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AN UPDATE ON MECHANISTIC MODES, DIAGNOSTIC APPROACH & DECIDE FOR SURGERY/VIV IN EARLY BIOPROSTHETIC VALVE FAILURE; A REVIEW

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ABSTRACT

The use of bioprosthetic heart valves has expanded considerably over the last 20 years, now are contributors of the maximum of valve replacements conducted worldwide. Whereas late structural valve degeneration continues to be the dominant mode of failure further than 10 years, early bioprosthetic valve failure (EBVF), defined as valve impairment making rearbitration imperative, resulting in robust haemodynamic diminishing or demise amongst 5 years of implantation, delineates a unique as well as escalatingly acknowledged clinical botheration. EBVF is multifactorial in origin in addition to portrays the interaction of three fundamental pathological events: i) accelerated structural valve degeneration guided by host immune reactions along with ii) dystrophic calcification; iii) valve thrombosis, both subclinical as well as clinical, inclusive of hypoattenuated leaflet thickening following transcatheter implantation; as well as prosthetic valve endocarditis, which carries unproportionate early mortality. Non-structural etiological factors inclusive of i) patient–prosthesis mismatch, ii) paravalvular regurgitation, in addition to iii) procedural malposition further aiding in, specifically with transcatheter valves. i) Younger recipients, ii) valves implanted in the mitralposition, iii) valve-in-valve procedures, iv) end-stage renal disease, along with iv) metabolic conditions are created risk factors. i) Multimodalityimaging, ii) incorporating transthoracic in addition to iii) transoesophageal echocardiography, iv) cardiac computed tomography, v) cardiac magneticresonance as well as nuclear imaging, has converted the early acknowledgement in addition to explore properties of EBVF. This review synthesises present insight i) of the mechanistic modes, ii) risk factors, iii) diagnostic strategy, along with iv) therapeutic implications of EBVF, with emphasis on the surgical viewpoint. A temporal-mechanistic strategy—associating time from implantation to plausible pathology—possesses the capability of refining diagnostic exactitude as well as guide correct selection of i) anticoagulation, ii) antimicrobial therapy, iii) redosurgery or iv) valve-in-valve arbitration.

KEYWORDS: Early Bioprosthetic Valve Failure (EBVF); Structural Valve Degeneration; Valve Thrombosis.

1. INTRODUCTION

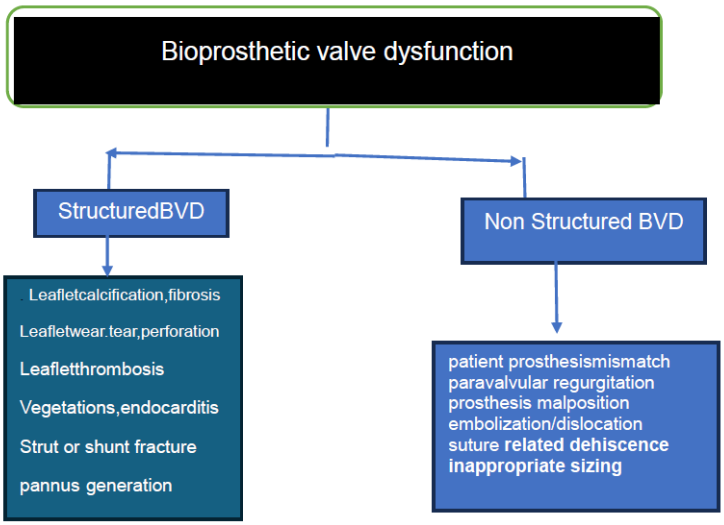
Surgical as well as transcatheter bioprosthetic heart valves (BHVs) have,over the past 2 decades, propagatively replaced mechanicalprostheses to assume the substitute of choice for maximum number of the subjects undertaking valve replacement.[1,2] The fundamental guides of such switching are the i) promising haemodynamic profile ofbiological valves, ii) the prevention of lifelong oral anticoagulation,in addition to the iii) rapid extension of transcatheter aortic valve

replacement(TAVR) into intermediate- along with low-risk surgical populations.[3,4]

Refinements in a) tissue engineering, b) anti-calcification therapies as well as c) stentless or d) sutureless fashions have further widened thepatient cohort believed to be appropriate for biological valves.[5] Even with such advancements, the time period course of BHVs continues to be **restricted**. The plausibility of structural inimicality escalates steeply further than ten years, as well as rearbitration rates amongst 10 in addition to 20 years vary broadly based on i) valve model, ii) position,along with iii) patient age.[3,6] Of greater botherations, yet, is the**surfacing** of a unique subsetof cases who faced bioprosthetic valve failure amongst months to a few years of implantation, an phenomenon referred to asearly bioprosthetic valve failure (EBVF). Earlier ignored in the form of narrative,EBVF is now escalatingly acknowledged in the era of younger, lowerrisk recipients as well as complicated valve-in-valve (ViV) methodologies.[7,8] The ten-year results of the NOTION trial have corroborated corresponding clinical results amongst TAVR as well as surgical aortic valve replacement in lesser -risk patients however with lesser rates of robust structural valve inimicality subsequent to TAVR[9], whereas the PARTNER 3 five-year outcomes have illustrated the expansionof TAVR into populations whose life anticipation considerably surpasses the anticipated time period course of a single bioprosthesis.[4]

Recent outcomes point that hemodynamic valve inimicality might be estimable in greater than 6 %of TAVR recipients amongst the first year, with miniscules valve size a meaningful anticipator.[10] Best appreciation of the **modern** epidemiology of EBVF is against the context of such panorama trials. In the PARTNER 3cardiac CT substudy, subclinical leaflet thrombosis was determined in13 % of TAVR recipients as well as 5 % of surgical recipients at 30 days, with continuation or recurrent disease at one year.[11]

Prosthetic valve endocarditis influence around 0.5 to 1% of bioprosthetic valves per year, with the maximum hinderance in the first six to twelve months.[12,13] Documented rates of moderate or robust patient–prosthesis mismatch vary from 20 to 70 % in surgical case groups, based on annular size in addition to implantation modality.[14,15] Agglomerating such mechanistic modes, present-day registries point that amongst 5, along with 12% of bioprostheticvalves form certain kinds of clinically germane impairment amongst the first five years, with the percentage propagating to absolute failure ranging from 1 to 4 %.[6,16,17] EBVF delineate's not a single pathology however an ultimatecommon pathwayfor plethora of unique events (Figure 1).[16]



Legend for Figure 1.

Courtesy ref no-16 - Notional classification of bioprosthetic valve dysfunction (BVD) as well as bioprosthetic valve failure (BVF). BVD is dividedinto i) structural (a) leaflet wear, b) calcification, c) thrombosis, d) endocarditis) along with ii) non-structural (a) patient–prosthesis mismatch, b) paravalvular regurgitation, c) malposition) categories. BV F delineates propagation to clinical sequelae consequence, inclusive of symptoms, robust haemodynamic inimicality, mediation or death. Adapted from VARC-3 and EAPCI/EACTS consensus.[19,20]

Exacerbated structural degeneration manipulated by i) foreign-body immune reactions, ii) dystrophic calcification, iii) valve thrombosis (both clinical as well as subclinical), iv) prosthetic valve endocarditis (PVE), v) patient–prosthesismismatch (PPM), in addition to methodological complications all add to the same. The germane significance of each varies according to i) valve kind, ii) anatomical position, along with iii) recipient properties.[17,18]

Discriminating among such causative factors has immediate clinical germaneness, in view of the suitable arbitration—i) anticoagulation forthrombus, ii) antibiotics as well as iii) plausible resurgery for endocarditis,iv) redo operation or v) transcatheter ViV for degeneration—dependent completely on exactitude dependent on diagnosis as per mechanistic modes.

This review incorporates the temporal phase of failure, the underlying mechanistic modes, as well as the treatment pathway into a single practical framework. It yield a current surgical viewpoint on the causative factor of EBVF,summarises the definitions in addition to terminology hypothesized by recent documents in agreement, explores the foundational mechanistic modes of early failure, discusses the diagnostic as well as management repercussions., along withhighlight all through the practical query clinician is confronted at the bedside: when a recently implanted bioprosthesis fails, i) what has gone wrong, and ii) what needs to be done?

2. Definitions along with Classification

2.1 Bioprosthetic valve impairment versus failure

A clear differentiation needs to be drawn amongst bioprosthetic valveimpairment (BVI) along with bioprosthetic valve failure (BVF) (Figure1). The 2017 European Association of Percutaneous Cardiovascular Arbitrations agreement in addition to the following 2021 Valve Academic Research Consortium-3 (VARC-3) guidelines define BVI in the form of anyaberrations of valve structure or working estimated on imaging, irrespective of clinical sequelae.[19,20] BVF, by contrast, details BVI which has propagated to a clinically meaningful endpoint: i) robust haemodynamic inimicality, ii) valve- associated symptoms, iii) rearbitration, or iv) demise.[17,20]

BVI is further subcategorized into i) structural as well as ii) non-structural divisions. Structural BVI incorporates i) leaflet wear, ii) tear, iii) prolapse, iv) fibrosis, v) calcification, vi) strut fracture, or vii) deformation, inclusive of alterations secondary to thrombosis or endocarditis.

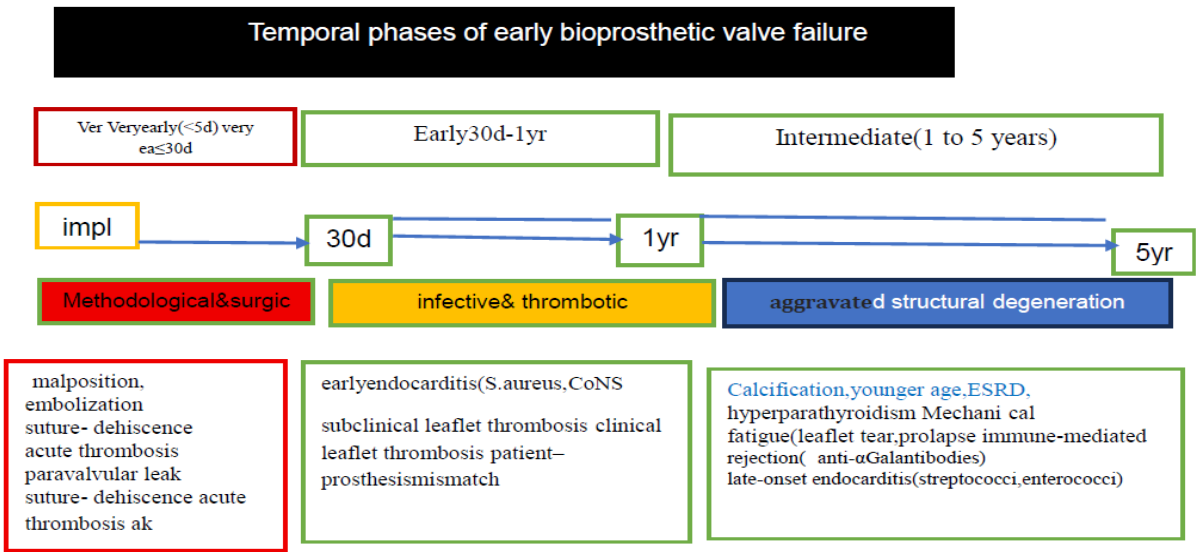
Non-structural BVI are inclusive of i) patient–prosthesis mismatch, ii) paravalvular regurgitation in the lack of leaflet pathology, iii) prosthesis malposition in addition to iv) embolization.[17]

2.2Definitions of “early” failure

There is no ubiquitously agreed upon temporal threshold for early BVF. Historical surgical case groups applied an arbitrary 30-day cut-off corresponding to operative mortality, whereas while more recent statementson agreement have posited wider windows delineating the natural history of variable failure modes.[20,21] Definition in the context of this review, of EBVF is in the form of bioprosthetic valve failure which takes place amongst five years of installation. This threshold is realistic instead of ubiquitous, chosen to catch the bulk of thrombotic as well as infective processes in addition to the occasional however unique occurrence of exacerbated structural inimicality in younger recipients along with the ones with metabolic comorbidities.[21,22]

Within this five-year window, three temporal phases can be acknowledged (Figure 2).

Figure 2: Temporal phases of early bioprosthetic valve failure within five years of implantation. Very early failure (≤30 days) is dominated by Methodological as well as surgical complications. Early failure (30 days to 1 year) possesses the properties of infective endocarditis, leaflet thrombosis along with and patient–prosthesis mismatch. Intermediate failure (1–5 years) delineates the onset of aggravated structural valve degeneration. Noticeably these phases are dominant but overlapping; greater than one mechanistic modes might be active at any acknowledged time point.



Legend for Figure 2.

Courtesy ref no-16: Temporal phases of early bioprosthetic valve failure within five years of implantation. Very early failure (≤30 days) is dominated by Methodological procedural as well as surgical complications. Early failure (30 days to 1 year) possesses the properties of infective endocarditis, leaflet thrombosis in addition to patient–prosthesis mismatch. Intermediate failure (1–5 years) delineates the onset of aggravated structural valve degeneration. Noticeably these phases are dominant but overlapping; greater than one mechanistic modes might be active at any acknowledged time point.

a)Very early failure (amongst 30 days) takes place predominately by methodological as well as surgical complications: i) malposition,ii) paravalvular leak, iii) suture- associated dehiscence in addition to iv) acute thrombosis.

b) Early failure (30 days to 1 year) escalatingly possesses the properties of i) infective endocarditis, ii) subclinical along with and iii) clinical leaflet thrombosis,as well as the haemodynamic sequelae of patient–prosthesis mismatch. c) Intermediate failure (1 to 5 years) portray the onset of aggravated structural degeneration in susceptible recipients, late-onset endocarditis in addition to continuous thrombus- modulated leaflet injury.[22,23] Such phases are dominant however, but overlapping; greater than one mechanistic modes might be active at any acknowledged time point.

2.3 Stages of structural valve degeneration

The **structured** three-stage classification of structural valve degeneration yields a parameter implementable to both early along with late failure.[20,24] Stage 1 SVD delineates morphological leaflet alterations (thickening, calcification or curtailed motion) without haemodynamic sequelae. Stage 2 portrays morphological aberrations associated with moderate stenosis or regurgitation. Stage 3, the threshold for symptomatic rearbitration, is by definition robust stenosis (mean gradient greater than 40 mmHg or efficacious orifice area lesser than 1cm² for the aortic position) or robust regurgitation.[24] When any of such stages takes place amongst five years of implantation, the patient might be believed tobe possessing early SVD, which itself comprises one of mechanistic modes of EBVF(see Table1).

Stages	Aortic bioprosthesis	Mitral bioprosthesis
Stage1 morphological without haemodynamic impact	Vmax<3m/s; mean gradient <20mmHg; DVI >0.35; EOA >1.2 cm² (BSA <1.6 m²); morphological leaflet abnormality without significant gradient rise.	Mean gradient <5 mmHg; MVA >1.5 cm²; morphological abnormality only.
Stage2 moderate haemodynamic impairment	Vmax 3–4 m/s; mean gradient 20–40 mmHg; DVI 0.25–0.35; ΔMG ≥10 mmHg vs baseline; or new moderate regurgitation.	Mean gradient >5 mmHg; ΔDVI ≥0.4 or ≥20%; ΔMVA ≥0.5 cm² or ≥25%; or new moderate regurgitation.
Stage3 robust haemodynamic impairment	Vmax >4 m/s; mean gradient >40 mmHg; ΔMG >20 mmHg vs baseline; EOA <1 cm² (BSA <1.6 m²); or new severe regurgitation.	Mean gradient >10 mmHg; ΔDVI ≥0.8 or ≥40%; ΔMVA ≥1.0 cm² or ≥50%; MVA <1.0 cm²; or new severe regurgitation.

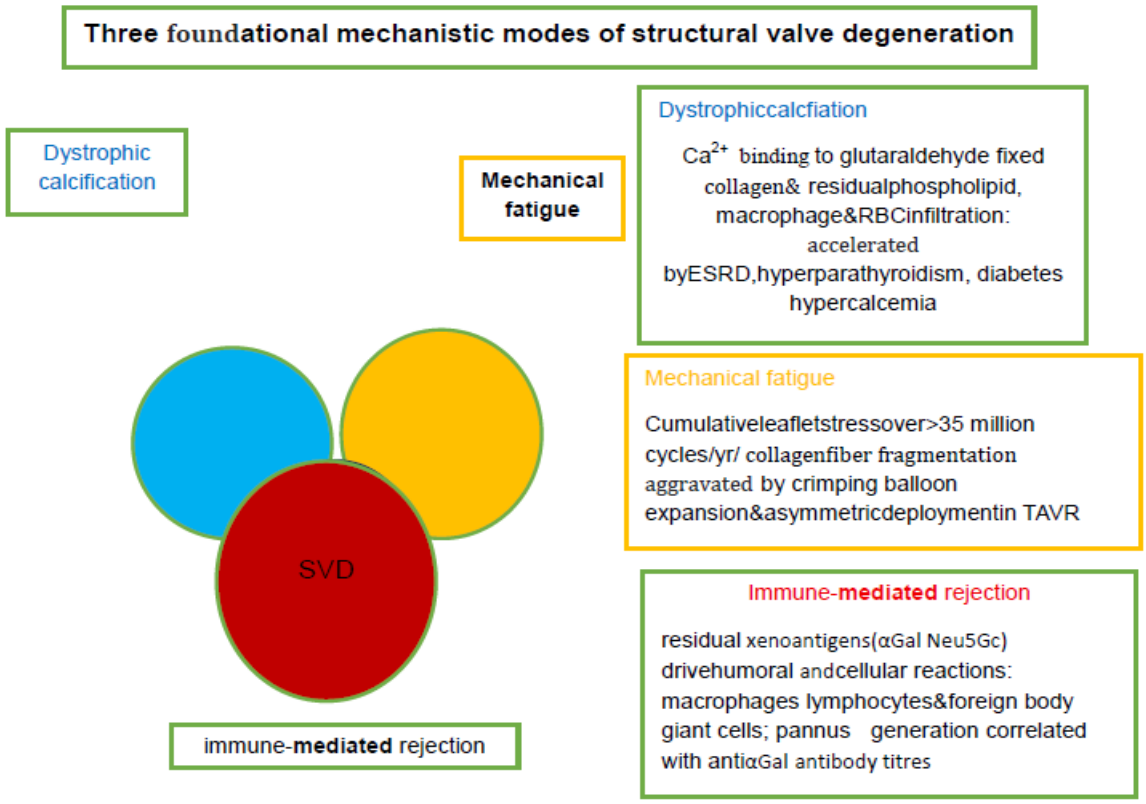
BSA, body surface area; DVI, Doppler velocity index; EOA, effective orifice area; MG, mean

Table1).

2.4 Exacerbated Structural Valve Degeneration

2.4a) Pathophysiology of early structural failure

Native valves are dynamic, self-renewing structures, whereas bioprosthetic leaflets are biologically inert in addition to do not possess the capability of healing, leaving them to bear accumulated mechanical, haemodynamic as well as immunological damages passively.[5,24] Such inter associated mechanistic modes buttress SVD (Figure 3).



Legend for Figure 3.

Courtesy ref no-16 The three principal pathological mechanisms of structural valve degeneration: dystrophic calcification, mechanical fatigue, in addition to immune-mediated rejection. Such events crosstalk along with augment one another, particularly in younger recipients along with patients withmetabolic susceptibility. crosstalk arrows amongst the three pathways illustrate that calcification, fatigue as well as immune activation are not autonomous however synergistic.

: i) dystrophic calcification, ii) mechanical fatigue, in addition to, iii) immune-mediated rejection. Such events crosstalk along with augment one another; early failure is canonically found when more than one event is active concomitantly, especially in younger recipients or the ones with metabolic susceptibility.

Calcification is started by the binding of calcium to remaining phospholipid cell membranes as well as to glutaraldehyde-treated collagen amongst the leaflet.[5,25,26] Glutaraldehyde fixation, whereas diminishing immunogenicity in addition to yielding tensile strength,further produces aldehyde groups which bind calcium ions as well as facilitate nucleation of hydroxyapatite. Macrophage in addition to red blood cell infiltration exacerbates such event by releasing intracellular calcium, along with aiding in iron-modulated oxidativedamage.[25] In recipients which possess end-stage renal disease(ESRD), hyperparathyroidism or considerably escalated calcium–phosphate products, calcification possesses the capability of propagating at a sharply exacerbated rate.[21,26]

Plethora of anti-calcification approaches have been integrated into modern bioprostheses. Such are inclusive of i) alpha-amino oleic acid treatment (Mosaic, Medtronic), ii) ethanol pretherapy (HancockII, Medtronic), iii) surfactant therapies (Trifecta, Abbott), as well as the greater recent iv) RESILIA tissue podium (Edwards Life sciences), that utilizes a glycerolisation step to cap remaining aldehyde groups in addition to aid in dry storage. The COMMENCE trial, along with its expansion cohorts have illustrated favourable mid-term time period course duration, with freedom from structural valve inimicality surpassing 99 percent at five years in addition to enthusiastic seven-year outcomes from the aorticcohort, despite direct comparable long-term corroboration withcanonical pericardium in randomised trials continues to be curtailed, as well as the time period course duration advantages in younger recipients needs greater follow-up.[27,28] If such therapies foundationally change the direction of EBVF in the youngest recipients, where calcification is maximum h)ostile, continues to be to be generated.

2Mechanical fatigue occur secondary to the repeated flexion of leaflets at the time of greater than 35 million cardiac cycles per year. Fibresof collagen propagatively fraction as well as elastic constituents disorganise, escalating susceptibility to i) leaflet tear, perforation, in addition to prolapse. In transcatheter heart valves, extra

stresses are added by i) crimping, ii) balloon expansion, as well as iii) post implementation leaflet asymmetry, total of that iii) iv) might exacerbate mechanical inimicality.[18,29]

3)Immune- modulated rejection has surfaced in the form of a third, escalatingly acknowledged, mechanistic mode. Although glutaraldehyde fixation,remaining xenoantigens (noticeably galactose-α-1,3-galactose in addition toN-glycolylneuraminic acid) evoke a sustenance adaptive immunereactions in human recipients.[30,31]

The resulting infiltration by lymphocytes, macrophages,along with foreign-body giant cells forms pannus, an inflammatory tissue overgrowth constituted of i) immune cells, ii) endothelial cells as well as iii) myofibroblasts that propagatively infringes on the leaflet base in addition to commissures.[31,32]

The original work of Senage et al[30], a recent publication in 2022 in Nature Medicine, isolated circulating IgG antibodies againstα-gal along with Neu5Gc in the maximum proportion of patients undergoing bioprosthetic valve replacement, with antibody titres escalating strikingly in the months subsequent to implantation [30]. In their cohort, the magnitude of the antibody reactions to α-gal at three monthspost-implantation was an autonomous anticipator following SVD across follow-up. Such observations has reframed SVD from a basically degenerative occurrence into one with an extensive immunological dimension, as well as has motivated endeavours to generate α-gal-insufficiency in porcine donors in addition to decellularised backbones with diminished antigenicity.[31]

Risk factors for accelerated structural valve degeneration.

recipient **factors** recipient **factors**	**Valve& position factors** **Valve& position factors**	**methodological factors** (TAVR)
Younger age at implantation	**Mitral position vs aortic**	**Valve in Valve procedure**
hyperparathyroidism	Bovinepericardium→.stenosis	residual paravalvular regurgitation,
Diabetesmellitus	porcine xenografts→regurgitation	underexpansion and asymmetric deployment
Hypertension& **Metabolic Syndrome**	Smaller valvular size/annulus	crimping **associated** leaflet**damage**
chronic inflammatory states	older generation glutaraldehyde fixation	post-deployment leaflet asymmetry
escalatedcalcium–phosphate **products**	Stented vsstentless	suboptimal anticoagulation

Legend for Figure 4
Courtesy ref no-16 Risk factors for accelerated structural valve degeneration. Recipient factors (younger age, end-stage renal disease,hyperparathyroidism, diabetes), valve factors (mitral position, bovine pericardium for stenosis, porcine for regurgitation), and proceduralfactors (valve-in-valve, paravalvular leak, underexpansion) all contribute. Surgical and TAVR-specific risk factors are presentedseparately for clarity.

2.4. Risk factors for accelerated SVD

Younger age at implantation is the one of maximum robust demographic risk factor (Figure 4). Patients below age 60 years' underwent SVD at considerably higher rates in contrast to older recipients, anoccurrence attributed to greater cardiac output, more leaflet stress, greater rigorous immune reactions, in addition to anticipated exposure for a greater time period course.[3,21] i) End-stage renal disease, ii) hyperparathyroidism, iii) diabetes mellitus as well as iv) chronic inflammatory states all escalate susceptibility to premature calcification.[20,25] Bovine pericardial valves possess a tendency to fail via stenosis guided by leaflet calcification, whereas porcine valves greater usually manifest with regurgitation from leaflet tear.[5]

Mitral position bioprostheses degenerate greater swiftly in contrast to aortic, delineating higher mechanical loading along with greater prevalence of atrial fibrillation with correlated stasis.[17,19]

In the transcatheter scenario, i) valve-in-valve implantation, ii) residualparavalvular regurgitation, iii) underexpansion and iv) asymmetric implementation have all been correlated with aggravated leaflet degeneration.[18,29,33] Prospective imaging studies utilizing $^{[18]}$F-sodium fluoride positron emission tomography $^{[18]}$F-NaF PET) have illustrated active microcalcification at the leaflet level amongst months of TAVR, with baseline tracer uptake anticipating following haemodynamic inimicality.[34,35]

3.1 Tissue Preservation Technologies along with Bioprosthetic Valve Fashion

The etiological factor of EBVF does not possess the capacity of being taken into account in identification from the engineering of the prosthesis itself. The i) biological substrate, ii) the fixation chemistry, iii) the stent or frame fashion, as well as the fashion manner iv) in which leaflets are configured allimpact the direction towardearly failure. Getting insight of such fashion deliberations is imperative for the operating dr in

reference to counselling patients regardingprosthesis selection.

3.2 Biological substrate along with fixation

Three fundamental xenograft tissues have been utilized clinically: i) porcineaortic valve leaflets, ii) bovine pericardium, in addition to iii) equine pericardium.a) Porcine valves perpetuate native valvular architecture however possess the tendency to fail via leaflet tear along with regurgitation. b) Bovine pericardium yields substantial tensile strength however possess the tendency to fail via i) diffuse calcification as well as ii) stenosis.[5,25] The inherent immunogenicity of such tissues is dominated by xenoantigens which i) survive fixation, noticeably ii) α-gal in addition to Neu5Gc.[30,31]

Glutaraldehyde has been the canonical fixative from its installationby Carpentier in the late 1960s. The occurrence labelled as the "Carpentier paradox"—that the same fixation was implicated regarding tissue time period course is further involved regarding its ultimatecalcification failure—has guided years of work into manipulations as well as alternatives.[24] Successive anti-calcification therapies have targeted particular facets of the calcification stepwise patterns, along with the maximum considerable advancement across the last 10 years is the RESILIA podium, that has illustrated attractive mid-term time period course in the COMMENCE trial.[27,28] Meaningfully RESILIA harnesses calcification however, does not directly result in modifications of xenoantigenicity, as well as therefore the assistance in immune-mediated rejection to failure is not clearly mitigated.

3.3 Stent Fashion along with the Trifecta background

Among stented surgical valves, the geometric association amongst leaflets and the stent frame is a pivotal influencer of time period course duration. for i) In internally mounted fashions (for instance. Carpentier-Edwards Perimount), the leaflets open amongst the lumen of the frame. ii) In externally mounted fashions (for instance the seminal Trifecta, Abbott fashions), the leaflet tissue is encompassed round the outside of the stent, yielding a greater efficacious orifice area however, exposing leaflets to direct touch in addition to frictional erosion against the stent posts. Such characteristics have been held responsible in the exacerbated structural inimicality found with the seminal Trifecta valve, where post-market surveillance isolated an unanticipately greater high rate of early failure amongst five to seven years of implantation, specifically in smallersizes.[32,36,37]

In February 2023, the United States Food and Drug Administration issued a safety communication to healthcare providers citing publications thatpointed a greater cumulative incidence of early SVD for the Trifecta valve in contrast to other commercially accessible surgical bioprostheses.[38] Following that, in July 2023, Abbott disclosed the omission along with removal from market of the Trifecta as well as Trifecta GT valves in the United States.[38] Such actions works in the form of a case study of fashion associated EBVF in addition to buttresses the fundamental that haemodynamic idealization along withtime period course duration are not autonomous aims. Surveillance of new valve fashions via the initial five to seven years of clinical use is hence imperative, owing to the failure modes of any innovative mounting geometry might not be obvious in the early post-implantationperiod.

3.4 Transcatheter valve fashion along with surfacing methodologies

Transcatheter heart valves face engineering hindrances which are not encountered with use of surgical valves. Crimping stimulates irreversible microdamageto leaflet collagen, with probability of escalating susceptibility to mechanical fatigue as well as aggravated calcification.[18,29,39] Asymmetric implementation organizes leaflet stress in a noneven manner as well as generates areas of stagnation which escalates susceptibility to leaflet thrombosis.[40] Current generation fashions inclusive of the SAPIEN 3 Ultra in addition to Evolut FX/PRO+ have considerably refined sealing in addition todiminished paravalvular regurgitation.[18,41] Polymer leaflet transcatheter valves delineate a materializing trajectory which might counter the immunogenicity along with calcification drawbacks of biological tissue,despite long-term human outcomes are still anticipated.[4]

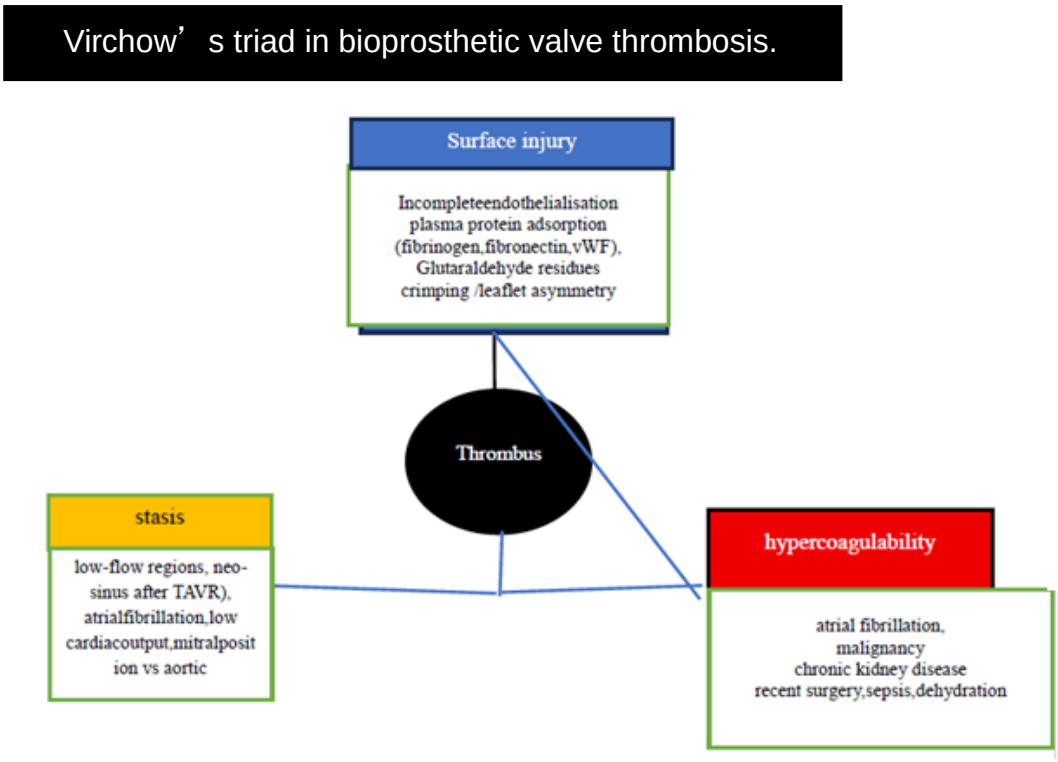
4.Bioprosthetic Valve Thrombosis

4.1Incidence along with clinical gamut

Valve thrombosis mirrors one of the maximum meaningful as well as plausiblyreversible aetiologies of EBVF. Symptomatic bioprosthetic valve thrombosis was historically believed tobe occasional, with adetermined incidence of roughly 0.03 %/ year.[42] Subclinical leaflet thrombosis, however, isolated by hypoattenuated leaflet thickening (HALT) on cardiac computed tomography(CT), is substantially greater prevalent, that takes place in 10 to 15% of patients subsequent to TAVR in addition to in as high as 7% subsequent to surgical aortic valve replacement.[11,43] It issignificant to emphasise that HALT resolution might take place spontaneously along with does not automatically warrant anticoagulation; the clinical germaneness of subclinical thrombosis continues to be controversial, however mounting corroboration points a correlation with later structural inimicality as well as a miniscule however estimable escalation in cerebrovascular processes.[11,44]

4.2 Mechanistic modes

Full three **constituents** of Virchow's triad accounts for generation of bioprosthetic thrombosis (Figure 5).



Legend for Figure 5.

Courtesy ref no-16 Schematic representation of Virchow’s triad in bioprosthetic valve thrombosis. Surface damage (incomplete endothelialisation,plasma protein adsorption), stasis (low-flow regions, neo-sinus), in addition to a hypercoagulable state (atrial fibrillation, malignancy, recentsurgery) interact to generate thrombus generation. Concomitant activity of all three components generates clinically significant thrombosis; partial activation underlies subclinical leaflet thrombosis (HALT).

Surface damage takes place via i) incomplete endothelialisation of the prosthesis, ii) remaining glutaraldehyde, iii) leaflet asymmetry subsequent to iv) crimping, as well as v) adsorption of plasma proteins.[39,45] Stasis is inherent to areas of low or recirculating flow, embodied by the neo-sinus generated amongst the transcatheter valve in addition to the native aortic root.[40] A hypercoagulable state,If primary or ii) associated with a) malignancy, b) chronic kidney disease,c) atrial fibrillation, or d) recent surgery, finishes the triad.[42,45]

4.2 Hypoattenuated leaflet thickening along with diminished leaflet motion

In case of contrast-enhanced cardiac CT, leaflet thrombus is seen in the form of a meniscus-shaped area of low attenuation beside the aortic surface of the leaflet, termed HALT. When curtailed motion (RELM, or hypoattenuation influencing motion, HAM), haemodynamic sequelae possesses greater probability.[11,46] Discriminating thrombus from chronic pannus is pivotal, owing to pannus does not react to anticoagulation along with canonically needs surgical revision; a Hounsfield unit threshold of 145 has been posited, with masses under such level enables thrombus generation attractive as well as the ones above pannus, despite such threshold is a useful driver instead of an unconditional distinguisher (Figure 6).[47]

Discriminating thrombus from pannus& vegetation			
characteristicc	thrombus	pannus	vegetation
Time course	Days-mths	Mths-years	Days-weeks
Echo appearance	Iso/hypoechogenicmass on Leaflet Surface	Hyperechoic,fixed,near ring/cusp base	Mobile mass on autonomous Leaflet motion
Leaflet motion	Diminished(HAM)	Diminished or normal	Normal or curtailed bymass
CT attenuation	<145(usually<90)	≥145	variable usually low
calcification	absent	might bepresent	absent
Clinical context	AF, low-flow,subideal anticoagulation	late manifestation,slow gradient rise	Fever,positive blood culture,embolism
initial treatments	Vitamin Kantagonist	Surgical revision	Targeted antibiotic± Surgical

Legend for Figure 6.

Courtesy ref no-16 Distinguishing characteristics of thrombus, pannus, as well vegetation on cardiac computed tomography as in addition to echocardiography.Hounsfield unit measurement on CT (threshold of 145) separates thrombus (lower attenuation) from pannus (higher attenuation), while echocardiographic characteristics, along with clinical circumstance drive the differentiation from infective vegetation. The HU threshold is a useful driver instead of an absolute distinguisher; clinical association is imperative.

4.3 Clinical course and management

Resolution of virtually 50%of subclinical thrombus episodes takes place spontaneously over weeks to months without particular mediation.[44] Beginning of vitamin K antagonist treatment usually reverses haemodynamicabnormalities in clinically significant cases, although recurrencesubsequent to withdrawal is well described.[11] Evoluation of chronic, organised thrombus might usually occur into fibrosis along with calcification, creating irreversible structural valve injury as well as transforming what started in the form of a thrombotic event into generated SVD.[19,44] The GALILEO in addition to ATLANTIS trials illustrated that routine direct oral anticoagulation subsequent to TAVR does not improve clinical results in addition to might escalate bleeding, embracing a targeted rather than ubiquitous strategy to anticoagulation.[48,49]

5. Prosthetic Valve Endocarditis

5.1 Epidemiology of early PVE

Prosthetic valve endocarditis (PVE) is a major aetiology of EBVF, contributing to as high as one-third of early rearbitrations in certain case groups.[12,13]

The cumulative incidence at one year is around 1 to 3%for both surgical as well as transcatheter aortic prostheses,in addition to apparently corresponding amongst mechanical along with biological valves.[12,13] Early PVE (amongst 12 months) is maximum frequently assignable to perioperative contamination, with dominant i) *Staphylococcus aureus*, ii) coagulase-negative staphylococci, as well as iii) Enterococcus species in the form of etiological factor.[12,50] Late PVE is maximum frequently community acquired along with possess causative factor like oral streptococci or enterococci. Subsequent TAVR, an extra risk gets obtained from the utilization of non-sterile milieus for instance catheterisation laboratories.[13,51]

5.2 Pathological patterns

In early PVE, the infective events canonically implicate the suture line as well as sewing ring, generating i) perivalvular abscess, ii) pseudoaneurysm,iii) fistula in addition to iv) dehiscence.[12] Late PVE maximum commonly influencesthe leaflets themselves. Subsequent TAVR, vegetations might generateon i) prosthetic leaflets, ii) the metallic stent frame, or iii) by extension to the anterior mitral leaflet; perivalvular complications takes place inabout 20% of TAVR-PVE subjects.[13,51]

5.3 Diagnostic challenges

The performance of modified Duke criteria is less proper in the prosthetic valve scenario, with sensitivity in early PVE diminished by acousticshadowing, small vegetations, along with negative blood cultures in patients getting verifiable antibiotics.[52,53] Transthoracic echocardiography possesses a sensitivity of roughly i) 70% per cent for vegetations as well as just ii) 50 per cent for abscesses; iii) transoesophageal echocardiography refines sensitivity to practically 90 per cent.[54]

Cardiac computed tomography offers excellent evaluationof characteristics ofperivalvular complications.[55] ^{18}F-fluorodeoxyglucose positron emission tomography (PET) combined with CT has considerably escalated diagnostic exactitude in PVE. The 2023 European Society of Cardiology criterion guidelines haveexpressly integrated ^{18}F -FDG PET/CT in the form of a major Duke guidelines for prosthetic valve endocarditis which takes place greater than three months subsequent to implantation, recognising that aberrant prosthetic or periprosthetic uptake possesses the capability of embracing the diagnosis of PVE.[53,56] Nonetheless, inferring precaution is needed in the early postoperative period, when sterile inflammation might generate false-positive uptake. White-cell labelled scintigraphy (WBC SPECT/CT) yields a complementary methodology with greater specificity, in addition to is specifically conducive when no conclusions can be drawn from FDG-PET or in the earlypost-operative window.[56,57]

5.4 RESULTS

Although, advancements made in diagnosis as well as management, PVE continues to be correlated with greater mortality. In-hospital mortality varies amongst 15 in addition to 25 %, along with one-year mortality reaches 40 % in certain series.[12,58] Surgery, when indicated by the existence of i) robust regurgitation, ii) perivalvular complications, iii) large vegetations, or iv) continuous infection, needs no postponement in suitable candidates.[53,58]

6. Non-structural Causes of Early Failure

6.1Patient–prosthesis mismatch

Patient–prosthesis mismatch (PPM) takes place when the efficacious orifice area of the implanted prosthesis is substantially miniscule germane to body surface area, generating remaining high transvalvular gradients although with normal valve working.[14] Robust PPM (indexed efficacious orificearea lesser than 0.65 cm^2/m^2 in the aortic position) is correlated with continuous i) left ventricular hypertrophy, ii) dysfunctional regression of

pulmonary hypertension, as well as iii) escalated early in addition to late mortality.[14,15] Approaches to ameliorate PPM are inclusive of i) preoperative computed tomography sizing, ii) root enlargement methodologies, in addition to iii) selection of supra-annular or iv) stentless prostheses in patients with miniscule annuli.[14,59]

6.2Paravalvular regurgitation

Paravalvular leak subsequent to surgical valve replacement maximum frequently delineates suture dehiscence in the circumstance of friable annular tissue. Subsequent TAVR, paravalvular regurgitation is usually a sequel of i) valve undersizing or ii) calcium- stimulated incomplete sealing, despite its incidence has considerably dropped with newer generation devices.[18,41] Even mild to moderate paravalvular regurgitation has been associated with diminishedsurvival as well as exacerbated structural leaflet degeneration.[18,41]

6.3 Methodological along with surgical factors

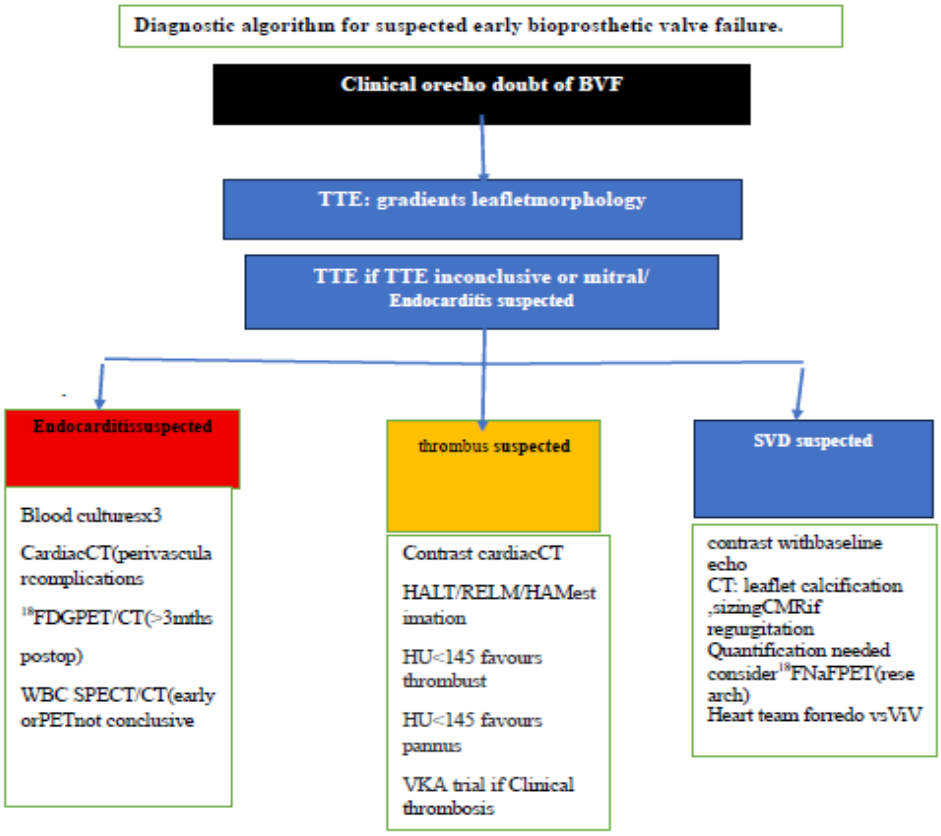
Technological factors operative amongst the perioperative periodare inclusive of i) valve malposition, ii)) embolisation, iii) inappropriate sizing, along with iv) surgical damage to neighbouring structures. Cardiac CT prior to redo or transcatheter arbitration is imperative to examine i) sternal proximity, ii) vascular access, as well as the iii) risk of coronary obstruction during valve in-valve methodologies, that is determined at 2.3 % in contrast to 0.7 % for de novo TAVR.[60,61] A virtual transcatheter heart valve to coronary ostium span of less than 4 mm isolates greater -risk anatomy.[60]

6.3a.Very early failure amongst 30 days

A subset of EBVF manifests amongst the first thirty postoperative days along with is virtually cent% assignable to identifiable technological or methodological factors instead of to disease events inherent to the prosthesis. Suture- associated complications are predominant in this particular early window in surgical setting practice. Prosthesis malposition incorporates both gross misalignment of a surgical valve as well as subideal implementation of a transcatheter device.[41] Acute valve thrombosis manifesting amongst days of implantation is infrequent however plausibly cataclysmic.[42,44] Iatrogenic damage that encompasses structures might not be acknowledged until the patient fails to get tapered of from cardiopulmonarybypass.[60]

6.4Diagnostic Approach to Suspected Early Failure

The asssessment of suspected EBVF begins with transthoracic echocardiography, which need to be contrasted to with a baseline study conducted before discharge or at six weeks (Figure 7).[62]



Legend for Figure 7.

Courtesy ref no-16 Suggested diagnostic algorithm for suspected early bioprosthetic valve failure. Transthoracic echocardiography is the firstline investigation, with escalation to transoesophageal echocardiography, cardiac CT, as well as nuclear imaging (^{18}F-FDG PET/CT, WBCSPECT/CT) based on the clinical question in addition to initial findings. This figure need to be be taken into account the central parameter of the manuscript,integrating the temporal-mechanistic approach with the multimodality imaging algorithm.

New or propagative escalation of i) transvalvular gradients,ii) new regurgitation, iii) leaflet thickening, iv) curtailed leaflet motion,v) paravalvular jets, vi) vegetation-like masses, as well as corroboration of vii) valve rocking need immediate further asssessment. Transoesophageal echocardiography is imperative whenever transthoracic imaging is suggestive however not conclusive, specifically in suspected endocarditis or mitral prosthesis impairment.[54,62]

Multimodality imaging extends the diagnostic reach. Cardiac computed tomography is specifically valuable for discriminating thrombus from pannus (Figure 6), isolating HALT, in addition to characterising perivalvular complications, along with planning remediation.[11,46,47,55] Cardiac magnetic resonance, whereas curtailed by metallic artefact, yields exactitude quantification of regurgitation robustness as well as ventricular remodelling.[63] Nuclear imaging, specifically ^{18}F-FDG PET/CT in addition to WBC SPECT/CT, has assumed irreplaceable place in the diagnostic algorithm for prosthetic endocarditis.[53,56,57] The 2023 ESC guidelines have expressly integrated FDG-PET/CT into the major Duke criteria for late prosthetic valve endocarditis, acknowledging that aberrant prosthetic or periprosthetic uptake possesses the capability of embracing the diagnosis, whereas taking precaution that postoperative inflammation in the early weeks subsequent to surgery need precaution in reference to inference.[53]

6.5 Suggestions to be taken into account for Management

Management of EBVF is decided by the mechanistic modes that lie beneath. Subclinical thrombus without haemodynamic sequelae might be found, whereas clinically meaningful thrombosis mandates vitamin K antagonist treatment with serial imaging.[11,44] Endocarditis needs continuous targeted antibiotic treatment guided by blood cultures, with surgical arbitration indicated for robust i) regurgitation, ii) perivalvular extension, iii) large vegetations, iv) uncontrolled infection, or v) recurrent embolism.[53,58] Generated structural valve degeneration,when symptomatic in addition to robust, needs either redo surgery or transcatheter valve-in-valve replacement, with the choice affected by surgical risk, anatomy, along with the risk of coronary obstruction or left ventricular outflow tract obstruction.[59,60,61]

Redo surgical aortic valve replacement carries documented in-hospital mortality amongst 5 as well as 13 per cent, whereas transcatheter valve in-valve attains methodological procedural success in about 95% of selected high-risk patients with one-year mortality of15 to 20% for aortic in addition to, mitral methodologies respectively.[59,61,64] Recent registry outcomes have buttressed the idea that redo-SAVR as well as ViV-TAVR work complementary parts amongst a lifetime management parameter, with patient selection driven by risk profile along with anatomical idealness instead of a competing archetypal.[64]

6.6 Heart team decision framework

The choice amongst i) redo surgery, ii) transcatheter valve-in-valve,as well as iii) persistent medical treatment in EBVF is occasionaly simple,in addition to is advantageous considerably from structured heart team review. Six things to be taken into account predominate the discussion: i) mechanistic modes that lie beneath, ii) patient surgical risk, iii) anatomical idealness for ViV (validated by gated cardiac CT with attention to coronary ostial height along with sinus measurements)[60], iv) the prosthesis label size of the original valve, v) the patient's life anticipated contemplated against time period course duration of a second tier mediation, along with mitral-particular screening for left ventricularoutflow tract obstruction.[59]

7. Future Directions

Plethora of generations yields the chance of diminishing the incidenceof EBVF. Anti-calcification therapies for instance the RESILIA tissue podium have illustrated attractive mid-term time period course duration, with the Indure Durability Registry presently exploring results inyounger recipients (≤60 years).[27,28] Tissue engineering with the objective of i) decellularisation, ii) elimination of α-gal antigens utilizing GTKO porcine donors, along with iii) refined fixation chemistries might reduce the immune accounting for structural failure.[29,30] Surveillance approaches integrating ^{18}F-sodium fluoride PET (^{18}F-NaF PET)to estimate early microcalcification, as well as serial cardiac CT for HALT determination,might allow risk-stratified follow-up.[11,34,35] Improvements intranscatheter valve fashion, inclusive of i) diminished -profile administration systems, ii) refined sealing skirts, in addition to iii) longtime period course duration polymer leaflets, apparently ARE attractive for both primary along with valve-in-valve methodologies.[4,18,29]

8. CONCLUSION

Having reviewed the different significant etiopathogenesis and role of different antiobesity agents, comprehensively, role of adipocytokines in HFpEF as well as HFrEF, Role of SGLT2 Inhibitors Beyond Glycosuria in Controlling Obesity, NAFLD Treatment, Pancreatic β Cell Protection Besides Therapy for Diabetes Mellitus, CVOT and Renoprotection including MACE withSGLT2 Inhibitors Molecular Modes

Implicated in Diastolic Impairment in early HFpEF as well as HFrEF, and epigenetics modifications in diabetic cardiomyopathy(DbCM), with Role of SGLT2 Inhibitors and GLP-1RA in therapy of DbCM particularly with Rajyoga Meditation[65-87], here we have detailed EBVFin detail.

Early bioprosthetic valve failure is multifactorial, incorporating i) aggravated structural degeneration, ii) thrombosis, iii) endocarditis,as well as iv) non-structural mechanistic modes inclusive of a) patient–prosthesis mismatch in addition to b) methodological complications. The clinical phenotype is usually non-particular, along with the acknowledgement in time of the mechanistic modes is based on systematic multimodality imaging (Figure7) as well as a high index of suspicion. Owing to bioprosthetic valves areescalatingly implanted in younger in addition to lower-risk patients, a) the early isolation, b) performance of studies on characteristics, along with c) therapy of EBVF would possess escalating clinical significance.Three fundamentals need highlighting. i) First, the temporal phase of failure yields significant diagnostic guidance (Figure 2, Table3): very early failure amongst 30 days is virtually always i) methodological,ii) infective in addition to iii) thrombotic mechanistic modes predominate the first year, as well as aggravated structural degeneration assumes prominence subsequently.ii) Second, neither of single imaging methodology is adequate. i) Transthoracic,ii) transoesophageal echocardiography, iii) cardiac CT (Figure 6),iv) cardiac magnetic resonance, as well as v) nuclear imaging all aid in unique knowledge, in addition to the diagnostic algorithm need to continue to be adaptive to the clinical query. iii) Third, therapy decisions in EBVF are not straightforward methodological however earnestly strategic (Table 2),with repercussions extending further than the prompt arbitration to the patient's lifetime direction of valve replacement; such decisions are best made amongst a structured heart team framework which incorporates i) surgical, ii) arbitrational, iii) imaging, in addition to iv) experience with infectious disease.

Table 2: Temporal-mechanistic guide to investigation of suspected EBVF.

Time from implant	maximum plausible etiologicalfactors	First escalation test
≤30 days	Malposition, PVL, dehiscence, acute thrombosis	TEE ± CT
30 days–1 year	PVE, HALT/thrombosis, PPM	TEE, CT, blood cultures
1–5 years	Accelerated SVD, pannus, late PVE	CT ± PET/CT

CT, computed tomography; HALT, hypoattenuated leaflet thickening; PET, positron emission tomography; PPM, patient–prosthesis mismatch;
PVE, prosthetic valve endocarditis; PVL, paravalvular leak; SVD, structural valve degeneration; TEE, transoesophageal echocardiography.

Table 3: Heart team factors favouring redo surgery versus transcatheter valve-in-valve in early bioprosthetic valve failure.

Factor	Favours redo surgery	Favours valve-in-valve
Patient age and life expectancy	Younger (<65 years), good longevity expected	Older (>75 years), limited life expectancy
Surgical risk	Low to intermediate (STS <4%)	High or prohibitive (STS >8%)
Original valve size	Small (≤21 mm) with risk of severe ViV PPM	Adequate (≥23 mm aortic)
Coronary ostial height (CT)	Low (<10 mm) — high obstruction risk for ViV	Adequate (>10 mm)
Mechanism of failure	Endocarditis with paravalvular extension; pannus; severe PVL	Pure SVD with central regurgitation or stenosis
Concomitant cardiac disease	Multiple lesions requiring surgery (e.g. CABG, mitral)	Isolated valve dysfunction
Prior sternotomy	Acceptable surgical access; minimal patent grafts at risk	Hostile re-entry; patent grafts crossing midline
Mitral position	Adequate neo-LVOT predicted; small or hostile annulus	Adequate predicted neo-LVOT (≥1.7 cm^2)

CABG, coronary artery bypass grafting; CT, computed tomography; LVOT, left ventricular outflow tract; PPM, patient–prosthesis mismatch;
PVL, paravalvular leak; STS, Society of Thoracic Surgeons risk score; SVD, structural valve degeneration; ViV, valve-in-valve.

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