Treatment Failure of Venous Stenting With or Without Direct Oral Anticoagulants (DOAC) / Non-Vitamin K Oral Anticoagulants (NOACs) in Patients With Deep Vein Thrombosis (DVT) in Term of the Stent Patency: Protocol for a Systematic Review

Bahram Mohebbi

Iran University of Medical Sciences

Jamal Moosavi

Iran University of Medical Sciences

Behshid Ghadrdoost

Iran University of Medical Sciences

Ayatollah Bayatian (✉ Bayatiandr@yahoo.com)

Iran University of Medical Sciences

Hooman Bakhshandeh

Iran University of Medical Sciences

Sima Besharat

Golestan University of Medical Sciences and Health Services <https://orcid.org/0000-0002-0540-6056>

Abbas Keshtkar

Tehran University of Medical Sciences

Parham Sadeghipour

Iran University of Medical Sciences

Protocol

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Abstract

Background: Venous stenting plays a significant role in the treatment of acute deep vein thrombosis (DVT). But the adjuvant anti-coagulant therapy could also help to more successful patency rate. We hope to elucidate the differences in the patency rate of venous stenting with or without direct oral anticoagulants (DOAC) / non-vitamin K oral anticoagulants (NOACs).

Methods: Studies that work on the stent patency rate in venous stent with or without DOAC / NOAC will be included. The primary studies (Cohort, case control, case-series or randomized/ non-randomized trials) will be included if the participants / patients have had acute or chronic DVT, with venous stenting (at least one study group or all of study subjects) who have received DOAC / NOAC agents. The stent patency rate should be reported in all of study subjects within a follow-up time, minimum for 1 year. We will perform an electronic search on published or in press articles, which have been published in MEDLINE / PubMed, Embase, the online Cochrane database, CENTRAL and searches of clinical trial registries: clinicalTrials.gov, EU Clinical Trials, ISRCTN registry, WHO network registry for trials. PROSPERO databases will be manually searched for protocols.

After screening of the relevant articles, selection and data extraction will be conducted in duplicate and independently. Methodological quality of the selected studies will be assessed using the Newcastle Ottawa Scale (NOS) tool. We will use "Hazard Ratio" (HR) as the optimum Effect Size (ES) in this meta-analysis, otherwise we will use or calculate "Risk Ratio" (RR) or "Odds Ratio" (OR) ES measures as the selected study specific ES.

Discussion: In this review, we hope to find the treatment failure/ success rate of venous stenting with or without DOAC / NOAC regards to the stent patency rate and will try to provide insights into the right choice of anti-coagulant therapy.

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Background

Deep vein thrombosis (DVT) presenting with swelling, skin changes, venous claudication, and ulcerations is one of the major types of venous thromboembolism (VTE) mostly occurs in the lower extremities. Post-thrombotic syndrome (PTS), the most common long term complication of DVT, seen in 20% to 50% of patients who have a history of DVT (1). Location of the venous lesions may affect the outcome, and Iliofemoral DVT (IF-DVT) would make the patient more susceptible to PTS compared to the popliteal or femoral veins especially when chronic venous disease (CVD) is present (2).

There have been different therapeutic methods for Iliofemoral Deep vein thrombosis (IF-DVT) including conservative management with anticoagulation therapy and graduated compression stockings at the early stages. These methods may reduce the risk of recurrent venous thromboembolism (VTE) but mostly

leads to the poor venous patency and an increased risk of post-thrombotic syndrome (PTS) of > 50 % within two year follow-ups (3).

Catheter-directed thrombolysis (CDT) is the major intervention claimed to be effective in removing the occluding thrombus, reducing the risk of moderate or severe PTS and preventing secondary valve damage. Venous stenting eliminates the obstructive vein and decreases the recurrence of DVT by reducing the triggered thrombosis in the damaged vein. Some studies assessed the role of anti-thrombotic drugs (AT) starting at the time of stenting especially when there are persistent risk factors for recurrence (2–4).

Venous patency rates 6-24 months after catheter based thrombus removal with or without stent placement in patients with IFDVT is the cornerstone of outcome assessment, ranged between 72% and 100%. In selected patients with acute IF-DVT and low risk of bleeding, early thrombus removal strategies plus venous stenting for residual obstructive vein lesions has been recommended as the first-line therapy. But this suggestions are based on the results of small randomized-controlled trials and prospective cohort studies (5).

There are different methods of anticoagulant treatment for VTE. The recommended anticoagulant therapy choices in the initial phase, administered in the immediate days after diagnosis of VTE include unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Recently, direct oral anticoagulants (DOAC) / non-vitamin K oral anticoagulants (NOACs) have also been used for initial therapy instead of the traditional Vitamin K antagonist (VKA). According to the guidelines (the 2016 ACCP guidelines and 2019 ESC guideline PE), there are a large body of evidence supporting the use of non-vitamin K oral anticoagulants (NOACs) over vitamin K antagonist (VKA) in the treatment of acute VTE, especially during the first 3 months for patients with proximal DVT of the leg or pulmonary embolism (PE) in non-cancerous patients (3,6,7).

Endovascular therapy consists of vein dilation and stent placement has been considered useful for a satisfactory relief of symptoms, reported in a recent meta-analysis (1). Using new anticoagulant drugs has been studied in a few studies and no unique result has been applied. So in this systematic review we aim to evaluate the rate of venous stent patency using DOAC (Direct Oral Anticoagulant)/ NOAC (Non-VKA Oral Anticoagulants) therapy started immediately after venous stenting.

OBJECTIVES

The primary objective of this study is to examine stent patency rate after treatment of DVT patients with Venous Stenting and DOAC / NOAC. Furthermore, we will examine secondary objectives as followings:

1. Stent patency rate after treatment of DVT patients with Venous Stenting and DOAC / NOAC based on the study designs (case-control, and cohort).
2. Stent patency rate after treatment of DVT patients with Venous Stenting and DOAC / NOAC based on adjusted and unadjusted effect sizes.

3. Stent patency rate after treatment of DVT patients with Venous Stenting and DOAC / NOAC based on the methodological quality of the primary studies.
4. and evaluate the methodological heterogeneity and its potential sources.

Methods

Eligibility criteria

Studies that work on the stent patency rate in venous stent with DOAC / NOAC will be included. The below outcomes are NOT mandatory but, if the any secondary outcomes were reported, we will record them: bleeding (major/minor), other vascular accidents like hemorrhagic cardiovascular accidents (CVA), perioperative complications: thrombotic events and non-thrombotic complications (access site complications, stent migration, back pain, retroperitoneal bleeding, and contrast extravasation), clinical outcomes (included pain and edema relief, ulcer healing, recurrence, and clinical–etiology–anatomy–pathophysiology (CEAP) clinical classification before and after procedure), and death.

Type of studies

The primary studies (Cohort, case control, case-series or randomized/ non-randomized trials) will be included if the participants / patients have had acute or chronic DVT, with venous stenting (at least one study group or all of study subjects) who have received DOAC / NOAC agents. The stent patency rate should be reported in all of study subjects within a follow-up time, minimum for 12 months (1 year).

Type of participants

This systematic review will focus on studies that evaluate the rate of stent patency in acute or chronic DVT patients (inpatients or outpatients) with venous stenting (at least one study group or all of study subjects) who have received DOAC / NOAC agents.

The relevant animal studies or review articles will be excluded

Search strategy

We will perform an electronic search on published or in press articles, which have been published in MEDLINE / PubMed, Embase, the online Cochrane database, CENTRAL and searches of clinical trial registries: clinicalTrials.gov, EU Clinical Trials, ISRCTN registry, WHO network registry for trials. PROSPERO databases will be manually searched for protocols. Reference lists of previous systematic reviews and the primary articles will be also checked manually. No geographical restrictions will be applied. Language restriction will not be applied, and non-English studies will be included if at least an English abstract is available. Mesh search and free-text method (asking experts' opinion, checking previous review articles, and similar systematic review) will be applied to find synonyms and related terms: due to the primary searches there are few primary articles in this field, so following searches will be carried out for "All fields" with no field restrictions to achieve the most comprehensive search.

"Deep Vein Thrombosis", "venous stenting" and "post thrombotic syndrome" will be the main components and important related terms including: Iliofemoral DVT, Anticoagulation therapy, valve incompetence, venous patency, Thrombolytic therapy, Catheter-directed Thrombolysis (CDT), Catheter-based Thrombectomy, Post-thrombotic Syndrome (PTS), Pharmacomechanical Thrombectomy (PMT), VKA (Vitamin K Antagonists): such as Warfarin; Coumarin; Acenocoumarol; NOAC (Non-VKA Oral Anticoagulants), DOAC (Direct Oral Anticoagulant). Search syntax for these keywords and/or Medical Subject Headings (MeSH) terms and free text method will be selected and combined by Boolean operators and applied in PUBMED. Search terms will be adjusted for other electronic databases. The following syntax will be used in the PubMed database:

((("Deep Venous" OR deep-vein OR "Deep Vein") AND Thrombos*) OR "Deep-Vein Thrombos*" OR Phlebothrombos* OR "Deep Venous Thrombos*" OR "venous thrombos*" OR "vein thrombos*" OR Postthrombotic OR Post-thrombotic OR "venous stasis") AND stent* AND "post thrombotic syndrome"

Study selection

Screening

It is noteworthy that prior to any screening, reviewers will undergo training to ensure a comprehensive understanding of the review question, and the inclusion and exclusion criteria.

In the first step, after exporting the search outputs into Endnote software, any duplicates will be removed. After that, the studies will be screened based on titles and /or abstracts for the relevant topic by two reviewers (S.B. and A.K.).

Selection of studies

Two reviewers (S.B. and A.K) will independently screen all articles through the inclusion criteria and independently classify the articles into three groups based on the eligibility criteria: relevant, irrelevant, and unsure. Irrelevant studies, which selected by both reviewers, will remove from the study. A third reviewer will decide against the final decision whenever the two reviewers had disagreement.

Assessing risk of bias

The eligible primary studies (Cohort or Follow-up studies) will be assessed by Newcastle-Ottawa Scale tool (Cohort version) (8). The included trials or experimental studies will be assessed by Cochrane Risk of Bias (ROB) assessment tool (version-1) (9).

The ROB assessment will be independently performed by two reviewers and any disagreements will be resolved by third expert reviewer.

Data extraction and Data synthesis

Two reviewers will independently extract data from papers using a template created in Microsoft Excel. Data extraction form for this review will include general information, study eligibility, method, the risk of bias assessment, and results of studies. Any discrepancies in the data will be addressed by a third expert reviewer who will check these two forms and their differences. An email will be sent to corresponding authors of studies for missing, unclear, and unreliable data. From each article, the following information will be extracted.

General information: first author name, publication year, journal title, volume and issue, article title, reference numbers

Study eligibility: location, time and duration of the study (name of country, total study duration), type of participants, sample size (total population recruited in the study), inclusion and exclusion criteria (in the study), age and gender of study population, procedure performed in the study, side of the limb where the intervention has been performed (left, right), technical success rate, access site, stent style, stent size, stent number, Imaging during the operation, randomization method, inclusion criteria, interventions performed, assessor blinding, follow-up, outcomes / end-points, rate of post thrombotic syndrome, statistical analysis, loss to follow-up, procedural complications

Method: Study design (traditional case-control, Nested case-control, any type of cohort study), ethical approval obtained for the study.

Risk of bias assessment (mentioned above).

Results of studies: (Odds Ratio, Risk Ratio, Rate Ratio, 95% confidence intervals, standardized mean differences).

Data synthesis

Primary analysis:

If there are clinical trials and observational studies included in this study, they will not be combined and the analysis will be performed separately. Based on data analysis in majority of the eligible primary studies (Time-to-event or survival analysis), we will use "Hazard Ratio" (HR) as the optimum Effect Size (ES) in this meta-analysis. We convert the survival graph extracted data (usually Kaplan-Meier graph) and the findings of Log-rank test (Chi square and ...) into HR based on previous method (10,11).

In the absence of survival analysis in the eligible studies, we will use or calculate "Risk Ratio" (RR) or "Odds Ratio" (OR) ES measures as the selected study specific ES. Furthermore the rare outcome assumption is addressed (the outcome frequency < 10%), we will combine the different types of "Relative Risk" ES family such as HR, RR, OR (12).

We will assess heterogeneity using Q Cochrane test and I squared measure. We will categorize I squared measure into 4 categories; mild (0-24.9%), moderate (25-49.9%), severe (50-74.9%) and highly severe (75-

100%) based on Higgin's suggestion (13).

We will explore the source(s) of heterogeneity using "Sub-group analysis" or "Meta-regression" based on the covariate data type.

Sensitivity analyses:

The sensitivity analysis will be performed by two approaches. First, we will use one-out remove method for the influence of any primary studies on the combined ES. Secondly, we will evaluate the effect(s) of methodological quality (score or categorical data) on the primary studies ES by sub-group analysis.

Publication bias:

We will assess reporting bias using the Funnel plot and Egger's test and plot (14). If the Egger's test has the p value < 0.10, we will use Trim & Fill method (15) for evaluating the publication bias effect.

Analysis of subgroups or subsets:

We consider the study type (observational versus interventional), the ROB status categories (Low ROB vs High ROB) and the different follow-up time in the included studies (1-3 years vs > 3 years) as sub-group variables.

If there are the minimum criteria of quantitative data synthesis (minimum 5 primary studies in one of cohort or trial studies AND no highly severe methodological heterogeneity), we will perform Meta-analysis.

Assessing certainty of evidence:

We will grade the strength of evidence as high, moderate, low, or very-low using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) rating system. In the GRADE system, RCTs begin as high-quality evidence but may be downrated according to the risk of bias assessment, inconsistency, indirectness, imprecision in the results, and publication bias. Certainty is uprated for estimates with large ($RR > 2.0$ or $RR < 0.5$) or very-large ($RR > 5.0$ or $RR < 0.2$) magnitude of effect (16).

Discussion

There are different concerns after treatment of DVT such as VTE, PTS and most importantly stent patency. Interventions have been applied to reduce the consequent risks and sequels after a successful removal of thrombosis and maintaining the venous stent patent. Venous stenting patency rate is an important outcome considered as an item in the success rate of the whole anti-thrombotic treatment (3, 6, 7). Although removal of the occluding thrombus plus underlying damaged vein through catheter-directed thrombolysis (CDT) and pharmacomechanical thrombectomy (PMT), may reduce the risk of moderate to severe PTS by eliminating the trigger of further occlusion (2). The most recent guidelines suggested DOAC/NOACs more efficient compared to the traditional Vitamin K antagonists (VKAs). But there are

controversies about the administration, duration and type of anti-coagulant therapy, regards to the few clinical trials performed yet.

In this systematic review, we hope to elucidate the differences in the patency rate of venous stenting with DOAC / NOAC. Therefore, this systematic review and meta-analysis will try to provide insights into the Stent patency rate after treatment of DVT patients with Venous Stenting and DOAC / NOAC.

Declarations

Competing interests:

The authors have no financial or non-financial competing interests.

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable

Availability of data and material:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

Authors declare no competing interests.

Funding:

None.

Authors' contributions:

All authors contributed equally in conceptualization, formulating the main question, searching databases, writing the manuscript and read and finalizing the last draft.

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