Rivaroxaban for management of venous thromboembolism in pediatric nephrotic syndrome; a case report and review of literature

Marie-Claude Pelland-Marcotte[1], Soumitra Tole[2], Eve Bouhelier[3], Susan Lee[4], Jessica Halparin[4], Cherry Mammen[4], Karen Lyons[4], and Ali Amid[4]

[1]Centre hospitalier universitaire de Québec-Université Laval
[2]London Health Sciences Centre Children's Hospital
[3]Research Center of the CHU de Quebec
[4]BC Children's Hospital

April 9, 2022

Abstract

Thromboembolism is a major complication of nephrotic syndrome (NS). Hypoalbuminemia, loss of anticoagulant proteins, increased procoagulant proteins, hemoconcentration, and platelet activation contribute to a hypercoagulable state. Despite being well-described, the optimal management of thromboembolism in NS remains unclear. Rivaroxaban, a direct factor-Xa inhibitor has recently been shown to be safe and efficacious in treating pediatric venous thromboembolism but has not been well studied in NS. We present an adolescent with steroid-dependent NS, deep vein thrombosis and submassive pulmonary embolism successfully treated with rivaroxaban. We perform a systematic review of the reported safety and efficacy of direct factor-Xa inhibitor in this population.

INTRODUCTION

Thromboembolism is a well-recognised and potentially life-threatening complication of nephrotic syndrome (NS). Several factors contribute to a hypercoagulable state, including the loss of anticoagulant proteins (notably antithrombin and protein S) as well as increased synthesis of procoagulant factors, platelet activation, and hemoconcentration.[1] There are no evidence-based guidelines for the prevention or management of thromboembolic complications in pediatric NS. Low molecular weight heparin (LMWH) and warfarin have been the therapies of choice. As LMWHs confer their antithrombotic action by inhibition of activated factor X through binding and activating antithrombin, they may not be ideal in patients with antithrombin deficiency including patients with active nephrotic syndrome. Furthermore, anticoagulation with warfarin requires frequent monitoring of INR. Recently, rivaroxaban, a direct factor-Xa inhibitor, has been shown to be safe and efficacious in treating children with venous thromboembolism, but has not been well studied in NS.[2] While as an antithrombin-independent anticoagulant, it may offer convenient, effective, and reliable oral anticoagulation in NS, rivaroxaban is primarily protein-bound, and thus its pharmacokinetic properties may be altered in NS.[3]

We present a case of an adolescent with NS who experienced a large proximal deep vein thrombosis (DVT) and submassive pulmonary embolism (PE), successfully treated with rivaroxaban. Additionally, we performed a systematic review of the literature to assess the safety and efficacy of direct factor-Xa inhibitors in patients with NS.

CASE DESCRIPTION

A 13-year-old boy with NS, who had been in a prolonged relapse, presented to the emergency department with one-week history of dyspnea, chest pain, and left leg edema.

The patient was diagnosed with NS at 18 months of age and had a frequently relapsing and steroid-dependent course. Consequently, he had received several steroid-sparing therapies including cyclophosphamide, tacrolimus, mycophenolate mofetil (MMF) and several courses rituximab prior to his current relapse. At presentation, he remained on high-dose prednisone, MMF, and furosemide, and intermittent intravenous albumin therapy for ongoing proteinuria and generalized edema. He had no prior thromboembolic events and was not on prophylactic anticoagulation.

Upon assessment, he had tachycardia (128 beats-per-minute), tachypnea (32 breath-per-minute), was afebrile, and normotensive (112/81 mmHg). His oxygen saturation was 97% on room air. He was alert, but dyspneic with moderate work of breathing. His left leg was considerably more edematous than the right.

On investigation, he had mild leukocytosis (WBC 12.3 x10e9/L) and a normal platelet count (175 x10e9/L). He had normal INR and aPTT, elevated fibrinogen (7.6 g/L, normal 1.7-4.4) and D-Dimer (>35000 microgram/L, normal<500). He had hyponatremia (125 mmol/L), hypoalbuminemia (21 g/L, normal 37-56) and very low antithrombin activity (0.42 unit, normal 0.85-1.25). His serum creatinine was normal for age (41 micromol/L).

Doppler ultrasound of the lower extremities followed by computed tomography (CT) of the chest and abdomen showed a left-sided extensive DVT extending from the infrarenal inferior vena cava down to the superficial femoral vein, as well as a saddle PE [Figure 1] with areas of pulmonary ischemia. His N-terminal-pro B-type natriuretic peptide (NT-proBNP) was elevated (264 ng/L, normal<160). Transthoracic echocardiography showed preserved left ventricular function (ejection fraction of 50%) with evidence of right heart strain, in keeping with submassive PE.

The patient was started on an unfractionated heparin (UFH) infusion and was admitted to the Pediatric Intensive Care Unit. As he was hemodynamically stable, had a high bleeding risk due to areas of pulmonary ischemia, and underlying renal dysfunction we elected to continue with anticoagulation alone rather than systemic or pharmacomechanical catheter-directed thrombolysis. Due to his low antithrombin activity, he required very high infusion rates of UFH (up to 42 IU/kg/hr) to reach the desired anti-Xa activity level of 0.35-0.70 IU. A. He finally achieved full remission of his NS relapse after several weeks of high-dose corticosteroids and Rituximab.

One week after starting anticoagulation, a CT scan showed marginal reduction in the PE clot burden. Considering the ongoing proteinuria and challenges with anticoagulation using UFH, his anticoagulation was changed to rivaroxaban 20mg once-daily, as an antithrombin-independent option and the only direct factor-Xa inhibitor licensed for the pediatric population in Canada, on day 15 of admission. Random rivaroxaban levels (12-hour) and anti-Xa activity were measured at 99 ng/ml and 0.14 IU/ml respectively.

After 3 months of anticoagulation, the patient was asymptomatic and still in remission of his NS. He did not experience any bleeding and had no clinically significant post-thrombotic syndrome of the lower extremity (Villalta score 2 for moderate venous ectasia).[4] Radiological assessment showed near-complete resolution of his PE [Figure 1], normalization of his echocardiogram, and significant reduction in his DVT with residual non-occlusive thrombus in the left external iliac and common femoral veins. On thrombophilia work-up, he was found to be heterozygous for factor-V Leiden. Ten months after diagnosis, the patient has remained in remission for his NS, and continues full-dose rivaroxaban as secondary thromboprophylaxis without thrombotic recurrence.

DISCUSSION

Thromboembolism is a well-recognized complication of NS. In children, post-pubertal status, severe proteinuria, congenital NS, and prior thrombotic events are recognized risk factors.[5,6] In adults, the degree of hypoalbuminemia and membranous nephropathy have also been identified as predictors of thrombosis.[7] NS creates a prothrombotic milieu through several mechanisms: massive urinary losses of proteins, notably

the anticoagulants antithrombin and protein S; increased hepatic synthesis of several procoagulants proteins, notably fibrinogen and coagulation factors V, VIII, and X, as well as fibrinolytics inhibitors such as lipoprotein(a) and α2-macroglobulin, and constitutive platelet activation.[1,7,8] Additionally, direct glomerular injury may locally increase the risk of renal vein thrombosis through the presence of endothelium-derived microparticles, depletion of endothelium-derived nitric oxide, increased generation of PECAM-1, etc.[8]

Rivaroxaban has recently been shown to be efficacious and safe to treat venous thrombosis in the pediatric population.[2,9]Advantages include oral administration, rapid onset of action, and independence from antithrombin to achieve its therapeutic effect. However, it remains unclear how the presence of NS may affect direct factor-Xa inhibitors' pharmacological properties. Notably, rivaroxaban is 90 to 95% protein-bound and apixaban 87% protein-bound, mostly to albumin. It is thus possible that direct factor-Xa inhibitors pharmacokinetics could be altered by urinary protein losses.[10,11] Some authors have hypothesized that an increase in the free portion of rivaroxaban may increase the risk of bleeding.[11] Secondly, the efficacy of rivaroxaban might be potentiated by the increased levels of factor X, the principal target of rivaroxaban.[10] Thirdly, approximately one-third of rivaroxaban is excreted through the kidney; underlying renal dysfunction may thus increase the area under the curve of rivaroxaban. Edema may also alter the volume of distribution of the drug.[12,13] However, a phase I study with a single dose of the apixaban has shown similar pharmacokinetic measures in adults and in healthy individuals with NS and similar peak thrombin generation.[14] We were unable to draw peak Rivaroxaban levels as our patient opted to take his dose in the evening. However, his 12-hour serum rivaroxaban level and anti-Xa activity were within the expected therapeutic window,[3] and the patient did not experience bleeding.

We performed a systematic review of the literature to review the safety and efficacy of thrombin and direct factor-Xa inhibitors in NS. We searched Medline and Embase databases (1990-2021), using subject headings and textword terms for nephrotic syndrome AND oral anticoagulants, or their possible substitutes. Reference lists of all included papers and abstracts were hand-searched to identify potentially relevant articles. The search identified 153 unique articles or abstracts, of which 23 were considered for full-text reviews and 15 are included in this analysis. [see Supplementary File].

We retrieved one pediatric case series, in abstract form, in which four children with NS and thromboembolic events were treated with rivaroxaban. No treatment failure and no major or clinically relevant bleeding were encountered.[15] Additionally, our search retrieved several case reports or case series and one small pilot randomized controlled trial [Table 1]. In this trial, the use of rivaroxaban led to similar thrombus dissolution at four weeks in adults with NS, compared to LMWH, with no major bleeding in either group.[16] Ten cases [six published articles, four abstracts] of venous thromboembolic events in adults treated with direct factor-Xa inhibitors were retrieved [median age: 38 years (range: 18-60); 80% male].[10,11,17-24] Four cases required additional antithrombotic therapy due to thrombus progression or recurrence, and no major bleeds or other adverse events were reported. One author reported sub-therapeutic levels of apixaban with standard dosing, but achieved favorable clinical outcomes with optimized dosing.[18] The current literature is limited to case reports and small case series, therefore raising the concern of publication bias. We did not retrieve studies reporting the use of direct thrombin inhibitors.

CONCLUSION

Rivaroxaban may provide an effective and safe anticoagulation option in children with NS. Further studies are needed to assess the pharmacokinetics, efficacy and safety of direct factor-Xa inhibitors in these children.

AUTHOR CONTRIBUTIONS:

LK, CM, JH, SL, and AA provided study material. EB performed the citation search of the electronic databases, MCPM and ST performed literature review. All authors contributed toward analysis, interpretation of the data, and review of the manuscript and approved the final draft of the manuscript.

ETHICS STATEMENT:

Informed consent has been obtained for the use of deidentified images and clinical information in this letter to the editor

DATA AVAILABILITY STATEMENT:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST:

All authors report no relevant conflict of interest for this publication.

FUNDING:

Dr. Amid's research is in part funded by Naiman-Vickars Endowment Fund and BCCHR Investigator Grant Award.

REFERENCES:

1. Kerlin BA, Haworth K, Smoyer WE. Venous thromboembolism in pediatric nephrotic syndrome. *Pediatr Nephrol.* 2014;29(6):989-997.

2. Male C, Lensing AW, Palumbo JS, et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. *The Lancet Haematology.* 2020;7(1):e18-e27.

3. Willmann S, Thelen K, Kubitza D, et al. Pharmacokinetics of rivaroxaban in children using physiologically based and population pharmacokinetic modelling: an EINSTEIN-Jr phase I study. *Thromb J.* 2018;16:32.

4. Kahn SR. Measurement properties of the Villalta scale to define and classify the severity of the post-thrombotic syndrome. *J Thromb Haemost.* 2009;7(5):884-888.

5. Kerlin BA, Blatt NB, Fuh B, et al. Epidemiology and risk factors for thromboembolic complications of childhood nephrotic syndrome: a Midwest Pediatric Nephrology Consortium (MWPNC) study. *J Pediatr.*2009;155(1):105-110, 110 e101.

6. Bérody S, Heidet L, Gribouval O, et al. Treatment and outcome of congenital nephrotic syndrome. *Nephrology Dialysis Transplantation.* 2019;34(3):458-467.

7. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *Clin J Am Soc Nephrol.* 2012;7(3):513-520.

8. Chen G, Liu H, Liu F. A glimpse of the glomerular milieu: from endothelial cell to thrombotic disease in nephrotic syndrome.*Microvasc Res.* 2013;89:1-6.

9. Monagle P, Lensing AW, Thelen K, et al. Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): results from three multicentre, single-arm, phase 2 studies. *The Lancet Haematology.* 2019;6(10):e500-e509.

10. Li Y, Chen Y, Qi X, Hu B, Du Q, Qian Y. Poor response to rivaroxaban in nephrotic syndrome with acute deep vein thrombosis: A case report.*Medicine (United States).* 2019;98(31) (no pagination).

11. Reynolds ML, Nachman PH, Mooberry MJ, Crona DJ, Derebail VK. Recurrent venous thromboembolism in primary membranous nephropathy despite direct Xa inhibitor therapy. *Journal of Nephrology.*2019;32(4):669-672.

12. Pincus KJ, Hynicka LM. Prophylaxis of thromboembolic events in patients with nephrotic syndrome. *Annals of Pharmacotherapy.*2013;47(5):725-734.

13. Sexton DJ, de Freitas DG, Little MA, et al. Direct-Acting Oral Anticoagulants as Prophylaxis Against Thromboembolism in the Nephrotic Syndrome. *KI Rep.* 2018;3(4):784-793.

14. Derebail VK, Zhu J, Martin KA, et al. Clinical pharmacology of apixaban in nephrotic syndrome. *Journal of the American Society of Nephrology.* 2020;31:722.

15. Telaraja D, Hennessey C, Meldau J, et al. Pediatric nephrotic syndrome-related thromboembolism: Role of anticoagulant thromboprophylaxis. *Pediatric Blood and Cancer.*2019;66(Supplement 2):S279.

16. Zhang L, Zhang H, Zhang J, Tian H, Liang J, Liu Z. Rivaroxaban for the treatment of venous thromboembolism in patients with nephrotic syndrome and low AT-III: A pilot study. *Experimental and Therapeutic Medicine.* 2018;15(1):739-744.

17. Dupree LH, Reddy P. Use of Rivaroxaban in a Patient With History of Nephrotic Syndrome and Hypercoagulability. *Annals of Pharmacotherapy.* 2014;48(12):1655-1658.

18. Wharin S, Gooding R. A case series of patients treated with escalated doses of doacs. *British Journal of Haematology.*2018;181(Supplement 1):142.

19. Basu A, Jain S, Patel D, Bodapati G, Venkatappa N, Bhattacharya P. Failure of anticoagulation in a case of nephrotic syndrome with recurrent thromboembolism. *Chest Conference: CHEST.* 2015;148(4 MEETING ABSTRACT).

20. Song Z, Wu H, Cao H, Tang M, Yang S, Qin L. Nephrotic syndrome with acute pulmonary embolism in young adults: Two case reports.*Medicine (United States).* 2018;97(29) (no pagination).

21. Phelan L, Martin S. A case of abdominal pain post subtotal colectomy. *Irish Journal of Medical Science.*2020;189(SUPPL4):S52.

22. Obata F, Abe H, Murakami T, et al. Direct oral anticoagulant successfully used to treat an adult nephrotic patient complicated with portal vein thrombosis. *CEN Case Reports.* 2019;8(2):134-138.

23. Shimada Y, Nagaba Y, Nagaba H, et al. Edoxaban was effective for treating renal vein thrombosis in a patient with nephrotic syndrome.*Internal Medicine.* 2017;56(17):2307-2310.

24. Han T, Han C, Thet Z. Warfarin vs new oral anticoagulant in primary adult nephrotic syndrome associated venous thormboembolism.*Nephrology.* 2017;22(Supplement 3):64.

25. Chengappa M, Graffe J, Chasky M, Nashat M. Acute renal vein thrombosis (RVT) secondary to SARS-CoV-2. *Journal of General Internal Medicine.* 2021;36(SUPPL 1):S192-S193.

26. Wills M, et al. "The direct use of oral anti-coagulants in membranous nephropathy.". *Nephrology Dialysis Transplantation.* 35(SUPPL 3):iii776.

27. Shahzad SR, Al-Ahmad M, Faris FA, Hongalgi K. Management of Arterial Thrombosis Secondary to Nephrotic Syndrome in a Patient on Chronic Apixaban. *American Journal of Kidney Diseases.*2020;75(4):633-634.

TABLE 1

Use of direct factor-Xa inhibitors in patients with nephrotic syndrome

Ref

Study type

n

Sex

Age

(years)

Histologic subtype

Agent used

Dosage,

(mg/day)

Clinical outcome of thrombosis

Follow-up (m)

Therapeutic

Zhang, 2018[13]

RCT

16

81% male

Mean: 28 Range: 20-48

Various

Rivaroxaban (8) Dalteparin (1)

30 mg 5000 UI

7/8 patients with thrombus dissolution in both groups

1

Telaraja, 2019[12]

CS

9

NA

NA

NA

Rivaroxaban (4) Enoxaparin (4) Warfarin (1)

NA

No treatment failure

NA

Index case

CR

1

M

13

Rivaroxaban

20

Favorable

8

Dupree, 2014[17]

CR

1

F

18

NOS

Rivaroxaban

20

Favorable

6

Wharin, 2018[18]

CR

1

M

19

MCD

Apixaban

30

Favorable

NA

Basu, 2015[19]

CR

1

F

21

Lupus

Rivaroxaban

NA

Progression

2

Song, 2018[20]

CR

1

M

24

MCD

Rivaroxaban

NA

Favorable

1

Phelan, 2020[21]

CR

1

M

34

NOS

Apixaban

NA

Favorable

12

Obata, 2019[22]

CR

1

M

38

MCD

Edoxaban

30

Favorable

8

Shimada, 2017[23]

CR

1

M

39

NOS

Edoxaban

30

Favorable

9

Reynolds, 2019[11]

CR

1

M

51

MN

Apixaban

5

Recurrence

12

Li, 2019[10]

CR

1

M

59

NOS

Rivaroxaban

NA

Progression

0.7

Han, 2017[25]

CR

1

M

60

MN

Rivaroxaban

20

Recurrence

5

Prophylactic

Wills, 2020[26]	RCS	26	65% male	Mean: 55 Range: 26-76	MN	Rivaroxaban (21) Apixaban (5)	NA	0.11 thrombosis/ patient year	Mean: 11
Sexton, 2018[13]	CS	2	F	28/49	MCD/MN	Apixaban	10	Favorable	2/3
Shahzad, 2020[27]	CR	1	M	58	MN	Apixaban	NA	Development of arterial thrombosis	NA

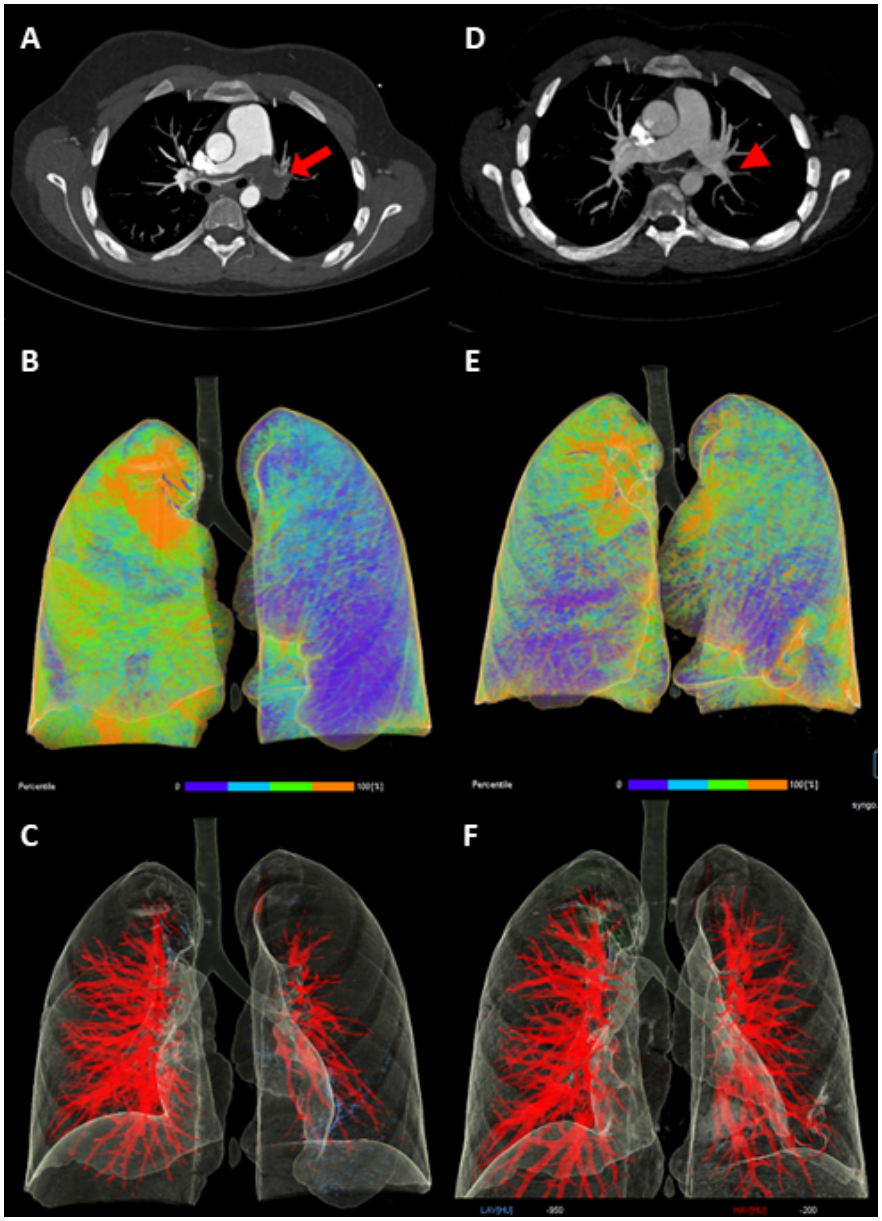
Abbreviations : CR: case report; CS: case series; RCS: retrospective cohort study; RCT: randomized controlled trial; F: female; M: male; MCD: minimal change disease; MN: membranous nephropathy; NOS: not otherwise specified; NA: Not available.

FIGURE LEGEND

Images depict two CT pulmonary angiograms performed at presentation (Panels A, B, C) and after 3 months of anticoagulation (Panels D, E, F).

On the original CT there is a saddle pulmonary embolism with complete occlusion of the left pulmonary artery (Panel A, arrow), associated with oligemia shown on a 3-D colour map (Panel B), and very asymmetric pulmonary arterial arborisation (Panel C). On the follow up CT, while there is no residual pulmonary arterial filling defect, but the left pulmonary artery is small than the right (Panel D, arrowhead), with only mild residual mosaicism (Panel E) and subtle but definite decreased arborisation on the left (Panel F).

FIGURE 1



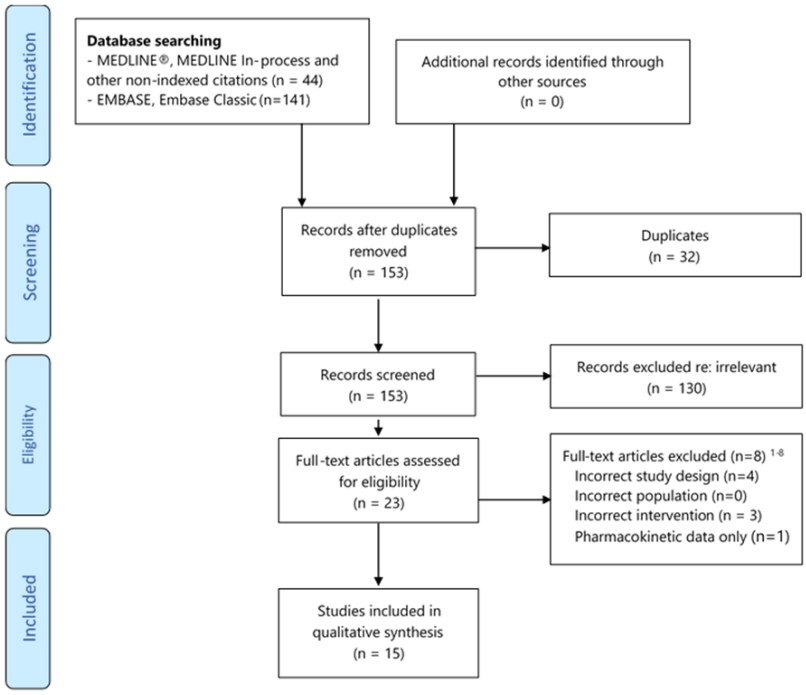
SUPPLEMENTARY FILE

Supplementary Table S1. Library search strategy for Embase

1	Nephrotic syndrome/ or (nephrotic adj1 syndrome*).ti,ab.
2	Anticoagulant agent/ or blood clotting factor 10a inhibitor/ or (anticoagulant* or (anticoagulation adj2 (agent or agen
3	Oral drug administration/ or (oral or buccal or sublingual).ti,ab.
4	2 and 3
5	1 and 4
6	Rivaroxaban/ or apixaban/ or betrixaban/ or edoxaban/ or dabigatran/ or ximelagatran/ or (rivaroxaban* or apixaba
7	1 and 6
8	(DOAC or DOACs or (direct adj1 (acting or oral) adj2 anticoagulant*)).ti,ab.
9	1 and 8
10	5 or 7 or 9

The search was limited to articles in English and French published between January 1,1990 and October 6, 2021.

Supplementary Figure S1. Study selection flow diagram



References

1. Cohen, O., et al. (2020). "Rivaroxaban for the treatment of venous thromboembolism in pediatric patients." Expert Review of Cardiovascular Therapy 18(11): 733-741.
2. Derebail, V. K., et al. (2020). "Role of direct oral anticoagulants in patients with kidney disease." Kidney International 97(4): 664-675.
3. Pincus, K. J. and L. M. Hynicka (2013). "Prophylaxis of thromboembolic events in patients with nephrotic syndrome." Annals of Pharmacotherapy 47(5): 725-734

4. Uppal, D., et al. (2019). "Direct Oral Anticoagulants (Doacs) and the Kidney." American Journal of Kidney Diseases 73(5): 743
5. El Hangouche, A. J., et al. (2018). "A complicated steroid resistant nephrotic syndrome: A large intracardiac thrombus with bilateral distal embolization." Pan African Medical Journal 31 (no pagination).
6. Kamran, H., et al. (2016). Venous and arterial thromboses in nephrotic syndrome: where only warfarin has walked. Journal of General Internal Medicine 31, 85–922
7. Suri, D., et al. (2014). "Thromboembolic complications in childhood nephrotic syndrome: a clinical profile." Clinical and Experimental Nephrology 18(5): 803-813
8. Derebail, V. K., et al. (2020). "Clinical pharmacology of apixaban in nephrotic syndrome." Journal of the American Society of Nephrology 31: 722