

New Negative Feedback Mechanism of Market Economy Operation, Econometric Ethics and Two Theorems of Welfare Economics

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Abstract

In the previous article "Prediction on Clopidogrel's Abnormal Behaviors and Pharmacobehavioral Economics", the authors propose to establish new disciplines such as pharmacobehavioral economics. Although the establishment of a new discipline normally brings about a breakthrough in the development of the field, from December 2012 to July 2021, this paper had been rejected by many journals, and the correct results of empirical studies turned into a hot potato. During this process, both invisible hand and visible hand became barriers to the formal publication of this article, justice and morality were ignored, and the market and regulators failed. So far, for clopidogrel whose global cumulative sales have exceeded \$90 billion, the treatment guidelines based on the incorrect results of Phase III CAPRIE cannot be corrected, and the global medical economic resources have been excessively consumed for a long time. Based on the prediction function combined with pharmacobehavioral economics or medical-behavioral economics and game theory, within one day of 2012, from massive data, we quickly found that there were serious evidence-based medicine data errors and illogical in another drug with abnormal behavior. The author designs a new economic system, which is the new negative feedback mechanism of market economy operation when the market and the government or regulation failed at the same time. The process of disclosing the illogical data and wrong results of the CAPRIE trial, which cannot be officially published so far, shows that absolute neoliberal economics should sometimes be just a skilled method or methodology for high IQ people or interest groups to transfer wealth as much as possible under the banner of freedom economics. In economic activities, "general disequilibrium theory", rather than "general equilibrium theory", widely exists in market economic activities. Therefore, it can be seen that the market economy in which capital participates is usually asymmetric, and asymmetric economics is the mainstream of market economy. In a discipline, the accurate interpretation of terms is crucial for communication of the discipline. It is suggested to replace "invisible hand" with "profit driven hand". This shows that in a free economy, even though there are thorough laws and institutions in place, invisible hand and visible hand will derail public interests, lead to more waste of public resources, bring more risk to patients and push back the public utilities instead of being necessarily able to accelerate the progress of public utilities.

Keywords: Behavioral economics · Game theory · Pharmacobehavioral economics · Clopidogrel · Aspirin Health behavioral economics · Medical behavioral economics · Econometric ethics · Metrometric business ethics · Metrometric management Ethics · Prospect theory · invisible hand · welfare economics · market failure · profit driven hand · regulation failure · negative feedback mechanism of market economy operation · general disequilibrium theory · general equilibrium theory · freedom economics · asymmetric economics

Nine years ago, we found evidences that the core data and results of the CAPRIE trial were seriously wrong and completely illogical.¹⁻³ Because clopidogrel involved huge economic benefits, the correct results obtained from empirical research on major problems became a thorny problem or hot potato. Both the invisible hand and the visible hand have become obstacles to the official publication of this paper. This led to the rejection of this paper by many journals that attached importance to empirical research from December 2012 to July 2021, and even the account of the papers published on the preprint platform for ten months was blocked.^{2,3} So far, the treatment guidelines based on the incorrect results of CAPRIE in the phase III clinical trial cannot be corrected, and the global medical economic resources have been excessively consumed for a long time. Thus, justice and morality are ignored, and the market and regulatory institutions fail.

However, these have stimulated the author's further research on behavioral economics in the field of medicine and health, the research on the negative feedback mechanism in the market economic system when the market and government fail, the research on liberal economics and relevant theorems of welfare economics, and the research on quantitative economic ethics or quantitative business ethics or quantitative management ethics. It is described as follows.

1. Treatment guidelines based on Non-EBM and Eight years of rejection

The treatment guidelines based on evidence-based medicine can be said to similarly represent a kind of medical fairness or justice. Clinicians prescribe anticoagulant clopidogrel to patients according to the treatment guidelines or specialists' consensus or previous medication habits, and the manufacturers and managing enterprises benefit from them. However, in today's medical world, it seems very easy to formulate treatment guidelines or consensus for a medicine. When the data of Phase III CAPRIE trial of clopidogrel became public, the treatment guidelines for clopidogrel were quickly released. This laid the foundation for clopidogrel to achieve cumulative annual sales of more than \$90 billion. On the contrary, after the CAPRIE trial data was found to be illogical, the paper has been refused to be published publicly for more than 8 years, and the relevant treatment guidelines have been unable to be revised. Although the summary of this paper was disclosed at a medical conference in 2013 and is also searchable globally,¹ no hospitals, medical colleges or regulators have carried out studies on pharmacovigilance, pharmacoeconomics, clinical economics or health economics based on this viewpoint.

2. Evidence of Non-EBM, big market and Invisible ADR of clopidogrel

Clopidogrel is increasingly being used for the secondary prevention of ischemic stroke according to the updated guidelines on acute stroke management.⁴ Many years of habit has also led many clinicians to use clopidogrel alone for anticoagulation. Some articles think that it is a common and multifactorial phenomenon of clopidogrel resistance, which seriously limits the efficacy of the antiplatelet agents.^{4,5,6} It needs a lot of energy and money to do such research. They didn't notice that the data from the phase III trial of clopidogrel were non-evidence-based medicine(Non-EBM). Looking back at the table 6 of phase III clinical CAPRIE trial, the data concerning subgroup No1, No 2 and No 3 of ischemic stroke are all wrong and illogical.^{1,2} How can some patients have good clinical results after taking it? May some patients with drug resistance be more severe or life-threatening? Google Scholar shows that the CAPRIE trial has been cited more than 6000 times, so far, however, no other professional has reported that the data is illogical and non-EBM.

It is unclear whether there are other problems behind the illogical CAPRIE trial data. Perhaps there are data problems with clopidogrel's adverse reactions. One of the teachers of the author of this article, a retired pharmaceutical chemist living in Australia now, read this article on the figshare preprint in March 2021.² After that, he told the author that he had taken clopidogrel for a period of time in 2020. Many bleeding points appeared on his skin, but disappeared after taking cheaper aspirin. Such side effect of clopidogrel, which is known in private discussions, has not been reported to the Therapeutic Goods and Administration (TGA) or FDA. It is relatively easy for experts with pharmaceutical background to change medication after finding adverse drug reactions (ADRs). However, if people without medical background take the medicine, it may be difficult to notice such ADRs in time. It is not known how many other people have similar problems after taking the medicine.

3. Non-evidence-based medicine problems in the CAPRIE trial and huge waste of public health resources

To our surprise and distress, the non-evidence-based medicine problems in the CAPRIE trial are somewhat esoteric and difficult to understand, and the top journals have greater influence than our correct proof. Some professors or doctors in the field of cardiology or pharmacology, or even epidemiologists with advanced degrees, still believed that the results of CAPRIE trial were correct after reading this article or were unable to determine whether the CAPRIE trial results were correct or not. Although some doctors trusted the results of articles published by top journals without thinking, some professors in the fields of cardiovascular, neuroscience, pharmacy or epidemiology were able to understand this article and confirmed that the core data and results of the CAPRIE trial were completely wrong and illogical. The resulting treatment guidelines have led to a huge waste of public health resources around the world. On such a key issue that is even difficult for medical or pharmaceutical experts to understand, in accordance with the principles of morality and justice, relevant journals or media or regulatory agencies should stand up and endorse the justice or evidence of EBM quickly. However, such a situation has not occurred yet.

4. "Invisible hand", visible hand and public interests

The traditional and universal view in economics is that as long as there is a good

legal and institutional guarantee, the free actions of economic men to maximize self-interest will unconsciously and effectively improve the public interest of society.⁷ The "invisible hand" unconsciously promotes the progress of public services.⁸ From more than eight years of submission experience, the game of fairness, justice and interests has been carried out many times. However, the results of establishing a fair clinical medication or medical insurance payment order with the cooperative game equilibrium as the core and ensuring the effective operation of the fair order have not appeared yet, which reflects that justice itself has fallen into a dilemma and it is not easy to achieve justice. This also reflects that the market economy itself has fallen into difficulties, and achieving a complete market economy is impossible. This shows that in an economic system, even though there are thorough laws and institutions in place, invisible hand and visible hand will derail public interests, lead to more waste of public resources, bring more risk to patients and push back the public utilities, which may not necessarily accelerate the development of public utilities.

5. Market failure and regulatory failure under the free economic system

From the above analysis, it is easy to see the difficulties of disclosing clopidogrel's problems and the constant waste of medical insurance resources. Isn't it market failure under the free economic system, coupled with regulatory failure?^{7,9,10} The asymmetries of information, public power, media control ability or the number of speakers lead to issues that cannot be solved for a long time. If we say that morality, justice and fairness are the necessity of a society, they seem to have not come for more than eight years. In economic activities with seemingly free competitions, fairness and justice or objective evidence, driven by tangible or intangible, direct or indirect interests, may also be influenced by invisible feet and visible feet, invisible brain and visible brain, as well as invisible heart and visible heart.

It can be seen that absolute Neo liberal economics should sometimes only be a professional method for highly intelligent people or interest groups to transfer wealth as much as possible under the banner of liberal economics.^{13,14} In economic activities, it is not the general equilibrium theory, but the 'general disequilibrium theory' that is widely or universally present in market economic activities.¹¹ It can be seen that the market economy in which capital participates is often asymmetric, and asymmetric economy is the mainstream of market economy.^{15,16} In a discipline, the accurate interpretation of terms is very important for the communication of disciplines. It is suggested to replace 'invisible hand' with 'profit driven hand'.

6 Prediction and Rapid Discovery of Another Non-EBM Drug by Pharmacobehavioral Economics etc. and Game Theory

John Nash, Nobel Laureate in economics, once said that it takes more than 50 years for a great economic theory to verify its significance.⁴ After we found and confirmed serious errors in the data of CAPRIE trial,^{1,2} we used the excellent prediction function of pharmacobehavioral economics or medical behavioral economics and game theory to make predictions that are normally impossible to predict under asymmetric information and quickly find out serious data errors and evidence of Non-EBM in another drug from the massive data within one day eight years ago.^{1,2} Although the author is very worried that this drug with seriously wrong

clinical trial data may seriously affect patients' health and consume medical insurance funds after it is widely used. Because the first article was not published, the second one was not submitted even though it had been completed. People who are interested in the topic could also do some research to see what the drug is in a day or three days or a week? But we don't want to predict or look for a third. We believe that these subjects will bring more brilliant positive significance.

7. New Negative Feedback Mechanism of Market Economy Operation

We believe that any economic operation is different from children's urination, and there is only one positive feedback direction. However, it is just like the athletes who finish the 110-meter hurdle race, many organs and tissues or signal systems make them stop running again, so that when the market and the government or supervision fail at the same time, there are other incentive mechanisms to make the economy return to an orderly track. Therefore, we need to design a new economic system to achieve effective negative feedback (**Fig 1**), which is the new negative feedback mechanisms of market economy operation. It can be expected that the bubble of stock price caused by irrational exuberance will burst after the normal operation of negative feedback mechanism of the market economy.

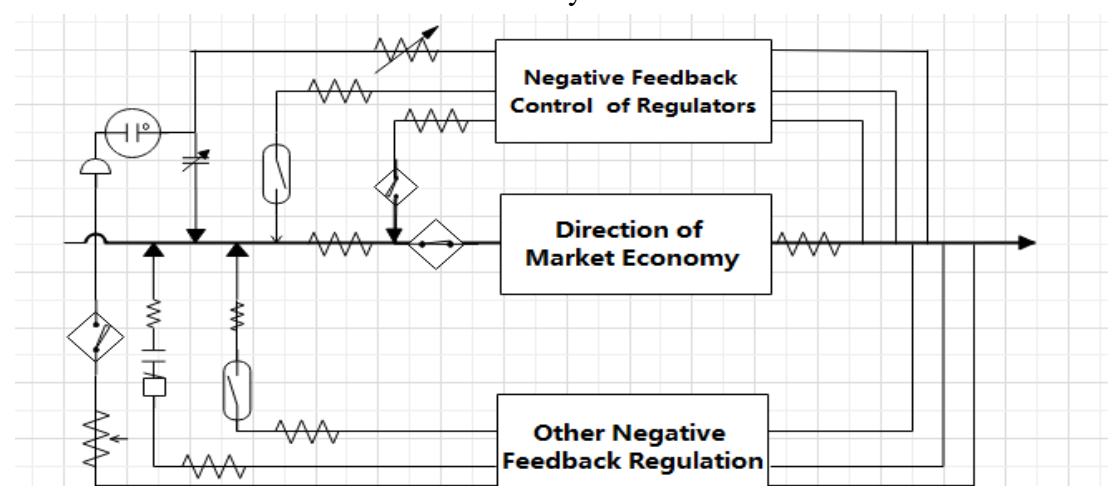


Fig 1. Negative Feedback Mechanisms of Market Economy Operation

8. Non-EBM and Quantitative Business Ethics or Econometric Ethics etc.

In modern medicine, whether it conforms to the principle of EBM is the fundamental principle to guide clinical medication. Clopidogrel brings huge economic benefits to drug manufacturers and other relevant units, which is fundamentally based on EBM evidence produced by CAPRIE trial. However, when we found that the core data of CAPRIE trial was completely illogical, it was not merely difficult for this article to enter the peer review process for a long time, but also to be publicly published in medical or pharmaceutical journals or comprehensive journals, as well as rejected by journals in economics or management that attach importance to the empirical study. Because the clopidogrel involved huge economic interests, the correct results obtained by empirical research for major issues seemed to become a tough nut or a hot potato. Both the invisible hand and visible hand became barriers to the formal and public publication of this article. “The invisible hand” is generally

regarded as a positive means of regulation. However, we believe that “the invisible hand” is also a negative signal in the operation of the market economy, which makes not merely the market fail, but also the government fails.

Therefore, we also suggest that an independent quantitative economic ethics or quantitative business ethics or quantitative management ethics (econometric ethics or metrological business ethics or metrological management ethics) should be established to study the problems in economic ethics or management ethics with the method of empirical research.^{4A-6A}

8. Evidence of non-EBM, Difficulty in Revising Treatment Guidelines or Consensus and Two Theorems of Welfare Economics

Through this empirical study and the current situation, we can clearly see that there are inconsistencies between the findings and the two theorems of welfare economics.^{10,12} The first theorem of welfare economics points out that under certain conditions, the competitive market equilibrium allocation is Pareto effective and conforms to Pareto optimal effect, which means market mechanism can solve the efficiency problem. Unconsciously, people will contribute to the optimal allocation of resources. The second theorem tells us that, satisfying certain conditions and given a certain endowment configuration, Pareto efficient configuration can be realized through the competitive market equilibrium. In other words, to achieve the objective of fairness, the initial endowment needs only to be adjusted and the rest should be left to the market. This also shows that fairness and efficiency can be balanced.

However, the fact that we have contributed for eight years since the clopidogrel came into the market shows that in real life, the Pareto optimal effect does not come and the market mechanism does not solve the efficiency problem. No institution has revised the treatment guidelines or specialists consensus of clopidogrel based on the wrong results of CAPRIE trial, adjusted its clinical medication methods, and rationally allocated public health resources to promote the optimal allocation of resources. This is obviously inconsistent with the first theorem of welfare economics. The competitive market equilibrium has also failed to achieve the objective of fairness, and the governments or regulatory authorities have not been able to effectively

The author believes that an economical theorem that requires too many assumptions (six or more) to be established does not seem to be a theorem anymore.

9 Discussions

Although the “invisible hand” or “profit driven hand” is usually regarded as a positive regulatory means.¹⁷ The conclusion of CAPRIE incident is that the “invisible hand” is also a negative signal in the operation of the market economy, which will not merely make the market fail, but also make the government fail. Although the traditional and general view of economics is that as long as there is good legal and institutional guarantee, the free action of economic man to maximize its own interests will unknowingly and effectively improve the social public interests. From the analysis of the profits, problems and supervision of clopidogrel since its listing, we can see that in the real clopidogrel problem, the Pareto optimal effect does not appear, and the market mechanism does not solve the issue of efficiency. No institution considered the wrong results of CAPRIE trial to modify the treatment guidelines

about clopidogrel, adjust clinical medication, and promote the rational and optimal allocation of public health resources; competitive market equilibrium also failed to achieve the goal of fairness. Obviously, it contradicts the first and second theorems of welfare economics. The author believes that the economic theorem that needs to establish too many assumptions (six or more) seems to be no longer a theorem, and the old theoretical basis of welfare economics needs to be abandoned and modified. In addition, we propose to establish independent econometric ethics or econometric business ethics or econometric management ethics to study the problems in economic ethics or management ethics with the method of empirical research.

In desperation, the author designed a new economic system, that is, a new negative feedback mechanism for the operation of the market economy when the market and the government or supervision fail at the same time, hoping to help the normal operation of the economy in the future. Naturally, it can be seen that absolute Neo liberal economics should sometimes be only a skilled method for highly intelligent people or interest groups to transfer wealth as much as possible under the banner of liberal economics, rather than a discipline. In economic activities, there is a general imbalance theory rather than a general equilibrium theory in market economic activities. It can be seen that the market economy in which capital participates is often asymmetric, and asymmetric economy is the mainstream of market economy. In a discipline, the accurate interpretation of terms is very important for the communication of disciplines. It is suggested to replace "invisible hand" with "profit driven hand".

^{4A} The Definition of Econometric Ethics (Quantitative economic ethics): A discipline that uses mathematical or mathematical statistics methods to conduct quantitative research on moral and ethical issues or phenomena in economic field.

^{5A} Econometric business ethics (metrological business ethics): a discipline that uses mathematical or mathematical statistics methods to conduct quantitative research on moral and ethical issues or phenomena in the field of business.

^{6A} Metrological management ethics (quantitative management ethics): A discipline that uses mathematical or mathematical statistics methods to conduct quantitative research on moral and ethical issues or phenomena in the field of management.

Conflict of Interest: As of the publication date of this paper, the authors declare that they have no conflict of interest. Current research has not received any financial supports.

Disclosure Statement

Most of the content has been disclosed on the preprint platform from 2021 to 2022 (Liu, L. (2021): Postscript: Ethical, Economic, Managerial and Political Reflections Triggered by New Discovery of Clopidogrel. figshare. Preprint. <https://doi.org/10.6084/m9.figshare.14954871.v1,-v26>; Li Liu. (2022). Postscript: Ethical, Economic, Managerial and Political Reflections Triggered by New Discovery of Clopidogrel. Zenodo. <https://doi.org/10.5281/zenodo.6416334>).

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