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Prevalence of Aspirin Resistance in Patients with Transcatheter Pulmonary Valve Replacement

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ABSTRACT

Background: Congenital heart disease (CHD) patients with pulmonary valve failure may undergo transcatheter pulmonary valve replacement (TPVR). Aspirin is often prescribed as long-term therapy after TPVR to prevent thromboembolic events (TE).

Aims: We aimed to examine the prevalence of aspirin resistance within the CHD TPVR population.

Methods: The VerifyNow point-of-care test quantifies platelet aggregation as Aspirin Reactivity Units (ARU). ARU values greater than 550 suggest aspirin resistance (AR). A retrospective chart review analyzed ARU test results from May 2022 through December 2023 in CHD patients following successful TPVR ($n = 48$). Lifelong TE history was collected. Association between AR and sex, race, and ethnicity was examined with Fisher's Exact test, and the Wilcoxon rank sum exact test analyzed associations between AR and age.

Results: Three of 45 (6.67%) CHD TPVR aspirin-compliant patients (average age 33.14 years; range 0.74−77.86 years, 47% females) were AR. Interestingly, all AR patients were females, suggesting higher AR prevalence in females ($p = 0.094$). No significant associations were found between AR and age ($p = 0.8$), race ($p = 0.077$), or ethnicity ($p = 0.2$). No AR patients had a documented history of TE. Five of 42 (11.9%) aspirin sensitive patients had TE while taking aspirin, including two females (not on birth control at time of event) and three males.

Conclusions: AR is prevalent in CHD TPVR patients, but TE occurrence did not correlate with AR. However, AR exclusively in females and TE in aspirin sensitive patients, suggests need for further investigations on the most effective TE prophylaxis in this population.

1 | Introduction

Since its commercial introduction, transcatheter pulmonary heart valve replacement (TPVR) has been growing in popularity as a minimally invasive treatment option with a high success rate for patients with right ventricular outflow tract (RVOT) dysfunction [1, 2]. TPVR has been shown to have comparable outcomes to surgical valve replacement and is also associated with shorter hospital stays, less time in intensive care, and lower mortality rates [3, 4].

Pulmonary valve dysfunction is not an uncommon finding in patients with congenital heart disease (CHD). Chronic pulmonary valve stenosis is seen in many CHD patients, either isolated or in combination with another defect [5]. Both pulmonary stenosis and pulmonary regurgitation cause increasing strain on the right ventricle, contributing to hypertrophy, tricuspid regurgitation, arrhythmias, exercise intolerance, and right ventricular failure [6, 7]. In these cases, patients may greatly benefit from a TPVR procedure.

With bioprosthetic valves (including TPVs), in-valve thrombosis remains a prevalent complication which can lead to premature valve failure. Additional anticoagulation measures, surgical re-intervention, or valve explant may be necessary if a thrombus occurs within the valve [8]. The materials within transcatheter valves increase the risk of thrombosis, especially in the first 3 months after implantation. Antithrombotic therapy improves patient outcomes, both in the short- and long-term [9–11].

In patients with heart disease, aspirin may be prescribed due to its antiplatelet effects. Aspirin limits the ability of arachidonic acid to bind to the active sites of the COX-1 and COX-2 enzymes, severely reducing the synthesis of thromboxane and prostaglandins. The decrease in thromboxane inhibits the platelet's ability to clot. The platelets are unable to make the appropriate proteins to effectively repair and replace the now inactive enzymes, thus making aspirin's effect irreversible for the remaining life of the cell. Clinical trials have also demonstrated that the effective dosing for antiplatelet therapy is lower than those for aspirin's pain relief and anti-inflammatory properties [12]. Aspirin has been shown to reduce the risk of thrombus-related complications in patients at risk for vascular disorders, including patients taking aspirin for thromboprophylaxis after placement of prosthetic heart valves [9, 13]. The drug is commonly prescribed during the post-operative period, with Shibbani et al. [11] reporting that physicians unanimously started patients on aspirin therapy post-TPVR.

Despite lacking a standard definition, the term “aspirin resistance” has generally been used to describe patients that have a reduced antiplatelet response to aspirin. These patients may still experience adverse ischemic events despite antiplatelet therapy and require a higher dose of aspirin to achieve desired results [14]. Some studies have suggested that aspirin resistance is associated with a higher risk of nonfatal adverse ischemic events, cardiovascular morbidity, and undesirable treatment outcomes [15–18]. Unfortunately, the prevalence of aspirin resistance is unknown. Previous studies have found varied percentages of patients with aspirin resistance, with Mansour et al. [14] finding a range of 5% to 29.9%. Other investigations have found rates of resistance as high as 70% in patients with major cardiac diagnoses such as congestive heart failure and acute myocardial infarction [19].

Various tests have been developed to evaluate aspirin resistance in patients. One such test is the VerifyNow assay. This point-of-care test uses cartridges loaded with platelet agonists and beads coated with fibrinogen. Results are obtained by placing collected blood into one of these cartridges and measuring the light transmission through it. If platelet aggregation occurs, the light transmission will decrease. The results of the VerifyNow assay are measured in aspirin reactivity units (ARU), with a value greater than or equal to 550 suggesting aspirin resistance [19, 20].

2 | Methods

This retrospective, single-center chart review was approved by the University of Iowa Institutional Review Board via expedited review with a full waiver of HIPAA authorization. Patients with diagnosed CHD and at least one ARU test following successful TPVR were included. All ARU tests included were performed between May 1, 2022 and December 14, 2023 at our institution. Patients that were non-compliant with aspirin or taking a dose greater than 81 mg per day at time of ARU testing were excluded.

Demographic data was collected on patient sex, race, ethnicity, and age at time of ARU draw. Charts were also reviewed for past thrombosis and stroke events. If an event was found, it was determined if the patient was taking aspirin at the time of the thrombus. Only events in which the patient was concurrently taking aspirin were included in analysis.

Aspirin resistance was defined as an ARU result of 550 or greater. Fisher's exact test was used to examine associations between aspirin resistance and sex, race, and ethnicity. The Wilcoxon rank sum exact test was used to examine the association between aspirin resistance and age.

3 | Results

Fifty initial CHD patients were identified with an ARU test post-TPVR (Figure 1). At the time of ARU draw, four patients were non-compliant with aspirin and 1 was taking a higher dose of aspirin (325 mg daily). Our final group included 45 patients. For patients with multiple ARU tests, only the first compliant test was used in statistical analysis. Forty-seven percent of this group were females. These patients covered a broad range of ages from 0.74 to 77.86 years with a mean age of 33.14 years.

Aspirin resistance was found in 3 of the 45 (6.7%) patients (Table 1). This group ranged from 19.76 to 50.28 years of age, with an average age of 33.86 years. All 3 aspirin resistant patients were female. The 42 other patients were aspirin sensitive, of which 16 (43%) were female. Aspirin sensitive patient ages ranged from 0.74 to 77.86 years, averaging 33.09 years. Six children under 18 years of age were found to be aspirin sensitive, and there were no aspirin resistant children (Figure 2).

History of thrombosis and stroke events was collected. To be included in analysis, the patient had to be taking aspirin at time of the event. These events occurred in 0 of 3 aspirin resistant patients and 5 of 42 (12%) of aspirin sensitive patients. The events included two peripheral vein thromboses, one thrombus within the RVOT, one thrombus within the implanted TPV, and one ischemic stroke (see Table 2).

4 | Discussion

Of the 45 patients included in our analysis, three were found to be resistant to aspirin (6.7%) and 42 were aspirin sensitive. Interestingly, all 3 resistant patients were female. In the overall cohort, 14% of all females were identified as aspirin resistant. All resistant patients were not prescribed oral birth control at the time of ARU draw. While not statistically significant ($p = 0.097$), this suggests that aspirin resistance may be more prevalent in females than males. Other studies have

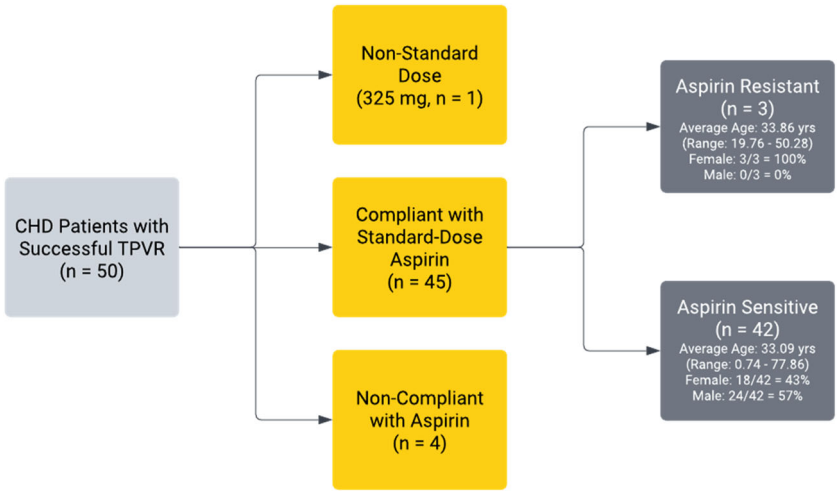

FIGURE 1 | Study inclusion flowchart with demographic information for included patients. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 | Demographics of aspirin resistant and aspirin sensitive patients.

Trait		Aspirin Resistant ($n = 3$)	Aspirin Sensitive ($n = 42$)	p value
Sex				0.094
	Female	3 (100%, 6.7%)	18 (43%, 40%)	
	Male	0 (0%, 0%)	24 (57%, 53%)	
Age				0.8
	Median	32	32	
	Interquartile Range	26, 41	20, 41	
Race				0.077
	White	1 (33%, 2.2%)	36 (86%, 80%)	
	Black or African American	1 (33%, 2.2%)	1 (2.4%, 2.2%)	
	Asian	0 (0%, 0%)	1 (2.4%, 2.2%)	
	American Indian or Alaska Native	0 (0%, 0%)	1 (2.4, 2.2)	
	Native Hawaiian or Other Pacific Islander	0 (0%, 0%)	0 (0, 0)	
	Multiracial/Two or More Races	0 (0%, 0%)	1 (2.4, 2.2)	
	Unknown/Any Race	0 (0%, 0%)	0 (0, 0)	
	Hispanic/Latino of Any Race	1 (33%, 2.2%)	2 (4.8, 4.4)	
Ethnicity				0.2
	Hispanic	1 (33%, 2.2%)	3 (7.1, 6.7)	
	Non-Hispanic	2 (68%, 4.4%)	39 (93, 87)	
	Declined to Answer	0 (0%, 0%)	0 (0%, 0%)	

Note: Values are *n* (*n*%, Overall %) unless otherwise stated.

found significant correlations between female sex and aspirin resistance in both healthy populations and people with cardiovascular disease [15, 20–23]. Further research is needed to determine the most effective thromboembolic prophylaxis in female patients.

In our cohort, there was no significant relationship between age and aspirin resistance ($p = 0.8$). This observation aligns with previous findings in cardiovascular patients, including a cohort study involving pediatric CHD patients with TPVR [21, 22, 24]. However, other studies have found a statistically significant relationship between aspirin resistance and increased age. Studies involving healthy patients, patients with coronary artery disease, and patients at elevated risk of thromboembolic events (TE) have all concluded that aspirin resistance is more prevalent in older patients [20, 23, 25]. Investigating the differences between these populations is necessary to understand when it is appropriate to use patient age to predict aspirin resistance.

Aspirin resistance was not found to have a significant link to patient race ($p = 0.077$) or ethnicity ($p = 0.2$). These results are

consistent with other literature involving populations with cardiovascular indications for aspirin therapy [26, 27].

Our study found that TEs while taking aspirin occurred exclusively in aspirin sensitive patients. This seems to indicate that aspirin resistance does not relate to the risk of thrombus formation. Roman-Gonzalez et al. found that although participants with a history of stroke were more likely to be aspirin resistant, there was no correlation between aspirin resistance and the presence of clinical risk factors for stroke [28]. However, other studies have concluded that aspirin resistant patients were more likely to experience ischemic strokes, transient ischemic attack episodes, and other adverse cardiovascular events [29, 30]. Five of 45 (12%) of our overall cohort were found to have a documented history of thrombosis or ischemic stroke post-TPVR while taking aspirin. None of the patients included in this study had one of these events before TPVR. There is a low occurrence of thrombotic events in the post-TPVR population, with larger studies finding less than 1% of their participants experiencing thrombosis or ischemic stroke events [31, 32]. One study found that the calculated prevalence of thrombosis in CHD patients at their center was approximately 2% [33]. Further investigation is necessary to determine the clinical implications of aspirin resistance in CHD patients with TPVR. Since TEs occurred exclusively in aspirin-sensitive patients, consideration for a second agent other than anti-platelet groups could be beneficial in preventing thromboembolism.

A recent study in Ireland examined the prevalence of aspirin resistance and clinical outcomes in a cohort of pediatric patients with TPVR and/or xenograft valve conduits. Aspirin resistance was measured with the quantitative platelet mapping assay thromboelastography with platelet mapping and light transmission aggregometry. Seven of 30 patients (23%) in their cohort were found to be aspirin resistant according to at least one of the two tests. For the patients found to be aspirin resistant, six underwent repeat testing. All but one of the repeat tests came back as aspirin sensitive. For the five patients that became aspirin sensitive on repeat testing, known reasons for the initial result included nonadherence to medication, draw being taken in the post-operative period, timing of dose, and resolution of discordant results on repeat testing. Due to these changes, prevalence of aspirin resistance may be as low as 6.7% in this patient population. Data on thromboembolic history was not collected [24]. This study's observation that 6.7% of pediatric TPVR patients are aspirin resistant aligns with the findings of our study involving both pediatric and adult TPVR patients. This similarity is especially interesting considering this pediatric study and our study used different tests to determine aspirin resistance.

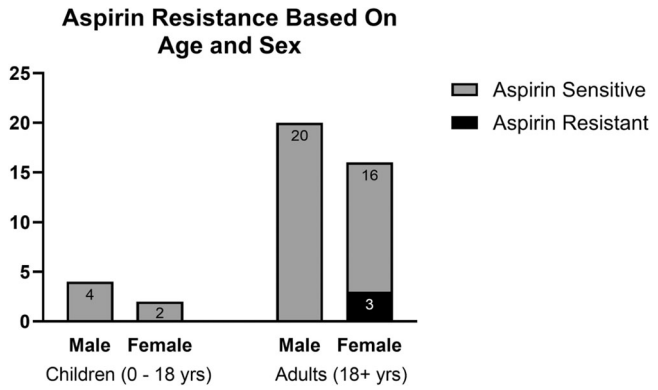

FIGURE 2 | Aspirin resistance sorted by age and sex.

5 | Limitations

This study was limited by a small sample size. There was no control group available for comparison, making it difficult to assess the prevalence of aspirin resistance relative to other populations. Due to the mechanism of the VerifyNow ARU assay, patients that were non-compliant with prescribed aspirin have an increased likelihood of producing false positive results for aspirin resistance. These patients were excluded, further limiting the sample population.

It is speculated that other drugs such as clopidogrel may rarely cause a reduction in a patient's ARU if taken in the previous 5 days [34, 35]. However, this reduction was not found to change a patient's classification from aspirin resistant to aspirin sensitive. Clopidogrel is commonly prescribed alongside aspirin for dual antiplatelet therapy, and this is the case for many patients in this study. Further investigation must be done to determine the full effects of clopidogrel therapy on ARU test results.

The nature of retrospective chart reviews also limits the information and results accessible to researchers. Documentation from outside centers may not be available within the patient's chart at our institution. This means that some adverse ischemic events and other outcomes may have been missed due to the

TABLE 2 | Location of clot, sex, and aspirin resistance status for patients with documented thromboembolic events.

Event Number	Location of Thrombus	Sex	Taking aspirin at time of event?	Aspirin Sensitive/ Resistant
1	Iliac Vein	Male	Yes	Sensitive
2	Right Ventricular Outflow Tract	Female	Yes	Sensitive
3	Subclavian Vein	Female	Yes	Sensitive
4	Inside Sapien 3 Valve	Male	Yes	Sensitive
5	Brain (Stroke)	Male	Yes	Sensitive

documents potentially disclosing this information not being available to members of the research team. Because it is impossible to retrospectively verify medication compliance, patients were assumed to be compliant with aspirin at the time of ARU if there was no documentation stating otherwise. This may have introduced additional confounding factors.

Aspirin resistance does not have a universal definition, making standardizing its measurement and distinction difficult. While this was mitigated by using an objective measurement unit such as ARU, it is still difficult to compare the prevalence of aspirin resistance when compared to other studies not using this test.

6 | Conclusion

In our retrospective observational study, aspirin resistance was found in 6.7% of CHD patients post-TPVR. Interestingly, aspirin resistance did not correlate with thrombosis and stroke. Thromboembolism solely in aspirin sensitive patients warrants a consideration whether an agent other than anti-platelet drugs could be beneficial in preventing thrombosis in TPVR patients. In addition, aspirin resistance exclusively in females, suggests a need for further investigation into the best mode of thromboembolic prophylaxis in this population.

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Conflicts of Interest

The authors declare no conflicts of interest.

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