Review Article

C1q tumor necrosis factor related proteins (CTRPs) in patients with cardiovascular diseases

Zahra Barmoudeh[1], Maryam Hashemi Shahraki[1], Hossein Pourghadamyari[2], Mina Rohani Borj[3], Amir Hossein Doustimotlagh[4,5*], Kazem Abbaszadeh-Goudarzi[6*]

[1] *Student Research Committee, Yasuj University of Medical Sciences, Yasuj, Iran*
[2] *Department of Clinical Biochemistry, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran*
[3] *Department of Clinical Biochemistry, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[4] *Medicinal Plants Research Center, Yasuj University of Medical Sciences, Yasuj, Iran*
[5] *Department of Clinical Biochemistry, Faculty of Medicine, Yasuj University of Medical Sciences, Yasuj, Iran*
[6] *Cellular and Molecular Research Center, Sabzevar University of Medical Sciences, Sabzevar, Iran*

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* **Corresponding Author:**

Amir Hossein Doustimotlagh, Department of Clinical Biochemistry, Faculty of Medicine, Yasuj University of Medical Sciences, Yasuj, Iran
Email:
amirhosseindoustimotlagh@gmail.com

Kazem Abbaszadeh-Goudarzi, Cellular and Molecular Research Center, Sabzevar University of Medical Sciences, Sabzevar, Iran
Email:
goudarzi63@gmail.com

ABSTRACT

Cardiovascular diseases (CVDs) are the major cause of death in both developed and developing countries. It is widely accepted that predicting CVDs in the early stages or before the onset of the diseases could be a central goal in the management, prevention, and treatment of these diseases. Adipokines, a large and diverse group of molecules secreted by adipose tissue that affect cardiovascular function, have played a crucial role in the cardiovascular system. C1q/tumor necrosis factor-related protein (CTRP) is a newly discovered family of adipokines that are paralogs of adiponectin. This family includes 15 members (CTRP1 to CTRP15). Recent studies have shown that CTRPs have diverse biological effects on the cardiovascular system. In this review, recent research on the expression of the CTRP gene superfamily in CVDs is examined to assess their potential as new CVD biomarkers. Given the growing data on the roles of CTRPs in the physiology and development of CVDs, this review discusses the role of various types of CTRPs, including CTRP1, CTRP2, CTRP3, CTRP6, CTRP9, CTRP12, and CTRP13 in the management, prevention, and treatment of CVDs.

Keywords: Cardiovascular diseases; C1q/ tumor necrosis factor related protein; CTRP; Adipokine

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Introduction

Cardiovascular diseases (CVDs) are the leading cause of death in both developed and developing countries (1, 2). According to recent epidemiological studies, there has been a dramatic increase in the prevalence and morbidity of CVDs over the past decades (3, 4). It is worth noting that CVDs also impose a huge financial burden on healthcare systems (3, 5). As such, these diseases require immediate attention as they have become a serious health problem. It is widely accepted that predicting CVDs in the early stages or before the onset of the diseases can be considered an important goal in the management, prevention, and treatment of these kinds of diseases (6, 7). To this end, a considerable amount of literature has been published recently on the prediction of CVDs using biomarkers (8, 9). These studies have introduced several biomarkers such as troponins (10), high sensitive C-reactive protein

(hsCRP) (11), pro-oxidant and antioxidant balance (PAB) (12), antibody against heat shock proteins (anti-HSPs) (13), myeloperoxidase (MPO) (14), oxidized LDL (15), and so on. Cardiovascular disease biomarkers are well-reviewed by Holten (2013) and by Serra (2018) (16, 17).

In this review, recent research on the expression of the complement C1q tumor necrosis factor-related proteins (CTRPs) gene superfamily in CVDs is examined to assess their potential as new CVD biomarkers. This highly conserved family of proteins has four distinct domains, similar to adiponectin domains (Figure 1). It has been reported that the CTRP family, as a cluster of adipokines, plays a vital role in the physiology and development of CVDs. Table 1 briefly shows the role of some CTRPs in CVDs.

CTRP1

C1q/tumor necrosis factor-related protein 1 (CTRP1) is a new adipokine synthesized in adipose tissue. In human tissues, the gene expression of CTRP-1 at the mRNA level is higher in the heart compared to the liver and kidney (18). In epididymal adipose tissue, CTRP-1 expression is up-regulated by lipopolysaccharide (LPS) and down-regulated by inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (19). Notably, CTRP-1 can prevent the activation and aggregation of platelets by binding to fibrillar collagen type I, as confirmed by recombinant human CTRP-1. More importantly, the binding tendency of GPVI-Fc4 and von Willebrand factor (VWF) to collagen is partially or completely inhibited by CTRP-1, respectively. In an experiment, it was shown that CTRP-1 prevented the accumulation of platelets on a surface coated with collagen but had no impact on a VWF-coated surface (20). These data suggest that by preventing VWF from binding to collagen, CTRP-1 can block platelet aggregation induced by collagen.

In nonhuman primates, using a model known as Folts vascular injury, it was demonstrated that CTRP-1 can inhibit platelet-induced thrombosis in vivo. This effect was achieved without changes in activated-clotting time (ACT) or template cut bleeding times. This result suggests that the anti-platelet thrombotic activity of CTRP-1 most likely acts by pacifying the thrombogenic site of vascular injury (20-22). These investigations show that CTRP-1 plays an important role in the plaque formation process in coronary heart disease (CHD).

In the acute coronary syndrome or stable angina pectoris group, the concentrations of CTRP-1 and IL-6 were increased. In plasma, CTRP-1 and IL-6 levels were higher in the single-, double-, and triple-vessel lesion group compared to the control group. The CTRP-1 concentration was positively associated with CRP and IL-6 levels and negatively with HDL-C (23). Notably, increases in CTRP-1 and IL-6 concentrations can powerfully predict CHD. The variation in plasma concentrations of CTRP-1 and IL-6 can be an important marker to reflect the stage of inflammation in CHD and the severity of coronary atherosclerosis. This finding suggests that there is a strong relationship between the occurrence of CHD and the combined evaluation of CTRP-1 and IL-6 (23).

It has been reported that high concentrations of CTRP1 in blood circulation are related to hypertension (24), metabolic syndrome (25), and inflammation (26). However, increases in CTRP1 levels are associated with severe inflammation and atherosclerosis in vivo, as well as dysfunction of angiogenic elements and reduced collateralization in coronary vasculature (27). Ying Shen et al. reported that after classifying participants based on the presence or absence of diabetes, significant differences in the levels of CTRP1 and hsCRP among patients with low and high collateralization were shown for both diabetic and non-diabetic patients. Moreover, the levels of CTRP3 and CTRP1 were negatively and positively related to the number of diseased coronary arteries, respectively (27). Research has also shown that an increase in CTRP1 is related to CVD and an

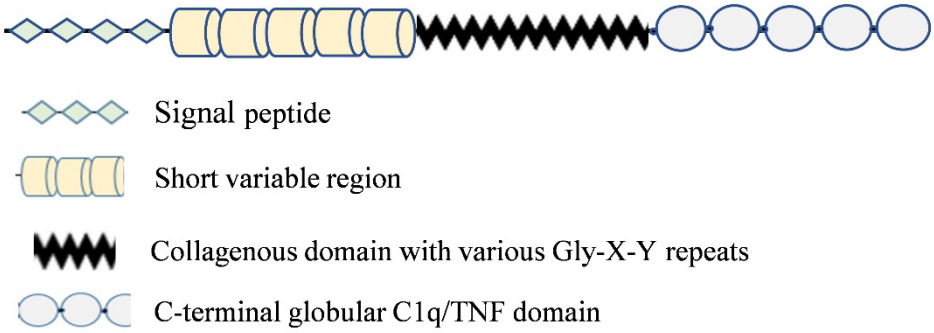

Figure 1: Structure of C1q tumor necrosis factor related proteins (CTRPs) family members. Domain structure of CTRPs is included a signal peptide (SP), variable region (V), collagen domain (Col – Gly-X-Y), and globular C1q/TNF domain. A signal peptide (white), a short variable region (purple), a collagenous domain with various length of Gly-X-Y repeats (grey), and a C-terminal globular domain homologous to complement C1q (green).

Table 1: The role of CTRP1, CTRP2, CTRP3, CTRP6, CTRP9, CTRP12, and CTRP13 in cardiovascular diseases

CTRP	type of disease	detection method	sample	gender	age	Results	ref
CTRP1	CAD	ELISA	Serum	Human	65±12	Increased serum level of CTRP1 is associated with low coronary collateralization instable angina patients	(27)
	Adverse cardiovascular events	ELISA	Serum	Human	69 [63–74]	Increased serum level of CTRP1 is associated with CVDs	(28)
	Atherosclerosis	ELISA, Immunohistochemistry	Serum	Human, animal	67.5+9.7	CTRP1 level increased in atherosclerotic tissues	(36)
	CHF	ELISA, Real time PCR	Plasma and tissue samples	Human	68±8	Increased plasma level of in CHF patients	(39)
	Ischemic injury	Real time PCR	Heart tissue	Cell line, Animal	-	CTRP1 protects the heart by reducing cardiomyocyte apoptosis and inflammatory response	(34)
CTRP2	Vascular			Animal		CTRP-1 showed antiplatelet thrombotic activity	(20)
	AMI	ELISA, Real-time PCR	H9c2 cell line	Cell culture, Animal	-	CTRP2 expressions reduced in H9c2 cells exposed to H_2O_2 And rats after AMI	(45)
CTRP3	CAD	ELISA	Plasma	Human	-	Serum CTRP 3 level elevated in CAD patients	(51)
	-		-	Cell culture	-	CTRP3 has role in the pathophysiology of neointimal hyperplasia	(11)
CTRP6	Cardiac fibrosis		-	Animal	-	CTRP6 decreased post-MI cardiac function	(56)
CTRP9	Ventricular remodeling	ELISA	Blood samples	Mice, Human	-	CTRP9 level decreased	(59)
	MI/R injury	ELISA	Plasma	Mice	-	CTRP9 inhibits ER stress-related apoptosis signaling during MI/R injury	(60)
	Carotid plaque	Western blot	Serum	Mice	-	CTRP9 play an anti-inflammation role against atherosclerosis	(61)
	AMI	Western blot, real-time PCR	Plasma, adipose tissue	Mice	10–12 weeks	CTRP9 production can be valuable for prevention or treatment of AMI	(62)
	Inflammation	Confocal images, real-time PCR	RAW cell line	Cell line	-	Anti-inflammatory effects	(63)
	Atherosclerosis	Western blot	Serum	Mice	8 weeks	Protective effect of CTRP9 in atherosclerosis	(68)
CTRP12	Vascular	ELISA, real-time PCR	Serum	Mice	8–12 weeks	Protects against the development of pathological vascular remodeling	(69)
	Diabetes and CAD	ELISA	Serum	human	45 -75	Link between CTRP12 and pathogenic mechanisms of atherosclerosis	(70)
CTRP13	Atherosclerotic plaque	ELISA	Serum	Mice	8–10 week	Prevented the atherosclerotic plaque formation	(71)

increased susceptibility to major adverse cardiovascular events (MACE) (28, 29).

It has been confirmed that in rodents, CTRP1 reduces blood glucose levels and increases fatty acid oxidation in skeletal muscles by activating the AMPK signaling cascade (30, 31). Based on the expression of CTRP1 induced by cytokines with inflammatory properties in adipose tissues, it has been confirmed that there is a significant association between CTRP1 expression and low-grade chronic inflammation (32).

Despite the vital impact of CTRP1 on whole-body energy homeostasis through its metabolic actions, different studies have confirmed that there is a positive relationship between CTRP1 levels and obesity-linked disorders, such as metabolic syndrome (MetS), type 2 diabetes (T2DM), hypertension, or non-alcoholic fatty liver disease (NAFLD) (25, 31, 33, 34). To a large extent, a close association between CTRP1 and obesity-related traits may contribute to the considerable linkage between the future risk of CVDs and CTRP1. Furthermore, this association may be part of a common pathway or present potential factors mediating the linkage between CTRP1 and MACE. However, analyses have shown a strong association between CTRP1 and MACE when inflammatory markers and metabolic parameters were evaluated in studies. Moreover, CTPR1 can predict the incidence of MACE as well as its relationship with an unfavorable metabolic profile (28). In the sera of hypertensive patients, the levels of CTRP1 are up-regulated and it mediates the production of aldosterone by angiotensin II (24, 35).

Recently, several investigations have confirmed that serum levels of CTRP1 are associated with coronary artery disease with impairment of collateralization(27). However, little information is available about the relation of CTRP1 with atherosclerosis and its underlying mechanisms. In patients with coronary artery disease (CAD), the levels of CTRP1, TNF-α, and hsCRP were significantly higher in comparison to control (36). However, the findings showed that higher CTRP1 levels were related to multi-vessel disease subgroup compared to one-vessel. Of note, the atherosclerosis extent index, CTRP-1 levels were associated with the number of diseased coronary arteries (36).

Congestive heart failure (CHF) is a complex clinical syndrome resulting from any structural or functional impairment of the ventricular in relation to filling or ejection of blood (37). In plasma and epicardial adipose tissue (EAT) of congestive heart failure (CHF) patients, CTRP1 levels were higher compared to controls. In relation to the levels of CTRP1, there is no difference in cardiomyocytes between the CHF group and the non-CHF group (38). Moreover, an investigation to explore survival analysis showed that more CTRP1 values led to a worse prognosis following discharge. Notably, in H295R cells, CTRP1 induced the overexpression of IL-6 gene in mRNA level (38). By modulation the levels of CYP11B2 protein and brain natriuretic peptide, CTRP1 activated ERK1/2 and Jak-2 in order to release aldosterone. Notably, through JAK2-STAT3 signaling pathways, brain natriuretic peptide repressed the aldosterone release induced by CTRP1. In the plasma, the levels of CTRP1 were increased in patients with CHF. By modulation of IL-6 levels and aldosterone release, CTRP1 may play an important role in the pathogenesis of CHF patients (38).

In diabetic rats, CTRP1 expression is stimulated by cytokines with inflammatory markers. Clinical evidence has confirmed that high levels of CTRP1 are positively related to MetS and T2DM (39). In patients with CAD, plasma levels of CTRP1 are enhanced (28, 40). Therefore, CTRP1 can be used as a vital biomarker for obesity-related complications (41). More importantly, several investigations have shown that CTRP1 improves glucose metabolism and insulin sensitivity in obese mice, proving CTRP1's role as a metabolic regulator (33, 42). To define the downstream signaling pathway of this adipokine, an investigation was conducted on acute ischemic injury using loss and gain of function with genetic manipulations. Treating cardiomyocytes with CTRP1 not only resulted in a reduction in apoptosis levels induced by hypoxia–reoxygenation but also an increase in cAMP production, which was reversed by the inhibition of sphingosine-1-phosphate (S1P) signaling (34, 43). Moreover, blocking the S1P signaling pathways led to reversing the inhibition of myocardial infarct size, apoptosis, and inflammation mediated by CTRP1 following myocardial ischemia-reperfusion (MI/R) injuries in vivo. In cardiomyocytes, CTRP1 protects against myocardial ischemic injury by decreasing apoptosis and inflammatory response via S1P/cAMP signaling pathways, indicating that CTRP1 has a vital impact on ischemic heart disease (34).

CTRP2

Functionally, it has been demonstrated that only CTRP2 is the most analogous to adiponectin in regulating whole-body metabolism (44). In H9c2 cells and acute myocardial infarction (AMI) rats, the expression of cardiac CTRP2 was significantly decreased in oxidative stress status. In the H9c2 cell line, myoblastic cells, the knockdown of CTRP2 significantly increased damages caused by oxidative stress, whereas the overexpression of CTRP2 significantly decreased them (45). However, the antioxidant inhibitor α-lipoic acid reverses CTRP2 expression during oxidative stress status, which in turn explains that CTRP2 production can be regulated by oxidative stress (45).

In vivo, CTRP2 administration to rats with AMI significantly decreased infarct size, apoptotic myocardial cells, reactive oxygen species (ROS) generation, and improved cardiac function. It also modulated the downstream of the ERK1/2 signaling pathway and

finally inhibited cytokine production such as TNF-α and IL-6. It should be noted that CTRP1 is a new survival molecule in the heart. CTRP2 overexpression is a potential approach to alleviate AMI injury (45).

Lei et al. (2019) used the knockout mouse (KO) model to determine the function of CTRP2, and their results showed that in CTRP2-KO mice, the metabolic rate and energy expenditure were significantly increased. They also found that the lack of CTRP2 led to the activation of lipolysis pathways (46). They reported that the KO model had severe weight loss due to high lipolysis. Moreover, in cultured adipocytes, CTRP2 treatment suppressed triglyceride (TG) hydrolysis, and its deficiency enhanced agonist-induced lipolysis in vivo. Their results provide the first in vivo evidence that CTRP2 regulates lipid metabolism in adipose tissue and liver (46).

In a recent study by Ilbeigi et al. (2020), the serum levels of CTRP2 were evaluated in patients with angiographically confirmed CAD and found that serum levels of CTRP2 were significantly higher than in control subjects. In addition, they reported a significant and positive correlation between the severity of the disease and the serum concentration of CTRP2. They, therefore, proposed CTRP2 as a novel biomarker and predictor of CAD severity (47).

CTRP3 and CTRP6

CTRP3, also known as cartonectin, cartducin, and CORS-26, has anti-inflammatory properties and has attracted attention for its potential impact on the pathogenesis of CAD (48, 49). Recent investigations on cardiac and vascular remodeling in mice have shown the protective properties of CTRP3 (50). However, there are few investigations about the relevance of CTRP3 with CAD. Recent research has shown that CTRP3 levels were significantly higher in CAD patients compared to non-CAD patients. Significant variations of CTRP3 levels were found in single-vessel and triple-vessel groups. New findings have also shown that CAD occurrence was correlated with CTRP3 levels as well as glucose and HDL cholesterol. Of note, there is a close association between CTRP3 levels and the prevalence/severity of CAD, suggesting it as a new biomarker for CAD (51). CTRP3 not only inhibits apoptosis in cardiomyocytes (52) but also increases cardiomyocyte survival and enhances angiogenesis (53). There are still some inconsistencies regarding the role of CTRP3 in heart disease.

CTRP6 is another factor that has been evaluated and reported to increase the oxidation of fatty acids by activating AMPK (54). CTRP6 is a 240-amino acid-secreted glycoprotein that is expressed in the heart, adipose tissue, and uterus (55). The activation of AMPK is responsible for the anti-fibrotic impacts mediated by CTRP6 via targeting the RhoA/MRTF-A pathway (56). It has also been confirmed that the expression of CTRP6 gradually decreases during adipocyte differentiation, and consequently, it is clear that CTRP6 knockdown inhibits adipogenesis. However, pretreatment with new compounds such as adenine 9-b-D-arabinofuranoside (AraA), an AMPK inhibitor, or LY294002, a phosphatidylinositol-3-kinase (PI3 K) inhibitor, inhibits the protective impacts of CTRP6 on profibrotic response induced by TGF-β1 (56). More importantly, CTRP6 causes interleukin-10 expression via the p42/44 mitogen-activated protein kinase-dependent pathway in human macrophages, indicating that CTRP6 might exert anti-inflammatory impacts (57, 58). All of these features are beneficial for heart patients and deserve further investigation.

CTRP9 and CTRP12

Recently, more evidence has suggested that CTRP9 has cardioprotective properties by protecting the heart from ventricular remodeling. However, it has been confirmed that b1-AA monoclonal antibodies (b1-AamAb) inhibit the expression of cardiac CTRP9 and enhance remodeling of cardiac tissue, presenting CTRP9 as a new target for therapeutic aims against remodeling in pathologic status in b1-AA–positive patients suffering from CHD (59). Data from a study showed that plasma CTRP9 decreases MI/R injury, reverses post-MI remodeling, and enhances vasorelaxation in an endocrine manner. It was demonstrated that CTRP9 is highly expressed in the heart, about 1.6-fold compared to the level of circulating CTRP9 (60).

In carotid mature plaques, lentiviral-CTRP9 delivery led to a reduction in macrophage and lipid contents as well as an increase in collagen contents and vascular smooth muscle cells. Notably, in mature plaques, pro-inflammatory cytokines were decreased by CTRP9. However, in macrophages, CTRP9 is overexpressed by decreasing cytokines with pro-inflammatory properties, which enhances the stability of plaque in ApoE KO mice. In order to stabilize plaque models, it is suggested that an increase in CTRP9 production can be a useful therapeutic approach (61).

In cardiac myocytes, CTRP9 plays an important role as a new regulator of heart damage caused by acute ischemic status through AMPK activation. Myocardial AMPK activation has been demonstrated to have salutary impacts on different heart diseases. It should be noted that CTRP9 is abundantly expressed in adipose tissue. It seems that CTRP9 endocranially affects cardiac AMPK signaling. The CTRP9/AMPK signaling axis may express a linkage between fat and heart tissue. In mice, the level of CTRP9 is down-regulated in correlation with insulin resistance, obesity, and hyperinsulinemia, which are associated with an increasing prevalence of CVD (62).

In many CVDs, CTRP9 acts as an adiponectin paralog,

showing regulatory roles. AMPK, as a molecule of intracellular signaling, mediates the biological functions of adiponectin. It is a fact that CTRP9, like adiponectin, imposes its beneficial impacts through AMPK on cardiovascular inflammation, endothelium relaxation, monocyte adhesion, and myocardial apoptosis. Recently, a study has shown that CTRP9 was a protective agent of atherosclerosis in humans independent of adiponectin. Moreover, it was revealed that CTRP9 played a major role in stabilizing atherosclerotic plaques. Notably, the mechanisms by which CTRP9 exerts its anti-inflammatory properties on macrophages have not been elucidated. New results suggest that supplementation with CTRP9 to treat atherosclerosis may be a useful strategy (63). Furthermore, it has been reported that CTRP9 prevents vascular smooth muscle cells from expanding through a process that relies on cAMP, so it is able to mitigate neointimal thickening after vascular damage. It was concluded that CTRP9 may be a major therapeutic target for preventing pathological vascular remodeling (64). There have also been other research in this field and nearly all of them affirm the function of CTRP9 as a preventive factor in pathological vascular remodeling, atrial inflammation and fibrosis (65-67).

Recently it has been found that plasma CTRP9 markedly decreased following AMI in mice and humans suffering from CAD, presenting that CTRP9 may have the potential for diagnostic value in CAD (67). More importantly, in advanced atherosclerotic mice, CTRP9 not only reduced the index of plaque vulnerability but also increased the stability of carotid plaque. Notably, in human primary hepatocytes, CTRP9 induced autophagy. It is common to use 3-methyladenine as an autophagy inhibitor to suppress autophagy outcomes, including endoplasmic reticulum (ER) stress and hepatic steatosis. By targeting autophagy, it is supposed that CTRP9 may play a protective role in the formation of atherosclerotic lesions. Therefore, this strategy can be used in the pathophysiological process of CVD (68).

It has been indicated that CTRP12 (adipolin) has the properties of an adipokine, including anti-inflammatory properties, which protect against pathological vascular remodeling. Particularly, in response to injury, serum CTRP12 was increased, resulting in decreased vascular inflammation and remodeling. Therefore, to treat and prevent vascular disorders, it can be a therapeutic approach to increase plasma levels of CTRP12 (69). In this regard, Fadaei et al (2019) reported a significant relation between CTRP12 and the pathogenic mechanisms of atherosclerosis (70). In this case, more detailed studies with a higher sample size should also be undertaken.

CTRP13

To date, it has been identified that out of all 15 CTRPs, CTRP13 is evolutionarily highly conserved with a difference of only one amino acid between mouse and human (71). Clinical investigations have shown that in T2DM and CAD, gene expression and serum levels of CTRP13 were considerably lower compared to healthy controls. In addition, it was suggested that decreased levels of CTRP13 appear to have an association with increased CAD risk (72). Also, Wang and colleagues in 2019 showed that CTRP13 levels were significantly lower in CAD patients as well as in the CAD animal model than in the normal control group. In addition, they showed that exogenous CTRP13 infusion in the CAD animal model significantly reduced inflammation and the severity of atherosclerotic lesions (71). However, more investigations are needed to understand the role of CTRP13 in atherosclerosis.

Conclusion

Taken together, these findings suggest an important role for CTRPs in the pathophysiology of CVDs. Several studies have confirmed the potential of CTRPs as new biomarkers for predicting and managing CVDs. However, further knowledge about the role of CTRPs in the pathogenesis of CVDs will be useful to develop a greater degree of accuracy on this matter.

Conflict of Interest

The authors declare that there is no conflict of interest.

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