.77); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)



Adverse hepato-bilary events

Study or Subgroup	Fibrate Events	Fibrate Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
ACCORD	52	2765	40	2753	27.3%	0.00 [-0.00, 0.01]
DAIS	3	207	0	211	16.2%	0.01 [-0.00, 0.03]
FIELD	22	4895	38	4900	29.7%	-0.00 [-0.01, -0.00]
LOCAT	9	197	0	198	9.1%	0.05 [0.02, 0.08]
Stockholm	5	279	0	276	17.6%	0.02 [0.00, 0.03]
Total (95% CI)		**8343**		**8338**	**100.0%**	**0.01 [-0.00, 0.02]**
Total events	91		78			

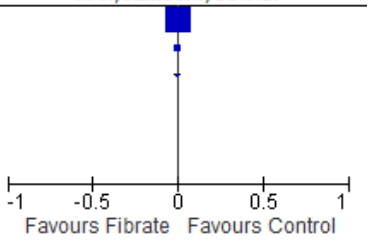
Heterogeneity: Tau² = 0.00; Chi² = 23.34, df = 4 (P = 0.0001); I² = 83%
Test for overall effect: Z = 1.76 (P = 0.08)



Myopathy Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
ACCORD	4	2765	3	2753	83.1%	0.00 [-0.00, 0.00]
BIP	5	1548	7	1542	15.2%	-0.00 [-0.01, 0.00]
DAIS	0	207	1	211	1.7%	-0.00 [-0.02, 0.01]
Total (95% CI)		**4520**		**4506**	**100.0%**	**0.00 [-0.00, 0.00]**
Total events	9		11			

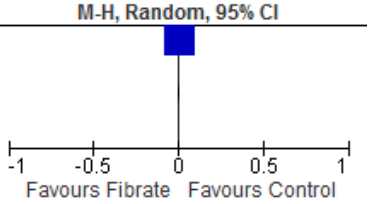
Heterogeneity: Tau² = 0.00; Chi² = 1.27, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)



Pancreatitis Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
FIELD	40	4895	23	4900	100.0%	0.00 [0.00, 0.01]
Total (95% CI)		**4895**		**4900**	**100.0%**	**0.00 [0.00, 0.01]**
Total events	40		23			

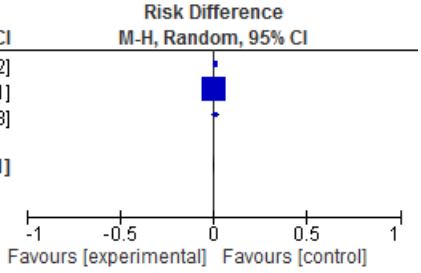
Heterogeneity: Not applicable
Test for overall effect: Z = 2.15 (P = 0.03)



Pulmonary Emboli Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
CDP	26	1103	37	2789	11.6%	0.01 [0.00, 0.02]
FIELD	53	4895	32	4900	84.2%	0.00 [0.00, 0.01]
VA-Neurology Section	4	268	1	264	4.3%	0.01 [-0.01, 0.03]
Total (95% CI)		**6266**		**7953**	**100.0%**	**0.01 [0.00, 0.01]**
Total events	83		70			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.92$, df = 2 (P = 0.38); $I^2 = 0\%$
Test for overall effect: Z = 3.07 (P = 0.002)

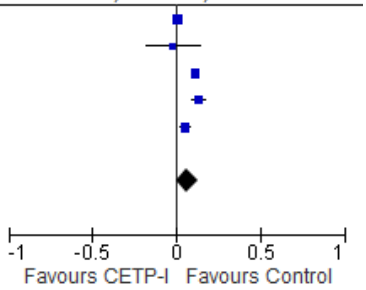


CETP Inhibitor

Reported Hypertension

Study or Subgroup	CETP Inhibitor Events	Total	Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
dal-OUTCOMES	578	7912	513	7907	23.2%	0.01 [0.00, 0.02]
Dal-Plaque	18	63	20	65	10.3%	-0.02 [-0.18, 0.14]
Illuminate	1411	7533	564	7534	23.1%	0.11 [0.10, 0.12]
Illustrate	140	591	63	597	21.3%	0.13 [0.09, 0.17]
Radiance 1	38	423	16	427	22.1%	0.05 [0.02, 0.09]
Total (95% CI)		**16522**		**16530**	**100.0%**	**0.07 [-0.00, 0.13]**
Total events	2185		1176			

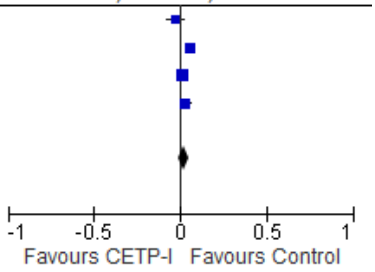
Heterogeneity: Tau² = 0.01; Chi² = 274.38, df = 4 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.89 (P = 0.06)



Rise in systolic BP more than 15mmHg

Study or Subgroup	CETP-I Events	Total	Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Define	354	802	377	797	18.2%	-0.03 [-0.08, 0.02]
Illustrate	53	591	19	597	26.1%	0.06 [0.03, 0.08]
Radiance 1	9	423	4	427	29.6%	0.01 [-0.00, 0.03]
Radiance 2	20	377	8	375	26.1%	0.03 [0.00, 0.06]
Total (95% CI)		**2193**		**2196**	**100.0%**	**0.02 [-0.01, 0.05]**
Total events	436		408			

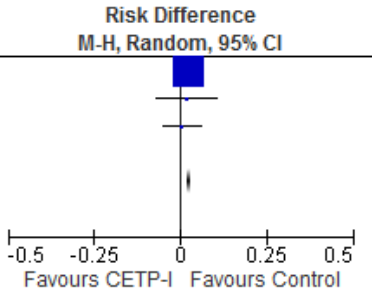
Heterogeneity: Tau² = 0.00; Chi² = 16.27, df = 3 (P = 0.0010); I² = 82%
Test for overall effect: Z = 1.31 (P = 0.19)



Diarrhoea Adverse Events

Study or Subgroup	CETP-I Events	Total	Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
dal-OUTCOMES	541	7912	342	7907	97.8%	0.03 [0.02, 0.03]
Dal-Plaque	5	63	4	65	0.6%	0.02 [-0.07, 0.11]
dal-Vessel	27	236	26	236	1.5%	0.00 [-0.05, 0.06]
Total (95% CI)		**8211**		**8208**	**100.0%**	**0.02 [0.02, 0.03]**
Total events	573		372			

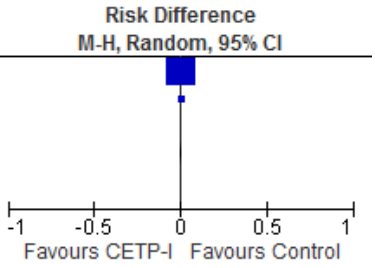
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 6.87 (P < 0.00001)



Myalgia Events

Study or Subgroup	CETP-I Events	Total	Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
dal-OUTCOMES	336	7912	319	7907	89.9%	0.00 [-0.00, 0.01]
Define	32	808	28	804	10.1%	0.00 [-0.01, 0.02]
Total (95% CI)		**8720**		**8711**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	368		347			

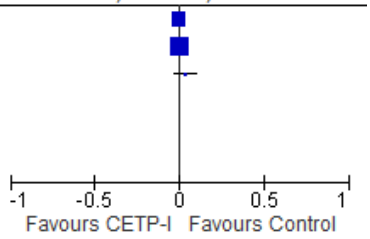
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.43)



Reported Infection Events

Study or Subgroup	CETP-I Events	CETP-I Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
dal-OUTCOMES	270	7912	288	7907	41.7%	-0.00 [-0.01, 0.00]
Illuminate	182	7533	177	7534	58.0%	0.00 [-0.00, 0.01]
Radiance 1	227	423	215	427	0.3%	0.03 [-0.03, 0.10]
Total (95% CI)		**15868**		**15868**	**100.0%**	**-0.00 [-0.00, 0.00]**
Total events	679		680			

Heterogeneity: Tau² = 0.00; Chi² = 1.64, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)



Adverse hepato-bilary events

Study or Subgroup	CETP-I Events	CETP-I Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Define	1	800	8	797	41.9%	-0.01 [-0.02, -0.00]
Illustrate	8	591	5	597	32.1%	0.01 [-0.01, 0.02]
Radiance 1	2	423	9	427	26.0%	-0.02 [-0.03, -0.00]
Total (95% CI)		**1814**		**1821**	**100.0%**	**-0.01 [-0.02, 0.00]**
Total events	11		22			

Heterogeneity: Tau² = 0.00; Chi² = 5.77, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 1.12 (P = 0.26)