ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV674

A Narrative Review on the Effect of TRT on Stroke and Cardiovascular Diseases

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Abstract:-

- ***Introduction***

Hypogonadism is a common condition in the general population, affecting males and females. Data on the effects of testosterone replacement therapy on stroke (cerebrovascular accident) and cardiovascular illnesses show conflicting results. The condition can be well managed but the controversy surrounding the use of TRT may cause delay or unwillingness in seeking treatment. The purpose of this narrative review is to ascertain how testosterone replacement medication affects the prevalence of stroke and cardiovascular disease as well as the risk factors causing these diseases.

- ***Measurements:***

Studies included in this project met the following criteria; males above 18 years, only original peer-reviewed research articles, online publications between 2000 and 2023, text in English. While non-human studies, not full text and abstract only studies were excluded.

- ***Findings:***

Research on the effects of testosterone replacement therapy on cardiovascular diseases and stroke has produced conflicting results, and the majority of the available data comes from retrospective studies. While many studies found no effect or reduced risk of stroke and cardiovascular diseases following the use of testosterone replacement therapy, a few other studies linked factors such as the route of administration (intramuscular) and period of exposure (within 2 years of treatment) to an increased risk of developing cardiovascular events such as myocardial infarction, heart failure, hypertension, coronary artery diseases and stroke.

Keywords:- *Testosterone Replacement Therapy, Coronary Artery Disease, Stroke, HRT And Cardiovascular Diseases, Hypogonadism, Testosterone.*

I. INTRODUCTION

Testosterone is an anabolic hormone which promotes bone density, builds muscle mass, and helps in the formation of sexual characteristics in the uterus, vagina, penis, and testes both at birth and during puberty. Additionally, it maintains these secondary sexual characteristics (Ahmed et al, 2020). About two-third of plasma testosterone is in the active form, attached to albumin, and just a small portion is in the free state. Approximately two thirds of testosterone circulates in the body as the inactive form, bound to sex hormone binding globulin (Belchetz et al, 2010). Symptoms of low testosterone include reduced libido, erectile dysfunction, osteoporosis, fatigue, and diminished vitality (Lu et al, 2019). About 25% of men are thought to be testosterone deficient, and many of these individuals are at an increased risk of developing cardiovascular diseases (Michael et al, 2019). There is a high incidence of hypogonadism each year in the United States and it is more common in men between the ages of 40 and 69 (Araujo et al, 2004). Morgentaler et al, 2015, reports that while normal plasma levels of testosterone are generally needed to maintain good health, its deficiency is associated with an increased risk of cardiovascular illnesses. People diagnosed with hypogonadism (low testosterone) are managed with testosterone replacement therapy. Testosterone activates calcium and potassium channels in the cardiovascular system. Many androgen receptors are thought to be present in cardiac cells, and these receptors, when activated, control the metabolism of calcium and produce ventricular contractility (Goodale et al, 2017).

II. LOW TESTOSTERONE AND THE CARDIOVASCULAR SYSTEM

An analysis of the prevalence and prognostic implications of testosterone deficit in males with chronic heart failure was conducted by Jankowska et al. (2006). Comparative studies were conducted between men with chronic heart failure, a low ejection fraction, New York Heart Association classes I, II, III, and IV and their healthy counterparts. They found that testosterone insufficiency, which is often prevalent in this population, was a poor predictive factor in patients with chronic heart failure. Keating et al. (2006) also discovered a correlation between an increased incidence of cardiovascular disorders such myocardial infarction and coronary artery disease and males with androgen deficit who underwent androgen ablation for prostate cancer. A higher risk of cardiovascular events, such as acute myocardial infarction and heart failure, was also noted by Martin-Merino et al. (2011) among males who had undergone androgen deprivation therapy. The association between endogenous testosterone levels and all-cause mortality in senior males was investigated by Laughlin et al. (2018). Men with low serum testosterone levels, aged 50-91, were included in the trial, and their mortality was monitored subsequently. It was shown that a lower testosterone level was associated with a higher risk of cardiovascular death. Khaw et al. (2007) conducted a larger comparable study to look at the relationship between endogenous testosterone

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV674

levels and mortality from cancer, cardiovascular disease, and all causes combined. The study involved 11,606 males, ages 40 to 79, participated in the study. Following correction for age, BMI, systolic blood pressure, and other demographic factors, the study found a negative correlation between baseline testosterone concentrations and cardiovascular disease death. Arnlov et al. (2006) examined the relationship between men's testosterone levels and their risk of cardiovascular disease. A baseline testosterone level was measured in 2084 middle-aged men without a history of cardiovascular disease and followed up on for ten years. The development of a cardiovascular incident was not substantially correlated with serum testosterone levels. The testosterone levels of males with and without coronary artery disease were compared by English et al. (2000). Ninety people made up the small sample size for the study. Men with coronary heart disease were reported to have had decreased testosterone levels. Men with heart failure were shown to have lower testosterone concentrations than people in good condition. Similarly, a cohort study conducted by Azoulay et al. (2011) included 22,310 males aged 40 and above who experienced their first transient ischemic attack or stroke after being on androgen deprivation therapy. Upon a 4-year follow-up, it was found that their risk of transient ischemic attack and stroke was higher than that of the control group. The findings suggested that a higher risk of stroke is linked to hypogonadism.

According to Kienitz and Quinkler (2008), although vasodilatation did occur during the early phase of testosterone exposure, prolonged testosterone use eventually causes vasoconstriction, atherosclerosis, and activation of the renin-angiotensin-aldosterone system, which may control blood pressure. In their study on testosterone, cardiomyopathies, and heart failure, Diaconu et al. (2021) found that while the effects of testosterone on the cardiovascular system are poorly understood, reported actions have been dependent on variables like underlying disease or physiological states. They also found that patients with heart failure and dilated cardiomyopathy have been observed to have reduced testosterone levels, suggesting that testosterone may have both beneficial and harmful effects on the cardiovascular system. Determining whether testosterone replacement therapy reduces the incidence of stroke and cardiovascular events or whether it is associated with cardiovascular events directly is therefore crucial.

III. LITERATURE REVIEW

A. Testosterone Replacement Therapy and CVD:

In a cohort study published in 2013, Vigen et al. examined the relationship between testosterone therapy and myocardial infarction and stroke in men who had underlying coronary artery disease and low testosterone levels. The underlying coronary artery disease was taken into account. The risk of myocardial infarction and stroke increased steadily over the course of each year of follow-up, with the testosterone treatment group showing a larger increase in risk than the non-treatment group. The team discovered a correlation between testosterone and both stroke and myocardial infarction. Earlier, a randomised controlled trial had been suspended. In that study, Basaria et al. (2010) evaluated the side effects linked to testosterone injection in their study. Twenty-nine males 65 years of age and older with low testosterone levels and limited mobility participated in the trial. For a period of six months, either testosterone gel or a placebo gel was applied to them at random. The testosterone group (23 men) experienced a higher rate of adverse cardiovascular events than the placebo group (5 men), which led to the early termination of this trial. The relative risk of experiencing cardiovascular events remained stable during the course of the 6-month treatment period. One drawback for general population use was the trial's limited size. According to Sarah et al. (2019), the use of exogenous testosterone is linked to worsened cardiovascular outcomes. A 53-year-old bodybuilder who experienced exertional dyspnea and a pan systolic murmur for three months was the subject of the study. Following an evaluation, an echocardiography showed a 15% left ventricular ejection fraction. It was said that he acknowledged using intramuscular testosterone. While the steroid was being stopped, he received treatment for heart failure. His testosterone level went back to normal, and his ejection fraction improved to 54%. They came to the conclusion that in young, healthy athletes, the use of testosterone (anabolic steroids) is an uncommon but treatable cause of cardiomyopathy. A related finding was also mentioned by Garner et al. (2018). A sixty-year-old Caucasian male bodybuilder was discovered to be abusing his medicine. He had a history of hypogonadism, was receiving testosterone replacement therapy, and was on treatment. He had no prior history of heart problems, and a year prior, his testosterone level was normal. Echocardiography throughout the study showed an ejection fraction of 25% to 30%, and cardiac catheterization confirmed cardiomyopathy. It was observed that his testosterone level (2872 ng/dL) was above average. The course of treatment was stopped. His ejection fraction had increased to 50% to 55% and his testosterone level had dropped significantly to 346 ng/dL at the 6-month follow-up. It has been discovered that testosterone abusers take five to thirty-nine times the authorised dosage. A cohort study by Finkle et al (2014) analysed the risk of acute non-fatal myocardial infarction following an initial total testosterone prescription in a large healthcare data-base. The incidence rate of myocardial infarction among young men and the elderly within a year of treatment was compared to that of the event within 90 days of treatment. Refilling the prescription for testosterone resulted in a two-fold increase in myocardial infarction risk for both older and younger men, whereas older men who did not refill their prescription saw a drop in risk within 91 to 180 days. Younger people with a history of heart disease were shown to be at increased risk. They found that men with pre-existing heart disease, regardless of age, had a higher risk of myocardial infarction. This was supported in another study. Etminan et al.'s (2015) extensive case-control study, which discovered a higher risk of myocardial infarction linked to first-time exposure—that is, the first testosterone prescription within 90 days—supported this. However, selection error was found to be a study limitation. In their 2018 study, Rosenberg et al. recruited 1019 healthy senior men in an effort to investigate the possible relationship between low testosterone and an increased risk of atrial fibrillation. It was found that atrial

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV674

fibrillation developed in one-third of these guys. Researchers found an inverse relationship between atrial fibrillation and testosterone, with lower testosterone levels being linked to a higher risk of atrial fibrillation. Men with low testosterone levels were found to have a higher chance of developing atrial fibrillation than men with high testosterone levels, even after adjusting for demographics, clinical risk factors, and left atrial diameter. They discovered a link between low testosterone and an elevated elderly risk of atrial fibrillation. A factor that has been considered as contributory to the outcome of testosterone replacement therapy on cardiovascular events is the formulation or route of administration. When Layton et al. (2015) examined 544,115 men beginning testosterone therapy; they found that those receiving transdermal testosterone gel were less likely to experience cardiovascular events than those receiving intramuscular injections. The relationship between endogenous testosterone and cardiovascular outcomes was examined by Magnani et al. (2014). They sought to look at the relationship between testosterone and the 10-year risk of atrial fibrillation. In this study, which included 1251 senior males, a sizable portion of the subjects experienced atrial fibrillation. According to the study, older men's testosterone levels were linked to an increased incidence of atrial fibrillation. By calculating the proportion of brachial artery flow-mediated dilatation, Matthews et al. (2019) investigated the connection between exogenous testosterone and vascular endothelia function (as well as cardiovascular illnesses). Men and women who had reached menopause and did not have any clinical cardiovascular problems were included in the study. They underwent measurement and correction of their testosterone levels for demographics, cardiovascular risk factors, and hormone therapy. They discovered a correlation in men without age differences between elevated serum levels of testosterone and a modest proportion of brachial artery flow-mediated dilatation (worse illness). This suggests that in elderly men, testosterone is associated with worse cardiovascular illnesses. Weightlifters have also tested positive for testosterone, a substance that is abused in sports.

In their cohort study, Sharma et al. (2017) examined the relationship between the risk of atrial fibrillation and total testosterone after treatment. Three groups were formed from the males whose total testosterone level was low. When testosterone was administered to one group, the serum level normalised; when testosterone was administered to another group, the serum level did not normalise; and the last group did not receive testosterone treatment. They reported a substantial reduction in the frequency of atrial fibrillation following testosterone replacement therapy, with total testosterone levels returning to normal. A similar beneficial impact was observed by Qingtao et al in 2019. They evaluated the relationship between hypertension and bioavailable, free, and total testosterone. In the study, 253 men between the ages of 40 and 79 took part. With or without adjustment for confounders including smoking, age, and physical activity, the data showed an inverse connection between total testosterone, free testosterone, and bioavailable testosterone and systolic blood pressure, diastolic blood pressure, and hypertension. Similarly, testosterone has been shown by Huisman et al. (2006) to help reduce the incidence of plaque formation in men. While there was a notable rise in high density lipoprotein (HDL), elevated testosterone was also linked to decreased triglycerides. However, they also discovered a connection between hypertension and increased testosterone levels in both males and females when compared to their normotensive counterparts. This rise in systolic blood pressure has been associated with elevated renin activity when elevated testosterone levels are present. Etminan et al. (2015) provided additional evidence for this finding in a sizable case-control study, whereby it was discovered that the first testosterone prescription within a 90-day period was linked to a higher risk of myocardial infarction. Selection mistake was noted as a study limitation (this was not dependent on low serum testosterone levels). An earlier study by Baillargeon et al. (2014) indicated that testosterone treatment did not raise the incidence of myocardial infarction, comparing 19,065 control individuals with 6,355 Medicare seniors aged 66 years who had received at least one testosterone injection. Rather, it was advantageous for males who were more likely to suffer a myocardial infarction. Similarly, Wallis et al. (2016) found that testosterone treatment was linked to a slightly lower incidence of major cardiovascular events (MI, CVA/stroke, and DVT) than control individuals, but the risk of these cardiovascular events increased in men with short-term exposure to testosterone. The study examined the impact of cumulative exposure to testosterone therapy in 10,311 men compared to 28,029 matched control individuals. In order to ascertain the relationship between endogenous testosterone levels and cardiovascular disorders such atherosclerosis, myocardial infarction, and ischemic heart disease, Ruige et al. (2011) conducted a meta-analysis of cohort and nested case-control studies. It was discovered that there was only a tenuous link between high testosterone levels and cardiovascular disease risk. Men under 70 years old did not show any correlation between their testosterone levels and cardiovascular diseases, whereas men over 70 years old showed some protection against cardiovascular diseases. Similarly, a 2013 study by Haring et al. suggested that the correlations observed between blood testosterone and cardiometabolic risk variables may be residual confounding rather than causative. Results from Wu et al. (2008) appear to corroborate this. They stated that data from the European Male Ageing project indicated that, even after controlling for confounding variables such BMI, smoking status, alcohol use, and co-morbidities, there was no longer any discernible correlation between age and serum testosterone levels.

Cheetham et al. (2017) carried out an analysis on the association between cardiovascular outcomes and testosterone replacement therapy prescribed by doctors for men with androgen insufficiency and administered topically, orally, or by injection. In the retrospective cohort study 8,808 men 40 years of age and older who had ever taken testosterone were included in the cohort trial, along with 35,527 men who had never received testosterone but had all suffered myocardial infarctions in the past. It was reported that these males had a lower chance of cardiovascular problems. When the outcome was limited to combination cardiac events (unstable angina, acute myocardial infarction) and combined stroke events (stroke and transient ischemic

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attack), similar findings were observed. Similarly, Oni et al. (2017) found in another study that same year that therapeutic serum testosterone concentration with testosterone replacement therapy conferred a lower risk of myocardial infarction compared to non-therapeutic treatment testosterone levels. The study examined the serum testosterone levels of over 12,000 veterans. In 1,482 males between the ages of 25 and 84, low testosterone levels were still inversely correlated with carotid artery intima-thickness even when age and conventional cardiovascular risk factors were taken into account. There was no correlation between the evolution of carotid intima-media thickness and blood testosterone concentrations at the 7-year follow-up. Toma et al, (2012) discovered that testosterone replacement therapy could improve exercise capacity, muscle strength significantly without causing any significant change in ejection fraction, systolic blood pressure or diastolic blood pressure. The progression of intima-media thickness of the common carotid artery was found to be inversely related to serum free testosterone in a smaller study that prospectively followed up on 196 elderly men for four years. This relationship was even stronger in the older men who also had low grade inflammation (Thiago and Shedzad, 2019). Testosterone has been demonstrated to enhance myocardial perfusion in addition to the favourable changes in ECG parameters. An MRI revealed a slight increase in myocardial perfusion in the area fed by unblocked coronary arteries in a randomised control trial including 22 men with coronary heart disease who received oral testosterone undecanoate for 8 weeks. The findings of Dockery et al. (2009) about the observed coronary vaso-relaxant impact of testosterone corroborate earlier studies that androgen deprivation therapy enhanced the stiffness of major arteries in individuals with prostate cancer. The application of these findings in the general population is limited because some of the trials had small participant numbers and others used testosterone administration methods like intracoronary infusion, which are not typically used in clinical practise. Despite the above findings suggesting that testosterone might have a beneficial coronary vascular effect (Shehzad and Thiago, 2019). Another factor that has been considered as contributory to the outcome of testosterone replacement therapy on cardiovascular events is the formulation or route of administration. When Layton et al. (2015) examined 544,115 men beginning testosterone therapy; they found that those receiving transdermal testosterone gel were less likely to experience cardiovascular events than those receiving intramuscular injections.

In a limited experiment, transdermal testosterone patches containing 5 mg were provided to 46 men with stable angina. The 12-week trial revealed improvements in the ECG during physical activity. Another study that examined the effects of exercise on ECG alterations in individuals with chronic stable angina and congestive heart failure, respectively, corroborated this. Testosterone replacement medication was found to have a favourable effect in both situations, protecting men from exercise-induced ischaemia, although these trials had small sample size (Malkin et al, 2006). In 2009, they conducted a follow-up study to examine the impact of testosterone on carotid intima-media thickness and exercise-induced ischemia. There were fifteen males with angina and hypogonadism who participated in the 12-month study. Two men were reported to have left the research early, while seven men received testosterone treatment and six received a placebo. In comparison to the placebo group, testosterone was found to lengthen the duration to ischemia and reduce the thickness of the carotid intima-media. The results were considered to be proof positive that testosterone therapy is safe. In a different study, Zoe et al. (2012) looked for a correlation between low testosterone and death from all causes. 3637 men between the ages of 70 and 88 took part in the study. They underwent a 5-year follow-up period during which their testosterone level was assessed. Out of 605 deaths, 207 were attributable to heart-related conditions. They found that whereas optimising testosterone may enhance cardiovascular outcome, low testosterone was linked to mortality from cardiovascular-related causes. The impact of long-acting testosterone therapy on exercise capacity and other functions in elderly people with chronic heart failure was studied by Caminiti et al. (2009). The subjects had decreased ejection fraction and persistent chronic heart failure. After the test, an echocardiography was performed on them. The left ventricular function of both the treatment and placebo groups did not significantly change. The findings indicated that even in the presence of underlying heart disease, long-acting testosterone therapy enhanced exercise capacity and other essential functions. This was corroborated once more by Scott et al. (2019), who found that individuals receiving testosterone therapy experienced improvements in their ejection fraction. It has also been suggested that testosterone may help heart failure patients live better and also have better cardiac function. Pugh et al, (2003) sought to determine the short term effects of testosterone therapy. 12 men who had moderate-to-severe left ventricular failure were prescribed 60mg of testosterone for 2 days. An improvement was noted in their cardiac output which was attributed to the testosterone's ability to reduce peripheral resistance. When 76 men with low ejection fractions were compared to those who did not receive testosterone treatment, it was found that the men's improved ejection fraction may have contributed to their increased functional capacity after a 12-month course of 5 mg testosterone patches. Additionally, a greater number of males in the therapy group showed improvement in at least one NYHA functional class, compared to approximately 25% of men in the non-treatment group (Malkin et al, 2006). While there was a widespread belief that having a male partner increases the risk of coronary artery disease, with men thought to be twice as likely to develop coronary heart disease as women, Nettleship et al. (2009) found that the risk of coronary atherosclerosis and other cardiovascular risk factors increases with age, particularly in areas where testosterone levels are known to be low. Additionally, there was a negative correlation found between atherosclerotic variables and testosterone. These results imply that atherosclerosis is linked to low testosterone levels rather than male sex. There have been reports of improved myocardial ischemia and improved treatment of atherosclerosis with testosterone therapy. A case control study comprising 934,283 men between the ages of 45 and 80 was conducted to look for a correlation between myocardial infarction and testosterone replacement treatment use—either for the first time, in the past, or currently. The study revealed no correlation between present or prior users

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV674

and no difference between various formulations in people who had a history of coronary artery disease, but it did find an increased risk in first-time users. Seven experiments from different universities comprised the set of testosterone trials that looked into the impact of testosterone replacement therapy on illnesses such as coronary artery disease, cognition, and other conditions. In the trial's cardiovascular-related studies, 138 men underwent CT angiography monitoring to measure the volume of non-calcified and calcified coronary artery plaque and their coronary artery calcium scores (Cruqui et al, 2014). After a year of testosterone replacement medication, there was no difference in the number of adverse cardiovascular events or an increase in calcified plaque between the two groups. Non-calcified plaque volume, however, does not indicate a higher risk of unfavourable cardiovascular events. Instead, these kinds of occurrences can be predicted by coronary artery calcium scores. The coronary calcium score did not show a difference between the two groups in the trials. A second research (TEAAM trial) with 308 men looked at common carotid artery thickness and coronary calcium scores. The trial found no variations in arterial thickness between the experimental and control groups. A significant trial by Lincoff et al. (2023) involved 5246 males between the ages of 45 and 80 who had pre-existing cardiovascular risk factors or diseases and were symptomatic or clinically diagnosed with hypogonadism. The trial was double-blind, placebo-controlled, and randomised. Randomly chosen participants were given either a placebo gel or transdermal 1.6% testosterone gel. The individuals were followed up with for 33 months after the study concluded, which lasted 21 months. It was discovered that testosterone therapy treatment did not significantly worsen the incidence of cardiovascular events when compared to placebo. The relationship between low plasma testosterone and high mortality in males with cardiovascular disease (ischemic artery disease) was also investigated by Soisson et al. (2013). Men over 65 who had baseline measurements of their total and bio-available testosterone made up the cohort. The study found that while a normal amount of testosterone is cardio-protective, high and low plasma testosterone levels were associated with an elevated risk of ischemic artery disease. However, a related study conducted by Ohlsson et al. (2011) looked at 2,416 males ages 69 to 81 to find a connection between low plasma testosterone and cardiovascular events. They underwent a 5-year follow-up after having their baseline testosterone tested. It has been suggested that testosterone and cardiovascular health are inversely related. It was discovered that men with higher testosterone levels were less likely to have cardiovascular illnesses. Shores et al. (2012) examined the relationship between hypogonadal men's testosterone levels and mortality. In the study, cohorts of 1,031 males 40 years of age and older with testosterone levels below normal were enrolled. After adjusting for age and underlying medical conditions, those who received testosterone treatment were compared to men who did not receive it. Without a discernible impact on coronary heart disease, it was found that the mortality rate in males who were not treated was double that of the treated group. Shores et al. (2014) conducted a study that examined the relationship between testosterone and ischemic stroke, which is a leading cause of morbidity and mortality in older men. A cohort of 1032 males aged 66 to 97, who had no prior history of heart disease and were monitored for ten years. There was no correlation found between elevated risk of stroke and either free or total testosterone.

B. Testosterone Replacement Therapy and Stroke

Studies examining the relationship between testosterone replacement therapy and stroke risk are few and far between. Observational research and randomised controlled trials have not yet conclusively demonstrated a link between testosterone therapy and stroke. Neither the testosterone group nor the control group saw a high frequency of stroke occurrences, according to a randomised control experiment. Because so few studies have been done in this area, the inquiry concluded that there was no evidence to support the risk of stroke in men, but it could not rule out a relationship between the two (Thiago and Basaria, 2019). Yeap et al. (2009) looked at the association between cardiovascular events and low testosterone levels. The study involved the recruitment of 3443 senior males. They found that older men with low testosterone had a higher risk of stroke and transient ischemic episodes, with the risk increasing with decreasing testosterone levels. Despite having underlying type II diabetes mellitus, Morgunov et al. (2011) found that testosterone therapy had a beneficial effect on patients who had ischemic strokes. Body mass index, glycated haemoglobin (HbA1c), cholesterol, triglycerides, and low-density lipoproteins all showed improvements, however the control group's incidence of stroke doubled compared to the treatment group. Loo et al. (2019) also assessed the risk of myocardial infarction, acute seizures, and ischemic stroke associated with testosterone replacement therapy in older men with low testosterone levels. A group of men, aged 45 and above, who did not exhibit any symptoms of hypogonadotrophic or testicular disease and had low testosterone levels were created. 850 individuals reported having a myocardial infarction, transient ischemic attack, or ischemic stroke during follow-up, out of the 5,401 males who took part in the trial. A greater risk of cardiovascular events has been associated with current testosterone replacement medication use compared with non-use. The greatest danger was discovered to occur within the first six months to two years of continuous use of testosterone replacement therapy. There was no negative impact or worsening of pre-existing myocardial infarction or stroke in patients who had received treatment when compared to non-treated patients, according to a different study by Tan et al. (2015) that looked at the relationship between testosterone therapy and new myocardial infarction and stroke events in patients who had hypogonadism, myocardial infarction, or stroke. They suggested that younger males without risk factors can safely use testosterone. Bias has been discovered in a few studies that examined the negative consequences of testosterone replacement medication. Among these biases are comparisons between individuals who received varying testosterone dosages and formulations; analysis of trials deemed to be of low or medium quality; and an inadequate assessment of the cardiovascular events (Thiago and Basaria, 2019). The goal of Srinath et al. (2016) was to ascertain whether ischemic strokes and low endogenous testosterone were related. 1558 middle-aged males who were overweight

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV674

but had no prior history of cardiovascular disease, stroke, or testosterone treatment usage. After controlling for atherosclerotic risk variables, the study revealed no correlation between lower testosterone levels and stroke or ischemic brain damage. However, lower testosterone levels were linked to hypertension and high density lipoprotein.

Chan et al. (2016) also investigated the relationship between low testosterone and death from cardiovascular disease in older males. 1804 men, the majority of whom were under 60, participated in the study. Men with lower baseline testosterone levels were included in the follow-up and outcome measures, which lasted for 15 years. 399 more cardiovascular events and 141 deaths linked to cardiovascular disease were reported. They stated that, in spite of the aforementioned findings, it was not possible to determine a relationship between the outcomes and testosterone levels in males of any age. Maggi et al. (2016) conducted a comprehensive study in the same year to investigate the cardiovascular safety of testosterone in the treatment of hypogonadal men. Men who took testosterone and those who did not were monitored for cardiovascular consequences. Out of the five documented deaths, two were untreated and three were receiving testosterone replacement medication. They stated that the patient's age and prior history of cardiovascular conditions had more bearing on the result than testosterone replacement therapy. Thirumalai and Anawalt's (2022) most recent prospective cohort study examined the effects of testosterone, both endogenous and exogenous, on cardiovascular health in men who were followed up for five to fifteen years. According to reports, there is no correlation or inverse relationship between cardiovascular events including myocardial infarction, coronary artery disease, and hypertension with endogenous testosterone or testosterone replacement treatment. They concluded from their research that neither endogenous testosterone nor testosterone replacement therapy, at treatment doses, had any negligible effects on the risk of cardiovascular diseases in the absence of underlying medical conditions or other cardiovascular events, such as stroke, deep vein thrombosis, or recent myocardial infarction. But they advised against the prescription of very high doses to patients who have minimal drop in their testosterone level.

IV. CONCLUSION

Testosterone plays vital roles in maintaining the body’s homeostasis. Men who have low testosterone level and diagnosed of hypogonadism, suffer from symptoms such as decreased energy, easy fatigability, clouding of memory, low libido, erectile dysfunction amongst others. There is a high prevalence of hypogonadism where it is reported that 1 in 4 men in the United States suffer from this condition. Associations have been reported between testosterone and cardiovascular events. Research shows that low testosterone level is associated with acute myocardial infarction, cardiomyopathy and coronary artery disease. This has been supported by other researches. Additionally, it has been noted that this insufficiency is a poor predictive factor for cardiovascular events, particularly in people with underlying cardiovascular disorders such chronic heart failure, where it has been shown to exacerbate the condition by lowering ejection fraction. Moreover, it has been connected to stroke, transient ischemic episodes, and mortality from cardiovascular disease. Additionally, a study has connected low testosterone to vasoconstriction, which raises blood pressure.

When a patient is diagnosed with hypogonadism, testosterone replacement therapy is typically started. Raising the plasma concentration to a normal level and managing the disease's symptoms are the objectives of treatment. According to reports, testosterone replacement therapy produces a number of negative side effects that impact various body systems and organs. Numerous studies have shown conflicting results supporting and refuting the use of testosterone replacement therapy. Its impact on the development of cardiovascular events and cerebrovascular events (strokes), as well as the risk factors for these illnesses, has been examined in this review. Some studies have revealed favourable effects or increased risk associated with testosterone, while others have found no association between the hormone and stroke or cardiovascular events.

Numerous researches documented the positive outcomes of testosterone replacement treatment. An investigation revealed a negative correlation between senior men's testosterone levels and their risk of cardiovascular conditions including atrial fibrillation. This conclusion was backed by data from other studies, which showed that a lower incidence of atrial fibrillation was linked to the normalisation of plasma testosterone. There is a documented inverse relationship between testosterone therapy and hypertension, diastolic blood pressure, and systolic blood pressure. Another study indicated that while normalised testosterone levels were associated with normal blood pressure and cardioprotection, elevated testosterone levels were linked to hypertension. It has been observed that testosterone therapy improves heart health. It was linked to a decrease in triglycerides and plaque development as well as an increase in HDL. A study claimed to have seen some protection against cardiovascular problems in older people, but it found no correlation between testosterone therapy and these conditions. Similarly, some additional studies found that testosterone therapy had a positive benefit that became more noticeable after a lengthy period of usage rather than increasing the risk of cardiovascular disease. Evidence also indicates that, even in the presence of congestive heart failure and underlying chronic stable angina, exercise improves myocardial perfusion and ECG abnormalities. Studies investigating the relationship between testosterone replacement therapy and stroke are extremely rare. Data indicates that testosterone replacement therapy does not induce stroke, but rather has a beneficial effect even in patients with underlying cardiovascular illnesses, despite reports linking low testosterone to cerebrovascular events.

A small number of studies documented negative consequences from testosterone replacement therapy. A cohort study found that both the testosterone treatment group and the control group had a significant increased risk of myocardial infarction and stroke, though the treatment

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV674

group's risk was higher and participants had an underlying coronary artery disease. An additional investigation revealed that cardiomyopathy accompanied by a noteworthy decrease in ejection fraction was a side effect of testosterone treatment. The testosterone treatment group saw a significant rate of cardiovascular events, as revealed by a randomised controlled trial, prompting the study's termination. There were only 209 participants in the study, which limits the study's applicability to the broader public. According to a study, there was a decrease in the risk of myocardial infarction when testosterone replacement medication was stopped after the first three months of treatment. However, this was observed when underlying cardiac illness was present. A different study's report, which indicated a higher risk of myocardial infarction in those receiving testosterone therapy for the first time, corroborated the aforementioned finding. Additionally, a study found a link between testosterone replacement treatment and deaths from cardiovascular diseases.

A few variables were found to have an impact on a few of the given results. The sample size is one of these variables. The majority of the research enrolled relatively few participants, which restricts the applicability of their conclusions. Another factor that was shown to be potentially responsible for the observed detrimental effect was the method of administration. According to a report, patients who received transdermal testosterone gel were less likely than those who received intramuscular injections to experience cardiovascular problems. As we await the result of a large clinical trial (TRAVERSE trial) which is thought to be able to address many of the unanswered questions surrounding the safety of testosterone replacement therapy, it is advised that physicians should adhere strictly to established guidelines and be guided by the principle of non-malfeasance when managing patients with hypogonadism

Based on the research that is now available, testosterone replacement treatment has more positive effects than negative ones. Similarly, there is a connection between cardiovascular events and low testosterone levels. Therefore, if a patient is diagnosed with hypogonadism, they should be urged to seek help and be willing to get treated. As we await the result of a large clinical trial (TRAVERSE trial) which is thought to be able to address many of the unanswered questions surrounding the safety of testosterone replacement therapy, it is advised that ph\ysicians should adhere strictly to established guidelines and be guided by the principle of non-malfeasance when managing patients with hypogonadism.

DECLARATION OF INTEREST STATEMENT

I, Omolu Ernest Chijioke, hereby declare that this dissertation entitled “A Narrative Review on the Effect of Testosterone Replacement Therapy on Stroke and Cardiovascular Diseases” is entirely my own work and that this dissertation has not been previously published and such materials as has been obtained from another source has been duly acknowledged in this dissertation. A more elaborate work was submitted to the department of sport medicine, as part of the master of Sport and Exercise Medicine under the supervision of “Dr Angell Peter “.

ACKNOWLEDGEMENTS

I am most grateful to God Almighty who has sustained my life and has made good things come to me.

I am thankful to my supervisor Dr Angell Peter for his help, patience and guidance. It was wonderful working with you.

My sincere appreciation goes to everyone in the department of Sport and Exercise Medicine, who indeed contributed to the success of my academic pursuit and formation at Liverpool Hope University.

I am grateful to my beautiful wife Nwamaka Linda Omolu and our children David, Daniel and Angela Omolu for their unending support.

And to my friends and acquaintances who were ever ready to help in every way possible.

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