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Coronary artery disease in patients undergoing TAVI - why not to treat

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KEYWORDS

- aortic stenosis
- coronary angioplasty
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- TAVI

Abstract

The management of coronary artery disease in the context of severe aortic stenosis in patients at increased surgical risk is an increasingly relevant problem in the transcatheter aortic valve implantation (TAVI) era. We review the current data on percutaneous coronary intervention (PCI) in TAVI patients and discuss how it has impacted upon our decision making, advocating that pre-TAVI revascularisation is not necessarily required.

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Introduction

Senile, calcific aortic stenosis (AS) is the most common valvular disease in the developed world and often co-exists with coronary artery disease (CAD) secondary to atherosclerosis[1,2]. This has been the subject of numerous studies in the field of surgical aortic valve replacement, and revascularisation through concomitant coronary artery bypass grafting for significant lesions is recommended[3]. It is also of great interest to clinicians performing transcatheter aortic valve implantation (TAVI), given that these patients are generally older and are characterised by higher risk profiles. Looking to improve both safety and efficacy outcomes for these patients, the question now is whether or not these patients should be revascularised prior to TAVI.

Comparative pathophysiology

Calcific AS and CAD share common processes, such as the involvement of low-density lipoprotein-mediated immune response and inflammatory cytokine release[4,5]. The risk factors for both conditions are also similar, predominantly age, male sex, hypertension, smoking and raised low-density lipoprotein (LDL) cholesterol levels[6]. However, whilst one may be a marker of risk for the other[7], the processes are distinct from each other. Indeed, the relevance of this common risk profile is evident when considering patients undergoing surgical aortic valve replacement (SAVR), where the incidence of CAD is known to increase with age and the degree of aortic calcification[7-9].

TAVI and CAD

Given this overlap, it is not surprising that CAD is a frequent finding in patients undergoing TAVI in the larger registries and randomised controlled trials[10-12]. However, there is no consensus in the literature regarding the significance of CAD in patients undergoing TAVI, the main problem being the variability in the actual definition of CAD used in the specific studies, which are summarised in **Table 1**.

Some groups have used the presence of previous revascularisation to define CAD[13,14]. This seems to have identified patients at higher risk, with more frequent peripheral vascular disease (PVD), renal impairment, greater anginal burden and lower left ventricular ejection fraction[13,14]. Unsurprisingly, these studies also found higher perioperative risk in the CAD patients.

There are also analyses using composite definitions of CAD in the literature, combining factors such as previous revascularisation or myocardial infarction and angiographic severity of stenoses[15,16]. Again, these patients were found to have an increased frequency of comorbidities associated with CAD but with no impact upon survival. The limitations of heterogeneity may also explain the results of a recent meta-analysis combining many of these studies which also found no effect of CAD status upon mortality[17].

Day by day in the cathlab we use anatomy to classify lesion severity prior to PCI and in assessing patients prior to SAVR[3,18]. Traditional cut-offs of stenosis severity, such as the 50% commonly used prior to surgery and 70% used in PCI, were found wanting in efforts to identify potentially modifiable risk factors[19,20], as was the use of lesion position and severity in the Duke Myocardial Jeopardy Score to assess the volume of myocardium at risk[21]. The complexity of CAD as measured by the SYNTAX score, however, may be more promising, though whether the risk is modifiable by treatment is as yet unclear[20,22].

Functional testing in the presence of aortic stenosis is more difficult, given the global subendocardial ischaemia which is often present. Myocardial perfusion scans can be falsely positive in up to 20% of cases[23]. Indeed, myocardial perfusion has been shown to be abnormal in the absence of coronary disease in severe AS on cardiac magnetic resonance imaging[24]. Fractional flow reserve is not validated in the presence of left ventricular hypertrophy or aortic stenosis[25], though it has been used in a small case series[26].

TAVI and PCI

PCI in patients with aortic stenosis has been shown to be feasible and safe in a historical cohort of 254 patients when compared to a propensity-matched cohort of patients without severe AS[27]. However, in this group of patients mainly comprising those with acute coronary syndromes or symptomatic angina thought to be predominantly due to CAD, those with LVEF ≤30% or an STS score ≥10 had a greatly increased 30-day mortality - an important consideration when approaching often high-risk patients for consideration for TAVI.

Historically, patients undergoing SAVR have been thought to benefit from concomitant coronary artery bypass grafting (CABG). Patients undergoing SAVR in early registries with unbypassed CAD have been shown to have poorer 10-year actuarial survival rates than those undergoing appropriate bypass or without the need of bypass[28]. There is, though, no randomised controlled trial to test this hypothesis in SAVR. However, the current guidelines suggest that myocardial revascularisation at the time of SAVR is a class I recommendation in the presence of stenoses of ≥70%, and a class IIa recommendation if the stenoses are 50-70% on angiography[18]. In the latest American guidelines this is a class IIa recommendation[3]. It should be noted that combined SAVR and CABG carries a greater risk than isolated SAVR[29], possibly due to features of the procedure and also the characteristics of patients with CAD.

But does the degree of revascularisation have any effect upon outcome in TAVI? A subgroup analysis of the Italian CoreValve registry found that revascularisation prior to TAVI (whether complete or partial) resulted in 12-month MACCE and mortality no different from those who were not revascularised[14]. The absence of a mortality benefit for revascularisation has been reflected in subsequent, smaller studies[16,22,30]. In fact, there is evidence to suggest the opposite, with one recent study comparing the outcomes of 65 patients who underwent TAVI+PCI (either staged or combined) against 346 patients who received isolated TAVI. Thirty-day cardiovascular mortality was higher in the PCI arm (15% vs. 5%, p=0.01), as was the rate of myocardial infarction (6% vs. 1%, p=0.01), driven by periprocedural MI (5% vs. 1%, p=0.05). Staged PCI also had higher rates of blood transfusion (50% vs. 29%), although this did not reach statistical significance[31].

Table 1. Summary of studies considering coronary artery disease in patients undergoing TAVI.

Study	Cohort	Definition of CAD	Findings	Conclusions
Previous revascularisation				
Dewey (2010)[13]	Single centre 171 patients with successful TAVI	Previous PCI or CABG CAD n=84 (49.1%) No CAD n=87 (50.9%)	CAD cohort had – More frequent PVD, CKD, previous MI – More angina – Higher logistic EuroSCORE – Greater use of TA approach – Lower LVEF	CAD patients had higher 30-day mortality (13.1% vs. 1.2%, p=0.002) CAD patients had more frequent adverse events (53.6% vs. 34.5%, p=0.02) CAD was independently associated with 30-day mortality (OR 10.1, 95% CI: 2.1-174.8, p=0.009) BUT not targets for revascularisation
Ussia (2013)[14]	Multicentre 659 patients receiving TAVI using the CoreValve system	Previous PCI or CABG CAD n=251 (38.1%) No CAD n=408 (61.9%) CAD group had more frequent "critical stenoses" (82.1% vs. 16.9%)	CAD cohort were – Older and more male – More frequent PVD, CKD, AF, previous MI – More angina – Higher logistic EuroSCORE – Lower LVEF	No difference in 30-day or 12-month MACCE or mortality CAD cohort had higher spontaneous MI at 12 months (2.4% vs. 0.2%, p=0.009)
See Table 2 for effects of revascularisation				
Anatomical				
Masson (2010)[21]	136 patients	Both by prior revascularisation and by Duke Myocardial Jeopardy Score (requires lesions of ≥70%) into 5 groups DMJS 0 & No CAD, DMJS 0 & CAD, DMJS 2, DMJS 4, DMJS 6-12	Groups with raised DMJS associated with – More male sex – More frequent PVD and CABG – Greater use of TA approach	No difference in 30-day mortality, NYHA status or rehospitalisation rate between groups No difference in Kaplan-Meier survival analysis up to 1 year between groups
Abdel-Wahab (2012)[19]	1,382 patients in German multicentre registry	859 patients (62.2%) had CAD defined by lesion(s) of ≥50% on CA	CAD cohort were – Younger – More male sex, diabetes – Greater anginal burden (CCS class)	CAD status had no impact upon angina post-TAVI Greater in-hospital mortality in CAD group (10.0% vs. 5.5%, p<0.01)
Khawaja (2014)[20]	Single centre 271 patients undergoing TAVI using the Edwards bioprosthesis	2 analyses (i) according to 70% lesions (or 50% LMS or SVG) by QCA (ii) 189 patients without CABG underwent SYNTAX scoring	CAD group associated with – Higher LES – More previous BAV TAVI just as successful with similar pre- and post-TAVI AV gradients	CAD status has no effect upon mortality on Kaplan-Meier analysis (=0.805) Mortality risk increases with SYNTAX risk tertile (p=0.007) SYNTAX >9 at TAVI has increased mortality (p=0.005)
Stefanini (2014)[22]	Single centre 445 patients with successful TAVI	SYNTAX score used to define groups as: (i) No CAD (n=158) (ii) SYNTAX 0-22 (n=207) (iii) SYNTAX >22 (n=80)	More severe CAD associated with – More male sex, diabetes, PVD, previous MI – More frequent previous revascularisation – Higher LES and STS scores – Lower LVEF and AVA	30-day outcomes were not affected by the SYNTAX score 12-month MACCE was higher in those with SYNTAX >22 than those with SYNTAX ≤22 or no CAD (29.6% vs. 16.1% vs. 12.5%; p=0.016) - driven by higher CV mortality
See Table 2 for effects of revascularisation				
Composite				
Gautier (2011)[15]	Single centre 230 patients referred for TAVI assessment with documented CAD status	144 (63%) had CAD defined as: Any of: – Previous MI – Previous PCI or CABG – Significant disease on CA (≥70% stenosis or ≥50% LMS lesion)	Only 145/230 underwent TAVI Of these the TAVI+CAD group had – More male sex, PVD, comorbidities – Were younger – Higher LES	CAD status had no effect upon procedural success, complications or mortality at 30 days, CAD status did not impact upon survival by Kaplan-Meier analysis up to 12 months (p=0.28)
Gasparetto (2012)[16]	Single centre 191 patients undergoing TAVI	113 (59.2%) had CAD defined as Any of: – Previous PCI or CABG – Stenosis of ≥50% on CA	CAD cohort had – More male sex – More cerebrovascular disease – Lower LVEF	CAD patients required more inotropic support (38.0% vs. 24.4%, p=0.04), CAD status had no effect upon 30-day safety or mortality outcomes
Meta-analysis				
D'Ascenzo (2013)[17]	2,472 patients in 7 studies	Heterogeneous, studies used any of: – Previous MI PCI, CABG – DMJS – Lesions on CA	CAD diagnosed in 52% (range 42%-65%)	No effect upon risk of death in a pooled analysis

AF: atrial fibrillation; CA: coronary angiography; CABG: coronary artery bypass graft; CAD: coronary artery disease; CCS: Canadian Cardiovascular Society anginal class; CKD: chronic kidney disease; MACCE: major adverse cardiovascular or cerebrovascular events; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; TAVI: transcatheter aortic valve implantation

Table 2. Summary of studies considering PCI in TAVI patients.

Study	Cohort	Extent of PCI	Conclusions
Gasparetto (2012)[16]	113 patients with active or historic CAD	38 patients (33.6%) were completely revascularised at time of TAVI 75 patients (76.4%) were incompletely revascularised	Complete revascularisation had no significant effect upon combined efficacy at 12 months OR 1.53 (95% CI: 0.66-3.50); p=0.32 (All-cause mortality OR prosthesis dysfunction OR hospitalisation for valve-related symptoms or cardiac decompensation)
Abdel-Wahab (2012)[30]	125 patients undergoing TAVI PCI to all lesions >50%	55/125 (44%) in TAVI+PCI arm 70/125 (56%) in TAVI alone arm	Patients requiring PCI (i.e., with more CAD) had greater anginal burden at baseline but after TAVI+PCI or TAVI alone ALL patients had ≤CCS 2 angina with no difference in distribution Similar effect upon NYHA class No significant difference in all-cause mortality at either 30 days or 6 months No difference in Kaplan-Meier survival curves up to 3 years (log-rank p=0.36)
Ussia (2013)[14]	275 patients with significant unrevascularised CAD	No revascularisation n=92 (33.4%) Partial revascularisation n=88 (32.0%) Complete revascularisation n=95 (34.5%)	No difference in 12-month MACCE (18.5% vs. 22.7% vs. 16.8%; p=NS) No difference in 12-month mortality (17.4% vs. 19.3% vs. 15.8%; p=NS) Higher 12-month spontaneous MI when no revascularisation (4.8% vs. 1.8% vs. 0.0%; p=0.05)
Stefanini (2014)[22]	445 patients undergoing TAVI 287 (64.5%) had ≥1 lesion ≥50%	48.4% of patients underwent PCI (for lesions ≥70% in a proximal segment) Analysis of effects of residual SYNTAX score at time of TAVI across all patients	Higher residual SYNTAX score at the time of TAVI had more frequent composite endpoint of CV mortality OR stoke OR MI No CAD (12.5%) vs. rSS 0-14 (16.5%) vs. rSS >14 (26.3%) - p=0.043 But outcomes of PCI patients vs. no PCI in patients with lesions ≥50% not published
Griese (2014)[31]	411 patients undergoing TAVI using the Edwards system in >90% of cases	65 patients underwent planned TAVI+PCI 346 patients underwent TAVI alone	Higher cardiovascular mortality at 30 days in PCI patients (15% vs. 5%, p=0.01) Higher rate of MI at 30 days in PCI patients (6% vs. 1%, p=0.01)

CAD: coronary artery disease; CCS: Canadian Cardiovascular Society anginal class; MACCE: major adverse cardiovascular or cerebrovascular events; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; TAVI: transcatheter aortic valve implantation

With respect to the main indication for PCI in non-valvular stable coronary artery disease, namely the treatment of angina, again we find that PCI prior to TAVI does not seem to help. Despite more severe angina at baseline in the PCI cohort of a study of 129 patients (21% of patients were Canadian Cardiovascular Society [CCS] class 3-4, compared to only 8% of patients in the no PCI group [p=0.01]), post TAVI neither group had any patients with CCS >2 symptoms, and there was no difference between the PCI and no PCI arms[30].

As to the question of timing of PCI, the vast majority of patients in these studies underwent PCI prior to TAVI in a staged procedure. Rates of hybrid PCI-TAVI are low in the reported literature at up to 14% of revascularisation, with the largest experience being only 46 patients[30-34]. However, the Pasic study did report promising one-year survival of 87.1% in this cohort, though without a comparator group to put that into context[33]. The most detailed inspection of this strategy was in the study by Griese et al. Outcomes and procedural details from 48 staged PCI were compared to 17 hybrid TAVI-PCI: they found no statistical difference between the groups with respect to 30-day outcomes, though the rate of myocardial infarction was higher in the hybrid group (12% vs. 4%) with the caveat of small numbers[31]. The results of PCI combining PCI and TAVI are summarised in **Table 2**.

What are the issues surrounding PCI in the context of TAVI?

Amongst the possible advantages of revascularisation prior to TAVI may be a protective effect against the ischaemic burden of the procedure, including, as it does, periods of hypotension. The absence of contractile reserve is associated with increased mortality after SAVR[35], and significant stenoses not intervened upon could contribute to this. Improving coronary flow in symptomatic patients with significant flow-limiting stenoses may maximise this beyond the valvular intervention. Invasive coronary haemodynamic studies have demonstrated a marked reduction in the diastolic suction wave in AS, which significant coronary stenosis may impair further[36].

The inherent risks of PCI are well-known to the cardiology community: death, myocardial infarction, stroke, vascular-access complications, renal insufficiency, allergy and stroke/TIA[37,38]. Even after successful PCI, there is the risk of stent thrombosis in up to 1% of cases with significant associated mortality[39]. PCI performed in the presence of severe aortic stenosis, whether staged or hybrid, runs the risk of the possibly detrimental effect AS may have upon the ability to withstand these. The need for dual antiplatelet therapy after PCI would be an important consideration in all access routes for TAVI, especially given the adverse outcomes associated with major bleeding[40]. Atrial fibrillation is common in these elderly patients, and so the issue of triple anticoagulation also arises to complicate matters. Acute kidney injury after TAVI is associated with increased mortality[41], and the risks of contrast administration prior to TAVI should not be underestimated. Contrast use in coronary angiography within 24 hours of cardiac surgery has been shown to increase the risk of acute kidney injury (AKI)[42]. This risk can even extend out to five days[43]. Whether state or privately funded, the cost of a second admission in the case of staged PCI with an increased total length of stay must be taken into consideration.

The literature does not currently support PCI prior to TAVI. Without data to suggest improved outcomes with PCI or revascularisation prior to TAVI, the inherent risks of PCI in patients with increased perioperative risk cannot be overlooked. As such, we have provided our own institutional algorithm **(Figure 1)**, describing how PCI is reserved only for those in whom unstable coronary disease or the most severe angina is the presenting complaint (in our experience, an uncommon scenario with dyspnoea more prominent). Given that unprotected left main stem (ULMS) lesions carry the worst prognosis of any coronary lesion and given the increased myocardium at risk[44], we would suggest that ULMS lesions should be considered by the Heart Team for revascularisation prior to TAVI irrespective of symptoms. Whilst applying this rationale in more than 450 patients, we have yet to require PCI for angina or its equivalents after TAVI. Perhaps the aorta is indeed the first coronary artery.

Access to the coronary ostia is possible with all the currently available commercial TAVI valves. However, one must carefully consider the relative anatomy of the aortic root, sinuses and the height of the ostia at the time of TAVI to ensure that future access is possible.

How to answer the known unknowns?

Randomised controlled trial data are clearly required. Both the PARTNER 2A and the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trials have revascularisation strategies within their designs. They will randomise patients between TAVI+PCI and SAVR+CABG if revascularisation is required.

The issue of TAVI and CAD is to be addressed specifically by the percutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantation (ACTIVATION) trial, a randomised, controlled, open-label trial of 310 patients who will be randomised to treatment of significant coronary artery disease by PCI (test arm) or no PCI (control arm) **(Figure 2)**. Significant coronary disease is defined as ≥1 lesion of ≥70% severity in a major epicardial vessel, or 50% in a vein graft or protected left main stem lesion. The trial hypothesis is that a lack of pre-TAVI PCI is non-inferior to treating coronary stenoses with PCI prior to TAVI. The primary outcome is a composite of 12-month mortality and rehospitalisation, and the trial is currently enrolling in centres across the UK and France (ISRCTN75836930)[44].

Summary

Overall, the literature suggests that percutaneous revascularisation has not been shown to improve outcome after TAVI nor more ably reduce angina. Given the inherent risks detailed above in performing PCI and the lack of compelling data, we have postulated that pre-TAVI PCI can be omitted in these patients. Whilst data from ACTIVATION, PARTNER IIA and SURTAVI trials are awaited we have detailed our own strategy for managing CAD in our patients.

In our opinion the current data do not unreservedly support revascularisation in most patients awaiting TAVI and we would advocate a more hands-off approach.

Conflict of interest statement

M. Khawaja is in receipt of a British Heart Foundation Clinical Research Training Fellowship (12/15/29380). M. Khawaja, M. Thomas and S. Redwood have received research funding grants

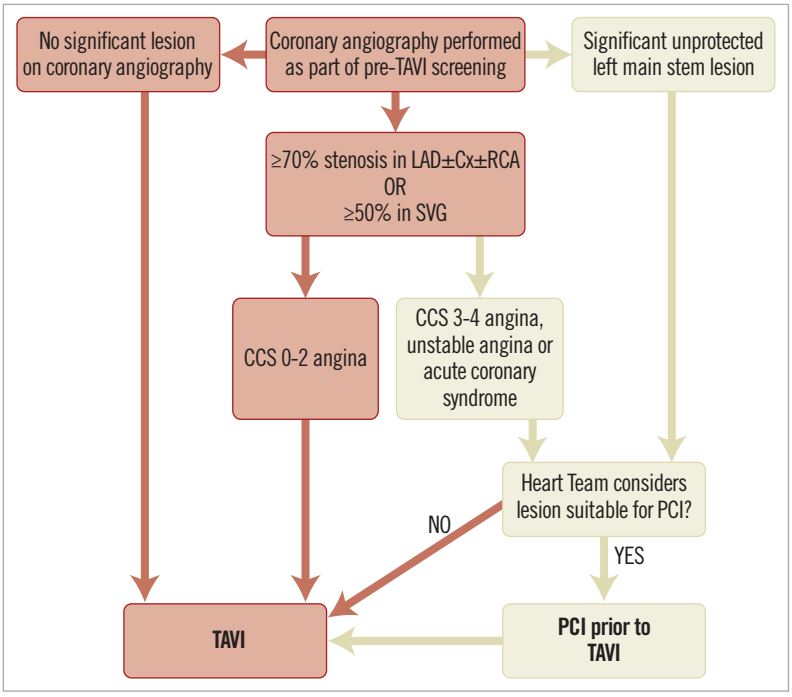

Figure 1. *An algorithm to manage coronary artery disease in patients undergoing TAVI.*

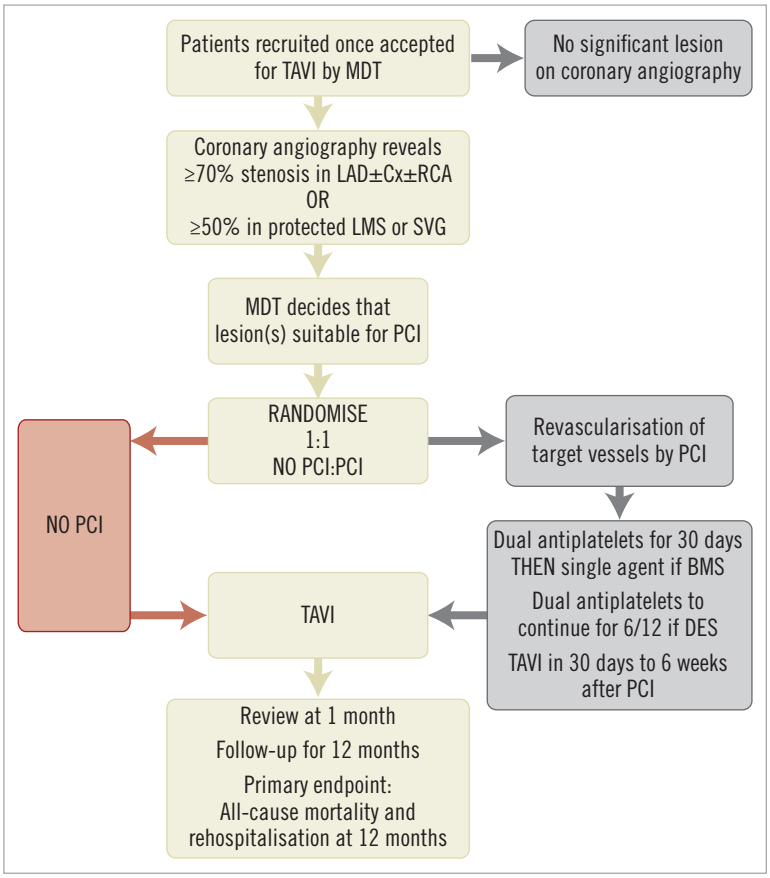

Figure 2. *The structure of the ACTIVATION randomised controlled trial of PCI prior to TAVI (adapted from Khawaja et al)*[45].

from Edwards Lifesciences and Boston Scientific. M. Thomas and S. Redwood are proctors for Edwards Lifesciences.

References

1. Ortlepp JR, Schmitz F, Bozoglu T, Hanrath P, Hoffmann R. Cardiovascular risk factors in patients with aortic stenosis predict prevalence of coronary artery disease but not of aortic stenosis: an angiographic pair matched case-control study. *Heart.* 2003;89:1019-22.

2. Beach JM, Mihaljevic T, Svensson LG, Rajeswaran J, Marwick T, Griffin B, Johnston DR, Sabik JF 3rd, Blackstone EH. Coronary artery disease and outcomes of aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol.* 2013;61:837-48.

3. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:2440-92.

4. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med.* 2005;352:1685-95.

5. Otto CM. Calcific aortic stenosis--time to look more closely at the valve. *N Engl J Med.* 2008;359:1395-8.

6. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol.* 1997;29:630-4.

7. Adler Y, Vaturi M, Herz I, Iakobishvili Z, Toaf J, Fink N, Battler A, Sagie A. Nonobstructive aortic valve calcification: a window to significant coronary artery disease. *Atherosclerosis.* 2002;161:193-7.

8. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics - 2013 update: a report from the American Heart Association. *Circulation*. 2013;127:e6-e245.

9. Kvidal P, Bergström R, Hörte LG, Ståhle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol.* 2000;35:747-56.

10. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, James J, Kleiman NS,

Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK; U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med.* 2014;370:1790-8.

11. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363:1597-607.

12. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, Eggebrecht H, Rubino P, Michev I, Lange R, Anderson WN, Wendler O. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation*. 2010;122:62-9.

13. Dewey TM, Brown DL, Herbert MA, Culica D, Smith CR, Leon MB, Svensson LG, Tuzcu M, Webb JG, Cribier A, Mack MJ. Effect of concomitant coronary artery disease on procedural and late outcomes of transcatheter aortic valve implantation. *Ann Thorac Surg.* 2010;89:758-67.

14. Ussia GP, Barbanti M, Colombo A, Tarantini G, Petronio AS, Ettori F, Ramondo A, Santoro G, Klugmann S, Bedogni F, Antoniucci D, Maisano F, Marzocchi A, Poli A, De Carlo M, Fiorina C, De Marco F, Napodano M, Violini R, Bortone AS, Tamburino C; CoreValve Italian Registry Investigators. Impact of coronary artery disease in elderly patients undergoing transcatheter aortic valve implantation: insight from the Italian CoreValve Registry. *Int J Cardiol.* 2013;167:943-50.

15. Gautier M, Pepin M, Himbert D, Ducrocq G, Iung B, Dilly MP, Attias D, Nataf P, Vahanian A. Impact of coronary artery disease on indications for transcatheter aortic valve implantation and on procedural outcomes. *EuroIntervention.* 2011;7:549-55.

16. Gasparetto V, Fraccaro C, Tarantini G, Buja P, D'Onofrio A, Yzeiraj E, Pittarello D, Isabella G, Gerosa G, Iliceto S, Napodano M. Safety and effectiveness of a selective strategy for coronary artery revascularization before transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* 2013;81:376-83.

17. D'Ascenzo F, Conrotto F, Giordana F, Moretti C, D'Amico M, Salizzoni S, Omedè P, La Torre M, Thomas M, Khawaja M, Hildick-Smith D, Ussia G, Barbanti M, Tamburino C, Webb J, Schnabel RB, Seiffert M, Wilde S, Treede H, Gasparetto V, Napodano M, Tarantini G, Presbitero P, Mennuni M, Rossi ML, Gasparini M, Biondi Zoccai G, Lupo M, Rinaldi M, Gaita F, Marra S. Mid-term prognostic value of coronary artery disease in patients undergoing transcatheter aortic valve implantation: a meta-analysis of adjusted observational results. *Int J Cardiol.* 2013;168:2528-32.

18. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Piérard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J.* 2012;33:2451-96.

19. Abdel-Wahab M, Zahn R, Horack M, Gerckens U, Schuler G, Sievert H, Naber C, Voehringer M, Schäfer U, Senges J, Richardt G. Transcatheter aortic valve implantation in patients with and without concomitant coronary artery disease: comparison of characteristics and early outcome in the German multicenter TAVI registry. *Clin Res Cardiol.* 2012;101:973-81.

20. Khawaja MZ, Asrress KN, Haran H, Arri S, Nadra I, Bolter K, Wilson K, Clack L, Hancock J, Young CP, Bapat V, Thomas M, Redwood S. The effect of coronary artery disease defined by quantitative coronary angiography and SYNTAX score upon outcome after transcatheter aortic valve implantation (TAVI) using the Edwards bioprosthesis. *EuroIntervention.* 2014 May 20. pii: 20131105-04. doi: 10.4244/EIJY14M05_09. [Epub ahead of print].

21. Masson J, Lee M, Boone RH, Al Ali A, Al Bugami S, Hamburger J, John Mancini GB, Ye J, Cheung A, Humphries KH, Wood D, Nietlispach F, Webb JG. Impact of coronary artery disease on outcomes after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* 2010;76:165-73.

22. Stefanini GG, Stortecky S, Cao D, Rat-Wirtzler J, O'Sullivan CJ, Gloekler S, Buellesfeld L, Khattab AA, Nietlispach F, Pilgrim T, Huber C, Carrel T, Meier B, Jüni P, Wenaweser P, Windecker S. Coronary artery disease severity and aortic stenosis: clinical outcomes according to SYNTAX score in patients undergoing transcatheter aortic valve implantation. *Eur Heart J.* 2014 Mar 28. [Epub ahead of print].

23. Demirkol MO, Yaymaci B, Debes H, Basaran Y, Turan F. Dipyridamole myocardial perfusion tomography in patients with severe aortic stenosis. *Cardiology.* 2002;97:37-42.

24. Steadman CD, Jerosch-Herold M, Grundy B, Rafelt S, Ng LL, Squire IB, Samani NJ, McCann GP. Determinants and functional significance of myocardial perfusion reserve in severe aortic stenosis. *JACC Cardiovasc Imaging.* 2012;5:182-9.

25. Pijls NH, Sels JW. Functional measurement of coronary stenosis. *J Am Coll Cardiol.* 2012;59:1045-57.

26. Stähli BE, Maier W, Corti R, Lüscher TF, Altwegg LA. Fractional flow reserve evaluation in patients considered for transfemoral transcatheter aortic valve implantation: a case series. *Cardiology.* 2012;123:234-9.

27. Goel SS, Agarwal S, Tuzcu EM, Ellis SG, Svensson LG, Zaman T, Bajaj N, Joseph L, Patel NS, Aksoy O, Stewart WJ, Griffin BP, Kapadia SR. Percutaneous coronary intervention in patients with severe aortic stenosis: implications for transcatheter aortic valve replacement. *Circulation*. 2012;125:1005-13.

28. Czer LS, Gray RJ, Stewart ME, De Robertis M, Chaux A, Matloff JM. Reduction in sudden late death by concomitant revascularization with aortic valve replacement. *J Thorac Cardiovasc Surg.*1988;95:390-401.

29. Gummert JF, Funkat A, Beckmann A, Schiller W, Hekmat K, Ernst M, Beyersdorf F. Cardiac surgery in Germany during 2009. A report on behalf of the German Society for Thoracic and Cardiovascular Surgery. *Thorac Cardiovasc Surg.* 2010;58:379-86.

30. Abdel-Wahab M, Mostafa AE, Geist V, Stöcker B, Gordian K, Merten C, Richardt D, Toelg R, Richardt G. Comparison of outcomes in patients having isolated transcatheter aortic valve implantation versus combined with preprocedural percutaneous coronary intervention. *Am J Cardiol.* 2012;109:581-6.

31. Griese DP, Reents W, Tóth A, Kerber S, Diegeler A, Babin-Ebell J. Concomitant coronary intervention is associated with poorer early and late clinical outcomes in selected elderly patients receiving transcatheter aortic valve implantation. *Eur J Cardiothorac Surg.* 2014;46:e1-7.

32. Wenaweser P, Pilgrim T, Roth N, Kadner A, Stortecky S, Kalesan B, Meuli F, Büllesfeld L, Khattab AA, Huber C, Eberle B, Erdös G, Meier B, Jüni P, Carrel T, Windecker S. Clinical outcome and predictors for adverse events after transcatheter aortic valve implantation with the use of different devices and access routes. *Am Heart J.* 2011;161:1114-24.

33. Pasic M, Dreysse S, Unbehaun A, Buz S, Drews T, Klein C, D'Ancona G, Hetzer R. Combined elective percutaneous coronary intervention and transapical transcatheter aortic valve implantation. *Interact Cardiovasc Thorac Surg.* 2012;14:463-8.

34. Conradi L, Seiffert M, Franzen O, Baldus S, Schirmer J, Meinertz T, Reichenspurner H, Treede H. First experience with transcatheter aortic valve implantation and concomitant percutaneous coronary intervention. *Clin Res Cardiol.* 2011;100:311-6.

35. Monin JL, Quéré JP, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Tribouilloy C, Guéret P. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation*. 2003;108:319-24.

36. Davies JE, Sen S, Broyd C, Hadjiloizou N, Baksi J, Francis DP, Foale RA, Parker KH, Hughes AD, Chukwuemeka A, Casula R, Malik IS, Mikhail GW, Mayet J. Arterial pulse wave dynamics after percutaneous aortic valve replacement: fall in coronary diastolic suction with increasing heart rate as a basis for angina symptoms in aortic stenosis. *Circulation*. 2011;124:1565-72.

37. Smith SC Jr, Feldman TE, Hirshfeld JW, Jacobs AK, Kern MJ, King SB, Morrison DA, O'Neil WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation*. 2006;113:e166-286.

38. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. *Eur Heart J.* 2012;33:2551-67.

39. Moreno R, Fernández C, Hernández R, Alfonso F, Angiolillo DJ, Sabaté M, Escaned J, Bañuelos C, Fernández-Ortiz A, Macaya C. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol.* 2005;45:954-9.

40. Doyle BJ, Rihal CS, Gastineau DA, Holmes DR Jr. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. *J Am Coll Cardiol.* 2009;53:2019-27.

41. Khawaja M, Thomas M, Joshi A, Asrress KN, Wilson K, Bolter K, Young CP, Hancock J, Bapat V, Redwood S. The effects of VARC-defined acute kidney injury after transcatheter aortic valve implantation (TAVI) using the Edwards bioprosthesis. *EuroIntervention.* 2012;8:563-70.

42. Hennessy SA, LaPar DJ, Stukenborg GJ, Stone ML, Mlynarek RA, Kern JA, Ailawadi G, Kron IL. Cardiac catheterization within 24 hours of valve surgery is significantly associated with acute renal failure. *J Thorac Cardiovasc Surg.* 2010;140:1011-7.

43. Del Duca D, Iqbal S, Rahme E, Goldberg P, de Varennes B. Renal failure after cardiac surgery: timing of cardiac catheterization and other perioperative risk factors. *Ann Thorac Surg.* 2007;84:1264-71.

44. Garg S, Stone GW, Kappetein AP, Sabik JF, Simonton C, Serruys PW. Clinical and angiographic risk assessment in patients with left main stem lesions. *JACC Cardiovasc Interv.* 2010;3:891-901.

45. Khawaja MZ, Wang D, Pocock S, Redwood SR, Thomas MR. The percutaneous coronary intervention prior to transcatheter aortic valve implantation (ACTIVATION) trial: study protocol for a randomized controlled trial. *Trials.* 2014;15:300.