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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.

REGISTRATION: URL: https://www.crd.york.ac.uk/PROSPERO/. Unique identifier: CRD42018106771.

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.3–5 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 It is not provided equally to all treatment groups.6–8 This unequal distribution of cointerventions might be caused by a failure to adequately blind participants and/or personnel.12 For example, if investigators know that a participant is receiving an active substance in a trial...
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 systematically reported in cardiovascular trials to assess the validity of the findings, particularly when trials are not fully blinded.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Definition |
|--------------|------------|
| 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 |

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.

Beyond the studied medication, each of which could affect outcomes, so cointerventions and in particular these comediations may play an important role in cardiovascular RCTs, especially if unblinded.5,8,20,21 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 binding of participants and personnel, binding of outcome assessors, information about cointerventions, implementation of study treatment, adherence to study treatment, cross-overs, statistical analysis conducted, and funding source (industry versus non-industry). Available information on cointerventions, binding 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).29,30,33 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 (i.e., 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 cointerventions29,30,33 (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 (e.g., “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 (i.e., partially reported) or missing (i.e., 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.).

**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.

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” (\(P=0.33\); Figure B).

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.
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. RCTs with inadequate blinding seem particularly at risk for unbalanced cointerventions, and reporting cointerventions is important because if they are unbalanced between treatment arms, they could introduce bias. 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. 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), an open-label trial evaluating the effect of ximelagatran versus warfarin on strokes and systemic embolic events and SPORTIF V, 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, 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, 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. However, cointerventions are among the data required to be collected in a Cochrane systematic review. In cardiovascular medicine, cointerventions may be particularly important because participants usually receive many different treatments that could reduce cardiovascular risk and change cardiovascular outcomes. In the Women’s Health Initiative, which

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.
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. 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). 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. 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 binding 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, and previous methodological reviews have used the same design. 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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SUPPLEMENTAL MATERIAL
Table S1. Literature search.

```sql
((("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)
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*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 | No Information | Both patients and caregivers were blinded |
| The method of masking was described and it was inappropriate (e.g. comparison of tablet versus injection with no double dummy) | 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”) | Detailed description about how the blinding status was established and maintained (either in published paper of in protocol): matching placebo or adequate description |
| | 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) | No specific adverse effects or methods to avoid unblinding included in the protocol |
| | Unblinding is possible (e.g. blood investigations, specific adverse effects) & no methods to avoid unblinding | |
Table S3. Description of 26 excluded studies.

| Author, y | Reason for exclusion |
|-----------|----------------------|
| Anderson, 2016 (PMID:27161018) | Primary outcome: death or disability defined through modified Rankin scale |
| He, 2014 (PMID: 24240777) | Primary outcome: death and major disability defined 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 |
| Reference                     | Description                                      |
|-------------------------------|--------------------------------------------------|
| 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 descriptions of reported and not reported co-interventions.

| PMID of the study | Interventions | Setting | Outcome | Co-intervention s in the protocol | Co-interventions reported | Timepoint | Co-interventions not reported | F U |
|-------------------|---------------|---------|---------|-----------------------------------|---------------------------|-----------|-------------------------------|-----|
| 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 death | 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.

| Study ID | Intervention | Patient Population | Endpoint | Protocol Information |
|----------|--------------|---------------------|----------|----------------------|
| 23803136 | Aspirin and Clopidogrel vs Aspirin | Patients with acute minor stroke or TIA | Stroke | Through day 90 (end of follow-up) |
| 24247616 | Varespladib vs Placebo | Patients with ACS | Composite of CV mortality, nonfatal MI, nonfatal stroke, or unstable angina with evidence of ischemia requiring | - | 3.1 |
| Study ID   | Treatment                          | Patients                              | Outcome Measure                                                                 | Notes                                                                 |
|-----------|------------------------------------|---------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------|
| 22082198  | Dronedaron 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.” |
| 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 discretion of physician” |
| 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” |

Notes:
- NI = No information
- No information on antihypertensives, antiplatelet agents or statins; No information on anticoagulation in patients with atrial fibrillation
- No extended protocol available; published study design: “All patients are given standard treatment in stroke units. Therapeutic agents other”
| Study ID | Treatment Comparison | Study Population | Outcome Measure | Notes |
|----------|----------------------|------------------|-----------------|-------|
| 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. |
| 24206459 | Bardoxolon vs Placebo | Patients with diabetes and chronic kidney disease | Composite of end-stage renal disease or CV death | “Investigator should not reduce or discontinue ACE inhibitors and/or ARBs unless indicated secondary to a medical contraindication (e.g. hyperkalemia). |
| 9        | 7                    |                  |                 |       |
| Study ID | Study Name | Patient Characteristics | Medication Assessment | Concomitant Medications | Notes |
|----------|------------|--------------------------|-----------------------|-------------------------|-------|
| 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, antiplatelet s) |
| 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, antiplatelet s, statins) |
| ID     | Study Description                                                                 | Patients                                      | Composite                                                                                                                                                                                                 | Note                                                                 | Details                                                                                                                                   |
|--------|----------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| 2347874 | Aliskiren vs Placebo                                                            | Patients with acute HF                        | Composite of CV death of HF rehospitalisation                                                                                                                                                    | NI                                                                  | No information on other antihypertensives, diuretics, aldosterone receptor inhibitors, antiplatelet s, statins                        |
| 2795971 | Low-dose Rivaroxaban and P2Y12 Inhibitor vs very low-dose Rivaroxaban            | Patients with atrial fibrillation undergoing PCI | Composite of CV death, MI, Stroke                                                                                                  | NI                                                                  | Concomitant therapies must be recorded throughout the study.                                                                         |
| 2255019 | Fish oil capsules vs Placebo                                                     | Patients with arteriovenous hemodialysis grafts | Composite of hemodialysis graft patency thrombosis and CV events                                                                     | NI                                                                  | No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins)                                      |
| 2130965 | Apixaban vs Aspirin                                                             | Patients with atrial fibrillation              | Composite of stroke or systemic embolism                                                                                            | NI                                                                  | Assessment of concomitant medications: 0, 12, end of FU                                                                              |

Change in antihypertensive medications: secondary outcome

Assessment of aspirin and clopidogrel in text

During follow-up

No information on antihypertensives, statins
| Study ID | Treatment Group | Patient Population | End Point | Protocol Details | Additional Information |
|----------|-----------------|--------------------|-----------|------------------|------------------------|
| 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 |
| 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: “managements was left to the discretion of the treating physician, including cardiovascular medications. We recommend 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/ARB, b-blockers, statins | During follow-up | - |
| 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) |
| Study Code | Description | Population | Outcome | Other Information | Endpoints | Other Information |
|------------|-------------|------------|---------|-------------------|-----------|------------------|
| 30279197   | 6 vs 12 months of dual treatment (Clopidogrel 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 | No informatio n on other cardiac preventive treatments (antihypertensives, statins) |
| 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. Informatio n about lipoprotein levels in table | End of follow-up | No informatio n on other cardiac preventive treatments (antihypertensives, antiplatelet s) |
| 30291013   | Albiglутide vs Placebo | Patients with CV disease | Composite of CV | Not extended protocol, Informatio n on other hypoglycemia | At different times of | No informatio n on other |
| Study ID | Treatment A vs Treatment B | Study Population | Outcomes | Concomitant Medications | Diuretics, ACEI/ARBs, β-blockers, aldosterone receptor inhibitors | Different time-points until the end of follow-up |
|----------|---------------------------|------------------|----------|-------------------------|------------------------------------------------------------------|-------------------------------------------|
| 21073363 | Eplerenone vs Placebo     | Patients with systolic HF and mild symptoms | Composite of CV death or hospitalisation for HF | Permitted concomitant medications may include angiotensin ACE-Is, ARBs, β-blockers, and diuretics. Digoxin, vasodilators, and inotropes may be used, as clinically indicated | NI | NI |
| 30146935 | Rivaroxaban vs Placebo    | Patients with HF and coronary disease | Composite of death from any cause, MI, or stroke | Different time-points until the end of follow-up | Diuretics, ACEI/ARBs, β-blockers, aldosterone receptor inhibitors | Different time-points until the end of follow-up |

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”
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
| Study ID   | Treatment                        | Patient Population                                                                 | Outcomes                                                                 | Antiplatelets, ACEI/ARBs, Potassium Channel Blockers, Calcium Channel Blockers, Nitrate, Anti-ischemic Drugs | Time Points | Information on Cardiac Preventive Treatments (Antihypertensives, Antiplatelets or Statins) at the End of Follow-Up |
|-----------|----------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-------------|----------------------------------------------------------------------------------------------------------------|
| 26474810  | Ranolazine vs Placebo           | Patients with incomplete revascularisation                                             | Composite of ischemia-driven revascularisation or ischemia-driven hospitalisation without revascularisation | Antiplatelets, ACEI/ARBs, statins, β-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 |
| 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, antihypertensives or statins                                             |
| Study ID | Intervention  | Population | Outcomes | Concomitant medications | Adverse Events | Notes |
|----------|---------------|------------|----------|--------------------------|----------------|-------|
| 28844192 | Rivaroxaban and Aspirin 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 |
| 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 aspirin-use in text. Only information on other cardiac preventive treatments (antihypertensives, statins) at some point during the study. | NI | NI |

| 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. |

| 28844192 | Rivaroxaban and Aspirin 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 |
| 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 aspirin-use in text. Only information on other cardiac preventive treatments (antihypertensives, statins) at some point during the study. | NI | NI |

| 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. |
| Study ID | Treatment | Patient Population | End Point | Protocol Details | Comparator | Follow-up | Adverse Events |
|----------|-----------|---------------------|-----------|-----------------|------------|-----------|----------------|
| 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, β-blockers | At 3 months | No information on diuretics, aldosterone receptor inhibitors, antiplatelet s, statins |
| 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, antiplatelet s, statins) |
| Study ID | Intervention | Patient Population | Composite Endpoints | Relevant Concomitant Medications | At the End of Follow-up | Notes |
|----------|--------------|---------------------|---------------------|----------------------------------|------------------------|-------|
| 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 cardiovascul ar 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 | - | |
| 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)” | | | No information on other cardiac preventive treatments (antihypertensives, antiplatelet s, statins) |
| Study ID   | Intervention                          | Population Description                                                                 | Outcomes                                                                 | Timepoint                  | N  |
|------------|---------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------|----|
| 27633186   | Semaglutide vs Placebo                 | Patients with type 2 diabetes                                                          | Composite of CV death, nonfatal MI, nonfatal stroke                      | At the end of follow-up   | 25 |
|            |                                       |                                                                                        | “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 |                            |                |
| 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                           | At 1-year, 2-year and at the end of follow-up | 25 |
|            |                                       |                                                                                        | “All patients will be treated to regional standards of care for cardiovascular risk factors (eg, blood pressure, lipids) and HbA1c. Investigator 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 |                            |                |
| Study ID  | Treatment Group  | Eligibility Criteria | Outcomes Measure | Randomization | Blinding | Other Relevant Information |
|----------|------------------|----------------------|------------------|---------------|---------|-----------------------------|
| 28514624 | Evacetrapib vs Placebo | Patients at high CV risk | Composite of CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina | Random allocation to medication type | NI | No information on other cardiac preventive treatments (antihypertensives, antiplatelet agents) |
| 28304224 | Evolocumab vs Placebo | Patients with CV disease | Composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization | Controlled trial design | NI | Only information about statins and ezetimibe during follow-up |

"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."

"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 baseline."

"Only information about statins and ezetimibe is provided during follow-up."

| Number | 26 |
|--------|----|
| NCT Number | Intervention | Study Population | Primary Endpoint | Comparator | Postbaseline Information |
|------------|--------------|------------------|------------------|------------|--------------------------|
| 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/ARB, renin inhibitors, diuretics, β-blockers, calcium channel inhibitors, anticoagulants, antidiabetics |
| 25176015   | Angiotensin- nepriysin 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 β-blocker (i.e., maximally tolerated dose) at a stable dose for at least 4 weeks. | NI | No information on diuretics, aldosterone receptor inhibitors, antiplatelet agents, statins |
| 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. |
|---|---|
| Patients with CV disease and type 2 diabetes or metabolic syndrome | Patients with CV death, MI, or stroke |
| Methotrexate vs Placebo | Composite of CV death, MI, or stroke |
| Ixabtaglumab, with stable nonfatal coronary artery disease | Composite of CV death, MI, or stroke |
| Patients selected for the study | No information on other cardiac preventive treatments (antihypertensives, antithrombotics, statins) |
| No information on other cardiac preventive treatments | No information on other cardiac preventive treatments |

Patients selected for the study should receive the treatments appropriate for their condition. Diverters should be made to keep the dose levels 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.
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."

| Study ID   | Treatment Comparison                                      | Endpoint Description                                                                 | Information Provided                                      | Follow-up Duration | Notes |
|------------|-----------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------|-------|
| 26954408   | Naltrexone-bupropion group vs Placebo                     | Overweight and obese patients with high CV risk                                     | 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. | During follow-up   | No information on potential differences between groups in text |
| 23473338   | Darbepoetin alfa vs Placebo                               | Patients with systolic heart failure and anemia                                    | "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, aldosterone |
| Study ID | Treatment Group | Patient Group | Endpoint | Protocol Details | Comparator | Results |
|----------|-----------------|---------------|----------|-----------------|------------|---------|
| 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)* |
| 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 |
| 25399658 | 12 or 30 months of dual | Patients who had undergone PCI | Composite of stent thrombosis and antiplatelet | “All anticoagulant and antiplatelet | NI | NI |

- Receptor inhibitors, antiplatelet(s), statins
| Study ID | Treatment | Patient Selection | Endpoints | Cox Proportional Hazards Model | Other Cardiac Preventive Treatments |
|----------|-----------|------------------|-----------|-------------------------------|-----------------------------------|
| 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 | No information on other cardiac preventive treatments (antihypertensives, antiplatelet agents, statins) |
| 25173516 | Darapladib vs Placebo | Patients with | Composite of | “It is recommend” | No difference | No information on other cardiac preventive treatments (antihypertensives, antiplatelet agents, statins) |
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"

| 22077192 | Rivaroxaban vs Placebo | Patients with recent ACS | Composite of CV death, MI or stroke | NI | NI | No information on other cardiac preventive treatments (antihypertensives, antiplatelet s, statins) | 31 |
managing clinician. It is advised that the appropriate guideline recommendations be followed for all other concomitant medication.

| Study ID | Treatment | Patient Group | Outcomes | 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 | Antiplatelets (aspirin, clopidogrel, ticlopidine, prasugrel), statins, b-blockers, ACEI/ARBs, diuretics, calcium channel blockers | At 3, 12, 24, 36 months | - | 31 |
| ID     | Drug Comparison                          | Study Population                                    | Outcome Measures                                                                 | Concomitant Medications Assessment | Follow-up | Other Information                                                                 |
|--------|------------------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------|-----------|-----------------------------------------------------------------------------------|
| 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” | At 12, 24, 36 months | -                                                                                 |
| 25781440 | Thienopyridine vs Placebo               | Patients following treatment with bare-metal stents or drug-eluting stents | Composite of death, MI, stroke                                                    | NI                                | NI        | No information on other cardiac preventive treatments (antihypertensives, statins) |
| 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” | At 12, 24, 36 months | No information on antiplatelet s                                                   |
| Study ID | Treatment 1 | Treatment 2 | Comparator | Comparator Description | Outcome Event | Outcome Event Description | Notes |
|----------|-------------|-------------|------------|------------------------|---------------|----------------------------|-------|
| 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 | 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, β-blockers, ACEIs or ARBs, and treatments for diabetes, hypertension, and smoking” | NI | No information on other cardiac preventive treatments (antihypertensives, antiplatelet s) | 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 | No information on other cardiac preventive treatments (antihypertensives, statins) | 34.1 |
| ID     | Treatment 1                  | Treatment 2                  | Participants                                      | Outcomes                                                                 | Notes                                                                 | Duration of follow-up | Other Cardiac Preventive Treatments |
|--------|-------------------------------|-------------------------------|---------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------|------------------------|-------------------------------------|
| 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 | Adequate description of other preventive treatments in text             | Concomitant drugs not allowed: Lipid-lowering drugs (other than the investigation 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 | During follow-up | -                                   |
| 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 | NI                                                                       | NI                                                                   | NI                     | No information on other cardiac preventive treatments (antihypertensives, antiplatelet, statins) | 36                                 |
| 27043774 | Aliskiren vs Enalapril | Patients with HF and reduced ejection fraction | Composite of CV death or HF hospitalisation | NI | NI | No information on diuretics, antiplatelet s, statins | 36.6 |

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.
| Study ID   | Intervention                      | Population Description                      | Outcome Measures                                                                 | Intervention Medications                                                                 | Follow-Up Duration | P Value |
|-----------|-----------------------------------|---------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------|---------|
| 28910237  | Exenatide vs Placebo              | Patients with type 2 diabetes               | Composite outcome death from CV causes, nonfatal MI, or nonfatal stroke           | 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                     | Lipid lowering, antihypertensives, anticoagulants, antiplatelets, hypoglycemic medications | Postbaseline      | -       |
|           |                                   |                                             |                                                                                 |                                                                                          |                   | 38.4    |
| ID    | Study Design                                                                 | Eligibility Criteria                                                                 | Outcomes                                                                 | Medications                                                                 | Follow-Up Measures                                                                 |
|-------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 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 syndrome, 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                                                                                     |
| 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 |NI                                                                                     | No information on other cardiac preventive treatments (antiplatelets, statins, which antihypertensives per group) |
| Study ID   | Intervention                          | Patient Population                                                                 | End Point                                             | Allocation | Follow-Up | No Information on other cardiac preventive treatments (antihypertensives, diuretics, aldosterone receptor inhibitors, antiplatelet agents, statins) |
|------------|---------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------|------------|-----------|--------------------------------------------------------------------------------------------------|
| 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 | NI         | NI        | No information on other cardiac preventive treatments (antihypertensives, diuretics, aldosterone receptor inhibitors, antiplatelet agents, statins) |
| 22931357   | Aspirin and Clopidogrel vs Aspirin    | Patients with recent lacunar stroke                                                | Composite of recurrent stroke, ischemic stroke and intracranial hemorrhage | NI         | Statins   | At any time of follow-up (antihypertensives as part of 2x2 factorial) |
| 22551105   | Warfarin vs Aspirin                   | Patients with HF and reduced ejection fraction                                     | Composite of ischemic stroke, intracerebral hemorrhage, death from any cause | NI         | NI        | No information on diuretics, aldosterone receptor inhibitors, statins |
| Study ID | Intervention | Participants | Outcome Measures | N1 | N2 | Notes |
|----------|--------------|--------------|-----------------|----|----|-------|
| 28605608 | Canagliflozin vs Placebo | Patients with type 2 diabetes | Composite of CV death, nonfatal MI, or nonfatal stroke | NI | NI | No information on other cardiac preventive treatments (antihypertensives, antiplatelets, statins) |
| 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 | 44.2 |

4.4.3 Management of Vascular Risk Factors

All patients will receive optimal treatment for hypertension, diabetes mellitus and hypercholesterolemia (See Procedure Manual).
| Trial ID     | Treatment                        | Eligibility Criteria                                                                 | Outcomes                          | Follow-up | Notes                                                                 |
|-------------|----------------------------------|--------------------------------------------------------------------------------------|-----------------------------------|-----------|-----------------------------------------------------------------------|
| 28845751    | Canakinum ab 50 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 | NI        | No information on other cardiac preventive treatments (antihypertensives, antiplatelet agents, statins) |
| 24678955    | Darapladib vs Placebo            | Patients with stable coronary heart disease                                           | Composite of CV death, MI, or stroke | Following informatio in the text “LDL levels and BP were balanced at the end of the study” | No information on antiplatelet agents |
| 27295427    | Liraglutide vs Placebo           | Patients with type 2                                                                 | Composite of CV death,             | End of follow-up | Lipid lowering, antihypert |

Note: LDL = Low Density Lipoprotein, MI = Myocardial Infarction, CV = Cardiovascular
| Study ID   | Intervention                          | Patient Population                                      | Primary Outcome                                                                 | Concomitant Drugs Required | Concomitant Drug Recording | Follow-up          |
|-----------|---------------------------------------|---------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------|----------------------------|--------------------|
| 25014686  | Niacin vs Placebo                     | Patients with CV disease                                | Composite of nonfatal MI, death from coronary causes, stroke or arterial revascularisation | 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 | Concomitant medications will be recorded at every visit, if any changes... | Until the end of follow-up |
| 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 revascularisation) | 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, β-blocker, α- | 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, β-blocker, α- | Until the end of follow-up |
| Study ID  | Treatment          | Intervention                                                                 | Primary Outcome                                                                 | Comparator 1 | Comparator 2 | OtherNotes                                                                 |
|----------|--------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------|--------------|---------------------------------------------------------------------------|
| 21388310 | Irbesartan vs Placebo | Patients with atrial fibrillation at risk for stroke | Composite of stroke, MI, or death from vascular causes | NI           | NI           | No information on other cardiac preventive treatments (statins) and anticoagulation in patients with atrial fibrillation |
| 28847206 | Anacetrapib vs Placebo | Patients with CV disease and low HDL | Composite of first major coronary event, a coronary death, MI, or coronary revascularization | NI           | NI           | No information on other cardiac preventive treatments (antihypertensives, antiplatelet s, statins) |
| Study Code | Treatment | Patients | Primary Endpoint | Prescribing Guide | Information About Other Treatments | During Follow-up | Other Information |
|------------|-----------|----------|------------------|-------------------|--------------------------------------|------------------|------------------|
| 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” | | | |
| 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 antihypertensive medications other than the study drugs… If blood pressure is not properly controlled, other antihypertensive medications can be” | NI | | No information on other cardiac preventive treatments (antiplatelets, statins) | 50.4
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..

| Study ID   | Intervention                          | Comparator                        | Endpoint Description                                                                 | NI | NI | NI | Other Cardiac Preventive Treatments |
|-----------|---------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------|----|----|----|-------------------------------------|
| 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, antiplatelet s, statins) |
| 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, antiplatelet s, statins) |
| 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 coronary heart disease | NI | NI | NI | No information on other cardiac preventive treatments (antihypertensives, antiplatelet s) and hypoglycemia |
| Study ID       | Treatment Group | Participants                                      | Outcome Measures                                                                 | Medications Provided                                                                                     | Follow-up Duration |
|---------------|-----------------|---------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-------------------|
| 26886418      | Pioglitazone vs Placebo | Patients with recent ischemic stroke or TIA | Composite of fatal or non-fatal stroke, MI, 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 until end of follow-up |
| 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, antiplatelet(s)) | 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 (antihypertensives, antiplatelet(s))         | 60.0 |
| Study ID | Intervention | Patients | Composite End Point | Concomitant Treatments | Duration |
|----------|--------------|----------|---------------------|------------------------|----------|
| 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) | ACEI/ARBs, statins, antiplatelets | 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 | NI | NI |
| 23121374 | Cinacalcet vs Placebo | Patients with chronic | Composite of death, MI, hospitalisation | "Concomitant therapy will be collected" | During follow-up |

Note: "NI" indicates no information on other cardiac preventive treatments (antihypertensives, statins).
| Kidney Disease | 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 |
|---|---|---|---|---|---|---|---|
| 26323937 | 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 informatio 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) |
| 27041480 | | | | | | |
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 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. | NI | NI | No information on other cardiac preventive treatments (antiplatelets) | 67.2 |
| Study ID | Treatment | Study Design | Outcome Measure | Follow-up | Concurrent Treatments | No information on other cardiac preventive treatments (antiplatelets) |
|----------|-----------|--------------|-----------------|-----------|-----------------------|--------------------------------------------------------------|
| 27040132 | Rosuvastatin vs Placebo | Patients with intermediate CV risk | Composite of CV death, nonfatal MI, or nonfatal stroke | 0, 24, end of FU | 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 and thiazide diuretics should be used. | 67.2 |
| Study ID   | Interventions | Study Design | Comparator | Concomitant Medications | CV Composite Events | Notes |
|-----------|---------------|--------------|------------|-------------------------|---------------------|-------|
| 2603952   | Simvastatin + Ezetimibe vs Simvastatin + 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 |
| 22686415  | N-3 fatty acids vs Placebo | Patients at risk for CV 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 |
| 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 indicated for the participant's welfare” | Lipid lowering, antihypertensives (Thiazid, ACEI/ARBs, b-blocker, other), antiplatelet | At the end of follow-up | - |

and thiazide diuretics should be used.."
| Study ID | Intervention | Participants | Endpoints | Criteria |
|----------|--------------|--------------|-----------|----------|
| 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" |
| 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" |
| 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" |

Other treatments 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: No informatio n on other cardiac preventive treatments (antihypertensives, statins, other antidiabetics, Statins, ACEI/ARBs, hypoglycemic medications, β-blockers, calcium channel blockers, diuretics (antiplatelets part of 2x2 factorial)
| Study ID | Intervention | Population | Primary Endpoints | Comparator | Endpoint Definition | Trial Specifics |
|---------|--------------|------------|-------------------|------------|-------------------|----------------|
| 2311777 5 | Multivitamin vs Placebo | Male physicians; subgroup with CV disease | Composite of MACE, including nonfatal MI, nonfatal stroke, and CVD mortality. | NI | 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 assignment, and any risk factors that are unbalanced”. | No information on other cardiac preventive treatments (antihypertensives, antiplatelet, statins) |
| 2704308 2 | Losmapimod vs Placebo | Patients with ACS | Composite of CV death, MI, or severe recurrent ischemia requiring urgent coronary revascularization | NI | “Investigator’s 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 | No information on procedural characteristics |

Long term follow-up (>1 month) with index procedure after randomization.
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”

| NCT Number | Study Design | Intervention | Outcomes | Procedure Characteristics | Procedural & At Discharge | Type of Stent | Notes |
|------------|--------------|--------------|----------|---------------------------|---------------------------|---------------|-------|
| 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 |
| 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 intervention s were recommend ed to be performed according to the current standard guidelines, and final procedure strategy was left entirely at the operators’ | Informati on about procedural characteri stics | Periprocedural | Access site per group is missing. Periproced ural medication s missing; Informati on o other cardiac preventive treatments (antihypert ensives, statins) at end of | 5, 9 |
| Study ID | Treatment Comparison | Participants | Primary Endpoint | Procedure Details | Discharge Details | Study Details |
|----------|----------------------|--------------|------------------|-------------------|------------------|---------------|
| 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 | No information on other cardiac preventive treatments (antihypertensives, antiplatelet s, statins) |
| 2954469 | 6 vs 12 months 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 predilution and antithrombotic medications during the procedure, and use of glycoprotein IIb/IIIa inhibitors will be up to operators discretion. The length and diameter of the stent will not be restricted” (from published study design) | Informatio n about procedural characteristics & medications: heparin, GpIIb/IIIa inhibitors and discharge medications: aspirin, clopidogrel, b-blockers, statins, ACEI/ARBs. | No information on other cardiac preventive treatments (antihypertensives, statins) at the end of follow-up; no information for balloon dilatation |
| 30166073 | Aspirin and Ticagrelor 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 discretion). Direct stenting and implant of multiple E-ZES were allowed” (from published study design) | Informatio n about procedural characteristics | No information on other cardiac preventive treatments (antihypertensives, antiplatelet s, statins) |
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 hospitalization, rehospitalization for HF, or "Associated treatments (antiplatelet 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, antiplatelet s, statins) at end of follow-up; Type of |
| Short term follow-up (<1 month) with index procedure after randomization | Procedural characteristics and periprocedural medications (P2Y12 inhibitors use, bivalirudin, heparin, fondaparinux, aspirin) | Periprocedural & at discharge |  |
|---|---|---|---|
| Cangrelor vs Clopidogrel | 2347369 | 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 | 0.2 |
| Study ID | Treatment                        | Patients Description                              | Outcome Measures                              | Procedural Characteristics | Periprocedural & Discharge | Type of Stent Not Reported |
|---------|----------------------------------|--------------------------------------------------|-----------------------------------------------|----------------------------|---------------------------|---------------------------|
| 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/IIIa inhibitors, β-blockers, statins, ACEI/ARBs | Periprocedural & at discharge | Type of stent not reported, balloon-dilatation not reported |
| 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) | ACEI/ARBs, aspirin, clopidogrel, statin at discharge and procedural characteristics and periprocedural medications (Aspirin, P2Y12-inhibitor loading dose, GpIIb/IIIa) | Periprocedural & at discharge | - | 1 |
| ID     | Treatment 1  | Treatment 2  | Outcome Measure                                      | Protocol Description                                                                                                                                                                                                                                                                                                                                 | Duration | N |
|--------|--------------|--------------|------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---|
| 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-adrenergic agonist & procedural characteristics (antiplatelets as part of factorial 2x2) | During the first 3 days | - |
| Study ID   | Treatment                        | Eligibility                      | Outcomes                                      | Main Findings                                                                 | Data Types | Interpretation                                                                 |
|-----------|----------------------------------|----------------------------------|-----------------------------------------------|------------------------------------------------------------------------------|------------|-------------------------------------------------------------------------------|
| 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 antiplatelet s, or procedural characteristics               |
| 2311776   | 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            | Periop procedures | No information on antiplatelet s                                               |
| 25775052  | Bivalirudin vs Heparin            | Patients undergoing              | Composite of MACE                              | “Anticoagulant agent” ACEI/ARB, aspirin, Periop procedures &                  | -          | 1                                                                             |
| 22077909 | Abciximab plus Heparin vs Bivalirudin | Patients with NSTEMI undergoing PCI | Composite outcomes: death, large recurrent MI, urgent target-vessel 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. β-blockers, | Procedural characteristics and periprocedural medications (GpIIb/IIIa inhibitors, bivalirudin, heparin, randomization after aspirin & P2Y12 was given) | Periprocedural | - | 1 |
| Study ID   | Intervention                        | Study Design | Outcomes                                                                 | Medications                                                                                     | Procedure Characteristics                                    | Results |
|-----------|------------------------------------|--------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|---------|
| 2185648 3 | 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/ARB S periprocedural and postprocedural characteristics | No info |
| 2245280 7 | Glucose-insulin-potassium vs Placebo| Patients with suspected ACS | MI                                                                      | NI (published study design)                                                                   | NI                                                                              | -       |
| 2417149 0 | 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 anticoagulation 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/ARB S at discharge and procedural characteristics and periprocedural medications (aspirin, P2Y12-inhibitor loading dose, heparin, bivalirubin, enoxaparin, GpIIb/IIIa inhibitors) | -       |
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"

| Study ID  | Intervention | Participant Details | Outcomes | Procedural Characteristics | Periprocedural Medications at Discharge | Type of Stent Missing |
|-----------|--------------|---------------------|----------|---------------------------|----------------------------------------|-----------------------|
| 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/IIIa inhibitors, b-blockers, statins, ACEI/ARBs, diuretics, antidiabetics) | 1 |
| 29525821  | Atorvastatin vs Placebo | Patients with ACS undergoing PCI | “Co-intervention: 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 & at discharge | 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. 

| Trial ID  | Study Description                  | Study Population                                                                 | Potential concomitant antiplatelet Therapy, antithrombotic drugs | Periprocedural Characteristics |
|-----------|------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------|--------------------------------|
| 26095867  | Low Molecular Weight Heparin vs Placebo | Patients with atrial fibrillation undergoing surgery                             | Aspirin, clopidogrel, NSAIDs, Cox-2, heparin, warfarin & procedural characteristics | -                              |
| 23991622  | Prasugrel vs Placebo               | Patients with NSTEMI undergoing PCI                                               | Procedural characteristics: Stent type is missing                | -                              |
| Study ID  | Intervention 1  | Intervention 2  | Outcome 1  | Outcome 2  |
|-----------|-----------------|-----------------|------------|------------|
| 26933848  | Aspirin vs Placebo | Patients undergoi ng 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 | Periprocessual & up to 7 days | 1 |
| 27774838  | Tranexamic acid vs Placebo | Patients undergoi ng 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, amiodarone | Periprocessual & 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”

| Code     | Treatment                                | Patients undergoing cardiac surgery | Composite of all-cause mortality, nonfatal stroke, or need for mechanical support for severe left ventricular dysfunctio n | “Standard local procedures for CABG surgery or associated preoperative and postoperative care were followed” (no protocol) | ACEI/ARB s, β-blockers, statins, clopidogrel, calcium channel blockers, nitrate, hypoglycemic medicatio ns | Periprocedural & at discharg e | No information on procedural characteristics | 1 |
|----------|------------------------------------------|-------------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-----------------------------|---------------------------------------------|---|
| 22782417 | Acadesine vs Placebo                     | Patients undergoing cardiac surgery | Composite of all-cause mortality, nonfatal stroke, or need for mechanical support for severe left ventricular dysfunctio n | “Standard local procedures for CABG surgery or associated preoperative and postoperative care were followed” (no protocol) | ACEI/ARB s, β-blockers, statins, clopidogrel, calcium channel blockers, nitrate, hypoglycemic medicatio ns | Periprocedural & at discharg e | 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 medicatio ns (inotropes, antifibrinolytic, non-study steroids, ACEI/ARB s, β-blockers, antiplatelets, statins, vitamin K antagonist s, PPIs, hypoglycemic medicatio ns | Periprocedural | - | 1 |
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-density 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 inhibitors, 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**<sup>*</sup> *(ref: Inadequate blinding)* |                      |          |          |                        |          |          |
| Adequate blinding                | 1.04                 | 0.47 to  | 0.93     | 0.99                   | 0.41 to  | 0.99     |
|                                  |                      | 2.27     |          |                        | 2.38     |          |
| **Risk of bias due to deviations of intended interventions**<sup>†</sup> *(ref: “At risk of bias”<sup>‡</sup>)* |                      |          |          |                        |          |          |
| “At low risk of bias”            | 1.47                 | 0.67 to  | 0.33     | 1.38                   | 0.52 to  | 0.52     |
|                                  |                      | 3.21     |          |                        | 3.69     |          |
| **Funding**                      |                      |          |          |                        |          |          |
| *(ref: Industry)*                |                      |          |          |                        |          |          |
| Non-Industry                     | 2.06                 | 0.86 to  | 0.10     | 2.24                   | 0.80 to  | 0.12     |
|                                  |                      | 4.92     |          |                        | 6.25     |          |
| **Trial design**                 |                      |          |          |                        |          |          |
| *(ref: Non-inferiority)*         |                      |          |          |                        |          |          |
| Superiority                      | 0.63                 | 0.26 to  | 0.32     | 0.38                   | 0.13 to  | 0.08     |
|                                  |                      | 1.55     |          |                        | 1.13     |          |
| **Follow-up**                    |                      |          |          |                        |          |          |
| *(ref: >1 month)*                |                      |          |          |                        |          |          |
| <1 month                         | 4.33                 | 1.63 to  | 0.003    | 3.63                   | 1.21 to  | 0.02     |
|                                  |                      | 11.52    |          |                        | 10.91    |          |

*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).

Records identified through database searching
Total: 1335 (Medline) & 812 (Embase)

Additional records identified through hand search
(n = 3)

Records after duplicates removed
(n = 1625)

Records excluded based on title and abstract
(n = 1476)

Records screened
(n = 1625)

Full-text articles assessed for eligibility
(n = 149)

Full-text articles excluded, with reasons
(n = 26)
- Not RCTs n = 12
- Other outcomes n = 13
Other comparisons n = 1

Studies included in qualitative synthesis
(n = 123)