PANEVĖŽIO KOLEGIJA ISSN 2029-1280, eISSN 2669-0071. Taikomieji tyrimai studijose ir praktikoje – Applied Research in Studies and Practice, 2022, 18.

THE ROLE OF TRIMETHYLAMINE N-OXIDE (TMAO) IN DIFFERENT CARDIOVASCULAR PHENOTYPES

Austėja Lieponytė[a], Karolis Ličkūnas[a], Ligita Gukauskienė[b]

[a]Lithuanian University of Health Sciences, Lithuania
[b]Panevėžio kolegija/University of Applied Sciences, Lithuania

Abstract. Cardiovascular diseases (CVDs) are the leading cause of death worldwide. Increased trimethylamine N-oxide (TMAO) levels have been shown to associate with cardiovascular disease and predict outcomes in the presence of multiple CVD phenotypes. The present review focuses on TMAO's involvement in the main pathogenetic pathways causing or aggravating the development and progression of different CVD phenotypes, as well as the correlation between higher TMAO values in a certain cardiovascular disorder and its prognostic value of future outcomes. Different studies demonstrate the importance of the TMAO in atherosclerotic and thrombotic processes which result in more severe peripheral artery disease and its worse outcomes. In addition to atherosclerosis, TMAO induced platelet hyper-reactivity and foam cell formation lead to myocardial ischemia manifesting as a stable coronary artery disease (CAD) or acute coronary syndrome (ACS). TMAO is also involved in the progression of heart failure (HF) as it directly promotes cardiac damage and indirectly exacerbates the procession of HF by causing renal impairment. The findings suggest assessing TMAO concentration for CVD prophylaxis purposes and using measured TMAO levels as a prognostic value and a valid mortality risk assessment independently as well as combined with other current clinical risk predictors.

Keywords: TMAO, CVD, atherosclerosis, heart failure, coronary artery disease

INTRODUCTION

According to World Health Organisation (WHO), cardiovascular diseases (CVDs) are the leading cause of death globally, taking an estimated 17.9 million lives each year (World Health Organisation [WHO], 2021). CVD includes various disorders, such as atherosclerosis, hypertension, platelet hyperactivity, stroke, hyperlipidemia, and heart failure (Writing Group Members et al., 2016). Despite a guidelines-based optimal primary and secondary prevention, several major cardiovascular events (MACE) keep happening. The nature of this considerable residual cardiovascular risk remains unknown (Guasti et al., 2021).

The diet-gut microbiome interactions are increasingly recognized for their contribution to CVD development and progression (Zhu et al., 2016). Studies revealing a potential causal link between the gut microbiome and CVD focused on trimethylamine N-oxide (TMAO) - a metaorganismal metabolite formed following ingestion of dietary nutrients abundant in a Western diet (eg, lecithin, choline, carnitine) (Witkowski, Weeks & Hazen, 2020). Circulating levels of TMAO have been shown to associate with CVD and predict outcomes in the presence of multiple CVD phenotypes, including peripheral artery disease, coronary artery disease, acute coronary syndrome and heart failure (Witkowski et al., 2020). Therefore understanding the role of the TMAO on CVD progression and pathogenesis could be an effective strategy in the treatment and prevention of CVD.

The objective of the research is to review the main pathways linking TMAO to CVD, the roles of the TMAO on the pathogenesis and progression of various CVD phenotypes and to overview the previous clinical trials and meta-analyses investigating how higher TMAO values correlate with current cardiovascular disorder and how it may predict its further outcomes.

Research methods: a literature review was undertaken using Google Scholar search engine in various databases: PubMed, MEDLINE, ProQuest, to perform a comprehensive search on the correlation between TMAO and cardiovascular risk. The only alternative search for trimethylamine N-oxide was TMAO. Keywords used for cardiovascular risk included atherosclerosis, peripheral artery disease, coronary artery disease, heart failure and CVD. The limitations placed on the search results were from 2011 to 2020 as well as refining the language to English only. Both animal and human studies were referenced. From all the results garnished, the titles and abstracts were analysed for their relevance to the topic and only those that specifically addressed the topic were included in the final reference list.

LINKING TMAO TO CVD

Trimethylamine N-oxide is an amine oxide mainly derived from the oxidation of trimethylamine (TMA), the intermediate product of the microbial metabolic pathway (Koeth et al., 2013). TMA is a waste

© 2022 Panevėžio kolegija

product generated in the gut from betaine, L-carnitine and its metabolite γ-butyrobetaine (GBB), choline and other choline-containing compounds, which are present in the diet (Zeisel & Warrier, 2017). Produced TMA is then carried via the portal circulation to the liver, where it is rapidly converted by a family of enzymes, host hepatic flavin monooxygenases (FMOs), into TMA N-oxide (TMAO) (Zhu et al., 2016).

In preclinical models TMAO accelerated atherosclerosis development and induced thrombosis, supporting a role for gut microbiota in the pathogenesis of atherosclerosis and its associated complications (Roncal et al., 2019). Nowadays, atherosclerosis is one of the major causes of CVD, so it is plausible to think that, if high plasma TMAO concentrations are related to the development of atherosclerosis, TMAO is therefore related to CVD as well (Janeiro et al., 2018).

As it was found by Guasti et al. in their systematic review, patients with high baseline TMAO plasma levels have three times increased risk of MACE and all-cause mortality compared to patients with low baseline TMAO plasma levels. It was estimated that the absolute risk of MACE was 15.50% in patients with a high baseline TMAO value and 10.0% in patients with a low baseline TMAO value. Meanwhile, the absolute risk of all-cause mortality was 10.75% and 3.27% in patients with a high and low baseline TMAO value, respectively (Guasti et al., 2021). A clinical study which enrolled 4007 participants ascertained that even after adjustment for traditional risk factors and separate analysis of the components of the major adverse cardiovascular events, elevated plasma levels of TMAO remained a significant predictor of the risk of major adverse cardiovascular events. These findings prove the possible benefit of the estimated TMAO value inclusion in cardiovascular risk estimation (Tang, 2013).

In conclusion, TMAO is closely related to the development of atherosclerosis which by itself leads to higher rates of MACE and overall mortality, making TMAO an independant predictor of cardiovascular risk.

TMAO AND PERIPHERAL ARTERY DISEASE (PAD)

Peripheral artery disease is defined as chronic arterial occlusive disease of lower extremity arteries with resultant arterial narrowing or occlusion due to atherosclerosis (Barnes, Eid, Creager & Goodney, 2020). TMAO has a wide range of molecular and physiological effects associated with the development of atherosclerosis and other CVD related pathologies (Chan et al., 2019). A critical role in the initiation and progression of atherosclerosis is played by endothelial dysfunction. TMAO promotes endothelial dysfunction by dysregulating vasorelaxation mechanisms, modulating lipid, cholesterol, bile acid metabolism, promoting oxidative stress and inflammation through cytokines, as well as upregulating adhesion molecules, immune cell recruitment factors and platelet aggregation (Iglesias-Carres et al., 2021). TMAO can promote atherosclerosis by inhibiting reverse cholesterol transport and enhanced macrophage foam cell formation in both the artery wall and peritoneal cavity, as well as promoting aortic root atherosclerotic plaque development. Also, new human data reported by Randrianarisoa et al have found that increased fasting serum TMAO levels were associated with increased carotid intima–media thickness, which is a marker of atherosclerosis (Senthong et al., 2018).

According to a study concluded in Spain, TMAO was associated to peripheral artery disease severity and cardiovascular mortality. The patients with a more severe condition (critical limb ischemia) showed higher TMAO and lower TMA/TMAO ratio levels compared to the patients with a milder condition (intermittent claudication). Furthermore, both groups of study individuals showed a higher risk of cardiovascular death that remained significant after adjustment for confounding factors (Roncal et al., 2019).

Another study aimed to determine the clinical prognostic value of plasma TMAO levels in a contemporary cohort of patients with established but stable PAD. It examined the relationship between fasting plasma TMAO and all-cause 5-year mortality. It was found that elevated plasma TMAO is a significant predictor of 5-year all-cause mortality risk among stable patients with a PAD since elevated TMAO levels were associated with 2.7-fold increased mortality risk. Following adjustments for traditional risk factors, inflammatory biomarkers, and history of coronary artery disease, the highest TMAO quartile remained predictive of 5-year mortality. Similar prognostic value for elevated TMAO was seen for subjects with carotid artery, non-carotid artery or lower extremity PAD (Senthong et al., 2018).

To sum up, the studies show a significant role of TMAO in atherosclerosis formation by promoting endothelial dysfunction, inhibiting reverse cholesterol transport and enhancing macrophage foam cell formation in the artery wall and peritoneal cavity. This is a cause of significant damage in peripheral artery disease, since patients with more severe conditions show higher levels of TMAO and the mortality risk, associated with these higher TMAO concentrations, was also significantly increased.

TMAO AND CORONARY ARTERY DISEASE (CAD)

CAD is an atherosclerotic disease which is manifested by stable angina, unstable angina, myocardial infarction (MI), or sudden cardiac death (Malakar et al., 2019). Stable coronary artery disease (CAD) refers to a reversible supply/demand mismatch related to ischemia, a history of myocardial infarction (MI), or the presence of plaque documented by catheterization or computed tomography angiography (Braun, Stevens & Barstow, 2018). Acute coronary syndrome (ACS) is an acute myocardial infarction (MI) or ischemia, usually from acutely disrupted coronary artery blood flow (Barstow, 2020). ACS encompasses unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) (Hedayati, Yadav & Khanagavi, 2018).

Studies have indicated that TMAO significantly induces platelet hyper-reactivity and increases the risk of thrombosis, promotes foam cell formation and aggravates atherosclerosis, sequently leading to the occurrence of myocardial ischemia or infarction (Zhang, Wang, Ke & Du, 2021). The results of large-scale human clinical studies with over 4,000 subjects proved that elevated TMAO levels are independently associated with incident
risk for thrombotic events (myocardial infarction or stroke) in subjects, even following adjustments for multiple risk factors, medication use, and CVD status (Zhu et al., 2016).

Zhao et al trial demonstrated that significantly increased TMAO levels were observed in patients with chronic stable angina (CSA) compared with that in healthy counterparts. TMAO accumulation deteriorated atherosclerosis through activating inflammatory responses, altering cholesterol metabolism and facilitating thrombogenesis (Zhao et al., 2021).

A study done in Beijing investigated the relationship between the culprit plaque morphology and plasma TMAO concentration in patients with ST-segment–elevation myocardial infarction (STEMI). The analysis found that plasma TMAO concentrations were significantly higher in patients with STEMI with plaque rupture than in those with plaque erosion as assessed by Optical coherence tomography (OCT). Elevated TMAO levels were found to be an independent predictor of plaque rupture, after adjustments for traditional risk factors. Moreover, analysis indicated that TMAO may be a potential biomarker for distinguishing plaque rupture from plaque erosion (Tan et al., 2019).

Another research found that plasma TMAO levels are significantly associated with the coronary atherosclerotic burden, as quantified by the number of diseased coronary vessels and the SYNTAX score (response to coronary atherosclerosis load), in patients with STEMI. Moreover, elevated TMAO levels serve as an independent predictor of a high SYNTAX score and the presence of multiple-vessel disease, even after adjusting for traditional risk factors (Sheng et al., 2019).

Matsuzawa et al found that the plasma TMAO levels were significantly increased from the acute to chronic phase of STEMI, the higher chronic-phase TMAO levels were associated with coronary plaque progression and the chronic-phase TMAO level was a significant and independent predictor of future cardiovascular events in patients after STEMI (Matsuzawa et al., 2019).

Importantly, higher TMAO levels were dose-dependently associated with increased platelet aggregation responsiveness, even in subjects on low-dose aspirin. This suggests that in subjects with elevated TMAO, the antiplatelet effects of aspirin may be attenuated, highlighting the possible involvement of TMAO in on-treatment platelet reactivity and so-called aspirin resistance (Witkowski, 2020).

To summarize, by inducing platelet hyper-reactivity, promoting foam cell formation and aggravating atherosclerosis, elevated TMAO levels lead to such thrombotic events as myocardial infarction or stroke. The elevation can be diagnosed not only in patients with an acute coronary condition like STEMI but also in chronic stable angina. The findings could be beneficial for prognostic measures in plaque progression, rupture, distinguishing it from plaque erosion, detecting multiple-vessel disease and also in treatment options when evaluating the possible TMAO effect on aspirin resistance.

TMAO AND HEART FAILURE (HF)

Heart failure is characterized by reduced cardiac output and insufficient blood supply to meet the body's demand. Reduced blood supply significantly affects the gut which eventually leads to a shifting composition of the gut microbiota and, consequently, higher TMAO levels. This results in aggravating the progress of HF by inducing myocardial hypertrophy and fibrosis, endothelial cell and vascular inflammation, as well as cardiac mitochondrial dysfunction. Also, TMAO indirectly exacerbates the procession of HF by causing renal interstitial fibrosis and dysfunction, promoting sodium and water retention (Zhang et al., 2021).

© 2022 Panevėžio kolegija

A study done in Japan connects the TMAO and heart failure through altered brown adipose tissue (BAT) function in which disorientation in choline metabolism occurs, causing elevation of plasma trimethylamine N-oxide levels. Administration of TMAO to mice led to significant reduction of phosphocreatine and ATP levels in cardiac tissue, while reduced plasma TMAO levels improved cardiac dysfunction in animals with left ventricular pressure overload. These results suggest that maintenance of BAT homeostasis and reducing TMAO production could be potential next-generation therapies for heart failure (Yoshida et al., 2022).

Another study investigating the relationship between fasting plasma trimethylamine-N-oxide (TMAO) and all-cause mortality over a 5-year follow-up in 720 patients with stable HF found that higher plasma TMAO levels were associated with a 3.4-fold increased mortality risk. Following adjustments for traditional risk factors and BNP levels, elevated TMAO levels remained predictive of 5-year mortality risk, as well as following the addition of estimated glomerular filtration rate to the model (Tang et al., 2014).

A research conducted by Suzuki et al proved TMAO contribution to prognostic values when combined with N-terminal pro B-type natriuretic peptide (NT-proBNP) and risk prediction of in-hospital mortality in acute heart failure (AHF) when combined with current clinical risk scores that include adjustment for renal function. Also, elevated TMAO levels were found to be an independent predictor of poor prognosis at 1 year (Suzuki et al., 2016).

In a study aimed to determine the prognostic value of TMAO and its dietary precursors in heart failure, plasma TMAO, choline, and betaine was measured by mass spectrometry in 112 patients with chronic systolic HF with comprehensive echocardiographic evaluation. The study revealed that higher TMAO levels predict incident adverse clinical events independently from age, estimated glomerular filtration rate, mitral E/septal Ea, and NT-proBNP levels (Tang et al., 2015).

All in all, the studies show an important role of TMAO in the progress of heart failure. It is believed that increased TMAO levels cause a significant reduction of phosphocreatine and ATP levels in cardiac tissue, which induces myocardial hypertrophy, fibrosis, endothelial cell and vascular inflammation, as well as cardiac mitochondrial dysfunction and indirect cardiac damage through renal function impairment. Measuring TMAO in such condition provides a prognostic value and a valid mortality risk assessment independently as well as combined with other current clinical risk predictors.

CONCLUSIONS

The results of this review prove that TMAO plays an important role in the pathogenetic mechanism of atherosclerosis leading to the development and progression of such cardiovascular disorders as PAD and CAD.

Increased TMAO levels exacerbate the progression of HF causing direct cardiac damage, as well as indirectly affecting the heart through the induction of renal dysfunction.

The evaluation of the gut microbial TMAO for preventative measures could expand the cardiovascular diseases diagnostic field, while assessment of TMAO combined with other predictors could be used as a prognostic value in order to avoid or slow down the progression of CVD.

REFERENCES

Barnes, J. A., Eid, M. A., Creager, M. A. & Goodney, P. P. (2020). Epidemiology and risk of amputation in patients with diabetes mellitus and peripheral artery disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 40(8), 1808–1817. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1161/ATVBAHA.120.314595

Barstow C. (2020). Acute coronary syndrome: presentation and diagnostic evaluation. FP Essentials, 490, 11–19. https://doi.org/10.1016/j.cmet.2012.12.011

Braun, M. M., Stevens, W. A., & Barstow, C. H. (2018). Stable coronary artery disease: treatment. American Family Physician, 97(6), 376–384.

Chan, M. M., Yang, X., Wang, H., Saaoud, F., Sun, Y., & Fong, D. (2019). The microbial metabolite trimethylamine N-oxide links vascular dysfunctions and the autoimmune disease rheumatoid arthritis. Nutrients, 11(8), 1821. https://doi.org/10.3390/nu11081821

Guasti, L., Galliazzo, S., Molaro, M., Visconti, E., Pennella, B., Gaudio, G. V., Lupi, A., Grandi, A. M., & Squizzato, A. (2021). TMAO as a biomarker of cardiovascular events: a systematic review and meta-analysis. Internal and Emergency Medicine, 16(1), 201–207. https://doi.org/10.1007/s11739-020-02470-5

Hedayati, T., Yadav, N., & Khanagavi, J. (2018). Non-ST-segment acute coronary syndromes. Cardiology Clinics, 36(1), 37–52. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1016/j.ccl.2017.08.003

Iglesias-Carres, L., Hughes, M. D., Steele, C. N., Ponder, M. A., Davy, K. P., & Neilson, A. P. (2021). Use of dietary phytochemicals for inhibition of trimethylamine N-oxide formation. The Journal of Nutritional Biochemistry, 91, 108600. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1016/j.jnutbio.2021.108600

Janeiro, M. H., Ramírez, M. J., Milagro, F. I., Martínez, J. A., & Solas, M. (2018). Implication of trimethylamine N-oxide (TMAO) in disease: Potential biomarker or new therapeutic target. Nutrients, 10(10), 1398. https://doi.org/10.3390/nu10101398

Koeth, R. A., Wang, Z., Levison, B. S., Buffa, J. A., Org, E., Sheehy, B. T., Britt, E. B., Fu, X., Wu, Y., Li, L., Smith, J. D., DiDonato, J. A., Chen, J., Li, H., Wu, G. D., Lewis, J. D., Warrier, M., Brown, J. M., Krauss, R. M., Tang, W. H., … Hazen, S. L. (2013). Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nature Medicine, 19(5), 576–585. https://doi.org/10.1038/nm.3145

Malakar, A. K., Choudhury, D., Halder, B., Paul, P., Uddin, A., & Chakraborty, S. (2019). A review on coronary artery disease, its risk factors, and therapeutics. Journal of Cellular Physiology, 234(10), 16812–16823. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1002/jcp.28350

Matsuzawa, Y., Nakahashi, H., Konishi, M., Sato, R., Kawashima, C., Kikuchi, S., Akiyama, E., Iwahashi, N., Maejima, N., Okada, K., Ebina, T., Hibi, K., Kosuge, M., Ishigami, T., Tamura, K., & Kimura, K. (2019). Microbiota-derived trimethylamine N-oxide predicts cardiovascular risk after STEMI. Scientific Reports, 9(1), 11647. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1038/s41598-019-48246-6

Roncal, C., Martínez-Aguilar, E., Orbe, J., Ravassa, S., Fernandez-Montero, A., Saenz-Pipaon, G., Ugarte, A., Estella-Hermoso de Mendoza, A., Rodriguez, J. A., Fernández-Alonso, S., Fernández-Alonso, L., Oyarzabal, J., & Paramo, J. A. (2019). Trimethylamine-N-oxide (TMAO) predicts cardiovascular mortality in peripheral artery disease. Scientific Reports, 9(1), 15580. https://doi.org/10.1038/s41598-019-52082-z

Senthong, V., Wang, Z., Fan, Y., Wu, Y., Hazen, S. L., & Tang, W. H. (2016). Trimethylamine N-oxide and mortality risk in patients with peripheral artery disease. Journal of the American Heart Association, 5(10), e004237. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1161/JAHA.116.004237

Sheng, Z., Tan, Y., Liu, C., Zhou, P., Li, J., Zhou, J., Chen, R., Chen, Y., Song, L., Zhao, H., & Yan, H. (2019). Relation of circulating trimethylamine N-oxide with coronary atherosclerotic burden in patients with ST-segment elevation myocardial infarction. The American Journal of Cardiology, 123(6), 894–898. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1016/j.amjcard.2018.12.018

Suzuki, T., Heaney, L. M., Bhandari, S. S., Jones, D. J., & Ng, L. L. (2016). Trimethylamine N-oxide and prognosis in acute heart failure. Heart (British Cardiac Society), 102(11), 841–848. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1136/heartjnl-2015-308826

Tan, Y., Sheng, Z., Zhou, P., Liu, C., Zhao, H., Song, L., Li, J., Zhou, J., Chen, Y., Wang, L., Qian, H., Sun, Z., Qiao, S., Xu, B., Gao, R., & Yan, H. (2019). Plasma trimethylamine N-oxide as a novel biomarker for plaque rupture in patients with ST-segment-elevation myocardial infarction. Circulation. Cardiovascular interventions, 12(1), e007281. https://doiorg.ezproxy.dbazes.lsmuni.lt/10.1161/CIRCINTERVENTIONS.118.00728

Tang, W. H., Wang, Z., Fan, Y., Levison, B., Hazen, J. E., Donahue, L. M., Wu, Y., & Hazen, S. L. (2014). Prognostic value of elevated levels of intestinal microbe-generated metabolite trimethylamine-N-oxide in patients with heart failure: refining the gut hypothesis. Journal of the American College of Cardiology, 64(18), 1908–1914. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1016/j.jacc.2014.02.617

Tang, W. H., Wang, Z., Levison, B. S., Koeth, R. A., Britt, E. B., Fu, X., Wu, Y., & Hazen, S. L. (2013). Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. The New England Journal of Medicine, 368(17), 1575–1584. https://doi.org/10.1056/NEJMoa1109400

Tang, W. H., Wang, Z., Shrestha, K., Borowski, A. G., Wu, Y., Troughton, R. W., Klein, A. L., & Hazen, S. L. (2015). Intestinal microbiota-dependent phosphatidylcholine metabolites, diastolic dysfunction, and adverse clinical outcomes in chronic systolic heart failure. Journal of Cardiac Failure, 21(2), 91–96. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1016/j.cardfail.2014.11.006.

Witkowski, M., Weeks, T. L., & Hazen, S. L. (2020). Gut microbiota and cardiovascular disease. Circulation Research, 127(4), 553–570. https://doi.org/10.1161/CIRCRESAHA.120.316242

World Health Organisation. (2021). Cardiovascular diseases (CVDs). https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1

Writing Group Members, Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., Das, S. R., de Ferranti, S., Després, J. P., Fullerton, H. J., Howard, V. J., Huffman, M. D., Isasi, C. R., Jiménez, M. C., Judd, S. E., Kissela, B. M., Lichtman, J. H., Lisabeth, L. D., Liu, S., … Stroke Statistics Subcommittee (2016). Heart disease and stroke statistics-2016 update: A report from the American Heart Association. Circulation, 133(4), e38–e360. https://doi.org/10.1161/CIR.0000000000000350

Yoshida, Y., Shimizu, I., Shimada, A., Nakahara, K., Yanagisawa, S., Kubo, M., Fukuda, S., Ishii, C., Yamamoto, H., Ishikawa, T., Kano, K., Aoki, J., Katsuumi, G., Suda, M., Ozaki, K., Yoshida, Y., Okuda, S., Ohta, S., Okamoto, S., Minokoshi, Y., … Minamino, T. (2022). Brown adipose tissue dysfunction promotes heart failure via a trimethylamine N-oxide-dependent mechanism. Scientific Reports, 12(1), 14883. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1038/s41598-022-19245-x.

Zeisel, S. H., & Warrier, M. (2017). Trimethylamine N-oxide, the microbiome, and heart and kidney disease. Annual Review of Nutrition, 37, 157–181. https://doi.org/10.1146/annurev-nutr-071816-064732

Zhang, Y., Wang, Y., Ke, B., & Du, J. (2021). TMAO: how gut microbiota contributes to heart failure. Translational Research: the Journal of Laboratory and Clinical Medicine, 228, 109–125. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1016/j.trsl.2020.08.007.

Zhao, X., Chen, Y., Li, L., Zhai, J., Yu, B., Wang, H., Yang, D., Wang, Q., Chang, Y., Li, J., Zhang, P., Zhang, H., & Li, Y. (2021). Effect of DLT-SML on chronic stable angina through ameliorating inflammation, correcting dyslipidemia, and regulating gut microbiota. Journal of Cardiovascular Pharmacology, 77(4), 458–469. https://doi-org.ezproxy.dbazes.lsmuni.lt/10.1097/FJC.0000000000000970

Zhu, W., Gregory, J. C., Org, E., Buffa, J. A., Gupta, N., Wang, Z., Li, L., Fu, X., Wu, Y., Mehrabian, M., Sartor, R. B., McIntyre, T. M., Silverstein, R. L., Tang, W., DiDonato, J. A., Brown, J. M., Lusis, A. J., & Hazen, S. L. (2016). Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. Cell, 165(1), 111–124. https://doi.org/10.1016/j.cell.2016.02.011

© 2022 Panevėžio kolegija