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SYSTEMATIC REVIEW AND META-ANALYSIS

Low Reporting of Cointerventions in Recent Cardiovascular Clinical Trials: A Systematic Review

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BACKGROUND: A cointervention in a randomized clinical trial (RCT) is medical care given in addition to the tested intervention. If cointerventions are unbalanced between trial arms, the results may be biased. We hypothesized that cointerventions would be more adequately reported in RCTs without full blinding or at risk of bias.

METHODS AND RESULTS: To describe the reporting of cointerventions and to evaluate the factors associated with their reporting, we did a systematic search of all RCTs evaluating pharmacological interventions on cardiovascular outcomes published in 5 high-impact journals. The reporting of cointerventions, blinding, and risk of bias were extracted and evaluated independently by 2 reviewers (E.M., L.A.). Cointerventions were inadequately reported in 87 of 123 RCTs (70.7%), with 56 (45.5%) providing no information on cointerventions and 31 (25.2%) providing only partial information. Of the RCTs, 52 (42.3%) had inadequate blinding of participants and/or personnel and 63 (51.2%) of the RCTs were judged at risk of bias. In univariable analysis, the reporting of cointerventions was not associated with blinding of participants and/or personnel (odds ratio [OR], 1.04; 95% CI, 0.47–2.27 for adequately versus inadequately blinded trials) or with risk of bias (OR, 1.47; 95% CI, 0.67–3.21 for at low risk of bias versus trials at risk of bias). In multivariable analysis, only a follow-up of <1 month was associated with the adequate reporting of cointerventions (OR, 3.63; 95% CI, 1.21–10.91).

CONCLUSIONS: More than two-thirds of recent major cardiovascular trials did not adequately report cointerventions. The quality of reporting was not better among trials that were not fully blinded or at risk for bias.

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Key Words: blinding ■ cardiovascular trials ■ cointerventions ■ competing treatments ■ reporting ■ risk of bias

Because randomized clinical trial (RCT) outcomes shape clinical guidelines and daily practice,[1,2] we expect them to meet the highest standards of methodological quality and provide us with robust results.[3,4] RCTs have benefitted from continuous improvement in methodological quality,[5] especially in random sequence generation and allocation concealment, which have freed them from baseline confounding.[5–7] However, randomization does not eliminate differences that may arise between treatment groups during follow-up. After randomization, bias can arise when participants receive medical care in addition to the intervention of interest (cointerventions)[6,8] if it is not provided equally to all treatment groups.[8–11]

When one group receives more cointerventions than another, the RCT results may be compromised by bias.[6–8,11] This unequal distribution of cointerventions might be caused by a failure to adequately blind participants and/or personnel.[12–14] For example, if investigators know that a participant is receiving an active substance in a trial

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CLINICAL PERSPECTIVE

What Is New?

- In this systematic review of major cardiovascular trials in 5 highly influential medical journals, cointerventions were inadequately reported in more than two-thirds of the trials, whereas the quality of reporting was not better among trials that were not fully blinded or at risk for bias.

What Are the Clinical Implications?

- Cointerventions should be systematically reported in cardiovascular trials to assess the validity of the findings, particularly when trials are not fully blinded.

Nonstandard Abbreviations and Acronyms

OR	odds ratio
RCT	randomized clinical trial
RR	relative risk
CONSORT	Consolidated Standards of Reporting Trials
INR	International normalized ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SPORTIF	Stroke Prevention Using the Oral Direct Thrombin Inhibitor Ximelagatran in Patients With Atrial Fibrillation

designed to prevent myocardial infarction (eg, new antidiabetic drugs), they might suggest that the participant take other medications that reduce cardiovascular risk (eg, statins). If a family doctor knows that a patient is not receiving the active substance, he or she might feel ethically bound to prescribe effective cointerventions.[8] If cointerventions affect one group more than another, the results could be biased in either direction.[6,8] To reduce the risk of bias, cointerventions should be reported in both unblinded (ie, open label) and in double-blind trials because blinding can be compromised during the course of even a double-blind RCT by, for example, drugs that are not adequately matched, specific side effects, or laboratory investigations (such as lipid measurements).[15–19] It is difficult to measure unblinding in a double-blind RCT, but we can and should quantify its possible consequences by reporting relevant cointerventions.[13,16,17]

Patients in cardiovascular trials often receive multiple treatments (eg, statins, antihypertensives, antiplatelets) beyond the studied medication, each of which could affect outcomes, so cointerventions and in particular these comedications may play an important role in cardiovascular RCTs, especially if unblinded.[6,8,20,21] After several years without new potent drugs for cardiovascular prevention, a number of large RCTs have demonstrated the benefit of recent drugs for cardiovascular prevention,[22–27] but in some there was risk that cointerventions were unbalanced between study groups. We designed this systematic review to evaluate the quality of cointervention reporting in recently published RCTs with cardiovascular outcomes and to evaluate potential explanatory factors for reporting. We hypothesized that cointerventions would be more adequately reported in RCTs that were not fully blinded or otherwise at risk of bias because unbalanced cointerventions between trial arms may be more likely in these studies and could compromise their findings.

METHODS

Selection of Articles

We searched MEDLINE and EMBASE for RCTs evaluating pharmacological interventions on binary cardiovascular outcomes (fatal and/or nonfatal myocardial infarction, fatal and/or nonfatal stroke, mortality as well as composite outcomes) published in the 5 general medical journals with the highest impact factors (*New England Journal of Medicine*, *Lancet*, *Journal of the American Medical Association*, *British Medical Journal*, and *Annals of Internal Medicine*) between 2011 and 2019 (see Table S1 for details of the search strategy). Our methods conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses.[28] The protocol is registered on PROSPERO (CRD42018106771). One reviewer (E.M.) screened all titles and abstracts, assessed the full text of eligible abstracts and articles, and identified relevant trials. Another investigator (L.A.) independently assessed the eligible abstracts. The data that support the findings of this study are available from the corresponding author upon request.

Assessment of Included RCTs

The following information was extracted: study design (superiority versus noninferiority/equivalence trials), number of patients, type of intervention and comparator, follow-up duration, outcomes, information concerning methods of blinding of participants and personnel, blinding of outcome assessors, information about cointerventions, implementation of study treatment, adherence to study treatment, cross-overs, statistical analysis conducted, and funding source (industry versus nonindustry). Available information on cointerventions, blinding of participants and/or personnel, adherence to study treatment, and statistical analysis was extracted

independently by 2 reviewers (E.M., L.A.). All available information was extracted from the original trial reports, supplementary material, and protocols (if available).

Definition of Cointerventions and Quality of Their Reporting

Two investigators (E.M., L.A.) independently assessed the cointervention reporting. Because we included RCTs with cardiovascular outcomes, we considered potential cointerventions whose modification has been shown to decrease cardiovascular risk (Box 1).[8,29–34] We defined cointerventions as concomitant medications (statins, antihypertensives, antiplatelets) over follow-up (Box 1). In addition, diuretics, antidiabetics, and anticoagulants were also included in the definition of "cointervention" if these patients were included in the trials (ie, patients with heart failure, diabetics, or atrial fibrillation). We also defined 2 special categories of cointerventions in (1) RCTs where there was an index procedure after randomization, in which case, in addition to concomitant medications (statins, antihypertensives, antiplatelets) over follow-up, procedural characteristics and periprocedural medications between the groups would also be cointerventions[29,30,33] (Box S1), and (2) in RCTs with an index procedure after randomization but with a follow-up of <1 month in which case cointerventions would be procedural characteristics and periprocedural medications without considering concomitant medications (statins, antihypertensives, antiplatelets; Box S1).[29,30,33] Although advice for smoking, diet, and physical activity are also effective cointerventions, they are difficult to quantify, are rarely assessed in the original studies, and are therefore not evaluated in the present study.

To evaluate the reporting quality of cointerventions in each RCT, cointerventions were judged as adequately reported if the authors reported all cointerventions across trial arms (as described in Box 1) or if the authors explicitly stated that cointerventions did not differ between groups or gave indirect evidence that cointerventions did not differ between groups (eg, "there were no differences between groups in blood-pressure or cholesterol levels") or that there were no cointerventions. We judged cointerventions as inadequately reported if information in the article or supplement was incomplete (ie, partially reported) or missing (ie, not reported). Trials that did report cointerventions were classed as either "balanced" if there were similar levels of cointerventions between both groups or "unbalanced" and were judged by 2 reviewers (E.M., L.A.) independently. Disagreements were resolved by consensus in discussions that involved a third author (M.F.).

Box 1. Definition of Reporting

The reporting was adequate if all of the following elements were reported and inadequate if 1 or more elements were missing.*
Cointerventions are defined as the following:

- Concomitant medications (statins, antihypertensives, antiplatelets) over follow-up.[31,32,34†]

Special conditions:

- If randomization before an index procedure‡ and follow-up >1 month: concomitant medications (statins, antihypertensives, antiplatelets†) over follow-up and procedural characteristics and periprocedural medications.[29,30,33§]
- If randomization before an index procedure‡ and follow-up <1 month: procedural characteristics and periprocedural medications.[29,30,33§]

*Information could be anywhere in main article or supplements. Cointerventions should be summarized by percentages or absolute number across groups or the authors should state explicitly in the main text that cointerventions did not differ across the groups.† Includes others depending on the condition under study, for example, antidiabetics in trials that included patients with diabetes mellitus or diuretics if heart failure or anticoagulants in trials that included patients with atrial fibrillation; see the detailed descriptions in Table S3.‡ Index procedures included percutaneous coronary–angiography (n=18), cardiac surgery (n=5), surgery (n=2), and ablation (n=1); see the detailed description in Table S3.§ For more detailed descriptions of procedural characteristics/periprocedural medications, see Box S1.

Assessment of Blinding and the risk of bias

We independently assessed the blinding of participants and/or personnel. We based our judgments about blinding participants and/or personnel on the Cochrane Collaboration risk of bias tool 2011 (Risk of bias 1.0) and instructions from Unverzagt et al (Table S2).[35] We classified RCTs into having adequate blinding or inadequate blinding.

Two authors (E.M., L.A.) used the risk of bias 2.0 tool to independently assess risk of bias caused by deviations from the intended interventions (effect of adhering to treatment),[13] and classified RCTs as at high risk of bias, some concerns, or at low risk of bias. For our analysis, we grouped together RCTs judged as "some concerns" and RCTs judged as "at high risk of bias" and classed them all as "at risk of bias."

In general, there was good agreement regarding the previous classifications: Cohen's κ score for interobserver variability was 0.84 for the reporting of cointerventions, 0.87 for blinding participants and/or personnel, and 0.76 for the RoB 2.0 assessment.

Statistical Analysis

We used descriptive statistics. Comparisons between groups were conducted using a chi-square test. We used univariable and multivariable logistic regressions to evaluate the association of reporting of cointerventions with blinding (adequately versus inadequately), risk of bias (trials at low risk of bias versus trials at risk of bias), funding (nonindustry funded versus industry funded), design (superiority versus noninferiority/equivalence), and duration of follow-up (≤1 month versus >1 month). Finally, in an analysis that was not prespecified in the protocol, we looked at RCTs that adequately reported cointerventions

and explored the aforementioned factors for their association with balanced cointerventions between treatment arms using univariable logistic regression. *P* values were 2-sided and considered significant if $P<0.05$. For data management, analysis, and graphics, we used Stata version 15.0.

RESULTS

General Characteristics of Included RCTs

The literature search identified 1625 potentially eligible reports. After screening titles and abstracts, we evaluated 149 full articles, of which 123 met the inclusion criteria (Figure S1). A detailed description of the excluded trials is provided in Table S3. Table S4 describes the main characteristics of the 123 included RCTs: 83 (67.5%) were published in the *New England Journal of Medicine*; 27 (21.9%) had a noninferiority/equivalence design; 94 (76.4%) were industry funded; 45 (36.6%) examined antithrombotics or anticoagulants; 16 (13.0%) involved antidiabetics; 14 (11.4%) involved antihypertensives; and 17 (13.8%) were lipid-modifying agents (Table S4). The primary end points of all trials were composite end points (Table S5), and all of the trials had blinded adjudication committees.

Reporting of Cointerventions

As seen in Table, cointerventions were inadequately reported in 87 of 123 RCTs (70.7%), with 56 (45.5%) providing no information on cointerventions and 31 (25.2%) providing only partial information (Table). Table S5 provides detailed descriptions of the potential cointerventions in the protocols, all cointerventions reported and not reported, and the time points of reporting in each RCT. As seen in Table S6, the results remained similar in a stratified analysis based on medication category. Assessing potential cointerventions at regular intervals, usually at each visit and the last visit, was often included in study protocols (Table S5). Protocols were not available in only 7 RCTs.

Table. Reporting of Cointerventions (n=123)

Variable*	Sample, n (%)
Adequately reported	36 (29.3)
Balanced	31/36 (86.1)
Unbalanced	5/36 (13.9)
Partially reported	31 (25.2)
Balanced	26/31 (83.9)
Unbalanced	5/31 (16.1)
Not reported	56 (45.5)

*"Adequately reported" indicates if cointerventions of interest were reported across trial arms; "partially reported" indicates if only part of the information was provided; "not reported" indicates if there was no reporting on potential cointerventions in the published article or the supplements (see Box 1).

The Reporting of Cointerventions in Relation to Quality of Blinding and Risk of Bias

A total of 71 (57.7%) RCTs adequately blinded participants and/or personnel, whereas 52 (42.3%) were inadequately blinded. Of the RCTs, 60 (48.8%) were at "low risk of bias"; 63 (51.2%) were "at risk of bias" (n=28, 22.8% as "some concerns"; n=35, 28.5% as "at high risk of bias") because they deviated from planned interventions. Among the 52 trials with inadequate blinding of participants and/or personnel, 15 (28.9%) adequately reported cointerventions versus 21 (29.6%) in those with adequate blinding (*P*=0.93; Figure A). Among the 63 trials "at risk of bias," 16 (25.4%) adequately reported cointerventions versus 20 (33.3%) in those "at low risk of bias" (*P*=0.33; FigureB).

Factors Associated With Adequately Reporting Cointerventions

As seen in Table S7, the odds ratio (OR) in the univariable analysis for adequately reporting cointerventions was 1.04 (95% CI, 0.47–2.27) comparing adequately versus inadequately blinded trials, 1.47 (95% CI, 0.67–3.21) comparing trials "at low risk of bias" versus trials "at risk of bias," 2.06 (95% CI, 0.86–4.92) comparing non-industry-funded trials versus industry-funded trials, 0.63 (95% CI, 0.26–1.55) comparing superiority trials versus noninferiority/equivalence trials, and 4.33 (95% CI, 1.63–11.52) comparing trials with a follow-up ≤1 month versus >1 month (Table S7). In multivariable analysis, only a follow-up of <1 month was associated with the adequate reporting of cointerventions (OR, 3.63; 95% CI, 1.21–10.91; Table S7).

Factors Associated With Balanced Cointerventions

As seen in Table, among the 36 RCTs that adequately reported cointerventions, cointerventions were balanced in 31 and unbalanced in 5 trials. All trials with unbalanced cointerventions were judged as inadequately blinded trials and were industry funded. As seen in Table S8, no other factor was associated with unbalanced cointerventions, even though the confidence intervals were large.

DISCUSSION

In this systematic review of recent RCTs on cardiovascular outcomes, more than two-thirds of RCTs did not adequately report cointerventions. Reporting was not better among trials that were not fully blinded

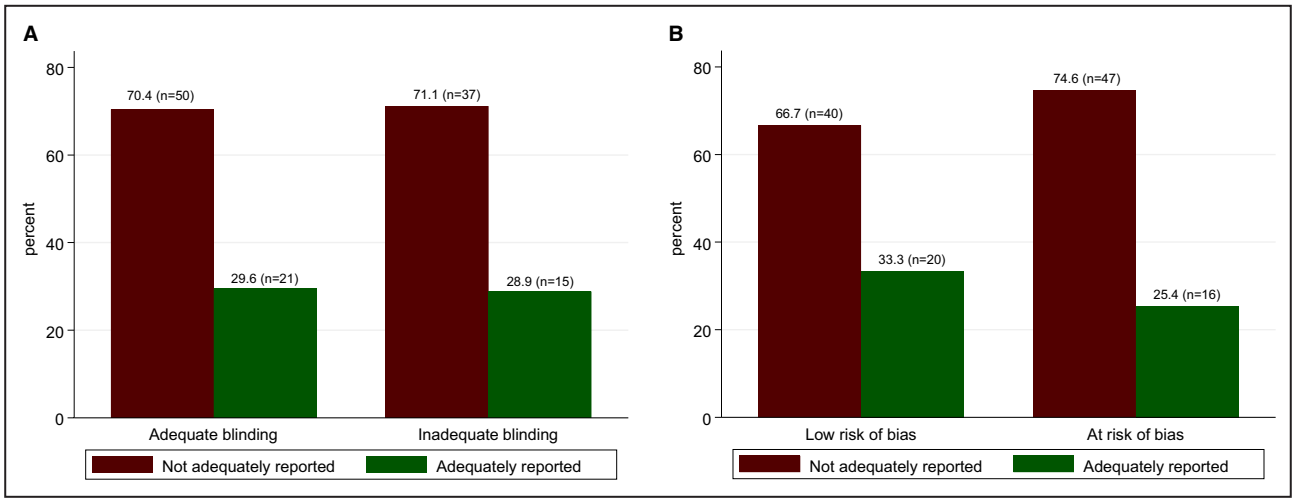

Figure. Proportion of trials reporting cointerventions according to blinding and risk of bias.
A, Proportion of trials reporting cointerventions according to blinding of participants and/or personnel (n=123). For the analysis, we grouped together the trials with no information on cointerventions and partial information and defined them as "not adequately reported"; *P*=0.93 for the comparison between groups. **B**, Proportion of trials reporting cointerventions according to risk of bias attributed to deviation of intended interventions (n=123). For the analysis, we grouped (1) trials with some concerns and at high risk of bias and defined them as "at risk of bias" attributed to the deviation of intended interventions and (2) trials with no information on cointerventions and partial information and defined them as "not adequately reported"; *P*=0.33 for the comparison between groups.

nor among RCTs at risk of bias in which the reporting of cointerventions would be particularly important to assess the validity of their results. Adequate reporting of cointerventions was more common in trials that followed patients for <1 month, perhaps because cointerventions are easier to assess over a short follow-up.

Lack of blinding could lead to biased results through many different ways. Indeed, an association between lack of blinding and positive results has been shown, especially when the outcomes were subject to ascertainment bias, that is, not "hard" outcomes.[36] RCTs with inadequate blinding seem particularly at risk for unbalanced cointerventions,[14] and reporting cointerventions is important because if they are unbalanced between treatment arms, they could introduce bias.[6,8,11,13] In an earlier systematic review of 12 complementary/alternative medicine RCTs, cointerventions (use of analgesics) were reported in 7 of these studies, and it was shown that not blinding participants was associated with an 1.55 increased risk (95% CI, 0.99–2.43) of receiving cointerventions.[12] The lack of blinding and cointerventions could also explain the differences in the effect sizes between SPORTIF III (Stroke Prevention Using the Oral Direct Thrombin Inhibitor Ximelagatran in Patients With Atrial Fibrillation),[21] an open-label trial evaluating the effect of ximelagatran versus warfarin on strokes and systemic embolic events and SPORTIF V,[20] a trial with otherwise similar design and end points with SPORTIF III, but double-blinded. Although the potential risk factors were well balanced across the treatment arms within each trial, the effect sizes were remarkably different between the 2 trials: SPORTIF III, primary event rate 1.6% per year with ximelagatran and 2.3% per year with warfarin (relative risk [RR], 0.71; 95% CI, 0.48–1.07) versus SPORTIF V, primary event rate 1.6% with ximelagatran per year and 1.2% with warfarin per year (RR, 1.38; 95% CI, 0.91–2.10). Outcome assessments were blinded in both trials. Indeed, in a pooled analysis of the 2 trials,[37] it was shown that the differences between the trials could be attributed to differences in cointerventions such as statins and differences in other risk factors (eg, hypertension), in addition to less variability in international normalized ratio (INR) control in SPORTIF V,[37,38] although ascertainment bias cannot be excluded. In our review, the reporting of cointerventions was scarce in both RCTs with adequate and inadequate blinding, and we found no association between blinding and the reporting of cointerventions. The reasons for this could be that the reporting of cointerventions in cardiovascular trials might have received less attention and/or be less standardized. Although the Consolidated Standards of Reporting Trials (CONSORT) statement recognizes that a lack of blinding may influence the use of cointerventions, subsequent reporting of cointerventions across groups is currently not mandatory.[14] However, cointerventions are among the data required to be collected in a Cochrane systematic review.[13,39]

In cardiovascular medicine, cointerventions may be particularly important because participants usually receive many different treatments that could reduce cardiovascular risk and change cardiovascular outcomes.[6,8] In the Women's Health Initiative, which

examined the effect of hormone therapy on cardiovascular outcomes, the differential use of statins showed significantly different effects on coronary heart disease and stroke, confounding the results.[6] A recently published RCT on the effects of coronary computer tomography on cardiovascular outcomes, which did not blind participants or personnel, found that the participants assigned to the intervention group were more likely to receive additional preventive treatments for cardiovascular disease (statins, antihypertensives, antiplatelets).[40] In a double-blind RCT designed to test the effects of fenofibrate versus placebo on hard cardiovascular end points, 17% of the participants on placebo were also treated with statins versus 8% in the fenofibrate group, which may have caused the results to be biased toward the null.[10] In many cardiovascular trials, depending on the type of intervention, the presence of cointerventions may reflect the effectiveness of the study treatment that occurs in a real world instead of a perfect hypothetical study scenario, and the blinding of participants and/or personnel may not always be possible. Nevertheless, as cointerventions may lead to an overestimation of treatment effect, this is of particular concern when the results of an RCT are used for the registration of a new drug. In addition, in this systematic review, we included RCTs with pharmacological interventions (and not surgery or with devices), so that in these cases blinding is usually feasible.

This study has limitations. First, the results were limited to cardiovascular trials published in major medical journals, which represent a minority of published clinical research. However, trials published in journals with high impact factors usually do better in terms of the quality of reporting,[5] and previous methodological reviews have used the same design.[41] Second, this study did not evaluate the reporting of cointerventions in medical fields other than cardiovascular. Third, the definition of which cointerventions should be reported is (to some extent) arbitrary. We proposed a definition (Box 1) that was easy to apply, reflected by a high interobserver agreement (Cohen's κ, 0.84).

CONCLUSIONS

More than two-thirds of recent major cardiovascular trials did not adequately report cointerventions. The quality of reporting was not better among trials that were not fully blinded or at risk of bias. Our review highlights the need for more standardized, systematic reporting of cointerventions in cardiovascular trials.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1-S8
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SUPPLEMENTAL MATERIAL

Table S1. Literature search.

((((("Annals of internal medicine"[Journal]) OR ("BMJ (Clinical research ed.)"[Journal]) OR ("JAMA"[Journal]) OR ("Lancet (London, England)"[Journal]) OR ("The New England journal of medicine"[Journal])) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals[mh] NOT humans[mh]))) AND (("Cardiovascular Diseases/drug therapy"[Mesh] OR "Cardiovascular Diseases/mortality"[Mesh] OR "Cardiovascular Diseases/prevention and control"[Mesh]) OR ("Myocardial Ischemia/drug therapy"[Mesh] OR "Myocardial Ischemia/mortality"[Mesh] OR "Myocardial Ischemia/prevention and control"[Mesh]) OR ("Myocardial Infarction/drug therapy"[Mesh] OR "Myocardial Infarction/mortality"[Mesh] OR "Myocardial Infarction/prevention and control"[Mesh]) OR ("Stroke/drug therapy"[Mesh] OR "Stroke/mortality"[Mesh] OR "Stroke/prevention and control"[Mesh]) OR ("Cerebrovascular Disorders"[Mesh:noexp]) OR ("Ischemic Attack, Transient"[Mesh]) OR ("Intracranial Embolism and Thrombosis"[Mesh]) OR ("Intracranial Arteriosclerosis"[Mesh:noexp]))) NOT ((comment[Publication Type]) OR (letter[Publication Type])) Filters: Publication date from 2011/01/01 to 2019/04/11

*The last update of the search was on 11.04.2019

Table S2. Adequate and inadequate blinding of participants and/or personnel.

*based on risk of bias due to lack of/insufficient blinding of participants and/or personnel of the Cochrane Collaboration risk of bias tool 2011 and on the basis of the instructions used from Unverzagt et al. (see ref. 35)

Inadequate		Adequate
High	Some concerns	Low
Open-label, Single-blind The method of masking was described and it was inappropriate (e.g. comparison of tablet versus injection with no double dummy)	No Information The authors stated that the study was double-blind but there was no adequate description in the text or in protocol (e.g. “matching placebo”) Treatments administered from care-givers (i.v. i.m. injections): with no other description concerning the preparation (e.g. similar colour or matched, opaque syringes or bottles) Unblinding is possible (e.g. blood investigations, specific adverse effects) & no methods to avoid unblinding	Both patients and caregivers were blinded Detailed description about how the blinding status was established and maintained (either in published paper of in protocol): matching placebo or adequate description No specific adverse effects or methods to avoid unblinding included in the protocol

Table S3. Description of 26 excluded studies.

Author, y	Reason for exclusion
Anderson, 2016 (PMID:27161018)	Primary outcome: death or disability define through modified Rankin scale
He, 2014 (PMID: 24240777)	Primary outcome: death and major disability through modified Rankin scale
Kirchhof, 2012 (PMID: 22713626)	Primary outcome: persistent atrial fibrillation or death
Sandercock, 2012 (PMID: 22632908)	Primary outcome: proportion of patients alive and independent, as defined by an Oxford Handicap Score
Torres, 2014 (PMID: 25399731)	Primary outcome: death, end-stage renal disease, or a 50% reduction from the baseline estimated GFR
Sabatine, 2015 (PMID: 25773607)	Other outcome;CV events assessed as prespecified exploratory analysis
Robinson, 2015 (PMID: 25773378)	Other outcome;CV events assessed as post hoc analysis
Beckett, 2011 (PMID: 22218098)	Extension of a randomised, clinical trial
Bonow, 2011 (PMID: 21463153)	Substudy
De Boer, 2011 (PMID: 22077236)	Extension of a randomised, clinical trial
Gerstein, 2014 (PMID: 25088437)	Analysis of data from other randomised, clinical trial
Leonardi, 2016 (PMID: 27677503)	Substudy
Scirica, 2012 (PMID: 22932716)	Substudy
Wang, 2016 (PMID: 27348249)	Substudy
Williamson, 2016 (PMID: 27195814)	Substudy/already included
Zannad, 2015 (PMID: 25765696)	Posthoc/already included
Zoungas, 2014 (PMID: 25234206)	Extension of a randomised, clinical trial
Macdougall, 2013 (PMID: 23343062)	Other outcome;CV events assessed only as safety
Newby, 2014 (PMID: 24930728)	Other outcome;CV events assessed only as safety

Cleland, 2011 (PMID: 21856481)	Other outcome;CV events assessed only as safety
Marchioli, 2013 (PMID: 23216616)	Combination of pharmaceutical and non pharmaceutical treatments
Ohman, 2017 (PMID: 28325638)	Other outcome; CV events as exploratory outcome
Anand, 2018 (PMID: 29132880)	Substudy/already included
Connolly, 2018 (PMID: 29132879)	Substudy/already included
Kudenchuch, 2016 (PMID: 27043165)	Other outcomes
Perkins, 2018 (PMID: 30021076)	Other outcomes

y: year, CV: cardiovascular

Table S4. Trial characteristics (n=123).

Variables	Sample (n) (%)
Journal	
New England Journal of Medicine	83 (67.5)
Lancet	14 (11.4)
Journal of the American Medical Association	24 (19.5)
British Medical Journal	1 (0.8)
Annals of Internal Medicine	1 (0.8)
Type of comparator	
Placebo only	72 (58.5)
Active (with the use of placebo)	34 (27.6)
Active only	14 (11.4)
Standard of care (no treatment only)	3 (2.5)
Trial Design	
Superiority	96 (78.1)
Non-inferiority/equivalence	27 (21.9)
Type of funding source	
Industry-sponsored	94 (76.4)
Non-industry	29 (23.6)
Type of intervention*	
Antihypertensives/diuretics/heart failure treatments	14 (11.4)
Antithrombotics/anticoagulants	45 (36.6)
Lipid-modifying medications	17 (13.8)
Antidiabetics	16 (13.0)
Antiinflammatory, antirheumatic, antineoplastic	12 (9.8)
Cardiac therapy†	3 (2.4)
Various‡	16 (13.0)

*Classified according to ATC Code; †includes antianginal treatment and antiarrhythmic medications ‡includes antiobesity preparations, medications for the treatment of bone disease, vitamins, and combination of different treatments (see Table S3)

Table S5. Detailed characteristics of 123 included Randomized Clinical Trials and decriptions of reported and not reported co-interventions.

PMID of the study	Intervention	Setting	Outcome	Co-interventions in the protocol	Co-interventions reported	Timepoint	Co-interventions not reported	FU
21732835	Nesiritide vs Placebo	Patients hospitalized with acute HF	Composite end point of rehospitalisation for HF or death	"If concomitant medication is used for HF, the medical therapy should remain as stable as possible during the first 6 hours after study drug initiation to allow for the evaluation of any potential effects of study drug. Diuretics, morphine and other vasoactive drugs may be used during this period if clinically warranted"	Information about the use of loop diuretics, inotropic agents, vasodilators in the first 24h in table	First 24h	No information on other antihypertensives, aldosterone receptor blockers	1
29766750	Clopidogrel and Aspirin vs Aspirin	Patients with acute ischemic stroke or high risk TIA	Composite of major ischemic events (ischemic stroke, MI, or death from an ischemic vascular event)	"Any treatment which is ongoing before randomization and/or prescribed or changed during the study must be recorded"	NI	NI	No information on antihypertensives, statins in patients with acute stroke	2.9
27160892	Tigagrelor vs Aspirin	Patients with acute ischemic stroke or high risk TIA	Composite of stroke, MI, death	"Recording of concomitant medications will be made at each visit. Medications of special interest including study	NI	NI	No information on antihypertensives, statins in patients with acute stroke	3

				medication, other antiplatelet medications, PPIs and statins will be captured in detail. There are no restrictions to other statin therapies (…). Investigators are advised to check lipid levels and adjust statin dosages per local practice and appropriate guidelines”				
23803136	Aspirin and Clopidogrel vs Aspirin	Patients with acute minor stroke or TIA	Stroke	“Any drugs other than those listed above are permitted (including anti-hypertensive medications), if considered necessary for the patient, with a stable dose (when possible), at the discretion of the Investigator”	Antiplatelets (aspirin, ticlopine, cilostazole, dipyridamole, GpIIb/IIIa inhibitors), heparin, anticoagulants, antihypertensives, lipid-lowering, hypoglycemic medications	Through day 90 (end of follow-up)	-	3
24247616	Varespladib vs Placebo	Patients with ACS	Composite of CV mortality, nonfatal MI, nonfatal stroke, or unstable angina with evidence of ischemia requiring	Not specified in the puplished study design (extended protocol not available)	Aspirin, clopidogrel, ticlopidine, prasugrel, b-blockers, ACEI/ARBs	During the treatment period	-	3.1

			hospitalisation					
22082198	Dronedarone vs Placebo	Patients with high-risk atrial fibrillation	Composite of stroke, MI, systemic embolism, or CV death	"Patients included in the study should receive the usual standard therapy (…) according to guidelines. Patients who received concomitant medications during the study drug period (…) will be summarized using same classes as those already defined for baseline medications"	NI	NI	No information on antihypertensives, antiplatelets or statins; No information on anticoagulation in patients with atrial fibrillation	3.5
21406646	High vs standard dose of Clopidogrel	Patients undergoing PCI	Composite of CV death, nonfatal MI, or stent thrombosis	No extended protocol available; published study design: "Concomitant medications: aspirin, periprocedural anticoagulation: left to the descrition of physician"	Antiplatelets, b-blockers, ACE/ARBs, statin, calcium channel inhibitors	Periprocedural	-	6
21316752	Candesartan vs Placebo	Patients with acute stroke	Composite of CV death, MI, or stroke	No extended protocol available; published study design: "All patients are given standard treatment in stroke units. Therapeutic agents other	Information about other antihypertensives in text	During follow-up	No information on antiplatelets for patients with acute stroke. No information on statins	6

				than ARBs can be administered during the treatment period.…"				
21780946	Apixaban vs Placebo	Patients with ACS	Composite of CV death, MI or ischemic stroke	"All subjects should receive evidence-based post-ACS care according to local standards of care and national practice guidelines (ACC/AHA, ESC, etc.). All subjects should receive single or dual antiplatelet therapy based on investigator discretion", "The use of clopidogrel and other approved antiplatelet agents will be left to investigator discretion and according to local guidelines"; Assess concomitant medications at each visit.	NI	NI	No information on cardiac preventive treatments (antihypertensives, antiplatelets or statins)	7.9
24206459	Bardoxolone vs Placebo	Patients with diabetes and chronic kidney disease 4	Composite of end-stage renal disease or CV death	"Investigators should not reduce or discontinue ACE inhibitors and/or ARBs unless indicated secondary to a medical contraindication (e.g. hyperkalemi	NI	NI	No information on cardiac preventive treatments (antihypertensives, antiplatelets or statins)	9

				a). Any concomitant medication with the exception of those listed below may be given at the discretion of the investigator", "the prescribing information for all concomitant medications should be reviewed carefully"				
28304242	Bocozizumab vs Placebo	Patients at high CV risk	Composite nonfatal MI, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or CV death	"All permitted concomitant medications should be recorded at each study visit: Lipid lowering: all patients will continue to take their prescribed lipid lowering treatment"; "Other concomitant treatment are permitted at the discretion of the physician according to local guidelines"	NI	NI	No information on cardiac preventive treatments (antihypertensives, antiplatelets)	10
29766772	Rivaroxaban vs Aspirin	Patients with recent embolic stroke of undetermined source	Stroke or systemic embolism	Concomitant medications assessment at visit 0, 12 and end of follow-up	NI	NI	No information on cardiac preventive medications (antihypertensives, antiplatelets, statins)	11

23478743	Aliskiren vs Placebo	Patients with acute HF	Composite of CV death of HF rehospitalisation	Not extended protocol, from published study design: “Standard therapy treatment will be left to the discretion of the treating physician but should include diuretics, ACE-Inhibitors or ARBs, beta-blockers, and aldosterone blocking agents, unless contraindicated”; “	NI	NI	No information on other antihypertensives, diuretics, aldosterone receptor inhibitors, antiplatelets, statins	12
27959713	Low-dose Rivaroxaban and P2Y12 Inhibitor vs very low-dose Rivaroxaban	Patients with atrial fibrillation undergoing PCI	Composite of CV death, MI, Stroke	Concomitant therapies must be recorded throughout the study..”	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	12
22550196	Fish oil capsules vs Placebo	Patients with arteriovenous hemodialysis grafts	Composite of hemodialysis graft patency thrombosis and CV events	Not extended protocol, from published study design: medication review at visit 0, 6,12. Change in antihypertensive medications: secondary outcome	NI	NI	No information on other cardiac preventive treatments (antiplatelets, statins)	12
21309657	Apixaban vs Aspirin	Patients with atrial fibrillation	Composite of stroke or systemic embolism	Assessment of concomitant medications: 0, 12, end of FU	Information for aspirin and clopidogrel in text	During follow-up	No information on antihypertensives, statins	13.2

28402745	Ularitide vs Placebo	Patients with acute HF	CV death	"Required medication for the treatment of concomitant diseases is unrestricted". Concomitant medications assessment at day 30.	NI	NI	No information on other antihypertensives, diuretics, aldosterone receptor inhibitors, antiplatelets, statins	15
29900874	Dabigatran vs Placebo	Patients with myocardial injury after non-cardiac surgery	Composite of vascular mortality and non-fatal MI, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism	Not extended protocol, from published study design: "management was left to the discretion of the treating physician, including cardiovascular medications. We recommended that all patients with MINS take low-dose acetylsalicylic acid (ASA) and a statin". Concomitant medications assessment every 6 months until end of FU.	Antiplatelets, ACEI/ARBS, b-blockers, statins	During follow-up	-	16
22920930	Prasugrel vs Clopidogrel	Patients with NSTEMI, who do not undergo PCI	Composite of CV death, MI, or stroke	"Other cardiac and non-cardiac medications not specifically excluded may be administered at the discretion of the treating physician"; The use of all concomitant	NI	NI	No information on other cardiac preventive treatments (antihypertensives, statins)	17

				medications will be recorded in the CRF;"The effect of concomitant medications on the primary efficacy endpoint will be assessed by conducting subgroup analyses on certain medication classes"				
30279197	6 vs 12 months of of dual treatment (Clopidorgel and Aspirin)	Patients with STEMI treated PCI and second generation zotarolimus-eluting stent	Composite of all cause mortality, MI, revascularisation, stroke, and thrombolysis MI major bleeding	Not extended protocol, from published study design: NI	NI	NI	No information on other cardiac preventive treatments (antihypertensives, statins)	18
23992602	Alogliptin vs Placebo	Patients with recent ACS and type 2 diabetes	Composite of CV death, nonfatal MI, or nonfatal stroke	"At each study visit, subjects will be asked whether they have taken any medication other than the study medication. Investigators will be encouraged to manage subjects according to regional guidelines for the …. …. Subjects will be instructed on proper nutrition and exercise"	Medications not provided. Information about lipoprotein levels in table	End of follow-up	No information on other cardiac preventive treatments (antihypertensives, antiplatelets)	18
30291013	Albiglutide vs Placebo	Patients with CV disease	Composite of CV	Not extended protocol,	Information on other hypoglyce	At different times of	No information on other	19.2

		and type 2 diabetes	death, MI, or stroke	from published study design: “Information on the use of concomitant medications is captured at each visit. Usual care providers are encouraged to follow most-up-to-date guidelines for diabetes and CV disease management according to local guidelines”	mic medicatio ns	follow-up	cardiac preventive treatments (antihypert ensives, antiplatelet s, statins)	
2107336 3	Eplerenon e vs Placebo	Patients with systolic HF and mild symptom s	Composite of CV death or hospitalisa tion for HF	Concomitan t medications : assessed at each visit. “Permitted concomitant medications may include angiotensin ACE-Is, ARBs, b-blockers, and diuretics. Digoxin, vasodilators , and inotropes may be used, as clinically indicated”	NI	NI	No informatio n on other antihypert ensives, other diuretics, antiplatelet s, statins	21
3014693 5	Rivaroxaba n vs Placebo	Patients with HF and coronary disease	Composite of death from any cause, MI, or stroke	“For each subject, the drug identity and dose of all CV therapies and proton pump inhibitors taken during the index hospitalizati on through the end of	Diuretics, ACEI/ARB s, b-blockers, aldosteron e receptor inhibitors	Different time-points until the end of follow-up	-	21 .1

				the study will be recorded on the appropriate page of the eCRF. Subjects must be receiving at a minimum for their HF: a diuretic and RAS inhibitor/vasodilator therapy (either an ACEI, ARB, or hydralazine/nitrate combination), and, unless contraindicated, the following:Beta blockers, which should be titrated to the maximum dose recommended by current guidelines., Aldosterone antagonists, which should be prescribed per guideline recommendations. Additional standard care treatments for HF and CAD (except anticoagulants) as prescribed by their managing physician are allowed. Subjects				

				should be receiving antiplatelet therapy as standard care for their CAD”				
26474810	Ranolazine vs Placebo	Patients with incomplete revascularisation	Composite of ischemia-driven revascularisation or ischemia-driven hospitalisation without revascularisation	Not extended protocol, from published study design: “After PCI, participants will be treated with standard recommended medical therapies, including antianginal therapies (other than ranolazine) per the discretion of the investigator (eg, aspirin, any second antiplatelet agent, a lipid-lowering agent, b-blocker, calcium-channel blockers, nitrates, angiotensin-converting enzyme inhibitors, and/or angiotensin receptor blockers)” Concomitant medications assessment every 3 months.	Antiplatelets, ACEI/ARBs, statins, b-blockers, calcium channel blockers, nitrate, anti-ischemic drugs	6 and 12 months	No information on cardiac preventive treatments (antihypertensives, antiplatelets or statins) at the end of follow-up	21.2
21870978	Apixaban vs Warfarin	Patients with atrial fibrillation at risk for stroke	Composite of stroke (ischemic or hemorrhagic) or	“The frequency of subjects receiving concomitant medications	NI	NI	No information on antiplatelets, antihypert	21.6

			systemic embolism	after randomization will be summarized by treatment group, medication class (anti-platelet, anti-coagulant/VKA, anti-arrhythmic, diuretic, ace inhibitor, beta blocker, alpha blocker, calcium channel blocker, ARB, lipid lowering, CYP3A4 inhibitor, hypoglycemic, anti-depressant, NSAID, other) and drug name"			ensives, statins	
28844192	Rivaroxaban and Aspirin vs Aspirin Rivaroxaban vs Aspirin	Patients with stable CV disease	Composite of CV death, stroke, or MI	"Subjects may receive all medications that their treating physicians believe are necessary" Concomitant medications assessed at screening, 9 months and end of FU.	NI	NI	No Information on other cardiac preventive treatments (antihypertensives, statins)	23
21830957	Rivaroxaban vs Warfarin	Patients with nonvalvular atrial fibrillation at risk of stroke	Composite of stroke or systemic embolism	"All medications not restricted or disallowed, as outlined below, are permitted" "Appropriate caution should be exercised with any changes in diet or for	Only information about aspirin-use in text	At some point during the study	No information on other cardiac preventive treatments (antihypertensives, statins)	23.2

				over-the-counter or prescription medications that might affect warfarin dosing..including the performance of INR testing as necessary to adjust dosing" Concomitant medications assessed at each visit.				
27367876	Escitalopram vs Placebo	Patients with HF and depression	Composite of all cause death or hospitalization	Not extended protocol, from published study design: NI	ACEI/ARBs, b-blockers	At 3 months	No information on diuretics, aldosterone receptor inhibitors, antiplatelets, statins	24
24682069	Aleglitazar vs Placebo	Patients with recent ACS and type 2 diabetes	Composite of CV death, nonfatal MI, nonfatal stroke	Extended protocol not available, from published study design: "Although statins may be adjusted throughout the trial according to LDL-C levels, investigators are encouraged to maintain other background lipid-modulating therapy (niacin, fish oil, bile acid sequestrants) at stable doses during the trial. Patients are counseled on diet and	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	24

				exercise based on guidelines"				
28605603	Degludec vs Glargine	Patients with type 2 diabetes	Composite of major CV event (death from CV causes, nonfatal MI, or nonfatal stroke)	"Relevant concomitant medications … diabetes and cardiovascular related diseases, (for example antihypertensives, lipid-lowering agents, aspirin and other antiplatelet agents) taken at trial entry and during the trial must be recorded"	Lipid lowering, antihypertensives, anticoagulants, antiplatelets, diuretics, hypoglycemic medications	At the end of follow-up	-	24
26630143	Lixisenatide vs Placebo	Patients with recent ACS and type 2 diabetes	Composite of CV death, MI, stroke, or hospitalisation for unstable angina	"Treatments in addition to the IP should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IP, they may be given at the discretion of the Investigator, with a stable dose (when possible)" "Change in concomitant medications will be assessed at each visit. The prior, on-study, and post-study medications will be	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	25

				presented on the randomized population. Medications will be summarized by treatment group”				
27633186	Semaglutide vs Placebo	Patients with type 2 diabetes	Composite of CV death, nonfatal MI, nonfatal stroke	“A broad spectrum of concomitant glucose-lowering treatments, as well as other treatments for co-morbidities and cardiovascular risk factors can be introduced in subjects based on individual requirements and at investigator’s discretion”	Lipid lowering, antihypertensives, anticoagulants, antiplatelets, diuretics, hypoglycemic medications	At the end of follow-up	-	25.2
23992601	Saxagliptin vs Placebo	Patients with CV disease or at high CV risk and type 2 diabetes	Composite of CV death, MI, or ischemic stroke	“All patients will be treated to regional standards of care for cardiovascular risk factors (eg, blood pressure, lipids) and HbA1c. Investigators will be duly informed of this requirement via…. Recording of concomitant medication with a duration of ≥3 months in the appropriate sections of	Lipid lowering, antihypertensives, antiplatelets, diuretics, hypoglycemic medications	At 1-year, 2-year and at the end of follow-up	-	25.2

				… will be according to type of medication"				
28514624	Evacetrapib vs Placebo	Patients at high CV risk	Composite of CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina	"Patients will be allowed to take any concomitant medications required except those listed in the ….. These therapies may include, but are not limited to, aspirin, other antiplatelet agents, H2 receptor blockers, proton pump inhibitors, antihypertensives, and appropriate diet and exercise and other nonpharmacologic measures"	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets)	26
28304224	Evolocumab vs Placebo	Patients with CV disease	Composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization	"Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. Subjects must remain on the same dose of atorvastatin with or without ezetimibe as taken at	Only information about statins and ezetimibe	During follow-up	No information on other cardiac preventive treatments (antihypertensives, antiplatelets)	26

				baseline from end of screening until the end of the study”				
30418475	Linagliptin vs Placebo	Patients with type 2 diabetes and high CV and renal risk	Composite of CV death, nonfatal MI, or nonfatal stroke	Not extended protocol, from published study design: “Investigators were also encouraged to treat all other CV risk factors (e.g. dyslipidemia, hypertension, albuminuria, smoking) in accordance with optimal local or regional guidelines and standards of care. Ultimately, changes in medication were at the discretion of the investigator and/or treating clinician”	Lipid lowering, ACEI/ARBS, renin inhibitors, diuretics, b-blockers, calcium channel inhibitors, anticoagulants, antidiabetics	Postbaseline	-	26.4
25176015	Angiotensin-neprilysin inhibition vs enalapril	Patients with class II, III, or IV HF and an ejection fraction of 40%	Composite of CV death or HF hospitalization	“The patient should be on an optimal medical regimen of background HF medications. This must include an individually optimized dose of a b-blocker (i.e., maximally tolerated dose) at a stable dose for at least 4	NI	NI	No information on diuretics, aldosterone receptor inhibitors, antiplatelets, statins	27

				weeks prior to study entry, unless contraindicated or not tolerated. Every effort should be made to keep the dose level of these background, life-saving HF medications stable throughout the entire study. However, if the patient's condition warrants a change in any of these medications, it is allowed at the discretion of the study investigator. Diuretics may be used and may be adjusted throughout the length of the study at the discretion of the investigator"				
30415610	Methotrexate vs Placebo	Patients with CV disease and type 2 diabetes or metabolic syndrome	Composite of CV death, MI, or stroke	NI	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	27.6
25176136	Ivabradine vs Placebo	Patients with stable coronary artery disease	Composite of CV death or nonfatal MI	"Patients selected for the study should receive the treatments appropriate	NI	NI	No information on other cardiac preventive treatments (antihypert	27.8

				to their cardiovascular condition. The concomitant treatments received by patients (and their respective doses) should not be modified during the study, unless there is a clinical need”			ensives, antiplatelets, statins)	
26954408	Naltrexone-bupropion group vs Placebo	Overweight and obese patients with high CV risk	MACE, defined as CV death, nonfatal stroke, or nonfatal MI	“The incidence of the use of certain medications (e.g., statins, antihypertensive agents, and antidiabetic agents) at screening, Visit 8 (Week 52)… and at study medication discontinuation … as applicable) will be summarized for each treatment group.The incidence of subjects with a change in these medications …may also be summarized ”	Information regarding CV risk factors and concomitant medications	During follow-up	No information on potential differences between groups in text	27.8
23473338	Darbepoetin alfa vs Placebo	Patients with systolic heart failure and anemia	Composite of death from any cause or hospitalisation for worsening HF	“Throughout the study, investigators may prescribe any concomitant medications or	Other treatments presented in the text	During follow-up	No information on other antihypertensives, other diuretics, aldosteron	28

				treatments deemed necessary to provide adequate supportive care except as specified in Section 6.4. Information on concomitant therapy will be collected on the appropriate CRF. Iron will be administered as tolerated according to … Administration of iron therapy will be recorded on the CRF”			e receptor inhibitors, antiplatelets, statins	
21616527	Terutroban vs Aspirin	Patients with recent ischemic stroke or TIA	Composite of fatal or non-fatal ischemic stroke, fatal or non-fatal MI, or other vascular death	Not extended protocol, from published study design: “Clinical examination is performed, and concomitant treatments are recorded at every visit”	“Furthermore, we recorded no differences between groups in mean blood pressure, heart rate, or laboratory parameters throughout the study (data not shown)”	Througout the study	-	28.3
24251359	Edoxaban vs Warfarin	Patients with atrial fibrillation	Composite of stroke or systemic embolism	“There are no concomitant medications required as part of the study design”	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	29.8
25399658	12 or 30 months of dual	Patients who had undergone PCI	Composite of stent thrombosis and	“All anticoagulant and antiplatelet	NI	NI	No information on other cardiac	30

	antiplatelet therapy	with drug-eluting stents	MACE and cerebrovascular events (composite of death, MI, stroke)	concomitant medications must be recorded in the subject's medical record and on the eCRFs. In addition to APT, beta-blockers, statins, ACEIs, ARBs, NSAIDs, COX-2, PPIs and warfarin will be captured on the eCRF. The information related to the concomitant medications will be recorded .. through the 33 month follow up visit"			preventive treatments (antihypertensives, statins)	
22443427	Vorapaxar vs Placebo	Patients with a history of CV disease	Composite of CV death, MI, or stroke	"The potential influence of baseline risk factors and concomitant therapies such as statins, thienopyridines, and aspirin dosing on the occurrences of the primary and key secondary efficacy endpoints will be explored using the Cox proportional-hazard model"	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	30
25173516	Darapladib vs Placebo	Patients with	Composite of	"It is recommend	No difference		No informatio	30

		recent ACS	coronary heart disease death, MI, or urgent coronary revascularization for MI	ed that subjects enrolled in the SOLID-TIMI 52 trial be treated according to the existing guidelines for patients after ACS. The background use of evidence-based medications including statins, antiplatelet drugs, and β-blockers is closely monitored throughout the course of the trial"	between the groups in lipids or blood pressure in the text		n on antiplatelets	
22077192	Rivaroxaban vs Placebo	Patients with recent ACS	Composite of CV death, MI or stroke	"For each subject, .. all concomitant therapies .. will be recorded on the appropriate page of the CRF. The duration of dual antiplatelet treatment is at the discretion of the investigator and may vary depending on the subject's diagnosis or whether a bare metal stent or drug eluting stent is implanted. All other concomitant medication use is at the discretion of the	NI	NI	No information on other cardiac preventive treatments (antihypertensives antiplatelets, statins)	31

				managing clinician. It is advised that the appropriate guideline recommendations be followed for all other concomitant medication"				
23126252	Dalcetrapib vs Placebo	Patients with recent ACS	Composite of death from coronary heart disease, nonfatal MI, ischemic stroke, unstable angina, or cardiac arrest with resuscitation	"Patients should receive contemporary evidence-based medical care for ACS, including anti-platelets, b-blockers, ACEIs, and statins, and medication for optimal control of hypertension, angina, and diabetes. Patients should also receive instructions on a heart healthy diet. Patients should also receive counseling on appropriate life style modifications such as weight control, physical activity, smoking cessation etc. The use of any concomitant medication will be recorded"	Antiplatelets (aspirin, clopidogrel, ticlopidine, prasugrel), statins, b-blockers, ACEI/ARBs, diuretics, calcium channel blockers	At 3 ,12, 24, 36 months	-	31

29527974	Febuxostat vs Allopurinol	Patients with gout and CV disease	Composite of CV death, nonfatal MI, nonfatal stroke, or unstable angina with urgent revascularization	“Concomitant medications assessed at each visit”	Antiplatelets (aspirin, clopidogrel), lipid-lowering, ACEI/ARBs	At 12, 24, 36 months	-	32
25781440	Thienopyridine vs Placebo	Patients following treatment with bare-meta stents or drug-eluting stents	Composite of death, MI, stroke	“Demographic, clinical, and procedural information at the time of enrollment are captured as well as subsequent clinical end points, serious adverse events, concomitant medications, and antiplatelet therapy compliance”	NI	NI	No information on other cardiac preventive treatments (antihypertensives, statins)	32.5
23121378	Aliskiren vs Placebo	Patients with type 2 diabetes and CV or renal disease	Composite of CV death or cardiac arrest with resuscitation; nonfatal MI; nonfatal stroke; unplanned HF hospitalisation; renal hard endpoints	“Patients should be treated with the target dose of the medications as per the guidelines relevant to his/her medical history and concomitant conditions. Concomitant treatment must include an ACEI or an ARB and treatment with statins is recommended”	ACEI/ARBS, b-blockers, diuretics, calcium channel blockers	At 12, 24, 36 months	No information on antiplatelets	32.9

25773268	Tigagrelor vs Placebo	Patients with prior MI	Composite of CV death, MI, or stroke	“Concomitant therapy with simvastatin or lovastatin at doses higher than 40 mg daily is not permitted. There are no restrictions to other statin therapies (ie, doses of simvastatin or lovastatin ≤40 mg daily or any dose of any other statin is permitted)”	NI	NI	No information on other cardiac preventive treatments (antihypertensives, statins)	33
30403574	Alirocumab vs Placebo	Patients with prior ACS	Composite of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization	“All patients should receive contemporary evidence-based treatment for ACS and chronic coronary heart disease as described in regional professional guidelines, including, but not limited to anti-platelet agents, b-blockers, ACEIs or ARBs, and treatments for diabetes, hypertension, and smoking”	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets)	33.6
27959716	Celecoxib vs Naproxen Celecoxib vs Ibuprofen	Patients at increased CV risk	Composite outcome of CV death (including hemorrhagic death), nonfatal MI, or	“Concomitant medications assessed at each visit”	NI	NI	No information on other cardiac preventive treatments (antihypertensives,	34.1

			nonfatal stroke				antiplatelets, statins)	
22085343	Niacin vs Placebo	Patients with CV disease and low HDL	Composite of death from coronary heart disease, nonfatal MI, ischemic stroke, hospitalisation for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization	“Concomitant drugs not allowed: Lipid-lowering drugs (other than the investigational drugs), such as statins, bile-acid sequestrants, fish oils, cholesterol absorption inhibitors (e.g., ezetimibe, except for its use as described above to achieve study protocol treatment goals for LDL-C), fibrates”	Adequate description of other preventive treatments in text	During follow-up	-	36
26052984	Sitagliptin vs Placebo	Patients with type 2 diabetes and CV disease	Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalisation for unstable angina	“In accordance with standard guidelines for care in all countries participating in the study, it is anticipated that all subjects will receive counseling about appropriate diet and exercise interventions as part ofusual care. Concomitant medications will be used at the discretion of the usual	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	36

				care physician, who will be informed of the participant's enrollment in the study, the use of blinded study medication, and the classes of AHAs which are contraindicated during the study period. Usual care physicians will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines"				
27043774	Aliskiren vs Enalapril Aliskiren/Enalapril vs Enalapril	Patients with HF and reduced ejection fraction	Composite of CV death or HF hospitalisation	"Every effort should be made by the investigator to keep the dose level of each patient's background heart failure medications (such as ARB's, beta blocker) stable throughout the entire study duration. However, if the clinical condition of the patient warrants a change in any of these medications	NI	NI	No information on diuretics, antiplatelets, statins	36.6

				, it is allowed at the discretion of the study investigator. Concomitant use of aldosterone receptor antagonists and ARB is prohibited”				
28910237	Exenatide vs Placebo	Patients with type 2 diabetes	Composite outcome death from CV causes, nonfatal MI, or nonfatal stroke	“Concomitant medications will be used at the discretion of the usual care physician (or investigator if also the usual care physician), …. Usual care physicians will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines…”	Lipid lowering, antihypertensives, anticoagulants, antiplatelets, hypoglycemic medications	During follow-up	-	38.4
26378978	Empagliflozin vs Placebo	Patients with type 2 diabetes and high CV risk	Composite outcome of CV death, nonfatal MI, or nonfatal stroke	“Beginning at the Screening Visit and every visit thereafter (except follow-up visit), patients will receive diet and exercise counselling based on local diet recommendations.	Lipid lowering, antihypertensives, anticoagulants, antiplatelets, hypoglycemic medications	Postbaseline	-	38.4

				Concomitant medications will be documented at each visit”				
26551272	Intensive BP Lowering vs Control	Persons with a systolic blood pressure of 130 mm Hg or higher and an increased CV risk, but without diabetes	Composite of MI, other acute coronary syndromes, stroke, HF, or CV death	“Information regarding the participants’ concomitant non-study medication therapy is collected .. at annual followup visits….Although data are collected on all current therapies, emphasis is placed on concurrent antihypertensive, cardiovascular, chronic kidney disease and dementia medications as well as background risk reduction therapy such as aspirin and lipid-lowering drugs”	NI	NI	No information on other cardiac preventive treatments (antiplatelets, statins, which antihypertensives per group)	39.1
30145941	Lorcaserin vs Placebo	Overweight or obese patients with CV disease or multiple CV risk factors	Composite of CV death, MI, or stroke	“Medications for the treatment of hypertension, dyslipidemia, or diabetes may be started, discontinued, or adjusted during the study according to local standards of care if, in	Information on CV risk factors	End of follow-up	No information on other cardiac preventive treatments (antihypertensives, antiplatelets)	39.6

				the judgment of the investigator or the subject's physician, such a change is medically indicated"				
24716680	Spironolactone vs Placebo	Patients with heart failure and a preserved left ventricular ejection fraction	Composite of CV death, aborted cardiac arrest, or hospitalisation for the management of HF	"Subjects will be treated with other medications at the discretion of their cardiologist and/or primary care provider. All medications will be recorded on the study forms. Concomitant medications are assessed regularly"	NI	NI	No information on other cardiac preventive treatments (antihypertensives, diuretics, aldosterone receptor inhibitors, antiplatelets, statins)	39.6
22931315	Aspirin and Clopidogrel vs Aspirin	Patients with recent lacunar stroke	Composite of recurrent stroke, (ischemic stroke and intracranial hemorrhage)	NI	Statins (antihypertensives as part of 2x2 factorial)	At any time of follow-up	-	40.8
22551105	Warfarin vs Aspirin	Patients with HF and reduced ejection fraction	Composite of ischemic stroke, intracerebral hemorrhage, death from any cause	"Unless contraindicated, all patients should receive optimal doses of angiotensin-converting enzyme inhibitors or equivalent and betaadrenergic antagonists.	NI	NI	No information on diuretics, aldosterone receptor inhibitors, statins	42

				4.4.3 Management of Vascular Risk Factors All patients will receive optimal treatment for hypertension, diabetes mellitus and hypercholesterolemia (See Procedure Manual)"				
28605608	Canagliflozin vs Placebo	Patients with type 2 diabetes	Composite of CV death, nonfatal MI, or nonfatal stroke	"All therapies different from the study drug must be recorded in the concomitant therapy section … of the CRF. During the 2-week single-blind placebo run-in period, investigators should adjust the subject's regimen as needed to optimize the subject's CV risk factors and thereby to reduce the need for adjustments of medications after randomization"	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	43.2
23726159	Intensive blood pressure lowering vs Control	Patients with recent lacunar stroke	Stroke (including ischemic strokes and intracranial hemorrhages)	NI	Mean number of antihypertensives (ACEI/ARBs, diuretics, calcium channel blockers, b-	At last visit	-	44.4

					blockers), statins			
2884575 1	Canakinum ab 50 mg vs Placebo Canakinum ab 150 mg vs Placebo Canakinum ab 300 mg vs Placebo	Patients with previous MI and a high-sensitivity C-reactive protein level of 2 mg or more per liter	Composite of nonfatal MI, nonfatal stroke, or CV death	"All medications and significant non-drug therapies (including physical therapy and blood transfusions) taken within 30 days of screening and administered after the patient has signed informed consent must be listed on the appropriate Concomitant Medications and or Procedures and Significant Non-Drug Therapies eCRF Prior & Concomitant Antidiabetic & CVD Medications : assessed at each visit"	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	44 .4
2467895 5	Darapladib vs Placebo	Patients with stable coronary heart disease	Composite of CV death, MI, or stroke	"All concomitant medications taken during the study will be recorded in the eCRF. The use of concomitant statin therapy will be …."	Following information in the text "LDL levels and BP were balanced at the end of the study"	End of follow-up	No information on antiplatelets	44 .4
2729542 7	Liraglutide vs Placebo	Patients with type 2	Composite of CV death,	"Non-investigational drugs that	Lipid lowering, antihypert	At the end of	-	45 .6

		diabetes and high CV risk	nonfatal MI, nonfatal stroke	are required will be prescribed to trial subjects in the usual fashion according to local health plans. Concomitant medication will be recorded at every visit, if any changes…However, the final choice of concomitant therapy and glucose-lowering intensification modalities will be at Investigator's discretion"	ensives, anticoagulants, antiplatelets, diuretics, hypoglycemic medications	follow-up		
25014686	Niacin vs Placebo	Patients with CV disease	Composite of nonfatal MI, death from coronary causes, stroke or arterial revascularisation	Only information about statins	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets)	46.8
30535217	Alfacalcidol vs control	Patients with chronic kidney disease	Composite of fatal and nonfatal CV events (MI, hospitalizations for congestive HF, stroke, aortic dissection/rupture, amputation of lower limb due to ischemia, cardiac sudden death; coronary revascular	"Concomitant drugs shall be recorded … shall also be recorded: 1) Drugs for abnormal mineral metabolism and hyperparathyroidism 2) Antihypertensive drugs (calcium channel blocker, ACE inhibitor, Angiotensin receptor blocker, ß-blocker, α-	Information about other treatments in appendix	Until the end of follow-up	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	48

			ization and leg artery revascularization)	blocker, loop diuretics, and others) 3) Other cardiovascular drugs (..) 4) Anti-platelet drugs (..) 5) Anti-coagulants (..) 6) Anti-diabetic drugs (…) 7) Lipid-lowering drugs (statin) 8) ESAs (…) 9) Iron preparations (…)"				
21388310	Irbesartan vs Placebo	Patients with atrial fibrillation at risk for stroke	Composite of stroke, MI, or death from vascular causes	"Assessed at 3,6,12,18,24 months. The incidence of the use of selected concomitant medications will be summarized in each treatment group"	NI	NI	No information on other cardiac preventive treatments (statins) and anticoagulation in patients with atrial fibrillation	49
28847206	Anacetrapib vs Placebo	Patients with CV disease and low HDL	Composite of first major coronary event, a coronary death, MI, or coronary revascularization	"Randomized participants who are receiving study atorvastatin at the lower doses and who, in the opinion of their managing doctors, require more intensive LDL-lowering therapy may have the dose of atorvastatin increased (to a	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	49.2

				maximum of 20 mg daily in Far East, 80 mg daily elsewhere).:..”				
30415602	Dapagliflozin vs Placebo	Patients with type 2 diabetes and CV disease or at high CV risk	Composite of CV death, MI, or ischemic stroke	“All patients should be treated according to regional standards of care for CV risk factors (e.g., blood pressure, lipids, antithrombotic treatment) and HbA1c. Other medication(s), which are considered necessary for the patient’s safety and well-being, may be given at the discretion of the Investigator”	Information about other antidiabetics across groups	During follow-up	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	50.4
25771069	Enalapril–folic vs Enalapril alone	Patients with hypertension	Stroke	“Any drugs other than use of folic acid are permitted. Proper control of blood pressure should be used as a goal for anti-hypertensive medications other than the study drugs. … If blood pressure is not properly controlled, other anti-hypertensive medications can be	NI Info about other antihypertensives in text not across groups	NI	No information on other cardiac preventive treatments (antiplatelets, statins)	54

				added based on the recommendation of the “Chinese Guidelines of Hypertension Management” published in 2005. Controlling of the blood pressure within a normal range is not mandatory. The first choices of anti-hypertensive drugs to be added are..”				
24490264	High-dose multivitamin vs Placebo	Patients with prior MI	Composite of total death, recurrent MI, stroke, coronary revascularization, or hospitalisation for angina	NI	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	55
23532240	EDTA Chelation solution vs Placebo	Patients with prior MI	Composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalisation for angina	NI	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	55
30415628	Icosapent Ethyl vs Placebo	Patients with CV disease or with diabetes and other risk factors	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or	“Any medications administered during the study period must be documented on the Concomitant Medication CRF. ..The	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets) and hypoglyce	56.5

			unstable angina	following products are allowed: statins, ezetimibe, and herbal products & dietary supplements not containing omega-3 fatty acids”			mic medications	
26886418	Pioglitazone vs Placebo	Patients with recent ischemic stroke or TIA	Composite of fatal or non-fatal stroke, MI	D.8.2 Definition and Management of Vascular Risk Factors D.8.2.1 Hypertension D.8.2.2 Elevated Blood Lipids D.8.2.3 Carotid Artery Disease D.8.2.4 Atrial Fibrillation D.8.2.5 Cigarette Smoking D.8.2.6 Diet, Exercise, and Weight D.8.3 Other Preventive Therapy	Statins, “on blood pressure goal”, anticoagulants or antiplatelets, hypoglycemic medications, smoking	Each year unti end of follow-up	-	57.6
21663949	Simvastatin plus Ezetimibe vs Placebo	Patients with chronic kidney disease	MACE (non-fatal MI or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure)	From published study design: NI	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets)	58.8
30158069	Aspirin vs Placebo	Patients with moderate CV risk	Composite outcome of time to first occurrence of CV death, MI,	No protocol	NI	NI	No information on other cardiac preventive treatments (antihypert	60

			unstable angina, stroke, or TIA				ensives, statins)	
23656645	N-3 fatty acids vs Placebo	Patients with multiple CV risk factors or atherosclerotic vascular disease but not MI	Composite of CV death or admission to the hospital for CV causes (revised)	“3.2 Terapie concomitanti Nonostante i molteplici effetti farmacologici degli n-3 PUFA, al dosaggio utilizzato nello studio, non sono note interazioni clinicamente rilevanti con i principali farmaci cardiovascolari compresi antiaggreganti, anticoagulanti e antiaritmici”	ACEI/ARBs, statins, antiplatelets	At the end of follow-up	-	60
25401325	Aspirin vs Control	Patients with hypertension, dyslipidemia, or type 2 diabetes	Composite of death from CV causes (MI, stroke, and other CV causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal MI	“Treatment to control hypertension, dyslipidemia, or diabetes (ie, the underlying risk factors for vascular events) was administered to all eligible patients at the screening visit and, in principle, throughout the study, in accordance with Japanese therapeutic guideline” (no protocol)	NI	NI	No information on other cardiac preventive treatments (antihypertensives, statins)	60.2
23121374	Cinacalcet vs Placebo	Patients with chronic	Composite of death, MI, hospitalisa	“Concomitant therapy will be collected	“The provision of antiplatele	During follow-up	-	64

		kidney disease	tion for unstable angina, HF, or a peripheral vascular event	from day 1 through the end of the study"	t agents, statins, beta-blockers, and inhibitors of the renin–angiotensin–aldosterone system did not materially change over time in either group" (text)			
26323937	Benznidazole vs Placebo	Patients with established Chagas' cardiomyopathy	Composite of death, resuscitated cardiac arrest, sustained ventricular tachycardia, insertion of a pacemaker or implantable cardioverter-defibrillator, cardiac transplantation, new HF, stroke, or other thromboembolic event	"Any concomitant therapy, including treatments demonstrated to be effective in the study population is permitted"	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins), diuretics, aldosterone receptor inhibitors	64.8
27041480	Candesartan/HCT vs Placebo	Patients with intermediate CV risk	Composite of CV death, nonfatal MI, nonfatal stroke	"Concomitant treatments assessed 0, 24, end of FU; Concurrent Treatments: There are no other restrictions to the use of additional therapies. If clinicians managing	Only information about other antihypertensives in table across groups	At 2 years and at the end of follow-up	No information on other cardiac preventive treatments (antiplatelets)	67.2

				individual study participants believe that lipid modifying or blood pressure lowering treatments are clinically indicated after randomization, open label lipid modifying or blood pressure lowering drug(s) can be added. Whenever possible, drugs other than statins, ARBs, ACE inhibitors and thiazide diuretics should be used.."				
27039945	Rosuvastatin and Candesartan/HCT vs Placebo	Patients with intermediate CV risk	Composite of CV death, nonfatal MI, or nonfatal stroke	"Concomitant treatments assessed 0, 24, end of FU; Concurrent Treatments: There are no other restrictions to the use of additional therapies. If clinicians managing individual study participants believe that lipid modifying or blood pressure lowering treatments are clinically indicated after randomizati	NI	NI	No information on other cardiac preventive treatments (antiplatelets)	67.2

				on, open label lipid modifying or blood pressure lowering drug(s) can be added. Whenever possible, drugs other than statins, ARBs, ACE inhibitors and thiazide diuretics should be used..”				
27040132	Rosuvastatin vs Placebo	Patients with intermediate CV risk	Composite of CV death, nonfatal MI, or nonfatal stroke	“Concomitant treatments assessed 0, 24, end of FU; Concurrent Treatments: There are no other restrictions to the use of additional therapies. If clinicians managing individual study participants believe that lipid modifying or blood pressure lowering treatments are clinically indicated after randomization, open label lipid modifying or blood pressure lowering drug(s) can be added. Whenever possible, drugs other than statins, ARBs, ACE inhibitors	NI	NI	No information on other cardiac preventive treatments (antiplatelets)	67.2

				and thiazide diuretics should be used..”				
26039521	Simvastatin plus Ezetimibe vs Simvastatin plus Placebo	Patients with recent ACS	Composite of CV death, nonfatal MI, unstable angina requiring rehospitalisation, coronary revascularization or nonfatal stroke	“CV Concomitant Medications Review in each visit. The use of any concomitant medication must relate to an adverse event or the subject's medical history”	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets)	72
22686415	N-3 fatty acids vs Placebo	Patients at for CV risk and impaired fasting glucose, impaired glucose tolerance, or diabetes	Composite of death from coronary heart disease, nonfatal MI, ischemic stroke, hospitalisation for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization	“Concomitant medications may be used at the discretion of the participant’s physician when indicated for the participant’s welfare. Participants will be formally asked about the types of concomitant treatments every year. As noted above, TZDs will not be permitted in combination with insulin glargine”	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins) and hypoglycemic medications	74.4
22686416	Insulin-glargine vs standard-care	Patients with CV risk factors plus impaired fasting glucose, impaired glucose	Composite of nonfatal MI, nonfatal stroke, or CV death	“Concomitant medications may be used at the discretion of the participant’s physician when	Lipid lowering, antihypertensives (Thiazid, ACEI/ARBs, b-blocker, other), antiplatele	At the end of follow-up	-	74.4

		tolerance, or type 2 diabetes		indicated for the participant's welfare. Participants will be formally asked about the types of concomitant treatments every year. As noted above, TZDs will not be permitted in combination with insulin glargine"	ts, other antidiabetics			
30146932	N-3 fatty acids vs Placebo	Patients with type 2 diabetes	Composite of serious vascular event (i.e., nonfatal MI or stroke, transient ischemic attack, or vascular death)	"Follow-up questionnaires asking about use of relevant non-study treatments will be sent 6-monthly with a further supply of the participant's allocated study treatment"	Statins, ACEI/ARBs, hypoglycemic medications, b-blockers, calcium channel blockers, diuretics (antiplatelets part of 2x2 factorial)	At the end of follow-up	-	88.8
30146931	Aspirin vs Placebo	Patients with type 2 diabetes	Composite of serious vascular event (i.e., nonfatal myocardial infarction or stroke, transient ischemic attack, or vascular death)	"Follow-up questionnaires asking about use of relevant non-study treatments will be sent 6-monthly with a further supply of the participant's allocated study treatment"	Statins, ACEI/ARBs, hypoglycemic medications, b-blockers, calcium channel blockers, diuretics	At the end of follow-up	-	88.8
30043065	Escitalopram vs Placebo	Patient with recent ACS and depression	Composite of all-cause mortality, MI, and percutaneous coronary	"Any change in concomitant medications or dosage will be documented	NI	NI	No information on other cardiac preventive treatments (antihypertensives,	97.2

			intervention	. Allowed drugs: …"			antiplatelets, statins)	
23117775	Multivitamin vs Placebo	Male physicians; subgroup with CV disease	Composite of MACE, including nonfatal MI, nonfatal stroke, and CVD mortality.	From published study design: "We will use the Cox proportional hazards model to compare event rates for each treatment group while controlling simultaneously for variable lengths of follow-up, other treatment assignments, and any risk factors that are unbalanced"	NI	NI	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	134
Long term follow-up (>1 month) with index procedure after randomization								
27043082	Losmapimod vs Placebo	Patients with ACS	Composite of CV death, MI, or severe recurrent ischemia requiring urgent coronary revascularization	"Investigators will manage the subjects according to standard of care, following local prescribing information. Close adherence to professional society guidelines for standard of care therapies in ACS will be	Aspirin, P2Y12 inhibitors, statin, b blocker, ACE/ARBs	At discharge	No information on procedural characteristics	5.5

				emphasized during study conduct, including anti-platelet therapy, statin medications, use of appropriate revascularization, ACEIs and b-blockers. All concomitant medications taken during the study will be recorded in the eCRF"				
28844201	Bivalirudin vs Heparin	Patients with ACS undergoing PCI	Composite of death from any cause, MI, or major bleeding	"Procedure strategies: All other treatments. are according to local tradition. GpIIb/IIIa inhibitors may be given as bailout treatment according to physician´s decision. After the index PCI, lifelong acetylsalicylic acid .. will be prescribed"	Periprocedural characteristics; aspirin, clopidogrel, GpIIb/IIIa inhibitors, b-blockers, statins, ACEI/ARBs, calcium channel blockers, anticoagulants	Periprocedural & at discharge	Type of stent is not reported	5.9
24177257	3 months vs 12 months of dual treatment	Patients undergoing PCI with zotarolimus-eluting stents	Net adverse clinical and cerebral events (MACE and major bleeding)	"All interventions were recommended to be performed according to the current standard guidelines, and final procedure strategy was left entirely at the operators'	Information about procedural characteristics	Periprocedural	Access site per group is missing. Periprocedural medications missing; Information o other cardiac preventive treatments (antihypertensives, statins) at end of	12

				discretion. Direct stenting and implant of multiple E-ZES were allowed" (from published study design)			follow-up missing	
22077816	Vorapaxar vs Placebo	Patients with NSTEMI	Composite of CV death, MI, stroke, recurrent ischemia with rehospitalisation, or urgent coronary revascularization	"In general, record in the eCRF those medications or therapies taken, used, or administered during the study.."	Only information about procedural characteristics	Periprocedural	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	16.5
29544699	6 vs 12 months of of dual treatment (Clopidorgel and Aspirin)	Patients with ACS undergoing PCI with drug-eluting stents	Composite of all-cause death, MI, or stroke	"Direct stenting or prediltion and antithrombotic medications during the procedure, and use of glycoprotein IIb/IIIa inhibitors will be up to operatos discretion. The length and diameter of the stent will not be restricted" (from published study design)	Information about procedural characteristics & medications; heparin, GpIIb/IIIa inhibitors and discharge medications: aspirin, clopidogrel, b-blockers, statins, ACEI/ARBs,	Periprocedural & at discharge	No information on other cardiac preventive treatments (antihypertensives, statins) at the end of follow-up; no information for balloon dilatation	18
30166073	Aspirin and Tigagrelor vs Aspirin and Clopidogrel	Patients undergoing elective or urgent PCI with drug-eluting stents	Composite of all-cause mortality or non-fatal new Q-wave MI	"Balloon angioplasty and stent implantation were performed according to standard techniques; direct stenting (without	Information about procedural characteristics	Periprocedural	No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)	24

				previous balloon dilatation) was allowed. Staged procedures were permitted ... Glycoprotein IIB/IIIA receptor inhibitors were to be administered only in patients who had periprocedural ischemic complications (i.e., no reflow or giant thrombus) after stenting. The use of unfractionated heparin (up to an arbitrary set maximum of 4000IU) during the index diagnostic angiogram was left at the discretion of the investigator. The use of other medications was per applicable professional guidelines"				
26321103	Cyclosporin vs Placebo	Patients with STEMI undergoing PCI (randomization before recanalization)	Composite of death from any cause, worsening of HF during the initial hospitalisation, rehospitalisation for HF, or	"Associated treatments (anti-platelets agents, anticoagulants, ACE-I, -blockers, statins, n-3 PUFA …) will be administered according	Procedural characteristics and periprocedural medications; lipid lowering, antihypertensives, anticoagulants,	Periprocedural & at discharge	No information on cardiac preventive treatments (antihypertensives, antiplatelets, statins) at end of follow-up; Type of	12

			adverse left ventricular remodeling at 1 year	to the current guidelines ..”; “Coronary angioplasty and stenting will be performed according to the usual procedures utilized by the cardiologist in charge….”	antidiabetics		stent is missing	
Short term follow-up (<1 month) with index procedure after randomization								
23473369	Cangrelor vs Clopidogrel	Patients undergoing urgent or elective PCI	Composite of death, MI, ischemia-driven revascularization or stent thrombosis	“All patients should receive standard of care antiplatelet therapy per ACC/AHA/ESC guidelines; The following allowed medications may constitute standard care and will be allowed as concomitant medications, including…. institution‘s standard practices during the index PCI procedure with the exception of medications prohibited	Procedural characteristics and periprocedural medications (P2Y12 inhibitors use, bivalirudin, heparin, fondaparinux, aspirin)	Periprocedural & at discharge	-	0.2

				under this protocol"				
23995608	Otamixaban vs Heparin plus eptifibatide	Patients with NSTEMI undergoing PCI	Composite of all-cause death or new MI	"In addition to study medication, all randomized patients must receive both aspirin and an oral adenosine diphosphate receptor antagonist given as per their local label or international guidelines. Both radial and femoral access for angiography and PCI are allowed. For patients having femoral access, if a closure device is used, the sheath ….."	Procedural characteristics and periprocedural medications (P2Y12 inhibitors use, bivalirudin, heparin, fondaparinux, aspirin) and aspirin, clopidogrel, Gp IIb/IIIAa inhibitors, b-blockers, statins, ACEI/ARBs	Periprocedural & at discharge	Type of stent not reported, balloon-dilatation not reported	0.23
25002178	Bivalirudin vs Heparin	Patients undergoing primary PCI	Composite of all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target lesion revascularisation	"The GP IIb/IIIa inhibitor, abciximab, was allowed for selective use in both groups as per the European Society of Cardiology guidelines (..). No other trial-related restrictions were imposed on the performance of angiography and PCI, which were done in accordance with	ACEI/ARBs, aspirin, clopidogrel, statin at discharge and procedural characteristics and periprocedural medications (Aspirin, P2Y12-inhibitor loading dose, GpIIb/IIIa)	Periprocedural & at discharge	-	1

				prevailing best local practice as determined by the attending interventional cardiologist" (no protocol)				
24679062	Aspirin vs Placebo	Patients undergoing noncardiac surgery	Composite of death or nonfatal MI	"All aspects of the patient's management are at the discretion of the attending physician. This includes all decisions on antiplatelet, anticoagulation, and anti-ischemic therapies. We will encourage physicians not to prescribe an alpha-2 agonist …. We will also encourage physicians not to prescribe antiplatelet therapy during the initial 7 days after surgery …."	Anticoagulants, NSAID, statin, Cox-2, b-blocker, P2Y12, perioperative antifibrinolytic & procedural characteristics	During the first 3 days	-	1
24679061	Clonidine vs Placebo	Patients undergoing noncardiac surgery	Composite of death or nonfatal MI	"All aspects of the patient's management are at the discretion of the attending physician. This includes all decisions on antiplatelet, anticoagulation, and anti-	B-blocker, Calcium-Channel blockers, statin, a2-adrenergiv agonist & procedural characteristics (antiplatelets as part of factorial 2x2)	During the first 3 days	-	1

				ischemic therapies. We will encourage physicians not to prescribe an alpha-2 agonist …. We will also encourage physicians not to prescribe antiplatelet therapy during the initial 7 days after surgery ….”				
27590218	Edoxaban vs Enoxaparin –warfarin	Patients undergoing cardioversion for atrial fibrillation	Composite of stroke, systemic embolic event, MI, CV death	“There are no concomitant medications required as part of the study design. The study procedures detailed below are for both TEE and non-TEE-guided subjects, unless specifically stated otherwise. As much as possible, procedures must be followed in the order listed”	NI	-	No information on antiplatelets, or procedural characteristics	1
23117776	Dexamethasone vs Placebo	Patients undergoing cardiac surgery	Composite of death, MI, stroke, renal failure, or respiratory failure	“Anesthesia and surgical treatment were performed according to the standard procedures of each participating center”. (no protocol)	B-blockers, statin, corticosteroid & procedural characteristics	Periprocedural	No information on antiplatelets	1
25775052	Bivalirudin vs Heparin	Patients undergoi	Composite of MACE	“Anticoagulant agent	ACEI/ARBs, aspirin,	Periprocedural &	-	1

	vs Heparin plus Tirofiban	ng primary PCI	or cerebral events (all-cause death, reinfarction, ischemia-driven target vessel revascularization, or stroke) or bleeding	(heparin, LMWH, etc.) post procedure is not recommended Provisional (bailout) tirofiban use is allowed in the bivalirudin and heparin alone arms for no-reflow, slow flow, visible thrombus or other thrombotic complication ”	clopidogrel, statin and procedural characteristics and periprocedural medications (aspirin, P2Y12-inhibitor loading dose, GpIIb/IIIa inhibitors)	at discharge		
22077909	Abciximab plus Heparin vs Bivalirudin	Patients with NSTEMI undergoing PCI	Composite of death, large recurrent MI, urgent target-sessel revascularisation, major bleeding	“Concomitant medication assessed at discharge. Post-interventionally Sheath should … respectively. After the intervention, all patients will receive 80-325 mg/day aspirin indefinitely, clopidogrel 75-150 mg until discharge (but no longer than 3 days) followed by at least 75 mg/day for at least 6 months and other cardiac medications according to the judgment of patient’s physician (e.g. ß-blockers,	Procedural characteristics and periprocedural medications (GpIIb/IIIa inhibitors, bivalirudin, heparin, randomization after aspirin & P2Y12 was given)	Periprocedural	-	1

				ACE-inhibitors, statins etc)"				
21856483	Enoxaparin vs Heparin	Patients with STEMI undergoing PCI	Composite of death, complication of MI, procedure failure, or major bleeding	Procedures described in paper (no protocol)	Aspirin, clopidogrel, Gp IIb/IIIa inhibitors, statins, b blocker, ACEI/ARBS periprocedural and periprocedural characteristics	Periprocedural	-	1
22452807	Glucose-insulin-potassium vs Placebo	Patients with suspected ACS	MI	NI (published study design)	NI	-	No information on medications (anticoagulants, antiplatelets) or procedural characteristics	1
24171490	Bivalirudin vs Heparin	Patients with STEMI undergoing PCI	Composite of death or major bleeding not associated with coronary-artery bypass grafting	"Once a patient has commenced treatment with an anti-thrombin (..) no change in strategy is recommended. In patients requiring ongoing anti-coagulation for reasons other than PCI then anticoagulation should be maintained as per local practice. Glycoprotein IIb/IIIa Inhibitor Management: In patients randomised to the	Aspirin, clopidogrel, b-blockers, statins, ACEI/ARBs at discharge and procedural characteristics and periprocedural medications (aspirin, P2Y12-inhibitor loading dose, heparin, bivalirubin, enoxaparin), GpIIb/IIIa inhibitors)	Periprocedural & at discharge	-	1

				control arm the use of a GPI will be classified as either “routine” (treatment of patients before or during angiography but not once PCI has commenced) or “bail out” (treatment of patients during or after PCI)”				
26324049	Bivalirudin vs Heparin	Patients with ACS undergoing PCI	Composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events	Only information on vascular access site: transfemoral access	Procedural characteristics; Periprocedural medications and medications at discharge (aspirin, clopidogrel, GpIIb/IIIAa inhibitors, b-blockers, statins, ACEI/ARBs, diuretics, antidiabetics)	Periprocedural & at discharge	Type of stent missing	1
29525821	Atorvastatin vs Placebo	Patients with ACS undergoing PCI	Composite of all-cause mortality, MI, stroke, and unplanned coronary revascularization	“Co-interventions: Concomitant treatment with ASA and clopidogrel will be recommended for all patients at discharge. Due to its pragmatic design, the co-intervention	Procedural characteristics, periprocedural medications: only heparin	Periprocedural	Procedural characteristics: Access site is missing. Medications: No information on GIIb/IIIa, unclear if aspirin, clopidogrel, b-blockers, ACEIs/ARBs on	1

				s choice will be at the medical staff discretion. Nevertheless, the use of the following agents listed below will be strongly recommended to all sites (except if contraindications are present). The percutaneous coronary intervention will be performed according to the current clinical practice of the Institution, using either the transfemoral or the transradial access. Stents implantation, as well as stent characteristics, will be at the interventional cardiologist discretion"			baseline table are before admission or periprocedural	
26095867	Low Molecular Weight Heparin vs Placebo	Patients with atrial fibrillation undergoing surgery	Arterial thromboembolism (stroke, systemic embolism, TIA)	Potential co-Interventions: information on other concomitant antiplatelet Therapy, antithrombotic drugs	Aspirin, clopidogrel, NSAIDs, Cox-2, heparin, warfarin & procedural characteristics	Periprocedural	-	1
23991622	Prasugrel vs Placebo	Patients with NSTEMI undergoing PCI	Composite of CV death, MI, stroke, urgent	Only information in the use of other antiplatelets	Procedural characteristic; periproced	Periprocedural	Procedural characteristics: Stent type is missing	1

			revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy (Gp IIbIIIa bailout)	drugs in protocol	ural medications: heparin, bivalirudin, fondaparinux, aspirin, clopidogrel, PPI, b-Blocker, statin, ACEI/ ARBs, clopidogrel, calcium channel blockers			
26933848	Aspirin vs Placebo	Patients undergoing cardiac surgery	Composite of death and thrombotic complications (nonfatal MI, stroke, pulmonary embolism, renal failure, or bowel infarction)	"All other perioperative clinical care will be according to standard practice as this is an effectiveness trial and some elements of the trial are deliberately left to the clinicians' discretion in order to reflect usual practice and maximise generalisability. Anaesthesia and surgery will be according to local practices…. All such relevant perioperative data will be recorded on the CRF"	ACEI/ARBs, aspirin, clopidogrel, statin, b-blocker, diuretics, digoxin, NSAID, amiodarone, and procedural characteristics	Periprocedural & up to 7 days	-	1
27774838	Tranexamic acid vs Placebo	Patients undergoing cardiac surgery	Composite of death and thrombotic complications (nonfatal MI, stroke, pulmonary	"All other perioperative clinical care will be according to standard practice as this is an effectiveness	ACEI/ARBs, aspirin, clopidogrel, statin, b-blocker, diuretics, digoxin, NSAID, amiodaron	Periprocedural & up to 7 days	-	1

			embolism, renal failure, or bowel infarction)	s trial and some elements of the trial are deliberately left to the clinicians' discretion in order to reflect usual practice and maximise generalisability. Anaesthesia and surgery will be according to local practices…. All such relevant perioperative data will be recorded on the CRF"	e, and procedural characteristics			
22782417	Acadesine vs Placebo	Patients undergoing cardiac surgery	Composite of all-cause mortality, nonfatal stroke, or need for mechanical support for severe left ventricular dysfunction	"Standard local procedures for CABG surgery or associated preoperative and postoperative care were followed" (no protocol)	ACEI/ARBs, b-blockers, statin, clopidogrel, calcium channel blockers, nitrate, hypoglycemic medications	Periprocedural & at discharge	No information on procedural characteristics	1
26460660	Methylprednisolone vs Placebo	Patients undergoing cardiac surgery	Mortality and a composite of death and major morbidity (ie, myocardial injury, stroke, renal failure, or respiratory failure)	No protocol available	Procedural characteristics; periprocedural medications (inotropes, antifibrinolytic, non-study steroids, ACEI/ARBs, b-blockers, antiplatelets, statins, vitamin K antagonists, PPIs, hypoglycemic	Periprocedural	-	1

					medicatio ns)			

ACEI**:** angiotensive converting enzyme inhibitors, ACS: acute coronary syndrome, ARBs: Angiotensin II receptor blockers**,** CV: cardiovascular, FU: follow-up, GpIIb/IIa: Glycoprotein IIb/IIIa, HDL: high-densitiy cholesterol, HF: heart failure, LDL: low-density cholesterol, MACE: major adverse cardiac events, MI: myocardial infarction, NI: no information, NSAID: non-steroidal anti-inflammatory, PCI: percutaneous coronary angiography, PPIs: Proton pump inhibitos, TIA: transient ischemic attack

Table S6. Reporting of co-interventions according to medication category (n=123).

Drug	Reported (%,n)	Not adequately reported (%,n)
Overall (n=123)	29.3 (36)	70.7 (87)
Antihypertensives/diuretics/heart failure (n=14)	14.3 (2)	85.7 (12)
Antithrombotics/anticoagulants (n=45)	35.6 (16)	64.4 (29)
Lipid-lowering treatment (n=17)	23.5 (4)	76.5 (13)
Antidiabetics (n=16)	56.3 (9)	43.7 (7)
Antiinflammatory, antirheumatic medication (n=12)	16.7 (2)	83.3 (10)
Cardiac treatments & various (n=19)	15.8 (3)	84.2 (16)

Table S7. Potential explanatory factors associated with the reporting of co-interventions (n=123).

	Univariable analysis			Multivariable analysis		
	OR	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Blinding of participants and/or personnel* **(ref: Inadequate blinding)**						
Adequate blinding	1.04	0.47 to 2.27	0.93	0.99	0.41 to 2.38	0.99
Risk of bias due to deviations of intended interventions† **(ref: "At risk of bias"‡)**						
"At low risk of bias"	1.47	0.67 to 3.21	0.33	1.38	0.52 to 3.69	0.52
Funding **(ref: Industry)**						
Non-Industry	2.06	0.86 to 4.92	0.10	2.24	0.80 to 6.25	0.12
Trial design **(ref: Non-inferiority)**						
Superiority	0.63	0.26 to 1.55	0.32	0.38	0.13 to 1.13	0.08
Follow-up **(ref: >1 month)**						
<1 month	4.33	1.63 to 11.52	0.003	3.63	1.21 to 10.91	0.02

*according to risk of bias due to lack of blinding of participants and/or personnel (RoB 1.0);†risk of bias due to deviations of the intended interventions: effect of adhering to treatment (RoB 2.0); ‡"at risk of bias": "some concerns" and "at high risk of bias"

Table S8. Factors associated with balanced co-interventions among RCTs with adequate reporting of co-interventions (n=36).

	Univariable analysis	
	OR	**95%CI**
Blinding of participants and/or personnel[†] (ref: Inadequate blinding)		
Adequate blinding*	Omitted[*]	
Risk of bias due to deviations of intended interventions (ref: "At risk of bias"[‡])		
"At low risk of bias"	6.33	0.63 to 63.63
Funding (ref: Industry)		
Non-Industry*	Omitted[*]	
Trial design (ref: Non-inferiority)		
Superiority	5.14	0.71 to 37.15
Follow-up (ref: >1 month)		
<1 month	2.19	0.22 to 22.19

[†] according to risk of bias due to lack of blinding of participants and/or personnel (RoB 1.0) ; [‡]risk of bias due to deviations of the intended interventions: effect of adhering to treatment (RoB 2.0);"at risk of bias": "some concerns" and "at high risk of bias";[*]All trials with unbalanced co-interventions were judged as inadequately blinded trials and were industry-funded.

Box S1. Detailed definition of procedural characteristics and periprocedural medications.

- If the index procedure is cardiac surgery, minimum of procedural characteristics to be reported are: duration of aortic-cross clamping, on or off-pump surgery, duration of cardiac surgery. Minimum periprocedural medications to be reported are: antiplatelets, ACEIs/ARBs, statins, b-blockers (see ref. 29)
- If the index procedure is percutaneous coronary angiography, minimum of procedural characteristics to be reported are: stents and type of stents (bare-metal stents, drug-eluting stents), balloon dilatation, arterial access site. –minimum of periprocedural medications to be reported are: Heparin or Bivalirubin, Aspirin, P2Y12 inhibitors drug use, Glycoprotein IIb/IIIa (see ref. 30)

Figure S1. Flow diagram of the systematic review (Study selection).