中国科学: 生命科学 2022 年 第 52 卷 第 6 期: 797 ~ 811
SCIENTIA SINICA Vitae lifecn.scichina.com
《中国科学》杂志社 SCIENCE CHINA PRESS
评 述 中医药与重大疾病防治专辑

病证结合与冠心病防治策略

李逸雯, 罗斌玉, 崔京, 朱梦梦, 刘玥*, 徐浩, 史大卓, 陈可冀*

中国中医科学院西苑医院, 国家中医心血管病临床医学研究中心, 北京 100091
* 联系人, E-mail: liuyueheart@hotmail.com; kjchenvip@163.com

收稿日期: 2021-10-26; 接受日期: 2022-02-10; 网络版发表日期: 2022-03-30
国家自然科学基金优秀青年基金(批准号: 82022076)和国家中医药管理局中医药创新团队及人才支持计划项目(批准号: ZYYCXTD-C-202007)、中国中医科学院科技创新工程项目(批准号: CI2021B004)资助

摘要 病证结合是中西医结合临床的最佳模式, 具有原始创新的重要价值. 冠心病是危害人类健康的重大疾病, 中医药以血瘀证为关键证候发展了冠心病病机新认识, 从定性到定量确立了冠心病病证结合量化标准及诊断新标志物, 以循证方法证实了相关药物的临床疗效与安全性, 采用现代科学技术方法深入探索了以活血化瘀中药为代表的中医药防治冠心病的作用机理, 构建了以病证结合为特色的冠心病中西医结合防治策略. 病证结合血瘀证诊断标准的制定实现了中医证候的定量诊断, 涌现了大量活血化瘀药物防治冠心病的随机对照研究(randomized controlled trial, RCT)用以证实其有效性与安全性. 冠心病血瘀证生物学实质与活血化瘀机理研究涉及血小板功能、炎症介质、氧化应激等多方面, 体现出中医药多靶点特征与优势. 本文以冠心病血瘀证和活血化瘀为病证结合研究的切入点, 系统梳理了60年来中西医结合防治冠心病的研究历程, 并对未来的研究方向进行展望, 以期为进一步完善、优化具有中国特色的冠心病防治的中国方案提供参考.

关键词 冠心病, 血瘀证, 活血化瘀, 病证结合, 中西医结合

冠心病是全球范围内死亡率及致残率最高的疾病之一, 在中国目前约有1100万人罹患该病[1]. 近30年来冠心病西医治疗手段不断丰富, 冠心病患者的生存率得到显著提高, 但同时冠心病慢病综合管理的需求也逐步增加. 随着社会老龄化的进展, 冠心病常合并糖尿病、高血压、卒中等多种慢病, 极大提高了疾病综合管理的难度[2], 中医药防治冠心病的临床实践优势不断显现, 值得深入研究. 冠心病中医药防治在20世纪60年代前长期处于以经验医学为主的医家各家争鸣状态, 未得到统一共识. 中西医的碰撞出于诊疗需求, 现代医学结合中医对疾病的病理状态认识, 形成以西医疾病与中医证候结合的“病证结合模式”[3]. 以陈可冀院士为代表的中国第一代中西医结合医学家在大量临床实践中发现, 冠心病患者的诸多表现与中医血瘀证候存在相似之处, 尝试使用活血化瘀中药治疗后取得较好临床疗效[4,5]. 中国中医研究院与中国医学科学院阜外医院协作开发活血化瘀代表性方剂冠心2号, 十多家医院临床大协作同时开展基础研究, 是首先在我国开展循证医学临床研究实践的项目[6], 从而正式开启了以“血瘀”为切入点的冠心病病证结合的系列研

引用格式: 李逸雯, 罗斌玉, 崔京, 等. 病证结合与冠心病防治策略. 中国科学: 生命科学, 2022, 52: 797–811
Li Y W, Luo B Y, Cui J, et al. Combination of disease and syndrome in coronary artery disease: prevention and treatment strategies (in Chinese). Sci Sin Vitae, 2022, 52: 797–811, doi: 10.1360/SSV-2021-0384

究. 经过数代人的不懈努力, 取得了一系列创新性成果, 丰富了冠心病的防治策略, 显著降低了冠心病病死率[7,8], 走出了一条具有原始创新的中西医结合研究之路.

1 走向共识: 冠心病中医病机与病证结合诊断标准

1.1 冠心病中医病机: 创新与发展

冠心病属于中医"胸痹"范畴, 中医经典古籍《金匮要略》中首次提出该病名, 且将胸痹的病机归纳为"阳微阴弦"(即上焦阳虚而阴寒内盛), 后世沿用此法治以通阳豁痰宣痹, 但临床疗效仍有很大的提高空间. 随着现代医学体系对中医药传统诊疗模式的巨大冲击和不断融合, 西医明确诊断结合中医辨证论治的"病证结合模式"成为最佳的中西医结合研究范式[3]. 20世纪60年代, 陈可冀等学者通过大量的临床实践发现, "血瘀"可能是冠心病发病及加重的关键中医病机, 应用活血化瘀中药治疗可明显减轻冠心病心绞痛患者的症状, 且可明显减少硝酸酯类药物的用量[9]. 冠状动脉病变严重程度、经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI)后再狭窄等情况与中医血瘀证密切相关[10,11], 尤其发现血瘀证患者存在更高的不良心血管事件(major adverse cardiovascular events, MACE)风险[12], 从而正式提出"血瘀"是冠心病中医核心病机的认识, 基于以上认识, 采用活血化瘀中药防治冠心病成为学界共识. 后续临床中又发现, 稳定性冠心病患者有的长期稳定, 有的却突发急性冠脉综合征(acute coronary syndrome, ACS), 单纯的血瘀并不能解释所有临床现象. 因此, 陈可冀院士带领团队研究发现, 中医"瘀毒理论"结合冠心病现代病理的炎症、氧化应激等机制, 以"毒"的内涵可以更全面概括解释冠心病突发炎症风暴继而引发病理性血栓破裂的过程, 从而提出了冠心病"瘀毒致变"的中医病机新认识, 即瘀为常, 毒为变[13,14], 遂采用活血解毒中药防治ACS, 显示出更为显著的临床效果[15,16]. 病证结合明确了血瘀、瘀毒等中医病机在冠心病发病中的关键地位, 并通过现代医学方法评价其临床应用价值. 中医病因病机认识学上的每一次发展和创新, 都会带来治疗学的改变和相应疾病防治效果的巨大进步, 从另一个角度来说, 冠心病的中医辨证也丰富了冠心病现代医学的分型策略, 为病证结合的定量研究提供了理论基础. 病证结合的代表性成果见图1.

1.2 冠心病病证结合诊断标准: 从主观判断到客观量化

从定性诊断到定量诊断, 以血瘀证为切入点, 围绕冠心病病证结合诊断标准的制定, 截至目前已发布7篇有指导意义的标准或专家共识, 可大致分为以下三个阶段: (ⅰ) 1982~2000年, 血瘀证的中医诊断标准确立. 主要基于回顾性或横断面研究数据及专家共识确定血瘀证各诊断依据的占比; (ⅱ) 2001~2015年血瘀证诊断标准开始广泛结合临床常用理化检查, 描述更精确; (ⅲ) 2016年正式发布冠心病血瘀证量化诊断标准. 舌质紫暗及瘀斑、面色唇色紫黑、脉涩及脉结代、体表肿块及肌肤甲错、疼痛性质、出血倾向及离经之血是中医血瘀证诊断的主体内容, 也是各版血瘀证诊断标准的共同点. 在对现代辅助检查结果的纳入上各版本情况不一, 2011年至今通过循证医学的方法对冠脉病变程度、凝血功能、血流动力学指标补充入血瘀证诊断, 丰富了临床血瘀证诊断的应用范围. 具体见表1.

2 循证评价: 以活血化瘀方药的临床研究为例

病证结合的临床研究通过引入循证医学和转化医学, 实现了药效的客观评价[30,31], 也证实中医药的临床应用可丰富冠心病的现代综合管理方案. 病证结合冠心病的临床研究始于对活血化瘀中药的临床评价, 中医药领域第一个随机对照研究(randomized clinical trial, RCT)于1982年在《中华心血管病杂志》发表, 该研究首次以多中心、双盲的方法评价了活血化瘀复方精制冠心片(丹参、赤芍、川芎、红花、降香)防治冠心病的效果[6], 显示其可显著改善冠心病的症状及心电图的变化结果, 明显减少硝酸甘油的使用.

随后的40年来, 临床研究涵盖多种治法方剂(活血化瘀、益气活血、活血解毒等)、不同剂型(水煎剂、中成药、喷雾剂、注射剂等)、冠心病不同类型或阶段(稳定型冠心病、不稳定性心绞痛、PCI术后再狭窄、缺血再灌注后无复流等). 众多RCT显示不同配伍的活血化瘀方剂可有效防治冠心病[32,33], 提示活血化瘀本身存在生物学机制的一致性, 胸痹皆瘀. 研究显

图 1　1949年后冠心病病证结合研究代表性成果[6~9,17~25](网络版彩图)

Figure 1　Representative research results of coronary artery disease of combination of disease and syndrome after 1949[6~9,17~25] (color online)

示, 同一活血化瘀药物可应用于不同冠心病疾病阶段, 如服用血府逐瘀相关制剂[34~36]及芎芍胶囊[17,18,37]不仅可明显改善稳定性心绞痛及不稳定性心绞痛的临床症状及心电图结果, 同时被证实可抑制PCI术后的血管再狭窄. 复方丹参滴丸[38~40]、速效救心丸[41]、愈心痛胶囊[42,43]等可有效缓解心绞痛症状, 减少硝酸甘油使用, 稳定ACS患者的临床症状. 通心络胶囊[44~46]保护心肌梗死后再灌注的心肌及微血管, 维持左室射血分数, 减少坏死心肌面积, 安全性良好. 因此活血化瘀治疗贯穿冠心病始终, 有重要的临床应用价值.

冠心病病程漫长, 病机多变, 在血瘀的基础上对合并气虚、痰浊、瘀毒病机的不断探索, 不仅丰富了冠心病病证结合研究的科学内涵, 对拓展冠心病的中医治法也提供了理论基础. 气虚血瘀是冠心病患者最为常见的证型之一, 临床治以益气活血, 其中抗心梗合剂[47]以益气养阴活血法治疗急性心肌梗死可提高患者抗休克耐力, 减少心律失常发生. 心悦胶囊联合复方丹参片[48]、参术冠心方[49]均通过益气活血改善心肌梗死血运重建后心肌灌注情况, 具有良好的心肌保护效果. 芳香温通、化痰活血用以治疗心绞痛急性发作, 宽胸气雾剂[50,51]、丹蒌片[52]可明显改善冠心病患者心绞痛症状, 抑制炎症反应、促进斑块稳定. 愈梗通瘀汤

表 1 血瘀证相关诊断标准简要情况

Table 1 Overview of diagnostic criteria for syndromes of blood stasis

名称	年份	量化诊断	实验室检查项目	影像学项目	共性内容
血瘀证诊断试行标准[21]	1983	否	无	(1) 头颅血管造影; (2) 头颅CT	(1) 舌质紫黯或舌体瘀斑、瘀点; (2) 面部、唇、齿龈及眼紫黑; (3) 肌肤甲错; (4) 脉涩, 或结、代, 或无脉; (5) 固定性疼痛; (6) 痛经伴色黑有血块或闭经; (7) 脏器肿大、新生物、病理性肿块; (8) 出血倾向、离经之血, 出血后引起的瘀血(包括外伤后出血)
血瘀证诊断标准[26]	1987	定量积分	(1) 血液流变学功能; (2) 微循环功能; (3) 凝血及纤溶功能; (4) 血小板功能; (5) 血流动力学功能	血管造影	
国际瘀血诊断标准试行方案[27]	1987	定性诊断	(1) 血液流变学功能; (2) 微循环功能; (3) 血小板功能; (4) 血液黏度	(1) 血管造影; (2) 心肌闪烁显像; (3) 骨盆腰椎X线异常	
血瘀证中西医结合诊疗共识[28]	2011	否	(1) 血液流变学功能; (2)血小板功能	血管造影	
实用血瘀证诊断标准[24]	2016	定性诊断	(1) 血液流变学功能; (2) 微循环功能; (3) 凝血及纤溶功能	(1) 血管造影; (2) 提示血栓、梗死、栓塞的证据	
冠心病血瘀证诊断标准[25]	2016	定量积分	凝血及纤溶功能	(1) 血管造影; (2) 心脏超声	
国际血瘀证诊断指南[29]	2021	定性诊断	(1) 血液流变学功能; (2) 微循环功能 (3) 凝血及纤溶功能; (4) 血小板功能	(1) 血管造影; (2) 提示血栓、梗死、栓塞的证据; (3) 胸部CT	

用于急性心肌梗死患者改善血流动力学紊乱、修复损伤心肌、缩小梗死面积从而减少心肌梗死并发症的出现, 显著改善心功能[53]. 由活血解毒中药组成的清心解瘀方可降低稳定性冠心病患者心源性死亡、非致命性心肌梗死及卒中的发生率, 并可降低稳定性冠心病患者心血管复合终点结局的发生率, 安全性良好[7], 并从细胞焦亡、炎症反应、肠道菌群等层面解释该方的作用机制[54~56].

目前虽已有大量活血化瘀中药防治冠心病的RCT发表, 但多数研究样本量小、随机化方法和结局指标选择不太恰当, 因此研究水平及证据级别有限, 但近年来亦有高水平的临床研究发表引起广泛关注. 一项纳入3505例患者的多中心随机双盲研究显示, 芪参益气滴丸对心血管复合终点、非致命性心肌梗死及卒中发生率与阿司匹林无统计学差异, 芪参益气滴丸可能具有类似阿司匹林的心肌梗死二级预防效果[8]. MUST研究[19]纳入97个中心的2674例患者, 进行24个月干预后MACE事件及心绞痛症状发生率均有统计学差异, 麝香保心丸的活血化瘀治疗可作为冠心病患者的长期治疗手段. QUEST研究[7]多中心纳入1500例患者, 经6个月随机双盲干预, 发现试验组心源性死亡、非致命性心肌梗死和缺血性卒中组成的复合终点事件发生率显著降低, 提示清心解瘀方对稳定性冠心病的临床防治具有重要价值.

3 机制研究: 血瘀证的生物学实质与活血化瘀现代机理的有益探索

冠心病病证结合研究不仅初步明确了冠心病血瘀证的生物学实质[57], 同时对活血化瘀中药的现代作用机理进行了有益的探索, 取得了一定的进展. 目前冠心病血瘀证相关生物标志物众多, 单一的指标变化无法充分显示冠心病血瘀证生物学实质的复杂性[58]. 随着多组学技术的快速发展和对冠心病不同分型及阶段病理状态间交互机制的深入认识, 目前的认知告诉我们冠心病血瘀证的生物学实质是多维度而非线性的. 活血化瘀的现代理解也包括两个层次, “活血”为改善生理功能, “化瘀”为消除病理变化. 从目前的研究结果来看, 活血化瘀中药可调节血小板功能[59,60], 抑制炎症反应[61], 抑制氧化应激[62], 改善血流动力学[63], 改善脂代谢异常[64], 调控表观遗传[65,66]等. 近3年来研究热点聚焦为线粒体, 外泌体, 非编码RNA, 如微小核糖核酸(microRNA, miRNA)及长非编码(long non-coding RNA, lncRNA)、细胞自噬、肠道菌群等[67~69].

3.1　血瘀证、活血化瘀与血小板功能

冠心病血瘀证及活血化瘀机理研究中最为核心的就是围绕血小板功能的探索. 血小板功能可影响凝血进程, 维持血管壁完整性, 调节血液流变学, 控制炎症因子释放, 调节单核-吞噬细胞系统等[70], 与血瘀证密切相关[71]. 冠心病血瘀证患者血浆代谢组学分析发现, 其存在明显的血小板聚集, 花生四烯酸、亚油酸表达显著增高, 血小板膜糖蛋白CD62P, GPⅡb/Ⅲa, CD40L活化[72], 血小板微粒(platelet microparticle)、内皮细胞微粒(endothelial microparticle, EMP)等表达增加[73]. 冠心病血瘀证患者血小板的吞噬乳胶颗粒数量减少、吞噬功能降低, 免疫清除功能降低[74], 致血小板活化、黏附及聚集性增强. 冠心病血瘀证血小板蛋白质组学的研究引起广泛关注[60].

血小板功能大致分为活化、黏附、聚集和炎症四部分, 多种活血化瘀中药具有其中一种或多种调节作用[75]. 现代研究中通过对血小板活化机制的分类, 将抗血小板药物分为环氧化酶(cyclooxygenase, COX)抑制剂、二磷酸腺苷(adenosine diphosphate, ADP)受体拮抗剂、血小板膜糖受体Ⅱb/Ⅲa(glycoprotein, GPⅡb/Ⅲa)抑制剂及磷酸二酯酶(phosphodiesterases, PDEs)抑制剂, 中医药多种药物在通路上与现有抗血小板药物存在机制互补, 尤其在GPⅡb/Ⅲa受体抑制等西药转化的瓶颈上[76]. 不同活血化瘀药物调节血小板功能机制可大致分为花生四烯酸(arachidonic acid, AA)通路、前列环素(prostaglandin I2, PGI-2)/环磷腺苷(adenosine cyclophosphate, cAMP)通路、$P2Y_{12}$/cAMP通路、血小板活化因子(platelet-activating factor, PAF)通路、Ca^{2+}相关通路以及多种血小板膜糖蛋白相关通路(CD62p, GPⅡb/Ⅲa)等[72,77]. 研究发现, 活血化瘀中药复方: 复方丹参滴丸[78]、大黄䗪虫丸[79]、血府逐瘀汤[80]、补阳还五汤[81]、桃红四物汤[82]、冠心Ⅱ号方[83]、芎芍胶囊[84]、通心络胶囊[46]; 活血化瘀中药注射液: 丹红注射液[76]、血塞通注射液[85]; 活血化瘀单药或其有效单体: 川芎[86,87]、鸡血藤[88]、丹参[89](丹参多酚酸盐[90]、丹参酮ⅡA[91])、赤芍[92]、三七(三七皂苷[93])、虎杖[94]、红花[95](红花黄色素[96])、蒲黄[97]、银杏[98]等可抑制血小板活化, 有良好的抗血小板作用, 其具体机制见图2.

3.2　血瘀证、活血化瘀与炎症介质

炎症反应在冠心病的发生发展过程中扮演了极为重要的角色, 不仅促进动脉粥样硬化的形成, 同时可诱发急性斑块破裂血栓形成. 炎症反应涉及靶点众多、受累细胞组织广泛, 目前相关药物研发仍存显著局限. 在丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)抑制剂、PLA2抑制剂、烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, NADPH)氧化酶抑制剂、肿瘤坏死因子(tumor necrosis factor, TNF-α)受体的研发折戟沉沙后[99~101], 秋水仙碱治疗冠心病临床试验[102]的成功提示植物来源的抗炎成分可能存在巨大潜力. 血瘀、痰热的程度可以提示患者炎症反应程度的差异[103~105], 活血化痰解毒治疗存在较为明确的抗炎效应[106], 具有进一步的研究价值. 川芎-赤芍配伍[107]、红花及丹参注射液[108,109]等联合冠心病二级预防药物较单纯西药治疗可显著降低稳定性冠心病患者的血清超敏C反应蛋白(hypersensitive C-reactive protein, hs-CRP)、TNF-α水平, 同时改善血脂异常.

活血、解毒中药改善炎症反应的机制近年来逐步得到初步阐明. 丹参酮诱导中性粒细胞凋亡, 促进中性粒细胞反向迁移[110], 通过调控Toll样受体4(Toll-like receptors 4, TLR4)-髓细胞分化初级反应蛋白88(myeloid differentiation primary response protein 88, MyD88)复合物及TLR4-TNF受体相关因子6(TNF receptor associated factor 6, TRAF6)-核因子-κB(nuclear factor-κB, NF-κB)信号通路发挥抗炎效应[111], 二氢丹参酮Ⅰ通过雷帕霉素的机制靶点(mechanistic target of rapamycin, mTOR)-转录因子EB(transcription factor EB, TFEB)-NF-κB信号通路改善心肌炎症[112]. 黄连小檗碱的抗炎作用可通过腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)通路[113]和沉默信息调节因子T1(silent information regulator T1, SIRT1)/衔接蛋白p66Shc[114]等发挥心血管保护效应. 丹参酮ⅡA不仅可以降低CRP、TNF-α、白介素6(interleukin-6, IL-6)等常见炎症指标, 同时可抑制血管紧张素Ⅱ(angiotensin Ⅱ, AngⅡ)介导的Ca^{2+}内流以调节NF-κB通路, 抑制基质金属蛋白酶(matrix metalloproteinases, MMPs)以稳定斑块延缓血管重塑等[115,116].

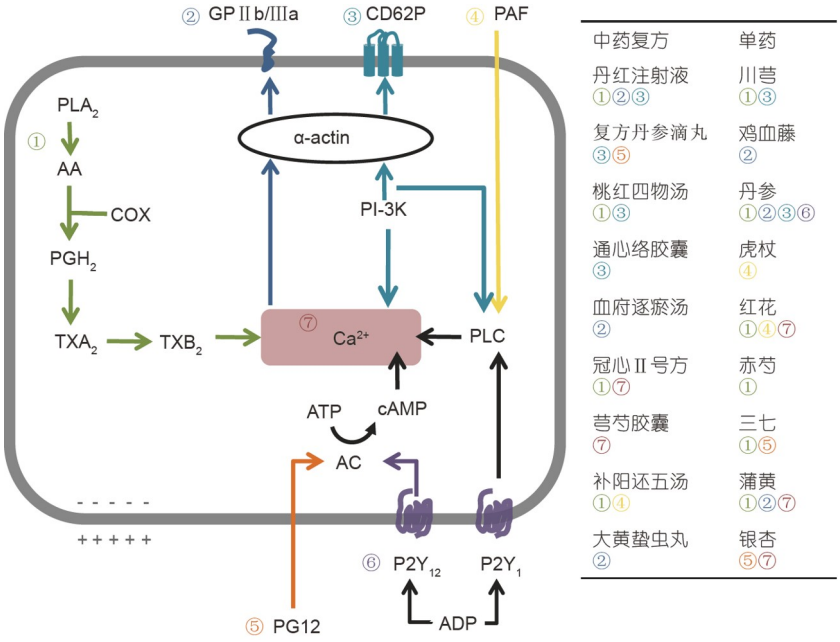

图 2 活血化瘀中药调节血小板功能的常见通路. 注: 边框内外表示血小板细胞膜内外的相关通路调节过程. 腺苷酸环化酶(adenylate cyclase, AC), 三磷酸腺苷(adenosine triphosphate, ATP), 磷脂酰肌醇激酶3(phosphatidylinositol 3-kinase, PI-3K), α-辅肌动蛋白(α-actin), 磷脂酶C(phospholipase C, PLC), 磷脂酶A_2(phospholipase A_2, PLA_2), 血栓素A_2(thromboxane A_2, TXA_2), 血栓素B_2(thromboxane B_2, TXB_2), 血小板糖蛋白Ⅱb/Ⅲa(GPⅡb/Ⅲa), P-选择素(P-selectin glycoprotein, CD62P)(网络版彩图)

Figure 2 Pathways of platelet function regulated by blood-stasis activating herbs. Note: the inside and outside of the border indicate the relevant pathways regulation process inside and outside the platelet cell membrane. AC (adenylate cyclase), ATP (adenosine triphosphate), PI-3K (phosphatidylinositol 3-kinase), PLC (phospholipase C), PLA_2 (phospholipase A_2), TXA_2 (thromboxane A_2), TXB_2 (thromboxane B_2), GPIIb/IIIa (glycoprotein IIb/IIIa), CD62P (P-selectin glycoprotein) (color online)

3.3 血瘀证、活血化瘀与氧化应激

氧自由基可以导致脂蛋白发生氧化修饰, 从而形成泡沫细胞, 促进细胞凋亡, 损伤内皮功能, 冠心病血瘀及痰浊证患者中存在氧化应激现象[63,64]. 目前多数抗氧化治疗心血管获益不如预期[117], 活血化瘀中药的干预或可弥补空白. 研究表明, 川芎嗪可增加细胞抗氧化能力, 调节线粒体Bcl-2通路降低超氧化物歧化酶(superoxide dismutase, SOD)、谷胱甘肽过氧化物酶(glutathion peroxidase, GSH-Px)活性[118], 降低线粒体一氧化氮合酶(nitric oxide synthase, NOS)活性, 从而减轻一氧化氮(nitric oxide, NO)所致的损伤, 减少脂质过氧化物的生成[118,119]. 当归补血汤能改善高脂饮食大鼠氧化应激, 上调肌浆网Ca^{2+}-ATP酶(sarcoplasmic reticulum Ca^{2+}-ATPase2a, SERCA2a)表达, 抑制活化转录因子6(activating transcription factor 6, ATF6)通路, 下调半胱氨酸蛋白酶-12(caspase protease-12, Cys-12), 从而心肌抗氧化能力并降低心肌组织氧化应激水平[120,121].

4 冠心病病证结合防治策略

虽然现代医学在冠心病的二级预防、经皮冠状动脉介入治疗、冠状动脉旁路移植术(coronary artery bypass grafting, CABG)等防治手段上取得显著进展, 然而目前临床仍然存在不能有效阻断冠脉临界病变、介入术后胸痛症状缓解不明显, 不能耐受二级预防的药物治疗、抗血小板药物抵抗, 无法血运重建的冠脉复杂病变、心梗后心衰的防治手段匮乏等现代医学亟待解决的临床关键科学问题[122]. 因此, 开展针对冠心病为核心的重大心血管疾病的中医药防治研究, 降低患病率和死亡率, 业已成为国家重大的公共卫生需求.

病证结合的系统化研究为冠心病的疾病分类提供了中医视角, 围绕冠心病血瘀证的生物学实质的探索为临床应用活血化瘀药物防治冠心病做出了范式. 中医药与冠心病二级预防药物联合使用可改善冠心病患者的生活质量, 且安全性良好[31], 目前冠心病病证结合防治策略以活血化瘀为主, 在此基础上衍生出益气

活血、行气活血、活血解毒等诸多治法，同时围绕其危险因素的防治，如高血压[123]、高脂血症[124]及糖尿病[125]等皆有相应临床证据，不断促进精准诊疗的实现. 虽然目前糖尿病及血脂异常的中医药治疗已进入西医防治指南[126,127]，但多数中医药的应用场景较为模糊，对中医药与西药联合应用的具体策略、获益与风险、应用周期等研究尚未有共识[128]，因此冠心病病证结合策略仍需不断探索，定位关键优势环节仍是一大挑战.

5　总结与展望

病证结合优化了现代中医药防治冠心病的研究模式，并成功确立了以血瘀证与活血化瘀为主体的中西医结合治疗学发展方向[129]，活血化瘀防治心血管疾病的理论创新与新药研究，是我国中西医结合领域60余年来研究最活跃、成果最突出的标志性成就之一，取得了一系列的创新性研究成果，在“血瘀证”病证结合诊断标准的制定、“活血化瘀”现代内涵的阐释、系列活血化瘀中药新药的研发、临床疗效评价及作用机制探究等方面获得了丰厚成果，推动了传统中医药的标准化和国际化进程，形成了高质量的临床转化应用证据[30]，为冠心病的中医药防治做出了突出贡献. 2011年，屠呦呦先生[130]在*Nature Medicine*发表的文章中专门提及活血化瘀中药防治冠心病是来自中医药的智慧.

病证结合中医药防治冠心病的临床转化研究需要不断进步，我们期望在以下方向能够开展深入的研究. 一是血瘀对早期血管衰老的识别、监测及早期干预具有重要意义，需要积极发挥中医药“治未病”的优势，开展“因瘀致衰”[131]及活血化瘀防治早期血管衰老的机制研究；二是随着代谢异常与心血管损害之间因果关系的不断明确，代谢性心血管病的理念[132,133]不断得到学界公认，心血管代谢风险的综合评估也越来越受到关注，研究糖脂代谢异常加重“血瘀”促进冠心病发展的机制对于阐明血瘀证生物实质，丰富活血化瘀的治疗内涵，拓展活血化瘀的应用范围意义重大；三是大数据技术与人工智能的快速发展为冠心病的中西医结合诊疗方案或临床指南的优化研究提供了技术支撑[134]，如何利用人工智能技术加速冠心病临床指南的制订流程，提高效率，创新其传播与实施模式，乃至改变指南的未来发展，已引起国内外学者的广泛关注[135]；四是关注冠心病防治的老药新用研究，利用网络药理学等技术[136]，预测老药新用的临床亮点开展系统化研究，对于缩短药物研发时间尽快服务于临床具有现实意义.

参考文献

1 The Writing Committee of the Report on Cardiovascular Health and Diseases in China. Summary of the China Cardiovascular Health and Disease Report 2020 (in Chinese). Chin Circ J, 2021, 36: 521–545 [中国心血管健康与疾病报告编写组. 中国心血管健康与疾病报告2020概要. 中国循环杂志, 2021, 36: 521–545]

2 Geriatric Medicine Branch of Chinese Medical Association, Writing Group of China Expert Consensus of Diagnosis and Treatment of Senile coronary Heart Disease. China expert consensus of diagnosis and treatment of senile coronary heart disease (in Chinese). Chin J Geriatr, 2016, 35: 683–691 [中华医学会老年医学分会, 高龄老年冠心病诊治中国专家共识写作组. 高龄老年冠心病诊治中国专家共识. 中华老年医学杂志, 2016, 35: 683–691]

3 Chen K J. The concept and clinical practice of combined disease and syndrome (in Chinese). Chin J Integr Med, 2011, 31: 1016–1017 [陈可冀. 病证结合治疗观与临床实践. 中国中西医结合杂志, 2011, 31: 1016–1017]

4 Chen K J. Traditional Chinese medicine treatment of angina pectoris and acute myocardial infarction in coronary heart disease (in Chinese). China J Intern Med, 1977, 16: 232–235 [陈可冀. 试谈冠心病心绞痛及急性心肌梗塞的中医治疗. 中华内科杂志, 1977, 16: 232–235]

5 Chen K J. Overview of blood stasis syndrome and the source of treatment methods of activating blood stasis (in Chinese). J Tradit Chin Med, 1979, 9: 51–57 [陈可冀. 瘀血证与活血化瘀治法源流概述. 中医杂志, 1979, 9: 51–57]

6 Chen K J, Qian Z H, Zhang W Q, et al. Effect of Jingzhi Guanxin tablets treating angina pectoris in coronary heart disease: a 112 cases double-blind, randomized controlled trial (in Chinese). Chin J Cardiovasc Dis, 1982, 10: 85–89 [陈可冀, 钱振淮, 张问渠, 等. 精制冠心片双盲法治疗冠心病心绞痛112例疗效分析. 中华心血管病杂志, 1982, 10: 85–89]

7 Li J, Gao Z, Zhang L, et al. Qing-Xin-Jie-Yu Granule for patients with stable coronary artery disease (QUEST Trial): a multicenter, double-

blinded, randomized trial. Complement Ther Med, 2019, 47: 102209
8 Shang H, Zhang J, Yao C, et al. Qi-shen-yi-qi dripping pills for the secondary prevention of myocardial infarction: a randomised clinical trial. Evid-Based Complement Alternat Med, 2013, 2013: 1–9
9 Preliminary report on the efficacy of Guanxin NO.2 formula in the treatment of angina pectoris in coronary heart disease (in Chinese). J Tradit Chin Med, 1972, 1: 29–32 [冠心2号方治疗冠心病心绞痛疗效的初步报告. 新医药学杂志, 1972, 1: 29–32]
10 Xu H, Lu X Y, Chen K J, et al. study on correlation of blood-stasis syndrome and its accompanied syndromes with pathological changes showed in coronary angiography and restenosis after percutaneous coronary intervention (in Chinese). J Tradit Chin Med, 2007, 27: 8–13 [徐浩, 鹿小燕, 陈可冀, 等. 血瘀证及其兼证与冠脉造影所示病变及介入治疗后再狭窄的相关性研究. 中国中西医结合杂志, 2007, 27: 8–13]
11 Shi L, Liu H X, Wang Z Y, et al. Study of correlation between coronary Gensini score and Chinese medicine syndromes in coronary heart disease (in Chinese). World J Integr Chin West Med, 2008, 3: 722–724 [时亮, 刘红旭, 王振裕, 等. 冠状动脉Gensini积分与冠心病患者中医证候相关性研究. 世界中西医结合杂志, 2008, 3: 722–724]
12 Chen K J, Shi D Z, Xu H, et al. The criterion of syndrome differentiation and quantification for stable coronary heart disease caused by etiological toxin of Chinese medicine (in Chinese), Chin J Integr Med, 2011, 31: 313–314 [陈可冀, 史大卓, 徐浩, 等. 冠心病稳定期因毒致病的辨证诊断量化标准. 中国中西医结合杂志, 2011, 31: 313–314]
13 Xu H, Shi D Z, Yin H J, et al. Blood-stasis and toxin causing catastrophe hypothesis and acute cardiovascular events: proposal of the hypothesis and its clinical significance (in Chinese). Chin J Integr Med, 2008, 28: 934–938 [徐浩, 史大卓, 殷惠军, 等. “瘀毒致变”与急性心血管事件: 假说的提出与临床意义. 中国中西医结合杂志, 2008, 28: 934–938]
14 Shi D Z, Xu H, Yin H J, et al. Combination and transformation of toxin and blood stasis in etiopathogenesis of thrombotic cerebrocardiovascular diseases (in Chinese). J Integr Med, 2008, 6: 1105–1108 [史大卓, 徐浩, 殷惠军, 等. “瘀”、“毒”从化——心脑血管血栓性疾病病因病机. 中西医结合学报, 2008, 6: 1105–1108]
15 Liu L T, Chen K J, Fu C G, et al. The etiology and pathogenesis of coronary heart disease from the perspective of “toxicity due to blood stasis” (in Chinese). Chin J Integr Med, 2015, 35: 1378–1380 [刘龙涛, 陈可冀, 付长庚, 等. 从“因瘀致毒”谈冠心病的病因病机. 中国中西医结合杂志, 2015, 35: 1378–1380]
16 Wang X, Hu D Y. Clinical study on the hypothesis of “endogenous collateral wind” on acute coronary syndrome (in Chinese). Chin J Tradit Chin Med Pharm, 2008, 23: 204–208 [王显, 胡大一. 急性冠脉综合征“络风内动”假说临床研究. 中华中医药杂志, 2008, 23: 204–208]
17 Xu H, Shi D Z, Chen K J, et al. Clinical Effect of Xiongshao Capsule on Preventing Restenosis Post-PTCA or/and Stenting (in Chinese). Chin J Integr Med, 2000, 20: 494–497 [徐浩, 史大卓, 陈可冀, 等. 芎芍胶囊预防冠状动脉介入治疗后再狭窄的临床研究. 中国中西医结合杂志, 2000, 20: 494–497]
18 Chen K, Shi D, Xu H, et al. XS0601 reduces the incidence of restenosis: a prospective study of 335 patients undergoing percutaneous coronary intervention in China. Chin Med J, 2006, 119: 6–13
19 Ge J B, Fan W H, Zhou J M, et al. Efficacy and safety of Shexiang Baoxin pill (MUSKARDIA) in patients with stable coronary artery disease: a multicenter, double-blind, placebo-controlled phase IV randomized clinical trial. Chin Med J (Engl), 2020, 134: 185–192
20 Reference standards for the syndromes of coronary heart disease (angina pectoris, myocardial infarction) in traditional Chinese medicine (revised in 1979) (in Chinese). J Med Res, 1979, 12: 19 [冠心病(心绞痛、心肌梗塞)中医辨证参考标准(1979年修订). 医学研究通讯, 1979, 12: 19]
21 The First National Conference on Blood Stasis and Activating Blood Circulation Association of Integrative Medicine. Trial criteria for the diagnosis of blood stasis Standards (in Chinese). Chin J Integr Med, 1983, 3: 2 [中国中西医结合研究会第一次全国活血化瘀学术会议. 血瘀证诊断试行标准. 中西医结合杂志, 1983, 3: 封2]
22 Cardiovascular Society of the Chinese Society of Integrative Medicine. Chinese syndrome differentiation criteria for coronary heart disease (in Chinese). Chin J Integr Med, 1991, 11: 257–257 [中国中西医结合学会心血管学会. 冠心病中医辨证标准. 中国中西医结合杂志, 1991, 11: 257–257]
23 Chen K J, Shi D Z. Guideline of TCM Clinical Identification Criteria and Prevention for Coronary Heart Disease and Acute Myocardial Infarction (in Chinese). Beijing: People's Medical Publishing House, 2014 [陈可冀, 史大卓. 冠心病及急性心肌梗死中医临床辨证标准及防治指南. 北京: 人民卫生出版社, 2014]
24 Xu H, Chen K J. Practical diagnostic criteria for blood stasis evidence (in Chinese). Chin J Integr Med, 2016, 6: 1163 [徐浩, 陈可冀. 实用血瘀证诊断标准. 中国中西医结合杂志, 2016, 6: 1163]

25 Shi D Z. Diagnostic criteria for blood stasis in coronary heart disease (in Chinese). Chin J Integr Med, 2016, 6: 1162 [史大卓. 冠心病血瘀证诊断标准. 中国中西医结合杂志, 2016, 36: 1162]

26 Revision of the Second National Academic Conference on Blood Stasis and Blood Stasis Research. Diagnostic criteria for blood stasis evidence (in Chinese). Chin J Integr Med, 1987, 7: 129 [第二届全国活血化瘀研究学术会议修订. 血瘀证诊断标准. 中国中西医结合杂志, 1987, 7: 129]

27 Xiao C X, Sang B S. Trial version of international blood stasis diagnostic criteria (in Chinese). Clin Focus,1987, 2: 558 [小川新, 桑滨生. 国际瘀血诊断标准试行方案. 临床荟萃,1987, 2: 558]

28 Du J X, Shi Z X. Consensus on combined Chinese and Western medicine treatment for blood stasis syndrome (in Chinese). Chin J Integr Med, 2011, 31: 839–844 [杜金行, 史载祥. 血瘀证中西医结合诊疗共识. 中国中西医结合杂志, 2011, 31: 839–844]

29 World Federation of Chinese Medicine Societies. The SCM standard of diagnostic guidelines for blood-stasis syndrome (in Chinese). [2021-12-16]. Available from URL: http://en.wfcms.org/index.php/show/21/3180.html [世界中医药学会联合会. 国际血瘀证诊断指南. [2021-12-16]. Available from URL: http://en.wfcms.org/index.php/show/21/3180.html]

30 Liu Y, Gao Z Y, Fu C G, et al. Blood-activating drugs against coronary artery disease: evidence-based and prospective (in Chinese). J Evid Based Med, 2018, 18: 1143–1150 [刘玥, 高铸烨, 付长庚, 等. 活血化瘀药物防治冠心病:循证与展望. 中国循证医学杂志, 2018, 18: 1143–1150]

31 Mao J Y, Wu Y J, Shi D Z. Clinical application guidelines for proprietary Chinese medicines in the treatment of coronary heart disease (2020) (in Chinese). Chin J Integr Med Cardio Cerebrovasc Dis, 2021, 19: 1409–1435 [毛静远, 吴永健, 史大卓. 中成药治疗冠心病临床应用指南(2020年). 中西医结合心脑血管病杂志, 2021, 19: 1409–1435]

32 Xu H, Wang A L, Luo J, et al. A practical randomized controlled study on the treatment of stable angina pectoris in coronary heart disease based on the blood stasis identification method of academician Chen Keji (in Chinese). Chin J Integr Med, 2017, 37: 1174–1180 [徐浩, 王安璐, 罗静, 等. 基于陈可冀院士血瘀证辨证方法治疗冠心病稳定性心绞痛的实用性随机对照研究. 中国中西医结合志, 2017, 37: 1174–1180]

33 Xu Y, Hu H, Li Y, et al. Effects of huoxin formula on the arterial functions of patients with coronary heart disease. Pharm Biol, 2019, 57: 13–20

34 Yu B, Chen K J, Mao J M, et al. Clinical study on the prevention and treatment of restenosis after coronary artery stenting in 43 cases of coronary artery disease with Xuefu Zhuyu Pill (in Chinese). Chin J Integr Med, 1998, 18: 585–589 [于蓓, 陈可冀, 毛节明, 等. 血府逐瘀浓缩丸防治43例冠心病冠脉内支架植入术后再狭窄的临床研究. 中国中西医结合杂志, 1998, 18: 585–589]

35 Zheng G H, Chen H Y, Chu J F, et al. Systematic review of randomized controlled trials of Xuefu Zhuyu capsules for the treatment of angina pectoris in coronary artery disease (in Chinese). J Tradit Chin Med, 2012, 53: 117–121 [郑国华, 谌海英, 褚剑锋,等. 血府逐瘀胶囊治疗冠心病心绞痛随机对照试验的系统评价. 中医杂志, 2012, 53: 117–121]

36 Xue M, Chen K J, Ma X J, et al. Effects of Xuefu Zhuyu Oral Liquid on hemorheology in patients with blood-stasis syndrome due to coronary disease and their relationship with human platelet antigen-3 polymorphism. J Chin Integr Med, 2008, 6: 1129–1135

37 Peng W, Shi D Z, Xue Y T, et al. Effect of Xiongshao capsule in treating 112 patients with coronary heart disease angina pectoris of xin-blood stasis syndrome (in Chinese). Chin J Integr Med, 2011, 31: 191–194 [彭伟, 史大卓, 薛一涛, 等. 芎芍胶囊治疗冠心病心绞痛心血瘀阻证112例临床研究. 中国中西医结合杂志, 2011, 31: 191–194]

38 Yang Y, Wang X L, Bi Y F, et al. Meta-analysis and grade evaluation of compound danshen dripping pills combined with western medicine in the treatment of unstable angina pectoris (in Chinese). J Tradit Chin Med, 2019, 60: 1815–1826 [杨颖, 王贤良, 毕颖斐, 等. 复方丹参滴丸联合西医常规治疗不稳定型心绞痛的Meta分析及GRADE评价. 中医杂志, 2019, 60: 1815–1826]

39 Zhong C M, Shi Z F, Dai Q Q, et al. Systematic review of the effect of compound Danshin dropping pill combined with western drugs on inflammatory factors and cardiac function after percutaneous coronary intervention for acute myocardial infarction (in Chinese). J Evid Based Med, 2021, 21: 662–668 [钟长鸣, 石兆峰, 代倩倩, 等. 复方丹参滴丸联合西药常规治疗对急性心肌梗死经皮冠状动脉介入术后炎症因子和心功能影响的系统评价. 中国循证医学杂志, 2021, 21: 662–668]

40 Luo J, Song W, Yang G, et al. Compound Danshen (*Salvia miltiorrhiza*) dripping pill for coronary heart disease: an overview of systematic reviews. Am J Chin Med, 2015, 43: 25–43

41 Duan X, Zhou L, Wu T, et al. Chinese herbal medicine Suxiao jiuxin wan for angina pectoris. Cochrane Database Syst Rev, 2013, 2013: CD004473

42 Wei L L. Clinical observation on the treatment of unstable angina pectoris with yuxintong capsule (in Chinese). Chin J Tradit Chin Med Pharm, 2009, 24: 1532–1533 [魏玲玲. 愈心痛胶囊治疗不稳定性心绞痛的临床观察. 中华中医药杂志, 2009, 24: 1532–1533]

43 Lei Y, Chen K J, Ke Y N, et al. Clinical study on the treatment of unstable angina pectoris with yuxintong capsule (in Chinese). Chin J Integr Med, 1996, 16: 580–584 [雷燕, 陈可冀, 柯元南, 等. 愈心痛胶囊治疗不稳定性心绞痛临床研究. 中国中西医结合杂志, 1996, 16: 580–584]

44 You S J, Chen K J, Yang Y J, et al. Clinical study on spontaneous improvement after blood flow reconstruction interfered by tongxinluo capsule in patients with early stage acute myocardial infarction(in Chinese). Chin J Integr Med, 2005: 604–607 [尤士杰, 陈可冀, 杨跃进, 等. 通心络胶囊干预急性心肌梗死早期血运重建后自发性改善的临床研究. 中国中西医结合杂志, 2005: 604–607]

45 Jia Y L, Zhang S K, Bao F F, et al. Systematic evaluation of indirect comparison between Tongxinluo capsule and Danshin drops for the treatment of angina pectoris in coronary heart disease (in Chinese). J Evid Based Med. 2011, 11: 919–931 [贾永亮, 张时开, 鲍菲飞, 等. 通心络胶囊与丹参滴丸治疗冠心病心绞痛间接比较的系统评价. 中国循证医学杂志, 2011, 11: 919–931]

46 Zhang L, Li Y, Yang B S, et al. A multicenter, randomized, double-blind, and placebo-controlled study of the effects of Tongxinluo capsules in acute coronary syndrome patients with high on-treatment platelet reactivity. Chin Med J, 2018, 131: 508–515

47 China Academy of Chinese Medical Sciences, Xiyuan Hospital,Beijing University of Chinese Medicine, Dongzhimen Hospital, China Academy of Chinese Medical Sciences, Guang'anmen Hospital, et al. Analysis of the efficacy of 118 cases of acute myocardial infarction treated with Kangxingeng formula (in Chinese). Chin J Intern Med, 1976, 1: 212–215 [中医研究院西苑医院内科, 东直门医院内科, 广安门医院内科, 等. 以"抗心梗合剂"为主治疗急性心肌梗塞118例疗效分析. 中华内科杂志, 1976, 1: 212–215]

48 Li Y Q, Jin M, Qiu S L, et al. Effect of Chinese drugs for supplementing Qi, nourishing Yin and activating blood circulation on myocardial perfusion in patients with acute myocardial infarction after revascularization. Chin J Integr Med, 2009, 15: 19–25

49 Xu D P, Wu H L, Lan T H, et al. Effect of Shenzhu Guanxin Recipe (参术冠心方) on patients with angina pectoris after percutaneous coronary intervention: a prospective, randomized controlled trial. Chin J Integr Med, 2015, 21: 408–416

50 Li L L, Dong G J, Ge C J, et al. Multicenter randomized controlled clinical study on relief of angina pectoris in coronary artery disease with broad chest aerosol (in Chinese). Chin J Integr Med, 2014, 34: 396–401 [李立志, 董国菊, 葛长江, 等. 宽胸气雾剂缓解冠心病心绞痛的多中心随机对照临床研究. 中国中西医结合杂志, 2014, 34: 396–401]

51 Yang Q N, Bai R N, Dong G J, et al. Effect of Kuanxiong aerosol (宽胸气雾剂) on patients with angina pectoris: a non-inferiority multi-center randomized controlled trial. Chin J Integr Med, 2018, 24: 336–342

52 Mao S, Wang L, Ouyang W, et al. Traditional Chinese medicine, Danlou tablets alleviate adverse left ventricular remodeling after myocardial infarction: results of a double-blind, randomized, placebo-controlled, pilot study. BMC Complement Altern Med, 2016, 16: 447

53 Li S M, Xu F Q. Six-month prognosis of patients with acute myocardial infarction with the effect of Yugeng Tongyu formula (in Chinese). Chin J Integr Med, 2019, 39: 927–931 [李思铭, 徐凤芹. 愈梗通瘀汤对急性心肌梗死患者半年预后的影响. 中国中西医结合杂志, 2019, 39: 927–931]

54 Wang Z, Zhang Z G, Zhang J. Clinical observation on curative effect of qingxin jieyu prescription on stable coronary heart disease and its effect on ANK1 and CD40L (in Chinese). J N Chin Med, 2020, 52: 51–54 [王贞, 张志国, 张君. 清心解瘀方治疗稳定性冠心病疗效观察及对ANK1、CD40L的影响. 新中医, 2020, 52: 51–54]

55 Ju J Q. Study on the mechanism of stabilizing atherosclerotic vulnerable plaques by regulating macrophage scorching with Qingxin jieju formula (in Chinese). Dissertation for Doctoral Degree. Beijing: Beijing University of Chinese Medicine, 2019 [鞠建庆. 清心解瘀方调控巨噬细胞焦亡稳定动脉粥样硬化易损斑块的机制研究. 博士学位论文. 北京: 北京中医药大学, 2019]

56 Wang A L. Study on the role and mechanism of intestinal flora modulation of lipid metabolism in atherosclerosis by Qingxin jieju formula (in Chinese). Dissertation for Doctoral Degree. Beijing: Beijing University of Chinese Medicine, 2019 [王安璐. 清心解瘀方重塑肠道菌群调节动脉粥样硬化脂质代谢作用及机制研究. 博士学位论文. 北京: 北京中医药大学, 2019]

57 Li L, Liu J X, Ren J X, et al. Corresponding study on the formula and evidence of coronary artery disease in small pigs with evidence of sputum-stasis interconnection (in Chinese). Acta Pharm Sin, 2017, 52: 1698–1704 [李磊, 刘建勋, 任建勋, 等. 小型猪痰瘀互结证冠心病的方证相应研究. 药学学报, 2017, 52: 1698–1704]

58 Yu G, Wang J. Current status and considerations on the systems biology of coronary heart disease with blood stasis confirmation (in Chinese). J Tradit Chin Med, 2012, 53: 2049–2051 [虞桂, 王阶. 冠心病血瘀证实质的系统生物学研究现状与思考. 中医杂志, 2012, 53: 2049–2051]

59 Liu Y, Yin H J, Chen K J. Platelet proteomics and its advanced application for research of blood stasis syndrome and activated blood circulation herbs of Chinese medicine. Sci China Life Sci, 2013, 56: 1000–1006

60 Liao W, Ma X, Li J, et al. A review of the mechanism of action of Dantonic® for the treatment of chronic stable angina. Biomed Pharmacother, 2019, 109: 690–700

61 Li S M, Li J G, Xu H. A new perspective for Chinese medicine intervention for coronary artery disease: targeting inflammation. Chin J Integr Med, 2019, 25: 3–8

62 Zhao A M, Ren J G, Liu J X. Mechanism of Yiqi Huoxue decoction in treating coronary heart disease with Qi deficiency and blood stasis syndrome (in Chinese). Chin J Exp Tradit Med Form, 2017, 23: 215–220 [赵爱梅, 任钧国, 刘建勋. 益气活血方治疗冠心病气虚血瘀证作用机制研究进展. 中国实验方剂学杂志, 2017, 23: 215–220]

63 Wang Y, Chen J R, An M S, et al. Efficacy of salvia polyphenolic acid salt in the treatment of angina pectoris in elderly people with coronary heart disease and its effects on lipid metabolism, hemodynamics and myocardial spectrum enzyme levels (in Chinese). Chin Arch Tradit Chin Med, 2021, 39: 199–202 [王彦, 陈加容, 安闵生, 等. 丹参多酚酸盐治疗老年冠心病心绞痛疗效及对血脂代谢、血流动力学和心肌谱酶水平的影响. 中华中医药学刊, 2021, 39: 199–202]

64 Peng J Q, Ren J G, Zhang Y N, et al. Correlation between monocyte/HDL cholesterol ratio and blood stasis syndrome in coronary heart disease (in Chinese). World Chin Med, 2021, 16: 2157–2162 [彭菊琴, 任钧国, 张艺楠, 等. 单核细胞/高密度脂蛋白胆固醇比值与冠心病血瘀证相关性研究. 世界中医药, 2021, 16: 2157–2162]

65 Liu L C, He Q Y, Chen H W, et al. Progress of genomic research on blood stasis in coronary heart disease (in Chinese). World Sci Technol-Modern Tradit Chin, 2020, 22: 3810–3818 [刘兰椿, 何庆勇, 陈恒文, 等. 冠心病血瘀证基因组学研究进展. 世界科学技术-中医药现代化, 2020, 22: 3810–3818]

66 Li J, Zhang S M, Zhang X Z, et al. Exploring susceptibility genes associated with blood stasis syndrome in early-onset coronary heart disease based on DNA hydroxymethylation modifications regulating mRNA expression (in Chinese). Chin J Tradit Chin Med Pharm 2020, 35: 5945–5948 [李杰, 张书萌, 张湘卓, 等. 基于DNA羟甲基化修饰调控mRNA表达探讨早发冠心病血瘀证相关易感基因. 中华中医药杂志, 2020, 35: 5945–5948]

67 Jia G, Hill M A, Sowers J R. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. Circ Res, 2018, 122: 624–638

68 Morales P E, Arias-Durán C, Ávalos-Guajardo Y, et al. Emerging role of mitophagy in cardiovascular physiology and pathology. Mol Aspects Med, 2020, 71: 100822

69 Witkowski M, Weeks T L, Hazen S L. Gut microbiota and cardiovascular disease. Circ Res, 2020, 127: 553–570

70 Rubenstein D A, Yin W. Platelet-activation mechanisms and vascular remodeling. Compr Physiol, 2018, 8: 1117–1156

71 Xin Q Q, Chen X, Yuan R, et al. Correlation of platelet and coagulation function with blood stasis syndrome in coronary heart disease: a systematic review and meta-analysis. Chin J Integr Med, 2021, 27: 858–866

72 Hu Y H, Jia Q L, Meng H, et al. Correlation of syndrome of blood stasis and the expressions of peripheral blood platelet microparticle membrane protein in patients with coronary heart disease unstable angina pectoris (in Chinese). J Tradit Chin Med, 2017, 58: 321–324 [胡元会, 贾秋蕾, 孟昊, 等. 冠心病不稳定型心绞痛患者血瘀证与外周血血小板微粒膜蛋白表达的相关性. 中医杂志, 2017, 58: 321–324]

73 Jia Q L, Meng H, Hu Y H, et al. Microparticles aggregates of peripheral blood in the unstable angina pectoris patients with blood stasis pattern (in Chinese). J Beijing Univ Tradit Chin Med, 2017, 40: 59–64 [贾秋蕾, 孟昊, 胡元会,等. 冠心病血瘀证患者外周血细胞微粒结合体水平的研究. 北京中医药大学学报, 2017, 40: 59–64]

74 Wu J, Chen K J, Wu Y K, et al. Observation of platelet phagocytosis in patients with coronary heart disease with blood stasis syndrome (in Chinese). Chin J Cardiovasc Dis, 1990, 18: 273–275 [吴锦, 陈可冀, 吴耀炯, 等. 冠心病血瘀证患者血小板吞噬能力的观察. 中华心血管病杂志, 1990, 18: 273–275]

75 Liu Y, Yin H J, Shi D Z, et al. The use of Chinese medicinal herbs and formulas that activate blood circulation and antiplatelet therapies (in Chinese). Chin Sci Bull, 2014, 59: 647–655 [刘玥, 殷惠军, 史大卓, 等. 活血化瘀中药与抗血小板治疗. 科学通报, 2014, 59: 647–655]

76 Fan H, Li M, Yu L, et al. Effects of Danhong Injection on platelet aggregation in hyperlipidemia rats. J Ethnopharmacol, 2018, 212: 67–73

77 Liu Y, Yin H, Chen K. Research on the correlation between platelet gelsolin and blood-stasis syndrome of coronary heart disease. Chin J Integr Med, 2011, 17: 587–592

78 Jin L. Effect of compound Danshen dropping drops on platelet activation function in patients with unstable angina pectoris with coronary artery disease (in Chinese). Chin J Integr Med, 2000, 20: 415–417 [金露. 复方丹参滴丸对冠心病不稳定性心绞痛患者血小板活化功能的影响. 中国中西医结合杂志, 2000, 20: 415–417]

79 Wang D S, Chen F P, He S L, et al. Study on the mechanism of anti platelet activation of Dahuang Zhechong Pill (in Chinese). Chin J Tradit Chin Med Pharm, 2008, 9: 818–821 [王东生, 陈方平, 贺石林, 等. 大黄蛰虫丸抗血小板活化的机制研究. 中华中医药杂志, 2008, 9: 818–

821]

80 Lei Y, Chen K J, Li Z W, et al. Correlation between the clinical efficacy and in vitro serum pharmacological effects of Xuefu Zhuyu Pill on anti-platelet activation (in Chinese). Chin J Integr Med, 2002, 22: 270–273 [雷燕, 陈可冀, 李中文, 等. 血府逐瘀浓缩丸抗血小板活化的临床疗效与体外血清药理作用的相关性研究. 中国中西医结合杂志, 2002, 22: 270–273]

81 Zhang J P, Li C L, Zhang Y P, et al. Effect of Buyang Huanwu formula on the content of platelet-activating factor in arterial blood before and after arterial thrombosis in rats (in Chinese). Chin J Integr Med, 1998, 18: 730–732 [张继平, 李长龄, 张玉萍, 等. 补阳还五汤对大鼠动脉血栓形成前后动脉血中血小板活化因子含量的影响. 中国中西医结合杂志, 1998, 18: 730–732]

82 Han L, Peng D Y, Xu F, et al. Study on the anti-thrombogenic effect of Taohong Siwu formula (in Chinese). J Anhui Univ Tradit Chin Med, 2010, 29: 47–49 [韩岚, 彭代银, 许钒, 等. 桃红四物汤抗血栓形成作用研究. 安徽中医学院学报, 2010, 29: 47–49]

83 Gao H L, Li Y K, Tong Y, et al. comparative study on the protective effects of different Guanxin Ⅱ formula on the acutemyocardial ischemia in dogs (in Chinese). Pharmacol Clin Chin Materia Med, 2007, 23: 1–4 [高会丽, 李贻奎, 仝燕, 等. 冠心II号系列组方对犬急性心肌缺血保护作用的比较研究. 中药药理与临床, 2007, 23: 1–4]

84 Li L Z, Liu J G, Ma L B, et al. Effects of rhizome capsules on lipid metabolism and platelet aggregation in a rabbit atherosclerosis model (in Chinese). Chin J Integr Med, 2008, 28: 1100–1103 [李立志, 刘剑刚, 马鲁波, 等. 芎芍胶囊对兔动脉粥样硬化模型脂质代谢及血小板聚集的影响. 中国中西医结合杂志, 2008, 28: 1100–1103]

85 Zhao X F, Wang P H, He S S. Effect of Xuesaitong injection on platelet parameters, cardiac function and blood rheology in patients with coronary artery disease (in Chinese). Chin J Thromb Hemost, 2020, 26: 40–42 [赵雄飞, 王培华, 何水胜. 血塞通注射液对冠心病患者血小板参数、心功能及血液流变学的影响. 血栓与止血学, 2020, 26: 40–42]

86 Shu B, Zhou C J, Ma Y H, et al. Advances in the pharmacological effects of the active ingredients in the Chinese medicine Chuanxiong (in Chinese). Chin Pharmacol Bull, 2006, 22: 1043–1047 [舒冰, 周重建, 马迎辉, 等. 中药川芎中有效成分的药理作用研究进展. 中国药理学通报, 2006, 22: 1043–1047]

87 Li L, Chen H, Shen A, et al. Ligustrazine inhibits platelet activation via suppression of the Akt pathway. Int J Mol Med, 2019, 43: 575–582

88 Yin X M, Zhao S Y, Rao L H, et al. Experimental study on the anti-AA-induced platelet aggregation effect of different components of Cockscomb (in Chinese). Exp Lab Med, 2016, 34: 422–424 [尹小明, 赵诗云, 饶丽华, 等. 鸡血藤不同成分抗AA诱导的血小板聚集作用的实验研究. 实验与检验医学, 2016, 34: 422–424]

89 Shan X X, Hong B J, Liu J, et al. Review of chemical composition, pharmacological effects, and clinical application of Salviae Miltiorrhizae Radix et Phizoma and prediction of its Q-markers (in Chinese). China J Chin Materia Med, 2021, 46: 5496–5511 [单晓晓, 洪帮振, 刘洁, 等. 丹参化学成分、药理作用、临床应用的研究进展及质量标志物的预测分析. 中国中药杂志, 2021, 46: 5496–5511]

90 Han J Y, Li Q, Ma Z Z, et al. Effects and mechanisms of compound Chinese medicine and major ingredients on microcirculatory dysfunction and organ injury induced by ischemia/reperfusion. Pharmacol Ther, 2017, 177: 146–173

91 Maione F, Cantone V, Chini M G, et al. Molecular mechanism of tanshinone IIA and cryptotanshinone in platelet anti-aggregating effects: an integrated study of pharmacology and computational analysis. Fitoterapia, 2015, 100: 174–178

92 Xie P, Cui L, Shan Y, et al. Antithrombotic effect and mechanism of *Radix paeoniae rubra*. Biomed Res Int, 2017, 2017: 1–9

93 Wang W, Yang L, Song L, et al. Combination of *Panax notoginseng* saponins and aspirin potentiates platelet inhibition with alleviated gastric injury via modulating arachidonic acid metabolism. Biomed PharmacoTher, 2021, 134: 111165

94 Yang Y M, Wang X X, Chen J Z, et al. Resveratrol attenuates adenosine diphosphate-induced platelet activation by reducing protein kinase C activity. Am J Chin Med, 2008, 36: 603–613

95 Yuan S J, Zhang Z W, Gao T H, et al. Study on antithrombotic mechanism of Honghua injection (in Chinese). Chin J Chin Materia Med, 2011, 36: 1528–1529 [袁淑娟, 张志伟, 高天红, 等. 红花注射液抗血栓作用机制研究. 中国中药杂志, 2011, 36: 1528–1529]

96 Chen W M, Jin M, Wu W, et al. Inhibition of safflor yellow on rabbit platelet activation induced by platelet activating factor (in Chinese). Chin Pharm J, 2000, 35: 741–744 [陈文梅, 金鸣, 吴伟, 等. 红花黄色素抑制血小板激活因子介导的血小板活化作用的研究. 中国药学杂志, 2000, 35: 741–744]

97 Yang H L, Li J. Effect of pollen typhae flavonoids on hemorheological parameters and platelet aggregation in rabbits (in Chinese). Chin J Exp Tradit Med Form, 2012, 18: 244–246 [杨慧玲, 李军. 蒲黄总黄酮对家兔血液流变学参数和血小板聚集的影响. 中国实验方剂学杂志, 2012, 18: 244–246]

98 Wang K L, Li Z Q, Cao Z Y, et al. Effects of ginkgolide A, B and K on platelet aggregation (in Chinese). Chin J Chin Materia Med, 2017, 42:

4722–4726 [王奎龙, 李卓琼, 曹泽彧, 等. 银杏二萜内酯A,B,K抗血小板聚集作用机制研究. 中国中药杂志, 2017, 42: 4722–4726]
99 White H D, Held C, Stewart R, et al. Darapladib for preventing ischemic events in stable coronary heart disease. N Engl J Med, 2014, 370: 1702–1711
100 O'Donoghue M L, Braunwald E, White H D, et al. Effect of darapladib on major coronary events after an acute coronary syndrome. JAMA, 2014, 312: 1006–1015
101 Padfield G J, Din J N, Koushiappi E, et al. Cardiovascular effects of tumour necrosis factor α antagonism in patients with acute myocardial infarction: a first in human study. Heart, 2013, 99: 1330–1335
102 Nidorf S M, Fiolet A T L, Mosterd A, et al. Colchicine in patients with chronic coronary disease. N Engl J Med, 2020, 383: 1838–1847
103 Wu H, Hong Y D, Wu W, et al. Discussion on the correlation between phlegm-heat syndrome and inflammatory factors in coronary heart disease (in Chinese). , 2004, 31: 542–543 [吴辉, 洪永敦, 吴伟, 等. 冠心病痰热证候与炎症因子相关性探讨. 辽宁中医杂志, 2004, 31: 542–543]
104 Zhao H H, Wang W, Guo S Z. Proteomics study on unstable angina pectoris patients with blood stasis syndrome (in Chinese). Chine J Arterioscl, 2008, 16: 545–548 [赵慧辉, 王伟, 郭淑贞. 冠心病不稳定型心绞痛血瘀证的蛋白质组学. 中国动脉硬化杂志, 2008, 16: 545–548
105 Ma X J, Yin H J, Chen K J, et al. Research progress of correlation between blood-stasis syndrome and inflammation (in Chinese). Chin J Integr Med, 2007, 27: 669–672 [马晓娟, 殷惠军, 陈可冀. 血瘀证与炎症相关性的研究进展. 中国中西医结合杂志, 2007, 27: 669–672]
106 Li H, Sureda A, Devkota H P, et al. Curcumin, the golden spice in treating cardiovascular diseases. Biotechnol Adv, 2020, 38: 107343
107 Zheng F, Zhou M X, Xu H, et al. 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 (in Chinese). Chin J Tradit Chin Med Pharm, 2009, 24: 1153–1157 [郑峰, 周明学, 徐浩, 等. 活血解毒中药对稳定期冠心病患者血清炎症标记物及血脂的影响. 中华中医药杂志, 2009, 24: 1153–1157]
108 Bi C, Li P L, Liao Y, et al. Pharmacodynamic effects of Dan-hong injection in rats with blood stasis syndrome. Biomed Pharmacother, 2019, 118: 109187
109 Liu J Z, Wang T, Zhao Y G, et al. Effect of *Salvia miltiorrhiza* ligustrazine injection on elderly patients with unstable angina pectoris and serum hs-CRP and lipid (in Chinese). Pharmacol Clin Chin Materia Med, 2015, 31: 237–239 [刘金柱, 王铁, 赵远贵, 等. 丹参川芎嗪注射液对老年不稳定型心绞痛患者的疗效和对血清hs-CRP、血脂的影响. 中药药理与临床, 2015, 31: 237–239]
110 Li S, Jiao Y, Wang H, 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, 7: 17451
111 Fang J, Little P J, Xu S. Atheroprotective effects and molecular targets of tanshinones derived from herbal medicine danshen. Med Res Rev, 2018, 38: 201–228
112 Wang X, Wang Q, Li W, et al. TFEB-NF-κB inflammatory signaling axis: a novel therapeutic pathway of Dihydrotanshinone I in doxorubicin-induced cardiotoxicity. J Exp Clin Cancer Res, 2020, 39: 93
113 Yao J, Kong W J, Jiang J D. Learning from berberine: treating chronic diseases through multiple targets. Sci China Life Sci, 2015, 58: 854–859
114 Feng X, Sureda A, Jafari S, et al. Berberine in cardiovascular and metabolic diseases: from mechanisms to therapeutics. Theranostics, 2019, 9: 1923–1951
115 Jiao Y, Li S M, Gao Z Y, et al. Sodium Tanshinone IIA sulfonate injection and inflammatory factors of coronary heart diseases (in Chinese). World Chin Med, 2013, 8: 1404–1406 [焦阳, 李思铭, 高铸烨, 等. 丹参酮ⅡA磺酸钠注射液与冠心病炎症因子的研究进展. 世界中医药, 2013, 8: 1404–1406]
116 Guo R, Li L, Su J, et al. Pharmacological activity and mechanism of tanshinone iia in related diseases. Drug Des Devel Ther, 2020, 14: 4735–4748
117 Kim B J, Lee E J, Kwon S U, et al. Prevention of cardiovascular events in asian patients with ischaemic stroke at high risk of cerebral haemorrhage (picasso): a multicentre, randomised controlled trial. Lancet Neurol, 2018, 17: 509–518
118 Yang B, Li H, Qiao Y, et al. Tetramethylpyrazine attenuates the endotheliotoxicity and the mitochondrial dysfunction by doxorubicin *via* 14-3-3γ/Bcl-2. Oxid Med Cell Longev, 2019, 2019: 1–20
119 Yang K, Zeng L, Ge A, et al. The effect of *Hedysarum multijugum maxim.-Chuanxiong rhizoma* compound on ischemic stroke: a research based on network and experimental pharmacology. Oxid Med Cell Longev, 2020, 2020: 1–24
120 Gong A G W, Lau K M, Zhang L M L, et al. Danggui Buxue Tang, Chinese herbal decoction containing astragali radix and angelicae sinensis radix, induces production of nitric oxide in endothelial cells: signaling mediated by phosphorylation of endothelial nitric oxide synthase. Planta Med, 2016, 82: 418–423

121 Guo J, Mo Y S, Wang Q, et al. Protective effect of Danggui Buxuetang on endothelial progenitor cells against oxidative stress injury induced by H_2O_2 (in Chinese). Chin J Exp Tradit Med Form, 2020, 26: 39–45 [郭静, 莫友胜, 王奇, 等. 当归补血汤对内皮祖细胞氧化应激损伤的保护作用. 中国实验方剂学杂志, 2020, 26: 39–45]
122 Bi Y F, Mao J Y, Wang X L, et al. Clinical advantages of TCM in prevention and treatment of coronary heart disease and thinking about its curative effect evaluation (in Chinese). J Tradit Chin Med, 2015, 56: 437–440 [毕颖斐, 毛静远, 王贤良, 等. 中医药防治冠心病临床优势及有关疗效评价的思考. 中医杂志, 2015, 56: 437–440]
123 Yang X, Xiong X, Yang G, et al. Songling Xuemaikang Capsule (松龄血脉康胶囊) for primary hypertension: A systematic review of randomized controlled trials. Chin J Integr Med, 2015, 21: 312–320
124 Depommier C, Everard A, Druart C, et al. Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat Med, 2019, 25: 1096–1103
125 Zhang Y, Gu Y, Ren H, et al. Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOTE study). Nat Commun, 2020, 11: 5015
126 Zhu J R, Gao R L, Zhao S P, et al. 2016 Chinese guideline for the management of dyslipidemia in adults (in Chiense). Chin J Gen Pract, 2017, 16: 15–35 [诸骏仁, 高润霖, 赵水平, 等. 中国成人血脂异常防治指南(2016年修订版). 中华全科医师杂志, 2017, 16: 15–35]
127 Chinese Diabetes Society. Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition) (in Chinese). Chin J Diabet Mellit, 2021, 13: 315–409 [中华医学会糖尿病学分会. 中国2型糖尿病防治指南(2020年版). 中华糖尿病杂志, 2021, 13: 315–409]
128 Standardization Project Team of Clinical Application Guide of Chinese Patent Medicine in Treatment of Dominant Diseases. Clinical application guide of Chinese patent medicine in treating coronary heart disease (2020) (in Chinese). Chin J Integr Med, 2021, 41: 391–417 [《中成药治疗优势病种临床应用指南》标准化项目组. 中成药治疗冠心病临床应用指南(2020年). 中国中西医结合杂志, 2021, 41: 391–417]
129 Zhang J, Ju J Q, Lin Q, et al. Knowledge graph analysis of blood stasis syndrome and blood circulation and blood stasis removal in recent 10 years (in Chinese). Chin J Integr Med, 2021, 1–7 [张杰, 鞠建庆, 林骞, 等. 近10年血瘀证与活血化瘀研究的知识图谱分析. 中国中西医结合杂志, : 1–7]
130 Tu Y. The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. Nat Med, 2011, 17: 1217–1220
131 Cui J, Li Y W, Liu Y, et al. Aging due to blood stasis and vascular aging (in Chinese). Chin J Integr Med, 2021, 1–5 [崔京, 李逸雯, 刘玥, 等. 因瘀致衰与血管衰老. 中国中西医结合杂志, 1–5]
132 Zhu Z M. Cardiometabolic diseases: concept, challenge and clinical practice (in Chinese). Chin J Cardiovasc Dis, 2021, 49: 650–655 [祝之明. 代谢性心血管病: 理念、挑战与实践. 中华心血管病杂志, 2021, 49: 650–655]
133 Cui J, Liu Y, Li Y, et al. Type 2 diabetes and myocardial infarction: recent clinical evidence and perspective. Front Cardiovasc Med, 2021, 8: 644189
134 Jiang Y, Zhao C, Zhang X Y, et al. Clinical research issues and countermeasures in Chinese medicine in the era of artificial intelligence (in Chinese). Chin J Integr Med, 2021, 41: 991–994 [蒋寅, 赵晨, 张晓雨, 等. 人工智能时代的中医临床研究问题与对策. 中国中西医结合杂志, 2021, 41: 991–994
135 Chen Y L, Luo X F, Shi Q L, et al. How will artificial intelligence lead the future of clinical practice guidelines (in Chinese). Med J Peking Union Med Coll Hosp, 2021, 12: 114–121 [陈耀龙, 罗旭飞, 史乾灵, 等. 人工智能如何改变指南的未来. 协和医学杂志, 2021, 12: 114–121]
136 Liu Y F, Sun M Y, Zhao Y K, et al. Network pharmacology in drug repositioning of Chinese medicines: application status and thinking (in Chinese). J Evid Based Med, 2017, 17: 1344–1349 [刘艳飞, 孙明月, 赵莹科, 等. 网络药理学在中药药物重定位研究中的应用现状与思考. 中国循证医学杂志, 2017, 17: 1344–1349]

Combination of disease and syndrome in coronary artery disease: prevention and treatment strategies

LI YiWen, LUO BinYu, CUI Jing, ZHU MengMeng, LIU Yue, XU Hao, SHI DaZhuo & CHEN KeJi

National Clinical Research Center for TCM Cardiology, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing 100091, China

The combination of disease and syndrome might be the optimal pattern for integration of Chinese and western medicine with highly innovative value. Coronary artery disease (CAD) is a major disease that endangers health. Traditional Chinese medicine (TCM) has developed a new understanding of the pathogenesis of CAD by taking blood stasis as the key syndrome (Zheng). Quantitative criteria and new diagnostic markers of CAD were established, from qualitative to quantitative aspects. Through evidence-based methods and biotechnological methods, the clinical efficacy, safety and the mechanism of TCM against CAD were confirmed. Represented by activating blood circulation and resolving blood stasis, the strategy combining Chinese and Western medicine was established for the prevention and treatment of CAD, featuring disease-syndrome combination. Several blood stasis criteria enabled the quantitative scoring of the degree of blood stasis. Innumerable randomized controlled trials (RCTs) using activating blood circulation as the interventions confirmed the efficacy and safety of this therapy. The mechanisms of activating blood circulation involve platelet function, inflammatory mediators, and oxidative stress, and numerous relevant targets need further elaboration. Here, we review the research progress of integration of Chinese and western medicine in the prevention and treatment of CAD over the past 60 years, starting from activating blood circulation as the entry point of the disease-syndrome combination research, providing an outlook on the future research direction and reference for further optimizing the Chinese solution for the prevention and treatment of CAD with Chinese characteristics.

coronary artery disease, syndrome of blood stasis, activating blood circulation, combination of disease and syndrome, integration of Chinese and western medicine

doi: 10.1360/SSV-2021-0384