Late coronary ischemic syndromes associated with transcatheter aortic valve implantation: A review of mechanistic and clinical aspects

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1. Introduction

Over the last decade, transcatheter aortic valve implantation (TAVI) has drawn an ever-growing interest as a novel option particularly for surgically high-risk subjects necessitating aortic valve intervention,1–5 and is probably the most popular and rapidly evolving topic in the arena of current interventional cardiology. On the other hand, TAVI is well known to be associated with a variety of coronary and non-coronary complications in the acute setting.1,5 A variety of life-threatening periprocedural complications including vascular injury, cerebrovascular events, acute kidney injury, paravalvular leak with hemodynamic compromise and conduction blocks, etc. have all been reported in large patient series.1,5

One of the most devastating acute complications associated with TAVI appears to be the device-related acute coronary ostial occlusion due to the device malapposition, plaque shift from the native valves as well as protrusion of native leaflets into the coronary ostia during the procedure requiring emergent coronary intervention.1,5–7 The risk of this deadly complication significantly increases in the setting of certain baseline features including low-take off coronary arteries (<10–12 mm), bulky and heavily calcified native valves, narrow aortic root with shallow sinuses.1 In the setting of TAVI, clinicians generally focus on periprocedural complications, and little is known about potential late complications and long-term pathophysiological alterations particularly involving the coronary arterial tree at the macro and microvascular levels. Therefore, the potential association between TAVI and late coronary ischemic syndromes needs to be further elucidated in terms of mechanisms and clinical implications. The term ‘late coronary ischemic syndrome’ used in this setting refers to any type, magnitude and duration of stable and unstable coronary ischemic syndromes arising at any time after TAVI with the particular exclusion of acute procedural coronary complications (acute ostial occlusion, guidewire-related coronary dissection, etc.). Accordingly, the present paper aims to discuss potential association of TAVI with late coronary ischemic events on the basis of mechanistic and clinical perspectives.

1.1. Clinical background: readmission of TAVI recipients with coronary ischemic events in major clinical trials and real life

In clinical practice, a significant portion of patients undergoing TAVI generally appear to be very elderly and frail suffering a variety
of significant multi-organ comorbidities. Importantly, a portion of these patients are generally rehospitalized after sometime following TAVI due to a variety of acute cardiac emergencies including acute coronary syndromes (ACS) and even sudden cardiac death, death.3,9 Interestingly, clinicians are generally inclined to consider these life-threatening readmissions as part of a natural and anticipated course of these high-risk patients, and do not contemplate over any specific triggers and mechanisms underlying these coronary ischemic syndromes emerging after TAVI. In our clinical practice, we also encounter such cases readmitted with acute coronary ischemic syndromes emerging without a specific trigger after TAVI.10 Similarly, readmissions with acute myocardial infarction (AMI) following TAVI were also reported in previous large-scale studies.8,8 Accordingly, a recent study has reported AMI readmission incidences of 0.0% and 0.8% for self and balloon expandable valves, respectively, at 1 month.8 On the other hand, the incidences of cardiovascular mortality at 1 month were reported to be 4.3% and 4.1% for self and balloon expandable valves, respectively, in the same study.8 In another recent study comparing different bioprostheses in terms of procedural success and clinical outcomes, rates of AMI at 1 month were found to be 0.5% and 1.5% along with the cardiac mortality rates of 8.3% and 7.4 at 1 year for self-expandable and balloon expandable valves, respectively (p > 0.05 for both).9 Moreover, a multicenter study comprising a population of around 4500, in-hospital rate of AMI after TAVI was reported to be less than 1%, and was similar for self and balloon expandable valves.11 However, this study exclusively focused on in-hospital outcomes, and did not report the AMI rates in the long-term among patients undergoing TAVI.11

On the other hand, studies with a relatively longer follow-up periods demonstrated a relatively higher incidence of ACs following TAVI.12,13 A recent multicenter study reported an overall mortality rate of 55% at 42 ± 15 months among patients undergoing TAVI.12 Among these mortal cases, 3.9% and 2.6% were reported to be due to AMI and sudden cardiac death (SCD), respectively.12 In another multicenter study reporting 5-year outcome of a self-expandable bioprosthesis, 5.8% of rehospitalizations appeared to be due to cardiac ischemia in a population of 353 patients undergoing TAVI.13 Very recently, a large-scale multicenter study comprising a population of 280 patients undergoing aortic valve intervention has made a comparison between TAVI and surgical aortic valve replacement (SAVR) in terms of clinical outcomes, and has demonstrated AMI incidences of 5.1% and 6.0% at 2-years in the TAVI and SAVR arms, respectively.4 Importantly, this was reportedly the first study directly comparing surgical and transcatheter aortic valve interventions in patients with a relatively low surgical risk.3 Taken together, the incidence of AMI might be relatively rare in the short and mid terms after TAVI, and appears to be comparable between self and balloon expandable valves.3,11 However, there exists an upward temporal trend in the incidence of AMI readmissions on longer clinical follow-up.12,13

Of note, not all cardiac ischemic signs and symptoms after TAVI exclusively appear as part of an urgent or emergent ACS presentation including AMI in clinical practice. Accordingly, a significant portion of coronary ischemic syndromes arising after TAVI might emerge with a relatively lenient and stable clinical symptomatology (including stable angina pectoris (SAP) or mild forms of unstable angina pectoris (USAP)) that do not generally prompt TAVI recipients to seek medical aid for their ischemic symptoms potentially leading to an underestimation of real incidence of these syndromes in this setting. More importantly, even though coronary ischemic syndromes emerging after TAVI might, to some extent, be regarded as a coincidental phenomenon arising spontaneously or due to a variety of stressors,8–13 TAVI, per se, may have the potential to directly account for or accelerate the emergence of coronary ischemia as well. Taken together, it seems reasonable that TAVI, at the cost of treating the diseased aortic valve, may potentially elicit a significant proclivity for late coronary ischemic events (even in the setting of an uneventful periprocedural course) in the short and long terms through a variety of subtle mechanisms particularly in the presence of certain risk factors (as described below). On the other hand, studies with longer follow-up periods directly comparing patients with and without TAVI with regard to the evolution of coronary ischemic syndromes are strongly needed to draw firm conclusions on this issue. Probably, these studies will also demonstrate which bioprosthetic valve type appears to be more favorable in this setting.

1.2. Late coronary ischemic syndromes after TAVI: potential mechanisms and associated risk factors

As mentioned previously, late coronary ischemic syndromes arising after TAVI should not always be regarded as independent and coincidental entities, and may be directly and strongly associated with the implanted device itself suggesting a variety of potential mechanisms and associated risk factors in this setting.

1.2.1. Coronary embolism: a multi-faceted phenomenon in the setting of TAVI

In the setting of TAVI, coronary embolization with histopathological confirmation of thrombus was previously reported in the literature.14 Accordingly, late coronary ischemic events due to coronary embolism might theoretically be based on potential detrimental effects of TAVI on aortic flow dynamics: a recent study investigating potential impact of various TAVI valves on flow dynamics in sinus of Valsalva demonstrated significant reductions in Valsalva flow during early valve opening and valve closure associated with blood stasis at the basal level of Valsalva sinuses.15 This stasis might even be more pronounced in the setting of complex interventions including valve-in valve procedures. These pathophysiological alterations provide a potential explanation on the higher incidence of embolic neurological events in patients following TAVI.15 On the other hand, subclinical leaflet thrombosis as demonstrated with reduced valve motion was suggested as a novel phenomenon potentially arising as an alternative cause of cerebrovascular emboli in these patients.4–6 In a recent large scale study, subclinical leaflet thrombosis (as determined with computed tomography (CT) scan) among TAVI recipients was found to be associated with transient ischemic attacks (TIAs) or stroke.7 More importantly, anticoagulant therapy was found to be more effective both in the prevention and treatment of subclinical leaflet thrombosis in comparison to dual antiplatelet therapy (DAPT) use in these patients.8 On the other hand, current guidelines on valvular heart disease recommend the use of DAPT (clopidogrel plus aspirin for the first 6 months followed by life-long aspirin), and not the routine use of anticoagulation in patients after TAVI.15 Accordingly, further studies are still needed to determine the best antithrombotic strategy (anticoagulation? DAPT? or both?) for the prevention of embolic events with or without subclinical valve thrombosis in these patients. Taken together, withholding or prematurely terminating dual antiplatelet and/or anticoagulant therapy may potentially give rise to such neurological, and by analogy, to coronary embolic events after TAVI. However, as expected, coronary emboli in this setting (potentially originating from the aortic root (due to device related stasis), bioprosthetic leaflet tissue or the stent frame of the valve) may be considered less likely to occur as compared with cerebrovascular emboli possibly due to the anatomical location of coronary arteries and supra-coronary positioning of most bioprosthetic valves.
1.2.2. Impaired coronary flow dynamics and in-situ coronary thrombus formation

Based on coronary wave intensity analysis, there exists two dominant waves in the coronary circulation: systolic forward flowing (pushing) wave (generated by enhanced aortic pressure during myocardial contraction) and diastolic backward flowing (suction) wave (largely due to the suction force of microcirculatory decompression during myocardial relaxation).\textsuperscript{18,19} The latter appears to serve as the fundamental determinant of coronary perfusion, and was recently shown to be significantly compromised in patients with severe aortic valve stenosis (AVS) during tachycardia largely contributing to the occurrence of exercise angina in these patients.\textsuperscript{19,20} Interestingly, however, during resting state, there exists a paradoxical increase in diastolic suction flow in patients with AVS possibly as a result of enhanced compensatory diastolic recoil.\textsuperscript{19,21} Interestingly, diastolic suction wave (both at rest and during exercise) is significantly blunted in the setting of left ventricular hypertrophy (LVH) without AVS.\textsuperscript{21} Taken together, relief of AVS (with TAVI or SAVR) might elicit a significant decline in systemic afterload and myocardial wall stress leading to immediate enhancement of coronary blood flow during exercise largely through potentiation of coronary flow reserve (CFR) (and hence; exercise diastolic suction flow) in the coronary microvasculature.\textsuperscript{22,23}

However, detrimental impact of TAVI may potentially outweigh its favorable effects in certain settings particularly in the long term: AVS patients with severe LVH might potentially incur persistence or even worsening of anginal symptoms after TAVI largely attributable to the deterioration of microvascular dysfunction associated with a significant and unopposed decline in resting diastolic suction flow (due to the loss of compensatory increase associated with AVS). Moreover, augmentation of exercise diastolic suction flow (and CFR) arising due to the relief of AVS generally appears to be trivial in the setting of severe LVH, and may not counterbalance the adverse impact of worsening microvascular dysfunction in this setting. Therefore, an existing severe LVH at baseline may be regarded as an important determinant of coronary microvascular dysfunction arising after TAVI. Accordingly, clinicians should also focus on therapeutic strategies aiming to reverse or mitigate severe LVH and associated anginal symptoms in the post-TAVI setting.

On the other hand, potential impact of TAVI at the macrovascular level may be considered as a relatively more common and striking phenomenon in the clinical setting. Accordingly, impaired epicardial coronary flow dynamics (including reduced flow with intra-coronary stasis) with or without in-situ coronary thrombus formation may emerge as a dominant mechanism of late coronary ischemic events emerging after TAVI.\textsuperscript{10} In the literature, in-situ coronary thrombus formation was previously suggested as a potential cause of acute and late-onset coronary ischemic symptoms after TAVI.\textsuperscript{10,22} Accordingly, a case of ACS arising a few days after a balloon expandable TAVI was previously attributed to a thrombus superimposed on a left main coronary artery (LMCA) atherosclerotic plaque.\textsuperscript{22} Similarly, a case of acute ST segment elevation myocardial infarction (STEMI) arising about 1 month after a valve-in-valve self expandable TAVI was also reported very recently.\textsuperscript{23} Importantly, STEMI in this case emerged without a specific trigger, and was attributed to an in-situ thrombus formation emerging in the proximal-mid portion of the left anterior descending (LAD) artery possibly as a result of impaired coronary flow dynamics.\textsuperscript{10}

Impaired epicardial coronary flow after TAVI might not always appear to be grossly visible, and might be attributable to a variety of mechanical and hemodynamic factors including compromising effects of valve struts on coronary ostia, coronary flow after TAVI might not always appear to be grossly visible, and might be attributable to a variety of mechanical and hemodynamic factors including compromising effects of valve struts on coronary ostia, coronary flow after TAVI might not always appear to be grossly visible, and might be

1.2.3. Hypersensitivity reactions against the device material

Interestingly, it was previously suggested that hypersensitivity reactions (including Kounis syndrome) against the implanted device material might also serve as a potential trigger of coronary thrombus formation in certain settings.\textsuperscript{23,24} Kounis syndrome is characterized by acute spasm and/or thrombotic occlusion of coronary arteries in response to certain allergic triggers (drugs, food, etc.) potentially associated with immunoglobulin E (IgE) mediated mast cell degranulation which, in turn, leads to excessive levels of proinflammatory substances including cytokines, leukotrienes, etc. as well as bioactive amines including histamine, etc., with a variety of detrimental effects on coronary vasomotion and atherosclerotic plaque stability.\textsuperscript{23,24} More importantly, implanted cardiac devices including coronary stents, TAVI bioprostheses, etc. may also be associated with Kounis type allergic reaction particularly triggered by the metallic content of these devices (mostly cobalt, nickel, chromium) in atopic recipients.\textsuperscript{23,24}

Importantly, device related antigens may induce Kounis syndrome through local as well as systemic routes.\textsuperscript{23} In the setting of systemic activation, metal anions released from the device into the circulation might interact with antigen presenting cells potentially located in a variety of arterial beds including coronary system, etc. ultimately triggering thrombotic occlusion somewhere along the coronary arterial tree.\textsuperscript{23,24} However, it seems likely that thrombotic occlusion due to local hypersensitivity reactions generally involve the anatomical surfaces in close contact
with the TAVI device including coronary ostium. In rare instances, bioprosthetic cusp thrombosis might also be attributable to the locally activated Kounis syndrome. On the other hand, hypersensitivity reactions generally arise during the very early stages after TAVI, and hence; fail to explain the very late TAVI-related coronary ischemic syndromes in the long term.

1.2.4. De-novo or accelerated atherogenesis

Mechanistically, it is well known that certain hemodynamic factors including shear stress is of utmost importance for the maintenance of endothelial functions and hence; atheroprotection along the arterial tree. Vascular shear stress is generally defined as the force exerted on per unit of the vascular wall by the blood flow, and hence; appears to be strongly dependent on coronary flow dynamics including flow velocity and blood viscosity. Accordingly, normal or supranormal wall shear stress along the coronary arteries was previously suggested to have a protective impact on endothelial functions through a variety of mechanisms including enhancement of local antioxidant and antiinflammatory milieu. Conversely, reduced shear stress in this setting was shown to promote local increases in angiostatin–2 levels and oxidative stress along with the expression of adhesion molecules and intimal lipid infiltration that are generally considered as the initial key steps in atherogenesis. Therefore, in a portion of patients undergoing TAVI, de-novo or accelerated atherogenesis (with or without plaque rupture) due to low coronary shear stress (associated with impaired coronary flow) should also be taken into consideration as a potential contributory mechanism.

1.2.5. Late mechanical complications associated with the device

Lastly, late ACs after TAVI might also occur as a consequence of device-related mechanical complications including acute and critical coronary ostial occlusion due to a late device malapposition. Interestingly, an ACS arising 9 months after the procedure due to a very late subluxation of the aortic bioprosthesis (leading to a subtotal occlusion of left coronary ostium) was recently reported. Similarly, acute left and right coronary ostial occlusions at 1 year and 6 months, respectively, after TAVI (with different types of devices) were also reported previously. In some instances, late device malapposition may also give rise to a significant paravalvular leak potentially creating a coronary steal phenomenon with ischemic signs and symptoms. Since calcification within the surrounding tissue also serves as a sustenance to the implanted device, less calcified native valves may potentially predispose to such device malappositions even long after TAVI. Moreover, late device malapposition may, to some extent, be associated with the type of the TAVI device. On the other hand, the issue of which devices are more prone to this late complication has yet remained to be established. However, late mechanical complications have been reported very rarely, and hence; not can be generalisable to the whole TAVI population to explain the mechanisms and increased incidence of late coronary ischemic events in this population. Tables 1 and 2 summarize potential mechanisms and risk factors, respectively, for the evolution of TAVI-related late coronary ischemic events in the clinical setting.

2. Prognostic and therapeutic implications

Emergence of late coronary ischemic syndromes after TAVI might potentially serve as an independent prognostic marker on top of other risk stratifiers in TAVI recipients, and might have a strong association with cardiac and total mortality in these subjects. Consistent with this, presence of baseline CAD was reported to serve as an independent predictor of mortality at 5 years among 870 TAVI recipients. Very recently, a multicentre study comprising 1444 TAVI recipients, an existing previous AMI was found to be strongly associated with 5-year mortality. It seems likely that detrimental effects of coronary ischemic syndromes (whether TAVI related or not) on these already frail and vulnerable population might be more striking as compared with other elderly patients.

Even though the direct relation between TAVI and late coronary ischemic syndromes currently remains to be fully established, suggested mechanisms and risk factors potentially associated with this relation may signify a variety of preventive and therapeutic measures as well:

- Life-long anticoagulation therapy (mostly warfarin) may be recommended in the setting of high-risk procedural features (for ins; valve-in-valve TAVI with self-expandable bioprostheses) to substantially reduce the risk of coronary embolism or in-situ coronary thrombus formation due to impaired flow dynamics.
- As opposed to the general consensus exclusively recommending the use of DAPT followed by aspirin, anticoagulation therapy (for a certain duration after TAVI) was recently suggested to prevent and manage subclinical leaflet thrombosis that might arise as a reversible cause of bioprosthesis dysfunction and systemic embolism mostly in the first few months after TAVI. In contrast, impaired flow dynamics arising after high-risk procedures (leading to stasis in the aortic root and coronary arteries) may possibly serve as a permanent and predominant source of coronary ischemic pathologies potentially requiring life-long anticoagulation.
- In patients intolerant to anticoagulant therapy, life-long DAPT may be the preferred strategy in the setting of high-risk

Table 1

| Potential mechanisms of TAVI-related late coronary ischemic syndromes. |
|---------------------------------------------------------------|
| Impaired coronary flow dynamics and coronary hypoperfusion |
| In situ coronary thrombus formation |
| Coronary embolism |
| De-novo or accelerated atherogenesis |
| Hypersensitivity reactions against the device material |
| Late device malapposition |

Table 2

| Potential risk factors for the evolution of TAVI-related late coronary ischemic syndromes. |
|---------------------------------------------|
| Implantation of self-expandable valves |
| Valve-in-valve TAVI |
| Premature cessation of dual antiplatelet therapy |
| Presence of hypercoagulable states (smoking etc.) |
| Recent coronary stent implantation |
| Severe coronary stenosis at baseline |
| CSF at baseline |
| Severe degree of LVH at baseline |
| History of allergic reactions |
| Absence of calcification within the native valvular tissue |

TAVI: transcatheter aortic valve implantation, CSF: coronary slow flow, LVH: left ventricular hypertrophy.

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- Despite the reportedly higher incidence of acute procedural coronary ostial occlusion with balloon-expandable valves, late impact of self-expandable valves on coronary system may be more striking in the long-term.
- Clopidogrel plus aspirin usually recommended for the first 6 months.
- Not amenable to percutaneous coronary intervention in the pre-TAVI setting.
- Kounis syndrome or other types of allergic reactions.
- Associated with device malapposition.
procedural features though it may not appear to be so efficient as anticoagulant therapy in this setting. Even in the setting of low-risk (single, balloon expandable valves), premature termination of DAPT should be strongly discouraged, and DAPT for 6 months after the procedure followed by lifelong aspirin therapy should be implemented in every patient unless strictly contraindicated as recommended by the recent guidelines.17

- As described previously, substantial reduction in coronary perfusion without coronary embolism or thrombus may be the predominant mechanism in a portion of patients with TAVI even in the absence of pre-existing coronary macro or microvascular disease. Therefore, therapies targeting enhancement of myocardial blood flow including newer generation calcium channel blockers26 etc. and other antischemics (beta blockers, ranolazine, trimethazidine)23,24 may be initiated soon after TAVI. It seems reasonable to initiate more intensive regimens much earlier in the setting of a pre-existing microvascular disease or a critical coronary stenosis that is not amenable to PCI in the pre-TAVI setting.

- Hypercoagulable states including smoking,35 etc. should be discouraged in a more strict manner. Accordingly, smoking was recently suggested as an important predictor of long-term mortality among TAVI recipients16 possibly due to its detrimental effects on coagulation/ thrombogenic procedures including elective coronary stent implantation.37 where necessary, should be performed in the pre-TAVI setting, and importantly; if possible, deferring TAVI until the implanted coronary stent is considered to be fully endothelialized, may be a safer strategy. Therefore, bare metal stents may be preferred over drug-eluting ones due to their higher rates of endothelialization.

- Since TAVI may have the potential to reduce coronary shear stress potentially associated with de-novo or accelerated atherogenesis, a variety of antiatherosclerotic drugs including statins, ACE inhibitors37 should also be initiated on a routine basis. Fortunately, majority of these patients already receive statin therapy prior to TAVI as part of a primary or secondary preventive strategy against stable CAD and ACS. Importantly, since TAVI candidates are generally frail and elderly people, statins are generally prescribed to these patients in small doses to avoid potential statin toxicity. However, statin therapy, in certain settings after TAVI, may need to be uptitrated with close monitoring to maximize its antiatherosclerotic efficacy.

- History of allergic reactions should be carefully sought preceding a planned TAVI with a particular attention on metal sensitivity.22 Potential allergic constituents of the device should also be documented in the pre-TAVI setting. Atopic patients with a high likelihood of hypersensitivity reactions, further tests particularly for the metal allergy should be implemented just as currently recommended prior to coronary stent implantation.23 In case of a Kounis syndrome evolving after TAVI, initiation of antihistaminics, mast cell stabilizing agents, steroids as well as desensitization protocols in certain settings might serve as an effective strategy on top of standard ACS protocol.24 On the other hand, beta-blockers should be regarded with caution in this setting due to their potential to induce coronary vasospasm (as a result of relative increase in unopposed alpha adrenergic activity).24 Novel agents particularly targeting quantity, structure and functions of mast cells might potentially serve as promising preventive strategies in the setting of Kounis syndrome28 associated with device implantation including TAVI.

- Since TAVI is generally considered as a last resort for high-risk surgical patients with severe AVS,21 every effort should be made to perform it in the most proper setting. On the other hand, deferral of TAVI until patient-related risk factors for late coronary ischemic syndromes (if any) have been completely eliminated or, at least, minimized, seems to be a plausible option in clinically stable patients requiring TAVI. Lastly; specifically designed, and hence; unique TAVI devices (including mechanically expanding bioprostheses) have been tested so far in an effort to improve outcomes of TAVI in the clinical setting.39 Within this context, further advancement in device technology (bioprostheses devoid of allergic, procoagulant characteristics, partially bioabsorbable frames, etc.) may possibly eradicate or mitigate the potential detrimental effects of TAVI on coronary physiology.

3. Conclusion

Major clinical studies as well as real life experiences have demonstrated variable rates of readmissions with ACS among TAVI recipients particularly with an increasing temporal trend in the long term. On the other hand, a significant portion of coronary ischemic syndromes arising after TAVI may be clinically stable, and may not result in readmissions and/or rehospitalizations suggesting potential underestimation and underreporting of these syndromes after TAVI.

Even though coronary ischemic syndromes emerging after TAVI might, to some extent, appear to be coincidental or attributable to a variety of stressors, there potentially exists a subtle and direct association between TAVI and late coronary ischemic events (both stable CAD and ACS) through a variety of diverse mechanisms that might, to a large extent, have gone unnoticed or overlooked so far in the clinical setting. This association may potentially suggest a more fundamental role of TAVI-related impaired coronary flow dynamics with or without intracoronary thrombus formation (as compared with other factors including coronary emboli, late device malapposition, hypersensitivity etc.) particularly in the setting of certain device and/or patient-related risk factors. Awareness of this potential association between TAVI and late coronary ischemic syndromes may help tailor patient-specific management strategies in TAVI recipients deemed as having high-risk for such an association. However, further investigations are strongly warranted to confirm this association along with its risk factors and implications.

Conflict of interest

None.

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