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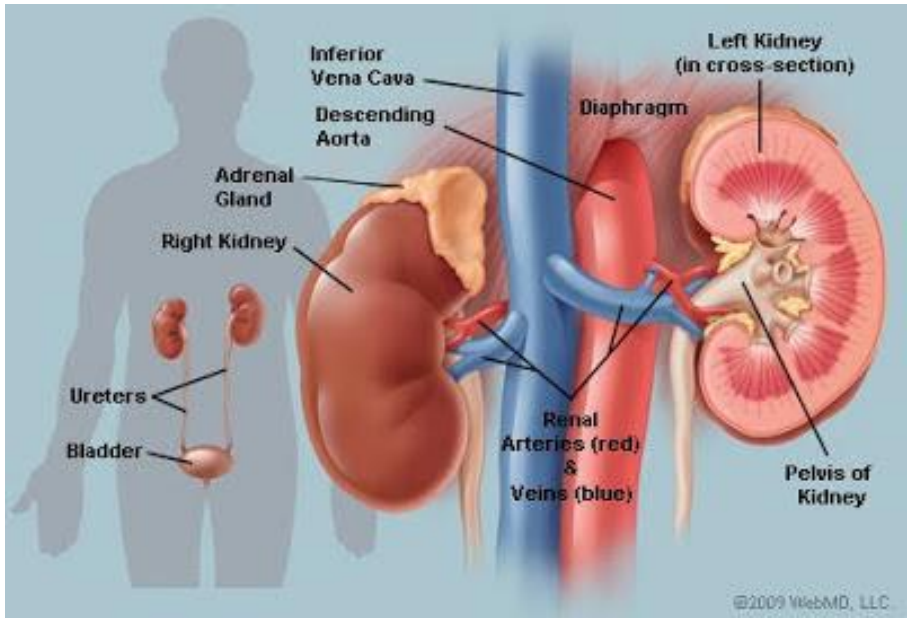
ÇOCUK

BÖBREK NAKLİ GÜNCELLEME SEMPOZYUMU - IV



Tromboz Riski Taşıyan Pediatrik Alıcıların Yönetimi

Hematolojik Yaklaşım

Prof. Dr. Yasemin Altuner Torun
İstinye Üniversitesi Tıp Fakültesi
Çocuk Hematoloji-Onkoloji BD

- Kronik böbrek hastalıkları tromboz ve hemostazda açısından risk taşır.
- GFR azalması venöz tromboz riskinde artar ile koreledir.
- Venoz tromboz gelişen KBY hastalarında yüksek mortalite gelişmektedir.
- VTE (DVT ve pulmoner emboli) yıllık 1000 de 0,75-2,69 arasında gözükmektedir
- Çocuk böbrek nakillerinde erken vasküler komplikasyonların başında tromboz gelir.
- Erken greft kayıplarının %35–50'sinden sorumludur.

Kronik Böbrek Hastalığında;

Hypercoagulation	Bleeding
Platelet activation	Platelet defects
Vascular endothelial damage	Impaired platelet-vessel wall activations
Microparticles and micro RNA	Vascular damage
Oxidative stress	Oxidative stress
Increased von Willebrand factor (vWF)	Defective binding of vWF to GPIIb/IIIa
Increased	Defective prostacyclin and NO synthesis
Increased factor XIIa and VIIa and thrombin formation	Anemia
Decreased protein C and protein S and anti-thrombin III	
Increased tissue factor and acute-phase proteins: fibrinogen, CRP	

Hypercoagulation	Bleeding
Decreased tissue plasminogen activator (tPA)	Increased tPA
Increased plasminogen activator inhibitor 1 (PAI1)	Decreased PAI1
Uremic toxins	Uremic toxins
Increased rennin-angiotensin-aldosterone (RAAS) activity	
Antiphospholipid antibodies	
- Pro-thrombotic gene mutations	Medications
- Factor V Leiden	- Beta-lactam antibiotics
- MTHFR	- Aspirin and NSAIDs
- 20210 prothrombin gene mutation	- Anticoagulants
- Protein C, S, and anti-thrombin deficiency	- Antiaggregants
Nephrotic syndrome	Amyloidosis, myeloma
Anemia	Anemia
Atherosclerosis: dyslipidemia, diabetes, arterial hypertension, peripheral vascular disease	Vasculitis
Corticosteroid treatment, cyclosporine A, cocaine	Corticosteroid treatment
Heparin-induced thrombocytopenia type II	
Hemodialysis and peritoneal dialysis	Hemodialysis and peritoneal dialysis

Risk faktörleri

Pediatrik vakalarda vasküler komplikasyon: %5–10 (erişkinlerde %1–5).

Renal ven trombozu en sık görülür.

2 yaş altı çocuklarda risk çok daha yüksektir.

Donör: kadavra böbrek, yaş uyumsuzluğu, genç verici yaşı (< 5 yıl), uzun iskemi süresi.

Alıcı: verici-alıcı damar uyumsuzluğu, genetik trombofili, antifosfolipid sendromu, genç alıcı yaşı(< 2 yaş), pozitif aile öyküsü

Cerrahi: anastomoz zorluğu, hipotansiyon.

Risk factors for the development of venous thrombosis in pediatric patients

Most common risk factors in pediatric patients
Central venous catheter
Congenital heart disease
Immobilization
Obesity
Estrogen-containing contraceptives
Malignancy (eg, leukemia)
Prematurity
Surgery, especially orthopedic
Systemic infection
Trauma
Other risk factors
Heart failure
Inflammatory bowel disease
Certain cancer therapies (eg, asparaginase)
Personal or family history of thrombosis
Inherited thrombophilia: ▪ Factor V Leiden mutation ▪ Prothrombin G20210A mutation ▪ Protein S deficiency ▪ Protein C deficiency ▪ Antithrombin deficiency
Antiphospholipid syndrome
Nephrotic syndrome
Pregnancy
Severe liver disease
Vascular abnormalities or malformations

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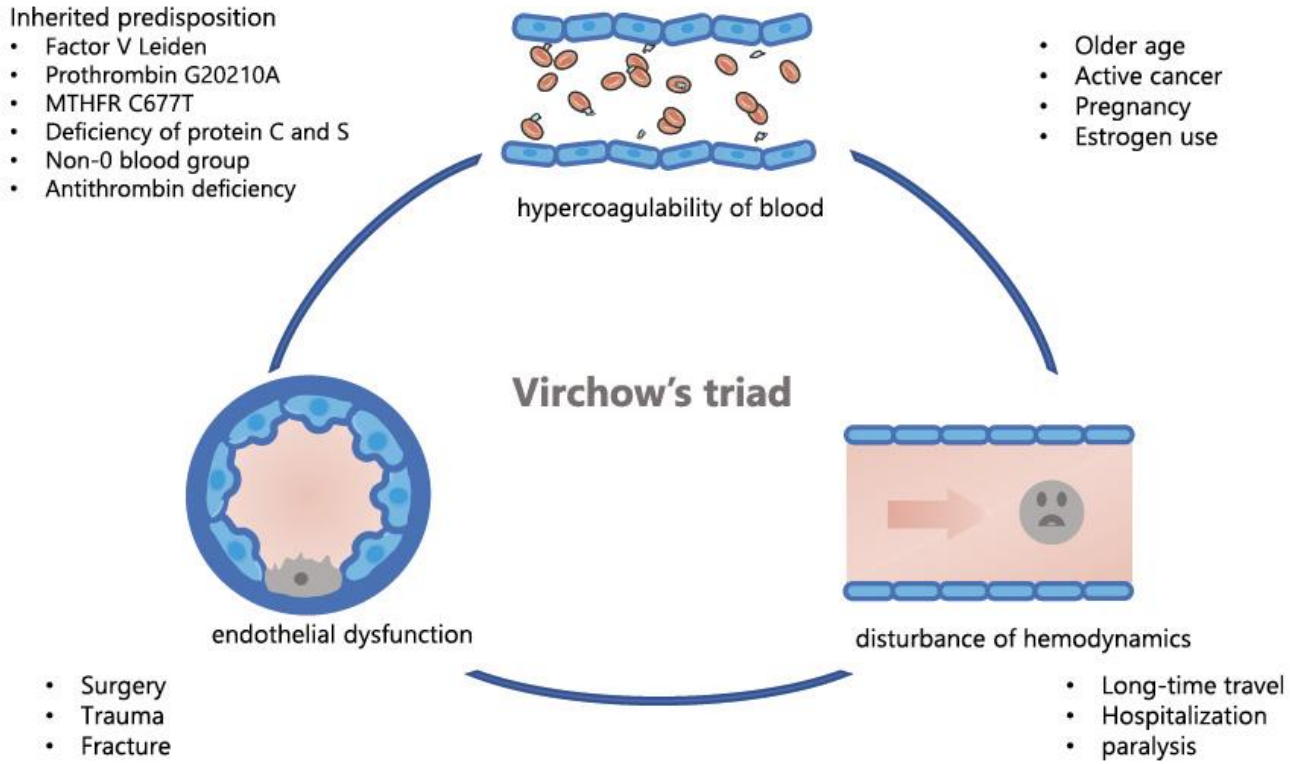
From: **Venous Thromboembolism in Kidney Diseases and Genetic Predisposition**



Kidney Dis. 2022;8(3):181-189. doi:10.1159/000523777

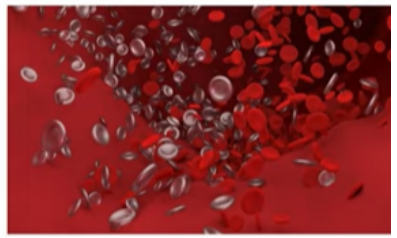
Genetik trombofili faktörleri

❖Prokoagülan ve antikoagülan sistem normalde denge halindedir.

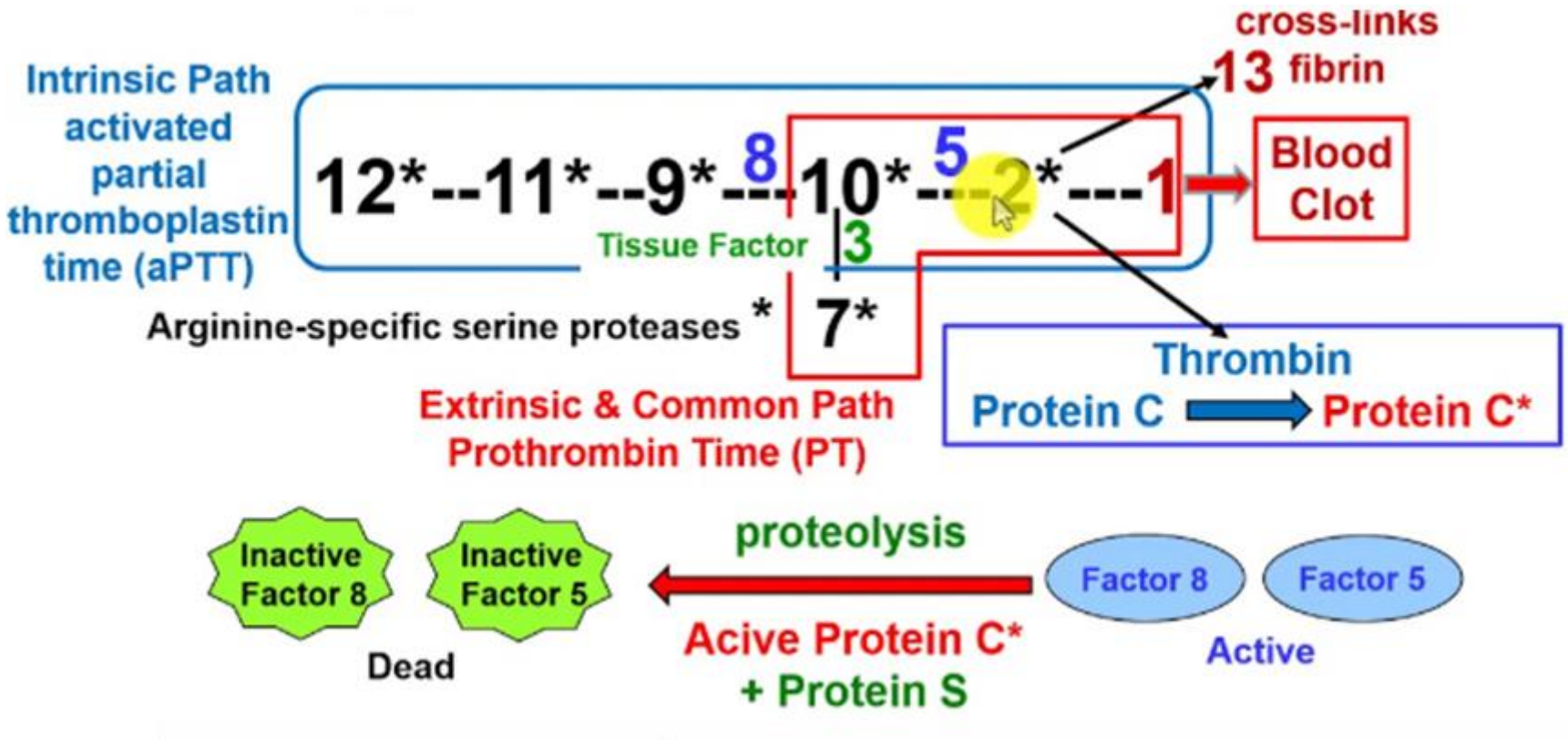
Faktör V Leiden Mutasyonu

Factor V Leiden (FVL): Introduction

- *Autosomal dominant* hematologic condition involving an increased risk of **thrombosis**
- Caused by a point mutation on **Factor V**
  - *FVL* mutations
    - R506Q mutation
  - Incomplete penetrance
- Most common inherited thrombophilic condition among Caucasians
  - Some estimates state upwards of 3-7% of Caucasians are heterozygotes
  - May be as little as 5% of heterozygotes will actually have issues with VTE

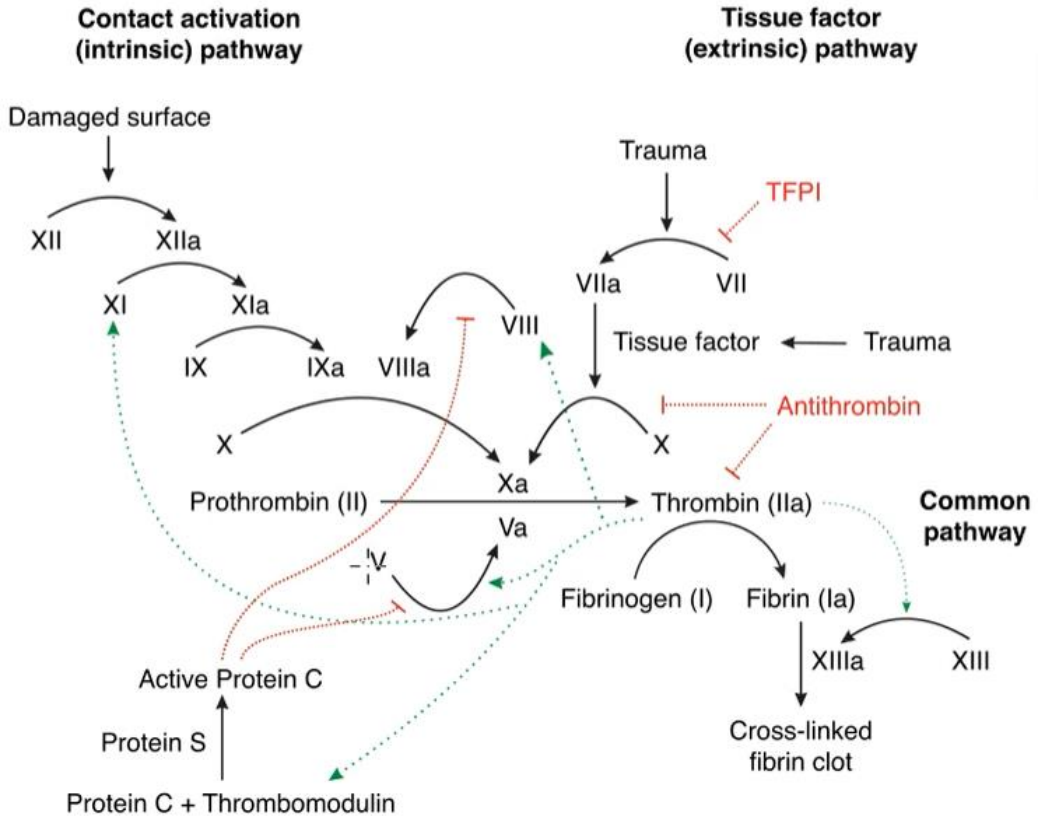


Heterozygous individuals are at a 7-fold increased risk of thrombosis
Homozygous individuals are at a 20-fold increased risk of thrombosis


cross-links
13 fibrin
Intrinsic Path
activated
partial
thromboplastin
time (aPTT)
12*--11*--9*--8--10*--5--2*---1
Blood
Clot
Tissue Factor
3
Arginine-specific serine proteases *
7*
Thrombin
Protein C
Protein C*
Extrinsic & Common Path
Prothrombin Time (PT)
proteolysis
Inactive
Factor 8
Inactive
Factor 5
Factor 8
Factor 5
Dead
Acive Protein C*
+ Protein S
Active

Protrombin G20210 Mutasyonu

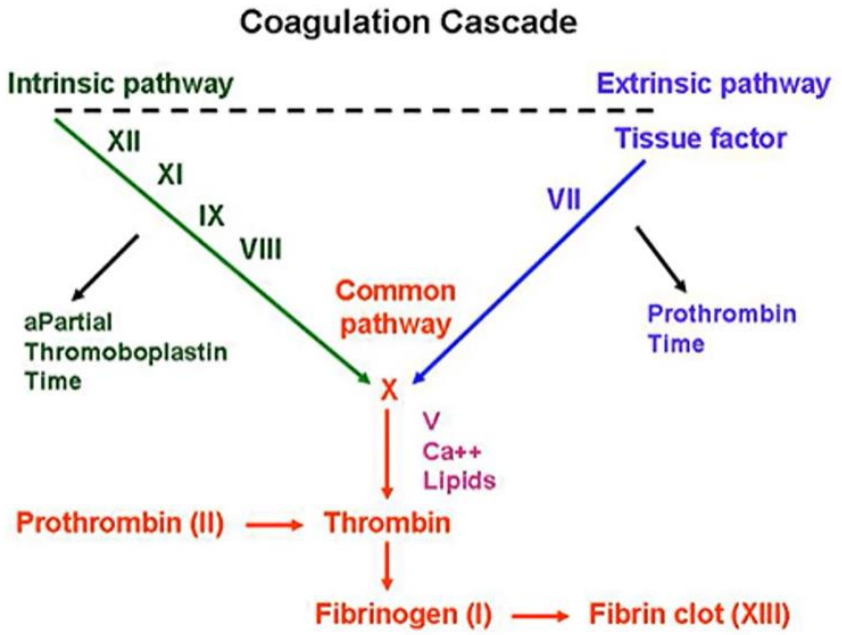
- Protrombin KC de sentezlenir. İnaktif formdadır.
- Trombin ve fibrinojen üzerinden hemostazı sağlar.
- PT G20210 tek nükleotid mutasyonu protein kod sekans üzerinde etkisi yoktur. Herhangi bir yapısal değişiklik olmadan protrombin üertimin arttırır.
- Tek başına 4 kat; Faktör V leiden mutasyonu ile birlikte ise 20 kat VTE riskini artırır.

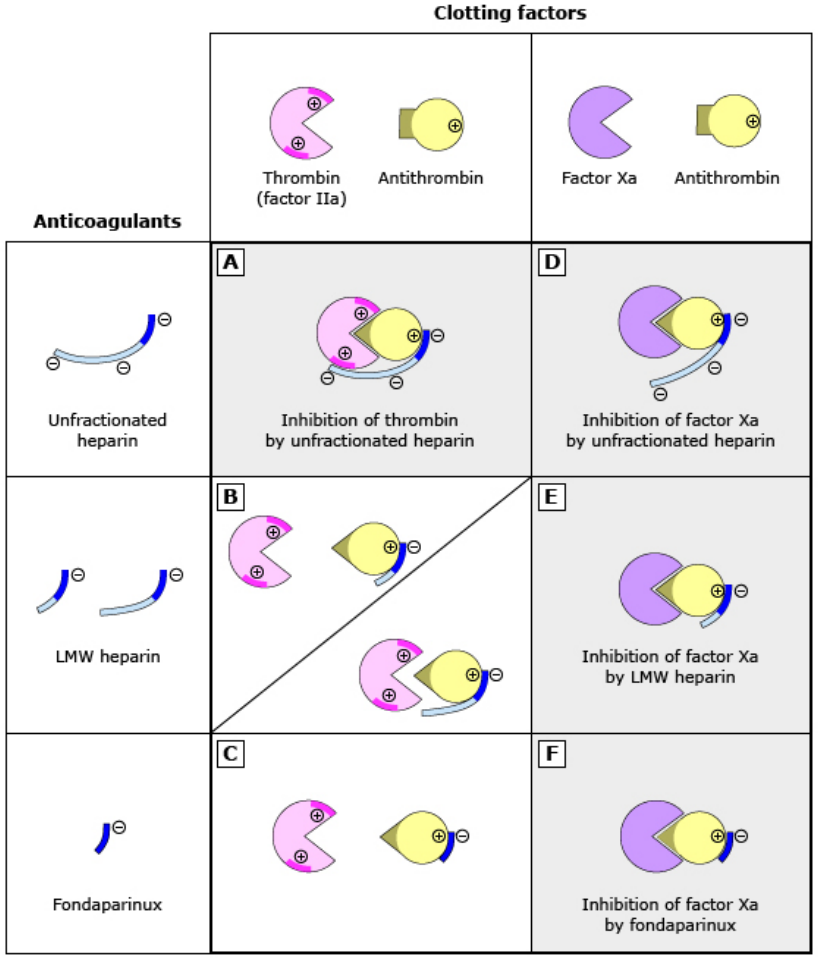


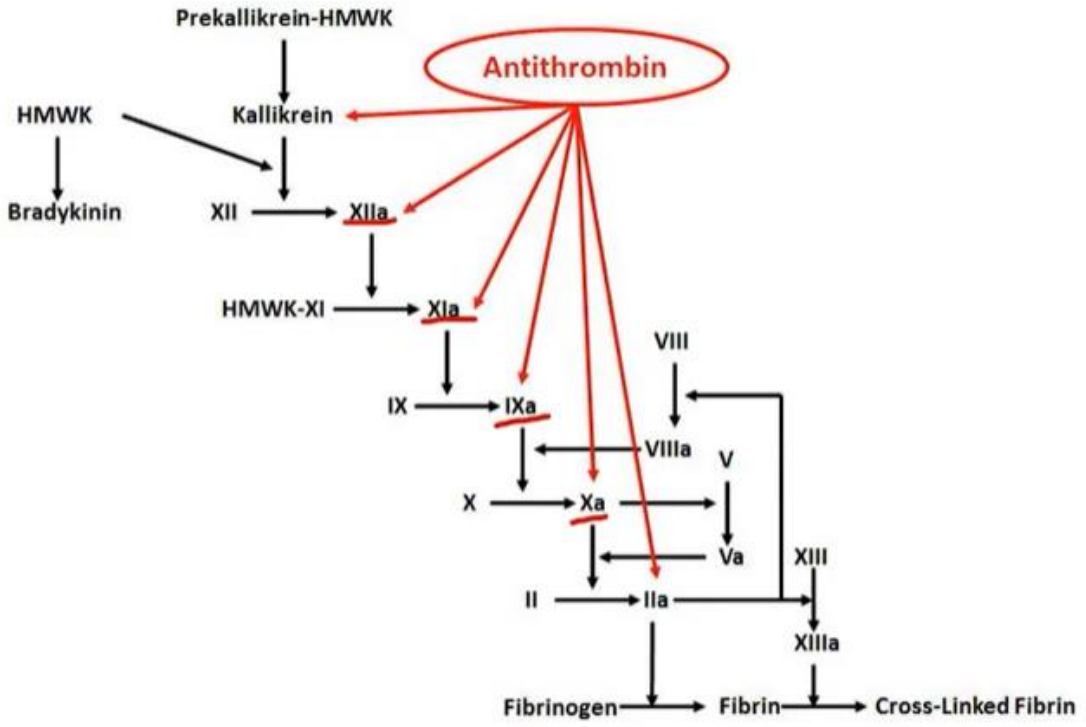
Antitrombin III eksikliği

AT trombini inhibe eder. Böylece koagülasyon yolunu inhibe etmiş olur.

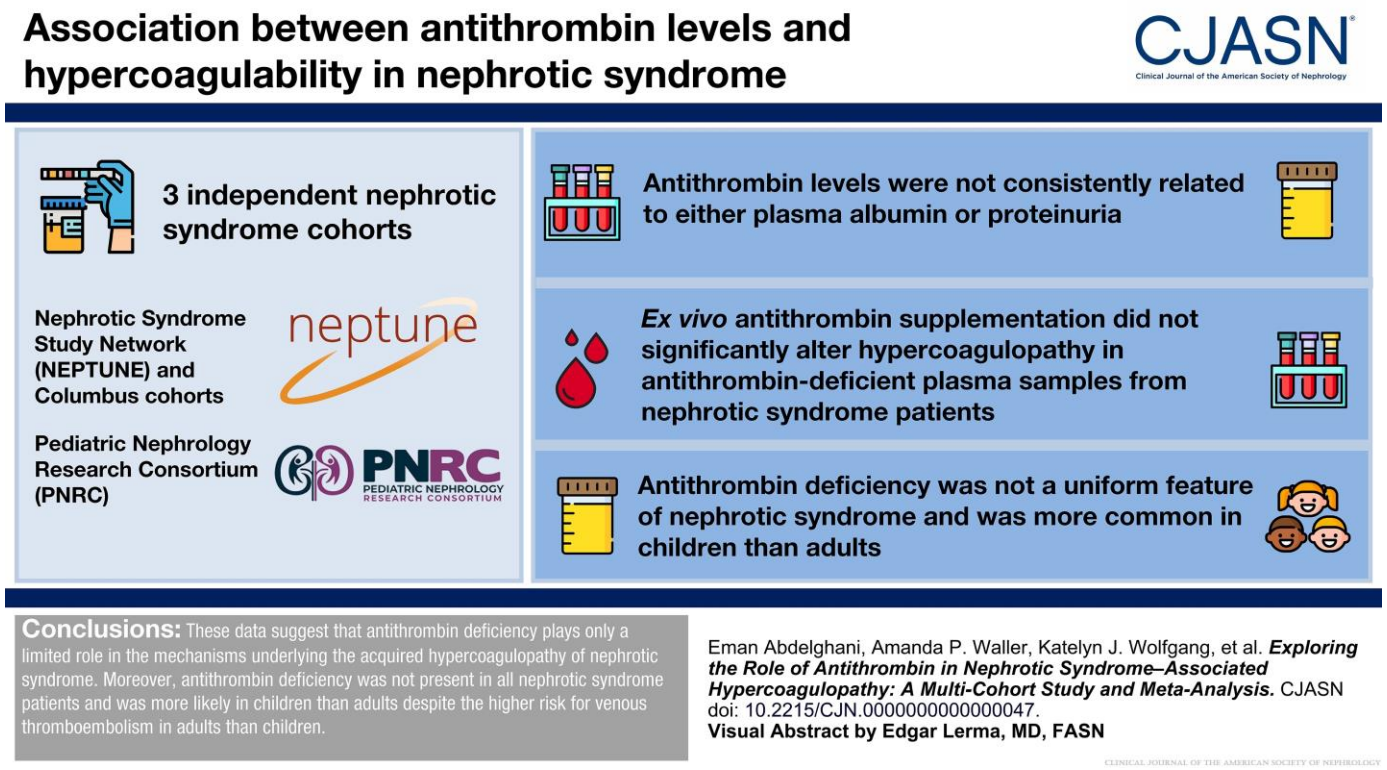
ATIII antikoagülan aktivitesi heparan sülfat tarafından stimule edildiğinde artar.







Schematic representation of anticoagulant mechanisms. Heparins bind to antithrombin (formerly called antithrombin III) and induce a conformational change that makes antithrombin an efficient inactivator of coagulation factors. Unfractionated heparin inhibits thrombin (factor IIa) by forming a ternary complex. The inhibitory effect of LMW heparins on thrombin is variable, with longer chain LMW heparins such as tinzaparin having greater inhibition than the shorter chain LMW heparins such as enoxaparin. All heparins and fondaparinux efficiently inactivate factor Xa. Refer to UpToDate for details regarding the use of heparins and fondaparinux.



Wolters Kluwer

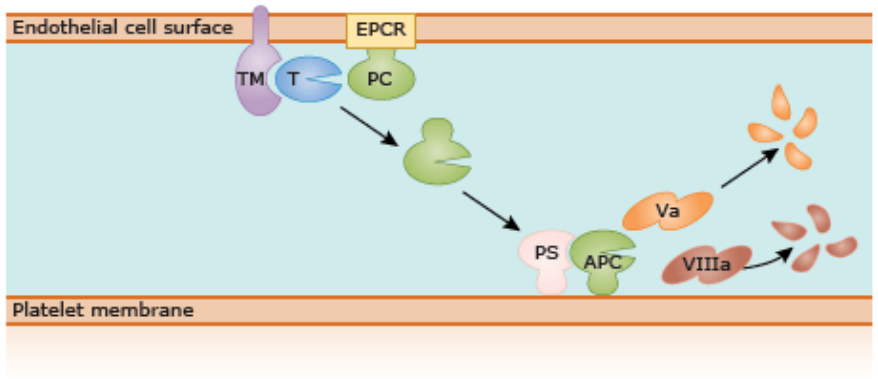
Exploring the Role of Antithrombin in Nephrotic Syndrome–Associated Hypercoagulopathy: A Multi-Cohort Study and Meta-Analysis

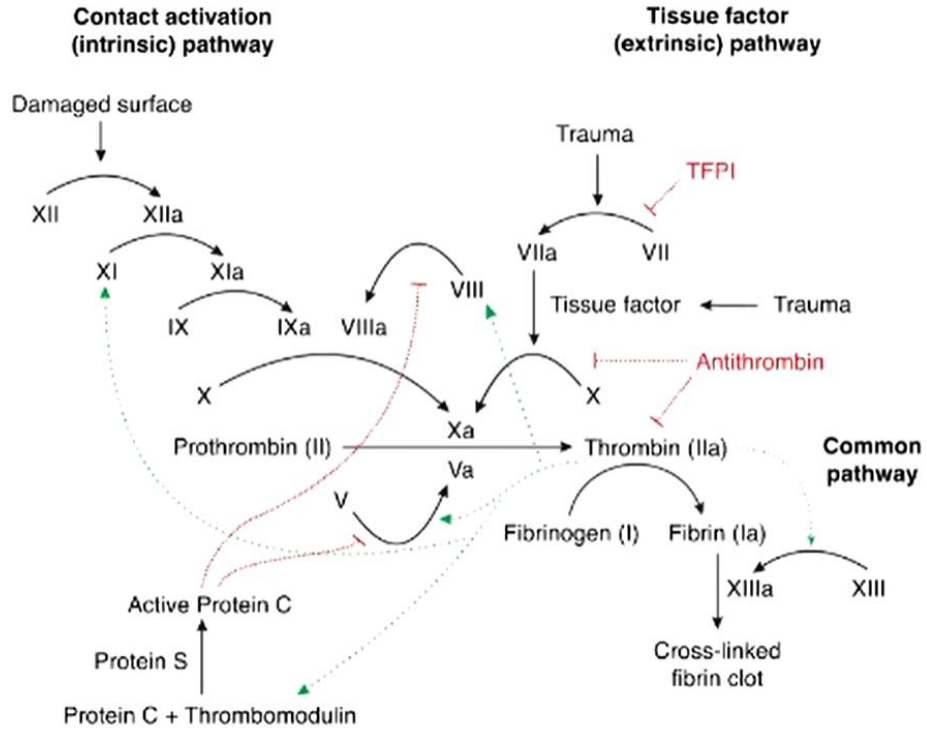
Abdelghani, Eman; Waller, Amanda P.; Wolfgang, Katelyn J.; Stanek, Joseph R.; Parikh, Samir V.; Rovin, Brad H.; Smoyer, William E.; Kerlin, Bryce A.; the PNRC Investigators,*; the NEPTUNE Investigators**; the PNRC Investigators,*; the NEPTUNE Investigators**

Clinical Journal of the American Society of Nephrology18(2):234-244, February 2023.

doi: 10.2215/CJN.0000000000000047

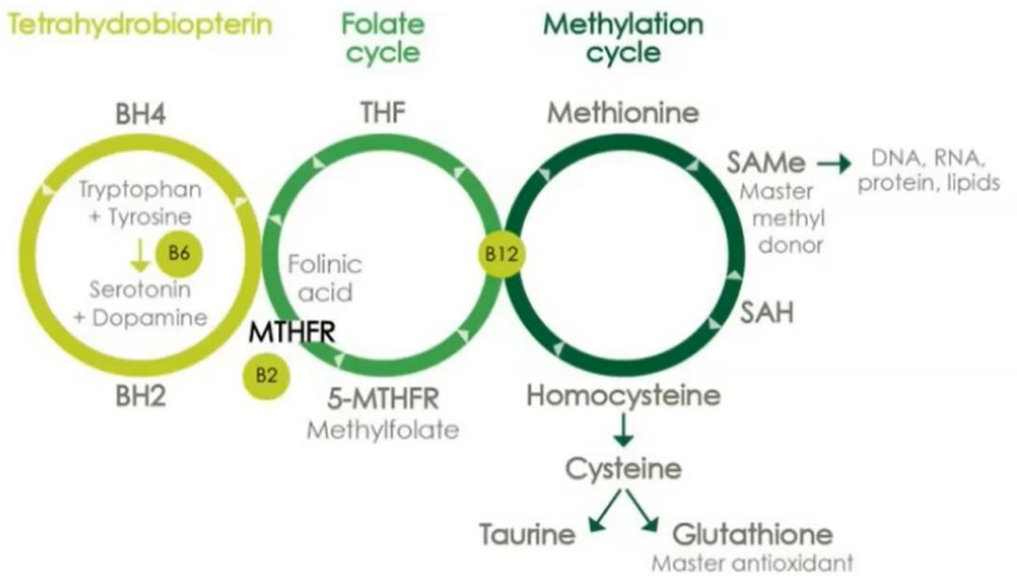
Protein C ve Protein S eksikliği

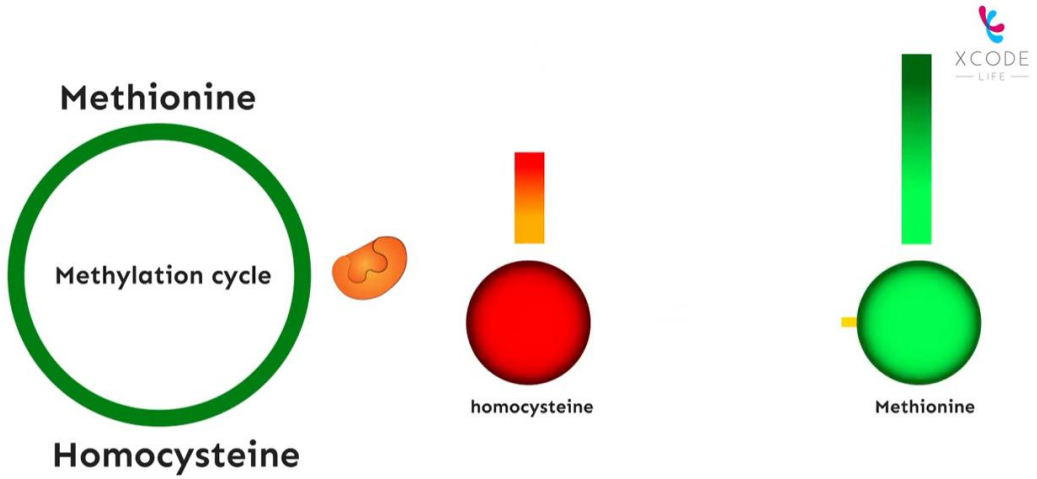




Protein C is activated on the endothelial cell membrane, where it is anchored by the endothelial protein C receptor. Activated protein C and protein S assemble on the platelet membrane. Protein S acts as a cofactor for protein C in proteolytically cleaving activated factors V and VIII (factors Va and VIIIa).

MTHFR c677T Mutasyonu





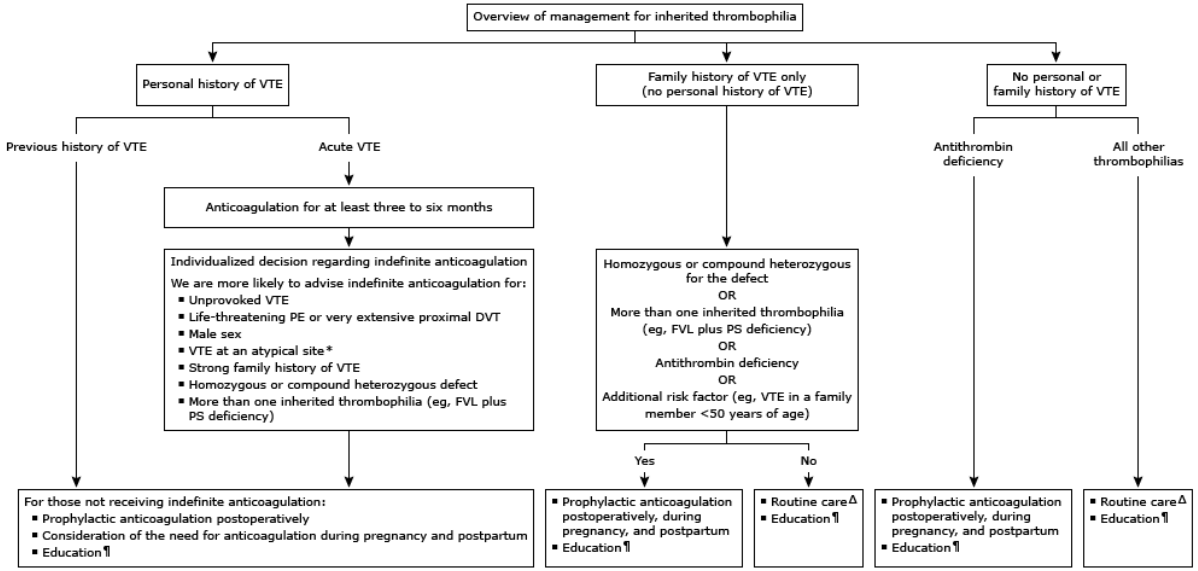
MTHFR C677T polimorfizmi enzim aktivitesini azaltır ve hiperhomosisteinemiyeneden olarak tromboza yol açar.

Genel olarak bakıldığında;

Prevalence of inherited thrombophilia and associated VTE risk

Thrombophilia	Prevalence (%)		Relative risk of a first episode of VTE compared with controls
	General population	Individuals with VTE	
AT deficiency	0.02 to 0.2%	1 to 7%	16-fold increased
Protein C deficiency	0.2 to 0.5%	2 to 5%	7-fold increased
Protein S deficiency	Unknown	1%	5-fold increased
Factor V Leiden*	2 to 5%	12 to 18%	4- to 5-fold increased
Prothrombin G20210A*	2%	5 to 8%	3- to 4-fold increased

Overview of management for patients with inherited thrombophilia



This algorithm applies to individuals with known inherited thrombophilia (factor V Leiden or prothrombin G20210A; protein S, protein C, or AT deficiency). It is a general overview of our approach and does not substitute for clinical judgment regarding the risks and benefits of anticoagulation for an individual patient. Consultation with a hematologist may be appropriate.

- Individuals with AT deficiency may have heparin resistance, and, if they require anticoagulation, it may be necessary to use a nonheparin anticoagulant and/or to provide AT replacement along with appropriate doses of heparin. Refer to the UpToDate topic on AT deficiency for details.
- Routine obstetrical care includes mechanical thromboprophylaxis and/or anticoagulation for women undergoing cesarean delivery. Routine postoperative care includes thromboprophylaxis in most cases; individuals with thrombophilia may require more aggressive prophylaxis than those without. Refer to UpToDate for indications for thrombophilia testing and other aspects of obstetric and postoperative management.
- Routine perioperative care includes thromboprophylaxis based on the procedure-associated risk of VTE.
- Atypical sites of VTE include mesenteric, portal, and cerebral veins.

VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; FVL: factor V Leiden mutation; PS: protein S; AT: antithrombin.

* Atypical sites of VTE include mesenteric, portal, and cerebral veins.

¶ All individuals with inherited thrombophilia should have education regarding signs and symptoms of VTE, attention to prophylaxis in high-risk situations (eg, certain surgeries, pregnancy, and postpartum for some women), risk assessment for first-degree relatives, and, for women, avoidance of estrogen-containing contraceptives.

Δ Routine care includes appropriate thromboprophylaxis for high-risk surgical procedures based on the procedure-associated risk of VTE.

Böbrek nakli özelinde;

- Böbrek nakillerindeki başarısızlığın %34'ü venöz tromboza bağlıdır.
- US renal database kayıtlarında nakil sonrası 1.5-3 yılda tromboz isidansı: 2.9 epizot/1000 hasta başı
- Kadın cinsiyet, sağ böbrek, ve otozomal polikistik böbrek hastalığında trombotik olay daha fazladır.
- Nakil sonrası bir yılda GFR <30 mL7dk/1.73 m2 olduğunda VTE 2.05 kat daha fazla görülme şansı vardır. Erken transplant kaybında en önemli genetik faktör faktör V leiden mutasyonudur.
- Birkaç mutasyon birlikteliği böbrek kayıp oranını daha fazla arttırmaktadır

Table 1. Risk factors for the development of VTE in kidney diseases

Risk factors	References
NS and VTE	[33–36]
MN	
FSGS	
Lupus nephritis	
Low albumin levels	
Sepsis	
Intravenous corticosteroid use	
BMI ≥30 kg/m^2	
AKI	
Female sex	
CKD and VTE	[43]
Immobilization	
Surgery	
Prothrombin G20210A	
Malignancy	
Factor V Leiden	
Low eGFR	
ESRD and VTE	[46, 47]
Receiving hemodialysis than patients with peritoneal dialysis	
Toxic nephropathy as the cause of ESRD	
Atrial fibrillation	
Female sex	
Kidney transplantation and VTE	[51, 53–54]
Recipient female gender	
eGFR less than 30 mL/min/1.73 m^2	
Right kidneys	
The ADPKD group	

Helantera I, Raiha J, Finne P, Lempinen M. Early failure of kidney transplants in the current era-a national cohort study. Transpl Int. 2018;31((8)):880–6. doi: 10.1111/tri.13115.

Abbott KC, Cruess DF, Agodoa LY, Sawyers ES, Tveit DP. Early renal insufficiency and late venous thromboembolism after renal transplantation in the United States. Am J Kidney Dis. 2004;43((1)):120–30. doi: 10.1053/j.ajkd.2003.08.047.

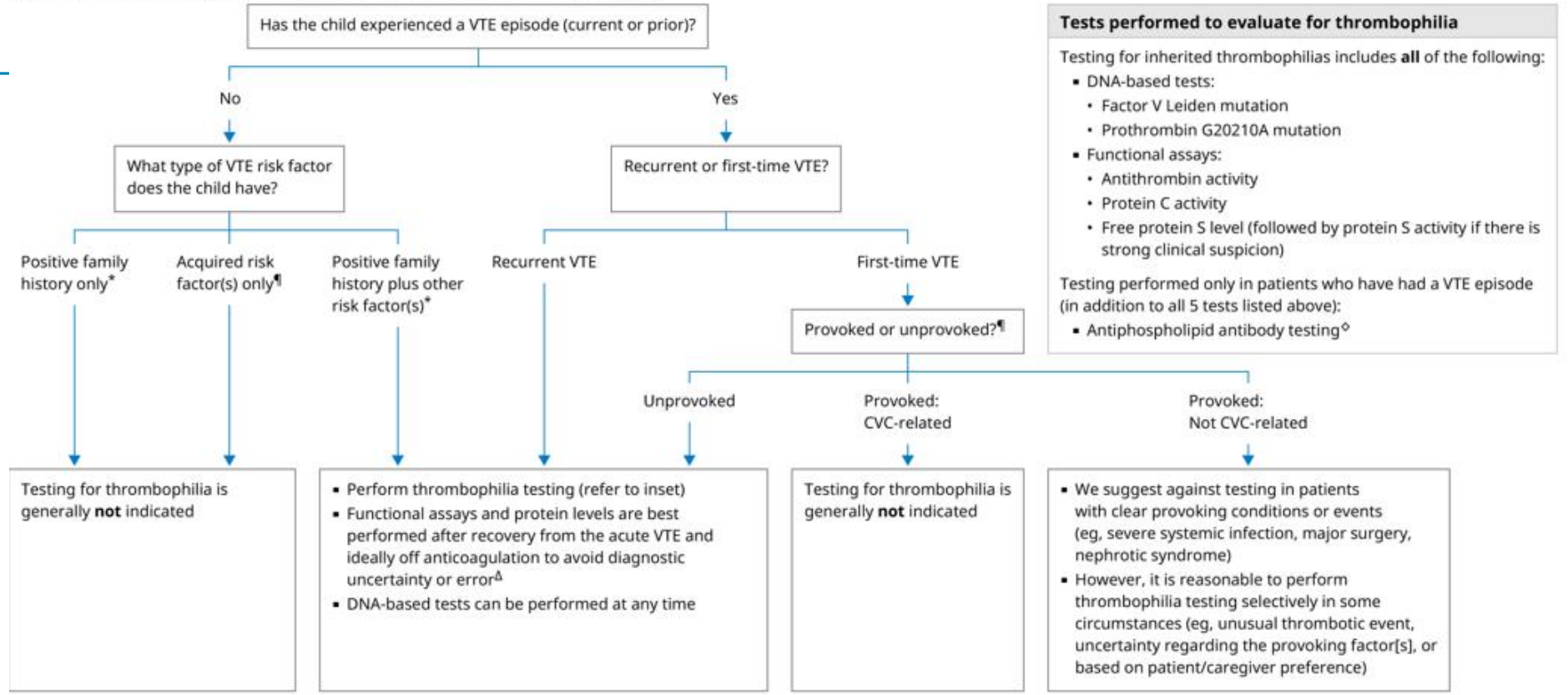
Lam NN, Garg AX, Knoll GA, Kim SJ, Lentine KL, McArthur E, et al. Venous thromboembolism and the risk of death and graft loss in kidney transplant recipients. Am J Nephrol. 2017;46((4)):343–54. doi: 10.1159/000480304.

Tüm alıcılarda genetik test yapalım mı?

Böbrek nakli yapılacak 100 hastada trombofili taraması yapılmış. Preoperatif taramanın ek bir faydası görülmemiştir. Sonuç olarak VTE hikayesi ve aile öyküsü olması durumunda tarama yapılması ön görülmüştür.

Bock ME, Bobrowski AE, Bhat R. Utility of thrombophilia screening in pediatric renal transplant recipients. Pediatr Transplant. 2019;23((1)):e13314.

Approach to thrombophilia testing in pediatric patients with or at risk for venous thromboembolism (VTE)



This figure summarizes our suggested approach to thrombophilia testing in children and adolescents. Thrombophilia testing may be under consideration in children currently or previously diagnosed with a VTE episode or in those with risk factors for VTE (including family history of VTE and/or acquired risk factors). This algorithm is intended for use in conjunction with other UpToDate content. Refer to UpToDate's topic on thrombophilia testing in children for additional details and for the rationale behind this approach.

APS: antiphospholipid syndrome; CVC: central venous catheter; DNA: deoxyribonucleic acid; DOAC: direct oral anticoagulant; Ig: immunoglobulin; IT: inherited thrombophilia; VTE: venous thromboembolism.

* For children and adolescents who have a strong family history of VTE or IT (eg, VTE in a first-degree relative <40 years old), we suggest IT testing only if there are additional risk factors or underlying medical problems that place the child or adolescent at risk for developing thrombosis (cancer, CVC, trauma, major surgery, currently using or considering an estrogen-containing contraceptive).

¶ Well-established acquired risk factors for thrombosis in children include CVCs, infection, cancer, major surgery or trauma, prolonged immobilization, history of surgical or transcatheter repair of congenital heart disease, nephrotic syndrome, inflammatory disorders, and others. Most VTE episodes in children are with associated with 1 or more of these provoking risk factors. This is referred to as "provoked" VTE. Unprovoked VTE (ie, VTE occurring in the absence of a clear provoking factor) is rare in childhood.

△ The exception is the patient in whom APS is clinically suspected (eg, adolescent patient with unprovoked or recurrent thrombotic episodes, immune mediated cytopenias, and/or underlying autoimmune condition). For such patients, we suggest testing for antiphospholipid antibodies earlier in the course since the results may impact treatment decisions (eg, warfarin is generally preferred over DOACs for treatment of VTE in patients with APS).

◇ Antiphospholipid antibody testing includes immunoassays for IgG and IgM antibodies to cardiolipin and beta2-glycoprotein I and functional assay for the lupus anticoagulant phenomenon. For further details, refer to separate UpToDate content on diagnosing APS.

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Original Clinical Science—General

Intra-abdominal Complications After Pediatric Kidney Transplantation: Incidence and Risk Factors

Amir Taher,[1] Benjamin Zhu,[1] Sophia Ma,[1] Albert Shun, MBBS,[1,2] and Anne Maria Durkan, MD[1,2]

Background. The incidence and types of intra-abdominal complications after pediatric transplantation are not well established, and specific risk groups have not been clearly identified. **Methods.** A retrospective chart review of all pediatric transplant recipients between 1995 and 2016 was undertaken. Intra-abdominal complications were grouped into 4 categories: fluid collections, gastrointestinal, vascular, and urogenital. Donor, recipient, and transplant characteristics were evaluated using univariate and multivariate logistic regressions. **Results.** There were 146 transplants meeting the inclusion criteria. The mean follow-up time was 4.6 ± 3.7 years (range, 0.3–18 y). The mean weight at transplantation was 31.5 ± 16.5 kg (range, 9–78), with 24 (16%) recipients being <15 kg and 23% younger than 5 years. Thirty-four (23%) patients had previous abdominal surgery. There were 32 complications identified in 27 (18%) transplant recipients. Fluid collections requiring surgical drainage developed in 9 (6.2%), gastrointestinal surgical complications in 12 (8.2%), vascular complications in 5 (3.5%), and urogenital complications in 6 (4.1%). There were only 3 graft losses due to abdominal complications, all after renal vein thrombosis. Weight <15 kg at the time of transplant ($P = 0.016$), previous abdominal surgery ($P = 0.047$), and intraperitoneal surgical technique ($P = 0.008$) were risk factors in the univariate analysis using Cox regression models, whereas only weight <15 kg ($P = 0.003$) and previous abdominal surgery ($P = 0.008$) were retained in the multivariate analysis. **Conclusions.** Intraabdominal complications occur in almost 1 in 5 pediatric renal transplant recipients. Weight <15 kg and previous abdominal surgery are risk factors for developing such complications.

(*Transplantation* 2019;103:1234–1239)

Thromboprophylaxis after kidney transplantation in children: Ten-year experience of a single Brazilian center

Julia Maimone Beatrice [1], Marcelo Straus Takahashi [2], Daniele Martins Celeste [1], Andreia Watanabe [3], Vera Hermina Kalika Koch [3], Jorge David Aivazoglou Carneiro [1]

Affiliations + expand

PMID: 34324760 DOI: 10.1111/petr.14101

Abstract

Background: Kidney transplantation is the gold standard treatment for children with end-stage chronic kidney disease. Graft thrombosis is an important cause of graft failure, with high morbidity, mortality, and impact on quality of life and to the health system. The role of thromboprophylaxis in this setting is still uncertain. We describe the demographic characteristics and thrombotic risk factors in pediatric renal transplant recipients, determining the rate of renal graft thrombosis, and discuss the role of thromboprophylaxis.

Methods: This retrospective study reviewed 96 pediatric renal transplantations between 2008 and 2017 in a single hospital. Patients were assigned to one of two groups: children who did not receive thromboprophylaxis after transplantation and those who did. We reported their characteristics, comparing the incidence of graft thrombosis and hemorrhagic complications between the groups.

Results: Forty-nine patients (51%) received thromboprophylaxis. Thrombosis occurred in 5 patients who did not receive thromboprophylaxis (5.2%) compared with none in the group that did ($p = .025$). In all patients, renal graft thrombosis resulted in early graft loss. Thirteen patients had hemorrhagic complications. Seven were unrelated to pharmacological thromboprophylaxis (2 major, 1 moderate, and 4 minor bleeding, which either did not receive thromboprophylaxis or had bleeding prior to thromboprophylaxis), while six occurred during heparinization (2 major, 1 moderate, and 3 minor bleeding). There was no significant difference in the rate of hemorrhagic complications between the groups ($p = .105$).

Conclusions: The rate of renal graft thrombosis was 5.2%. Thrombosis remains an important cause of early graft loss. Thromboprophylaxis was associated with a reduction in graft thrombosis without increased risk of bleeding.

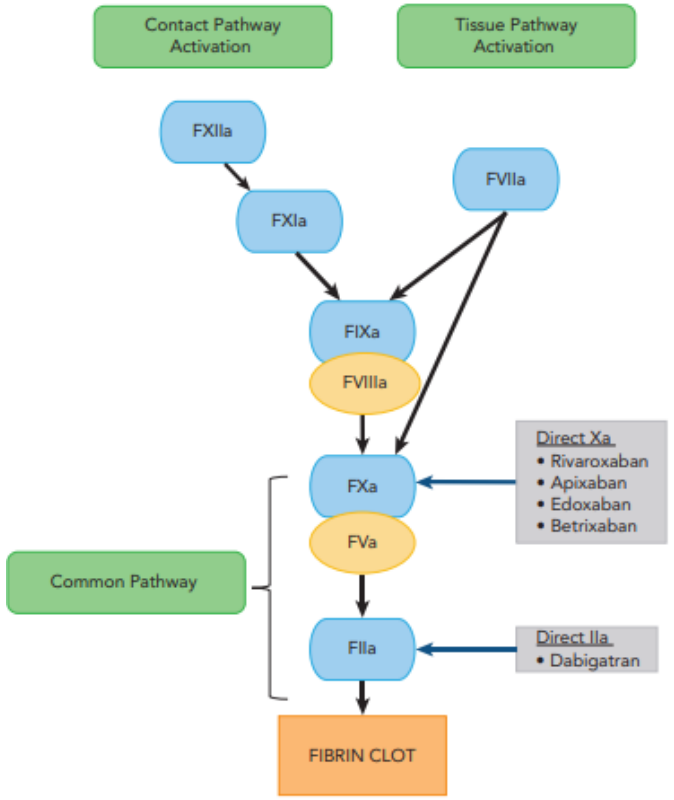
Tromboproflaksi için ne kullanalım?

Unfractionated Heparin vs LMWH

Unfractionated Heparin		Low Molecular Weight Heparin (LMWH)
Activates anti-thrombin III which forms a complex inhibiting clotting factors IIa and Xa, as well as IX, XI, XII	Mechanism of action	Examples include *enoxaparin, tinzaparin* *Fondaparinux* is a synthetic derivative of LMWH Activates anti-thrombin III which forms a complex inhibiting clotting factor Xa
Intravenous (IV)	Mode of administration	Subcutaneous (SC)
Shorter (~1 hour)	Half-life	Longer (~3-6 hours) Fondaparinux ~17-21 hours
Bleeding, osteoporosis, thrombocytopenia (HIT), hyperkalemia (due to hypoaldosteronism)	Side effects	Bleeding, osteoporosis, thrombocytopenia (HIT), hyperkalemia (due to hypoaldosteronism)
Rapidly reversible by protamine sulphate Useful in situations where rapid reversal required	Reversibility	Partially reversible by protamine sulphate
Useful in renal failure	Use in renal failure	Use with caution/avoid if GFR <30 due to increased risk of bleeding
Higher risk compared to LMWH	Risk of HIT	Lower risk of HIT No risk of HIT when using fondaparinux

HIT – Heparin-induced thrombocytopenia

GRAM PROJECT



Benefits of anticoagulation prophylaxis in children undergoing kidney transplant: systematic review and meta-analysis

Ahmad H. Al-Huniti[1] | Caroline Malcolmson[2] | Valerie Langlois[3] | Ashlene M. McKay[4] | Armando Lorenzo[5] | Zhen Wang[6] | Suzan Williams[2] | Chia Wei Teoh[4] | Leonardo R. Brandão[2,7]

[1]Division of Pediatric Hematology/Oncology, Mayo Clinic, Rochester, Minnesota, USA

[2]Division of Pediatric Haematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada

[3]Division of Pediatric Nephrology, McGill University Health Centre, Montreal, Quebec, Canada

[4]Division of Pediatric Nephrology, The Hospital for Sick Children, Toronto, Ontario, Canada

[5]Division of Pediatric Urology, The Hospital for Sick Children, Toronto, Ontario, Canada

[6]Department of Health Care Delivery Research, Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota, USA

[7]Department of Paediatrics, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

Correspondence
Ahmad H. Al-Huniti, Division of Pediatric Hematology/Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA.
Email: Al-Huniti.Ahmad@mayo.edu

Abstract

Background: Graft thrombosis is a preventable cause of early allograft loss after pediatric kidney transplant, but the role of primary thromboprophylaxis is uncertain.

Objectives: This study aimed to determine the effectiveness and safety of thromboprophylaxis in preventing graft thrombosis among children (0-21 years) undergoing kidney transplant.

Methods: We performed a systematic literature review of MEDLINE, Embase, and Cochrane Libraries from inception until September 2024. The primary outcome assessed by meta-analysis was graft thrombosis, and the secondary outcome was major bleeding (per International Society on Thrombosis and Haemostasis criteria).

Results: Twenty-five observational studies (21 retrospective and 4 prospective) describing 2094 patients (1659 cases and 435 controls) met eligibility criteria. Thromboprophylaxis was used universally (ie, all kidney recipients in the study) in 64% (1055/1659) or only in high-risk patients (eg, recipient weight <20 kg and age <5 years) in 36% (604/1659). Compared with no preventive measures for thrombosis, thromboprophylaxis was associated with reduced risk of graft thrombosis (odds ratio, 0.31; 95% CI, 0.18-0.53). Subgroup analyses of heparinoid-only, universal thromboprophylaxis, and high risk only protocols revealed similar findings. Thromboprophylaxis was not associated with increased risk of bleeding resulting in surgical exploration or graft loss. The overall risk of bias was moderate. Studies showed high clinical and methodologic heterogeneity in study populations and thromboprophylaxis protocols.

Conclusion: Primary thromboprophylaxis appears effective in preventing kidney graft loss from vascular thrombosis in pediatric recipients. This benefit may be offset by the risk of bleeding, although clarity on bleeding risk factors is lacking. We identified

North American Pediatric Renal Trials and Collaborative (1987 -2017) renovasküler tromboz oranı %10.5

United States Renal Data System(1995-2014), renovasküler tromboz oranı transplant sonrası ilk bir yılda %18.6

Standart proflaktik doz UFH: 10 unite/kg/saat enoksiparin: 0.5 - 0.75 mg/kg günde 2 kez

Tromboz

Tromboproflaksi grubunda graft trombozu 614 hastanın 24 ‘ünde (%3.9) – graft kaybı 23 hastada görüldü.

Standart bakım grubunda 435 hastanın 56’sında(%12) tromboz ve 55 hastada graft kaybı görüldü.

Kanama %15.4 (867 hastada)--%15.4 Eritrosit transfüzyonu-%2 cerrahi eksplorasyon%0.8 graft kaybı (3 hasta) yaşandı.

Tromboflaksi grubunda bir hastada fatal kanama gözlendi.

TABLE 4 Thromboprophylactic regimens used in the included studies.

Study	Thromboprophylactic regimen
Broyer et al., 1991 [35]	Enoxaparin started 24 h after grafting in the absence of any bleeding, at a dose of 0.4 mg/kg by subcutaneous injection every 12 h. Subsequently, the dosage was adjusted according to the anti-Xa plasma activity aiming for a trough level of 0.2 U/mL and a peak level at 4 h of 0.4 U/mL.
Gagnadoux et al., 1993 [36]	LMWH
Gagnadoux et al., 1994 [25]	LMWH
Ohta et al., 2000 [37]	Dipyridamole (5 mg/kg) is administered per oral solution in 3 divided daily doses starting 1 wk after transplantation.
Kranz et al., 2002 [38]	Children without thrombophilia received heparin 200 U/kg/d (low dose) for 2 wk, followed by ASA 3-5 mg/kg 3 times per wk in the first year after kidney transplantation. Children with thrombophilia were treated more intensively, with UFH started intraoperatively and adjusted to a partial thrombin time of 50-60 s. This regimen was followed by LMWH given subcutaneously for 6 wk, before switching to ASA 3-5 mg/kg 3 times per week until 1 y after kidney transplantation.
Pape et al., 2004 [39]	Heparin was administered at a low dose of 100-200 IU/kg/d, aiming for an APTT of 30-40 s, during the first 2 wk after transplantation.
Vester et al., 2004 [40]	Low-dose prophylactic UFH therapy was given routinely for 14 d to every patient. In cases with an identified thrombosis risk factor, UFH therapy was intensified (APTT prolonged to 50-60 s) for 14 d, followed by LMWH for another 4 wk.
Kranz et al., 2006 [41]	Children without thrombophilia received low-dose heparin (200 IU/kg/d) postoperatively for the first 14 d without prolongation of the APTT. Afterward, ASA (3-5 mg/kg 3 times per wk) was introduced for the first year after transplant. In children with thrombophilia, heparin was initiated intraoperatively and adjusted to obtain an APTT of 50-60 s during the first 14 d. Anticoagulation was continued with LMWH for another 8 wk (anti-Xa target level, 0.4-0.7 U/mL) before switching to ASA.
Pape et al., 2006 [42]	UFH 200 IU/kg/d (≈8 U/kg/h) over 2 wk
Afanetti et al., 2012 [43]	UFH was used early postoperatively.
Esfandiar et al., 2012 [44]	UFH 50 U/kg was administered every 8 h, for 7 postoperative d, and aspirin 5 mg/kg/d, 3 times per wk, from day 3 of transplantation for 3 mo.
ElSheemy et al., 2014 [21]	Prophylactic anticoagulation was given as LMWH at a dose of 0.1 mg/kg every 12 h for the first 4 d, then converted to oral antiplatelet (ASA) at 5 mg/kg/d for 1-3 mo postoperatively.
Zhao et al., 2014 [45]	Continuous infusion of heparin at 5 U/kg/h for the first week after transplantation, after which ASA with or without clopidogrel was given daily. For the first week, the APTT was maintained at <1.5 times prolonged compared with baseline value.
Sui et al., 2016 [46]	UFH 10 U/kg/h for the first week, with APTT <1.5× upper limit, followed by ASA 50 mg/d beginning the second wk.
Kim et al., 2019 [47]	UFH 10 U/kg/h for 5-7 d starting intraoperatively or within 1 h after the operation.
Al Midani et al., 2020 UFH [48]	UFH given subcutaneously after induction of anesthesia with 3× daily administration thereafter (3000 U/d for children <15 kg; 4500 U/d for children 15-20 kg; and 7500 U/d for children >20 kg). APTT was maintained at less than twice the control baseline value. UFH was discontinued when patients were fully mobile at 7 to 10 d posttransplant
Al Midani et al., 2020 ASA [48]	Oral ASA prophylaxis (1 mg/kg, with maximum dose of 75 mg/d) from induction until at least 1 mo after transplant (unless bleeding problems occurred). ASA was not discontinued for renal allograft biopsies (most performed urgently, preventing elective antiplatelet discontinuation before the procedure).
Amesty et al., 2020 [20]	Enoxaparin sodium 0.5-1 mg/kg/24 h, starting 6-12 h posttransplant for 5-7 days (exception for patients with contraindication due to active bleeding), switching to ASA 1-2 mg/kg/d for 1-3 months. For patients with prothrombotic risk factors, prophylaxis was individualized.
Su et al., 2020 [49]	Similar anticoagulation protocols were used by 2 centers. First Affiliated Hospital of Sun Yat−sen University: all recipients received LWMH (50-100 IU/kg/d) for 1-5 d, with dose adjustments for postoperative drainage volume around the allograft and/or follow-up graft ultrasound findings. LMWH was switched to oral antiplatelet, then gradually discontinued. First Affiliated Hospital of Zhengzhou University: donor age <1 y or recipient age <5 y, LMWH (50-100 IU/kg/d) for 1-5 d posttransplant, with dosage adjustments according to drainage volume and thromboelastography. LMWH was switched to oral antiplatelet therapy, then gradually discontinued.

Gander et al., 2022 [52]	Three thrombosis risk groups were defined: low, intermediate, and high. Antithrombotic prophylaxis used only for intermediate-risk and high-risk groups with oral/endovenous ASA. ASA 2 mg/kg/d or UFH 10 U/kg/h were administered as a continuous infusion, respectively. All patients receiving a second or subsequent kidney transplant were classified as at least intermediate risk and received antithrombotic prophylaxis with ASA. ASA was maintained until 1 mo after kidney transplant. Low thrombotic risk (must meet all criteria): - First transplant without vascular anomalies - Donor weight and recipient weight >15 kg - Deceased donor transplant - Absence of identified thrombophilic factor, active nephrotic syndrome, and a history of thrombotic events and intraoperative complications Intermediate thrombotic risk (must meet only 1 criterion) - Second or subsequent transplant - Vascular anomalies - Donor or recipient weight <15 kg - Living-related donor transplant - Intraoperative complications of moderate risk of thrombosis (at discretion of the surgical team) High thrombotic risk (must meet only 1 criterion) - Congenital thrombophilia - Prothrombotic immunologic disease - Active nephrotic syndrome - Fabry disease - History of thrombosis of 2 or more vessels - Receiving prophylactic or therapeutic anticoagulants Intraoperative complications of high risk of thrombosis (at discretion of the surgical team)

Study	Thromboprophylactic regimen
Cetiner et al., 2021 [19]	IV UFH (200 IU/kg/d) for 2 wk, starting 4 h posttransplant, followed by oral ASA. In case of thrombophilia, IV heparin was started during transplantation, and doses were adjusted to achieve APTT 1.5-fold higher than baseline. After 2 wk, subcutaneous LMWH (enoxaparin) was administered for an additional 6 wk (target anti-Xa activity, 0.2-0.4), and thereafter, oral ASA.
Beatrice et al., 2021 [50]	Patients at low risk for thrombosis (no clinical risk factors and negative thrombophilic tests): prophylaxis with IV UFH 10 U/kg/h postoperatively for 7 d, followed by oral ASA at 3-5 mg/kg/d 3 times weekly for 1 y. Patients at high risk for thrombosis (history of thrombosis or positive thrombophilic tests): IV UFH at 10 U/kg/h for 7 d, followed by LMWH subcutaneously (enoxaparin) at 1 mg/kg/d for 8 wk, then oral ASA at 3-5 mg/kg/d 3 times weekly for 1 year. APTT ratio was maintained at <1.5 times baseline to monitor the UFH dose; anti-Xa was maintained between 0.2 and 0.4 U/mL in patients receiving LMWH.
Wen et al., 2022 [51]	Prophylactic anticoagulation with heparin (5-10 U/kg/h), initiated immediately after surgery, with dosage adjusted according to the baseline coagulation test (APTT, target value 28-40 s). Subcutaneous heparin followed, replaced by oral ASA (100 mg per night) 1 wk postoperatively.

Ghidini et al., 2023 [53]	Perioperative UFH infusion 5-10 U/kg/h if thrombophilia detected during pretransplant blood screening, considerable mismatch between donor and recipient, vascular anomalies, or intraoperative finding of graft venous congestion after implantation.
Schild et al., 2024 [54]	Did not specify the antithrombotic protocol. The mean daily dose administered was ASA 2.4 mg/kg, UFH 140 U/kg, and LMWH 1.1 mg/kg. The median initiation times for these medications were 160 h for ASA, 1 h for UFH, and 72 h for LMWH.
Ramirez-Amoros et al., 2024 [55]	Anticoagulation therapy was individualized according to the thrombotic risk. If no added risk was present, LMWH started 12-24 h postoperatively and maintained until the patient restarted walking (≈postoperative day 8), then switching to antiaggregation with ASA.

APTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; IV, intravenous; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

Tromboproflaksi ile greft trombozu %12 den %4'e düşmektedir.

5 | CONCLUSION

Our systematic review suggests that primary thromboprophylaxis is effective in preventing kidney graft loss secondary to graft thrombosis in pediatric kidney transplants. This benefit of thromboprophylaxis should be balanced with the risk of bleeding. However, the study findings are limited by the heterogeneity and quality of the available studies. Our study also identified knowledge gaps, including the absence of optimal thromboprophylaxis regimens/duration and inability to identify patients at risk for major bleeding.

Current practice of antithrombotic prophylaxis in pediatric kidney transplantation—Results of an international survey on behalf of the European Society for Paediatric Nephrology

Kathrin Buder[1] | Matthias Zirngibl[2] | Sascha Bapistella[2] | Silvio Nadalin[3] | Burkhard Tönshoff[4] | Marcus Weitz[2] | Members of the "Transplantation Working Group" of the European Society for Paediatric Nephrology (ESPN)*

[1]Pediatric Nephrology Department, University Children`s Hospital Zurich, Zurich, Switzerland

[2]Department of General Pediatrics and Hematology/Oncology, University Hospital Tübingen, University Children`s Hospital, Tübingen, Germany

[3]Department of General, Visceral and Transplant Surgery, University Hospital Tübingen, Tübingen, Germany

[4]Department of Pediatrics I, University Children's Hospital Heidelberg, Heidelberg, Germany

Correspondence
Marcus Weitz, University Hospital Tübingen, University Children`s Hospital, Department of General Pediatrics and Hematology/Oncology, Hoppe-Seyler-Str. 1, D – 72076 Tübingen, Germany.
Email: marcus.weitz@med.uni-tuebingen.de

Abstract

Background: Renal graft thrombosis (RGT) is one of the main causes for early graft loss in pediatric kidney transplantation (KTx). Despite the lack of evidence-based recommendations, antithrombotic prophylaxis (aP) is used to prevent RGT.

Methods: An online survey supported by the European Society for Pediatric Nephrology was developed to investigate the current practice of aP in pediatric KTx recipients <18 years.

Results: A total of 80 pediatric KTx centers from 37 countries participated in the survey. Antithrombotic prophylaxis was performed in 96% of the pediatric renal transplant centers (all/selected patients: 54%/42%). The main overall used drugs were as follows: low-molecular-weight heparin (89%), unfractionated heparin (UFH) (69%), and acetylsalicylic acid (ASS) (55%). Ten different aP management strategies were identified as follows: 51% used a single drug and 48% combined two drugs sequentially. The corresponding centers started aP predominantly within 24 hours after pediatric KTx; 51% preferred UFH for starting aP. In centers switching to a second drug (51%), this change was performed after 10 ± 6 days; of these 57% preferred ASS for maintenance aP. Reported median aP duration was 51 days (range 1-360).

Conclusions: Despite the use of aP in almost all responding pediatric KTx centers, there is no uniform management strategy. Notwithstanding, UFH seems to be the preferred drug for the early post-operative period of pediatric KTx, and ASS for maintenance prophylaxis following pediatric KTx. Prospective studies are needed to further evaluate the benefits and risks of aP, preferably resulting in guidelines for the management in pediatric KTx.

Analysis of Factors Related to the Success of Pediatric Kidney Transplantation: A 35 Years Experience

Natália Dalsenter Avilez[a], Ana Beatriz Pereira De Souza[a], Bruno Ricardo Di Domenico[a], Liliane Cury Prates[b], Marilda Mazzali[c], and Marcelo Lopes De Lima[a*]

[a]Department of Urology, University of Campinas - UNICAMP - Sao Paulo, Brazil; [b]Department of Pediatric Nephrology, University of Campinas - UNICAMP - Sao Paulo, Brazil; and [c]Department of Nephrology, University of Campinas - UNICAMP - Sao Paulo, Brazil

ABSTRACT

Background. Despite the significant improvement results over the past 20 years, pediatric kidney transplantation remains a challenge. Chronic rejection, thrombosis, and recurrence of the primary disease are frequent causes of graft loss that have been little studied. Therefore, our objective is to analyze factors related to a better prognosis, which can be used to improve future strategies to allow higher pediatric transplant success rates.

Methods. A retrospective cohort study with patients under 15 years old submitted for kidney transplantation at the Hospital das Clínicas da UNICAMP between January 1, 1987, and January 1, 2022. Age, patient weight, time and type of dialysis, use of anticoagulation, complications, ischemia time, and donor weight were analyzed and related to graft loss. The significance level adopted for the statistical tests was 5%.

Results. One hundred ninety-two medical records were anaThe mean follow-up time was 11 years, and the mean graft duration was ration 8.5 years. The main causes of graft loss were chronic dysfunction, thrombosis, and acute cellular rejection. Thrombosis presented significantly with the donor's body mass index and second transplantation. There was no correlation between the analyzed variables and chronic dysfunction or acute cellular rejection.

Discussion. Thrombosis remains the main cause of early graft loss, followed by acute cellular rejection. Measures such as thrombophilia screening and thromboprophylaxis have been proposed to improve results. However, they are still not standardized.

Conclusion. The main causes of graft loss were chronic dysfunction, thrombosis, and acute cellular rejection. Only the thrombosis was related to the donor's body mass index and a second transplantation.

Table 3. Early Complications

Complication	Result
Thrombosis	19 (9.9%)
Bleeding >500 mL	7 (3.6%)
Renal artery stenosis	4 (2%)
Urinary fistula	1 (0.5%)
Lymphocele	1 (0.5%)
Surgical wound infection	1 (0.5%)

Thrombosis is the main cause of early graft loss; for this reason, some measures have been proposed to reduce this risk. Some studies have proposed the systematic screening of patients for thrombophilia [4,29] and pharmacologic thromboprophylaxis in high-risk cases. However, there is no consensus on the ideal anticoagulation protocol. Low molecular weight heparin, unfractionated heparin, and aspirin were used in different studies for a period that varied from 1 month to 1 year, showing (in some cases) a reduction in the incidence of thrombosis without an increase in bleeding rates [30,31]. Other studies pointed out a decrease in the risk of thrombosis but with an increase in the hemorrhagic risk [32], and others showed no evidence of a thrombosis index [26,29,33]. In our study, 14.54% of the patients had a personal history of thrombosis, and 7.22% had a family history. Reports on antecedents and anticoagulation were scarce and, therefore, could not be analyzed.

Dinlediğiniz için teşekkürler