**Strategies for primary prevention of cardiovascular diseases in adults with type 2 diabetes mellitus: role of cardiac troponin**

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**Abstract**

People with type 2 diabetes mellitus (T2DM) have two- to four-fold increased cardiovascular mortality in comparison to the general population. With the identification of new therapeutic targets and hypoglycemic drugs for T2DM, the need of a better stratification of CVD risk has emerged to select patients who may need intensive or specific treatment. At present, risk stratification is based on clinical, demographic and biochemical factors. High sensitivity cardiac troponin (hs-cTn) increases after several ischemic and non-ischemic insults and it is considered a marker of myocardial injury. This review summarizes the main findings about hs-cTn utilization for risk stratification in people with T2DM and no clinical CVD. Several large observational studies have documented the association between hs-cTn and adverse cardiovascular outcomes in both the general population and in patients with T2DM. Lifestyle interventions, and particularly promotion of physical activity and adoption of healthy nutritional habits, have been associated to a significant benefit on hs-cTn release in the general population. Randomized controlled trials suggested that hypoglycemic, anti-hypertensive and lipid-lowering therapy may influence the degree of T2DM-induced cardiac injury. Besides these promising findings, the efficacy of an hs-cTn-based approach for CVD prevention in T2DM patients still requires more investigations.

**Keywords:** Diabetes Mellitus; Troponin; Cardiovascular Diseases; Risk Factors; Biomarkers; Primary Prevention

## 1. Introduction

Cardiovascular diseases (CVD) are the main cause of mortality in people with type 2 diabetes mellitus (T2DM), who have two- to four-fold increased cardiovascular mortality when compared with the general population [1]. In clinical practice, T2DM is considered as a "coronary heart disease equivalent", meaning that it is a risk factor for Coronary Heart Disease (CHD) of the same magnitude of prior CHD itself [2, 3]. Controlling cardiovascular risk factors, such as dyslipidemia, hypertension, obesity, represents a milestone for the prevention of cardiovascular complications in people with T2DM. For this reason, it is recommended that people with T2DM, even if asymptomatic, undergo to annual physical examination to detect and manage cardiovascular risk factors [4].

The main cardiovascular complications in patients with T2DM are heart failure, with both preserved or reduced ejection fraction, and atherosclerotic vascular disease, namely coronary artery disease, atherosclerotic cerebrovascular disease and peripheral artery disease[5]. Although different mechanisms have been proposed to explain the onset of these conditions, hyperglycemia may be a common factor. The relationship between hyperglycemia and CVD is probably more complex than expected, being T2DM itself a risk factor for CVD. In addition, patients with Acute Myocardial Infarction (AMI) are at higher risk of developing T2DM in comparison to non-AMI patients, suggesting that a vicious loop may exist between vascular damage and T2DM-associated metabolic disturbances [6].

Overall, the management of T2DM includes both lifestyle modifications, being extremely effective for reducing metabolic imbalances and CVD risk, and pharmacological interventions that should consider clinical, demographic and psychological factors with a personalized, patient-centered approach [5, 7]. Primary prevention of CVD starts with the identification and management of modifiable risk factors such as overweight and obesity, hypertension, dyslipidemia, smoking habit, non-healthy diet. Basically, secondary prevention in patients with T2DM and known CVD consists in a switch toward intensive interventions from the ones used for primary prevention. In any case, management of hyperglycemia remains a milestone in the treatment of T2DM, and the choice of the antihyperglycemic therapy should consider if the patient has already experienced CVD. At this regard, the new drugs sodium- glucose co-trasporter 2 (SGLT-2) inhibitors

and glucagon-like peptide 1 (GLP-1) receptor agonists are effective in reducing glycemia with demonstrated cardiovascular benefit [8-10]. At the same time, the need of a better stratification of CVD risk has emerged to select patients who need intensive or specific treatment. For example, the reduction of estimated glomerular filtration rate (eGFR) and the occurrence of albuminuria, biomarkers of hyperglycemia-associated microvascular alterations, have emerged as important risk factors for macrovascular disease and they are commonly used to identify patients that could specifically benefit from the therapy with SGLT-2 inhibitors, recently associated to renoprotective effects [9]. Similarly, it has been speculated that other biomarkers may be useful to discriminate patients at high CVD risk needing intensive treatment in order to reduce mortality. Specifically, cardiac biomarkers, such as cardiac troponin, represent an inexpensive (if compared with other diagnostic tests such as imaging), and non-invasive way to detect vascular and/or cardiac damage underlying subclinical cardiovascular diseases.

**2. Biochemical features of cardiac troponins**

Troponins are small proteins expressed in striated and cardiac muscle that participate to muscle contraction by the interaction with tropomyosin and actin. The molecular complex of troponins is composed by three isoforms, troponin I, troponin T, and troponin C, forming together a functional and structural unit. When low concentration of $Ca^{++}$ is present in the cardiomyocyte, troponin I interacts with actin inhibiting ATPase. When $Ca^{++}$ is released in cytoplasm of cardiomyocytes to promote contraction, troponin C binds $Ca^{++}$ inducing a conformational change of the troponin complex that brings troponin T nearby tropomyosin. When troponin T binds tropomyosyn, the latter is stretched leaving specific site of actin free for the interaction with myosin, a key event of muscle contraction [11]. Overall, troponin I inhibits contraction when $Ca^{++}$ concentration is low; troponin C binds $Ca^{++}$ when contraction is required; troponin T binds tropomyosin allowing the exposure of actin for its interaction with myosin. Myocardiocytes express specific isoforms of troponin T and troponin I, making them myocardium-specific biomarkers [11].

Several mechanisms of protein release from myocardiocytes have been described in relation to different pathophysiological processes. Only a small proportion of soluble troponin is present in cytoplasm, while the vast majority forms complexes on the thin filament of myocardial tissue. After a reversible stress, such as

after a strenuous physical exercise or a transient ischemia, a modest release of the soluble troponin pool can be observed, probably through apoptotic mechanisms and membrane blebbing [12]. When cellular stress became irreversible, such as after a prolonged ischemic insult, necrosis occurs, leading to the complete and uncontrolled release of the entire cellular content, including structural proteins such as troponin. Not only ischemia can lead to cellular necrosis. Indeed, several stimulus, both clinical and subclinical, can lead to myocardial injury and, thus, to the increase of circulating troponin [13-16]. Conceptually, every release of troponin, irrespective of the underlying pathophysiologic mechanism that has induced it, can document a myocardium injury. Nevertheless, the exact clinical implications of these events are to be clarified.

**3. High sensitivity assays**

Cardiac troponin has been the cornerstone for the diagnosis of Acute Coronary Syndromes (ACS) since 2000s, and particularly for identifying Acute Myocardial Infarction (AMI) and differentiating Non-ST elevation Myocardial Infarction (NSTEMI) from unstable angina or non-ACS conditions [17]. Nowadays, it is widely accepted that the increase of circulating troponin above the 99$^{th}$ percentile in patients with clinical symptoms of acute myocardial ischemia defines AMI, according to its fourth universal definition [18]. Moreover, troponin has a prognostic value being the magnitude of its increase associated to extension of cardiac necrotic area [19]. With the introduction of high sensitivity assays for the measurement of cardiac troponin in plasma (hs-cTn), its clinical use has been expanded behind the diagnosis of ACS. Firstly, in acute settings, hs-cTn allows a faster management of patients with suspected AMI referring to the Emergency Department, allowing a safe exclusion of AMI after just 1-2 hours from aT2DMission due to its high negative predictive value [20]. Secondly, a dynamic or stable increase of hs-cTn in absence of any clinical evidence of acute ischemia defines “myocardial injury”, introducing the concept that hs-cTn can effectively identify subclinical damage of myocardium reporting to clinicians useful pathological information [18]. An increase of hs-cTn above the reference limit can be observed in some chronic non-ACS-related conditions, including stable CHD and heart failure, T2DM, chronic kidney disease, cardiotoxicity of anticancer drugs [21]. At present, although the diffusion of hs-cTn is still far from being widespread, its routine use has been accepted in many medical institutions worldwide. hs-cTn detects very small amounts of circulating troponin

that were undetectable with previously available assays. Actually, some hs-cTn assays can measure troponin in 80-99% of healthy individuals with no clinical CVD, and hs-cTn increase has been associated to higher cardiovascular mortality in the general population [22, 23]. It means that hs-cTn may be used to stratify patients at risk of CVD with subclinical myocardial injury. Although several cardiac biomarkers have been proposed to detect myocardial injury, hs-cTn remain the most effective one for clinical applications [24-26].

In the last decades several assays fulfilling the definition of "high sensitivity" have been developed. According to this definition, the assay must assure a Coefficient of Variation (CV%) less than 10% at the concentration corresponding to the the 99$^{th}$ percentile of the distribution of cTn values measured in healthy individuals. Nevertheless, significant differences has been documented among available hs-cTn assays in terms of both analytical and diagnostic performances [27], leading to the proposal of a different definition of high sensitivity assay based on clinical performance instead of the analytical one [28]. At present, one hs-cTnT and several hs-cTnI assays are available for clinical diagnostic applications [29]. Although their clinical accuracy for the diagnosis of AMI is comparable [30], hs-cTnI assays seem more suitable for the detection of chronic subclinical cardiac injury, probably for their high analytical sensitivity [31].

**4. Mechanisms of cardiac troponin release in diabetes mellitus**

Chronic hyperglycemia has deleterious effects on myocardium [32]. Several mechanisms contribute to the chronic release of cardiac troponin (cTn) in patients with T2DM. Cardiac injury can arise from atherosclerotic coronary disease with subsequent reduction of blood flow in the cardiac tissue and hypoxia. The release of cTn into the bloodstream could be also the result of the direct cytotoxic effect of hyperglycemia on cardiac tissue, leading to necrosis of myocardiocytes and cardiac dysfunction. Moreover, chronic kidney disease, which is recognized as one of the main microvascular complication of T2DM, is associated to persistently increased hs-cTn concentrations [33], probably due to both reduced clearance of troponin by the kidney and increased cardiac release [34]. Overall, it seems reasonable that multiple mechanisms may act synergically increasing plasma hs-cTn in patients with T2DM.

Chronic hyperglycemia stimulates accelerated atherosclerosis through several pathways, including activation of the polyol pathway; synthesis of AGEs; activation of protein kinase C (PKC); activation of the hexosamine pathway with increased *N*-acetylglucosamine (O-GlcNAc); increased oxygen utilization and subsequent mithocondrial dysfunction (Figure 1). Some of these pathways converge on vascular production of Reactive Oxygen Species (ROS), which are considered important mediators of the pathological processes underlying accelerated atherosclerosis in T2DM. ROS arise in part from autoxidation of glucose, but also from an increased utilization of oxygen by mithocondrial electron transport chain, mithocondrial respiratory dysfunction and prolonged production of superoxide, which have been associated to cardiac damage and dysfunction. Also AGEs production and fatty acid oxidation, which are both increased in T2DM due to the excess of glucose and its metabolic utilization, contribute to the generation of ROS [35].

Chronic hyperglycemia activates the synthesis of methylglyoxal through the polyol pathway. Methylglyoxale is derived from the utilization of glucose by the glycolytic pathway and it is one of the most important precursor of AGEs, accounting for the majority of glycated adducts in tissues from patients with T2DM [36]. Some of these glycated adducts are used in clinical practice as biomarkers of chronic hyperglycemia, such as glycated hemoglobin (HbA1c) or glycated albumin [37, 38]. Nevertheless, the accumulation of AGEs in plasma and in vasculature has important pathological implications because it induces the synthesis of ROS which, in turn, activates the synthesis of pro-inflammatory cytokines, adhesion molecules, and LDL oxidation [39]. The utilization of glucose in excess leads to the accumulation of diacylglycerol (DAG), a glycolytic intermediate. DAG, together with ROS, is considered one of the main activator of PKC, which in turn modulates the activity of endothelial NO synthase (eNOS) promoting endothelial dysfunction [40]. eNOS activity is also reduced by post-translation modification by O-GlcNAcylation [41]. All these mechanisms participate to the atherosclerotic plaque formation and progression and, indirectly, can cause a reduction of oxygen supply to cardiac tissue with subsequent hypoxic damage and cellular necrosis.

Together with atherosclerotic vascular disease, T2DM is associated to morphological and functional changes of myocardium, defined “diabetic cardiomyopathy”. The clinical manifestation of diabetic cardiomyopathy is heart failure, which often represents the first clinical manifestation of cardiovascular complications in

patients with T2DM or coexists with atherosclerotic vascular disease. In animal models of "diabetic cardiomyopathy", accumulation of AGEs, ROS, pro-inflammatory cytokines and pro-fibrotic factors has been documented [42]. Moreover, altered $Ca^{++}$ homeostasis and $Ca^{++}$ reuptake in cardiomyocytes have been observed in animal models of T2DM, probably due to increased post-translational modification by oxidation and O-GlcNAcylation of proteins involved in these pathways [43]. Also cardiac lipotoxicity has been associated to cardiomyocytes apoptosis in T2DM [44]. Increased lipid accumulation has been observed in both animal models and human tissue from patients with T2DM and it involves not only triglycerides but also lipid metabolism intermediates such as ceramides and oxidized phospholipids [45]. Most of these pathways converge on cell death through apoptosis or necrosis. It is reasonable that both apoptosis and necrosis, independent of the stimulus that has induced them, may lead to the release of troponin in the bloodstream.

**5. Observational studies**

With the introduction of high sensitivity assays for cTn measurement, quantifying plasma cTn in individuals without AMI has become possible. Therefore, many clinical studies exploring the clinical significance of plasma cTn concentration in absence of any acute cardiac condition have been conducted. Overall, a large body of evidence has demonstrated that hs-cTn is an independent risk factor for CVD and mortality in the general population, supporting its introduction in clinical practice for the selection of individuals at high risk [23, 46-48]. Based on this evidence, the role of hs-cTn has been explored in other populations considered at high risk for CVD, including patients with T2DM.

The vast majority of people with T2DM but not clinically confirmed CHD, had coronary atherosclerosis, suggesting that T2DM may act as a trigger for the atherosclerotic process and may accelerate the progression of atherosclerotic lesions [49]. Tang *et al.* examined 1,275 patients with T2DM undergoing to coronary angiography and found that 22% of them had subclinical myocardial necrosis, defined by a hs-cTnI value above the limit of detection and below the diagnostic cut off for AMI [50]. Interestingly, patients with the highest hs-cTnI had a 3-years increased risk of all-cause mortality, non-fatal MI or stroke independent of glycemic control, supporting a role of hs-cTnI for stratifying patients with T2DM requiring intensive

interventions for CVD prevention. A sub-analysis of the Atherosclerosis Risk in Communities (ARIC) study including almost 10,000 individuals without clinically evident CHD or heart failure, demonstrated that HbA1c was correlated to hs-cTnT [32]. This association remained significant also after the adjustment for the main cardiovascular risk factors and when it was restricted to patients with T2DM, confirming that chronic hyperglycemia was associated to a progressive myocardial injury in persons with no clinically relevant CHD. Nevertheless, these results could be underpowered by the limited percentage of individuals with detectable hs-cTnT (66.3%) included in the study. Subsequent prospective analyses conducted on a cohort from the ARIC population, demonstrated that persons with T2DM had higher incidence of high hs-cTnT (hs-cTnT>14 ng/L) than persons without, even after adjustment for cardiovascular risk factors [51]. Patients with incident high hs-cTnT and T2DM had also substantially increased risk of cardiovascular outcomes (heart failure, CHD) and all-cause mortality during a 6-years follow-up in comparison to persons with no incident hs-cTnT elevation and T2DM [51]. Again, in more than 1,500 individuals with T2DM and no prevalent CVD from the ARIC population, hs-cTnT improved the discriminatory ability of traditional risk factors for CVD, including ECG abnormalities and conventional complications of T2DM, to detect individuals at risk of CHD, heart failure or stroke over a median follow-up of about 13 years [52].

Taken together, these results showed that myocardial injury, also in absence of clinically relevant CVD, is associated to adverse cardiovascular outcomes and it can be effectively detected by non-invasive biochemical tests, such as hs-cTn.

The Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) study investigators found that in patients with T2DM and stable CHD with mild or no symptoms of angina, hs-cTnT was associated with increased mortality (both cardiovascular and all-causes), risk of AMI, stroke, and heart failure, even after adjustment for the main cardiovascular risk factors, confirming the role of myocardial injury, detected by hs-cTnT, for the stratification of patients with T2DM at high risk of adverse outcomes [53]. The BARI 2D study was originally designed for comparing the efficacy of prompt coronary revascularization plus intensive medical therapy versus intensive medical therapy alone and showed that no significant benefit arose from one approach in comparison with the other. In this ancillary study, the Authors

found that this lack of benefit was observed both in patients who had high hs-cTnT at baseline and in patients who didn't [53].

Similar results have arisen from a secondary analysis of the SAVOR-TIMI-53 study. In this subanalysis, patients with established CVD or multiple risk factors for vascular disease were included. Specifically, in 2,691 patients with risk factors only, high hs-cTnT identified persons at high risk of the composite primary outcome, namely cardiovascular death, AMI, hospitalization for heart failure, but not ischemic stroke, during a follow-up of 2 years [54].

In the Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection (ARTEMIS) study, a large prospective study including 1,243 patients with stable CHD, patients were stratified according to glucose metabolism impairment. The predictive value of several biomarkers, including hs-cTnT, high sensitivity C Reactive Protein (hsCRP), B-type natriuretic Peptide (BNP), and Galectin-3, was evaluated. The Authors found that in the group with T2DM hs-cTnT was the strongest predictor of the primary end-point, defined as cardiac death and hospitalization for congestive heart failure during the 2-year follow-up [55].

In a prospective observational study with a follow-up of about 12 years, hs-cTnT was an independent predictor of all-cause mortality and CVD in patients with type 1 diabetes mellitus and albuminuria, but this association was not replicated in patients without nephropathy [56]. Notably, in patients with no nephropathy hs-cTnT median value was close to the limit of detection of the assay, suggesting that the lack of association in that group could be partially explained by analytical issues. Hendriks *et al* evaluated the association between hs-cTnT and mortality in patients with T2DM stratifying the population study according to hs-cTnT levels. The Authors found that hs-cTnT was associated to both cardiovascular and all-cause mortality in a model adjusted for the main confounding factors, and the strength of this association was higher in the group of patients with the highest hs-cTnT values than in the other groups [57]. Interestingly, most of the studies in this field has evaluated hs-cTnT, while very few studies have focused on hs-cTnI and cardiovascular outcomes in persons with T2DM, especially in the setting of primary prevention. Given the higher sensitivity

of hs-cTnI assays in comparison to the hs-cTnT one, it is reasonable that more insights on the involvement of myocardial injury in persons with T2DM but asymptomatic for CVD may arise from such investigations.

Another important consideration that arises from the studies on myocardial injury in patients with T2DM is that frequently these patients have higher hs-cTn than those with no T2DM. Therefore, a large proportion of patients with T2DM, ranging from about 10 - 40%, has hs-cTn values above the diagnostic cutoff for AMI (Table 1). It means that hs-cTn concentrations in patients with T2DM presenting at Emergency Department with chest pain and suspected AMI should be considered with caution and the diagnostic cut-off used for the general population may be not appropriate in this specific population, making the diagnosis of AMI particularly challenging in these cases. For example, in the study of Rubin *et al*, in patients with T2DM the hs-cTnT 99$^{th}$ percentile was 54 ng/L [32], significantly higher than the value of 14 ng/L, the one proposed by the manufacturer and accepted in several clinical institutions where hs-cTnT is used for routine clinical applications. The appropriateness of common hs-cTn diagnostic cutoffs for AMI in patients with and without T2DM hasn't been investigated yet. It is reasonable that in patients with T2DM and acute chest pain the typically increasing/decreasing kinetics of hs-cTn release, hallmark of acute coronary conditions [18], may be particularly informative, especially when a high baseline value is observed.

**6. Lifestyle interventions**

Lifestyle interventions represent the first-line strategy to contain CVD risk factors in people with T2DM [7]. Basically, these interventions are focused on reducing body weight, controlling dyslipidemia and hypertension, reaching glycemic targets. The most powerful approaches are: i) promoting regular physical exercise; ii) adopting healthy nutritional habits through self-managed education and support. Overall, lifestyle interventions have been associated to a reduction of cardiac injury. Results from the Atherosclerosis Risk In Communities Study have documented that in individuals free form CVD at baseline, adoption of healthy lifestyle effectively reduced hs-TnT, supporting the efficacy of lifestyle interventions in reversing cardiac damage [58].

Healthy nutritional habits have unquestionable beneficial effects on the achievement and maintenance of glycemic targets and on the reduction of body weight, dyslipidemia, hypertension, with well-recognized benefits on cardiovascular outcomes. Given the involvement of ROS and AGEs-induced inflammation in the pathogenesis of cardiac damage in T2DM (Figure 1), it is not surprising that both endogenous and dietary micronutrients (e.g., vitamin A, vitamin C, vitamin E, beta-carotene, lycopene, lutein, selenium and manganese), that contribute to the antioxidant arsenal of human cells, have been proposed as modulators of the beneficial effect of the nutritional regimens that contain them in large quantity, such as the Mediterrean diet. It has been proven that Mediterranean diet reduces the incidence of cardiometabolic outcomes in subjects with T2DM [59]. For example, polyphenols, substances contained in foods such as extra virgin olive oil and nuts, are likely to elicit antioxidant protection, as suggested by the decrease of inflammatory biomarkers in individuals at risk of T2DM, as demonstrated in the PREDIMED study [60]. The relationship between diet and myocardial injury in patients with T2DM is still poorly investigated. For example, a low glycemic index diet had comparable effect on hs-cTnI than a high-cereal fiber diet [61], and in the OmniHeart study hs-cTnI levels were reduced by a carbohydrate-rich diet, a protein-rich diet and by an unsaturated fat-rich diet to a similar extent [62]. Taken together, these findings suggest that healthy diets, irrespective of macronutrients composition, may have beneficial effects on cardiac injury. Nevertheless, none of these trials have specifically considered people with T2DM.

The relationship between cardiac injury and physical exercise is complex. It has been fully documented that long, strenuous exercise induces a release of hs-cTn, but the pattern of this release is typically transient and with limited clinical significance. Nevertheless, the long-term effect of regular exercise training on cardiac injury is still debated [63, 64]. Aerobic interval training program seems to have beneficial effects on arterial function in patients with type 2 T2DM [65], but its effect on cardiac injury in these patients hasn't been fully elucidated yet.

**7. Clinical trials**

Given the linear association between plasma hs-cTn levels and the risk of cardiovascular outcomes and mortality in patients with T2DM, hs-cTn may be used to identify patients at high risk that may need more

intensive pharmacological strategies to reduce cardiovascular outcomes. In the recent Guidelines of The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) on the management of CVD risk in patients with T2DM, patients with T2DM and organ damage, or T2DM with at least three major risk factors, are considered at very high risk of developing CVD [4]. The Authors considered hs-cTnT a predictor of 10-years cardiovascular mortality, nevertheless the addition of hs-cTnT to the conventional risk assessment algorithms is considered of limited clinical value [4]. At present, routine assessment of circulating biomarkers is not recommended for CV risk stratification (class of recommendation III; level of evidence B), probably because the evidence, especially arising from clinical trials, is still limited. Moreover, few data is now available on the effect of treatments of hyperglycemia on plasma hs-cTn and it is not clear if hs-cTn reduction after hypoglycemic treatments may correspond to a parallel risk reduction. In a randomized, double-blind, placebo-controlled study assessing the efficacy and safety of canaglifozin, a new SGLT2 inhibitor, Januzzi *et al* demonstrated that hs-cTnI gradually increased in placebo group during a 2-years follow-up and that canaglifozin attenuated this increase [66]. Notably, the same trend was observed also for NT-proBNP, a well-recognized marker of cardiac dysfunction in both general population and people with T2DM. Although the reduction of cardiovascular outcomes and mortality in patients with T2DM has been a major health issue in the last years, intensive strategies have failed to decrease cardiovascular mortality effectively [67]. In light of these considerations, Srivastava et al investigated the effect of treatment with metformin plus insulin in patients with type 2 T2DM and found that metformin alone decreased hs-cTnT to a larger extent than insulin alone or insulin plus metformin [68]. In the trial conducted by Salahuddin *et al*, a different behavior of plasma hs-cTnT concentration was observed when rosiglitazone treatment was tested. Patients with type 2 T2DM were randomized to receive placebo versus rosiglitazone, an hypoglycemic agent recently associated to increased risk of heart failure [69]. Although hs-cTnT showed a modest increase after rosiglitazone treatment as well as after placebo, this increase was of the same magnitude in both groups. Although interesting, this pivotal result should be confirmed at longer follow-up to document that rosiglitazone doesn’t induce myocardial injury itself.

In addition to hypoglycemic therapies, specific interventions for controlling dyslipidemia and hypertension represent a cornerstone in the management of cardiovascular risk in patients with T2DM. At present, the effect of these interventions on hs-cTn levels as markers of myocardial injury has been poorly evaluated. In a sub-analysis of the RADAR study, the effect of 18-months treatment with rosuvastatin and atorvastatin on hs-cTnI was assessed [70]. The Authors found that atorvastatin decreased hs-cTnI while rosuvastatin didn't, showing that they could have a different effect in reducing the T2DM-induced cardiac damage. In the TEAMSTA Protect I-Trial (A TElmisartan and AMlodipine STudy to Assess the cardiovascular PROTECTive effects as measured by endothelial dysfunction in hypertensive at-risk patients beyond blood pressure) the effect of antihypertensive treatment beyond blood pressure reduction was evaluated. Particularly, patients were randomized receiving an angiotensin-converting-enzyme inhibitor plus a thiazide diuretic or a dihydropyridine calcium-channel blocker for 6 months. The Investigators found that at 6-months follow-up, both treatments reduced blood pressure, and that hs-cTnI was modestly but significantly reduced in both groups, especially in responders [71]. Interestingly, hs-cTnT didn't show the same trend, with no difference between the baseline value and the one after treatment. Interestingly, after the publication of the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline for the prevention, detection evaluation, and management of hypertension, the use of biomarkers for the identification of patients who may benefit from pharmacological treatment was investigated [72]. In a large, pooled cohort analysis, Pandey *et al* showed that individuals with hypertension or high blood pressure actually not recommended for antihypertensive medication with high hs-cTnT have a higher 10-year cardiovascular incidence rate than those without high hs-cTnT [72]. The Authors concluded suggesting the introduction of hs-cTnT in the risk assessment of patients with high blood pressure and hypertension and provide the evidence that hs-cTnT could help allocating patients to the best intervention strategy. Although this analysis was intended for individuals from the general population and not specifically for people with T2DM, it represents an interesting example of the incremental value of biomarkers for the management of CVD risk factors.

## 8. Conclusions

With the introduction of the new high sensitivity assays for the determination of cTn in plasma, a faster management of patients presenting with suspected AMI is possible. Moreover, these assays are useful for the stratification of patients with chronic, subclinical myocardial injury, allowing their allocation to the best interventions for containing cardiovascular risk and reducing adverse outcomes. These new high sensitivity assays also permit the identification of the cTn release into the bloodstream as a consequence of hyperglycemia-induced, subclinical, myocardial damage. Several clinical studies have confirmed the association between hs-cTn and cardiovascular mortality in both general population and in individuals with T2DM. Nevertheless, the efficacy of reducing hs-cTn through hypoglycemic agents or other pharmacological interventions commonly used to manage CVD risk in patients with T2DM, requires more confirmation by large, randomized, controlled clinical trials.

**Table 1.** Summary of the observational studies evaluating hs-cTn concentration in patients with T2DM.

| **Reference** | **Study population** | **Sample size** | **Persons with detectable hs-cTn at baseline, %** | **Persons with T2DM and hs-cTn > 99$^{th}$ percentile, %** |
|---|---|---|---|---|
| Rubin *et al* [32] | General population, no CHD (ARIC study) | 9,661 | 66.3% | 21.8% |
| Selvin *et al* [51] | General population, hs-cTnT<14ng/l and no CHD (ARIC study) | 9.051 | NA | 10.8% (at follow-up) |
| Gori *et al* [52] | General population, no CHD (ARIC study) | 1,510 | NA | 14% |
| Everett *et al* [53] | People with T2DM and stable ischemic heart disease (BARI 2D trial) | 2,368 | 98.7% | 39.3% |
| Lepojarvi *et al* [55] | Patients with stable CHD | 1,243 | NA | 11.3% |

| | | | | |
|---|---|---|---|---|
| Galsgaard *et al* [56] | Patients with type 1 T2DM with/without nephropathy | 900 | 88.3% | NA |
| Hendriks *et al* [57] | Patients with T2DM | 1,133 | 54% | 14.7% |
| Scirica *et al* [54] | Patients with T2DM and CVD or risk factors | 12,310 | 99.7% | 46.2% in patients with CVD; 31.6 % in patients with risk factors only |
| Cavender *et al* [73] | Patients with T2DM with established CHD | 3,808 | 93% | 16% |
| Salahuddin *et al* [69] | Patients with type 2 T2DM with or at risk of CHD | 150 | 93% | 23% |

ACS: acute coronary syndrome; CHD: coronary heart disease; T2DM: diabetes mellitus; NA: not available

**Figure legend**

**Figure 1**. Molecular mechanisms linking hyperglycemia to accelerated atherosclerosis, cardiomyopathy, and cardiac troponin release.

AGE: advanced glycation end-products; AMI: acute myocardial infarction; BNP: brain natriuretic peptide; DAG: diacylglycerol; eNOS: endothelial nitric oxide synthase; GlcNAc: *N*-acetylglucosamine; PKC: protein kinase C; ROS: reactive oxygen species.

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