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ASSESSMENT OF METHODOLOGICAL QUALITY IN RANDOMIZED CARDIOVASCULAR CLINICAL TRIALS

Doctoral (PhD) Dissertation Odgerel Baasan M.D.

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Abbreviations

ACC	American college of cardiology
AHA	American heart association
CENTRAL	Cochrane central register of controlled trials
CONSORT	Consolidated standard of reporting trials
CVD	Cardiovascular disease
DM	Diabetes mellitus
DMC	Data monitoring committee
ESC	European society of cardiology
EBM	Evidence based medicine
FDA	Food and drug administration
ICD	International classification of diseases
MI	Myocardial infarction
RCT	Randomized controlled trial
RoB	Risk of bias
RG	Reporting guideline
SPIRIT	Standard protocol items: Recommendation for interventional trials
TR	Trial registration
WHO	World health organization
WHF	World Heart Federation

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1. Introduction

As in all clinical fields, clinical trials are essential in cardiology in order to provide the information needed to answer questions that arise in clinical practice. However, inappropriate design and conduct of clinical trials will result in distorted information that will affect medical decision-making and, in extreme cases, may lead to patients not receiving the most appropriate treatment.

In this chapter I provide a general background to the thesis and present the main context of the chosen topic. This includes an overview of cardiovascular disease epidemiology, an introduction to evidence-based research in cardiovascular medicine and a brief overview of the problem of design, conduct and reporting of clinical trials.

1.1 Cardiovascular disease epidemiology and risk factors

Cardiovascular disease (CVD) is the leading cause of death globally, taking an estimated 17.9 million lives each year. CVD is covering a range of disorders such as coronary heart disease (angina, myocardial infarction (MI), and heart failure), rheumatic heart disease, peripheral arterial disease, and other conditions. More than four out of five CVD deaths are due to heart attacks and strokes, and one third of these deaths occur prematurely in people under 70 years of age [1].

CVD is complex, though there is variety of traditional and non-traditional risk factors. Traditional factors include obesity, hyperlipidemia, arterial hypertension, diabetes mellitus (DM), physical inactivity, depression, family history, older age, and male sex, while emerging non-traditional factors include oxidative stress, endothelial dysfunction, insulin resistance, anemia, proteinuria, and arterial stiffening [2].

Cardiovascular disease prevention and management

There are three types of prevention mechanisms to prevent and reduce the impacts of a disease. Primary prevention refers to the steps taken by an individual to prevent the onset of the disease. This is achieved by maintaining a healthy lifestyle choice such as diet and exercise. Secondary prevention focuses on reducing the impact of the disease by early diagnosis prior to any critical and permanent damage. This facilitates avoiding life threatening situations and long- term impairments from a disease. Tertiary prevention is used once long-term effects set in, by helping the patients to manage pain, increase life expectancy, and increase the quality of life [3].

Cardiovascular disease management includes pharmacotherapies, electrophysiological treatment such as cardiac ablation, cardiac resynchronization therapy, and left atrial appendage closure, implantable cardioverter defibrillator and pacemaker implantation, surgical options such as coronary angioplasty, coronary artery bypass grafting and valve disease surgery.

1.2 Randomized clinical trials in cardiovascular medicine

Evidence-based medicine (EBM) in cardiology refers to the application of the best available research to clinical care, which requires the integration of scientific evidence with clinical expertise and patient values. The best available research highlights the accuracy and precision of diagnostic tests, predicts the importance of prognostic markers, and enables the efficacy and safety of therapeutic, rehabilitative, or preventive healthcare strategies. The main goal of EBM is to provide the best available treatment to the patient and integrating scientific evidence with patient's preferences, concerns, and expectations [4]. As cardiovascular medicine has moved toward evidence-based decision making, the number of randomized clinical trials (RCTs) has increased. RCT is regarded as the gold standard trial for evaluating the effectiveness of interventions (Figure1.) and the cornerstone for therapeutic decision making strategies [5].

The European Society of Cardiology (ESC), American Heart Association (AHA), World Heart Federation (WHF), and American College of Cardiology (ACC) are committed to ensuring that high quality trials continue to provide the best clinical practice guideline that improves the clinical care of all patients across different race and gender identities, socioeconomic strata, and geographies [6].

RCTs are widely recognized as the most optimal methodology for causal inference, where humans are prospectively included and randomly allocated to groups to evaluate the efficacy and safety of an intervention [7]. In the last three decades, the cardiovascular RCT has emerged as the principal method by which new therapies are evaluated [8]. RCTs have been widely used to provide reliable knowledge on the best treatment strategies, such as therapies which are able to improve patient's symptoms, correct disease markers, and improve clinical outcomes [9,10].Evidence generated from RCTs has greatly influenced the diagnosis and treatment of many heart diseases

including arterial hypertension, arrhythmias, acute myocardial infarction, heart failure, and coronary revascularization [11-13]. As RCTs constitute the foundational background of modern medical practice, the increasing prevalence of cardiovascular disease around

the world requires high quality of clinical research and translation of its findings into new therapeutic and diagnostic strategies [14]. Unfortunately, although there was a significant increase in the quantity of scientific literature concerning cardiovascular disease published in recent years, it was indicated that this has not resulted in guideline recommendations with more certainty and supporting evidence. The American College of Cardiology and the American Heart Association (ACC/AHA) clinical practice guidelines are still based on a lower quality of evidence and expert opinions, indicating the lack of high-quality studies with relevant data [15]. Also the RoB has not been assessed in these studies. Several tools exist that support researchers to plan and conduct high-quality research and make trial results completely and transparently available. Guidelines for clinical trial protocols (e.g., SPIRIT) facilitate trial planning in all important details. Reporting guidelines (e.g., CONSORT for RCTs) have the aim of decreasing the risk of non-reporting bias, i.e., facilitating that clinical trial methods are described as they were conducted, and trial results are fully published [16]. Mandatory RCT registration by the International Committee of Medical Journal Editors (ICMJE) has been put forward [17], with detailed registration before commencing the RCTs enabling more transparent and complete reporting and the European Medicines Agency and WHO also support clinical trial registration [18,19]. In the field of cardiology, insufficient registration tendencies were reported [11]. Cardiac and cardiovascular system journals infrequently require, recommend, and enforce the use of obligatory clinical trial registration [20]. Methodological flaws in the design, conduct, analysis, and reporting of RCTs can cause the true intervention effect to be underestimated or overestimated. This is why these systemic errors (defined as the RoB) are assessed when systematic reviews are conducted, or evidence-based guidelines are developed [21]. Concerns arising due to the high RoB in trials included in evidence syntheses lead to the downgrading of evidence level and consequently will decrease our certainty in the pooled results.The strength of the RCTs comes from the randomization procedure, which ensures that all participants have the same chance of being assigned to each of the study groups and guarantees that the characteristics of the participant are similar through the different groups at the baseline [22].

However, the extent to which we can draw final conclusions based on RCTs strongly depends on how rigorous study methodology is; methodological inaccuracies during trial planning and conduct will subsequently reduce the reliability of results and their usability in medical practice. Biased results can finally lead to the underestimation or overestimation of the true intervention effect [23].

The RoB reflects the degree to which the results of a trial should be believed [24,25]. To reduce the possibility of RoB in RCT's, the Cochrane Collaboration introduced a tool designed to appraise RoB [26,27], involving six domains related to the internal validity of a trial: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other" potential threats to validity [24,26]. The RoB assessment enables the assessment of flaws in the trial design, conduct, and analysis that may affect study results [28].

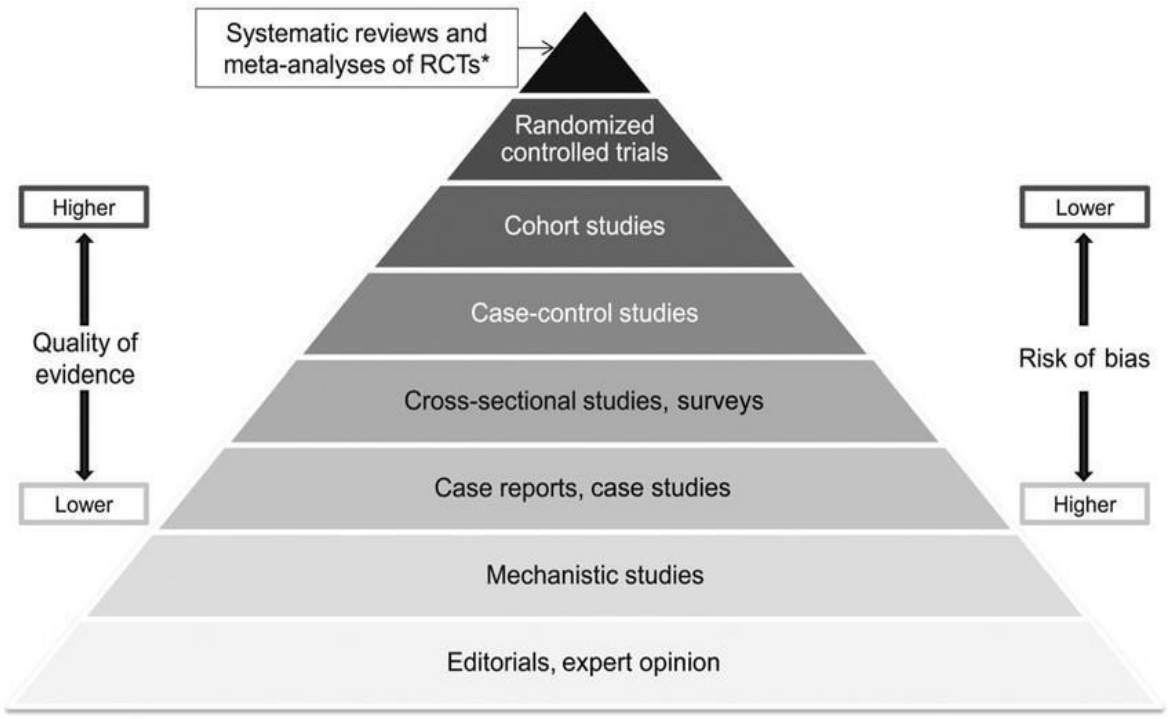

FIGURE 1. Hierarchy of evidence pyramid

Source: (Yetley, Elizabeth & MacFarlane, Amanda & Greene-Finestone, Linda & Garza (2016). Options for basing Dietary Reference Intakes (DRIs) on chronic disease endpoints: report from a joint US-/Canadian-sponsored working group. American Journal of Clinical Nutrition. 105. 10.3945/ajcn.116.139097.)

1.3 Risk of bias in randomized clinical trial

The reliability of results of the cardiovascular RCTs depends on the extent to which potential sources of bias have been avoided. In epidemiology "bias" represents a systematic error [29]. The bias translates in a deviation from the truth, which will consequently be incorporated in the results of a study. One of the main characteristics of bias is that it can lead to underestimation or overestimation of the true intervention effect [30]. Cochrane's risk of bias (RoB) tool contains six (Figure 2.) domain (including seven items): selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting) and other sources of bias [23].

Selection bias

Selection bias refers to systematic differences between baseline characteristics of the groups that are compared. Successful randomization prevents selection bias in allocating interventions to participants. A rule for allocating interventions to participants must be specified, based on some chance (random) process, which is called sequence generation. One suitable method for assigning interventions would be to use a simple random sequence, and to conceal the upcoming allocations from those involved in enrolment into the trial.

Performance bias

Performance bias refers to systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest. After enrolment into the study, blinding (or masking) of study participants and personnel may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcomes. Effective blinding can also ensure that the compared groups receive a similar amount of attention, treatment, and diagnostic investigations.

Detection bias

Detection bias refers to systematic differences between groups in how outcomes are determined. Blinding (or masking) of outcome assessors may reduce the risk that

knowledge of which intervention was received, rather than the intervention itself, affects outcome measurement.

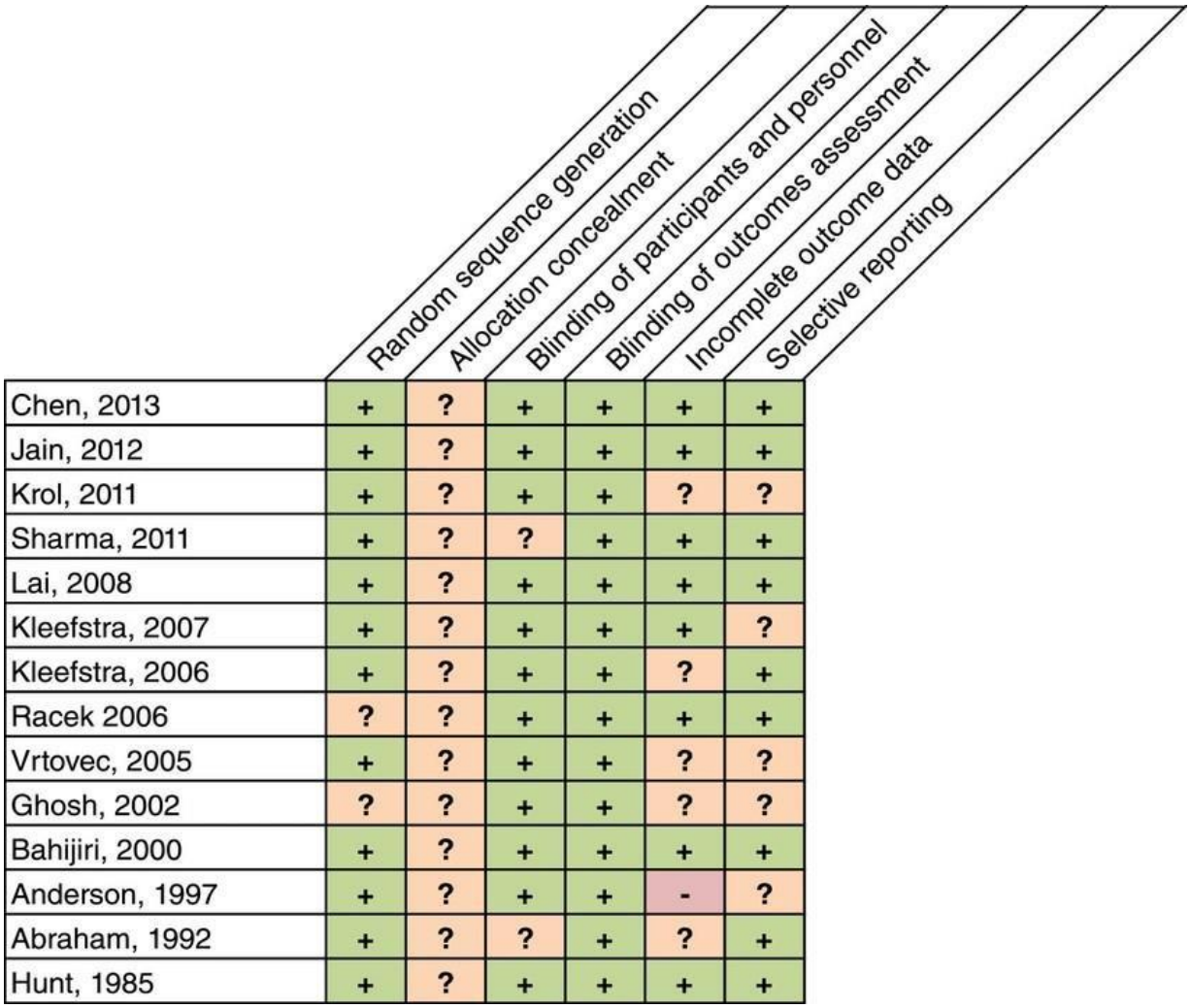

FIGURE 2. Cochrane risk of bias assessment tool.

Six domains are evaluated, random sequence generation, allocation concealment, blinding of participants and personnel, blind of outcomes assessment, incomplete outcome data and selective reporting. – , ? and + represents either a high, unknown or low risk of bias, respectively.

Source: (Yin, Raynold & Phung, Olivia. (2015). Effect of chromium supplementation on glycated hemoglobin and fasting plasma glucose in patients with diabetes mellitus. Nutrition Journal. 14. 10.1186/1475-2891-14-14.)

Attrition bias

Attrition bias refers to systematic differences between groups in withdrawals from a study.Withdrawals from the study lead to incomplete outcome data. Attrition refers to situations in which outcome data are not available.

Reporting bias

Reporting bias refers to systematic differences between reported and unreported findings. Within a published report those analyses with statistically significant differences between interventions groups are more likely to be reported than non-significant differences. This sort of bias is usually known as outcome reporting bias or selective reporting bias [24].

Other biases

In addition, there are other sources of bias that are relevant only in certain circumstances. These relate mainly to particular trial designs (e.g. recruitment bias in cluster-randomized trials or bias due to the lack of an adequate washout period in RCTs with a cross-over design); and there may be sources of bias that are only found in a particular clinical setting.

1.4 Reporting and trial registration for randomized clinical trials

Although the quality and completeness of reporting has been improving in the recent years, many studies have shown the lower quality of reporting across various topics and study types. Poor reporting also limits the RoB assessment validity, making poorly reported items to be generally evaluated at "unclear RoB" in the assessment. With insufficient reporting, studies are also less likely to be properly considered for inclusion in synthesis of the results for prospective clinical guidelines to properly inform clinicians or health policy makers [31].

To address the issue of poor reporting, the research community has developed organized guidance for scientific writing such as Consolidated Standards of Reporting Trials (CONSORT) Statement reporting guidelines [32]. Checklists with preferred information to be reported about a clinical trial are available, facilitating the work of the authors as well as that of journal editors and readers. Randomized trial registration improves identification of gaps in clinical trials research and leads to improvements in

the quality of clinical trials by making it possible to detect potential problems early in the research process [33].

1.5 Role of randomized controlled trial in the prevention, diagnosis and treatment of cardiovascular disease

Randomized controlled trials (RCTs) are the main source for evidence on the efficacy and safety of clinical interventions, and systematic reviews and clinical guidelines synthesize their results. Clinical trials have contributed largely to the development of treatment strategies for cardiovascular disease [34].However, many RCTs have methodological faults, and results are often biased [35]. Unbiased randomisation is the key methodological basis of randomised controlled trials. Across RCTs, there are main problems are with randomization, allocation concealment, and blinding [36].

Recently, it was indicated that almost one third of RCTs had at least one domain at high risk which shows avoidable waste of research is related to inadequate methods [37]. The most common key quality factors were allocation concealment and blinding for RCTs in several medical fields [38]. Studies show a decrease in poor reporting and inadequate methods over time for RCTs [39], however evidence on trends of RCT characteristics and methodological quality in cardiovascular medicine over time is currently lacking.

Increasing cardiovascular disease morbidity and mortality worldwidely requires only well designed and efficient randomised trials to distinguish between worthwhile, useless, and harmful interventions. We must support the conduct of high methodological quality trials in cardiovascular medicine by ensuring adequate support from both regulatory and academic institutions; by making randomised controlled trials more efficient by reducing waste.

2. Aims

We aimed to describe the reliability of cardiovascular diseases evidence using a representative sample of cardiovascular RCTs published in 2017 and 2012.

Specific objectives:

1. To examine the reliability of published cardiovascular clinical trials using RoB tool.
2. To define specific trial characteristics which increase the likelihood of unclear/high RoB.
3. To reveal any potential differences in methodological issues between cardiovascular RCTs funded by the industry or the academy.
4. To investigate tendencies over time to answer whether there was an improvement in measures of methodological quality and reporting in RCTS between 2012 and 2017.
5. To assess how well cardiovascular RCTs were able to estimate the true intervention effect in 2017 as compared to 2012.

3. Methods

3.1 Methodological Quality and Risk of Bias Assessment of Cardiovascular Disease Research: Analysis of Randomized Controlled Trials Published in 2017

3.1.1 Selection of studies

We used the Cochrane CENTRAL Register of Controlled Trials to search for RCTs published in 2017 using subject headings and keywords related to adults (aged ≥ 18 years) and CVDs (such as, atherosclerosis, arrhythmia, cardiomyopathy, heart failure, hypertension, ischemic heart disease, heart attack, angina, sudden death, cardiac arrest, hypercholesterolemia, high blood pressure, CVD, ejection fraction, echocardiography, pericarditis, coronary artery disease, angioplasty, and angiography(Table1). The search and the screening of identified studies for eligibility were conducted by the first author (OB). Our search yielded a total of 2,556 studies (Figure 3.).

Following deduplication, 2,419 studies underwent further analysis. Cochrane CENTRAL was the priority search source as it is the most comprehensive resource available of RCTs, containing publications from MEDLINE and EMBASE, as well as hand-search results, and gray literature [24,25]. Results of the search were randomly ordered in Excel, by the following method: after exporting the search result as an Excel file from Cochrane CENTRAL, we assigned a random number between 0 and 1 to each record using Excel's random number generator, then reordered them from the smallest to the highest number [40]. As a next step, we screened studies consecutively for eligibility, and the first 250 (10%) RCTs matching our prespecified inclusion criteria were selected (Table 2). Trials were eligible for inclusion if they were published in the year 2017, were written in English, the described results of an RCT in the field of cardiovascular medicine, and included participants aged ≥ 18 years. Decision on the inclusion of a study was made after a careful consideration of the methodology in the full text.

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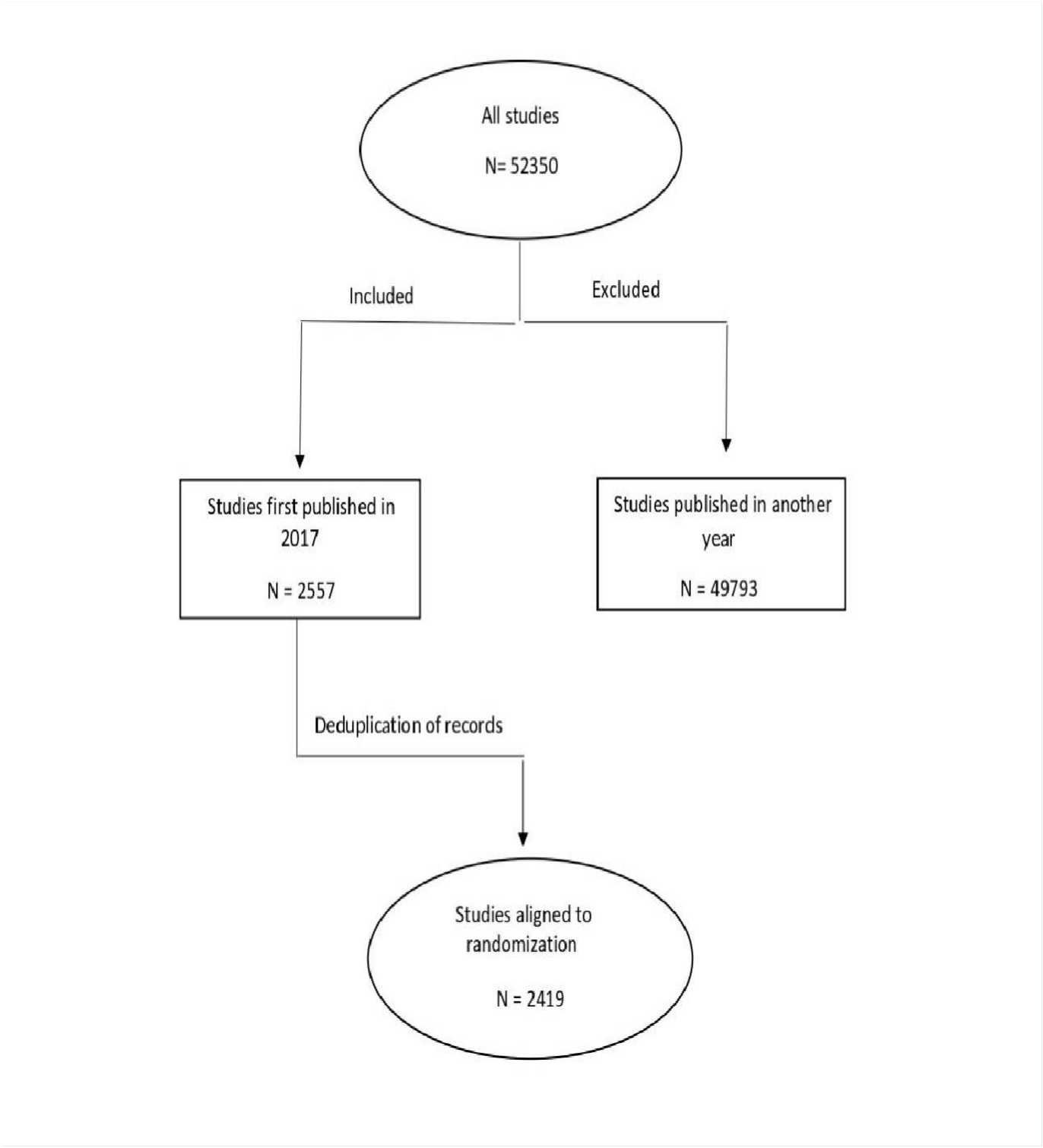

FIGURE 3. Flow diagram of the search

TABLE 1. Search strategy for Embase from January 2017 to December 2017

Number	Search Term	Results
#1	(atherosclerosis):ti in Trials	2108
#2	(arrhythmia):ti in Trials	681
#3	(cardiomyopathy):ti in Trials	1522
#4	(heart failure):ti in Trials	15450
#5	(hypertension):ti in Trials	21366
#6	(ischemic heart disease):ti in Trials	980
#7	(heart attack):ti in Trials	303
#8	(angina):ti in Trials	4861
#9	(sudden death):ti in Trials	319
#10	(cardiac arrest):ti in Trials	1459
#11	(hypercholesterolemia):ti in Trials	2352
#12	(High blood pressure):ti in Trials	983
#13	(cardiovascular disease):ti in Trials	3713
#14	(ejection fraction):ti in Trials	1776
#15	(echocardiography):ti in Trials	1151
#16	(angioplasty):ti	3216
#17	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 #10 or #12 or #13 or #14 or #15 with Publication Year from 2017 to 2017, in Trials	2557

TABLE 2. All included trials published in 2017 year (N=250).

№	First Author	Title	Journal
1.	Magnuson	Cost-Effectiveness of Long-Term Ticagrelor in Patients With Prior Myocardial Infarction Results From the PEGASUS-TIMI 54 Trial	J Am Coll Cardiol. 2017;70(5):527-538.doi: 0.1016/j.jacc.2017.05.063..
2.	St Pierre	The effect of an electronic cognitive aid on the management of ST-elevation myocardial infarction during caesarean section: a prospective randomized trial	*BMC Anesthesiol*. 2017;17(1):46.Published 2017 doi:10.1186/s12871-017-0340-4.
3.	Meischke	Simulation training to improve 9-1-1 dispatcher identification of cardiac arrest: A randomized controlled trial.	Resuscitation. 2017 ;119:21-26doi:10.1016/j.resusc itation.
4.	Priti	Ivabradine vs metoprolol in patients with acute inferior wall myocardial infarction- "Expanding arena for ivabradine	Cardiovasc Ther. 2017 ;35(4). doi: 0.1111/1755-5922.12266.
5.	Kuramitsu	Effect of sitagliptin on plaque changes in coronary artery following acute coronary syndrome in diabetic patients: the ESPECIAL-ACS study	Journal of Cardiology , Volume69, Issue 1,Pages 369-376, Japan , English
6.	Jayo- Montoya	Effects of different high intensity aerobic interval training programs with Mediterranean diet recommendations in post-myocardial infarct patients: preliminary results of INTERFARCT controlled trials	European journal of preventive cardiology
7.	Maldonado- Martin	Effects of Low-Dose Recombinant Human Brain Natriuretic Peptide on Anterior Myocardial Infarction Complicated by Cardiogenic Shock.	Braz J Cardiovasc Surg. 2017 ;32(2):96-103.doi: 10.21470/1678-9741-2016-0007
8.	Kopec	Improving Prediction of Postoperative Myocardial Infarction With High- Sensitivity Cardiac Troponin T and NT- proBNP	Anesth Analg. 2017 ;124(2):398-405.doi: 10.1213/ANE.0000000000001736.
9.	Scales	Prehospital cooling to improve successful targeted temperature management after cardiac arrest: A randomized controlled trial	Resuscitation. 2017 ;121:187-194.doi: 10.1016/j.resuscitati on.2017.10.002.
10.	OJHA	A RANDOMIZED ACTIVE CONTROLLED CLINICAL STUDY TO EVALUATE EFFICACY AND SAFETY OF RESVERATROL AS AN ADJUVANT THERAPY IN PATIENTS WITH HYPERTENSION	Asian journal of Pharmaceutical and Clinical research, 2017;10;1.
11.	Omar	Ratio of Systolic Blood Pressure to Right Atrial Pressure, a Novel Marker to Predict Morbidity and Mortality in Acute Systolic Heart Failure.	1068. doi: 10.1016/j.amjcard.2 016.11.062.
12.	Mazereeuw	Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients.	Brain Behav Immun. 2017 ;60:136-141.doi: 10.1016/j.bbi.2016.10.005. Epub 2016.
13.	Han	Treatment of Pulmonary Arterial Hypertension Using Initial Combination Therapy of Bosentan and Iloprost,	Respir Care. 2017;62(4):489-496.doi: 10.4187/respcare.05, 280.
14.	Kim	Haemodynamic effects of riociguat in inoperable/recurrent chronic thromboembolic pulmonary hypertension. Kim NH, D'Armini AM, Grimminger F, Grünig E, Hoeper MM, Jansa P, Mayer E, Neurohr C, Simonneau G, Torbicki A, Wang C, Fritsch A, Davie N, Ghofrani HA	Heart. 2017;103(8):599-606. doi: 10.1136/heartjnl-2016-309621.
15.	Taborsky	Red or white wine consumption effect on atherosclerosis in healthy individuals (In Vino Veritas study).	2017;118(5):292-298. doi: 10.4149/BLL_2017 _072.
16.	Tani	The effects of increasing calcium channel blocker dose vs. adding a diuretic to treatment regimens for patients with uncontrolled hypertension.	Hypertens Res. 2017 ;40(10):892-898. doi: 10.1038/hr.2017.56.

17.	Wang	Efficacy of ezetimibe combined with atorvastatin in the treatment of carotid artery plaque in patients with type 2 diabetes mellitus omplicated with coronary heart disease.	Int Angiol. 2017 ;36(5):467-473. doi: 10.23736/S0392-9590.17.03818-4.
18.	Rudolph	Prasugrel as opposed to clopidogrel improves endothelial nitric oxide bioavailability and reduces platelet-leukocyte interaction in patients with unstable angina pectoris: A randomized controlled trial.	Int J Cardiol. 2017 ;248:7-13.doi: 10.1016/j.ijcard.2017.06.099.
19.	Auscher	Effects of Intensive Statin Therapy on Left Ventricular Function in Patients with Myocardial Infarction and Abnormal Glucose Tolerance.	Cardiology. 2017;138(1):16-25.doi: 10.1159/000469657.
20.	Lybeck	Prognostic significance of clinical seizures after cardiac arrest and target temperature management	Resuscitation. 2017 ;114:146-151.doi: 10.1016/j.resuscitati on.2017.01.017.
21.	Gallagher	Telemonitoring Adherence to Medications in Heart Failure Patients (TEAM-HF): A Pilot Randomized Clinical Trial	Clinical Trial. J Card Fail. 2017 ;23(4):345-349. doi: 10.1016/j.cardfail.2 016.11.001.
22.	Jaguszewski	The REMEDEE-OCT Study: An Evaluation of the Bioengineered COMBO Dual-Therapy CD34 Antibody-Covered Sirolimus-Eluting Coronary Stent Compared With a Cobalt-Chromium Everolimus-Eluting Stent in Patients WithAcute Coronary Syndromes: Insights From Optical Coherence Tomography Imaging Analysis.	JACC Cardiovasc Interv. 2017 ;10(5):489-499. doi: 10.1016/j.jcin.2016.11.040.
23.	Gotsman	Patient-Specific Tailored Intervention Improves INR Time in Therapeutic Range and INR Variability in Heart Failure Patients.	Am J Med. 2017 ;130(8):982-989. doi: 10.1016/j.amjmed.2 017.02.030.
24.	Packer	Long-Term Effect of Endothelin Receptor Antagonism With Bosentan on the Morbidity and Mortality of Patients With Severe Chronic Heart Failure: Primary Results of the ENABLE Trials.	JACC Heart Fail. 2017 ;5(5):317-326.doi: 10.1016/j.jchf.2017.
25.	Boriani	MORE-CARE Study Investigators. Effects of remote monitoring on clinical outcomes and use of healthcare resources in heart failure patients with biventricular defibrillators: results of the MORE-CARE multicentre randomized controlled trial.	Eur J Heart Fail. 2017 ;19(3):416-425. doi: 10.1002/ejhf.626.
26.	Packer	Fisher L. Long-Term Effects of Flosequinan on the Morbidity and Mortality of Patients With Severe Chronic Heart Failure: Primary Results of the PROFILE Trial After 24 Years. JACC Heart Fail.	2017 ;5(6):399-407. doi: 10.1016/j.jchf.2017. 03.003.
27.	Kuck	Impact of Substrate Modification by Catheter Ablation on Implantable Cardioverter-Defibrillator Interventions in Patients With Unstable Ventricular Arrhythmias and Coronary Artery Disease: Results From the Multicenter Randomized Controlled SMS (Substrate Modification Study).	Circ Arrhythm Electrophysiol. 2017 Mar;10(3):e004422.doi: 10.1161/CIRCEP.116.004422.
28.	Dufour	Open-label therapy with alirocumab in patients with heterozygous familial hypercholesterolemia: Results from three years of treatment.	Int J Cardiol. 2017 1;228:754-760.doi: 10.1016/j.ijcard.2016.11.046.
29.	Kim	Haemodynamic effects of riociguat in inoperable/recurrent chronic thromboembolic pulmonary hypertension.	Heart. 2017 ;103(8):599-606. doi: 10.1136/heartjnl- 2016-309621.
30.	Damman	Plasma Neutrophil Gelatinase-Associated Lipocalin and Predicting Clinically Relevant Worsening Renal Function in Acute Heart Failure.	Int J Mol Sci. 2017 ;18(7):1470. doi: 10.3390/ijms18071470.
31.	Wang	Efficacy and Safety of Shensong Yangxin Capsules for Frequent VPCs in Congestive Heart Failure Study	Chin Med J (Engl). 2017 ;130(14):1639-1647.

		Group. Effects of Traditional Chinese Medicine Shensong Yangxin Capsules on Heart Rhythm and Function in Congestive Heart Failure Patients with Frequent Ventricular Premature Complexes: A Randomized, Double-blind, Multicenter Clinical Trial.	doi: 10.4103/0366-6999.209906.
32.	Grüble	Effects of Vitamin D3 on asymmetric- and symmetric dimethylarginine in arterial hypertension.	J Steroid Biochem Mol Biol. 2018 ;175:157-163.doi: 10.1016/j.jsbmb.2016.12.014.
34.	de Leeuw	The effects of missed doses of amlodipine and losartan on blood pressure in older hypertensive patients.	Hypertens Res. 2017 ;40(6):568-572. doi: 10.1038/hr.2016.190.
35.	Steinhoff	PERFECT Trial Investigators Group, Börgermann J, David R, Garbade J, Große J, Haverich A, Hennig H, Kaminski A, Lotz J, Mohr FW, Müller P, Oostendorp R, Ruch U, Sarikouch S, Skorska A, Stamm C, Tiedemann G, Wagner FM, Wolkenhauer O. Cardiac Function Improvement and Bone Marrow Response: Outcome Analysis of the Randomized PERFECT Phase III Clinical Trial of Intramyocardial CD133+ Application After Myocardial Infarction2	017 ;22:208-224. doi: 10.1016/j.ebiom.20 17.07.022.
36.	Massberg	Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting Versus Zotarolimus- Eluting Stents (ISAR-TEST 5) Investigators. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial..	Circulation. 2011;124(5):624-32. doi: 10.1161/CIRCULA TIONAHA.111.026 732.
37.	Fujiwara	Comparative effects of valsartan plus either cilnidipine or hydrochlorothiazide on home morning blood pressure surge evaluated by information and communication technology-based nocturnal home blood pressure monitoring.	J Clin Hypertens (Greenwich). 2018 ;20(1):159-167.doi: 10.1111/jch.13154.
38.	Derkach .	Effects of dietary sodium on metabolites: the Dietary Approaches to Stop Hypertension (DASH)-Sodium Feeding Study.	Am J Clin Nutr. 2017 ;106(4):1131-1141. doi: 10.3945/ajcn.116.150136.
39.	Safdar	Ranolazine and Microvascular Angina by PET in the Emergency Department: Results From a Pilot Randomized Controlled Trial.	Clin Ther. 2017 ;39(1):55-3.doi:.1016/j.clinthera. 2016.12.002.
40.	Toyoda	Protective effects of bisoprolol against myocardial injury and pulmonary dysfunction in patients with chronic heart failure.	Int J Cardiol. 2017 ;1;226:71-76.doi: 10.1016/j.ijcard.2016.
41.	Sanati	Intracoronary versus Intravenous eptifibatide during percutaneous coronary intervention for acute ST-segment elevation myocardial infarction; a randomized controlled trial.	Cardiovasc Interv Ther. 2017 ;32(4):351-357. doi: 10.1007/s12928-016-0418-9.
42.	Glantz	Effect of CPAP on diastolic function in coronary artery disease patients with nonsleepy obstructive sleep apnea: A randomized controlled trial.	Int J Cardiol. 2017 ;241:12-18.doi: 10.1016/j.ijcard.2017.03.100.
43.	Krustrup .	Broad-spectrum health improvements with one year of soccer training in inactive mildly hypertensive middle-aged women.	Scand J Med Sci Sports. 2017 ;27(12):1893-1901. doi: 10.1111/sms.12829.
44.	Cheung	Effects of Intensive BP Control in CKD.	J Am Soc Nephrol. 2017 ;28(9):2812-2823. doi: 10.1681/ASN.2017020148.
45.	Mehra	A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure.	N Engl J Med. 2017 ;376(5):440-450. doi: 10.1056/NEJMoa16,10426.
46.	Lee	Efficacy and tolerability of two different formulations of atorvastatin in Korean patients with hypercholesterolemia: a multicenter, prospective, randomized clinical trial..	Drug Des Devel Ther. 2017 ;11:2277-2285.doi: 10.2147/DDDT.S11 2241.
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3.1.2 Data Extraction

For data extraction, we used a data extraction sheet already tested and described in a previous study [41], data extracting guide available here: https://doi.org/10.1016/j.jpeds.2017.09.014 [40]. The following data were extracted: journal type (e.g., specialty cardiovascular, or general medical), the publication details and characteristics of the published trials (such as study design, intervention, trial conduct, study sample, sample size, presence of a data monitoring committee, research outcomes, and conclusions). Further, we collected information about trial registration. Data extraction was completed by two reviewers (OB, OF): the first reviewer extracted the data and then, the second reviewer double-checked the sample. Conflicts were resolved through discussion and by reaching a consensus. Trial registration and protocol availability were investigated by retrieving information from the publications and via additional Internet searches (in Google and Google scholar). For the internet searches, we used the trial register number, the investigators' names, and keywords describing the intervention or the condition.

3.1.3 Assessment of Methodological Quality and Reporting

We used the Cochrane RoB assessment tool [42] to evaluate the methodological quality of included RCTs. This tool assesses seven domains as mentioned above in details. We used the Cochrane RoB tool to assess RoB for the primary outcome. When the primary outcome was not clearly defined, we presumed it was the outcome either (1) described under aims/objectives of the study, (2) the outcome used to determine the sample size, or (3) the first outcome reported in the publication. One researcher performed a RoB assessment, while a second researcher was assigned to ensure the correctness of the assessments for each study. Following Cochrane procedures [25], we classified each domain as low, unclear, or high risk. Then, the overall RoB was determined as follows: low when all domains were assessed as low RoB; unclear when at least 1 domain was assessed as unclear, and no domains were assessed as high RoB; and high if any domain was assessed as high RoB [25].

3.1.4 Statistical Analysis

Statistical analyses were conducted by the statistical software R version 4.1.2 [43]. The data were analyzed descriptively, using means and standard deviations (SDs), medians and ranges for continuous variables and proportions for categorical variables. A multivariable logistic regression analysis was conducted to investigate the association between pre-specified study characteristics and the odds of high/unclear RoB. The value of $p < 0.05$ was considered as a significant result.

3.2 Change over Five Years in Important Measures of Methodological Quality and Reporting in Randomized Cardiovascular Clinical Trials

3.2.1 Sample selection and data extraction

We conducted two searches to identify RCTs published in either 2012 or 2017. As mentioned above in details we used same methodology to identify our studies. Our search resulted in 2566 trials. We included the first 250 (about 10%) eligible RCTs for both year 2012 and 2017. We used a data extraction tool that was developed for assessing the methodological quality of RCTs in child health research [55].

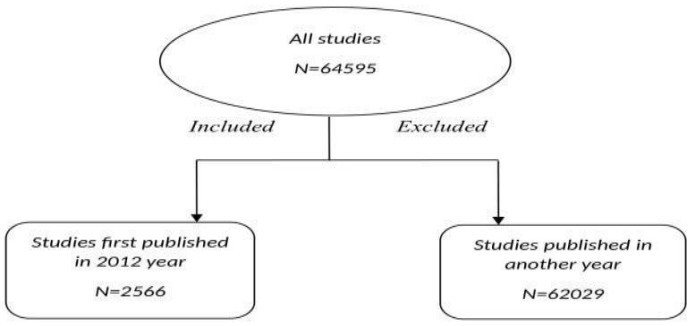

Figure 4. Flow diagram of the search (2012 year)

TABLE 3. All included trials published in 2012 year (N=250)

Number	First Author	Title	Journal
1.	Mora	Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study	Circulation. 2012 ;125(16):1979-87. doi: 10.1161/CIRCULATIONAHA.111.088591.
2.	Schwartz	Effects of dalcetrapib in patients with a recent acute coronary syndrome.	N Engl J Med. 2012 ;367(22):2089-99. doi: 10.1056/NEJMoa1206797. /
3.	Waters	Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes	J Am Coll Cardiol. 2013 ;61(2):148-52. doi: 10.1016/j.jacc.2012.09.042.
4.	Nidorf	Low-dose colchicine for secondary prevention of cardiovascular disease	J Am Coll Cardiol. 2013 29;61(4):404-410. doi: 10.1016/j.jacc.2012.10.027.
5.	Okin	Racial differences in sudden cardiac death among hypertensive patients during antihypertensive therapy: the LIFE study	Heart Rhythm. 2012 ;9(4):531-7. doi: 10.1016/j.hrthm.2011.11.008.
6.	Chardoli	Echocardiography integrated ACLS protocol versus conventional cardiopulmonary resuscitation in patients with pulseless electrical activity cardiac arrest.	Chin J Traumatol. 2012;15(5):284-7. PMID: 23069099
7.	Bishu	Biomarkers in acutely decompensated heart failure with preserved or reduced ejection fraction	Am Heart J. 2012 ;164(5):763-770.e3. doi: 10.1016/j.ahj.2012.08.014.
8.	Lam	Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial	Circ Heart Fail. 2012 ;5(5):571-8. doi: 10.1161/CIRCHEARTFAILURE.112.970061.
9.	Greene	EVEREST Trial Investigators. Prognostic value of monocyte count in patients hospitalized for heart failure with reduced ejection fraction (from the EVEREST Trial).	Am J Cardiol. 2012 ;110(11):1657-62. doi: 10.1016/j.amjcard.2012.07.035
10.	Mentz	The impact of chronic obstructive pulmonary disease in patients hospitalized for worsening heart failure with reduced ejection fraction: an analysis of the EVEREST Trial	J Card Fail. 2012 Jul;18(7):515-23. doi: 10.1016/j.cardfail.2012.04.010. Epub 2012 Jun 4. PMID: 22748484.
11.	Vaduganathan	EVEREST trial investigators. Predictive value of low relative lymphocyte count in patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial	Circ Heart Fail. 2012 Nov;5(6):750-8. doi: 10.1161/CIRCHEARTFAILURE.112.970525. Epub 2012 Oct 9. PMID: 23051949
12.	Mentz	Atrial fibrillation or flutter on initial electrocardiogram is associated with worse outcomes in patients admitted for worsening heart failure with reduced ejection fraction: findings from the EVEREST Trial..	Am Heart J. 2012 Dec;164(6):884-92.e2. doi: 10.1016/j.ahj.2012.09.011. Epub 2012 Oct 29. PMID: 23194489
13.	Loncar	Effect of beta blockade on natriuretic peptides and copeptin in elderly patients with heart failure and preserved or reduced ejection fraction: results from the CIBIS-ELD trial.	Clin Biochem. 2012 ;45(1-2):117-22. doi: 10.1016/j.clinbiochem.2011.11.010.
14.	Solomon	Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial.	Lancet. 2012 ;380(9851):1387-95. doi: 10.1016/S0140-6736(12)61227-6.
15.	Rector	Assessment of long-term effects of irbesartan on heart failure with preserved ejection fraction as measured by the minnesota living with heart failure questionnaire in the irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial.	Circ Heart Fail. 2012 ;5(2):217-25. doi: 10.1161/CIRCHEARTFAILURE.111.964221.
16.	Sandri	Age-related effects of exercise training on diastolic function in heart failure with reduced ejection fraction: the Leipzig Exercise Intervention in Chronic Heart Failure and Aging (LEICA) Diastolic Dysfunction Study.	Eur Heart J. 2012 ;33(14):1758-68. doi: 10.1093/eurheartj/ehr469
17.	Andrews	L-arginine cardioplegia reduces oxidative stress and preserves diastolic function in patients with low ejection fraction undergoing coronary artery surgery.	Anaesth Intensive Care. 2012 ;40(1):99-106. doi: 10.1177/0310057X1204000110.
18.	Thomas	Prospective randomized comparison of conventional stress echocardiography and real-time perfusion stress echocardiography in detecting significant coronary artery disease.	J Am Soc Echocardiogr. 2012 (11):1207-14. doi: 10.1016/j.echo.2012.08.016.
19.	Oliveira	Impact of continuous positive airway pressure treatment on right ventricle performance in patients with obstructive sleep apnoea, assessed by three-dimensional echocardiography.	Sleep Med. 2012 ;13(5):510-6. doi: 10.1016/j.sleep.2011.12.010.
20.	Oh JK	Core lab analysis of baseline echocardiographic studies in the STICH trial and recommendation for use of echocardiography in future clinical trials.	J Am Soc Echocardiogr. 2012 ;25(3):327-36. doi: 10.1016/j.echo.2011.12.002.
21.	Kong	intravenous hydration strategies for the prevention of contrast-induced nephropathy in patients undergoing	Acta Cardiol. 2012 ;67(5):565-9. doi:

		coronary angiography or angioplasty: a randomized clinical trial	10.1080/ac.67.5.2174131.
22.	Hoffmann	Coronary CT angiography versus standard evaluation in acute chest pain.	N Engl J Med. 2012;367(4):299-308. doi: 10.1056/NEJMoa1201161.
23.	Pichler	Ivabradine versus metoprolol for heart rate reduction before coronary computed tomography angiography.	Am J Cardiol. 2012 ;109(2):169-73. doi: 10.1016/j.amjcard.2011.08.025.
24.	Rochitte	Diltiazem as an alternative to beta-blocker in coronary artery computed tomography angiography..	Arq Bras Cardiol. 2012;99(2):706-13. English, Portuguese. doi: 10.1590/s0066-782x2012005000059.
25.	Ray	Blood pressure monitoring technique impacts hypertension treatment	J Gen Intern Med. 2012 ;27(6):623-9. doi: 10.1007/s11606-011-1937-9.
26.	Kim	Everolimus-eluting stent implantation for unprotected left main coronary artery stenosis. The PRECOMBAT-2 (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) study.	JACC Cardiovasc Interv. 2012 ;5(7):708-17. doi: 10.1016/j.jcin.2012.05.002.
27.	Botden	Red wine polyphenols do not lower peripheral or central blood pressure in high normal blood pressure and hypertension.	Am J Hypertens. 2012 ;25(6):718-23. doi: 10.1038/ajh.2012.25.
28.	Thiele	Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI Trial).	Eur Heart J. 2012 ;33(16):2035-43. doi: 10.1093/eurheartj/ehr418.
29.	Dimeo	Aerobic exercise reduces blood pressure in resistant hypertension..	Hypertension. 2012 ;60(3):653-8. doi: 10.1161/HYPERTENSIONAHA.112.197780.
30.	Shaw	Impact of left ventricular function and the extent of ischemia and scar by stress myocardial perfusion imaging on prognosis and therapeutic risk reduction in diabetic patients with coronary artery disease: results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial.	J Nucl Cardiol. 2012 ;19(4):658-69. doi: 10.1007/s12350-012-9548-3.
31.	Krysiak	Different effects of perindopril and enalapril on monocyte cytokine release in coronary artery disease patients with normal blood pressure.	Pharmacol Rep. 2012;64(6):1466-75. doi: 10.1016/s1734-1140(12)70944-1.
32.	Rittger	. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study..	J Am Coll Cardiol. 2012 10;59(15):1377-82. doi: 10.1016/j.jacc.2012.01.015.
33.	Bulpitt	Blood pressure control in the Hypertension in the Very Elderly Trial (HYVET).	J Hum Hypertens. 2012 ;26(3):157-63. doi: 10.1038/jhh.2011.10..
34.	van Onzenoort	Electronic monitoring of adherence, treatment of hypertension, and blood pressure control.	Am J Hypertens. 2012 ;25(1):54-9. doi: 10.1038/ajh.2011.153.
35.	Moreno-Luna	Olive oil polyphenols decrease blood pressure and improve endothelial function in young women with mild hypertension..	Am J Hypertens. 2012 ;25(12):1299-304. doi: 10.1038/ajh.2012.128.
36.	Cushman	Home and clinic blood pressure responses in elderly individuals with systolic hypertension	J Am Soc Hypertens. 2012;6(3):210-8. doi: 10.1016/j.jash.2012.03.001.
37.	Logan	Effect of home blood pressure telemonitoring with self-care support on uncontrolled systolic hypertension in diabetics.	Hypertension. 2012 ;60(1):51-7. doi: 10.1161/HYPERTENSIONAHA.111.188409.
38.	Cicero	Predictors of the short-term effect of isoleucine-proline-proline/valine-proline-proline lactotripeptides from casein on office and ambulatory blood pressure in subjects with pharmacologically untreated high-normal blood pressure or first-degree hypertension.	Clin Exp Hypertens. 2012;34(8):601-5. doi: 10.3109/10641963.2012.681731.
39.	Tarantini	Postconditioning during coronary angioplasty in acute myocardial infarction: the POST-AMI trial.	Int J Cardiol. 2012 ;162(1):33-8. doi: 10.1016/j.ijcard.2012.03.136.
40.	Gayda	Effects of sauna alone and postexercise sauna baths on blood pressure and hemodynamic variables in patients with untreated hypertension.	J Clin Hypertens (Greenwich). 2012 ;14(8):553-60. doi: 10.1111/j.1751-7176.2012.00637.x.
41.	Cushman	Azilsartan medoxomil plus chlorthalidone reduces blood pressure more effectively than olmesartan plus hydrochlorothiazide in stage 2 systolic hypertension..	Hypertension. 2012 ;60(2):310-8. doi: 10.1161/HYPERTENSIONAHA.111.188284.
42.	Rosenbaum	Olmesartan medoxomil combined with hydrochlorothiazide improves 24-hour blood pressure control in moderate-to-severe hypertension.	Curr Med Res Opin. 2012 ;28(2):179-86. doi: 10.1185/03007995.2011.644626.
43.	Gong	. Hypertension susceptibility loci and blood pressure response to antihypertensives: results from the pharmacogenomic evaluation of antihypertensive responses study.	Circ Cardiovasc Genet. 2012 ;5(6):686-91. doi: 10.1161/CIRCGENETICS.112.964080.

44.	Hanayama	Losartan/hydrochlorothiazide combination therapy surpasses high-dose angiotensin receptor blocker in the reduction of morning home blood pressure in patients with morning hypertension.	Acta Med Okayama. 2012;66(6):449-59. doi: 10.18926/AMO/49041.
45.	Kanaki	Low-dose atorvastatin reduces ambulatory blood pressure in patients with mild hypertension and hypercholesterolaemia: a double-blind, randomized, placebo-controlled study.	J Hum Hypertens. 2012 ;26(10):577-84. doi: 10.1038/jhh.2011.80..
46.	Fukutomi	Differential effects of strict blood pressure lowering by losartan/hydrochlorothiazide combination therapy and high-dose amlodipine monotherapy on microalbuminuria: the ALPHABET study	J Am Soc Hypertens. 2012 ;6(1):73-82. doi: 10.1016/j.jash.2011.09.004.
47.	Rayner	G-protein-coupled receptor kinase 4 polymorphisms predict blood pressure response to dietary modification in Black patients with mild-to-moderate hypertension.	J Hum Hypertens. 2012 ;26(5):334-9. doi: 10.1038/jhh.2011.33.
48.	Piette	Hypertension management using mobile technology and home blood pressure monitoring: results of a randomized trial in two low/middle-income countries..	Telemed J E Health. 2012 ;18(8):613-20. doi: 10.1089/tmj.2011.0271.
49.	Brener	Diabetes mellitus, myocardial reperfusion, and outcome in patients with acute ST-elevation myocardial infarction treated with primary angioplasty (from HORIZONS AMI).	Am J Cardiol. 2012 ;109(8):1111-6. doi: 10.1016/j.amjcard.2011.11.046.
50.	Chevalier	One-year results of the CRISTAL Trial, a randomized comparison of cypher sirolimus-eluting coronary stents versus balloon angioplasty for restenosis of drug-eluting stents	J Interv Cardiol. 2012 ;25(6):586-95. doi: 10.1111/j.1540-8183.2012.00769.x..
51.	Black	Aliskiren alone or in combination with hydrochlorothiazide in Hispanic/Latino patients with systolic blood pressure 160 mm Hg to <180 mm Hg (Aliskiren Alone or in Combination with Hydrochlorothiazide in Patients with Stage 2 Hypertension to Provide Quick Intensive Control of Blood Pressure [ACQUIRE] substudy).	J Clin Hypertens (Greenwich). 2012 ;14(8):514-21. doi: 10.1111/j.1751-7176.2012.00672.x.
52.	Epstein	Determinants and consequences of adherence to the dietary approaches to stop hypertension diet in African-American and white adults with high blood pressure: results from the ENCORE trial.	J Acad Nutr Diet. 2012 ;112(11):1763-73. doi: 10.1016/j.jand.2012.07.007.
53.	Souza	Self measurement of blood pressure for control of blood pressure levels and adherence to treatment.	Arq Bras Cardiol. 2012 ;98(2):167-74. English, Portuguese. doi: 10.1590/s0066-782x2012005000010.
54.	Ke YN	Improved blood pressure control with nifedipine GITS/valsartan combination versus high-dose valsartan monotherapy in mild-to-moderate hypertensive patients from Asia: results from the ADVISE study, a randomized trial.	Cardiovasc Ther. 2012 Dec;30(6):326-32. doi: 10.1111/1755-5922.12003.
55.	Heisler	Improving blood pressure control through a clinical pharmacist outreach program in patients with diabetes mellitus in 2 high-performing health systems: the adherence and intensification of medications cluster randomized, controlled pragmatic trial.	Circulation. 2012 ;125(23):2863-72. doi: 10.1161/CIRCULATIONAHA.111.089169.
56.	Fuchs	Efficacy of isolated home blood pressure monitoring for blood pressure control: randomized controlled trial with ambulatory blood pressure monitoring - MONITOR study.	J Hypertens. 2012 ;30(1):75-80. doi: 10.1097/HJH.0b013e32834e5a4f.
57.	Sugiura.	Candesartan-based therapy and risk of cancer in patients with systemic hypertension (Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease [HIJ-CREATE] substudy	Am J Cardiol. 2012 ;109(4):576-80. doi: 10.1016/j.amjcard.2011.09.050.
58.	Patti	Comparison of safety and efficacy of bivalirudin versus unfractionated heparin in high-risk patients undergoing percutaneous coronary intervention (from the Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty-Bivalirudin vs Heparin study)..	Am J Cardiol. 2012 ;110(4):478-84. doi: 10.1016/j.amjcard.2012.04.017.
59.	Bhan	Efficacy of early invasive management post-fibrinolysis in men versus women with ST-elevation myocardial infarction: a subgroup analysis from Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI)..	Am Heart J. 2012 ;164(3):343-50. doi: 10.1016/j.ahj.2012.05.022.
60.	Song	Randomized comparison of conservative versus aggressive strategy for provisional side branch intervention in coronary bifurcation lesions: results from the SMART-STRATEGY (Smart Angioplasty Research Team-Optimal Strategy for Side Branch Intervention in Coronary Bifurcation Lesions) randomized trial.	JACC Cardiovasc Interv. 2012 ;5(11):1133-40. doi: 10.1016/j.jcin.2012.07.010.
61.	Carr	The predictive ability of blood pressure in elderly trial patients	J Hypertens. 2012 ;30(9):1725-33. doi: 10.1097/HJH.0b013e3283568a73.
62.	Smith	Blood pressure responses and metabolic effects of hydrochlorothiazide and atenolol	Am J Hypertens. 2012 ;25(3):359-65. doi: 10.1038/ajh.2011.215.
63.	Tzoulaki	A nutrient-wide association study on blood pressure.	Circulation. 2012 ;126(21):2456-64. doi: 10.1161/CIRCULATIONAHA.112.114058.
64.	Renda	Genetic determinants of blood pressure responses to caffeine drinking..	Am J Clin Nutr. 2012 ;95(1):241-8. doi: 10.3945/ajcn.111.018267.

65.	Teunissen-	Protein supplementation lowers blood pressure in overweight adults: effect of dietary proteins on blood pressure (PROPRES), a randomized trial.	Am J Clin Nutr. 2012 ;95(4):966-71. doi: 10.3945/ajcn.111.029116.
66.	Verdecchia	Blood pressure and other determinants of new-onset atrial fibrillation in patients at high cardiovascular risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease studies	J Hypertens. 2012 ;30(5):1004-14. doi: 10.1097/HJH.0b013e3283522a51..
67.	Levitan	Blood pressure measurement device, number and timing of visits, and intra-individual visit-to-visit variability of blood pressure	J Clin Hypertens (Greenwich). 2012 Nov;14(11):744-50. doi: 10.1111/jch.12005.
68.	Barzilay.	Intensive blood pressure treatment does not improve cardiovascular outcomes in centrally obese hypertensive individuals with diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial.	Diabetes Care. 2012 Jul;35(7):1401-5. doi: 10.2337/dc11-1827.
69.	Bolognese	Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced nephropathy and tissue reperfusion in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the Contrast Media and Nephrotoxicity Following Primary Angioplasty for Acute Myocardial Infarction [CONTRAST-AMI] Trial	Am J Cardiol. 2012 Jan 1;109(1):67-74. doi: 10.1016/j.amjcard.2011.08.006.
70.	Bhammar	Effects of fractionized and continuous exercise on 24-h ambulatory blood pressure.	Med Sci Sports Exerc. 2012 ;44(12):2270-6. doi: 10.1249/MSS.0b013e3182663117.
71.	Sirvinskas.	The influence of mean arterial blood pressure during cardiopulmonary bypass on postoperative renal dysfunction in elderly patients.	Perfusion. 2012 ;27(3):193-8. doi: 10.1177/0267659112436751.
72.	Lin	Heart rate variability biofeedback decreases blood pressure in prehypertensive subjects by improving autonomic function and baroreflex.	J Altern Complement Med. 2012 ;18(2):143-52. doi: 10.1089/acm.2010.0607.
73.	Inrig..	Impact of higher hemoglobin targets on blood pressure and clinical outcomes: a secondary analysis of CHOIR.	Nephrol Dial Transplant. 2012 ;27(9):3606-14. doi: 10.1093/ndt/gfs123.
74.	Acelajado	Both morning and evening dosing of nebivolol reduces trough mean blood pressure surge in hypertensive patients..	J Am Soc Hypertens. 2012 ;6(1):66-72. doi: 10.1016/j.jash.2011.09.001.
75.	Zhang	Blood pressure variability in relation to autonomic nervous system dysregulation: the X-CELLENT study..	Hypertens Res. 2012 ;35(4):399-403. doi: 10.1038/hr.2011.203.
76.	Arima	Effects of blood pressure lowering on intracranial and extracranial bleeding in patients on antithrombotic therapy: the PROGRESS trial..	Stroke. 2012 ;43(6):1675-7. doi: 10.1161/STROKEAHA.112.651448.
77.	Tuttle	Dietary amino acids and blood pressure.	Am J Kidney Dis. 2012 ;59(6):803-9. doi: 10.1053/j.ajkd.2011.12.026.
78.	Kerby	Adherence to blood pressure telemonitoring in a cluster-randomized clinical trial.	J Clin Hypertens (Greenwich). 2012 ;14(10):668-74. doi: 10.1111/j.1751-7176.2012.00685.x
79.	Dobrosielski	Effect of exercise on blood pressure in type 2 diabetes: a randomized controlled trial.	J Gen Intern Med. 2012 ;27(11):1453-9. doi: 10.1007/s11606-012-2103-8.
80.	Hodgson	Long-term effects of a protein-enriched diet on blood pressure in older women	Br J Nutr. 2012 ;107(11):1664-72. doi: 10.1017/S0007114511004740.
81.	Wessel	'Diagnostic mode' improves adherence to the home blood pressure measurement schedule.	Blood Press Monit. 2012 ;17(5):214-9. doi: 10.1097/MBP.0b013e328357352a.
82.	Stewart	Effect of intensive structured care on individual blood pressure targets in primary care: multicentre randomised controlled trial.	BMJ. 2012 ;345:e7156. doi: 10.1136/bmj.e7156.
83.	Kim	Can acupuncture affect the circadian rhythm of blood pressure? A randomized, double-blind, controlled trial.	J Altern Complement Med. 2012 ;18(10):918-23. doi: 10.1089/acm.2011.0508.
84.	Molmen-Hansen.	Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients.	Eur J Prev Cardiol. 2012 ;19(2):151-60. doi: 10.1177/1741826711400512.
85.	Chiva-Blanch	Dealcoholized red wine decreases systolic and diastolic blood pressure and increases plasma nitric oxide: short communication	Circ Res. 2012 ;111(8):1065-8. doi: 10.1161/CIRCRESAHA.112.275636.
86.	Kushiro	Blood pressure control status and effects of pravastatin on cardiovascular events occurrence in patients with dyslipidaemia.	J Hum Hypertens. 2012 ;26(6):388-95. doi: 10.1038/jhh.2011.49.
87.	Okamoto	Synergistic effect of norepinephrine transporter blockade and α-2 antagonism on blood pressure in autonomic	Hypertension. 2012 ;59(3):650-6. doi:

		failure.	10.1161/HYPERTENSIONAHA.111.184812.
88.	Cosselman	Blood pressure response to controlled diesel exhaust exposure in human subjects	Hypertension. 2012 ;59(5):943-8. doi: 10.1161/HYPERTENSIONAHA.111.186593.
89.	Shiraishi	Cardio-cerebrovascular protective effects of valsartan in high-risk hypertensive patients with coronary artery disease (from the Kyoto Heart Study).	Am J Cardiol. 2012 ;109(9):1308-14. doi: 10.1016/j.amjcard.2011.12.025.
90.	Dong	Effect of prostaglandin E1 on pulmonary arterial hypertension following corrective surgery for congenital heart disease.	J Cardiovasc Pharmacol Ther. 2012 ;17(3):303-7. doi: 10.1177/1074248411429966.
91.	Sandoval	Safety and efficacy of sitaxsentan 50 and 100 mg in patients with pulmonary arterial hypertension..	Pulm Pharmacol Ther. 2012 ;25(1):33-9. doi: 10.1016/j.pupt.2011.10.002.
92.	Larstorp	Association of pulse pressure with new-onset atrial fibrillation in patients with hypertension and left ventricular hypertrophy: the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study.	Hypertension. 2012 ;60(2):347-53. doi: 10.1161/HYPERTENSIONAHA.112.195032.
93.	Houle	Effect of a pharmacist-managed hypertension program on health system costs: an evaluation of the Study of Cardiovascular Risk Intervention by Pharmacists-Hypertension (SCRIP-HTN).	Pharmacotherapy. 2012 Jun;32(6):527-37. doi: 10.1002/j.1875-9114.2012.01097.x.
94.	Borer	Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT Study.	Eur Heart J. 2012 ;33(22):2813-20. doi: 10.1093/eurheartj/ehs259.
95.	Austin	Patterns of fatigue in elderly heart failure patients measured by a quality of life scale (Minnesota living with heart failure).	Eur J Cardiovasc Nurs. 2012 ;11(4):439-44. doi: 10.1016/j.ejcnurse.2011.04.002.
96.	Bart	Ultrafiltration in decompensated heart failure with cardiorenal syndrome.	N Engl J Med. 2012 ;367(24):2296-304. doi: 10.1056/NEJMoa1210357.
97.	Guimarães	Pilates in heart failure patients: a randomized controlled pilot trial..	Cardiovasc Ther. 2012 ;30(6):351-6. doi: 10.1111/j.1755-5922.2011.00285.x.
98.	Alves	Exercise training improves diastolic function in heart failure patients.	Med Sci Sports Exerc. 2012 ;44(5):776-85. doi: 10.1249/MSS.0b013e31823cd16a..
99.	Nolan	Therapeutic benefit of internet-based lifestyle counselling for hypertension.	Can J Cardiol. 2012 ;28(3):390-6. doi: 10.1016/j.cjca.2012.02.012.
100.	Wagner	Personal health records and hypertension control: a randomized trial..	J Am Med Inform Assoc. 2012 ;19(4):626-34. doi: 10.1136/amiajnl-2011-000349.
101.	Hobolth L	Carvedilol or propranolol in portal hypertension? A randomized comparison.	Scand J Gastroenterol. 2012 ;47(4):467-74. doi: 10.3109/00365521.2012.666673.
102.	Mao	Therapeutic effect of forest bathing on human hypertension in the elderly.	J Cardiol. 2012 ;60(6):495-502. doi: 10.1016/j.jjcc.2012.08.003.
103.	Zeng	Atorvastatin in Pulmonary Arterial Hypertension (APATH) Study Group. Atorvastatin in pulmonary arterial hypertension (APATH) study.	Eur Respir J. 2012 ;40(1):67-74. doi: 10.1183/09031936.00149011.
104.	Hebert	Nurse-led disease management for hypertension control in a diverse urban community: a randomized trial.	J Gen Intern Med. 2012 ;27(6):630-9. doi: 10.1007/s11606-011-1924-1.
105.	Nozue	Impacts of conventional coronary risk factors, diabetes and hypertension, on coronary atherosclerosis during statin therapy	Coron Artery Dis. 2012 ;23(4):239-44. doi: 10.1097/MCA.0b013e328351f919.
106.	Guo	Effects of high thoracic epidural sympathetic blockade for the treatment of severe chronic heart failure due to dilated cardiomyopathy.	Acta Cardiol. 2012 ;67(5):533-9. doi: 10.1080/ac.67.5.2174127.
107.	Larstorp	Regression of ECG-LVH is associated with lower risk of new-onset heart failure and mortality in patients with isolated systolic hypertension; The LIFE study.	Am J Hypertens. 201 ;25(10):1101-9. doi: 10.1038/ajh.2012.86.
108.	Okin.	Effect of changing heart rate during treatment of hypertension on incidence of heart failure.	Am J Cardiol. 2012 ;109(5):699-704. doi: 10.1016/j.amjcard.2011.10.026.
109.	Chen.	Acute effects of nicardipine and esmolol on the cardiac cycle, intracardiac hemodynamic and endothelial shear stress in patients with unstable angina pectoris and moderate coronary stenosis: results from single center, randomized study.	Cardiovasc Ther. 2012 ;30(3):162-71. doi: 10.1111/j.1755-5922.2011.00298.x.
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219.	Palta	Evaluation of a mindfulness-based intervention program to decrease blood pressure in low-income African-American older adults.	J Urban Health. 2012 ;89(2):308-16. doi: 10.1007/s11524-011-9654-6.
220.	Larson	Acute, quercetin-induced reductions in blood pressure in hypertensive individuals are not secondary to lower plasma angiotensin-converting enzyme activity or endothelin-1: nitric oxide.	Nutr Res. 2012 ;32(8):557-64. doi: 10.1016/j.nutres.
221.	Eriksson	Comparison of blood pressure measurements between an automated oscillometric device and a Hawksley random-zero sphygmomanometer in the northern Sweden MONICA study.	Blood Press Monit. 2012 ;17(4):164-70. doi: 10.1097/MBP.0b013e328356ef58.
222.	Zhang	Neuropeptide Y promoter polymorphism modifies effects of a weight-loss diet on 2-year changes of blood pressure: the preventing overweight using novel dietary strategies trial.	Hypertension. 2012 ;60(5):1169-75. doi: 10.1161/HYPERTENSIONAHA.112.197855.
223.	Cicero	Effect of a combined nutraceutical containing Orthosiphon stamineus effect on blood pressure and metabolic syndrome components in hypertensive dyslipidaemic patients: a randomized clinical trial.	Complement Ther Clin Pract. 2012 ;18(3):190-4. doi: 10.1016/j.ctcp.2012.02.002.
224.	Coles	Effect of beetroot juice on lowering blood pressure in free-living, disease-free adults: a randomized, placebo-controlled trial	Nutr J. 2012 ;11:106. doi: 10.1186/1475-2891-11-106.
225.	Lazich	Effects of combining simvastatin with rosiglitazone on inflammation, oxidant stress and ambulatory blood pressure in patients with the metabolic syndrome: the SIROCO study.	Diabetes Obes Metab. 2012 ;14(2):181-6. doi: 10.1111/j.1463-1326.2011.01510.x.
226.	Bogdanski	Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters	Nutr Res. 2012 ;32(6):421-7. doi:

		associated with insulin resistance in obese, hypertensive patients.	10.1016/j.nutres.2012.05.007.
227.	Swift.	The effect of different doses of aerobic exercise training on endothelial function in postmenopausal women with elevated blood pressure: results from the DREW study.	Br J Sports Med. 2012 ;46(10):753-8. doi: 10.1136/bjsports-2011-090025.
228.	Kommuri	Relationship between improvements in heart failure patient disease specific knowledge and clinical events as part of a randomized controlled trial.	Patient Educ Couns. 2012 ;86(2):233-8. doi: 10.1016/j.pec.2011.05.019.
229.	D'Alto	Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology.	Int J Cardiol. 2012;155(3):378-82. doi: 10.1016/j.ijcard.2010.10.051.
230.	Angermann	Mode of action and effects of standardized collaborative disease management on mortality and morbidity in patients with systolic heart failure: the Interdisciplinary Network for Heart Failure (INH) study.	Circ Heart Fail. 2012 Jan;5(1):25-35. doi: 10.1161/CIRCHEARTFAILURE.111.962969.
231.	Szabo de Edelenyi .	. Effect of B-vitamins and n-3 PUFA supplementation for 5 years on blood pressure in patients with CVD.	Br J Nutr. 2012;107(6):921-7. doi: 10.1017/S0007114511003692.
232.	Sandset.	Relation between change in blood pressure in acute stroke and risk of early adverse events and poor outcome.	Stroke. 2012 ;43(8):2108-14. doi: 10.1161/STROKEAHA.111.647362.
233.	West.	Diets containing pistachios reduce systolic blood pressure and peripheral vascular responses to stress in adults with dyslipidemia.	Hypertension. 2012 ;60(1):58-63. doi: 10.1161/HYPERTENSIONAHA.111.182147.
234.	Koren	The effect of sitagliptin versus glibenclamide on arterial stiffness, blood pressure, lipids, and inflammation in type 2 diabetes mellitus patients.	Diabetes Technol Ther. 2012 ;14(7):561-7. doi: 10.1089/dia.2011.0296.
235.	Lewin.	Nebivolol withdrawal results in blood pressure returning toward pretreatment levels, but without rebound symptoms: phase IV randomized trial.	J Am Soc Hypertens. 2012;6(3):228-36. doi: 10.1016/j.jash.2012.02.002.
236.	Asayama	Electrical Devices of Blood Pressure (HOMED-BP). Cardiovascular outcomes in the first trial of antihypertensive therapy guided by self-measured home blood pressure	Hypertens Res. 2012 ;35(11):1102-10. doi: 10.1038/hr.2012.125.
237.	Miller	The impact of the catechol-O-methyltransferase genotype on vascular function and blood pressure after acute green tea ingestion.	Mol Nutr Food Res. 2012 ;56(6):966-75. doi: 10.1002/mnfr.201100726.
238.	Marketou	TLR2 and TLR4 gene expression in peripheral monocytes in nondiabetic hypertensive patients: the effect of intensive blood pressure-lowering.	J Clin Hypertens (Greenwich). 2012 ;14(5):330-5. doi: 10.1111/j.1751-7176.2012.00620.x.
239.	Hobbs	Blood pressure-lowering effects of beetroot juice and novel beetroot-enriched bread products in normotensive male subjects.	Br J Nutr. 2012 ;108(11):2066-74. doi: 10.1017/S0007114512000190.
240.	Hyman	Effect of a physician uncertainty reduction intervention on blood pressure in uncontrolled hypertensives--a cluster randomized trial.	J Gen Intern Med. 2012 ;27(4):413-9. doi: 10.1007/s11606-011-1888-1.
241.	Dow.	The effects of daily consumption of grapefruit on body weight, lipids, and blood pressure in healthy, overweight adults.	Metabolism. 2012 Jul;61(7):1026-35. doi: 10.1016/j.metabol.2011.12.004.
242.	Düsing	Sustained decrease in blood pressure following missed doses of aliskiren or telmisartan: the ASSERTIVE double-blind, randomized study.	J Hypertens. 2012;30(5):1029-40. doi: 10.1097/HJH.0b013e328351c263..
243.	Hassellund	Effects of anthocyanins on blood pressure and stress reactivity: a double-blind randomized placebo-controlled crossover study.	J Hum Hypertens. 2012 ;26(6):396-404. doi: 10.1038/jhh.2011.41.
244.	Soejima.	Aspirin reduces cerebrovascular events in type 2 diabetic patients with poorly controlled blood pressure.	Circ J. 2012;76(6):1526-32. doi: 10.1253/circj.cj-11-1033.
245.	Franks	Comparison of the effects of energy drink versus caffeine supplementation on indices of 24-hour ambulatory blood pressure.	Ann Pharmacother. 2012 ;46(2):192-9. doi: 10.1345/aph.1Q555..
246.	Turner	Power to identify a genetic predictor of antihypertensive drug response using different methods to measure blood pressure response.	J Transl Med. 2012 13;10:47. doi: 10.1186/1479-5876-10-47
247.	Sica	Blood pressure-lowering efficacy of the fixed-dose combination of azilsartan medoxomil and chlorthalidone.	J Clin Hypertens (Greenwich). 2012 ;14(5):284-92. doi: 10.1111/j.1751-7176.2012.00616.
248.	Miyauchi	Management of home blood pressure by amlodipine combined with angiotensin II receptor blocker in type 2 diabetes.	Circ J. 2012;76(9):2159-66. doi: 10.1253/circj.cj-11-1406.
249.	van Dieren	Effects of blood pressure lowering on cardiovascular outcomes in different cardiovascular risk groups among participants with type 2 diabetes.	Diabetes Res Clin Pract. 2012 ;98(1):83-90. doi: 10.1016/j.diabres.2012.05.002.
250.	Poortvliet	Blood pressure variability and cardiovascular risk in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER).	PLoS One. 2012;7(12): e52438. doi: 10.1371/journal.pone.0052438.

3.2.2 Statistical Analysis

Statistical analyses were conducted by the statistical software R version 4.1.2 (R Development Core Team 2021) [45]. To analyze for 5-year changes in main study characteristics, we compared the 2017 sample with 250 RCTs published in 2012 [55]. All collected binomial variables were analyzed using logistic regression analyses with generalized linear models. All collected categorical variables with more than two categories were analyzed with multinomial regression models. For these models, a single p-value for the entire model was presented to provide a concise overview of the overall significance. Variables of methodological quality and report were analyzed with separate univariable logistic regressions. Model assumptions on residuals were checked using "model-checking plots". Statistical significance tests in the models were carried out with Chi-square tests. The value of $p < 0.05$ was considered as a significant result.

4. Results

4.1 Methodological Quality and Risk of Bias Assessment of Cardiovascular Disease Research: Analysis of Randomized Controlled Trials Published in 2017

4.1.1 Study Design and Reporting Characteristics of the Study Sample

Out of the 2,419 studies identified via search, we included the first 250 randomly selected trials, which met our search inclusion criteria as shown in Figure 1. The publication and trial characteristics of our sample are shown in Table 4.

TABLE 4. Publication and trial characteristics (N = 250).

Study characteristics	**N (%)**
The geographical location of the corresponding author	
Asia	65 (26.0%)
North America	69 (27.6%)
Europe (Excluding United Kingdom)	93 (37.2%)
South America	13 (5.2%)
Australia	2 (0.8%)
United Kingdom	8 (3.2%)
Type of journal **Specialty cardiovascular journal**	**100 (40.0%)**
General cardiovascular journal	46 (18.4%)
Specialty medical journal	49 (19.6%)
General medical journal	41 (16.4%)
Non-medical journal	14 (5.6%)
Study design	
Parallel	231 (92.4%)
Crossover	15 (6.0%)
Factorial	4 (1.6%)
Study type	
Efficacy/Superiority	237 (94.8%)
Equivalence	3 (1.2%)
Non-inferiority	4 (1.6%)
None of the above	6 (2.4%)
Intervention	

Drug	139 (55.6%)
Prevention or screening	20 (8.0%)
Device	23 (9.2%)
Other	68 (27.2%)
Placebo-controlled	
Yes	68 (27.2%)
No	182 (72.8%)
Number of centers	
Multicenter	157 (62.8%)
Single center	93 (37.2%)
Data Monitoring Committee	
Yes	105 (42.0%)
No	94 (37.6%)
Unclear	51 (20.4%)
Funding source	
Academic or Research institute	94 (37.6%)
Pharmaceutical	48 (19.2%)
Government	24 (9.6%)
Industry for device	10 (4.0%)
No external funding	4 (1.6%)
Private	50 (20.0%)
Unclear	21 (8.4%)
Primary outcome explicitly specified	
Yes	157 (62.8%)
No	93 (37.2%)
Intervention favored	
Treatment	139 (55.6%)
Control	9 (3.6%)
None	104 (41.6%)
Sample size calculation reported	
Yes	151 (60.4%)
No	99 (39.6%)
Was there at least one statistically significant outcome?	
Yes	215 (86.0%)
No	35 (14.0%)
Was the primary outcome statistically significant?	
Yes	173 (69.2%)
No	77 (30.8%)
Overall authors conclusion	
Positive	170 (68.0%)
Negative	34 (13.6%)
Neutral	46 (18.4%)
Adverse events	
Reported	170 (68.0%)
Non-reported	82 (32.8%)
Trial registered	
Yes	209(83.6%)

Most of the included trials had a parallel design (92.4%) and were efficacy trials (94.8%). Overall, 20.8% were placebo-controlled trials. An important part of the results of the trial was published in specialty cardiovascular journals (40.0%). In 139 studies (55.6%), the main goal was to evaluate the effects of pharmacological interventions. All geographic areas were represented; the majority of authors were from Europe (37.4%) and North America (26.0%). The funding source was specified in 91.6% of the included trials: most of the trials were funded by an academic grant or a research institute (37.6%), while industrial and pharmaceuticals funding were reported in 23.2% of the trials.

When analyzing the main results of trials, we observed that at least one statistically significant result was reported in 86.0% of the studies; in these studies, the primary outcome was reported to be statistically significant in 69.2% of the cases. The treatment was favored in 55.6% and control in 3.6%. At least one adverse event was reported in 68% of the trials. A data monitoring committee was reported in 42% and sample size calculation in 60.4%. A total of 83.6% of the studies were registered in one of the clinical trials registries out of the 77.5% were registered in clinicaltrials.gov.

4.1.2 Risk of Bias Assessment

Table 5 shows the RoB assessment results. Overall, 29.2% of the studies were deemed as low RoB, while the remaining studies were at either unclear (39.6%) or high risk (31.2%). We rated the domains sequence generation, allocation concealment, and selective reporting to be the domains most often at high RoB (13.2, 9.6, and 10.4%, respectively). We investigated whether the RoB was associated with the following variables: type of the intervention (drug vs. non-drug); single or multiple study centers; sample size; the presence of a Data Monitoring Committee; statistical significance of the primary outcome and trial registration (Table 6).

TABLE 5. Risk of bias (RoB) assessments by domain (n=250).

Domain	Risk of bias assessment N (%)		
	High	**Unclear**	**Low**
Sequence generation	33 (13.2%)	68 (27.2%)	149 (59.6%)
Allocation concealment	24 (9.6%)	51 (20.4%)	175 (70.0%)
Blinding: participant and personnel	11 (4.4%)	112 (44.8%)	127 (50.8%)
Blinding: outcome assessor	11 (4.4%)	33 (13.2%)	206 (82.4%)
Incomplete outcome data	8 (3.2%)	57 (22.8%)	185 (74.0%)
Selective reporting	26 (10.4%)	67 (26.8%)	157 (62.8%)
Other bias	36 (14.4%)	106 (42.4%)	108 (42.8%)
Overall RoB	78 (31.2%)	99 (39.6%)	73 (29.2%)

TABLE 6. Multivariable regression analyses for all included trials, and trials with and without stated funding from the industry*.

	All trials (N = 250)		**Industry-funded trials (N = 106)**		**Non-industry funded trials (N = 119)**	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Drug trial (vs. non-drug trial)	0.53 (0.29 – 0.97)	0.04	0.49 (0.18 – 1.27)	0.15	0.50 (0.20 – 1.20)	0.12
Multicentre (vs. single center)	0.39 (0.18 – 0.80)	0.01	0.13 (0.02 – 0.61)	0.02	0.80 (0.32 – 2.00)	0.64
Sample size (>500 vs. smaller)	0.67 (0.34 – 1.31)	0.24	0.60 (0.23 – 1.56)	0.29	1.72 (0.52 – 6.86)	0.40
Data Monitoring Committee (yes vs. no)	0.59 (0.32 – 1.09)	0.09	0.36 (0.13 – 0.96)	0.045	0.91 (0.37 – 2.27)	0.84
Primary outcome statistically significant (vs. not)	0.92 (0.48 – 1.74)	0.80	0.52 (0.81 – 1.11)	0.49	1.36 (0.54 – 3.38)	0.51
Trial registration reported (vs. not reported)	0.06 (0.003 – 0.31)	<0.01	0.19 (0.01 – 1.28)	0.15	1.13 (0.01 – 0.75)	0.06

*Funding was not reported in N = 25 studies

TABLE 7. Risk of bias assessments by domain in studies funded by the industry or non-industry (N = 250).

RoB domain	Funding source (industrial vs. non-industrial)				
	Industrial	**N (%)**	**Non-industrial**	**N (%)**	**P value**
Random sequence generation	Low	66 (62.3)	Low	71(59.7)	0.4533
	Unclear	32 (30.2)	Unclear	33 (27.7)	
	High	8 (7.5)	High	15 (12.6)	
Allocation concealment	Low	90 (84.9)	Low	76 (63.9)	0.0014*
	Unclear	13 (12.3)	Unclear	32 (26.9)	
	High	3 (2.8)	High	11 (9.2)	
Blinding participant and personnel	Low	70 (66.0)	Low	51 (42.9)	0.0001*
	Unclear	35 (33.0)	Unclear	61 (51.3)	
	High	1 (0.94)	High	7 (5.9)	
Blinding outcome assessor	Low	95 (89.6)	Low	95 (79.8)	0.1198
	Unclear	8 (7.5)	Unclear	19 (16.0)	
	High	3 (2.8)	High	5 (4.2)	
Incomplete outcome data	Low	86 (81.1)	Low	91 (76.5)	0.1734
	Unclear	14 (13.2)	Unclear	25 (21.0)	
	High	6 (5.7)	High	3 (2.5)	
Selective reporting	Low	80 (75.5)	Low	86 (72.3)	0.8598
	Unclear	23 (21.7)	Unclear	29 (24.4)	
	High	3 (2.8)	High	4 (3.4)	
Other bias	Low	55 (51.9)	Low	47 (39.5)	0.1659
	Unclear	41 (38.7)	Unclear	56 (47.1)	
	High	10 (9.4)	High	16 (13.4)	
Overall RoB	Low	42 (39.6)	Low	30 (25.2)	0.0587
	Unclear	41 (38.7)	Unclear	53 (44.5)	
	High	23 (21.7)	High	36 (30.3)	
Statistical analysis was made by regression analysis. *Statistically significant results ($p < 0.001$).					

Of these variables, trial registration influenced overall RoB to the greatest extent (odds ratio [OR] 0.06, 95% CI 0.03–0.31). Drug trials were more likely to have a low RoB than non-drug trials (OR 0.53, 95% CI 0.29–0.97), and multicenter trials more likely than single center trials (OR 0.39, 95% CI 0.18–0.80).

When we investigated individual RoB intems separately: drug trials (OR 0.39, 95% CI 0.22–0.66) and registered trials (OR 0.39, 95% CI 0.18–0.83) were more likely to have low RoB for random sequence generation.

Drug trials (OR 0.51, 95% CI 0.28–0.93), registered trials (OR0.49, 95% CI 0.26–0.91), and multicenter trials (OR 0.49, 95% CI 0.26–0.91) were more likely to have low RoB for allocation concealment, while trials with a statistically significant result were more likely to have unclear or high RoB (OR 2.59, 95% CI1.34–5.31).

Registered trials (OR 0.18, 95% CI 0.06–0.43), trials larger than 500 participants (OR 0.47, 95% CI 0.24–0.92), and trials with a Data Monitoring Committee (OR 0.50, 95% CI 0.28–0.87) had more often low RoB for the blinding of participants and personnel while the blinding of outcome assessors was more often low RoB in multicenter trials (OR 0.42, 95% CI 0.19–0.89) and registered trials (OR 0.27, 95% CI 0.12–0.63).

There were no factors that increased the likelihood of low RoB for incomplete outcome data; however, trials with statistically significant results decreased the likelihood of low RoB for incomplete outcome data (OR 2.40, 95% CI 1.18–5.21).

Larger trials with more than 500 participants were more likely to have low RoB for selective reporting (OR 0.44, 95% CI 0.19–0.95).

Registered trials (OR0.23, 95% CI 0.08–0.56) and multicenter trials (OR 0.31, 95% CI0.16–0.59) were more likely to have low RoB for other biases.

4.1.3 Risk of Bias According to a Funding Source

When funding source was added as an additional independent variable to the multivariable regression model, funding did not seem to influence the likelihood of overall low RoB (industry funding: OR 0.76, 95% CI 0.40–1.45).

In the sub-group of industry-funded trials, multicenter trial and Data Monitoring Committee were factors that increased the likelihood of overall low RoB. None of the investigated factors influenced the overall RoB within the sub-group of trials with non-industry funding (Table 6). Compared with non-industry funded studies more industry funded studies were rated as low RoB (84.9 vs. 63.9%) and less were rated as unclear

(12.3 vs. 26.9%) or high RoB (2.8 vs. 9.2%) for allocation concealment ($p < 0.001$) (Table 7). More industry funded studies were rated low (66.0 vs.42.9%) and fewer were rated as unclear (33.0vs 51.3%) or high risk (0.94vs 5.9%) for the blinding of participants and personnel ($p<0.001$).

4.2 Change over Five Years in Important Measures of Methodological Quality and Reporting in Randomized Cardiovascular Clinical Trials

4.2.1 Descriptive Analysis

The main characteristics of included cardiovascular RCTs are shown in Table 8. Data from 2017 have been previously partly reported [55]. Values from 2012, some data on additional measures of methodological quality and reporting for both years and statistical comparisons were novel.

TABLE 8. Characteristics of cardiovascular trials from 2012(n=250) and 2017(n=250)

Characteristics	**2012, n (%)**	**2017, n (%)**	**p Value**
Type of Journal			<0.001
Specialty cardiovascular journal	96 (38.4%)	100 (40.0%)	
General cardiovascular journal	41 (16.4%)	46 (18.4%)	
Specialty medical journal	26 (10.4%)	49 (19.6%)	
General medical journal	50 (20.0%)	41 (16.4%)	
Other	37 (14.8%)	14 (5.6%)	
Continent of corresponding author			<0.05
Africa	3 (1.2%)	0 (0.0%)	
Asia	57 (22.8%)	65 (26.0%)	
Australia	10 (4.0%)	2 (0.8%)	
Europe (excluding UK)	70 (28.0%)	93 (37.2%)	
North America	89 (35.6%)	69 (27.6%)	
South America	8 (3.2%)	13 (5.2%)	

United Kingdom	13 (5.2%)	8 (3.2%)	
Total	250 (100%)	250 (100%)	
Study type			0.093
Efficacy/Superiority	244 (97.6%)	237 (94.8%)	
Equivalence	2 (0.8%)	3 (1.2%)	
Non-inferiority	4 (1.6%)	4 (1.6%)	
None of the above	0 (0.0%)	6 (2.4%)	
Study design			<0.01
Cluster	7 (2.8%)	0 (0.0%)	
Parallel	201 (80.4%)	231 (92.4%)	
Crossover	34 (13.6%)	15 (6.0%)	
Factorial	5 (2.0%)	4 (1.6%)	
Other	3 (1.2%)	0 (0.0%)	
Intervention type			<0.001
Alternative therapeutic	24 (9.6%)	32 (12.8%)	
Behavioral	0 (0.0%)	2 (0.8%)	
Cell therapy	0 (0.0%)	1 (0.4%)	
Communication,	4 (1.6%)	13 (5.2%)	
Device	17 (6.8%)	23 (9.2%)	
Diet, nutrition	26 (10.4%)	10 (4.0%)	
Drug	117 (46.8%)	139 (55.6%)	
Prevention or screening	43 (17.2%)	20 (8.0%)	
Rehabilitation or psychosocial	18 (7.2%)	6 (2.4%)	
Surgery or radiotherapy	1 (0.4%)	3 (1.2%)	
Other	0 (0.0%)	1 (0.4%)	
Type of control			0.628
Active intervention	153 (61.2%)	160 (64.0%)	
No intervention	10 (4.0%)	21 (8.4%)	
Placebo	86 (34.4%)	68 (27.2%)	
Other	1 (0.4%)	1 (0.4%)	

Was the study multicenter?			0.063
Yes	117 (46.8%)	157 (62.8%)	
No	131 (52.4%)	93 (37.2%)	
Unclear	2 (0.8%)	0 (0.0%)	
Was the study multinational?			<0.05
Yes	45 (18.0%)	69 (27.6%)	
No	205 (82.0%)	181 (72.4%)	
Where were participants recruited from?			<0.001
Developing country	3 (1.2%)	21 (8.4%)	
Transitional country	8 (3.2%)	13 (5.2%)	
Established market economy	239 (95.6%)	216 (86.4%)	
Who funded the study?			<0.001
Academic or Research institute	113 (45.2%)	94 (37.6%)	
Government	44 (17.6%)	24 (9.6%)	
Industry for device	4 (1.6%)	10 (4.0%)	
No external funding	3 (1.2%)	4 (1.6%)	
Pharmaceutical	36 (14.4%)	48 (19.2%)	
Private	13 (5.2%)	50 (20.0%)	
Unclear	37 (14.8%)	21 (8.4%)	
How was the study population selected?			0.775
Inpatients	144 (57.6%)	133 (53.2%)	
Outpatients	98 (39.2%)	116 (46.4%)	
Unclear	7 (2.8%)	1 (0.4%)	
Primary diagnostic category in the study			0.971
Circulatory system	250 (100%)	244 (97.6%)	
Congenital malformations	0 (0.0%)	1 (0.4%)	
Factors influencing health status	0 (0.0%)	2 (0.8%)	
Metabolic disease	0 (0.0%)	2 (0.8%)	
Unclear	0 (0.0%)	1 (0.4%)	

Footnote: Intervention categories were defined based on Wood et al., 2008 [56] Multicenter trials were defined as trials with two or more administratively distinct study centers. Multinational applied to the countries from which patients were enrolled. The economic status of the country was defined based on Panagiotou et al., 2013 [57].

TABLE 9. Changes in important measures of methodological quality and reporting

Study Characteristics	2012, *n* (%)	2017, *n* (%)	*P Value*
Funding source			0.002
Specified	243 (97.2%)	229 (91.6%)	
Not specified	7 (2.8%)	21 (8.4%)	
Consent obtained			0.895
Reported	250 (100%)	248 (99.2%)	
Not reported	0 (0.0%)	2 (0.8%)	
Number of patients approached to participate in the study			0.854
Reported	2 (0.2%)	12 (4.8%)	
Not reported	248 (99.8%)	238 (95.2%)	
Number of patients consented to participate in the study			0.534
Reported	2 (0.2%)	12 (4.8%)	
Not reported	248 (99.8%)	238 (95.2%)	
Number of participants randomized			0.972
Reported	2 (0.2%)	2 (99.8%)	
Not reported	248 (99.8%)	248 (2.0%)	
Number of participants analyzed			0.887
Reported	2 (0.2%)	1 (0.4%)	
Not reported	248 (99.8%)	249 (99.6%)	
Sample size calculation			<0.01
Reported	124 (49.6%)	151 (60.4%)	
Not reported	126 (50.4%)	99 (39.6%)	
Data Monitoring Committee			<0.001
Yes	86 (34.4%)	105 (42.0%)	
No	39 (15.6%)	94 (37.6%)	
Unclear	125 (50.0%)	51 (20.4%)	

Analysis described as intention to treat			0.120
Yes	232 (92.8%)	222 (88.8%)	
No	18 (7.2%)	28 (11.2%)	
Primary outcome specified in trial registry			0.823
Yes	135 (54.0%)	157 (62.8%)	
No	115 (46.0%)	93 (37.2%)	
Primary outcome was objective			0.652
Objective	247 (98.8%)	248 (99.2%)	
Subjective	3 (1.2%)	2 (0.8%)	
Type of primary outcome			0.124
Behavioural	20 (8.0%)	6 (2.4%)	
Biomarker	40 (16.0%)	21 (8.4%)	
Physiological	172 (68.8%)	206 (82.4%)	
Psychological	5 (2.0%)	5 (2.0%)	
Techniques/Training	8 (3.2%)	6 (2.4%)	
Quality of life	3 (1.2%)	1 (0.4%)	
Other	2 (0.8%)	3 (1.2%)	
At least one statistically significant outcome			0.899
Yes	213 (85.2%)	215 (86.0%)	
No	37 (14.8%)	35 (14.0%)	
Significant statistical primary outcome			<0.01
Yes	197 (78.8%)	173 (69.2%)	
No	53 (21.2%)	77 (30.8%)	
The author's overall conclusion			<0.01
Negative	32 (12.8%)	34 (13.6%)	
Neutral	18 (7.2%)	46 (18.4%)	
Positive	193 (77.2%)	170 (68.0%)	
Insufficient evidence (intermediate)	7 (2.8%)	(0.0%)	
Planning to collect adverse effects/events or side effects			<0.001

Reported	185 (74.0%)	121 (48.4%)	
Not reported	65 (26.0%)	129 (51.6%)	
Harms reported			<0.001
Yes	130 (52.0%)	170 (68.0%)	
No	120 (48.0%)	80 (32.0%)	
Blinding performed			0.087
Yes	126 (50.4%)	145 (58.0%)	
No	124 (49.6%)	105 (42.0%)	
Trial registered			0.238
Yes	135 (54.0%)	192 (76.8%)	
No	115 (46.0%)	58 (23.24%)	
Primary register			0.031
clinicaltrials.gov	124 (68.9%)	164 (78.4%)	
Other	56 (31.1%)	45 (21.6%)	
Primary outcome stated the same in trial registry and in the publication			<0.001
Yes	132 (52.8%)	183 (73.2%)	
No	76 (30.4%)	26 (10.4%)	
N/A	42 (16.8%)	41 (16.4%)	

The behavioral outcome included attitudes and specific (e.g., eating) behaviors; biomarkers were defined as markers measured as an indicator of biological or pathogenic processes or pharmacologic responses to an intervention; physiological outcomes reflected how a patient feels, functions, or survives; psychological and quality of life outcomes included different scales measuring these variables. We used ’no’ when something hasn’t been done when it could have been possible; and used ‘N/A’ when it doesn’t apply to that particular trial.

We observed significant differences in the country of origin defined based on the first author's affiliation between 2012 and 2017. In our 2017 sample, more publications were published in specialty medical journals (19.6% compared to 10.4%; the logistic regression result on the Type of Journal variable was: $p < 0.001$). In 2017 we included more RCTs with parallel design (92.4% compared to 80.4%; $p < 0.01$), and among the interventions there were more drug trials (55.6% compared to 46.8%) and surgical interventions (1.2% compared to 0.4%), ($p < 0.001$). In the 2017 sample, we had a larger number of multinational trials (27.6% compared to 18%), ($p < 0.05$) where developing (8.4% compared to 1.2%) and transitional economy countries (5.2% compared to 3.2%) were more often concerned ($p < 0.001$). In 2017 included trials were more often funded by pharmaceutical companies or industry ($p < 0.001$). Table 9 shows changes in important measures of methodological quality and reporting.

4.2.2 Change in Important Measures of Methodological Quality and Reporting

As compared to 2012, we observed an improvement in 2017 in the reporting of the presence of a data monitoring committee (42.0% compared to 34.4%; $p < 0.001$). As compared to 2012, there was a positive change in registering trials in trial registries in 2017 and, among clinical trial registries, the clinicaltrials.gov database had increased popularity (registration rate in clinicaltrials.gov was: 78.4% compared to 68.9%; $p = 0.03$). Also, significantly more RCTs reported sample size calculation (60.4% compared to 49.6%; $p < 0.01$) in 2017 as compared to 2012. Although fewer RCTs specified plan to collect adverse effects in 2017 (48.4% compared to 74%; $p < 0.001$), they reported harms more often in 2017 (68% compared to 52%; $p < 0.001$).

When we investigated the reporting of results, we observed that the number of RCTs with statistically significant results of the primary outcome was lower in the 2017 sample (69.2% compared to 78.8%; $p <0.01$). Further, there were more publications with neutral conclusions in 2017 (18.4% compared to 7.2%; $p < 0.01$). There were no statistically significant differences between 2012 and 2017 in the number of intentions to treat analyses, in the type of outcomes (as most outcomes were objective), or specific types of primary outcomes.

4.2.3 Change in Risk of Bias

We provided a RoB assessment by each domain for trials published in 2012 and 2017 year (Table 10). Compared with 2012, more 2017 RCTs were rated low (70.4% compared to 38.8%) and fewer were rated unclear (20.4% compared to 50%; $p < 0.001$) risk for allocation concealment. Fewer 2017 RCTs were rated low (50.8% compared to 65.6%; $p < 0.001$) risk for blinding of participants and personnel, for blinding of outcome assessors (82.4% compared to 90.8%; $p < 0.001$), and selective outcome reporting (62.8% compared to 80.0%; $p < 0.001$). A similar proportion of 2017 RCTs were rated low risk for random sequence generation (59.6% compared to 56.0%), and for incomplete outcome data (74% compared to 73.6%;) compared to 2012. In 2017, more RCTs were rated low (42.8% compared to 33.6%) risk for other RoB ($p < 0.01$). More trials were rated low (29.2% compared to 21.2%) for overall RoB in 2017 compared to 2012 ($p < 0.01$).

In 2017, multicenter trials (OR 0.39, 95% CI 0.18 to 0.80), drug trials (OR 0.53, 95%CI 0.29 to 0.97), and registered trials (OR 0.06, 95% CI 0.003 to 0.31) were also more likely to have a low overall RoB. In 2012, there was not yet a significant difference between multicenter or single-center trials (OR 0.52, 95% CI 0.24 to 1.22), drug trials, and non-drug trials (OR 0.82, 95% CI 0.44 to 1.56). Trial registration was not yet shown to have positive effects on RoB in 2012 either (OR 0.85, 95% CI 0.38 to 1.84).

TABLE 10. Risk of bias assessments by domain in 2012 (n = 250) and in 2017 (n = 250)

	N (%) in 2012	RoB Domains	N (%) in 2017
Random sequence generation			0.381
Low	140 (56.0%)	149 (59.6%)	
Unclear	95 (38.0%)	68 (27.2%)	
High	15 (6.0%)	33 (13.2%)	
Allocation concealment			<0.001
Low	97 (38.8%)	175 (70.0%)	
Unclear	125 (50.0%)	51 (20.4%)	
High	28 (11.2%)	24 (9.6%)	
Blinding participants and personnel			<0.001
Low	164 (65.6%)	127 (50.8%)	
Unclear	73 (29.2%)	112 (44.8%)	
High	13 (5.2%)	11 (4.4%)	
Blinding outcome assessors			<0.001
Low	227 (90.8%)	206 (82.4%)	
Unclear	19 (7.6%)	33 (13.2%)	
High	4 (1.6%)	11 (4.4%)	
Incomplete outcome data			0.469
Low	184 (73.6%)	185 (74.0%)	
Unclear	60 (24.0%)	57 (22.8%)	
High	6 (2.4%)	8 (3.2%)	
Selective outcome reporting			<0.001
Low	200 (80.0%)	157 (62.8%)	
Unclear	48 (19.2.0%)	67 (26.8%)	

High	2 (0.8%)	26 (10.4%)	
Other bias			<0.01
Low	84 (33.6%)	108 (42.8%)	
Unclear	131 (52.4%)	106 (42.4%)	
High	35 (14.0%)	36 (14.4%)	
Overall bias			<0.01
Low	53 (21.2%)	73 (29.2%)	
Unclear	142 (56.8%)	99 (39.6%)	
High	55 (22.0%)	78 (31.2%)	

5. Discussion

5.1 Methodological Quality and Risk of Bias Assessment of Cardiovascular Disease Research: Analysis of Randomized Controlled Trials Published in 2017

5.1.1 Summary of Main Findings

To our knowledge, this is the first research evaluating the RoB and its association with specific trial characteristics in a randomly selected sample of clinical trials in adult cardiovascular disease. Included trials were mainly parallel RCTs investigating the efficacy of an intervention, with a very diverse trial scope and published in a variety of cardiovascular and general medical journals. Of the 250 studies included, more than 85% have reported at least one statistically significant result, with the primary outcome significant in 69%. Treatment was favored in 55% of the studies, and adverse events were reported in 68%. Less than one-third of our samples were overall low RoB, while the other two-thirds were unclear or high RoB. Sequence generation, allocation concealment, and selective reporting were the RoB domains most frequently rated at high risk. Trial registration influenced overall RoB to the greatest extent. Drug trials were more likely to be at low RoB than non-drug trials, and multicenter trials were more likely at a low risk RoB than single-center trials. In the subgroup of industry-funded trials, multicenter trial and Data Monitoring Committee were factors that increased the likelihood of overall low RoB, while none of the investigated factors influenced the overall RoB within the subgroupof non industry funded trials. Significant differences were found in the RoB for the domains allocation concealment and the blinding of participants and personnel between industry-funded and nonindustry funded trials, with industry funded trials more often rated at low risk.

5.1.2 Strengths and Weakness of the Study

This study has several strengths. We aimed to select a sample of studies representative for all randomized controlled trials published in 2017; we did not exclude published trials based on the country, type of journal, type of participants, or type of intervention. Included trials were randomly selected from all eligible trials. We used the most well recognized tool for methodological assessment and the results indicated several areas of

methodological weaknesses. To increase the reliability of findings, both data extraction and RoB assessment were conducted by two independent researchers. However, there are some weaknesses also. This study was not pre-registered. Our study is limited by the included trials published in the English language only; conclusions cannot be generalized to trials published in other languages. We could not identify register entries or trial protocols for a subsample of trials, and it was difficult to properly evaluate the selective outcome reporting in these trials. We have not contacted the authors to get additional information about their trials; therefore, the assessments are solely based on published information. Additionally, our studies focused on the internal validity of trials, but have not assessed factors that may impact the external validity.

5.1.3 Discussion of Findings Considering Other Studies

Of the 250 analyzed trials, more than two-thirds (70.8%) were at high or unclear RoB, which is consistent with previous study results [44,45]. The RoB domains sequence generation, allocation concealment, and selective reporting was rated most often to be at high risk in our study. Trial registration had the most beneficial effect on RoB in our study. In previous studies, random sequence generation, allocation concealment, and selective reporting were shown to differ between registered and unregistered gynecology and fertility trials [46]. Registration was shown to be a factor influencing all RoB domains except selective outcome reporting in a sample of pediatric research trials [41]. Trial registration is a factor that has the potential to facilitate higher methodological quality [47]. We found that drug trials were more likely at a low RoB than non-drug trials. This might be in connection with the strict regulations surrounding drug trials. Differences in protocol quality [48] registration and publication tendencies were described already in previous publications [49,50], between trials with regulated and non-regulated interventions. In our study, multi-center trials have demonstrated lower RoB compared with single-center trials. This is consistent with the conclusions of Landoni et al., who underlined bias issues characteristic for single-center trials (e.g., local effect bias, selection and performance bias, detection and reporting bias, analysis and attrition bias, concomitant therapy bias, low fragility index, and publication bias). Caution is advised for the results of single-center RCTs [51].

The source of funding may have an important impact on trial planning, conduct, and reporting [52-54]. In our study, we investigated the role of funding sources on RoB by

comparing trials funded or not by the industry. In our study, industry funded studies were rated more often low for the allocation concealment and the blinding of participants and personnel, as non-industry- funded studies. Our findings on the higher probability of industry-funded trials to have adequate blinding are supported by the results of a similar study conducted in pediatric RCTs [24,54]. The blinding of participants and personnel may not always be feasible; however, studies should attempt blinding wherever possible.

5.1.4 Implications for Practice and Future Research

Our results underline the need of further improvement in the process of planning and performing a clinical trial in the field of CVD research. Trial registration was associated with a larger likelihood of low RoB, therefore mandatory trial registration should be endorsed and enforced by ethic committees, funders, and journal editors. Further favorable trial features associated with the lower RoB were multicenter trials, larger trials with more than 500 participants, and trials with a Data monitoring Committee. Trials not funded by the industry were more often at a high RoB for the allocation concealment and the blinding of participants and personnel, indicating, that studies without industry involvement need to pay greater attention to following certain methodological recommendations. The same is applicable for cardiovascular research trials investigating the effects of a non-drug intervention. In the present study, we focused on the methodological quality of CVD research trials but did not assess reporting issues in detail. This may need further assessed in the future.

5.2 Change over Five Years in Important Measures of Methodological Quality and Reporting in Randomized Cardiovascular Clinical Trials

5.2.1 Summary of Main Findings

We observed that cardiovascular RCTs changed significantly from 2012 to 2017 years in several characteristics related to their study design and reporting. Respectively, RCTs in the 2017 sample were published mostly in specialty cardiovascular journals with a higher number of authors from Asia and Europe compared to trials published in 2012. The 2017 sample included more parallel trials evaluating drug interventions. The number of

industry-funded clinical trials increased from 2012 to 2017, while the number of trials funded by the academy decreased. In the 2017 sample, more trials were from developing and transitional economy countries. Multinational trials had a significantly higher proportion in the 2017 sample compared with 2012.As compared to 2012, in 2017 there were significant changes in important measures of methodological quality and reporting, including an improvement in the reporting of the presence of a data monitoring committee, and a positive tendency of registering trials in trial registries. Also, we observed that significantly more RCTs reported sample size calculations in 2017 as compared to 2012. We also observed notable changes over five years in the ability of cardiovascular RCTS to properly estimate the true intervention effect. The 2017 trials were more likely to have a low RoB than 2012 for overall RoB. However, the 5-year change was not clearly in the direction of improvement, as we observed a lower number of RCTs with a low RoB for blinding of participants and personnel and blinding of outcome assessors in 2017 as compared to 2012. In 2017, multicenter trials drug trials, and registered trials were also more likely to have a low overall RoB than single center, non-drug, non-registered trials. In 2012, these RoB differences were not yet present between RCTs with specific characteristics.

5.2.2 Strengths and Weaknesses of the Study

For both investigated publication years we selected our sample randomly from Cochrane CENTRAL as the most comprehensive resource of RCTs. The samples covered areas of the prevention, diagnosis, and treatment of cardiovascular diseases, including acute myocardial infarction, heart failure, arrhythmia, coronary revascularization, and chronic coronary artery disease. Most of our trials were registered in clinical trial registries, so essential trial details were double checked in both the full text article and the registry. We used the most accurate tool for RoB (methodological quality) assessment including RCTs. Two independent reviewers performed data extraction and RoB assessment; discrepancies were always resolved by discussion.

This study has also some limitations. Our sample included about 10% from all eligible cardiovascular disease trials published in the years 2012 and 2017 only in the English language. This study was not pre-registered with a detailed statistical analysis plan. We have chosen cardiovascular trials with participants aged 18years or older, therefore our results are not applicable to pediatric trials in cardiovascular medicine.

As we started our research in the year 2018 and intended to evaluate changes over time, we decided to investigate publications from 2017, and from five years earlier, from 2012. However, since 2017, the publication characteristics may have changed further. It also has to be emphasized that the 2017 sample differed from the 2012 sample in many study design and reporting features, which may have impacted our RoB results. Although we have collected supplementary information from trial registries and published protocols, this was not detailed enough to compare information across these different information sources.

5.2.3 Discussion of Findings Considering Other Studies

The RoB in CVD RCTs generally decreased over the 5 years. This is consistent with the conclusions of Vinkers et al. [58], who reported significant improvement in the level of RoB of RCTs over the past years in connection with increased knowledge about mandatory trial registration and journal requirements. Our study revealed that trial registration positively influenced RoB. This finding is in line with prior research investigating clinical trial registration and the RoB. A study among clinical trials included in Cochrane systematic reviews of interventions published between 2014 and 2019 found that clinical trial registration was associated with a low RoB or all bias domains examined except for attrition bias, and for overall RoB [59]. Registered trials were at lower RoB than non-registered trials in Latin America and the Caribbean [60]. Prospectively registered trials had a significantly lower RoB compared to unregistered trials across all domains of health research [61].We found that multicenter trials were more likely at low RoB than single center trials. This could be associated with that multicenter studies allow for better control of study quality than single center studies [62]. Our findings are consistent with Tamborska et al., who found that RCTs at lower RoB were more likely to use multicenter recruitment in neurology trials [63]. Our investigation has shown that drug trials had a more favorable impact on RoB than non-drug trials, which might be related to the strict regulations these pharmaceutical trials must follow. Similarly, Cho Y et al. found that most drug trials were at low RoB for blinding participants and personnel, while almost two-thirds of non-drug trials were at high RoB for blinding participants and personnel in cardiopulmonary resuscitation and emergency cardiovascular care [64]. Existing differences and the positive beneficial impact of regulations can be observed in the planning phase of trials when regulated clinical trial protocols were described to

follow reporting guidelines to a greater extent than non- regulated trials [65].

5.2.4 Implication for Practice and Future Research

We observed some improvements with respect to some important study design features and some specific RoB domains over 5 years. However, there were also some methodological features and RoB domains that changed in an unfavorable direction or remained unchanged. This points to the need to continue to pay close attention to the planning and conduct of RCTs in the field of cardiovascular clinical research.

This study identified several features of clinical trial planning and conducting that need further improvement in the field of cardiovascular research. Improvements in study design, conduct, and reporting will decrease research waste and support the realization of evidence-based decisions in the field of cardiology. Journal adoption of existing reporting guidelines may lead to potential mechanisms to ensure improvements in overall clinical trial quality. We would emphasize that a paper that adheres to reporting guidelines better places a clinical decision-maker to assess the quality of the trial design and conduct and to interpret its findings accurately, improving the potential of the research to be impactful and meaningful to patients and clinical practice.

5.2.5 Conclusion

Almost two-thirds of RCTs published in 2017 in the field of CVD research were at high or unclear RoB. This indicates a need for more rigorous trial planning and conduct. Prospective trial registration is a factor that predicts the lower RoB.

We call cardiovascular disease researchers to try to avoid possible risks of bias during planning and conducting their cardiovascular RCTs and follow reporting guidelines when communicating their results to ensure the validity of trial results and their effective translation to evidence-based cardiovascular patient care.

6. Novel findings and practical applications

1. Our results underline the need of further improvement in the process of planning and performing a clinical trial in the field of CVD research.
2. Trial registration was associated with a larger likelihood of low RoB, therefore mandatory trial registration should be endorsed and enforced by ethic committees, funders, and journal editors.
3. Favorable trial features associated with the lower RoB were multicenter trials, larger trials with more than 500 participants, and trials with a Data Monitoring Committee.
4. Trials funded by the academy were more often at a high RoB for the allocation concealment and the blinding of participants and personnel than those funded by the industry, indicating, that studies without industry involvement need to pay greater attention to following certain methodological recommendations. The same is applicable for cardiovascular research trials investigating the effects of a non-drug interventions.
5. Our study identified several features of clinical trial planning and conducting that need further improvement in the field of cardiovascular research, including a lower number of RCTs with a low RoB for blinding of participants and personnel and blinding of outcome assessors in 2017 as compared to 2012. Improvements in study design, conduct, and reporting will decrease research waste and support the realization of evidence-based decisions in the field of cardiology.
6. As compared to 2012, in 2017 there were significant changes in important measures of methodological quality and reporting, including an improvement in the reporting of the presence of a data monitoring committee, and a positive tendency of registering trials in trial registries. Also, we observed that significantly more RCTs reported sample size calculations in 2017 as compared to 2012.

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8. List of publications

8.1 Articles related to the thesis

- ***Baasan O,*** *Freihat O, Nagy DU and Lohner S. Methodological Quality and Risk of Bias Assessment of Cardiovascular Disease Research: Analysis of Randomized Controlled Trials Published in 2017. Front. Cardiovasc. Med. 2022; 9:830070. doi: 10.3389/fcvm.2022.830070 (IF$_{2022}$:* ***3.6)***
- ***Baasan O.*** *Freihat O, Nagy D, Lohner S. Change over Five Years in Important Measures of Methodological Quality and Reporting in Randomized Cardiovascular Clinical Trials. J. Cardiovasc. Dev. Dis. 2024; 11, 2. https://doi.org/10.3390/ jcdd11010002 (IF$_{2022}$:* ***2.4)***

8.2 Additional articles

- *Sándor-Bajusz KA, Kraut A,* ***Baasan O.*** *Márovics G, Berényi K, Lohner S. Publication of clinical trials on medicinal products: follow-up on trials authorized in Hungary. Trials. 2022 Apr 21;23(1):330. doi: 10.1186/s13063-022-06268-y. PMID: 35449017; PMCID: PMC9022244. (IF$_{2022}$:* ***2.5)***

8.3 Abstracts and oral presentations

- ***Odgerel Baasan 1.*** *Szimonetta Lohner 1The Conduct and Reporting of*

  Cardiovascular Disease Research: An Analysis of Randomized Controlled Trials Published in 2017 and Evaluation of Change over 5Years. ***Medical Conference for PhD Students and Experts of Clinical Sciences: Book of abstracts Pécs, Hungary:*** *University of Pécs Doctoral Student Self-Government, (2018) 111 p. pp.6-6,1p*
- ***Odgerel Baasan1****, Omar Freihat PhD1, Dávid Nagy PhD2, Szimonetta Lohner,MD, PhD1, 2 A descriptive analysis of randomized controlled trials of cardiovascular disease research published in 2017.* ***10 th INTERDISCIPLINARY DOCTORAL CONFERENCE 2021 BOOK OF ABSTRACTS****. Pécs, Hungary : Doctoral Student Association of the University of Pécs (2018) 361 p. pp.110-110 , 17*

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Submission of the doctoral dissertation and declaration of the originality of the dissertation

The undersigned,
Name: ODGEREL BAASAN
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on this day submitted my doctoral dissertation entitled: ASSESSMENT OF METHODOLOGICAL QUALITY IN RANDOMIZED CARDIOVASCULAR CLINICAL TRIALS

to the FOOD SCIENCES, NUTRITION, DIETETICS, AND HYDRATION Programme
PR-8

of the Doctoral School of Health Sciences, Faculty of Health Sciences, University of Pécs.

Names of the supervisor(s): DR. SIMONETTA LOHNER

At the same time, I declare that
- I have not submitted my doctoral dissertation to any other Doctoral School (neither in this country nor abroad),
- my application for degree earning has not been rejected in the past two years,
- in the past two years I have not had unsuccessful doctoral procedures,
- my doctoral degree has not been withdrawn in the past five years,
- my dissertation is independent work, I have not presented others' intellectual work as mine, the references are definite and full, on preparation of the dissertation I have not used false or falsified data.

Furthermore, I declare that I contribute to the request of DOI identification of my doctoral dissertation.

Dated: 30 th January 2024

Odgerel

signed by Candidate

Supervisor

Co-supervisor