Bivalirudin in TAVI patients for the reduction of thromboembolic events: Rationale and design of the BIVITAL trial

Mao C, Jialing H, Zhengang Z, Yong P, Yanbiao L, Wenyu L, Yuan Feng

Mao C, Jialing H, Zhengang Z, et al. Bivalirudin in TAVI patients for the reduction of thromboembolic events: Rationale and design of the BIVITAL trial. Clin Cardiol J. 2018;2(1):10-14.

ABSTRACT

Transcatheter Aortic Valve Implantation (TAVI) is a main treatment for Aortic Valve Stenosis (AS). Randomized clinical trials had proven that TAVI was significantly advanced to Surgical Valve Replacement (SAVR), despite of which, there are still room for further improvements of TAVI in the safety and clinical effects. Thrombosis is a common complication after TAVI, including valve thrombosis, subclinical valve thrombosis, myocardial infarction, myocardial injury, stroke and micro embolism of brain, significantly impair prognosis of patients. Using unfractionated heparin (UFH) for anticoagulation during TAVI was a conventional strategy. However, lots of studies in Percutaneous Coronary Intervention (PCI) showed the incidence of postoperative myocardial infarction and ischemic stroke is noninferior to UFH in use of Bivalirudin, a direct thrombin inhibitor, as an anticoagulant. BRAVO-3 study indicated that the rate of myocardial infarction within 48 hours was significantly lower in Bivalirudin group than UFH group (0% *vs.* 1.3%, p=0.03). In previous PCI studies, there is no standard criteria of using bivalirudin. A study limit bivalirudin using time in 4-12 hours after PCI resulting in slightly lower incidence of stent thrombosis than the UFH group. Additionally, no studies refined thrombosis into asymptomatic events including subclinical leaflet thrombosis, brain micro embolism and myocardial injury, which is not only with higher incidence in patients, but also capable to predict adverse prognosis. Therefore, we speculate that the rational use of Bivalirudin during TAVI procedure may reduce the risk of thrombosis compared with UFH in patients with aortic valve stenosis in China. The BIVITAL trial is the first prospective, masked, randomized study of Bivalirudin versus UFH in Chinese TAVI patient. The BIVITAL trial uses 7 days or before discharging thromboembolic events as primary endpoint, including valve thrombosis, subclinical leaflet thrombosis (Hypo attenuated leaflet thickening, HALT or reduced leaflet motion, RELM), myocardial infarction, myocardial injury, stroke, transient ischemic attacks (TIA), the number of new brain embolisms with average volume >205 mm^3 more than 5. Safety endpoint are 7 days or before discharge any bleeding or hemoglobin levels dropping more than 2.0 g/dl and all-cause mortality. We intend to recruit AS patient planning to receive transfemoral (TF) TAVI procedure, randomized into Bivalirudin group and UFH group in 1:1 fashion. By outcome comparison of two groups, we intend to prove bivalirudin can reduce thromboembolic events.

Key Words: *Aortic valve stenosis; TAVI; Bivalirudin; Heparin; Thromboembolic event*

INTRODUCTION

Aortic valve stenosis (AS) is common and potentially fatal in elderly patients. Aging of population brings more AS patients up, especially in China, which is calculated carrying more than two million AS patients burden. For a long time, surgical aortic valve replacement (SAVR) was the only efficient treatment for AS, although there were still plenty of inoperable or high-risk patients who cannot receive it. About 30-50% of AS patients were rejected by SAVR because of Older age, poor heart function, diabetes, renal insufficiency, chronic obstructive pulmonary disease (1). Conventional treatment, including balloon aortic valvuloplasty, was inefficient with an annual mortality rate exceeding 50% (2).

The advent of TAVI has brought the gospel to patients who are not suitable for surgical thoracotomy. Compared with SAVR, TAVI does not need thoracotomy and extracorporeal circulation resulting in obvious advantages, such as less trauma, shorter operation time and quicker recovery after operation. A number of randomized controlled trials, including PARTNER I (Placement of aortic transcatheter valves), showed that TAVI was superior to conservative treatment in patients with severe AS who were unable to perform surgery, as 1-year mortality rate was reduced by 45% (2). for patients with high surgical risk, TAVI was not inferior to or even superior to SAVR (3,4). With the improvement of devices and the accumulation of experience, the technology has been used to treat patients with lower risk surgery. PARTNER II and Notion (Nordic aortic Valve intervention) randomized controlled trials indicated that TAVI is also not inferior to or even superior to SAVR (5,6). Currently, TAVI has been widely applied in European and American AS patients as the main treatment modality. Up to now, the whole world has completed about 400,000 TAVI cases.

However, there is still room for further improvement in the safety and clinical effects of TAVI. It was estimated about 40% of TAVI patients are suffering from complications after surgery. Thrombosis is a common complication, and the generalized thrombosis includes valve thrombosis, coronary artery thrombosis and cerebral vascular thrombosis.

Valve thrombosis

Valve thrombosis is a hot topic discussed in recent years, and its incidence fluctuates between 0.03% to 7% (1,7). Valve thrombosis can exacerbate symptoms, biological prosthesis insufficiency, stroke, heart failure and weaken prosthesis durability (8). Makkar et al., believed that reduced leaflet motion (RLM) was the imaging manifestation of subclinical valve thrombosis, and their study showed that patients with lower RLM had a higher incidence of stroke and TIA (9).

Coronary artery thrombosis

The direct result of coronary artery thrombosis is myocardial infarction (MI) and myocardial injury, in PARTNER I trial, the incidence of 30-day MI after TAVI was 1.2% (6) in U.K. TAVI trial, 30 days after TAVI, the rate of MI reached 1.3% (10). Myocardial infarction can lead to poor prognosis and even direct death in patients. Rodés-cabau and others found that 99% of the patients had increased the level of troponin (TNT) after TAVI, and 77% had an increase in creatine kinase isoenzyme (CKMB) after surgery (11). The increase in myocardial enzymes was associated with postoperative adverse outcomes, with an increase of more than 5 times independently predicting 30-day and late-stage cardiovascular mortality (12).

Cerebral vascular thrombosis

The incidence of transient ischemic attack (TIA) and stroke was 6.4% in PARTNER trial, and stroke rate was 4.1% in U.K. TAVI study (10). Stroke

Department of Cardiology, West China Hospital, Sichuan University, P.R. China

Correspondence: Mao Chen, Department of Cardiology, West China Hospital, Sichuan University, P.R. China. Telephone 86-28-85423362, e-mail: hmaochen@vip.sina.com

#All the authors contributed equally to this work.

Received: September 29, 2018, Accepted: October 03, 2018, Published: October 09, 2018

events can lead to a 3.5 times-fold increase in mortality. Kahlert et al. found that 84% of patients with new cerebral infarction lesions according to cranial MRI 3 days post TAVI, this proved that of the presence of the micro embolism of brain which doesn't cause clinical symptoms (13). However, some researchers believed those micro embolisms may impair the cognitive function (6,9).

As with percutaneous coronary intervention (PCI), in TAVI clinical practice, common UFH is used as standard intraoperative anticoagulant by physicians' experience. According to the latest expert consensus, the first dose of UFH should be given before inserting the sheath, during which the Activation Clotting Time (ATC) should be monitored, and the target ACT value was 250-300 seconds (14). Although the strategy was widely used, it has not been supported by evidence-based medical evidence, and there are some limitations in the strategy itself (1). The molecular structure of UFH has heterogeneity, only one-third of the molecule has anticoagulant activity, the molecular size and the pharmacokinetic characteristics are inconsistent, resulting in the drug half-life ranging between 60-90 minutes (15). Therefore, in the process of cardiovascular intervention, the use of UFH is often to give an initial amount, after then, the use was flexible to small doses according to operation time and ATC. Besides, the optimal ATC value is controversial and has regional difference. In recent years, PCI has been more used in the range of 220-250 seconds, which was not clearly defined in TAVI, mainly depends on the experience of operators (2). Another limitation of UFH in anticoagulation is that the metabolic time is difficult to predict. The total scavenging time of UFH was 2-5 hours, which is affected by the patient's characteristic and ACT peak. In addition, UFH molecule binding to endothelial cells and plasma proteins, further leads to the pharmacokinetic non-linear characteristics and individual differences of UFH (16). These characteristics may have adverse effects on postoperative bleeding complications (3). UFH use may lead to UFH-induced thrombocytopenia (HIT) (15). About 30% of the patients receiving UFH anticoagulant were associated with non-immune-related thrombocytopenia, while the incidence of HIT was only 1-3%. Although the incidence of HIT is low, it can lead to poor outcome. (4) For patients with extremely high bleeding risk, the anticoagulant effect of UFH can be reversed in time by Protamine. However, because the half-life of protamine (about 7 minutes) is significantly shorter than that of normal UFH (17), it may lead to a rebound in anticoagulant effect during the course of use. At the same time, protamine itself also has side effects, such as hypotension, bradycardia, allergies, can increase the risk of death of patients (18).

Bivalirudin is a direct thrombin inhibitor with low molecular mass (20 amino acid residues) and short half-life period (25 minutes), and has superior pharmacokinetic characteristics compared to normal UFH. The mechanism of anticoagulation is directly combining with thrombin to inhibit fibrinogen transforming into fibrin. In a result, Bivalirudin has more stable dose-response curve, the anticoagulant effect can be predicted, and doesn't have to monitor any coagulation index during use (19). In addition, because BIvalirudin dosen't interact with platelet factor-4, so there is no risk of causing HIT.

A large number of studies have been made in patients with coronary heart disease treated with PCI in comparison with the use of Bvalirudin as an anticoagulant compared with UFH. there were similar incidence of myocardial infarction and ischemic stroke (20,21).

Based on the superior characteristics of Bivalirudin over UFH and the clinical results observed in PCI patients, it is speculated that the use of TAVI to replace UFH as anticoagulant is expected to reduce the incidence of thromboembolic events in TAVI during perioperative period. The BRAVO-3 study included 802 patients who had been treated with TAVI and randomly assigned to the Bivalirudin group and UFH group, the incidence of myocardial infarction in 48 hours post operation was 0% *vs.* 1.3% (p=0.03) respectively. Obviously, the effect of Bivalirudin in reducing thromboembolic events was better than that of UFH. A recent meta-analysis showed a lower myocardial infarct rate than in the UFH group (OR 0.41, 95%CI 0.20-0.87, p=0.02) in patients with aortic valve interventional therapy (22). These results suggest that TAVI can replace UFH in the TAVI. However, in BRAVO trial, Bivalirudin did not show superiority over UFH in 30day outcome regarding to MI and stroke, it may because of the various time duration of Bivalirudin using.

There is no study to evaluate the efficacy and safety of the use of TAVI in the Asian population compared with UFH anticoagulant. In most of previous studies, the use time of was uncertain, so it was hard to identify optimal using time of Bvalirudin in BRAVE-4 trial, Bivalirudin was applied 4-12 hours after PCI, and the incidence of stent thrombosis was slightly lower than that in the UFH group (1.12% *vs.* 1.45%, p=0.98) (23). At the same time, no study has been developed to refine thrombosis into asymptomatic events, such as subclinical leaflet thrombosis, brain micro-embolism, myocardial injury, the hint of which is more acute, not only with higher incidence in patients, but also capable to predict adverse prognosis. Our study is the first prospective, masked, randomized study of Bivalirudin versus UFH in Chinese AS patient during TAVI, including endpoints of thromboembolic events, bleeding complications and total death in 30 days, in order to explore the best anticoagulation strategy in the patients with aortic stenosis in China, optimize the TAVI therapeutic effect and eventually benefit the TAVI patients.

MATERIALS AND METHODS

The BIVITAL trail design is a prospective, single center, single blind, randomized controlled clinical trial enrolling in patients with severe AS in proposal of transfemoral (TF) access TAVI treatment. The patients will randomly be assigned to the Bivalirudin anticoagulant group or UFH anticoagulant group, respectively in 1:1 fashion. in the postoperative 1 days, 2 days, after discharge or 7 days after operation (whichever occurs earlier) and 30 days after operation, we will observe patients from two groups respectively of thromboembolic events, any bleeding events or hemoglobin level decreased more than 2.0 g/dl, all-cause mortality and other outcomes. By comparison outcome of two groups, we intend to provide evidence for the hypothesis that bivalirudin can reduce thromboembolic events compared with UFH.

All patient ≥ 18 years of age undergoing TF TAVI in our center are screened for the BIVITAL trial. Inclusion and exclusion criteria are listed in detail in Tables 1 and 2. To screen for eligible patients, pre-TAVI evaluation will performed, including history, electrocardiography, medicine taking (especially antiplatelet and cardiovascular medication), society of Thoracic Surgeon (STS) score, fragility assessment and imaging evaluation. fragility assessment requires BMI, cognitive function (A simple cognitive assessment of Alzheimer's disease), Strength and Balance (Use of a wheelchair, the walking speed of 5m walk of the patient, the times of falls in the past 6 months, Maximum grip strength (kg) of the dominant hand measured using Jamar portable dynamometer) and daily activity (Katz index). Imaging evaluation consist of transthoracic Doppler echocardiography (aortic valve effective area, the average pressure gradient, the aortic peak velocity, aortic regurgitation, mitral regurgitation, left ventricular ejection fraction, the left ventricular diastolic and end systolic diameters, the injection rate of tricuspid regurgitation and left atrial volume. For low flow low gradient AS, dobutamine can be used to assess the extent of aortic stenosis, the largest dose of which is 20 mcg/kg/min), coronary angioplasty (completed within 356 days, meanwhile aortic angiography and hemodynamic examination should be performed), and Cardiovascular enhanced CT (performed with 180 days if 90 days is impossible). Once enrolled in the BIVATAL trial, patients will further complete Laboratory tests of blood routine, biochemistry, coagulation (PT/PTT), myocardial enzymes (CK, CKMB, TNT), N-terminal B-type brain natriuretic peptide (NT-PRO-BNP) levels, and brain MRI (completed within 30 days).

In UFH group, initial-dose UFH will be injected through sheath or vein after vascular approach is successfully built, which is usually 50 u/kg. Monitoring ACT during procedure to maintain an ACT value of 250-300 seconds and adjusting UFH doses according to ACT. In Bivalirudin group, for patients with GFR ≥ 60 ml/min, Bivalirudin injection with an initial dose of 0.75 mg/kg started through sheath or vein after vascular approach completion, following with 1.75 mg/kg/h within 4 hours, after then change into 0.2 mg/kg/h for another 6 hours. The upper limit of bivalirudin usage is 20 hours, which is maintained by clinical physicians. ACT monitor initiate 5 minutes after venous injection aiming at an ACT value of 250-300 seconds, following another 0.3 mg/kg Bivalirudin injection if necessary. For patients with GFR in the range of 30-59 ml/min, the initial amount is 0.75 mg/kg, following by 1.4 mg/kg/h of continuous drug delivery for 4 hours, then 0.2 mg/kg/h for another 6 hours for patient with GFR<30 ml/min, the initial dose 0.75 mg/kg, following by 1.0 mg/kg/h of continuous drug delivery for 4 hours, then 0.2 mg/kg/h for another 6 hours (drug delivery duration less than 20 hours).

Double antiplatelet is applied before TAVI, usually aspirin 100 mg per day and clopidogrel 75 mg per day. For patients who don't complete pre-TAVI 72 hours' aspirin or clopidogrel taking, they will be given a load dose of aspirin (300 mg) or clopidogrel (300 mg) respectively before TAVI. Double antiplatelet therapy after TAVI is aspirin 100 mg per day combined with clopidogrel 75 mg per day for a period of 6-12 months, followed by the long-term use of aspirin 100 mg per day or clopidogrel 75 mg per day.

The primary endpoint is 7 days or before discharge (whichever earlier)

TABLE 1

Inclusion and exclusion criteria of the BIVITAL trial

Inclusion criteria
1. Patient age is ≥ 18-years-old.
2. Diagnosis of aortic valve stenosis (defined as aortic valve effective area ≤ 1.0 cm^2, or pressure gradient ≥ 40 mmHg, or peak velocity ≥ 4.0 m/s) and has obvious related clinical symptoms If the patients who meet the above criteria are accepted by Balloon aortic valvuloplasty) prior to the baseline operation, and no longer meet the criteria discussed above, the patients can still be screened according to pre-BAV echocardiography results.
3. The Heart team (including an interventional specialist and a heart surgeon) assessed that the patient was unsuitable for surgical thoracotomy or had a high risk of surgery, or that the patient had any of the following:
• STS Score ≥ 4%
• If STS scores <4%, had any of the following:
• Thoracic deformity
• Porcelain Aorta
• Severe pulmonary hypertension (>60 mmHg)
• History of thoracic radiation therapy
• The risk of reoperation for coronary artery bypass surgery
• Severe lung disease (oxygen required, FEV1<50% expected value, DLCO<60% or other evidence of severe pulmonary dysfunction)
• Neuromuscular disorders that can lead to mechanical ventilation or rehabilitation risk after SAVR
• Orthopedic diseases that can lead to the rehabilitation risk after SAVR
• Child A or Child B liver disease
• At least one of the following tips for patients with weakness: 5 meters walk ≥ 6 seconds, Katz ADL score of 3/6 or lower, BMI <21, wheelchair dependency, unable of living independently
• Age ≥ 80 years
• ther evidence of patient is inoperable or high risk for SAVR
4. The anatomy of aortic root and the condition of peripheral blood vessel were unavailable for TF TAVI evaluated by CT cardiovascular enhancement scan
5. The patient volunteered to join the trial and sign an informed consent letter.
Exclusion criteria
1. Patient has the contradiction of Bivalirudin
2. An AMI within 30 days before TAVI (defined as the total CK elevation of up to twice of the normal value, accompanied with:
• Q-wave and CKMB and/or troponin elevation.
• Non-Q wave MI
3. Prior PCI within 3 months before TAVI
4. History of cerebrovascular accident or transient ischemic attack within 6 months before TAVI
5. Patients with end-stage renal disease, undergoing hemodialysis treatment or serum creatinine >3 mg/dl.
6. Severe (4+) tricuspid or mitral insufficiency.
7. Undergoing anticoagulation therapy because of prior mechanical valve replacement, atrial fibrillation or other reasons.
8. Patient need emergency surgery for any reason.
9. Evidence of endocarditis or other systemic infection or sepsis within 6 months prior to operation.
10. Echocardiography shows a new form of cardiac neoplasm or ventricular thrombosis or valvular thrombosis, requiring treatment.
11. hemoglobin <7 g/dL, platelet <50,000 cells/mm^3 or >700,000 cells/mm^3 or white blood cell <1,000 cells/mm^3
12. Patient who had been hospitalized or transfused in the past 1 month, or had significant bleeding tendencies or blood clotting disorders, is unable to accept the required antiplatelet therapy, or refuse to receive blood transfusions
13. Patient is allergic to contrast agent, aspirin, all P2Y12 inhibitors, heparin, nickel, tantalum, titanium, or polyurethane and cannot carry out appropriate desensitization treatment
14. Life expectancy is less than 12 months assessed by the researchers.
15. Hypertrophic obstructive cardiomyopathy.
16. Severe left ventricular insufficiency, ejection fraction <15%.
17. Severe calcification of the iliac femoral artery, or femoral artery diameter <6 mm.
18. Establishment of vascular pathway through surgical incision (not puncture).
19. Aortic arch has a thick (>5 mm) protrusion, or an ulcer atherosclerotic plaque.
20. Drug abuse problems (e.g. alcohol, etc.).
21. Patient with untreated conduction system diseases, and need pacemaker's implantation, after which, patient is allowed to enter the group.
22. Patient has serious dementia of disability.

thromboembolic events including valve thrombosis, subclinical leaflet thrombosis (hypo attenuated leaflet thickening, HALT or reduced leaflet motion, RELM), myocardial infarction, myocardial injury, stroke, transient ischemic attacks (TIA), the new brain embolisms. The safety endpoint is 7 days or before discharge (whichever earlier) any bleeding or hemoglobin levels dropping more than 2.0 g/dl and all-cause mortality. The definition of all-cause mortality, myocardial infarction, transient ischemic attack, stroke and hemorrhage in the main endpoint and safety endpoint was defined by the second edition of Valve Academic study consortium (VARC-2) (24) recommended definition. The secondary endpoints are bleeding defined by BARC (bleeding academic, Consortium) (25), TIMI (thrombolysis in myocardial infarction) (7), GUSTO (Global utilization of streptokinase and tissue plasminogen for occluded coronary arteries) (26), and ACUITY/HORIZONS-AMI (Acute Catheterization and Urgent Intervention Triage Strategy/Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) (27,28). Major adverse cardiovascular events occurred at 30 days, including all-cause mortality, myocardial infarction and stroke, all-cause mortality, myocardial infarction, stroke, Cardiovascular death. The definition of all-cause mortality, cardiovascular death, myocardial infarction and stroke in the secondary endpoints defined by VARC-2 recommendation. Other additional endpoints included are severe vascular complication, acute kidney injury, new onset atrial fibrillation and degree of hemoglobin decrease, which are defined by VARC-2. Figure 1 shows the flow of BIVITAL trial.

STATISTICAL ANALYSIS

The continuous variables in the baseline and result (the mean ± standard deviation, the median and interquartile range, observations, minimum and maximum values), and discrete variables (percentages and events/samples) are summarized by descriptive statistics, and independent sample T-Test or chi-square test is used for statistical testing according to the variable type.

For the primary endpoint and safety endpoint of our research, Kaplan-Meier method is also used to compare two groups by rank sum test. All endpoints will be analyzed on the basis of the intention to Treat (ITT). For ITT analysis, all patients who have signed informed consent and enrolled in this trail will be included in the analysis sample.

Data for the feasibility study phase will be analyzed separately. For a VARC-2-defined thromboembolic events that occurs during hospitalization or within 7 days, a superiority test will be carried out; for the endpoint of any bleeding

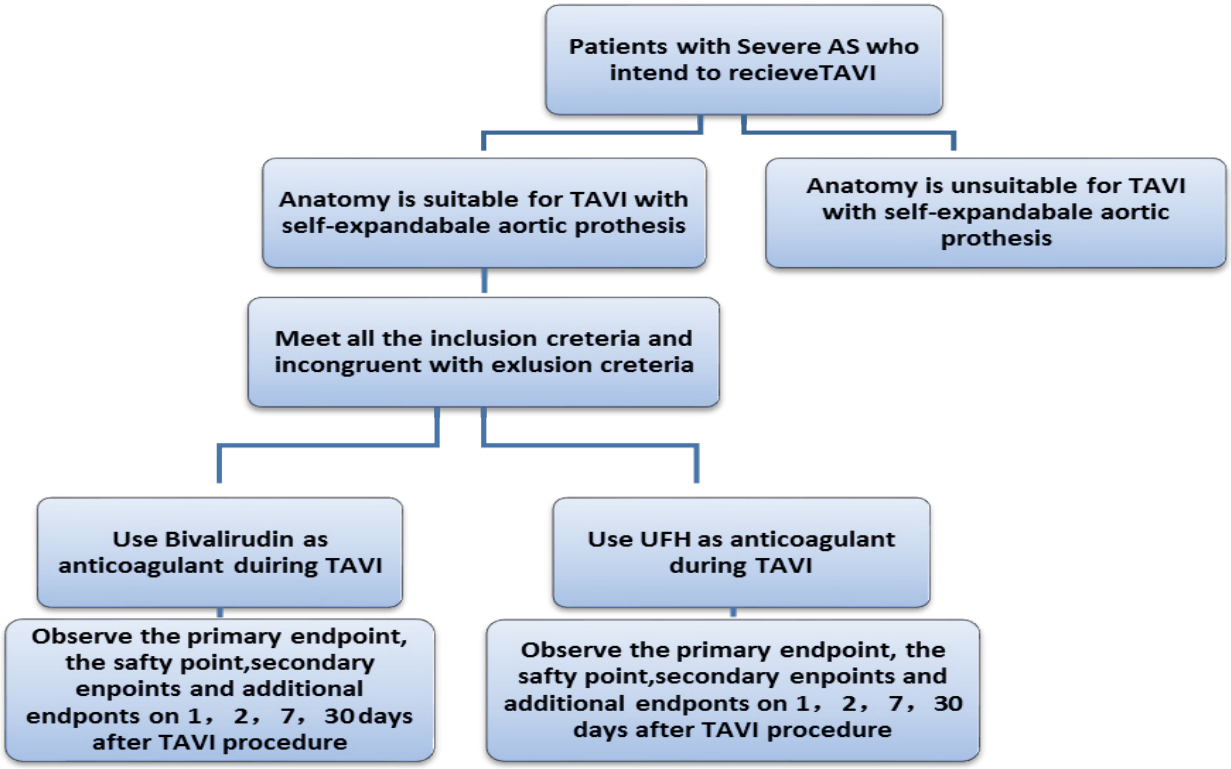

Figure 1) *The design of the BIVITAL trial*

TABLE 2
Definition of primary endpoints

Primary endpoint: Composite outcome of 7 days or before discharge (whichever earlier) thromboembolic events:
Subclinical leaflet thrombosis
• Hypo attenuated Leaflet Thickening (HALT): Hypoattenuating opacities involve the periphery and base of the leaflet and towards the edges of the leaflet. Or
• Reduced leaflet motion(RELM) : Mildly reduced (<50% reduction), moderately reduced (50 -70% reduction), severely reduced (>70% reduction), or immobile (lack of motion in at least one valve leaflet).
Valve thrombosis:
• Mobile mass detected by CT or echocardiography on valve suspicious of thrombus, in the absence of infection.
• Mean aortic valve pressure gradient (PG mean) ≥ 20 mm Hg or aortic valve area <1.2 cm^2 or peak velocity (Vmax) ≥ 3 m/s or moderate/severe valve regurgitation secondary to thrombosis diagnosed based on anticoagulation therapy response, CT or echocardiography findings, or histopathology findings.
Myocardial injury
• Elevation of troponin 15-fold to the upper limit; CKMB 5-fold to the upper limit.
Myocardial infarction: (abbreviated from VARC2)
Within 72 hours:
• Elevated Cardiac biomarkers within 72 hours (a peak value exceeding 15-fold as the upper reference limit for troponin or 5-fold for CK-MB).
• New ischemic symptoms or new ischemic signs (ECG or echocardiography findings) More than 72 hours.
• Elevated or fall of cardiac markers more than 72 hours.
• Ischemic symptoms or ischemic ECG or echocardiography findings or unexpected cardiac death or pathological findings.
Cerebral microembolism
• The total volume of new lesions ≥ 294 mm^3
Stroke and TIA: (abbreviated from VARC2)
• Stroke: Duration of a focal or global neurological deficit (e.g. change of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs) ≥ 24 h or <24 h if available neuroimaging documents a new infarct; OR the neurological deficit results in death.
• TIA: Duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate an infarct.

events or hemoglobin level decline over 2.0g/ld events and all-cause mortality will receive non-inferiority Test first, If the difference is statistically significant ($p<0.05$), then the superiority test will be performed further. A comparison of the primary and safety endpoint of the study will also be performed in a specific subgroup, including sex, age greater than or less than 75 years old, diabetes mellitus, hypertension, coronary heart disease, peripheral vascular disease, chronic obstructive pulmonary disease, chronic kidney disease, STS score greater than or less than 10%, LVEF is greater than or less than 35%. The interaction between the grouping factor and the comparison result will be analyzed by logistic regression.

RESULT AND DISCUSSION

The statistical hypothesis of this study is thromboembolic events involving the use of BIivalirudin as an anticoagulant group during hospitalization or within 7 days after operation (whichever occurs first) is lower than using UFH as anticoagulant group. The incidence of any bleeding events or hemoglobin level decreased more than 2.0 g/dl and all-cause mortality in Bivalirudin group are not higher than that of UFH group.

Following an initial assumption of 72.5% thromboembolic events rate in UFH group, and 26.5% thromboembolic events rate in Bivalirudin group with a hypothetical reduction rate of 46.0%. Considering a 5% of missing rate. The BIVITAL trial require in total of 164 patients,82 patients per group, to achieve 80% power to detect a significant difference between two groups.

CONCLUSION

In summary, the BIVITAL trial is the first prospective, single-blind, randomized trial aiming at Chinese severe AS patients, to compare the anticoagulation efficiency of Bivlairudin and UFH. The heterogeneity of UFH leading to difficulty to control while applying, however the Bivalirudin is relatively stable and controllable avoiding protamine reversal adverse. Past PCI study showed that the Bivalirudin was not inferior to UFH in inhibiting the thromboembolic events. Therefore, we speculate that the rational use of bivalirudin during TAVI can reduce the occurrence of thromboembolism events compared to UFH. In this study, the clinical and subclinical embolism events were selected as composite endpoints, which could be more accurate and sensitive to thromboembolism events.

REFERENCES

1. Iung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: Why are so many denied surgery? European Heart Journal. 2005;26:2714-20.
2. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363:1597-607.
3. Kaul S. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014;371:967.
4. Smith CR, Leon MB, Mack MJ, et al. Transcatheter *versus* surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364:2187-98.
5. Thyregod HGH, Steinbruchel DA, Ihlemann N, et al. Transcatheter *versus* surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. J Am Coll Cardiol. 2015;65:2184-94.
6. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374:1609-20.
7. Rao SV, O'Grady K, Pieper KS, et al. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. J Am Coll Cardiol. 2006;47:809-16.
8. Nch MD, Elgm PH, Hram DM, et al. Transcatheter aortic valve thrombosis. J Am Coll Cardiol. 2016;68:2059-69.
9. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med. 2015;373:2015-24.
10. Moat NE, Ludman P, Belder MA, et al. Long-Term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis. J Am Coll Cardiol. 2011;58:2130-8.
11. Rodés-Cabau J, Gutiérrez M, Bagur R, et al. Incidence, predictive factors, and prognostic value of myocardial injury following uncomplicated transcatheter aortic valve implantation. J Am Coll Cardiol. 2011;57:1988-99.
12. Barbash IM, Dvir D, Ben-Dor I, et al. Prevalence and effect of myocardial injury after transcatheter aortic valve replacement. J Am Coll Cardiol. 2013;111:1337-43.
13. Kahlert P, Knipp SC, Schlamann M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: A diffusion-weighted magnetic resonance imaging study. American Heart Association. 2010;121:870-8.
14. Agnihotri A. ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement: Executive summary. J Thorac Cardiovasc Surg. 2012;144:534-7.
15. Hirsh J, Anand SS, Halperin JL, et al. Guide to anticoagulant therapy, Heparin: A statement for healthcare professionals from the American Heart Association. Circulation. American Heart Association, Inc. 2001;103:2994-18.
16. Shimada YJ, Nakra NC, Fox JT, et al. Relation of race (Asian, African-American, European-American, and Hispanic) to activated clotting time after weight-adjusted bolus of heparin during percutaneous coronary intervention. Am J Cardiol. 2010;105:629-32.
17. Butterworth J, Lin YA, Prielipp RC, et al. Rapid disappearance of protamine in adults undergoing cardiac operation with cardiopulmonary bypass. Ann Thorac Surg. 2002;74:1589-95.
18. Guyatt GH, Akl EA, Crowther M, et al. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:1129.
19. Abdel-Wahab M, Richardt G. Safety of bivalirudin in patients with coronary artery disease. Expert Opinion on Drug Safety. 2011;11:141-50.
20. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med. 2008;13:1-13.
21. Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or unfractionated heparin in acute coronary syndromes. N Engl J Med. 2015;373:997-1009.
22. Villablanca PA, Al-Bawardy R, Mohananey D, et al. Bivalirudin *versus* heparin in patients undergoing percutaneous transcatheter aortic valve interventions: A systematic review and meta-analysis. J Interven Cardiol. 2017;30:586–94.
23. Schulz S, Richardt G, Laugwitz KL, et al. Prasugrel plus bivalirudin *vs.* clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. European Heart Journal. 2014;35:2285-94.
24. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. Euro Intervention. 2012;8:782-95.
25. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the bleeding academic research consortium. Circulation. American Heart Association, Inc. 2011;123:2736-47.
26. Investigators TG. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med. 1993;329:673-82.
27. Stone GW, Bertrand M, Colombo A, et al. Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial: Study design and rationale. Am Heart J. 2004;148:764-75.
28. Mehran R, Brodie B, Cox DA, et al. The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial: Study design and rationale. Am Heart J. 2008;156:44-56.