Redundant Clinical Trials Challenging Research Ethics and Hurting Patients: An Example of Clinical Trials Conducted in China Evaluating Statins among Patients with Coronary Artery Disease

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Redundant Clinical Trials Challenging Research Ethics and Hurting Patients

An Example of Clinical Trials Conducted in China Evaluating Statins among Patients with Coronary Artery Disease

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Summary Box

Section 1 Redundant clinical research wastes resources and hurts patients who may be denied effective treatment, especially in the settings of placebo-controlled trials. It has been suspected that redundancy has become a serious challenge in clinical research from mainland China, the biggest producer of scientific publications.

Section 2 Nearly 2,000 redundant trials have been initiated in mainland China since 2007 when clinical practice guidelines recommended statins to all patients with coronary artery

disease. Patients treated in the control group have experienced 3,032 extra major adverse cardiac events owing to deprivation of statins, including 534 deaths, 838 cases of myocardial infarction, and 185 cases of stroke. The unprecedented redundancy of clinical trials necessitates urgent reform to protect patients.

Abstract

Objective The Chinese Medical Association has developed two clinical practice guidelines (CPGs) to recommend statins therapy to all patients with coronary artery disease (CAD) since 2007. Clinical trials conducted thereafter may be redundant and unethical. The objective of the study was to estimate the number of extra major adverse cardiac events (MACEs) owing to deprivation of statins among patients who were treated in the control group of redundant clinical trials conducted in mainland China.

Design Cross-sectional study**.**

Methods We defined redundant clinical trials as randomized or quasi-randomized trials that have been initiated to compare statins with placebo or no treatment among patients with any subtype of CAD in mainland China since 2008, i.e., one year after statins were recommended by CPGs. We searched bibliographic databases, including PubMed, Embase, the Cochrane Controlled Register of Trials, and SinoMed, for redundant trials.

Main Outcome and Measure The number of extra MACEs that were attributable to the deprivation of statins among patients in the control groups of redundant trials.

Results Since 2008, 1,954 redundant clinical trials had been initiated or continued recruiting, in which 87,787 patients received placebo or no treatment (control group) for 20,915 person-years. More than 4,116 extra clinical events were reported, including 3,032 MACEs and 1,084 other or unspecified events. The 3,032 MACEs included 534 deaths, 838 cases of myocardial infarction, 185 cases of stroke, 91 cases of revascularization, 376 cases of heart failure, and 1,019 cases of recurrent or deteriorated angina pectoris.

Conclusions Nearly two thousand redundant clinical trials on statins among patients with CAD were identified from mainland China. Such trials have been harming patients, who have experienced thousands of unnecessary MACEs, including hundreds of deaths. The scale of redundancy may be much larger in the entire clinical research community, which necessitates urgent reform to protect patients.

Introduction

When investigators overlook existing evidence, clinical trials may be initiated to address treatment uncertainty that has already been solved by previous studies.[1] Failing to establish equipoise, such clinical trials are deemed redundant and inappropriate by the research community as they waste resources and unnecessarily put patients at risk of harm. This unnecessary replication is highly problematic in the context of placebo-controlled trials, which are legitimate only if there is no known treatment option.[2,3] Otherwise, patients in the control group who only take placebo are denied an known effective treatment, violating the ethical principles of the conduct of clinical trials.[4]

Cumulative meta-analysis can be used to show how the overall estimate of an effect of a treatment changes overtime as individual trials are added to the evidence pool chronologically.[5] Cumulative meta-analysis has been adapted to evaluate when sufficient evidence has accrued to reach a conclusion and, subsequently, to identify the redundancy of additional trials.[5] However, it is challenging for investigators to decide the adequacy of existing evidence solely based on cumulative meta-analysis, not only because of the varied methodological preference and interpretation of results, but also because of the possibility of the overall estimates at early stages being overridden by subsequent trials.[6] Instead, clinical practical guidelines (CPGs), which ideally are both consensus-oriented and systematic review-based, take into account the balance of potential harms and benefits as well as other issues such as feasibility and patient values. As such, the recommendations in CPGs are more comprehensively adopted by the research community, and therefore address treatment uncertainty more convincingly.[7]

Recently the research community has been witnessing a proliferation of scientific publications from China.[8] However, there are concerns over the redundancy of the research, both at the primary and secondary levels of evidence.[9] In this study, we evaluated the potential redundancy of clinical trials from mainland China. Specifically, we identified randomized or quasi-randomized controlled trials (RCTs) evaluating statins for treating coronary artery disease (CAD) which were conducted after the benefits of statins were affirmed by CPGs. We estimated the extra clinical events, including the major adverse cardiac events (MACEs), that were experienced by patients who did not receive statins in the redundant trials.

Methods

In this cross-sectional study we retrieved redundant trials from bibliographic databases, therefore it was not subject to institutional review board approval. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[10] Because this study was a literature review based on open-source data and did not include research participants, it was not subject to institutional review board approval. The study was conducted without involvement of patients or the public.

Inclusion/Exclusion Criteria

We conducted a literature review to identify eligible trials, defined as RCTs or quasi RCTs[11] comparing statins with placebo or no treatment among patients with CAD, including stable angina pectoris (SAP), acute coronary syndrome (ACS), unstable angina pectoris (UAP), and myocardial infarction (MI) (e.g., acute MI, old MI, non-ST elevation MI, and ST elevation MI). We excluded ischemic heart failure because the benefits of statins were not confirmed among those patients.[12] Trials assessing seven types of statins were eligible: lovastatin, simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin, and pitavastatin. We also included trials comparing statins and other pharmacological interventions, including herbal medicine, as a combination therapy as long as the control group was placebo or no treatment. Trials were excluded if surgical procedures, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), were conducted as part of the intervention.

We included trials published as journal articles in Chinese or English until December 2019. Systematic reviews and meta-analyses were excluded. We focused on trials recruiting patients from mainland China, meantime, we included similar trials outside of China as a comparison.

Literature search

We searched three English bibliographic databases – PubMed, Embase, and Cochrane Controlled Register of Trials (CENTRAL) – plus one Chinese bibliographic database – SinoMed (formerly known as Chinese Biomedical Database). The search strategy and search terms were developed by informationists from the Welch Medical Library at the Johns Hopkins University and the Medical Library at the Peking Union Medical College. We performed the initial search on January 1st, 2020 and completed an updated search on March 1st, 2020.

Screening and Data Abstraction

We screened titles/abstracts, and full-text articles with two authors (YJ and JW) independently and resolved all discrepancies through discussion with a third author (XW). We extracted the following items from eligible trials inside China: type of statins, type of CAD, sample size, follow-up, recruitment period, ethics committee approval, trial registration, number of centers, allocation scheme, and clinical events if reported. Only sample size was extracted from trials outside China.

Primary Analysis

In March and April 2007, two CPGs developed by the Chinese Society of Cardiology (a branch of the Chinese Medical Association) were published which strongly recommended (based on

Grade A evidence) statins therapy for patients with SAP and ACS, respectively.[13,14] We defined redundant trials as those that were either initiated or continued recruiting new patients from mainland China at least one year after CPGs were published. The one-year lag was added to allow trialists to adopt the CPGs and terminate the trials accordingly. Thus, March 2008 was the cutoff timepoint for SAP only, while April 2008 as the cutoff timepoint for other subtypes of CAD.

The primary outcome of the study was the absolute number of extra clinical events, including MACEs, that were experienced by patients who did not receive statins in the redundant trials inside of China. We recorded all types of clinical events as reported by eligible trials. A broad MACE was defined to include all-cause mortality or cardiac-related mortality, new or recurrent MI, stroke, re-hospitalization, revascularization, and recurrent or exacerbated angina pectoris (AP), to accommodate the wide range of MACEs reported by individual trials. The extra clinical events were estimated by risk difference between the statins group and the control group from individual trials, i.e., the difference between the number of actual clinical events in the control group and the expected clinical events if patients in the control group were treated as in the statins group. We only included the patients recruited after the cutoff timepoints in partially redundant trials, assuming a constant recruiting process.

We compared the trials between inside and outside of China by the number of trials and the patients treated in the control group by year of publication. We used the Mann-Whitney test for comparisons of non-Gaussian distributions. The data analysis was conducted in SAS 9.4.

Sensitivity Analysis

We explored multiple cutoff timepoints to define redundant trials, including immediately, 6 months, 2 years, and 5 years after the CPGs were published. Additionally, we conducted three cumulative meta-analyses with random effect to estimate the timepoints when sufficient evidence was accrued to show that statins could statistically significantly reduce the incidence of a combination of all-cause mortality, MI, and revascularization among patients with SAP, UAP, and MI, respectively,[15] then applied those timepoints to define redundant trials. We used the more recent timepoint when the patients in a trial were covered by multiple cumulative meta-analyses. We estimated the absolute number of extra clinical events, including MACEs, that were experienced by patients who did not receive statins in the redundant trials under each of these scenarios.

Results

Characteristics of Eligible Trials

By December 2019, 2481 trials about use of statins for CAD were published from mainland China whereas 78 were published from elsewhere (Figure 1 and Supplement 1). There were 239,222 patients treated in the trials inside of China, of which 115,823 were in control groups that did not receive statins. In comparison, 45,825 patients were treated in similar trials outside of China, 22,766 of which were in control groups. The number of the trials and the patients treated in the control group are compared between inside and outside of China chronologically in Figure 2-3.

The characteristics of trials are shown in Table 1. Of 2,481 trials inside of China, 963 (38.81%) recruited patients with unspecified subtypes of CAD, while more than a half (1,392, 56.11%) evaluated Atorvastatin. Most trials (2,465, 99.36%) were published in Chinese, were randomized (2,406, 96.98%), and reaffirmed the benefits of statins (2,478, 99.88%) by concluding superiority of statins over the control intervention. Only 88 (3.54%) trials reported funding source, mainly from government agencies (79, 89.77%), and only 249 (10.04%) trials reported approval from local ethics committee. None of the trials were registered in trial registries.

Table 1 Characteristics of Eligible Trials Inside of China

Item		All Eligible Trials		Trials Reported Clinical Events		Trials Not Reported Clinical Events	
		No.	%	No.	%	No.	%
No. of Eligible Trials		2481	100.00	568	100.00	1913	100.00
No. of Trials Reported IRB Approval		249	10.04	43	7.57	206	10.77
No. of RCTs		2406	96.98	548	96.48	1858	97.12
Disease Condition	CAD	963	38.81	134	23.59	829	43.34
	AP	795	32.04	170	29.93	625	32.67
	ACS	431	17.37	156	27.46	275	14.38
	MI	251	10.12	106	18.66	145	7.58
	Other	41	1.65	2	0.35	39	2.04
Type of Statins	Atorvastatin	1392	56.11	246	43.31	1146	59.91
	Simvastatin	578	23.30	192	33.8	386	20.18
	Rosuvastatin	259	10.44	42	7.39	217	11.34
	Other or Unclear	252	10.16	88	15.49	164	8.57

Total No. of Patients Treated	86*	70 – 110**	86*	70 – 110**	86*	70 – 110**
No. of Patients Treated in the Control Group	42*	33 – 53**	40*	32 – 52**	42*	34 – 53**
Follow-up (Day)	56*	28 – 90**	90*	56 – 180**	42*	28 – 84**

*Median.

**Upper and Lower Quartiles.

Only 568 (22.89%) trials inside of China reported clinical events, in which 27,156 patients were treated in the control group for 14,406 person-years. The median follow-up, in days, of trials reporting clinical events was longer than the ones not reporting clinical events (90 vs. 42, χ^2=367, P<0.01). In total the trials reported 7,469 extra clinical events, including 5,673 MACEs and 1,796 other or unspecified events. The MACE consisted of 939 deaths, 1,636 cases of MI, 376 cases of revascularization, 297 cases of stroke, 550 cases of HF, and 1,878 cases of recurrent or deteriorated AP.

Primary Analysis

The cutoff timepoints to define redundant trials in the primary analysis were set at March and April 2008, one year after the two CPGs were released on SAP and ACS, respectively. After the cutoff timepoints, 1,954 trials were initiated or continued recruiting, in which 87,787 patients were treated in the control group for 20,915 person-years.

In total 376 (19.24%) redundant trials reported clinical events, in which 16,288 patients were in the control group for 6,817 person-years. More than 4,116 extra clinical events were reported, including 3,032 MACEs and 1,084 other or unspecified events. The MACEs consisted of 534 deaths, 838 cases of MI, 185 cases of stroke, 91 cases of revascularization, 376 cases of HF, and 1,010 cases of recurrent or deteriorated AP (Table 2).

Table 2 Number of Extra Clinical Events

Item		Primary Analysis	Sensitivity Analysis				
		1-Year Lag	Based on CMA	No Lag	6-Month Lag	2-Year Lag	5-Year Lag
Cutoff Timepoint for Stable Angina Pectoris		March 2008	Jan 2003	March 2007	Sep 2007	March 2009	March 2012
Cutoff Timepoint for Other CAD		April 2008	Jan 2005	April 2007	Oct 2007	April 2009	April 2012
All Trials Recruiting After the Cutoff Timepoint							
No. of Trials		1954	2273	2064	1969	1843	1408
No. of Participants Recruited*		87787	103283	93047	90581	81365	60364
Person-Years Followed		20915	25854	22403	21702	19001	13161
Trials Reporting Clinical Events							
No. of Trials		376	478	410	387	341	232
No. of Participants Treated in the Control Group		16288	21395	17825	17090	14406	9377
Person-Years Followed		6817	9936	7629	7217	5818	3396
No. of Extra Clinical Events							
	Total	3032	4158	3393	3211	2614	1626
	Death	534	712	591	562	464	261
	MI	838	1188	958	897	708	433
MACE	Revascularization	91	147	115	104	63	21
	Stroke	185	235	204	193	172	138
	HF	376	456	394	384	349	238
	AP	1010	1422	1134	1072	860	537
Other Events		1084	1427	1168	1124	980	665
Total Events		4116	5585	4561	4335	3594	2291

Abbreviations

CMA: Cumulative Meta-Analysis; MACE: Major Adverse Cardiac Events; CPG: Clinical Practice Guideline; MI: Myocardial Infarction; HF: Heart Failure; AP: Angina Pectoris

*Patient recruited after the cutoff timepoint.

Sensitivity Analysis

Even allowing for a 5-year lag after the CPGs were released, i.e., after March/April 2012, there were 1408 redundant trials with 2,291 extra clinical events, including 1,626 MACEs and 665 other or unspecified events. The MACEs consisted of 261 deaths, 433 cases of MI, 138 cases of stroke, 21 cases of revascularization, 238 cases of HF, and 537 cases of recurrent or deteriorated AP (Table 2).

The cumulative meta-analyses showed that statins were known to reduce the incidence of MACEs statistically significantly among patients with UAP by 2002 and among patients with SAP or MI by 2004 (Supplement 2-4). After the time at which statins were shown to be effective by cumulative meta-analyses, 5,585 extra clinical events were reported by 478 redundant trials, including 4,158 MACEs and 1,427 other or unspecified events. The 4,158 MACEs consisted of 712 deaths, 1,188 cases of MI, 235 cases of stroke, 147 cases of revascularization, 456 cases of HF, and 1,422 cases of recurrent or deteriorated AP (Table 2).

Discussion

Our study identified thousands of redundant clinical trials conducted in mainland China causing thousands of extra clinical events experienced by patients owing to deprivation of statins during the trials. The unexpected scale of redundancy raises serious concerns over the ethical foundation of clinical research in mainland China.

Multiple system failures may lead to such a large scale of redundant trials. First, investigators may not be trained to realize the importance of clinical equipoise and consideration of existing evidence before initiating clinical trials. Second, investigators are under tremendous pressure to

produce publications which may also explain why only 20% of included trials reported clinical events; it is much easier and faster to conduct clinical trials on surrogate laboratory outcomes.[16,17] Third, where ethics approval is reported, the committees reviewing trial protocols fail in their responsibility to check the scientific foundation and protect participants from enrolling in harmful trials, and among the vast majority of trials that did not report ethics approval the investigators may have failed to obtain approval at all.[3,18] Fourth, journal editors fail to adequately evaluate the scientific value of the publications and by accepting manuscripts from such trials, have provided a means for redundant trials to be published and thereby validated the redundancy as acceptable. One possible explanation for this may be that some journals are so-called “predatory journals”, and may be more interested in pursuing profits rather than scientific merits.[19] Fifth, only a small proportion of trials reported funding source, most of which were either central or local government agencies, who failed to evaluate the scientific value of the redundant trials.[20] Last, none of included trials were registered in trial registries, of which a function is to reduce resource waste by declaring and presenting what has been conducted and what is currently being done in the clinical trial community.[21]

Our study confirmed previous studies which have suggested that external evidence, including systematic reviews, may be overlooked by researchers before initiating new clinical trials on similar topics.[22-24] However, even if systematic reviews confirm the benefits of a treatment in early stages of clinical research, it is challenging to know whether future trials may modify, or even reverse, that early conclusion, due to exaggerated positivity of early trials and the fact that later trials often comparatively have reduced effect sizes.[25] Consequently, it may not be appropriate to label some clinical trials as 'redundant' or 'unethical'. In our study however,

these concerns may be alleviated for two reasons. First, the redundant trials in our study consistently reaffirmed the benefits of statins among patients with CAD. This is quite unusual and differs from findings of other studies using cumulative meta-analyses to identify redundant trials, in which a proportion of subsequent trials were in favor of the control group.[5,23] The consistency of findings undermines the treatment uncertainties that are required to support the clinical equipoise to initiated subsequent clinical trials on similar topics. Second, most redundant trials in our study were initiated after CPGs were released (versus those trials that continued recruiting). The release of CPGs strongly recommending statins to all patients with CAD should completely disturb the clinical equipoise required to justify starting such trials. Moreover, we only included clinical trials conducted in mainland China so the redundant trials could not be justified by the unsatisfactory representativeness of Asian populations recruited in clinical trials in Western countries.[26]

We also confirmed a deep gap between Chinese and English literature.[27,28] Most of the included trials were published in Chinese and only indexed in Chinese bibliographic databases, while none of them was registered in trial registries. This may explain why systematic reviews that fail to search Chinese bibliographic databases often fail to include Chinese trials, even when Chinese trials on the clinical question exist.[29] It was also notable that most redundant trials inside of China were conducted years after the landmark trials outside of China were published, a phenomenon that could be possibly and partially explained by the language barrier.

Our findings may be only the tip of an iceberg. First, nearly 80% of eligible trials did not report clinical events, even with follow-up of more than one year. It is unclear whether no clinical events occurred in those trials, the events were not collected, or the events were simply not

reported. Second, the evidence is scarce on the publication rate of clinical trials in mainland China: it is challenging to estimate how many trials may have been conducted but not published. Third, our study was limited to only one drug class, one disease condition, one type of comparator, and only RCTs or quasi-RCTs. The scale of the redundancy remains unclear over the entire clinical trial community and it is unclear if similar redundancy exists among general biomedical research in mainland China.

There are several limitations of our study. First, we did not conduct a risk of bias assessment, a standard process in systematic reviews, because our primary goal was to estimate the absolute number of extra clinical events rather than the precise treatment effect on the population level and our study was not designed as a systematic review. In case of information bias, e.g., lack of masking, the extra clinical events may still be attributed to the treatment assignment, e.g., patients in the control group did not receive as much attention as fellow patients in the treatment group, which we believe would not threaten the validity of the conclusion.[30] On the other hand, selection bias, which may be from inappropriate randomization,[31] was not addressed. It is unclear how much impact these potential sources of bias may have on our results. Second, there are several reasons why we may have underestimated the extra clinical events, for example: we only searched one major Chinese bibliographic database[32] and it is possible we missed some eligible trials even though the coverage of SinoMed is reasonably sufficient;[28] we excluded trials that were not clearly specified as either RCTs or quasi-RCTs; and it is likely that some redundant trials failed to report clinical events, but we believed it would be inappropriate to extrapolate the number of events by assuming a similar incidence of clinical events between the trials reporting such events and those which did not. Third, we did not

evaluate the quality of the two CPGs as the anchor to define redundancy. It is possible that some researchers might not consider those CPGs, the only ones on CAD available at that time, as trustworthy, and therefore not follow them or consider that treatment uncertainty remains.

Unfortunately, we found redundant clinical trials initiated as recently as 2018. It is very likely that we will see more redundant trials being published in the near future unless dramatic actions are taken by stakeholders in mainland China, which may include, but are not limited to, altering the method to evaluate academic performance of researchers, legislating the responsibilities and requirements of ethic committees, reaching consensus about publishing requirements for journals, adapting the funding system, and mandating trial registration.

Conclusion

Nearly two thousand redundant clinical trials on statins among patients with CAD were identified from mainland China. Such trials have been harming patients, who have experienced thousands of unnecessary MACEs, including hundreds of deaths. The scale of redundancy may be much larger in the entire clinical research community, which necessitates urgent reform to protect patients.

Conflicts of Interest

None of the authors have reported conflicts of interest.

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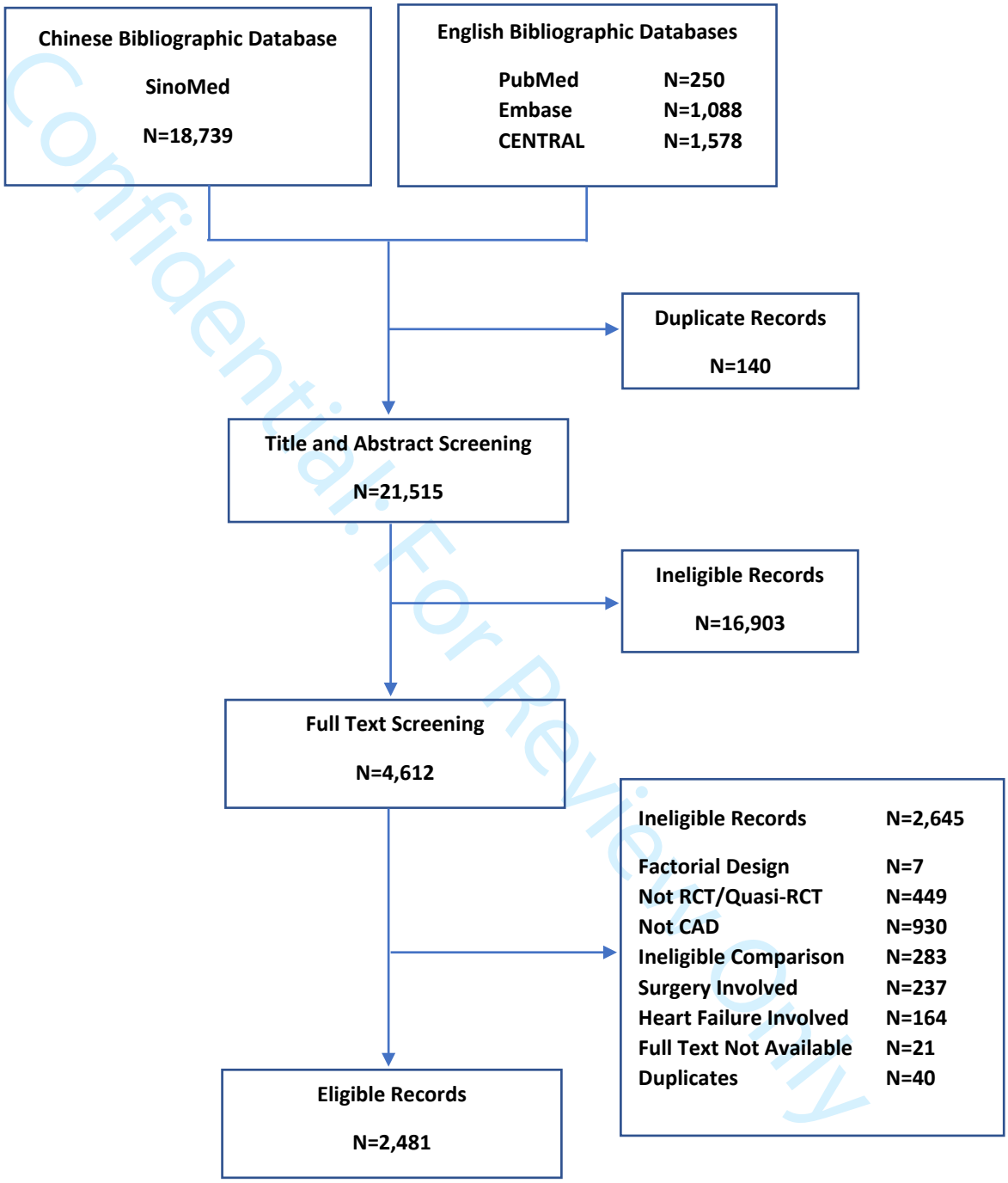
Figure 1 Selection of Eligible Trials Conducted Inside of China



Abbreviations

CENTRAL: the Cochrane Controlled Register of Trials; RCT: Randomized Controlled Trials; CAD: Coronary Artery Disease.

Figure 2 Comparison of the Number of Eligible Trials between Inside and Outside of China

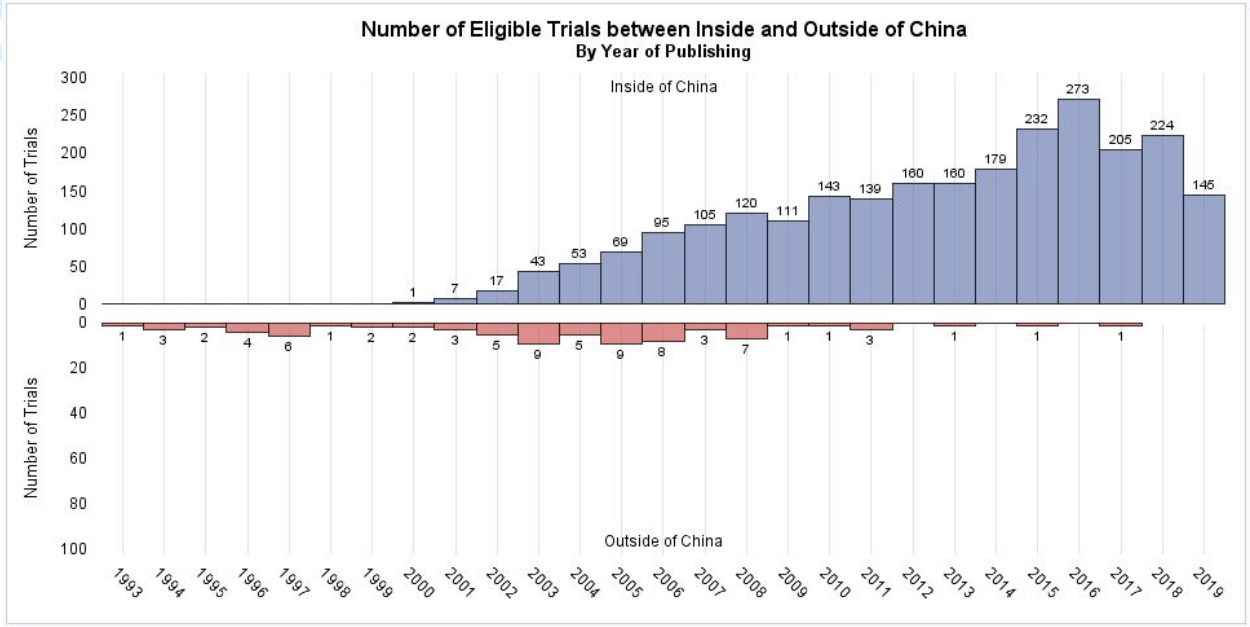
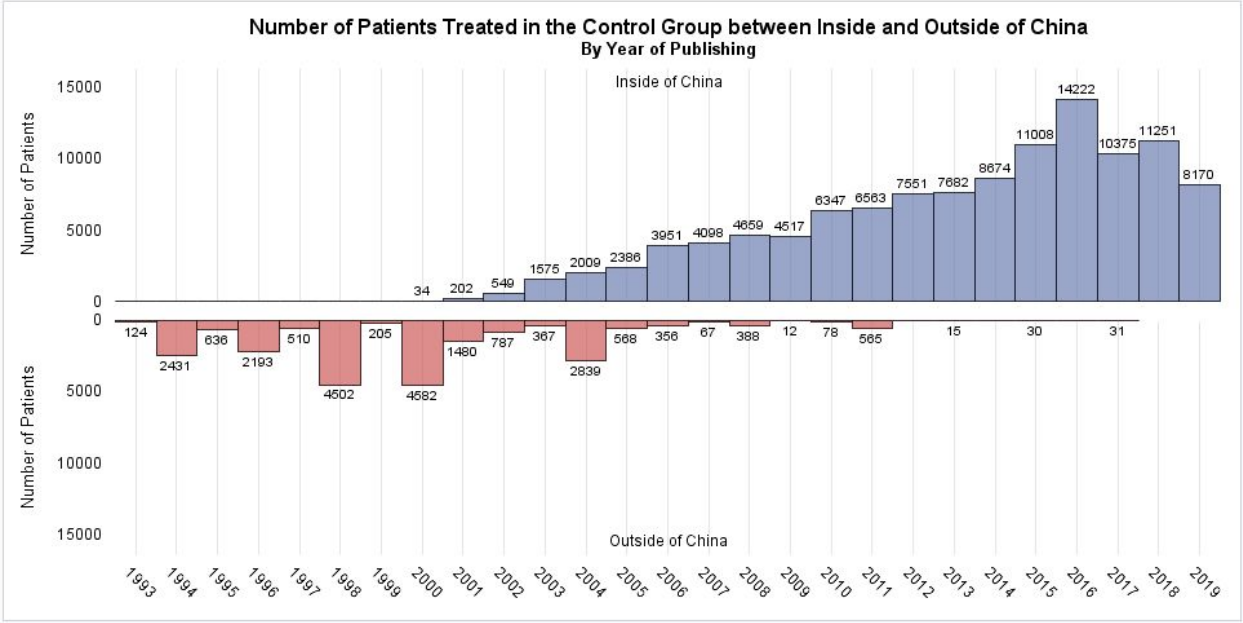
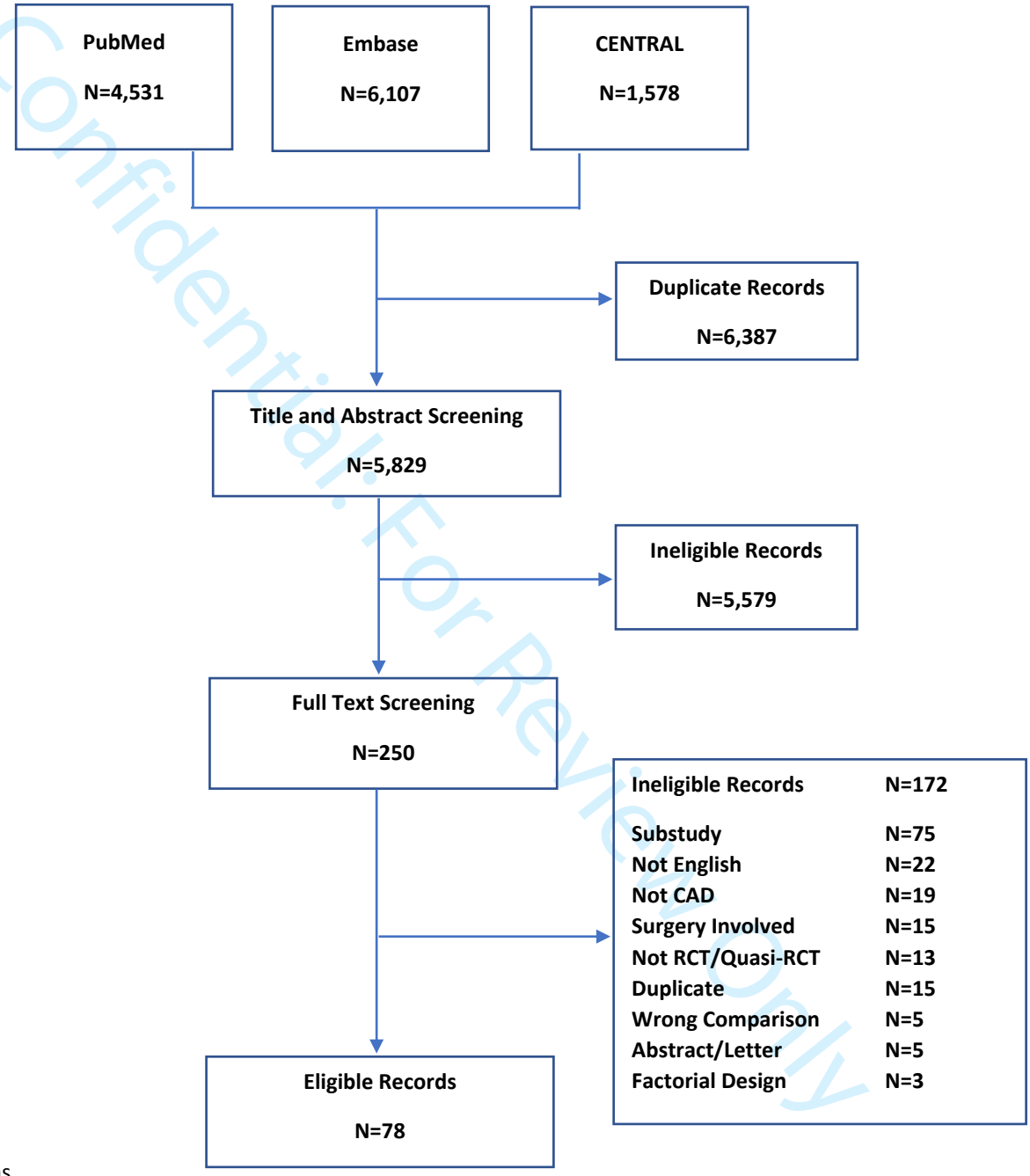


Figure 3 Comparison of the Number of Patients Treated in the Control Group between Inside and Outside of China



Supplement 1 Selection of Eligible Trials Conducted Outside of China

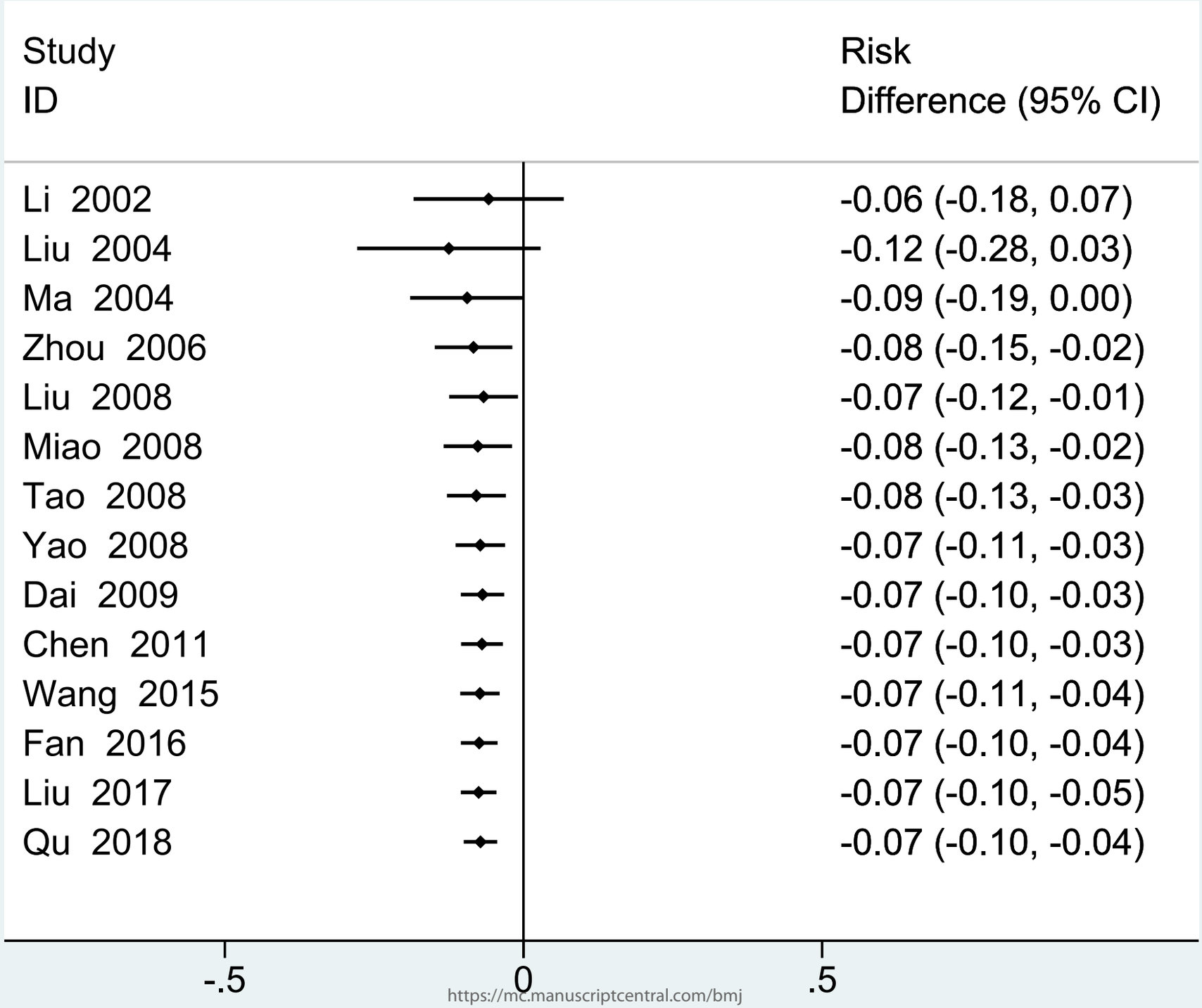


Abbreviations

CENTRAL: the Cochrane Controlled Register of Trials; RCT: Randomized Controlled Trials; CAD: Coronary Artery Disease.

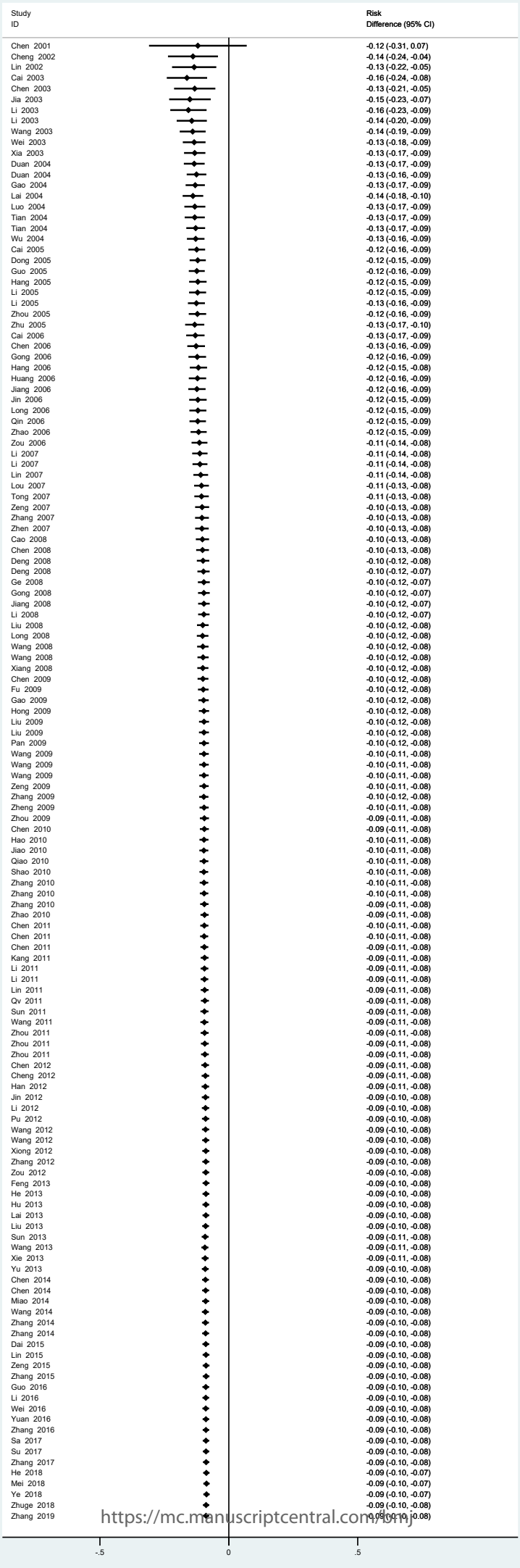
Cumulative Meta-Analysis

Patients with Stable Angina Pectoris



Cumulative Meta-Analysis

Patients with Unstable Angina Pectoris



Cumulative Meta-Analysis

Patients with Myocardial Infarction