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Research Article

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Complications of Streptokinase Therapy in Iranian Patients with ST-elevation Myocardial Infarction Patients: A Systematic Review and Meta-analysis

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Abstract

Objective
This study was conducted to investigate the pattern of adverse drug reactions caused by streptokinase treatment and related risk factors in patients with acute ST-elevation myocardial infarction (STEMI), considering the critical conditions in patients with AMI and the complications of streptokinase *therapy*.

Methods
Here we presented a systematic investigation and meta-analysis based on PRISMA principles. We searched for studies published in English in MEDLINE, PubMed, EMBASETM, Ovid, The Cochrane Library, and the TRIP database. We searched national databases of Iran (Magiran and SID) (KoreaMed and LILACS) for published literature in other languages.

Results
Our meta-analysis showed that the most prevalent complication after streptokinase therapy was arrhythmia 52%(95%CI:48-55) followed by hypotension 26%(95%CI:23-29), bradycardia 7%(95%:6-9), and allergy 2%(95%CI:1-3).

Conclusion
In the current research, it can be concluded that the most common side effect was hypotension. Other less common side effects were minor bleeding and mild allergic reaction.

Keywords: Streptokinase,ST-elevation Myocardial Infarction, Complication

Introduction

In 1998, Adverse drug reactions (ADRs) were recognized as the top 4-6 causes of death in the United States that impose costs on the health care system [1]. Furthermore, in the UK, data showed that 1/16 hospital admissions were related to an ADR at an annual cost of £466 million. *Adverse drug reactions* are causes of about 0.15% of hospital deaths *death [2]*. Therefore, the diagnosis and prevention of ADRs have an important role in improving treatment outcomes.

Streptokinase, a metabolic product of Beta-hemolytic Streptococcus, is an indirect fibrinolytic agent that interacts with Plasminogen and forms an active complex with protease activity that converts Plasminogen to plasmin [3]. The efficacy of streptokinase in patients with acute myocardial infarction (AMI) has been demonstrated in large Placebo-controlled trials [4, 5].

In GISSI-1, the first large thrombolytic trial that evaluated streptokinase therapy versus no treatment in AMI patients, a significant mortality benefit of streptokinase was registered as follows: 8.2%-15.4% for patients *receiving* streptokinase during 1 hour of symptom onset. In total, 9.2-12% of patients were treated within three hours, and 11.7-14.1% of patients were treated between 3-6 hours (4). In the ISIS-2 trial, similar benefits for streptokinase were observed in more than 17,000 patients with symptoms of acute myocardial infarction (MI) for 24 hours [5]. This drug has some side effects such as allergic reactions, hypotension, and bleeding despite reduced mortality in AMI patients treated with streptokinase

Streptokinase is an extracellular protein, and Its presence in the circulatory system can lead to severe anaphylactic reactions, including death [6,7]. The risk of this immune response depends on the level of anti-streptokinase circulating antibodies. This immunogenicity limits streptokinase treatments [8,9]. This study was conducted to investigate the pattern of adverse drug reactions caused by streptokinase treatment and related risk factors in patients with acute ST-elevation myocardial infarction (STEMI), considering the critical conditions in patients with AMI and the complications of streptokinase *therapy*.

Methodology

Here we presented a systematic investigation and meta-analysis based on PRISMA principles. The search for eligible studies was performed using the following search strategy: Searches were conducted by two independent researchers to find relevant studies published between January 1, 2010, to Aug 31, 2022. We searched for studies published in English in MEDLINE, PubMed, EMBASETM, Ovid, The Cochrane Library, and the TRIP database. We searched national databases of Iran (Magiran and SID) (KoreaMed and LILACS) for published literature in other languages. Specific search strategies were developed using a Health Sciences Databases for systematic review searches using MESH terms and open terms according to PRESS standards. Results were compared using searches in other databases after finalizing the MEDLINE strategy plan.

Data screening and extraction

Two researchers independently screened the terms and abstracts extracted from the databases using predetermined criteria. Disputes between the two researchers were resolved through discussion. The relevant articles' full text was further evaluated to identify eligible studies after initial screening. The study selection process was presented using an adopted PRISMA chart. The data extraction process was performed using a standardized data collection form for all studies. Extracted data include general characteristics of studies, the prevalence of ADRs, and when they were reported.

Data analysis

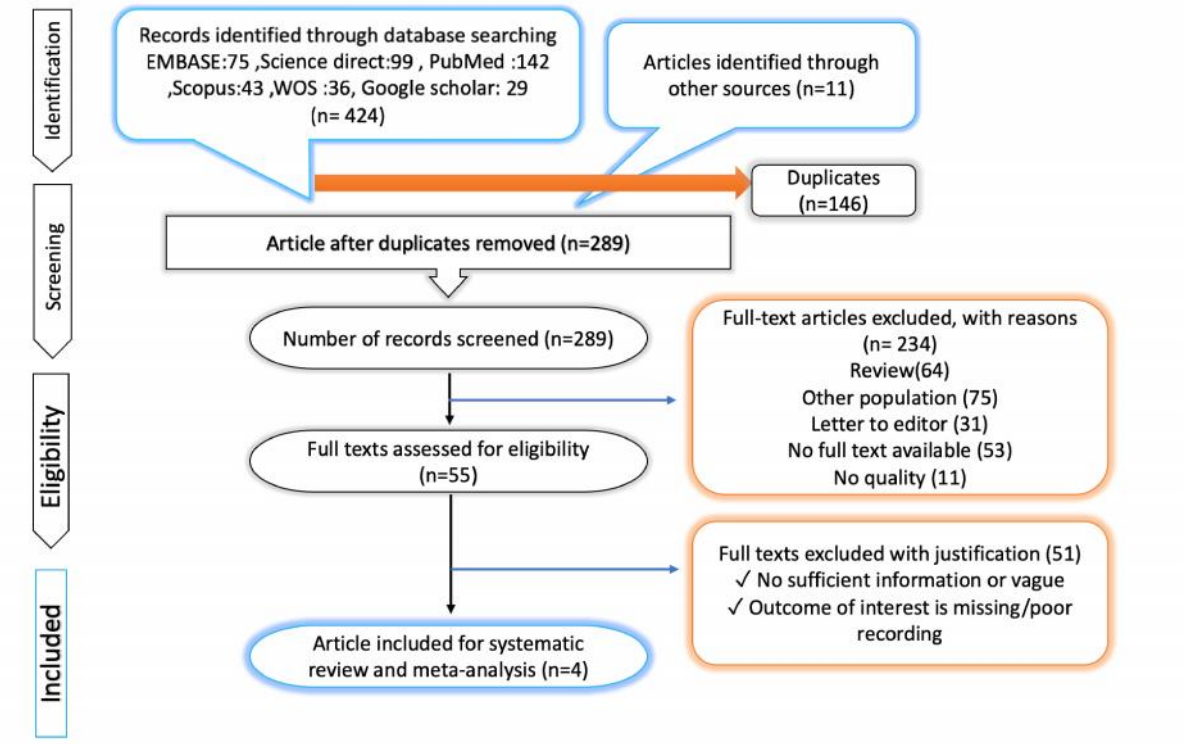
A random effects model was used to calculate the *combined* prevalence of ADRs. Heterogeneity between studies was evaluated using the *Stata 15*

version 1.0 *software*. Subgroup and meta-regression analyzes were performed to explore potential sources of heterogeneity such as age groups, ADRs detection methods, ADRs definitions, settings, study quality, and sample size. All analyzes were performed in Stata 15 *software*

Results

In total, the search and selection of studies were retrieved from electronic databases and other sources. After removing similar cases, 289 studies remained for evaluation. Title and abstract screening and evaluation resulted in eligible records for evaluation full-text. Finally, a total of 4 studies were reviewed in this systematic review.

Figure 1. PRISMA flow diagram

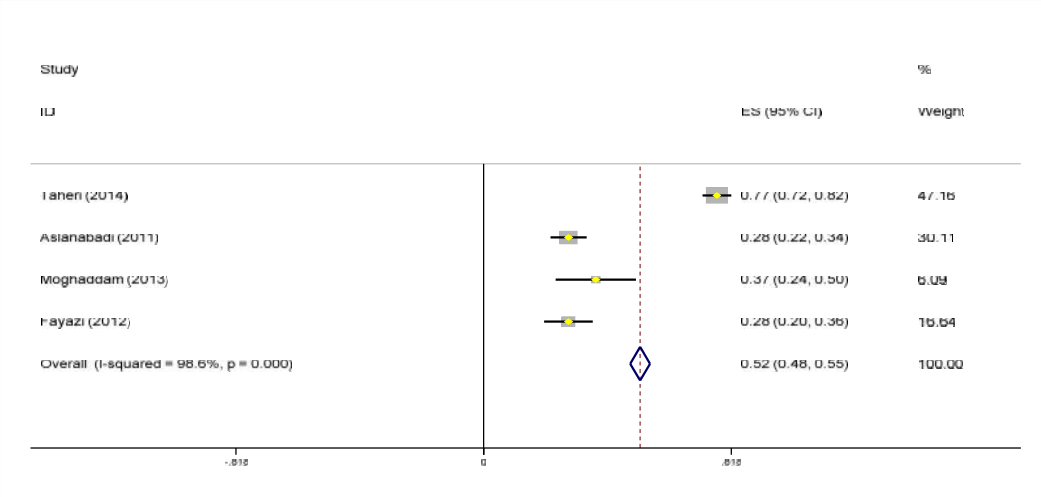


Meta-analysis of the prevalence of complications of streptokinase therapy in Iranian MI patients

Our meta-analysis showed that the most prevalent complication after streptokinase therapy was arrhythmia 52%(95%CI:48-55) followed by hypotension 26%(95%CI:23-29), bradycardia 7%(95%:6-9), and allergy 2%(95%CI:1-3).

Table 1. Characteristics of included studies regarding the complications of streptokinase therapy in Iranian MI patients

Author	Year	Province	Sample size	Design	Mean age	Arrhythmia	Allergy	Bleeding	Hypotension	Bradycardia	Nausea and Vomiting
Taheri	2014	Isfahan	300	N/A	46.15 ±8.11	76.6%	0.7%	6.7%	21.3%	10.7%	21.3%
Aslanabadi	2018	Tabriz	217	Cross-sectional	60.5 ± 12	28.2%	2.8%	5.1%	34.6%	9.7%	10.9%
Behnam moghadam	2013	Ghazvin	51	Cross-sectional	61.24 ±11.08	36.7%	5.8%	11.7%	47%	9.8%	45%
Fayazi	2012	Ahvaz	120	Cross-sectional	N/A	28.3%	2.5%	17.5%	20.5%	3.3%	6.4%



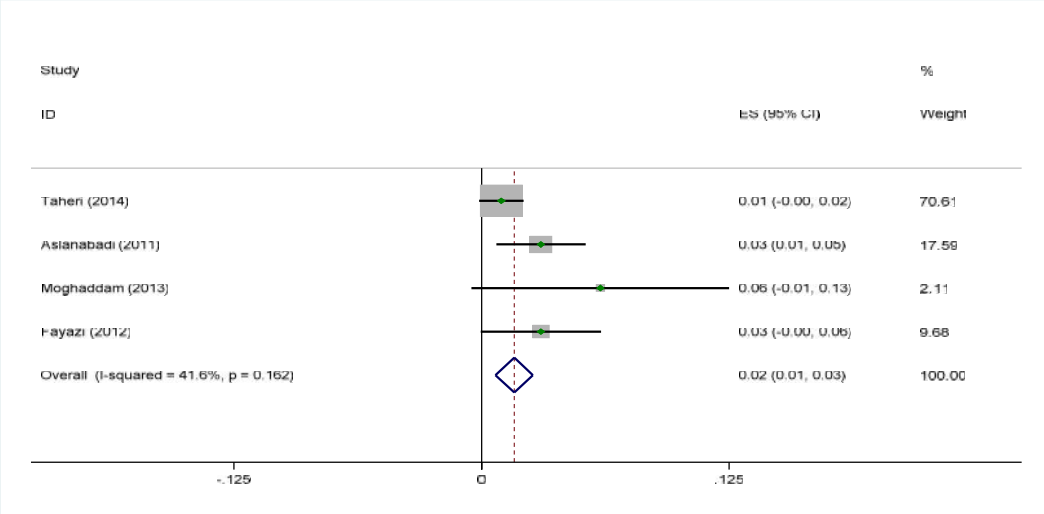
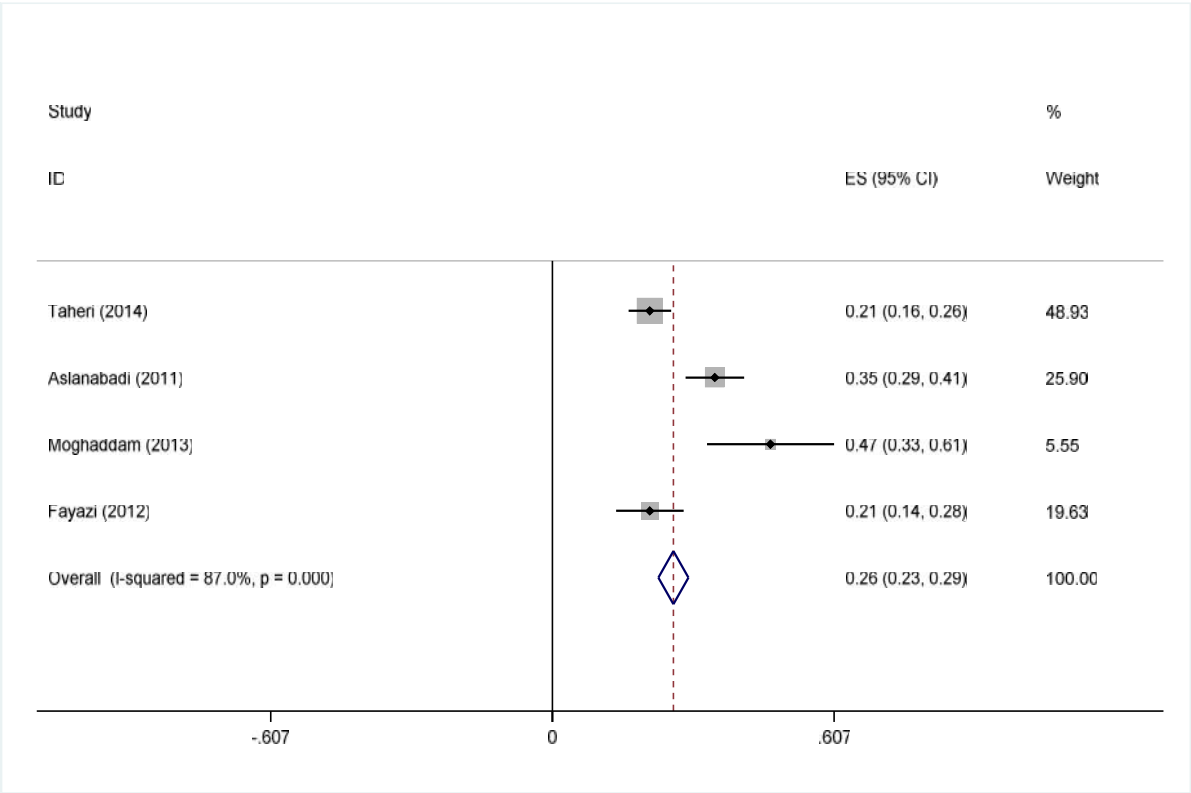


Figure 2. Meta-analysis of the prevalence of arrhythmia and allergy among Iranian MI patients after streptokinase therapy



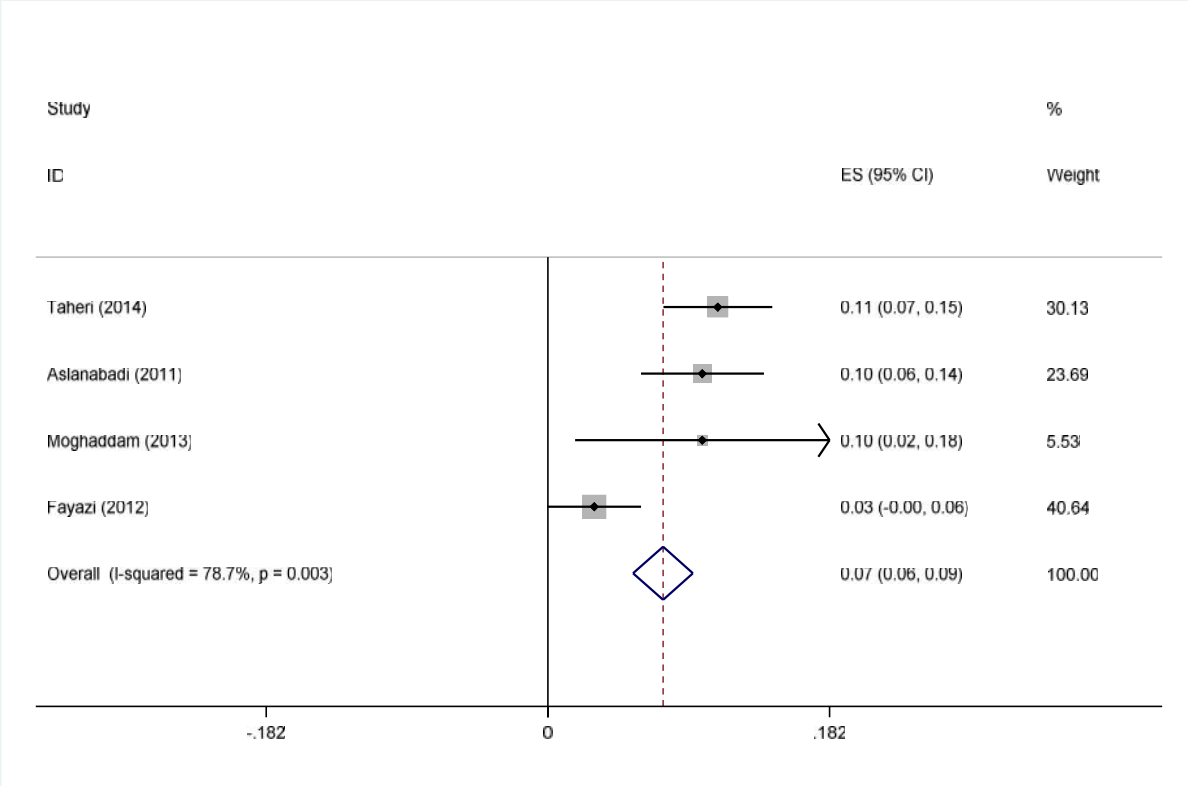


Figure 3. Meta-analysis of the prevalence of hypotension and bradycardia among Iranian MI patients after streptokinase therapy

Discussion

Hypotension (26%) was the most common complication after arrhythmia in our study. This disease was also reported in another study as the most common complication in *people aged 60 years andolder* [10]. The *prevalence of hypotension* with streptokinase was higher in other studies [13-10]. However, in the Gruppo Italiano (GISSI) trial [4], 3% of patients suffered from hypotension. While in the second international study of the *Infarct Survival (ISIS-2)* trial, 10% of patients had Orthostatic hypotension [5].

Studies have shown that hypotension during streptokinase infusion is free of blood pressure and *Bradycardia* during referral [13]. This finding is also confirmed by the ISIS2 test [4]. Some studies showed there is a significant correlation between inferior myocardial infarction (MI) and hypotension during streptokinase injection compared to anterior MI. The reduction of systolic blood pressure in patients with lower MI can also be attributed to the simultaneous occurrence of right ventricular infarction [13, 14]. Lu et al. showed that there is no significant relationship between hypotension during streptokinase injection and MI site [15].

Hemorrhagic strokewas the most serious effect during hospitalization after streptokinase injection. Hemorrhagic stroke was reported in only 3 cases (0.3%) in a prospective and self-reported Pharmacovigilance program in Cuba among 792 patients receiving streptokinase [16]. In GISI-1 and ISIS-2 trials, *severe* bleeding, such as hemorrhagic stroke, was reported at about 0.3-0.5% [4,5]. In addition, Maggioni et al. [17] reported the various forms of stroke in patients treated with streptokinase equal to 0.94%. The main factors for stroke include *drug-related* problems such as

bleeding complications as well as host-related factors such as older age, female gender, previous MI, history of smoking, and hypertension [17].

Bleeding is another common side effect associated with streptokinase therapy. In the present study, 8 out of 164 patients (4.9%) had bleeding. This finding is consistent with the two major trials of SK administration, GISSI-l (1986) and the ISIS-2 trial (1988), in which 515 of 14,452 (3.6%) patients experienced bleeding events. Bleeding occurs mainly in the skin and subcutaneous tissue. Other less common sites are the urinary system, gastrointestinal tract, and upper respiratory tract. Severe bleeding requiring blood transfusion occurred in only 65 streptokinase recipients (0.4%) in the combination trials, compared with 0.2% in the placebo group ISIS-2 [4,5].

Bleeding is another common side effect associated with streptokinase therapy. In the present study, 26%of patients had bleeding.
Since streptokinase is a streptococcal protein, potentially *severe* allergic reactions are possible but rare. There were no confirmed cases of anaphylactic shock in 8592 streptokinase recipients in the ISIS-2 trial [5]. Minor allergic reactions, including chills, fever, or rash, occurred in 4.4% of receiving patients during injection of streptokinase compared to 0.9% of those receiving placebo [5]. This finding is very comparable to our study where 2% of patients understand minor allergic reactions. In contrast, the GISSI study (1986) reported non-fatal anaphylactic reactions in 5860 patients receiving streptokinase, of which 99 patients (1.7%) with allergic reactions were excluded from the treatment [4].
In the present study, the incidence of different ADRs was reported by streptokinase, which is significantly higher than in other reports. For example, in the retrospective cohort study of Devi et al. And in the prospective study by Mohebbi et al., which was conducted in the *cardiacintensive care unit* (CICU), the most ADRs by streptokinase were 60% [18,19].

Conclusion

In the current research, it can be concluded that the most common side effect was hypotension. Other less common side effects were minor bleeding and mild allergic reaction.

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