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Not all arrestins are created equal: Therapeutic implications of the functional diversity of the β -arrestins in the heart

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Abstract

The two ubiquitous, outside the retina, G protein-coupled receptor (GPCR) adapter proteins, β -arrestin-1 and -2 (also known as arrestin-2 and -3, respectively), have three major functions in cells: GPCR desensitization, *i.e.*, receptor decoupling from G-proteins; GPCR internalization *via* clathrin-coated pits; and signal transduction independently of or in parallel to G-proteins. Both β -arrestins are expressed in the heart and regulate a large number of cardiac GPCRs. The latter constitute the single most commonly targeted receptor class by Food and Drug Administration-approved cardiovascular drugs, with about one-third of all currently used in the clinic medications affecting GPCR function. Since β -arrestin-1 and -2 play important roles in signaling and function of several GPCRs, in particular of adrenergic receptors and angiotensin II type 1 receptors, in cardiac myocytes, they have been a major focus of cardiac biology research in recent years. Perhaps the most significant realization coming out of their studies is that these two GPCR adapter proteins, initially thought of as functionally interchangeable, actually exert diametrically opposite effects in the mammalian myocardium. Specifically, the most abundant of the two β -arrestin-1 exerts overall detrimental effects on the heart, such as negative inotropy and promotion of adverse remodeling post-myocardial infarction (MI). In contrast, β -arrestin-2 is overall beneficial for the myocardium, as it has anti-apoptotic and anti-inflammatory effects that result in attenuation of post-MI adverse remodeling, while promoting cardiac contractile function. Thus, design of novel cardiac GPCR

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ligands that preferentially activate β -arrestin-2 over β -arrestin-1 has the potential of generating novel cardiovascular therapeutics for heart failure and other heart diseases.

Key words: Adverse remodeling; β -arrestin; Biased signaling; Cardiac myocyte; Cardiac fibroblast; contractility; Functional divergence; G protein-coupled receptor; Heart failure; Hormone; Myocardial infarction; Signal transducer

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Core tip: Presumed functionally similar for a long time, we now know that the two β -arrestins display significant functional diversity in several organs and tissues, including in the cardiovascular system. Their functional distinction also in the mammalian heart has been clearly documented over the past few years. β -arrestin-1, which is far more abundant than β -arrestin-2 in almost every tissue including the myocardium, opposes the cyclic adenosine monophosphate (cAMP)-dependent pro-contractile signaling of the β_1 adrenergic receptor (β_1 AR), and promotes cardiac apoptosis, inflammation, and other adverse remodeling-associated processes post-myocardial infarction. Conversely, β -arrestin-2 promotes catecholamine-dependent cardiac contractility directly, via SERCA2a potentiation, and indirectly, by leaving β_1 AR's cAMP-dependent pro-contractile signaling unaffected.

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INTRODUCTION

Out of the four mammalian arrestins, only the two ubiquitous (outside the retina) arrestin-2 and -3, also known as β -arrestin-1 and -2 respectively, are expressed in the mammalian cardiovascular system. Like in almost every tissue, β -arrestin-1 protein is approximately 10-15-fold more abundant than β -arrestin-2 in the circulatory system, as well^[1]. Both β -arrestins regulate all non-opsin G protein-coupled receptors (GPCRs), also known as seven transmembrane-spanning receptors (7TMRs), including those responsible for neurohormonal regulation of cardiovascular physiology^[2,3]. For instance, cardiac function (contractility) is tightly controlled by the activity of β -adrenergic receptors (β ARs) located in the membranes of cardiac myocytes^[4-8]. Cardiac structure and morphology are regulated by angiotensin II (AngII) type 1 receptors (AT₁Rs) present (mainly) in cardiac fibroblast and endothelial cell membranes^[4,7]. Even the production and release of the regulatory hormones per se, whether it be catecholamine and corticosteroid release by the adrenal glands or activation of the renin-angiotensin-aldosterone system by the juxtaglomerular apparatus of the kidneys or release of neurotransmitters by central and peripheral neurons innervating cardiovascular organs, is under tight regulation by various GPCRs^[1,4,7].

Cardiovascular GPCRs can signal either through G-proteins or β -arrestins with the natural, endogenous agonist hormones activating both signal transducers at each receptor fully and equally^[1,9]. Several "biased" GPCR ligands have been discovered that (relatively) selectively activate either G proteins or β -arrestins^[1,9]. This "bias" in terms of the activated signal transducer is always relative but the concept of "biased" signaling and its attainability for therapeutic purposes has been challenged recently. Specifically, recent studies have shown that receptors can activate both G-proteins and β -arrestins at the same time^[10] or that β -arrestins do not even need to bind the agonist-activated receptor to get ("catalytically") activated^[11]. Additionally, it was very recently clearly demonstrated that G-protein activation is absolutely necessary, at least initially upon agonist activation, for β -arrestin activation and signaling to follow^[12,13]. This sequence of activation of the two signal transducers, *i.e.*, G-proteins being activated first followed by activation of β -arrestins, is also corroborated well by the majority of structural studies on mechanisms of GPCR activation done to date.

Specifically, the receptor seems to require the interaction with the heterotrimeric G-protein in order to become fully activated by the agonist. In other words, in the absence of a G-protein, agonist binding per se is simply insufficient for the receptor to break the huge energy barrier that prevents it from reaching the active state^[2,14]. Taken together, G-protein activation and signaling appears to be a prerequisite for β -arrestin signaling by GPCRs and thus, discrimination between these two families of signal transducers for any given GPCR ligand, which represents the foundation of the “biased signaling” concept for GPCRs, is essentially unfeasible. However, whereas the selective stimulation of G-protein vs. β -arrestin signaling for therapeutic purposes is most likely impossible, selective stimulation of β -arrestin-1 *vs* β -arrestin-2 might be feasible, similarly to the selective stimulation (or inhibition) of various $G\alpha$, which is pharmacologically achievable and currently exploited therapeutically. The first hint at signaling and functional differences between the two β -arrestins came over a decade ago with the realization that β -arrestin-1, but not β -arrestin-2 which has a nuclear export signal sequence (NES), can translocate to the nucleus where it regulates gene transcription^[15]. Since then, the experimental evidence supporting functional divergence between the signaling properties of the two β -arrestins both *in vitro* and in several tissues and organs *in vivo*, including in the heart, has been mounting at an accelerating pace. Thus, β -arrestin isoform-selective targeting may have a place in the design and development of novel drugs. Below, we review this evidence known so far for the cardiac β -arrestins and discuss what it could signify for heart failure drug development. Given that almost all of the *in vivo* studies on cardiac β -arrestins done so far are in relation to the effects of these two proteins on β AR and AT_1R signaling in the heart, the evidence for cardiac β -arrestins’ functional diversity reviewed below pertains exclusively to cardiac β ARs and AT_1R s.

FUNCTIONAL DIFFERENCES BETWEEN THE TWO BETA ARRESTINS IN CARDIAC BETA-AR SIGNALING

The β_1AR is by far the predominant β AR subtype in human adult cardiac myocytes, representing 75%-80% of total β AR density, followed by the β_2AR , which comprises about 15-18% of total cardiomyocyte β ARs and the remaining 2%-3% is β_3AR s^[4,7,16]. β_1AR stimulation by catecholamines results in the dissociation of the stimulatory G protein alpha subunit (G_{α_s}) from $G_{\beta\gamma}$. G_{α_s} stimulates adenylyl cyclase (AC) to produce cyclic adenosine monophosphate (cAMP), which, in turn, activates protein kinase A (PKA) and regulates different intracellular, sarcolemmal and myofibrillar substrates^[4,5,7]. Thus, cAMP-dependent signaling in cardiomyocytes mediates the cellular effects of β_1AR activation on stimulation of cardiac chronotropy, inotropy, dromotropy, and lusitropy (Figure 1)^[4,5,7]. As co-factors of GPCR-kinases (GRKs) in β AR desensitization/downregulation, β -arrestins normally diminish the inotropic and β -adrenergic reserves of the failing heart and their inhibition should theoretically be beneficial in acute decompensated heart failure (ADHF)^[4,7]. Indeed, genetic deletion of β -arrestin-1 in the heart results in several desirable therapeutic effects in heart failure, such as dramatic improvements in both cardiac β -adrenergic and inotropic reserves, amelioration of adverse remodeling and increased survival post-myocardial infarction (MI) (Figure 1)^[17,18]. In contrast however, cardiac β -arrestin-2 has been shown to be cardio-protective, as it inhibits cardiac apoptosis, inflammation, and significantly attenuates overall adverse remodeling post-MI (Figure 1)^[19]. One of the underlying mechanisms for the anti-inflammatory effects of cardiac β -arrestin-2 is nuclear factor-kappaB (NF κ B) inhibition in cardiac myocytes, which, again, appears to be mediated only by β -arrestin-2 and not by β -arrestin-1 in the heart (Figure 1)^[19,20]. Importantly, β_1AR -stimulated β -arrestin-2 was also recently documented to increase cardiac contractility both directly and indirectly (Figure 1)^[20]. Directly, by interacting with Sarco/Endoplasmic Reticulum Ca^{2+} -ATPase (SERCA)-2a leading to enhanced Small Ubiquitin-related Modifier (SUMO)-ylation of the latter^[20]. This process, deficient in human heart failure, is known to directly stimulate SERCA2a activity, thereby increasing cardiac contractility^[21]. β -arrestin-2 also increases cardiac function indirectly by leaving the β_1AR -stimulated cAMP-dependent pro-contractile signaling intact (*i.e.*, not desensitizing it) in cardiac myocytes *in vitro* and in post-MI heart failure mice *in vivo* (Figure 1)^[20]. Importantly, these effects are not shared by the vastly more abundant in the human heart β -arrestin-1^[22].

One of the salient mechanisms for the anti-apoptotic effects of cardiac β -arrestin-2 is transactivation of the epidermal growth factor receptor (EGFR) by the cardiac β_1AR (Figure 1)^[18,23]. β -arrestin-1 seems again unable to stimulate this and instead, promotes cardiac apoptosis post-MI (Figure 1)^[18]. Older studies had reported that mice expressing a mutant β_1AR that cannot undergo GRK-dependent desensitization or

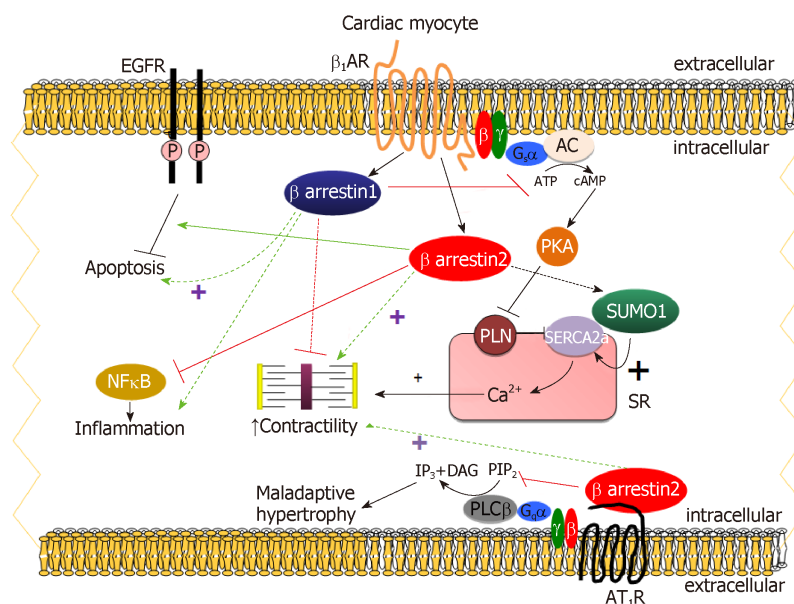


Figure 1 The functional distinction between β -arrestin-1 and β -arrestin-2 in cardiac myocytes. ATP: Adenosine triphosphate; P: Phosphorylation; SR: Sarcoplasmic reticulum; SUMO1: Small ubiquitin-like modifier protein-1; PLN: Phospholamban; PIP_2 : Phosphatidyl-inositol 4,5-bisphosphate; IP_3 : Inositol 1,4,5-trisphosphate; DAG: 1,2-Diacylglycerol; EGFR: Epidermal growth factor receptor; AR: Adrenergic receptor.

activate β -arrestins in their hearts lack cardiac EGFR transactivation and suffer from massive cardiac apoptosis and left ventricular dilatation compared to wild type controls^[23]. Interestingly, the β -blocker drug carvedilol, an inverse agonist towards G-protein activation^[16], is a weak β -arrestin-biased agonist that activates ERKs (Extracellular signal-Regulated Kinases) *via* EGFR transactivation also^[24,25]. It should be pointed out though that carvedilol's "biased" β -arrestin agonism has been demonstrated only in heterologous recombinant cell systems without cardiovascular (or any other physiological) relevance (mostly, transfected HEK293 cells). However, if this holds true in actual cardiomyocytes *in vivo*, it might be part of the mechanism for this β -blocker's cardio-protective effects. However, several studies do not lend support to this notion; sustained β_1 AR activation by catecholamines, markedly more potent activators of β -arrestin-dependent ERKs in the heart than carvedilol, increases cardiac adverse remodeling even in the absence of cardiac injury^[26]. Moreover, carvedilol is also a β_2 - and α_1 AR antagonist, which may interfere with its β -arrestin-activating properties in the heart^[27]. On the other hand, carvedilol's effects in the heart are virtually exclusively mediated by the β_1 AR, due to its relative selectivity for the human β_1 AR over the other human AR subtypes (β_2 AR and α_1 AR) and to the vast preponderance of the β_1 AR over the rest of AR subtypes in the human adult myocardium^[16]. Last but not least, recent studies have been unable to directly detect β -arrestin interactions with either β_1 AR or β_2 AR bound to carvedilol, including a study reporting the intriguing finding that carvedilol requires G_{ai} protein recruitment to the β_1 AR in order to induce EGFR transactivation *via* β -arrestins^[28-31]. Nevertheless, carvedilol has been shown to selectively recruit β -arrestin-2 to the hyperfunctional human polymorphic Arg389 β_1 AR in cardiomyocytes *in vitro*^[32]. Therefore, the more robust, compared to its Gly389 counterpart, pro-contractile signaling of this β_1 AR variant^[33] might be, at least partly, due to its unique β -arrestin-2-interacting tropism. In this vein, very recent data from our lab indicate that carvedilol-bound β_1 AR uniquely stimulates β -arrestin-2-dependent SERCA2a activity and fractional shortening of cardiomyocytes *in vitro*^[34].

FUNCTIONAL DIFFERENCES BETWEEN THE TWO BETA-ARRESTINS IN CARDIAC AT_1R SIGNALING

Despite its very low abundance in adult human myocardium (density ratio of $\text{AT}_1\text{R}/\beta_1\text{AR}$ in the non-failing human heart: approximately 1:15)^[16], the AT_1R plays important regulatory roles in the heart, but mainly *via* actions in cardiac fibroblasts and endothelial cells, rather than in cardiomyocytes^[4,7,35-37]. The AngII peptide analog SII ([Sar¹-Ile⁴-Ile⁸]-AngII) does not elicit G_q protein signaling when bound to the

AT₁R^[9,38]. When it was discovered to induce β -arrestin signaling from the AT₁R, the concept of biased signaling was introduced and ushered in a completely new field in cardiovascular drug development with companies designing novel “biased” AT₁R ligands that only activate β -arrestins while retaining G-protein-blocking properties. SII has now been documented to not be completely β -arrestin-“biased”, as it can activate some G-protein types (*e.g.*, G_s, G_i) from the AT₁R^[9]. Nevertheless, studies have shown that AT₁R-elicited β -arrestin-dependent signaling in cardiac myocytes leads to cardiomyocyte proliferation without hypertrophy, which is G_{q/11} protein signaling-dependent, and may even result in positive inotropy and lusitropy depending on which GRK isoform is involved (the so-called receptor “bar-coding” by GRKs). Interestingly, which β -arrestin is engaged is also crucial^[39,40]. Specifically, GRK2-dependent phosphorylation followed by β -arrestin-1 binding seems to reduce, whereas GRK6-dependent phosphorylation followed by β -arrestin-2 interaction seems to promote AT₁R-induced contractility in primary murine adult cardiomyocytes (Figure 1)^[39]. However, AT₁R-activated β -arrestins have no effect on contractility in isolated Langendorff-perfused cardiac preparations^[41]. Furthermore, a recombinant AT_{1A}R capable of only signaling through β -arrestins inhibits myocardial apoptosis and fibrosis, and enhances cardiomyocyte hypertrophy, upon transgenic overexpression in mouse hearts^[42]. Interestingly, a β -arrestin-2-“biased” ligand at the AT₁R is very beneficial in mice suffering from dilated cardiomyopathy as it prevents maladaptive signaling and improves myofilament Ca²⁺ sensitivity^[43]. Thus, cardiac AT₁R promotes hypertrophy and cardiomyocyte proliferation *via* the classic G_q protein/phospholipase C- β -signaling pathway, which is inhibited by the β -arrestins (classic AT₁R desensitization), and, at the same time, β -arrestin-2 (but not β -arrestin-1) can increase cardiac function *via* its cardiac AT₁R-dependent signaling (Figure 1).

Based on the above studies, several SII-derivative peptides have been synthesized and tested in animal models of ADHF with promising initial results^[44,45]. Unfortunately, these compounds failed in large phase III clinical trials (BLAST-AHF, ClinicalTrials.gov number, NCT01966601). There are probably several reasons for this. First, findings in animal models do not always translate into humans. Second, the compounds might have not been completely β -arrestin-“biased” (*i.e.*, maybe they had some weak, residual activity towards certain G-proteins). One intriguing possibility is that, due to the significantly lower abundance of the cardioprotective β -arrestin-2, compared to the cardio-toxic β -arrestin-1, in human cardiomyocytes^[22], these β -arrestin-“biased” compounds stimulated, in reality, β -arrestin-1 instead of β -arrestin-2 in the patients’ hearts and that’s why their clinical outcomes were not the desired ones. Finally, it is very likely that these compounds stimulated the AT₁R only in cardiac fibroblasts, which would preclude any clinical benefit for ADHF patients. In fact, both β -arrestins have been shown to regulate human cardiac fibroblast differentiation and to mediate collagen synthesis in human failing left ventricle-derived fibroblasts, thereby promoting the adverse remodeling process of cardiac fibrosis^[46].

Notably, β -arrestins have been reported to mediate signaling by the mechanical stretch-activated (unliganded) cardiac AT₁R^[47], which has been suggested to underlie one of the fundamental laws of cardiac physiology, the Frank-Starling mechanism of cardiac contractility^[48]. Although intriguing, this finding is very difficult to interpret, given that the Frank-Starling mechanism is hemodynamically/biomechanically governed rather than dependent on hormonal receptors/effects. Besides, if it was mediated by a cardiac GPCR, then that receptor would definitely be the β_1 AR, the by far most abundant GPCR (and at least 15-fold more abundant than the AT₁R) in cardiomyocytes^[46].

Finally, β -arrestin-mediated signaling by the AT₁R that can regulate cardiac function occurs in the adrenal cortex, as well. Specifically, the AT₁R promotes the adrenocortical production of aldosterone, a cardio-toxic hormone elevated in chronic human heart failure, *via* both G_{q/11}-proteins and β -arrestin-1^[35,49-51]. In fact, adrenal β -arrestin-1 is essential for aldosterone production, since, in mice lacking the *β -arrestin-1* gene, circulating aldosterone levels do not increase even in the presence of MI^[18]. Interestingly, the prototypic AT₁R antagonist (ARB, angiotensin receptor blocker) losartan is a relatively G protein-“biased” antagonist, which means it cannot suppress β -arrestin-1-dependent aldosterone production^[51-54]. In contrast, candesartan and valsartan are potent β -arrestin-inverse agonists at the adrenal AT₁R and very effective at suppressing aldosterone *in vitro* and *in vivo*^[52,53]. These differences among ARBs, which are all orthosteric antagonists, in their potency at blocking AT₁R-activated β -arrestin signaling may reflect their differential abilities to suppress β -arrestin signaling by the unliganded (*i.e.*, constitutively active) AT₁R^[47,55]. In other words, the ARBs seem to be inverse agonists not only for G-proteins but also for β -arrestins at the AT₁R.

THERAPEUTIC IMPLICATIONS IN HEART FAILURE

It becomes clear from the above that the signaling effects of the two β -arrestins in the heart are not just different but actually diametrically opposite. This is true for several other mammalian organ systems and tissue types^[56-58] and is completely corroborated by molecular, biophysical, crystallographic, and proteomic studies^[59-62]. It also makes sense from the evolutionary point of view, as functional redundancy of proteins is usually not favored by natural selection. Only during embryonic development might the two β -arrestins be able to compensate for each other, since single β -arrestin-knockout mice (either β -arrestin-1- or β -arrestin-2-knockouts) are viable and breed normally but the double β -arrestin-knockout mouse is embryonic-lethal^[63].

Regarding the myocardium, all the functional studies on β -arrestins done so far are in relation to either β ARs or the AT_1R . Studies on β -arrestin signaling from other cardiac GPCRs in cardiac cells are lacking. Based on the available data for β_1AR , β_2AR , or AT_1R signaling through β -arrestins in cardiac cells, it can be safely concluded that β -arrestin-1 is the arrestin responsible for the classic desensitization of the cAMP-dependent pro-contractile signaling of the β_1AR . This quite simply means that β -arrestin-1 exerts overall negative inotropy and is responsible (together with the elevated in human heart failure cardiac GRK2) for the diminished inotropic and adrenergic reserves of the failing human heart. In addition, β -arrestin-1 promotes cardiac apoptosis, inflammation, and accelerates cardiac adverse remodeling post-MI. In direct contrast, β -arrestin-2 promotes β_1AR -mediated cardiac contractility both directly and indirectly. Directly, *via* augmentation of SERCA2a activity, and indirectly, by leaving the β_1AR 's cAMP-dependent pro-contractile signaling intact (*i.e.*, no desensitization). On the other hand, it inhibits apoptosis and inflammation, and overall attenuates cardiac adverse remodeling post-MI, *via* stimulation of a variety of molecular pathways, such as EGFR transactivation and NF κ B inhibition, which β -arrestin-1 does not activate. Induction of ERK and of other mitogenic/proliferative molecular signaling pathways in cardiomyocytes play auxiliary roles in β -arrestin-2's reverse remodeling effects, as well. Of note, the same functional distinction between the two cardiac β -arrestins (*i.e.*, β -arrestin-1 being detrimental, β -arrestin-2 being beneficial) applies to cardiac AT_1R signaling, too. Regardless of how small the contribution of this GPCR to the overall contractile function of the cardiac myocyte is, β -arrestin-2 again appears to promote contractility and cardiomyocyte survival in response to AT_1R activation. Conversely, β -arrestin-1 (again in conjunction with GRK2) opposes the AT_1R -dependent pro-contractile signaling in cardiac myocytes. However, β -arrestin-1 might exert an indirect beneficial effect in the hypertrophic heart by desensitizing (reducing) the pro-hypertrophic signaling of the cardiac AT_1R through $G_{q/11}$ -proteins. In conclusion, based on their observed effects on the signaling of both β_1AR s and AT_1R s in cardiac myocytes, documented either directly (in β -arrestin-knockout mice) or indirectly (with the use of "biased" receptor ligands), cardiac β -arrestin-2 stimulation and/or β -arrestin-1 inhibition might be valid therapeutic strategies in human heart failure. By the way, it is interesting to note here that probably the exact opposite is the case in the systemic vasculature. In vascular smooth muscle cells, β -arrestin-1 appears beneficial in terms of vasodilation and attenuation of hyperplasia and β -arrestin-2 seems to promote hypertrophy/hyperplasia^[58]. This should not come as a surprise at all, given the different cellular machineries and GPCR types involved in β -arrestin signaling between cardiomyocytes (mainly β_1AR) and vascular smooth muscle cells (mainly AT_1R and, to a lesser extent, β_2AR). Besides, this is exactly what happens with the major second messenger cAMP: stimulated by the β_1AR , it is pro-contractile in cardiomyocytes, but stimulated by the β_2AR , it is pro-dilatory in vascular smooth muscle.

CONCLUSION

In the adult myocardium, the actions of β -arrestin-1 are detrimental, since they result in depletion of the functional and adrenergic reserves of the heart. In contrast, β -arrestin-2 is beneficial, since it can increase both of these cardiac reserves or at least preserve them in the face of a cardiac insult/damage, such as an MI. Thus, from the therapeutic standpoint, cardiac β -arrestin-1 blockade or β -arrestin-2 stimulation should be pursued for heart disease treatment. Of course, there are at least three very important questions awaiting answer in future studies in order to fully validate these strategies as therapeutic options for human heart failure. First, the effects of the two β -arrestins on the signaling of other important cardiac GPCRs in the heart, *i.e.*, beyond the β ARs and the AT_1R , need to be elucidated. The second issue to resolve is what the effects of the two β -arrestins in other tissues/components of the cardiovascular

system are, *e.g.*, vasculature, platelets, adrenals, *etc.* This is particularly important if the pharmacological targeting of the β -arrestins with systemically administered agents is being explored. For instance, β -arrestin-2 is beneficial in the heart, in platelets, and in vascular endothelium but might be detrimental in vascular smooth muscle^[58]. Its exact effects in all of these tissues need to be thoroughly investigated and determined, if a drug that stimulates this β -arrestin isoform is to be designed and developed. Finally, the third and therapeutically salient unanswered question pertains to the expression levels of the cardiac β -arrestins in the failing human heart. Although β -arrestin-2 protein is significantly under-expressed, compared to β -arrestin-1, in the non-failing human adult myocardium^[22,64], which makes cardiac-specific β -arrestin-2 gene transfer an enticing approach for heart failure treatment, its protein levels (and if they change) in human heart failure remain unknown. However, given that it is significantly expressed at the mRNA level, and in fact at levels comparable to those of β -arrestin-1 mRNA, in the failing human heart^[64], it is quite plausible that it might be upregulated at the protein level, similarly to GRK2, as a homeostatic mechanism of the failing human myocardium to confer cardioprotection. The only study done to date investigating β -arrestin expression in failing human hearts is quite old (was published almost 25 years ago) and could not detect any changes in the protein levels of either β -arrestin^[64]. Nevertheless, although β -arrestin-1 protein probably does not change in human heart failure, because it is already highly expressed in normal, healthy human hearts, that study failed to detect any β -arrestin-2 protein at all, even in normal healthy human hearts, probably due to technical deficiencies of the antibody it used^[64]. Therefore, it is rather inconclusive with regard to cardiac β -arrestin-2 protein expression in humans and whether cardiac β -arrestin-2 protein changes in human heart failure remains an open question. In fact, a much more recent study done in human cardiac fibroblasts isolated from left ventricles of heart failure patients hinted at β -arrestin-2 protein being upregulated in human failing hearts^[46]. In any case, more studies are certainly warranted, especially in human cardiac specimens, to unravel the full spectrum of physiological (and pathophysiological) actions of the two cardiac β -arrestins, beginning with the answering of the three outstanding questions mentioned above. Only then will the true potential of individual cardiac β -arrestin isoform targeting for heart failure therapy be revealed, so that the pharmaceutical industry can begin its realization.

REFERENCES

- Desimine VL, McCrink KA, Parker BM, Wertz SL, Maning J, Lymperopoulos A. Biased Agonism/Antagonism of Cardiovascular GPCRs for Heart Failure Therapy. *Int Rev Cell Mol Biol* 2018; **339**: 41-61 [PMID: 29776604 DOI: 10.1016/bs.ircmb.2018.02.007]
- Hilger D, Masureel M, Kobilka BK. Structure and dynamics of GPCR signaling complexes. *Nat Struct Mol Biol* 2018; **25**: 4-12 [PMID: 29323277 DOI: 10.1038/s41594-017-0011-7]
- Peterson YK, Luttrell LM. The Diverse Roles of Arrestin Scaffolds in G Protein-Coupled Receptor Signaling. *Pharmacol Rev* 2017; **69**: 256-297 [PMID: 28626043 DOI: 10.1124/pr.116.013367]
- Lymperopoulos A, Rengo G, Koch WJ. Adrenergic nervous system in heart failure: pathophysiology and therapy. *Circ Res* 2013; **113**: 739-753 [PMID: 23989716 DOI: 10.1161/CIRCRESAHA.113.300308]
- Lymperopoulos A, Garcia D, Walklett K. Pharmacogenetics of cardiac inotropy. *Pharmacogenomics* 2014; **15**: 1807-1821 [PMID: 25493572 DOI: 10.2217/pgs.14.120]
- Siryk-Bathgate A, Dabul S, Lymperopoulos A. Current and future G protein-coupled receptor signaling targets for heart failure therapy. *Drug Des Devel Ther* 2013; **7**: 1209-1222 [PMID: 24143078 DOI: 10.2147/DDDT.S35905]
- Capote LA, Mendez Perez R, Lymperopoulos A. GPCR signaling and cardiac function. *Eur J Pharmacol* 2015; **763**: 143-148 [PMID: 25981298 DOI: 10.1016/j.ejphar.2015.05.019]
- Lymperopoulos A, Bathgate A. Arrestins in the cardiovascular system. *Prog Mol Biol Transl Sci* 2013; **118**: 297-334 [PMID: 23764059 DOI: 10.1016/B978-0-12-394440-5.00012-7]
- Whalen EJ, Rajagopal S, Lefkowitz RJ. Therapeutic potential of β -arrestin- and G protein-biased agonists. *Trends Mol Med* 2011; **17**: 126-139 [PMID: 21183406 DOI: 10.1016/j.molmed.2010.11.004]
- Ranjan R, Dwivedi H, Baidya M, Kumar M, Shukla AK. Novel Structural Insights into GPCR- β -Arrestin Interaction and Signaling. *Trends Cell Biol* 2017; **27**: 851-862 [PMID: 28651823 DOI: 10.1016/j.tcb.2017.05.008]
- Eichel K, Jullié D, Barsi-Rhine B, Latorraca NR, Masureel M, Sibarita JB, Dror RO, von Zastrow M. Catalytic activation of β -arrestin by GPCRs. *Nature* 2018; **557**: 381-386 [PMID: 29720660 DOI: 10.1038/s41586-018-0079-1]
- Grundmann M, Merten N, Malfacini D, Inoue A, Preis P, Simon K, Rüttiger N, Ziegler N, Benkel T, Schmitt NK, Ishida S, Müller I, Reher R, Kawakami K, Inoue A, Rick U, Kühl T, Imhof D, Aoki J, König GM, Hoffmann C, Gomez J, Wess J, Kostenis E. Lack of beta-arrestin signaling in the absence of active G proteins. *Nat Commun* 2018; **9**: 341 [PMID: 29362459 DOI: 10.1038/s41467-017-02661-3]
- Luttrell LM, Wang J, Plouffe B, Smith JS, Yamani L, Kaur S, Jean-Charles PY, Gauthier C, Lee MH, Pani B, Kim J, Ahn S, Rajagopal S, Reiter E, Bouvier M, Shenoy SK, Laporte SA, Rockman HA, Lefkowitz RJ. Manifold roles of β -arrestins in GPCR signaling elucidated with siRNA and CRISPR/Cas9. *Sci Signal* 2018; **11**: pii: eaat7650 [PMID: 30254056 DOI: 10.1126/scisignal.aat7650]
- Weis WI, Kobilka BK. The Molecular Basis of G Protein-Coupled Receptor Activation. *Annu Rev Biochem* 2018; **87**: 897-919 [PMID: 29925258 DOI: 10.1146/annurev-biochem-060614-033910]

- 15 **Ma L**, Pei G. Beta-arrestin signaling and regulation of transcription. *J Cell Sci* 2007; **120**: 213-218 [PMID: [17215450](#) DOI: [10.1242/jcs.03338](#)]
- 16 **Yoshikawa T**, Port JD, Asano K, Chidiak P, Bouvier M, Dutcher D, Roden RL, Minobe W, Tremmel KD, Bristow MR. Cardiac adrenergic receptor effects of carvedilol. *Eur Heart J* 1996; **17** Suppl B: 8-16 [PMID: [8733065](#) DOI: [10.1093/eurheartj/17.suppl_B.8](#)]
- 17 **Conner DA**, Mathier MA, Mortensen RM, Christe M, Vatner SF, Seidman CE, Seidman JG. beta-Arrestin1 knockout mice appear normal but demonstrate altered cardiac responses to beta-adrenergic stimulation. *Circ Res* 1997; **81**: 1021-1026 [PMID: [9400383](#) DOI: [10.1161/01.RES.81.6.1021](#)]
- 18 **Bathgate-Siryk A**, Dabul S, Pandya K, Walklett K, Rengo G, Cannavo A, De Lucia C, Liccardo D, Gao E, Leosco D, Koch WJ, Lymperopoulos A. Negative impact of β -arrestin-1 on post-myocardial infarction heart failure via cardiac and adrenal-dependent neurohormonal mechanisms. *Hypertension* 2014; **63**: 404-412 [PMID: [24218435](#) DOI: [10.1161/HYPERTENSIONAHA.113.02043](#)]
- 19 **Watari K**, Nakaya M, Nishida M, Kim KM, Kurose H. β -arrestin2 in infiltrated macrophages inhibits excessive inflammation after myocardial infarction. *PLoS One* 2013; **8**: e68351 [PMID: [23861891](#) DOI: [10.1371/journal.pone.0068351](#)]
- 20 **McCrink KA**, Maning J, Vu A, Jafferjee M, Marrero C, Brill A, Bathgate-Siryk A, Dabul S, Koch WJ, Lymperopoulos A. β -Arrestin2 Improves Post-Myocardial Infarction Heart Failure via Sarco(endo)plasmic Reticulum Ca^{2+} -ATPase-Dependent Positive Inotropy in Cardiomyocytes. *Hypertension* 2017; **70**: 972-981 [PMID: [28874462](#) DOI: [10.1161/HYPERTENSIONAHA.117.09817](#)]
- 21 **Kho C**, Lee A, Jeong D, Oh JG, Chaanine AH, Kizana E, Park WJ, Hajjar RJ. SUMO1-dependent modulation of SERCA2a in heart failure. *Nature* 2011; **477**: 601-605 [PMID: [21900893](#) DOI: [10.1038/nature10407](#)]
- 22 **McCrink KA**, Maning J, Vu A, Jafferjee M, Marrero C, Brill A, Bathgate-Siryk A, Dabul S, Koch WJ, Lymperopoulos A. Cardiac β arrestin2 Improves Contractility and Adverse Remodeling in Heart Failure, But Is Underexpressed in Humans. *J Am Coll Cardiol* 2017; **70**: 2948-2949 [PMID: [29216991](#) DOI: [10.1016/j.jacc.2017.10.008](#)]
- 23 **Noma T**, Lemaire A, Naga Prasad SV, Barki-Harrington L, Tilley DG, Chen J, Le Corvoisier P, Violin JD, Wei H, Lefkowitz RJ, Rockman HA. Beta-arrestin-mediated beta1-adrenergic receptor transactivation of the EGFR confers cardioprotection. *J Clin Invest* 2007; **117**: 2445-2458 [PMID: [17786238](#) DOI: [10.1172/JCI31901](#)]
- 24 **Kim IM**, Tilley DG, Chen J, Salazar NC, Whalen EJ, Violin JD, Rockman HA. Beta-blockers alprenolol and carvedilol stimulate beta-arrestin-mediated EGFR transactivation. *Proc Natl Acad Sci USA* 2008; **105**: 14555-14560 [PMID: [18787115](#) DOI: [10.1073/pnas.0804745105](#)]
- 25 **Wisler JW**, DeWire SM, Whalen EJ, Violin JD, Drake MT, Ahn S, Shenoy SK, Lefkowitz RJ. A unique mechanism of beta-blocker action: carvedilol stimulates beta-arrestin signaling. *Proc Natl Acad Sci USA* 2007; **104**: 16657-16662 [PMID: [17925438](#) DOI: [10.1073/pnas.0707936104](#)]
- 26 **Kaur K**, Parra S, Chen R, Charbeneau RA, Wade SM, Jay PY, Neubig RR. Gai2 signaling: friend or foe in cardiac injury and heart failure? *Naunyn Schmiedeberg's Arch Pharmacol* 2012; **385**: 443-453 [PMID: [22411356](#) DOI: [10.1007/s00210-011-0705-z](#)]
- 27 **Carr R**, Schilling J, Song J, Carter RL, Du Y, Yoo SM, Traynham CJ, Koch WJ, Cheung JY, Tilley DG, Benovic JL. β -arrestin-biased signaling through the β 2-adrenergic receptor promotes cardiomyocyte contraction. *Proc Natl Acad Sci USA* 2016; **113**: E4107-E4116 [PMID: [27354517](#) DOI: [10.1073/pnas.1606267113](#)]
- 28 **Littmann T**, Göttele M, Reinartz MT, Kälble S, Wainer IW, Ozawa T, Seifert R. Recruitment of β -arrestin 1 and 2 to the β 2-adrenoceptor: analysis of 65 ligands. *J Pharmacol Exp Ther* 2015; **355**: 183-190 [PMID: [26306764](#) DOI: [10.1124/jpet.115.227959](#)]
- 29 **Shukla AK**, Westfield GH, Xiao K, Reis RI, Huang LY, Tripathi-Shukla P, Qian J, Li S, Blanc A, Oleskie AN, Dosey AM, Su M, Liang CR, Gu LL, Shan JM, Chen X, Hanna R, Choi M, Yao XJ, Klink BU, Kahsai AW, Sidhu SS, Koide S, Penczek PA, Kossiakoff AA, Woods VL, Kobilka BK, Skiniotis G, Lefkowitz RJ. Visualization of arrestin recruitment by a G-protein-coupled receptor. *Nature* 2014; **512**: 218-222 [PMID: [25043026](#) DOI: [10.1038/nature13430](#)]
- 30 **O'Hayre M**, Eichel K, Avino S, Zhao X, Steffen DJ, Feng X, Kawakami K, Aoki J, Messer K, Sunahara R, Inoue A, von Zastrow M, Gutkind JS. Genetic evidence that β -arrestins are dispensable for the initiation of β 2-adrenergic receptor signaling to ERK. *Sci Signal* 2017; **10**: pii: eal3395 [PMID: [28634209](#) DOI: [10.1126/scisignal.aal3395](#)]
- 31 **Wang J**, Hanada K, Staus DP, Makara MA, Dahal GR, Chen Q, Ahles A, Engelhardt S, Rockman HA. Gai is required for carvedilol-induced β 1 adrenergic receptor β -arrestin biased signaling. *Nat Commun* 2017; **8**: 1706 [PMID: [29167435](#) DOI: [10.1038/s41467-017-01855-z](#)]
- 32 **McCrink KA**, Brill A, Jafferjee M, Valero TR, Marrero C, Rodriguez MM, Hale GM, Lymperopoulos A. β 1-adrenoceptor Arg389Gly polymorphism confers differential β -arrestin-binding tropism in cardiac myocytes. *Pharmacogenomics* 2016; **17**: 1611-1620 [PMID: [27643874](#) DOI: [10.2217/pgs-2016-0094](#)]
- 33 **Liggett SB**, Miale-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, Nelson B, Morrison J, Domanski MJ, Wagoner LE, Abraham WT, Anderson JL, Carlquist JF, Krause-Steinrauf HJ, Lazzaroni LC, Port JD, Lavori PW, Bristow MR. A polymorphism within a conserved beta(1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. *Proc Natl Acad Sci USA* 2006; **103**: 11288-11293 [PMID: [16844790](#) DOI: [10.1073/pnas.0509937103](#)]
- 34 **Lymperopoulos A**, Desimine VL, McCrink KA, Maning J, Wertz SL, Markan U, Pasupuleti S, Brill A, Parker BM. Positive cardiac inotropy by carvedilol via unique beta-arrestin2-dependent SERCA2a stimulation. *Eur Heart J* 2018; **39**: Suppl_1, 1 [DOI: [10.1093/eurheartj/ehy563.3144](#)]
- 35 **Maning J**, Negussie S, Clark MA, Lymperopoulos A. Biased agonism/antagonism at the AngII-AT1 receptor: Implications for adrenal aldosterone production and cardiovascular therapy. *Pharmacol Res* 2017; **125**: 14-20 [PMID: [28511989](#) DOI: [10.1016/j.phrs.2017.05.009](#)]
- 36 **Lymperopoulos A**. Beta-arrestin biased agonism/antagonism at cardiovascular seven transmembrane-spanning receptors. *Curr Pharm Des* 2012; **18**: 192-198 [PMID: [22229558](#) DOI: [10.2174/138161212799040475](#)]
- 37 **Thomas WG**, Thekkumkara TJ, Baker KM. Cardiac effects of AII, AT1A receptor signaling, desensitization, and internalization. *Adv Exp Med Biol* 1996; **396**: 59-69 [PMID: [8726686](#) DOI: [10.1007/978-1-4899-1376-0_7](#)]
- 38 **Saulière A**, Bellot M, Paris H, Denis C, Finana F, Hansen JT, Altie MF, Seguelas MH, Pathak A, Hansen JL, Sénard JM, Galès C. Deciphering biased-agonism complexity reveals a new active AT1 receptor entity. *Nat Chem Biol* 2012; **8**: 622-630 [PMID: [22634635](#) DOI: [10.1038/nchembio.961](#)]

- 39 **Rajagopal K**, Whalen EJ, Violin JD, Stiber JA, Rosenberg PB, Premont RT, Coffman TM, Rockman HA, Lefkowitz RJ. Beta-arrestin2-mediated inotropic effects of the angiotensin II type 1A receptor in isolated cardiac myocytes. *Proc Natl Acad Sci USA* 2006; **103**: 16284-16289 [PMID: [17060617](#) DOI: [10.1073/pnas.0607583103](#)]
- 40 **Zidar DA**, Violin JD, Whalen EJ, Lefkowitz RJ. Selective engagement of G protein coupled receptor kinases (GRKs) encodes distinct functions of biased ligands. *Proc Natl Acad Sci USA* 2009; **106**: 9649-9654 [PMID: [19497875](#) DOI: [10.1073/pnas.0904361106](#)]
- 41 **Aplin M**, Christensen GL, Schneider M, Heydorn A, Gammeltoft S, Kjølbye AL, Sheikh SP, Hansen JL. Differential extracellular signal-regulated kinases 1 and 2 activation by the angiotensin type 1 receptor supports distinct phenotypes of cardiac myocytes. *Basic Clin Pharmacol Toxicol* 2007; **100**: 296-301 [PMID: [17448114](#) DOI: [10.1111/j.1742-7843.2007.00064.x](#)]
- 42 **Zhai P**, Yamamoto M, Galeotti J, Liu J, Masarekar M, Thaisz J, Irie K, Holle E, Yu X, Kupersmidt S, Roden DM, Wagner T, Yatani A, Vatner DE, Vatner SF, Sadoshima J. Cardiac-specific overexpression of AT1 receptor mutant lacking G alpha q/G alpha i coupling causes hypertrophy and bradycardia in transgenic mice. *J Clin Invest* 2005; **115**: 3045-3056 [PMID: [16276415](#) DOI: [10.1172/JCI25330](#)]
- 43 **Ryba DM**, Li J, Cowan CL, Russell B, Wolska BM, Solaro RJ. Long-Term Biased β -Arrestin Signaling Improves Cardiac Structure and Function in Dilated Cardiomyopathy. *Circulation* 2017; **135**: 1056-1070 [PMID: [28104714](#) DOI: [10.1161/CIRCULATIONAHA.116.024482](#)]
- 44 **Violin JD**, DeWire SM, Yamashita D, Rominger DH, Nguyen L, Schiller K, Whalen EJ, Gowen M, Lark MW. Selectively engaging β -arrestins at the angiotensin II type 1 receptor reduces blood pressure and increases cardiac performance. *J Pharmacol Exp Ther* 2010; **335**: 572-579 [PMID: [20801892](#) DOI: [10.1124/jpet.110.173005](#)]
- 45 **Boerrigter G**, Soergel DG, Violin JD, Lark MW, Burnett JC. TRV120027, a novel β -arrestin biased ligand at the angiotensin II type I receptor, unloads the heart and maintains renal function when added to furosemide in experimental heart failure. *Circ Heart Fail* 2012; **5**: 627-634 [PMID: [22891045](#) DOI: [10.1161/CIRCHEARTFAILURE.112.969220](#)]
- 46 **Li J**, Philip JL, Xu X, Theccanat T, Abdur Razzaque M, Akhter SA. β -Arrestins regulate human cardiac fibroblast transformation and collagen synthesis in adverse ventricular remodeling. *J Mol Cell Cardiol* 2014; **76**: 73-83 [PMID: [25134464](#) DOI: [10.1016/j.yjmcc.2014.08.006](#)]
- 47 **Rakesh K**, Yoo B, Kim IM, Salazar N, Kim KS, Rockman HA. beta-Arrestin-biased agonism of the angiotensin receptor induced by mechanical stress. *Sci Signal* 2010; **3**: ra46 [PMID: [20530803](#) DOI: [10.1126/scisignal.2000769](#)]
- 48 **Abraham DM**, Davis RT, Warren CM, Mao L, Wolska BM, Solaro RJ, Rockman HA. β -Arrestin mediates the Frank-Starling mechanism of cardiac contractility. *Proc Natl Acad Sci USA* 2016; **113**: 14426-14431 [PMID: [27911784](#) DOI: [10.1073/pnas.1609308113](#)]
- 49 **Lymperopoulos A**, Aukshi B. Angiotensin receptor blocker drugs and inhibition of adrenal beta-arrestin-1-dependent aldosterone production: Implications for heart failure therapy. *World J Cardiol* 2017; **9**: 200-206 [PMID: [28400916](#) DOI: [10.4330/wjcv.9.i3.200](#)]
- 50 **Lymperopoulos A**, Rengo G, Zincarelli C, Kim J, Soltys S, Koch WJ. An adrenal beta-arrestin 1-mediated signaling pathway underlies angiotensin II-induced aldosterone production in vitro and in vivo. *Proc Natl Acad Sci USA* 2009; **106**: 5825-5830 [PMID: [19289825](#) DOI: [10.1073/pnas.0811706106](#)]
- 51 **Lymperopoulos A**, Rengo G, Zincarelli C, Kim J, Koch WJ. Adrenal beta-arrestin 1 inhibition in vivo attenuates post-myocardial infarction progression to heart failure and adverse remodeling via reduction of circulating aldosterone levels. *J Am Coll Cardiol* 2011; **57**: 356-365 [PMID: [21232674](#) DOI: [10.1016/j.jacc.2010.08.635](#)]
- 52 **Lymperopoulos A**, Sturchler E, Bathgate-Siryk A, Dabul S, Garcia D, Walklett K, Rengo G, McDonald P, Koch WJ. Different potencies of angiotensin receptor blockers at suppressing adrenal β -Arrestin1-dependent post-myocardial infarction hyperaldosteronism. *J Am Coll Cardiol* 2014; **64**: 2805-2806 [PMID: [25541135](#) DOI: [10.1016/j.jacc.2014.09.070](#)]
- 53 **Dabul S**, Bathgate-Siryk A, Valero TR, Jafferjee M, Sturchler E, McDonald P, Koch WJ, Lymperopoulos A. Suppression of adrenal β -arrestin1-dependent aldosterone production by ARBs: head-to-head comparison. *Sci Rep* 2015; **5**: 8116 [PMID: [25631300](#) DOI: [10.1038/srep08116](#)]
- 54 **Valero TR**, Sturchler E, Jafferjee M, Rengo G, Magafa V, Cordopatis P, McDonald P, Koch WJ, Lymperopoulos A. Structure-activity relationship study of angiotensin II analogs in terms of β -arrestin-dependent signaling to aldosterone production. *Pharmacol Res Perspect* 2016; **4**: e00226 [PMID: [27069636](#) DOI: [10.1002/prp2.226](#)]
- 55 **Tóth AD**, Prokop S, Gyombolai P, Várnai P, Balla A, Gurevich VV, Hunyady L, Turu G. Heterologous phosphorylation-induced formation of a stability lock permits regulation of inactive receptors by β -arrestins. *J Biol Chem* 2018; **293**: 876-892 [PMID: [29146594](#) DOI: [10.1074/jbc.M117.813139](#)]
- 56 **Srivastava A**, Gupta B, Gupta C, Shukla AK. Emerging Functional Divergence of β -Arrestin Isoforms in GPCR Function. *Trends Endocrinol Metab* 2015; **26**: 628-642 [PMID: [26471844](#) DOI: [10.1016/j.tem.2015.09.001](#)]
- 57 **Lymperopoulos A**, Negussie S. β Arrestins in cardiac G protein-coupled receptor signaling and function: partners in crime or "good cop, bad cop"? *Int J Mol Sci* 2013; **14**: 24726-24741 [PMID: [24351844](#) DOI: [10.3390/ijms141224726](#)]
- 58 **Lymperopoulos A**. Arrestins in the Cardiovascular System: An Update *Prog Mol Biol Transl Sci* 2018; In press [DOI: [10.1016/bs.pmbts.2018.07.003](#)]
- 59 **Zhan X**, Gimenez LE, Gurevich VV, Spiller BW. Crystal structure of arrestin-3 reveals the basis of the difference in receptor binding between two non-visual subtypes. *J Mol Biol* 2011; **406**: 467-478 [PMID: [21215759](#) DOI: [10.1016/j.jmb.2010.12.034](#)]
- 60 **Zhuo Y**, Vishnivetskiy SA, Zhan X, Gurevich VV, Klug CS. Identification of receptor binding-induced conformational changes in non-visual arrestins. *J Biol Chem* 2014; **289**: 20991-21002 [PMID: [24867953](#) DOI: [10.1074/jbc.M114.560680](#)]
- 61 **Gurevich VV**, Gurevich EV. Extensive shape shifting underlies functional versatility of arrestins. *Curr Opin Cell Biol* 2014; **27**: 1-9 [PMID: [24680424](#) DOI: [10.1016/j.ceb.2013.10.007](#)]
- 62 **Xiao K**, McClatchy DB, Shukla AK, Zhao Y, Chen M, Shenoy SK, Yates JR, Lefkowitz RJ. Functional specialization of beta-arrestin interactions revealed by proteomic analysis. *Proc Natl Acad Sci USA* 2007; **104**: 12011-12016 [PMID: [17620599](#) DOI: [10.1073/pnas.0704849104](#)]
- 63 **Luttrell LM**, Gesty-Palmer D. Beyond desensitization: physiological relevance of arrestin-dependent signaling. *Pharmacol Rev* 2010; **62**: 305-330 [PMID: [20427692](#) DOI: [10.1124/pr.109.002436](#)]
- 64 **Ungerer M**, Parruti G, Böhm M, Puzicha M, DeBlasi A, Erdmann E, Lohse MJ. Expression of beta-

arrestins and beta-adrenergic receptor kinases in the failing human heart. *Circ Res* 1994; **74**: 206-213
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Percutaneous devices for left atrial appendage occlusion: A contemporary review

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Abstract

Patient with atrial fibrillation (AF) are at risk of developing stroke with the left atrial appendage (LAA) being the most common site for thrombus formation. If left untreated, AF is associated with 4 to 5 folds increase in the risk of ischemic stroke in all age groups. About 5% to 15% of AF patients have atrial thrombi on transesophageal echocardiography, and 91% of those thrombi are located in the LAA in patient with nonrheumatic AF. Although oral anticoagulants are the gold-standard treatment for stroke prevention in patients with non-valvular AF, some patients are at high risk of bleeding and deemed not candidates for anticoagulation. Therefore, LAA occlusion (LAAO) has emerged as alternative approach for stroke prevention in those patients. Surgical LAAO is associated with high rate of unsuccessful closure and recommended only in patients with AF and undergoing cardiac surgery. Percutaneous LAAO uses transvenous access with trans-septal puncture and was first tested using the PLAATO device. Watchman is the most common and only Food and Drug Administration (FDA) approved device for LAAO. LAAO using Watchman device is non-inferior to warfarin therapy in preventing ischemic stroke/systemic thromboembolism. However, it is associated with lower rates of hemorrhagic stroke, bleeding and death. Amplatzer is another successful LAAO device that has CE mark and is waiting for FDA approval. Optimal antithrombotic therapy post LAAO is still under debate and highly patient-specific. The aim of this paper is to systematically review the current literature to evaluate the efficacy and safety of

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different LAAO devices.

Key words: Left atrial appendage; Atrial fibrillation; Anticoagulation; Stroke; Mortality

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Core tip: Left atrial appendage occlusion (LAAO) is a reasonable alternative approach that is used in patients with atrial fibrillation who are not candidates for anticoagulation. A number of key trials have shown that Watchman device is non-inferior to warfarin therapy in preventing ischemic stroke/systemic thromboembolism. However, it is associated with lower rates of hemorrhagic stroke, bleeding and death. Multiple retrospective and prospective studies of Amplatzer device (ACP and Amulet) reported high success rates in device implantation and stroke prevention. Our objective is to consolidate the current literature to better delineate the safety, efficacy and indication of LAAO for stroke prevention.

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INTRODUCTION

Atrial fibrillation (AF) affects 2.7 to 6.1 million in the United States and 33.5 million worldwide^[1-3]. The projected prevalence of AF in the United States is expected to be 12.1 million by 2030^[4]. AF-associated stroke is the most feared complication and the leading cause of disability in the United States^[5]. If left untreated, AF is associated with 4 to 5 folds increase in the risk of ischemic stroke in all age groups^[5,6]. Furthermore, AF is associated with increased risk of extracranial thromboembolic events to the aorta; and renal, mesenteric, and peripheral arteries^[7]. The proportion of strokes attributed solely to AF increases with age and may reach up to 23.5%^[6,8]. Oral anticoagulants (OACs) remain to be the gold standard treatment for stroke prevention, and their role in preventing AF-related strokes is well established^[9,10]. Yet, OACs are contraindicated in a subset of patients who are at high risk of bleeding. As a result, left atrial appendage occlusion (LAAO) has emerged as an alternative approach in this group. In the current article, we present the most updated studies describing safety, efficacy and outcome of different LAAO devices.

LITERATURE SEARCH

A systematic literature search was conducted using PubMed, EMBASE, and Cochrane Library to identify relevant articles from 1990 to 2018. The following search terms were used: "atrial fibrillation", "stroke", "left atrial appendage", "occlusion" or "closure", and "percutaneous" or "surgical." A total of 78 studies were included for review. Of the included studies on LAAO, 3 studies contained surgical LAAO, two contained Atriclip device, two contained Tiger Paw system, 6 contained Lariat device, 4 contained PLAATO device, 19 contained Watchman device, and 12 contained Amplatzer (ACP/Amulet) device.

LEFT ATRIAL APPENDAGE AND THROMBUS FORMATION

Left atrial appendage (LAA) is trabeculated long tubular structure that has narrow junction with the venous component of left atrium. it varies greatly in sizes and shapes and has bent or spiral axis in 70% of patients^[11]. Anatomically, LAA is best divided into the ostium, neck, and lobar region^[12]. In patients with chronic AF, remodeling of LAA leads to dilation, stretching and reduction in pectinate muscle volume^[13].

Approximately, 5% to 15% of AF patients have atrial thrombi on Transesophageal

echocardiography (TEE)^[14-17], and 91% of those thrombi are located in LAA in patients with nonrheumatic AF^[18]. The reason for LAA predilection for thrombus formation in AF is still not well known. One theory suggests that the extent of LAA filling and emptying is influenced more by changes in the left ventricular (which is impaired in AF) than LAA function^[19]. Ventricular filling creates intracavitary suction effect which influences the emptying and filling of left atrium and LAA.

IMAGING ASSESSMENT OF LAA

Accurate assessment of anatomic LAA characteristics is crucial prior to LAAO due to substantial variations in LAA anatomy that impact device selection and efficacy. TEE is the most widely used imaging tool for periprocedural LAA assessment. It is used for the detection of thrombi in the LA and LAA as well other cardiac masses and thrombi prior to LAAO^[12,20]. Features on TEE associated with increased risk of thrombus formation include: reduced LAA flow velocity, spontaneous left atrial contrast, and aortic atheroma^[16]. TEE is very important imaging to support fluoroscopy during device implantation. 3D TEE has shown to be more accurate than 2D TEE in LAA assessment and thrombi detection^[21,22]; and therefore, it is recommended for the guidance of LAAO^[23]. It is used to guide trans-septal puncture, verify catheter and sheath position in the LAA, aid device delivery and positioning, confirm adequate LAA sealing, and detect complications^[12]. Follow-up TEE is also recommended after LAAO to reassess the implanted device, confirm complete LAA closure, and rule out complications. Intracardiac echocardiography (ICE) is comparable imaging to TEE for guiding LAAO and performing the tasks typically provided by TEE during implantation. In one study LAA measurements by ICE during LAAO were significantly correlated to angiography and TEE (Pearson correlation coefficient $r = 0.94$, $P < 0.0001$ for both)^[24].

Multidetector computed tomography is another imaging modality that is used for the assessment of thrombus formation, LAA anatomy and function, device assessment and detection of complications post procedure^[12]. It provides 3D images of the heart by using numerous planes at different points in time during the cardiac cycle and has 100% sensitivity for excluding LAA thrombus^[25]. However, its use is limited due to ionizing radiation, lower temporal resolution than TEE and inability to perform during device deployment. angiography has been used for in LAA thrombi detection^[26]. However, it is expensive and invasive procedure, and rarely used nowadays due to presence of TEE and other less invasive imaging modalities.

GUIDELINE THERAPY FOR STROKE PREVENTION

The 2014 American Heart Association/American College of Cardiology (AHA/ACC) guidelines for management of AF recommends the use of anticoagulation for prevention of thromboembolism when CHA₂DS₂-VASc score is ≥ 2 [class I (A)]^[16]. The 2016 European Society of Cardiology (ESC) guidelines differentiate between males and females regarding anticoagulation recommendations^[27]. While anticoagulation is class I (A) indication for males with a score ≥ 2 and females with a score ≥ 3 , it's considered class IIa (B) indication for males with a score of 1 and females with a score of 2. Both American and European guidelines recommend considering surgical excision of LAA in patients who have AF and undergoing cardiac surgery [class IIb (level of evidence is "C" in AHA/ACC and "B" in the ESC guidelines)]^[16,27]. While AHA/ACC guidelines have no recommendations for LAAO, the ESC guidelines have class IIb (B) recommendation for LAAO in patients with AF and contra-indications for long-term anticoagulation^[27]. Similarly, National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand state that LAAO may be considered for stroke prevention in patients with non-valvular AF at moderate to high risk of stroke and with contraindications to OAC (GRADE quality of evidence: Low; GRADE strength of recommendation: Strong)^[28].

LAA SURGICAL CLOSURES/EXCISION

Surgical exclusion of LAA is recommended for patients with AF and undergoing concomitant cardiac surgeries. Different surgical methods to isolate LAA include: suture ligation, excision and suture closure, and stapling exclusion with or without excision^[29,30]. Surgical isolation of LAA is associated with high rate of unsuccessful closure. For instance, a previous study reported only 40% (55 out of 137) complete

LAA closure noted on TEE following surgical closure^[30]. Despite that, Friedman *et al*^[31] reported a lower risk of readmission for thromboembolism (4.2% *vs* 6.2%, HR = 0.67; 95%CI: 0.56-0.81) and all-cause mortality (17.3% *vs* 23.9%, HR = 0.88; 95%CI: 0.79-0.97) among Medicare patients (age > 65) with AF undergoing concomitant cardiac surgery and surgical LAAO, compared with no surgical LAAO. This the largest study to date supporting the role of surgical LAAO during cardiac surgery as a mean of preventing thromboembolism in patients over the age of 65 with AF.

The Atriclip Device System (Atricure, Inc., West Chester, OH, United States) is a surgical LAA exclusion device composed of self-closing, sterile, implantable clip with a reusable deployment tool (Figure 1). It is applied epicardially by either an open surgical or a minimally-invasive technique and placed at the base of the appendage. The clip is made of 2 parallel rigid titanium tubes with elastic nitinol springs covered with a knit-braided polyester sheath (Table 1)^[32,33]. The EXCLUDE study (Exclusion of LAA with AtriClip Exclusion Device in Patients Undergoing Concomitant Cardiac Surgery) is a nonrandomized multicenter trial that included 70 patients to evaluate the efficacy of Atriclip device^[33]. They enrolled adult patients undergoing elective primary cardiac operations via median sternotomy (coronary artery bypass grafting, valve re- pair or replacement, surgical Maze procedures, or atrial septal defect repair) and have CHADS₂ > 2. 67 out of 70 patients (95.7%) had successful intraoperative LAA exclusion, and 60 out of 61 patients (98.4%) had successful LAA exclusion seen on computed tomography angiography or TEE imaging after 3 mo^[33]. Tiger Paw System (Terumo Cardiovascular Systems, Ann Arbor, MI, United States) is another LAA exclusion device that is used as a concomitant procedure during open cardiac surgical procedures (Figure 1). The device contains implantable fastener of titanium connectors that staples the LAA tissue and is embedded in two rims of silicone that adapts to the LAA morphology and seals the puncture sites (Table 1)^[34]. Despite its efficacy in achieving complete LAA closure on prior study^[34], a class 1 recall from the market by FDA was made in 2015 due to device malfunction^[35].

LARIATE DEVICE CLOSURE SYSTEM

Lariat device (SentreHEART, Inc., Redwood City, California) is LAA closure system that is approved by the United States Food and Drug Administration (FDA) for soft tissue closure, but not LAAO (Figure 1). It is composed of 15-mm compliant occlusion balloon catheter (EndoCATH), 0.025-inch and 0.035-inch magnet-tipped guidewires (FindrWIRZ), and a 12-F suture delivery device (LARIAT) (Table 1). During the procedure, magnet-tipped guidewires are advanced through epicardial and transvenous accesses and connected in the LAA. Then, a suture fashioned as a Lariate or lasso is advanced over the epicardial access guidewire and tightened to occlude LAA base^[29,36]. The largest prospective study of Lariate device included patients who: were ≥ 18-year-old; had nonvalvular AF; had CHADS₂ ≥ 1; were poor candidate for or failed warfarin therapy; and had a life expectancy of at least 1 year^[36]. They reported 95% (81 of 85 patients) complete LAA closure documented on TEE one month after the procedure. 98% of those who underwent TEE (*n* = 65) had complete LAA closure after 1 year, including cases of incomplete closure at earlier time. Complications in the same study were limited to only two cases of severe pericarditis, two cases of strokes, and one case with pericardial effusion^[36]. Another study demonstrated similar efficacy of the Lariate device for stroke prevention^[37]. Dar *et al*^[38] demonstrated that LAAO using Lariate device might improve the mechanical function of the left atrium (LA) and reverse LA remodeling based on 2-dimensional speckle tracking echocardiography (a novel method for functional assessment of the LA). However, due to steep learning curve for device deployment (especially epicardial access), LAA leak and lack of direct efficacy comparison with oral anticoagulation, the device was not widely used in the United States^[39-42].

PERCUTANEOUS LAA CLOSURE

The most commonly used percutaneous LAAO devices are shown in figure 1 and described in Table 1. Percutaneous LAAO uses transvenous access with trans-septal puncture and was first tested using the Percutaneous LAA Transcatheter Occlusion (PLAATO) device (Appriva Medical Inc., Sunnyvale, CA) in 2001.

PLAATO device

This device consists of self-expanding nitinol cage that is covered with polymeric membrane in order to close off blood flow into the LAA (Table 1)^[43,44]. It was first

Table 1 Comparison of left atrial appendage occlusion devices

Device	Study	Year of Introduction	Description	Approach	Approval
Atriclip Device System (Atricure)	EXCLUDE study ^[33]	2008	Self-closing, sterile, implantable clip, with a reusable deployment tool applied pericardially.	Epicardial	CE Mark
Tiger Paw System (Terumo Cardiovascular Systems)	Slater <i>et al</i> ^[34]	Introduced in 2009 and recalled in 2015	Implantable fastener of titanium connectors that staples the LAA tissue plus rims of silicone that seal the puncture sites.	Epicardial	Recalled
Lariat device (SentreHEART)	Bartus <i>et al</i> ^[36] ; Massumi <i>et al</i> ^[37] ; Dar <i>et al</i> ^[38]	2009	Multicomponent system including: transvenous and epicardial balloon catheters, magnet tipped guidewires, and suture delivery system	Epicardial and transvenous	FDA approval for soft tissue closure not LAAO CE mark
PLAATO (Appriva Medical)	Sievert <i>et al</i> ^[43] ; Ostermaye <i>et al</i> ^[44] ; Bayard <i>et al</i> ^[45] ; Park <i>et al</i> ^[46]	Introduced in 2001 and discontinued in 2007	Self-expanding nitinol cage covered with polymeric membrane (ePTFE) designed to be placed in the orifice of the LAA	Transvenous, trans-septal	Discontinued
Watchman (Boston Scientific)	Pilot study ^[47] ; PROTECT AF study ^[48-50] ; PREVAIL study ^[51,52] ; CAP 1 registry ^[53] ; CAP 2 registry ^[54] ; EWOLUTION registry ^[55-57] ; RELEXAO Registry ^[72] ; ASAP study ^[58] ; ASAP TOO study ^[59]	2005	Self-expanding nitinol frame structure with fixation barbs and a permeable polyester fabric that covers the atrial facing surface of the device	Transvenous, trans-septal	FDA approved and CE Mark
ACP (St. Jude Medical)	Urena <i>et al</i> ^[67] ; Gloekler <i>et al</i> ^[60] ; Abualsaud <i>et al</i> ^[61] ; Korsholm <i>et al</i> ^[64] ; Berti <i>et al</i> ^[65] ; RELEXAO; Registry ^[72]	2008	Self-expanding distal lobe (6.5mm in length) and proximal disc (4-6mm larger than distal lobe) nitinol mesh with articulating waist	Transvenous, trans-septal	CE Mark
Amplatzer Amulet (St. Jude Medical)	Gloekler <i>et al</i> ^[60] ; Abualsaud <i>et al</i> ^[61] ; Landmesser <i>et al</i> ^[62] ; Tzikas <i>et al</i> ^[63] ; Korsholm <i>et al</i> ^[64] ; Berti <i>et al</i> ^[65] ; Kleinecke <i>et al</i> ^[66] ; RELEXAO; Registry ^[72]	2013	Self-expanding distal lobe and proximal disc nitinol mesh with articulating waist, and more anchors	Transvenous, trans-septal	CE Mark

LAAO: Left atrial appendage occlusion; FDA: Food and drug administration; ACP: Amplatzer cardiac plug.

tested on 15 patients with non-valvular AF and contraindication to warfarin therapy and are at high risk of thromboembolism based on CHADS₂ score^[43]. Successful occlusion of LAA was observed in all cases and no device related complications were reported. A larger prospective study enrolled patients using similar inclusion criteria to undergo LAAO using PLAATO device^[44]. Similarly, they reported high successful device Implantation in 108 out of 111 patients (97.3%) with only 2 patients developed stroke on follow up (2.2% annual risk of stroke). Subsequently, the European PLAATO2 trial reported successful LAAO in 90% (126 out of 140) of patients with reduction of stroke rate from 6.6% (based on CHADS₂ score) to 2.3% per year^[45]. Besides, a single center prospective study on 73 cases who had PLAATO device reported death due to device embolization in one patient and implant instability requiring open heart surgery in another one^[46]. Interestingly, there was no incidence of stroke for 24 mo of follow-up in the same study. Despite this success, the device was discontinued for unspecified reasons and replaced by Watchman device.

Watchman device

The Watchman device (Boston Scientific, Marlborough, MA), is the only FDA-approved percutaneous device for LAAO. The device is composed of self-expanding

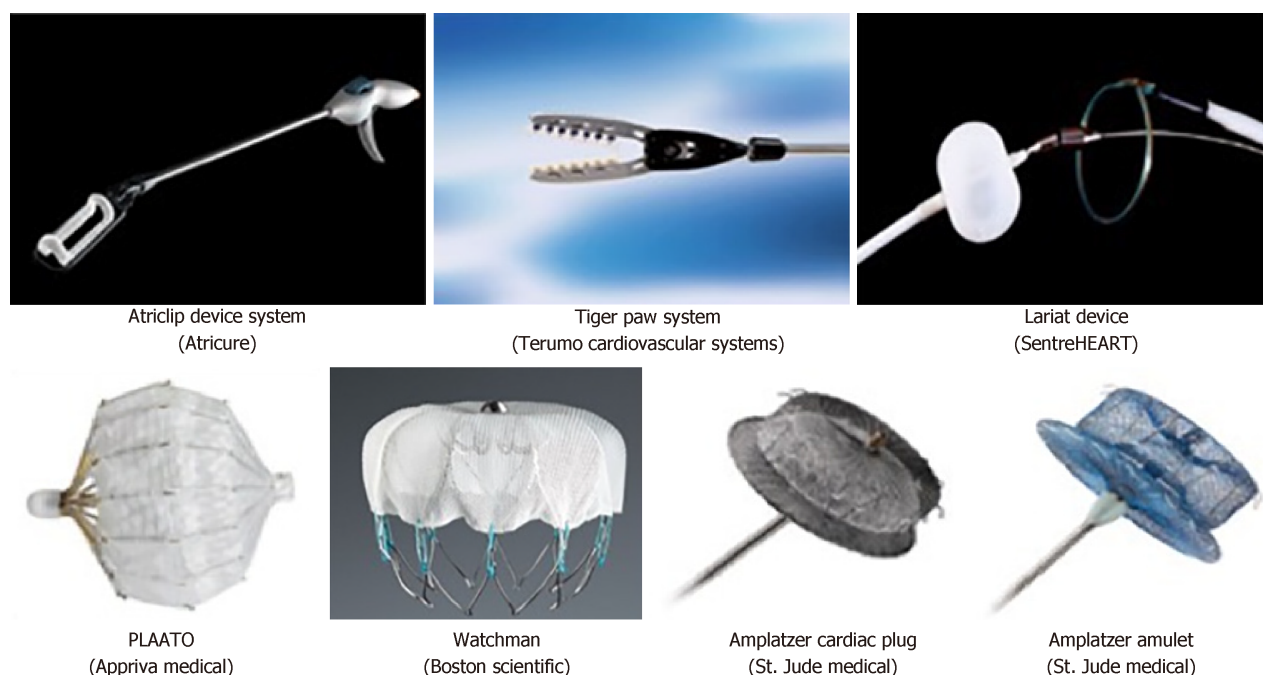


Figure 1 Surgical and percutaneous devices that are used for left atrial appendage occlusion.

nitinol frame structure with fixation barbs and a permeable polyester fabric that covers the atrial facing surface of the device (Table 1)^[47]. Multiple trials were done to evaluate the safety, efficacy and outcomes of watchmen device.

Pilot study was a non-randomized trial that included 75 patients and was done to assess the feasibility and safety of watchman device^[47]. They enrolled adult patients who: had non-valvular AF for 2 years, were eligible for warfarin therapy, and had CHADS₂ of at least 1. Although this was the first human trial to evaluate the efficacy and safety of Watchman device, the success rate of LAAO was very high and complications were relatively low. 88% of patients had successful device implantation and 93% of them had complete LAAO. Reported complications included; device embolization in 2 patients, device-related thrombus formation in 4 patients, and transient ischemic attack in 2 patients. There was no reported major strokes or procedure-related mortality.

PROTECT AF study (WATCHMAN LAA System for Embolic Protection in Patients with Atrial Fibrillation) was the first randomized trial to compare the efficacy and safety of LAAO using Watchman device with chronic warfarin therapy in patients with non-valvular AF and had CHADS₂ of 1 or more^[48]. Exclusion criteria included contraindications to warfarin, chronic warfarin use, LAA thrombus, a patent foramen ovale with atrial septal aneurysm and right-to-left shunt, mobile aortic atheroma, and symptomatic carotid artery disease. This trial enrolled 707 patients from 59 centers worldwide and assigned them randomly to LAAO with Watchman device ($n = 463$) or warfarin therapy ($n = 244$) with INR goal of 2 to 3. Watchman group was treated with warfarin for 45 d after device deployment to allow proper endothelialization. Warfarin was discontinued if TEE showed complete closure or significantly decreased flow around the device. Afterward, patients were given aspirin and clopidogrel for 6 mo followed by lifelong aspirin. At 1065 patient-years (PY) of follow-up (mean follow up 18 mo), Watchman device was non-inferior to warfarin for primary efficacy endpoint of stroke (either ischemic or hemorrhagic), cardiovascular death, or systemic thromboembolism. The Event rates of primary efficacy endpoint were 3% and 4.9% for Watchman and warfarin groups, respectively. Since then, two studies were published with two different follow up period^[49,50]. At 2.3 ± 1.1 years (2621 PY), Watchman device continued to be non-inferior to warfarin therapy with 3% and 4.3% event rates of primary efficacy endpoint for Watchman and warfarin groups, respectively^[49]. The second trial with 3.8 ± 1.7 years of follow up (2621 PY) showed event rate of 2.3% in the watchman group and 3.8% in the warfarin group ($P = 0.0348$), leading to 40% risk reduction in primary efficacy endpoint with Watchman device^[50].

PREVAIL study (Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation *vs* Long Term Warfarin Therapy) was another randomized trial that assessed the safety and efficacy of Watchman device in patients non-valvular AF^[51]. Investigators included a higher risk patients than PROTECT AF (CHADS₂ score

of 1 plus any of the following higher-risk characteristics: female age ≥ 75 years, baseline ejection fraction $\geq 30\%$ but $< 35\%$, age 65 to 74 years and either diabetes or coronary disease, and age ≥ 65 years with congestive heart failure). Patients were assigned randomly to receive LAAO using Watchman ($n = 269$) or warfarin therapy ($n = 138$) in 2:1 ratio. Warfarin and antiplatelet therapy post device implantation was in a similar fashion to PROTECT AF trial. Although non-inferiority criteria was not achieved for overall efficacy endpoint (stroke, systemic embolization or cardiovascular death), the rate of second efficacy endpoint (stroke or systemic embolization) was 2.5% in the Watchman group and 2% in the warfarin group at 18 mo follow-up, achieving criteria for non-inferiority. Compared to PROTECT AF study, procedural success increased from 90.9% to 95.1% ($P = 0.04$), while all 7-d procedure-related complications (composite of cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications) decreased from 8.7% to 4.2% in PREVAIL ($P = 0.004$).

PROTECT AF and PREVAIL results were pooled for patient level meta-analysis and with combined follow-up of 5 years (4343 PY)^[52]. The primary efficacy endpoint (stroke, systemic embolization or cardiovascular death) was similar between LAAO and warfarin groups (2.8 *vs* 3.4 events/100 PY; $P = 0.27$). In subgroup analysis of the same meta-analysis, the rate of all stroke or systemic embolism was similar between both groups (1.7 *vs* 1.8 events/100 PY; $P = 0.87$). However, there was statistically significant decrease in the rates of hemorrhagic stroke (0.17% *vs* 0.87%, $P = 0.002$), disabling / fatal stroke (0.37% *vs* 0.94%, $P = 0.027$), cardiovascular/unexplained death (1.3% *vs* 2.2%, $P = 0.027$), all-cause death (3.6% *vs* 4.9%, $P = 0.035$), and post-procedure bleeding (1.7% *vs* 3.6%, $P = 0.0003$) in LAAO arm when compared with warfarin arm. This meta-analysis underscores the mortality reduction and stroke prevention, particularly hemorrhagic stroke, associated with LAAO using Watchman device.

Continued Access to PROTECT AF (CAP)^[53] and Continued Access to PREVAIL (CAP2)^[54] Registries were designed to treat patients with similar baseline characteristics and according to same protocols after PROTECT AF and PREVAIL trials enrollment had been completed. Procedural performance and associated medications were identical in each registry. However, registries did not mandate 1-year neurological assessment. A Meta-analysis of 2406 patients from the PROTECT AF and PREVAIL trials and their respective registries (CAP and CAP2) with 5,931 PY of follow-up (mean of 2.69 years) reported: similar rate of all-cause stroke between both arms (1.75 *vs* 1.87 events/100 PY, $P = 0.94$); higher rate of ischemic stroke in Watchman group (1.6 *vs* 0.9 events/100 PY, $P = 0.05$); and lower rates of hemorrhagic stroke, cardiovascular death (1.1 *vs* 2.3 events/100 PY, $P = 0.006$), and non-procedural bleeding (6.0% *vs* 11.3%, $P = 0.02$) in Watchman group^[54]. Although the rate of all-cause stroke was similar between both arms, the reduction in hemorrhagic stroke with Watchman device was balanced by a relative increase in ischemic stroke rates. This may relate to possible technical failures of the device: failure to completely obliterate LAA flow, anatomical remodeling of the LAA ostium over time resulting in more leaks, or the development of thrombus on the device^[54]. Compared with the pooled results of PROTECT AF and PREVAIL trials mentioned above, the difference in ischemic stroke rate was not observed between LAAO and warfarin groups at longer and combined follow-up of 5 years^[52].

EWOLUTION study (Registry on Watchman Outcomes in Real-Life Utilization) is a multicenter, prospective, non-randomized cohort that aimed to collect peri-procedural and long-term outcome data for patients implanted with Watchman device for LAAO^[55]. This world-wide registry enrolled 1025 patients at 47 centers from the United States, Europe, Middle east and Russia who are more than 18-year-old and require LAAO based on ESC guidelines^[55-57]. The device was successfully implanted in 98.5% and complete LAAO was achieved in 99.3% noted on TEE^[56,57]. The rates of procedure-related serious adverse events (defined as; perforation, tamponade, embolism, neurological events, thrombosis, and bleeding) were 2.8% at 7 d and 3.6% at 30 d with bleeding being the most common adverse event^[57]. This is lower than the 7-d procedure-related serious adverse events observed in PROTECT AF (8.7%) and PREVAIL (4.2%) trials. At 1 year follow up; mortality was 9.8%, device-related thrombus was seen in 3.7% of patients, and 1.1% of patients suffered from ischemic stroke, leading to 84% risk reduction of stroke. There was no hemorrhagic stroke observed during follow-up^[56].

The ASAP study (ASA Plavix Feasibility Study with Watchman LAA Closure Technology Trial to assess) was a European multicenter, prospective, non-randomized study of Watchman device in patients with non-valvular AF who had CHADS₂ score ≥ 1 and were not eligible for OACs^[58]. After the device implantation, participants were given thienopyridine antiplatelet agent (clopidogrel or ticlopidine) for 6 mo and aspirin indefinitely. Out of 150 patients, 142 (94.7%) had successful implantation and 13 (8.7%) developed device-related adverse event. During mean follow up of $14.4 \pm$

8.6 mo, 4 patients developed strokes (2.3% per year) and 3 of them were ischemic (1.7% per year). There was 77% risk reduction in stroke compared to expected stroke risk based on CHADS₂ score (7.3% per year). Till this moment, there is no published randomized data on the safety and efficacy of LAAO in patients with contraindications to anticoagulation. The ASAP TOO study (The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation) is ongoing multicenter prospective randomized trial plan is to enroll up to 888 patients with non-valvular AF who are not candidate for OAC and have CHA₂DS₂-VAS_c ≥ 2 ^[59]. The study will randomize patients to Watchman *vs* control. Control patients will be prescribed single antiplatelet therapy, or no therapy based on physician discretion.

Amplatzer cardiac plug and amulet

Amplatzer cardiac plug (ACP) (AGA, St. Jude Medical, Minneapolis, MN, United States) is another LAAO device that consists of a lobe and disc made of nitinol mesh and polyester patch, connected by central waist. Amulet® is a second-generation device of the Amplatzer with several incremental design improvements. It is larger in size and has higher number of stabilizing wires, which allows successful closure of more LAA anatomies (Table 1). Comparative studies have shown similar results with ACP and Amulet AMPLATZER devices in terms of safety, implantation success and appropriate LAAO^[60,61]. Multiple retrospective and prospective studies for ACP and Amulet reported successful device implantation in 95% to 100% patients, with major periprocedural adverse events (death, stroke/TIA, device embolization, MI/perforation/tamponade/effusion, and major bleeding) ranging from 3.2% to 8%^[62-67]. An FDA approval trial is currently ongoing, with the aim of collecting randomized controlled data from the Amulet and Watchman devices from 1,600 patients worldwide. PRAGUE 17 is another ongoing prospective, multicenter, randomized trial That plan to enroll 396 patients with non-valvular AF and assign them to LAAO using Amulet or Watchman *vs* non-vitamin K oral anticoagulants (NOACs). The aim at 24 mo of follow-up is to determine whether LAAO is non-inferior to NOACs in terms of primary efficacy endpoint and peri-procedural complications^[68].

COMPARISON OF MULTIPLE LAA OCCLUSION DEVICES

A meta-analysis on 2779 patients who had percutaneous LAAO with multiple devices [PLAATO (18%), Watchman (57%), and ACP (24%)] showed successful implantation in 2611 patients (94%). The adjusted pooled incidence of stroke was 1.2 per 100 PY (95%CI: 0.9-1.6/100) and the combined efficacy outcome (stroke, systemic embolism, or cardiovascular death) rate was 2.7 per 100 PY (95%CI: 1.9-3.4/100). For combined adverse events, the random effect pooled rate was 6.5% (95%CI: 4.9%-8.2%)^[69]. One single-center retrospective study in Italy compared the use ACP *vs* Watchman in 156 patients (ACP in 99 and watchman in 66 patients) and demonstrated procedural success in 99.4%. During follow-up, only 1 patient suffered from transient ischemic attack and 2 from cardiac death. Furthermore, the data showed excellent safety and efficacy with similar clinical outcomes in both devices^[70]. Another multicenter retrospective registry for LAAO using various devices showed an overall success of 92.5%. The combined adverse event rate was 3.5%, leading to annual relative risk reduction for ischemic stroke, thromboembolic events, and major bleeding of 90.1%, 87.2%, and 92.9%, respectively^[71]. RELEXAO (Registry on Real-Life Experience With LAA Occlusion) registry is a French retrospective cohort of patients with AF who were treated with LAAO^[72]. In the study cohort from RELEXAO, Fauchier *et al*^[72] reported no differences in death, ischemic stroke, major bleeding, or device related thrombus between Watchman and Amplatzer devices. Those studies underscore the high success rate in placing various LAAO devices, and their safety and efficacy in preventing strokes and adverse events.

ANTITHROMBOTIC THERAPY AFTER DEVICE IMPLANTATION

Optimal anticoagulation/antiplatelet protocol post LAAO is highly patient-specific and recommended for a limited period post LAAO to prevent device associated thrombus^[72]. Different anticoagulation strategies have been described in multiple studies including: warfarin, NOACs, DAPT, single antiplatelet (SAPT), or no therapy at all (Table 2). The anticoagulation protocol described in PROTECT AF and PREVAIL trials consists of warfarin for 45 d followed by aspirin and clopidogrel for 6 mo, then aspirin indefinitely^[48-51]. In EWOLUTION registry for example, anticoagulation

regimens post LAAO were variable and included: warfarin in 16%, NOAC in 11%, DAPT in 60%, single antiplatelet (SAPT) in 7%, and no therapy in 6%^[56]. A study on post LAAO anticoagulation in patients from EWOLUTION registry demonstrated that NOAC and DAPT were similar to warfarin in terms of device thrombus, stroke or bleeding risks^[73]. Compared with EWOLUTION registry, antithrombotic regimen post LAAO in RELEXAO registry was different and included: OACs 28.8%, SAPT in 36.2%, DAPT in 23.2%, OACs plus DAPT in 4.3%, and no therapy in 7.5%. In ASAP study, patients were given DAPT for 6 mo followed by aspirin indefinitely as they were ineligible for OACs^[58]. A Questionnaire sent by European Heart Rhythm Association Electrophysiology to the participating centers to assess the indications and anticoagulation regimen post LAAO, showed that DAPT for 6 wk to 6 mo followed by aspirin monotherapy as the most common regimen^[74]. Interestingly, 41% of centers would prescribe no therapy and less than 10% followed PROTECT AF and PREVAIL protocol. The European Heart Rhythm Association/European Association of Percutaneous Cardiovascular Interventions (EHRA/EAPCI) expert consensus statement recommends treatment with DAPT for 1 to 6 mo followed by aspirin indefinitely in patients with high bleeding risk^[75].

COMPLICATIONS

Complications related to LAAO are either acute or delayed and most of them can be detect by peri-procedural imaging. **Table 3** summarizes LAAO related complications, their incidence and treatment options.

CONCLUSION

LAAO is a reasonable alternative approach that is used for preventing embolic events in patients with AF who are deemed not eligible for anticoagulation. While AHA/ACC guidelines have no recommendations for LAAO, the ESC guidelines have class IIb (B) recommendation for LAAO in patients with AF and contra-indications for long-term anticoagulation. Similarly, Australian guidelines recommend considering LAAO in patients with non-valvular AF at moderate to high risk of stroke and with contraindications to OAC. Watchman is the only FDA approved device for LAAO and indicated to reduce the risk of thromboembolism from the LAA in patients with non-valvular AF who: are at increased risk for stroke and systemic embolism based on CHADS₂ or CHA₂DS₂-VASc scores; are deemed by their physicians to be suitable for warfarin; and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin. Amplatzer is another successful LAAO device that has CE mark and is waiting for FDA approval. Optimal antithrombotic regimen post LAAO is highly patient-specific and recommended to prevent device associated thrombus. Due to wide variety of shapes, sizes, indications, and implantation techniques in different LAAO devices, there is a need for further research to identify the best type of LAAO device that suites each patient profile. We believe that the development of established clinical guidelines and expert consensus supporting the use of LAAO in the foreseeable future will ultimately improve patient outcomes.

Table 2 Antithrombotic therapy regimens following left atrial appendage occlusion

Study/reference	Regimen
PROTECT AF trial ^[48-50]	Warfarin for 45 d followed by aspirin and clopidogrel for 6 mo, then aspirin indefinitely
PREVAIL trial ^[51]	Warfarin for 45 d followed by aspirin and clopidogrel for 6 mo, then aspirin indefinitely
EWOLUTION registry ^[56]	warfarin in 16%, NOAC in 11%, DAPT in 60%, SAPT in 7%, and no therapy in 6%
RELEXAO registry ^[72]	OACs in 28.8%, SAPT in 36.2%, DAPT in 23.2%, OACs plus DAPT in 4.3%, and no therapy in 7.5%.
ASAP trial ^[58]	DAPT for 6 mo followed by aspirin indefinitely
EHRA/EAPCI expert consensus ^[75]	DAPT for 1 to 6 mo followed by aspirin indefinitely

OAC: Oral anticoagulant; NOAC: Non-vitamin K oral anticoagulant; SAPT: Single antiplatelet; DAPT: Dual antiplatelet; EHRA/EAPCI: European Heart Rhythm Association/European Association of Percutaneous Cardiovascular Interventions.

Table 3 Complications related to left atrial appendage occlusion

Complication	Incidence	Treatment
Pericardial effusion/tamponade that require intervention ^[47,48,50,51,53,56-58,63,76]	1.2% to 5%	Pericardiocentesis
Device embolization ^[47,48,50,51,56-58,63,76]	0% to 3.7%	Transcatheter removal or surgery
Device related thrombus ^[47,56-58,63]	Up to 14%	Anticoagulation
Persistent ASD ^[77]	11% at 6 mo and 7% at 12 mo	Usually small no need for treatment
Cardiac perforation ^[51]	0% to 0.4%	surgery
Procedure related stroke ^[47,48,51,53,56-58,76]	0% to 1.1%	Stroke management

ASD: Atrial septal defect.

REFERENCES

- Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; **285**: 2370-2375 [PMID: 11343485 DOI: 10.1001/jama.285.18.2370]
- Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006; **114**: 119-125 [PMID: 16818816 DOI: 10.1161/CIRCULATIONAHA.105.595140]
- Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014; **129**: 837-847 [PMID: 24345399 DOI: 10.1161/CIRCULATIONAHA.113.005119]
- Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol* 2013; **112**: 1142-1147 [PMID: 23831166 DOI: 10.1016/j.amjcard.2013.05.063]
- Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017; **135**: e146-e603 [PMID: 28122885 DOI: 10.1161/CIR.0000000000000485]
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; **22**: 983-988 [PMID: 1866765 DOI: 10.1161/01.STR.22.8.983]
- Frost L, Engholm G, Johnsen S, Møller H, Henneberg EW, Husted S. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. *Arch Intern Med* 2001; **161**: 272-276 [PMID: 11176743 DOI: 10.1001/archinte.161.2.272]
- Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003; **290**: 1049-1056 [PMID: 12941677 DOI: 10.1001/jama.290.8.1049]
- Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; **131**: 492-501 [PMID: 10507957 DOI: 10.7326/0003-4819-131-7-199910050-00003]
- Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; **154**: 1449-1457 [PMID: 8018000 DOI: 10.1001/archinte.1994.00420130036007]

- 11 **Al-Saady NM**, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. *Heart* 1999; **82**: 547-554 [PMID: [10525506](#)]
- 12 **Wunderlich NC**, Beigel R, Swaans MJ, Ho SY, Siegel RJ. Percutaneous interventions for left atrial appendage exclusion: options, assessment, and imaging using 2D and 3D echocardiography. *JACC Cardiovasc Imaging* 2015; **8**: 472-488 [PMID: [25882576](#) DOI: [10.1016/j.jcmg.2015.02.002](#)]
- 13 **Shirani J**, Alaeddini J. Structural remodeling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: Implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. *Cardiovasc Pathol* 2000; **9**: 95-101 [PMID: [10867359](#) DOI: [10.1016/S1054-8807\(00\)00030-2](#)]
- 14 **Manning WJ**, Silverman DI, Keighley CS, Oettgen P, Douglas PS. Transesophageal echocardiographically facilitated early cardioversion from atrial fibrillation using short-term anticoagulation: final results of a prospective 4.5-year study. *J Am Coll Cardiol* 1995; **25**: 1354-1361 [PMID: [7722133](#) DOI: [10.1016/0735-1097\(94\)00560-D](#)]
- 15 **Leung DY**, Black IW, Cranney GB, Hopkins AP, Walsh WF. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. *J Am Coll Cardiol* 1994; **24**: 755-762 [PMID: [8077549](#) DOI: [10.1016/0735-1097\(94\)90025-6](#)]
- 16 **January CT**, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; **64**: e1-76 [PMID: [24685669](#) DOI: [10.1016/j.jacc.2014.03.022](#)]
- 17 **Klein AL**, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF; Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001; **344**: 1411-1420 [PMID: [11346805](#) DOI: [10.1056/NEJM200105103441901](#)]
- 18 **Blackshear JL**, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996; **61**: 755-759 [PMID: [8572814](#) DOI: [10.1016/0003-4975\(95\)00887-X](#)]
- 19 **Predictors of thromboembolism in atrial fibrillation: II.** Echocardiographic features of patients at risk. The Stroke Prevention in Atrial Fibrillation Investigators. *Ann Intern Med* 1992; **116**: 6-12 [PMID: [1727097](#) DOI: [10.1016/0736-4679\(92\)90169-T](#)]
- 20 **Manning WJ**, Weintraub RM, Waksmonski CA, Haering JM, Rooney PS, Maslow AD, Johnson RG, Douglas PS. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. *Ann Intern Med* 1995; **123**: 817-822 [PMID: [7486462](#) DOI: [10.7326/0003-4819-123-11-199512010-00001](#)]
- 21 **Müller S**, Feuchtnr G, Bonatti J, Müller L, Laufer G, Hiemetzberger R, Pachinger O, Barbieri V, Bartel T. Value of transesophageal 3D echocardiography as an adjunct to conventional 2D imaging in preoperative evaluation of cardiac masses. *Echocardiography* 2008; **25**: 624-631 [PMID: [18652008](#) DOI: [10.1111/j.1540-8175.2008.00664.x](#)]
- 22 **Asch FM**, Bieganski SP, Panza JA, Weissman NJ. Real-time 3-dimensional echocardiography evaluation of intracardiac masses. *Echocardiography* 2006; **23**: 218-224 [PMID: [16524392](#) DOI: [10.1111/j.1540-8175.2006.00196.x](#)]
- 23 **Perk G**, Lang RM, Garcia-Fernandez MA, Lodato J, Sugeng L, Lopez J, Knight BP, Messika-Zeitoun D, Shah S, Slater J, Brochet E, Varkey M, Hijazi Z, Marino N, Ruiz C, Kronzon I. Use of real time three-dimensional transesophageal echocardiography in intracardiac catheter based interventions. *J Am Soc Echocardiogr* 2009; **22**: 865-882 [PMID: [19647156](#) DOI: [10.1016/j.echo.2009.04.031](#)]
- 24 **Berti S**, Paradossi U, Meucci F, Trianni G, Tzikas A, Rezzaghi M, Stolkova M, Palmieri C, Mori F, Santoro G. Periprocedural intracardiac echocardiography for left atrial appendage closure: a dual-center experience. *JACC Cardiovasc Interv* 2014; **7**: 1036-1044 [PMID: [25234677](#) DOI: [10.1016/j.jcin.2014.04.014](#)]
- 25 **Martinez MW**, Kirsch J, Williamson EE, Syed IS, Feng D, Ommen S, Packer DL, Brady PA. Utility of nongated multidetector computed tomography for detection of left atrial thrombus in patients undergoing catheter ablation of atrial fibrillation. *JACC Cardiovasc Imaging* 2009; **2**: 69-76 [PMID: [19356536](#) DOI: [10.1016/j.jcmg.2008.09.011](#)]
- 26 **Sakamoto I**, Hayashi K, Matsunaga N, Ogawa Y, Matsuoka Y, Okimoto T, Takagi M, Yano K, Toda G, Miyahara Y. Coronary angiographic finding of thrombus in the left atrial appendage. *Acta Radiol* 1996; **37**: 749-753 [PMID: [8915287](#) DOI: [10.1177/02841851960373264](#)]
- 27 **Kirchhof P**, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; **37**: 2893-2962 [PMID: [27567408](#) DOI: [10.1093/eurheartj/ehw210](#)]
- 28 **NHFA CSANZ Atrial Fibrillation Guideline Working Group**. Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C, Freedman B, Ferguson C, Hall T, Haqqani H, Hendriks J, Hespe C, Hung J, Kalman JM, Sanders P, Worthington J, Yan TD, Zwar N. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. *Heart Lung Circ* 2018; **27**: 1209-1266 [PMID: [30077228](#) DOI: [10.1016/j.hlc.2018.06.1043](#)]
- 29 **Holmes DR**, Lakkireddy DR, Whitlock RP, Waksman R, Mack MJ. Left atrial appendage occlusion: opportunities and challenges. *J Am Coll Cardiol* 2014; **63**: 291-298 [PMID: [24076495](#) DOI: [10.1016/j.jacc.2013.08.1631](#)]
- 30 **Kanderian AS**, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. *J Am Coll Cardiol* 2008; **52**: 924-929 [PMID: [18772063](#) DOI: [10.1016/j.jacc.2008.03.067](#)]
- 31 **Friedman DJ**, Piccini JP, Wang T, Zheng J, Malaisrie SC, Holmes DR, Suri RM, Mack MJ, Badhwar V, Jacobs JP, Gaca JG, Chow SC, Peterson ED, Brennan JM. Association Between Left Atrial Appendage Occlusion and Readmission for Thromboembolism Among Patients With Atrial Fibrillation Undergoing Concomitant Cardiac Surgery. *JAMA* 2018; **319**: 365-374 [PMID: [29362794](#) DOI: [10.1001/jama.2017.20125](#)]
- 32 **Salzberg SP**, Plass A, Emmert MY, Desbiolles L, Alkadhi H, Grünenfelder J, Genoni M. Left atrial

- appendage clip occlusion: early clinical results. *J Thorac Cardiovasc Surg* 2010; **139**: 1269-1274 [PMID: 19880144 DOI: 10.1016/j.jtcvs.2009.06.033]
- 33 **Ailawadi G**, Gerdisch MW, Harvey RL, Hooker RL, Damiano RJ, Salamon T, Mack MJ. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. *J Thorac Cardiovasc Surg* 2011; **142**: 1002-1009, 1009.e1 [PMID: 21906756 DOI: 10.1016/j.jtcvs.2011.07.052]
- 34 **Slater AD**, Tatroles AJ, Coffey A, Pappas PS, Bresticker M, Greason K, Slaughter MS. Prospective clinical study of a novel left atrial appendage occlusion device. *Ann Thorac Surg* 2012; **93**: 2035-8; discussion 2038-40 [PMID: 22632497 DOI: 10.1016/j.athoracsur.2011.12.077]
- 35 **Ventosa-Fernandez G**, Quintana E, Castellá M, Pereda D. Exclusion of the left atrial appendage with the TigerPaw II system: a word of caution. *Interact Cardiovasc Thorac Surg* 2015; **21**: 803-804 [PMID: 26395944 DOI: 10.1093/icvts/ivv256]
- 36 **Bartus K**, Han FT, Bednarek J, Myc J, Kapelak B, Sadowski J, Lelakowski J, Bartus S, Yakubov SJ, Lee RJ. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *J Am Coll Cardiol* 2013; **62**: 108-118 [PMID: 23062528 DOI: 10.1016/j.jacc.2012.06.046]
- 37 **Massumi A**, Chelu MG, Nazeri A, May SA, Afshar-Kharaghan H, Saeed M, Razavi M, Rasekh A. Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. *Am J Cardiol* 2013; **111**: 869-873 [PMID: 23312129 DOI: 10.1016/j.amjcard.2012.11.061]
- 38 **Dar T**, Afzal MR, Yarlagadda B, Kutty S, Shang Q, Gunda S, Samanta A, Thummalur J, Arukala KS, Kanmanthareddy A, Reddy M, Atkins D, Bommana S, Dawn B, Lakkireddy D. Mechanical function of the left atrium is improved with epicardial ligation of the left atrial appendage: Insights from the LAFIT-LARIAT Registry. *Heart Rhythm* 2018; **15**: 955-959 [PMID: 29477973 DOI: 10.1016/j.hrthm.2018.02.022]
- 39 **Giedrimas E**, Lin AC, Knight BP. Left atrial thrombus after appendage closure using LARIAT. *Circ Arrhythm Electrophysiol* 2013; **6**: e52-e53 [PMID: 23962862 DOI: 10.1161/CIRCEP.113.000532]
- 40 **Briceno DF**, Fernando RR, Laing ST. Left atrial appendage thrombus post LARIAT closure device. *Heart Rhythm* 2014; **11**: 1600-1601 [PMID: 24184785 DOI: 10.1016/j.hrthm.2013.10.053]
- 41 **Truesdell AG**, Patel CP, Maini BS. Late-occurring left atrial appendage thrombus after ligation using LARIAT. *J Interv Card Electrophysiol* 2014; **41**: 101 [PMID: 24928486 DOI: 10.1007/s10840-014-9916-9]
- 42 **Pillai AM**, Kanmanthareddy A, Earnest M, Reddy M, Ferrell R, Nath J, Pillariseti J, Vallakati A, Lakkireddy D. Initial experience with post Lariat left atrial appendage leak closure with Amplatzer septal occluder device and repeat Lariat application. *Heart Rhythm* 2014; **11**: 1877-1883 [PMID: 24993460 DOI: 10.1016/j.hrthm.2014.06.035]
- 43 **Sievert H**, Lesh MD, Trepels T, Omran H, Bartorelli A, Della Bella P, Nakai T, Reisman M, DiMario C, Block P, Kramer P, Fleschenberg D, Krumdorf U, Scherer D. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. *Circulation* 2002; **105**: 1887-1889 [PMID: 11997272 DOI: 10.1161/01.CIR.0000015698.54752.6D]
- 44 **Ostermayer SH**, Reisman M, Kramer PH, Matthews RV, Gray WA, Block PC, Omran H, Bartorelli AL, Della Bella P, Di Mario C, Pappone C, Casale PN, Moses JW, Poppas A, Williams DO, Meier B, Skanes A, Teirstein PS, Lesh MD, Nakai T, Bayard Y, Billinger K, Trepels T, Krumdorf U, Sievert H. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. *J Am Coll Cardiol* 2005; **46**: 9-14 [PMID: 15992628 DOI: 10.1016/j.jacc.2005.03.042]
- 45 **Bayard YL**, Omran H, Neuzil P, Thuesen L, Pichler M, Rowland E, Ramondo A, Ruzyllo W, Budts W, Montalescot G, Brugada P, Serruys PW, Vahanian A, Piéchaud JF, Bartorelli A, Marco J, Probst P, Kuck KH, Ostermayer SH, Büschek F, Fischer E, Leetz M, Sievert H. PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. *EuroIntervention* 2010; **6**: 220-226 [PMID: 20562072]
- 46 **Park JW**, Leithäuser B, Gerk U, Vrsansky M, Jung F. Percutaneous left atrial appendage transcatheter occlusion (PLAATO) for stroke prevention in atrial fibrillation: 2-year outcomes. *J Invasive Cardiol* 2009; **21**: 446-450 [PMID: 19726815]
- 47 **Sick PB**, Schuler G, Hauptmann KE, Grube E, Yakubov S, Turi ZG, Mishkel G, Almany S, Holmes DR. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 2007; **49**: 1490-1495 [PMID: 17397680 DOI: 10.1016/j.jacc.2007.02.035]
- 48 **Holmes DR**, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009; **374**: 534-542 [PMID: 19683639 DOI: 10.1016/S0140-6736(09)61343-X]
- 49 **Reddy VY**, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, Halperin JL, Holmes D; PROTECT AF Investigators. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation* 2013; **127**: 720-729 [PMID: 23325525 DOI: 10.1161/CIRCULATIONAHA.112.114389]
- 50 **Reddy VY**, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, Huber K, Whisenant B, Kar S, Swarup V, Gordon N, Holmes D; PROTECT AF Steering Committee and Investigators. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA* 2014; **312**: 1988-1998 [PMID: 25399274 DOI: 10.1001/jama.2014.15192]
- 51 **Holmes DR**, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014; **64**: 1-12 [PMID: 24998121 DOI: 10.1016/j.jacc.2014.04.029]
- 52 **Reddy VY**, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, Horton RP, Buchbinder M, Neuzil P, Gordon NT, Holmes DR; PREVAIL and PROTECT AF Investigators. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. *J Am Coll Cardiol* 2017; **70**: 2964-2975 [PMID: 29103847 DOI: 10.1016/j.jacc.2017.10.021]
- 53 **Reddy VY**, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure:

- results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation* 2011; **123**: 417-424 [PMID: 21242484 DOI: 10.1161/CIRCULATIONAHA.110.976449]
- 54 **Holmes DR**, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, Valderrabano M, Reddy VY. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: A Patient-Level Meta-Analysis. *J Am Coll Cardiol* 2015; **65**: 2614-2623 [PMID: 26088300 DOI: 10.1016/j.jacc.2015.04.025]
 - 55 **Boersma LV**, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, Stein KM, Bergmann MW. EWOLUTION: Design of a registry to evaluate real-world clinical outcomes in patients with AF and high stroke risk-treated with the WATCHMAN left atrial appendage closure technology. *Catheter Cardiovasc Interv* 2016; **88**: 460-465 [PMID: 26719158 DOI: 10.1002/ccd.26358]
 - 56 **Boersma LV**, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, Gori T, Meincke F, Protopopov AV, Betts T, Foley D, Sievert H, Mazzone P, De Potter T, Vireca E, Stein K, Bergmann MW; EWOLUTION Investigators. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm* 2017; **14**: 1302-1308 [PMID: 28577840 DOI: 10.1016/j.hrthm.2017.05.038]
 - 57 **Boersma LV**, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, Pokushalov E, Kische S, Schmitz T, Stein KM, Bergmann MW; EWOLUTION investigators. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J* 2016; **37**: 2465-2474 [PMID: 26822918 DOI: 10.1093/eurheartj/ehv730]
 - 58 **Reddy VY**, Möbius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, Sick P, Sievert H. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013; **61**: 2551-2556 [PMID: 23583249 DOI: 10.1016/j.jacc.2013.03.035]
 - 59 **Holmes DR**, Reddy VY, Buchbinder M, Stein K, Elletson M, Bergmann MW, Schmidt B, Saw J. The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) trial. *Am Heart J* 2017; **189**: 68-74 [PMID: 28625383 DOI: 10.1016/j.ahj.2017.03.007]
 - 60 **Glockler S**, Shakir S, Doblies J, Khattab AA, Praz F, Guerios É, Koermendy D, Stortecky S, Pilgrim T, Buellesfeld L, Wenaweser P, Windecker S, Moschovitis A, Landmesser U, Nietlispach F, Meier B. Early results of first versus second generation Amplatzer occluders for left atrial appendage closure in patients with atrial fibrillation. *Clin Res Cardiol* 2015; **104**: 656-665 [PMID: 25736061 DOI: 10.1007/s00392-015-0828-1]
 - 61 **Abualsaud A**, Freixa X, Tzikas A, Chan J, Garceau P, Basmadjian A, Ibrahim R. Side-by-Side Comparison of LAA Occlusion Performance With the Amplatzer Cardiac Plug and Amplatzer Amulet. *J Invasive Cardiol* 2016; **28**: 34-38 [PMID: 26716593]
 - 62 **Landmesser U**, Schmidt B, Nielsen-Kudsk JE, Lam SCC, Park JW, Tarantini G, Cruz-Gonzalez I, Geist V, Della Bella P, Colombo A, Zeus T, Omran H, Piorkowski C, Lund J, Tondo C, Hildick-Smith D. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. *EuroIntervention* 2017; **13**: 867-876 [PMID: 28649053 DOI: 10.4244/EIJ-D-17-00493]
 - 63 **Tzikas A**, Gafoor S, Meerkin D, Freixa X, Cruz-Gonzalez I, Lewalter T, Saw J, Berti S, Nielsen-Kudsk JE, Ibrahim R, Lakkireddy D, Paul V, Arzamendi D, Nietlispach F, Worthley SG, Hildick-Smith D, Thambo JB, Tondo C, Aminian A, Kalarus Z, Schmidt B, Sondergaard L, Kefer J, Meier B, Park JW, Sievert H, Omran H. Left atrial appendage occlusion with the AMPLATZER Amulet device: an expert consensus step-by-step approach. *EuroIntervention* 2016; **11**: 1512-1521 [PMID: 27107315 DOI: 10.4244/EIJV11I113A292]
 - 64 **Korsholm K**, Nielsen KM, Jensen JM, Jensen HK, Andersen G, Nielsen-Kudsk JE. Transcatheter left atrial appendage occlusion in patients with atrial fibrillation and a high bleeding risk using aspirin alone for post-implant antithrombotic therapy. *EuroIntervention* 2017; **12**: 2075-2082 [PMID: 27973336 DOI: 10.4244/EIJ-D-16-00726]
 - 65 **Berti S**, Pastormerlo LE, Rezzaghi M, Trianni G, Paradossi U, Cerone E, Ravani M, De Caterina AR, Rizza A, Palmieri C. Left atrial appendage occlusion in high-risk patients with non-valvular atrial fibrillation. *Heart* 2016; **102**: 1969-1973 [PMID: 27492943 DOI: 10.1136/heartjnl-2015-309150]
 - 66 **Kleinecke C**, Park JW, Gödde M, Zintl K, Schnupp S, Brachmann J. Twelve-month follow-up of left atrial appendage occlusion with Amplatzer Amulet. *Cardiol J* 2017; **24**: 131-138 [PMID: 28198520 DOI: 10.5603/CJ.a2017.0017]
 - 67 **Urena M**, Rodés-Cabau J, Freixa X, Saw J, Webb JG, Freeman M, Horlick E, Osten M, Chan A, Marquis JF, Champagne J, Ibrahim R. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. *J Am Coll Cardiol* 2013; **62**: 96-102 [PMID: 23665098 DOI: 10.1016/j.jacc.2013.02.089]
 - 68 **Osmancik P**, Tousek P, Herman D, Neuzil P, Hala P, Stasek J, Haman L, Kala P, Poloczek M, Branny M, Chovancik J, Cervinka P, Holy J, Vancura V, Rokyta R, Taborsky M, Kovarnik T, Zemanek D, Peichtl P, Haskova S, Jarkovsky J, Widimsky P; PRAGUE-17 Investigators. Interventional left atrial appendage closure vs novel anticoagulation agents in patients with atrial fibrillation indicated for long-term anticoagulation (PRAGUE-17 study). *Am Heart J* 2017; **183**: 108-114 [PMID: 27979034 DOI: 10.1016/j.ahj.2016.10.003]
 - 69 **Xu H**, Xie X, Wang B, Ma S, Wang F. Efficacy and Safety of Percutaneous Left Atrial Appendage Occlusion for Stroke Prevention in Nonvalvular Atrial Fibrillation: A Meta-analysis of Contemporary Studies. *Heart Lung Circ* 2016; **25**: 1107-1117 [PMID: 27199213 DOI: 10.1016/j.hlc.2016.03.016]
 - 70 **Figini F**, Mazzone P, Regazzoli D, Porata G, Ruparelia N, Giannini F, Stella S, Ancona F, Agricola E, Sora N, Marzi A, Aurelio A, Trevisi N, Della Bella P, Colombo A, Montorfano M. Left atrial appendage closure: A single center experience and comparison of two contemporary devices. *Catheter Cardiovasc Interv* 2017; **89**: 763-772 [PMID: 27567013 DOI: 10.1002/ccd.26678]
 - 71 **Betts TR**, Leo M, Panikker S, Kanagaratnam P, Koa-Wing M, Davies DW, Hildick-Smith D, Wynne DG, Ormerod O, Segal OR, Chow AW, Todd D, Cabrera Gomez S, Kirkwood GJ, Fox D, Pepper C, Foran J, Wong T. Percutaneous left atrial appendage occlusion using different technologies in the United Kingdom: A multicenter registry. *Catheter Cardiovasc Interv* 2017; **89**: 484-492 [PMID: 27651124 DOI: 10.1002/ccd.26782]
 - 72 **Fauchier L**, Cinaud A, Brigadeau F, Lepillier A, Pierre B, Abbey S, Fatemi M, Franceschi F, Guedeney P,

- Jacon P, Paziaud O, Venier S, Deharo JC, Gras D, Klug D, Mansourati J, Montalescot G, Piot O, Defaye P. Device-Related Thrombosis After Percutaneous Left Atrial Appendage Occlusion for Atrial Fibrillation. *J Am Coll Cardiol* 2018; **71**: 1528-1536 [PMID: [29622159](#) DOI: [10.1016/j.jacc.2018.01.076](#)]
- 73 **Bergmann MW**, Betts TR, Sievert H, Schmidt B, Pokushalov E, Kische S, Schmitz T, Meincke F, Stein KM, Boersma LVA, Ince H. Safety and efficacy of early anticoagulation drug regimens after WATCHMAN left atrial appendage closure: three-month data from the EWOLUTION prospective, multicentre, monitored international WATCHMAN LAA closure registry. *EuroIntervention* 2017; **13**: 877-884 [PMID: [28606886](#) DOI: [10.4244/EIJ-D-17-00042](#)]
- 74 **Tilz RR**, Potpara T, Chen J, Dobreanu D, Larsen TB, Haugaa KH, Dagres N. Left atrial appendage occluder implantation in Europe: indications and anticoagulation post-implantation. Results of the European Heart Rhythm Association Survey. *Europace* 2017; **19**: 1737-1742 [PMID: [29016910](#) DOI: [10.1093/europace/eux254](#)]
- 75 **Meier B**, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C, Glikson M. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *EuroIntervention* 2015; **10**: 1109-1125 [PMID: [25169595](#)]
- 76 **Reddy VY**, Gibson DN, Kar S, O'Neill W, Doshi SK, Horton RP, Buchbinder M, Gordon NT, Holmes DR. Post-Approval U.S. Experience With Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation. *J Am Coll Cardiol* 2017; **69**: 253-261 [PMID: [27816552](#) DOI: [10.1016/j.jacc.2016.10.010](#)]
- 77 **Singh SM**, Douglas PS, Reddy VY. The incidence and long-term clinical outcome of iatrogenic atrial septal defects secondary to transseptal catheterization with a 12F transseptal sheath. *Circ Arrhythm Electrophysiol* 2011; **4**: 166-171 [PMID: [21248245](#) DOI: [10.1161/CIRCEP.110.959015](#)]

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Heart valve disease in elderly

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Abstract

The incidence of heart valve disease increases significantly with age. Degenerative abnormalities associated with severe aortic stenosis and mitral and tricuspid regurgitation are found in not less than 10% of the population aged ≥ 75 years. Surgical treatment has been considered for years to be the treatment of choice. However, it was not uncommonly associated with high perioperative morbidity and mortality due to frequent comorbidities and overall frailty conditions of these patients. Conventional risk scores such as Society of Thoracic Surgeons and European System for Cardiac Operative Risk Evaluation may underestimate the risk of surgery in elderly patients, leading to inappropriate surgical indication. On the other hand, at least 30% of patients with severe conditions are left untreated due to prohibitive surgical risk. Interventional procedures, which are in continuous development, may be actually considered for high risk patients and, as recent results suggest, also for intermediate risk patients.

Key words: Valve diseases; Elderly; Surgery; Interventional cardiology

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Core tip: Severe heart valve diseases are not uncommon in the elderly and often treatment may be challenging due to high risks related both to relevant comorbidities and the frailty condition of elderly patients. Although surgery is still the first choice for most conditions, interventional strategies are emerging as a valid alternative both in high and intermediate risk patients. Careful evaluation is needed for each individual patient in order to establish a more appropriate strategy considering that the impact on the quality of life may be more relevant in this population than the effects on survival, which is already limited by decreased life expectancy related to ageing.

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INTRODUCTION

Progressive ageing of a population is associated with an increased prevalence of chronic degenerative diseases. Among these, heart valve abnormalities represent an important public-health problem leading to high morbidity and mortality. The Euro Heart Survey on valve heart disease (VHD) published in 2003 included 5001 adults from 25 countries suffering from moderate to severe heart valve disease^[1]. Native VHD was found in about 4000 patients. The remaining had had previous valve surgery. Degenerative process was the main cause of aortic involvement and mitral regurgitation (MR). Mitral stenosis (MS) was mainly due to rheumatic disease. Incidence of valvular disease increased with age. Incidence of VHD was 6% for both mitral and aortic disease in patients aged ≥ 75 years, while in younger patients (aged < 64 years), the incidence was less than 1%. Importantly, according to the Survey, more than 30% of subjects with severe, symptomatic, single VHD, usually elderly with relevant comorbidities, did not undergo surgery.

More recently, Nkomo *et al*^[2] reported the results of echocardiographic examinations in 11911 randomly selected adults who had been prospectively assessed in three large population-based epidemiological studies^[3-5]. Moreover, included in the study were 16501 adults who were assessed in community by clinically indicated echocardiography. In the first group, 615 patients (5.1%) had moderate or severe valve disease. There were no gender related differences. Prevalence of valve disease increased significantly with age from 0.7% in the group comprised of 18-year-olds to 44-year-olds to 13.3% in the group of those 75 years and older ($P < 0.0001$). A significant increase of VHD was reported for each increment of 10 years of ageing. This was particularly evident for aortic stenosis (AS) (hazard ratio (HR) = 2.51; 95% confidence interval (CI): 2.02 to 3.12; $P < 0.0001$). MR was the most frequent VHD in elderly patients (9.3%) followed by AS (2.8%), aortic regurgitation (AR) (2.0%), and finally MS (0.2%).

In the community group, valve disease was diagnosed in 1505 patients. Prevalence of valve diseases increased considerably with age also in this group (0.3% in 18-44 years old, 11.7% in those aged ≥ 75 years). There was a trend that showed a lower rate of diagnosis in women than in men. Both in the population and in the community study, valve disease was associated with an increased mortality risk ratio (RR) (1.36, 95% CI: 1.15-1.62; $P = 0.0005$ and respectively 1.75, 95% CI: 1.61-1.90; $P < 0.0001$). Incidence of heart valve disease in 500 consecutive patients aged > 8 years referred to our Center for hip fracture is reported in [Figure 1](#).

Due to increased life expectancy in the elderly population, AS prevalence is expected to increase further. according to recent projections from The OxVALVE population cohort study in the United Kingdom, the number of elderly people with moderate or severe valvular heart disease will more than double by 2056^[6].

A retrospective study from Scotland showed that among all patients hospitalized from 1 January 1997 to 31 December 2005, a final diagnosis of non-congenital aortic valve disease was made in a total of 19733 adults^[7]. Discharge diagnosis was AS in 13220 (67.0%) and AR in 2807 (14.2%). Mixed aortic valve disease, or unspecified aortic valve disease, occurred respectively in 699 (3.5%) and 3007 (15.2%). Elderly patients, aged 80 and older, accounted for most of the patients included in the study. More than half had died by 31 December 2006. The risk of death (and heart failure) was 20% higher in AS in comparison to aortic insufficiency or mixed aortic valve disease. Only 19.4% of patients included in the study had aortic valve replacement during follow-up, three out four for AS. Age, female gender, and co-morbidity influenced replacement rate.

Despite the relevance of VHD as a cause of heart failure and death, the first European Heart Valve Disease survey demonstrated that the awareness and knowledge of heart valve disease in the general population was alarmingly low, and only 3.8% really knew what AS was^[8]. Two years later, the second European Heart Valve Disease survey showed a mild improvement in general knowledge of heart valve disease in comparison to 2015. Despite this finding, the correct understanding of AS decreased significantly (2015: 7.2% vs 2017: 3.8%; $P < 0.001$)^[9].

Treatment of VHD in the elderly requires careful evaluation since other than the effects on survival, already limited by decreased life expectancy related to ageing, the impact on the quality of life should be considered a relevant aspect. In elderly people, clinical outcome after surgical treatment is significantly influenced by concomitant

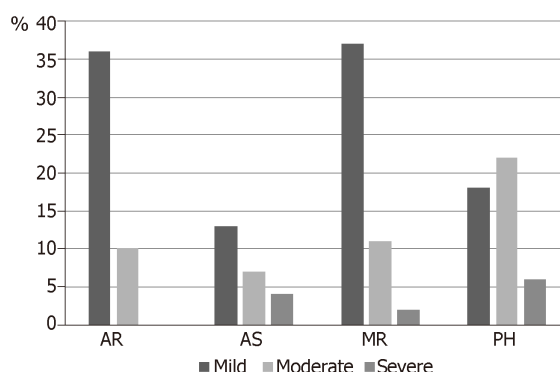


Figure 1 Incidence of valve heart disease in 500 consecutive patients aged > 80 years referred for hip fracture.

severe comorbidities [diabetes mellitus, chronic kidney disease, cerebrovascular disease, and atrial fibrillation (AF), *etc*] that may impair postoperative recovery, leading to worse outcomes^[10]. A multidisciplinary approach involving cardiologists, interventional cardiologists, surgeons, anesthesiologists, and geriatricians may improve the decisional process.

AORTIC VALVE

AS

Epidemiology and pathophysiology: In the elderly, degenerative AS is one of the most common types of valvular heart disease. The prevalence of AS has been reported to be between 12% and 26% depending on the diagnostic criteria employed^[1,11]. In the study by Lindroos *et al*^[12], critical AS was defined as a valve area < 0.8 cm² or velocity ratio of < 0.35. In the 75- to 86-year-old group, the reported prevalence of disease was 2.9% (95% CI: 1.4% to 5.1%). Overall, 40% of patients with severe AS were considered to be at high surgical risk. It must be emphasized that although AS is clearly associated with adverse outcomes, even aortic sclerosis can create an increased risk of cardiovascular morbidity and mortality mainly by its being a significant risk factor for progression to AS. Degenerative calcific disease accounts for most cases of severe AS; however, a large study reported that 22% percent of octogenarians presenting for surgery for isolated AS had bicuspid valve disease^[13-15].

Calcific aortic valve disease evolves over the years at a different rate in every subject. The development and progression of AS is at least in part related to active processes that have pathophysiological mechanisms in common with atherosclerotic disease^[14]. First, several studies suggested that calcific degenerative AS and atherosclerosis have common risk factors such as age, smoking, hypertension, hypercholesterolemia, diabetes mellitus, and metabolic syndrome^[15-18]. Since valve leaflets may have anatomic heterogeneity, different shear stresses may lead to endothelial dysfunction at the ventricular surface of the valve. Second, the loss of endothelial integrity allows lipid accumulation and cellular migration (inflammatory cells, macrophages, and T cells) in the subendothelial matrix^[19] with neurohormonal activation^[20]. Plaque-like subendothelial deposits may lead to downward displacement and fragmentation of the subjacent elastic lamina. The osteoblast-like activity of interstitial cells may be responsible for valvular calcification over time with a decrease in leaflet mobility^[21].

AR

Epidemiology and pathophysiology: Isolated AR is significantly less common than pure AS. Degenerative and bicuspid aortic valve disease shows a different degree of both regurgitation and left ventricular obstruction; however, stenosis is usually pre-eminent. More frequently, AR is a consequence of aortic dilation and the deformation of the annulus valve. Overall prevalence of significant native AR has been reported in between 2.0% and 2.5% of patients 70 years to 83 years of age, without gender differences^[22,23] although smaller studies reported a higher incidence of up to 13%. Age, aortic valve fibrocalcification, and female sex were considered independent factors related to AR, while several studies failed to find a relationship with arterial hypertension^[24].

Treatment of aortic valve diseases: Surgical aortic valve replacement (SAVR) has been, for a long time, the treatment of choice for severe aortic valve disease. Improved survival and quality of life have been clearly demonstrated even in elderly patients^[25-27]. Nevertheless, a non-negligible number of elderly patients are considered at very high or prohibitive risk for conventional surgical procedures, and about 30% of symptomatic subjects will never undergo surgery^[1].

Non-surgical options, in particular transcatheter aortic valve replacement (TAVR), have developed as a suitable alternative to SAVR. In humans, the first transcatheter aortic stent valve was implanted in 2002, using femoral vein access and a transeptal approach^[28]. In 2005, technical developments allowed for changing the approach to the transfemoral artery^[29]. Transapical TAVR (TA-TAVR) has been proposed in patients with unsuitable vascular access. Several studies compared safety and efficacy between the transfemoral TAVR (TF-TAVR) and TA-TAVR. The transfemoral approach, whenever feasible, should be considered the preferable access route^[30].

Initially, the indication for TAVR was limited to severely symptomatic AS with high surgical risk according to validated risk scores [Society of Thoracic Surgeons (STS) or European System for Cardiac Operative Risk Evaluation (EuroSCORE)]. At present, indications for percutaneous treatment may be extended to intermediate risk subjects. Nevertheless the use of STS-risk score (or EuroSCORE) may be misleading in very old people (aged > 80 years) since a high risk of perioperative complications may exist due to overall age and frailty *per se*^[31-33]. Frailty, limited functional capacity according to Barthel scale, inadequate nutrition, and the need for non-cardiac surgery (most frequently oncologic or orthopedic surgery) are good indicators for TAVR, which allows a faster recovery and improved quality of life.

The randomized PARTNER 1B study first showed a decrease in death from any cause and death from cardiovascular causes in patients who underwent TAVR *vs* a conservative treatment^[34]. The PARTNER 1A trial randomized 699 high-risk patients with severe AS to TAVR (using transfemoral or the transapical approach) or SAVR^[35]. Death from any cause at 1 year was similar in the two groups, while major vascular complications (11.0% *vs* 3.2%, $P < 0.001$) and stroke (8.3% *vs* 4.3%, $P < 0.05$) were more frequent in TAVR than in SAVR. At 2 years follow-up, TAVR was associated with an increased late mortality mainly related to mechanical complications of the valve such as paravalvular leak. With first generation devices, residual AR due to para-valvular leaks was found postoperatively in about 20% of patients. Minimally invasive aortic valve replacement was proposed to manage carefully selected patients with the aim of decreasing permanent pacemaker implantation and other vascular complications that would be critical to changing patient prognosis.

In the study by Hirji *et al*^[36], 1028 octogenarians underwent isolated aortic valve replacement between 2002 and 2015. Three hundred and six were treated by TAVR and 722 by SAVR (344 conventional and 378 minimally invasive valve replacement). Median follow-up was 35 mo. TAVR patients were relatively older (86.2 years *vs* 84.2 years) and in more cases had several co-morbidities. Operative mortality and mid-term survival were similar for TAVR (regardless of approach), SAVR, and minimally invasive aortic valve replacement after adjustment for confounding factors. The median in-hospital length of stay was statistically higher for the SAVR group ($P < 0.05$). Independent predictors of mortality were age, class III/IV New York Heart Association (NYHA), preoperative creatinine, severe chronic lung disease, and prior cardiac surgery (all $P < 0.05$). The authors concluded that treatment decisions should be addressed by a multi-disciplinary heart team, taking into account patient comorbidities, frailty, and quality of life.

Recently were reported the results of the FRENCH Aortic National CoreValve and Edwards (FRANCE-2) registry. In the study were included 2254 patients > 80 years of age who underwent TAVR. Thirty-day and 1-year mortality were not significantly different among patients aged 80 to 84 years, 85 to 89 years, and finally > 90 years (10.3% *vs* 9.5% *vs* 11.2%; $P = 0.53$ and respectively 19.8% *vs* 26.1% *vs* 27.7%; $P = 0.16$)^[37].

A recent study compared carefully selected patients > 90 years old, without many comorbidities, *vs* younger patients who underwent TAVR. Major complications were similar, and all-cause mortality at 30 days and 1 year was not statistically different (2.9% and 12.5% in patients aged ≥ 90 *vs* 2.8% and 12.3% in patients aged < 90, respectively)^[38].

The effects of TAVR were evaluated more recently in low-intermediate risk populations. An Italian observational, multicenter, “real-world” study included 1300 patients in a propensity-matched population. The authors did not find significant differences in mortality or major adverse cardiac and cardiovascular events between SAVR and TAVR^[39].

In the PARTNER 2A randomized trial, TAVR was compared with SAVR in 2032 intermediate-risk patients. The primary endpoints were all-cause mortality or disabling stroke at 2 years. The authors did not find differences between groups.

Although major vascular complications and paravalvular regurgitation were more frequent in TAVR, surgical replacement was associated with higher rates of acute kidney injury, severe bleeding, and new-onset AF^[40].

The multicenter Surgical Replacement and Transcatheter Aortic Valve Implantation trial was a randomized, clinical trial that included 1746 patients at intermediate surgical risk, of whom 1660 underwent TAVR or surgical operation^[41]. The primary endpoint, a composite of death from any cause or disabling stroke at 24 mo, was 12.6% in TVAR and 14% in SAVR respectively. On the basis of these results, 2017 American Heart Association/American College of Cardiology gave a IIa indication for the TAVR procedure in intermediate surgical risk^[42].

Data from studies of a low-risk group for surgery, showed that SAVR is still more advantageous than TAVR. Rosato *et al*^[43] reported that survival at 3 years was 72.0% after TAVR and 83.4% after SAVR ($P = 0.0015$). Further studies with new generation valve prostheses are necessary before expanding indications of TAVR in lower-risk patients.

Effects of coronary artery disease: Coronary artery disease (CAD) is frequently associated with AS, in particular in elderly patients^[44]. The coexistence of CAD leads to a worse prognosis for AS of comparable severity. Surgical treatment allows correction of valve disease and at the same time coronary revascularization. Data regarding elderly subjects are limited. Less is known about the effects of CAD in elderly patients undergoing TAVR.

To evaluate the effect of age on combined AVR and concomitant coronary artery bypass graft (CABG), 452 consecutive patients (mean age 64 years) were divided into three groups: Young ($n = 114$), middle-aged ($n = 225$), and elderly ($n = 113$). CAD was more extensive in the elderly group. Only 62.8% of elderly patients had complete myocardial revascularization in comparison to 94.1% and 76.2%, respectively, of the other two groups ($P < 0.05$). In-hospital mortality was 6.4% in the elderly in comparison to 2.0% and 5.3%, respectively in the other groups. Freedom from cardiac-related death at 12 mo and 60 mo was higher in young and middle-aged patients than in elderly patients^[45].

How CAD impacts patient survival following TAVR has been investigated by a recent meta-analysis. Fifteen studies including 8013 patients were examined. The median age of patients was 81.3 years, 46.6% were men, and 3899 (48.7%) had CAD. All-cause mortality at 30 days post TAVR was not significantly different between patients with and without CAD. All-cause mortality however was significantly higher at 1 year in patients with CAD in comparison with patients without CAD (OR = 1.21; 95% CI: 1.07–1.36; $P = 0.002$). These results suggest the need to revisit the revascularization strategies for concomitant CAD in patients with TAVR^[46].

AS and MR

In the elderly, AS is frequently associated with concomitant MR (22%–48%). In severe cases affecting both valves, surgical valve replacement has usually been considered the treatment of choice. Data regarding elderly subjects is limited. In the study by Yu *et al*^[47], 43 high-risk patients with severe AS, aged 80 ± 6 years, underwent concomitant SAVR and mitral valve (MV) surgery. Nineteen (44%) had prior cardiac surgery, and 39 (91%) were in congestive heart failure. Five patients (11.6%) died during hospitalization or at 30 days. Mortality was 25% at 6 mo, 35% at 1 year, and 45% at 2 years. Patients often needed prolonged ventilation, and 10% developed new renal failure requiring dialysis. When AS in patients at high or prohibitive surgical risk is treated by percutaneous TAVR, concomitant significant MR usually is not corrected^[48,49]. Untreated MR is associated with a significant increase in mortality and morbidity^[50].

The recent availability of percutaneous devices for treating MV disease may offer an alternative for the management of MR after TAVR^[51]. Few limited case series reported a procedural success (decrease of degree of MR $< 2+$) comprised between 92% and 100% for edge to edge MV repair with MitraClip™ (Abbott Vascular, Menlo Park, CA, United States)^[52]. Recurrent 3+ MR at 1 year however occurred in 21.4%. One year survival rate was 66.5%.

In conclusion, concomitant MV surgery in patients with MV disease undergoing aortic valve replacement did not give better results on long term survival than TAVR without correction of MV regurgitation. Therefore, individual assessment should guide procedural strategy in treating MR associated with severe AS.

MV

Epidemiology and pathophysiology

Several conditions may damage the MV in older patients, such as degeneration of valve leaflets, calcification of the mitral annulus commonly involving the posterior leaflet, ischemia, and rheumatic heart disease.

Anatomo-functional abnormalities of the MV apparatus may result in valve stenosis or, more frequently, regurgitation. The most common etiology of MS is rheumatic heart disease; however, it is not common that the disease remains undiagnosed up until an advanced age^[53]. Degenerative MV annulus calcification is more frequent in the elderly, but it is unclear how frequent a significant hemodynamic impact might be. Functional MS related to massive annular calcification and reduced leaflet excursion has been reported in 2.5% to 18.0% of elderly patients^[54]. Degenerative MS accounted for 12.5% of MS cases according to data of the Euro Heart Survey^[1]. The severity of calcification has significant implications for surgery. Debridement of the posterior annulus may be challenging, and residual calcium may not allow adequate suturing of the MV prosthesis with the risk of post-operative paravalvular regurgitation due to suture dehiscence. Moreover, there is the non-negligible risk of extensive damage and posterior disruption of the left ventricle and that of death.

In industrialized countries, MR is the most frequent valvular heart disease in patients over the age of 65 years^[1,2]. Elderly patients account for about 40% of all patients with MR and 4.5% are over 80 years of age. Heart failure, arrhythmia, and death may occur in patients with severe disease. Prevalence of moderate MR in the Framingham study was 11.1% in men 70 years to 83 years of age^[23]. In the study, no information was reported regarding valve morphology. Secondary MR has been reported in about 25% of patients after myocardial infarction and in more than 50% in heart failure with depressed ejection fraction.

Treatment

Etiology of MV regurgitation plays a relevant role in the decision-making process, particularly in elderly patients. MV surgery is indicated only if the balance between expected clinical improvement exceeds increased operative risk related to ageing and comorbidities. Surgical treatment is clearly suggested by American guidelines for patients with primary valve disease, while no indications are provided by ESC guidelines^[42,55]. A high operative mortality (15%) was reported by a recent meta-analysis including 5572 octogenarian patients^[56]. Therefore, a careful multidimensional preoperative evaluation is needed for risk stratification since STS and EuroSCORE may effectively underestimate effective surgery related risks in elderly, frail patients. Left ventricular dysfunction is more frequent with concomitant CAD. Surgical revascularization increases the risk of both early and late mortality after surgery.

Secondary MR in those aged > 75 years is likely to be more frequent than primary valve disease. In this case, no clear indication for surgery exists as the clinical benefit is uncertain. When concomitant coronary artery bypass grafting is not planned, surgical intervention may be recommended only in patients with refractory symptoms after optimization of medical therapy and eventual cardiac resynchronization therapy^[57,58].

MV-repair at present is the generally accepted “gold standard” treatment for degenerative MV disease. Several studies demonstrated the superiority of repair over MV replacement (MVR)^[59,60]. Patients with extensive bi-leaflet or anterior leaflet prolapse and myxomatous degeneration without extensive calcification are considered good candidates for MV repair. Nevertheless, in elderly patients MV-repair as suggested by administrative American databases was performed in less than 50%. Advanced age was as an independent predictor of valve replacement^[61].

The lower technical complexity of valve replacement with shorter cardio pulmonary bypass times and decreased risk of failure with need of reintervention may explain the lower rate of MV repair than expected in elderly patients. These aspects are particularly relevant due the limited life expectancy of aged patients. Nevertheless, MVR has a high short-term mortality of 25% to 30%, frequently due to congestive heart failure possibly related to alteration of the left ventricular dimensions and geometry.

Differences in long-term clinical outcomes between surgery and conservative management were evaluated by Kang *et al*^[62] in 157 patients with severe MR aged ≥ 70 years. Median follow-up was 5.4 years. Surgery was associated with a lower mortality (HR 0.31; 95%CI: 0.13 to 0.73; $P = 0.007$) other than with a decrease in overall cardiac event (HR 0.26; 95%CI: 0.13 to 0.53; $P < 0.001$).

In a single center retrospective study in 2015, consecutive patients with moderate to severe MR were divided into two groups^[63]. Patients aged > 60 years (mean age 66.98 ± 5.94 years) were considered as the elderly group ($n = 680$) and compared to patients < 60 years (control group, $n = 1061$). In total, 308/680 elderly MR were denied

surgery, which was much higher than the rate of denial observed in the control group (45.29% *vs* 36.10%, $P < 0.001$). The factors associated with decreased probability of undergoing surgery were increased age, diabetes, and high risk stratification according to EuroSCORE-II. Of the 275 elderly patients with severe MR included in this study, 75 (27.27%) did not undergo surgery.

A database from the University Centre of Leipzig, Germany was examined and assessed to identify all patients aged > 70 years who underwent MV surgical procedures between 1999 and 2009. In 97% of the 2503 patients, MR was the primary indication for operation^[64]. MV repair was performed in 64%. Mortality rate at 30 days was 3.1%, and survival at 5 years was 55.2%. Coronary revascularization was associated with an early and long-term poorer outcome. Several factors, such as diabetes, chronic obstructive lung disease, left ventricular function $< 30\%$, preoperative hemodialysis, presence of endocarditis, MVR, concomitant TV procedures, urgent or emergent procedures, aortic procedures, aortic valve replacement, and CABG, were independently related younger late death^[64].

A recent retrospective study by Silashi *et al*^[65] reviewed the results after MV surgery in elderly patients treated over the past 20 years. Excluded from the study were patients with repeat cardiac surgery, endocarditis, and concomitant aortic valve replacement. Of 1776 patients with MV disease, 341 were aged ≥ 75 years. Two hundred and twenty-one underwent MV-repair and 120 MVR. One hundred thirty-five patients had concomitant coronary artery bypass grafting (39.6%). Fifty had tricuspid valve (TV) surgery (14.7%). Thirty-day mortality associated with MV repair was 5.4% *vs* 9.2% for MVR ($P = 0.26$). Concomitant CABG was more frequently performed in patients undergoing MV-repair (43.9% *vs* 31.7%, $P = 0.03$). In 27 patients, planned MV-repair was converted to MVR, mainly after invasive inspection of the MV. Moderate/severe MR was observed at follow-up in 15 cases after MV-repair (6.8%), of which four needed reintervention. After MVR, significant MR was observed in only 3 cases (2.5%). Overall 1- and 5-year survival was 90.7% and 74.2% *vs* 81.3% and 61.0%, respectively ($P < 0.01$).

In a propensity adjusted analysis of outcomes after MV surgery in patients aged > 80 years (mean age 83 years), overall operative mortality was 11% after MV-repair in comparison to 18.9% for MVR^[66]. It must be underlined that this study also included patients with endocarditis (1.8% in MV-repair and 13.7% in MVR) and ischemic MV disease (32.2% in MV-repair).

Included in a meta-analysis by Shang *et al*^[67] were seven observational clinical studies published after 2000 comparing MVP and MVR in the elderly (aged 70 years or older). Overall, 1809 patients were considered. Thirty-day mortality was significantly lower after MV repair (RR: 0.40, 95%CI: 0.25–0.64). Moreover, repair was associated with length of postoperative hospital stay and less postoperative complications in comparison to MVR. Finally long-term (1- and 5-year survival) were higher in MV-repair.

Patients at high-prohibitive risk for surgery may benefit, when technically feasible, by percutaneous interventional treatment. MitraClipTM therapy is at present the most widely used technique. The device allows for building a bridge between the anterior and posterior mitral leaflet thus mimicking the surgical technique of the Alfieri stitch. In patients treated for degenerative MR, despite good periprocedural results, the rate of recurrent severe MR after MitraClipTM therapy has been reported close to 55% at 12 mo^[68]. The need for re-operations may exceed 20% at 4 years of follow-up^[69].

Failure of MitraClipTM procedures may be related to the absence of concomitant annuloplasty. Failed MitraClipTM procedures may complicate eventual future MV-repair. In particular when treatment included more than one clip valves, which are often not repairable. Further techniques, such as transcatheter MV-in-ring implantation, may be considered in selected cases after failure on MV repair.

Surgery must be considered the initial “gold standard” treatment for elderly patients with degenerative MR and acceptable surgical risk should be considered. A multidisciplinary “Heart Team” should discuss the patient’s condition and various treatment opportunities. New interventional treatment options may be considered for symptomatic high risk patients.

TV

Tricuspid regurgitation (TR) is the second most common VHD after MR with an incidence of 1.2% to 1.5% in the general population^[1,2]. The prevalence increases with age and in particular in females. In the group of 70 to 83 year-olds, incidence is 5.6% in women as compared to 1.5% in men^[23]. Severe TR is associated with higher 1-year mortality and poorer outcomes independent of age and other comorbid conditions^[70].

Primary valve disease accounts for 25% of TR. This is more common in younger patients suffering from anatomic valve abnormalities (congenital, rheumatic, neoplastic, traumatic, infective endocarditis, and endomyocardial fibrosis). Other causes of TR are lead implantation for pacing or leaflet damage due to RV biopsy^[71]. In elderly subjects, functional or secondary TR due to left heart disease, often MR or AS, is by far the more common etiology of TR^[70]. TR secondary to left heart valve disease is often associated with poor prognosis and difficult therapeutic choices. Pulmonary hypertension, right ventricular infarction, chronic right ventricular pacing, and history of AF are other common causes of secondary TR. The term “functional” may be misleading for TV disease. As with the MV, annular dilatation of the tricuspid annulus and/or dislocation of papillary muscles plays just as important of a role in causing valve malfunction^[72]. Annular dilatation occurs along the anterior and posterior TV leaflet implantation; therefore, the annulus becomes more circular and planar. Geometrical abnormalities may be different between secondary TR and the so-called “idiopathic TR,” commonly attributed to ageing and AF^[73,74]. In idiopathic TR, basal RV dilatation with relatively normal RV length and marked annular dilatation but with normal tenting height of leaflets is commonly observed. Where there is functional TR in patients with pulmonary hypertension, there is a spherical RV deformation, with less evident annular dilation but significantly greater tenting height. These morpho-functional differences have significant implications for treatment.

Treatment

A conservative (no touch) approach to TR was proposed in the 1960s. It was conceivable that the hemodynamic improvement related to the correction of the left-sided valve disease would result in a decrease of secondary TR. The experiences that followed, however, demonstrated that regression of TR is not the rule, and regurgitation may further increase in particular when the mitral and/or aortic valve diseases are not completely or adequately resolved during surgery. Moreover, it must be stressed that an isolated severe TR is now increasingly recognized even in patients with normal left heart valve function after either MV annuloplasty or replacement. The degree of right ventricular dysfunction indicated by annular dilatation may be related to impaired regression of further increased degree of valve regurgitation. Preoperative evaluation may give information whether TR will resolve after successful mitral surgery. Four hundred and thirteen patients with rheumatic heart disease, who did not have preoperative severe TR, underwent MVR without concomitant TV repair and were then followed for a median period of 13 years^[75]. Forty-six patients (11.1%) had new severe TR. Independent predictors for new severe TR were preoperative moderate TR (HR 2.401; $P = 0.008$) and AF (HR 2.119; $P = 0.018$). Patients with new severe TR had larger right ventricles and higher pulmonary artery pressures on echocardiography.

Right ventricular failure is associated with a higher surgical mortality (from 5% to 11% and from 8% to 22% during follow-up)^[76]. Preoperative right ventricular dysfunction and persisting TR are associated with a minor relief of symptoms and an impaired cardiac output response to exercise after correction of valve diseases.

Although it has been suggested that functional TR may be untreated in patients with a significant predictable decrease in the pulmonary resistance, at present we have no reliable methods to predict reversibility of the TR after correction of the left heart valve dysfunction. Moreover, methods of measuring and quantifying the degree of TR are still not reliable and repeatable. The clinical assessment may add information to echocardiography. Finally, there is no satisfactory method to assess true right ventricular function.

Often, in elderly patients with long standing disease, TR frequently poses a challenging treatment dilemma^[77]. Severe TR may be tolerated for many years and sometimes managed conservatively until severe right heart failure and ascites develop. It is then often too late for correction since any therapy comes with extremely high risk, with unacceptable operative mortality. Moreover, the likelihood of functional recovery is poor. American College of Cardiology/American Heart Association guidelines do not give any Class I indications for isolated TV surgery^[42]. Operative risk is high in these patients with a mortality rate of 7.9% at 30 days. Age is an independent predictor according to multivariable analysis. Reduction of right ventricle afterload after treatment of a left-sided valve lesion may lead to an improvement, even if often unpredictable, of severe TR. TV repair during left sided surgery does not appreciably increase the risks of surgery. TR repair is currently recommended in patients undergoing left-sided valve surgery. Effects of depressed right ventricular function on results of TV repair were examined by Subbotina *et al*^[78]. Eighty-two out of 191 patients (43%) had decreased tricuspid annular plane systolic excursion (TAPSE) (13.3 ± 3.3 mm *vs* 20.2 ± 4.9 mm; $P < 0.001$). In both groups, 91%

underwent ring annuloplasty. Patients with depressed right ventricular function had a higher incidence of low cardiac output syndrome after surgery (10% *vs* 27%, $P=0.005$) and a higher early mortality. Functional improvement, expressed as change in NYHA class, was more evident in patients with preserved right ventricular function. Of 173 patients who underwent MV surgery and radiofrequency ablation of AF, only age and concomitant TV repair were independently associated with mortality according to multivariate analysis^[79].

In the last years, numerous percutaneous transcatheter repair and replacement devices were developed to treat this large group of high surgical risk patients. To improve prognosis in severe TR, an earlier diagnosis and referral for treatment are essential, as are a better understanding of the different stages of disease and potential treatment options, proven safe and efficacious percutaneous options, and an evidence base for earlier surgical or percutaneous intervention of significant TR, irrespective of symptoms. The use of MitraClip™ in the tricuspid position is associated with unpredictable results. Data reported from a recent registry showed a > 50% reduction in effective regurgitant orifice area after treatment with MitraClip™. The procedure was associated with significant clinical improvement with decrease in the NYHA functional class and longer 6 minute walking distance^[80]. Other transcatheter therapies are being tested in feasibility trials. Among these the Trialalign system (MitrAlign, Tewksbury, Massachusetts, United States) that mimics the surgical Kay annuloplasty *via* a pair of pledgeted sutures delivered percutaneously through the right internal jugular vein.

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REFERENCES

- 1 **Iung B**, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003; **24**: 1231-1243 [PMID: 12831818 DOI: 10.1016/S0195-668X(03)00201-X]
- 2 **Nkomo VT**, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006; **368**: 1005-1011 [PMID: 16980116 DOI: 10.1016/S0140-6736(06)69208-8]
- 3 **Hughes GH**, Cutter G, Donahue R, Friedman GD, Hulley S, Hunkeler E, Jacobs DR, Liu K, Orden S, Pirie P. Recruitment in the Coronary Artery Disease Risk Development in Young Adults (Cardia) Study. *Control Clin Trials* 1987; **8**: 68S-73S [PMID: 3440391 DOI: 10.1016/0197-2456(87)90008-0]
- 4 **The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives**. The ARIC investigators. *Am J Epidemiol* 1989; **129**: 687-702 [PMID: 2646917 DOI: 10.1093/oxfordjournals.aje.a115184]
- 5 **Fried LP**, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991; **1**: 263-276 [PMID: 1669507 DOI: 10.1016/1047-2797(91)90005-W]
- 6 **Berry C**, Lloyd SM, Wang Y, Macdonald A, Ford I. The changing course of aortic valve disease in Scotland: temporal trends in hospitalizations and mortality and prognostic importance of aortic stenosis. *Eur Heart J* 2013; **34**: 1538-1547 [PMID: 23111418 DOI: 10.1093/eurheartj/ehs339]
- 7 **Coffey S**, d'Arcy JL, Loudon MA, Mant D, Farmer AJ, Prendergast BD; OxVALVE-PCS group. The OxVALVE population cohort study (OxVALVE-PCS)-population screening for undiagnosed valvular heart disease in the elderly: study design and objectives. *Open Heart* 2014; **1**: e000043 [PMID: 25332795 DOI: 10.1136/openhrt-2014-000043]
- 8 **Gaede L**, Di Bartolomeo R, van der Kleij F, Elsässer A, Iung B, Möllmann H. Aortic valve stenosis: what do people know? A heart valve disease awareness survey of over 8,800 people aged 60 or over. *EuroIntervention* 2016; **12**: 883-889 [PMID: 27283409 DOI: 10.4244/EIJY16M06_02]
- 9 **Gaede L**, Aarberge L, Brandon Bravo Bruinsma G, Macarthy P, Musumeci F, Zamorano P, Möllmann H. Heart Valve Disease Awareness Survey 2017: what did we achieve since 2015? *Clin Res Cardiol* 2019; **108**: 61-67 [PMID: 29943272 DOI: 10.1007/s00392-018-1312-5]
- 10 **Osnabrugge RL**, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 2013; **62**: 1002-1012 [PMID: 23727214 DOI: 10.1016/j.jacc.2013.05.015]
- 11 **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**: 630-634 [PMID: 9060903 DOI: 10.1016/S0735-1097(96)00563-3]
- 12 **Lindroos M**, Kupari M, Heikkilä J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol* 1993; **21**: 1220-1225 [PMID: 8459080 DOI: 10.1016/0735-1097(93)90249-Z]
- 13 **Roberts WC**, Janning KG, Ko JM, Filardo G, Matter GJ. Frequency of congenitally bicuspid aortic valves in patients ≥80 years of age undergoing aortic valve replacement for aortic stenosis (with or without aortic regurgitation) and implications for transcatheter aortic valve implantation. *Am J Cardiol* 2012; **109**: 1632-1636 [PMID: 22459301 DOI: 10.1016/j.amjcard.2012.01.390]

- 14 **Otto CM**, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. *Circulation* 1994; **90**: 844-853 [PMID: [7519131](#) DOI: [10.1161/01.CIR.90.2.844](#)]
- 15 **Pahkala K**, Hietalampi H, Laitinen TT, Viikari JS, Rönnemaa T, Niinikoski H, Lagström H, Talvia S, Jula A, Heinonen OJ, Juonala M, Simell O, Raitakari OT. Ideal cardiovascular health in adolescence: effect of lifestyle intervention and association with vascular intima-media thickness and elasticity (the Special Turku Coronary Risk Factor Intervention Project for Children [STRIP] study). *Circulation* 2013; **127**: 2088-2096 [PMID: [23613255](#) DOI: [10.1161/CIRCULATIONAHA.112.000761](#)]
- 16 **Spring B**, Moller AC, Colangelo LA, Siddique J, Roehrig M, Daviglus ML, Polak JF, Reis JP, Sidney S, Liu K. Healthy lifestyle change and subclinical atherosclerosis in young adults: Coronary Artery Risk Development in Young Adults (CARDIA) study. *Circulation* 2014; **130**: 10-17 [PMID: [24982115](#) DOI: [10.1161/CIRCULATIONAHA.113.005445](#)]
- 17 **Xanthakis V**, Enserro DM, Murabito JM, Polak JF, Wollert KC, Januzzi JL, Wang TJ, Tofler G, Vasan RS. Ideal cardiovascular health: associations with biomarkers and subclinical disease and impact on incidence of cardiovascular disease in the Framingham Offspring Study. *Circulation* 2014; **130**: 1676-1683 [PMID: [25274000](#) DOI: [10.1161/CIRCULATIONAHA.114.009273](#)]
- 18 **Loprinzi PD**, Branscum A, Hanks J, Smit E. Healthy Lifestyle Characteristics and Their Joint Association With Cardiovascular Disease Biomarkers in US Adults. *Mayo Clin Proc* 2016; **91**: 432-442 [PMID: [26906650](#) DOI: [10.1016/j.mayocp.2016.01.009](#)]
- 19 **Bossé Y**, Mathieu P, Pibarot P. Genomics: the next step to elucidate the etiology of calcific aortic valve stenosis. *J Am Coll Cardiol* 2008; **51**: 1327-1336 [PMID: [18387432](#) DOI: [10.1016/j.jacc.2007.12.031](#)]
- 20 **New SE**, Aikawa E. Molecular imaging insights into early inflammatory stages of arterial and aortic valve calcification. *Circ Res* 2011; **108**: 1381-1391 [PMID: [21617135](#) DOI: [10.1161/CIRCRESAHA.110.234146](#)]
- 21 **O'Brien KD**, Reichenbach DD, Marcovina SM, Kuusisto J, Alpers CE, Otto CM. Apolipoproteins B, (a), and E accumulate in the morphologically early lesion of 'degenerative' valvular aortic stenosis. *Arterioscler Thromb Vasc Biol* 1996; **16**: 523-532 [PMID: [8624774](#) DOI: [10.1161/01.ATV.16.4.523](#)]
- 22 **Dweck MR**, Jones C, Joshi NV, Fletcher AM, Richardson H, White A, Marsden M, Pessotto R, Clark JC, Wallace WA, Salter DM, McKillop G, van Beek EJ, Boon NA, Rudd JH, Newby DE. Assessment of valvular calcification and inflammation by positron emission tomography in patients with aortic stenosis. *Circulation* 2012; **125**: 76-86 [PMID: [22090163](#) DOI: [10.1161/CIRCULATIONAHA.111.051052](#)]
- 23 **Singh JP**, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999; **83**: 897-902 [PMID: [10190406](#) DOI: [10.1016/S0002-9149\(98\)01064-9](#)]
- 24 **Palmieri V**, Bella JN, Arnett DK, Roman MJ, Oberman A, Kitzman DW, Hopkins PN, Paranicas M, Rao DC, Devereux RB. Aortic root dilatation at sinuses of valsalva and aortic regurgitation in hypertensive and normotensive subjects: The Hypertension Genetic Epidemiology Network Study. *Hypertension* 2001; **37**: 1229-1235 [PMID: [11358933](#) DOI: [10.1161/01.HYP.37.5.1229](#)]
- 25 **Shapira OM**, Kelleher RM, Zelingher J, Whalen D, Fitzgerald C, Aldea GS, Shemin RJ. Prognosis and quality of life after valve surgery in patients older than 75 years. *Chest* 1997; **112**: 885-894 [PMID: [9377949](#) DOI: [10.1378/chest.112.4.885](#)]
- 26 **Brennan JM**, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, Douglas PS, Peterson ED; DEClIDE AVR (Developing Evidence to Inform Decisions about Effectiveness—Aortic Valve Replacement) Research Team. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. *Circulation* 2013; **127**: 1647-1655 [PMID: [23538379](#) DOI: [10.1161/CIRCULATIONAHA.113.002003](#)]
- 27 **Brennan JM**, Edwards FH, Zhao Y, O'Brien SM, Douglas PS, Peterson ED; Developing Evidence to Inform Decisions About Effectiveness—Aortic Valve Replacement (DEClIDE AVR) Research Team. Long-term survival after aortic valve replacement among high-risk elderly patients in the United States: insights from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, 1991 to 2007. *Circulation* 2012; **126**: 1621-1629 [PMID: [22907936](#) DOI: [10.1161/CIRCULATIONAHA.112.091371](#)]
- 28 **Cribier AG**. The Odyssey of TAVR from concept to clinical reality. *Tex Heart Inst J* 2014; **41**: 125-130 [PMID: [24808769](#) DOI: [10.14503/THIJ-14-4137](#)]
- 29 **Webb JG**, Binder RK. Transcatheter aortic valve implantation: the evolution of prostheses, delivery systems and approaches. *Arch Cardiovasc Dis* 2012; **105**: 153-159 [PMID: [22520798](#) DOI: [10.1016/j.acvd.2012.02.001](#)]
- 30 **Biancari F**, Rosato S, D'Errigo P, Ranucci M, Onorati F, Barbanti M, Santini F, Tamburino C, Santoro G, Grossi C, Covello RD, Ventura M, Fusco D, Seccareccia F; OBSERVANT Research Group. Immediate and Intermediate Outcome After Transapical Versus Transfemoral Transcatheter Aortic Valve Replacement. *Am J Cardiol* 2016; **117**: 245-251 [PMID: [26639038](#) DOI: [10.1016/j.amjcard.2015.10.036](#)]
- 31 **Fried LP**, Hadley EC, Walston JD, Newman AB, Guralnik JM, Studenski S, Harris TB, Ershler WB, Ferrucci L. From bedside to bench: research agenda for frailty. *Sci Aging Knowledge Environ* 2005; **2005**: pe24 [PMID: [16079413](#) DOI: [10.1126/sageke.2005.31.pe24](#)]
- 32 **Prêtre R**, Turina MI. Cardiac valve surgery in the octogenarian. *Heart* 2000; **83**: 116-121 [PMID: [10618352](#) DOI: [10.1136/heart.83.1.116](#)]
- 33 **Cheitlin MD**, Gerstenblith G, Hazzard WR, Pasternak R, Fried LP, Rich MW, Krumholz HM, Peterson E, Reves JG, McKay C, Saksena S, Shen WK, Akhtar M, Brass LM, Biller J. Database Conference January 27-30, 2000, Washington D.C.—Do existing databases answer clinical questions about geriatric cardiovascular disease and stroke? *Am J Geriatr Cardiol* 2001; **10**: 207-223 [PMID: [11455241](#) DOI: [10.1111/j.1076-7460.2003.00696.x](#)]
- 34 **Smith CR**, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011; **364**: 2187-2198 [PMID: [21639811](#) DOI: [10.1056/NEJMoa1103510](#)]
- 35 **Kodali SK**, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012; **366**: 1686-1695 [PMID: [22443479](#) DOI: [10.1056/NEJMoa1200384](#)]
- 36 **Hirji SA**, Ramirez-Del Val F, Kolkailah AA, Ejiofor JI, McGurk S, Chowdhury R, Lee J, Shah PB,

- Sobieszczyk PS, Aranki SF, Pelletier MP, Shekar PS, Kaneko T. Outcomes of surgical and transcatheter aortic valve replacement in the octogenarians-surgery still the gold standard? *Ann Cardiothorac Surg* 2017; **6**: 453-462 [PMID: 29062740 DOI: 10.21037/acs.2017.08.01]
- 37 **Yamamoto M**, Mouillet G, Meguro K, Gilard M, Laskar M, Eltchaninoff H, Fajadet J, Iung B, Donzeau-Gouge P, Leprince P, Leuguerrier A, Prat A, Lievre M, Chevreul K, Dubois-Rande JL, Teiger E; FRANCE-2 Registry Investigators. Clinical results of transcatheter aortic valve implantation in octogenarians and nonagenarians: insights from the FRANCE-2 registry. *Ann Thorac Surg* 2014; **97**: 29-36 [PMID: 24140210 DOI: 10.1016/j.athoracsur.2013.07.100]
- 38 **Tamburino C**, Barbanti M, D'Errigo P, Ranucci M, Onorati F, Covello RD, Santini F, Rosato S, Santoro G, Fusco D, Grossi C, Seccareccia F; OBSERVANT Research Group. 1-Year Outcomes After Transfemoral Transcatheter or Surgical Aortic Valve Replacement: Results From the Italian OBSERVANT Study. *J Am Coll Cardiol* 2015; **66**: 804-812 [PMID: 26271063 DOI: 10.1016/j.jacc.2015.06.013]
- 39 **Abramowitz Y**, Chakravarty T, Jilaihawi H, Kashif M, Zadikany R, Lee C, Matar G, Cheng W, Makkar RR. Comparison of Outcomes of Transcatheter Aortic Valve Implantation in Patients ≥ 90 Years Versus < 90 Years. *Am J Cardiol* 2015; **116**: 1110-1115 [PMID: 26235927 DOI: 10.1016/j.amjcard.2015.06.033]
- 40 **Leon MB**, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG; PARTNER 2 Investigators. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 2016; **374**: 1609-1620 [PMID: 27040324 DOI: 10.1056/NEJMoa1514616]
- 41 **Reardon MJ**, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP; SURTAVI Investigators. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 2017; **376**: 1321-1331 [PMID: 28304219 DOI: 10.1056/NEJMoa1700456]
- 42 **Nishimura RA**, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM, Thompson A. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017; **135**: e1159-e1195 [PMID: 28298458 DOI: 10.1161/CIR.0000000000000503]
- 43 **Rosato S**, Santini F, Barbanti M, Biancari F, D'Errigo P, Onorati F, Tamburino C, Ranucci M, Covello RD, Santoro G, Grossi C, Ventura M, Fusco D, Seccareccia F; OBSERVANT Research Group. Transcatheter Aortic Valve Implantation Compared With Surgical Aortic Valve Replacement in Low-Risk Patients. *Circ Cardiovasc Interv* 2016; **9**: e003326 [PMID: 27154298 DOI: 10.1161/CIRCINTERVENTIONS.115.003326]
- 44 **Enriquez-Sarano M**, Klotz E, Garratt KN, Bailey KR, Tajik AJ, Holmes DR. Secular trends in coronary atherosclerosis--analysis in patients with valvular regurgitation. *N Engl J Med* 1996; **335**: 316-322 [PMID: 8663854 DOI: 10.1056/NEJM199608013350504]
- 45 **Perek B**, Casadei V, Puślecki M, Stefaniak S, Maison D, Gwizdała A, Perek A, Szarpak Ł, Jemielity M. Clinical presentation, surgical management, and outcomes of patients treated for aortic stenosis and coronary artery disease. Does age matter? *Kardiologia Pol* 2018; **76**: 655-661 [PMID: 29313564 DOI: 10.5603/KP.2018.0005]
- 46 **Sankaramangalam K**, Banerjee K, Kandregula K, Mohanany D, Parashar A, Jones BM, Jobanputra Y, Mick S, Krishnaswamy A, Svensson LG, Kapadia SR. Impact of Coronary Artery Disease on 30-Day and 1-Year Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement: A Meta-Analysis. *J Am Heart Assoc* 2017; **6**: pii: e006092 [PMID: 29021275 DOI: 10.1161/JAHA.117.006092]
- 47 **Yu PJ**, Mattia A, Cassiere HA, Esposito R, Manetta F, Kohn N, Hartman AR. Should high risk patients with concomitant severe aortic stenosis and mitral valve disease undergo double valve surgery in the TAVR era? *J Cardiothorac Surg* 2017; **12**: 123 [PMID: 29284509 DOI: 10.1186/s13019-017-0688-z]
- 48 **Nombela-Franco L**, Ribeiro HB, Urena M, Allende R, Amat-Santos I, DeLarochelière R, Dumont E, Doyle D, DeLarochelière H, Laflamme J, Laflamme L, García E, Macaya C, Jiménez-Quevedo P, Côté M, Bergeron S, Beaudoin J, Pibarot P, Rodés-Cabau J. Significant mitral regurgitation left untreated at the time of aortic valve replacement: a comprehensive review of a frequent entity in the transcatheter aortic valve replacement era. *J Am Coll Cardiol* 2014; **63**: 2643-2658 [PMID: 24681140 DOI: 10.1016/j.jacc.2014.02.573]
- 49 **Cortés C**, Amat-Santos IJ, Nombela-Franco L, Muñoz-García AJ, Gutiérrez-Ibanes E, De La Torre Hernández JM, Córdoba-Soriano JG, Jiménez-Quevedo P, Hernández-García JM, González-Mansilla A, Ruano J, Jiménez-Mazuecos J, Castrodeza J, Tobar J, Islas F, Revilla A, Puri R, Puerto A, Gómez I, Rodés-Cabau J, San Román JA. Mitral Regurgitation After Transcatheter Aortic Valve Replacement: Prognosis, Imaging Predictors, and Potential Management. *JACC Cardiovasc Interv* 2016; **9**: 1603-1614 [PMID: 27491611 DOI: 10.1016/j.jcin.2016.05.025]
- 50 **Khawaja MZ**, Williams R, Hung J, Arri S, Asstress KN, Bolter K, Wilson K, Young CP, Bapat V, Hancock J, Thomas M, Redwood S. Impact of preprocedural mitral regurgitation upon mortality after transcatheter aortic valve implantation (TAVI) for severe aortic stenosis. *Heart* 2014; **100**: 1799-1803 [PMID: 25155800 DOI: 10.1136/heartjnl-2014-305775]
- 51 **Schofer J**, Siminiak T, Haude M, Herrman JP, Vainer J, Wu JC, Levy WC, Mauri L, Feldman T, Kwong RY, Kaye DM, Duffy SJ, Tübler T, Degen H, Brandt MC, Van Bibber R, Goldberg S, Reuter DG, Hoppe UC. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. *Circulation* 2009; **120**: 326-333 [PMID: 19597051 DOI: 10.1161/CIRCULATIONAHA.109.849885]
- 52 **David TE**, Ivanov J, Armstrong S, Christie D, Rakowski H. A comparison of outcomes of mitral valve repair for degenerative disease with posterior, anterior, and bileaflet prolapse. *J Thorac Cardiovasc Surg* 2005; **130**: 1242-1249 [PMID: 16256774 DOI: 10.1016/j.jtcvs.2005.06.046]
- 53 **Kodali SK**, Velagapudi P, Hahn RT, Abbott D, Leon MB. Valvular Heart Disease in Patients ≥ 80 Years of Age. *J Am Coll Cardiol* 2018; **71**: 2058-2072 [PMID: 29724358 DOI: 10.1016/j.jacc.2018.03.459]
- 54 **Ukita Y**, Yuda S, Sugio H, Yonezawa A, Takayanagi Y, Masuda-Yamamoto H, Tanaka-Saito N, Ohnishi H, Miura T. Prevalence and clinical characteristics of degenerative mitral stenosis. *J Cardiol* 2016; **68**:

- 248-252 [PMID: [26546498](#) DOI: [10.1016/j.jjcc.2015.09.021](#)]
- 55 **Kristensen SD**, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, Ford I, Gonzalez-Juanatey JR, Gorenk B, Heyndrickx GR, Hoeft A, Huber K, Jung B, Kjeldsen KP, Longrois D, Lüscher TF, Pierard L, Pocock S, Price S, Roffi M, Simes PA, Sousa-Uva M, Voudris V, Funck-Brentano C; Authors/Task Force Members. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J* 2014; **35**: 2383-2431 [PMID: [25086026](#) DOI: [10.1093/eurheartj/ehu282](#)]
 - 56 **Biancari F**, Schifano P, Pighi M, Vasques F, Juvonen T, Vinco G. Pooled estimates of immediate and late outcome of mitral valve surgery in octogenarians: a meta-analysis and meta-regression. *J Cardiothorac Vasc Anesth* 2013; **27**: 213-219 [PMID: [23507013](#) DOI: [10.1053/j.jvca.2012.11.007](#)]
 - 57 **Acker MA**, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, Smith PK, Hung JW, Blackstone EH, Puskas JD, Argenziano M, Gammie JS, Mack M, Ascheim DD, Bagiella E, Moquete EG, Ferguson TB, Horvath KA, Geller NL, Miller MA, Woo YJ, D'Alessandro DA, Ailawadi G, Dagenais F, Gardner TJ, O'Gara PT, Michler RE, Kron IL; CTSN. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med* 2014; **370**: 23-32 [PMID: [24245543](#) DOI: [10.1056/NEJMoa1312808](#)]
 - 58 **Dayan V**, Soca G, Cura L, Mestres CA. Similar survival after mitral valve replacement or repair for ischemic mitral regurgitation: a meta-analysis. *Ann Thorac Surg* 2014; **97**: 758-765 [PMID: [24370200](#) DOI: [10.1016/j.athoracsur.2013.10.044](#)]
 - 59 **Mick SL**, Keshavamurthy S, Gillinov AM. Mitral valve repair versus replacement. *Ann Cardiothorac Surg* 2015; **4**: 230-237 [PMID: [26309824](#) DOI: [10.3978/j.issn.2225-319X.2015.03.011](#)]
 - 60 **Vassileva CM**, Mishkel G, McNeely C, Boley T, Markwell S, Scaife S, Hazelrigg S. Long-term survival of patients undergoing mitral valve repair and replacement: a longitudinal analysis of Medicare fee-for-service beneficiaries. *Circulation* 2013; **127**: 1870-1876 [PMID: [23569153](#) DOI: [10.1161/CIRCULATIONAHA.113.002200](#)]
 - 61 **Badhwar V**, Peterson ED, Jacobs JP, He X, Brennan JM, O'Brien SM, Dokholyan RS, George KM, Bolling SF, Shahian DM, Grover FL, Edwards FH, Gammie JS. Longitudinal outcome of isolated mitral repair in older patients: results from 14,604 procedures performed from 1991 to 2007. *Ann Thorac Surg* 2012; **94**: 1870-7; discussion 1877-9 [PMID: [22858278](#) DOI: [10.1016/j.athoracsur.2012.05.105](#)]
 - 62 **Kang DH**, Heo R, Lee S, Baek S, Kim DH, Song JM, Song JK, Lee JW. Initial surgery versus conservative management of symptomatic severe mitral regurgitation in the elderly. *Heart* 2018; **104**: 849-854 [PMID: [28982717](#) DOI: [10.1136/heartjnl-2017-311759](#)]
 - 63 **Zhuge RQ**, Hou XP, Qi XL, Wu YJ, Zhang MZ. Clinical features and treatment options for mitral regurgitation in elderly inpatients. *J Geriatr Cardiol* 2018; **15**: 428-433 [PMID: [30108615](#) DOI: [10.11909/j.issn.1671-5411.2018.06.005](#)]
 - 64 **Seeburger J**, Falk V, Garbade J, Noack T, Kiefer P, Vollroth M, Mohr FW, Misfeld M. Mitral valve surgical procedures in the elderly. *Ann Thorac Surg* 2012; **94**: 1999-2003 [PMID: [22835550](#) DOI: [10.1016/j.athoracsur.2012.05.069](#)]
 - 65 **Silaschi M**, Chaubey S, Aldalati O, Khan H, Uzzaman MM, Singh M, Baghai M, Deshpande R, Wendler O. Is Mitral Valve Repair Superior to Mitral Valve Replacement in Elderly Patients? Comparison of Short- and Long-Term Outcomes in a Propensity-Matched Cohort. *J Am Heart Assoc* 2016; **5**: pii: e003605 [PMID: [27468927](#) DOI: [10.1161/JAHA.116.003605](#)]
 - 66 **Chikwe J**, Goldstone AB, Passage J, Anyanwu AC, Seeburger J, Castillo JG, Filsoufi F, Mohr FW, Adams DH. A propensity score-adjusted retrospective comparison of early and mid-term results of mitral valve repair versus replacement in octogenarians. *Eur Heart J* 2011; **32**: 618-626 [PMID: [20846993](#) DOI: [10.1093/eurheartj/ehq331](#)]
 - 67 **Shang X**, Lu R, Liu M, Xiao S, Dong N. Mitral valve repair versus replacement in elderly patients: a systematic review and meta-analysis. *J Thorac Dis* 2017; **9**: 3045-3051 [PMID: [29221278](#) DOI: [10.21037/jtd.2017.08.43](#)]
 - 68 **Feldman T**, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Lohin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011; **364**: 1395-1406 [PMID: [21463154](#) DOI: [10.1056/NEJMoa1009355](#)]
 - 69 **Dal-Bianco JP**, Inglessis I, Melnitchouk S, Daher M, Palacios IF. Percutaneous Mitral Valve Edge-to-Edge Repair for Degenerative Mitral Regurgitation. *Curr Treat Options Cardiovasc Med* 2015; **17**: 389 [PMID: [26070587](#) DOI: [10.1007/s11936-015-0389-7](#)]
 - 70 **Taramasso M**, Vanermen H, Maisano F, Guidotti A, La Canna G, Alfieri O. The growing clinical importance of secondary tricuspid regurgitation. *J Am Coll Cardiol* 2012; **59**: 703-710 [PMID: [22340261](#) DOI: [10.1016/j.jacc.2011.09.069](#)]
 - 71 **Cohen SR**, Sell JE, McIntosh CL, Clark RE. Tricuspid regurgitation in patients with acquired, chronic, pure mitral regurgitation. II. Nonoperative management, tricuspid valve annuloplasty, and tricuspid valve replacement. *J Thorac Cardiovasc Surg* 1987; **94**: 488-497 [PMID: [3657251](#)]
 - 72 **Girard SE**, Nishimura RA, Warnes CA, Dearani JA, Puga FJ. Idiopathic annular dilation: a rare cause of isolated severe tricuspid regurgitation. *J Heart Valve Dis* 2000; **9**: 283-287 [PMID: [10772049](#) DOI: [10.1016/S1053-2498\(99\)00135-7](#)]
 - 73 **Topilsky Y**, Khanna A, Le Tourneau T, Park S, Michelena H, Suri R, Mahoney DW, Enriquez-Sarano M. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. *Circ Cardiovasc Imaging* 2012; **5**: 314-323 [PMID: [22447806](#) DOI: [10.1161/CIRCIMAGING.111.967919](#)]
 - 74 **Mahmood F**, Kim H, Chaudary B, Bergman R, Matyal R, Gerstle J, Gorman JH, Gorman RC, Khabbaz KR. Tricuspid annular geometry: a three-dimensional transesophageal echocardiographic study. *J Cardiothorac Vasc Anesth* 2013; **27**: 639-646 [PMID: [23725682](#) DOI: [10.1053/j.jvca.2012.12.014](#)]
 - 75 **Q Tri HH**, Vinh PN. Progression of Tricuspid Regurgitation after Mitral Valve Replacement for Rheumatic Heart Disease. *J Heart Valve Dis* 2017; **26**: 290-294 [PMID: [29092113](#)]
 - 76 **Zack CJ**, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, Miller VM, Nishimura RA. National Trends and Outcomes in Isolated Tricuspid Valve Surgery. *J Am Coll Cardiol* 2017; **70**: 2953-2960 [PMID: [29241483](#) DOI: [10.1016/j.jacc.2017.10.039](#)]
 - 77 **Nath J**, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004; **43**: 405-409 [PMID: [15013122](#) DOI: [10.1016/j.jacc.2003.09.036](#)]
 - 78 **Subbotina I**, Girdauskas E, Bernhardt AM, Sinning C, Reichenspurner H, Sill B. Comparison of

- Outcomes of Tricuspid Valve Surgery in Patients with Reduced and Normal Right Ventricular Function. *Thorac Cardiovasc Surg* 2017; **65**: 617-625 [PMID: [28841733](#) DOI: [10.1055/s-0037-1604450](#)]
- 79 **Rostagno C**, Gelsomino S, Stefano PL, Padeletti L. Rhythmic and haemodynamic determinants of long-term survival after radiofrequency ablation of atrial fibrillation in mitral valve surgery. *Eur Heart J Qual Care Clin Outcomes* 2016; **2**: 285-290 [PMID: [29474714](#) DOI: [10.1093/ehjqcco/qcw021](#)]
- 80 **Nickenig G**, Kowalski M, Hausleiter J, Braun D, Schofer J, Yzeiraj E, Rudolph V, Friedrichs K, Maisano F, Taramasso M, Fam N, Bianchi G, Bedogni F, Denti P, Alfieri O, Latib A, Colombo A, Hammerstingl C, Schueler R. Transcatheter Treatment of Severe Tricuspid Regurgitation With the Edge-to-Edge MitraClip Technique. *Circulation* 2017; **135**: 1802-1814 [PMID: [28336788](#) DOI: [10.1161/CIRCULATIONAHA.116.024848](#)]

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Retrospective Study

Prevalence and clinical characteristics associated with left atrial thrombus detection: Apixaban

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Abstract

BACKGROUND

The prevalence of left atrial appendage (LAA) thrombus detection by transesophageal echocardiogram (TEE) in patients with non-valvular atrial fibrillation (AF) anticoagulated with apixaban is not well defined and identification of additional risk factors may help guide the selection process for pre-procedural TEE. The purpose of our study was to retrospectively analyze the prevalence of LAA thrombus detection by TEE in patients continuously anticoagulated with apixaban for ≥ 4 wk and evaluate for any cardiac risk factors or echocardiographic characteristics which may serve as predictors of thrombus formation.

AIM

To retrospectively analyze the prevalence of LAA thrombus detection by TEE in patients continuously anticoagulated with apixaban.

METHODS

Clinical and echocardiographic data for 820 consecutive patients with AF undergoing TEE at Augusta University Medical Center over a four-year period were retrospectively analyzed. All patients (apixaban: 226) with non-valvular AF and documented compliance with apixaban for ≥ 4 wk prior to index TEE were included.

RESULTS

Following ≥ 4 wk of continuous anticoagulation with apixaban, the prevalence of

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LAA thrombus and LAA thrombus/dense spontaneous echocardiographic contrast was 3.1% and 6.6%, respectively. Persistent AF, left ventricular ejection fraction < 30%, severe LA dilation, and reduced LAA velocity were associated with thrombus formation. Following multivariate logistic regression, persistent AF (OR: 7.427; 95%CI: 1.02 to 53.92; $P = 0.0474$), and reduced LAA velocity (OR: 1.086; 95%CI: 1.010 to 1.187; $P = 0.0489$) were identified as independent predictors of LAA thrombus. No Thrombi were detected in patients with a CHA₂DS₂-VASc score ≤ 1 .

CONCLUSION

Among patients with non-valvular AF and ≥ 4 wk of anticoagulation with apixaban, the prevalence of LAA thrombus detected by TEE was 3.1%. This suggests that continuous therapy with apixaban does not completely eliminate the risk of LAA thrombus and that TEE prior to cardioversion or catheter ablation may be of benefit in patients with multiple risk factors.

Key words: Atrial fibrillation; Anticoagulation; Left atrial appendage thrombus; Transesophageal echocardiography

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Core tip: The prevalence of left atrial appendage (LAA) thrombus detection by transesophageal echocardiogram (TEE) in patients with non-valvular atrial fibrillation (AF) anticoagulated with apixaban is not well defined and identification of additional risk factors may help guide the selection process for pre-procedural TEE. At our institution, the prevalence of thrombus detection in patients compliant with apixaban was 3.1%. Persistent AF, left ventricular ejection fraction < 30%, severe LA dilation, and reduced LAA velocity were associated with thrombus formation. Following multivariate logistic regression, persistent AF and reduced LAA velocity were identified as independent predictors of thrombus detection.

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased risk of systemic thromboembolism due to the development of left atrial (LA) and LA appendage (LAA) thrombi^[1,2]. Among patients with non-valvular AF, 90% of atrial thrombi are seen within the LAA^[3]. Transesophageal echocardiography (TEE) is the most sensitive and specific imaging modality for the detection LA thrombi and is routinely utilized in patients undergoing elective cardioversion or catheter ablation to reduce the risk of thromboembolic events^[1,2,4-7]. Risk factors such as structural heart disease, left atrial size, reduced left ventricular ejection fraction (LVEF), persistent AF, an CHA₂DS₂-VASc score have been reported as independent predictors of LAA thrombus detection by TEE^[8-13].

Several randomized trials have demonstrated the efficacy of non-vitamin K dependent oral anticoagulants (NOACs) to reduce rates of stroke and systemic thromboembolism compared to warfarin, however, their impact on the detection of LA thrombi by TEE is less well established^[14,15]. In patients receiving ≥ 3 wk of continuous anticoagulation with warfarin, the prevalence of LA thrombus detection is reported to be between 1.55% and 7.7%^[8,12,13,16-20]. Recent data has helped to elucidate the prevalence of LA thrombi in patients anticoagulated with NOACs, particularly in patients prescribed dabigatran or rivaroxaban prior to catheter ablation^[18-20]. With regards to apixaban, data remains limited^[18-22]. With at least one study reporting a decline in utilization of TEE prior to catheter ablation and prescription rates for NOACs increasing on a yearly basis, further analysis of patients prescribed apixaban could have clinically meaningful implications^[22,23]. Identification of additional risk

factors which may predict LAA thrombus detection in patients prescribed apixaban is of particular interest as it could help identify a population which would be at increased risk of adverse outcomes should intervention be performed without TEE.

MATERIALS AND METHODS

Study population

Following institutional review board approval, we retrospectively identified 820 consecutive patients with a diagnosis of AF undergoing TEE at Augusta University Medical Center between January 1, 2014 and September 30, 2017 (Figure 1). We excluded 146 patients who were not on any anticoagulation, 183 patients anticoagulated with other NOACs (Rivaroxaban: 122, Dabigatran: 60, Edoxaban: 1), 221 patients anticoagulated with Warfarin, and 15 patients who were determined to be incorrectly coded as AF and in whom TEE was performed for an alternative indication. Two hundred fifty-five patients were anticoagulated with apixaban. Within this cohort, 13 patients were excluded due to documented non-compliance with continuous oral anticoagulation in the 4 wk preceding index TEE, 8 for LAA ligation, 2 for valvular AF, and 6 patients with incomplete echocardiographic data. The final study population included 226 patients anticoagulated with apixaban.

Data extraction and baseline assessment

A detailed chart review was conducted in accordance with the study protocol targeting cardiac risk factors, anticoagulant therapy, and echocardiographic data. A CHA₂DS₂-VASc score was calculated for each patient in accordance with Lip *et al*^[24] AF lasting ≤ 7 d or > 7 d was defined as paroxysmal and persistent, respectively^[1,2]. All physician notes in the four weeks preceding TEE were reviewed. Any patient with documented medication noncompliance was excluded from the study.

Cardiac imaging

TEE Imaging was performed using Phillips EPIQ 7 ultrasound machine and Phillips IE33 ultrasound transducer (Andover, Massachusetts). Standard TEE images were acquired including focused imaging of the LA and LAA. Technique routinely used at our institution involves acquisition of at least two orthogonal views of the LAA. All TEEs were reviewed by at least one of two echocardiographers with strong agreement between observers (Cohen's kappa: 0.89). A thrombus was reported if a well-circumscribed, echo-reflective mass distinct from the LA endocardium or pectinate muscles was present in the appendage or body of the LA^[4]. Spontaneous echo contrast (SEC) was classified as dense, clearing, or absent correlating with 3-4+, 1-2+, or 0 as graded by Fatkin *et al*^[25] SEC was classified as dense if a dense swirling pattern was observed in the LAA and was detectable throughout the cardiac cycle (with variable intensity). SEC was classified as clearing if minimal echodensity was observed in the LAA and was detectable transiently during the cardiac cycle. LAA velocities were determined based on peak velocities averaged over a minimum of two full cardiac cycles in the view which was most parallel to the LAA ostium. LA size was assessed semi-quantitatively and documented as normal, mildly, moderately, or severely dilated.

Follow up

For any patient with LA or LAA thrombi identified on TEE, data was collected for 180 d following index study. If a subsequent TEE was performed between 30 and 180 d following diagnosis of LA or LAA thrombi, then follow up data was collected including changes in oral anticoagulation, antiplatelet therapy, and resolution of thrombus.

Statistical analysis

All statistical computations and hypothesis tests were performed using R 3.4.3 (<https://www.r-project.org/>). To compare demographics and echocardiographic variables between groups, Fisher's exact test was used for categorical variables and Welch's *t*-test was used for the continuous variables. All hypothesis tests were performed at 5% significance level. Univariate logistic regression model was used to associate the odds of occurrence of an event (LAA thrombus formation, dense SEC) to demographic and echocardiographic factors. For scenarios where the odds of the event are zero, pseudo-data points were added to obtain valid estimates and test statistics. Significance of the factors was determined using a two-sided *z*-test. For each univariate model, a two-sided 95% confidence interval (CI) is reported. Using the variables deemed as significant, a multivariate logistic regression was fit to study independence of the variables.

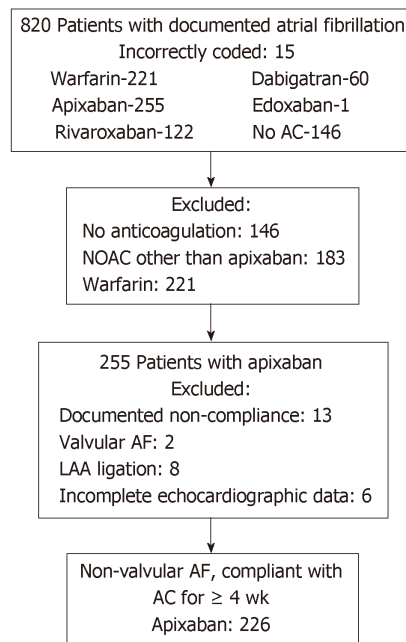


Figure 1 Study population. AC: Anticoagulation; AF: Atrial fibrillation; LAA: Left atrial appendage; NOAC: Non-vitamin K oral anticoagulant.

RESULTS

Population demographics and echocardiographic characteristics

Patient demographics, cardiac risk factors and echocardiographic characteristics for patients with and without thrombus detection are reported in Table 1. The presence of end-stage renal disease, persistent AF, reduced LAA velocities, severe LA dilation, and dense SEC were more common in patients found to have LAA thrombus. Overall, the study population was at meaningful risk of thromboembolic events as 181 (80.1%) patients had CHA₂DS₂-VASc score ≥ 2 .

Prevalence of LAA thrombus and SEC

In patients compliant with apixaban, the prevalence of LAA thrombus and LAA thrombus/Dense SEC was 3.1% and 6.6%, respectively. Full data for the study population based on prevalence of thrombus is provided in Table 1. A similar table, based on the prevalence of thrombus/dense SEC, is available in the online materials (Supplementary Table 1). Among patients with LVEF $< 30\%$ and $\geq 50\%$, thrombus was detected in 9.1% and 2.0% ($P = 0.074$), respectively. The prevalence of LAA thrombus based on CHA₂DS₂-VASc score is summarized in Supplementary Table 2. Notably, no thrombi were identified in the 45 (19.9%) patients with a CHA₂DS₂-VASc score ≤ 1 .

Univariate and multivariate predictors of LAA thrombus

In patients anticoagulated with apixaban, persistent AF, LVEF $< 30\%$, severe LA dilation, and reduced LAA velocity were identified as univariate predictors of LAA thrombus detection (Table 2). On multivariate logistic regression, persistent AF (OR: 7.427; 95%CI: 1.02 to 53.92; $P = 0.0474$), and reduced LAA velocity (OR: 1.086; 95%CI: 1.010 to 1.187; $P = 0.0489$) remained independent predictors of LAA thrombus detection. On further analysis, the OR for each 10% decrease in LVEF was 1.517 (95%CI: 0.971 to 2.369; $P = 0.067$). For the combined endpoint of LAA thrombus detection/dense SEC, reduced LAA velocity (OR: 1.131; 95%CI: 1.031 to 1.235; $p = 0.0061$), was a significant independent predictor on multivariate logistic regression with persistent AF (OR: 4.665; 95%CI: 0.81 to 27.0; $P = 0.0856$) and severe LA dilation (OR: 5.915; 95%CI: 0.74 to 46.98; $P = 0.0927$) approaching significance (Supplementary Table 3).

Subsequent cardiac imaging and thrombus resolution

Six patients had a subsequent TEE performed 30-180 d following the diagnosis of LAA thrombus and documented compliance with continuous anticoagulation. Anticoagulation and echocardiographic data, as well as, CHA₂DS₂-VASc score for each patient is provided in Table 3. These patients were anticoagulated for a mean of

Table 1 Cardiac risk factors and echocardiographic characteristics by presence of thrombus

	Study population (n = 226)	Apixaban-thrombus (n = 7)	Apixaban - no thrombus (n = 219)	P-value ¹
Age	65.8 ± 11.9	68.1 ± 8.0	65.7 ± 11.9	0.458
Race				
White	190 (84.1)	4 (57.1)	186 (84.9)	0.0825
Black	34 (15.0)	3 (42.9)	31 (14.2)	0.0712
Hispanic	0 (0)	0 (0)	0 (0)	-
Asian	2 (0.9)	0 (0)	2 (0.9)	1
Most recent Cr	1.01 ± 0.33	1.18 ± 0.82	1.01 ± 0.32	0.662
ESRD	6 (2.7)	2 (28.5)	4 (1.8)	0.012
Clopidogrel	7 (3.1)	0 (0)	7 (3.2)	1
Aspirin	83 (36.7)	2 (28.5)	81 (37.0)	1
CHA ₂ DS ₂ -VASc	2.83 ± 1.62	3.43 ± 1.40	2.81 ± 1.62	0.354
CHF	88 (34.5)	3 (42.9)	75 (34.2)	0.695
Hypertension	184 (81.4)	7 (100)	177 (80.8)	0.353
Age > 75	50 (22.1)	1 (14.3)	49 (22.4)	1
Diabetes	50 (22.1)	2 (28.5)	48 (21.9)	0.652
Stroke	11 (4.9)	0 (0)	11 (5.0)	1
Vascular disease	26 (11.5)	1 (14.3)	25 (11.4)	0.580
Age > 65	145 (64.2)	6 (85.7)	139 (63.5)	0.426
Female	87 (38.5)	2 (28.5)	85 (38.8)	0.710
Persistent AF	59 (26.1)	5 (71.4)	54 (24.7)	0.014
Echocardiographic data				
LVEF	47.8 ± 14.3	38.6 ± 19.3	48.1 ± 14.1	0.241
LVEF < 30	33 (14.6)	3 (42.9)	30 (13.7)	0.066
LVEF 30-49	44 (19.5)	1 (14.3)	43 (19.6)	1
LVEF ≥ 50	149 (65.9)	3 (42.9)	146 (66.7)	0.233
LAA velocity	48.4 ± 18.1	27.8 ± 10.5	49.0 ± 18.0	0.001
LAA velocity < 40 cm/s	71 (31.4)	6 (85.7)	65 (29.7)	0.004
SEC classification				
None	206 (91.2)	1 (14.3)	205 (93.6)	<0.001
Clearing	7 (3.1)	1 (14.3)	6 (2.7)	0.200
Dense	13 (5.8)	5 (71.4)	8 (3.7)	<0.001
LA dilation				
Moderate	66 (29.2)	1 (14.3)	65 (29.7)	0.677
Severe	59 (26.1)	6 (85.7)	53 (24.2)	0.001
Mitral Regurgitation				
Moderate	53 (23.5)	1 (14.3)	52 (23.7)	1
Severe	5 (2.2)	1 (14.3)	4 (1.8)	0.147

¹P-values denote differences between cohorts with and without thrombus. AF: Atrial fibrillation; CHF: Congestive heart failure; Cr: Creatinine; ESRD: End-stage renal disease; LA: Left atria; LAA: Left atrial appendage; LVEF: Left ventricular ejection fraction; SEC: Spontaneous echo contrast.

94.0 d and thrombus resolution occurred in 83.3%.

DISCUSSION

The purpose of our study was to retrospectively analyze the prevalence of LAA thrombus in patients continuously anticoagulated with apixaban for ≥ 4 wk and evaluate for any cardiac risk factors or echocardiographic characteristics which may serve as predictors of thrombus formation.

Prevalence of LAA thrombus detection

To date, there remains limited data on the prevalence of LAA thrombus detection by TEE amongst patients with non-valvular AF on apixaban therapy. Multiple recent retrospective analyses have helped to elucidate the prevalence of LAA thrombus in

Table 2 Univariate and multivariate predictors of left atrial appendage thrombus

Apixaban						
Variable	Unadjusted (univariate analysis)			Adjusted (multivariate analysis)		
	OR	95%CI	P-value	OR	95%CI	P-value
CHF	1.440	0.31-6.60	0.6388			
Hypertension	1.933	0.24-15.87	0.5396			
Age > 65	3.453	0.41-29.20	0.2552			
Age > 75	0.578	0.07-4.92	0.6160			
Diabetes	1.425	0.27-7.58	0.6778			
Stroke	2.177	0.25-18.85	0.4800			
Vascular disease	1.293	0.15-11.19	0.8152			
CHA ₂ DS ₂ -VASc	1.261	0.80-2.00	0.3240			
Gender (female)	0.631	0.12-3.32	0.5866			
Persistent AF	7.639	1.44-40.51	0.0169 ¹	7.427	1.02-53.92	0.0474
LVEF < 30%	4.725	1.01-22.17	0.0489 ¹	0.726	0.10-5.12	0.7480
LVEF < 50% ²	2.667	0.58-12.23	0.2069			
Severe left atrial dilation ¹	8.877	1.27-61.85	0.0275 ¹	5.901	0.69-50.62	0.1054
LAA velocity (decrease) ¹	1.110	1.031-1.19	0.0032 ¹	1.086	1.010-1.187	0.0489
LAA velocity < 40 cm/s ²	14.215	1.68-120.40	0.0149 ²			

¹Significant factor in the univariate model which is used in the multivariate model;

²Significant factor in the univariate model but not considered in the multivariate model. AF: Atrial fibrillation; CHF: Congestive heart failure; CI: Confidence interval; LAA: Left atrial appendage; LVEF: Left ventricular ejection fraction; OR: Odds ratio.

patients treated with NOACs, in particular, patients undergoing catheter ablation^[18-20,22]. However, apixaban is often the least represented oral anticoagulant in these studies with a reported prevalence of 0% to 2.9%^[21]. In our study population, the prevalence of LAA thrombus was 3.1% despite ≥ 4 wk of continuous anticoagulation which is consistent with previously published data from smaller cohorts when risk factors are considered. The cohort was at considerable risk given mean CHA₂DS₂-VASc 2.83 ± 1.62 and 80.1% of patients with CHA₂DS₂-VASc ≥ 2 .

Predictors of LAA thrombus detection

The presence of persistent AF, reduced LVEF, severe LA dilation, and reduced LAA velocity were identified as univariate predictors of LA thrombus detection in the apixaban cohort. Following evaluation with multivariate logistic regression, persistent AF and reduced LAA velocity were identified as independent predictors of LA thrombus detection. Commonly identified independent predictors of thrombus formation in recent studies include CHF, persistent AF, reduced LVEF, and elevated CHA₂DS₂-VASc score^[18-20]. Of note, apixaban was often the least represented NOAC in these studies and made minimal contribution to the population with thrombus. Finally, these analyses pooled vitamin K antagonist and NOAC data in order to perform multivariate analysis with one exception, in which the authors describe only 1 independent predictor and report small sample size as a limitation^[18-20]. CHA₂DS₂-VASc score was not identified as a univariate predictor which is likely a result of the relatively small number of low-risk patients in our study population as only 19.9% of patients had CHA₂DS₂-VASc score < 2. Of note, reduced LVEF < 30% was identified as a significant univariate predictor in both analyses, however was not determined to be a significant independent predictor. We believe that reduced LVEF is a significant predictor of thrombus formation as identified in similar studies with variable anticoagulation strategies and rates of compliance^[9,13,19,20]. However, our result likely reflects a limitation of sample size as well as an inherent relationship between advanced cardiomyopathy and clinical/echocardiographic findings most prevalent in high-risk patients with AF.

Rate of LAA thrombus resolution

Data regarding thrombus resolution in patients prescribed apixaban has thus far been limited to case reports and small cohorts^[19,20,26,27]. While data regarding thrombus resolution in patients prescribed warfarin is more prevalent, rates of resolution range

Table 3 Clinical characteristics and thrombus resolution

Study ID	AC after thrombus identification	Thrombus resolution	Duration of AC (d)	P2Y12 inhibitor	Aspirin	LVEF (%)	LA dilation	Spontaneous contrast	LAA velocity (cm/s)	Duration of A-fib	CHADS-VASc score
Apixaban following index TEE (<i>n</i> = 6)											
LA-011	Apixaban	Yes	143	No	No	55	Moderate	None	30.4	Paroxysmal	3
LA-016	Apixaban	Yes	38	Yes	Yes	15	Severe	Severe	14.4	Paroxysmal	2
LA-017	Apixaban	Yes	175	No	Yes	15	Severe	Mild	34.0	Paroxysmal	4
LA-019	Apixaban	Yes	40	No	No	30	Severe	None	26.5	Paroxysmal	2
LA-020	Apixaban	Yes	56	No	Yes	25	Severe	Moderate	28.0	Persistent	3
LA-005	Apixaban	No	112	No	No	65	Moderate	Moderate	49.2	Persistent	4
		5/6 (83.3%)	Mean 94.0 Median 84.0								

AC: Anticoagulation; A-fib: Atrial fibrillation; LA: Left atrium; LAA: Left atrial appendage; LVEF: Left ventricular ejection fraction; TEE: Transesophageal echocardiogram.

from 55% to 82%^[16,17,28]. In our limited cohort, we identified thrombus resolution in 83.3% of patients anticoagulated with apixaban (*n* = 6). Although all patients were confirmed to be compliant with continuous anticoagulation throughout the follow up period, there was significant heterogeneity in the duration of therapy prior to repeat cardiac imaging which limits our ability to draw conclusions regarding the optimal duration of anticoagulation. Regardless, apixaban appears to be a reasonable anticoagulation strategy in this population and warrants further investigation in prospective trial.

Application of study findings

A recent expert consensus statement recommends that current anticoagulation guidelines as they pertain to cardioversion of AF should be observed for patients presenting with AF prior to catheter ablation and that TEE is reasonable despite ≥ 3 wk of continuous anticoagulation^[1,2,7]. Two recent surveys, one including 16 Canadian centers and the other including 521 ablation centers in 24 countries, report that > 70% of ablation centers routinely utilized pre-procedure TEE in all patients^[29,30]. One cost-effectiveness analysis reports an incremental cost-effectiveness ratio of \$226608 per quality-adjusted life year for routine use of TEE in an unselected population prior to pulmonary vein isolation modeled with a 4% prevalence of thrombus. While the prevalence is likely overestimated, this analysis highlights the need to better identify patients with a high pretest probability of LAA thrombus despite continuous anticoagulation in order to improve the cost-benefit ratio of the procedure^[31]. A trend toward more conservative use of pre-procedural TEE appears to be underway as one large ablation center reports a significant decline in the routine utilization of TEE from 86% to 42% over a 5 year period^[22]. While another recent study completely eliminated pre-procedural TEE in favor of intracardiac echocardiography prior to AF ablation. Despite adequate imaging of the LAA in only 71% of patients, the authors report excellent outcomes^[32]. This study is retrospective and meant to explore variables which could be predictors of thrombus formation in patients treated with apixaban. A prospective randomized trial would be needed to conclusively determine and validate a scoring system and/or various cutoffs. However, this may not be practical given the low event rate in this population. Nonetheless, we hope that our work can provide evidence to help guide the selection of patients for pre-procedural TEE.

Study limitations

Our study is limited by the retrospective nature of the data collected. In addition, we cannot objectively confirm 100% compliance with apixaban therapy as quantitative assays are not routinely used in clinical practice. Although we took great effort to exclude any patients with documented non-compliance, our ability to do so would be limited by the history provided and documentation of health care professionals.

In patients with non-valvular AF and a minimum of 4 wk continuous oral

anticoagulation with apixaban, the prevalence of LAA thrombus and LAA thrombus/dense SEC detected by TEE was 3.1% and 6.6%, respectively. Both persistent AF and reduced LAA velocity were identified as independent predictors of LA thrombus detection in patients anticoagulated with apixaban. In addition, LVEF < 30% and severe LA dilation were identified as univariate predictors. We hope that the presence or absence of these clinical findings in addition to established risk factors can help guide the selection process for utilization of pre-procedural TEE in future patients with non-valvular AF anticoagulated with apixaban.

ARTICLE HIGHLIGHTS

Research background

The prevalence of left atrial appendage (LAA) thrombus detection by transesophageal echocardiogram (TEE) in patients anticoagulated for ≥ 4 wk with apixaban is not well defined and predictors of LAA thrombus detection are not completely understood. Furthermore, the efficacy of apixaban to resolve pre-existing LAA thrombi is not well documented.

Research motivation

Prescriptions rates for non-vitamin K dependent oral anticoagulants are increasing on a yearly basis and further analysis of patients prescribed apixaban could have clinically meaningful implications. We aimed to identify significant predictors of LAA thrombus detection on TEE to aid in the selection process for screening in future patients undergoing direct current cardioversion or catheter ablation.

Research objectives

The purpose of our study was to retrospectively analyze the prevalence of LAA thrombus detection by TEE in patients continuously anticoagulated with apixaban for ≥ 4 wk and evaluate for any cardiac risk factors or echocardiographic characteristics which may serve as predictors of thrombus formation.

Research methods

Clinical and echocardiographic data for 820 consecutive patients with atrial fibrillation (AF) undergoing TEE at Augusta University Medical Center over a four-year period were retrospectively analyzed. All patients (apixaban: 226) with non-valvular AF and documented compliance with apixaban for ≥ 4 wk prior to index TEE were included.

Research results

Following ≥ 4 wk of continuous anticoagulation with apixaban, the prevalence of LAA thrombus and LAA thrombus/dense spontaneous echocardiographic contrast was 3.1% and 6.6%, respectively. Persistent AF, left ventricular ejection fraction < 30%, severe LA dilation, and reduced LAA velocity were associated with thrombus formation. Following multivariate logistic regression, persistent AF (OR: 7.427; 95%CI: 1.02 to 53.92; $P = 0.0474$), and reduced LAA velocity (OR: 1.086; 95%CI: 1.010 to 1.187; $P = 0.0489$) were identified as independent predictors of LAA thrombus. No Thrombi were detected in patients with a CHA₂DS₂-VASc score ≤ 1 .

Research conclusions

Among patients with non-valvular AF and ≥ 4 wk of anticoagulation with apixaban, the prevalence of LAA thrombus detected by TEE was 3.1%. This suggests that continuous therapy with apixaban does not completely eliminate the risk of LAA thrombus and that TEE prior to cardioversion or catheter ablation may be of benefit in patients with multiple risk factors.

Research perspectives

Compliance with non-vitamin K oral anticoagulants reduces but does not eliminate the prevalence of thrombus detection by TEE. However, available cost-effectiveness analysis reports that pre-procedural TEE is unlikely to be cost-effective in an unselected population. Therefore, there is a need to better identify patients with increased pretest probability of LAA thrombus in order to improve the cost-benefit ratio of the procedure. It is our hope that identification of additional clinical and echocardiographic characteristics; in addition to established risk factors, can help guide the selection process for utilization of pre-procedural TEE

REFERENCES

- 1 January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellnor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014; **130**: e199-e267 [PMID: 24682347 DOI: 10.1161/CIR.0000000000000041]
- 2 Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in

- collaboration with EACTS. *Eur Heart J* 2016; **37**: 2893-2962 [PMID: [27567408](#) DOI: [10.1093/eurheartj/ehw210](#)]
- 3 **Al-Saady NM**, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. *Heart* 1999; **82**: 547-554 [PMID: [10525506](#) DOI: [10.1136/hrt.82.5.547](#)]
 - 4 **Manning WJ**, Weintraub RM, Waksmonski CA, Haering JM, Rooney PS, Maslow AD, Johnson RG, Douglas PS. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. *Ann Intern Med* 1995; **123**: 817-822 [PMID: [7486462](#) DOI: [10.7326/0003-4819-123-11-199512010-00001](#)]
 - 5 **Manning WJ**, Silverman DI, Gordon SP, Krumholz HM, Douglas PS. Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. *N Engl J Med* 1993; **328**: 750-755 [PMID: [8437595](#) DOI: [10.1056/NEJM199303183281102](#)]
 - 6 **Klein AL**, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF; Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001; **344**: 1411-1420 [PMID: [11346805](#) DOI: [10.1056/NEJM200105103441901](#)]
 - 7 **Calkins H**, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot NMSN, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2017; **14**: e275-e444 [PMID: [28506916](#) DOI: [10.1016/j.hrthm.2017.05.012](#)]
 - 8 **Wallace TW**, Atwater BD, Daubert JP, Voora D, Crowley AL, Bahnson TD, Hranitzky PM. Prevalence and clinical characteristics associated with left atrial appendage thrombus in fully anticoagulated patients undergoing catheter-directed atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2010; **21**: 849-852 [PMID: [20158561](#) DOI: [10.1111/j.1540-8167.2010.01729.x](#)]
 - 9 **Puwanant S**, Varr BC, Shrestha K, Hussain SK, Tang WH, Gabriel RS, Wazni OM, Bhargava M, Saliba WJ, Thomas JD, Lindsay BD, Klein AL. Role of the CHADS2 score in the evaluation of thromboembolic risk in patients with atrial fibrillation undergoing transesophageal echocardiography before pulmonary vein isolation. *J Am Coll Cardiol* 2009; **54**: 2032-2039 [PMID: [19926009](#) DOI: [10.1016/j.jacc.2009.07.037](#)]
 - 10 **Yamamoto M**, Seo Y, Kawamatsu N, Sato K, Sugano A, Machino-Ohtsuka T, Kawamura R, Nakajima H, Igarashi M, Sekiguchi Y, Ishizu T, Aonuma K. Complex left atrial appendage morphology and left atrial appendage thrombus formation in patients with atrial fibrillation. *Circ Cardiovasc Imaging* 2014; **7**: 337-343 [PMID: [24523417](#) DOI: [10.1161/CIRCIMAGING.113.001317](#)]
 - 11 **Calvo N**, Mont L, Vidal B, Nadal M, Montserrat S, Andreu D, Tamborero D, Pare C, Azqueta M, Berrueto A, Brugada J, Sitges M. Usefulness of transoesophageal echocardiography before circumferential pulmonary vein ablation in patients with atrial fibrillation: is it really mandatory? *Europace* 2011; **13**: 486-491 [PMID: [21186230](#) DOI: [10.1093/europace/euq456](#)]
 - 12 **Scherr D**, Dalal D, Chilukuri K, Dong J, Spragg D, Henrikson CA, Nazarian S, Cheng A, Berger RD, Abraham TP, Calkins H, Marine JE. Incidence and predictors of left atrial thrombus prior to catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2009; **20**: 379-384 [PMID: [19017348](#) DOI: [10.1111/j.1540-8167.2008.01336.x](#)]
 - 13 **McCready JW**, Nunn L, Lambiase PD, Ahsan SY, Segal OR, Rowland E, Lowe MD, Chow AW. Incidence of left atrial thrombus prior to atrial fibrillation ablation: is pre-procedural transoesophageal echocardiography mandatory? *Europace* 2010; **12**: 927-932 [PMID: [20304842](#) DOI: [10.1093/europace/euq074](#)]
 - 14 **Savarese G**, Giugliano RP, Rosano GM, McMurray J, Magnani G, Filippatos G, DelleGrottaglie S, Lund LH, Trimarco B, Perrone-Filardi P. Efficacy and Safety of Novel Oral Anticoagulants in Patients With Atrial Fibrillation and Heart Failure: A Meta-Analysis. *JACC Heart Fail* 2016; **4**: 870-880 [PMID: [27614940](#) DOI: [10.1016/j.jchf.2016.07.012](#)]
 - 15 **Ruff CT**, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; **383**: 955-962 [PMID: [24315724](#) DOI: [10.1016/S0140-6736\(13\)62343-0](#)]
 - 16 **Jaber WA**, Prior DL, Thamilarasan M, Grimm RA, Thomas JD, Klein AL, Asher CR. Efficacy of anticoagulation in resolving left atrial and left atrial appendage thrombi: A transesophageal echocardiographic study. *Am Heart J* 2000; **140**: 150-156 [PMID: [10874278](#) DOI: [10.1067/mhj.2000.106648](#)]
 - 17 **Seidl K**, Rameken M, Drögemüller A, Vater M, Brandt A, Schwacke H, Bergmeier C, Zahn R, Senges J. Embolic events in patients with atrial fibrillation and effective anticoagulation: value of transesophageal echocardiography to guide direct-current cardioversion. Final results of the Ludwigshafen Observational Cardioversion Study. *J Am Coll Cardiol* 2002; **39**: 1436-1442 [PMID: [11985904](#) DOI: [10.1016/S0735-1097\(02\)01785-0](#)]
 - 18 **Wyrembak J**, Campbell KB, Steinberg BA, Bahnson TD, Daubert JP, Velazquez EJ, Samad Z, Atwater BD. Incidence and Predictors of Left Atrial Appendage Thrombus in Patients Treated With Nonvitamin K Oral Anticoagulants Versus Warfarin Before Catheter Ablation for Atrial Fibrillation. *Am J Cardiol* 2017; **119**: 1017-1022 [PMID: [28153350](#) DOI: [10.1016/j.amjcard.2016.12.008](#)]
 - 19 **Frenkel D**, D'Amato SA, Al-Kazaz M, Markowitz SM, Liu CF, Thomas G, Ip JE, Sharma SK, Yang H, Singh P, Lerman BB, Cheung JW. Prevalence of Left Atrial Thrombus Detection by Transesophageal Echocardiography: A Comparison of Continuous Non-Vitamin K Antagonist Oral Anticoagulant Versus Warfarin Therapy in Patients Undergoing Catheter Ablation for Atrial Fibrillation. *JACC Clin Electrophysiol* 2016; **2**: 295-303 [PMID: [29766887](#) DOI: [10.1016/j.jacep.2016.01.004](#)]
 - 20 **Da Costa A**, Delolme C, Guichard JB, Gerbay A, Pierrard R, Romeyer-Bouchard C, Isaaz K. Comparison of prevalence and management of left atrial appendage thrombi under old and new anticoagulants prior to left atrial catheter ablation. *Am Heart J* 2017; **193**: 8-15 [PMID: [29129259](#) DOI: [10.1016/j.ahj.2017.07.016](#)]

- 21 **Flaker G**, Lopes RD, Al-Khatib SM, Hermosillo AG, Hohnloser SH, Tinga B, Zhu J, Mohan P, Garcia D, Bartunek J, Vinereanu D, Husted S, Harjola VP, Rosenqvist M, Alexander JH, Granger CB; ARISTOTLE Committees and Investigators. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *J Am Coll Cardiol* 2014; **63**: 1082-1087 [PMID: 24211508 DOI: 10.1016/j.jacc.2013.09.062]
- 22 **Balouch M**, Gucuk Ipek E, Chrispin J, Bajwa RJ, Zghaib T, Berger RD, Ashikaga H, Calkins H, Nazarian S, Marine JE, Spragg DD. Trends in Transesophageal Echocardiography Use, Findings, and Clinical Outcomes in the Era of Minimally Interrupted Anticoagulation for Atrial Fibrillation Ablation. *JACC Clin Electrophysiol* 2017; **3**: 329-336 [PMID: 29759444 DOI: 10.1016/j.jacep.2016.09.011]
- 23 **Marzec LN**, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, Hsu JC, Maddox TM. Influence of Direct Oral Anticoagulants on Rates of Oral Anticoagulation for Atrial Fibrillation. *J Am Coll Cardiol* 2017; **69**: 2475-2484 [PMID: 28521884 DOI: 10.1016/j.jacc.2017.03.540]
- 24 **Lip GY**, Nieuwlaet R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; **137**: 263-272 [PMID: 19762550 DOI: 10.1378/chest.09-1584]
- 25 **Fatkin D**, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol* 1994; **23**: 961-969 [PMID: 8106703 DOI: 10.1016/0735-1097(94)90644-0]
- 26 **Dobashi S**, Fujino T, Ikeda T. Use of apixaban for an elderly patient with left atrial thrombus. *BMJ Case Rep* 2014; **2014**: pii: bcr2014203870 [PMID: 24962484 DOI: 10.1136/bcr-2014-203870]
- 27 **Miwa Y**, Minamishima T, Sato T, Sakata K, Yoshino H, Soejima K. Resolution of a warfarin and dabigatran-resistant left atrial appendage thrombus with apixaban. *J Arrhythm* 2016; **32**: 233-235 [PMID: 27354873 DOI: 10.1016/j.joa.2016.01.009]
- 28 **Corrado G**, Tadeo G, Beretta S, Tagliagambe LM, Manzillo GF, Spata M, Santarone M. Atrial thrombi resolution after prolonged anticoagulation in patients with atrial fibrillation. *Chest* 1999; **115**: 140-143 [PMID: 9925075 DOI: 10.1378/chest.115.1.140]
- 29 **Cappato R**, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010; **3**: 32-38 [PMID: 19995881 DOI: 10.1161/CIRCEP.109.859116]
- 30 **Awad S**, Mohajer K, Baranchuk A, Pal RS. Current clinical practice of transesophageal echocardiography and cardiac computed tomography prior to atrial fibrillation ablation in Canada. *Int J Cardiol* 2015; **189**: 300-301 [PMID: 25967570 DOI: 10.1016/j.ijcard.2015.03.318]
- 31 **Gula LJ**, Massel D, Redfearn DP, Krahn AD, Yee R, Klein GJ, Skanes AC. Impact of routine transoesophageal echocardiography on safety, outcomes, and cost of pulmonary vein ablation: inferences drawn from a decision analysis model. *Europace* 2010; **12**: 1550-1557 [PMID: 20716548 DOI: 10.1093/europace/euq306]
- 32 **Di Biase L**, Briceno DF, Trivedi C, Mohanty S, Gianni C, Burkhardt JD, Mohanty P, Bai R, Gunda S, Horton R, Bailey S, Sanchez JE, Al-Ahmad A, Hranitzky P, Gallingshouse GJ, Reddy YM, Zagrodzky J, Hongo R, Beheiry S, Lakkireddy D, Natale A. Is transesophageal echocardiogram mandatory in patients undergoing ablation of atrial fibrillation with uninterrupted novel oral anticoagulants? Results from a prospective multicenter registry. *Heart Rhythm* 2016; **13**: 1197-1202 [PMID: 26994940 DOI: 10.1016/j.hrthm.2016.03.024]

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