Summer 7-12-2022

Utilizing Vitamin D Supplementation in Heart Failure

Rachel Alexanian

Utilizing Vitamin D Supplementation in Heart Failure

Rachel Alexanian, PA-S2

George Fox University

School of Graduate Health Sciences

Department of Physician Assistant Medicine

Doctor of Medical Science Program

Dr. Justin M. Gambini, DMSc, MSPAS, PA-C, DFAAPA

ARP II: Dissertation Manuscript

Scholarly Project: Draft Manuscript

July 12, 2022

Utilizing Vitamin D Supplementation in Heart Failure

Target journal: Circulation: Heart Failure (from AHA)

Type of paper: Review article

Manuscript requirements:

- ≤6000 words
- Max of 100 references
- Max of 8 display items
- Unstructured abstract ≤250 words

Prior to submission, please gather the following items:

- A single PDF including all elements including text, figures, and tables
- Alternately, individual Manuscript files can be provided:
    1. Manuscript text file.
    2. Tables: May be either embedded within the manuscript (preferred) or submitted as separate files. Tables should be provided as editable text, not as images.
    3. Figures: May be either embedded within the manuscript (preferred) or submitted separately. Please note that only PDF, EPS, and TIFF files will be allowed for publication, but any sufficiently clear image format is acceptable for initial submission.
    4. Supplemental Files
- All author information, including:
    - Full names
    - Affiliations
    - E-mail addresses

Manuscript Preparation Guidelines

The following are additional manuscript preparation guidelines for the AHA/ASA journal portfolio. Please note that these guidelines are provided as an aid and authors that adhere to the Minimum Submission Requirements provided above will have their manuscript considered for review.

Organize manuscripts in this order:

1. Title Page
2. Abstract
3. Introduction
4. Methods
5. Results
6. Discussion
7. Acknowledgments
8. Sources of Funding
9. Disclosures
10. References
11. Tables
12. Figures with Figure Legends

Number all pages—including Figures with legends and Tables. Abbreviations must be defined at first mention.

It is recommended for manuscripts to be typed, double-spaced using a 12-point font, including references, figure legends, and tables. Leave 1-inch margins on all sides.

Full title:

Utilizing Vitamin D Supplementation in Heart Failure

Authors' names, academic degrees, and affiliations:

Rachel Alexanian, PA-S2, George Fox University

Heather Rollins, DMSc, PA-C, George Fox University

Tim Aylward, MPAS, PA-C, George Fox University

Justin M. Gambini, DMSc, MSPAS, PA-C, DFAAPA, George Fox University

Short title:

Vitamin D Supplementation in Heart Failure

Corresponding author information:

Rachel Alexanian

[REDACTED]

Total word count:

3,168

ABSTRACT

Background: The purpose of this article is to procure a literature review on a relatively new area of research, ultimately aimed at improving the lives of those with heart failure. This article sheds light on the benefits of vitamin D supplementation, and it contributes significantly to the conversation regarding mitigating the complications of heart failure. Herein we aim to offer insight into whether vitamin D supplementation is beneficial for a patient with heart failure.

Method: PubMed, MeSH, and PLOS One literature searches were conducted with the following search terms: heart failure, hospitalization, vitamin D, quality of life, and cardiovascular disease. Nine pertinent articles were ultimately retrieved and serve as the backbone for this article. To find the most up-to-date data, inclusion criteria included research conducted within the past 5 years. Two exceptions published within the past 10 years were made to this inclusion criteria due to their invaluable pertinence to the topic at hand.

Results: This is novel research because science has only recently begun to seriously consider vitamin D as a legitimate adjunct therapy in heart failure. Studies herein indicate the potential for Vitamin D supplementation to improve quality of life and cardiac functioning, and decrease mortality, serum inflammatory markers, and left ventricular remodeling in patients with heart failure.

Conclusion: There is growing evidence for a positive correlation between vitamin D levels and cardiovascular health. Vitamin D is unlikely to replace today's medical therapy, but preliminary data indicates the potential of vitamin D to decrease hospitalization rates, improve quality of life, and even reduce mortality in patients with heart failure. Collectively, this data suggests vitamin D supplementation may be a beneficial augment to traditional medical therapy to improve

outcomes in heart failure. Additional research is needed to parse out the benefit of vitamin D supplementation in the different stages and classifications of heart failure.

Keywords: Heart failure, hospitalization, vitamin D, quality of life, and cardiovascular disease.

NONSTANDARD ABBREVIATIONS AND ACRONYMS

ACC	American College of Cardiology Foundation
ACEi	Angiotensin-converting enzyme inhibitor
AHA	American Heart Association
ARB	Angiotensin receptor antagonist
ARNi	Angiotensin receptor-neprilysin inhibitor
BNP	B-type natriuretic peptide
eGFR	Estimated glomerular filtration rate
HFimpEF	Heart failure with improved ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reserved ejection fraction
HFSA	Heart Failure Society of America
MRA	Mineralocorticoid receptor antagonist
RAAS	Renin-angiotensin-aldosterone system
SGLT2i	Sodium-glucose cotransporter 2 inhibitors
SNS	Sympathetic nervous system
VITAL Trial	Vitamin D and OmegA-3 Trial

INTRODUCTION

Heart failure is one of the top three cardiovascular diseases worldwide. It is technically challenging to manage and often precipitates hospitalizations in those who are afflicted. Vitamin D deficiency is one of the most common vitamin deficiencies worldwide. The benefits of vitamin D on cardiovascular health are not well understood but there is growing evidence that vitamin D may be valuable for cardiovascular health. Thus, the importance of identifying the potential role of vitamin D supplementation in heart failure through evidence-based research cannot be underestimated. This paper will break down the basic science of heart failure and vitamin D and conclude by highlighting various studies on the relationship between vitamin D and heart failure. The list of studies is in no way exhaustive but rather highlights the potential benefit of vitamin D supplementation in heart failure patients.

HEART FAILURE: DEFINITION AND CLASSIFICATION

The American Heart Association, American College of Cardiology Foundation, and Heart Failure Society of America (AHA/ACC/HFSA) have jointly defined heart failure as "a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood."[1] From this overarching definition comes the different stages of heart failure, outlined in Table 1. [1]

Table 1. Stages of Heart Failure

Stage	**Definition**
Stage A	At risk for heart failure
Stage B	Pre-heart failure
Stage C	Symptomatic heart failure

Stage D	Advanced heart failure

In addition to these stages is the New York Heart Association Classification of heart failure, which is used to assess both the symptoms and function of patients in stage C or stage D of heart failure. Heart failure can also be classified by left ventricular ejection fraction, as detailed in Table 2.[1]

Table 2. Classification of HF by LVEF

Type of HF according to LVEF	**Criteria**
HFrEF (HF with reduced EF)	LVEF ≤ 40%
HFimpEF (HF with improved EF)	Previous LVEF ≤ 40% and a follow up measurement of LVEF > 40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%-49% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HR with preserved EF)	LVEF ≥ 50% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

HEART FAILURE: DIAGNOSIS

The 2022 AHA/ACC/HFSA Guidelines for the Management of Heart Failure recommends an extensive workup, including a CBC, UA, serum electrolytes, BUN, serum

creatinine, glucose, lipid profile, liver function tests, iron studies, TSH, B-type natriuretic peptide (BNP) or N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), 12-lead EKG, chest x-ray and transthoracic echocardiography (TTE).[1] This in-depth workup can clue providers in to the most accurate classification of heart. The specific reasons for the above workup are outlined in Table 3.[1]

Table 3. Work Up For Heart Failure

Specific Work Up	**Rationale**
Labs (CBC, UA, serum electrolytes, BUN, serum creatinine, glucose, lipid profile, liver function tests, iron studies, TSH)	Helpful for indicating comorbidities, qualification/exclusion from certain treatments, causes/complications of heart failure, and the likely severity and prognosis of the heart failure
BNP or NT-proBNP	Higher levels associated with increased adverse outcomes in heart failure, including cardiovascular and all-cause death, as well as major cardiovascular events
12-lead EKG	Reveals rate and rhythm, QRS status, and possible cause and prognosis of heart failure
Chest x-ray	Assesses for cardiomegaly, pulmonary venous congestion, and edema. May also reveal other causes for a patient's symptoms that are not due to heart failure
TTE	Identifies structural abnormalities that in turn can predict subsequent clinical risks

HEART FAILURE: PATHOPHYSIOLOGY

Heart failure is a progressive process marked by structural and functional cardiovascular remodeling over time.[2] Increased ventricular pressure and volume overload collectively result in remodeling mechanisms including the release of neuroendocrine signals, signaling peptides, and inflammatory cytokines, and increase myocardial wall stress and oxidative stress.[2] This remodeling initially serve to compensate in the short term but eventually adds to disease progression. The results is hypertrophy or apoptosis of myocytes, interstitial fibrosis, alteration of calcium-handling and cytoskeletal function, higher levels of ventricular wall stress, and re-expression of fetal genes.[2] In addition to these mechanisms, long-term activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) eventually contribute to the remodeling of the heart, blood vessels, and kidneys, in addition to other organs, thereby resulting in symptomatic heart failure.[2] Thus, the progressive nature of heart failure puts patients at increased risk of many complications that may necessitate hospitalization and additional treatment, including cardiac cachexia, impaired renal function, pulmonary congestion, arrhythmias, angina, myocardial infarction, and pulmonary edema, among others.[3]

HEART FAILURE: CURRENT TREATMENT RECOMMENDATIONS

The treatment of heart failure is complicated, often requiring close monitoring and medication changes. The 2022 AHA/ACC/HFSA general guidelines for therapeutics are outlined in Table 4.[1]

Table 4. 2022 AHA/ACC/HFSA General Guidelines For Therapeutics in Heart Failure

Medication	**Reasoning For Use**
Angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor antagonists (ARB)/angiotensin receptor-neprilysin inhibitor (ARNi)	Reduce morbidity and mortality in HFrEF

Beta blockers	Reduce • Risk of death • Combined risk of death/hospitalization in HFrEF
Mineralocorticoid receptor antagonists (MRAs)	Reduce • All-cause mortality • Heart failure hospitalizations • Sudden cardiac death in HFrEF
Sodium-glucose cotransporter 2 inhibitors (SGLT2i)	Reduce the rates of hospitalization in heart failure when compared to placebo
Diuretics as needed (loop diuretics preferred)	Assist in the reduction of fluid retention, increase urine sodium excretion, and improve quality of life, exercise tolerance, and symptoms

The specific regimen varies from patient to patient depending on multiple factors, including the classification of heart failure as well as the patient's eGFR, electrolyte levels, known drug allergies, etc. The complicated and individualized treatment regimen of heart failure is a testament to its extensive pathology. Thus, it is prudent to consider other possible therapies to augment the current regimen, even something as seemingly simple as vitamin D supplementation.

VITAMIN D: SYNTHESIS AND PHYSIOLOGIC FUNCTIONS

Vitamin D (1,25-dihydroxyvitamin D) is more accurately referred to as a hormone than a vitamin because it can be synthesized endogenously (in the skin).[4] Upon exposure to UV light, 7-dehydrocholesterol undergoes a reaction to yield previtamin D_3 and then cholecalciferol, which

is then absorbed into blood and becomes the active metabolite 1,25-dihydroxyvitamin D (calcitriol) via hydroxylation reactions in the liver and kidney.[5]

The effects of vitamin D on the body are extensive. Vitamin D receptors are found throughout most tissues, thereby maintaining the normal function of cell proliferation and differentiation, the immune system, cardiomyocytes, and inflammatory responses, in addition to the endocrine and skeletal systems.[6] While the role of vitamin D on cardiovascular health is not well understood, experimental models have revealed multiple benefits of vitamin D supplementation: anti-hypertrophic properties, inhibition of myocyte proliferation and RAAS, and anti-hypertensive functions, among other positive cardiovascular impacts. [7] In addition to this, there are multiple hypothetical processes connecting vitamin D and cardiovascular disease, as summarized in *Figure 1*.[7]

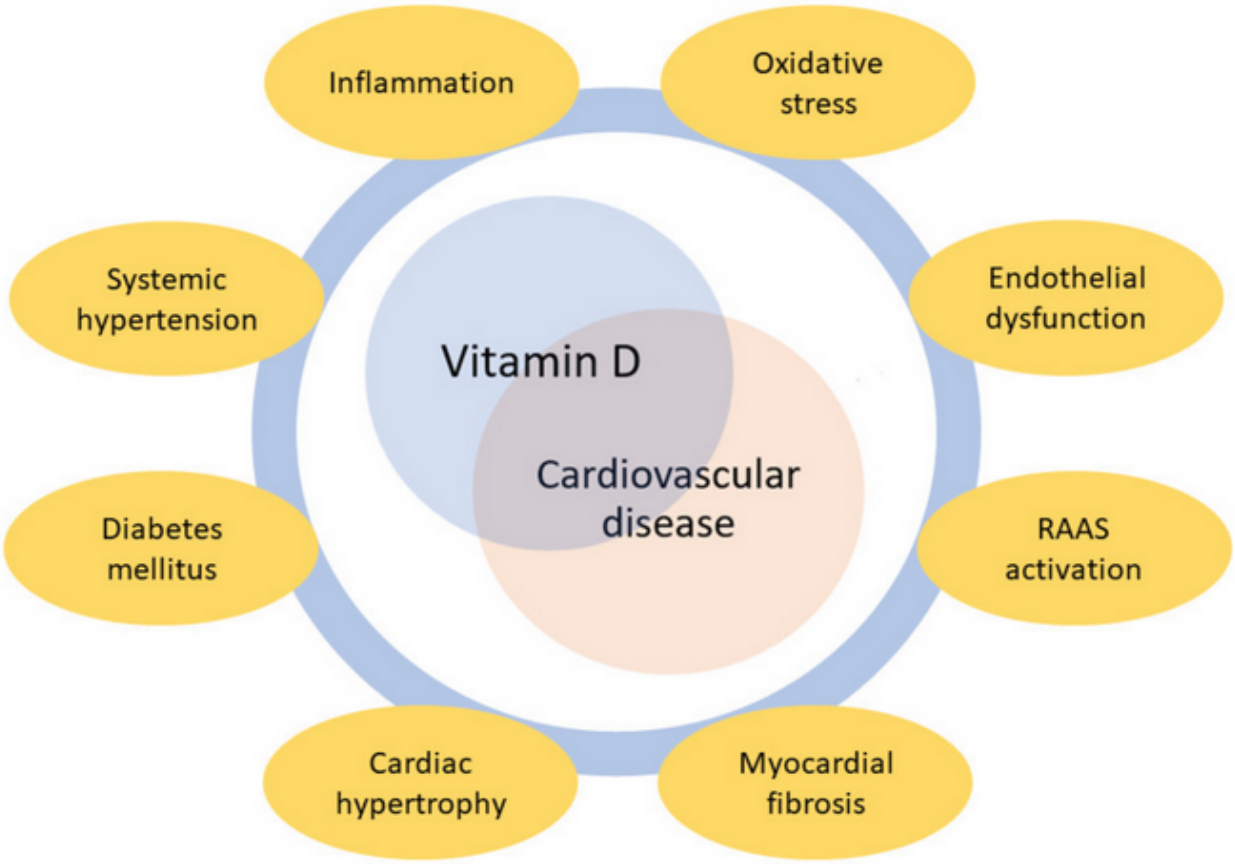

Figure 1. Major hypothetical mechanisms underlying the association between vitamin D and cardiovascular disease. RAAS – renin-angiotensin-aldosterone system.

VITAMIN D: DEFICIENCY

Vitamin D levels are measured by testing the serum level of 25-dihydroxyvitamin D, also referred to as 25(OH) vitamin D. Despite being the most common vitamin deficiency worldwide, there is no universal definition for vitamin D "deficiency." Some epidemiologic and experimental data advocates a 25(OH) vitamin D level > 20 ng/mL to be sufficient for most individuals, but other experts advocate a level > 30 ng/mL.[6] In spite of a definitive definition of vitamin D deficiency, it is widely accepted that low levels of vitamin D have a negative effect on health.

Vitamin D deficiency creates a cascade of potential problems. Typically, mild and even moderate vitamin D deficiency is asymptomatic. But in addition to fatigue, muscle and joint

aches, and mood changes, patients with a long-standing deficiency can experience hypocalcemia, secondary hyperparathyroidism, impaired skeletal mineralization, and proximal myopathy."[4] Deficiency in vitamin D has also been shown to increase overall mortality including cardiovascular causes.[4]

VITAMIN D SUPPLEMENTATION IN HEART FAILURE

The idea of supplementing vitamin D in patients with heart failure is a relatively new concept, evidenced by the overall limited data on the subject and lack of a substantial number of long-term studies. Cosentino et al[7] reviewed multiple studies detailing the relationship between vitamin D deficiency and heart failure, concluding at the end of their study, "vitamin D insufficiency seems to be associated not only with higher HF prevalence and risk but also with its clinical severity and risk of hospitalization."

Witte et al[8] conducted a randomized placebo-controlled double-blind trial on 229 patients with chronic heart failure due to LVSD and a vitamin D deficiency of < 20 ng/ml. These patients were on optimal medical therapy at the time of the study. Patients were given either 4,000 IU of vitamin D3 or a non-calcium based placebo every day for one year.[8] The primary endpoint studied was to see if there was any change in 6-minute walk distances. "secondary endpoints included change in LV ejection fraction at 1 year, and safety measures of renal function and serum calcium concentration assessed every 3 months."[8] This study[8] found that while vitamin D supplementation did not improve 6-minute walk distances, it did improve cardiac function (improvement LV ejection fraction of +6.07%) and helped reverse LV remodeling and diameter.

Moretti et al[9] conducted a "6-month, parallel group, double-blind, placebo-controlled, single clinic center, randomized trial of supplemental vitamin D3 using a dose of 10,000 IU daily or placebo in 40 vitamin D deficient or insufficient (25(OH)D level ≤ 32 ng/ml) patients with

stable New York Heart Association Class II-III HF in a specialty cardiology clinic" to determine quality of life and hormonal indices. Quality of life was determined using the Kansas City Cardiomyopathy (KCCQ) tool that is "sensitive and specific for assessment of change in health-related QOL," administered at the beginning of treatment and then at the 6-month interval. [9]

The results supported the potential role of vitamin D3 supplementation benefitting heart failure patients. BNP levels were significantly improved with therapeutic vitamin D3 treatment compared to placebo. This is a significant result because "BNP has been shown to be strongly associated with recurrent hospitalization and mortality in this patient population."[9] Additionally, KCCQ scores in the vitamin D supplementation group were significantly improved in the domains of physical, quality of life, overall summary, and clinical summary. The study[9] concluded that further research is necessary to determine whether heart failure patients need vitamin D supplementation only in cases where 25(OH)D levels are < 20–30 ng/ml at baseline (the generally accepted definition of vitamin D insufficiency), or if all heart failure patients would benefit from supplementation regardless of their baseline status.

Gotsman et al[10] compared heart failure patients vs non-heart failure patients at Clalit Health Services in Jerusalem, Israel. They evaluated the vitamin D levels of patients between January 2006 and June 2010 who were 45 years old and older. Patients with the diagnosis of heart failure were compared with those who were not diagnosed with heart failure in order to study "the impact of both vitamin D deficiency and vitamin D supplementation on survival in [heart failure] patients."[10] They found that vitamin D deficiency was more prevalent among the patients with heart failure, and vitamin D deficiency is a predictor of mortality in this patient population.[10] In light of these findings, it is not surprising the study also concluded vitamin D supplementation to be useful in improving the outcomes of heart failure patients.

Cubbon et al[11] prospectively examined vitamin D deficiency in 1,802 patients with heart failure secondary to a left ventricular ejection fraction less than or equal to 45%. They found 73% of patients to be deficient in vitamin D. While they did not show supplementation to improve outcomes, they noted that "during a mean follow-up period of 4 years, each 2.72-fold increment in 25[OH]D concentration (for example from 32 to 87 nmol/L) is associated with 14% lower all-cause mortality (95% confidence interval (CI) 1, 26%; $p = 0.04$)"[11]

Wang et al[12] wrote a meta-analysis of 10 randomized controlled trials regarding the use of vitamin D supplementation for patients with chronic heart failure (CHF). They concluded that while a pooled analysis of supplementation of vitamin D didn't reduce the mortality or improve left ventricular function, it did decrease inflammatory markers within the blood and improved the quality of life for patients with heart failure. They called for future studies to determine therapeutic levels of vitamin D and calcium levels in heart failure patients.

Zitterman et al[13] wrote a post-hoc analysis of the EVITA trial, which was a randomized clinical trial over a period of three years conducted to determine whether 4000 IU of vitamin D given daily affects left ventricular end-diastolic and end-systolic diameter and left ventricular ejection fraction in those with advanced heart failure and serum 25-hydroxyvitamin D levels < 75 nmol/L (< 30 ng/ml). The results indicated vitamin D supplementation likely will not improve cardiac function in *all* patients with advanced heart failure. However, in the subset of patients 50 years of age and older, the left ventricular ejection fraction did increase by a max of 2.60% at 36 months post-randomization.[13]

Djousse et al[14] conducted an ancillary study to the Vitamin D and OmegA-3 Trial (VITAL trial) to determine how vitamin D and omega-3 supplements affect heart failure hospitalization incidence. The primary outcome was hospitalization for heart failure after

randomization, and a secondary outcome was recurrent hospitalization secondary to heart failure. The results of this study[14] concluded neither vitamin D nor omega-3 fatty acid supplements helped to significantly reduce the first heart failure hospitalization rates, although the authors also acknowledged the limitation that they could not parse out the efficacy of vitamin D on heart failure with preserved ejection fraction vs reduced ejection fraction.

Additionally, only 45% of patients in the original VITAL trial with a baseline serum 25-hydroxyvitamin D levels had levels < 30 ng/ml (and only 12.7% had < 20 ng/ml). Djousse et al[14] did not specify in the ancillary study how many of their participants were vitamin D deficient at baseline. Thus this study[14] should be taken with a certain level of caution when trying to apply it to the overarching consideration of vitamin D supplementation in heart failure.

The 2022 AHA/ACC/HFSA guidelines[1] briefly discuss vitamin D supplementation in heart failure, stating that routine supplementation has not proven beneficial. However, two out of the three articles they cited for this conclusion did in fact indicate some potential benefit in certain heart failure populations, as discussed above regarding Wang et al[12] and Zittermann et al[13]. The third article cited, Djoussé et al[14], only looked at vitamin D supplementation effects on initial and subsequent hospitalization rates in those with heart failure. There is admittedly a lack of substantial evidence from randomized trials but there is also lack of evidence for any significant harm with such supplementation, and many studies indicate supplementation may actually be beneficial at least to some degree. Thus, is it reasonable to consider vitamin D supplementation in the effort to reach therapeutic levels in heart failure patients because it may prevent complications, is unlikely to cause adverse effects, and could result in the improvement of quality of life and a slower disease process.

CONCLUSION

Approximately 6 million Americans have heart failure and that number is estimated to be nearly 8 million by 2030 (a 46% increase).[16] Even heart failure patients on optimal medical therapy suffer setbacks and complications as part of the disease process. Vitamin D is a hormone that is necessary for the proper function of many systems within the body, including but not limited to endocrine, musculoskeletal, immune, and cardiovascular. Deficiency of this hormone results in fatigue, muscle aches, mood swings, and significant deficiency may result in hypocalcemia, secondary hyperparathyroidism, impaired mineralization of bone, proximal myopathy, and increased mortality with cardiovascular involvement.

Researchers have spent years studying whether vitamin D is a good adjuvant therapy for those with heart failure, and there is ample data to show a positive correlation between normal vitamin D levels and cardiovascular health. Vitamin D is unlikely to replace today's medical therapy, but preliminary data indicates the potential of vitamin D to decrease hospitalization rates, improve quality of life, and even reduce mortality in patients with heart failure. Future research should parse out the benefit of vitamin D supplementation in the different stages of heart failure, and in heart failure with and without preserved ejection fraction. Studies should also be intentional about homogeneous study designs for the sake of consistency and easy comparison. These parameters for future studies will collectively prove beneficial for helping to determine which subset of patients with heart failure are most likely to benefit from vitamin D supplementation.

Acknowledgments

We thank George Fox University for providing support.

Sources of Funding

None.

Disclosures

None.

REFERENCES

1. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18). doi:10.1161/cir.0000000000001063
2. Givertz MM, Mehra MR. Heart Failure: Pathophysiology and Diagnosis. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson J. eds. *Harrison's Principles of Internal Medicine 21e*. McGraw Hill; 2022. Accessed August 03, 2022. https://accessmedicine-mhmedical-com.georgefox.idm.oclc.org/content.aspx?bookid=3095&sectionid=265451573
3. Heart failure: Complications. University Health Care. https://www.universityhealth.org/heart-failure/complications/. Accessed February 27, 2022.
4. Bringhurst F, Kronenberg HM, Liu ES. Bone and Mineral Metabolism in Health and Disease. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson J. eds. *Harrison's Principles of Internal Medicine 21e*. McGraw Hill; 2022. Accessed August 02, 2022. https://accessmedicine-mhmedical-com.georgefox.idm.oclc.org/content.aspx?bookid=3095&sectionid=265446402
5. Bender DA. Micronutrients: Vitamins & Minerals. In: Rodwell VW, Bender DA, Botham KM, Kennelly PJ, Weil P. eds. *Harper's Illustrated Biochemistry, 31e*. McGraw Hill; 2018. Accessed August 02, 2022. https://accessmedicine-mhmedical-com.georgefox.idm.oclc.org/content.aspx?bookid=2386&sectionid=187836268

6. Suter PM. Vitamin and Trace Mineral Deficiency and Excess. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson J. eds. *Harrison's Principles of Internal Medicine 21e*. McGraw Hill; 2022. Accessed August 02, 2022. https://accessmedicine-mhmedical-com.georgefox.idm.oclc.org/content.aspx?bookid=3095&sectionid=264532114
7. Cosentino N, Campodonico J, Milazzo V, De Metrio M, Brambilla M, Camera M, Marenzi G. Vitamin D and Cardiovascular Disease: Current Evidence and Future Perspectives. *Nutrients*. 2021; 13(10):3603. https://doi.org/10.3390/nu13103603
8. Witte KK, Byrom R, Gierula J, et al. Effects of Vitamin D on Cardiac Function in Patients With Chronic HF: The VINDICATE Study. *J Am Coll Cardiol*. 2016;67(22):2593-2603. doi:10.1016/j.jacc.2016.03.508
9. Moretti HD, Colucci VJ, Berry BD. Vitamin D_3 repletion versus placebo as adjunctive treatment of heart failure patient quality of life and hormonal indices: a randomized, double-blind, placebo-controlled trial. *BMC Cardiovasc Disord*. 2017;17(1):274. doi:10.1186/s12872-017-0707-y
10. Gotsman I, Shauer A, Zwas DR, et al. Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome. *Eur J Heart Fail*. 2012;14(4):357-366. doi:10.1093/eurjhf/hfr175. Accessed April 9, 2022.
11. Cubbon RM, Lowry JE, Drozd M, et al. Vitamin D deficiency is an independent predictor of mortality in patients with chronic heart failure. *Eur J Nutr*. 2019;58(6):2535-2543. doi:10.1007/s00394-018-1806-y

12. Wang T, Liu Z, Fu J, Min Z. Meta-analysis of vitamin D supplementation in the treatment of chronic heart failure. Scandinavian Cardiovascular Journal. 2019;53(3):110-116. doi:10.1080/14017431.2019.1612084
13. Zittermann A, Ernst JB, Prokop S, et al. Vitamin D supplementation of 4000 IU daily and cardiac function in patients with advanced heart failure: The EVITA trial. International Journal of Cardiology. 2019;280:117-123. doi:10.1016/j.ijcard.2019.01.027
14. Djoussé L, Cook NR, Kim E, et al. Supplementation with vitamin D and omega-3 fatty acids and incidence of heart failure hospitalization. Circulation. 2020;141(9):784-786. doi:10.1161/circulationaha.119.044645
15. Manson JAE, Cook NR, Lee I-M, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. New England Journal of Medicine. 2019;380(1):33-44. doi:10.1056/nejmoa1809944
16. Understand your risk for heart failure. American Heart Association. https://www.heart.org/en/health-topics/heart-failure/causes-and-risks-for-heart-failure/understand-your-risk-for-heart-failure. Published May 17, 2021. Accessed August 4, 2022.