

The Appropriate Interpretation of Recent Clinical Trials -How to Read RCT in the Era of Advertizing-based Medicine-

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ABSTRACT

Although evidence-based medicine (EBM) has changed medical therapy from experience- or experiment-based medicine to the modern science-based medicine, nowadays it seems to be used as a tool of advertizing strategy of industries. Clinical trial is a fundamental component of EBM and it costs very much and are mostly conducted by the financial support of pharmaceutical industries at a tremendous expense. If anticipated results for the sponsor were not shown in the trial, a “spin” has been used to mislead readers as if positive results for test drugs or devices were obtained by emphasizing subgroup analysis, or searching favorable endpoint by post-hoc analysis. Clinical trials on angiotensin receptor blocker (ARB) are continuing succession of defeat all over world except two Japanese clinical trials, JIKEI HEART and KYOTO HEART studies. However, in both trials, subjective soft endpoints, such as angina pectoris or congestive heart failure were used despite of prospective randomized, open labeled, blinded endpoint design. In the era of advertizing-based medicine, It is important to read clinical trial data with critical view points.

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Key Words: Evidence-based medicine, Prospective randomized open labeled blinded endpoint, Randomized controlled trials, Post-hoc analyses, Angiotensin receptor blocker

Nearly two decades have passed since the introduction of the concept of “evidence-based medicine (EBM)” in therapeutic medicine. Without a doubt, EBM has dramatically changed the clinical practice of physicians from experience-based or experiment-based medicine to science-based medicine, which has markedly contributed to the establishment of modern era of medicine.

For example, based on scientific data from clinical large-scale trials¹⁾ beta-blockers are now considered standard

of care for congestive heart failure (CHF), a shift from when beta-blockers were considered as contraindicated based on theory, that negative inotropic action would be harmful. A class of anti-arrhythmic drugs, encainide and flecainide, were found to have a significant long-term mortality risk due to their proarrhythmic action in patients with myocardial infarction by the Cardiac Arrhythmia Suppression (CAST) trial,²⁾ in contrast to its theoretical effects. Clinical trials, the Systolic Hypertension in the Elderly Program (SHEP)³⁾ trial proved that strict blood pressure control with anti-hypertensive treatment in the hypertensive elderly prevents cardiovascular events.

However, from the beginning, there were concerns that evidence-based medicine might be used for marketing

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strategies by the pharmaceutical industry or political strategies by governments. Nowadays, the former concern seems to be realized as intensified global competition has led to intensified marketing by pharmaceutical companies and their support of clinical trials.

Concerns and cautions about clinical trials supported by the pharmaceutical industry

Most of the large-scale clinical trials were supported by the pharmaceutical industry. Although the extremely high cost to conduct large-scale clinical trials is well known, the motive of the pharmaceutical company for providing the financial support for a trial is too often for the purpose to gain positive clinical evidence to support the sales of their drug. Ridker and Torres⁴⁾ reported that recent cardiovascular trials funded by for-profit organizations are more likely to report positive findings than trials funded by not-for profit organizations, as are trials using surrogate rather than clinical end points (Fig.1).

If anticipating result was not obtained, report was often unpublished, such as the Prospective Randomized Amlodipine Survival Evaluation (PRAISE)-2,⁵⁾ financial support was withdrawn such as the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE),⁶⁾

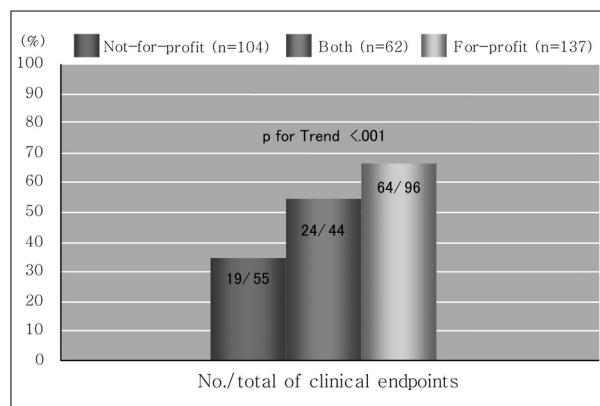


Fig. 1. Proportion of trials significantly favoring newer treatments over standard of care.⁴⁾

so-called “spin” were used in science article, as used in many randomized controlled trials (RCT) reports sponsored by pharmaceutical companies.

“Spin” can be defined as specific reporting that could distort the interpretation of results and mislead readers in RCT with statistically nonsignificant results for primary endpoint.⁷⁾

Example of “spin” are;¹⁾ emphasizing only favorable secondary endpoint obtained by subgroup analysis,²⁾ searching favorable points for marketing from post-hoc analyses,³⁾ interpreting statistically nonsignificant results for the primary outcomes as showing treatment equivalence or comparable effectiveness,⁴⁾ modifying original results by adjusting by various factors.

Secondary endpoints is nothing but newly-generated hypothesis, to be solved

The fundamental goal of a clinical trial is to prove an hypothesis, which is defined as the primary endpoint. Thus, the result of the clinical trial should only be the primary endpoint. As the secondary endpoint is very likely to be incidental, it is hypothesis-generating and a new theme to be solved in future trials.

Although the examples of trials whose secondary endpoints have been emphasized even when the primary endpoint was negative are too numerous to elaborate, a few are shared here.

The PRAISE trial⁵⁾ tested the ability of amlodipine, compared to placebo, to prevent total mortality and cardiovascular events in patients with severe CHF. Although the primary endpoint of total mortality of amlodipine was comparable with placebo, sub-analyses, dividing CHF patients into ischemic and non-ischemic, showed that amlodipine had significant preventive effect on total mortality in patients with non-ischemic CHF, but not in ischemic CHF patients.

The PRAISE-2⁸⁾ was planned and conducted to confirm whether amlodipine prevents death in patients with non-ischemic CHF. Although the number of patients in PRAISE-2 was 8-times more than in PRAISE, amlodipine could not prove a mortality benefit in these patients-thus did not support the finding of the PRAISE sub-analysis. However, the results of the PRAISE sub-analysis were published in the medical literature, while the negative results of PRAISE-2 were not published.

The Evaluation of Losartan in the Elderly Study (ELITE)⁹⁾ and ELITE-II¹⁰⁾ studies provide another example of the unreliability of secondary endpoints. Angiotensin receptor blockers (ARBs) appeared with the great expectation of achieving optimal cardiovascular protection by blocking the renin-angiotensin system (RAS) at the receptor level without the adverse effect of cough which is associated with angiotensin converting enzyme inhibitors (ACE-I).

ELITE⁹⁾ was conducted to verify the usefulness and safety of angiotensin II receptor blocker (ARBs) in elderly patients with CHF compared to ACE-I, and the primary endpoint was a worsening of the renal function (increase in serum creatinine > 0.3 mg/dL). ELITE received significant attention because it was the first trial to compare the effectiveness of new class of drugs, losartan with ACE-inhibitor, captopril. A comparable increase in serum creatinine was found in the ARB- and ACE-I treated groups. However, the secondary endpoints of total death or hospitalization due to CHF was significantly lower in the ARB group compared to the ACE-I group. This result was welcomed by the many investigators who had been engaged in the study of the renin-angiotensin system in animal experiments and the pharmaceutical companies hoping to sell ARBs as a blockbuster drug.

ELITE-II,¹⁰⁾ however, with total death as its primary endpoint, 4-times more patients than in ELITE, and 74-week study period, found no significant difference between the ARB and ACE-I to prevent death in elderly patients with CHF (Fig. 2).

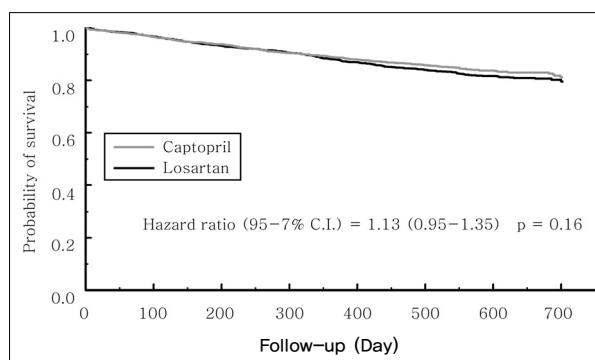


Fig. 2. Evaluation of Losartan in the Elderly Study II, Primary endpoint: All-cause mortality.¹⁰⁾

To date, no clinical trial has been published that shows an ARB to be better than an ACE-I to prevent cardiovascular (CV) events and death in CHF.

Emphasis of favorable secondary endpoints or modified endpoints: commercial-based medicine

The VALUE trial¹¹⁾ compared the cardiovascular protective effect of the ARB valsartan and the calcium channel blocker (CCB) amlodipine. The working hypothesis of the trial was that the cardioprotective effect of an ARB, by its RAS blockade plus antihypertensive action, is superior to a CCB to prevent CV events. Therefore, the trial sought to prove “beyond the blood pressure lowering” effects of the ARB.

Unexpectedly, the primary endpoint defined as the composite of cardiac mortality and morbidity, was similar in both treatment groups. Further, the incidence of myocardial infarction (MI) was significantly higher in the valsartan group than the amlodipine group, and the incidence of stroke tended to be higher with valsartan than with amlodipine, probably because of the difference in blood pressure levels during the first 6 months after randomization. However, the published results emphasized the lower rate of new-onset diabetes in the valsartan group, distracting readers attention from the high incidence of the hard endpoints of MI, stroke in valsartan group as shown in Fig. 3. It is unusual for a surrogate endpoint, such as new-onset diabetes, to be

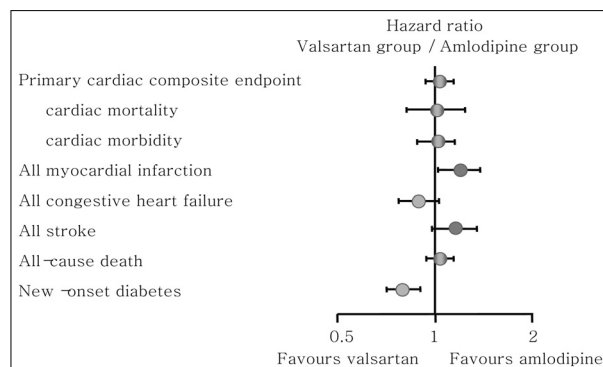


Fig. 3. VThe Valsartan Antihypertensive Long-term Use Evaluation: hazard ratio of primary and secondary endpoints.¹⁰⁾

	Valsartan	Amlodipine		HR (95% CI)	p
Composite cardiac events	408/5006	455/5006		0.90 (0.79-1.03)	0.111
Stroke	146/5006	144/5006		1.02 (0.81-1.28)	0.899
Death	423/5006	442/5006		0.96 (0.84-1.10)	0.566
Myocardial infarction	187/5006	193/5006		0.97 (0.80-1.19)	0.791
Heart failure	172/5006	213/5006		0.81 (0.66-0.99)	0.040

Fig. 4. Hazard ratios (HR) for major endpoints in patients on valsartan or amlodipine based therapies. Events occurring after a baseline translocated to the 6 months point of the trial (after adjustment designed to achieve BP control) in 5006 treatment cohort pairs matched by SBP, age, sex and the presence or absence of prior coronary disease, stroke and diabetes.¹²⁾ CI, confidence interval.

included with hard endpoints.

Further, the analysis of the hard endpoints was performed using the hazard ratio, while the odds ratio was used for surrogate endpoint of new-onset diabetes. This suggests that new-onset diabetes was not a pre-defined endpoint in the study protocol.

Modified post-hoc data from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) was published in *The Lancet*¹²⁾ as a research letter, as shown in Fig. 4. The intention was to show adjusted blood pressure data that excluded the outcomes which occurred more often in Valsartan group during the first 6 months after randomi-

zation, when a difference in blood pressure between the groups was observed. The modified data showed that the rate of CV events, MI, and stroke were similar in the valsartan and amlodipine groups, in contrast to the originally reported data. From the view of EBM, such post-hoc analyses modified for various factors are not feasible and should be prohibited.

True “VALUE” of ARBs

ARBs entered the market nearly 10 years ago with great expectation of perfect cardio-protection by blocking the action of the RAS at the receptor level and as an alternative to ACE-I with the adverse effect of cough. However, theory and practice are now always consistent, and recent clinical trials continue to show negative results with ARBs, contrary to expectations.

The VALUE trial did not show superiority of valsartan over amlodipine to prevent CV events. Further, the incidence of MI or angina pectoris was significantly higher with valsartan compared to amlodipine in high-risk patients. Although the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET)¹³⁾ showed non-inferiority for the ARB telmisartan compared to the ACE-I ramipril to prevent CV events, the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease (TRANSCEND) trial¹⁴⁾ failed to prove the cardioprotective effect of telmisartan is superior to placebo. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial¹⁵⁾ failed to prove the protective effect of valsartan for the recurrence of atrial fibrillation. The Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE)¹⁶⁾ did not show a preventive effect for irbesartan on left ventricular diastolic function. The Prevention regimen for effectively avoiding second strokes (PROFESS)¹⁷⁾ failed to show that telmisartan prevented the

recurrence of stroke, and showed a higher incidence of atrial fibrillation with telmisartan compared placebo. In the Renin–Angiotensin System Study (RASS) trial,¹⁸⁾ losartan was not superior to placebo for renoprotection, as shown by biopsy.

In the NAVIGATE trial,¹⁹⁾ valsartan was not cardioprotective in patients with impaired glucose tolerance.

Miracle ARB or magic trials?

– soft endpoint in PROBE design trials –

Exceptionally, two Japanese trials, JIKEI HEART²⁰⁾ and KYOTO HEART,²¹⁾ showed remarkable benefit with the ARB valsartan over non-ARB treatment for the prevention of the composite cardiovascular primary endpoint. The JIKEI HEART and KYOTO HEART studies had the same primary endpoint: composite of angina pectoris, CHF, or transient ischemic attack. These are subjective, soft endpoints. Notably, the only positive results found with valsartan were for the subjective, soft endpoints, while for the hard endpoints of MI and CV death no significant difference was found between groups (Fig. 5).

The inclusion of soft endpoints in the primary endpoint could contribute to earlier termination of a clinical trial because of reaching the pre-specified number of endpoints more quickly. However, because such an endpoint included soft and hard endpoints, it could magnify the effect of the studied drug.

Both JIKEI HEART and KYOTO HEART used the prospective randomized, open labeled, blinded endpoint (PROBE) method. In terms of EBM, trials using the non-randomized PROBE method, should not include subjective, soft endpoints. The results of the trial can be too easily affected by confounding factors, including the subjective judgment of the treating physician.

Notably, the incidence of angina pectoris was remarkably different between the JIKEI HEART and KYOTO HEART studies and the VALUE trial¹¹⁾ which was double-blinded and randomized. In JIKEI HEART²⁰⁾ and KYOTO HEART,²¹⁾ angina pectoris incidence was significantly lower with valsartan compared to non-ARB treatment (primarily CCBs), whereas in VALUE the incidence of angina pectoris was significantly higher with valsartan compared to amlodipine.

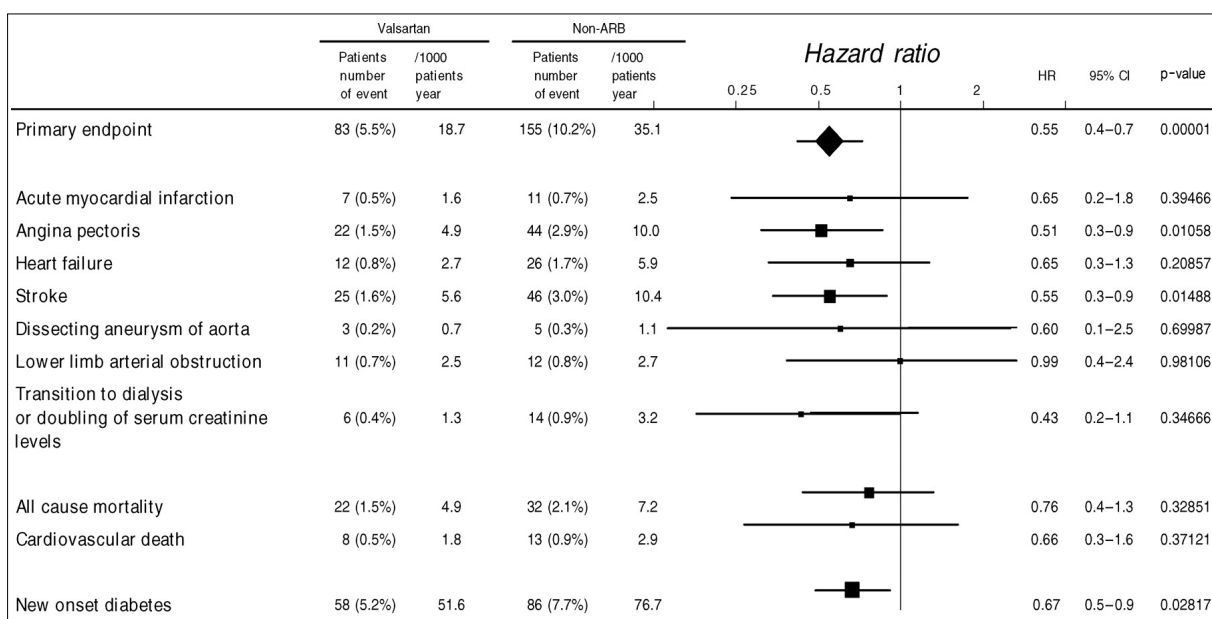


Fig. 5. KYOTO HEART study. Hazard ratio and 95% confidence intervals adjusted for sex, age, diabetes, smoking, dyslipidemia, and concomitant antihypertensive treatment.²¹⁾ ARB, angiotensin receptor blocker.

The reasons for this difference are not clear, but could include racial differences and trial methodologies.

The true purpose of antihypertensive medication: prevention of diabetes or prevention of myocardial infarction?

Antihypertensive agents can be classified into three groups according to their influence on glucose tolerance:

- Favorable influence on glucose tolerance
 - Alpha blocker, ACE-I, and ARB
- Exacerbate glucose tolerance
 - Thiazide diuretic, beta blocker
- Neutral on glucose tolerance

The goal of antihypertensive treatment is the prevention of cardiovascular complications by reducing blood pressure. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial²²⁾ clearly demonstrated that drugs with a favorable influence on glucose tolerance is not always associated with the prevention of CV and those with an unfavorable influence are not always associated with an increase of CV events. That is, in ALLHAT, the alpha-blocker, reported to have a favorable effect on glucose tolerance was discontinued early in the trial²³⁾ because of an increase in CV events compared to the thiazide diuretics, which are well-known to have a negative effect on glucose tolerance. Finally, ALLHAT demonstrated that the thiazide antihypertensive drug is not inferior but superior to a CCB or ACE-I.

The SHEP trial³⁾ was the first to demonstrate the usefulness of a thiazide diuretic in elderly patients with hypertension. Although the study period was 5-years, it continued for another 10 years as an open-label trial. After 14 years, in patients with diabetes treated with a thiazide diuretic compared to patients without diabetes, the rate of death was similar and the prognosis was better.²⁴⁾ This result clearly

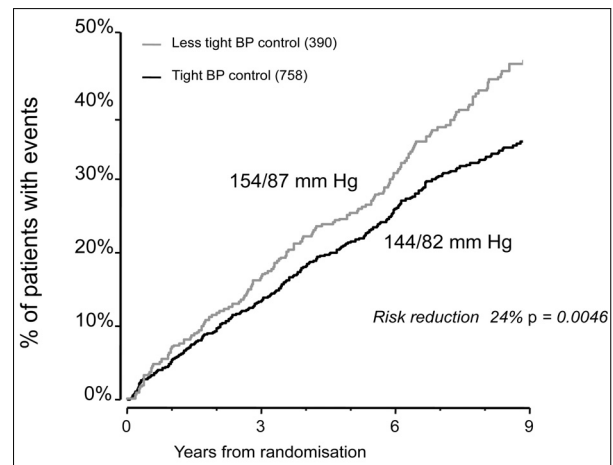


Fig. 6. Any diabetes-related endpoints.²⁶⁾

demonstrates that strict control of blood pressure is important in patients with diabetes even if any antihypertensive drug is used.

In the UK Prospective Diabetes Study (UKPDS),^{25,26)} the value of strict blood pressure was compared to the value of strict blood sugar control to determine which best reduces CV events and improves prognosis. Patients with type 2 diabetes were randomized to tight or less tight blood pressure control and followed for an average of 8.4 years. Tight BP control was defined as less than 144/82 mm Hg and less tight control as less than 154/87 mm Hg. Diabetes-related endpoints were significantly reduced in the tight BP control group by 24%, microvessel disease by 37%, and stroke by 44%, compared to the less tight BP control group. Further, tight blood sugar control (HbA1c 7.0%) was associated with significant reductions in diabetes-related endpoint by 12%, microvessel disease by 25%, and MI by 16%. Strict BP control produced a greater reduction in major vessel outcomes compared to strict blood sugar control (Fig. 6).

An era of new challenges for clinical trials

The Heart Outcomes Prevention Evaluation (HOPE) trial,²⁷⁾ published in 2000, was a landmark trial that showed a

remarkable reduction in CV events in high-risk patients, even with very small reductions in blood pressure, and it suggested a “beyond the blood pressure lowering” cardiovascular protection by RA System blockade. However, the Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) trial²⁸⁾ published in 2004, did not demonstrate that the long-acting ACE-I trandorapril, compared to placebo, was cardio-protective.

Notably, cardiovascular events in the placebo group of PEACE trial, reported in 2000 were lower than that the active group of HOPE trial, reported in 2004, as shown in Fig. 7.

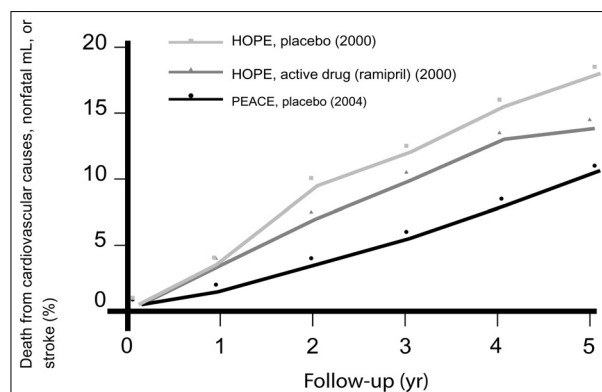


Fig. 7. ACE inhibitors in stable coronary artery disease. Comparison of outcomes in the PEACE and HOPE trials.²⁸⁾ ACE, angiotensin converting enzyme; HOPE, Heart Outcomes Prevention Evaluation; PEACE, Prevention of Events with Angiotensin-Converting Enzyme inhibition.

Table 1. Changing therapy for coronary disease

Concomitant therapy (%)	HOPE (2000)	PEACE (2004)	ONTARGET (2008)	TRANSCEND (2008)
Statin	29	70	62	55
Antiplatelets	76	90	76	80
Beta blocker	39	60	58	58
Coronary revascularization	40	72	51	46

() : year of reporting.

HOPE, Heart Outcomes Prevention Evaluation; PEACE, Prevention of Events with Angiotensin-Converting Enzyme inhibition; ONTARGET, The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease.

What happened in those four years? Table 1 shows remarkable increase in the rate of prescription of other drugs shown to be cardio-protective in clinical trials, including statins, antiplatelets, and beta-blockers. Thus, in just a short time, the incidence of CV events were reduced, making it more difficult to show the benefit, even incremental, of new drugs.

Conclusion

Clinical trials now face a new challenge: how to design a trial that has a sufficient number of events to show a statistical benefit of a new drug, even compared to placebo, in an era where patients are well-treated and fewer CV events occur. The consistent negative trial results with ARB may be attributable in part to the lower occurrence of endpoints. This seems to have led to sponsors of clinical trials relying on variable interpretation of secondary endpoints or subanalyses for their marketing. This so-called “spin” means the medical literature can provide the impression of positive results in the absence of the negative results being published. Recently Boutron, et al.⁷⁾ reported that “spin” was observed in 37.5% and 58.3% of the results and interpretation of 205 published randomized controlled trials published in PubMed. Physicians must read articles the medical articles with caution using critical view and a full awareness of the lack of publishing negative results in this era of advertising-based medicine, not evidence-based medicine.

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