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**Review Article**

# Lumbrokinase Reduced the Fibrinogen Concentration in Ischemic Cerebrovascular Disease Patients: A Systematic Review and Meta-Analysis

**Yedy P. Sukmawan**
Department of Clinical Pharmacy and Pharmacology,
Bakti Tunas Husada College of Health Sciences, Tasikmalaya, Indonesia

**Abstract**
Lumbrokinase has been used to treat stroke and cardiovascular disease. Fibrinogen elevation is a known risk factor and a powerful predictor of ischemic cerebrovascular disease. The objective of this study was to conduct a systematic review and meta-analysis of the effects of lumbrokinase treatment on fibrinogen concentration and blood and plasma viscosities. The search strategy included articles indexed by PubMed and other resources (Google Search), using medical subject headings (MeSH) and text words. A total of 185 articles were identified; however, only two articles were included in the final analysis, including 727 patients. The results demonstrated a significant reduction in the fibrinogen concentration (–0.67, 95% confidence interval [95% CI] [–1.22, –0.12]; p=0.02) and a significant reduction in plasma viscosity (–0.77, 95% CI [–1.06, –0.48]; p=0.00001) for the lumbrokinase-treatment group compared with the control group. However, no significant difference in blood viscosity was observed between the two groups (–0.61, 95% CI [–1.33, 0.11]; p=0.10). Lumbrokinase may be effective as an adjuvant drug alongside the standard treatment for ischemic cerebrovascular disease. However, these results should be interpreted with caution due to high heterogeneity, and further randomized controlled trials are necessary.

**Keywords:** Fibrinogen, ischemic cerebrovascular disease, lumbrokinase

# Lumbrokinase Menurunkan Konsentrasi Fibrinogen pada Pasien Penyakit Iskemik Serebrovaskular: Kajian Sistematik dan Meta-Analisis

**Abstrak**
Lumbrokinase telah digunakan untuk penatalaksanaan strok dan penyakit kardiovaskular. Peningkatan konsentrasi fibrinogen telah diketahui sebagai faktor risiko dan prediktor yang sangat kuat untuk penyakit iskemik serebrovaskular. Tujuan *review* sistematik dan meta-analisis ini adalah untuk menganalisis efek lumbrokinase terhadap konsentrasi fibrinogen, viskositas darah dan viskositas plasma. Strategi pencarian artikel meliputi pencarian artikel pada *database PubMed* dan sumber lainnya (*Worldwide Website/Google Search*) dengan menggunakan *medical subject heading* (MeSH) dan *textword*. Sebanyak 185 artikel teridentifikasi, tetapi hanya 2 artikel (melibatkan 727 pasien) yang memenuhi kriteria inklusi. Hasil analisis menunjukkan bahwa lumbrokinase dapat menurunkan konsentrasi fibrinogen dibandingkan terhadap kelompok kontrol (–0,67, 95% CI [–1,22, –0,12] ; p=0,02). Selain itu, lumbrokinase juga dapat menurunkan viskositas plasma secara signifikan bila dibandingkan dengan kelompok kontrol (–0,77, 95% *confidence interval* [95% CI] [–1,06, –0,48]; p=0,00001). Efek lumbrokinase terhadap viskositas darah, meskipun terjadi penurunan terhadap viskositas darah, tidak menunjukkan signifikansi bila dibandingkan kelompok kontrol (–0,61, 95% CI [–1,33, 0,11]; p=0,10). Lumbrokinase mungkin efektif untuk penyakit iskemik serebrovaskular, namun hasil ini harus diinterpretasikan dengan hati-hati disebabkan heterogenitas yang tinggi, selain itu diperlukan lebih banyak penelitian dengan desain *randomized controlled trial*.

**Kata kunci:** Fibrinogen, lumbrokinase, penyakit iskemik serebrovaskular

**Correspondence:** apt. Yedy P. Sukmawan, M.Si., Department of Clinical Pharmacy and Pharmacology, College of Health Sciences, Tasikmalaya, West Java 46115, Indonesia, email: *yedipur@gmail.com*
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## Introduction

Fibrinogen is a thrombin-coagulable glycoprotein found in the blood of vertebrates (340-kDa plasma protein), comprised of two sets of disulfide-bridged alpha, beta, and gamma chain.[1–3] Fibrinogen is synthesized in the liver and is essential for hemostasis, wound healing, inflammation, angiogenesis, and matrix interactions.[4] In addition to normal physiological functions, fibrinogen has been associated with disease pathology. Fibrinogen elevation is a known risk factor and a powerful predictor of ischemic stroke, with a pooled hazard ratio (HR) for values above the median of 1.34 (95% confidence interval [95% CI] [1.13, 1.60]; p=0.001).[5–7] Moreover, fibrinogen elevation has been associated with early neurological deterioration (END) and may be associated with poorer prognoses within 1 year after stroke.[8,9]

Lumbrokinase was isolated and purified from different species of earthworms, has been used as a traditional medicine in several countries, and is recognized as a fibrinolytic agent which can be used to treat various conditions associated with thrombosis.[10] Lumbrokinase has been used to treat stroke and cardiovascular diseases because it is a fibrinolytic enzyme and has the capability of directly dissolving fibrinogen and fibrin clots, inhibiting platelet activation and aggregation, converting plasminogen into plasmin, and increasing native tissue plasminogen activator (t-PA) activity to dissolve fibrin clots.[10–12] In addition, lumbrokinase plays a role in the modulation of the condition after cerebral ischemia.[13] Therefore, this study performed a systematic review and meta-analysis to examine the effects of lumbrokinase on fibrinogen levels in ischemic cerebrovascular disease patients.

## Methods

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The search strategy included articles indexed by PubMed and other resources (Google Search), with study selection based on the Patient, Intervention, Comparison, Outcome (PICO) model, using the medical subject heading (MeSH) "lumbrokinase" and the following text words: "vermis kinase"; "boluoke"; "earthworm fibrinolytic enzyme component A protein, Eisenia fetida"; "EFE component A protein, Eisenia fetida"; "Aspirin"; "Acetylsalicylic"; "2-(Acetyloxy) benzoic Acid"; "Acylpyrin"; "Aloxiprimum"; "Colfarit"; "Dispril"; "Easprin"; "Ecotrin"; "Endosprin"; "Magnecyl"; "Micristin"; "Polopirin"; "Polopiryna"; "Solprin"; "Solupsan"; "Zorprin"; and "Acetysal". The last date that a search was performed was 28 November 2018.

The studies were examined for the following inclusion criteria: (1) the use of lumbrokinase as an adjuvant therapy in addition to standard treatment; (2) ischemic cerebrovascular disease patients (ischemic stroke); (3) randomized controlled trial (RCT) study design; (4) fibrinogen levels as a reported outcome (mean±SD); (5) original article; and (6) study published in an English language publication. The following data were extracted from each included publication: the study source (year); study design; sample size (number of subjects); duration of treatment; outcome; fibrinogen level; blood viscosity; plasma viscosity; and article quality. The risk of bias was assessed based on the parameters of randomization, double-blind status, allocation concealment, withdrawal, and dropout.

### Data analysis

Data were analyzed using RevMan 5.3. Data were expressed as standard mean difference, using a 95% CI. A p-value <0.05 was defined as being statistically significant for all outcomes.

## Results

Description of trials

The process used for the article selection is shown in Figure 1. The total number of articles identified by the initial search was 185, of which 179 were excluded based on the title and abstract for the following reasons: no lumbrokinase; no ischemic cerebrovascular disease; preclinical study; and no original research. A total of six articles remained for full-text review. After full-text review, four articles were excluded due to no ischemic cerebrovascular disease, preclinical trials, no mention of the mean and SD for fibrinogen, and lumbrokinase as a primary prevention measure for ischemic cerebrovascular disease (instead of as a treatment for ischemic cerebrovascular disease). Two studies were included in the final analysis that fulfilled the inclusion criteria. These randomized controlled trials study enrolled 763 patients (727 total patients were analyzed after patient withdrawal/dropout was considered) with ischemic cerebrovascular disease who received standard stroke treatment either with or without additional lumbrokinase (capsule) (Table 1).

We included two studies in the quantitative analysis. Assessment of the article quality for the study performed by Cao et al. (2013) showed well-reported randomization, allocation concealment, and withdrawal and dropout details; however, this study did not utilize a double-blind design, which may contribute to performance bias. The study was a parallel and multicenter center. Assessment of the article quality for the study performed by Pang et al. (1993) showed well-reported randomization, double-blind, and withdrawal and dropout details; however, allocation concealment was not well-reported, which may contribute to selection bias.

Lumbrokinase reduced fibrinogen concentration

Data results from the two trials, which included 727 patients, demonstrated a significant reduction in fibrinogen concentration for the lumbrokinase group compared with the

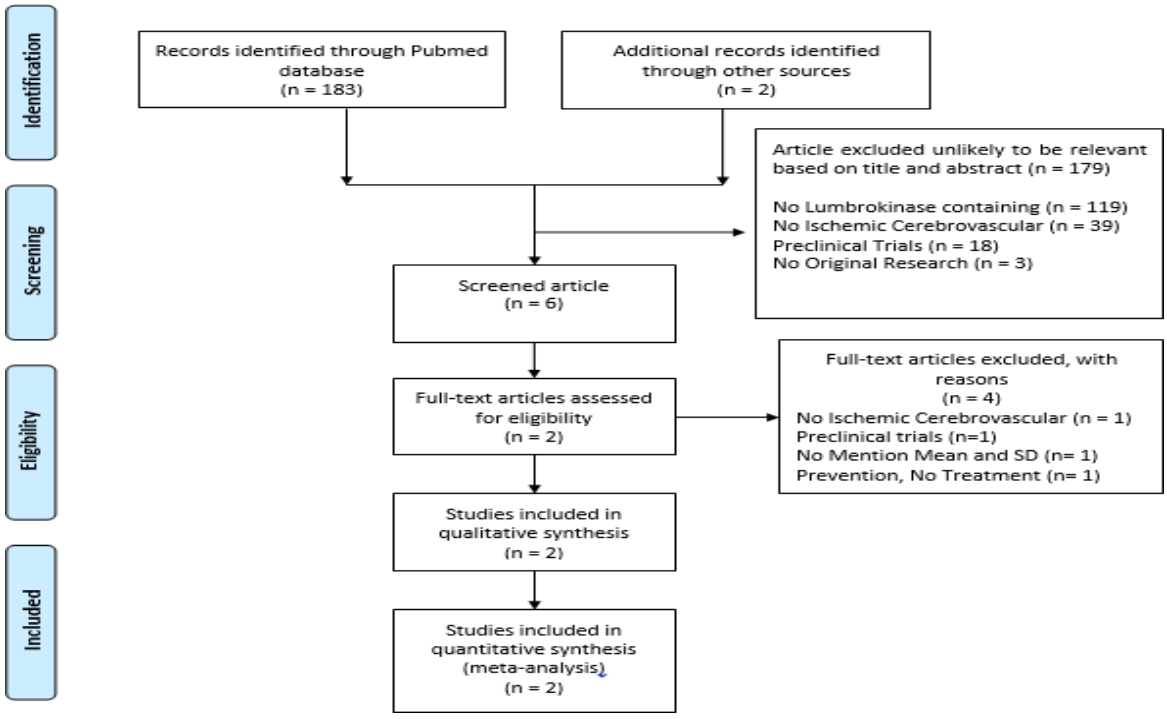


**Figure 1 Article Selection Process**

**Table 1 Basic Characteristics of the Included Studies**

| Study (Year) | Study Design | Number of Subject (Completed) | Duration of Treatment | Results | Fg Level | | Blood Viscosity | | Plasma Viscosity | | Article Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | L | C | L | C | L | C | |
| Cao et al. (2013)[15] | Multicenter, Randomized, Controlled Study | 310 (274) | 12 (Three times a day) | Long-term oral fibrinogen depletion therapy may be beneficial for secondary ischemic stroke prevention | 2.68 ± 0.95 | 3.56 ± 0.86 | 4.49 ± 0.80 | 5.23 ± 0.67 | 1.46 ± 0.23 | 1.67 ± 0.22 | Randomization (Well-Reported)<br>Double-Blind (No)<br>Allocation Concealment (Well-Reported)<br>Withdrawal and Dropout (Well-Reported) |
| Pang et al. (1993)[16] | Randomized, Controlled, Double-blind Study | 453 (453) | 21 days (Three times a day) | Lumbrokinase can serve as an effective drug for the prevention of thrombosis and as a safe and beneficial antithrombotic agent | 3.27 ± 0.80 | 3.61 ± 0.98 | 5.23 ± 1.44 | 5.57 ± 1.23 | 1.73 ± 0.14 | 1.83 ± 0.19 | Randomization (Well-Reported)<br>Double-Blind (yes)<br>Allocation Concealment (Unclear)<br>Withdrawal and Dropout (Well-Reported) |

L=Lumbrokinase; C=Control

control group (–0.67, 95% CI [–1.22, –0.12]; p=0.02). However, the trials demonstrated significant heterogeneity (Figure 2).

Lumbrokinase effects on blood viscosity

The blood viscosity of the lumbrokinase group did not differ significantly from that of the control group (–0.61, 95% CI [–1.33, 0.11]; p=0.10) and demonstrated significant heterogeneity between the trials (Figure 3).

Lumbrokinase effects on plasma viscosity

The lumbrokinase group demonstrated a significant reduction in plasma viscosity reduction compared with the control group (–0.77, 95% CI [–1.06, –0.48]; p=0.00001), with no obvious statistical heterogeneity among trials (p=0.07) (Figure 4).

## Discussion

Meta-analysis results demonstrated a significant reduction in fibrinogen concentration after lumbrokinase treatment. This result indicated that lumbrokinase may be effective for the treatment and prevention of ischemic cerebrovascular disease. In addition to that, fibrinogen reductions may improve prognoses and neurological functions. The reduction in the fibrinogen level was accompanied by reductions in plasma and blood viscosities, which resulted in improved blood flow and

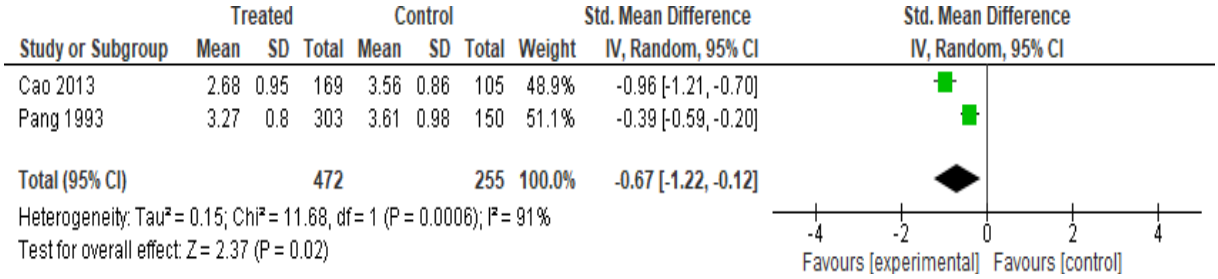


**Figure 2 Meta-Analysis of Lumbrokinase-mediated Fibrinogen Concentration Reductions**

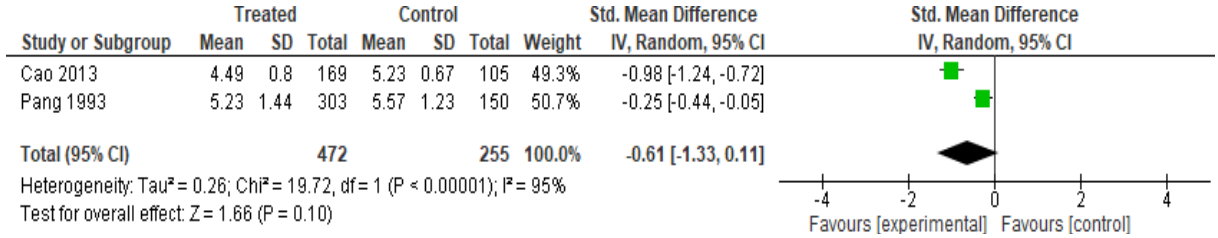


**Figure 3 Meta-Analysis of Lumbrokinase-mediated Effects on Blood Viscosity**

may help remove blood clots and re-establish blood flow.[17] A previous study by Ji et al. (2008) demonstrated that the antiplatelet activity of lumbrokinase may involve the following three mechanisms: (1) significantly elevating intracellular cAMP levels and enhancing the activity of adenylate cyclase to inhibit aggregation; (2) protecting against ischemic injury by enhancing Janus kinase 1 [JAK1] mRNA levels and decreasing signal transducer and activator of transcription 1 [STAT1] mRNA levels; (3) significantly inhibiting the expression of intracellular adhesion molecule 1 (ICAM-1) in human umbilical vein endothelial cells (HUVEC), which protects against injury, interfering with the interaction between fibrinogen and its receptors on platelet surfaces, in vitro, and inhibits the expression of P-selectin and glycoprotein IIB/IIIA. Therefore, this mechanism may protect against events that occur after ischemic events, such as platelet activation and aggregation and the activation of the JAK1/STAT1 signaling pathway, the activation of adenosine 3′, 5′-cyclic monophosphate (cAMP) and guanosine 3′, 5′-cyclic monophosphate (cGMP) levels, $Ca^{2+}$ overload, the overexpression of adhesion molecules in endothelial cells, and fibrinogen elevation.[11,18] Fibrinogen elevation contributed to the obstruction of the microvascular due to the coagulation cascade and change in the blood rheological properties.[19] In addition, this condition causes excessive clumping

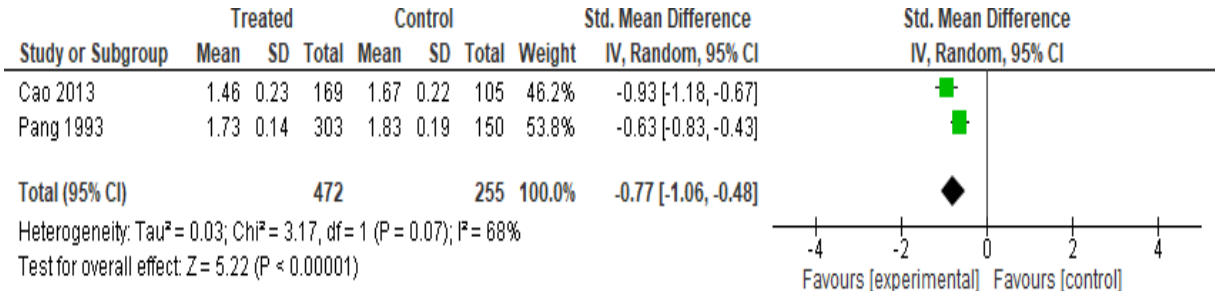


**Figure 4 Meta-Analysis of the Lumbrokinase-mediated Effects on Plasma Viscosity**

of blood cells, resulting in formation of abnormal clots in the artery and may lead to the development of the hemorrhagic stroke.[20] Plasma fibrinogen levels were significantly increased (both men and women) in ischemic stroke patients when compared to controls, and act as a risk factor and contribute to the pathogenesis of ischemic stroke.[18] The carotid artery stenosis and risk of death within 1 year after stroke are significantly associated with elevated fibrinogen levels.[21]

Limitations of this study are the high degree of heterogeneity ($p<0.05$), the inclusion of relatively few studies, and the use of the Google search engine. This heterogeneity may be due to clinical heterogeneity (due to variation in participants, interventions, and outcomes) or methodological heterogeneity (due to variations in study design and bias).[13] Google search engine was used to identify gray literature. Therefore, results of this study should be interpreted with caution.

## Conclusion

Lumbrokinase treatment resulted in significant fibrinogen concentration and plasma viscosity reductions, which indicate that this agent may be effective as an adjuvant drug in addition to standard treatment for ischemic cerebrovascular disease. However, these results should be interpreted with caution due to high heterogeneity, and more randomized controlled trials are necessary.

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## Conflict of Interest

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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