The Decline Effect in Cardiovascular Medicine: Is the Effect of Cardiovascular Medicine and Stent on Cardiovascular Events Decline Over the Years?

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The term decline effect is referred to a diminution of scientifically discovered effects over time. Reasons for the decline effect are multifaceted and include publication bias, selective reporting, outcomes reporting bias, regression to the mean, scientific paradigm shift, overshadowing and habituation, among others. Such effects can be found in cardiovascular medicines through medications (e.g., aspirin, antithrombotics, proton pump inhibitor, beta-blockers, statins, estrogen/progestin, angiotensin converting enzyme inhibitor etc.), as well as with interventional devices (e.g., angioplasty, percutaneous coronary intervention, stents). The scientific community should understand the various dimensions of the decline effects, and effective steps should be undertaken to prevent or recognize such decline effects in cardiovascular medicines. (Korean Circ J 2013;43:443-452)

KEY WORDS: Cardiovascular drug; Stents; Percutaneous coronary intervention.

Introduction

In the 1930s, the term of ‘decline effect’ was first discovered, statistical significances of purported evidence for psychic ability declined as studies were repeated within parapsychology. Jonathan Schooler defined that ‘decline effect’ refers to scientifically discovered effects published in the literature which diminish with time and/or when tests are repeated. In other scopes, several scientific results were rigorously proven and acceptance levels decreased in later studies. It mean decline effect size statistically over time. Issues arose from Jonah Lehrer’s article on decline effects, while many scientists pointed out meaningful implications to medicines, especially for cardiovascular medicines. Because pharmacutical drugs and interventional devices in cardiovascular diseases (CVDs) cannot ignore declining effects, controversial debates on the application of drugs and devices continued.

This effect is originated from more complicated and multi-dimensional causes. The most likely explanation for the decline regression suggests that some scientists attribute decline effects to initial self-corrected exaggerated outcomes. If early results are reported when errors were combines to magnify the apparent effects, then published studies are likely to indicate systematic bias towards the initially exaggerated findings, which are subsequently self-corrected. Such tendency of the scientists knowing the ideal results may influence the possible results received. Replicated tests are probably corrections of these flaws. If results of falsification are written in textbooks, it cannot be proven.

Academic incentive modifications after the scientific paradigm repositions will disapprove the theory. After a new paradigm is proposed, the peer review process will be tilted toward positive results. In a consecutive experiment by Jonathan Schooler, he called such phenomenon of verbal overshadowing and habituation. Joseph Bank Rhine called this decline effect which diminished over time through his experiments on sensory perception ability tests. And he also tested a parapsychological phenomenon known as precognition. Jennions and Theodore Sterling commented that decline effect is majority of publication bias, selective reporting, and outcome reporting bias. Publication bias also plays key role in the decline effect. Tenden-
cies of scientists and scientific journals indicate preference of positive data over null results. Publication bias can distort the available evidence on research questions, which leads to misleading inferences within reviews and meta-analysis. Palmer reported that smaller sample sizes were not random at all but skewed heavily towards positive results, and selective reporting was one of the subtle omissions and unconscious misperceptions, as researchers struggle to make sense of their results. Ioannidis claimed that selective reporting is rooted in fundamental cognitive flaws, similarly in situations where we tend to prove ourselves right and avoid the facts of being wrong, especially when related to our careers. Other explanation for decline effects include unreported aspects of methods. If exclusive results were reported first, then the next researcher may use rigorous methodologies in the later study, and thus resulting errors due to experimental bias and failures of replicated study.

John Crabbe performed a series of experiments and addressed that many extraordinary scientific data are nothing but noise. The decline effect is actually a decline of illusion.

Cardiovascular Medicine

Ioannidis found that forty-one percent had either been directly contradicted or had their effect sizes significantly downgraded in the evaluation study for original clinical search studies in 3 major general clinical journals and high-impact-factor specialty journals in 1990-2003 and have been cited more than 1000 times in the literature. The trials with contradicted or initially strong effects had significantly smaller sample sizes and tended to be older than those with replicated or unchallenged findings.

The cardiovascular fields are worth noting within this report. Subjects of his study included 49 highly-cited original clinical research studies in which 31 (63.3%) were of cardiovascular fields. From the 31 eligible highly cited studies with efficacy claims, 5 (16.1%) were contradicted by subsequent research, and another 4 (12.9%) were found to have initially stronger effects. In all these 9 cases, subsequent studies were either larger or better controlled. The results of 13 highly cited articles (41.9%) were replicated and 6 (19.4%) had remained unchallenged.

Initial cohort study and small randomized trials on the estrogen/progestin reported a 44% relative risk reduction in coronary heart disease (CHD), but large randomized trials found that estrogen and progestin significantly increased the relative risk of coronary events by 29% among postmenopausal women with refuting results.

In case of vitamin E, initial studies reported significant associations with decreased risk of coronary artery disease (CAD) and a 47% relative risk reduction for cardiovascular deaths or CHD, however large randomized clinical trials (RCTs) showed no beneficial effects of vitamin E for CAD. The early study results showed that immediate angioplasty achieved a 58% relative risk reduction for death or reinfarction, but a subsequent studies suggested that the benefit is probably much smaller (30%) and does not show any sizeable benefit. Two randomized trials showed that stents can reduce with 31% and 42% relative risk for revascularization, but next meta-analysis suggested that the benefit is probably much smaller (approximately 10%) due to unblinding designs. In studies of flavonoids, an effect to reduce relative risks for CAD from 68% in initial studies to only 20% in subsequent meta-analysis of prospective cohorts.

Aspirin

Aspirin for the primary prevention of CHD have always been controversial. The primary preventive application of aspirin depends on the benefit and the risk of adverse events induced by aspirin in adults at risk for CHD. The overall benefit in the reduction of CVD events with aspirin use depends on baseline CVD risks and risks for gastrointestinal bleeding. There were several trials and meta-analysis on the effect of aspirin to prevent CHD. They found that aspirin for primary prevention of CHD was beneficial among patients with high risk but not for clinical CVD.

In 2002, the United States Preventive Services Task Force (USPSTF) concluded that aspirin of primary prevention for high-risk patients reduces the risk of CHD by 28%, and strongly recommended that clinicians discuss aspirin preventions with adults for increased CHD risk, defined as a 5-year risk of 3% or more.

In 2008, a meta-analysis of about 10000 patients with stable CVD also support benefit. Thus, aspirin remains an essential part of the treatment and secondary prevention of ischemic syndromes.

The USPSTF found good evidence that aspirin decreases the incidence of myocardial infarction (MI). In 2011, the USPSTF recommends the use of aspirin for men aged 45 to 79 years when potential benefits due to a reduction in MIs outweighs the potential harms due to an increase in gastrointestinal hemorrhage. And the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of aspirin for CVD prevention in men and women of 80 years or older. The USPSTF recommends against the use of aspirin for MI prevention for men younger than 45 years. Shared decision making is strongly encouraged with persons whose risk is close to these estimates of 10-year risk levels. As the potential CVD reduction benefit increases above harms, the recommendation to take aspirin should become stronger. Current guidelines do not recommend aspirin therapy in low-risk subjects. Despite these data, the role of aspirin in primary preventions continues to
be investigated.20

The debate on the optimal dose of aspirin for patients undergoing revascularization or after an acute coronary syndrome (ACS) event continues. Large scaled randomized trials were conducted after the mid-2000s.20,21 In the absence of recurrent ischemia, low-dose aspirin should be the treatment of choice for maintenance therapy within all patients following ACS, irrespective of whether an invasive of medical approach is undertaken or not.21

Antithrombotics

Risks of antithrombotic therapies remain due to the result of multifaceted interactions among patients' co-morbidities, drug combinations, multifaceted dosing adjustments, and the complexity of the care environment despite great advances. Thus, many challenges exist in developing antithrombotic drugs. Acute care setting; treating patients early, complexity of health systems, length of stay, drug combinations, monitoring effects, interplay with invasive strategy, patient comorbidities, dosing and bleeding. Pharmacodynamics/pharmacokinetics outcomes in acute care setting: bleeding and tolerability, adherence issues and costs, events over time, patient morbidities, monitoring effects, drug combinations, surgeries and procedures, multiple providers. Pharmacodynamics/pharmacokinetics outcomes in chronic care setting.30

Intravenous Glycoprotein IIb/IIIa Inhibitors (GPIs) are potent antiplatelet agents that inhibit fibrinogen-mediated platelet aggregation. GPIs is recommended in cases of moderate or high-risk non-ST-segment elevation acute coronary syndromes (NSTE-ACS), especially when an early invasive strategy is planned.21

Clopidogrel bisulfate is a thienopyridine derivative, which is adenosine diphosphate antagonist for the P2Y1 receptors. Combined therapies of clopidogrel and aspirin has become the standard adjunctive regimen in prevention of thrombotic events after intracoronary stenting.24,25 Clopidogrel is a well-known drug that has a wide inter-individual variability which is determined according to genetics, patient's characteristics, and interactions with proton pump inhibitors (PPIs), although the latter remains controversial.26 Questions of appropriate dosing, length of therapy, and use of combination therapy are the most pressing and considerable debates regarding the variability of response to antiplatelet therapy, including the definition, measurement, and clinical relevance of responsiveness. Despite of the exist controversies, antplatelet therapy with aspirin and/ or clopidogrel remains a proven and essential therapeutic tool for safe and effective management of atherothrombotic risk in specific clinical setting.27

Despite the paradigm shift for additional therapy of clopidogrel to aspirin therapy, clopidogrel has certain limitations which are related with adverse thrombotic events for variability in patients with CYP2C19*2 genetic polymorphisms.28 New P2Y12 receptor antagonists of adenosine diphosphate (prasugrel, ticagrelor) confer greater platelet inhibitions than clopidogrel. However, greater and faster platelet inhibitory medicine like cangrelor and elinogrel comes with an increased risk of hemorrhagic complications. And P2Y12 receptor antagonists have reduced use of GPIs, which block the final pathway leading to platelet aggregation and thrombosis. A further study to determine such way into clinical use will be necessary.

Low molecular weight heparins (LMWHs) are fragments of unfractioned heparin (MW: approximately 5000 daltons) that exert their anticoagulant effects indirectly via antithrombin. There have been several studies evaluating LMWHs in the setting of additional adjunctive pharmacologic therapies,38-41 further questions remain regarding the use of LMWHs in other settings. Direct thrombin inhibitors (DTIs) act by binding to thrombin, blocking the formation of fibrin from fibrinogen by action of thrombin and the feedback activation of coagulation factors by thrombin, and inhibit the thrombin-induced components of platelet aggregation. However, LMWHs may lead to the risk of rebound because upstream prothrombotic elements may accumulate during DTI activities conceptually. Several kinds of DTIs are being examined in clinical trials which evaluate the use in deep venous thrombosis, ischemic heart disease, and atrial fibrillation (AF). The developments of effective, safe and orally available DTIs have always been a major challenge for the pharmaceutical industry.39 New anticoagulants can be divided into 3 groups based on their primary target in coagulation cascades: inhibitors of initiation of coagulation, inhibitors of the propagation of coagulation, and thrombin inhibitors. Nimjee et al.40 suggests that anticoagulation can be readily and predictably achieved and that the effects can be immediately reversed when administering an appropriately designed/matched antidote which also relies upon the aptamer technology. As new therapies are introduced, rigorous evidences will be essential to ensure improved patient care with both the current and new antithrombics.21

Anticoagulant with Aspirin

There are little evidences in combination warfarin-acetylsalicylic acid (ASA) therapy for the presence of both chronic fibrillation and CAD despite of its widespread use. Such combination therapy confers therapeutic benefits compared with warfarin alone, however approximately 1.5- to 2-fold increased risk for serious bleeding.42 Combination therapy should be used cautiously in selected patients who have an acute coronary event, a recent percutaneous coronary intervention (PCI) or coronary artery bypass in whom an antiplatelet drug may be of benefit to prevent acute coronary in-stent or bypass
Proton Pump Inhibitor and Aspirin

Aspirin therapy for primary prevention depends on trade-offs between its ability to reduce nonfatal MI and its potential to increase the risk of hemorrhage in cranial and extracranial sites. There are several kinds of evidences for mitigation and the possible reduction of gastrointestinal bleeding. Acid-suppressive therapy can reduce the risk of upper GI bleeding. Saini et al. suggested that low-cost omeprazole regimen of patients 65 years or older who are using aspirin for secondary prevention may be cost-effective.

Usage of PPIs for antiplatelet therapy is effective in addressing the problems of gastrointestinal bleeding. Earnshaw et al. found that adding PPI therapy does not appear to be cost-effective for those patients with low or average risks for GI bleeding but may be valuable for those with a GI bleeding risk over 4 per 1000 per year in cost-utility analysis of aspirin and PPIs for primary prevention. He found out that treatment with aspirin for CHD prevention is less costly and more effective than no treatment for men aged 45 to 55 years. The 10% CHD risks suggested that further efforts to include aspirin for secondary prevention may be cost-effective.

Beta-Blockers

For over three decades, hypertension guidelines have proposed including β-blockers as a first line therapeutic option. Beta-blockers were documented to reduce reinfarction rates and to have protective effects for a broad spectrum of cardiovascular indications such as hypertension, diabetes, angina, AF as well as perioperatively in patients undergoing surgery. However, despite lowering blood pressure, beta-blockers have never shown to reduce morbidity and mortality in uncomplicated hypertensions. Also, beta-blockers do not prevent heart failures in hypertension any better than any other antihypertensive drug classes. There are many controversies in the use of beta-blockers in CVDs.

Beta-blockers are catecolamine competitive inhibitors and act through alpha and beta adrenergic receptors blockade. The most important therapeutic effects of beta-blockers are on cardiovascular system, where they act as negative chronotropic and inotropic agents, lowering cardiac work and improving oxygen demand/supply ratio. For their anti-ischemic activity, beta-blockers are used as anti-anginal drugs and in acute and previous MI for preventing total and cardiovascular mortality. Beta-blockers are useful in numerous cardiovascular conditions.

The first compound had severe opposing effects preventing their use until propranolol was introduced. It was found effective for treatment of angina pectoris since not all patients with hypertension responded to monotherapy with a meaningful reduction of pressure.

Actually this viewpoint is becoming increasingly subjective to controversy. The recent literature indicates that the absence of sufficient data and of solid evidence does not support using of β-blockers as monotherapy or as first line treatment, especially not in the elderly population.

Lindholm et al. reported that the effect of beta-blockers is less than optimum with a raised risk of stroke in comparison with other antihypertensive drugs, and they proposed that beta-blockers should not remain as first choice in the treatment of primary hypertension and should not be used as reference drugs in future. De Caterina and Leone explained several causes of their mild cardioprotective effects, such as their unfavorable metabolic properties, a lack of efficacy on left ventricular hypertrophy regression and endothelial dysfunction, and reduced patient compliance. Beta blocker effects on cardiovascular morbidity and mortality in hypertensive patients remains controversial and their use in uncomplicated hypertension is currently still under debate.

However, this doesn’t preclude their predominant places in complicated hypertension, after MI, congestive heart failure and in the presence of arrhythmias.

There is no indication in treating primary non-complicated hypertension with beta-blockers as first-line drugs. Different metabolic effects of selective and non-selective beta-blockers are actually being debated. Traditional β-blockers (e.g., atenolol, metoprolol, propranolol) affect only the β-adrenergic receptors, whereas carvedilol and labetalol mediate vasodilation through blockade of the α-
adrenergic receptor. Other drugs like nebivolol may exert vasodilatations via stimulation of nitric oxide. Vasodilation may be important not only for blood pressure reductions, but also for tolerability. Current evidence suggests that older beta-blockers, such as atenolol and propranolol, may not be preferred as antihypertensive drugs. However, newer beta-blockers, especially with vasodilatory properties (carvedilol, nebivolol), should be considered in hypertensive patients. Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are effective at reducing perioperative ischemia and cardio-vascular complications may not benefit patients as expected and may actually be harmful to some individuals. Currently, the best evidence supports beta-blocker use in two patient groups: patients undergoing vascular surgery with known ischemic heart disease or multiple risk factors, and, for patients already receiving beta-blockers for known cardiovascular conditions.

Statins

Statins are the treatment of choice for managing hypercholesterolaemia because of their proven efficacy and safety profile. They also have an increasing role in managing cardiovascular risks in patients with relatively normal levels of plasma cholesterol. However there is less clear evidence supporting the use of statins. Statins are efficient in preventing first cardiovascular events, but the cost-efficiency of primary prevention remains controversial. In primary prevention particularly, the pros and cons of statin therapy should be weighted by considering patient-specific life circumstances and assessing the individual cardiovascular risks, as provided by risk calculators. Since diabetes mellitus poses a high risk even in the absence of known CADs, the statin treatment is generally indicated within these patients. There is no lower LDL threshold defining the limit of treatment benefits; rather, LDL target levels should be sought according to individual cardiovascular risks. Despite recent evidences that statin treatment is associated with a small risk of incident diabetes mellitus, this disadvantage is outweighed by vascular benefits.

Statins have pleiotropic effects, such as anti-inflammatory properties, improved endothelial function, stabilize plaques, reduced coronary artery thrombus formation, and influence myocardial protection and remodeling. It is still debated to what extent these effects translate into cardiovascular risk reduction beyond being conferred by LDL reductions. Although all statins share a common mechanism of action, they differ in terms of their chemical structures, pharmacokinetic profiles, and lipid-modifying efficacy.

There is controversy over the correct dose, the time of initiation of therapy, and the utility of the treatment-to-goal approach. Many questions remain unanswered despite substantial evidences supporting early initiation of statin therapy. Current guidelines recommend initiating high dose statin therapy pre-discharge regardless of the baseline LDL levels in patients with acute coronary syndromes. It is prudent to recommend low-to-moderate-dose statin therapy as the most appropriate choice for achieving cardiovascular risk reduction in the majority of individuals without incurring adverse effects, whereas intensive-dose statin therapy may be reserved for those that do not respond to low-to-moderate-dose statins.

In coronary syndromes, it does not confer benefits in terms of the hard clinical outcomes of MI and strokes, it is associated with increased liver and muscle-related adverse outcomes leading to increased withdrawals and suboptimal long-term adherences. The adherence rate to statin therapy in 1 year ranged from 26% to 85%, with rapid declines in adherence rates typically observed within the first few months of several cohort studies. Although, only 3% of patients in randomized research studies develop intolerance, clinical practices up to 15% of outpatients receiving statins have reported muscle pain. Study results on the mechanisms and treatments of statin intolerance have been limited.

The time of statin initiation varied in many researches and several reports showed negative results for early statin therapy for ACS patients. The idea that polypill therapy consisting of cholesterol-lowering (statins), antihypertensive, and antiplatelet agents together would simultaneously lower multiple risk factors has generated much controversy and debates over the past decade. It is an unclear and controversial topic that whether the current wide use of polypill for CVD prevention, especially during primary prevention, is a threat or opportunity to public health. More external validation is required regarding the benefits, risks, costs, convenience, and acceptability of the polypill because these are key practical components in implementing and sustaining interventions.

Angioplasty, Percutaneous Coronary Intervention, and Stents

Since the 1970s, coronary artery bypass grafting (CABG) is the standard revascularization choice for unprotected left main coronary
States and other countries after the developments of coronary artery (ULMCA) disease based on the efficacy and survival advantage of CABG in reference to medical therapy.\(^{79,80}\) In 1977, the practice of PCI was introduced, and it impacted on significant changes in revascularization strategy of CADs.

Percutaneous coronary intervention has led to a viable alternative treatment for ULMCA disease, because of the anatomically easy accessibility, relatively large caliber of the left main coronary artery (LMCA), technical advances in both PCI and stent technology like radiographic imaging, stent composition, deployment, and drug-eluting stents (DES).

Mayo Clinic (2010) had divided 4 eras according to the dominant interventional strategy at the time; 1979-1989 percutaneous transluminal coronary angioplasty, 1990-1996 early stent era. 1997-2003 the bare-metal stent (BMS), 2003-2006 contemporary practice include DES.\(^{79}\)

Current evidence from clinical trials and extensive off-label experiences indicates that stenting yields mortality and morbidity rates that compare favorably with CABG, by updating the current guidelines for LMCA revascularization, it might have prompted many interventional cardiologists to choose PCI with DES as a good treatment option for patients with LMCA diseases.\(^{81}\) There have been several studies that have cited both an increase in PCI and a decrease in CABG surgery volumes in the treatment of CAD within the United States and other countries after the developments of coronary angioplasty 3 decades ago.\(^{82}\)

Percutaneous coronary intervention in the setting of ACS has proven mortality benefits. Introduction of coronary stents has revolutionized the field of interventional cardiology by reducing the incidence of restenosis after balloon angioplasty.\(^{83}\)

Several randomized controlled trials have demonstrated that coronary stenting reduces mortality when compared to thrombolysis in ST-segment elevation myocardial infarction. Meta-analysis of RCTs has also shown a reduction of mortality in non-ST-segment elevation myocardial infarction. As a result, intracoronary stents has become the preferred treatment for eligible patients with ACS.\(^{83,84}\) However, controversy exists regarding the clinical impacts of early inflammatory responses on in-stent restenosis after coronary stent implantation,\(^{85}\) procedural choices, and particularly stent choices. Implanted stent is a strong inflammatory stimulus in which the stent facilitates arterial intimal cellular proliferation and extracellular matrix synthesis that is mediated largely by inflammatory processes.\(^{86}\)

Drug-eluting stents were introduced in the United States in 2003 and have been widely adopted based on profound reductions in restenosis.\(^{87}\)

Randomized clinical trials and population-based studies suggest that DES appear safe and more effective than BMS in the setting of acute myocardial infarction (AMI). However, DES are commonly used in AMI, there has been significant debates in the clinical community regarding their true efficacy and long-term safety. Longer follow-ups of these studies (>2 years) will be important to confirm the ongoing safety, and more data on new DES will be essential as clinical practice evolves.\(^{88}\)

The long-term safety and efficacy of DES for patients with AMI remain controversial because the incidences of late stent thrombosis (LST) and deaths could be higher in DES than BMS despite of DES has been shown to be associated with significant reduction in restenosis and target vessel revascularization.\(^{89}\)

Premature discontinuation of clopidogrel after DES is one of the most important predictors of LST. Improving compliances with dual-antiplatelet therapy and procedural practices can improve outcomes for both DES and BMS in AMI. The scientific ‘battle’ (for the optimal reperfusion therapy in AMI) between pharmaco-oriented and balloon-oriented cardiologists has already been ongoing for 16 years.\(^{90}\)

Randomized and meta-analysis studies demonstrated that PCI with DES for unprotected left main trunk diseases, when compared with BMS, could be more strongly associated with a significant reduction for target lesion revascularization needs without any additional adverse outcomes, although there are limitations on indications.\(^{91}\) Further investigation is needed on PCI for ULMCA diseases, along with further analysis of remote-stage outcomes of BMS.\(^{92}\)

The primary use of DES has become the routine clinical practice for CAD, but the use in peripheral arteries has to be further studied.\(^{93}\)

First-generation DES with controlled releases of sirolimus or paclitaxel from durable polymers compared with BMSs have been consistently shown to reduce the risks of repeat revascularization procedures due to restenosis. Newer generation DES have been developed with the goal to further improve upon the safety profiles of first-generation DES while maintaining efficacy. These platforms include DES with improved and more biocompatible durable polymers, DES using bio-absorbable polymers for drug-release, DES with polymer-free drug release, and fully bio-absorbable DES. This innovative concept remains an evidence for clinical applications.\(^{94}\)

Interventional cardiology has utilized balloon catheters, bare metal- and DES to recanalize narrowed vessels for the past 30 years. However, the quest and answer for outcome optimization is ongoing for specific lesions and patients.

Drug-eluting balloons are among the latest technologies proposed to overcome the limitations of DES, such as stent thrombosis and the dependency on long-term dual antiplatelet therapy.\(^{95}\)

Implication and Conclusion

Dwan et al.\(^{96}\) investigated that 68.8% series of cohort studies were publication biased and 31.3% of randomized controlled trials were

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outcome reporting biased. And they found strong empirical evidences of an association between significant results and publications; studies that report positive or significant results are more likely to be published and outcomes that are statistically significant have higher odds of being fully reported.\textsuperscript{94} Publication bias will lead to overestimation of treatment effects. Study results without statistical significances take longer to activate publication than those with significant results, thus furthering bias evidences. It is either time lag biased or pipeline biased.\textsuperscript{99,100}

Many studies tried to assess the relationship between publication and funding. Stern and Simes,\textsuperscript{97} Dickersin et al.,\textsuperscript{98} and Decullier and Chapuis\textsuperscript{99} reported that external fundings lead to a higher rate of publications. But other studies found reverse results; the probability of publications decreased when the study was commercially funded,\textsuperscript{100} government funded results were more likely to have statistical significances but no effects on publication.\textsuperscript{101} no differences in funding mechanism,\textsuperscript{94} no differences in whether data was managed by the pharmaceutical industry or federally sponsored organizations.\textsuperscript{102} Ioannidis\textsuperscript{102} found that positive trials were published significantly more rapidly after submission than negative trials.

Selective reporting bias is defined as the selection on the basis of the results of a subset of the original variables recorded for inclusion in a publication.\textsuperscript{103} There are several kinds of selective reporting bias: examples, intention to treat analysis, per-protocol analysis, and different time points or subgroups.\textsuperscript{104} Randomized controlled trials is known as the most powerful study designed to evaluate the effectiveness of a treatment in medical research.\textsuperscript{105,106} This also can be biased by selective outcome reporting.

The bias from missing outcome data which may affect a meta-analysis are non-publications in a study level and selective for non-reporting of outcomes on an outcome level.\textsuperscript{4}

In cardiovascular medicines, there are more complicated situations on decline effects, because of technological innovation updates, new published evidences, and updated guidelines with traditional problems of studies. We should understand various dimensions of decline effect in cardiovascular medicine.

Schooler\textsuperscript{11} suggests an open-access repository for all research findings for improving and testing decline effect of results. He concluded and proposed that these database could identify the current scientific processes on how scientist design experiments, how they write, and how journals decide what to publish based on peer reviews and experimental replications, thus, succeeds in distinguishing grounded truth from unwarranted fallacy.

In systematic review of the empirical evidences on study publication bias and outcome reporting bias, authors recommend researchers to use the flow diagram as the standard for reporting of future similar studies. Such studies overlook publication bias and outcome reporting bias so that reviewers scrutinize trials with missing outcome data and contacts trialists when results are not reported. Statisticians should be involved for data extraction of more complex outcomes, develop methods to assess the robustness of conclusions, systemic reviews to outcome reporting bias, being cautious for missing data in meta-analysis, setup clinical trial registers and detailed protocols for advanced publications.\textsuperscript{9}

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