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Erectile Dysfunction Complicating Cardiovascular Risk Factors and Disease

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1. Introduction

Erectile Dysfunction (ED) is the persistent inability to achieve and or maintain penile erection sufficient for satisfactory sexual Intercourse. ¹ In 1995 it was estimated that 152 million men world-wide experienced ED and it was projected that by 2025, the prevalence worldwide would be 320 million.² In the United states alone, 34 million men suffer from ED³ while in China, according to Yang et al, ⁴ prevalence is reported to be 73.1% in the general population. Shaeer et al ⁵ in their study of the prevalence of ED in diverse nationalities representing a wide range of cultural, religious, racial and socio-economic backgrounds concluded that prevalence rates from various countries are difficult to compare because of variable definition and age range. So far, the most comprehensive epidemiological study of ED has been the Massachusetts male aging study⁶ which reported ED to be present in 10% of men aged between forty and fifty years and almost 70% in Men aged 70% years and above.

	COUNTRIES	PREVALENCE
1.	Malaysia	17.0%
2.	Germany	19.0%
3.	Japan	34.0%
4.	United States of America	52.0%
5.	Morocco	53.6%
6.	Nigeria	57.4%
7.	Egypt	63.6%
8.	Turkey	64.3%
9.	China	73.1%
10.	Pakistan	80.8%

Table 1. Reported Prevalence of ED in selected Countries.

In the early 1980s, issues of quality of life (Qol) were brought into the fore of medical practice prompting the rise of ED into prominence as a diagnostic entity. According to Pomerville ⁷ '20 years ago, ED did not exist as a diagnostic term. Its former name 'Impotence' carried a heavy connotation - an impotent man was powerless, worthless, less than a man. Impotence was seldom discussed in the locker rooms or bed rooms of nations" Impotence was relegated and considered to be due to the wears and tears of the aging process for which there is no treatment. This is strongly supported by the following statement by Wyne et al:⁸ "for centuries, sexual medicine was a taboo subject practiced by quasiscientists, back alley charlatans and village shamans. Because of a paucity of basic knowledge about the anatomy, Physiology and Pharmacology of the erectile process, many myths on causation and therapy were promulgated through time."

This perception has changed remarkably due to research into ED in the last century which led to the discovery that certain factors are associated with ED with a cause- effect relationship.^{9 10} Currently, there is a better understanding of the incidence, prevalence, etiology and risk factors for ED.

ED is classified as psychogenic, neurological and vasculogenic. Vasculogenic erectile dysfunction, similar to coronary artery disease, is usually due to atherosclerosis, in the case of ED, atherosclerosis of the branches of the pudendal artery. Cardiovascular risk factors are so classified because of their propensity for causing atherosclerosis¹² which may involve the coronary artery thereby predisposing the heart to myocardial hypoperfusion disease. The common denominator in ED and CAD therefore, is atherosclerosis whose main causes are these life style abnormalities referred to as cardiovascular risk factors. The implication of this is that the risk factors for ED and CAD are similar or are in fact the same.^{13 14 15}

Hypertension, Diabetes mellitus, dyslipidemia and cigarette smoking have been well documented as predisposing to atherosclerosis of the coronary artery which has earned them the term 'cardiovascular risk factors". Currently, reduced androgen level, particularly testosterone, is under intense research as another risk factor because of the vascular changes associated with it.¹⁶ Several epidemiological studies have demonstrated that ED is more prevalent in men with atherosclerotic disease than the general population. ¹⁷ It is now generally accepted that ED, like CAD, results from the endothelial dysfunction which usually co-exist with or predates true atherosclerotic vascular changes.¹⁸

Documented Risk Factors	CVS RISK FACTOR BEING EVALUATED
Cigarette smoking Dyslipidemia Diabetes Mellitus Hypertension	Low testosterone level

Table 2. CVS risk factors.

In spite of the adverse effects of ED on quality of life of the affected men, the disease is generally under-reported and under-treated¹⁹ due to poor self reporting as a result of cultural taboos, fear of stigmatization, ignorance on the part of the patient or physician and unavailability of specialists in the area. Erectile dysfunction is a treatable disease and many

men have been treated and have returned to normal life especially with the advent of the phosphodiesterase 5 inhibitors.²⁰ This chapter focuses on erectile dysfunction and its cardiovascular system correlates.

2. Neuroanatomy and physiology of penile erection

The human penis is made up of two dorsally located corpora cavernosa and one ventrally placed corpus spongiosum.²¹ The corpus spongiosum expands proximally to form the bulb of the penis while distally it expands to form the glans penis, the most sensitive part of the organ. Proximally, the two corpora cavernosa diverge laterally and are attached, one on each side, to the inferior surface of the ischio pubic rami.²² The erectile tissue proper is located in the corpora cavernosa and surrounded by a tough fibrous tissue called the tunica albuginea.

The corpora cavernosa consist of sinusoids with smooth muscle lined internally by endothelium similar to that of blood vessels. The helicine arteries, the terminal branches of the cavernosal arteries, open directly into the sinusoids. The blood is drained by veins which course beneath the tunica albuginea before piercing it. These join the dorsal vein complex.

The penis is innervated by both autonomic and somatic nerves; the latter supplies the skin while the former sub serves the erectile tissue proper.²³ Somatic supply consist of free nerve endings (receptors) in the skin of the penis, usually up to ten times as numerous in the penile skin and the glans particularly. These receptors coalesce to form the dorsal nerve of the penis, a branch of the pudendal nerve which originates from the dorsal rami of S2 -4.²⁴ The nerve fibres are mainly unmyelinated C and A delta fibres which sub serve the sensation of pain, pressure and touch (tactile stimulus), the stimulus responsible for reflexogenic erection. The para sympathetic pathway which serves the cavernosa arises from neurons in the S2- 4²⁵ and follow the ventral rami. This group of cells constitutes the Onuf nucleus and their preganglionic fibres join the sympathetic fibers from the hypogastric plexus to form the pelvic plexus (pelvic splanchnic nerves). The post ganglionic fibres (nervi erigentis) arise from the pelvic plexus and passing anterior to the rectum and posteriolateral to the prostate, they pierce the pelvic membrane to reach the corpora cavernosa. They are often damaged during surgical procedures which involve total removal of the prostate and the rectum because of which these procedures are often complicated by erectile dysfunction.²⁶

The sympathetic pathway whose fibres are mainly inhibitory originate from T11 - L2 spinal segment. The fibres pass through the white rami to the sympathetic ganglion. Some of these fibres reach the inferior mesenteric and superior hypogastric plexus through the lumbar splanchnic nerves. From the hypogastric plexus, some fibres reach the pelvis and join the parasympathetic fibres to form the pelvic plexus. The fibres from the pelvic plexus which reach the carvenosa along with those from S2-4 are mainly from T10 -12.²⁷ These fibres also carry impulses which control ejaculation and may be damaged during radical retro peritoneal dissection as they course behind the peritoneum.²⁸

The central control of penile erection depends on the input from somatic and autonomic pathways and environmental factors, which include smell, sight and thought of Sex. Tactile impulses from the dorsal nerve of the penis travel via the spino thalamic and spino reticular pathways to the thalamus and sensory cortex for sensory interpretation. Studies have shown that the medial pre-optic area and the para ventricular nucleus of the hypothalamus are the

integration centre for erection and sexual activity.²⁹ It is currently suggested that there may be projections from the hypothalamic nuclei to the sacral erection centre, S2 - 4, as is found in animals. Other centres which contribute to control of sexual activity also abound in the mid brain and medulla.³⁰

Several neuro transmitters are involved in penile erection and control of sexual activity. The neuro transmitter traditionally associated with the parasympathetic (parasympathetic finally control erection) is acetylcholine while nor- adrenaline and adrenaline are involved in sympathetic transmission. Other neuro-transmitters secreted at the level of the autonomic nervous system in the genito-urinary tract are vaso- active intestinal peptide (VIP) and several prostaglandins. These neurotransmitters do not however, completely account for the events that lead to penile erection. Currently, the substance which is considered to act as the neurotransmitter involved in penile erection is a non adrenergic, non cholinergic (NANC) and it is now known to be nitric oxide (NO).³¹

Nitric oxide is a ubiquitous neuro-transmitter in the lower urinary tract³² and its role in penile erection process is presently well documented. It is formed from L-arginine under the control of Nitric oxide synthase.³³ There are three isoforms of Nitric oxide synthase; eNos, nNos and iNos depending on the cell in which it is synthesized. Neural stimulation causes release of Nitric oxide from neurons while its release from endothelium is in response to sheer stress.³⁴ The neurotransmitters involved in the central control of penile erection and sexual activity include oxytocin, gama aminobutyric acid and serotonin.

In the flaccid state, the smooth muscle of the cavernosa is semi contracted under the tonic influence of the sympathetic system, its intrinsic myogenic activity and endothelium derived factors such as prostaglandin F₂ alpha.³⁷ In this state, the blood flow to the penis is kept at the barest minimum required to meet its nutritional needs at a pCo₂ of 35mmHg.³⁸ Following sexual stimulation, the non adrenergic non cholinergic fibres which accompany the parasympathetic to the cavernosa, release nitric oxide which triggers the erectile process³⁹.

- Central (smell, thought) and tactile (penile skin) stimulus
- Processing of resulting impulses by the Onuf nucleus.
- Activation of the effector pathway (nervi-erigentes).
- Release of neuronal NO following neuronal NO Synthase activation.
- Activation of the NO-cGMP pathway.
- Increase blood flow into the cavernous sinus-penile erection.
- Increase flow stimulates release of endothelial NO- sustained erection

Table 3. Summary of physiology of penile erection.

Nitric oxide is a potent vasodilator which readily diffuses into the cell to initiate a series of bio-chemical events. Nitric oxide modulates the activities of guanylate cyclase,⁴⁰ an action which leads to the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). The latter, acting as a second messenger, regulates calcium channel activities including those of intracellular contractile proteins that lead to the relaxation of corpus cavernosal smooth muscle.⁴¹ Specifically, cGMP activates protein

Kinase G leading to a decrease in calcium influx into the cell which in turn causes activation of myokinase and finally, relaxation of corpora smooth muscle, a sine qua non in the erectile process⁴².

Penile erection is classified as: Central, reflexogenic and Nocturnal.⁴³ In central erection, the stimulus is from thought, sight and smell related to Sexual intercourse which activates the spinal centres, the impulses of which travel through the parasympathetic to the corpora. Reflexogenic erection results from tactile stimulation of the dorsal nerve of the penis. The afferent pathway reaches the onuf nucleus which then activates the erectile parasympathetic pathway via the same process as in central erection. Nocturnal Penile tumescence (NPT) is currently poorly understood. It occurs during rapid eye movement sleep and it is presently thought to play a key role in keeping the erectile tissue perfused.³

Following central or reflexogenic stimulus, there is activation of the parasympathetic erectile pathway with the release of nitric oxide and the consequent cascade of events which lead to relaxation of cavernous smooth muscle and the helicine arteries. The ensuing rapid influx of blood into the sinusoids leads to increased intra cavernosal pressure and compression of the sub tunical venous system against the tunica albuginea. There is reduced outflow in the presence of markedly increased inflow and the penis becomes firm and increased in size - phase of full erection. Through the pudendal nerve, sexual impulses also reach the ischio carveranosus and bulbospongiosus muscles which contract vigorously, further impeding venous drainage - phase of rigid erection.

Penile detumescence is a consequence of the intense, diffuse sympathetic discharge which heralds orgasm, emission and ejaculation. The catecholamines released in the process cause smooth muscle contraction, thereby terminating erection. The smooth muscle contraction leads to reduced blood flow into the sinusoids, reduced intra cavernosa pressure and the opening of the venous channels. There is therefore increased venous outflow in the presence of reduced arterial inflow. The trapped blood in the sinusoids is expelled and the penis becomes flaccid²³.

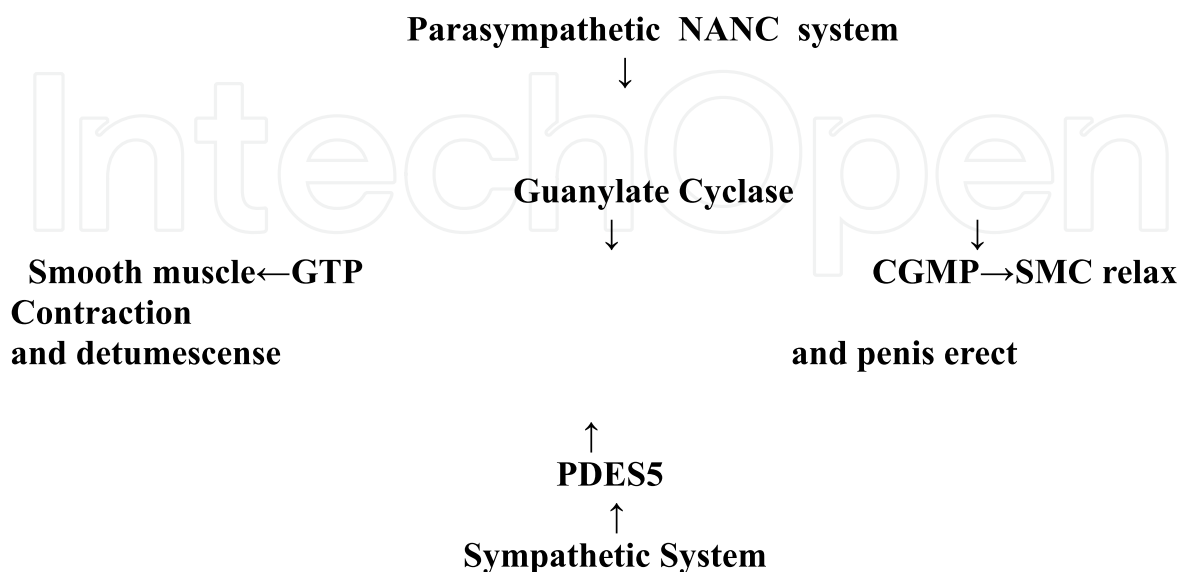


Fig. 1. Penile tumescence and detumescence

3. Atherosclerosis

Arteries vary in wall thickness and size and based on these, they are classified as⁴⁵ (A) Elastic or large arteries. A typical example is the aorta, Innorminate, subclavian and illiac arteries (b) Medium sized arteries typical of which are coronary arteries (c) Small arteries. These are usually less than 2mm in diameter, coursing for most of their path through the substance of the issue or organ. A good example is the pudental and cavernosa arteries which supply the penile erectile tissue and upon which erection depends. The arterial wall, independent of class, is made up of three layers namely;

1. Adventitia. This is a fibrous tissue which covers the artery externally and separates it from the surrounding structures or tissues.
2. The media. This is responsible for most of the wall thickness and consists mostly of smooth muscle cells (SMC) which are under the tonic control of the endothelium.⁴⁶ It is from this layer that SMC are recruited in the formation of atheroma.
3. The intima. This consists of a single layer of endothelium which rests on a basement membrane. The endothelial cells are joined together by tight junctions which are normally impermeable to most substances in the blood.

The endothelium is physiologically endowed to control the vessel in order to vary blood flow according to tissue, organ and regional requirements. It is in most part, responsible for the smooth flow of blood and therefore has profound effect on vascular reactivity and thrombogenesis. It inhibits platelet aggregation, reduces the recruitment of inflammatory cells into the intima and the entry of lipids into the arterial wall.

The endothelium secretes a wide variety of substances with paracrine effect while also expressing receptors for various substances in the blood stream, the latter including hormones, local mediators and vasoactive substances. Based on these, the endothelium is capable of sensing and responding to local changes either by causing vasodilatation or constriction. The overall effect of endothelial reactivity is however vasodilatation or a tendency to vasodilatation reaching up to 80% in the penile arterial bed as against 15% in other tissues.^{47 48}

Nitric oxide (NO) is a major neurotransmitter produced by the endothelium and is responsible for the endothelium derived vasodilatation. It is produced, as a neurotransmitter, in most parts of the lower urinary tract either normally or pathologically.⁴⁹ It inhibits cytochrome C oxidase, reduces oxygen consumption by the vasculature and inhibits or modifies the endothelial cells for circulating white blood cells. Its release is stimulated by acetyl choline, bradykin, substance P and sheer stress on the arterial wall.

- Endothelial dysfunction is defined as a state of altered phenotype which leads to impairment of vascular reactivity or an induced surface which is thrombogenic or abnormally adhesive for inflammatory cells.⁴⁵ This change may predate or co-exist with atherosclerosis and is characterized by loss of vascular reactivity. The initial phase is characterized by decreased bioavailability of nitric oxide either due to reduced production or increased breakdown. There is therefore loss of the endothelium derived smooth muscle relaxation with a tendency to vasoconstriction and increased peripheral resistance. These effects have been implicated in hypertension, diabetes mellitus, cigarette smoking and hyperlipidemia, all of which are risk factors for ED and CAD.

Endothelial dysfunction is a systemic disease and it is usually as a result of diverse injury including sheer stress, trauma and inflammation. It occurs in the initial and subsequent phases of atherosclerosis. Though all arterial beds are affected, the effects manifests earlier in the smaller vessel beds⁵⁰ such as the pudendal artery which supply the erectile tissue of the penis. In the presence of endothelial dysfunction, the endothelium becomes unduly permeable, allowing substances such as lipids, proteins and macrophages into the intima, a *sin-qua non* for atherosclerotic changes.

- Atherosclerosis is characterized by intimal lesion called atheroma or atheromatous plaques or fibrofatty plaques which project into the lumen of the vessel. It forms the common pathway through which the well documented cardiovascular risk factors cause their deleterious effects on the heart, cerebrum and the erectile tissues. Endothelial dysfunction results from inhibition of dimethyl arginine dimethyl amino hydrolase which catalyses the hydrolysis of asymmetric dimethyl arginine, an inhibitor of endothelial nitric oxide synthase. The subsequent uncoupling of eNos leads to endothelial oxidative stress and formation of peroxy nitrates, oxidation of pro-inflammatory nuclear factor Kappa B and hence cellular inflammation.⁵¹

Endothelial inflammation causes increase permeability of the endothelial cells and the tight junctions. The subsequent increased movement of lipids, protein and inflammatory cells, particularly macrophages into the intima, initiates the process of atherosclerosis which affects all the arterial bed. Timing of clinical appearance however depends on the severity and size of the affected vessel as up to 75% of the vessel lumen maybe occluded before effects become obvious.⁵² Smaller vessels such as the pudendal artery may be occluded up to ten years before bigger vessels like the coronary arteries are affected. This explains why erectile dysfunction usually precedes the occurrence of coronary artery diseases or stroke.

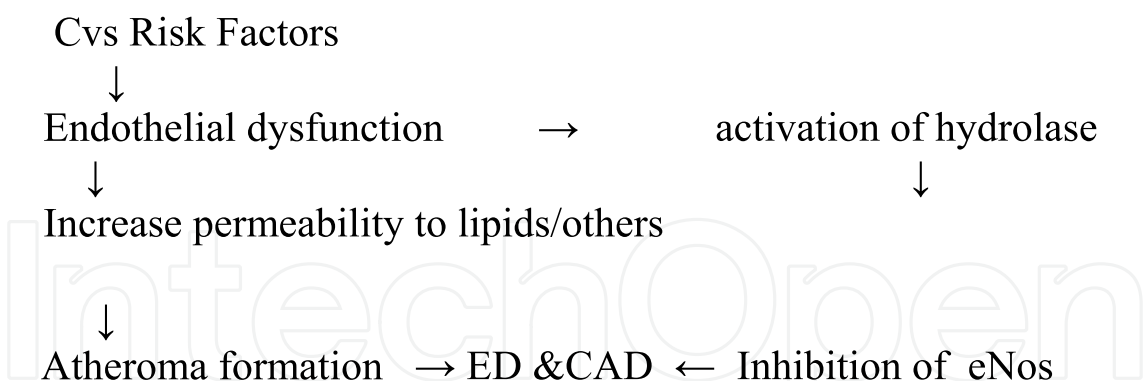


Fig. 2. Mechnisms by which CVS risk factors cause ED and CAD

4. Cardiovascular risk factors and erectile dysfunction

4.1 Diabetes mellitus

Diabetes mellitus(DM) is defined as persistent hyperglycemia secondary to relative or absolute insulin deficiency. This has a profound effect on protein, lipid and carbohydrate metabolism with a myriad of complications of which ED is one. These complications can broadly be classified as vascular or neurologic and ED has been documented in both classes. In DM, neurologic damage which may predispose to ED usually result from peripheral

neuropathy and ED is well known to be associated with both somatic and autonomic neuropathies.⁵³ Both types of autonomic neuropathies ie, axonal and demyelinating, occur in DM and are responsible for the 'failure to initiate' type of ED.

Vascular damage from DM causes the 'failure to fill' type of erectile dysfunction. This results from endothelial dysfunction and or atherosclerosis both of which are companions of diabetes mellitus. Diabetes mellitus is associated with low grade inflammation, dyslipidemia, hypertension and the metabolic syndrome all of which, as independent entities, are risk factors for ED. This low grade inflammatory state in DM has been well documented by many authors who have demonstrated elevated c-Reactive protein, Tumor Necrosis Factor alpha (TNF) and interleukin 6 (IL-6) in diabetic patients with ED who have no other risk factors.^{54 55 56}

The low grade inflammation in DM causes endothelial dysfunction which leads to an endothelium that is more thrombogenic and permeable to lipids, inflammatory cells such as macrophages. This initiates the process of atherosclerosis which is usually diffuse and occurs earlier in diabetic patients. (The reader is referred to standard vascular texts for the pathology of atherosclerosis) The ensuing diffuse atherosclerosis and micro-angiopathy is responsible for the nephropathy, retinopathy, stroke, coronary artery disease and ED that accompany DM. According to Meng et al,⁵⁷ higher glucose levels induces apoptosis in endothelial cells while Di Filippo et al⁵⁸ conclude that DM is associated with increased cardiovascular disease due to established risk factors such as dyslipidemia, hypertension and atherosclerosis as a result of increased inflammation. This leads to the production of free oxygen radicals, impaired NO metabolism and increased movement of lipids into the intima leading to early and diffuse atherosclerosis. Through this atherosclerotic damage, cerebral, cardiac, renal and erectile function maybe impaired.

The pathophysiologic relationship between diabetes mellitus and erectile dysfunction, according to Moore et al,⁵⁹ is multifactorial. They proposed the mechanism of ED in DM to include elevated advance glycation end products, increased level of free oxygen radicals, impaired NO synthesis, increased endothelin B binding sites and ultrastructural changes, up regulated Rhoa/ Rho-Kinase pathway, NO dependent selective nitregic nerve degeneration and impaired c-GMP dependent kinase. Overall, there is impaired flow mediated dilatation in DM patients which is in part secondary to increased inflammation and endothelial and platelet activation⁶⁰

- Other associated CVS risk factors e.g. hypertension, dyslipidemia.
- Low grade inflammation causing endothelial dysfunction.
- Production of free O₂ radicals, impaired NO metabolism.
- Elevated advance glycation end products.
- Increased endothelin B receptor binding sites.
- Up regulation of RhOA/Rho-Kinase Pathway.
- Nitric oxide dependent selective nitregic nerve degeneration.

Table 4. Summary of Causes of ED in DM.

ED is highly common in type 2 DM (T2DM) patients and the duration of DM is usually longer in ED patients. The atherosclerotic process is usually ongoing, dynamic and progressive⁶¹ making the clinical course of ED in DM gradual and ED may be the only sign⁶². As DM, especially type 2, maybe present for years before diagnosis, many patients already have complications before or at presentation and this may include ED. Based on these, it has been proposed that ED should be regarded as an observable marker of DM. In a study of ED In diabetics, Sun et al⁶³ concluded that men with ED are more than twice likely to have DM, strongly so for men 45 years and below but not for men older than 66 years. Twelve percent of men studied by Deutsch et al⁶⁴ were found to have unrecognized DM while the Massachusetts Male Aging Study (MMAS)⁶⁵ showed that the probability of ED is three times more common in men who reported being treated for DM and figures as high as three quarters of all diabetics have been documented. DM has other complications such as leg ulcers which impact negatively on psyche and quality of life and in such patients, ED may be partly psychogenic. This should not be underestimated in the course of evaluation.

4.2 Hypertension

Essential hypertension is the leading risk factor for mortality worldwide accounting for 13% of all deaths globally.⁶⁶ It is the most common non communicable disease in Nigeria⁶⁷ and according to Essien et al,⁶⁸ the mean venous blood glucose level of hypertensive adult Nigerians is higher than their normotensive counterparts. According to recent studies, approximately 67-68% of men with hypertension have some degree of erectile dysfunction.⁶⁹

Erectile dysfunction in hypertension, similar to diabetes mellitus, results from endothelial dysfunction and or atherosclerosis. Endothelial dysfunction in hypertension is caused by the sheer stress of elevated blood pressure on the vessel wall.⁷⁰ This endothelial damage causes the impairment of endothelium derived relaxation. The inflammation which accompanies endothelial dysfunction leads to altered NO metabolism, formation of free oxygen radicals and an increased movement of lipids into the intima, a necessity for atheromatous vascular damage. Hypertension is associated with structural and functional changes in the arterial wall and this is responsible for the mortality and morbidity associated with it.⁷¹

In a number of cardiovascular pathologies, such as hypertension and heart failure, according to Boulanger et al,⁷² the balance in the endothelial production of vasodilating mediators is altered. The underlying dysfunction is likely to be the consequence of the high blood pressure and could facilitate the maintenance of elevated peripheral resistance with subsequent development of atherosclerosis. The ensuing arterial stiffness is an independent cardiovascular risk factor.⁷³ From this perspective, it can be deduced that hypertension is an independent risk factor for coronary heart disease and vasculogenic erectile dysfunction. In the work of Modebe⁷⁴ in Nigeria, 8% of the untreated hypertension population had erectile dysfunction while this was 61% in the treated group. Treatment, rather than the hypertension therefore, may be responsible for the ED and may account for the non compliance with treatment frequently seen in this group of patients who may want to maintain their potency. This agrees with the opinion of Shiri et al⁷⁵ who in their study concluded that the risk of ED is higher in men suffering from treated hypertension and heart disease than in those with the untreated condition

Erectile function and neuromuscular transmission are calcium dependent phenomena, which to a large extent, depends on the general physical well being of the man. Erectile

dysfunction is associated with the use of calcium channel blockers, angiotensin II antagonist, non selective alpha blockers and diuretics. The continuous use of diuretics, particularly thiazide diuretics, is often accompanied by dehydration, electrolyte imbalance and elevated blood sugar all of which may lead to ED or aggravate an already existing mild disease. ED is however not currently known to be associated with the use of organic nitrates, angiotensin converting enzymes (ACE) inhibitors, selective alpha blockers and drugs that lower serum lipid levels.

- Ultrastructural changes in the vessel wall.
- Endothelial dysfunction and atherosclerosis.
- Medication side effect e.g. diuretics.
- Target organ damage e.g. stroke and heart failure.

Table 5. Summary of causes of ED in hypertension

The preliminary report of the telmisartan alone, and in combination with ramipril global end point trial/telmisartan randomized assessment study in ACE - intolerant subjects with cardiovascular disease (ONTARGET/TRACEND) study⁷⁶ has shown that on the contrary, calcium channel blockers tend to have a significant adverse effect on erectile function whereas diuretics, beta blockers, ACE inhibitors, ATI antagonist and alpha blockers do not. Treatment with ACE inhibitors and ATI antagonist or a combination of both is suggested to improve erectile function in cardiovascular high risk patients.

On the overall, hypertension is complicated by numerous vascular conditions which impact negatively on the quality of life of the affected men. Apart from coronary heart disease and erectile dysfunction, conditions such as hypertensive renal damage, intermittent claudication, retinal damage and heart failure often complicate hypertension and lower the quality of life of these men, with severe effect on their psyche. Like DM therefore, the contribution of psychogenic erectile dysfunction in hypertensives should not be underestimated in the course of treatment.

5. Cigarette smoking/dyslipidemia

Cigarette smoking is currently a major health concern and in spite of the vigorous campaign against it, more people continue to take to smoking in many countries of the world. The most well mentioned and documented toxin of cigarette smoke is nicotine but others exist. Cigarette smoke is directly toxic to vascular endothelium⁷⁷ and this culminates in vascular endothelial dysfunction, functional and architectural changes in the vessel wall.⁷⁸ The cascade of events which follow this endothelial dysfunction is similar to that in DM and hypertension. The end result is atherosclerosis and its deleterious effect on penile erectile, cardiac and cerebral function.

According to Chen et al,⁷⁹ an increased ED prevalence has been reported in patients with chronic obstructive airway diseases and sustained inflammation seem to play a central role in this linkage. Cigarette smoking has traditionally been associated to chronic obstructive airway disease (chronic bronchitis, emphysema) and through this mechanism, it may contribute significantly to the burden of ED. These conditions, similar to DM, are

accompanied by low level chronic inflammation, elevated c-Reactive protein and may be followed by diffuse endothelial dysfunction and atherosclerosis.⁸⁰ This low grade inflammatory state allow increase in low density lipoprotein transport across the endothelium into the intima, thereby initiating the process of atherosclerosis.

- Direct toxicity to vascular endothelium.
- Functional and structural changes in vessel wall.
- Chronic obstructive airway disease.
- Endothelial dysfunction and atherosclerosis.
- Reduction in concentration of NO synthase.

Table 6. Summary of causes of ED in cigarette smoking and Dyslipidemia

Dyslipidemia and obesity are major components of the metabolic syndrome (MS) which is currently well documented as being accompanied by a low systemic inflammatory state which predisposes to vascular endothelial dysfunction.⁸¹ This is the underlying mechanism of ED in men who have the metabolic syndrome and concomitant ED. This is evidenced by the presence of raised level of inflammatory markers in the affected men. MS and obesity are linked to lowered serum testosterone⁸² in a double edge manner and low serum testosterone as an independent cardiovascular risk factor, is presently being examined. It is considered to be due to the reduced level of sex hormone binding globulin. Additionally, in obesity which is often present in MS, there is increased level of low density lipoprotein as a result of abnormal insulin metabolism.⁸²

A third of citizens of the United States are presently considered, by current definition, to be obese⁸³ and the prevalence of MS in ED population is 45% compared with 24% in matched control.⁸⁴ Conversely, the prevalence of ED in MS population is 34 - 43% and this depends on the number of independent risk factors-⁸⁵ dyslipidemia, hypertension and diabetes mellitus. Dyslipidemia is also often an accompaniment of DM and hypertension in different combinations. However, dyslipidemia is an independent risk factor for ED and CAD.⁸⁶ Hypercholesterolemia has a well established link with endothelial dysfunction with oxidized low density lipoprotein being a key mediator.⁸⁷ According to Brunner et al,⁷⁷ in familial hypercholesterolemia, endothelial dysfunction is present prior to clinical arterial disease. Endothelial dysfunction is related to particle size and concentration,⁸⁸ transport across the endothelium being inversely related to the particle size and directly to the concentration. This explains why low density lipoprotein, and not high density lipoproteins,⁸⁹ is incriminated in endothelial dysfunction. Low density lipoprotein leads to reduction in endogenous NO synthase⁹⁰ which in turn causes a reduced bioavailability of the endothelium derived relaxation factor, NO, probably by enhancing super oxide anion. Lipoproteins are transported across the endothelium by the process of transcytosis and in the presence of endothelial dysfunction, reduced NO bioavailability and increased concentration of LDL, this process is enhanced leading to atherosclerotic vascular changes. In contrast, HDLs are presently considered to enhance endothelial function and a low concentration may predispose to endothelial dysfunction.⁹¹

6. Coronary Artery Disease (CAD)

In Britain, approximately a quarter of all deaths among men and one-fifth of all deaths among women are due to ischemic heart diseases.⁹² In England and Wales, 30% of all deaths among men and 22% among women are as a result of ischemic heart diseases.⁹³ Through atherosclerotic narrowing, cardiac ischemia precipitates cardiac malfunction and sometimes infarction of the myocardium. The major risk factors for endothelial dysfunction and atherosclerosis, which are also the cause of CAD and ED, are hypertension DM, dyslipidemia and cigarette smoking and these life style abnormalities have been traditionally documented as cardiovascular risk factors.

ED is related to CAD in a double edged manner. ED represents an independent risk factor for feature CVS event independent of classic risk factors such as hypertension, DM and dyslipidema⁹⁴. The common denominator for ED, CAD and these cardiovascular risk factors is endothelial dysfunction which is usually diffuse, affecting several arterial beds such as the pudendal and coronary arteries and thereafter culminating in atherosclerosis. In 2003 Montorsi et al⁹⁵ proposed the small artery theory to explain the earlier occurrence of ED than CAD. Coronary arteries, being larger than the pudendal arteries, take a longer period for occlusion from endothelial dysfunction and atherosclerotic vascular narrowing to occur. Eventually, as the atherosclerosis progresses, larger vessels such as the cerebral, coronary and renal arteries become involved and this precipitates target organ damage.

Several studies have documented this with clear evidence. In the study by Pritzter,⁹⁶ of 20 men, out of a study group of 50 who were investigated angiographically following self reported ED without any other complaints, all have demonstrable disease. They compared sexual function to the penile stress test as a window to the hearts of men. Vlachopoulos et al⁹⁷ investigated men whose only complaint was ED and found angiographically silent CAD in 19%. Bensal et al⁹⁸ also in their work documented 56% asymptomatic CAD in an ED population. Ultimately, in some of these men, CAD become overt, and as documented by Rodriguez et al⁹⁹ in DM, taking an average period of 38.8 months. According to their study, 100% of DM men experienced ED prior to onset of CAD. Based on this premise, ED is currently considered a sentinel event for CAD as both have their origin from endothelial dysfunction and atherosclerosis.¹⁰⁰ These are mounting evidence therefore, that ED is an early predictor of CAD and that there is need for physicians to evaluate men who present with ED, with no other cardiovascular symptom, for CAD and its risk factors.¹⁰¹

CAD is an independent risk factor for ED and the prevalence of ED in CAD population is remarkable. James et al¹⁰² studied the relation between ED and CAD in men referred for stress myocardial perfusion single-photon emission computed tomography (MPS). They concluded that men sent for MPS have a higher prevalence of ED. Also, men with ED exhibited a higher prevalence of severe CAD and left ventricular dysfunction than those without ED. In the work of Bensal,⁹⁸ 75% of men with CAD have symptoms of ED and 91% of their ED populations have cardiovascular risks. This has implication for men who have CAD and who intend to engage in sexual activity. Herschorn¹⁰⁰ in his work on cardiovascular safety of phosphodiesterase 5 inhibitors said that "in general, sexual activity has an effect similar to mild-moderate exercise in increasing heart rate, blood pressure, cardiac output and respiratory rate. The degree of change in these physiologic parameters however, is greater than expected because of disproportionate increase in sympathetic

activation. The absolute risk of sexual activity triggering a myocardial infarction (MI) is low. Men with CAD or previous MI have a 10-fold higher risk, which means that during sexual inter-course, the probability of such a man having MI is 20/Million/hour".

7. Heart failure (HF)

Several cardiovascular disorders cause heart failure which may be left or right sided failure. These include hypertension, congenital and acquired heart defects and cardiomyopathies. Left side failure usually results from hypertension, mitral and aortic valvular abnormalities which may be acquired or congenital. Eventually, left sided failure leads to pulmonary hypertension and with continued back pressure, right sided failure which is referred to as congestive cardiac failure (CCF). Heart failure may occur independent of traditional cardiovascular risk factors or in association with one or more of them. For instance, Ukoh¹⁰³ et al in their study observed hyperlipidemia in three groups of patients. (1) Hypertensive's with or without heart disease (2) patients with ischemic heart disease and (3) those with hypertensive cardiomyopathy. ED may therefore occur in men with heart failure not because of the failure itself, but because of the background cardiovascular risk factors present.

The prevalence of heart failure (HF) in the United States, according to the American Heart Association, is estimated at 5.3 million.¹⁰⁴ ED is present, estimatedly, in 60.8% of heart failure patients and prevalence ranging from 81 to 91% has been documented in this group.¹⁰⁵ In CCF, there is peripheral venous stasis, decreased venous return, reduced stroke volume and cardiac output, a must situation for physical in-activity or under-activity. Most patients with chronic cardiovascular disease experience decreased libido and frequency of sexual activity as well as ED.

- Endothelial dysfunction.
- Reduced cardiac output.
- Exercise in tolerance from PH.
- Associated CVS Risk factors.
- Drug side effect.

Table 7. Causes of ED in Heart Failure

The ED in HF patients is multifactorial in origin. Anxiety or depression may lead to performance fears and therefore psychogenic ED. The reduced pulmonary and cardiac reserve in CCF patients makes exercise intolerable, bearing in mind that sexual activity involve mild to moderate exercise and that most of erectile function is CVS event. Treatment of heart failure may lead to ED as a side effect of the drugs used. Diuretics, particular thiazides,¹⁰⁶are associated with ED through unknown mechanism which may not be unconnected with the accompanying electrolyte imbalance. Beta blockers, Digoxin and aldosterone are also documented as causing ED. Heart failure is accompanied by endothelial dysfunction which as an independent factor, may cause ED in these men.¹⁰⁷

8. Treatment of ED complicating CVS risk factors and disease

Following the evaluation of these men (this is beyond the scope of this chapter), there is need for treatment in order to improve their quality of life. Gerald et al¹⁰⁸ evaluated the sexual attitudes and beliefs of middle aged and older adults in non-European 'Westernized' countries in their work. Approximately 85% of men and women felt that satisfactory sexual intercourse is essential for the maintenance of a relationship. Most respondents felt that it is acceptable for older men to use medication to enable them to continue to enjoy sexual activity. By extension, this is necessary if they are to continue to maintain spousal relationship which at this age has profound effect on quality of life and longevity.

ED is multifactorial in terms of etiology, the implication of which is that treatment should be holistic. It is based on this premise that David et al¹⁰⁹ proposed a multifaceted approach with the argument that no single agent has proven to be highly efficacious. He supported this with the work of Goldstein et al¹¹⁰ in which though, 84% of men had improved function following treatment with sildenafil, they achieved a fully rigid erection only four times per month. This is limiting for a couple and may therefore not be enough to maintain a satisfactory relationship.

9. Life style modification

9.1 Smoking and alcohol

According to Feldman et al,⁶ smoking doubles the risk of developing ED. Cigarette smoking increases the risk of death from CAD and according to Derling et al,¹¹¹ also the incidence of ED. Traditionally, alcohol has been associated with the capacity to lower serum cholesterol and therefore improve erectile function. Alcohol has a central sedating effect which may be over powering. It is also associated with lowered NO production.¹¹² Men who smoke and drink alcohol should be advised to cease smoking and alcohol consumption. The later may be restricted to a single daily drink, preferably, red wine which has been documented to improve NO production.

9.2 Regular exercise

Regular exercise is beneficial to all body tissues and organs particularly in healthy individuals. During exercise, the cardiac output, the chronotropic and inotropic activity of the heart increase and the circulation therefore becomes more rapid. The blood supply to different organs and tissues, particularly the heart and muscles, increase with remarkable improvement in tissue perfusion. A sedentary life style is three times as likely to lead to ED where as moderate physical activity reduces the risk of ED by two-thirds.¹¹³ The sheer stress of increase blood flow stimulates the production of NO, an effect which lasts for up to 2-7days with a magnitude in the order of fourfold.¹¹⁴ During penile erection, the increase in flow is more than this, implying a more increased production of NO. On this premise, some studies have shown improved erectile function in men with regular and frequent sexual activity.

Regular exercise also may help control weight gain, obesity, dyslipidimia and the metabolic syndrome. Reduction in weight in the already obese men may lead to regularization of testosterone concentration and correct the loss of libido often associated with ED in the obese. Men with ED should therefore be advised on regular physical exercise and sexual activity.

9.3 Modification of diet

Diet has a profound effect on the general well being and it is part of general healthy living that men should be mindful of what they eat. Diet modification can help control weight gain, glucose level in diabetes and cholesterol level in dyslipidemic men. When combined with regular exercise, the effect may be synergistic with remarkable weight loss and it has been documented that about one-third of obese men with ED are able to improve sexual function through life style changes.¹¹⁵ Dietary modification should involve the services of a trained dietician who should set a target from the beginning, bearing in mind existing co-morbidities and the age of the patients.

9.4 Principles of medical treatment

The medical treatment for erectile dysfunction complicating CVS risk factors and disease should necessarily include treating for the underlying risk factors¹⁰⁷. These include the control of hypertension, diabetes mellitus, dyslipidemia, heart failure and coronary artery disease. Although this therapeutic approach, according to Tikkanen et al¹¹⁶, appears justified, relatively few intervention studies have investigated the effect of risk factor reduction on established ED. However, in the work by Saltzman et al¹¹⁷, artovastatin treatment of men with hyperlipidemia as the only risk factor, for instance, led to an improvement in erectile function. The medical treatment of these risk factors is beyond this chapter but a few guiding principles need to be explained.

Route of Administration	Drugs Used
1. Oral	a. Phosphodiesterase 5 inhibitors 1. Sildenafil 2. Vardanefil 3. Tadalafil b. Peripheral alpha 1 blockers 1. Phentolamine Mesylate c. Central Alpha2 antagonist 1. Yohimbine d. Dopamine agonists 1. Apomorpine
2. Intra-Urethral	a. Direct smooth muscle relaxant 1. Aprostadil (PGEI)
3. Intra-cavernosal (injectable)	a. Phosphodiesterase Inhibitor 1. Papaverine b. Peripheral alpha 1 blocker 1. Phentolamine c. Direct smooth muscle relaxant 1. Aprostadil (PGEI) 2. Vaso-active intestinal peptide (VIP).

Table 8. Summary of Drugs used in Pharmacotherapy for ED

There are conflicting reports on the effects of the drugs used for specific therapy of these risk factors and disease on ED. Statins have been reported to improve erectile function due to their positive effect on endothelial function.¹¹⁸ There are however observational reports associating statin use with ED.¹¹⁹ Diuretics, calcium channel blockers and beta blockers used for the treatment of hypertension and digoxin used for heart-failure have all been reportedly linked with ED. The preliminary report of the telmisartan alone, and in combination with ramipril global end point trial/telmisartan randomized assessment study in ACE-intolerant subjects with cardiovascular Disease (CONTARGET/TRANCEND) study⁷⁶ shows that calcium channel blockers tend to have a significant adverse effect on erectile function while treatment with beta blockers, diuretics, ACE inhibitors, ATI antagonist and alpha antagonist do not. Treatment with ACE inhibitors, ATI antagonist or a combination of both is suggested to improve erectile function in cardiovascular high risk patients. Based on this premise, the treating physician is advised to document the base-line erectile function at the commencement of treatment as subsequent development of ED is often quoted as responsible for non compliance by the affected men who may wish to maintain their potency. In the course of treatment, these men should be questioned directly about erectile function, and if this wanes or the patients complain, the drugs should be withdrawn. If erectile function returns, the drug/drugs can then be documented as the culprit and permanently withdrawn. This emphasizes the need for individualization of the management of these men.

Erectile dysfunction has social implications for the couple and any treatment regimen should necessarily take the female partner into consideration¹¹⁴. Some modalities of treatment may require the co-operation of the female partner due to their psychosocial and medical side effects which may be distressful to the couple. For instance, apomorphine may cause nausea and or vomiting sometimes necessitating the use of anti-emetics. Table 8 shows some of the drugs for the treatment of ED, their mode of administration and some of their side effects. Also, the use of phosphodiesterase 5 inhibitors is associated with diverse reaction which may threaten life.

9.5 Treatment of ED in CAD and HF patients; Use of PDE 5 inhibitors

The development and approval for use of the phosphodiesterase 5 inhibitors has revolutionized the treatment of erectile dysfunction, but this is not without short-comings especially in men with HF and CAD. The main stay of the treatment of CAD is the use of nitrates which dilate the coronary arterial bed. The active factor in the nitrates is the nitric-oxide which it releases and which is also the endothelium dependent vasodilator and neurotransmitter mostly responsible for penile erection in man. The phosphodiesterase 5 inhibitors inhibit the breakdown of nitric oxide, an action which potentiates that of the nitrates used for the treatment of CAD.

Patients with heart disease have a reduced exercise tolerance because of which there is need to assess and advise them on fitness to undergo sexual activity. They should be stratified into low risk, intermediate risk and high risk based on the presence and number of risk factors, angina, previous MI and their New York Heart Association classification status¹²¹. The amount of energy required for sexual activity has been shown to be about 20-40 metabolic equivalent of the tasks which is equivalent to doing easy house hood work or climbing a flight of stairs. This should guide the physician in advising patients with heart

failure provided that aortic stenosis and obstructive valvular cardiomyopathy have been excluded.

Opinions are varied as to whether the phosphodiesterase 5 inhibitors should be used in patients who have coronary artery disease and concomitant erectile dysfunction. According to George et al¹²¹, on the basis of the pharmacokinetic profile of sildenafil for instance, the co-administration of a nitrate within the first 24 hours is likely to produce a severe, potentially, life threatening hypotensive response and it is therefore contradicted. However, Parker et al¹²² insist in their work that though contradicted, there are occasions when a patient who has recently taken a phosphodiesterase 5 inhibitor might need intravenous nitroglycerin treatment with the proviso that such patients should be closely monitored and should have stable CAD. In the work by Webb et al,¹²³ when sublingual nitroglycerin was administered, there was a fourfold decrease in systolic blood pressure in patients with sildenafil treatment. Their conclusion was that sildenafil potentiated the hypotensive effect of nitrates and their concomitant use was absolutely contra indicated. According to Velasquez et al¹²⁴ adverse cardiac event associated to sildenafil use, for instance, include MI, angina, ventricular tachycardia and death. Therefore, the use of phosphodiesterase 5 inhibitors and nitrates in men with ED and concomitant CAD should be done with caution, individualized and in consultation between the physician and Urologist in order to optimize care.

10. Surgical treatment

Surgical treatment of ED has been relegated to the background as the last option with the advent of effective medical therapy. The main-stay of surgical treatment includes the use of penile implants and penile arterial revascularization procedures.¹²⁵ Infection is a major setback in the use of penile implants particularly in DM. Penile revascularization procedures may be complicated by numbness of the glans and penile skin, defeating the aim of the surgery. Penile venous surgery is presently considered historical.

11. Use of vacuum erection devices

These devices induce erection by increasing corporal perfusion and or impeding venous return.¹²⁶ Their efficacy profile is good but non compliance by patients is high due to difficulty with operating them and the associated ejaculatory problems. In truth, vacuum erection devices cause a hinged erection and the penis is rather truly not rigid.

12. Conclusion

Endothelial dysfunction and atherosclerosis are the pathways through which cardiovascular risk factors predispose to coronary artery disease, stroke and erectile dysfunction, the ED occurring earlier because of the small size of the pudendal artery which supplies the cavernous bed. As atherosclerosis is a progressive and dynamic disease, larger vessels are eventually involved and this often includes the coronary artery with the development of CAD. ED is presently regarded as a sentinel event for CAD and patients who present with ED with no other risk factors should be evaluated for silent CAD. The drugs used for the treatment of CVS risk factors may have ED as side effect and patients should therefore be questioned directly for the occurrence of ED. The concomitant use of nitrates and phosphodiesterase 5 inhibitors calls for caution.

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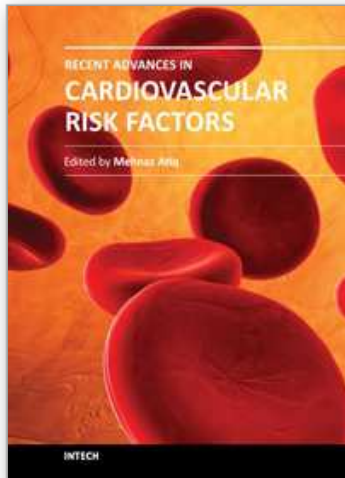
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Recent Advances in Cardiovascular Risk Factors

Edited by Prof. Mehnaz Atiq

ISBN 978-953-51-0321-9

Hard cover, 522 pages

Publisher InTech

Published online 21, March, 2012

Published in print edition March, 2012

Among the non-communicable diseases, cardiovascular disorders are the leading cause of morbidity and mortality in both the developed and the developing countries. The spectrum of risk factors is wide and their understanding is imperative to prevent the first and recurrent episodes of myocardial infarction, stroke or peripheral vascular disease which may prove fatal or disabling. This book has tried to present an update on risk factors incorporating new research which has thrown more light on the existing knowledge. It has also tried to highlight regional diversity addressing such issues. It will hopefully be resourceful to the cardiologists, general practitioners, family physicians, researchers, graduate students committed to cardiovascular risk prevention.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Irekpita Eshiobo, Emeka Kesieme and Taofik Salami (2012). Erectile Dysfunction Complicating Cardiovascular Risk Factors and Disease, Recent Advances in Cardiovascular Risk Factors, Prof. Mehnaz Atiq (Ed.), ISBN: 978-953-51-0321-9, InTech, Available from: <http://www.intechopen.com/books/recent-advances-in-cardiovascular-risk-factors/erectile-dysfunction-complicating-cardiovascular-risk-factors-and-disease->

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