

# Effects of Alpha-Tocopherol (Vitamin E) Treatment on Cardiovascular Biomarkers: A Comprehensive Review

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## ABSTRACT

This comprehensive review explores that subjoining of alpha-tocopherol (vitamin E) have improved effect on cardiovascular biomarkers in the human subjects, focusing on its potential role in addressing cardiovascular diseases (CVDs), which are major global health challenges exacerbated by risk factors such as dyslipidaemia and hypertension. Systematic analysis of various randomized controlled trials, evaluates alpha-tocopherol's effects on LDL cholesterol, HDL cholesterol, systolic blood pressure, triglycerides, total cholesterol levels etc. The synthesis of current literature consistently indicates that alpha-tocopherol treatment leads to significant reductions in systolic blood pressure compared to control groups. Furthermore, substantial evidence supports alpha-tocopherol's ability to increase HDL-cholesterol levels and decrease LDL-cholesterol concentrations, suggesting beneficial impacts on lipid profiles. The review also discusses alpha-tocopherol's influence on additional cardiovascular biomarkers such as Troponin I, B-type Natriuretic Peptide (BNP), N-terminal pro-BNP, Troponin T, C-reactive Protein (CRP), Lipoproteins, Creatine Kinase-MB (CK-MB), Myoglobin, and Fibrinogen, highlighting its potential broader effects on cardiovascular health indicators. Overall, this review underscores alpha-tocopherol's potential as an adjunctive therapy for managing cardiovascular risk factors, particularly hypertension and dyslipidemia. The findings suggest that alpha-tocopherol supplementation may induce favourable changes in cardiovascular biomarkers, offering insights into its therapeutic potential and calling for further investigation in clinical settings.

**Keywords:** Alpha-Tocopherol, Triglycerides, HDL Cholesterol, LDL Cholesterol, Systolic blood pressure, Total Cholesterol, Creatine Kinase-MB, C-reactive protein, CRP, NT-pro BNP

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## INTRODUCTION

Vitamin E, encompassing four tocopherols and four tocotrienols among which four tocopherols are  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ - and four tocotrienols are  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ - among which  $\alpha$ -tocopherol is biologically more active form, has played a crucial role in scientific research since its initial identification in the 1920s for its ability to prevent neonatal mortality in rats<sup>1,2</sup>. In human diet also its essential to have lipid soluble antioxidants, Vitamin E exists in various forms, with alpha-tocopherol being the primary variant utilized by the human body. Its fundamental role lies in its antioxidant function, where it neutralizes unstable electrons known as "free radicals," thereby protecting cells from oxidative damage<sup>3,4,5</sup>. Additionally, vitamin E contributes to enhancing immune system function, preventing blood clot formation in coronary arteries, and supporting platelet and coagulation systems<sup>6,7</sup>. With advancements in medicine and healthcare delivery systems, the main causes of mortality as well as morbidity have transferred from infectious disease to non-communicable disease (NCDs). Over the past two decades. Among NCDs, cardiovascular disease (CVD) has

remained a leading health burden globally<sup>8,9,10</sup>. The COVID-19 pandemic has further exacerbated this burden, straining healthcare resources and increasing morbidity and mortality rates among individuals with established CVD<sup>11,12</sup>. The virus responsible for COVID-19 is SARS-CoV-2 which has been also connected with an elevated risk of sudden heart attacks by directly damaging heart cells, triggering inflammation and scarring, and heightening the vulnerability to irregular heartbeats and myocardial infarctions<sup>11,12</sup>. The recognition of antioxidant vitamins, including vitamin E, gained prominence in the 1980s with the understanding of their role in early stage of Atherosclerosis in mitigating free radical damages, characterized by arterial narrowing<sup>13,14</sup>. Various Research also shows presence of the free radicals in the conditions like various chronic diseases, pathogenesis of cancers and vision impairments.<sup>15,16</sup> Vitamin E plays major role in protecting cells from the oxidative stress and modulate free radical generation under specific conditions underscores its potential therapeutic relevance in mitigating these chronic ailments. This introduction sets the stage for understanding

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the multifaceted action of vitamin E in various diseases and health of human, highlighting its antioxidant properties and relevance amidst evolving healthcare challenges and emerging infectious threats like COVID-19. Cardiovascular biomarkers are the biological molecules detectable in various body fluids, blood and tissue that provide critical insights into the state of the cardiovascular system. These markers have a crucial role in, monitoring and diagnosing the disease conditions as well as for the treatment of particular diseases by revealing various processes such as inflammation, tissue damage, or pathological changes within the heart and blood vessels<sup>17</sup>. Commonly utilized cardiovascular biomarkers are Troponins in which 2 troponins are included Troponin I and Troponin T. Troponins are the proteins released when the muscles of heart is damaged, making them essential for diagnosing myocardial infarction (heart attacks)<sup>18</sup>. N terminal pro-BNP and B type natriuretic peptide are the hormones get released when any stress or stretching occurs in any chamber of the heart., aiding for the diagnosis and treatment of failure of heart.<sup>19</sup> C reactive protein which also act as effective marker, indicating arterial inflammation and correlating with increased risk of Heart related problems<sup>20</sup>. Lipoproteins such as High-density lipoproteins and Low-density lipoproteins are crucial in assessing cholesterol and triglyceride levels, providing insights for having the risk of coronary artery disease as well as Artherosclerosis<sup>21</sup>. In the muscles of heart there is Creatine Kinase- MB enzyme which gets elevated during myocardial infarction, further aiding in its diagnosis<sup>22</sup>. Myoglobin, released into the blood following heart or skeletal muscle injury, serves as good marker for diagnosing heart related problems like Myocardial Infarction<sup>23</sup>. Fibrinogen, a blood clotting factor, indicates an increased risk of cardiovascular events when elevated<sup>24</sup>. These biomarkers collectively give a good direction to medical field with valuable guidance for the clinical interventions and clinically make decisions, thereby improving patient outcomes in cardiovascular health.

#### **Role of Cardiovascular Biomarkers**

Cardiovascular biomarkers have a pivotal role for the early diagnosis and quicker treatment and management of various heart related problems like myocardial infarction and other acute coronary syndromes. Troponin I and Troponin T are effective indicators of heart muscle damage, essential for diagnosing myocardial infarction with precision<sup>25</sup>. Myoglobin and CK-MB, though less specific than troponins, also contribute to the diagnostic process of acute coronary syndromes<sup>26</sup>. C-reactive protein (CRP) is utilized to assess cardiovascular risk in apparently healthy individuals by indicating inflammation levels which indicates increased risk of various cardiac problems like coronary heart disease and atherosclerosis<sup>27</sup>. Various researches indicated and given insights that severity and prognosis of heart failure is also corelated with the N terminal pro BNP and B type natriuretic peptide, with higher levels correlating to poorer outcomes<sup>28</sup>. Lipoprotein levels, such as high-density lipoproteins and low-density lipoproteins cholesterol, are routinely monitored to gauge the effectiveness of lipid-lowering therapies and to assess ongoing risks of atherosclerotic cardiovascular disease<sup>29</sup>.

These biomarkers are integral in guiding treatment decisions; for example, BNP levels can determine the necessity for aggressive interventions in heart failure management<sup>30</sup>. Elevated fibrinogen levels may prompt the initiation of anticoagulant therapy to mitigate the risk of thrombotic events<sup>31</sup>. Regular monitoring of biomarkers facilitates the management of chronic cardiovascular conditions, enabling clinicians to detect disease progression and evaluate the efficacy of therapeutic strategies in patients with stable coronary artery disease<sup>32</sup>. In summary, cardiovascular biomarkers serve as essential tools in clinical practice, aiding in early diagnosis, risk assessment, and treatment decision-making, ultimately improving patient outcomes in cardiovascular health.

#### **Alpha tocopherol**

Alpha-tocopherol ( $\alpha$ -tocopherol) stands out as the most active form of Vitamin E, renowned for the role as a fat-soluble antioxidant. Its molecular formula,  $C_{29}H_{50}O_2$ , reflects its chemical structure—a chromanol ring housing a hydroxyl group at the 6-position, pivotal for its antioxidant prowess, and a lengthy phytol tail that enhances its solubility in lipids<sup>33</sup>. This compound serves a crucial function in cellular protection by intercepting lipid radicals generated during lipid peroxidation, thereby thwarting the propagation of presence of free radicals and preserving cellular growth<sup>34</sup>. Beyond its antioxidant activities, alpha-tocopherol influences diverse physiological processes, including immune function, DNA repair mechanisms, and various metabolic pathways<sup>35</sup>. The absorption of alpha tocopherol occurs in small intestine which integrates in chylomicrons, specialized lipoproteins that fat soluble vitamins and ferry dietary fats throughout the body<sup>36</sup>. Once in circulation, it travels predominantly bound to high- and low-density lipoproteins, which aid for the distribution to tissues<sup>37</sup>. The liver assumes a pivotal role in regulating alpha-tocopherol levels by incorporating it into VLDL which known as very low-density lipoproteins, subsequently processed into LDL for systemic distribution<sup>38</sup>. Research studies also indicates that with the help of cytochrome P450 enzymes metabolically alpha-tocopherol primarily transform into liver, leading to production of metabolites like alpha-carboxyethyl hydroxy chroman (alpha-CEHC) that are excreted in urine<sup>39</sup>. This tightly regulated process ensures optimal levels of alpha-tocopherol, essential for maintaining cellular homeostasis. Moreover, alpha-tocopherol exerts influence at the genetic level, modulating gene expression which are involved in antioxidant defences, inflammation and signalling pathways of cell<sup>40</sup>. It interacts with PPAR $\gamma$  and NF- $\kappa$ B which known as the transcription factors shows pivotal role in the inflammatory responses and lipid metabolism, thereby impacting broader physiological outcomes<sup>41</sup>. Furthermore, alpha-tocopherol enhances immune function by shielding immune cells from oxidative stress and regulating cytokine production, fostering robust immune responses across different age groups<sup>42</sup>. This multifaceted role underscores alpha-tocopherol's significance not only as an antioxidant but also as a pivotal regulator of cellular and metabolic processes critical for overall health and well-being.

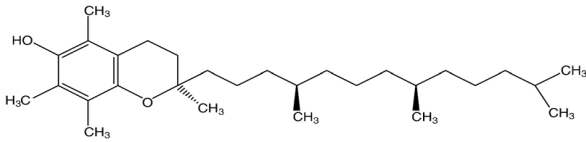


Figure: 1 Molecular Composition of Alpha Tokoferol

## DISCUSSION

Alpha tocopherol has tremendous effect on cardiovascular biomarkers reveals a multifaceted landscape. This review has highlighted its potential benefits in improving lipid profiles, reducing oxidative stress markers, modulating inflammatory cytokines, and enhancing endothelial function. These findings align with previous studies that have demonstrated alpha-tocopherol's role in mitigating cardiovascular problems. However, clinical significance of these effects remains subject to ongoing debate and scrutiny.

Various research studies highlighted in this review consistently show alpha-tocopherol supplementation leads to favourable changes in HDL-cholesterol levels and decreases in LDL-cholesterol concentrations, indicating its potential in managing lipid profiles. Moreover, its antioxidant properties contribute to reducing oxidative stress markers and inflammatory cytokines, which are helped in the diagnosis and treatment aspect of various cardiovascular disease conditions. Additionally, improvements in endothelial function further underscore alpha-tocopherol's potential cardiovascular benefits. Despite these promising findings, challenges in translating biomarker improvements into clinically meaningful outcomes persist. Questions remain regarding the optimal dosage, duration of supplementation, and specific patient populations that may benefit most from alpha-tocopherol therapy. Moreover, variability in study designs and participant characteristics across clinical trials complicates the interpretation of results. In conclusion, while alpha-tocopherol shows promise as an adjunctive therapy for cardiovascular risk management, although randomized control trails required to perform its crucial role in cardiovascular disease prevention and treatment.

### Alpha tocopherol and CRP

Alpha-tocopherol, a potent antioxidant, functions by scavenging free radicals and thereby reducing oxidative stress within cells. This stress, if left unchecked, can activate inflammatory pathways, leading to increased production of C-reactive protein (CRP)<sup>44</sup>. Alpha tocopherol inhibits the activation of nuclear factor kappa B which known as transcription factor involved in the process of inflammation by mitigating the oxidative stress, a critical transcription factor involved in inflammation. This inhibition may consequently decrease the synthesis of CRP in the liver. However, few experimental research studies shows the effects of supplementation of alpha-tocopherol on CRP levels produced varied outcomes. Some research indicates a modest reduction in CRP levels with vitamin E supplementation, especially among individuals with elevated baseline CRP or those at risk of cardiovascular disease<sup>43</sup>. For instance, a study demonstrated that treatment of vitamin E for six months reduced C reactive protein

among the adults who were smoking and admitted with acute coronary syndrome, conditions where bio markers related to inflammation are predictive of adverse cardiovascular events within the initial six months post-syndrome<sup>44</sup>. Meta-analyses of randomized controlled trials further support this result, suggesting that alpha and gamma both tocopherol supplementation could lower serum CRP levels<sup>45</sup>. These insights underscore the potential of vitamin E supplementation in modulating inflammatory markers associated with cardiovascular risk, though further rigorous clinical experiments are required to finding its clinical effectiveness utility and optimal therapeutic applications.

**Alpha tocopherol and Troponin:** Alpha-tocopherol, known for its potent antioxidant effect, functions by mitigating the free radicals that arise during ischemia-reperfusion injury, thereby reducing lipid peroxidation as well as oxidation stress in cardiac tissues. This effect of alpha tocopherol acting as antioxidants is a major benefactor to myocardial damage and subsequent release of troponin into circulation<sup>46</sup>. By mitigating oxidative damage, alpha-tocopherol potentially lessens the severity of myocardial injury, which could impact troponin release levels. However, the relationship between alpha-tocopherol supplementation and troponin levels in myocardial infarction is intricate and involves interactions not only with oxidative stress but also with inflammatory pathways and cellular signaling mechanisms [46]. Research investigating exercise effects combined with additional supplementation of vitamin E on cardiac troponin alterations performed on rats following intense exercise supports this notion, it shows supplementation of vitamin E may attenuate myocardial troponin alterations due to exercise<sup>47</sup>. These findings highlight the role of vitamin E is very much strong against myocardial damage induced by strenuous exercise, suggesting its relevance for athletes and individuals engaging in vigorous physical activity. Still the studies are warranted to elucidate more clear mechanism as well as practical implications of alpha-tocopherol's role in mitigating troponin release and myocardial injury in various cardiovascular contexts.

### Alpha tocopherol and Myoglobin and CKMB

Alpha-tocopherol, known for its potent antioxidant effects, shows crucial agent in mitigating damage occurs due to oxidative stress to cardiac cells during ischemia and reperfusion events. By scavenging free radicals and reducing lipid peroxidation, alpha-tocopherol may help decrease the release of myoglobin into circulation, potentially attenuating the severity of myocardial injury by reducing lipid peroxidation and mitigating the free radicals<sup>48</sup>. The isoform of creatine kinase is known as Creatine kinase -MB predominantly found in the muscles of heart., serves as a biomarker for myocardial damage, particularly in conditions like myocardial infarction. Elevated CK-MB levels in the blood indicate myocardial injury, and alpha-tocopherol's antioxidant properties are the reason to protect cardiac cells from damage occurs due to oxidative stress, thereby possibly reducing CK-MB leakage into the bloodstream [48]. Supporting this, a study examining effectivity of additional diet support of vitamin

E on rats fed a diet increased in fat demonstrated significant reductions in plasma levels of CRP and CK-MB, suggesting potential protective effects against inflammatory and cardiovascular risks associated with high-fat diets<sup>49</sup>. These findings underscore the therapeutic potential of alpha-tocopherol in protecting cardiac function if the cause is damage due to oxidative stress and myocardial injury, warranting further investigation into its clinical applications in cardiovascular health.

#### **Alpha tocopherol and Lipoproteins**

Alpha-tocopherol, a potent soluble in fat antioxidant shows a critical agent in protecting lipoproteins if damage occurs due to oxidative stress within the bloodstream. It is primarily transported by LDL and HDL particles, where free radicals mitigated by it and it also prevents oxidation of lipids carried by these particles. Oxidized lipoproteins, particularly oxidized LDL (oxLDL), are known contributors to the development of atherosclerosis, a leading cause of cardiovascular diseases<sup>50</sup>. The distribution of alpha-tocopherol among lipoproteins is influenced by various factors including dietary intake, absorption efficiency, and metabolic demands within the body. Initially incorporated into chylomicrons during intestinal absorption, alpha-tocopherol is subsequently redistributed among lipoproteins through complex metabolic processes<sup>51</sup>. Facilitating this redistribution is TTP which known as tocopherol transfer protein plays a pivotal role in maintaining adequate level of plasma of alpha-tocopherol by facilitating its transfer from lipoproteins to peripheral tissues, thereby ensuring efficient antioxidant protection throughout the body<sup>52, 53</sup>. This intricate interplay underscores the importance of alpha-tocopherol in mitigating the oxidative stress and its active role in preventing progression of cardiovascular diseases associated with lipoprotein oxidation

#### **Alpha tocopherol and Fibrinogens**

Alpha-tocopherol, renowned for its antioxidant properties, exerts potential influence over fibrinogen levels, a critical glycoprotein involved in blood clotting. Research suggests that alpha-tocopherol may contribute to reducing fibrinogen concentrations, thereby potentially mitigating the risk of cardiovascular diseases. This effect is primarily attributed to its ability to combat inflammation and damages occurs due to oxidative stress, this both factors are implicated in elevating fibrinogen levels<sup>54</sup>. Moreover, studies examining alpha-tocopherol's impact on platelet aggregation, a process intricately linked with fibrinogen function in coagulation, further underscore its potential role in modulating fibrinogen dynamics<sup>55</sup>. Additionally, the anti-inflammatory properties of alpha-tocopherol may contribute to lowering fibrinogen levels by suppressing inflammatory cytokines<sup>56</sup>. N terminal pro- BNP and B type natriuretic peptides are also plays a role as effective biomarkers in heart failure management, alpha-tocopherol's antioxidant prowess has been explored for its potential protective effects in cardiovascular health. It is posited that alpha-tocopherol, by mitigating oxidative stress, could influence BNP and NT-proBNP levels, offering insights into its therapeutic potential in heart failure<sup>57, 58</sup>. These findings underscore the multifaceted role of alpha-tocopherol in cardiovascular

health, warranting further exploration of its clinical implications in managing cardiovascular biomarkers and disease progression.

#### **Alpha tocopherol and Blood pressure**

Alpha-tocopherol, known for its antioxidant properties, is implicated in influencing blood pressure by its antioxidant effect as it directly acts in oxidative stress which can impair the function of endothelium and contribute to hypertension<sup>59</sup>. The endothelium, crucial for regulating vascular tone, can be damage occurs due to oxidative stress, leading to dysfunction of vascular system and elevated blood pressure levels<sup>59</sup>. Few research studies also explored potential of supplementation of vitamin E to lower the blood pressure, with varying results. For instance, Mahadik et al. demonstrated significant reductions in systolic blood pressure among hypertensive patients following vitamin E supplementation [59]. Similarly, one meta-analysis of various randomized control trials done by Jafarnejad reported a modest but inconsistent reduction in systolic blood pressure with vitamin E supplementation<sup>60</sup>. Moreover, research by Devaraj et al. indicated that addition of diet containing of vitamin E improved endothelial function among hypertensive individuals, indicates a possible process in which it helps to blood pressure regulation<sup>61</sup>. These findings underscore the potential role of alpha-tocopherol in managing blood pressure through its antioxidant effects and warrant further investigation into its clinical implications for hypertension management.

#### **CONCLUSION**

Globally cardiovascular disease is the leading cause of death, responsible for approximately 19.91 million deaths annually which have bed impact on public health worldwide. In United States alone, about 605,000 people experience their first heart attack each year, and approximately 200,000 suffer from recurrent attacks. Recent data underscores the escalating burden of heart disease in India due to lifestyle changes, urbanization, and rising rates of obesity and diabetes. Alpha-tocopherol supplementation has shown promising results in positively influencing various cardiovascular biomarkers. Found abundantly in foods such as almonds, sunflower seeds, hazelnuts, and leafy greens like spinach and kale, alpha-tocopherol intake can potentially benefit cardiovascular health through dietary counseling and recommendations. However, the efficacy of alpha-tocopherol in cardiovascular prevention and treatment requires further exploration through extensive and long-term studies. Clinicians should carefully evaluate individual patient factors before recommending alpha-tocopherol supplementation, considering its potential benefits and the need for evidence-based guidelines in cardiovascular care.

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