



## **A SYSTEMATIC REVIEW OF EVOLOCUMAB FOR STROKE PREVENTION IN PATIENTS WITH DYSLIPIDEMIA**

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### **AUTHORS' CONTRIBUTIONS**

This work was carried out in collaboration between both authors. Author RTP designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author RLRS managed the analyses of the study and manage literature searches. Both authors read and approved the final manuscript.

### **ARTICLE INFORMATION**

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### **ABSTRACT**

**Introduction:** Evolocumab is a human monoclonal immunoglobulin G2 (IgG2) directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9). By inactivating PCSK9, evolocumab upregulates low-density lipoprotein receptor (LDLR) causing increased catabolism of low-density lipoprotein cholesterol (LDL-C) and the consequent reduction of LDL-C levels in the blood.

**Objective:** This systematic review aimed to identify the effectiveness of evolocumab for stroke prevention in patients with dyslipidemia.

**Method:** PubMed and Cochrane Library were searched to identify relevant studies. The keywords were the combination of the following words: evolocumab, PCSK9, stroke, and dyslipidemia. The inclusion criteria of the study i.e : patients with dyslipidemia, was a randomised controlled trial (RCT), published within ten (10) years (from 2008 to 2018), concerned on evolocumab and compared to other pharmacologic agents for the management of dyslipidemia or placebo. The quality of selected studies was assessed using Jadad score.

**Results:** There are only two studies matched with inclusion and exclusion criteria. The name of the trial was OSLER and FOURIER. Both studies used a subcutaneous injection of evolocumab with 2 types of dosage: 140 mg in every 2 weeks or 420 mg once in a month. OSLER was using standard dyslipidemia therapy, whereas FOURIER was using placebo as a control. Both studies were conducted for 12 months.

**Conclusion:** Subcutaneous injection of evolocumab is effective for the lowered LDL-C level. It is also effective for stroke prevention in patients with dyslipidemia.

**Keywords:** Stroke; evolocumab; PCSK9; dyslipidemia.

## 1. INTRODUCTION

Cardiovascular disease (CVD) remains one of the most familiar sources of morbidity and mortality in the world [1]. Atherosclerosis is characterised by cholesterol deposition in the arterial intima, with subsequent plaque formation and arterial disease. Low-density lipoprotein cholesterol (LDL-C) plays the most important role in the atherogenesis process, which is the substrate of cardiovascular disease, including stroke, and is the leading cause of death worldwide [2]. Reduction of LDL-C is of vital importance for the prevention of CVD [3].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is initially secreted as an inactive enzyme precursor which undergoes intramolecular autocatalytic cleavage in the endoplasmic reticulum for activation. The matured PCSK9 moves out of the endoplasmic reticulum of the hepatic cells to be further handled by the Golgi apparatus of hepatic cells before entering the circulation [4]. PCSK9 binds surface LDL receptor (LDLR) and targets it toward lysosomal degradation. As a consequence, the number of LDLRs at the cell surface get decreased, and LDL-cholesterol (LDL-C) clearance is reduced [5]. Inhibiting PCSK9 results in improved LDLR recycling, increased LDLR availability on hepatocyte cell surfaces, and reduced blood LDL-C levels, makes PCSK9 inhibition a novel therapeutic strategy for managing hypercholesterolemia [6].

PCSK9 is an inhibitor of LDL(R). PCSK9 binds with LDL(R) on the liver cell surface and escorts it to the lysosomal system of liver cells for the destruction of LDL(R), which thus cannot return back to the surface of liver cells. The net result is a decrease in the population of LDL(R). Hence, less number of LDL(R)s are available at the liver cell surface to mop up LDLc for further metabolism [4].

To date, statins remain the first-choice therapy, as they have been shown to reduce the risk of major vascular events by lowering LDL-C. However, due to adherence to statin therapy or statin resistance, many patients do not reach LDL-C target levels [7]. In 2015, the US Food and Drug Administration (FDA) approved the anti-PCSK9 monoclonal antibodies, alirocumab and evolocumab, to treat patients with hypercholesterolemia and mixed dyslipidemia [8]. Evolocumab is a fully human monoclonal immunoglobulin G2 (IgG2), directed against human PCSK9. By inactivating PCSK9, evolocumab upregulates LDLR causing increased catabolism of LDL-C and the consequent reduction of LDL-C levels in the blood [9].

Although evolocumab is highly effective at numeric reduction of LDL cholesterol, most trials have not investigated clinically important patient-centred outcomes such as myocardial infarction, stroke, or premature death from cardiovascular disease [10]. Systematic review of evolocumab for stroke prevention in Indonesia has not yet performed. This systematic review aimed to identify the effectiveness of evolocumab for stroke prevention in patients with dyslipidemia.

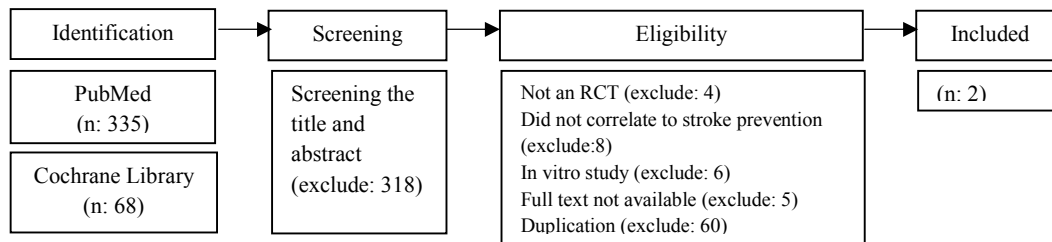
## 2. MATERIALS AND METHODS

PubMed and Cochrane Library were searched to identify relevant studies. Two researchers were involved in the process of data extraction, review process, and quality assessment. The keywords were the combination of the following words: evolocumab, PCSK9, stroke, and dyslipidemia. The systematic review process complied with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PRISMA checklist consists of 27 essential item to make a transparent systematic review and meta-analysis [11]. Fig. 1 showed the selection process based on PRISMA guideline. The inclusion criteria of the study i.e.

- (i) Study population: patients with dyslipidemia
- (ii) Study design: randomised controlled trial (RCT)
- (iii) Study time: published within ten (10) years (from 2008 to 2018).
- (iv) Study intervention: evolocumab
- (v) Study control: other pharmacologic agents for the management of dyslipidemia or placebo.

Studies were excluded if the full text was not available and did not use English as the main language. The efficacy outcomes of interest were percentage change from the baseline in LDL-C and stroke events. A study that did not discuss the incidence of stroke was excluded. The safety outcomes of interest were any adverse event (AE) and serious AE. Other variables for which data were sought included number of subjects, subjects' characteristics (mean age and gender), and length of the study.

The quality of selected studies was assessed using a Jadad score. A Jadad score consists of 5 items. One point will be added if the study fulfil each item, thus the maximum score is 5 [12]. The study will be excluded if the score is less than 3. A score up to 2 indicates a low-quality design.



**Fig. 1. Selection process of the studies**

### 3. RESULTS

There were total 335 journals from PubMed and 68 journals from Cochrane Library. After checking for the title and abstract, there were 318 journals that were excluded and remains 85 journals. Four journals were excluded because those journals were not an RCT, 8 journals did not correlate to stroke prevention, 6 journals were an in vitro studies, 5 journals did not fully accessible, and 60 journals showed duplication with other study or a same journal published in different journal database.

There are only two studies matched with inclusion and exclusion criteria. The name of the trial was OSLER and FOURIER. Table 1 showed a Jadad score for each study. Other well known trials such as MENDEL-2 (Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2), DESCARTES (Durable Effect of PCSK9 Antibody Compared with Placebo Study), YUKAWA, GAUSS-2 (Goal Achievement After Utilising an Anti-PCSK9 Antibody in Statin Intolerant Subjects-2) and LAPLACE-2 (LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy) were excluded because did not evaluate the effectiveness of evolocumab for stroke prevention.

Table 2 showed the summary of each study. Both studies used a subcutaneous injection of evolocumab with 2 type of dosage: 140 mg in every 2 weeks or 420 mg once in a month. OSLER was using standard dyslipidemia therapy, whereas FOURIER was using placebo as a control. Both studies were conducted for 12 months. Both studies concluded that evolocumab lowered LDL-C level significantly compared to the control group. Subcutaneous injection of evolocumab has also reduced the incidence of a cardiovascular event including stroke.

## 4. DISCUSSION

### 4.1 Evolocumab for LDL-C level

In OSLER study, the median baseline LDL cholesterol was 120 mg/dl. At the 12<sup>th</sup> week,

evolocumab, as compared with standard therapy, reduced the LDL-C level by 61% (95% CI: 59-63;  $p < 0.001$ ), for a mean absolute reduction of 73 mg/dl to a median of 48 mg/dl. At 12 weeks, the LDL-C level was reduced to 100 mg/dl or less in 90.2% of patients and 70 mg per deciliter or less in 73.6% of patients in the evolocumab group, as compared with 26.0% and 3.8%, respectively, in the standard-therapy group [13].

The median LDL cholesterol level at baseline in FOURIER study was 92 mg per deciliter. At 48 weeks in the evolocumab group, the LDL cholesterol level was reduced to  $\leq 70$  mg/dl in 87% of the patients, to  $\leq 40$  mg/dl in 67% of the patients, and to  $\leq 25$  mg/dl in 42% of the patients, as compared with 18%, 0.5%, and less than 0.1%, respectively, of the patients in the placebo group ( $p < 0.001$  for all comparisons of evolocumab vs placebo) [14].

### 4.2 Evolocumab for Stroke Prevention

At the baseline, 2.7% in evolocumab and 2.5% in the standard-therapy group had a stroke. About 80.4% of the subjects had at least one cardiovascular risk factor (hypertension, diabetes mellitus, metabolic syndrome, current cigarette use, family history of premature coronary artery disease, and known familial hypercholesterolemia). Patients in the evolocumab group had a significantly lower rate of all cardiovascular events than patients in the standard-therapy group (Kaplan–Meier Estimates at 1 year, 0.95% and 2.18%, respectively; HR: 0.47, 95% CI: 0.28-0.78;  $p = 0.003$ ). The incidence of stroke occurred in 3 subjects (0.1%) in the evolocumab group and 2 subjects (0.1%) in the control group. The incidence of TIA occurred in 1 subjects (0.0%) in the evolocumab group and 5 subjects (0.3%) in the control group [13].

Similar to the OSLER study, evolocumab significantly reduced the risk of the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation in the FOURIER study (9.8% vs 11.3%, HR: 0.85, 95%CI: 0.79-0.92,  $p < 0.001$ ). The secondary endpoint of

Table 1. Jadad score of selected studies

Author, Year (Name of Study)	Was the study described as randomised?	Was the method used to generate the sequence of randomisation described and appropriate?	Was the study described as double blind?	Was the method of double blinding described any appropriate?	Was there a description of withdrawal and dropout?	Total Score
Sabatine, et al.,2015 (OSLER)	Yes	Yes	No	No	Yes	3
Sabatine, et al.,2017 (FOURIER)	Yes	Yes	Yes	Yes	Yes	5

Table 2. Summary of selected studies

Authors (Year)	Trial Name	Intervention	Control	Number of Subject	Length of Study	Conclusion
Sabatine, et al. (2015)	OSLER	Evolocumab SC 140 mg every 2 weeks or 420 mg once a month + standard therapy (mean age: 57.8 ± 11.0, 50.1% male)	Standard therapy (Mean age: 58.2 ± 10.9, 51.4% male)	4465	12 months	The use of evolocumab plus standard therapy significantly reduced LDL cholesterol levels and reduced the incidence of cardiovascular events.
Sabatine, et al. (2017)	FOURIER	Evolocumab SC 140 mg every 2 weeks or 420 mg once a month (mean age: 62.5 ± 9.1, 75.4% male)	Placebo (Mean age: 62.5 ± 8.9, 75.5% male)	27564	12 months	Inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels and reduced the risk of cardiovascular events.

OSLER: Open-Label Study of Long-Term Evaluation against LDL Cholesterol FOURIER: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk, SC: subcutaneous, LDL: Low-Density of Lipoprotein, PCSK9: Pro-protein convertase subtilisin/kexin type 9

cardiovascular death, myocardial infarction, or stroke was also lower in the evolocumab group (5.9% vs 7.4%, HR: 0.80, 95% CI: 0.73-0.88,  $p < 0.001$ ). Stroke event in the evolocumab group was lower than the placebo group (1.5% vs 1.9%), and it was statistically significant ( $p < 0.01$ ) [14].

### 4.3 Safety and Adverse Event

Adverse events occurred in 69.2% subjects in the evolocumab group and 64.8% in the standard-therapy group. Serious adverse events occurred in 7.5% subjects in the evolocumab group and in 7.5% subjects in the standard-therapy group. Injection-site reactions were reported in 4.3% subjects in the evolocumab group (the only group in which such events were analysed) and led to the discontinuation of evolocumab in 6 patients (0.2%) [13].

No significant between-group differences were seen in the overall rates of adverse events, serious adverse events, or adverse events thought to be related to the study agent and leading to discontinuation of the study regimen. Injection-site reactions were rare, but they were more frequent with evolocumab (2.1% vs 1.6%). The rates of allergic reactions also did not differ significantly between the groups (3.1% vs 2.9%) [14].

## 5. CONCLUSION

Subcutaneous injection of evolocumab is effective for the lowered LDL-C level. It is also effective for stroke prevention in patients with dyslipidemia. However, the safety level of the evolocumab should be reviewed further.

## CONSENT AND ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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