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Feature Article

A New Perspective for Chinese Medicine Intervention for Coronary Artery Disease: Targeting Inflammation*

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ABSTRACT Inflammation, which plays a critical role in atherosclerosis and the occurrence of acute cardiovascular events, may be a new target for treatment of coronary artery disease (CAD) to reduce residual cardiovascular risk. Recently, Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease (CANTOS), the largest scale clinical trial that targeted inflammation but not lipids, has affirmed for the first time the inflammatory hypothesis of artherosclerosis and marked the advent of an exciting era of targeting inflammation for the prevention and treatment of cardiovascular diseases. Chinese medicine (CM) is a promising adjuvant therapy for CAD in light of its safety and pleiotropic effect of anti-inflammation, anti-platelet, lipid-regulating, endothelium-protection, microcirculation-improving, etc. In recent years, exploration of anti-inflammatory treatment of CAD with CM has been going on from theory to practice. Taking CANTOS as an example, the design strategy to combine CM and Western medicine to inhibit inflammation were discussed in this paper, which might provide a new perspective for CM intervention on CAD.

KEYWORDS coronary artery disease, inflammation, Chinese medicine

Lowering plasma level of low density lipoprotein cholesterol (LDL-C) has been the focus of almost all recent studies on coronary artery disease (CAD) and results of these studies seem to support the concept that lower is better. Therefore, target LDL-C levels recommended by guidelines has reduced from less than 100 mg/dL (2.6 mmol/L) to less than 70 mg/dL (1.8 mmol/L) for patients at very high risk, and for patients at extreme risk, less than 55 mg/dL (1.4 mmol/L).[1-4] Undoubtedly, the lowering of LDL-C level has greatly improved prognosis for patients with CAD. However, it seems that further reduction of LDL-C to extremely low levels only generate limited benefits and there are still substantial residual cardiovascular risk. For example, in Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT), reduction of LDL-C from 2.4 to 1.4 mmol/L only resulted in an absolute risk reduction of 2%, and the 7-year event rates for primary outcome (death from cardiovascular causes, major coronary event, or nonfatal stroke) was still 32.7% in the ezetimibe plus simvastatin group;[5] In Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER), reduction of LDL-C from 2.4 to 0.78 mmol/L only generated an absolute risk reduction of 1.5%, and 2.2-year event rate for the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization was still 11.3%.[6] Besides, clinical and experimental data support a critical role for inflammation in atherosclerosis (AS) and the occurrence of acute cardiovascular events.[7-10]

Inflammation: A New Target for Treatment of CAD

The understanding of the biology of AS has incorporated the inflammatory hypothesis for more than 20 years.[8,11] Inflammatory cells and factors play a critical role in the initiation, growth of atherosclerotic plaque and occurrence of acute cardiovascular

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events. Inflammatory reactions could increase plaque instability, probablly resulting in plaque rupture, fissuring, or erosion preceding myocardial infarction, stroke, and cardiovascular death. These insights led to the recognition that inflammation accounts for a substantial proportion of unexplained residual cardiovascular risk. Therefore, many scholars believe that in addition to plasma cholesterol, the most promising intervention target for AS is inflammation.[12-14] The main components involved in the inflammatory process of AS are: (1) cells such as mononuclear cells, macrophages, lymphocytes, vascular endothelial cells, vascular smooth muscle cells, platelets, and so on; (2) pro-inflammatory factors, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), angiotensin-Ⅱ, interferon-gamma, endothelium cell adhesion factor 1, intercellular adhesion factor-1; (3) inflammatory markers like C-reactive protein (CRP).[15]

Multiple prospective and epidemiological studies have found that the level of CRP/high-sensitivity C reactive protein (hs-CRP) mainly reflected the stability of coronary atherosclerotic plaques and was closely related to acute cardiovascular events.[16-20] CRP/hs-CRP is the mostly recognized inflammatory marker currently and an independent risk factor for cardiovascular events.[21-23] CRP can induce endothelial cells to express cell adhesion molecules, IL-6 and endothelin-1 (ET-1), etc., increase the uptake of LDL-C by macrophages, inhibit the formation of nitric oxide (NO) and angiogenesis, increase the expression of vascular smooth muscle angiotensin 1 receptor and inhibit the release of prostacyclin by endothelial cells. These processes are directly related to the occurrence and development of AS and plaque rupture.

The most intriguing results for inflammation is from Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. In JUPITER, investigators found that among patients with an elevated level of hs-CRP and normal lipid profiles, statins (rosuvastatin) treatment decreased hs-CRP by 37% and resulted in a lower incidence of major vascular events than placebo.[24] However, because the level of LDL-C was also lowered from baseline, it was impossible to conclude that the reduction of hs-CRP or the inhibition of inflammation was responsible for the clinical benefit. IL-1β is a cytokine that is central to the inflammatory response and plays a critical role in AS through IL-6 and CRP. Canakinumab, which has been approved for clinical use in rheumatologic disorders, is a human monoclonal antibody against IL-1β. Therefore, Ridker, et al[25] conducted the Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease (CANTOS) trial to directly test the inflammatory hypothesis of atherothrombosis. In the trial, 10,061 patients with previous myocardial infarction and hs-CRP ⩾2 mg/L were randomly assigned to 3 doses of canakinumab (50, 150, 300 mg) or placebo, administered subcutaneously every 3 months. The median follow-up time was 3.7 years compared with placebo, canakinumab reduced the hs-CRP level from baseline in a dose-dependent fashion (26%, 37% and 41% lower than placebo, respectively), with no reduction in the LDL-C level. The 150-mg dose of canakinumab significantly lowered incidence of the primary end point (a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) compared with placebo.

CANTOS, the largest scale double-blinded, placebo-controlled, randomized clinical trial that targeted inflammation but not lipids, has affirmed for the first time the inflammatory hypothesis of artherosclerosis and marked that we are entering an exciting era of targeting inflammation for the prevention and treatment of cardiovascular diseases.[26]

Anti-inflammatory Treatment of CAD with CM: from Theory to Practice

Despite the scientific and clinical excitement about canakinumab for CAD, some concerns should be noticed. First of all, fatal infection occurred more often in patients who received canakinumab than in those who received placebo. Besides, the agent now is too expensive (costs $200,000 a year) to limit its clinical application. Lastly, targeting one mediator (IL-1β) by canakinumab can not block all inflammatory pathways implicated in AS since inflammatory signaling pathways have considerable redundancy, which may be an important reason why it failed to reduce cardiovascular death. Therefore, there is a need to find anti-inflammatory agents that is as or more effective but safer and cheaper than Canakinumab.

Blood stasis syndrome (BSS) is the most common CM syndrome in patients with CAD. However, although the blood stasis theory could perfectly accout

for the biology of platelet aggregation and activation, increased blood viscosity, hypercoagulability and thrombosis in AS, it can not explain inflammation, endothelial injury, oxidative stress and tissue necrosis involved in AS, etc. Therefore, the research team led by academician CHEN Ke-ji proposed the "blood-stasis and toxin causing deterioration" hypothesis: BSS is ubiquitous in the atherothrombotic process in CAD, and is also the basic CM pathology in stable CAD. If the blood stasis persists, it leads to heat-transmission and toxin-formation and then causes "blood-stasis and toxin" status. Untreated or mistreated, and stimulated by exopathic factors, this "blood-stasis and toxin" status will block the circulation of qi and blood in heart and lead to adverse events such as unstable angina, acute myocardial infarction or sudden cardiac death. On the basis of this hypothesis, a large sample cohort study was conducted to establish the blood-stasis and toxin syndrome differentiation criteria for stable CAD, which provided the theoretical basis for anti-inflammatory treatment of CAD with CM.[27]

In some previous experimental researches, CM herbs or extracts with blood activating and detoxifying or heat-clearing and detoxifying property such as prepared *Radix et Rhizoma Rhei* with wine,[28,29] *Andrographis Paniculata* P.E,[30] red yeast rice,[31] effective components of *Chuanxiong Rhizome* and red Peony root,[32] and Qingre Quyu Granule,[33] were found to have anti-inflammatory, antiischemic and plaque stabilizing effects.

Small-sample clinical studies showed that Chinese patent medicine like Danhong Injection (丹红注射液) and Compound Danshen Injection (复方丹红注射液),[34] Safflower Yellow Injection (红花注射液),[35] Xuefu Zhuyu Oral Liquid (血府逐瘀口服液),[36] Xinqingning Tablets (新清宁片)[37] could effectively relieve angina pectoris and inhibit the inflammatory reaction of CAD patients. However, none of these studies used inflammatory markers as the main endpoints. All the subjects in these studies were not with increased inflammatory reaction or elevated hs-CRP level and those with high risk of infection or other systemic inflammatory diseases were not excluded. Consequently, these studies can not fully confirm the clinical efficacy of CM with anti-inflammatory property in the treatment of CAD.

CM with activating blood circulation (ABC) properties is widely used in CAD treatment. Among them, *Salvia miltiorrhiza* preparation was most extensively studied. Since 1830s, the chemical composition of *Salvia miltiorrhiza* and their biological activity have been widely studied. More than 30 liposoluble components and 30 water-soluble components were identified and extracted from *Salvia miltiorrhiza*, among which tanshinone ⅡA sulfate (TS) is one of the most active component.

Previous preclinical researches showed that TS had anti-inflammatory and plaque stabilizing effects.[38,39] Other studies also demonstrated the anti-inflammatory effect of TS, including the chronic inflammation in CAD.[40] Robertson, et al[41] found that TS had most potent anti-inflammatory effects *in vivo* both by induction of neutrophil apoptosis and by promoting reverse migration of neutrophils. Although this research is not within field of CAD, it provides evidence that TS is a promising anti-inflammatory agents. To assess the effectiveness and sustained effect of TS on hs-CRP and other inflammatory markers in patients with unstable CAD, we conducted a prospective small sample randomized open-label trial.[42] As hs-CRP more than 3 mg/L is considered an independent risk factor for cardiovascular events and more than 15 mg/L may be more suggestive of infection,[43] only patients of non-ST elevation acute coronary syndrome (NSTE-ACS) with hs-CRP level between 3 and 15 mg/L were enrolled. Patients were randomly assigned to atorvastatin-based standard medical therapy or standard therapy plus Sodium Tanshinone ⅡA Sulfate (STS) Injection (80 mg, once daily for 14 consecutive days) with 1-month follow-up. Patients with infection and taking any antibiotics or any CM with the function of clearing heat and removing toxins were excluded. After 14-day treatment, the levels of hs-CRP in the experimental group were significantly lower than that in the control group (1.72 *vs*. 3.20 mg/L, P=0.0191), and lower levels of IL-6, chemotactic protein-1 (MCP-1), and soluble CD40 ligand were also observed in the experimental group.[44] Besides, angina symptoms were also better improved in the experimental group (P<0.01). At 30 days after treatment completion, MCP-1 levels remained lower in the experimental group than in the control group (313.88 *vs*. 337.91 pg/mL, P=0.0078). Notably, no serious adverse events occurred. The study suggests that STS may alleviate the symptoms of angina pectoris by further reducing elevated hs-CRP and other circulating inflammatory markers

(IL-6, MCP-1, sCD40L) and stabilizing AS plaque in NSTE-ACS patients with increased inflammatory response. The apparent additive effect of STS in reducing the level of MCP-1 even persisted to 30 days after the completion of treatment. Since no previous high-quality study has evaluated the effect of TS on hs-CRP and other inflammatory markers in CAD patients, the findings shed light on the benefit and safety of an adjunct therapy of TS regimen for CAD patients with enhanced inflammatory reaction, thereby offering potential implications for clinical practice from anti-inflammatory perspective.

In addition, there is another trial which found that Qingxin Jieyu Decoction (清心解瘀汤, QXJY, with the effect of blood circulation activating and detoxifying effects) in addition to conventional treatment can reduce inflammatory markers (hs-CRP, IL-6, sCD40L, matrix metalloprotein-9) level of stable CAD.[45] Accordingly, a multicenter, randomized, double-blind pacebo-controlled trial (QUEST Trial) is carried out to test if QXJY combined conventional treatment is more superior to reduce inflammation of AS and finally lead to the reduction of major adverse cardiac event (MACE) in high-risk stable CAD patients.[46] It will undoubtedly provide an evidence-based complementary therapeutic approach for anti-inflammation and contribute to further reducing MACE for CAD.

Prospect

For quite a long time, anti-inflammatory therapy for CAD mainly rests on preclinical studies and results of many clinical studies targeting inflammation are not satisfactory. For example, some anti-inflammatory medicine failed to reduce the incidence of cardiovascular events (such as darapladib, a lipoprotein phospholipase A2 antagonism,[47,48] and losmapimod, a p38 mitogen-activated protein kinase inhibitor[49]), and some even bring harm to patients with CAD (anakinra, an IL-1 receptor inhibitor[50] and varespladib, a secretory phospholipase A2 inhibitor,[51,52] may increase the risk of cardiovascular events; etancept, a TNF-α antagonism, may increase the activity of platelets[53]). All these cases impeded wide acceptance of the inflammation hypothesis and application of anti-inflammatory agents in clinical practice. Since the CANTOS trial proved the clinical benefit of an agent targeting inflammation and autoimmunity, this old-tree-new-buds field is opened to further investigation and definitely will receive more and more attention.

CM is a promising adjuvant therapy for CAD in light of its safety and pleiotropic effect of anti-inflammation, anti-platelet, lipid-regulating, endothelium-protection, microcirculation-improving and anti-myocardial ischemia. The above clinical trial of TS undoubtedly provides a novel integrative strategy to combine CM and Western medicine to inhibit inflammation, thus provding a new perspective to safely reduce residual cardiovascular risk in patients with CAD. Considering the small scale of present clinical trials, whether the reduction of inflammatory factors by CM in CAD patients will ultimately reduce future cardiovascular events and yield long-term prognostic benefit should be investigated by future clinical trials. So far, QUEST Trial might be the only registered clinical trial of CM intervention sponsored by the national funding of China to evaluate CM in combination with conventional treatment on inhibiting inflammatory response and reducing MACE in high-risk stable CAD patients. We are looking forward to more and more strictly designed clinical trials assessing effects of CM with anti-inflammatory effects on cardiovascular event in the future.

REFERENCES

1. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel Ⅲ Guidelines. Circulation 2004;110:227-239.
2. European Association for Cardiovascular Prevention and Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32:1769-1818.
3. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J 2013;34:2949-3003.
4. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 2017;23:479-497.

5. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-2397.
6. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-1722.
7. Li JJ, Fang CH. Atherosclerosis is a more rational term for the pathological entity currently known as atherosclerosis. Med Hypotheses 2004;63:100-102.
8. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115-126.
9. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685-1695.
10. Libby P, Ridker PM, Hansson GK; Leducq Transatlantic Network on Atherothrombosis. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol 2009;54:2129-2138.
11. Alexander RW. Inflammation and coronary artery disease. N Engl J Med 1994;331:468-469.
12. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature 2011;473:317-325.
13. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitive C-reactive protein: rationale and design of the JUPITOR trial. Circulation 2003;108:2292-2297.
14. Li JJ, Li YS, Fang CH, Hui RT, Yang YJ, Cheng JL, et al. Effects of simvastatin within two weeks on anti-inflammatory cytokine interleukin-10 in patients with unstable angina. Heart 2006;92:529-530.
15. Li JJ. Inflammation and atherosclerosis. Chin J Front Clin Sci (Elect version, Chin) 2011;3:4-6.
16. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005;352:29-38.
17. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352:20-28.
18. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132-140.
19. Musunuru K, Kral BG, Blumenthal RS, Fuster V, Campbell CY, Gluckman TJ, et al. The use of high sensitivity assays for C-reactive protein in clinical practice. Nat Clin Pract Cardiovasc Med 2008;5:621-635.
20. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-1565.
21. KoenigW. High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. Int J Cardiol 2013;168:5126-5134.
22. Kaptoge S, Seshasai SR, Gao P, Freitag DF, Butterworth AS, Borglykke A, et al. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. Eur Heart J 2014;35:578-589.
23. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003;107:363-369.
24. Ridker, P. M, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195-2207.
25. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-1131.
26. Peter Libby. Interleukin-1 beta as a target for atherosclerosis therapy: biological basis of CANTOS and beyond. J Am Coll Cardiol 2017;70:2278-2289.
27. Chen KJ, Shi DZ, Xu H, Yin HJ, Zhang JC. The criterion of syndrome differentiation and quantification for stable coronary heart disease caused by etiological toxin of Chinese medicine. Chin J Integr Tradit West Med (Chin) 2011;31:313-314.
28. Wen C, Xu H, Huang QF, Chen KJ. Effect of drugs for promoting blood circulation on blood lipids and inflammatory reaction of atherosclerotic plaques in ApoE gene deficiency mice. Chin J Integr Tradit West Med (Chin) 2005;25:345-349.
29. Wen C, Xu H, Huang QF, Chen KJ, Li P, Sheng X. Effects of herbs of activation blood on atherosclerotic plaque morphology in ApoE gene-deficient mice. Chin J Pathophysiol (Chin) 2005;21:864-867.
30. Li SS, Zhao HY, Guo ZL. Study on the effective component API0134 of *Andrographis paniculata* to prevent reocclusion after coronary artery thrombolysis in dogs (Abstract). Chin Circ J (Chin) 1999;14:5-6.
31. Wu M, Zhang WG, Liu LT. Red yeast rice prevents atherosclerosis through regulating inflammatory signaling pathways. Chin J Integr Med 2017;23:689-695.
32. Huang Y, Yin HJ, Ma XJ, Wang JS, Liu Q, Wu CF, et al. Correlation between Fc γ R Ⅲ a and aortic atherosclerotic plaque destabilization in ApoE knockout mice and intervention effects of effective components of *Chuanxiong rhizome* and red Peony root. Chin J Integr Med 2011;17:355-360.

33. Wang Y, Cheng WL, Wang Y, Peng JP, Yuan J, Chen L, et al. Qingre Quyu Granule stabilizes plaques through inhibiting the expression of tenascin-C in patients with severe carotid stenosis. Chin J Integr Med 2015;21:339-345.
34. Liu JH, Muo GH, Tang L. Clinical study of Danhong Injection on coronary heart disease with angina pectoris. J Chin Physici (Chin) 2006;8:1715-1719.
35. Lin P, Ren QY. Effect of Safflower Yellow Injection on the inflammatory factor and blood lipids of old patients with coronary heart disease. Chin Hosp Pharm J (Chin) 2009;29:652-653.
36. Liu JG, Xu H, Dong GJ, Shi DZ, Zhou GH, Zhu JH, et al. Xuefu Zhuyu Oral Liquid on vascular endothelium function and hemorrheologic influence in patients with angina pectoris and blood- stasis syndrome. Chin J Integr Med Cardio Cerebrovasc Dis (Chin) 2006;4:659.
37. Zheng F, Zhou MX, Xu H, Chen KJ. Effects of herbs with function of activating blood circulation and detoxication on serum inflammatory markers and blood lipids in stable patients with coronary heart disease. China J Tradit Chin Med Pharm (Chin) 2009;24:1153-1157.
38. Zhou MX, Xu H, Chen KJ, Pan L, Wen C, Liu JG. Effects of some active ingredients of Chinese drugs for activating blood circulation and detoxicating on blood lipids and atherosclerotic plaque inflammatory reaction in ApoE-gene knockout mice. Chin J Integr Med Cardio-/Cerebrovasc Dis (Chin) 2007;5:1202-1205.
39. Gao S, Liu Z, Li H, Little PJ, Liu P, Xu S. Cardiovascular actions and therapeutic potential of tanshinone ⅡA. Atherosclerosis 2012;220:3-10.
40. 40. Li HZ, Lu YH, Huang GS, Chen Q, Fu Q, Li ZL. Tanshinone II A inhibits dendritic cell-mediated adaptive immunity: potential role in anti-atherosclerotic activity. Chin J Integr Med 2014;20:764-769.
41. Robertson AL, Holmes GR, Bojarczuk AN, Burgon J, Loynes CA, Chimen M, et al. A zebrafish compound screen reveals modulation of neutrophil reverse migration as an anti-Inflammatory mechanism. Sci Transl Med 2014;6:225ra29.
42. Shang QH, Wang H, Li SM, Xu H. The effect of sodium tanshinone ⅡA sulfate and simvastatin on elevated serum levels of inflammatory markers in patients with coronary heart disease: a study protocol for a randomized controlled trial. Evid Based Complement Alternat Med 2013;2013:756519.
43. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151:483-495.
44. Li SM, Jiao Y, Wang H, Shang Q, Lu F, Huang L, et al. Sodium tanshinone ⅡA sulfate adjunct therapy reduces high-sensitivity C-reactive protein level in coronary artery disease patients: a randomized controlled trial. Sci Rep 2017:17451.
45. Gao X. Clinical Study of Qing-Xin-Jie-Yu Decoction on elevated serum levels of inflammatory markers in patients with stable coronary heart disease [dissertation]. Beijing: Chin Academy of Chinese Medical Sciences; 2017.
46. Li SY, Guo M, Mao HM, Gao ZY, Xu Hao, Shi DZ. Qing-Xin-Jie-Yu Granules in addition to conventional treatment for patients with stable coronary artery disease (QUEST Trial): study protocol for a randomized controlled trial. Trials 2016;17:451.
47. White HD, Held C, Stewart R. Darapladib for preventing ischemic events in stable coronary heart disease. N Engl J Med 2014;370:1702-1711.
48. O'Donoghue ML, Braunwald E, White HD, Lukas MA, Tarka E, Steg PG, et al. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. JAMA 2014;312:1006-1015.
49. Newby LK, Marber MS, Melloni C, Sarov-Blat L, Aberle LH, Aylward PE, et al. Losmapimod, a novel p38 mitogen-activated protein kinase inhibitor, in non-ST-segment elevation myocardial infarction: a randomised phase 2 trial. Lancet 2014;384:1187-1195.
50. Morton AC, Rothman AM, Greenwood JP, Gunn J, Chase A, Clarke B, et al. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. Eur Heart J 2015;36:377-384.
51. Koenig W, Khuseyinova N. Lipoprotein-associated and secretory phospholipase A2 in cardiovascular disease: the epidemiological evidence. Cardiovasc Drugs Ther 2009;23:85-92.
52. Nicholls SJ, Kastelein JJ, Schwartz GG, Bash D, Rosenson RS, Cavender MA, et al. Varespladib and cardiovascular events in patients with an acute coronary syndrome: the VISTA-16 randomized clinical trial. JAMA 2014;311:252-262.
53. Padfield GJ, Din JN, Koushiappi E, Mills NL, Robinson SD, Cruden NM, et al. Cardiovascular effects of tumour necrosis factor alpha antagonism in patients with acute myocardial infarction: a first in human study. Heart 2013;99:1330-1335.

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