Supplementary References

S1) Sans-Atxer L, Joly D. Tolvaptan in the treatment of autosomal dominant polycystic kidney disease: patient selection and special considerations. *Int J Nephrol Renov Dis*. 2018;11:41-51. doi:10.2147/IJNRD.S125942

S2) Christiansen CF, Schmidt M, Lamberg AL, et al. Kidney disease and risk of venous thromboembolism: a nationwide population-based case-control study. *J Thromb Haemost JTH*. 2014;12(9):1449-1454. doi:10.1111/jth.12652

S3) O'Sullivan DA, Torres VE, Heit JA, Liggett S, King BF. Compression of the inferior vena cava by right renal cysts: an unusual cause of IVC and/or iliofemoral thrombosis with pulmonary embolism in autosomal dominant polycystic kidney disease. *Clin Nephrol*. 1998;49(5):332-334.

S4) Iguchi S, Kasai A, Kishimoto H, et al. Thrombosis in Inferior Vena Cava (IVC) Due to Intra-cystic Hemorrhage into a Hepatic Local Cyst with Autosomal Dominant Polycystic Kidney Disease (ADPKD). *Intern Med*. 2004;43(3):209-212. doi:10.2169/internalmedicine.43.209

S5) Maeda T, Uchida Y, Oyamada K, Nakajima F. Thrombosis in Inferior Vena Cava Due to Enlarged Renal Cysts in Autosomal Dominant Polycystic Kidney Disease. *Intern Med*. 2010;49(17):1891-1894. doi:10.2169/internalmedicine.49.3748

S6) Yin X, Blumenfeld JD, Riyahi S, et al. Prevalence of Inferior Vena Cava Compression in ADPKD. *Kidney Int Rep*. 2021;6(1):168-178. doi:10.1016/j.ekir.2020.10.027

S7) Bhupalan A, Talbot K, Forbes A, Owen M, Samson D, Murray-Lyon IM. Budd-Chiari syndrome in association with polycystic disease of the liver and kidneys. *J R Soc Med*. 1992;85(5):296-297.

S8) Clive DM, Davidoff A, Schweizer RT. Budd-Chiari syndrome in autosomal dominant polycystic kidney disease: a complication of nephrectomy in patients with liver cysts. *Am J Kidney Dis Off J Natl Kidney Found*. 1993;21(2):202-205. doi:10.1016/s0272-6386(12)81094-8

S9) Torres VE, Rastogi S, King BF, Stanson AW, Gross JB, Nogorney DM. Hepatic venous outflow obstruction in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol JASN*. 1994;5(5):1186-1192. doi:10.1681/ASN.V551186

S10) Barbier L, Ronot M, Aussilhou B, et al. Polycystic liver disease: Hepatic venous outflow obstruction lesions of the noncystic parenchyma have major consequences. *Hepatol Baltim Md*. 2018;68(2):652-662. doi:10.1002/hep.29582

Supplementary Methods

Study Design and Data Source

The study was conceived as an observational, retrospective pharmacovigilance analysis using adverse events (AEs) recorded in the US Food and Drug Administration Adverse Event Reporting System (FAERS). The FAERS archive is a global pharmacovigilance database successfully exploited in the recent past for accurate and timely real-world safety assessment of drugs, including a) early detection of safety concerns for newly marketed drugs, which may not be fully appreciated in the pre-marketing setting [S11, S12], b) continuous monitoring of safety issues for old drugs, c) signal detection of nonserious AEs, to which little attention is usually given [S13].

When properly designed, the accuracy of pharmacovigilance analyses through FAERS is noteworthy (i.e., the ability to actually distinguish true from false negatives) [S14], and a recent study found that risk estimates from meta-analyses and pharmacovigilance analyses correlate in some cases [S15], thus supporting the role of FAERS in designing targeted pharmaco-epidemiological studies or exploring the underlying pharmacological basis [S16].

The FAERS repository collects solicited and unsolicited AEs (including medication errors) submitted by healthcare professionals, patients and manufacturers. It gathers more than 20 million raw reports and covers virtually worldwide population (relevant catchment area includes also serious reports from EU and other non-US Countries) [S17, S18]. Data can be analyzed both through interactive web-based tool (the so-called FAERS public dashboard) or by downloading raw data for customized search, as performed in the present study. To this purpose, publicly-available quarterly data were downloaded as ASCII files from the FDA website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html) and pre-processed to remove duplicates (i.e., reports overlapping in key pre-specified fields, including active substance(s), AEs, event date, age, gender, reporter country, weight), and standardize drugs names into relevant active substances (using the WHODrug Dictionary, as downloaded in March 2020, and integrating manually for misspellings and new drugs to obtain a translation of 97% of drug entries) [S19]. The analysis covered the period up to September 2020.

In this study, exposure assessment considered all role codes, i.e., tolvaptan can be recorded as suspect (primary or secondary suspect), concomitant or interacting. Only the reports recording tolvaptan as Jynarque® and Jinarc® were selected (using relevant brand names or congenital cystic kidney disease as indication. Therefore, reports recording tolvaptan as Samsca® has a different posology and not comparable indications: i.e., it is always approved in adults for the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion, and in some countries, it is also indicated for heart failure.

Case definition

Cases (i.e., thromboembolic events) were identified using dedicated Standardized Medical Dictionary for Regulatory Activities Queries (SMQs), a common approach in pharmacovigilance as recommended by the so-called Good Signal Detection Practices in Pharmacovigilance [S20].

The following SMQ was used: "embolic and thrombotic events" (comprehensive search), which allows a high sensitivity search. Individual signs/symptoms, named Preferred Terms (PTs), were then analyzed as they offer a clinical perspective by specifically describing the nature and origin of the event (e.g., deep vein thrombosis, myocardial infarction, cerebrovascular accident). The full list of PTs can be found in a recent publication [S21].

Descriptive analysis

Thromboembolic events were described in terms of demographic characteristics: age, sex, reporter country (US, Europe, Asia), reporter type (e.g., clinician vs consumer), seriousness, namely resulting in death (i.e., death reported as the outcome), life-threating event, disability, hospitalization, requiring intervention, or another serious event.

The following clinical features were inspected: latency (i.e., time to onset expressed in days with interquartile range –IQR–, calculated as the difference between the date of the first administration and the date the event occurred), discontinuation, dechallenge (clinical improvement after the offending agent is suspended), rechallenge (occurrence of a similar reaction after re-administration, usually unintentional).

Analysis of concomitant medications

A focus was devoted to co-reported drugs, including cardiovascular agents and anti-gout agents. These concomitant drugs can be used as a proxy of underlying comorbidities such as cardiovascular diseases, or suggestive of AEs (i.e., hyperuricemia/gout attack, expected for tolvaptan). Additional co-reported drugs were identified a priori as having a strong evidence of thromboembolic risk or being proxy of a disease as a risk factor for thrombosis: diuretics (not recommended considering the potential synergism with acquaretic AEs on dehydration), sex hormones (contraceptives/estrogens/progestogens), glucocorticoids, antidepressants, antidiabetics, angiogenesis inhibitors, erythropoiesis-stimulating agents. Moreover, concomitant antithrombotic drugs (antiplatelet agents, heparins, vitamin K antagonists, direct oral anticoagulants) were checked

as potential proxy of pre-existing thromboembolic risk/event or indicative of management strategies (if the date of administration followed the onset date of the thrombotic event). Finally, co-reported acquaretic events were also analyzed as a potential proxy of an underlying susceptibility to thrombosis (due to the aforementioned dehydration).

Causality assessment

Individual cases were assessed for causality (categorized as highly probable, probable, possible, unlikely) according to an adaptation of the standardized WHO-UMC system, a probabilistic algorithm (https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf). Highly probable cases were those with plausible time to onset (i.e., the event was recorded after tolvaptan initiation), alternate drugs ruled out, and positive dechallenge and/or rechallenge.

Table S1. Adapted WHO-UMC Causality Categories.

ASSESSMENT	TIME SEQUENCE[$]	ALTERNATE CAUSES RULED OUT[#]	DECHALLENGE[*]
HIGHLY PROBABLE	√	√	√
PROBABLE	√	√	
POSSIBLE	√		
UNLIKELY			

EXPLANATORY NOTES

Please note that, as compared to the original version, we decided to avoid the term "certain", considering that no firm causality can be inferred.

$ This information can vary depending on the underlying event of interest). For the purpose of this study, also considering published case reports, we accepted also acute onset (i.e., 1 day) as plausible time relationship to drug intake, and thus no report was assessed as unlikely. When a drug was reported to be administered after the event occurred, the causality link was considered impossible, and the report was not included in the analysis.

Alternative causes are all reasonably ruled out. For this study, we considered both drugs which are themselves pro-thrombotic (e.g., sex hormones, glucocorticoids, angiogenesis inhibitors), and drugs which are a proxy of prothrombotic diseases (e.g., diabetes and depression). Cardiovascular agents and anti-gout agents were not considered as drug-related risk factors.

* Positive dechallenge (the event improved after drug discontinuation). For this study rechallenge was not used, since it is unlikely to occur in clinical practice (ethical issue) unless unintentional.

References

S11) Raschi E, Gatti M, Gelsomino F, et al. Lessons to be learnt from real world studies on immune-related adverse events with checkpoint inhibitors: a clinical perspective from pharmacovigilance. Target Oncol 2020, 15, 449-466.

S12) Raschi E, Poluzzi E, Salvo F, et al. Pharmacovigilance of sodium-glucose co-transporter-2 inhibitors: What a clinician should know on disproportionality analysis of spontaneous reporting systems. Nutr Metab Cardiovasc Dis 2018, 28, 533-542.

S13) Fukazawa C, Hinomura Y, Kaneko M, Narukawa M. Significance of data mining in routine signal detection: Analysis based on the safety signals identified by the FDA. Pharmacoepidemiol Drug Saf. 2018 Dec;27(12):1402-1408.

S14) Harpaz R, DuMouchel W, LePendu P, et al. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. Clin Pharmacol Ther 2013, 93, 539-546.

S15) Khouri C, Petit C, Tod M, et al. Adverse drug reaction risks obtained from meta-analyses and pharmacovigilance disproportionality analyses are correlated in most cases. J Clin Epidemiol 2021, 134, 14-21.

S16) Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol. 2011 Dec;72(6):905-908

S17) Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of the public version of the FDA adverse event reporting system. Int J Med Sci. 2013;10(7):796–803.

S18) Raschi E, Moretti U, Salvo F et al. Evolving roles of spontaneous reporting systems to assess and monitor drug safety. In: Kothari CS, Shah M, Patel RM (eds) Pharmacovigilance. Intech; 2019:1-28. Available from: https://www.intechopen.com/books/pharmacovigilance/evolving-roles-of-spontaneous-reporting-systems-to-assess-and-monitor-drug-safety

S19) Poluzzi E, Raschi E, Piccinni C et al. Data mining techniques in pharmacovigilance: analysis of the publicly accessible FDA adverse event reporting system (AERS). In: Data mining applications in engineering and medicine. Karahoca A, Ed. Croatia, InTech; 2012: 267-301. Available from: https://www.intechopen.com/books/data-mining-applications-in-engineering-and-medicine/data-mining-techniques-in-pharmacovigilance-analysis-of-the-publicly-accessible-fda-adverse-event-re

S20) Wisniewski AF, Bate A, Bousquet C, et al. Good Signal Detection Practices: Evidence from IMI PROTECT. Drug Saf 2016, 39, 469-490.

S21) Raschi E, Fusaroli M, Ardizzoni A, Poluzzi E, De Ponti F. Thromboembolic Events with Cyclin-Dependent Kinase 4/6 Inhibitors in the FDA Adverse Event Reporting System. *Cancers*. 2021; 13(8):1758. https://doi.org/10.3390/cancers13081758