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CORRELATION BETWEEN DEGENERATIVE AORTIC VALVE DISEASE AND SEVERITY OF CORONARY ARTERY DISEASE ASSESSED BY SYNTAX SCORE

By

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ABSTRACT

Background: The degree of degenerative aortic valve disease (DAVD) can play a significant role as an independent risk factor for coronary artery disease. Therefore, it can be directly linked to coronary artery disease (CAD) severity making its assessment and measurement a critical step before the invasive investigations to diagnose CAD.

Objective: The present work aimed to assess the relationship between DAVD by transthoracic echocardiography (TTE) on the aortic valve, and the severity and complexity of coronary artery disease assessed by SYNTAX score.

Patients and Methods: This prospective study included 100 patients with Echocardiographic evidence of DAVD, and risk of coronary artery disease indicated for coronary angiography at Al-Azhar University (Assiut branch) between November 2020 to December 2021. Informed consent, detailed history, complete physical examination, resting ECG, full labs, complete transthoracic echocardiographic examination, particular emphasis on degenerative aortic valve assessment, and coronary angiography were performed. Assessment of severity of CAD was done for all patients using SYNTAX score, number of affected vessels, and degree of stenosis were also assessed.

Results: There were a statistically significant positive strong correlation between DAVD degree with both SYNTAX score and number of affected vessels.

Conclusion: Aortic valve sclerosis, calcification, and degeneration were strongly correlated with the extent of coronary artery disease and may predict it. Echocardiographic detection of DAVD in patients undergoing coronary angiography could be applied as a new surrogate marker of the extent of coronary atherosclerosis. DAVD was associated with atherosclerosis risk factors like age, dyslipidemia, DM, and hypertension.

Keywords: Degenerative aortic valve diseases (DAVD), coronary artery disease (CAD), SYNTAX score transthoracic echocardiography (TTE), coronary angiography.

INTRODUCTION

Degenerative aortic valve disease (DAVD) is characterized by lipid deposition and calcific infiltration on the edge of aortic leaflets without significant restriction of motion. DAVD incidence has increased with the aging population and common echocardiography use *(Martinsson et al., 2015)*. However, studies showed that DAVD is not only important because of aging, but it may also advance aortic stenosis and may be related to coronary artery diseases (CAD). Studies have demonstrated that the risk factors for CAD formation and progression may also be the risk factors for DAVD development and progression to CAD *(Milin et al., 2014)*. Atherosclerosis is a major health problem affecting cardiovascular system, which makes CAD the leading cause of death in developed countries and one of major health problems in developing countries. It is a degenerative disease affecting blood vessels and leads to catastrophic cardiovascular events. It is characterized by basement membrane disruption, inflammation, cell infiltration, lipid deposition and calcification *(Sanchis-Gomar et al., 2016)*. Being the site of frequent turbulence and mechanical stress Aortic valve serves as a focus for the deposition of lipids involved in the process of atherosclerosis. Many studies focused on aortic valve sclerosis as a degenerative disease sharing common histopathological mechanisms with coronary artery atherosclerosis *(Topcu et al., 2017)*. It has the advantage of being proceeding CAD and can be a mirror of what is happening inside coronary arteries. Furthermore, it can be directly linked to CAD severity making its assessment and measurement an important step before invasive investigations to diagnose CAD *(Nabati et al., 2019)*.

The present work aimed to assess the relationship between DAVD by Transthoracic echocardiography (TTE) on aortic valve and the severity and complexity of CAD assessed by SYNTAX score.

PATIENTS AND METHODS

This prospective study included 100 patients with Echocardiographic evidence of DAVD, with risk of CAD and indicated for coronary angiography at cardiology department of al-Azhar University at Assiut between the periods from November 2020 to December 2021.

Inclusion criteria: Echocardiographic evidence of DAVD for patients with risk of CAD prepared for coronary angiography within any age group and both genders are accepted.

Exclusion criteria: Hemodynamically unstable patients, patients with end-stage liver or renal disease or hemodialysis, patients with hyperparathyroidism, vit.D disorders, patients with known hypercalcemia due to any cause, very poor acoustic windows, known rheumatic valvular disease, bicuspid aortic valve, congenital heart disease, cardiac valve replacement, and diseases associated with high bone turnover rate, e.g. multiple myeloma, Paget's disease, tuberculosis or sarcoidosis.

Methods: Each patient was subjected to informed consent, full history, clinical examination and full lab investigations including S.Cr, CBC, INR, viral serology(B,C viral hepatitis, and HIV), RBS and lipogram, twelve-lead electrocardiogram (ECG), and trans-Thoracic Echocardiography (TTE). All TTE measurements represented the average of three consecutive beats between normal HR ranges, 60–100 beat per minute. The results were confirmed by an echo cardiographer who is blind to the patient's information. Images were acquired from the standard views in left lateral decubitus position. Aortic valve assessment: Zoom view of the parasternal short-axis window of the aortic valve, which was fully closed at end-diastole, was used to determine the aortic valve sclerosis score. Gain settings were adjusted in modes to optimize image quality and avoid effect of tissue harmonic imaging which can give a false impression of increased valve cusps thickness and sclerosis. Aortic valve disease was defined as focal areas of increased echogenicity and thickening of the aortic valve leaflets that did not restrict leaflet motion and had a velocity of less than 2.5 m/s across the aortic valve (at least one abnormal leaflet per valve). The score was classified as: **Grade 0:** Normal reflectance, no thickening, thickness < 2mm, **Grade 1:** Non-calcified, thickened valve, thickness < 2mm, **Grade 2:** Mildly calcified valve (<1/3 of valve area), thickness < 2mm, **Grade 3:** Moderately calcified valve (1/3–2/3 of valve area), thickness > 4 mm, and **Grade 4:** Markedly calcified valve (>2/3 of valve area), thickness > 6 mm. For the purposes of the following analysis, the presence of aortic sclerosis was defined as an average aortic valve sclerosis score index (AVSSI). According to *(Yousry et al., 2015)*, The grading of the sclerosis score was determined for each cusp, including the non-coronary, right coronary, and left coronary cusps, individually. The average of aortic valve sclerosis score index (AAVSSI) was used for each patient to define their overall average. According AAVSSI studied population assigned into 3 groups, **group A** (AVSSI (0-1)), **group B** (AVSSI (1-2)), and **group C** (AVSSI (>2)). Lastly Coronary angiography and SYNTAX score calculation was performed for measuring the complexity and intensity of coronary artery disease (CAD). Coronary arteries having a diameter greater than 1.5 mm and a stenosis of 50% were evaluated. The SYNTAX score was calculated using the most recent updated version available online (www.SYNTAXscore.com, accessed in October 2014). SYNTAX scores were classified into two categories (low SYNTAX: < 22 and high SYNTAX: ≥ 22).

The study was conducted in full agreement with principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and within the laws and regulations of Egypt. The study protocol was reviewed and approved by the research ethics committee of the Faculty of Medicine Al-Azhar University (Assiut branch). All patients signed informed written consents before recruitment in the study.

Statistical analysis: SPSS version 25.0 was used for data management and data analysis. Quantitative variables were first subjected to the normality test (Kolmogoro v Smirmov). Continuous variables were presented as means, and standard deviations. Continuous variables in 2 groups were calculated by independent t-test, if it was normally distributed, and Mann–Whitney U test test if not. Also, dependent continuous variables in >2 group were estimated by One-way ANOVA test if it was normally distributed, and Kruskal Wallis test if not. Categorical variables were described as numbers (percentage), and were compared by Chi-square test and Fisher`s Exact test. Correlation analysis of variables was calculated by Spearman's correlation. The demographics and laboratory data with significant differences between groups were assessed by univariate and multivariate logistic regression analysis to discover risk factors associated. P values >0.05 was considered significant.

RESULTS

Demographic variables, DAVD risk factors, some baseline laboratory results, echocardiographic and angiographic characteristics of the study population **(Table 1)**.

Table (1): Demographic variables, DAVD risk factors, some Baseline laboratory, Echocardiographic and angiographic characteristics of the study population

Variables		**Patients (n=100)**	
Age (mean ±SD)		67.70 ±4.7	
Gender n (%)	**males**	71	71.0%
	females	29	29.0%
Hypertension n (%)		55	55%
Smoking n (%)		45	45%
Diabetes n (%)	IDDM	29	29%
	Non-IDDM	8	8%
Triglycerides (mg/dl) (mean ±SD)		194.48 ±27.40	
Cholesterol (mg/dl) (mean ±SD)		198.00 ±15.40	
LDL (mg/dl) (mean ±SD)		94.65 ±15.83	
EF (%) modified Simpson's method (mean ±SD)		49.06 ±4.76	
E/e ratio (mean ±SD)		9.09 ±0.92	
Aortic valve sclerosis score index (mean ±SD)		1.72 ±0.86	
Number of Vessels Affected n (%)	**single**	20	20.0%
	2 vessels	62	62.0%
	Multi vessels	18	18.0%
SYNTAX score (mean ±SD)		14.57 ±5.26	

Descriptive and statistical analysis were assigned into three groups according AAVSSI obtained from echocardiographic results of studied population **Figure (1)**, Thirty-two patients in group A (AVSSI (0-1)), Thirty-five patients in group B (AVSSI (1-2)), and thirty-three patients in group C (AVSSI (>2)), then evaluated as regards their patient characteristics, laboratory data results, echocardiographic and angiographic characteristics **(Table 2)**.

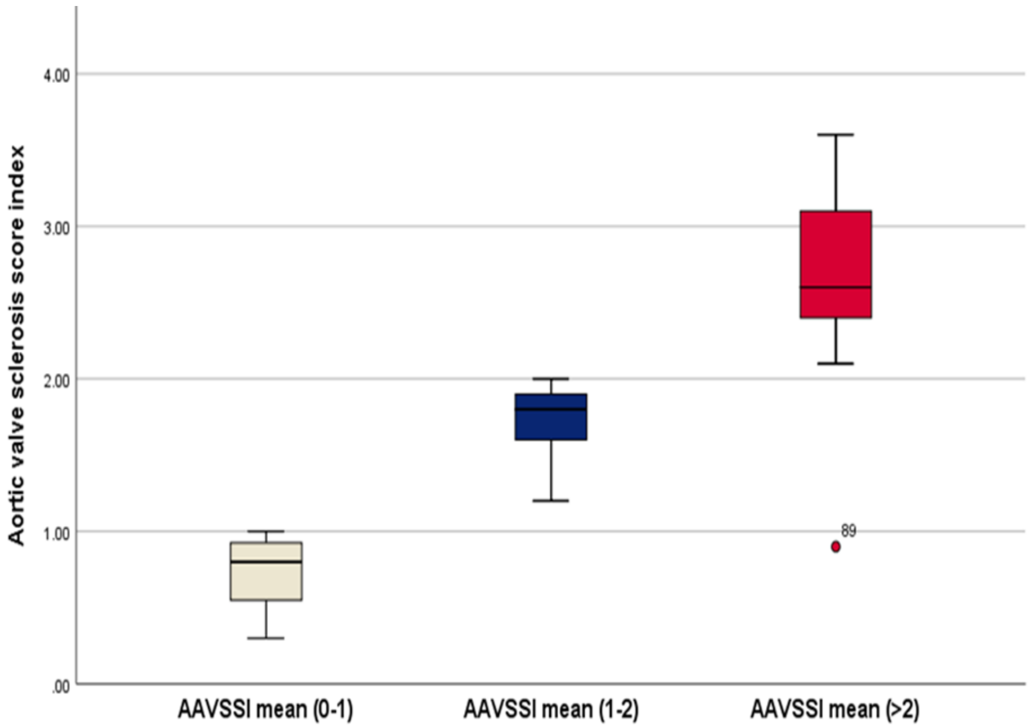

Figure (1): Aortic valve sclerosis score index of studied groups

Table (2): Demographic data, some laboratory data results, echocardiographic and angiographic differences between studied groups according to AVSSI

Variables \ Groups		Group A AVSSI (0-1) (N=32)		Group B AVSSI (>1-2) (N=35)		Group C AVSSI (>2) (N=33)		P value
Age (years)		64.66 ±3.6		66.80 ±4.2		71.61 ±3.5		**<0.001***
		n	%	n	%	n	%	
Gender	males	20	62.5%	26	74.3%	25	75.8%	0.434
	females	12	37.5%	9	25.7%	8	24.2%	
Hypertension		12	37.5%	19	54.3%	24	72.7%	**0.017***
Smoking		11	34.4%	16	45.7%	18	54.5%	0.262
Diabetes mellitus		13	40.6%	13	37.1%	11	33.3%	0.831
Triglycerides (mg/dl)		190.47 ±27.99		194.91 ±23.30		197.91 ±30.97		0.550
Cholesterol (mg/dl)		191.38 ±14.17		193.54 ±13.64		197.03 ±18.04		0.563
LDL (mg/dl)		96.59 ±16.16		93.11 ±13.23		94.39 ±18.17		0.630
EF (%)		48.97 ±4.69		49.11 ±4.57		49.09 ±5.14		0.971
E/e ratio		8.30 ±0.63		9.26 ±0.56		9.68 ±0.93		**<0.001***
Number of vessels affected	Single	16	50.0%	4	11.4%	0	0%	**<0.001***
	2 vessels	16	50.0%	26	74.3%	20	60.6%	
	Multi vessel	0	0.0%	5	14.3%	13	39.4%	
SYNTAX score		10.62 ±3.89		14.66 ±4.47		20.27 ±4.80		**<0.001***

Continuous data are presented as means± SD.
*P value is significant if <0.05.

There were non-significance differences between groups (P>0.05) regarding gender, smoking and D.M, triglycerides, cholesterol, LDL, and EF (%). There were significance differences as regards age, hypertension, E/e ratio, number of vessels affected, and SYNTAX score (P<0.001) between the studied groups.

The number of aortic valve sclerosis cases between low and high SYNTAX scores demonstrated in **(Table 3** and **Figure 2)**.

Table (3): Number of aortic valve sclerosis cases between low and high SYNTAX scores

AAVSSI \ Groups	SYNTAX score < 22 (N=78)		SYNTAX score ≥ 22 (N=22)		P value
	n	%	n	%	
AAVSSI mean (0-1)	32	41.0%	0	0.0%	**<0.001***
AAVSSI mean (1-2)	31	39.7%	4	18.2%	
AAVSSI mean (>2)	15	19.2%	18	81.8%	

Continuous data are presented as means± SD.
*P value is significant if <0.05.

There were significance differences as regards AAVSSI and the number of aortic valve sclerosis cases between low and high SYNTAX scores.

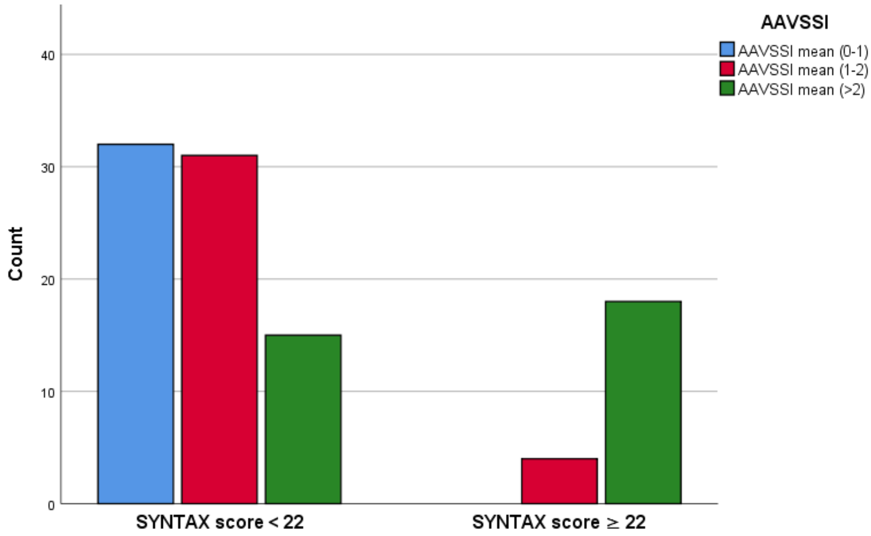

Figure (2): Numbers of aortic valve sclerosis cases between low and high SYNTAX scores

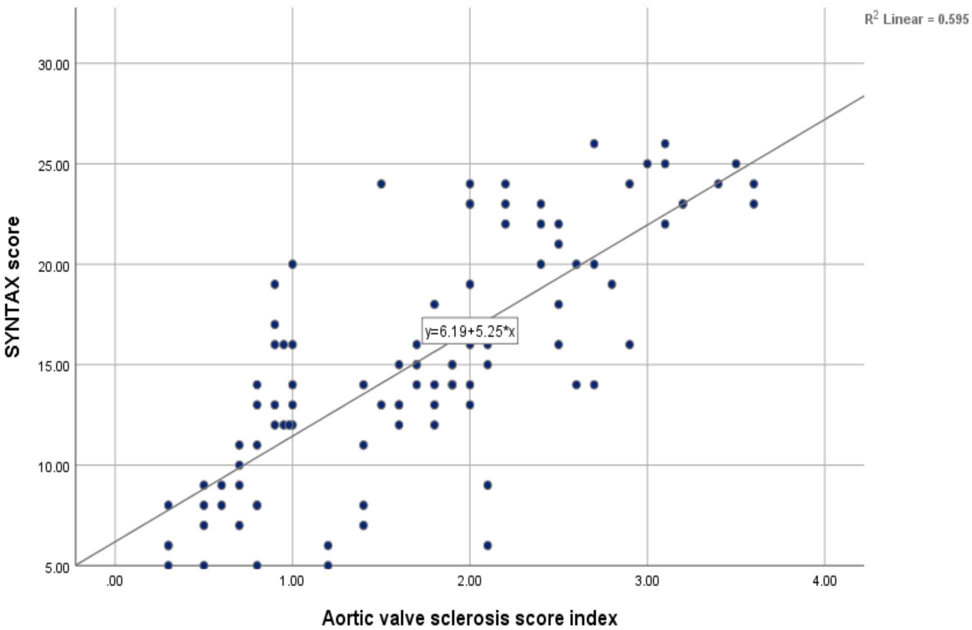

Figure (3): Correlation between SYNTAX scores and Aortic valve sclerosis score index

The univariate logistic regression analysis showed that age, gender (males), hypertension, diabetes, diastolic function, triglycerides (mg/dl), cholesterol (mg/dl), E/e ratio and AAVSSI were associated with high SYNTAX score.

Subsequently, all the above univariate analysis parameters with statistical significances were integrated for in-depth analysis into the multivariate logistic regression model. In the multivariate logistic regression model, considering the likelihood of over fitting, we assumed a stepwise forward method for logistic regression analysis to decrease the number of independent variables entering the model to decrease the probability of over fitting the model. The results showed that the early independent predictors for high SYNTAX score were gender, number of vessels affected and aortic valve sclerosis score index upon entry, while the role of other parameters were unclear **(Table 6)**.

Table (6): Binary Logistic regression model of the predictors for high SYNTAX score

Parameters / Variables	Univariable Odds ratio	95% C.I		P value	Multivariable Odds ratio	95% C.I		P value
		lower	upper			lower	upper	
Age	1.182	1.056	1.322	**0.004**	1.013	.738	1.389	**0.938**
Gender (male)	5.294	1.150	24.365	**0.032**	13.588	1.647	15.987	**0.029**
Hypertension	2.667	.944	7.529	**0.048**	3.228	.255	40.821	0.365
Diabetes	3.300	1.021	10.663	**0.046**	.513	.016	16.374	0.705
Number of Vessels Affected	2.868	1.233	6.670	**0.014**	887.615	3.803	987.517	**0.015**
Triglycerides (mg/dl)	1.022	1.004	1.041	**0.020**	1.061	.990	1.138	0.095
Cholesterol (mg/dl)	1.047	1.014	1.082	**0.005**	1.064	.948	1.194	0.293
E/e ratio	10.241	3.687	28.449	**<0.001**	3.509	.867	14.191	0.078
Aortic valve sclerosis score index	17.027	5.024	57.705	**<0.001**	601.913	15.522	23341.727	**0.001**

DISCUSSION

With AAVSI it was found that age and hypertension was higher in group c than in groups with lower score index. In contrast, it was found that there were no statistically significant differences with gender, smoking and diabetes in comparison between three groups. This typically agreed with *Nabati and Favaedi. (2018)*, *Sengeløv et al. (2018)*, and *Ibrahim et al. (2020)*, and partially in agreement with a study by *El Moneum. (2019)* who showed that the incidence of AAVSI increases with the presence of more risk factors that including as HTN, DM, dyslipidemia, male gender, aging, family history, and smoking. We found also there were no significant differences as regards EF%, mean triglycerides, cholesterol, and LDL levels between groups with different AAVSI. However, E/e ratio, AAVSI, number of vessels affected and SYNTAX score were significantly increase in in group with AAVSI <2 than in group with AAVSI <0 – 1, and group with AAVSI <1 - 2. These results were in agreement with *El Moneum (2019)*, and *Ibrahim et al. (2020)*. In contrast to our findings, *Bhatt et al. (2015)* discovered that the presence of AVS was not associated with the number of obstructive vessels, degree of stenosis in epicardial arteries, or SYNTAX. Moreover, we reported AAVSSI mean (0-1) in 41.0% of SYNTAX score < 22 versus 0.0% in SYNTAX score ≥ 22, AAVSSI mean (<1-2) were 39.7% in SYNTAX score < 22 vs 18.2% in SYNTAX score ≥ 22, AAVSSI mean (>2) 19.2% in SYNTAX score < 22 versus 81.8% in SYNTAX score ≥ 22. Interestingly, the results of *El Moneum (2019)* documented that there was a statistically significant difference as regard the mean SYNTAX score in AVSSI>1 compared to AVSSI ≤ 1. Unexpectedly, this study noticed non-significant differences between groups. Also, *Topcu et al. (2017)* stated a strong positive correlation between the AAVSSI and SYNTAX scores and the number of vessels affected. A similar pattern of results was obtained by *Ibrahim et al. (2020)*. Finally, the univariate logistic regression analysis showed that the age, gender (male), hypertension, DM, diastolic function, triglycerides, cholesterol, E/e ratio and AAVSI were associated with high SYNTAX score. All the above parameters showed a statistical significance in the univariate analysis incorporated into the multivariate logistic regression. These findings were consistent with that of *Ibrahim et al. (2020)*. All study variables were combined to create a logistic regression model in order to identify the true predictors of a high SYNTAX score in the study population. In our study model, hypertension and a high AAVSSI were found to be strong predictors of severe coronary artery lesions that are also in agreement with *Topcu et al. (2017)*.

CONCLUSION

Aortic valve sclerosis, calcification and degeneration were strongly correlated with the extent of coronary artery disease and may predict it. Echocardiographic detection of DAVD in patients undergoing coronary angiography could be applied as a new surrogate marker of the extent of coronary atherosclerosis. DAVD was associated with atherosclerosis risk factors like age, dyslipidemia, DM, and hypertension.

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العلاقه بين مرض الصمام الأبهرى التنكسى وشدة مرض الشريان التاجى مقيمة بواسطة معيار سنتاكس

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خلفية البحث: تلعب درجة تنكس الصمام الأبهرى دوراً كبيراً كعامل من عوامل خطورة الاصابة بمرض تصلب الشرايين التاجيه للقلب وتعد مرتبطة به ارتباطاً وثيقاً. لذا متابعة وقياس درجة هذا التنكس تعد خطوة هامة لتشخيص أمراض شرايين القلب التاجية قبل اللجوء للفحوصات المكلفة والأكثر خطورة لتشخيص ذلك.

الهدف من البحث: تقييم مدى ارتباط تنكس الصمام الأبهري بشدة مرض و إصابة الشريان التاجي بواسطة معيار سينتاكس.

المرضى وطرق البحث: قمنا بدراسة 100 مريضًا يعانون من وجود تنكس بالصمام الأبهرى مصاحباً لمرضهم بقصور شرايين القلب التاجية والمحدد لهم إجراء القسطرة التشخيصية أوالعلاجية بقسم القلب والاوعية الدموية بجامعه الأزهر فرع أسيوط فى الفترة من نوفمبر 2020م إلى ديسمبر 2021م. تم توقيع كل مريض على إذن كتابي لإجراء البحث بعد توضيح الهدف من الدراسة والمخاطر المحتملة لكل مشارك. تم مراجعة لجنة أخلاقيات البحث العلمى بكلية الطب بجامعة الأزهر فرع أسيوط لشروط وإجراءات السلامة والخصوصية المتعلقة بإجراء الدراسة. تم أخذ التاريخ المرضي كاملاً. خضع المريض إلى فحص طبى عام وفحص طبى خاص بالقلب. تم إجراء التحاليل للمريض خاصةً خريطة دهون الدم، تحليل سكر صيامى, سيولة بالدم, وظائف كلى، صورة دم كاملة. رسم قلب عادي. أشعة إيكو (موجات فوق صوتية على القلب)عن طريق الصدر مع تقييم حالة الصمام الأبهرى ودرجة تنكسة.إجراء القسطرة التشخيصية أو العلاجية على

شـــرايين القلـــب مـــع حســـاب نســـبة معيـــار ســـينتاكس وتقيـــيم شـــده إصـــابة شـــرايين القلب التاجية.

نتـــائج البحـــث: تبـــين وجـــود علاقـــة إحصـــائية قويـــة بـــين زيـــادة درجـــة تـــنكس الصـــمام الأبهـــرى وإصـــابة شـــرايين القلـــب التاجيـــة وعـــدد الشـــرايين التاجيـــة المصابة أيضا.

الاســـتنتاج: هنـــاك علاقـــة وثيقـــة بـــين تصـــلب الصـــمام الأبهـــرى التنكســـى وشـــدة إصـــابة شـــرايين القلـــب التاجيـــة و وجـــود تصـــلب الصـــمام الأبهـــرى التنكســـي أثنـــاء الفحـــص بالموجـــات الفـــوق صـــوتية علـــى القلـــب قـــد يكـــون مؤشـــر وأداة للتنبـــؤ بوجود إصابة شديدة بشرايين القلب التاجية.

الكلمـــات الدالـــة: مـــرض الصـــمام الأبهـــرى التنكســـى، مـــرض الشـــريان التـــاجى، معيـــار ســـنتاكس، فحـــص الموجـــات فـــوق صـــوتية علـــى القلـــب عـــن طريـــق الصـــدر (الايكو، صدى القلب)، قسطرة شرايين القلب التاجية.