

# Pulmonary Embolism in a Patient With ADPKD Treated With Tolvaptan: From the Clinical Experience to the Analysis of the Food and Drug Administration Adverse Event Reporting System Registry



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## BACKGROUND

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder (estimated prevalence of 1 per 1000–1 per 2500 live births)<sup>1</sup> characterized by the development and growth of multiple bilateral cysts eventually leading to end-stage renal disease and renal replacement therapy.<sup>1</sup>

Tolvaptan, a selective vasopressin V2 receptor antagonist, is currently the only pharmacologic agent approved for ADPKD capable of slowing the kidney cyst growth and the progression of kidney disease.<sup>2</sup> The resulting aquaretic adverse events (AEs) (polyuria, pollakiuria, and nocturia) may cause dehydration and did not seem to diminish over time,<sup>2</sup> thus supporting the need to inform patients for adequate liquid intake and maintaining long-term vigilance.

Data on the risk/benefit profile of tolvaptan in ADPKD come mainly from randomized controlled trials and small real-world studies.<sup>3</sup> The latest prospective, multinational, open-label safety study enrolling subjects who completed previous trials (median exposure 651 days) confirmed the occurrence of treatment-emergent aquaretic AEs and the importance of tight

hepatic monitoring as effective risk minimization strategy.<sup>4</sup>

Therefore, postmarketing studies are needed to evaluate rare and unexpected AEs, which are not fully appreciated in randomized controlled trials.<sup>5</sup>

We herein describe the occurrence of acute pulmonary thromboembolism in a patient with risk factors exposed to tolvaptan. To evaluate the possible association between tolvaptan and thromboembolism, we also analyzed the Food and Drug Administration Adverse Event Reporting System.

## CASE PRESENTATION

A 44-year-old woman presented to the emergency department with persistent dyspnea and chest pain on July 2020. She referred a past medical history of portal vein and caudal vena cava thrombosis during estrogen-progestogen therapy in 2009, treated with warfarin for 11 months. A heterozygous mutation for factor V Leiden was found. The patient was also affected by ADPKD and started administration of tolvaptan 60 mg/daily in October 2019 (120 mg/daily at hospital admission).

On physical examination, tachycardia of 139 beats per minute and increased respiratory rate of 30/min

with slight reduction of oxygen saturation level (96%) were observed, without signs of heart failure. Burning pain on lower limbs, without clinical signs of deep vein thrombosis, was referred. Kidney function was stable (creatinine 1.09 mg/dl, estimated glomerular filtration rate 62 ml/min) with signs of fibrinolysis as D-dimer was 2.97 mg/l (normal value <0.55 mg/l). Troponin I was 12.8 ng/l with normal B-type natriuretic peptide (30 pg/ml).

In the suspicion of acute pulmonary embolism, a contrast-enhanced computed tomography angiogram was performed and confirmed the presence of bilateral massive pulmonary thromboembolia. Inferior vena cava compression by hepatic or right renal cysts was ruled out by computed tomography and magnetic resonance imaging. Results of echocardiography performed revealed mild dilation and hypokinesia of the right ventricle with positive McConnell's sign (hypokinetic right ventricular free wall with sparing of the apex); the inferior vena cava was completely collapsed. Troponin I was 12.8 ng/l (the 99th percentile upper reference limit was 11.6 ng/l). The patient was deemed at intermediate high-risk pulmonary embolism, so anticoagulation treatment with low-molecular-weight heparin (enoxaparin 8000 U twice daily) was started plus i.v. fluid loading. Her kidney function was stable (creatinine = 0.86 mg/dl), with slightly elevated liver function enzymes (aspartate transaminase = 42 U/l, alanine transaminase = 78 U/l, gamma-glutamyl transferase = 66 U/l). Tolvaptan was discontinued, and enoxaparin was switched to a direct oral anticoagulant, rivaroxaban 20 mg.

She was discharged on day 17 with stable medical condition (creatinine = 0.8 mg/dl, aspartate transaminase/alanine transaminase/gamma-glutamyl transferase = 40/82/55 U/l), without resuming tolvaptan. After 3 months of anticoagulation therapy, reduction of the thrombus at the main pulmonary trunk and partial occlusion at the left pulmonary artery with left lung infarct lesions was found; some segmental filling defects were also revealed in the right pulmonary basilar branches. At the cardiologic assessment at 6 months, the patient was still symptomatic and despite echocardiogram results revealed a normal right ventricle size and contractile function with normal pulmonary artery pressure (15 + 5 mm Hg), the complete workup for chronic thromboembolic pulmonary hypertension was completed according with both guidelines of the European Society of Cardiology on acute pulmonary embolism and pulmonary hypertension.<sup>6</sup> Finally, chronic thromboembolic disease (persistence of thromboembolic burden but without pulmonary hypertension at rest) was

confirmed and the patient received lifelong anti-coagulation therapy for 2 previous venous thromboembolism episodes not related to major transient or reversible risk factors. Kidney and liver function enzymes were in normal range (creatinine = 0.93 mg/dl, aspartate transaminase = 15 U/l, alanine transaminase = 23 U/l, gamma-glutamyl transferase = 23 U/l).

### Food and Drug Administration Adverse Event Reporting System Analysis

The Food and Drug Administration Adverse Event Reporting System is a publicly available global spontaneous reporting system collecting real-world data on suspected adverse drug reactions. We retained reports of interest, specifically "embolic and thrombotic events," up to September 2020, building on previous experience in pharmacovigilance.<sup>7</sup> The cases were described in terms of demographic and clinical information, including causality assessment (see [Supplementary Methods](#)).

Overall, 57 thromboembolic events were found (24 explicitly venous and 21 arterial), involving mostly the lung (in 32% of the cases), periphery (23%), nervous system (21%), and heart (18%), with pulmonary embolism being the most frequently reported AE (13 cases).

There were 32 cases (61.5% of the reports specifying sex) that occurred in males, 61.4% were submitted by physicians, and the median age was 51 years. It should be noted that 12 cases concerned people of more than 60 years of age, but this is in line with the lack of age limits for reimbursement in multiple countries (6 of these reports are from Japan and 2 from France).<sup>S1</sup> Most of the reports were serious (65%), such as resulting in death (6 cases), life-threatening event, disability, hospitalization, requiring intervention, or another serious event. Median latency (i.e., time from the prescription of tolvaptan and the onset of AE), calculated on 19 cases, was approximately 5 months, with 50% of the thromboembolic events occurring between 2 months and 10 months. In 34 cases (59.6%) tolvaptan was discontinued (positive dechallenge result in 17 cases).

Cardiovascular drugs, mainly amlodipine, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, were recorded in 35 cases, and antigout agents were found in 15 cases. Potential risk factors were recorded in 16 cases (28%), mostly sex hormones and diuretics (11% each). In 11 cases (19.3%), antithrombotic therapy was documented (in 3 cases specified as therapy for the thromboembolic event). Most frequently co-reported events were thirst and pollakiuria (6 cases each). A highly probable/

**Table 1.** Individual case assessment

| Case <sup>a</sup>        | Thromboembolic event                     | Country <sup>a</sup> | Age | Sex | Latency (d) | Discontinuation | Risk factors               | Antithrombotics | Aquaretic events                             | Seriousness | Causality       |
|--------------------------|------------------------------------------|----------------------|-----|-----|-------------|-----------------|----------------------------|-----------------|----------------------------------------------|-------------|-----------------|
| Venous thromboembolism   |                                          |                      |     |     |             |                 |                            |                 |                                              |             |                 |
| 1                        | Deep vein thrombosis                     | NL                   | 48  | M   |             | Y               |                            |                 |                                              |             | Probable        |
| 2                        | Pulmonary embolism                       | US                   | 51  | M   | 54          | N               | Citalopram                 |                 |                                              | HO          | Possible        |
| 3                        | Pulmonary embolism; thrombosis           | DE                   |     | F   |             | N               | Desogestrel                |                 |                                              | HO          | Possible        |
| 4                        | Deep vein thrombosis; pulmonary embolism | US                   | 46  | M   | 1035        | Y (D)           |                            |                 | Acute kidney injury                          | HO          | Highly probable |
| 5                        | Deep vein thrombosis; pulmonary embolism | DE                   | 46  | M   | 468         | Y               |                            |                 |                                              | HO          | Probable        |
| 6                        | Deep vein thrombosis                     | GB                   | 48  | F   |             | N               | Desogestrel                |                 |                                              |             | Possible        |
| 7                        | Pulmonary embolism                       | FR                   | 67  | M   | 1           | Y (D)           | Escitalopram; furosemide   | ASA             |                                              | HO          | Possible        |
| 8                        | Pulmonary embolism                       | FR                   | 67  | M   | 69          | Y (D)           |                            |                 |                                              | HO          | Highly probable |
| 9                        | Deep vein thrombosis                     | US                   | 42  | M   |             | Y               |                            | Enoxaparin      |                                              |             | Probable        |
| 10                       | Budd-Chiari syndrome                     | DE                   | 51  | F   |             | Y               | Spironolactone; torasemide | Enoxaparin      |                                              | HO          | Possible        |
| 11                       | Pulmonary embolism; thrombosis           | CA                   | 33  | F   |             | Y (D)           | Medroxyprogesterone        |                 |                                              | HO          | Possible        |
| 12                       | Pulmonary embolism                       | US                   | 51  | M   |             | N               |                            |                 | Pollakiuria                                  |             | Probable        |
| 13                       | Pulmonary thrombosis                     | US                   | 58  | F   |             | N               |                            |                 |                                              | HO          | Highly probable |
| 14                       | Pulmonary embolism                       | ES                   |     | M   |             | N               |                            |                 |                                              | DEA         | Probable        |
| 15                       | Portal vein occlusion                    | US                   | 35  | M   |             | Y               | Erythropoietin             |                 | Thirst                                       | LT          | Possible        |
| 16                       | Portal vein occlusion                    | US                   | 35  | M   |             | N               |                            |                 |                                              |             | Probable        |
| Venous thromboembolism   |                                          |                      |     |     |             |                 |                            |                 |                                              |             |                 |
| 17                       | Pulmonary thrombosis                     | AU                   |     | F   |             | N               |                            |                 | Nocturia                                     |             | Probable        |
| 18                       | Pulmonary thrombosis                     | US                   |     | M   |             | N               | Testosterone               |                 |                                              | HO          | Possible        |
| 19                       | Pulmonary thrombosis                     | US                   | 77  | M   | 101         | N               | Testosterone               |                 | Polydipsia, pollakiuria, nocturia, dry mouth | DEA         | Possible        |
| 20                       | Pulmonary thrombosis                     | AU                   |     | F   |             | N               |                            |                 | Thirst, nocturia, dry mouth                  |             | Probable        |
| 21                       | Deep vein thrombosis; pulmonary embolism | JP                   | 58  | M   | 144         | Y (D)           |                            |                 | Hypnatremia, dehydration                     | HO          | Highly probable |
| 22                       | Pulmonary embolism                       | JP                   | 43  | M   |             | Y (D)           |                            | Warfarin        |                                              |             | Highly probable |
| 23                       | Pulmonary embolism                       | FR                   | 40  | F   |             | Y               |                            |                 |                                              |             | Probable        |
| 24                       | Pulmonary embolism                       | DE                   |     |     |             | N               |                            |                 |                                              |             | Probable        |
| Arterial thromboembolism |                                          |                      |     |     |             |                 |                            |                 |                                              |             |                 |

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**Table 1.** (Continued) Individual case assessment

| Case <sup>a</sup>                  | Thromboembolic event                         | Country <sup>a</sup> | Age | Sex | Latency (d) | Discontinuation | Risk factors        | Antithrombotics | Aquaretic events                                                     | Seriousness | Causality       |
|------------------------------------|----------------------------------------------|----------------------|-----|-----|-------------|-----------------|---------------------|-----------------|----------------------------------------------------------------------|-------------|-----------------|
| 1                                  | Hepatic artery thrombosis                    | BE                   | 45  | F   | 201         | Y               | Nomegestrol         |                 |                                                                      |             | Possible        |
| 2                                  | Retinal artery occlusion                     | JP                   | 75  | M   |             | Y (D)           |                     |                 |                                                                      | HO          | Highly probable |
| 3                                  | Myocardial infarction                        | DE                   | 51  |     |             | Y               |                     |                 |                                                                      |             | Probable        |
| 4                                  | Cerebellar infarction; stress cardiomyopathy | JP                   | 66  | F   | 271         | Y (D)           |                     |                 |                                                                      | HO          | Highly probable |
| 5                                  | Myocardial infarction                        | FR                   | 57  | M   | 184         | Y (D)           |                     |                 |                                                                      | HO          | Highly probable |
| 6                                  | Amaurosis                                    | DE                   |     | M   | 298         | Y (D)           |                     | ASA             |                                                                      | HO          | Highly probable |
| 7                                  | Transient ischemic attack                    | JP                   | 62  | F   | 315         | Y (D)           |                     |                 |                                                                      | HO          | Highly probable |
| 8                                  | Lacunar infarction                           | JP                   | 57  | M   |             | Y               | Furosemide          |                 | Hypernatremia                                                        | HO          | Possible        |
| Arterial thromboembolism           |                                              |                      |     |     |             |                 |                     |                 |                                                                      |             |                 |
| 9                                  | Transient ischemic attack                    | JP                   | 50  | F   |             | Y (D)           |                     |                 |                                                                      |             | Highly probable |
| 10                                 | Myocardial infarction                        | IT                   | 40  | M   |             | Y (D)           |                     |                 |                                                                      | HO          | Highly probable |
| 11                                 | Myocardial infarction                        | CA                   |     |     |             |                 |                     | Warfarin        |                                                                      | DEA         | Probable        |
| 12                                 | Blindness transient                          | CA                   | 55  | F   | 1           | N               | Hydrochlorothiazide |                 | Pollakiuria; hypotension                                             |             | Possible        |
| 13                                 | Acute myocardial infarction                  | SE                   | 44  | F   |             | N               |                     |                 |                                                                      | HO          | Probable        |
| 14                                 | Myocardial infarction                        | US                   | 65  | M   | 155         | Y               |                     |                 |                                                                      |             | Probable        |
| 15                                 | Retinal vein occlusion                       | FR                   | 44  |     |             | N               |                     |                 |                                                                      |             | Probable        |
| 16                                 | Myocardial infarction                        | CA                   | 49  | M   |             | N               |                     | Warfarin        |                                                                      | DEA         | Probable        |
| 17                                 | Amaurosis fugax                              | AT                   | 61  | F   |             | N               | Hydrochlorothiazide |                 |                                                                      | HO          | Possible        |
| 18                                 | Peripheral artery occlusion                  | AU                   | 47  | M   |             | N               |                     |                 | Pollakiuria                                                          |             | Probable        |
| 19                                 | Stress cardiomyopathy                        | IT                   | 45  | F   |             | Y (D)           |                     |                 |                                                                      | HO          | Highly probable |
| 20                                 | Acute myocardial infarction                  | KR                   | 36  | M   |             | N               |                     |                 |                                                                      | DEA         | Probable        |
| 21                                 | Transient ischemic attack                    | US                   | 66  | M   |             | Y (D)           | Fluticasone         | Clopidogrel     | Thirst; hypotension; hypernatremia; dehydration; acute kidney injury | HO          | Possible        |
| Other nonspecified thromboembolism |                                              |                      |     |     |             |                 |                     |                 |                                                                      |             |                 |
| 1                                  | Cerebral infarction                          | JP                   | 59  | M   |             | Y               |                     |                 | Hypovolemia                                                          | HO          | Probable        |
| 2                                  | Disseminated intravascular coagulation       | JP                   | 51  | F   | 146         | Y               |                     |                 | Dehydration; acute kidney injury                                     | DEA         | Probable        |
| Other nonspecified thromboembolism |                                              |                      |     |     |             |                 |                     |                 |                                                                      |             |                 |
| 3                                  | Thrombosis                                   | US                   | 40  | F   |             | Y               | Escitalopram        | Apixaban        | Thirst; pollakiuria                                                  | HO          | Possible        |
| 4                                  | Cerebral infarction                          | JP                   | 58  | F   |             | Y               |                     | clopidogrel     |                                                                      |             | Probable        |

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**Table 1.** (Continued) Individual case assessment

| Case <sup>a</sup> | Thromboembolic event     | Country <sup>a</sup> | Age | Sex | Latency (d) | Discontinuation | Risk factors | Antithrombotics | Aquaretic events     | Seriousness | Causality       |
|-------------------|--------------------------|----------------------|-----|-----|-------------|-----------------|--------------|-----------------|----------------------|-------------|-----------------|
| 5                 | Cerebral infarction      | JP                   | 66  | M   |             | Y               |              |                 |                      | DS          | Probable        |
| 6                 | Thrombosis               | US                   | 56  | M   | 1           | N               |              |                 |                      | HO          | Probable        |
| 7                 | Cerebral infarction      | JP                   | 80  | M   |             |                 |              |                 |                      | HO          | Probable        |
| 8                 | Thrombosis               | CA                   | 49  | M   | 1           |                 |              |                 | Polydipsia; nocturia | HO          | Probable        |
| 9                 | Thrombosis               | US                   | 32  | M   |             | N               |              | Apixaban        |                      | HO          | Probable        |
| 10                | Cerebral infarction      | JP                   | 63  | M   |             | Y               | Furosemide   |                 |                      | HO          | Possible        |
| 11                | Cerebrovascular accident | TW                   | 41  | F   | 83          | Y (D)           |              |                 |                      | HO          | Highly probable |
| 12                | Cerebrovascular accident | US                   |     |     | 441         | N               |              |                 |                      |             | Probable        |

ASA, acetylsalicylic acid; AT, Austria; AU, Australia; BE, Belgium; CA, Canada; D, dechallenge; DE, Germany; DEA, death; DS, disability; ES, Spain; F, female; FR, France; GB, United Kingdom; HO, hospitalization; ISD, International Organization for Standardization; IT, Italy; JP, Japan; KR, South Korea; LT, life threatening; M, male; N, no; NL, Netherlands; SE, Sweden; TW, Taiwan; US, United States; Y, yes.

<sup>a</sup>Countries are coded using their ISO 3166-1 alpha-2 code.

probable causality was found in 51% of the cases and probable in 49% (Table 1).

## DISCUSSION AND CONCLUSION

After the publication of TEMPO 3:4 trial, tolvaptan was approved worldwide to slow the progression of cyst development and end-stage renal disease of ADPKD in adults. Aquaretic events and liver injury were key treatment-emergent AEs, whereas thromboembolism was not identified as a safety issue.

To our knowledge, this is the first comprehensive real-world characterization of thromboembolic events to tolvaptan in patients with ADPKD collected from a real-world global spontaneous reporting system. Only 1 case report was published, in which venous thromboembolism occurred in a 60-year-old man after 6 days of persistent watery diarrhea, a likely cause of prothrombotic dehydration.<sup>8</sup>

It should be noted that chronic kidney disease is a well-established risk factor for venous thromboembolism. Notably, for chronic kidney disease and end-stage renal disease, this increased risk is due to increased tissue factor and fibrinogen levels, enhanced activation of factors XIIa and VIIa, and reduced tissue plasminogen activator.<sup>4,7-9</sup> Furthermore, many known conditions in patients with ADPKD may add up and raise the risk of thrombosis, such as erythrocytosis,<sup>S2</sup> inferior vena cava compression,<sup>S3-S6</sup> and hepatic venous outflow obstruction with or without Budd-Chiari syndrome.<sup>S7-S10</sup> Therefore, it could be stated that tolvaptan may have a contributory rather than a causative role in thromboembolism, although the association is quite unclear. More studies on the matter are required to better understand thromboembolic risk in these patients and help stratify them to identify those who could be more at risk of developing this life-threatening condition.

The following 2 clues emerged from our data: (i) concomitant aquaretic events (including the use of diuretics) and drug-related risk factors (especially sex hormones) were recorded in a nonnegligible proportion of thromboembolic events and (ii) even in the presence of increased patient susceptibility (i.e., Leiden V factor mutation and previous thromboembolism during estrogen-progestogen therapy), the onset was delayed up to 9 to 10 months. Regarding arterial and non-specified thromboembolic events, the highest ratio of patients older than 60 years (29% and 25%, respectively, vs. 13% in venous events) may suggest a possible confounding or contributory role of age for nonvenous cases.

Taken together, these data (i) strengthen the importance of routine medication review to minimize

potential toxic synergism; (ii) support long-term monitoring by nephrologists to timely diagnose signs and typical symptoms, such as edema, sudden leg swelling, thrombophlebitis, shortness of breath, hypoxia, chest pain, polypnea, and tachycardia; and (iii) call for constant epidemiologic surveillance and clarification by means of dedicated registries. Whether formal thrombophilic assessment should be performed when prescribing tolvaptan, particularly in subjects with previous events or other risk factors (including concomitant drugs), remains an unresolved question; further studies of the prevalence of hypercoagulable states in patients with ADPKD are needed.

We acknowledge the limitations of our study, which do not allow to provide incidence rates. Moreover, clinical features (genetics body mass index, patient's history, comorbidities, inferior vena cava syndrome, infections) and instrumental assessment (ultrasonography and laboratory parameters) to support diagnosis and risk stratification/prediction cannot be fully analyzed. Therefore, causal association cannot be firmly inferred.

In conclusion, although tolvaptan could be effective in retarding the progression of ADPKD, a signal of thromboembolism emerged from the Food and Drug Administration Adverse Event Reporting System. Nephrologists should monitor the occurrence of thromboembolic events for timely assessment and prompt management, including medication review and tolvaptan discontinuation.

## DISCLOSURE

All the authors declared no competing interests.

## SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplemental References.](#)

[Supplementary Methods.](#)

**Table S1.** Adapted World Health Organization-Uppsala Monitoring Centre causality categories.

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