



Review

# Urine Aquaporin-2: A Promising Marker of Response to the Arginine Vasopressin Type-2 Antagonist, Tolvaptan in Patients with Congestive Heart Failure

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**Abstract:** Aquaporin-2, a member of the aquaporin family, is an arginine vasopressin-regulated water channel expressed in the renal collecting duct, and a promising marker of the concentrating and diluting ability of the kidney. The arginine vasopressin type-2 antagonist, tolvaptan, is a new-generation diuretic; it is especially indicated in patients with decompensated heart failure refractory to conventional diuretics. However, the ideal responders to tolvaptan have not yet been identified, and non-responders experience worse clinical courses despite treatment with tolvaptan. Urine aquaporin-2 has recently been demonstrated as a promising predictor of response to tolvaptan. We here validated aquaporin-2-guided tolvaptan therapy in patients with decompensated heart failure. Long-term efficacy of tolvaptan treatment in the responders defined by aquaporin-2 needs to be validated in the future prospective study.

**Keywords:** heart failure; congestion; chronic kidney disease; hyponatremia

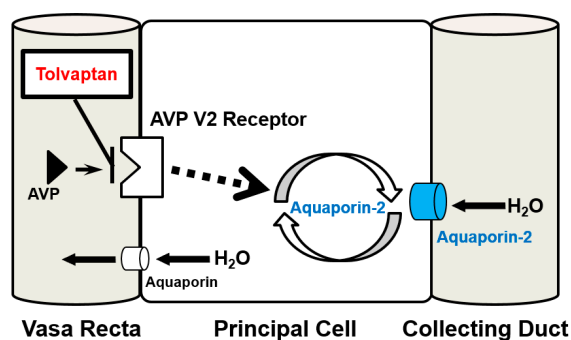
## 1. Aquaporin-2 in Patients with Congestive Heart Failure (HF)

The aquaporin family has various activities in the human body, such as mediating water transport, and cell adhesion, migration, proliferation, and differentiation [1]. Of the aquaporin family members, aquaporin-2 has been characterized as an arginine vasopressin (AVP)-regulated water channel protein translocating between the apical plasma membrane and subapical vesicles in the principal cells of the collecting duct [2].

The mechanisms of aquaporin-2-mediated water retention have been studied for the past 20 years [3]. Secreted AVP binds to the AVP type-2 ( $V_2$ ) receptor located at the basolateral membrane of principal cells (Figure 1). Activation of the  $V_2$  receptor triggers the trafficking of aquaporin-2 from intracellular storage vesicles to the apical membrane by cAMP-dependent phosphorylation of aquaporin-2 [4,5]. Translocation of aquaporin-2 to the apical membrane increases water permeability, thereby increasing urine osmolality (U-OSM) [6].

Approximately 3% of aquaporin-2, in particular phosphorylated and translocated aquaporin-2, in the kidney tissue is excreted in urine [7]. Therefore, urine aquaporin-2 is considered a marker of collecting duct responsiveness to AVP [8].

Several techniques have been developed to quantify urine aquaporin-2, such as radioimmunoassay, Western blotting, and sandwich enzyme-linked immunosorbent assay [7,9,10], and urine aquaporin-2 has been quantified in various clinical conditions including pregnancy [11], liver cirrhosis [12], syndrome of inappropriate secretion of antidiuretic hormone [5], diabetes insipidus [4], and HF [13,14].



**Figure 1.** The relationship between arginine vasopressin, aquaporin-2, and tolvaptan in the collecting duct. AVP, arginine vasopressin.

In patients with congestive HF, AVP is inappropriately secreted through the activation of a non-osmotic pathway owing to reduced effective circulating volume, despite peripheral water retention [15–18]. Secreted AVP stimulates the expression and translocation of aquaporin-2 at the apical membrane of the collecting duct [4,5], thereby facilitating water retention and successive hypervolemic hyponatremia (Figure 1) [15]. Therefore, urine aquaporin-2 level increases in patients with HF owing to inappropriately elevated serum AVP level. Plasma level of AVP increases in association with HF progression, accompanied by activation of the renin-angiotensin-aldosterone system and sympathetic nerve system, which facilitate water retention [15–17,19]. Many studies have demonstrated that hyponatremia is a predictor of morbidity and mortality in patients with HF [20–23].

## 2. Tolvaptan and Its Responsiveness

Tolvaptan, the only commercially available vasopressin  $V_2$  receptor antagonist, thus far, has been recently developed as a promising agent to treat patients with congestive HF refractory to conventional diuretics [24]. It has a unique therapeutic target: it blocks AVP-aquaporin-2 pathway, and increases the excretion of electrolyte-free water in urine (Figure 1). Many studies have demonstrated the short-term efficacy and safety of tolvaptan; it also ameliorates symptomatic congestion, normalizes hyponatremia to maintain hemodynamics and the sparing renal function, and terminates the vicious cycle of HF described above [25–35]. However, these benefits may not be expected in non-responders, whose urine volume does not increase despite the administration of tolvaptan [36]. Tolvaptan could not normalize serum sodium concentration, ameliorate symptomatic congestion, and improve renal function in non-responders. Moreover, indeterminate administration of tolvaptan to non-responders may result in a loss of the optimal timing of intensive treatment [37].

Tolvaptan was not found to be superior to placebo in terms of long-term survival rate in the Efficacy of Vasopressin Antagonist in HF Outcome Study with Tolvaptan (EVEREST) trial [38]. Considering that tolvaptan demonstrated improved survival rate over the placebo in patients with hyponatremia in this subanalysis [39], it may improve long-term prognosis only in a specific population. Therefore, it is necessary to identify the optimal population, *i.e.*, responders [40,41].

## 3. Tolvaptan and Aquaporin-2

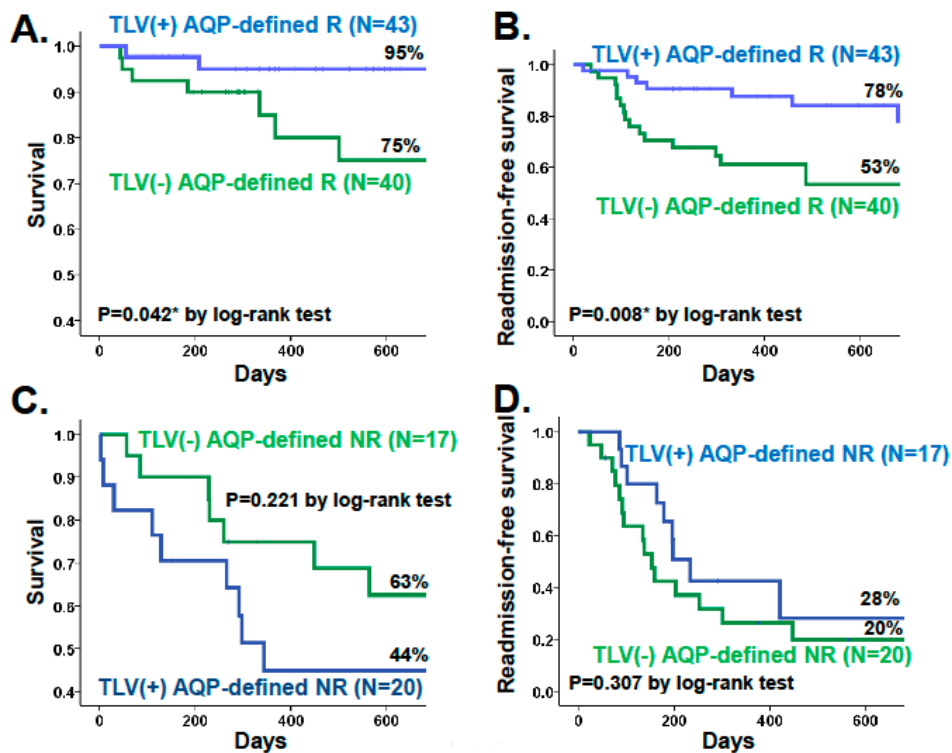
Several studies recently demonstrated that unresponsiveness to tolvaptan is associated with decreased renal function [42–44]. Older patients with chronic kidney disease have a trend of physiological insipidus mellitus, and have reduced urine concentrating ability. Tolvaptan may not be able to inhibit the already-extinct AVP-aquaporin-2 system in the collecting duct, and the residual function of the collecting duct is essential for response to tolvaptan [40,45]. Therefore, urine aquaporin-2 has been evaluated as a predictive “marker” of responsiveness to tolvaptan [46].

We recently demonstrated that higher urine aquaporin-2 level at baseline relative to plasma AVP was a novel predictor of responsiveness to tolvaptan [37], because urine aquaporin-2 level increases in

association with AVP stimulation under the well-preserved function of the collecting duct. Higher level of urine aquaporin-2 is associated with elevated U-OSM in the responders [37]. Thus, U-OSM could be an alternative to urine aquaporin-2 for the prediction of responses to tolvaptan [40].

In contrast, urine aquaporin-2 levels in non-responders were not detectable, regardless of serum AVP level [37]. In general, expression level of aquaporin-2 decreases in patients with chronic kidney disease [47]. Sato *et al.* showed that aquaporin-2 is not expressed in the renal tissue of non-responders with diabetes nephropathy [48]. However, not all patients with chronic kidney disease have reduced urine excretion of aquaporin-2. Some patients have preserved function of the collecting duct despite decreased glomerular filtration ratio, and such patients are classified as responders to tolvaptan [37]. However, several studies reported that even patients with advanced chronic kidney disease responded to tolvaptan [43–45,49,50]. Therefore, urine aquaporin-2 could be a novel predictor to estimate the responders to tolvaptan especially among those with chronic kidney disease.

Long-term improvements in survival and re-admission-free survival rate were observed in the responders receiving tolvaptan, who were defined by urine aquaporin-2, although the study was retrospective (Figure 2A,B) [37]. In this study, potential response was defined as baseline urine aquaporin-2/serum AVP level  $>1.4 \times 10^3$  L/gCre, and those receiving tolvaptan were compared with propensity score-matched control group. In contrast, non-responders, whose urine aquaporin-2/serum AVP level  $<1.4 \times 10^3$  L/gCre, could neither achieve improvement in survival nor in re-admission-free survival rate despite tolvaptan administration, compared with propensity score-matched non-responders without tolvaptan (Figure 2A,B). Tolvaptan ameliorated symptomatic congestion, normalized hyponatremia, improved renal function, and reduced the dose of diuretics in the aquaporin-defined responders. These effects may improve patients' prognosis during long-term tolvaptan treatment. Prospective randomized trials are warranted to evaluate long-term improvement in the prognosis of the aquaporin-defined responders receiving tolvaptan.



**Figure 2.** Kaplan-Meier curves showing survival and readmission-free survival rate stratified by the administration of tolvaptan in responders (A,B) and non-responders (C,D). R, responder; NR, non-responder; TLV, tolvaptan, AQP, aquaporin.

Measurement of urine aquaporin-2 is also useful in confirming the response to tolvaptan in a timely fashion. Martin *et al.* showed that urine aquaporin-2 level decreased accompanied by an increase in urine volume from 2 h after the administration of tolvaptan [14]. Udelson *et al.* demonstrated a decrease in urine osmolality at 4 h after tolvaptan administration, which indicates decreased aquaporin-2 activity [31]. The decreased level of urine aquaporin-2 is restored the next morning, but does not reach the baseline level, which may indicate prolonged blockade of V<sub>2</sub> receptor by tolvaptan for >24 h [51]. In contrast, urine aquaporin-2 remained undetectable during tolvaptan treatment in the non-responders [51]. Persistent undetectable level of urine aquaporin-2 regardless of tolvaptan administration indicates lack of response to tolvaptan.

#### 4. Conclusions

In conclusion, urine aquaporin-2 is a novel predictor of responsiveness to tolvaptan, and the responders achieved amelioration of symptomatic congestion, normalization of hyponatremia, and improvement in renal function during tolvaptan treatment. Long-term prognosis in the aquaporin-defined responders during tolvaptan treatment should be confirmed in a prospective randomized trial in the future.

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**Author Contributions:** Koichiro Kinugawa designed and reviewed the study; Teruhiko Imamura designed the study and wrote the paper

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#### Abbreviations

HF	heart failure
AVP	arginine vasopressin
U-OSM	urine osmolality

#### References

1. Ishibashi, K.; Kondo, S.; Hara, S.; Morishita, Y. The evolutionary aspects of aquaporin family. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2011**, *300*, R566–R576. [[CrossRef](#)] [[PubMed](#)]
2. Park, E.J.; Kwon, T.H. A minireview on vasopressin-regulated aquaporin-2 in kidney collecting duct cells. *Electrol. Blood Press.* **2015**, *13*, 1–6. [[CrossRef](#)] [[PubMed](#)]
3. Ishikawa, S.E. Hyponatremia associated with heart failure: Pathological role of vasopressin-dependent impaired water excretion. *J. Clin. Med.* **2015**, *4*, 933–947. [[CrossRef](#)] [[PubMed](#)]
4. Kanno, K.; Sasaki, S.; Hirata, Y.; Ishikawa, S.; Fushimi, K.; Nakanishi, S.; Bichet, D.G.; Marumo, F. Urinary excretion of aquaporin-2 in patients with diabetes insipidus. *N. Engl. J. Med.* **1995**, *332*, 1540–1545. [[CrossRef](#)] [[PubMed](#)]
5. Ishikawa, S.; Saito, T.; Fukagawa, A.; Higashiyama, M.; Nakamura, T.; Kusaka, I.; Nagasaka, S.; Honda, K.; Saito, T. Close association of urinary excretion of aquaporin-2 with appropriate and inappropriate arginine vasopressin-dependent antidiuresis in hyponatremia in elderly subjects. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 1665–1671. [[CrossRef](#)]
6. Robertson, G.L.; Mahr, E.A.; Athar, S.; Sinha, T. Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. *J. Clin. Investig.* **1973**, *52*, 2340–2352. [[CrossRef](#)] [[PubMed](#)]
7. Rai, T.; Sekine, K.; Kanno, K.; Hata, K.; Miura, M.; Mizushima, A.; Marumo, F.; Sasaki, S. Urinary excretion of aquaporin-2 water channel protein in human and rat. *J. Am. Soc. Nephrol.* **1997**, *8*, 1357–1362. [[PubMed](#)]
8. Elliot, S.; Goldsmith, P.; Knepper, M.; Haughey, M.; Olson, B. Urinary excretion of aquaporin-2 in humans: A potential marker of collecting duct responsiveness to vasopressin. *J. Am. Soc. Nephrol.* **1996**, *7*, 403–409. [[PubMed](#)]

9. Umenishi, F.; Summer, S.N.; Cadnapaphornchai, M.; Schrier, R.W. Comparison of three methods to quantify urinary aquaporin-2 protein. *Kidney Int.* **2002**, *62*, 2288–2293. [[CrossRef](#)] [[PubMed](#)]
10. Sasaki, S.; Ohmoto, Y.; Mori, T.; Iwata, F.; Muraguchi, M. Daily variance of urinary excretion of AQP2 determined by sandwich elisa method. *Clin. Exp. Nephrol.* **2012**, *16*, 406–410. [[CrossRef](#)] [[PubMed](#)]
11. Buemi, M.; D'Anna, R.; di Pasquale, G.; Floccari, F.; Ruello, A.; Aloisi, C.; Leonardi, I.; Frisina, N.; Corica, F. Urinary excretion of aquaporin-2 water channel during pregnancy. *Cell. Physiol. Biochem.* **2001**, *11*, 203–208. [[CrossRef](#)] [[PubMed](#)]
12. Ivarsen, P.; Frokiaer, J.; Aagaard, N.K.; Hansen, E.F.; Bendtsen, F.; Nielsen, S.; Vilstrup, H. Increased urinary excretion of aquaporin 2 in patients with liver cirrhosis. *Gut* **2003**, *52*, 1194–1199. [[CrossRef](#)] [[PubMed](#)]
13. Funayama, H.; Nakamura, T.; Saito, T.; Yoshimura, A.; Saito, M.; Kawakami, M.; Ishikawa, S.E. Urinary excretion of aquaporin-2 water channel exaggerated dependent upon vasopressin in congestive heart failure. *Kidney Int.* **2004**, *66*, 1387–1392. [[CrossRef](#)] [[PubMed](#)]
14. Martin, P.Y.; Abraham, W.T.; Lieming, X.; Olson, B.R.; Oren, R.M.; Ohara, M.; Schrier, R.W. Selective V<sub>2</sub>-receptor vasopressin antagonism decreases urinary aquaporin-2 excretion in patients with chronic heart failure. *J. Am. Soc. Nephrol.* **1999**, *10*, 2165–2170. [[PubMed](#)]
15. Imamura, T.; Kinugawa, K.; Hatano, M.; Fujino, T.; Inaba, T.; Maki, H.; Kinoshita, O.; Nawata, K.; Kyo, S.; Ono, M.; *et al.* Low cardiac output stimulates vasopressin release in patients with stage D heart failure. *Circ. J.* **2014**, *78*, 2259–2267. [[CrossRef](#)] [[PubMed](#)]
16. Goldsmith, S.R.; Francis, G.S.; Cowley, A.W., Jr.; Levine, T.B.; Cohn, J.N. Increased plasma arginine vasopressin levels in patients with congestive heart failure. *J. Am. Coll. Cardiol.* **1983**, *1*, 1385–1390. [[CrossRef](#)]
17. Szatalowicz, V.L.; Arnold, P.E.; Chaimovitz, C.; Bichet, D.; Berl, T.; Schrier, R.W. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. *N. Engl. J. Med.* **1981**, *305*, 263–266. [[CrossRef](#)] [[PubMed](#)]
18. Pruszczyński, W.; Vahanian, A.; Ardaillou, R.; Acar, J. Role of antidiuretic hormone in impaired water excretion of patients with congestive heart failure. *J. Clin. Endocrinol. Metab.* **1984**, *58*, 599–605. [[CrossRef](#)] [[PubMed](#)]
19. Nakamura, T.; Funayama, H.; Yoshimura, A.; Tsuruya, Y.; Saito, M.; Kawakami, M.; Ishikawa, S.E. Possible vascular role of increased plasma arginine vasopressin in congestive heart failure. *Int. J. Cardiol.* **2006**, *106*, 191–195. [[CrossRef](#)] [[PubMed](#)]
20. Bettari, L.; Fiuzat, M.; Shaw, L.K.; Wojdyła, D.M.; Metra, M.; Felker, G.M.; O'Connor, C.M. Hyponatremia and long-term outcomes in chronic heart failure—An observational study from the duke databank for cardiovascular diseases. *J. Card. Fail.* **2012**, *18*, 74–81. [[CrossRef](#)] [[PubMed](#)]
21. Konishi, M.; Haraguchi, G.; Ohigashi, H.; Sasaoka, T.; Yoshikawa, S.; Inagaki, H.; Ashikaga, T.; Isobe, M. Progression of hyponatremia is associated with increased cardiac mortality in patients hospitalized for acute decompensated heart failure. *J. Card. Fail.* **2012**, *18*, 620–625. [[CrossRef](#)] [[PubMed](#)]
22. Sato, N.; Gheorghiadu, M.; Kajimoto, K.; Munakata, R.; Minami, Y.; Mizuno, M.; Aokage, T.; Asai, K.; Sakata, Y.; Yumino, D.; *et al.* Hyponatremia and in-hospital mortality in patients admitted for heart failure (from the attend registry). *Am. J. Cardiol.* **2013**, *111*, 1019–1025. [[CrossRef](#)] [[PubMed](#)]
23. Gheorghiadu, M.; Abraham, W.T.; Albert, N.M.; Gattis Stough, W.; Greenberg, B.H.; O'Connor, C.M.; She, L.; Yancy, C.W.; Young, J.; Fonarow, G.C.; *et al.* Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: An analysis from the OPTIMIZE-HF registry. *Eur. Heart J.* **2007**, *28*, 980–988. [[CrossRef](#)] [[PubMed](#)]
24. Izumi, Y.; Miura, K.; Iwao, H. Therapeutic potential of vasopressin-receptor antagonists in heart failure. *J. Pharmacol. Sci.* **2014**, *124*, 1–6. [[CrossRef](#)] [[PubMed](#)]
25. Imamura, T.; Kinugawa, K.; Minatsuki, S.; Muraoka, H.; Kato, N.; Inaba, T.; Maki, H.; Hatano, M.; Yao, A.; Komuro, I. Tolvaptan can improve clinical course in responders. *Int. Heart J.* **2013**, *54*, 377–381. [[CrossRef](#)] [[PubMed](#)]
26. Imamura, T.; Kinugawa, K.; Shiga, T.; Kato, N.; Endo, M.; Inaba, T.; Maki, H.; Hatano, M.; Yao, A.; Hirata, Y.; *et al.* Correction of hyponatremia by tolvaptan before left ventricular assist device implantation. *Int. Heart J.* **2012**, *53*, 391–393. [[CrossRef](#)] [[PubMed](#)]



27. Imamura, T.; Kinugawa, K.; Kato, N.; Minatsuki, S.; Muraoka, H.; Inaba, T.; Maki, H.; Shiga, T.; Hatano, M.; Yao, A.; *et al.* Successful conversion from thiazide to tolvaptan in a patient with stage D heart failure and chronic kidney disease before heart transplantation. *Int. Heart J.* **2013**, *54*, 48–50. [[CrossRef](#)] [[PubMed](#)]
28. Kinugawa, K.; Imamura, T.; Komuro, I. Experience of a vasopressin receptor antagonist, tolvaptan, under the unique indication in Japanese heart failure patients. *Clin. Pharmacol. Ther.* **2013**, *94*, 449–451. [[CrossRef](#)] [[PubMed](#)]
29. Costello-Boerrigter, L.C.; Smith, W.B.; Boerrigter, G.; Ouyang, J.; Zimmer, C.A.; Orlandi, C.; Burnett, J.C., Jr. Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. *Am. J. Physiol. Ren. Physiol.* **2006**, *290*, F273–F278. [[CrossRef](#)] [[PubMed](#)]
30. Schrier, R.W.; Gross, P.; Gheorghade, M.; Berl, T.; Verbalis, J.G.; Czerwiec, F.S.; Orlandi, C. Tolvaptan, a selective oral vasopressin V<sub>2</sub>-receptor antagonist, for hyponatremia. *N. Engl. J. Med.* **2006**, *355*, 2099–2112. [[CrossRef](#)] [[PubMed](#)]
31. Udelson, J.E.; Orlandi, C.; Ouyang, J.; Krasa, H.; Zimmer, C.A.; Frivold, G.; Haught, W.H.; Meymandi, S.; Macarie, C.; Raef, D.; *et al.* Acute hemodynamic effects of tolvaptan, a vasopressin V<sub>2</sub> receptor blocker, in patients with symptomatic heart failure and systolic dysfunction: An international, multicenter, randomized, placebo-controlled trial. *J. Am. Coll. Cardiol.* **2008**, *52*, 1540–1545. [[CrossRef](#)] [[PubMed](#)]
32. Berl, T.; Quittnat-Pelletier, F.; Verbalis, J.G.; Schrier, R.W.; Bichet, D.G.; Ouyang, J.; Czerwiec, F.S.; Investigators, S. Oral tolvaptan is safe and effective in chronic hyponatremia. *J. Am. Soc. Nephrol.* **2010**, *21*, 705–712. [[CrossRef](#)] [[PubMed](#)]
33. Kinugawa, K.; Sato, N.; Inomata, T.; Shimakawa, T.; Iwatake, N.; Mizuguchi, K. Efficacy and safety of tolvaptan in heart failure patients with volume overload. *Circ. J.* **2014**, *78*, 844–852. [[CrossRef](#)] [[PubMed](#)]
34. Matsuzaki, M.; Hori, M.; Izumi, T.; Fukunami, M.; Tolvaptan, I. Efficacy and safety of tolvaptan in heart failure patients with volume overload despite the standard treatment with conventional diuretics: A phase III, randomized, double-blind, placebo-controlled study (quest study). *Cardiovasc. Drugs Ther.* **2011**, *25*, S33–S45. [[CrossRef](#)] [[PubMed](#)]
35. Imamura, T.; Kinugawa, K. Mid-term administration of tolvaptan improves renal function accompanied by dose-reduction in furosemide in aquaporin-defined responders. *Int. Heart J.* **2015**, *56*, 686–687. [[CrossRef](#)] [[PubMed](#)]
36. Imamura, T.; Kinugawa, K.; Kato, N.; Minatsuki, S.; Muraoka, H.; Inaba, T.; Maki, H.; Shiga, T.; Hatano, M.; Hosoya, Y.; *et al.* A case with recovery of response to tolvaptan associated with remission of acute kidney injury and increased urine osmolality. *Int. Heart J.* **2013**, *54*, 115–118. [[CrossRef](#)] [[PubMed](#)]
37. Imamura, T.; Kinugawa, K.; Fujino, T.; Inaba, T.; Maki, H.; Hatano, M.; Yao, A.; Komuro, I. Increased urine aquaporin-2 relative to plasma arginine vasopressin is a novel marker of response to tolvaptan in patients with decompensated heart failure. *Circ. J.* **2014**, *78*, 2240–2249. [[CrossRef](#)] [[PubMed](#)]
38. Konstam, M.A.; Gheorghade, M.; Burnett, J.C., Jr.; Grinfeld, L.; Maggioni, A.P.; Swedberg, K.; Udelson, J.E.; Zannad, F.; Cook, T.; Ouyang, J.; *et al.* Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The everest outcome trial. *JAMA* **2007**, *297*, 1319–1331. [[CrossRef](#)] [[PubMed](#)]
39. Hauptman, P.J.; Burnett, J.; Gheorghade, M.; Grinfeld, L.; Konstam, M.A.; Kostic, D.; Krasa, H.B.; Maggioni, A.; Ouyang, J.; Swedberg, K.; *et al.* Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. *J. Card. Fail.* **2013**, *19*, 390–397. [[CrossRef](#)] [[PubMed](#)]
40. Imamura, T.; Kinugawa, K.; Shiga, T.; Kato, N.; Muraoka, H.; Minatsuki, S.; Inaba, T.; Maki, H.; Hatano, M.; Yao, A.; *et al.* Novel criteria of urine osmolality effectively predict response to tolvaptan in decompensated heart failure patients—Association between non-responders and chronic kidney disease. *Circ. J.* **2013**, *77*, 397–404. [[CrossRef](#)] [[PubMed](#)]
41. Imamura, T.; Kinugawa, K.; Minatsuki, S.; Muraoka, H.; Kato, N.; Inaba, T.; Maki, H.; Shiga, T.; Hatano, M.; Yao, A.; *et al.* Urine osmolality estimated using urine urea nitrogen, sodium and creatinine can effectively predict response to tolvaptan in decompensated heart failure patients. *Circ. J.* **2013**, *77*, 1208–1213. [[CrossRef](#)] [[PubMed](#)]
42. Toda, H.; Nakamura, K.; Nakahama, M.; Wada, T.; Watanabe, A.; Hashimoto, K.; Terasaka, R.; Tokioka, K.; Nishii, N.; Miyoshi, T.; *et al.* Clinical characteristics of responders to treatment with tolvaptan in patients

- with acute decompensated heart failure: Importance of preserved kidney size. *J. Cardiol.* **2015**, *67*, 177–183. [[CrossRef](#)] [[PubMed](#)]
43. Tanaka, A.; Katsuno, T.; Ozaki, T.; Sakata, F.; Kato, N.; Suzuki, Y.; Kosugi, T.; Kato, S.; Tsuboi, N.; Sato, W.; *et al.* The efficacy of tolvaptan as a diuretic for chronic kidney disease patients. *Acta Cardiol.* **2015**, *70*, 217–223. [[PubMed](#)]
44. Tominaga, N.; Kida, K.; Matsumoto, N.; Akashi, Y.J.; Miyake, F.; Kimura, K.; Shibagaki, Y. Safety of add-on tolvaptan in patients with furosemide-resistant congestive heart failure complicated by advanced chronic kidney disease: A sub-analysis of a pharmacokinetics/pharmacodynamics study. *Clin. Nephrol.* **2015**, *84*, 29–38. [[CrossRef](#)] [[PubMed](#)]
45. Iwatani, H.; Kawabata, H.; Sakaguchi, Y.; Yamamoto, R.; Hamano, T.; Rakugi, H.; Isaka, Y. Urine osmolality predicts the body weight-reduction response to tolvaptan in chronic kidney disease patients: A retrospective, observational study. *Nephron* **2015**, *130*, 8–12. [[CrossRef](#)] [[PubMed](#)]
46. Imamura, T. Aquaporin-2-guided tolvaptan therapy in patients with congestive heart failure accompanied by chronic kidney disease. *Int. Heart J.* **2014**, *55*, 482–483. [[CrossRef](#)] [[PubMed](#)]
47. Jensen, J.M.; Mose, F.H.; Kulik, A.E.; Bech, J.N.; Fenton, R.A.; Pedersen, E.B. Abnormal urinary excretion of NKCC2 and AQP2 in response to hypertonic saline in chronic kidney disease: An intervention study in patients with chronic kidney disease and healthy controls. *BMC Nephrol.* **2014**, *15*, 101. [[CrossRef](#)] [[PubMed](#)]
48. Sato, E.; Nakamura, T.; Amaha, M.; Nomura, M.; Matsumura, D.; Yamagishi, H.; Ono, Y.; Ueda, Y. Effect of tolvaptan in patients with chronic kidney disease due to diabetic nephropathy with heart failure. *Int. Heart J.* **2014**, *55*, 533–538. [[CrossRef](#)] [[PubMed](#)]
49. Hirano, D.; Kakegawa, D.; Yamada, A.; Ito, A.; Miwa, S.; Ida, H. Tolvaptan in a pediatric patient with diuretic-resistant heart and kidney failure. *Pediatr. Int.* **2015**, *57*, 183–185. [[CrossRef](#)] [[PubMed](#)]
50. Otsuka, T.; Sakai, Y.; Ohno, D.; Murasawa, T.; Sato, N.; Tsuruoka, S. The effects of tolvaptan on patients with severe chronic kidney disease complicated by congestive heart failure. *Clin. Exp. Nephrol.* **2013**, *17*, 834–838. [[CrossRef](#)] [[PubMed](#)]
51. Imamura, T.; Kinugawa, K.; Komuro, I. Tolvaptan prolongs blockage of the vasopressin type II receptor over 24 hours in responders with stage D heart failure. *Int. Heart J.* **2016**. in press. [[CrossRef](#)] [[PubMed](#)]



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