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2019/2020

João António dos Reis Rego Diniz

Endovascular Treatment of Iliofemoral Deep Venous Thrombosis – Is There Enough Evidence to Support It? A Systematic Review with Meta-Analysis

Maio, 2020

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Mestrado Integrado em Medicina

Área: Ciências Médicas e da Saúde – Medicina Clínica

Angiologia e Cirurgia Vascular

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Doutor Armando Amílcar Pires Mansilha Rodrigues de Almeida

E sob a Coorientação de:

Dra. Andreia Sofia Martins Pires Coelho

Trabalho organizado de acordo com as normas da revista:

International Angiology

Maio, 2020

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UC Dissertação/Projeto (6º Ano) – DECLARAÇÃO DE REPRODUÇÃO

NOME

João António dos Reis Bogo Diniz

NÚMERO DE ESTUDANTE

201404331

E-MAIL

joaoreisdiniz@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Ciências Médicas e da Saúde - Medicina Clínica

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Endovascular Treatment of Widespread Dix Hours Thrombosis - Is There Enough Evidence to Support It? A Systematic Review with Meta-Analysis

ORIENTADOR

Armando Aníbal Peres Marcilha Rodrigues de Almeida

COORIENTADOR (se aplicável)

Andreia Sofia Martins Pires Coelho

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Dedicatória

À minha mãe, pelo apoio incondicional que sempre me prestou.

À minha irmã, por sempre ter acreditado em mim.

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International Angiology 2019 mese;38(0):000–000
DOI: 10.23736/S0392-9590.19.04298-6

REVIEW
SECTION

Endovascular treatment of iliofemoral deep venous thrombosis: is there enough evidence to support it? A systematic review with meta-analysis

João DINIZ *, Andreia COELHO, Armando MANSILHA

Department of Angiology and Vascular Surgery, Faculty of Medicine, University of Porto, Porto, Portugal

*Corresponding author: João Diniz, Faculty of Medicine, University of Porto, Al. Prof. Hernâni Monteiro 4200, 319 Porto, Portugal. E-mail: joaoregodinis@gmail.com

ABSTRACT

Introduction: Post-thrombotic syndrome (PTS) and iliofemoral (IF) patency reduction are common complications of iliofemoral deep venous thrombosis (IFDVT). Recent studies suggested that endovascular treatment, such as catheter-directed thrombolysis (CDT) and pharmacomechanical thrombectomy (PMT) can effectively reduce the risk and morbidity of PTS in IFDVT patients. This article aims to review the current literature on the subject, focusing on the long-term outcomes of endovascular treatment techniques in IFDVT patients.

Evidence acquisition: A thorough systematic review of the literature was conducted using PubMed/Medline and Scopus, according to PRISMA statement guidelines. Forty articles were included, according to their scientific relevance, for the qualitative analysis. From this initial set of articles, nine articles were included for the quantitative analysis.

Evidence synthesis: Endovascular treatment with CDT or PMT is related to a decreased risk of PTS development, when compared to standard anticoagulation treatment (OR=0.71; 95% CI=0.54-0.92). Furthermore, IF patency presents superior rates in patients treated with CDT or PMT, instead of anticoagulation (OR=3.20; 95% CI=1.80 -5.71). There are no significant differences in the risk of PTS and IF patency between patients treated with CDT and PMT. Complications such as bleeding, pulmonary embolism and death, don't seem to differ between endovascular treatment and anticoagulation, as well as between CDT and PMT procedures.

Conclusions: Endovascular techniques seem to have satisfactory long-term outcomes in IFDVT, regarding to PTS risk and IF patency. However, further investigation with prospective randomized clinical trials with large populations and long follow-ups is necessary.

(*Cite this article as:* Diniz J, Coelho A, Mansilha A. Endovascular treatment of iliofemoral deep venous thrombosis: is there enough evidence to support it? A systematic review with meta-analysis. Int Angiol 2019;38:000–000. DOI: 10.23736/S0392-9590.19.04298-6)

Key words: Venous thrombosis; Iliac vein; Femoral vein; Thrombolytic therapy.

Introduction

Acute deep vein thrombosis (DVT) of the lower limbs is a common and significant cause of morbidity and mortality with major physical sequelae for patients.[1] It has an estimated incidence of about 1.0 person per 1000 people per year.[2] Most of these patients are treated with systemic anticoagulation, which effectively prevents thrombus extension, pulmonary embolism, recurrence and death.[3] However, iliofemoral DVT (IFDVT) presents more severe acute symptoms and a higher risk of Post-Thrombotic Syndrome (PTS), when compared to distal DVT. Despite the use of best medical treatment, PTS can develop within 2 years in nearly 50% of the patients with proximal DVT.[3, 4]

Conventional therapy for IFDVT with anticoagulation alone does not promote clot dissolution or valve patency preservation.[5] Recent studies suggested that additional catheter-directed thrombolysis (CDT) to standard anticoagulation treatment could improve vein recanalization and valve function in patients with acute IFDVT, which seems to reduce the risk and morbidity of PTS and to provide persistent and long-term clinical benefit.[2, 5] Pharmacomechanical thrombectomy (PMT) also has emerged as a potentially faster, less invasive and safer alternative for patients who cannot be submitted to thrombolytic therapy.[5] Early thrombus removal by both of these endovascular procedures seems to reduce the risk of PTS development.

Up to date, there is no clinical consensus regarding whether endovascular treatment is able or not to improve the long-term outcomes of patients with IFDVT, regarding to the risk of PTS, the preservation of iliofemoral (IF) patency and overall quality of life.

Through this article, we aim to review the current evidence on the long-term outcomes of the application of additional endovascular procedures to treat IFDVT.

Evidence acquisition

Methods

This systematic review with meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[6] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate the strength and quality of evidence.[7]

Literature research

A thorough literature search was carried using PubMed/Medline and Scopus databases, including articles published up to February 2019 and using the following keywords: "Venous Thrombosis," "Iliac Vein," "Femoral Vein" and "Thrombolytic Therapy." From this initial research, 370 articles were obtained. Only English articles published since January 2000 were included and all reviews and case reports were excluded from the quantitative analysis. Three articles were manually included by backward-citation from the initial group of references, according to its scientific relevance (Srinivas *et al.*,[8] Huang *et al.*[9] and Gagne *et al.*[10]).

The specified inclusion criteria for the obtained studies were: 1) study groups that included CDT/PMT and anticoagulation *vs.* anticoagulation alone or study groups that included CDT *vs.* PMT; 2) studies with a randomized clinical trial, comparative prospective or comparative retrospective designs; and 3) intention to treat analysis. The specified exclusion criteria were: 1) duplicated data; 2) review articles; 3) case reports; and 4) ongoing clinical trials without final results. From this initial selection, 223 articles were excluded.

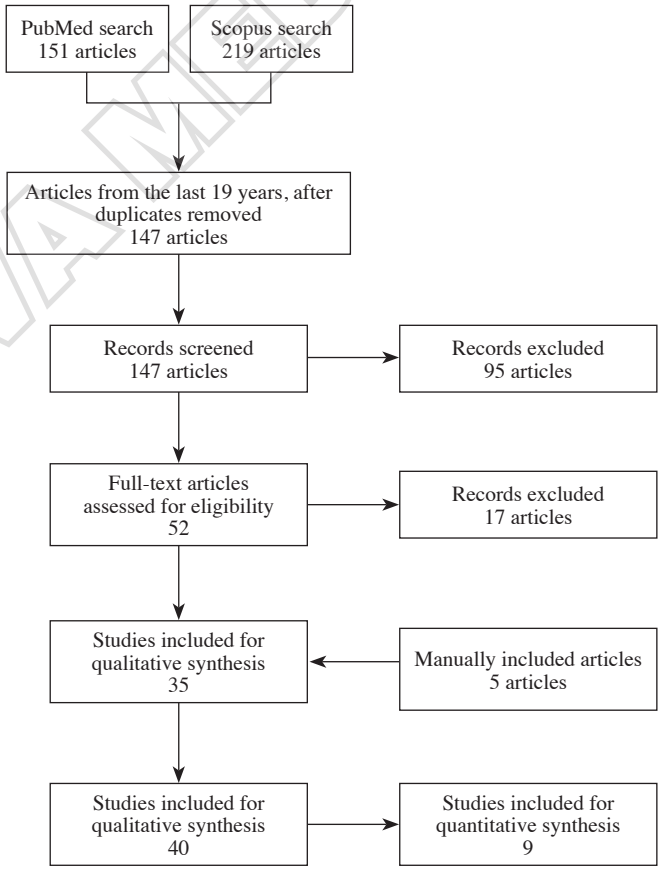

Figure 1.—Flow chart of evidence acquisition, according to PRISMA.

All remaining 147 abstracts were accessed and 95 articles were excluded for not being directly related to the subject.

From the remaining 52 articles, 40 articles were included in the qualitative analysis of this study, according to their scientific relevance. A total of 9 articles were included in the quantitative analysis: 4 randomized clinical trials, 2 nonrandomized prospective studies and 3 nonrandomized retrospective studies.

Every article was adequately reviewed in order to assure that eligibility and quality criteria were met. The schematic of evidence acquisition is represented in Figure 1.

Data extraction

Data extraction was performed based on a pre-defined set of clinical variables and outcomes.

The pre-specified clinical variables were: 1) number of patients; 2) sex; 3) age; 4) device used for thrombolysis; 5) thrombolytic agent; 6) anticoagulation regimen; and 7) follow-up.

The pre-specified primary outcomes were 1) overall rate of PTS; and 2) IF patency; The pre-specified secondary outcomes were 3) bleeding events; 4) pulmonary embolism; and 5) death.

Two independent reviewers were responsible for the selection and extraction of the pre-specified data from every study. Blinding of the reviewers was not performed. In case of disagreement, a third reviewer was responsible for the analysis of the study and extracted data in cause and a team discussion was made in order to achieve common consensus to whether the study was adequate or not to be included in the meta-analysis, according to selection and quality criteria.

Risk of bias

The risk of bias of each included randomized clinical trial was accessed using the revised Cochrane Risk-of-Bias Tool for Randomized Clinical Trials (RoB 2). This tool determines the overall risk of bias at the expense of the interpretation of five specific domains of each study: 1) the randomization process; 2) the deviation from the intended interventions; 3) the missing outcome data; 4) the measurement of the outcome and 5) the selection of the reported result.

In order to evaluate the risk of bias of the included nonrandomized observational prospective and retrospective studies we used the Newcastle-Ottawa Scale (NOS), which evaluates the quality of the study based in selection, comparability and outcome criteria.

The risk of bias assessment of the 4 included randomized clinical trials and the 5 non-randomized comparative studies is presented in Table I, II,[5, 8, 9, 11-14] respectively.

Quality assessment

The quality of the content of all of the included articles were reviewed. Only articles with adequate, useful and non-biased information were used for the elaboration of the meta-analysis. This assessment was made using RoB2 and NOS tools.

TABLE I.—*Risk of bias assessment of the included randomized clinical trials, according to the Cochrane Risk-of-Bias Tool for Randomized Clinical Trials (RoB2).*[11, 12]

	CaVenT[2]	Haig *et al.*[11]	ATTRACT[4]	Elsharawy *et al.*[12]
Randomization process	+	+	+	+
Deviation from the intended intervention	+	+	?	+
Missing outcome data	+	+	-	+
Measurement of the outcome	+	+	-	+
Selection of reported result	?	?	+	+

+low bias risk; ?some concerns; -high risk of bias.

TABLE II.—*Risk of bias assessment of the included nonrandomized clinical trials, according to the NewCastle Ottawa Scale (NOS).*[5, 8, 9, 13, 14]

	Srinivas *et al.*[8]	Kuo *et al.*[5]	Lin *et al.*[13]	Huang *et al.*[9]	Martinez *et al.*[14]
Selection	****	***	****	****	****
Comparability	**	**	**	**	**
Outcome	***	***	***	***	***

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Statistical analysis

The statistical analysis was performed with Winpepi software. In order to perform the quantitative analysis of the included articles an intention-to-treat approach for all outcomes was considered. The extracted data was analyzed and interpreted according to CDT, PMT and anticoagulation subgroups. A Mantel-Haenszel fixed effect model was used for meta-analysis. The Odds Ratios (ORs) and respective 95% Confidence Intervals (CI 95) were estimated. No sensitive analysis or meta-regression was performed. No funnel plot was elaborated, due to the reduced number of included articles.

Evidence synthesis

Study designs and baseline characteristics

After the performed literature research and data extraction, 9 articles met all the criteria previously defined for the quantitative analysis. From these studies, 4 are prospective randomized clinical trials, 2 are nonrandomized prospective comparative studies and 3 are nonrandomized retrospective comparative studies. They had not only different study designs and population baseline characteristics, but also different technical and pharmacological approaches for the endovascular studied interventions. The most relevant characteristics of each of these studies are described in Table III.[2, 4, 5, 8, 9, 11-14]

CaVenT[2] and Haig *et al.*[11] are two different trials that studied the same baseline population. In order to avoid including duplicated data in the statistical analysis, we only included Haig *et al.*[11] data in the meta-analysis, because of the longer follow-up period of this study. However, due to the lack of results of bleeding rates of Haig *et al.*,[11] we used the obtained bleeding rates of CaVenT[2] for the elaboration of the meta-analysis.

The CaVenT trial was the first multicenter, open-label, randomized controlled clinical trial that studied the efficacy and safety of additional CDT with alteplase to treat patients with a first time acute DVT.[2] This study was performed in 2012 and included 209 patients aged between 18 to 75 years old, from 20 hospitals in Norwegian southeast-

TABLE III.—*Baseline characteristics of the included studies for meta-analysis.*[2, 4, 5, 8, 9, 11-14]

Study	Year	Interventions	N	Mean age (years)	Sex (male)	Device	Thrombolytic agent	Anticoagulation regimen	Follow-up (months)
CaVenT[2]	2012	CDT and anticoagulation *vs.* anticoagulation alone	90/99	53/50	58/61	UniFuse Angiodynamics	Alteplase	UFH, LMWH or warfarin	24
Haig *et al.*[11]	2016	CDT and anticoagulation *vs.* anticoagulation alone	87/89	58/53	57/53	UniFuse Angiodynamics	Alteplase	UFH, LMWH, or warfarin	36
ATTRACT[4]	2017	CDT/PMT and anticoagulation *vs.* anticoagulation alone	336/355	52/53	205/221	Trellis Peripheral Infusion System	Alteplase	UFH, LMWH, warfarin or NOAC	24
Elsharawy *et al.*[12]	2002	CDT and anticoagulation *vs.* anticoagulation alone	18/17	44/49	6/5	Jet lysis Catheter	Streptokinase	UFH, LMWH or warfarin	6
Srinivas *et al.*[8]	2014	CDT+PMT *vs.* anticoagulation	25/26	39/53	14/16	Judkin's Right Guiding Catheter	Streptokinase	UFH, LMWH, warfarin or nicoumalone	6
Kuo *et al.*[5]	2016	CDT *vs.* PMT	31/30	64/67	17/18	AngioJet Device	Urokinase	UFH or LMWH	24
Lin *et al.*[13]	2006	CDT *vs.* PMT	44/49	49/45	19/22	AngioJet Device	Alteplase, retaplase or urokinase	UFH, LMWH or warfarin	96
Huang *et al.*[9]	2015	CDT *vs.* PMT	18/16	64/63	12/9	AngioJet Device	Urokinase	UFH, LMWH or warfarin	12
Martinez *et al.*[14]	2008	CDT *vs.* PMT+CDT	21/22	53/44	14/7	Trellis Catheter	Alteplase, reteplase or tenecteplase	UFH, LMWH or warfarin	48

CDT: catheter-directed thrombolysis; PMT: pharmacomechanical thrombectomy; UFH: unfractionated heparin; LMWH: low molecular weight heparin; NOAC: new oral anticoagulant.

ern health region. Patients were randomly assigned to conventional anticoagulation treatment or to additional CDT and randomization was stratified for the involvement of the pelvic veins. The two primary outcomes were frequency of overall PTS (measured by Villalta Score at 24 months follow-up) and IF patency (measured after 6 months follow-up).[2] This study was extended, in 2016, with a larger follow-up period of 5 years in which 176 patients of the 209 patients originally randomized were included.[11]

The ATTRACT Trial was a multicenter, randomized, open-label, assessor-blinded, controlled clinical trial, performed in 2017. Patients from 56 clinical centers of the USA, between 16 and 75 years old were included in this study.[4] This trial counted with a total of 692 patients, being the trial with the highest number of participants in our meta-analysis. Patients were randomly assigned to either standard anticoagulation alone or anticoagulation with pharmacomechanical thrombolysis (CDT or device-mediated intrathrombus delivery of rt-PA and thrombus aspiration or maceration, with or without stenting). The primary studied outcome was the development of overall PTS between 6 and 24 months follow-up.[4]

Elsharawy *et al.* is a randomized clinical trial that was performed in 2002 and the main objective of this study was to compare the clinical outcomes of CDT and anticoagulation to anticoagulation alone in the treatment of IFDVT.[12] A consecutive series of 35 patients with less than 70 years old were randomized to either the experimental or control group.[12]

Srinivas *et al.* is a prospective and comparative study from 2014 that included patients with recent lower limb DVT (between 1 and 8 weeks) and with ages between 12 and 85 years old. A total of 64 patients were included in this study, 4 of which were excluded for having an upper limb DVT. After randomization, 30 patients were assigned to the PMT treatment arm and 30 patients were assigned to the anticoagulation treatment arm. The primary endpoint of this study was to determine the efficacy of PMT (CDT and mechanical thromboaspiration) in comparison to standard anticoagulation alone.[8]

Kuo *et al.* included 61 patients with acute ilieofemoral DVT in a prospective study with the main objective of comparing the efficacy, long-term outcomes and complications of CDT and PMT treatment.[5] In this trial, performed in 2016, 3 patients were submitted to CDT and 31 patients were submitted to PMT, pursuant to each patient's decision. After the intervention, each patient was followed up for at least 2 years.[5]

Lin *et al.* was a retrospective study made in 2006 that evaluated the clinical records of all patients with symptomatic lower leg DVT undergoing CDT or PMT interventions for a 8 year period.[13] A total of 93 patients who were submitted to these endovascular procedures were included in the study. CDT was performed in 44 patients and PMT in 49 patients. The purpose of this study was to compare the treatment outcomes of both endovascular treatments.[13]

Huang *et al.* was undertaken in 2015 as a retrospective comparative study that aimed to determine and compare the outcomes of patients with acute proximal DVT treated with CDT or PMT.[9] From an initial set of 39 patients, 34 were followed for more than a year and the received endovascular treatment depended of each patient (Table III).[9]

Recently, isolated segmental PMT has emerged as a treatment option for patients with extensive ilieofemoral DVT.[14] Martinez *et al.* is a random clinical trial from 2008, in which 21 patients were treated with percutaneous CDT and 22 patients were treated with isolated segmental PMT plus CDT. The main objective of this study was to determine and quantify the advantages of PMT in comparison to CDT.[14]

Results

After 24 months follow-up, CaVenT Trial revealed 41.1% of patients allocated to additional CDT presented PTS, compared to 55.6% of patients in the control group.[2] There was no difference in the long term quality of life between groups and CDT was related to a slightly increase in the risk of bleeding.[2]

The results of ATTRACT Trial showed no significant difference in the percentage of patients with PTS, between experimental and control group, after 6 to 24 months follow-up. In this trial, CDT led to an increased risk of major bleeding events within 10 days.[4] However, this study had various limitations such as the use of a binary classification for PTS (present or not present, not including the severity degree of PTS), inclusion of femoro-popliteal DVT and a significant lost of follow-up.[4] This major drawbacks may have compromised the results of the trial and the ability to draw adequate conclusions.

Elsharawy *et al.* presented similar conclusions to the CaVenT Trial, revealing that in short-term, patients treated with CDT presented better vein patency and competence than those treated with standard anticoagulation treatment alone.[12]

The administration of streptokinase with additional mechanical thrombectomy (CDT+PMT) is also an effective treatment for lower extremity DVT with satisfactory clini-

cal results, according to Srinivas *et al.*[8] Vein patency was increased from 23% to 80% at 6 months follow-up in this trial. This strategy can be used safely in acute situations, as it is only associated to a slightly increase in the risk of bleeding. Nevertheless, two deaths occurred allegedly due to pulmonary embolism, following CDT. The use of prophylactic IVC filter implantation previous to endovascular interventions should be considered to prevent these complications.[8]

With the democratization of CDT and PMT for lower limb IFDVT patients, it becomes important to compare the efficacy of each of these techniques to one another. Kuo *et al*.[5] and Huang *et al.*[9] both found that CDT and PMT have similar venous outcomes in the treatment of IFDVT, but PMT is related to a greater reduction in the severity of PTS. PMT also reduces the need for intensive care unit treatment, total hospital length stay and hospital costs (due largely to a reduction in the number of venograms performed per patient), according to Lin *et al.*[13]

The use of isolated segmental PMT also has emerged as a treatment option for extensive DVT. Martinez *et al.* showed isolated segmental PMT with CDT offers a greater effectiveness in thrombus removal in less time and with a lower dose of thrombolytic agent.[14] However, in this study there was no evidence of a decrease in hospital or intensive care unit length stay.[14]

Many strategies using thrombolytic endovascular treatment incorporate mechanical techniques in order to facilitate thrombus removal. However, in most patients, the exclusive use of mechanical techniques is not enough to promote thrombus resolution.

The primary and secondary outcomes of the included studies for the quantitative analysis are presented in Table IV, V,[2, 4, 5, 8, 9, 11-14] respectively.

Our meta-analysis revealed that endovascular treatment with CDT/PMT is related to a decreased PTS development rate, when compared to standard anticoagulation treatment (OR=0.71; 95% CI=0.54-0.92) (Figure 2).[2, 4, 8] On the other hand, there were no statistically significant differences between the overall rates of PTS in patients treated with CDT, when compared to PMT (OR=1.19; 95% CI=0.54-2.60) (Figure 3).

Patients treated with CDT/PMT also presented higher rates of IF patency when compared to standard anticoagu-

TABLE IV.— *Primary outcomes of the included studies for the quantitative analysis.*[2, 4, 5, 8, 9, 11-14]

Study	Overall PTS N. (%)	P value	IF Patency (%)	P value
CaVenT[2]	37 (41.1)/55 (55.6)	0.047	58 (65.9) / 45 (47.4)	0.012
Haig *et al.*[11]	37 (42.5)/63 (70.8)	<0.0001	68 (79.1) / 61 (70.9)	0.218
ATTRACT[4]	157 (47)/171 (48)	0.56	—	—
Elsharawy *et al.*[12]	—	—	13 (72)/2 (12)	<0.001
Srinivas *et al.*[8]	5 (20)/19 (77)	<0.01	20 (80)/7 (23)	<0.01
Kuo *et al.*[5]	6 (19.4)/6 (20)	1.000	19 (61.3)/21 (70)	0.474
Lin *et al.*[13]	—	—	28 (64)/33(68)	—
Huang *et al.*[9]	9 (50)/5 (31.3)	—	16 (88.9)/15 (93.8)	0.648
Martinez *et al.*[14]	6 (28.6)/3 (13.6)	0.0183	—	—

The first value corresponds to the obtained rates in the experimental group and second value to the rates obtained in the respective control group.
PTS: post-thrombotic syndrome; IF: iliofemoral.

TABLE V.—*Secondary outcomes of the included studies for the quantitative analysis.*[2, 4, 5, 8, 9, 11-14]

Study	Bleeding (%)	Pulmonary embolism (%)	Death (%)
CaVenT[2]	20 (22.2)/0 (0)	0 (0)/1 (1.01)	0 (0)/0 (0)
Haig *et al.*[11]	0 (0)/0 (0)	9 (5) *	3 (3.4)/9 (10.1)
ATTRACT[4]	46 (14)/38 (11)	—/—	7 (2)/8 (2)
Elsharawy *et al.*[12]	0 (0)/0 (0)	0 (0 /1 (6)	0 (0)/0 (0)
Srinivas *et al.*[8]	13 (48)/—	4 (15)/6 (21)	2 (7)/2 (7)
Kuo *et al.*[5]	7 (22.6)/14 (46.7)	—/—	0 (0)/0 (0)
Lin *et al.*[13]	2 (4)/3 (6)	—/—	0 (0)/0 (0)
Huang *et al.*[9]	1 (5.6)/0 (0)	0 (0)/0 (0)	3 (16.7)/0 (0)
Martinez *et al.*[14]	5 (23)/4 (19)	—/—	—/—

The first value corresponds to the obtained rates in the experimental group and second value to the rates obtained in the respective control group.
*This value represents the total number of cases in the intervention and control groups.

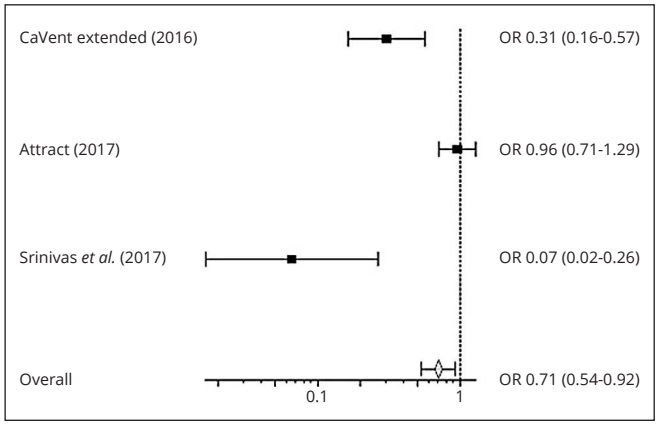

Figure 2.— Forest Plot showing the odds ratio of PTS in anticoagulation *vs.* CDT/PMT groups. A Mantel-Haenszel fixed effect model was used for meta-analysis. Odds ratio are shown with 95% confidence interval.[2, 4, 8] OR: Odds Ratio.

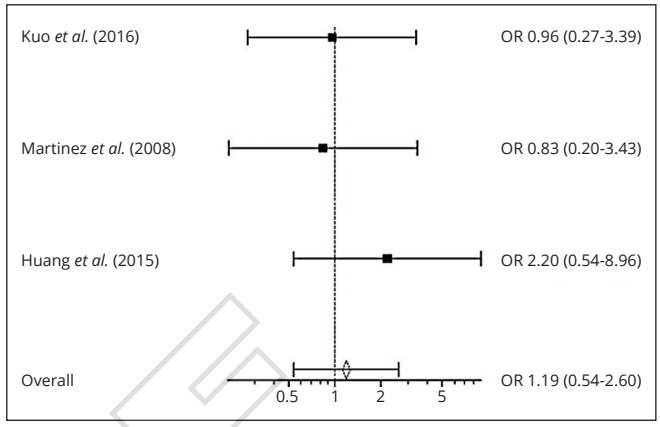

Figure 3.—Forest Plot showing the odds ratio of PTS in CDT *vs.* PMT groups. A Mantel-Haenszel fixed effect model was used for meta-analysis. Odds ratio are shown with 95% confidence interval. OR: Odds Ratio.

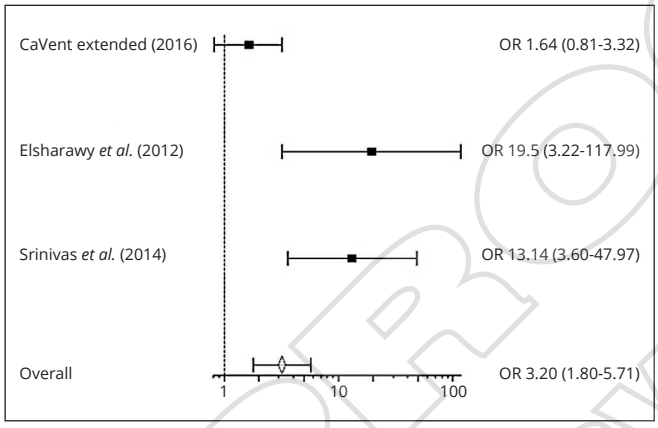

Figure 4.—Forest Plot showing the odds ratio of Iliofemoral Patency in anticoagulation *vs.* CDT/PMT groups. A Mantel-Haenszel fixed effect model was used for meta-analysis. Odds ratio are shown with 95% confidence interval. OR: Odds Ratio.

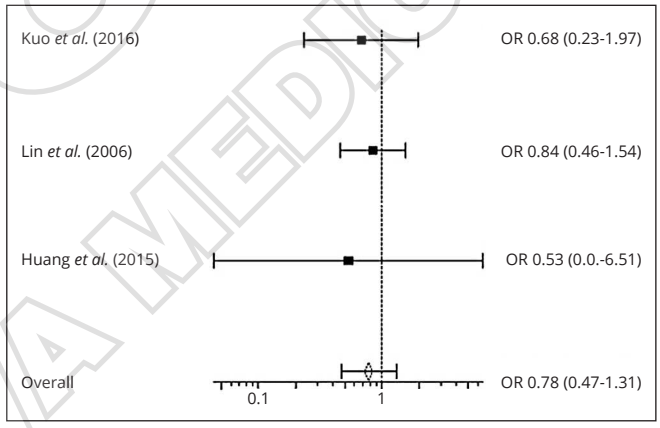

Figure 5.—Forest Plot showing the odds ratio of Iliofemoral Patency in CDT *vs.* PMT groups. A Mantel-Haenszel fixed effect model was used for meta-analysis. Odds ratio are shown with 95% confidence interval. OR: Odds Ratio.

lation (OR=3.20; 95% CI=1.80-5.71) (Figure 4) but no statistically significant differences between the rates of IF patency in patients treated with CDT and PMT were found (OR=0,78; 95% CI=0.47-1.31) (Figure 5).

There were also no statistically significant differences in bleeding rates between anticoagulation and CDT/PMT groups (OR=1.28; 95% CI=0.82-2.02) (Figure 6) and between CDT and PMT groups (OR=0.67; 95% CI=0.28-1.59) (Figure 7).

Also, pulmonary embolism rates did not present statistically significant differences between CDT/PMT and anticoagulation groups (OR=0.53; 95% CI=0.16-1.76) (Figure 8). Only one of the included articles, Huang *et al.*, presented adequate results to compare the rates of pulmonary embolism between CDT and PMT (OR=0.89; 95% CI=0.02-47.53). As for death rates, no statistically significant differences between CDT/PMT and anticoagulation groups (OR=0.67; 95% CI=0.32-1.42) (Figure 9) and between CDT and PMT groups (OR=2.56; 95% CI=0.33-20.03) (Figure 10) were obtained.

Discussion

PTS

PTS is a chronic disease and a common complication of DVT, especially after IFDVT. Several studies have shown frequencies of PTS of 30% to 40%, despite anticoagulation therapy in IFDVT patients.[15] This syndrome can cause

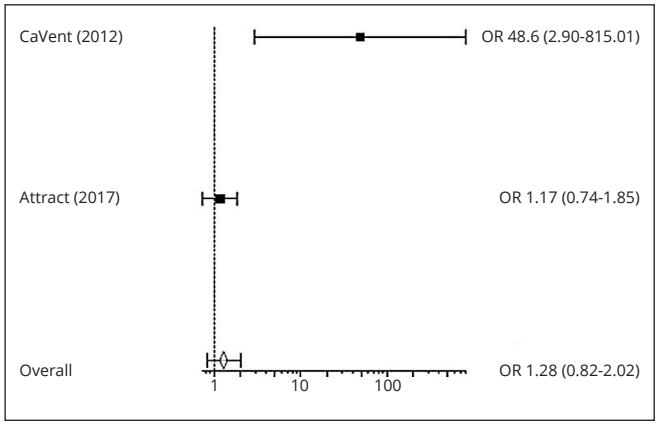

Figure 6.—Forest Plot showing the odds ratio of Bleeding in anticoagulation *vs.* CDT/PMT groups. A Mantel-Haenszel fixed effect model was used for meta-analysis. Odds ratio are shown with 95% confidence interval. OR: Odds Ratio.

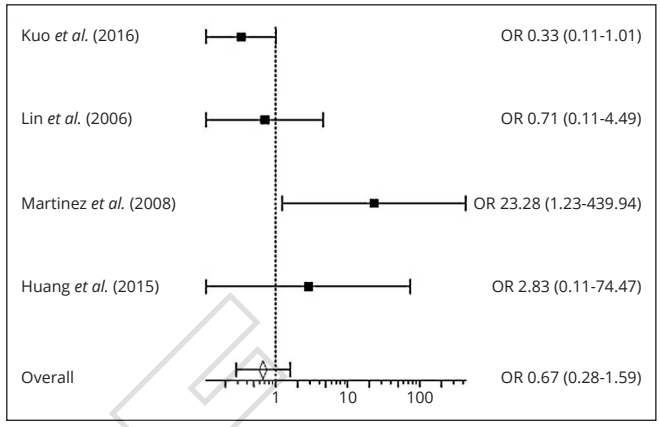

Figure 7.—Forest Plot showing the odds ratio of Bleeding in CDT *vs.* PMT groups. A Mantel-Haenszel fixed effect model was used for meta-analysis. Odds ratio are shown with 95% confidence interval. OR: Odds Ratio.

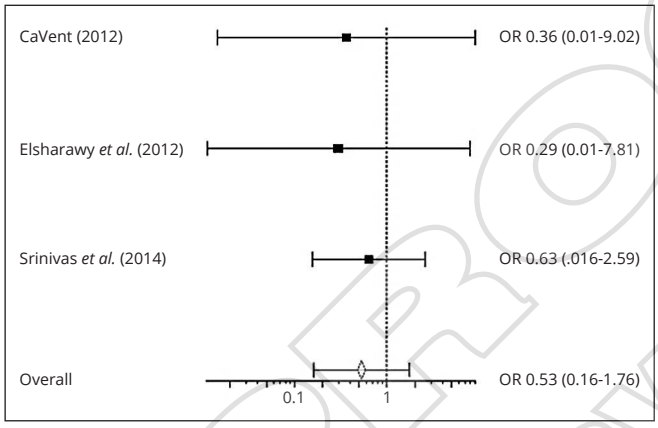

Figure 8.—Forest Plot showing the odds ratio of Pulmonary Embolism in anticoagulation *vs.* CDT/PMT groups. A Mantel-Haenszel fixed effect model was used for meta-analysis. Odds ratio are shown with 95% confidence interval. OR: Odds Ratio.

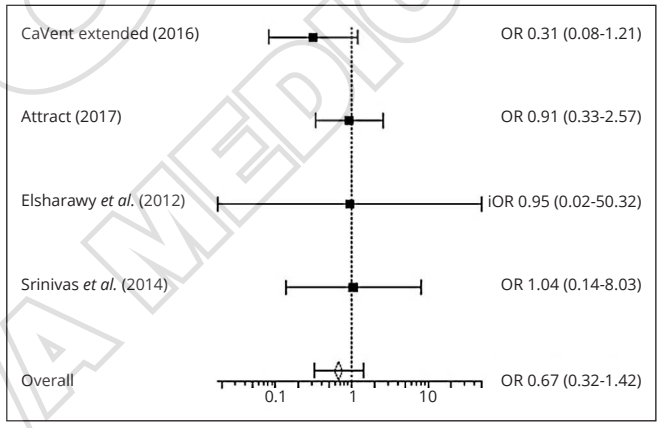

Figure 9.—Forest Plot showing the odds ratio of Death in anticoagulation *vs.* CDT/PMT groups. A Mantel-Haenszel fixed effect model was used for meta-analysis. Odds ratio are shown with 95% confidence interval. OR: Odds Ratio.

chronic limb pain, swelling, edema, pigmentation, sensation of heaviness and skin ulcers, in severe cases.[2, 4]

The pathophysiology of this condition is explained by ambulatory venous hypertension due to valvular incompetence and/or luminal obstruction.[4] The acute thrombotic occlusion in DVT causes an inflammatory response that destroys the vein valves and damages the vein wall, which leads to venous insufficiency and to the development of PTS.[2]

In order to avoid the development of this condition, it is essential to restore venous patency and maintain valve function by eliminating the thrombi in the deep venous system.[16] The standard of care for IFDVT to prevent PTS is anticoagulation, which relies on the endogenous fibrinolytic system to dissolve the clot.[2, 3] However, only 5% of patients treated with this therapy have significant or complete clot lysis.[3] Systemic thrombolysis was considered an alternative treatment that reduced the incidence of PTS in patients with IFDVT, but such treatment was related to an unacceptable risk of bleeding.[2, 7] The lack of effectiveness of anticoagulant and systemic thrombolytic therapies, made expectations rise with the development of local CDT and PMT for DVT treatment, due to the efficacy of selective thrombolysis and associated endovascular therapy, which resulted in faster thrombus dissolution and reduced hemorrhagic complications compared to systemic infusion.[7]

In fact, early clot removal by additional endovascular

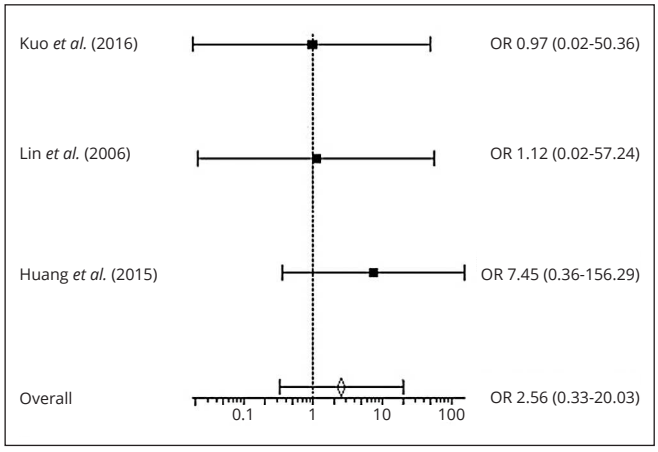

Figure 10.—Forest Plot showing the odds ratio of Death in CDT *vs.* PMT groups. A Mantel-Haenszel fixed effect model was used for meta-analysis. Odds ratio are shown with 95% confidence interval. OR: Odds Ratio.

procedures, such as CDT or PMT, can prevent persistent venous obstruction and damage of the vein valves, both important causes of secondary venous hypertension, which is considered pivotal in the development of chronic post-thrombotic leg complications.[11]

Endovascular techniques and clinical outcomes

CDT is a recent technique in which a catheter is percutaneously inserted into the affected vein and advanced through the thrombotic segment. The catheter has multiple side-holes, which allows the delivery of reduced doses of thrombolytic drugs directly into the clot.[2, 8] Several studies about this modality have shown promising results, focusing mostly on the feasibility of the method in terms of patency of the treated vein segments.[17]

PMT combines endovascular thrombectomy and CDT and appears to be an effective treatment option to treat acute DVT without the bleeding risks related to thrombolysis.[18, 19] This therapy improves functional outcomes of patients with contraindications for lytic therapy.[20] In patients undergoing CDT, PMT does not adversely affect valve function when compared to CDT, but there is a high number of reflux in the uninvolved limb.

Thrombectomy devices that make mechanical declotting are being produced by multiple centers and seem to be a good alternative to patients that can´t receive conventional thrombolytic therapy.[21] However, these devices have risks of venous wall and valve injury, due to the mechanical forces applied.[22, 23] Recent rotator thrombolysis devices have shown to reduce in-hospital mortality and to decrease PTS morbidity, due to rapid restoration of patency and sustained valve function.[24, 25] Further prospective studies with larger populations and data are needed to determine the long-term outcomes of patients treated with these devices.[14, 26] There should also be an improvement in mechanical devices to allow treatment with low bleeding complications to increase the patient population eligible for thrombolysis.[1, 20]

AngioJet® is an effective option for thrombus removal that may increase the efficiency of thrombus clearance and lower the necessary infusion dose and time for thrombolytic drugs to act. However, it may cause hemolysis, hemoglobinuria and vessel wall and valve damage.[25] The use of large-sized catheters, like 9French (F) or 10F, may be a safe and effective strategy to aproach acute lower limb DVT for aspiration thrombectomy. Additional intravenous thrombolysis can improve the efficacy of this procedure and does not seem to be related to a higher risk of bleeding in these cases.[25] Mechanical thrombectomy with simultaneous stenting can avoid complications related to residual stenosis and has excellent long-term outcomes.[27, 28] More prospective studies with large sample sizes and long follow-up periods should be performed to claim the real safety and effectiveness of large-catheter use in aspiration thrombectomy.

Technique variations There are many ways to perform CDT and PMT and multiple trials have been made to determine which techniques are related to more favorable outcomes.

The type of thrombolytic drug, thrombectomy device and venous access all vary depending on patient clinical and anatomical characteristics. The concomitant administration of argatroban and tPa is a safe and effective regimen for the treatment of massive DVT.[29, 30]

The DUTCH-CAVA Trial is an ongoing prospective randomized and multicenter study that aims to assess if CDT can safely and effectively reduce PTS morbidity after one year, in patients with acute IFDVT. In this trial, patients allocated to the intervention group are going to be treated with Ekos Endowave® System, while patients allocated to the control group will be treated with standard anticoagulation treatment.

Thrombolytic effect monitoring

Endovascular techniques of clot lysis or removal also reduce the high rate of DVT recurrence. The quantity of residual thrombus at the completion of CDT is directly correlated with recurrent episodes of DVT.[31] PTS risk and morbidity is also correlated to the residual thrombus volume and the complete clearance of the thrombi avoids the

development of this syndrome.[3, 32] IFDVT typically has a higher volume of thrombus occlusion than DVT in other locations, which explains the higher tendency for IFDVT recurrence.[31]

Adequate post-procedure imaging allows identification and treatment of residual clot burden and underlying venous pathology, which can ensure the short and long-term success of the intervention.[10] For this purpose, the standard imaging techniques rely on venography.[33] Intravascular ultrasound (IVUS) has also been used as an alternative or adjunctive imaging technique.[19] IVUS is more sensitive than venography in the detection of residual thrombus and venous lesions after PMT.[10, 19] The routine use of IVUS may improve the clinical outcomes of DVT patients.

Measuring the soluble products of fibrin lysis, such as D-dimers, is a potential alternative method of noninvasive monitoring to access the effect of fibrinolytic therapy.[22] There is a correlation between the amount of venous thrombus lysed during CDT and both the peak of D-dimer concentration and time integrated-value.[22] Further assessment should be made in prospective studies, in order to prove the validity of this procedure.

Clinical complications

CDT most common complication is bleeding, which has a very high risk to occur in certain patients. However, the prevalence of this adverse effect is relatively low, affecting up to 1.7% of patients who have a formal indication for CDT.[4] Other disadvantages of this technique include long time for clot lysis, long hospital stay and heavy economic costs incurred by the need for close clinical monitoring.[34]

There is also a theoretical risk of pulmonary embolism after treatment with thrombolytic therapy, caused by clot dissolution. The incidence of symptomatic pulmonary embolism has been reported to be 4.5% in these patients.[35] Patients with previous silent venous thromboembolism and with heart disease have a higher risk of developing symptomatic pulmonary embolism after CDT.[18] Selective IVC filter placement is considered an appropriate approach for these patients.[18]

Patient selection

The published literature about this subject fails to identify which patients will benefit the most from CDT or PMT. According to current data, incomplete clot lysis, recent surgery, male gender, phlegmasia and malignant diseases are the factors more related to immediate or mid-long term failure of this therapy.[36]

Patients with IFDVT will often have concomitant involvement of the popliteal and tibial veins. The presence of thrombus extension to these vessels does not have any adverse effect on symptom relief, thrombus recurrence or development of PTS in patients treated with thrombolytic therapy.[37] Also, inferior vena cava (IVC) thrombus extension does not have an impact on the technical success of CDT for iliofemoral DVT patients.[12] However, the presence of thrombosed IVC filters used to prevent pulmonary thromboembolism seems to make CDT failure more likely.[38] Bleeding complications, IVC agenesis and chronic DVT are related to a failure rate of 9.8% in IFDVT patients.[2, 10] The presence of malignancy is considered by some centers as an exclusion criteria for PMT due to uncertain or short life expectancy, increased risk of bleeding and high recurrence of DVT related to cancer.[39]

Patients with a symptom duration less than 2 weeks, absence of chronic post-thrombotic lesions and the use of pulse-spray technique during CDT were associated to a better primary vein patency in long-term.[40]

Meta-analysis

Our meta-analysis revealed that endovascular treatment with CDT or PMT reduces the risk of development of PTS, while improving IF patency, when compared to standard anticoagulation treatment. There seems to be no differences between CDT and PMT groups, when it comes to these two primary outcomes.

As for the analyzed secondary outcomes, no differences were found between not only CDT or PMT and standard anticoagulation, but also between CDT and PMT groups, in the rates of complications such as bleeding, pulmonary embolism and death.

Meta-bias

The limited number of articles included for the quantitative analysis did not justify the elaboration of a funnel-plot, in order to evaluate the risk of publication bias across studies.

Strength of the body of evidence

Most of the included studies have low or unclear risk of bias and the presented bias of each study is unlikely to lower the confidence in the measured outcomes of this article. For that reason and according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) systematic approach for certainty of evidence, we consider that the presented limitations across studies do not downgrade the obtained level of evidence.[7]

Limitations of this study

We admit some limitations to this study: 1) only two databases were searched; 2) studies with different designs were included in the quantitative analysis; 3) different thrombectomy devices were used in the included studies; 4) different thrombolytic agents were used in the included studies; 5) different follow-up periods were considered for the included studies. Such limitations can potentially explain the heterogeneity presented in our analysis. However, the systematic review methodology we followed, along with the performed statistical analysis strongly support the presented results.

Conclusions

PTS and IF patency reduction are frequent complications of IFDVT with significative physical burden and economical costs, that affects the overall quality of life of patients.[2, 4] Endovascular treatment of IFDVT is an effective treatment option for the acute phase of the disease, whether it is made by thrombolytic or mechanical procedures.

The results of this systematic review and meta-analysis support the benefit of CDT and PMT in the treatment of IFDVT, regarding the prevention of PTS development and to the maintenance of IF patency. There seems to be no significant differences between the rates of bleeding, pulmonary embolism and death, when comparing CDT and PMT to anticoagulation or CDT directly to PMT.

To conclude this review, endovascular therapy for IFDVT seems to have excellent long-term results. However, further investigation should be made about this subject, with prospective randomized clinical trials with large populations and long-term follow-ups. The results of some ongoing trials, such as the DUTCH-CAVA trial, will be able to provide additional information on the subject.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—João Diniz: manuscript design and conception, article writing, final approval of the manuscript; Andreia Coelho: manuscript design and conception, article writing, final approval of the manuscript; Armando Mansilha: manuscript design and conception, final approval of the manuscript.

Article first published online: _____. - Manuscript accepted: October 14, 2019. - Manuscript received: October 1, 2019.

Agradecimentos

Gostaria de expressar o meu agradecimento ao professor Armando Mansilha, pela disponibilidade que teve para orientar este trabalho e por toda a ajuda que prestou no decorrer do seu desenvolvimento.

Gostaria também de agradecer à Dr. Andreia Coelho, pelo papel imprescindível que desempenhou na elaboração do presente artigo.

Por fim, gostaria de prestar o meu agradecimento à minha família, pela sua presença constante e apoio incondicional ao longo de todo o meu percurso académico, bem como aos colegas e amigos que me acompanharam no decorrer destes anos.

Anexos

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pISSN 0392-9590

eISSN 1827-1839

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Original articles. These should be original contributions to the subject. The text should be 3000-5500 words (8 to 16 typed, double-spaced pages) not including references, tables, figures. No more than 50 references will be accepted. The article must be subdivided into the following sections: introduction, materials (patients) and methods, results, discussion, conclusions. The introduction should describe the theoretical background, the aim of the study and the hypothesis to be tested. The materials and methods section should describe in a logical sequence how the study was designed and carried out, how the data were analyzed (what hypothesis was tested, what type of study was carried out, how randomization was done, how the subjects were recruited and chosen, provide accurate details of the main features of treatment, of the materials used, of drug dosages, of unusual equipments, of the statistical method ...). In the results section the answers to the questions posed in the introduction should be given. The results should be reported fully, clearly and concisely supported, if necessary, by figures, graphs and tables. The discussion section should sum up the main results, critically analyze the methods used, compare the results obtained with other published data and discuss the implications of the results. The conclusions should briefly sum up the significance of the study and its future implications. For randomised controlled trials it is suggested to the authors to conform the structure of their paper to the checklist requirements of the following guidelines reported by the CONSORT statement: **http://www.consort-statement.org**.

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Identify methodologies, equipment (give name and address of manufacturer in brackets) and procedures in sufficient detail to allow other researchers to reproduce results. Specify well-known methods including statistical procedures; mention and provide a brief description of published methods which are not yet well known; describe new or modified methods at length; justify their use and evaluate their limits. For each drug generic name, dosage and administration routes should be given. Brand names for drugs should be given in brackets. Units of measurement, symbols and abbreviations must conform to international standards. Measurements of length, height, weight and volume should be given in metric units (meter, kilogram, liter) or their decimal multiples. Temperatures must be expressed in degrees Celsius. Blood pressure must be expressed in millimeters of mercury. All clinical chemistry measurements should be expressed in metric units using the International System of Units (SI). The use of unusual symbols or abbreviations is strongly discouraged. The first time an abbreviation appears in the text, it should be preceded by the words for which it stands.

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Sutherland DE, Simmons RL, Howard RJ. Intracapsular technique of transplant nephrectomy. Surg Gynecol Obstet 1978;146:951-2.

- Organization as author

International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Ann Int Med 1988;108:258-65.

- Issue with supplement

Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. Semin Oncol 1996;23(1 Suppl 2):89-97.

Books and monographs

For occasional publications, the names of authors, title, edition, place, publisher and year of publication must be given.

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Rossi G. Manual of Otorhinolaryngology. Turin: Edizioni Minerva Medica; 1987.

- Chapter from book

De Meester TR. Gastroesophageal reflux disease. In: Moody FG, Carey LC, Scott Jones R, Ketly KA, Nahrwold DL, Skinner DB, editors. Surgical treatment of digestive diseases. Chicago: Year Book Medical Publishers; 1986. p. 132-58.

- Congress proceedings

Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15-19; Kyoto, Japan. Amsterdam: Elsevier; 1996.

Electronic material

- Standard journal article on the Internet

Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. Ann Intern Med [Internet]. 2006 Jul 4 [cited 2007 Jan 4];145(1):62-9. Available from: http://www.annals.org/cgi/reprint/145/1/62.pdf

- Standard citation to a book on CD-ROM or DVD

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