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PERSPECTIVE

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Erectile dysfunction and testosterone deficiency as cardiovascular risk factors?

Summary

Graham Jackson introduced the concept that erectile dysfunction was a marker for undiagnosed cardiovascular disease and future events. Unfortunately this had had modest impact on CVD management as ED is not incorporated into current risk calculators. In this paper, we examine recent evidence as to whether ED should be upgraded to a risk factor, especially with the high predictive value in younger men. In the Princeton 3 guidelines, he recognised the important impact of testosterone deficiency (TD) on all-cause and cardiovascular mortality. Recent evidence suggests that testosterone therapy to target levels and for sufficient duration, reduces cardiovascular events. In this paper, we also produce a case for testosterone deficiency to be considered as an independent risk factor. The evidence for inclusion of both ED and TD may now be stronger than accepted risk factors and have the advantages of being easily assessed, being quantitative, symptomatic and clinically relevant, especially in younger men.

1 | INTRODUCTION

A risk factor is any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury. Some examples of the more important risk factors are overweight, unsafe sex, high blood pressure, tobacco and alcohol consumption, and unsafe water, sanitation and hygiene.

One of the most important areas of medical research is the identification of risk factors for specific disorders. Such research is usually aimed at discovering new causes of a disease, but risk factors can also be used as screening tests. A risk factor must be very strongly associated with a disorder if it is to be a worthwhile screening test.

2 | CORRELATION AS DISTINCT FROM CAUSATION

Risk factors or determinants are correlational and not necessarily causal, because correlation does not prove causation. For example, being young cannot be said to cause childhood infections, but young people have a higher rate of childhood infections because they are less likely to have developed immunity by previous exposure. Statistical methods are frequently used to assess the strength of an association and to provide causal evidence (eg in the study of the link between smoking and lung cancer). Statistical analysis along with the biological sciences can establish that risk factors are causal. The term risk factor has been used to describe causal determinants of increased rates of disease, and for unproven links to be called possible risks, associations.[1]

Risk factors are determined by research descriptions, and identification of risk factors can be a strategy for medical screening.

To be a worthwhile screening test, a risk factor must be strongly associated with a disorder.

The strength of association between a risk factor and a disorder can be quantified by the relative risk or relative odds (odds ratio).

A risk factor can also be considered as a screening test, and its association with the disorder can be quantified as the detection rate for a specified false-positive rate.

There is a direct numerical equivalence between the relative odds and the detection rate for specified false-positive rate that does not depend on the incidence or prevalence.

A risk marker is a variable that is quantitatively associated with a disease or other outcome, but direct alteration of the risk marker does not necessarily alter the risk of the outcome. For example, driving-while-intoxicated (DWI) history is a risk marker for pilots as epidemiologic studies indicate that pilots with a DWI history are significantly more likely than their counterparts without a DWI history to be involved in aviation crashes.[2,3]

While risk factors are those antecedents that are thought to have a causal role in the development of the disorder, risk markers are biological or neuropsychological traits that indicate a genetic tendency towards developing the illness. Thus, a risk marker can be thought of as a form of risk factor that is not causal.

The concept of risk factors for CVD and their modification was introduced by the authors of the Framingham Heart study [4] and further developed by the INTERHEART Study.[4] The authors suggested that a large body of epidemiologic studies has clearly demonstrated a link between certain risk markers and CVD. These can be classified into 2 categories: (i) those that have been proven to be causal (risk factors), and (ii) those that show associations with CVD but for whom a cause and effect association is yet to be proven (risk markers). These markers could be classified as predisposing (eg obesity which may work through raising blood pressure, glucose and lipids) or direct (eg smoking).[4]

However, the utility of a risk factor for practical application must be based on sound clinical judgement, not simply statistical tests. Risk factor assessments are useful only to the extent that they affect therapeutic decision making. That should remain the keystone for decisions

regarding the utility of newly defined risk factors. A marker may become a recognised risk factor in part because of the ease with which it is measured.[1]

The importance of this distinction is that risk factors tend to form the basis of health screening and markers do not. Papers frequently refer to "risk factor modification" but rarely to "risk marker modification".

3 | THE ACCEPTED MODIFIABLE RISK FACTORS AND MARKERS FOR CVD

The INTERHEART study[5] defined the following as causal risk factors for CVD:

- Tobacco consumption
- Elevated LDL
- Reduced HDL
- High blood pressure
- Elevated blood glucose
- Physical inactivity
- Obesity
- Diet

Factors 6-8 were clarified as "predisposing risk factors" as they work, at least in part through other risk factors that work directly. The important point is that despite being "predisposing" and difficult to quantify, especially in the case of diet, these factors form vitally important components of cardiovascular risk modification programmes and risk calculators.

Smoking, high blood pressure, diabetes, physical inactivity, overweight/obesity and dyslipidaemia are described as *modifiable* risk factors where there is evidence from clinical trials that altering the risk factor impacts on the subsequent incidence or severity of CVD.

Risk factors that show associations include low socioeconomic status, elevated prothrombotic factors such as fibrinogen and PAI-1, markers of infection and inflammation, elevated homocysteine, elevated lipoprotein (a) and a number of imprecise "psychological factors".

4 | CONVENTIONAL RISK ASSESSMENT AND MANAGEMENT IN PRIMARY CARE

In the UK, GPs opportunistically screen men for cardiovascular risk, during ad hoc consultations or at contracted over 40 medicals. Assessment tools have developed from Framingham Score,[4] through Q risk [6] and now JBS3 (Figure 2).[7] The concept of JBS3 is that the patient becomes involved in the consultation, as heart age and healthy life expectancy are calculated based on the current acknowledged modifiable risk factors using an interactive tool. By inputting the impact of proposed interventions, the patient can see the potential improvements in heart age. JBS3 unfortunately contains no questions about ED; however, it is highlighted in the ESC guidelines 2016.[8]

Matthew is 42 and has not seen a doctor for 22 years. He has become tired and lethargic and has given up physical activity, for over 5 years because of reduced strength and endurance. He is now longer engaging in any sort of physical activity. He feels tired at work as a factory worker and often needs to sleep in the afternoon. He falls asleep easily and has not initiated sex for 3 years and has lost his morning erections.

5 | ERECTILE DYSFUNCTION, A RISK FACTOR RATHER THAN A RISK MARKER—THE CLINICAL EVIDENCE

Erectile dysfunction, defined as the consistent inability to reach and maintain an erection satisfactory for sexual activity, is common, affecting almost 40% of men >40 years of age (with varying degrees of severity), and increasing in frequency with age. ED and CVD share common risk factors, including age, hypercholesterolaemia, hypertension, insulin resistance and DM, smoking, obesity, metabolic syndrome, sedentary lifestyle and depression. CVD and ED also share a common pathophysiological basis of aetiology and progression.[9]

Graham Jackson was the first cardiologist to describe the links between ED and subsequent cardiovascular events.[10] Meta-analyses of studies involving 36, 744 subjects concluded that the odds ratio for CVD in men with ED vs matched controls is 1.48, 1.35 for stroke and 1.19 for all-cause mortality.[11] ED has been shown to predict CV events over the next 3-5 years and the severity of ED has been shown to be closely correlated with the atheromatous burden found at angiography.[12,13] The predictive value of incident ED has been shown to be particularly strong in men under 50, with the effect decreasing in older men.[12,14]

The European Male Ageing Study (EMAS) concluded that ED (and hypogonadism) independently predicted men at a significantly higher risk of early death.[12] A prospective population study of 95,038 men over 45 without prior CVD,[13] showed a RR of IHD of 1.6, PVD 1.92 but 8-fold for heart failure. Risk was closely related to increasing severity of ED. Subsequent hospital admissions were strongly related to incident ED and also closely related to ED severity with RR 1.71 for angina, 1.81 for chronic ischaemic heart disease and 4.4 for heart failure, associated with ED. Reduction in hospital admissions is regarded as a stronger argument for health economic benefit than reduced mortality.[15]

In men with T2DM, and no known CVD, the predictive value of incident ED for CVD was found to be stronger than hypertension, dyslipidaemia and microalbuminuria.[16]The predictive ability of ED is higher in younger ED patients despite the fact that the probability of ED increases with age, and it most likely identifies a group of patients with early CVD.

A positive response to a question on ED should result in the measurement of a morning testosterone level, in line with all published

European guidelines. In 2008, NICE included advice that" all men with type 2 diabetes should be asked annually about ED [17] and in 2013, ED was included in the Quality Outcome Framework for type 2 diabetes as an annual assessment standard, only to be removed in 2014, in the name of "simplification".[18]

The Princeton Consensus documents [9] underscored the fact that "a man with ED and no known cardiac disease should be considered a cardiac patient until proven otherwise". Inman et al. found a high predictive value of ED for subsequent CVD in younger men, otherwise potentially missed by conventional risk assessment.[17]

Despite what appears to be a strong evidence base, routine assessment of ED is still not part of routine medical management and excuses of "embarrassment" and lack of "education" are still used as justification for not routinely recoding data on ED.[18] The likely reasons is that terms like "sentinel marker with shared risk factors", "harbinger" or "barometer of health" are simply not strong enough to influence established practice and that only recognition as an independent or predisposing risk *factor* will change current practice.[19]

6 | ED AND CVD—EVIDENCE FOR CAUSATION AND THE IMPACT OF MODIFICATION?

Improvement in ED is achievable by lifestyle modification, drug therapy, sex therapy or a combination of all these interventions.[20,21] Davey Smith et al. first identified a link between sexual frequency and cardiovascular death,[22] subsequently confirmed in men with a without ED.[23,24] The Princeton 3 consensus described sexual activity as equivalent to 3-4 METS or walking a mile in 20 minutes, a level of activity associated with an expected small effect of CVD risk.[9] There is therefore considerable evidence that there are CV benefits from sexual activity that are lost in the presence of ED.[23,24] These studies also concluded that resuming sexual activity might be associated with enhanced relationship benefits that might equate to additional health benefit in terms of mood and well-being.[23,24]

Gazzaruzo [12] was the first to describe a potential reduction in cardiovascular events with PDE5is in men with T2DM and angiographically proven CAD. Anderson et al. [25] who followed up 5956 men (PDE5I prescribing at 22.8%) with T2DM over 6.9 years. A 31% reduction in all-cause mortality and 26% reduction in MI were reported. Incident MI rate was 8.5% in the non-PDE5i group v 5.2% in the PDE5i group ($P < .0001$) and mortality from incident MI was 40% lower.

Andersson et al. [26] followed up 43,415 men after first myocardial infarction for 5 years and found significant reduction in all-cause and cardiovascular mortality and 30% reduction in new diagnosis in heart failure and related admissions, in men prescribed PDE5 inhibitors. The benefits appeared dose related and were not seen with other ED therapies.

These results were confirmed by Hackett et al[27] in 857 men with T2DM, 4-year mortality rate was 14.7% in the non-PDE5i group and 1.7% in the PDE5i group (OR 0.25 $P = .0007$), with greatest benefit seen in older patients. The authors suggested the urgent need for a RCT of daily dosing of PDE5i for cardio-prevention. PDE5is, already licensed to treat LUTS/BPH and Pulmonary Hypertension, have been shown to have benefits on endothelial dysfunction,[28] heart failure,[29] renal disease [30] and even cancer prevention.[31]

7 | LOW TESTOSTERONE, A RISK FACTOR OR RISK MARKER—THE CLINICAL IMPORTANCE

Evidence has emerged over the last 20 years that ED and TD are important predictors of increased cardiovascular risk but while ED is widely accepted as a "marker", the position of TD remains controversial.[32-34] Recent evidence demonstrates that ED and TD may be useful and relevant in terms of early diagnosis of CVD and effective management to target risk reduction.[32]

The Princeton 3 guidelines,[9] highlighted that measurement of testosterone was mandatory in all men with ED and suggested that TT was an independent marker for future CV events. Multiple long-term longitudinal studies have shown that low TT and FT is associated with increased cardiovascular and all-cause mortality,[33-36] after adjusting for other CV risk factors,[35,36] especially in men with preexisting metabolic disease and T2DM.[37] Five-year follow-up from the EMAS study concluded that ED and low TT independently predicted mortality and that men with both conditions were at particularly high risk.[32]

Several longitudinal studies have shown that low levels of TT and FT independently predict the later development of T2DM.[38,39] Holmboe et al.[40] reported on 5250 men from the Danish population followed up for 29 years and showed that low TT and low SHBG were strongly associated with incident T2DM. As there was no effect of LH, the authors concluded that *primary hypogonadism* was not a risk *factor* for T2DM but that low TT should be considered a risk *marker* for T2DM. As EMAS[41] found a prevalence of primary HG of 2% and secondary HG of 11%, a logical conclusion might be that secondary HG might be at risk factor for T2DM or a predisposing CV risk factor as it would be increasing the risk of an established risk factor. As there were no data on T therapy reported by Holmboe et al,[40] a causal relationship could not be established. Recently meta-analyses have reported the positive impact of T therapy on insulin resistance and glycaemic control in men with diabetes and metabolic disease (Figure 3).[37] Six well-conducted studies have evaluated patients properly diagnosed and treated to target levels for sufficient duration.[26,27,42–45]

A prospective study of 587 men with T2DM involved 5.8 years of follow-up.[42] Low testosterone was defined as TT <10.4 nmol/L. Fifty-eight men were treated with testosterone for 2 years or more. The mortality rate was 20% in the untreated group and 9.1% in the normal group independent of comorbidities and therapies. Mortality was 8.6% in the treated group. A similar retrospective USA study involved 1031 hypogonadal men, with 372 on T therapy. The cumulative mortality was 21% in the untreated group vs 10% in the treated group, with the greatest effect in younger men and those with T2DM.[43] Both papers were criticised for possible selection bias, but strengths were reliable pretreatment diagnosis and accurate reporting of medications.

Hackett et al followed up 857 men with T2DM for 4 years following baseline testosterone measurement. Patients had been randomised to long-acting testosterone undecanoate (TU) or placebo assessment during a randomised controlled study. The investigators confirmed that low baseline TT and FT were associated with increased all-cause mortality over 4 years of follow-up. They reported that T therapy and the use of phosphodiesterase 5 inhibitors (PDE5is) were independently associated with reduced all-cause mortality, with greatest benefit from both T therapy and PDE5is being seen in older men.[27]

Anderson et al[44] searched electronic medical records between 1996 and 2011 to identify 5695 men who had a low initial TT level, a subsequent testosterone level, and >3 years of follow-up. Levels were correlated with testosterone supplement use. Primary outcomes were a composite of death, non-fatal MI and stroke, major adverse cardiovascular events (MACE) and death alone. T therapy in men with low testosterone was associated with reduced MACE and death over 3 years compared with no or ineffective supplementation. This study suggested that the favourable impact of T therapy was predominantly on mortality, rather than number of events, and benefits were associated with achieving therapeutic levels of testosterone, defined as a range between 212 and 742 ng/dl with no suggestion of increased risk with sustained higher serum levels. The same study showed significant reduction in cardiovascular events in a cohort of hypogonadal men with angiographically diagnosed coronary artery disease.

Sharma et al[45] retrospectively evaluated 83 010 male veterans with documented low TT levels. The subjects were categorised into 3 groups: T therapy with resulting normalisation of TT levels (group 1), defined as the lower limit of the laboratory reference range; T therapy without normalisation of TT levels (group 2); and did not receive T therapy (group 3). The all-cause mortality (HR 0.53, 95% CI 0.50–0.55), risk of MI (HR 0.82, 95% CI0.71–0.95) and stroke (HR 0.70, 95% CI 0.51–0.96) were significantly lower in group 1 vs group 2 (n = 25 701, median age 66 years, mean follow-up 4.6 years).

Wallis et al.[46] reported a 5-year follow-up of 10 311 men on long-term T replacement compared with a 28 029 control group and found a decreased risk in all-cause mortality (HR 0.67 95% CI 0.62-0,73), cardiovascular events (HR 0.84 95% CI 0.72-0.98) and new cases of prostate cancer (HR 0.60 95% CI 0.45-0.80) after treatment for 12 months or longer. There appeared to be slight increased risk of CV events in the first 6 months that could have been related to increased risk caused by low T before patients reached therapeutic targets.

These longitudinal studies suggest that T therapy is associated with a reduction in all-cause and cardiovascular mortality in men with clearly defined HG treated for sufficient duration (>1 year) to the mid-upper normal range.

Recently, Budoff et al[47] reported a cohort of 170 men from the T trial with 138 completing the 12 month study and available for the primary analysis. The mean (SD) age was 71.2 (5.7) years. At baseline, 70 men (50.7%) had a coronary artery calcification score higher than 300 Agatston units, reflecting severe atherosclerosis. For the primary outcome, testosterone treatment compared with placebo was associated with a significantly greater increase in non-calcified plaque volume from baseline to 12 months (204 to 232 mm^3 vs 317to 325 mm^3, respectively; estimated difference, 41 mm^3; 95% CI, 14 to 67 mm^3; P = .003). For the secondary outcomes, the median total plaque volume increased from baseline to 12 months from 272 mm^3 to 318 mm^3 in the testosterone group vs from 499 to 541 mm^3 in the placebo group (estimated difference, 47 mm^3; 95% CI, 13 to 80 mm^3; P = .006), and the median coronary artery calcification score decreased from 255 to 244 Agatston units and increased in the testosterone group vs 494 to 503 Agatston units in the placebo group (estimated difference, −27 Agatston units; 95% CI, −80 to 26 Agatston units). There are several issues with this study. There was a greater than 50% difference in baseline plaque burden suggesting that these were not equivalent groups and that the changes observed might reflect normal patterns with differing degrees of atheroma. The coronary calcium score improved on testosterone and worsened on placebo. Most importantly it is unlikely that a discovery of severe coronary atheroma in 50% of men was not associated with a single intervention or medication change over a 12-month period.

8 | WHAT THIS MEANS FOR PATIENTS—THE CASE OF MATTHEW

How would the recognition of ED and low T work when integrated into current screening regimes?

His wife Tracy is concerned and makes an appointment for him to have an over-40 medical check. He sees his GP, who takes his history but does not ask about his erections or sexual function. Matthew is too embarrassed to raise the issue as his doctor is running late and seems stressed. Some routine measurements and blood tests are arranged.

Matthew—results

- Weight 110 Kg, BMI 34 kg/m^2. Total Cholesterol 6.6 LDL-Cholesterol 5.4.
- HDL-cholesterol 0.95 mmol/L TGs 2.78 mmol/L. IFCC 45%. HbA1c 6.4%.
- The data used in the JBS3 calculator (Figure 1) confirm that he has a heart age 50 with a 4.7% 10 year risk of a cardiovascular event. He has metabolic syndrome and prediabetes. An exercise and dietary regime is advised with follow-up in 3 months. Matthew returns home and tells his wife that the doctor said that he is “overweight”, but his heart is not too bad.
- Matthew decides not to attend for the follow-up visit.

Had the GP asked about his erections, she would have found that he had severe ED with a SHIM score of 7. This would have led to mandatory measurement of his testosterone level which would have shown a level of 7.2 nmol/L with SHBG 19 nmol/L. LH 2.0 iu/L. This would have led to the recognition that his multiple symptoms were because of testosterone deficiency. Had he been offered a symptom questionnaire, an Aging male Symptoms Score of 63 would have confirmed that

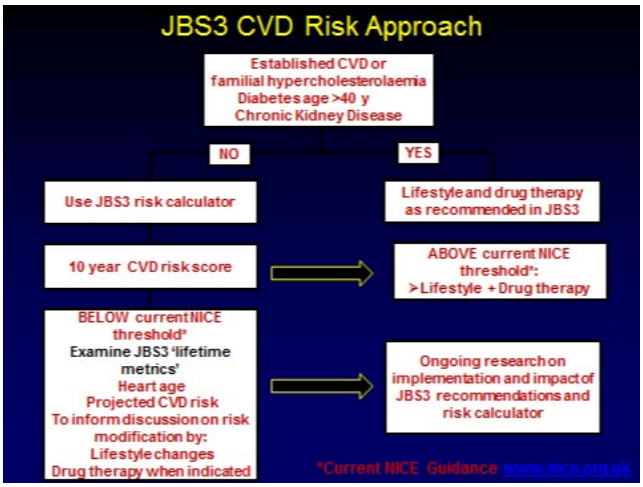

FIGURE 1 The use of the JBS3 risk calculator in primary care

he had symptomatic hypogonadism. Traditional teaching that men such as Matthew should be managed by weight loss in the first instance, has been challenged by a recent RCT showing that men treated with diet alone lose lean substantial lean muscle mass compared with men treated with diet plus testosterone.[46] Preservation of lean muscle is an important component in cardiovascular performance and in the prevention of frailty in ageing men (Figure 2).[48-50] As loss of physical strength was a major complaint, the optimal treatment for Matthew would be lifestyle advice, testosterone therapy plus a PDE5 inhibitor and a statin, as the presence of ED increases risk by 50%.[51,52] Recognition and treatment of his ED would also guarantee attendance at follow-up medical assessments.

9 | CONCLUSIONS

The Princeton Guidelines remind us that "A man with ED and no known CVD is a cardiac patient until proven otherwise" and the case of Matthew demonstrates precisely this point.[9] The Olmsted Country study showed that younger men with ED and no prior CVD could have up to 50-fold additional risk [14] and EMAS concluded that "detecting ED and low testosterone in younger men without known CVD detects a group of men at particularly high risk of early death".[32] In addition, we know that conventional risk calculators are of less value in younger men.[9,11,50-54] Such patients may be candidates for Coronary Calcium Scoring and or CT angiography (Figure 3).[53,54] These reviews concluded that ED was associated with shared risk factors for CVD, but highlighted the practical importance of ED in cardiovascular assessment. The reality is that little has changed in everyday practice despite the acceptance of ED as a "marker" of increased risk. We believe that recent evidence from 3 longitudinal studies concluding that treating

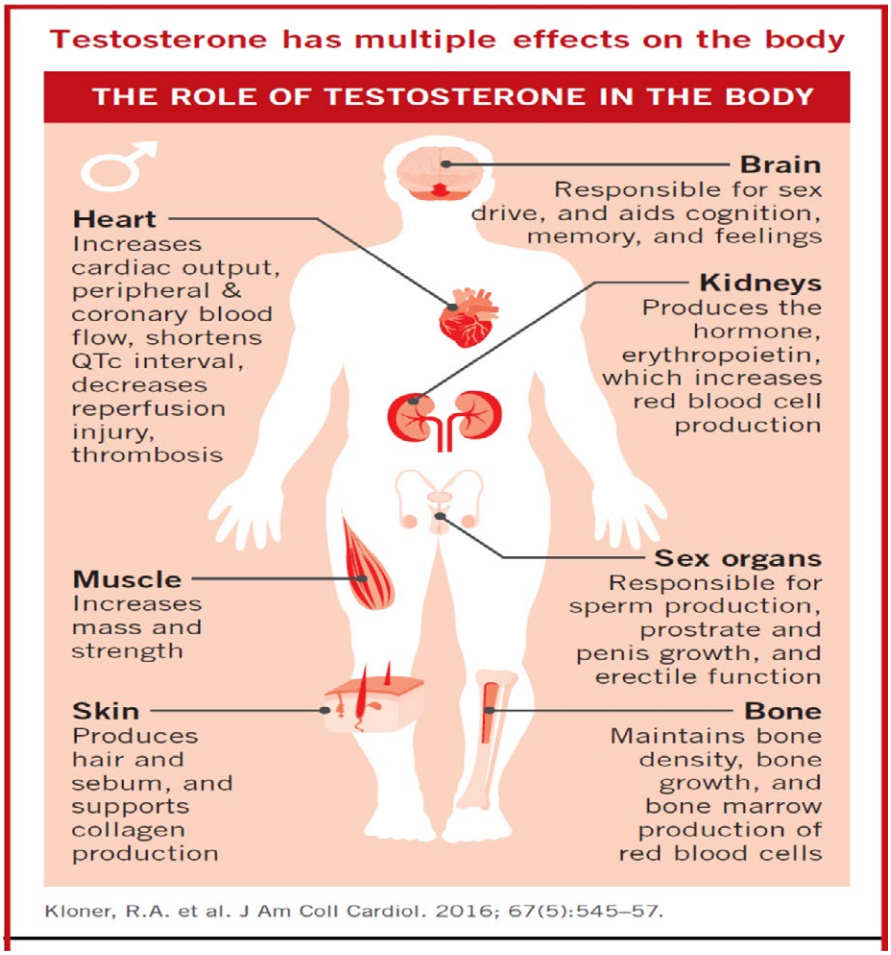

FIGURE 2 The pleomorphic effects of testosterone on cardiovascular risk and frailty

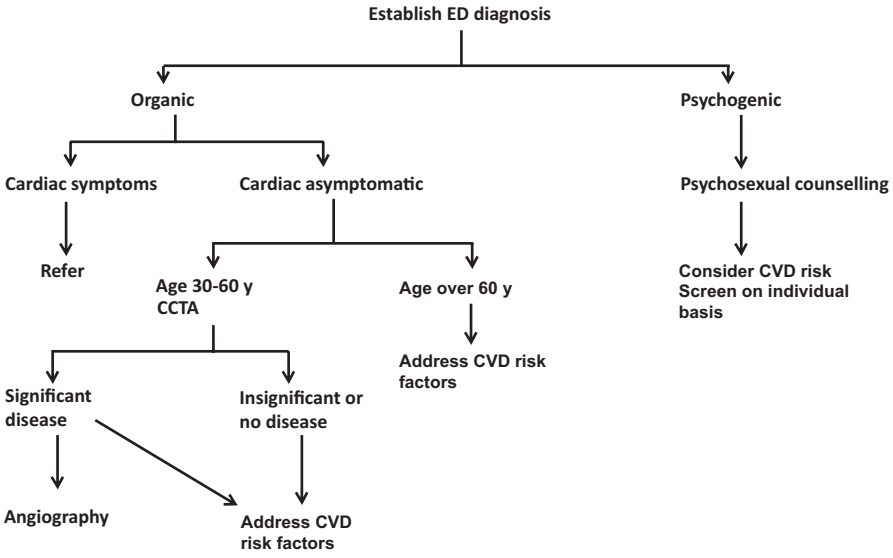

FIGURE 3 Algorithm for cardiovascular risk demonstrating the high predictive value of ED especially in younger men (Jackson et al. Ref. [51])

ED with PDE5is reduces cardiovascular and all-cause mortality should lead to a re-evaluation of this position.

In the case of testosterone deficiency, the associations with CVD and all-cause mortality is strong and the argument for causality now seems much more convincing than even 5 years ago.

Now that ED guidelines advise mandatory measurement of testosterone in all men with ED, the co-administration of ED therapy and testosterone has become common practice where T deficiency is found in men with ED, particularly with poor response to PDE5is.[51] There may be issues around the inclusion of single gender "risk factors", but there are already adjustments in place for metabolic syndrome criteria, waist circumference and alcohol variations between men and women.[5,52]

For risk reduction programmes to be practical, consideration should be given to factors that are *relevant*, *easily assessed* and *measured*, be *quantifiable* and be *modifiable*. There is now strong evidence that both ED and testosterone deficiency fulfil these criteria and that both should, at the very least, now be considered as *predisposing risk factors* for cardiovascular disease. ED and low testosterone are symptomatic conditions that patients would expect to be fully assessed and treated. Motivation to comply with ED and T therapy is relatively high, in contrast with other risk factors modification regimes. The reality is that, unless risk "markers" are not reclassified as "risk factors" then they will not be seen as relevant in every day practice. These issues are particularly important in younger men where current risk calculators are of less value.

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