# C-reactive protein and cardiovascular disease: From animal studies to the clinic (Review)

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**Abstract.** C-reactive protein (CRP) and cardiovascular disease (CVD) have long been important research topics. CRP is an acute phase protein, while CVD is an inflammatory condition. The association between CRP and CVD remains controversial and has been attracting increasing attention. Traditionally, the main marker of CVD is considered to be low-density lipoprotein cholesterol. However, due to its unique characteristics, CRP may represent a novel marker or a new therapeutic target for CVD. Clinical studies have demonstrated that CRP is a predictor of CVD, but whether it is directly involved in the development and progression of CVD has yet to be fully elucidated. Recent clinical studies have demonstrated that lowering plasma CRP levels may reduce the incidence of CVD. The aim of the present review was to investigate the association between CRP and CVD, particularly atherosclerosis, from laboratory animal studies to clinical research.

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## 1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide (1). According to the Global Burden of Disease Study, the number of deaths from CVD reached 17.9 million in 2015, which was markedly higher compared with the 12.3 million deaths from CVD reported in 1990 (2,3). Due to its high mortality and morbidity rates, it is crucial to predict the risk of CVD. Atherosclerosis is the pathological basis of several CVDs, including coronary heart disease, peripheral vascular disease and cerebral infarction. Atherosclerosis is a chronic inflammatory disease, chiefly manifested by activation of endothelial cells, adhesion and migration of monocytes, accumulation of foam cells, formation of atherosclerotic plaques, plaque rupture and thrombosis (4). C-reactive protein (CRP) is an acute phase reactive protein. The association between CRP as an acute phase response protein and CVD has been controversial. The aim of the present review was to investigate whether CRP is merely a biomarker of inflammatory diseases, or if it is causally associated with CVD and, thus, directly involved in the pathogenesis of CVD.

## 2. CRP

Tillett and Francis (5) first observed in 1930 that a protein in the serum of patients with acute inflammation reacted with the 'C' carbohydrate antibody of pneumococcus, giving rise to the name 'CRP'. CRP is mainly produced by the liver (6), has a ring-shaped pentamer symmetrical structure and the protoplasts are joined by non-covalent bonds (7). CRP is a highly sensitive marker of inflammation and tissue damage, and it is considered an acute phase protein (8). When inflammation occurs in the body, the CRP levels increase with the inflammatory response. In healthy adult volunteers, the median CRP concentration is 0.8 mg/l, with 90% of the cases at <3 mg/l and 99% at <10 mg/l (9). However, following acute phase stimulation, the CRP levels may increase 100- or even 500-fold (10). When CRP aggregates or binds to macromolecule ligands, the classical pathway of complement activation can be achieved through interactions with C1q (11,12). CRP levels are routinely assessed in the clinic. In clinical studies, the 'high-sensitivity' CRP (hs-CRP) detection method has come to be considered as

a more sensitive method for detecting atherosclerotic inflammation. The reason for this is that in order to detect CRP with high sensitivity, the detection limit needs to be minimized as far as possible (13-15). The US Centers for Disease Control and Prevention has previously issued a statement that classifies hs-CRP levels and risk categories as follows: low risk <1.0 mg/l; intermediate risk 1.0-3.0 mg/l; and high risk >3.0 mg/l (16,17).

## 3. CVD

CVD is a term used to collectively describe diseases involving the heart and/or vasculature. CVD mainly includes diseases caused by atherosclerosis (1). The Emerging Risk Factors Collaboration is based on a large number of population studies and has found that CRP concentrations are closely associated with coronary arterial disease, cancer, ischemic stroke and vascular diseases (18). However, more noteworthy is the comparison between men and women, as men develop CVD earlier and the risk of CVD increases with age (19). Atherosclerosis is a chronic inflammatory disease that is initially asymptomatic. Early atherosclerosis is associated with limited plaque formation, which does not affect the blood circulation (20). However, the plaques forming on the inner arterial wall gradually increase in size, causing narrowing of the arterial lumen and/or thrombus formation. At this stage, the blood supply to each organ may become compromised, causing manifestations of CVD (4,20). Atherosclerosis is the main cause of the high mortality rates of CVD (21). When CVD occurs in the body, the CRP levels increase; therefore, it may be inferred that there is an association between CRP and CVD (22-29). Based on a large number of animal experiments and clinical studies, CRP is a pathogenic factor that warrants further investigation (27,30-34). The association between CVD and CRP, and whether CRP can be used as a novel marker or target for the treatment of CVD, must be further verified in animal experiments and clinical studies.

## 4. Animal studies

Mice, rats and rabbits are frequently used to construct animal models in several preclinical studies investigating CVD (35), whereas the majority of the animal models that study CRP use mice and rabbits (36). To reveal the phylogenetic relationships of CRP, the CRP protein sequence of 14 most frequently used animal models in CVD research, including human (NP_000558.2), chimpanzee (XP_001170732.2), Rhesus monkey (XP_001117250.2), crab-eating macaque (NP_001306322.1), rabbit (NP_001075734.1), guinea pig (XP_003466601.1), naked mole-rat (XP_004858808.1), rat (NP_058792.1), golden hamster (XP_005078251.1), mouse (NP_031794.3), cattle (NP_001137569.1), sheep (XP_027821246.1), dog (NP_001301045.1), horse (XP_023496680.1) were downloaded from the NCBI protein database (https://www.ncbi.nlm.nih.gov/protein/). Subsequently, the phylogenetic tree of maximum likelihood was constructed using MEGA7 (37) (Fig. 1). Except for non-human primates, it may be inferred that rabbits and humans were placed in the same cluster. Rats and mice were in relatively far clusters, suggesting the genetic priority of rabbits and non-human primates as animal models in studies of CRP-related CVD.

There is controversy regarding the association between CRP and CVD in animal experiments. Several studies have demonstrated that CRP can promote the pathological process of atherosclerosis (30,31,38). Using a rat carotid angioplasty model, an experiment revealed that CRP can promote the migration and proliferation of vascular smooth muscle cells, an increase in the collagen content and the production of neointima (38). Paul *et al* (30) also suggested that human CRP over expression accelerates the progression of atherosclerosis in apolipoprotein E knockout ($ApoE^{-/-}$) mice and that CRP in lesions is associated with increased C3, angiotensin type 1 receptor (AT1-R), vascular cell adhesion molecule 1 and collagen content. However, a previous study by Hirschfield *et al* (39) demonstrated that after 56 weeks of observation, male $ApoE^{-/-}$ mice expressing human CRP did not display promotion of the development of atherosclerosis, but human CRP and mouse complement deposition were found in the plaques. Of note, it has been previously suggested that human CRP does not promote atherosclerosis, but rather may reduce the development of atherosclerosis (40). By contrast, Teupser *et al* (41) suggested that the absence of CRP in mice exacerbates atherosclerotic lesions.

Our group at the Research Institute of Atherosclerotic Disease has also performed animal studies to explore the role of CRP in CVD (31,42). High-cholesterol feed was used to induce atherosclerosis in rabbits and the association between CRP and atherosclerosis was investigated. The results demonstrated that the CRP content was positively correlated with the size of the atherosclerotic lesions (31). When an acute embolic stroke occurs in rabbits, the level of CRP in the plasma increases with increasing infarct size, and the CRP level in the plasma is closely associated with the area occupied by the infarcted lesion (42). In addition, we also found that decreased plasma CRP levels did not affect the development of atherosclerosis (43). These results indicate the presence of a close association between CRP and CVD.

However, several studies have failed to demonstrate a correlation between CRP and atherosclerosis, and it has been reported that CRP does not affect the development of atherosclerosis (43-48). Tennent *et al* (44) and Reifenberg *et al* (45) found no significant difference in the formation of atherosclerotic lesions in $ApoE^{-/-}$ mice between transgenic human and rabbit CRP. It has also been reported that CRP does not play a role even in early atherosclerosis (46,47). However, initial studies have revealed that mouse models for studying CRP may carry certain disadvantages, as the CRP levels in the plasma of mice stimulated by inflammation were markedly low compared with those in humans and rabbits (49). Compared with mice, the lipoprotein metabolism of rabbits and the response of CRP, an acute phase reactant, were more similar to that in humans (50,51).

In subsequent animal experiments, researchers have generally turned to the study of transgenic rabbits. Koike *et al* (48) observed that CRP did not affect the formation of aortic or coronary atherosclerotic lesions in transgenic rabbits. This suggests that, even at higher levels, CRP does not affect the occurrence and development of atherosclerosis. We found that, although antisense oligonucleotides to CRP were used

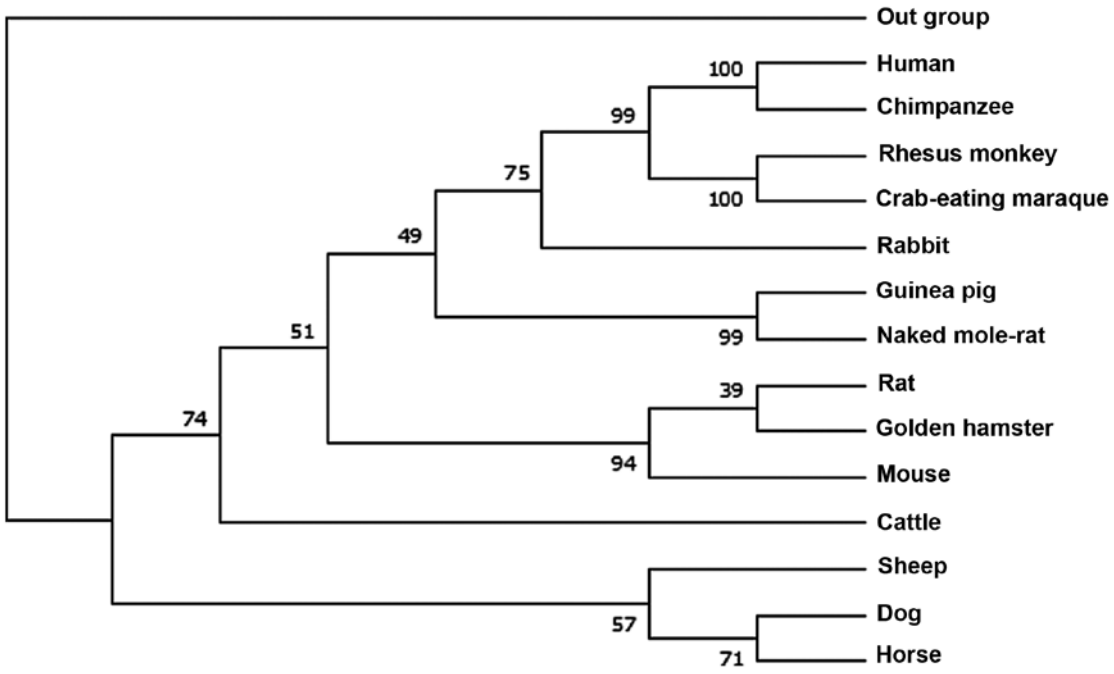


Figure 1. Molecular phylogenetic analysis animal models commonly used in CRP and CVD studies.

to reduce the plasma level of CRP, the progression of atherosclerosis in the aorta and coronary artery of rabbits was not affected (43). Therefore, in laboratory animals (mice, rats and rabbits) studies, it has not been confirmed that an increase or decrease in CRP levels affects the progression of atherosclerotic lesions. The major animal studies between CRP and CVD are summarized in Table I. However, concerning the currently available experimental studies, the results of mouse experiments have been contradictory. Most researchers have not demonstrated that CRP affects CVD lesions (39,41,44-47). Therefore, the results of animal experiments have failed to determine whether there is a correlation or a causal association between CRP and CVD, and further studies are required.

## 5. Clinical studies

A large volume of clinical data indicates that the detection of hs-CRP is of predictive value in CVD (22-26) and is also a risk factor and biomarker for CVD (27-29,52). Studies have demonstrated that the detection of CRP levels may help identify early complications in patients with acute myocardial infarction and acute coronary artery disease (33,34). Similarly, Hutchinson *et al* (53) found in early large-scale clinical studies that age increases are directly proportional to CRP levels, suggesting that CRP may be closely associated with an increased risk of CVD. Ridker *et al* (27) monitored the CRP levels of 27,939 patients for up to 8 years and suggested that the probability of CVD increased with increasing CRP levels. In subsequent study, a follow-up analysis of >6,000 patients revealed an increased risk of acute cardiovascular events in patients with higher CRP levels (54). These larger population studies have suggested that CRP may be a predictor of CVD.

For patients with stable or unstable angina, detecting serum CRP levels may also predict coronary events (55), and real-time detection of CRP plasma levels in patients with unstable angina after discharge can effectively predict the risk of recurrent coronary events (56). Therefore, CRP can predict the severity of CVD and the detection of the CRP levels may effectively prevent CVD (27,57,58). However, whether CRP is merely a predictive biomarker of inflammation in CVD, or whether reducing the level of CRP is beneficial in the treatment of CVD, have yet to be clearly determined. Previous studies have demonstrated that long-term use of statins can indeed reduce serum CRP levels in patients with acute myocardial infarction, which may prove beneficial in the treatment of acute myocardial infarction (52,59). In the well-known Justification for use of statins in prevention: An intervention trial evaluating Rosuvastatin (JUPITER) trial, the use of statins significantly reduced the level of CRP in patients by 37%, while the level of cholesterol was also significantly reduced, leading to a lower incidence of CVD (60). This result has also been reported in other clinical studies (59,61-64).

However, the JUPITER study did not clearly demonstrate whether the cause of CVD protection was a decrease in cholesterol or a consequence of a decrease in CRP levels. A previous study reported that CRP appeared to predict CVD better than low-density lipoprotein cholesterol levels (27). Earlier studies have also reported that CRP and interleukin-6 are strongly associated with an increased risk of CVD (22,25). This hypothesis was further confirmed by Ridker *et al* (65) in the recent Canakinumab antiinflammatory thrombosis outcome study (CANTOS) trial study, where patients with a history of myocardial infarction were treated with canakinumab, an anti-inflammatory human monoclonal antibody targeting interleukin-1β. Canakinumab treatment significantly reduced the level of CRP in plasma without lowering lipid levels *in vivo*, thereby reducing the incidence of recurrent CVD. This is a significant finding, showing a potential new method for the treatment of atherosclerotic diseases in the future. There

Table I. The main animal experiments to explore the relationship between CRP and atherosclerosis.

| Authors, year | Genotype | Sex | Diet | CRP, $\mu$g/ml | Significance | Refs. |
|---|---|---|---|---|---|---|
| Paul *et al*, 2004 | huCRPtg$^{+}$/ApoE$^{-/-}$ | M + F | SD | M: >100[a]<br>F: 70[a] | P<0.02 (M)<br>proatherogenic | (30) |
| Reifenberg *et al*, 2005 | rbCRPtg$^{+}$/ApoE$^{-/-}$ | M + F | Protein-rich diet | M: 29.3±18.2[b]<br>F: 29.0±25.1[b] | ns | (45) |
| Trion *et al*, 2005 | huCRPtg$^{+}$/E3L | M + F | Hypercholesterolemic diet | M: 10.2±6.5[b]<br>F: 0.2±0.1[b] | ns | (47) |
| Hirschfield *et al*, 2005 | huCRPtg$^{+}$/ApoE$^{-/-}$ | M | SD | <30[a] | ns | (39) |
| Tennent *et al*, 2008 | huCRPtg$^{+}$/ApoE$^{-/-}$ | M | SD | 1.76-31.79[a] | ns | (44) |
| Kovacs *et al*, 2007 | huCRPtg$^{+}$/LDLR$^{-/-}$ | M | SD | 24.0-51.8[a] | P<0.05<br>antiatherogenic | (40) |
| Torzewski *et al*, 2008 | huCRPtg$^{+}$/LDLR$^{-/-}$ | M | WTD | 7.4±4.4 -12.8±4.8[b] | ns | (46) |
| Teupser *et al*, 2011 | CRP$^{-/-}$/ApoE$^{-/-}$, - CRP$^{-/-}$/LDLR$^{-/}$ | M + F | Low fat, semisynthetic diet | 7.5[a] | ns | (41) |
| Koike *et al*, 2009 | huCRPtg$^{+}$ rabbits | M | Cholesterol-rich diet | 57.8±20.6[b] | ns | (48) |
| Yu Q *et al*, 2014 | WHHL rabbits | M | SD | <30[a] | ns | (43) |

CRP, C-reaction protein; hu, human; rb, rabbit; WHHL rabbits, Watanabe heritable hyperlipidemic rabbits; M, male; F, female; SD, standard diet; WTD, Western type diet; ns, not significant; [a]range; [b]the mean ± SD.

is a close association between CRP and CVD: The detection of CRP levels may better predict the incidence of CVD and a decrease in CRP levels may lead to a reduced risk of CVD. A summary of the results of previous major clinical studies is shown in Table II.

**6. Possible mechanism of CRP in atherosclerosis**

As Ridker *et al* (65) suggested, a number of publications have also indicated that CRP may not be simply a predictor, but that it may also be directly involved in the pathogenesis of CVD and play a role in promoting the development of atherosclerotic lesions (66-68). Pasceri *et al* (69) were the first to demonstrate that increased CRP levels can induce the production of monocyte chemotactic protein 1. Moreover, previous studies have shown the expression of adhesion molecules in human endothelial cells (70-72). It has also been demonstrated that when injecting human CRP into mice and rats, the increase in CRP in the body affected endothelial nitric oxide synthase activity and led to endothelial cell dysfunction (73-76). CRP may also reduce the expression of endothelial nitric oxide synthase in endothelial cells (77,78), and significantly increase the expression levels of vascular cell adhesion molecule, intracellular adhesion molecule and monocyte chemokine (79), thus inhibiting angiogenesis (80). Teoh *et al* (81) confirmed this finding in mice over-expressing CRP transgenes, further suggesting that CRP can cause endothelial cell dysfunction. In clinical studies, CRP levels have also been associated with impaired endothelial vascular activity (82-84). Although there is a clear correlation between CRP and endothelial cells, it is not clear whether CRP affects the development and progression of atherosclerosis. Other studies have also demonstrated that CRP may play a direct role in the pathogenesis of atherosclerosis by activating endothelial cells (69,72,77,79,80). Subsequently, Devaraj *et al* (85) found through studying human aortic endothelial cells, that CRP can participate in the process of atherosclerosis by upregulating nuclear factor (NF)-κB, inducing the synthesis of interleukin-8. Endothelial cells are markers of early atherosclerosis and the occurrence of atherosclerotic diseases is closely associated with endothelial cells, monocytes/macrophages and vascular smooth muscle cells (86). Thus, studies on those types of cells may support the role of CRP in atherosclerosis. However, there is controversy regarding the source of CRP, as it may be argued that activating endothelial cells produces CRP, while human coronary artery smooth muscle cells can also synthesize CRP following stimulation by inflammatory cytokines (87). In atherosclerotic diseases, the migration and proliferation of smooth muscle cells is an important pathological event (88). CRP can upregulate the expression of AT1-R in vascular smooth muscle and further promote the migration and proliferation of vascular smooth muscle cells (38). Subsequent study have demonstrated that CRP can activate the function of FcγRIIa and NADPH oxidase 4 through a pro-inflammatory mechanism, thereby inducing vascular smooth muscle cells to produce reactive oxygen species (89). However, Liu *et al* (90,91) found that CRP can activate the NF-κB signaling pathway through toll-like receptor 4 and promote the expression of inflammatory cytokines in rat vascular smooth muscle cells. Other researchers suggested that CRP can induce monocytes to express tissue factor and stimulate the release of matrix in monocytes/macrophages, further promoting the rupture of atherosclerotic plaques and, eventually, leading to the occurrence of CVD (92-94). Ballou and Lozanski (95) demonstrated that CRP can induce the release of inflammatory cytokines from human monocytes. Torzewski *et al* (96) considered that CRP deposition in early atherosclerotic lesions may occur earlier than monocyte

Table II. Main clinical studies exploring the relationship between CRP and atherosclerosis.

| Authors, year | Medical history | Sex | Number of participants | CRP, $\mu$g/ml | Correlation between CRP and CVD | Refs. |
|---|---|---|---|---|---|---|
| Ridker *et al*, 1997 | Healthy population | M | 543 | 1.51-1.13[a] | Prediction | (22) |
| Haverkate F *et al*, 1997 | Outpatients with angina | M + F | 2,121 | >3.6[a] | Prediction | (55) |
| Ridker PM *et al*, 1999 | Cholesterol and recurrent events; randomly selected participants | M + F | 472 | <4.5[a] | Positive CRP↓CVD↓ | (52) |
| Koenig, W *et al*, 1999 | General population | M | 936 | 0.05-90.8[a] | Prediction | (23) |
| Danesh, J *et al*, 2000 | General population | M | 1,531 | >2.4[a] | Prediction | (24) |
| Ridker PM *et al*, 2002 | Healthy population | F | 27,939 | 1.4-2.3[a] | Prediction | (27) |
| Danesh J *et al*, 2004 | Cardiovascular disease population | M + F | 18,569 | 1.75±5.3[b] | Prediction | (54) |
| Ridker *et al*, 2008 | Healthy population (hyperlipidemia, hs-CRP level) | M + F | 17,802 | ~4.2[a] | Positive CRP↓ CVD↓LDL↓ | (60) |
| Ridker PM *et al*, 2017 | Previous myocardial infarction, hs-CRP level | F | 10,061 | ~4.2[a] | Positive CRP↓ CVD↓ | (65) |

M, male; F, female; CRP, C-reaction protein; CVD, cardiovascular diseases; LDL, low density lipoprotein cholesterol; ↓, reduction; [a]range; [b]the mean ± SD.

infiltration, which is a characteristic of early atherosclerotic lesions, indicating that CRP may play a key role in the production of monocytes.

The presence of CRP in human atherosclerotic plaques has been confirmed (32,87,97-99), and complement activation has been detected in atherosclerotic plaques (100-102). Torzewski *et al* (103) demonstrated the presence of complement proteins in plaques by studying early atherosclerotic lesions in humans and animals. Whether the CRP detected in atherosclerotic plaques indicates that CRP is implicated in the development of atherosclerosis and promotes plaque formation by activating the complement system requires further confirmation in future studies.

## 7. Discussion

As for the association between CRP and CVD, CRP has been confirmed as a predictor of CVD. However, the causal relationship between CRP and CVD has yet to be confirmed. The results of animal and clinical studies to date have been contentious. Due to the differences between animals and humans, the results of animal models require further research. CRP has long been used in clinical research as an acute phase protein, and CRP detection shows predictive value in CVD research (27,57). Several researchers have classified CRP as a clinical predictor of CVD (56,104-106). However, CRP has been found to be associated with the function of endothelial cells, monocytes/macrophages and smooth muscle cells, and it has also been detected in atherosclerotic plaques (38,81,85,90,92,97). Previous studies have demonstrated that CRP is produced by the liver and it is released in the blood and delivered to the corresponding tissue when there are inflammatory symptoms (107-110). However, whether there is another source of CRP remains unknown. If CRP can promote the migration and proliferation of endothelial cells, monocytes/macrophages and vascular smooth muscle cells, and then activate the complement system and participate in the occurrence of CVD, the association between CRP and CVD would constitute a major discovery. However, most researchers believe that the involvement of CRP in the pathogenesis of atherosclerosis by activating endothelial cells requires further confirmation. Based on the current experimental results, the causal association between CRP and CVD is uncertain. Research has long been performed using mouse models, but these models carry certain disadvantages when studying the association between CRP and CVD (45,111,112). In order to better simulate the human inflammatory response, better animal models must be designed, to simulate the overall or local mechanisms of action of CRP. Currently, the role of CRP in inflammation depends on synthetic sources (113), which may be the key to the current controversy between CRP and CVD. The results of this study show that CRP secreted by the liver is difficult to enter extrahepatic tissues, so CRP may be produced by extrahepatic tissues and transported back to the blood (113).

However, other animal models are required for future studies, including rabbits and non-human primates. Animal model studies using different species are valuable. However, these animal models are all systemic studies, so it is unknown whether the local effects caused by the expression or deletion of genes in animal models can more closely simulate human disease. There is evidence that the level of circulating CRP mainly reflects the underlying inflammatory state, the expression of local CRP is closely associated with the development of the disease, and with locally increased CRP at different sites potentially causing inflammation (114). Therefore, studying the local effects of CRP may be a better model of human disease. The clinical CANTOS experiment was the first to demonstrate that CVD can be effectively treated by anti-inflammatory drugs and that by reducing the level of CRP, it may be possible to reduce the risk of CVD (65). However, there is a limitation in that the risk of CVD is reduced following anti-inflammatory

therapy, but this inflammatory suppression may affect the treatment of other diseases. This requires more thorough research in the clinical setting.

## 8. Conclusion

In animal and clinical studies, CRP plays an important role in CVD. Although the CANTOS study shows that drugs can reduce CRP levels and the risk of CVD (65), its cardiovascular effects have not been clearly determined. A large number of animal studies and clinical conclusions have confirmed CRP as a biomarker, but whether CRP suppression exerts cardiovascular protective effects and whether it affects the occurrence and development of other diseases requires further comprehensive assessment.

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## Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the NCBI protein database, [https://www.ncbi.nlm.nih.gov/protein/. human (NP_000558.2), chimpanzee (XP_001170732.2), Rhesus monkey (XP_001117250.2), crab-eating macaque (NP_001306322.1), rabbit (NP_001075734.1), guinea pig (XP_003466601.1), naked mole-rat (XP_004858808.1), rat (NP_058792.1), golden hamster (XP_005078251.1), mouse (NP_031794.3), cattle (NP_001137569.1), sheep (XP_027821246.1), dog (NP_001301045.1), horse (XP_023496680.1)].

## Authors' contributions

YF wrote the manuscript. YW and EL reviewed and revised the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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