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Review Article

Acute graft thrombosis in patients who underwent renal transplant and received anticoagulant or antiplatelet agents. A systematic review and meta-analysis

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Abstract: Objectives: Thrombosis is a major cause of early allograft loss in renal transplantation. Herein, we assessed the frequency of acute graft thrombosis in patients who underwent renal transplant and received anticoagulant or antiplatelet agents. Methods: We performed a systematic review of all available case series studies of anticoagulant and/or antiplatelet prophylaxis of thrombosis in renal transplantation. The data were pooled in a proportional meta-analysis. Results: Twenty-one case series were identified from 7,160 retrieved titles. A total of 3,246 patients were analyzed (1,718 treated with antiplatelet and/or anticoagulant agents and 1,528 non-treated control subjects). Allograft thrombosis occurred in 7.24% (95% CI 3.45 to 12.27%) of the patients receiving no intervention compared with 3.38% (95% CI 1.45 to 6.1%), 1.2% (95% CI 0.6 to 2.1%) and 0.47% (95% CI 0.001 to 1.79%) of the patients in the anticoagulant, aspirin, and aspirin + anticoagulant groups, respectively. The bleeding complication rate for anticoagulants was significantly higher than in the other groups. Conclusions: Our data suggests that anticoagulants, and aspirin, either alone or in association with an anticoagulant, seem to have a low frequency of acute allograft thrombosis after kidney transplantation. Higher hemorrhagic complication rates might occur when anticoagulants are used.

Keywords: Anticoagulants, aspirin, kidney transplantation, meta-analysis, thrombosis

Introduction

Renal transplantation is the gold-standard treatment for end-stage renal disease, with better overall survival and quality of life compared to chronic dialysis [1]. Due to its complexity, renal transplantation is prone to various possible complications within the clinical, nephrological, vascular and urological scopes [2]. Renal allograft thrombosis, either arterial or venous, is expected to occur in 1-6% of cases and is the main factor responsible for renal allograft loss in the first month after transplantation [3]. The chance of graft loss is virtually 100%, [4, 5] as timely diagnosis and prompt treatment are unlikely, and parenchymal damage with permanent renal dysfunction rapidly occurs.

Risk factors, such as the presence of thrombophilia, very young age and other predisposing factors, can be pinpointed, although allograft thrombosis may still occur without these contributors [3]. In such a setting, it would be extremely desirable to establish effective preventive measures. The adequacy of the surgical technique is clearly paramount, but the use of antiplatelet drugs and anticoagulants could also be useful for thrombosis prevention [6], and both have been tested clinically, either alone or combined, with conflicting results from individual series.

Unfractionated heparin and low-molecular-weight heparins (LMWHs) are widely used in deep venous thrombosis (DVT) prophylaxis in the initial postoperative periods of major surgi-

cal procedures. Their use is now well established, with guidelines to assess the risk of DVT for different types of surgical procedures and clinical situations and to direct the indication of anticoagulant prophylaxis [7]. The importance of aspirin use in preventing thrombotic events related to atherosclerosis is also well established, particularly in the management of arterial occlusive conditions, such as coronary artery disease and carotid obstruction [8, 9].

These pharmacological interventions are very simple, inexpensive, effective and safe, with a measurable positive impact in these settings. However, a definite protocol specifically tailored to preventing acute thrombosis of a transplanted kidney is still not available. Clinical practice is currently based mostly on case series studies along with two insufficiently sampled randomized clinical trials (RCTs) [10, 11], leading to a very heterogeneous practice amongst different institutions, with largely diverse protocols [12].

We aimed to assess the frequency of acute graft thrombosis in patients who underwent renal transplant and received anticoagulant or antiplatelet agents.

Methods

Our review protocol was registered at PROSPERO-International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/prospero/index.asp), under registration number CRD42014010145, and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was followed.

Study eligibility

The inclusion criteria were as follows: (i) case series studies (with the number of reported patients in each study greater than one); (ii) patients undergoing kidney transplantation, regardless of the modality (living or deceased donor), baseline renal disease, age or the presence of thrombophilic conditions or any other risk factors for allograft thrombosis; (iii) the use of any antiplatelet and/or anticoagulant agent, such as aspirin, heparin, warfarin or others; and (iv) the studies specified a measure of the occurrence of allograft thrombosis. Studies with incomplete data were scrutinized for the inclusion of the actual available information in the final analysis.

Either arterial or venous allograft thrombosis, when occurring up to three months after renal transplantation, was the outcome of interest; these conditions were considered together. We also quantified the hemorrhagic complication rates from each included study, when available, such as transfusion rates, abnormally high bloody drainage, perirenal hematomas and reoperations due to bleeding.

Search strategy

There were no language or publication status restrictions. Studies were obtained from the US National Library of Medicine (MEDLINE, 1966 to nowadays), the Excerpta Medica Database (EMBASE, 1980 to nowadays) and the Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS, 1982 to nowadays) to identify all case series of allograft thrombosis prophylaxis with the use of either antiplatelet or anticoagulant agents in renal transplantation.

The databases were accessed using a comprehensive search strategy for renal transplantation and antiplatelet or anticoagulant use with MeSH (Medical Subject Headings) terms and free text words, along with an exhaustive list of synonyms (**Appendix**). The search strategy was adapted for each database to achieve higher sensitivity. The bibliographic references in relevant articles were also examined for eligible studies. We contacted specialists in the field for additional studies and the authors of the included articles to request unpublished data.

Study selection and data collection

Two reviewers independently screened the titles identified by the literature search, and any discrepancies were resolved by discussion. The following information was extracted independently by two reviewers: authors and year of publication, country, number of participants, mean patient age, body weight or body mass index, the modality of renal transplantation (living or deceased donor), the presence of risk factors for thrombosis (e.g., hypercoagulable states, previous venous thrombosis, miscarriages, systemic lupus erythematosus, peripheral arterial disease, intraoperative vascular technical issues, multiple allograft arteries,

children or adolescents), the type and dosage of antiplatelet or anticoagulant agent, the administration regimen and the outcomes of interest.

If there was more than one published report of the same group of patients, the articles were analyzed to verify whether they reported different outcomes. If they presented the same outcomes, we extracted the data from the most complete report. Mean age, when reported, was calculated based on the mean age of the included studies. Children were computed as a high-risk population *per se* and were also included in the high-risk group along with patients with other risk factors for thrombosis; both populations were further analyzed as separate subgroups. Patients under 17 years old were considered children.

Measures of treatment effects

The proportional meta-analysis was performed using StatsDirect software, version 2.8.0. The outcomes of interest were treated as dichotomous variables with their respective 95% confidence intervals (CIs).

The pooled analysis of proportions from case series was performed as previously detailed by El Dib *et al*. [13]. Because of clear differences among the included studies and several uncontrollable variables, a random-effects model [14] was used to perform the pooled analysis of proportions.

Forest plot charts were presented to summarize the data. Each horizontal line on the graph represents a case series included in the meta-analysis. The estimated effect is marked with a solid black square, and the size of the square represents the weight of the corresponding study plotted in the meta-analysis. The combined total estimate is marked with an unfilled diamond at the bottom of the forest plot [13].

The possibility of publication bias was assessed with Egger tests, as they are useful adjuncts to meta-analyses. The resulting funnel plots indicate whether the positive results of the included articles could have influenced their chance of being published, which would translate graphically as dots plotted outside the inverted funnel.

Statistical heterogeneity

Statistical heterogeneity was assessed using the I^2 statistical test, and significance was assumed when I^2 was greater than 50%. This measurement illustrates the percentage of the variability in effect estimates resulting from heterogeneity rather than sampling error [15]. We also considered $P<0.05$ as statistically significant for the calculation of heterogeneity.

Results

The literature search identified 7,160 titles. After screening by title and then abstract, we obtained full-text copies of 68 studies on antiplatelet and/or anticoagulant use in renal transplantation that were potentially eligible for inclusion in the review. However, most of these studies (60.3%) were off-topic because they did not actually evaluate allograft thrombosis, and 7.4% were classified as review articles. Finally, a total of 22 case series studies [16-37] met all of the methodological requirements, but only 21 studies were included in the review because one was a duplicate publication [37] of Murphy 2001 (**Figure 1**).

Description of the included studies

Twenty-one case series with a total of 3,246 patients were included in this review. A total of 1,718 patients were treated with either antiplatelet or anticoagulant agents or a combination, and the remaining 1,528 were control subjects who underwent no further preventive treatment for allograft thrombosis in addition to the standard post-transplantation measures of care. No placebo was given to the controls in any of the series (**Table 1**).

The case series studies considered mostly adult renal allograft recipients (83.6% of total); although some studies specifically addressed the pediatric population [16, 20, 22, 27, 31] the mean age was not consistently reported (mean of the reported age ranged from 26.4 to 35.0 among the three studied intervention groups). Only one pediatric case series study reported body weight. The high-risk group (n=1,097) largely outnumbered the lower risk population (n=366) present in the total selected case series. However, the risk assessment was not reported and thus was unavailable in 1,783 patients (54.9% of total). Deceased

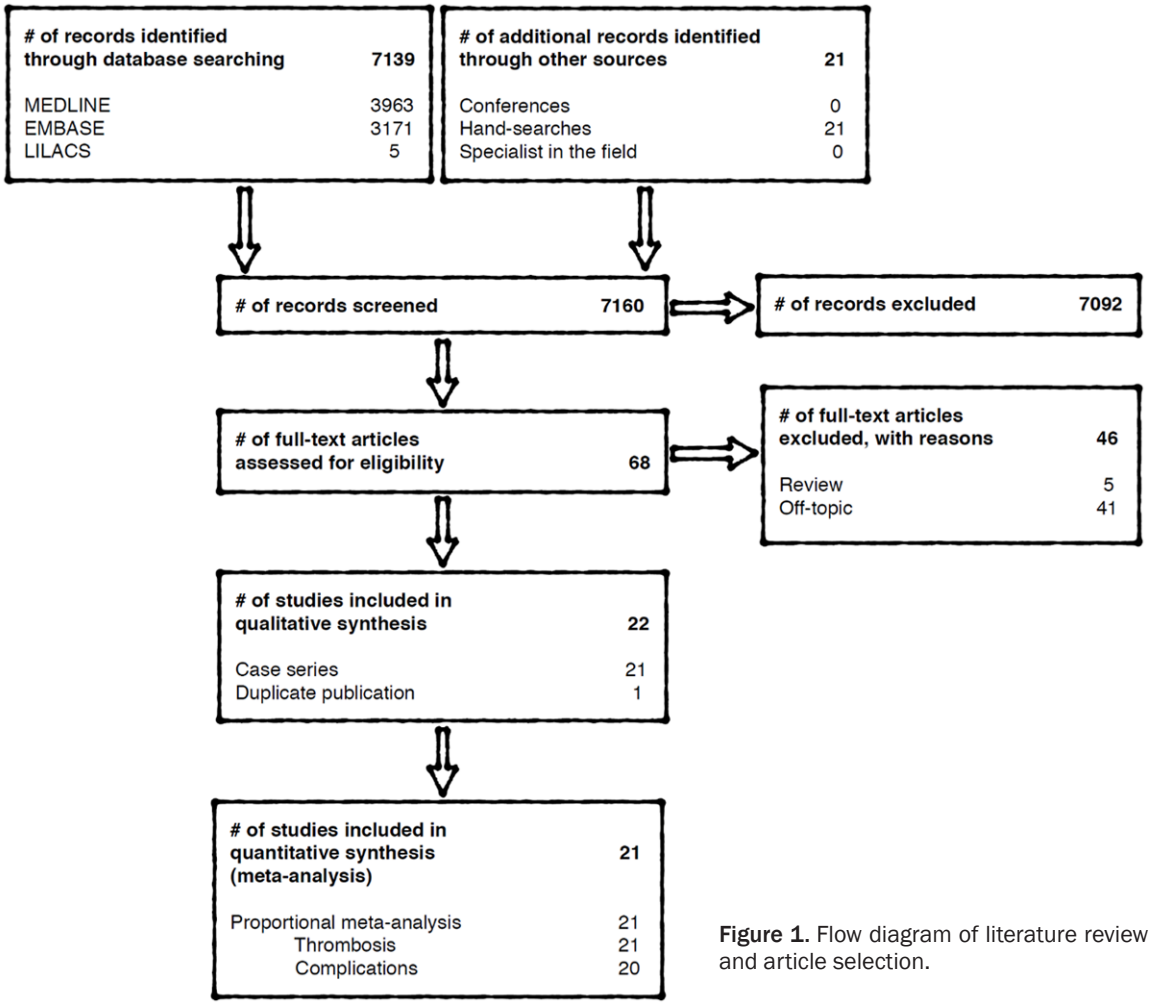

Figure 1. Flow diagram of literature review and article selection.

donor grafting was predominant in the overall reported case series studies (76.8% of 1,555 kidneys), approaching approximately three times the number of living donors. Nevertheless, a considerable number of patients (n=1,691) had no report of their transplant modality.

Types of intervention

There was high diversity in the way interventions were administered, with no single protocol exactly replicated among the studies (the only exception was for aspirin alone, with two studies from the same group). Aspirin alone, aspirin in association with anticoagulants (heparin, LMWH or both), and parenteral anticoagulants (followed or not by a period of oral anticoagulants) were all described. Full or prophylactic doses of heparin and LMWH (enoxaparin, dalteparin or others) were both used.

The dosages and administration schedules were largely uneven among studies. Argatroban (a low-molecular-weight direct thrombin inhibitor) was occasionally used to replace heparin in a few studies [20, 32] other than aspirin, no other antiplatelet agent was used.

Regarding the timing of intervention, no study proposed preoperative intervention alone. One study evaluated the administration of intravenous heparin only during the intraoperative period [28]. The majority of studies [17, 18, 30-36, 19, 20, 22-27] adopted postoperative intervention, with only a few [16, 21, 24, 29, 33] combining immediate preoperative introduction with postoperative maintenance of the drug. Two studies mixed patients undergoing only postoperative care with other patients combining pre- and postoperative intervention [24, 33].

Table 1. Characteristics of patients undergoing renal transplantation: comparison among different regimens of allograft thrombosis prophylaxis

	Antiplatelet	Anticoagulant	Antiplatelet + Anticoagulant	No intervention
Total case series	2[10, 22]	15[5-9, 11, 13, 14, 16-20, 23, 24]	6[12, 13, 15, 21, 23, 25]	13[5, 6, 9, 10, 12, 13, 17-20, 23-25]
Number of patients	881	614	223	1528
Mean age (years)	-	34.9[7-9, 13, 16-18, 20, 24]	26.4[12, 15, 21, 23, 25]	29.2[9, 12, 13, 17, 18, 20, 24, 25]
Not reported	2[10, 22]	__[5, 6, 11, 14, 19, 23, 25]	__[13, 23]	__[5, 6, 10, 19, 23]
Number of children	0[22]	177[5, 7, 16-18, 24]	90[15, 21, 25]	265[5, 17, 18, 24, 25]
Not specified	__[10]	__[6, 8, 9, 11, 13, 14, 19, 20, 23]	__[12, 13, 23]	NR[6, 9, 10, 12, 13, 19, 20, 23]
Kidney donor				
Living	90[22]	124[6, 7, 9, 16-18, 23, 24]	41[12, 21, 25]	105[6, 9, 12, 17, 18, 23-25]
Deceased	311[22]	308[6, 7, 9, 16-18, 23, 24]	154[12, 21, 25]	422[6, 9, 12, 17, 18, 23-25]
NR	480[10]	182[5, 8, 11, 13, 14, 19, 20]	28[13, 15, 23]	1001[5, 10, 13, 19, 20]
Low risk patients	NR[10, 22]	165[5-9, 11, 14, 16-20, 23, 24]	12[12, 15, 21, 23, 25]	189[5, 6, 9, 12, 17, 18, 20, 23-25]
High risk patients	NR[10, 22]	405[5-9, 11, 14, 16-20, 23, 24]	199[12, 15, 21, 23, 25]	493[5, 6, 9, 12, 17, 18, 20, 23-25]
NR	881[10, 22]	44[13]	12[13]	846[10, 13, 19]
Drug used (# of patients)	Aspirin 881 Other -	Heparin 259 LMWH 236 Heparin + LMWH 18 Heparin + Oral Anticoagulant 69 Others 32	ASA + Heparin 108 ASA + LMWH 97 ASA + Heparin + LMWH 18	-
Dosage	75-150 mg	Full 34.7% Prophylactic 65.3%	Full 7.8% Prophylactic 92.2%	-
Timing of intervention (# of patients)				
Preoperative	0	0	0	-
Intraoperative	0	100	0	
Postoperative	881	434	106	
Pre + Postoperative	0	80	117	
Country (# of studies)				
Netherlands	0	1	0	
UK	2	1	1	
USA	0	7	1	
Egypt	0	0	0	
France	0	1	0	
Germany	0	1	1	
Ireland	0	1	0	
Australia	0	1	0	
Turkey	0	1	0	
Iran	0	0	1	
Sweden	0	1	1	

Effects of interventions

A total of 136 allograft thrombosis episodes were recorded amongst all selected series. The mean rate of thrombosis in treated patients (regardless the type of intervention) was 1.86%. For 75 patients, there was no mention of whether the thrombosis was arterial, venous or both, but there was a larger number of patients with venous thrombosis (50 venous vs. 11 arterial).

Allograft thrombosis occurred in 7.24% (95% CI 3.45 to 12.27%) of the no intervention group patients compared to 3.38% (95% CI 1.45 to 6.1%), 1.2% (95% CI 0.6 to 2.1%) and 0.47% (95% CI 0.001 to 1.79%) in the anticoagulant, aspirin, and aspirin + anticoagulant groups, respectively (**Figure 2**).

There was a significantly lower rate of allograft thrombosis among patients who used aspirin, in combination or not with an anticoagulant, when compared to no intervention (reaching a decrease of almost seven-fold). However, those patients who used anticoagulants in monotherapy did not achieve a significant difference from the controls, as their CIs overlapped (**Figure 3A**).

From the available data, it was possible to analyze children and all high-risk patients as sub-

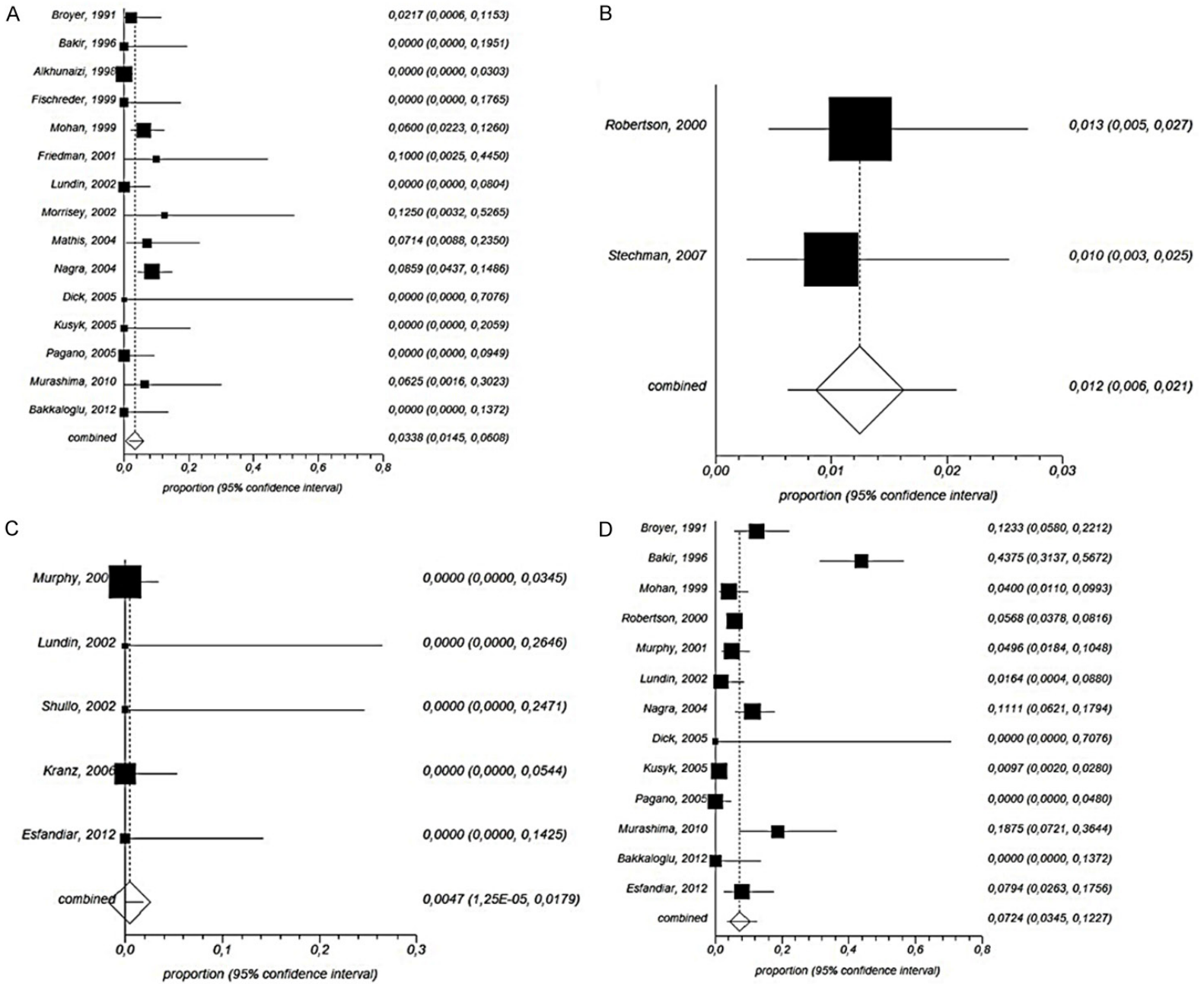
A
Broyer, 1991
Bakir, 1996
Alkhunaizi, 1998
Fischreder, 1999
Mohan, 1999
Friedman, 2001
Lundin, 2002
Morrisey, 2002
Mathis, 2004
Nagra, 2004
Dick, 2005
Kusyk, 2005
Pagano, 2005
Murashima, 2010
Bakkaloglu, 2012
combined
0,0217 (0,0006, 0,1153)
0,0000 (0,0000, 0,1951)
0,0000 (0,0000, 0,0303)
0,0000 (0,0000, 0,1765)
0,0600 (0,0223, 0,1260)
0,1000 (0,0025, 0,4450)
0,0000 (0,0000, 0,0804)
0,1250 (0,0032, 0,5265)
0,0714 (0,0088, 0,2350)
0,0859 (0,0437, 0,1486)
0,0000 (0,0000, 0,7076)
0,0000 (0,0000, 0,2059)
0,0000 (0,0000, 0,0949)
0,0625 (0,0016, 0,3023)
0,0000 (0,0000, 0,1372)
0,0338 (0,0145, 0,0608)
0,0 0,2 0,4 0,6 0,8
proportion (95% confidence interval)
B
Robertson, 2000
Stechman, 2007
combined
0,013 (0,005, 0,027)
0,010 (0,003, 0,025)
0,012 (0,006, 0,021)
0,00 0,01 0,02 0,03
proportion (95% confidence interval)
C
Murphy, 200
Lundin, 2002
Shullo, 2002
Kranz, 200
Esfandiar, 2012
combined
0,0000 (0,0000, 0,0345)
0,0000 (0,0000, 0,2646)
0,0000 (0,0000, 0,2471)
0,0000 (0,0000, 0,0544)
0,0000 (0,0000, 0,1425)
0,0047 (1,25E-05, 0,0179)
0,0 0,1 0,2 0,3
proportion (95% confidence interval)
D
Broyer, 1991
Bakir, 1996
Mohan, 1999
Robertson, 2000
Murphy, 2001
Lundin, 2002
Nagra, 2004
Dick, 2005
Kusyk, 2005
Pagano, 2005
Murashima, 2010
Bakkaloglu, 2012
Esfandiar, 2012
combined
0,1233 (0,0580, 0,2212)
0,4375 (0,3137, 0,5672)
0,0400 (0,0110, 0,0993)
0,0568 (0,0378, 0,0816)
0,0496 (0,0184, 0,1048)
0,0164 (0,0004, 0,0880)
0,1111 (0,0621, 0,1794)
0,0000 (0,0000, 0,7076)
0,0097 (0,0020, 0,0280)
0,0000 (0,0000, 0,0480)
0,1875 (0,0721, 0,3644)
0,0000 (0,0000, 0,1372)
0,0794 (0,0263, 0,1756)
0,0724 (0,0345, 0,1227)
0,0 0,2 0,4 0,6 0,8
proportion (95% confidence interval)

Figure 2. Allograft thrombosis: forest plots (random effects proportional meta-analysis). A. Anticoagulants; B. Aspirin; C. Aspirin + Anticoagulants; D. Controls.

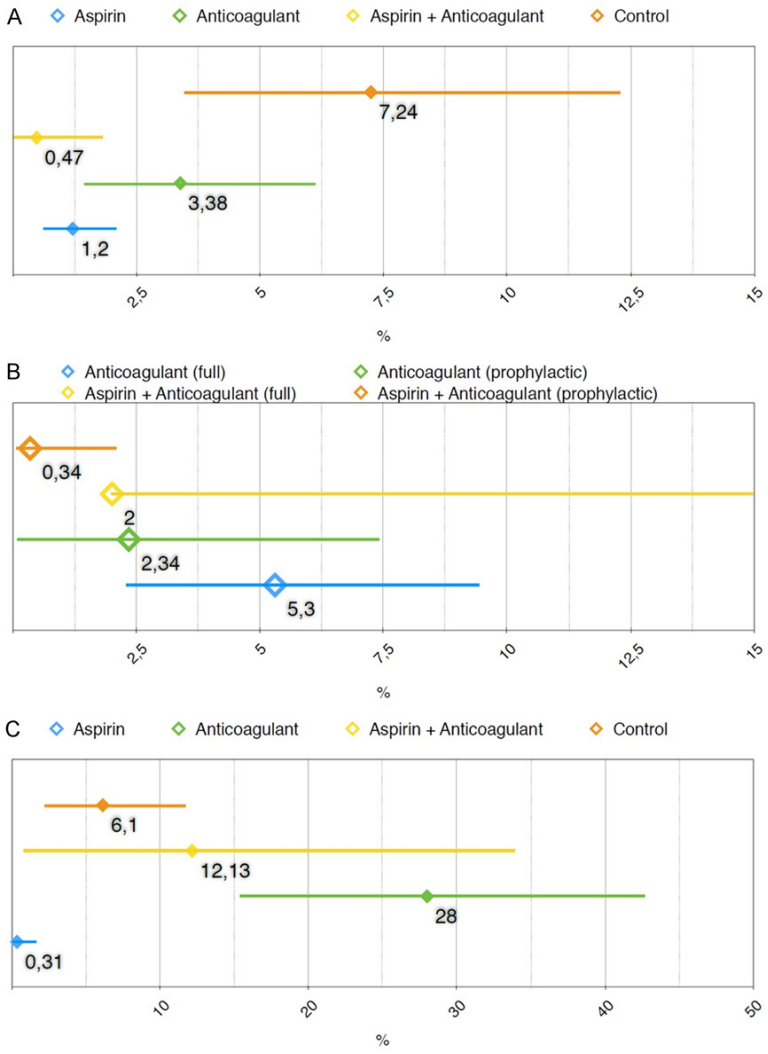

Figure 3. Comparison of the plotted proportional meta-analysis (incidence rates and 95% confidence intervals), according to prophylaxis regimen. A. Allograft thrombosis. B. Allograft thrombosis, with different anticoagulant dosages. C. Hemorrhagic complications.

groups, but only comparing anticoagulants to aspirin + anticoagulants because the aspirin-only studies did not report on age and risk status. Among either subgroup, aspirin + anticoagulants achieved significantly lower thrombosis rates than anticoagulants alone or controls, while anticoagulant CIs overlapped with those of the controls (**Table 2**).

There was no difference in the thrombosis rates with the use of full vs. prophylactic dosages of anticoagulants, either combined with aspirin or not, as all of the CIs overlapped (**Figure 3B**; **Table 2**).

The bleeding complication rate was 28.0% (95% CI 15.4 to 42.7%) for anticoagulants compared to 12.13% (95% CI 0.8 to 33.93%) for aspirin + anticoagulant, 0.31% (95% CI 0.0001 to 1.32%) for aspirin, and 6.1% (95% CI 2.2 to 11.7%) for the control group (**Table 2**; forest plots not shown). The 95% CIs for bleeding among treatment groups and controls obtained from the proportional meta-analysis of series reporting hemorrhagic complications are shown in **Figure 3C**.

The funnel plots for both anticoagulant and anticoagulant plus aspirin treatments were symmetrical, revealing a "well-behaved" data set in which publication bias is unlikely to have occurred (**Figure 4**). The bleeding complication data on aspirin alone should be used with caution; only two studies used aspirin alone, and a corresponding funnel plot could not be drawn.

There were significant differences in heterogeneity for both anticoagulant and control groups: I^2=53.6% from 15 studies with a total of 614 patients (P= 0.0073) and I^2=89.6%% from 13 studies with a total of 1,528 patients (P<0.0001), respectively, reflecting the inconsistency of clinical and methodological aspects among the studies included in the meta-analysis. However, in the anticoagulant + aspirin group, heterogeneity was not detected because there were no events (thrombosis) within the included studies. A heterogeneity analysis was not performed for the aspirin group due to the low number of included series.

Table 2. Analysis of outcomes, according to prophylaxis regimen and subgroups

	Studies* (n)	Events (n)	Patients (n)	Proportional Meta-analysis % (confidence interval)
Thrombosis (all patients)				
Aspirin	2	10	881	1.2 (0.6-2.1)
Anticoagulant	15	22	614	3.38 (1.45-6.08)
Aspirin + Anticoagulant	5	0	223	0.47 (0.001-1.79)
Controls	13	102	1528	7.24 (3.45-12.27)
Thrombosis (high risk patients)				
All treatments	12	16	399	3.42 (1.31-6.49)
Anticoagulant	9	16	296	4.97 (2.23-8.71)
Aspirin + Anticoagulant	3	0	103	0.64 (0.02-3.05)
Controls	5	56	329	16.0 (6.0-31.0)
Thrombosis (children)				
All treatments	5	12	267	3.03 (0.32-8.35)
Anticoagulant	3	12	177	6.86 (3.32-11.56)
Aspirin + Anticoagulant	2	0	90	0.52 (0.09-3.0)
Controls	4	28	265	11.0 (8.0-15.0)
Thrombosis (anticoagulant dosage)				
Full	7	10	202	5.3 (2.3-9.4)
Prophylactic	5	12	338	2.34 (0.1-7.4)
Full + Aspirin	1	0	13	2.0 (2.0-15.0)
Prophylactic + Aspirin	2	0	129	0.34 (0.07-2.06)
Bleeding Complications (all patients)				
Aspirin	2	3	881	0.31 (0.0001-1.32)
Anticoagulant	14	136	600	28.0 (15.4-42.7)
Aspirin + Anticoagulant	5	14	220	12.13 (0.8-33.93)
Controls	8	40	669	6.1 (2.2-11.7)

*Only studies with available data for each subgroup were considered.

Discussion

From our findings, it is apparent that aspirin use after renal transplantation indeed reduces the occurrence of allograft thrombosis. Moreover, aspirin seems to be the most important agent for that purpose because anticoagulants alone could not demonstrate a better effect than the absence of prophylaxis, and their concomitant use with aspirin was also no better than aspirin alone. When focusing on only high-risk patients and children, the result was similar, although the only possible comparison was between anticoagulants alone and aspirin + anticoagulants, as there were no series assessing aspirin alone in these groups.

Counterintuitively, we were not able to uncover any difference between anticoagulant dosages because there were significant differences in the incidence of thrombosis between prophylactic and full doses, whether or not they were associated with aspirin. Furthermore, when associated with aspirin, prophylactic regimens showed better results than full doses of anticoagulants. We attribute this effect to the low number of series that could be reliably analyzed in this regard, and this question would need to be addressed in further clinical studies.

The complications of anticoagulant and antiplatelet use would inherently be related to bleeding. In this regard, we achieved the expected result that the likelihood of bleeding complications is much increased by anticoagulants when compared to aspirin alone or untreated controls. The 95% CI of the aspirin + anticoagulant group overlaps with both those of the anticoagulant and control groups, which

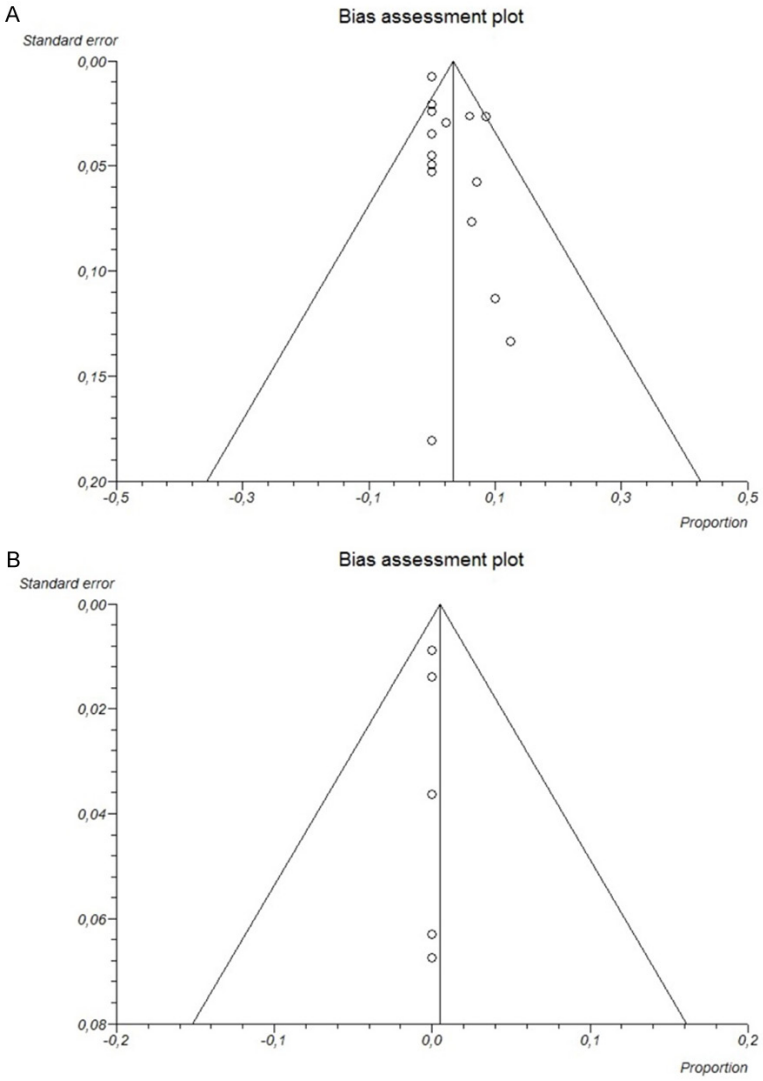

Figure 4. Bias assessment plot ("funnel plot") for the use of anticoagulant (A) and aspirin combined with anticoagulant (B).

could reflect a low number of included series (five) or perhaps a tendency to administer lower doses of heparin when combined with aspirin. We obtained bleeding rates with aspirin use alone that were actually lower than those of the controls, which could be related to report bias. Concerning the analysis of bleeding complications, our results may be limited by the fact that the search strategy that we used was not specifically directed to locate related articles.

There are still some shortcomings of our study. The current evaluation of the impacts of antiplatelet and anticoagulant agents on the occurrence of acute kidney allograft thrombosis is unfortunately poor and consists mainly of clinical series with inadequate control groups [16-37], consequently reaching only low levels of evidence.

In such a setting, we believe that a complementary and organized overview of the data presented by case series is meaningful, providing provisional conclusions that could aid clinical decision making while more definitive evidence is still to come. For that purpose, a systematic and initially wide search strategy had to be implemented within various databases, followed by the strict selection of related reports and the retrieval of adequate data. The reference lists were also scrutinized; thus, a low probability of having missed important series is expected. The effects of this scrutiny are further demonstrated by the assessment of the funnel plots, which had symmetrical inverted funnel shapes (**Figure 4**). However, the possibility of bias cannot be ruled out due to the high heterogeneity found in two of the treated groups. We cannot overemphasize that our findings, due to the inherent low level of the included studies, are subject to bias and therefore constitute no definite substitute for the data eventually provided by future RCTs.

To summarize the data from the case series and to achieve more reliable results, we used an analysis of proportions to measure the effects of and to compare interventions. Because high heterogeneity is inherent to the use of case series as the source of clinical and methodological data, a random effects model of proportional meta-analysis was chosen to acknowledge this fact and to minimize probable distortions derived from it. Recent research based on this approach in other fields has been published, and we perceive this as an interesting alternative that allows for new insights into

the currently available literature, enriched with statistical support that goes beyond a simple comparison of the incidence rates of outcomes among individual series.

To date, no prospective RCT has addressed aspirin use, and only two RCTs studied the use of heparin and LMWH, both limited to prophylactic dosages, in this setting. None of these studies could demonstrate any benefits from these interventions, although both failed to provide adequately sized samples and, thus, both lack the statistical power to disclose any eventual positive effect on reducing thrombotic complications [10, 11]. Therefore, we suggest to use anticoagulants, aspirin, or the combination, until more reliable evidence emerges from adequately designed and conducted RCTs.

In summary, our data suggests that anticoagulants, and aspirin, either alone or in association with an anticoagulant, seem to have a low frequency of acute allograft thrombosis after kidney transplantation, though higher hemorrhagic complication rates might occur when anticoagulants are used. From our systematic review, it is also evident that future research should focus on new well-designed RCTs that takes in consideration of patient heterogeneity, surgical variations and complications in adult and pediatric populations.

Disclosure of conflict of interest

None.

Abbreviations

CI, Confidence interval; LMWHs, Low-molecular-weight heparins; DVT, Deep venous thrombosis; RCT, Randomized clinical trial.

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SEARCH STRATEGY

((Kidney Transplantation) OR (Renal Transplantation) OR (Renal Transplantations) OR (Kidney Grafting) OR (Kidney Transplantations) OR ((Kidney OR Kidneys) AND ((Homologous Transplantations) OR Allograft OR Allografts OR Homograft OR Homografts OR (Homologous Transplantation) OR (Allogeneic Transplantation) OR (Allogeneic Transplantations) OR Allografting))) AND ((preventive therapy) OR prophylaxis OR (preventive measures) OR prevention OR control OR aspirin OR (Acetylsalicylic Acid) OR Alprostadil OR Dipyridamole OR Disintegrins OR Epoprostenol OR Iloprost OR Ketanserin OR Milrinone OR Pentoxifylline OR S-Nitrosoglutathione OR S-Nitrosothiols OR Ticlopidine OR Trapidil OR (Platelet Aggregation Inhibitors) OR (Blood Platelet Antiaggregants) OR (Platelet Antiaggregants) OR (Blood Platelet Aggregation Inhibitors) OR (Platelet Inhibitors) OR (Antiplatelet Agents) OR (Antiplatelet Drugs) OR (Platelet Antagonists) OR (Blood Platelet Antagonists) OR Anticoagulants OR (Anticoagulant Agents) OR (Anticoagulant Drugs) OR (Indirect Thrombin Inhibitors) OR Heparin OR (Unfractionated Heparin) OR (Heparinoid Acid) OR Liquaemin OR (Sodium Heparin) OR (Heparin Sodium) OR (alpha-Heparin) OR (alpha Heparin) OR (Heparin Cofactor II) OR Heparinoids OR dalteparin OR enoxaparin OR nadroparin OR LMWH OR (Low Molecular Weight Heparin) OR (Low-Molecular-Weight Heparin) OR 4-Hydroxycoumarins OR Acenocoumarol OR Ancrod OR (Antithrombin III) OR (Antithrombin Proteins) OR (beta 2- Glycoprotein I) OR (Blood Coagulation Factor Inhibitors) OR (Citric Acid) OR Coumarins OR (Dermatan Sulfate) OR Dextrans OR Dicumarol OR (Edetic Acid) OR (Ethyl Biscoumacetate) OR (Fibrin Fibrinogen Degradation Products) OR Gabexate OR Hirudins OR (Pentosan Sulfuric Polyester) OR Phenindione OR Phenprocoumon OR warfarin)