Antithrombotic therapy in TAVI

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Abstract

Transcatheter aortic valve implantation (TAVI) carries a significant thromboembolic and concomitant bleeding risk, not only during the procedure but also during the periprocedural period. Many issues concerning optimal antithrombotic therapy after TAVI are still under debate. In the present review, we aimed to identify all relevant studies evaluating antithrombotic therapeutic strategies in relation to clinical outcomes after the procedure. Four randomized control trials (RCT) were identified analyzing the post-TAVI antithrombotic strategy with all of them utilizing aspirin lifelong plus clopidogrel for 3–6 months. Seventeen registries have been identified, with a wide variance among them regarding baseline characteristics, while concerning antiplatelet therapy, clopidogrel duration was ranging from 3–12 months. Four non-randomized trials were identified, comparing single vs. dual antiplatelet therapy after TAVI, in respect of investigating thromboembolic outcome events over bleeding complications. Finally, limited data from a single RCT and a retrospective study exist with regards to anticoagulant treatment during the procedure and the optimal antithrombotic therapy when concomitant atrial fibrillation. In conclusion, due to the high risk and frailty of the treated population, antithrombotic therapy after TAVI should be carefully evaluated. Diminishing ischaemic and bleeding complications remains the main challenge in these patients with further studies to be needed in this field.

Keywords: Antithrombotic; Bleeding; Stroke; Transcatheter aortic valve implantation

1 Introduction

Transcatheter aortic valve implantation (TAVI) has been established as the main treatment option for high-risk or inoperable patients with symptomatic severe aortic stenosis (AS), for whom conventional surgical replacement has been previously denied.[1–4] Despite the early encouraging results regarding the patients’ outcome after TAVI, the risk of major periprocedural complications such as ischemic events and bleedings remains high in this frail population.[5] At the same time, many issues concerning optimal antithrombotic therapy are still under debate.[1,6–10]

A widely used, authority based practice is to prescribe lifelong aspirin in addition to clopidogrel for a 3-to 6-month period.[11,12] However, a variety of recent studies have questioned this practice regarding antiplatelet treatment.[13] Antithrombotic therapeutic approach becomes further more complex when there is a need for concomitant anticoagulant treatment. The usual clinical scenario of such a requirement is the presence of concomitant atrial fibrillation (AF).[14] Thus, considering that bleeding complications have a major effect on long-term outcomes in that population, it is of paramount importance to obtain data on optimal antithrombotic therapy in patients undergoing TAVI.[15–18]

There is a paucity of data derived from randomized control trials (RCTs) or registries concerning the appropriate antithrombotic regimen in patients undergoing TAVI, with no specific guidelines established up to now regarding these emerging issues.[19,20] In the present review, we aimed to identify all relevant studies evaluating antithrombotic therapeutic strategies in relation to clinical outcomes after TAVI.

2 Methods

A standardized protocol was used for study selection. We performed a systematic search of EMBASE, MEDLINE for
the following search terms: (TAVI or TAVR) and (anti-thrombotic or antiplatelet). Studies were included in the study selection if they fulfilled the criteria of a Valve Academic Research Consortium (VARC)-reporting study and the outcomes or endpoints were defined according to the updated VARC.21,22

2.1 Thromboembolic events and pathophysiology in TAVI

Similar to most of other vascular or surgical interventions, TAVI carries a significant thromboembolic and concomitant bleeding risk not only during the procedure but also during the periprocedural period. Despite the fact that stroke rates are relative low after TAVI (about 3%), ischemic events documented with cerebral imaging methods remain of high frequency (66%–86%).6,23 Indeed, the risk of stroke remains high during the periprocedural period due to the mechanics of valve implantation. Stenotic aortic valve is characterized by increased calcification and simultaneously large burden of tissue factor and thrombin, increasing inflammation, all of them predisposing to peripheral embolization.24 Insertion and crossing of a bulky device through this high thrombogenic environment, in addition to frequently required corrective maneuvers makes TAVI a high embolic risk procedure.

Accordingly, in the PARTNER (Placement of Aortic Transcatheter Valve) trial, TAVI was shown initially to have a higher risk for cerebrovascular events (CVEs) compared to surgical therapy.3,25 These events have been post-procedurally correlated with adverse outcomes at 1, 12, and 24 months.26,27 Almost half of all CVEs occur > 24 h after TAVI. Apart from artificial surface exposure, flow turbulence through the valve orifice and hemostatic activation due to vessel wall disruption are considered the main factors contributing to this late ongoing thrombogenicity, while AF, chronic or paroxysmal, add further to the embolic risk.27–29

2.2 Bleeding in TAVI

Similarly to thromboembolic risk, bleeding risk is a major and common threat for patients undergoing TAVI. According to VARC criteria, the incidence of periprocedural major and life-threatening bleeding is estimated around 15%–32% and 5%–16%, respectively.25,30 Either with transfemoral access where large sheath sizes are used and bulky vessel calcification exists, or with transapical access due to inadequate apical repair, bleeding risk remains a major factor affecting patient outcome.

Nevertheless, about 50% of severe aortic stenosis patients present with anemia at baseline, either due to gastrointestinal loss (Heyde’s syndrome), or no obvious source of bleeding.31–33 As a consequence, these patients often receive blood transfusions after TAVI.

2.3 Antithrombotic current recommendations in TAVI

Regarding anticoagulation during TAVI, unfractionated heparin (UFH) is widely administered, while the American College of Cardiology Foundation/American Association for Thoracic Surgery/Society for Cardiovascular Angiography and Interventions/Society of Thoracic Surgeons (ACCF/AATS/SCAI/STS) expert consensus document on TAVI advises maintenance of an activated clotting time (ACT) > 300 s with subsequent reversal using protamine sulfate (Table 1).34

Concerning antiplatelet therapy, the American guidelines recommend low-dose aspirin (81 mg qD) indefinitely and clopidogrel (75 mg qD) at short-term (3-6 months) after TAVI, while the European guidelines confirm that a combination of low dose aspirin and thienopyridine is required followed by a regimen consisting of aspirin or clopidogrel alone, despite the lack of firm data.34,35 Finally, the Canadian statement on TAVI suggests the use of the same dose of aspirin indefinitely and clopidogrel (75 mg qD) for 30–90 days (Table 1).36

With regards to more complex scenario of patients requiring simultaneous anticoagulation therapy (concomitant AF), the American guidelines recommend low-dose aspirin in addition to oral anticoagulant (OAC) but avoidance of any other antiplatelet therapy whenever possible, while the European consensus document suggests that this population should be treated as if they have been stented without TAVI.34,37 However, the Canadian recommendations discourage prescription of triple antithrombotic regimens (Table 1).36

3 Results

3.1 Randomized control trials

After study selection, four published RCTs mentioning the post-TAVI antithrombotic strategies have been finally identified (Table 2).38 The Placement of Aortic Transcatheter Valves (PARTNER) trials A and B compared TAVI to SAVR and optimal medical therapy.3,25 In both trials aspirin was given indefinitely (75–100 mg) and clopidogrel (75 mg) for six months. In the Medtronic CoreValve U.S. Pivotal Trial (CUSPT), in which TAVI vs. SAVR (surgical aortic valve replacement) were compared, aspirin (81–325 mg) indefinitely plus clopidogrel (75 mg) for three months was used.39 In the comparison of transcatheter heart valves in high-risk patients with severe aortic stenosis: Medtronic CoreValve vs. Edwards SAPIEN XT (CHOICE) trial,
Table 1. Recommendations for antithrombotic therapy in TAVI.

|                          | European guideline and consensus | AHA/ACC guidelines | ACCF/AATS/SCAI/STS consensus | CCS          |
|--------------------------|---------------------------------|--------------------|-----------------------------|--------------|
| Aspirin                  | Low-dose, indefinitely          | Low-dose (75–100 mg qD), indefinitely | Low-dose (81 mg qD), indefinitely | Low-dose, indefinitely |
| Additional anti-platelet therapy | Thienopyridine for 6 months     | Clopidogrel 75 mg qD for 6 months | Thienopyridine for 1–3 months | *Avoid triple therapy |
| Combination of OAC and aspirin or thienopyridine is generally used, but should be weighed against increased risk of bleeding. | No clopidogrel | *Avoid triple therapy unless definite indication exists |

*Triple therapy: dual antiplatelet therapy plus vitamin K antagonist; AF: atrial fibrillation; CCS: Canadian Cardiovascular Society; OAC: oral anticoagulant; TAVI: transcatheter aortic valve implantation.

Table 2. Current RCTs mentioned in the antiplatelet regimen.

|                          | PARTNER A[3] | PARTNER B[25] | CUSPT[39] | CHOICE[40] |
|--------------------------|--------------|---------------|-----------|------------|
| Year                     | 2011         | 2010          | 2014      | 2014       |
| Sample size, n           | 348          | 179           | 394       | 238        |
| Demographics             |              |               |           |            |
| Age, yrs                 | 84           | 83            | 83        | 81         |
| Female                   | 42%          | 54%           | 47%       | 64%        |
| EuroSCORE                | 29%          | 26%           | 18%       | 22%        |
| Stroke                   | 29%          | 27%           | 13%       | 20%        |
| AF                       | 41%          | 33%           | 41%       | 28%        |
| Procedure                |              |               |           |            |
| TF/TA/other              | 70%/30%/0    | 100%/0/0      | 82%/0/18% | 100%/0/0   |
| CRS/ESV                  | 0/100%       | 0/100%        | 100%/100% | 50%/50%    |
| Regimen                  |              |               |           |            |
| Aspirin, mg              | 75–100       | 75–100        | 81–325    | 100        |
| Clopidogrel, mg          | 300          | 300           | 300       | NR         |
| Maximal ACT, s           | ≥ 250        | ≥ 250         | ≥ 250     | NR         |
| Regimen post             |              |               |           |            |
| *Aspirin, mg/months      | 75–100/~     | 75–100/~      | 81–325/3  | 100/~      |
| Clopidogrel, mg/months   | 75/6         | 75/6          | 75/3      | 75/3       |
| OAC                      | NR           | NR            | NR        | Clopidogrel for three months |
| Outcomes                 |              |               |           |            |
| 30-day all-cause mortality | 3.4%        | 5.0%          | 3.3%      | 7.9%       |
| 30-day cardiovascular mortality | 3.2%        | 4.5%          | 3.1%      | 7.2%       |
| 1-year all-cause mortality | 24.2%       | 30.7%         | 14.2%     | NR         |
| 1-year cardiovascular mortality | 14.3%       | 19.6%         | 10.4%     | NR         |
| Myocardial infarction at 30 days | 0.0         | 0.0           | 0.8%      | 0.7%       |
| Myocardial infarction at 1 year | 0.4%        | 0.6%          | 1.9%      | NR         |
| Stroke at 30 days        | 4.7%         | 6.7%          | 4.9%      | 7.2%       |
| Stroke at 1 year         | 6.0%         | 10.0%         | 8.8%      | NR         |
| Major VASC at 30 days    | 11.0%        | 16.2%         | 5.9%      | 18.1%      |
| Minor bleeding at 30 days | NR           | NR            | NR        | 14.5%      |
| Major bleeding at 30 days | 9.3%         | 16.8%         | 28.1%     | 30%        |
| Major bleeding at 1 year | 14.7%        | 22.3%         | 29.5%     | NR         |
| LTB at 30 days           | NR           | NR            | 13.6%     | 17.4%      |
| LTB at 1 year            | NR           | NR            | 16.6%     | NR         |

*All recommend aspirin to be given indefinitely except for CUSPT, which recommends a duration of at least three months; ~: indefinitely. ACT: activated clotting time; CRS: Medtronic CoreValve revalving system; ESV: Edwards Sapien valve; LTB: life threatening bleeding; NR: not reported; OAC: oral anticoagulant; TA: transapical; TF: transfemoral; VASC: vascular access site related complication. Adapted from Nijenhuis, et al.[38]
which compared TAVI with a balloon vs. a self-expandable prosthesis, suggested lifelong low-dose aspirin (100 mg) plus clopidogrel for three months.\(^{[40]}\) Furthermore, in patients requiring concomitant oral OAC therapy, clopidogrel was prescribed for three months without aspirin (Table 2).

Between the aforementioned trials, baseline characteristics are comparable. Despite the fact that thromboembolic events seem comparable, vascular complications are lower in the CUSPT compared to the PARTNER trials. However, major bleedings rate at 30 days are higher in the CUSPT and CHOICE trial compared to the PARTNER trials [28.1% and 30% vs. 9.3% and 16.8%, respectively] (Table 2).

### 3.2 Registries

Regarding published registries about TAVI, overall seventeen have been identified and finally, out of them, only six were VARC-reporting studies (Table 3).\(^{[30,41-45]}\) Among them, there is a wide variance in baseline characteristics. While concerning antiplatelet therapy, the loading dose of aspirin is not stated in most of them. Clopidogrel loading dose ranges from 300 mg to 600 mg while its' duration ranges from 3–6 to 6–12 months. Concerning procedural anticoagulation, the maximal reported ACT was > 200 s or 250–300 s.

Among these VARC-reporting studies, major bleeding rates range from 1.6% to 20.9%, while life-threatening bleeding rates range from 1.2% to 13.9%. However, thromboembolic events seem comparable [myocardial infarction (MI) 0 to 2% and stroke 2% to 6.1%]. Finally, mortality rates at 1-month vary from 2.4% to 9.7% (Table 3).

### 3.3 Non-randomized studies for antiplatelet therapy

Four studies concerning antiplatelet regimens after TAVI

| Table 3. Registries mentioning the antiplatelet regimen after TAVI. |
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| **Nombela-Franco, et al.\(^{[27]}\)** | **Borz, et al.\(^{[43]}\)** | **Tchetche, et al.\(^{[42]}\)** | **Gilard, et al.\(^{[30]}\)** | **Griese, et al.\(^{[44]}\)** | **Abramowitz, et al.\(^{[41]}\)** |
| **Year** | 2012 | 2013 | 2012 | 2012 | 2013 | 2014 |
| **Sample size** | 214 | 250 | 943 | 3195 | 162 | 249 |
| **Demographics** | | | | | | |
| **Age, yrs** | 80 | 83 | 81 | 83 | 82 | 83 |
| **Female** | 50% | 54% | 46% | 49% | 70% | 47% |
| **Euroscore** | 14% | 23% | 21% | 22% | 17% | 26% |
| **AF** | 30% | NR | NR | 27% | 33% | NR |
| **Stroke** | 91% | NR | 16% | 10% | 8% | 8% |
| **Procedure** | | | | | | |
| **TF/TA/other** | 97%/0%/3% | 76%/24%/0 | 84%/9%/6% | 76%/18%/6% | 100%/0%/0 | NR |
| **CRS/ESV/other** | 100%/0%/0 | 0%/100%/0 | NR | 32%/68%/0 | 19%/81%/0 | NR |
| **Pre-regimen** | | | | | | |
| **Aspirin, mg** | 80 | 250 | NR | ≤ 160 | 100 | NR |
| **Clopidogrel, mg** | 600 | 300 | 300 | 300 | NR | NR |
| **Maximal ACT, s** | 250-300 | NR | 200-300 | NR | ≥ 250 | NR |
| **Post-regimen** | | | | | | |
| **Aspirin, mg/months** | 80/6 | NR | NR | ≤ 160 | 100/NR | 100/NR |
| **Clopidogrel, mg/months** | 75/6 | NR/1 | 75/1-6 | 75/1 | 75/NR | 75/6 |
| **Outcomes at 30 days** | | | | | | |
| **All-cause mortality** | 8.4% | 7.6% | 7.2% | 9.7% | 5.6% | 2.4% |
| **Myocardial infarction** | NR | 2.0% | 1.6% | 1.2% | NR | 0.0 |
| **Stroke** | 6.1% | 2.4% | 2.6% | 4.1% | NR | 2.0% |
| **Major VASC** | NR | 6.4% | 10.7% | 4.7% | 4.3% | 3.2% |
| **VASC** | NR | 18% | 22.2% | 9.7% | 9.9% | 10.0% |
| **Minor bleeding** | NR | 4.8% | 10.8% | 7.4% | 14.2% | NR |
| **Major bleeding** | NR | 9.2% | 20.9% | 4.5% | 3.7% | 1.6% |
| **LTB** | NR | 13.2% | 13.9% | 1.2% | 9.9% | NR |

\(^{a}\)Antiplatelet therapy (aspirin and clopidogrel) without anticoagulant therapy was maintained in seven patients (36%) in whom the risk of bleeding was considered greater than the risk of thromboembolism. ACT: activated clotting time; AF: atrial fibrillation; ESV: Edwards Sapien Valve; CRS: Medtronic CoreValve revalving system; LTB: life threatening bleeding; NR: not reported; PAD: peripheral artery disease; TA: transapical; TAVI: transcatheter aortic valve implantation; TF: transfemoral; VASC: vascular Access Site related Complication. Adapted from Nijenhuis, et al.\(^{[38]}\)
Table 4. Studies comparing aspirin vs. DAPT after TAVI.

| Group          | 2012 | 2014 | 2013 | 2014 |
|---------------|------|------|------|------|
| Number of patients | Aspirin | DAPT | Aspirin | DAPT | Aspirin | DAPT | Aspirin | DAPT |
| Age, yrs      | 81%  | 80%  | 81%  | 80%  | 82%  | 82%  | 83%  | 85%  |
| Female        | 59%  | 50%  | 60%  | 67%  | 54%  | 55%  | 45%  | 60%  |
| EuroSCORE     | 21%  | 23%  | 25%  | 23%  | NR   | NR   | NR   | 20%  |
| AF            | 15%  | 10%  | 0    | 0    | 11%  | 28%  | 23%  | 35%  |
| Stroke        | 10%  | 5%   | NR   | NR   | NR   | NR   | 8%   | 9%   |
| PAD           | 10%  | 8%   | NR   | NR   | NR   | NR   | 17%  | 8%   |
| Ejection fraction | 54%  | 51%  | 51%  | 52%  | NR   | NR   | NR   | NR   |

Demographics

| Procedure      | 2012 | 2014 | 2013 | 2014 |
|----------------|------|------|------|------|
| TF             | 100% | 95%  | NR   | NR   | NR   | NR   | 84%  | 77%  |
| TA             | 0    | 0    | NR   | NR   | NR   | NR   | NR   | 15%  |
| Other          | 0    | 5%   | NR   | NR   | NR   | NR   | 1%   | 0    |
| CRS            | 100% | 100% | 0    | 0    | 100% | 100% | 33%  | 0    |
| ESV            | 0    | 0    | 100% | 100% | 0    | 0    | 67%  | 100% |

Regimen pre

| Aspirin, mg   | 100  | 100  | 75–160 | 75–160 | 300  | 300  | 75   | 75   |
| Clopidogrel (loading dose in mg) | -    | 300  | NR    | NR    | -    | 300  | 300  | 300  |
| INR           | NR   | NR   | NP    | NP    | NR   | NR   | <1.5 | <1.5 |
| Maximal ACT, s | 200–250 | 200–250 | >250  | >250  | NR   | NR   | NR   | NR   |

Regimen post

| *Aspirin, mg  | 100  | 100  | 75–160 | 75–160 | 75   | 75   | 75   | 75   |
| Clopidogrel, mg/months | -    | 75/3 | 75/6  | 75/6  | -    | 75/6 | -    | 75/1 |
| OAC           | NR   | NR   | NP    | NP    | NR   | NR   | One month aspirin + single dose clopidogrel (300 mg) |

Outcomes

| 30-day all-cause mortality | 10.0% | 10.0% | 3.3%  | 1.7%  | 3.3%  | 6.9%  | 7.9%  | 9.4%  |
| 6 month all-cause mortality | 13.0% | 10.0% | 5.0%  | 5.0%  | NR    | NR    | NR    | NR    |
| Myocardial infarction at 30 days | 0    | 0    | 0    | 0    | NR    | NR    | NR    | 1.2%  |
| Stroke at 30 days           | 5.0% | 3.0%  | 3.3%  | 1.7%  | 2.2%  | 3.4%  | 1.2%  | 4.7%  |
| Major VASC at 30 days       | NR   | NR   | 0.0   | 5.0%  | 3.3%  | 5.2%  | 5.5%  | 10.2% |
| Minor bleeding at 30 days   | 10.0% | 8.0%  | 1.7%  | 5.0%  | NR    | NR    | 2.4%  | 5.5%  |
| Major bleeding at 30 days   | 30%  | 5.0%  | 3.3%  | 3.3%  | NR    | NR    | 2.4%  | 13.3% |
| Life-threatening bleeding at 30 days | 5.0%  | 5.0%  | 5.0%  | 6.6%  | NR    | NR    | 3.7%  | 12.5% |
| All bleeding at 30 days     | 18.0% | 18.0% | 10.0% | 15.0% | 8.8%  | 19.0% | 8.5%  | 31.3% |

*All recommend aspirin to be given indefinitely. ACT: activated clotting time; AF: atrial fibrillation; CRS: Medtronic CoreValve revalving system; DAPT: dual antiplatelet therapy; ESV: Edwards Sapien Valve; INR: not reported; NP: not performed; OAC: oral anticoagulant; PAD: peripheral artery disease; TA: transapical; TAVI: transcatheter aortic valve implantation; TF: transfemoral; VASC: vascular access site related complication. Adapted from Nijenhuis, et al.[38]

have been identified mainly comparing aspirin single anti-platelet therapy (SAPT) to dual antiplatelet therapy (DAPT) (Table 4). In the study from Ussia, et al.,[13] aspirin was prescribed indefinitely (100 mg) in all patients, while clopidogrel was added for three months (75 mg qD) in the clopidogrel-arm group. No further information concerning
oral anticoagulant therapy is provided by the authors. At 30 days post procedure, bleeding was comparable between the two groups (18% vs. 18%). Besides, no difference was observed in composite endpoint of one month mortality, MI, and stroke.

In a similar design non-randomized study [single antiplatelet for TAVI (SAT-TAVI) trial], SAPT with clopidogrel was administered for six months in one arm, while DAPT was administered in the second arm. Accordingly, bleeding at 30 days was not statistical different between two groups (10% for SAPT vs. 15% for DAPT). Similarly, 30-day rates for mortality, MI, and stroke results were comparable. However, in the SAT-TAVI trial, vascular access related complications (VASC) were reported significant lower for aspirin monotherapy vs. DAPT (5% vs. 13%, P < 0.05). In this study, patients requiring OACs were excluded.

In a third non-randomized study, Poliacikova et al. compared retrospectively aspirin monotherapy vs. DAPT. Specifically, aspirin was administered indefinitely in all patients while clopidogrel was prescribed for six months in DAPT arm. Concerning thrombotic events and 30-day mortality, no difference between groups was recorded. Contrary to that, bleeding at 30 days was higher in DAPT vs. SAPT group (19% vs. 8.8%, P = 0.069). As well, the composite endpoint of all-cause mortality, acute coronary syndrome, stroke and major bleeding was higher in DAPT vs. aspirin group (27.6% vs. 12.1%, respectively).

Finally, in a multi-center study (FRANCE 2 registry), aspirin monotherapy vs. DAPT were prospectively compared. The antithrombotic therapeutic regimens were as follows. In both groups, aspirin administration began the day before TAVI (75 mg without loading) and was given indefinitely. In the DAPT group, additionally to aspirin, clopidogrel was started (300 mg) the day prior to TAVI and continued for one month (75 mg qD). For patients requiring OACs, if in SAPT group, aspirin was administered for 30 days and if in DAPT group, except for 30 days aspirin (as in the SAPT group) a loading dose of 300 mg clopidogrel was given without continuation. Compared to the SAPT group, major and minor vascular access site related complications (VASC) were more frequent in the DAPT group (10% for DAPT vs. 6% for SAPT and 9% for DAPT vs. 2% for SAPT, respectively). Similarly, major and life-threatening bleedings were also recorded more frequent in the DAPT vs. SAPT group (13% vs. 2% and 13% vs. 4%, respectively). Accordingly, the number of patients needed blood transfusions was higher among the DAPT group (25% vs. 7%). However, mortality rates and thromboembolic events were not statistical different between the two groups.

### 3.4 Anticoagulant treatment

Concerning anticoagulation during implantation, only one published RCT has been finally identified. The BRAVO-3 trial investigated whether a direct thrombin inhibitor, bivalirudin, offers an alternative to heparin as the procedural anticoagulant agent in patients undergoing TAVI. A total of 802 patients were randomized to undergo transfemoral TAVI with bivalirudin versus unfractionated heparin administered during the procedure. Regarding the two primary endpoints of major bleeding within 48 h or before hospital discharge (whichever occurred first) and 30-day net adverse clinical events (combination of all-cause mortality, myocardial infarction, or stroke and major bleeding), no significant difference was recorded between the two groups (6.9% for bivalirudin vs. 9.0% for UFH, P = 0.27 for major bleeding and 14.4% for bivalirudin vs. 16.1% for UFH, P = 0.50 for combined adverse clinical events). However, at 48 h, the bivalirudin group had significantly fewer MI but more acute kidney injury events than the UFH group; at 30 days, these differences were no longer significant.

Finally, regarding long term antithrombotic therapy in TAVI patients with concurrent AF, Vavuranakis et al. have published a single center experience with the following therapeutic combination regimen; the AF-group patients were prescribed clopidogrel (75 mg/day) plus OAC for the first three months. Consequently, aspirin (100 mg/day) plus OAC were recommended until follow-up contact. Non-AF group patients were treated with DAPT for the first three months (clopidogrel 75 mg/day plus aspirin 100 mg/day), followed by SAPT with aspirin until follow-up. In a mean follow-up of 23.4 ± 14 months no statistical difference was found between groups concerning the primary endpoint of major adverse cardiac events (death, MI, coronary revascularization and stroke) (P = 0.705, phi coefficient = 0.06). Similarly, no difference between groups was found concerning the secondary end-point of major bleeding, as defined by Bleeding Academic Research Consortium (BARC) definition (P = 0.658, phi-coefficient = 0.14).

### 3.5 Forthcoming studies

Further evidence is needed in order to establish the appropriate antithrombotic treatment in patients undergoing TAVI, whether anticoagulation is required or not. Ongoing trials attempt to clarify this debated issue.

The dual antiplatelet therapy versus oral anticoagulation for a short time to prevent cerebral embolism after TAVI
(AUREA) (NCT01642134) trial assesses the efficacy of aspirin 80 mg/day plus clopidogrel 75 mg/day for three months, compared with acenocumarin in preventing cerebral thromboembolism identified by magnetic resonance (primary endpoint) at three months in patients without indication for anticoagulation. The Antiplaetelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPopular-TAVI) (NCT02247128) trial is a prospective randomized, controlled, open-label multicenter clinical trial to test the hypothesis that monotherapy with aspirin or OAC after TAVI is safer than the addition of clopidogrel for three months, without compromising clinical benefit.

Future studies will also need to investigate the potential role of newer antiplatelet (ticagrelor, prasugrel) or OAC regimens (dabigadran, rivaroxaban, apixaban and edoxaban) in antithrombotic strategy during and after TAVI.

4 Discussion

Undeniably, the concern for antithrombotic therapy after TAVI is of increasing importance especially after the knowledge that transcatheter heart valve thrombosis is more frequent than initially believed, with a frequency of 1%–5% for asymptomatic cases and much higher (40%) for symptomatic patients. The importance for optimal antithrombotic therapy is further underlined by the close correlation between asymptomatic transcatheter heart valve thrombosis and asymptomatic embolic events.

Use of dual antiplatelet therapy with aspirin plus clopidogrel after TAVI has been loosely based on coronary and peripheral vascular therapies. Furthermore, there is no evidence on duration of therapy or what agents should be used. Simultaneously with severe aortic stenosis, a high proportion of these patients suffer from AF, stroke and coronary artery disease with recent MI or coronary intervention. Thus, all these issues make difficult the development of a systemic antithrombotic approach.

Current clinical practice on antithrombotic therapy after TAVI remains empirical and/or authority based. Despite the lack of evidence, the American guidelines suggest aspirin (81 mg qd) indefinitely and clopidogrel for 3–6 months, while the Canadian statement on TAVI recommends the use of clopidogrel for 1–3 months. Similarly, the European guidelines confirm the above treatment, despite the lack of evidence.

Direct comparison of the different antithrombotic regimens is challenging, because of the significant variety in the baseline characteristics of the available study populations. Besides, especially in RCTs mentioned above, antithrombotic therapy remains quite vague. Finally, antithrombotic strategy in cases with need for OAC is not definitely reported, while major outcomes or bleeding events are often not reported according to VARC.

Antithrombotic treatment is initiated during implantation procedure for protection from embolic events, possibly occurring at this period. However, results from BRAVO-3 trial do not preconceive the use of bivalirudin instead of UFH for procedural anticoagulation, but have proven the safety of bivalirudin in this high frailty group of patients.

In case of concomitant AF, long term antithrombotic therapy is a challenging and complex field. Evaluation of the thrombotic (CHA2DS2-VASc score) and bleeding (HAS-BLED score) risk remains the optimal patient approach with simultaneous assessment of patient frailty. Combination of OAC plus usually aspirin in the first 3 months is generally used in high thrombotic risk patients (CHA2DS2-VASc score ≥ 2). Contrary to that, in cases of low risk (CHA2DS2-VASc score < 2) exclusive antiplatelet therapy is preferred, while in high bleeding risk patients (HAS-BLED ≥ 3) left atrial appendage closure remains an option.

Data regarding the exact mechanism of thromboembolic events after TAVI are lacking. It remains unclear whether clot formation is platelet or thrombin based. It has been shown that the endothelialization of the valve stent probably occurs within the first three months after implantation. This is in line with the observation that thromboembolic events are greater within this early post intervention period and supports the strategy of more intense early antithrombotic therapy. However, the use of DAPT during that period after TAVI must be further tested with well organized RCTs. Existing data from aforementioned small non-RCTs do not demonstrate any superiority of DAPT in comparison to aspirin monotherapy. Cerebrovascular events rates are similar whereas bleeding events may happen even more frequently.

It has been recently supported that rationale for anticoagulation therapy apart from concomitant AF, is further based on high stroke rates of TAVI patients and ‘subclinical leaflet thrombosis’. The implanted valve is a complex device with metal frame, biologic prosthesis and remaining native valve with complex flow patterns and possible embolic complications. Thus, “subclinical leaflet thickening or thrombosis” has been observed in quite remarkable rates (20%). Accordingly, anticoagulation directed at reducing stroke risk and possible leaflet thrombosis may be a novel investigation field in the near future.

Finally, as transcatheter based treatment for aortic steno-
sbs is targeting at lower age and lower risk patients, optimal antithrombotic therapy becomes of paramount importance. It seems that in these populations, long term valve durability and elimination of possible leaflet thrombosis are highlighted as the main pursued issues, in parallel with diminishing bleeding complications. Individualized antithrombotic regimens according to patient characteristics will be probably the optimal approach in the near future.

In conclusion, diminishing ischaemic and bleeding complications after TAVI remains the main challenge in patients undergoing TAVI. Due to the high risk and frailty of the treated population antithrombotic therapy after TAVI should be carefully evaluated. The inconsistency of clinical and demographic characteristics of these patients makes a head-to-head comparison of alternative antithrombotic regimens quite challenging. Current practice supports DAPT for up to 6 months and is mainly based on experience from coronary and peripheral vascular therapies without existing evidence of additional protection from dual antiplatelet therapy. Use of anticoagulants directed at reducing stroke risk and valve thrombosis is still debatable and well-organized RCTs are needed in this field.

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