Brief Report

Calcium and vitamin D supplementation impact on survival in patients with moderate concomitant aortic and mitral valve disease

Andrew Gaballa[1], Adel Hajj Ali[2], Joseph El Dahdah[1], Zoran Popovic[1], Tom K. Wang[1], Grant Reed[1], Leonardo Rodriguez[1], Brian Griffin[1], A. Marc Gillinov[1], Samir R. Kapadia[1], Lars G. Svensson[1], Milind Y. Desai[1]

[1]Heart Vascular Thoracic Institute (HVTI), Cleveland Clinic, Cleveland, OH, USA; [2]Department of Internal Medicine, Indiana University, Indianapolis, IN, USA

Correspondence to: Milind Y. Desai, MD, MBA. Heart Vascular Thoracic Institute (HVTI), Cleveland Clinic, 9500 Euclid Avenue, Desk J1-5, Cleveland, OH 44195, USA. Email: desaim2@ccf.org.

Abstract: Calcium supplement intake, with or without vitamin D supplementation, has risen amongst the older population, who are more likely to have deficiencies. Our aim was to investigate how the supplementation of calcium and vitamin D is associated with survival in patients with moderate concomitant aortic and mitral valve disease. A total of 3,257 patients (mean age of 71.73 years; 55.2% male; 83.1% White) were diagnosed with moderate concomitant aortic and mitral valve disease at Cleveland Clinic between January 2010 and December 2020 and were included in this study. The patients were divided into two groups based on their supplement intake. Further subgroup analysis was performed, focusing on the aortic valve, leading to the stratification of patients into two subgroups—group 1: aortic stenosis (AS) combined with either mitral stenosis or regurgitation, and group 2: aortic regurgitation (AR) combined with either mitral stenosis or regurgitation. The study's primary outcome was the combined event of all-cause mortality and heart failure hospitalization. Of the 3,257 patients who were included, 70% of them (2,273 patients) did not receive supplements, and 30% (984 patients) had received calcium and vitamin D supplementation. The supplement intake was associated with a greater risk of all-cause mortality [hazard ratio (HR), 1.114; 95% confidence interval (CI): 1.003–1.237, P=0.043], but no significant association with heart failure hospitalization was observed (HR, 1.003; 95% CI: 0.884–1.139, P=0.96). The subgroup analysis based on the aortic valve showed that among the 1,045 patients in group 1, 67% did not receive supplements, and 33% received supplementation. Calcium and vitamin D supplementation was significantly associated with a greater risk of all-cause mortality in patients with AS (HR, 1.203; 95% CI: 1.017–1.425, P=0.03). Contrarywise, in group 2 of patients with AR consisting of 2,212 patients, 71% did not receive any supplementation, and 29% received supplementation, with no significant association observed (HR, 1.044; 95% CI: 0.913–1.193, P=0.53). To conclude, in patients diagnosed with moderate concomitant aortic and mitral valve disease, the use of calcium and vitamin D supplements was associated with a greater mortality rate, particularly in AS patients.

Keywords: Valvular heart disease (VHD); calcium; vitamin D supplements; aortic valve disease; mitral valve disease

Submitted Jul 26, 2024. Accepted for publication Nov 20, 2024. Published online Feb 25, 2025.
doi: 10.21037/cdt-24-324
View this article at: https://dx.doi.org/10.21037/cdt-24-324

Concomitant aortic and mitral valve disease presents complex challenges for treatment and predicting outcomes. This clinical scenario is frequent yet remains poorly studied, as most clinical guidelines for valvular heart disease (VHD) management primarily focus on single valve diseases (1). The lack of substantial data makes it challenging to understand how concomitant valve diseases affect the function of the left ventricle and how modifiable risk factors, as well as vitamin supplementation, especially calcium and vitamin D, can impact the outcomes in this population, notably, given that the effect of calcium and vitamin D supplementation on cardiovascular (CV) health, at large, continues to be a subject of ongoing controversy (2).

The simultaneous use of calcium and vitamin D supplements to optimize bone health is widespread, with more than one-third of adults in the United States incorporating these supplements into their routine. This prevalence is even more pronounced among the elderly population (3,4). Due to their wide availability, affordability, and increasing usage among older adults, particularly those at risk of deficiencies, the impact of these supplements on CV health is a matter of significant interest from both clinical and public health perspectives, with a focus on promoting heart health and ensuring CV safety (5,6).

There have been numerous observational studies that have consistently and independently associated decreased levels of vitamin D in the blood, measured by serum 25-hydroxyvitamin D (25[OH]D), with a higher risk of developing cardiovascular disease (CVD) (7-9). After conducting multiple sizable randomized controlled trials (RCTs) and analyzing the data from these trials, it was found that vitamin D supplementation did not provide any beneficial CV effect, even for subgroups with insufficient vitamin D levels (10-12). Given the absence of RCT findings, currently, it is broadly accepted that the previously observed correlations between elevated serum 25[OH]D levels and improved impact on CV health were probably influenced by various further confounders.

The interchange between vitamin D supplementation and calcium supplements is complex. Over 40% of adults take calcium supplements and vitamin D to improve bone density (4). Sufficient calcium supplement intake is vital to sustain bone density. While vitamin D supplements are generally safe at normal levels, some studies concluded a significant association between calcium supplements and a higher risk of CV events, which was not observed with calcium intake obtained from dietary sources (12-15).

While most studies investigated the effects of calcium and vitamin D supplementation on CV outcomes in the general population, the literature lacks studies on patients with VHD, which is a higher-risk population for CV complications. In this context, we are investigating how calcium and vitamin D supplement intake might influence the outcomes of patients, particularly those with moderate concomitant aortic and mitral valve disease.

Our observational study comprised 3,257 patients diagnosed with moderate concomitant aortic and mitral valve disease. Data was collected from the Cleveland Clinic's medical records and imaging databases between January 2010 and December 2020. Inclusion criteria comprised patients aged 18 years or older with echocardiographic evidence of moderate stenosis or regurgitation involving both the aortic and mitral valves. Patients with mild or severe valve disease or other significant comorbidities were excluded from the analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Institutional Review Board (IRB) of Cleveland Clinic (No. 21-1234). Individual consent for this retrospective analysis was waived.

Clinical and demographic data, including age, gender, medical history, and presenting symptoms, were extracted from electronic medical records. Echocardiographic parameters were recorded, including valve morphology, degree of stenosis or regurgitation, and ventricular function. In addition, comorbidities such as diabetes mellitus, chronic kidney disease, hypertension, and coronary artery disease (CAD), as well as surgical data, were collected.

The study's observational period was instigated with the date of the patients' initial baseline echocardiogram at our facility. The patients were monitored via chart review, and their last follow-up or death date was documented. Mortality information was collected from available medical records or obituary databases. The study's primary endpoint was the combined event: heart failure hospitalization or all-cause mortality.

Consequently, the patients were divided into two groups based on their simultaneous vitamin D and calcium supplement intake: (I) not supplemented and (II) supplemented. A further subgroup analysis based on the aortic valve was then performed to differentiate between cases of aortic stenosis (AS) with mitral regurgitation or stenosis in group 1 and cases of aortic regurgitation (AR) with mitral regurgitation or stenosis in group 2.

Continuous data were expressed as mean ± standard deviation or median based on the distribution and were analyzed using Student's *t*-test or analysis of variance

(ANOVA). In contrast, categorical variables were analyzed using the Chi-squared test and presented as frequencies and percentages. Survival curves were constructed using the Kaplan-Meier survival analysis and compared utilizing the log-rank statistic. Cox proportional hazard analyses were performed to consider the association between potential predictors and survival outcomes, reporting hazard ratios (HRs), and 95% confidence intervals (CIs). Subgroup analyses were performed based on the aortic valve disease, whether AS or AR. All statistical analyses were conducted using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Results were considered statistically significant if the P value was less than 0.05, indicating a significance level of α=0.05.

Our study involving 3,257 patients observed a significant incidence of adverse outcomes. Specifically, all-cause mortality ensued in 1,611 patients (49.5%), heart failure hospitalization occurred in 1,119 patients (34.4%), and the composite event, comprising either all-cause mortality or heart failure hospitalization occurred in 1,926 patients (59.1%) (P<0.001). Baseline characteristics of the population are reported in *Table 1*. The mean age of the patients was 71.73±12.9 years; 55.2% were male, and 83.1% were White. Patients were followed up for a median period of 21.8 months, ranging from 1 to 155.8 months.

Of the total cohort comprising 3,257 patients, 2,518 (77.3%) were on beta blockers, 2,329 (71.5%) were on diuretics, 999 (30.7%) on calcium channel blockers, and 1,038 (31.9%) on angiotensin-converting enzyme (ACE) inhibitors. Of the 3,257 participants included in the study, 2,273 patients (70%) did not receive calcium or vitamin D supplements, while 984 patients (30%) did. Patients who were supplemented with calcium and vitamin D had a significantly increased risk of all-cause mortality (HR, 1.114; 95% CI: 1.003–1.237, P=0.043) (*Figure 1*). Nonetheless, the supplementation did not exhibit any significance with heart failure hospitalization (HR, 1.003; 95% CI: 0.884–1.139, P=0.96).

Additional subgroup analysis based on aortic valve disease provided further insights. Patients in group 1, diagnosed with AS concomitant with either mitral stenosis or regurgitation, included 1,045 patients (32%). From this group, 701 patients (67%) were not supplemented, and 344 (33%) received supplementation. In this subgroup, vitamin D and calcium supplementation was associated with a significantly increased risk of all-cause mortality (HR, 1.203; 95% CI: 1.017–1.425, P=0.03) (*Figure 2*).

In group 2, patients diagnosed with AR concomitant with either mitral stenosis or regurgitation comprised 2,212 patients (68%). From this group, 1,572 patients (71%) were not supplemented, and 640 patients (29%) were supplemented with calcium and vitamin D. In this subgroup, no significant association was found between supplementation and all-cause mortality (HR, 1.044; 95% CI: 0.913–1.193, P=0.53) (*Figure 3*).

In this observational study comprising 3,257 patients diagnosed with moderate concomitant aortic and mitral valve disease, followed over a median duration of 22 months, we found that calcium supplement intake combined with vitamin D supplementation was significantly associated with all-cause mortality. Specifically, patients with AS concomitant with either mitral regurgitation or stenosis had an increased risk of all-cause mortality. Strengthened by its large sample size, our study shows that calcium accompanied by vitamin D supplementation reflects a higher all-cause mortality rate.

The mechanism behind the increased CV risk from calcium supplements is still not clear. However, the current understanding of the mechanism is that with calcium supplementation, there is transient hypercalcemia following a single large dose. This may activate a coagulation cascade or cause calcium to be deposited inside the vessels, affecting the endothelial integrity and resulting in arterial stiffness (16). This is supported by the Mendelian randomization study that included 60,801 cases of CAD and 123,504 controls, which has shown that a genetic predisposition to increased serum calcium levels has been associated with a higher risk of myocardial infarction and CAD (17). In other observational studies, increased serum calcium levels showed a significant association with increased risk for stroke, CAD, diabetes, and heart failure (18-21). Another study has previously stated that 8.8% of participants experienced hypercalcemia, and 30.6% experienced hypercalciuria while taking 1,200 mg/day of calcium supplements. This suggests that even when adhering to recommended calcium doses, patients may still be susceptible to the adverse effects of elevated calcium levels (22).

Many meta-analyses have concluded that calcium supplementation increases CV risk, whether with or without vitamin D. A meta-analysis of 15 RCTs (n≥100 participants taking calcium supplements ≥500 mg/day, mean age ≥40 years, with a duration of the study ≥1 year) showed that supplementation with calcium alone without vitamin D was significantly associated with a higher risk of myocardial infarction (23). Given the increased risk of CV events with the probable negative impact on hip fracture

Table 1 Basic demographic, clinical, echocardiographic, and surgical characteristics

Variables	Total population (n=3,257)	AS (group 1) (n=1,045)	AR (group 2) (n=2,212)	Calcium/vitamin D supplement intake	
				No (n=2,273)	Yes (n=984)
Age (years)	71.73±12.9	74.6±11.4	70.5±13.24	70.62±13.44	74.30±11.09
Sex					
Male	1,797 (55.2)	590 (56.5)	1,207 (54.6)	1,374 (60.4)	423 (43.0)
Female	1,460 (44.8)	455 (43.5)	1,005 (45.4)	899 (39.6)	561 (57.0)
White	2,706 (83.1)	925 (88.5)	1,781 (80.5)	1,872 (82.4)	834 (84.8)
Ever smoked	1,652 (50.7)	544 (52.1)	1,108 (50.1)	1,167 (51.3)	485 (49.3)
Diabetes	879 (27.0)	387 (37.0)	492 (22.2)	1,690 (74.4)	688 (69.9)
Hypertension	2,545 (78.1)	832 (79.6)	1,713 (77.4)	1,733 (76.2)	812 (82.5)
Hyperlipidemia	2,076 (63.7)	733 (70.1)	1,343 (60.7)	1,378 (60.6)	698 (70.9)
Chronic kidney disease	915 (28.1)	341 (32.6)	574 (25.9)	597 (26.3)	318 (32.3)
Congestive heart failure	2,079 (63.8)	685 (65.6)	1,394 (63.0)	1,452 (63.9)	627 (63.7)
Atrial fibrillation	1,783 (54.7)	578 (55.3)	1,205 (54.5)	1,226 (53.9)	557 (56.6)
Coronary artery disease	1,921 (59.0)	719 (68.8)	1,202 (54.3)	1,335 (58.7)	586 (59.6)
Serum calcium (mg/dL)	9.18±0.69	9.11±0.70	9.21±0.59	9.15±0.68	9.23±0.71
LVEF (%)	48.92±14.7	48.7±14.3	47.7±14.7	48.42±14.79	50.08±14.37
RVSP (mmHg)	44.96±15.7	47.7±17.6	43.8±15.1	45.18±16.28	44.46±14.35
New York Heart Association class					
I	1,002 (30.8)	293 (28.0)	708 (32.0)	715 (31.5)	286 (29.1)
II	1,222 (37.5)	383 (36.7)	839 (37.9)	845 (37.2)	377 (38.3)
III	852 (26.2)	301 (28.8)	551 (24.9)	587 (25.8)	265 (26.9)
IV	181 (5.6)	68 (6.5)	113 (5.1)	126 (5.5)	55 (5.6)
Surgical interventions					
Aortic valve intervention	1,274 (39.1)	378 (36.2)	896 (40.5)	919 (40.4)	355 (36.1)
Mitral valve intervention	958 (29.4)	278 (26.6)	680 (30.7)	714 (31.4)	244 (24.8)
CABG	599 (18.4)	214 (20.5)	385 (17.4)	441 (19.4)	158 (16.1)
PCI	236 (7.2)	108 (10.3)	126 (5.7)	161 (7.1)	75 (7.6)

Data are presented as frequency (%) or mean ± standard deviation. AS, aortic stenosis; AR, aortic regurgitation; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; RVSP, right ventricular systolic pressure.

incidence, as well as the relatively small overall effectiveness in fracture reduction (approximately a 10% decrease), the study implies the need to reassess the role of calcium supplements in preventing and treating osteoporosis (23). Furthermore, a 2019 meta-analysis of 9 systematic reviews and 4 recent RCTs aimed to study the effects of calcium supplements not alone but combined with vitamin D on CV outcomes. It showed that combining calcium with vitamin D supplements was found to increase the risk of stroke (24). Additionally, a recent meta-analysis conducted in 2020, which included 16 RCTs and 26 observational studies, found that while calcium intake from dietary sources does not elevate the risk of CVD, calcium supplement intake may potentially raise CVD risk, especially in relation to myocardial infarction. This risk of CVD is even greater with the increase of the supplementation doses of

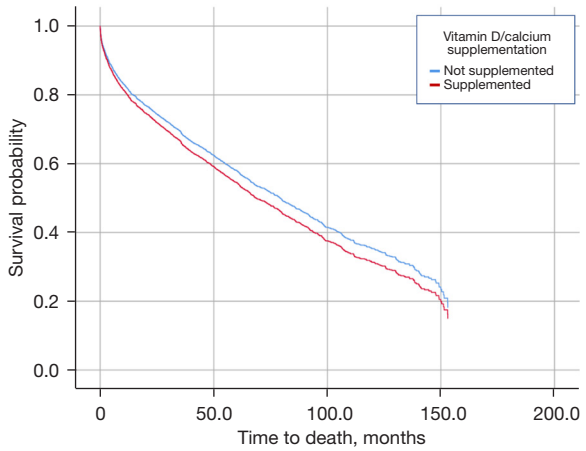

Figure 1 Kaplan-Meier curve of all-cause mortality for patients diagnosed with moderate concomitant aortic and mitral valve disease.

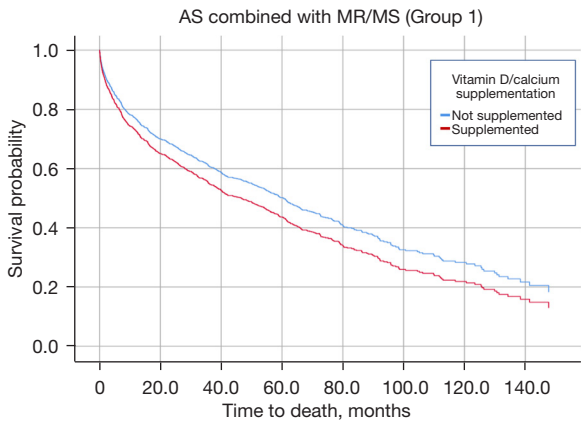

Figure 2 Kaplan-Meier curve of all-cause mortality for patients diagnosed with aortic stenosis combined with either mitral regurgitation or mitral stenosis (group 1: AS with MR/MS). AS, aortic stenosis; MR, mitral regurgitation; MS, mitral stenosis.

≥1,000 mg/day. They also concluded that men tend to be more adversely affected by calcium supplements than women (15).

Numerous cohort studies also found that users of calcium supplements have a higher risk for CV events compared to non-users. In Multi-Ethnic Study of Atherosclerosis (MESA), a higher risk of coronary artery calcification was found to be associated with the intake of calcium supplements (relative risk, 1.22; 95% CI: 1.07–1.39) (21). Conversely, increased calcium intake from food sources has not shown any significant association with an increased

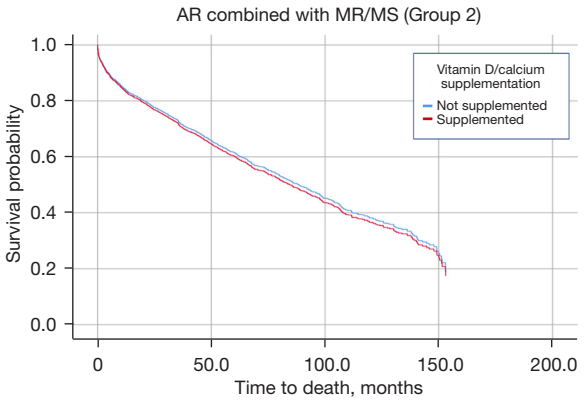

Figure 3 Kaplan-Meier curve of all-cause mortality for patients diagnosed with aortic regurgitation combined with either mitral regurgitation or mitral stenosis (group 2: AR with MR/MS). AR, aortic regurgitation; MR, mitral regurgitation; MS, mitral stenosis.

CV risk (12). An additional study was conducted on 23,980 participants from the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study, aged 35–64 years and free of major CVD events at recruitment. It concluded that increasing calcium intake from dietary sources shows no significant CV benefits. In contrast, participants who took calcium supplements were found to have a significantly higher risk of myocardial infarction, prompting these supplements to be taken with caution (25).

Previously discussed literature, whether meta-analyses or observational studies, conducted these studies on generally healthy populations. A recent study was conducted on 2,657 patients with mean age ≥60 years diagnosed with mild to moderate AS. It has concluded that oral calcium supplementation, whether alongside vitamin D or not, is associated with reduced survival and increased need for aortic valve replacement (AVR) in older patients with mild to moderate AS. They have also reported that their conclusions imply that calcium supplementation does not show CV benefit in this population; on the contrary, these supplementations ought to be carefully evaluated, given the increasing evidence and concern for CV harm (26).

Recently, Michos *et al.* concluded that while vitamin D does not seem to have a detrimental effect on CV health, the lack of an evident benefit from using supplements in RCTs should discourage their usage for this purpose. Instead, it's better to focus on optimizing vitamin D levels through diet and moderate sunlight exposure and to reserve the supplementation of vitamin D solely for confirmed

25[OH]D deficiency. Also, Michos *et al.* concluded that while calcium supplements are widely utilized to enhance bone density, they are associated with a potential risk to CV health. As a result, calcium supplementation should be approached with caution and care, and efforts should be made to achieve the recommended daily calcium intake from dietary sources (27).

Few studies show that calcium intake, whether from dietary sources or supplements with or without vitamin D, does not show a relationship, whether favorable or detrimental, to the risk of CVD, stroke, mortality, or all-cause mortality; however, the population was only generally healthy adults, not patients diagnosed with any valvular disease or any cardiothoracic morbidity in general (28,29). Among the few studies investigating the impact of calcium supplementation on aortic valve and coronary artery calcification, one has concluded that calcium supplements do not affect the progression of aortic valve calcification or coronary artery calcification. However, the exceedingly small sample sizes and insufficient follow-up periods constitute constraining factors in this study due to the gradual nature of disease progression (30).

To date, no study has investigated the risks of these supplements in our specific population diagnosed with moderate concomitant aortic and mitral valve disease. Our research stands out due to its innovative approach to effectively addressing these constraints. However, there are some limitations to this study. The analysis lacks some variables, such as the etiology of valvular disease, serum vitamin D, phosphate, alkaline phosphatase, bone density, and osteoporosis history. Potential confounders might affect the results, such as osteoporosis, as it is more prevalent among patients who consume calcium and vitamin D supplements. Being a retrospective analysis, inherent biases such as selection and ascertainment bias could affect the findings. Also, manually reviewing charts to determine whether patients were taking their supplements made it challenging to track unrecorded usage and dietary intake, potentially impacting the accuracy of estimated supplement effects on study results. Another limitation is that the analysis did not account for specific dosages of supplements at baseline or over time. Finally, the absence of cause-of-death data for a substantial patient subset introduces bias in mortality-related analyses, necessitating cautious interpretation.

In conclusion, our study showed that calcium and vitamin D supplement intake was associated with a greater mortality rate in patients diagnosed with moderate concomitant aortic and mitral valve disease. Furthermore, patients with AS exhibited worse outcomes in comparison to those with AR. This finding can help us better understand how calcium and vitamin D supplements might affect cardiac health. Specifically, concomitant aortic and mitral valve disease patients should be cautious before taking these supplements. Further research is warranted to explore the underlying mechanisms and to investigate whether personalized approaches to supplementation based on individual patient characteristics and the type of valvular disease may be necessary to optimize outcomes.

Acknowledgments

The abstract of this article was previously submitted and presented at the European Society of Cardiology (ESC) Congress 2023, followed by its publication in the European Heart Journal abstract supplement.

Footnote

Peer Review File: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-324/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-324/coif). M.Y.D. is a consultant and has research agreements with Bristol Myers Squibb, Tenaya, Viz AI, Edgewise, and Cytokinetics. G.R. receives honoraria from Boston Scientific, Edwards Lifesciences, and Abbott Laboratories. A.M.G. receives a grant from NIH—Cardiothoracic Surgical Trials Network, part of Cleveland Clinic funding unrelated to this manuscript. A.M.G. is a consultant with research agreements with Edwards Lifesciences, Medtronic, Artivion, Abbott, ClearFlow, AtriCure, Corcym, Johnson and Johnson, Baxter, and serves as a member of the Board of Directors at the American Association for Thoracic Surgery. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Institutional

Review Board (IRB) of Cleveland Clinic (No. 21-1234). Individual consent for this retrospective analysis was waived.

References

1. Roberts WC, Ko JM. Some observations on mitral and aortic valve disease. Proc (Bayl Univ Med Cent) 2008;21:282-99.
2. Chung M, Tang AM, Fu Z, et al. Calcium Intake and Cardiovascular Disease Risk. Ann Intern Med 2016;165:856-66.
3. Kantor ED, Rehm CD, Du M, et al. Trends in Dietary Supplement Use Among US Adults From 1999-2012. JAMA 2016;316:1464-74.
4. Bailey RL, Dodd KW, Goldman JA, et al. Estimation of total usual calcium and vitamin D intakes in the United States. J Nutr 2010;140:817-22.
5. Tankeu AT, Ndip Agbor V, Noubiap JJ. Calcium supplementation and cardiovascular risk: A rising concern. J Clin Hypertens (Greenwich) 2017;19:640-6.
6. Chin K, Appel LJ, Michos ED. Vitamin D, Calcium, and Cardiovascular Disease: A"D"vantageous or "D"etrimental? An Era of Uncertainty. Curr Atheroscler Rep 2017;19:5.
7. Wang L, Song Y, Manson JE, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes 2012;5:819-29.
8. Lutsey PL, Michos ED, Misialek JR, et al. Race and Vitamin D Binding Protein Gene Polymorphisms Modify the Association of 25-Hydroxyvitamin D and Incident Heart Failure: The ARIC (Atherosclerosis Risk in Communities) Study. JACC Heart Fail 2015;3:347-56.
9. Michos ED, Misialek JR, Selvin E, et al. 25-hydroxyvitamin D levels, vitamin D binding protein gene polymorphisms and incident coronary heart disease among whites and blacks: The ARIC study. Atherosclerosis 2015;241:12-7.
10. Barbarawi M, Kheiri B, Zayed Y, et al. Vitamin D Supplementation and Cardiovascular Disease Risks in More Than 83 000 Individuals in 21 Randomized Clinical Trials: A Meta-analysis. JAMA Cardiol 2019;4:765-76.
11. Manson JE, Cook NR, Lee IM, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med 2019;380:33-44.
12. Anderson JJ, Kruszka B, Delaney JA, et al. Calcium Intake From Diet and Supplements and the Risk of Coronary Artery Calcification and its Progression Among Older Adults: 10-Year Follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Heart Assoc 2016;5:e003815.
13. Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ 2008;336:262-6.
14. Bolland MJ, Grey A, Avenell A, et al. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011;342:d2040.
15. Yang C, Shi X, Xia H, et al. The Evidence and Controversy Between Dietary Calcium Intake and Calcium Supplementation and the Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis of Cohort Studies and Randomized Controlled Trials. J Am Coll Nutr 2020;39:352-70.
16. Reid IR, Bolland MJ, Avenell A, et al. Cardiovascular effects of calcium supplementation. Osteoporos Int 2011;22:1649-58.
17. Larsson SC, Burgess S, Michaëlsson K. Association of Genetic Variants Related to Serum Calcium Levels With Coronary Artery Disease and Myocardial Infarction. JAMA 2017;318:371-80.
18. Lutsey PL, Alonso A, Michos ED, et al. Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 2014;100:756-64.
19. Lind L, Skarfors E, Berglund L, et al. Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. J Clin Epidemiol 1997;50:967-73.
20. Rooney MR, Pankow JS, Sibley SD, et al. Serum calcium and incident type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Am J Clin Nutr 2016;104:1023-9.
21. Foley RN, Collins AJ, Ishani A, et al. Calcium-phosphate levels and cardiovascular disease in community-dwelling

adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 2008;156:556-63.
22. Gallagher JC, Smith LM, Yalamanchili V. Incidence of hypercalciuria and hypercalcemia during vitamin D and calcium supplementation in older women. Menopause 2014;21:1173-80.
23. Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010;341:c3691.
24. Khan SU, Khan MU, Riaz H, et al. Effects of Nutritional Supplements and Dietary Interventions on Cardiovascular Outcomes: An Umbrella Review and Evidence Map. Ann Intern Med 2019;171:190-8. Erratum in: Ann Intern Med 2020;172:75-6.
25. Li K, Kaaks R, Linseisen J, et al. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). Heart 2012;98:920-5.
26. Kassis N, Hariri EH, Karrthik AK, et al. Supplemental calcium and vitamin D and long-term mortality in aortic stenosis. Heart 2022;108:964-72.
27. Michos ED, Cainzos-Achirica M, Heravi AS, et al. Vitamin D, Calcium Supplements, and Implications for Cardiovascular Health: JACC Focus Seminar. J Am Coll Cardiol 2021;77:437-49.
28. Kopecky SL, Bauer DC, Gulati M, et al. Lack of Evidence Linking Calcium With or Without Vitamin D Supplementation to Cardiovascular Disease in Generally Healthy Adults: A Clinical Guideline From the National Osteoporosis Foundation and the American Society for Preventive Cardiology. Ann Intern Med 2016;165:867-8.
29. Hsia J, Heiss G, Ren H, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007;115:846-54.
30. Bhakta M, Bruce C, Messika-Zeitoun D, et al. Oral calcium supplements do not affect the progression of aortic valve calcification or coronary artery calcification. J Am Board Fam Med 2009;22:610-6.

Cite this article as: Gaballa A, Hajj Ali A, El Dahdah J, Popovic Z, Wang TK, Reed G, Rodriguez L, Griffin B, Gillinov AM, Kapadia SR, Svensson LG, Desai MY. Calcium and vitamin D supplementation impact on survival in patients with moderate concomitant aortic and mitral valve disease. Cardiovasc Diagn Ther 2025;15(1):265-272. doi: 10.21037/cdt-24-324