Beraprost sodium versus clopidogrel for preventing vascular thromboembolic events of arteriovenous fistula in uraemic patients: a retrospective study with a mean 3-year follow-up

Ziming Wan[1],*, Ying Zhu[2],*, Ruikun Yang[3],
Yongjian Zhang[4],*, Chen Yang[5], Lei Cao[6],*,
Wenjing Yan[7],*, Qi Wang[6],*, Ning Li[8],*,
Mingdong Zhao[9], Keke Gui[9] and Min Xiong[9]

Abstract

Objective: This study aimed to evaluate the efficacy of beraprost sodium (BPS) or clopidogrel (CL) using vascular thromboembolic events (VTEs) of arteriovenous fistula as a primary endpoint in patients with end-stage renal disease (ESRD) undergoing arteriovenous fistula surgery.

[1]Department of Nephrology, The First Affiliated Hospital of Chongqing Medical University, Yuzhong District, Chongqing, China
[2]Radiology Department, The First Affiliated Hospital, Sun Yat-sen University, Yuexiu District, Guangzhou, China
[3]Department of Pediatrics, The First Affiliated Hospital, Sun Yat-sen University, Yuexiu District, Guangzhou, China
[4]Department of Thoracic surgery, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Jianghan District, Wuhan, Hubei, China
[5]Department of Physical Examination, The First Affiliated Hospital, Sun Yat-sen University, Yuexiu District, Guangzhou, China

[6]Department of Anesthesiology, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Jianghan District, Wuhan, Hubei, China
[7]The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Jianghan District, Wuhan, Hubei, China
[8]Department of Neurology, The Affiliated Hospital of Hebei University, Baoding, Hebei, China
[9]Department of Orthopaedics, Jinshan Hospital, Fudan University, Jinshan District, Shanghai City, China

*These authors contributed equally to this work.

Corresponding author:
Mingdong Zhao, Department of Orthopaedics, Jinshan Hospital, Fudan University, No. 1508 Longhang Road, Jinshan District, Shanghai 201508, China.
Email: zhaonissann@163.com

Methods: We performed a multicentre, retrospective cohort study from August 2012 to August 2016. We studied patients with ESRD who underwent arteriovenous fistula surgery and received peroral administration of 40 μg BPS, three times per day, for 1 month, or 75 mg CL (initial dose of 300 mg), one time per day, for 1 month. The time to first on-study VTE was the primary endpoint.

Results: The BPS-treated cohort had a significantly delayed time to first VTE compared with the CL-treated cohort (hazard ratio 0.33, 95% confidence interval 0.18–0.56). An increased incidence of VTEs was detected in the 1-month follow-up, with rates of 2.4% and 8.7% for BPS and CL, respectively. This difference persisted over time, with rates of 8.0% and 18.1% at the final follow-up, respectively.

Conclusion: CL-treated patients with ESRD have a greater risk of VTEs compared with BPS-treated patients. CL-treated patients also tend to experience a VTE within the first month after cessation of oral administration.

Introduction

Uraemia is a potent risk factor for inducing vascular thromboembolic events (VTEs). VTEs manifest as endovascular thrombosis following interventions for arteriovenous fistula, and only inadequate antithrombotic medications pose a greater risk. Uraemia independently increases the risk of thrombosis by four to eight fold, implicating renal failure-specific prothrombotic mediators.[1–4] The estimated incidence of end-stage renal disease (ESRD) in China in 2017 was 300,00 patients, of whom almost 60% eventually died, which is partially related to common delays in diagnosis. Intervention for arteriovenous fistula, which is regarded as a lifeline of patients with ESRD, establishes permanent vascular access for these patients.[5,6] In recent years, the use of artificial blood vessels and semi-permanent tube surgery in patients with ESRD has rapidly developed.[7,8] However, this method has short-term effects, increased complications, and is expensive. Therefore, there has been an increase in these patients' mental and economic burden, which can have serious effects on their quality of life.[9,10] Previous studies have shown that the failure rate of intervention for arteriovenous fistula is 20% to 54%, mainly due to thrombosis, non-maturation, and mature obstruction of arteriovenous fistula.[11,12] The incidence of thrombus in arteriovenous fistula is more frequent within 30 days after surgery.[7] Previous studies have provided proof-of-concept that vascular access dysfunction is a major cause of morbidity and hospitalization in patients with uraemia, and this can be attributed to venous stenosis caused by neointimal hyperplasia after vascular access surgery.[11] Thrombosis caused by stenosis of an internal fistula in the forearm is common in the 3- to 4-cm venous end of the internal fistula.[8,9] Although several studies have advocated a characteristic of pharmacological agents, including anti-platelet drugs in preventing thrombosis, these studies have provided inconsistent findings.[13] Recently, pharmacological agents have been recommended to be used to decrease neointimal hyperplasia for improving vascular access

patency in patients with uraemia on haemo-dialysis.[13,14] Among these agents, beraprost sodium (BPS), which is an oral compound synthesized as a prostacyclin (prostaglandin I_2) derivative, shows strong anti-platelet activity (reduction in platelet aggregation and blockade of platelet adhesion). BPS is used to maintain vascular access patency because it inhibits neointimal formation after vascular surgery.[15–17] However, whether BPS can maintain vascular access patency in patients with uraemia on haemodialysis is unknown.[16,18] Clopidogrel (CL), which is an antithrombotic medication, is successfully used in preventing arteriovenous fistula failure caused by thrombosis. However, patients with uraemia on CL have increased vascular risk factors.[19,20] Previous randomized, controlled trials that compared CL with a placebo showed that patients with uraemia on CL have reduced rates of arteriovenous fistula thrombosis.[11,21]

To the best of our knowledge, direct comparison between BPS and CL has infrequently been described in the published literature.[8,11] Conventional antithrombotic medications have reduced effectiveness in patients with uraemia and thrombotic complications or the occurrence of VTEs. BPS and CL are promising options to reduce these uraemia-related thrombotic complications or occurrence of VTEs. However, several unanswered questions remain. This study aimed to evaluate the efficacy of BPS or CL, with the time to the first VTE of arteriovenous fistula as the primary endpoint, in patients with uraemia who underwent arteriovenous fistula surgery in an Asian population. We ultimately hope to provide a reference for clinical treatment.

Materials and methods

Setting

We followed the reporting guidelines for observational studies in the STROBE guidelines for this retrospective, comparative study. The study was approved by the institutional ethics review boards (the First Affiliated Hospital of Sun Yat-sen University, Jinshan Hospital, Fudan University, and the First Affiliated Hospital of Chongqing Medical University). An exemption for informed consent was obtained from these institutional ethics review boards.

Study population

We retrospectively collected data of 367 patients with ESRD who were diagnosed as having ESRD in line with standard criteria.[21] The patients were admitted to three hospitals from August 2012 to August 2016. The criteria that were used to decide on creation of arteriovenous fistula were based on previous literature.[14] The type of drug treatment that a patient received depended on power analysis before the study. The inclusion criteria were as follows: age of 20 to 95 years; either sex; patients with ESRD requiring maintenance haemodialysis; access to the cephalic vein fistula via end-to-side anastomosis of the radial artery, which was performed according to acceptable surgical techniques as previously described;[22] and a diameter of the fistula anastomosis of 7 to 10 mm. Further, the patients underwent dialysis three times/week for 3 to 4 hours using heparin or low-molecular-weight heparin anticoagulation. After dialysis, proper compression (no bleeding and palpable tremor) of the puncture point was performed for 15 to 20 minutes. Preoperative evaluation (physical with duplex scanning) was performed in all patients. Within 1 month before surgery, no anticoagulant or vasodilator was used in any patient. All of the patients underwent arteriovenous fistula surgery under general anaesthesia. The patients received peroral administration of 40 µg BPS (Beijing Ted Pharmaceutical Co., Ltd., China, drug

specification: 20 μg) three times per day[16,18] for 1 month or 75 mg CL (initial dose of 300 mg; Hangzhou Sanofi Pharmaceutical Co., Ltd., Hangzhou, China, drug specification: 75 mg) once per day for 1 month.[19,20] BPS or CL was applied on the day before surgery. The main exclusion criteria were as follows: incomplete data; previous use of the study drug (BPS or CL) or any anticoagulant drug that affects coagulation function during 3 months before surgery; non-healed or planned surgery; combined severe infection; severe liver disease; chemotherapy for other diseases; cardio-cerebrovascular diseases; circulatory system diseases; malignant tumours; further deterioration of the kidneys during anticoagulation drug treatment or during the follow-up period; modification, discontinuation or interruption of BPS or CL treatment; lactating and pregnant patients; life expectancy < 1 year; co-occurring mental illness; and an American Society of Anesthesiologists score of IV or V.

Definitions of main descriptive variables

Duplex scanning of VTEs, which was confirmed by a chief physician of the Ultrasound Department, was carried out within 1 week, every 2 weeks thereafter, and at the final follow-up. VTEs were defined as an interruption of blood flow due to thrombus or anastomotic stenosis, which was confirmed by duplex scanning. An independent review committee that was masked to the study group adjudicated whether the VTEs were due to thrombus or anastomotic stenosis (or attributable to investigation of suspected VTEs) to compare the incidence of VTEs between groups. Primary patency, strong tremors, and a strong vascular murmur at the anastomotic location were defined as occurring from the interval from the time of access placement to any intervention that was required to maintain or re-establish

patency. Patency was assessed by duplex scanning. If the internal diameter of the venous vessels was ≥5 mm, it could meet the requirements of dialysis. In contrast, if the internal diameter was < 5 mm, the fistula tended to be blocked. The success rate of the internal fistula = patency number/ total number × 100%.

Statistical analysis

Continuous data are presented as the mean and standard deviation or as the median and quartiles. Comparisons between the two groups were performed using Pearson's chi-square test (Fisher's exact test was used when necessary) or the Mann–Whitney U test for continuous variables. The time to first on-study VTE of vascular access was compared using Kaplan–Meier analysis and the log-rank test. The analyses were based on the data up to the primary analysis cut-off. All P values were two sided and a P value < 0.05 was used as the threshold for statistical significance. IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA) was used to conduct all analyses.

Results

Patients' characteristics

After the exclusion criteria were applied, 252 cases of uraemia were identified among 367 consecutive patients with uraemia who underwent arteriovenous fistula surgery and received peroral administration of 40 μg BPS or 75 mg CL (initial dose of 300 mg) (Figure 1). These cases included 125 patients with a mean age of 43.7 ± 7.24 years who received peroral administration of 40 μg BPS. There were 127 patients with a mean age of 44.1 ± 8.11 years who received peroral administration of 75 mg CL (initial dose of 300 mg). The patients' demographics are shown in
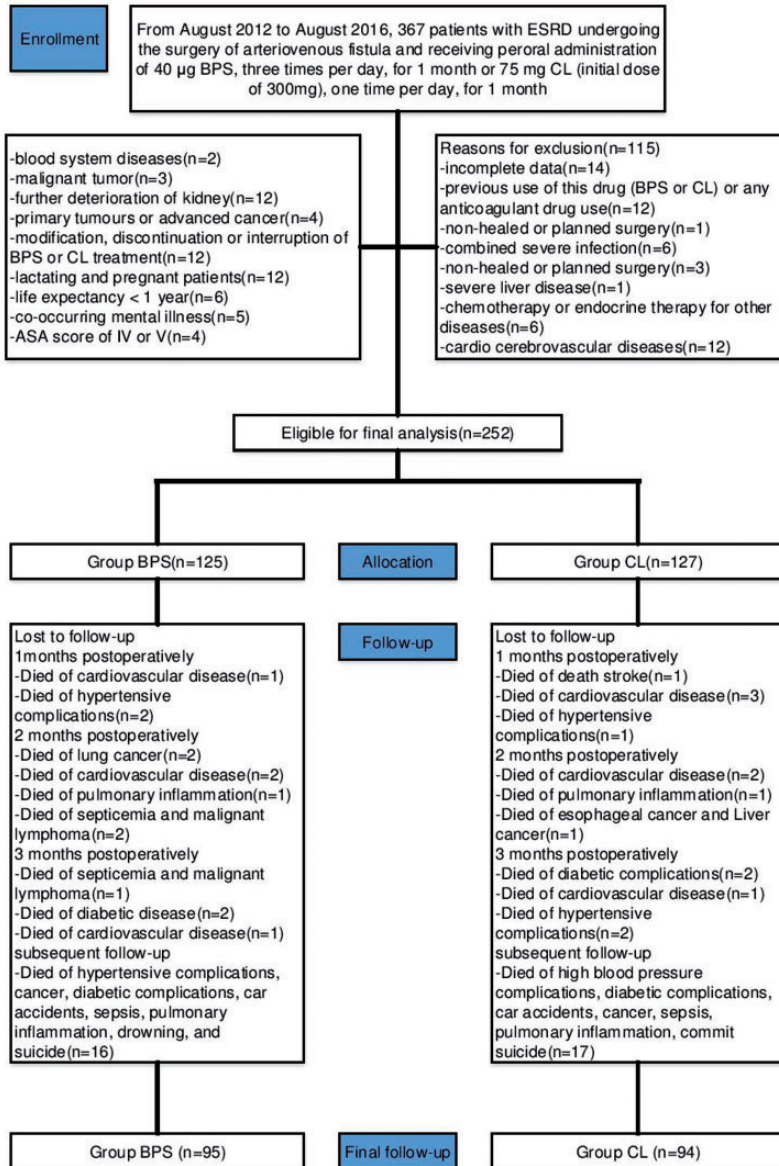
Figure 1. Flow diagram showing methods for identifying studies to assess the efficacy of BPS or CL using VTEs of arteriovenous fistula as the primary endpoint. Patients with ESRD who underwent arteriovenous fistula surgery in an Asian population were studied. BPS: beraprost sodium; CL: clopidogrel; VTEs: vascular thromboembolic events; ESRD: end-stage renal disease.

Tables 1 and 2. There were no significant differences in the proportion of patients with medical diseases (i.e., hypertension, diabetes mellitus, or peripheral vascular diseases) between the groups after initiation of drug prevention (Table 1). There were also no significant differences in laboratory parameters between the groups (Table 2).

Table 1. Comparison of patients' demographics between the groups.

Variable	BPS (n = 125)	CL (n = 127)	P value
Age (years)			0.70[a]
20–39	37	35	
40–59	47	48	
60–79	26	28	
80–95	15	16	
Sex (n), M/F	64/61	65/62	1.00[b]
Current smoker (n)	33	37	0.63[b]
Systolic BP (mmHg)	153.12 ± 21.32	152.76 ± 25.63	0.26[c]
Diastolic BP (mmHg)	90.17 ± 15.46	89.72 ± 16.84	0.10[c]
Causes of end-stage renal disease (n)			0.82[a]
Diabetes mellitus	34	36	
Chronic glomerulonephritis	49	44	
Hypertension	22	25	
Others	20	22	
Access flow rate (mL/minute)	962 ± 537	954 ± 671	0.29[c]
eGFR (mL/minute/1.73 m^2)	12.21 ± 2.71	12.18 ± 2.95	0.53[c]
BUN (mg/dL)	41.81 ± 13.57	42.10 ± 12.16	0.13[c]
Hb (g/dL)	9.91 ± 1.61	10.15 ± 2.18	0.29[c]
Creatinine (mg/dL)	11.17 ± 2.35	10.93 ± 2.69	0.41[c]
Dialysis duration with respective access (months)	14.61 ± 6.92	14.57 ± 7.01	0.37[c]
Urea kinetics, single-pool Kt/V[#]	1.82 ± 0.53	1.83 ± 0.49	0.35[c]
Type of dialysis (n)			0.66[b]
Haemodialysis	123	124	
Peritoneal dialysis	2	3	
Haemodialysis duration (months)	31.46 ± 7.36	31.24 ± 6.53	0.14[c]
ASA level			0.80[a]
1	45	44	
2	49	50	
3	31	33	
Ambulatory status (n)			0.45[a]
Normal walking	113	111	
Walking with assistive devices	12	16	
Completely restricted walking	0	0	
Diabetes mellitus			
Duration (years)	21 (13–25)	20 (12–26)	0.11[c]
Type 2 (n)	19	21	0.77[b]
Insulin use (n)	11	14	0.57[b]
HMG-CoA reductase inhibitors (n)	32	35	0.73[b]
ACEIs or ARBs (n)	27	29	0.81[b]
Beta-blockers (n)	23	26	0.68[b]
Calcium channel blockers (n)	17	19	0.76[b]
Aspirin (n)	37	39	0.85[b]
Erythropoietin, Unit/kg/week	142 ± 71	143 ± 69	0.43[c]
BMI (kg/m^2)	25.23 ± 3.71	25.15 ± 4.42	0.17[c]
BMD	-2.34 ± 0.26	-2.35 ± 0.11	0.28[c]
Diuretics (n)	43	44	0.97[b]

Table 1. Continued.

Variable	BPS (n = 125)	CL (n = 127)	P value
Personal history of VTEs (n)	11/125	12/127	0.86[b]
Family history of VTEs (n)	13/125	15/127	0.72[b]

Values are mean ± standard deviation or median and interquartile range. [a]Analysed using the Mann–Whitney test; [b]analysed using the chi-square test; [c]analysed using the independent samples t-test. [#]K: dialyzer blood urea clearance in L/h; t: dialysis session length in hours; V: urea distribution volume in litres. BPS: beraprost sodium; CL: clopidogrel; M: male; F: female; BP: blood pressure; eGFR: estimated glomerular filtration rate; BUN: blood urea nitrogen; Hb: haemoglobin; ASA: American Society of Anesthesiologists; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; BMI: body mass index; BMD: bone mineral density; VTEs: vascular thromboembolic events.

Table 2. Comparison of laboratory data between the two groups.

Laboratory data	BPS (n = 125)	CL (n = 127)	P value
Platelets, ×1000/mm^3	173 ± 52	168 ± 67	0.12[a]
White blood cells, /mm^3	7583 ± 1458	7402 ± 1772	0.35[a]
Haemoglobin, g/dL	11.12 ± 0.43	10.81 ± 0.26	0.17[a]
Serum albumin, g/dL	3.15 ± 0.26	2.99 ± 0.75	0.22[a]
Phosphate, mg/dL	4.92 ± 0.47	5.10 ± 0.93	0.37[a]
Uric acid, mg/dL	9.21 ± 2.04	8.92 ± 1.52	0.41[a]
Total cholesterol, mg/dL	132 ± 46	136 ± 35	0.20[a]
Triglycerides, mg/dL	100 (76–144)	99 (74–147)	0.37[a]
Ferritin, ng/mL	170 (111–347)	172 (122–352)	0.45[a]
Haemoglobin A1c, %	5.11 ± 1.22	4.97 ± 1.84	0.72[a]
Low-density lipoprotein cholesterol, mg/dL	74 ± 16	76 ± 13	0.24[a]
High-density lipoprotein cholesterol, mg/dL	42 ± 11	44 ± 16	0.28[a]
Total calcium, mg/dL	126 ± 23	128 ± 16	0.36[a]
Parathyroid hormone, pg/mL	134 (100–186)	137 (97–192)	0.51[a]
Bicarbonate, mEq/L	26.40 ± 2.73	25.92 ± 2.25	0.33[a]
Transferrin saturation, %	20 (19–27)	22 (18–25)	0.76[a]

Values are mean ± standard deviation or median and interquartile range. [a]Analysed using the independent samples t-test. BPS: beraprost sodium; CL: clopidogrel.

The mean duration at the cut-off date of the primary analysis was 36.2 months (interquartile range: 36–38) and 36.8 months (interquartile range: 36–38) for the BPS- and CL-treated cohorts, respectively.

Incidence and risk of VTEs

The incidence rate of the first on-study VTEs in the BPS-treated cohort was significantly lower than that in the CL-treated cohort (8.0% [10/125] versus 18.1% [23/127], P = 0.02) (Table 3). The mean time to the first on-study VTE was 2.7 months (95% confidence interval [CI] 14.3–45.3) and 1.5 months (9.9–45.6 months) for the BPS- and CL-treated cohorts (hazard ratio [HR] 0.31, 95% CI 0.24–0.67; P = 0.001). There was an appreciably delayed time to first on-study VTE in

Table 3. Comparison of the incidence of VTE between the two groups.

Variable	BPS (n = 125)	CL (n = 127)	P value
Total incidence of VTEs	10/125	23/127	0.02
Incidence of VTEs			
Within the first month	3/125	11/127	0.03
Within the second month	4/125	4/127	0.98
From the third month to the final follow-up	3/125	8/127	0.13

Values were analysed using the chi-square test. BPS: beraprost sodium; CL: clopidogrel; VTEs: vascular thromboembolic events.

the BPS-treated cohort compared with the CL-treated cohort (HR 0.33, 95% CI 0.18–0.56; P = 0.001).

The BPS-treated cohort had a lower occurrence of first on-study VTEs compared with the CL-treated cohort at the final follow-up (10 versus 23, P = 0.02). Within the first month after the end of CL therapy, 11 (11/23) patients suffered from a VTE. Within the second month after the end of CL therapy, four (4/23) patients suffered from a VTE and eight (8/23) patients suffered from a VTE from the third month to the final follow-up. VTEs mainly occurred within the first month after cessation of oral administration. There was a time distribution characteristic (tended to suffer from a VTE within the first month) in the occurrence of VTEs after the end of CL therapy. In contrast, the occurrence of VTEs and the time after the end of BPS therapy failed to show obvious distribution characteristics. Within the first month after the end of BPS therapy, three (3/10) patients had a VTE. Within the second month after the end of BPS therapy, four (4/10) patients had a VTE and three (3/10) patients had a VTE from the third month to the final follow-up. BPS reduced the risk of a first on-study VTE by 47% compared with CL (HR 0.22, 95% CI 0.15–0.29; P = 0.001) (Figure 2). The risk of a first on-study VTE in the CL-treated cohort was approximately three times higher than

that in the BPS-treated cohort (HR 3.14 [17.53/5.58], P = 0.001) (Table 4).

Discussion

In our study involving patients with ESRD, the most important finding was that CL-treated patients with uraemia had an increased risk of VTEs. Additionally, CL-treated patients had more VTEs within the first month after cessation of oral administration compared with BPS-treated patients.

A recently published study on preventing VTEs in patients with uraemia suggested that factors, such as advanced age, hypertension, anaemia, arteriosclerosis, abnormal lipid metabolism, and accumulation of uraemic toxins in the body, could result in a patient's poor vascular elasticity and vascular endovascular stenosis.[23] During surgery, traction of the arteries can lead to postoperative vasospasm, decreased blood flow, and endovascular damage.[24,25] These factors contribute to formation of thrombus after fistula formation, which results in failure of internal fistula function.[14] A recent study reported by Kim et al.[26] showed that BPS could improve the success rate of arteriovenous fistula in older patients and the efficacy was improved. Furthermore, previous studies have shown that several vascular anti-proliferative agents (including dipyridamole, statins, and fish oil) that affect the patency rate of
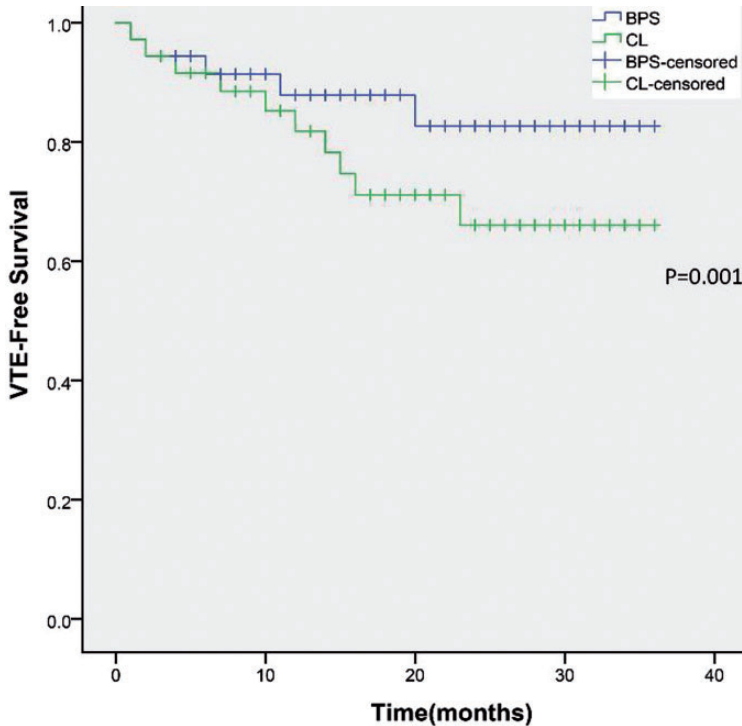
Figure 2. Kaplan–Meier estimates of VTEs of arteriovenous fistula between the groups. At the final follow-up, the incidence of VTEs was higher in the CL group than in the BPS group (P = 0.001). VTEs: vascular thromboembolic events; BPS: beraprost sodium; CL: clopidogrel.

Table 4. VTE risk ratio between the two groups.

Variable	BPS (n = 125)	CL (n = 127)	P value
HR (95% CI) for total VTEs	5.58	17.53	0.001
	(3.25–14.37)	(2.54–22.14)	
HR (95% CI) for VTEs			
Within the first month	3.33	8.27	0.003
	(1.21–6.67)	(1.49–15.11)	
Within the second month	32.54	36.76	0.151
	(5.43–154.86)	(6.24–97.44)	
From the third month	36.64	37.32	0.221
to the final follow-up	(4.65–83.31)	(3.12–88.34)	

VTEs: vascular thromboembolic events; BPS: beraprost sodium; CL: clopidogrel; HR: hazard ratio; CI: confidence interval.

arteriovenous fistula have the potential for benefits in anti-neointimal hyperplasia patients on haemodialysis. Additionally, the proportion of patients with diabetic nephropathy who undergo maintenance haemodialysis is increasing every year.[27] Patients with diabetic nephropathy are more prone to developing thrombosis and

other complications because of their poor blood flow, difficulty in establishing arteriovenous fistula, tendency to merge metabolic disorders, malnutrition, vascular sclerosis, increased release of von Willebrand factor, platelet aggregation, or vascular endothelial cell injury.[27–30]

BPS has the advantages of a stable structure, long half-life, and convenient oral administration. BPS is mainly used in clinical treatment of lower extremity arteriosclerosis occlusion diseases, pulmonary hypertension, diabetic peripheral neuropathy, and diabetic nephropathy.[17,28] The curative effect of BPS is distinct.[28] Prostacyclin can be combined with prostacyclin receptors on platelets and vascular smooth muscle and activates adenylate cyclase. Prostacyclin increases intracellular adenosine monophosphate concentrations, and inhibits the influx of calcium and production of thromboxane A_2, which can play a role in anti-platelet aggregation and dilating blood vessels.[18,26–28] Prostaglandin E_1 is produced by vascular endothelial cells, and can regulate calcium activity of vascular smooth muscle and prevent noradrenaline release from sympathetic nerve terminals to dilate blood vessels. Prostaglandin E_1 also has the effects of inhibiting platelet aggregation, protecting vascular endothelial cells, and preventing atherosclerosis.[31,32] Additionally, prostaglandin E_1 has an obvious targeting distribution to damaged vessels. This can improve vasospasm of the radial artery, increase blood flow of an internal fistula, and promote maturation of an internal fistula.[31,32]

Thrombosis is the major cause of failure of arteriovenous fistulas in patients on haemodialysis.[8,14] Formation of vortices induced by vascular intimal injury at the anastomotic site promotes adhesion of monocyte macrophages, which exacerbates the vicious cycle of fibrosis and atherosclerosis.[5,14] In turn, formation of haematomas and local infection make the local injury site

difficult to repair, thereby having a detrimental effect on the patency of blood vessels.[26] CL, which is an inactive prodrug, is converted into active components by the cytochrome $P_{450}3A4$ enzyme. The cytochrome $P_{450}3A4$ enzyme can selectively inhibit binding of adenosine diphosphate with its platelet membrane receptor. Ultimately, CL prevents fibrinogen from binding to glycoprotein receptors.[11] In addition to adenosine diphosphate, CL can inhibit platelet aggregation induced by other agonists by blocking expansion of platelet activation caused by adenosine diphosphate.[11,20] Additionally, CL has a certain anti-inflammatory effect and can effectively reduce thrombosis.[21]

BPS compared with CL in prevention of VTEs in patients with uraemia and ESRD has been the focus of several previous studies.[8,14,25] However, potential disadvantages in the majority of these studies are the relatively small sample size and/or short-term follow-up. Consequently, making conclusions about the relative superiority of one drug over the other using the time to first on-study VTE as the primary outcome might be incorrect. Chue et al.[32] showed that, in patients with ESRD, BPS was inferior to CL in delaying the time to first on-study VTE (HR 1.43; P = 0.001). However, Coleman et al.[13] further assessed the finding from Chue et al's.[32] study and showed that the rate of VTEs was 9% (n = 108) for BPS versus 11% (n = 110) for CL. BPS delayed the first on-study VTE by 19% versus 11% for CL (HR, 0.33; 95% CI, 0.21–0.76; P = 0.022). In our study, the VTE rate in the CL-treated cohort was considerably higher than that in the BPS-treated cohort, regardless of whether the evaluation was performed during drug use, after the cessation of drug use, or during the follow-up period. The incidence of VTEs in the BPS- and CL-treated cohorts was 8.0% (10/125) and 18.1% (23/127), respectively, at the final follow-up. These values

were not higher than 19.2% (10-month follow-up) and 22.7% (16-month follow-up) in other studies.[14,30]

Our study has certain limitations that should be considered in the interpretation of our results. First, this study was retrospective in nature with the inherent limitations of retrospective studies. These limitations include the quality of imaging at different centres and variable follow-up of patients. However, we collected data accurately via chart review and electronic records. Second, this study had a small sample size, it was a double-centre study, and the population was largely limited to patients with uraemia who underwent arteriovenous fistula for the first time. Therefore, our findings might not be applicable to general populations of patients with uraemia, such as those who received arteriovenous fistula for the second time. Third, we had no data on important risk factors, such as smoking status, blood pressure, and lipoproteins. Fourth, the analyses did not eliminate imperceptible VTEs that occurred before the endpoint, although the study was powered to detect differences in VTEs.

At the time of the cut-off date for this analysis, we conclude, as expected, that BPS significantly reduced the risk of VTEs compared with CL in patients with uraemia, regardless of whether the patients were followed for 3 years or less. This finding provides further evidence of the superior ability of BPS to prevent VTEs versus CL. Further investigation of the long-term use of BPS and CL is necessary.

Declaration of conflicting interest

Funding

References

1. Kai Y, Hamada J, Morioka M, et al. Arteriovenous fistulas at the cervicomedullary junction presenting with subarachnoid hemorrhage: Six case reports with special reference to the angiographic pattern of venous drainage. *AJNR Am J Neuroradiol* 2005; 26: 1949–1954.
2. Faiyaz R, Abreo K, Zaman F, et al. Salvage of poorly developed arteriovenous fistulae with percutaneous ligation of accessory veins. *Am J Kidney Dis* 2002; 39: 824–827.
3. Almasi-Sperling V, Galiano M, Lang W, et al. Timing of first arteriovenous fistula cannulation in children on hemodialysis. *Pediatr Nephrol* 2016; 31: 1647–1657.
4. Chou CY, Tseng YH, Shih CM, et al. Influence of intravenous drug abuse on native arteriovenous fistula thrombosis in chronic hemodialysis patients. *Ther Apher Dial* 2008; 12: 152–156.
5. Usta E, Elkrinawi R, Salehi-Gilani S, et al. Risk factors predicting the successful function and use of autogenous arteriovenous fistulae for hemodialysis. *Thorac Cardiovasc Surg* 2013; 61: 438–444.
6. Persic V, Ponikvar R and Buturovic-Ponikvar J. Preoperative ultrasonographic mapping of blood vessels before arteriovenous fistula construction in elderly patients with end-stage renal disease. *Ther Apher Dial* 2009; 13: 334–339.
7. Park SC, Song R, Kim S, et al. Fabrication of artificial arteriovenous fistula and analysis of flow field and shear stress by using mu-PIV technology. *J Mech Sci Technol* 2016; 30: 5503–5511.
8. Chanliau J, Charasse C, Rose C, et al. Clinical evaluation of an expert system for arteriovenous fistula assessment. *Int J Artif Organs* 2014; 37: 809–815.
9. Afsar B and Elsurer R. The primary arteriovenous fistula failure-a comparison between diabetic and non-diabetic patients: glycemic control matters. *Int Urol Nephrol* 2012; 44: 575–581.

10. Glassock RJ. Uremia (end-stage renal disease): how cost-effective are preventive strategies? *J Ren Nutr* 2010; 20(5 Suppl): S131–S134.

11. Dember LM, Beck GJ, Allon M, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis - a randomized controlled trial. *JAMA* 2008; 299: 2164–2171.

12. Vora AN, Stanislawski M, Grunwald GK, et al. Association between chronic kidney disease and rates of transfusion and progression to end-stage renal disease in patients undergoing transradial versus transfemoral cardiac catheterization-an analysis from the veterans affairs Clinical Assessment Reporting and Tracking (CART) program. *J Am Heart Assoc* 2017; 6: e004819.

13. Coleman CI, Tuttle LA, Teevan C, et al. Antiplatelet agents for the prevention of arteriovenous fistula and graft thrombosis: a meta analysis. *Int J Clin Pract* 2010; 64: 1239–1244.

14. Vachharajani N, Wise P, Klingensmith M, et al. Vascular access creation and maintenance in the USA. *J Vasc Access* 2015; 16(Suppl 9): S1–S4.

15. Matsumoto T, Iwasa K, Kyuragi R, et al. The efficacy of oral beraprost sodium, a prostaglandin I-2 analogue, for treating intermittent claudication in patients with arteriosclerosis obliterans. *Int Angiol* 2010; 29: 49–54.

16. Murakami M, Watanabe M, Furukawa H, et al. The prostacyclin analogue beraprost sodium prevents occlusion of bypass grafts in patients with lower extremity arterial occlusive disease: A 20-year retrospective study. *Ann Vasc Surg* 2005; 19: 838–842.

17. Mohler ER 3rd, Hiatt WR, Olin JW, et al. Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I-2 analogue - a double-blinded, randomized, controlled trial. *J Am Coll Cardiol* 2003; 41: 1679–1686.

18. Shimamura M, Miyakawa J, Doi M, et al. The pharmacokinetics of beraprost sodium following single oral administration to subjects with impaired kidney function. *J Clin Pharmacol* 2017; 57: 524–535.

19. Chemla ES and Morsy M. A European perspective on the Dialysis Access Consortium (DAC) study regarding the effects of clopidogrel on early failure of arteriovenous fistulas for hemodialysis. *J Vasc Access* 2008; 9: 229–230.

20. Gilpin V. Review of an article: effects of clopidogrel on early failure of arteriovenous fistulas for hemodialysis by Dember, LM, Beck, GJ, & Allon, M., et al. JAMA 2008; 299(18): 2164–71. *J Vasc Nurs* 2009; 27: 78.

21. Ismail A, Abushouk AI, Bekhet AH, et al. Regional versus local anesthesia for arteriovenous fistula creation in end-stage renal disease: a systematic review and meta-analysis. *J Vasc Access* 2017; 18: 177–184.

22. Rajan DK, Ebner A, Desai SB, et al. Percutaneous creation of an arteriovenous fistula for hemodialysis access. *J Vasc Interv Radiol* 2015; 26: 484–490.

23. Schinstock CA, Albright RC, Williams AW, et al. Outcomes of arteriovenous fistula creation after the fistula first initiative. *Clin J Am Soc Nephrol* 2011; 6: 1996–2002.

24. Ghorbani A, Aalamshah M, Shahbazian H, et al. Randomized controlled trial of clopidogrel to prevent primary arteriovenous fistula failure in hemodialysis patients. *Indian J Nephrol* 2009; 19: 57–61.

25. Al-Balas A, Lee T, Young CJ, et al. Predictors of initiation for predialysis arteriovenous fistula. *Clin J Am Soc Nephrol* 2016; 11: 1802–1808.

26. Kim M, Kim JU, Kim SM, et al. Effectiveness of beraprost sodium in maintaining vascular access patency in patients on hemodialysis. *Int Urol Nephrol* 2017; 49: 1287–1295.

27. Shima A, Miyamoto M, Kubota Y, et al. Beraprost sodium protects against diabetic nephropathy in patients with arteriosclerosis obliterans: a prospective, randomized, open-label study. *J Nippon Med Sch* 2015; 82: 84–91.

28. Na KY, Kim DK, Kim SG, et al. Effect of beraprost sodium on arterial stiffness in patients with type 2 diabetic nephropathy. *Trials* 2013; 14: 275.

29. Oudiz RJ, Benza RL, Delcroix M, et al. Long-term follow-up in PAH patients dosed with beraprost sodium modified release (BPS-MR) tablets, an oral twice

daily prostacyclin analogue. *Am J Respir Crit Care Med* 2011; 183: A5905.

30. Sugawara A, Kudo M, Saito A, et al. Novel effects of beraprost sodium on vasculatures. *Int Angiol* 2010; 29: 28–32.

31. Hashiguchi M, Ohno K and Saito R. Studies on the effectiveness and safety of cilostazol, beraprost sodium, prostaglandin E-1 for the treatment of intermittent claudication. *Yakugaku Zasshi* 2004; 124: 321–332.

32. Chue KM, Thant KZ, Luo HD, et al. Comprehensive comparison of the performance of autogenous brachial-basilic transposition arteriovenous fistula and prosthetic forearm loop arteriovenous graft in a multi-ethnic Asian hemodialysis population. *Biomed Res Int* 2016; 2016: 8693278.