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世界中医药学会联合会

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通络药物系统干预心血管事件链专家共识

Expert consensus on the intervention of the cardiovascular continuum by Luobing theory-based Chinese medicine formula

（草案，以出版稿为准 Draft）

世界中联技术报告

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引　言

近 30 年来，心血管疾病作为重大公共卫生问题一直是全球死亡的主要原因[1,2]。《健康中国 2030 规划》[3]提出降低心血管疾病等重大慢性病过早死亡率的目标，实现该目标需要西医、中医等多学科共同参与，最大限度遏制心血管疾病的发生发展。20 世纪 90 年代美国心脏病专家 *Braunwald* 教授提出“心血管事件链”概念[4]，带来心血管疾病全程干预理念的思维转变，也对单靶点、单因素、单环节的药物治疗提出挑战[5-9]，这与中医整体系统的理论特色相契合。近年来，中医络病理论指导下的通络药物在心血管疾病防治方面取得系列重大突破[10]，为更好促进中西医理念的更新与融合，为系统干预心血管事件链提供具有中国特色的中西医结合临床药物治疗方案，进一步提高心血管疾病防治水平，特此发布通络药物系统干预心血管事件链专家共识。

0.1 心血管事件链概念及其对相关疾病的防治意义

“心血管事件链”[4]是指以动脉粥样硬化为基础的心血管疾病由高危因素聚集导致动脉硬化，易损斑块破裂引起心肌梗死，出现心律失常、心力衰竭（以下简称心衰）直至死亡的全过程，呈现出多因素、多环节作用下因果相连、递进发展、事件突发、后果严重的病变特点[5-9]。该概念的提出反映了心血管疾病整体性与复杂性的系统特征，带来防治理念由既往关注单因素、单环节、单靶点干预，向整体、连续、动态、全程干预的系统思维转变。围绕心血管事件链关键病理环节重大疾病，聚焦高危因素、冠状动脉易损斑块、急性心肌梗死再灌注治疗后心肌保护、心律失常及慢性心衰，在解决当前病变瓶颈难题的同时，控制上游危险因素，防止病变向下游传变，形成治中寓防、防中寓治、防治结合的系统干预方案，有助于从根本上阻断心血管事件链，遏制心血管疾病的发生率及死亡率。

0.2 脉络学说的提出及对防治心血管事件链的意义

脉络学说是传承中医血脉理论创立的指导血管病变防治的原创理论，中医学在两千多年学术发展过程中虽有关于血管病变防治的相关理论记载，但由于历史原因造成血脉与脉络学说的缺位，致使关于血脉及脉络病变的理论认识和治疗方药缺乏整理，未形成系统的理论学说，导致对血管病变防治具有重要作用的该理论未能发挥其应有的指导作用。中医脉络学说在整体观的指导下，吴以岭院士将其进一步发展。脉络学说指出，从心血管事件链的早期阶段到严重的心血管事件发生，都与血管微循环障碍有关。从中医角度看，脉络学说不仅关注病症表象，更重视从深层次上关注和解决微循环障碍，改善内皮功能，从而缓解中血管、大血管以及心肌的问题。脉络学说强调从源头改善微循环，与心血管事件链的理念一脉相承。脉络学说研究领域包括胸痹、中风、心悸、心水等，涵盖了心脑血管病、心律失常、心衰等心血管事件链重大疾病，脉络学说指导有助于发挥中医整体系统理论特色，实现心血管事件链系统干预[11,12]。

0.3 脉络学说指导下通络药物防治心血管事件链的理论基础

0.3.1 脉络学说核心营卫理论揭示心血管事件链传变与组方用药规律

基于脉络学说的核心内容——营卫理论，提出心血管事件链“凝”→“壅”→“塞”→“不通”的传变规律，与高危因素聚集、动脉易损斑块、急性心梗，心律失常、慢性心衰等关键病理环节具有高度相关性。基于古今医案数据挖掘，揭示心血管事件链“凝”→“壅”→“塞”→“不通”传变特点：营卫“由络以通、交会生化”异常是始动因素并贯穿全程，引起津血输布代谢异常，湿、痰、瘀、水交互影响，形成“凝”→“壅”→“塞”→“不通”传变过程，构成心血管事件链由脉络功能障碍至结构损伤、由自身病变继发心肌组织损伤的连续病变过程。

依据数据挖掘确定的症候类型、核心病机及“调营卫津血”组方用药规律，确立了通络药物系统干预心血管事件链的用药方案：“健脾运津”治法及代表药物津力达颗粒用于干预心血管事件链的源头“凝”——高危因素聚集所致血液凝聚；“搜剔疏通”治法及代表药物通心络胶囊干预“壅”——冠脉易损斑块和“塞”——急性心肌梗死、脑梗死；“温清补通”治法及代表药物参松养心胶囊干预“不通”——心律失常；“气血水同治分消”治法及代表药物芪苈强心胶囊干预“不通”——慢性心衰。形成针对心血管事件链“凝”→“壅”→“塞”→“不通”中医传变规律核心病机的干预药物[13-15]。

0.3.2 脉络学说营卫理论指导提出心血管事件链系统干预策略

系统干预新策略的提出汲取了中医治未病思想，《黄帝内经》首提“治未病”概念，东汉张仲景发展《内经》“治未病”思想提出重在“防传变”。基于中医“治未病、防传变”提出“治本病、防未病”——防上游因素、治当前病变、控下游传变的心血管事件链系统干预新观点，深入研究“调其营卫”治法及通络药物通过防上游因素、治当前病变、控下游传变，发挥防中寓治、治中寓防、防治结合的干预作用，对整体、连续、动态、全程实现心血管事件链系统干预具有重大理论指导价值[14]。

在过去三十多年的临床实践中，现代西医学提出的针对心血管疾病不同阶段的一、二、三级预防理念与措施在心血管疾病防治中发挥了重大作用，但由于心血管疾病整体性与复杂性的系统特征，也为单因素、单环节、单靶点干预带来了挑战。心血管高危因素多呈现个体聚集及多代谢异常的特点，显著增加动脉硬化发病风险[16]；易损斑块残余炎症风险显著增加心血管事件，调脂联合抗感染治疗将为冠状动脉粥样硬化性心脏病（以下简称冠心病）高危患者提供更大获益[17-19]；再灌注治疗时代急性心肌梗死心肌无再流/慢血流及缺血再灌注损伤严重影响预后，属国际医学界面临的挑战[20,21]；相对于导管消融的快速进展，强调阻抑、对抗的抗心律失常药物治疗未有显著突破，持续性心房颤动导管消融术后复发率高达 30%，减少复发成为亟待解决国际难题[22-24]；慢性心衰标准治疗 5 年死亡率仍近 50%，降低心血管死亡陷入国际瓶颈[25,26]，也面临着百年来治疗理念的进一步更新问题。“心血管事件链”概念提示解决上述瓶颈难题需要向整体系统的思维转变与回归，这恰恰与传承中医学两千多年血脉理论基础上系统构建的脉络学说的理论特色相吻合，也为脉络学说指导下研发的通络药物解决上述瓶颈难题实现系统干预奠定了理论基础。

本文件的研究方法和技术路线见附录 A，临床研究文献筛选标准和证据级别见附录 B。

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通络药物系统干预心血管事件链专家共识

1 范围

本文件描述了系列通络药物（包括津力达颗粒、通心络胶囊、参松养心胶囊、芪苈强心胶囊）系统干预心血管事件链相关疾病（如糖尿病、脑卒中、冠心病、心律失常、心力衰竭等）的作用机制和临床应用建议。

本文件适用于内分泌、心血管内科、神经内科及相关专业临床医生在治疗糖尿病、脑卒中、冠心病、心律失常、心力衰竭等疾病时应用。

2 规范性引用文件

下列文件中的内容通过文中的规范性引用而构成本文件必不可少的条款。其中，注日期的引用文件，仅该日期对应的版本适用于本文件；不注日期的引用文件，其最新版本（包括所有的修改单）适用于本文件。

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3 术语和定义

下列术语和定义适用于本文件。

3.1

糖尿病

由于胰岛素分泌绝对或相对不足（胰岛素分泌缺陷），以及机体靶组织或靶器官对胰岛素敏感性降低（胰岛素作用缺陷）引起的以血糖水平升高，可伴有血脂异常等为特征的代谢性疾病。

注：糖尿病属于中医“消瘅”、“消渴病”等范畴。

[来源：SCM 18-2017，3.3]

3.2

冠状动脉粥样硬化性心脏病（冠心病）

由于冠状动脉硬化导致供养心脏的血液循环障碍，引起心肌缺血、缺氧而引起的心脏病。

3.3

缺血性脑卒中

各种脑血管病变所致脑部血液供应障碍，导致脑组织缺血、缺氧性坏死，而迅速出现相应神经功能缺损的一类临床综合征。

3.4

心房颤动（房颤）

临床最常见的心律失常之一，以心房电活动紊乱、心房失去有效收缩功能为特征，导致心室率不规则并伴随多种并发症风险。

3.5

室性早搏

又名室性期前收缩，一种常见的心律失常，是指房室束分叉以下部位过早发生的，提前使心肌除极的单个或成对的心搏。

3.6

心力衰竭（心衰）

由多种原因导致心脏结构和（或）功能的异常改变，使心室收缩和（或）舒张功能发生障碍，引起的一组复杂临床综合征。

[来源：SCM/TR 0008-2025，3.1]

4 通络药物与心血管事件链

4.1 通络药物

中医脉络学说指导研发的通络药物包括津力达颗粒（以下简称津力达）、通心络胶囊（以下简称通心络）、参松养心胶囊（以下简称参松养心）、芪苈强心胶囊（以下简称芪苈强心），针对心血管事件链不同阶段进行干预。津力达“健脾运津”治法用于干预心血管事件链的源头“凝”——高危因素聚集所致血液凝聚；通心络以“搜剔疏通”治法干预心血管事件链环节“壅”——冠脉易损斑块和“塞”——急性心肌梗死、脑梗死；参松养心以“温清补通”治法干预“不通”——心律失常；芪苈强心以“气血水同治分消”遣药组方规律干预“不通”——慢性心衰。形成针对心血管事件链“凝”→“壅”→“塞”→“不通”中医传变规律核心病机的干预药物。[13-15]

4.2 通络药物与糖尿病及糖尿病前期

4.2.1 津力达“健脾运津”组方特色

基于“凝”——高危因素阶段证候特征和临床表现，确立“健脾运津”治法代表药物津力达作为干预药物。方中集中应用中医治脾诸方，人参补气健脾；黄精、麦冬益脾阴，苍术、佩兰燥脾湿，荔枝核畅脾气，苦参、黄连清脾热，仙灵脾温脾阳，葛根升脾气，辅以丹参通脉络，发挥“运脾津，通脉络”的功效，为其防治糖尿病实现全程干预提供了组方依据[12]。

4.2.2 津力达改善 2 型糖尿病的作用机制

4.2.2.1 改善胰岛素敏感性

抗氧化：宋光耀等研究提示[27-30]，津力达上调沉默信息调节因子 3（sirtuin 3, SIRT3）表达，增强超氧化物歧化酶（superoxide dismutase, SOD）、谷胱甘肽过氧化物酶（Glutathione peroxidase, GSH-Px）等抗氧化酶活性，降低活性氧（reactive oxygen species, ROS）与丙二醛（malondialdehyde, MDA）水平，缓解氧化应激对胰岛素信号的干扰。

抗炎：唐艳阁等研究显示[31]，津力达有效抑制核因子κB（nuclear factor kappa-B, NF-κB）信号通路活化，减少白介素（interleukin, IL）1β、IL-6 等促炎因子的释放，减轻慢性低度炎症所致的胰岛素抵抗，从而改善胰岛素敏感性，达到调节血糖的作用。

缓解脂毒性：宋光耀等研究发现[32]，津力达通过激活 AMP 依赖的蛋白激酶

（AMP-activated protein kinase, AMPK），促进乙酰辅酶 A 羧化酶（Acetyl CoA carboxylase, ACC）磷酸化及激素敏感性脂肪酶（hormone-sensitive lipase, HSL）/脂肪甘油三酯脂肪酶（adipose triglyceride lipase, ATGL）表达，增强脂肪酸氧化效率；张会欣等研究提示[33]，津力达下调脂肪酸转位酶（fatty acid translocase, FAT/CD36）表达，减少游离脂肪酸摄取，降低骨骼肌中甘油三酯和非酯化脂肪酸的沉积，缓解脂毒性，改善胰岛素敏感性。

4.2.2.2 保护胰岛 β 细胞

抗β细胞凋亡：乐岭等研究表明[34,35]，津力达通过抑制 Smad2/3 磷酸化，上调 B 淋巴细胞瘤-2（B-cell lymphoma-2, Bcl-2）等抗凋亡蛋白表达及下调促凋亡蛋白[如半胱天冬酶-3（caspase-3）、Bcl-2 相关的 X 蛋白（Bax）]，并显著减轻高糖诱导的β细胞凋亡；同时改善胰岛微血管内皮细胞功能，优化胰岛β细胞生存环境，保护胰岛功能，从而达到保护胰岛β细胞的作用。

4.2.2.3 多通路协同调控糖脂代谢网络

高怀林等研究显示[36-45]，一方面津力达激活成纤维细胞生长因子（fibroblast growth factor 21, FGF21）/AMPK 信号通路，抑制肝脏二酰甘油酰基转移酶 1（diacylglycerol acyltransferase, DGAT1）表达，减少甘油三酯合成与堆积；同时上调解偶联蛋白（uncoupling protein 1,UCP1）、PR 结构域蛋白 16（PR domain containing 16, PRDM16）等棕色脂肪产热相关基因，促进脂肪酸氧化与能量消耗，改善肝脏及脂肪组织的代谢状态。另一方面，津力达上调过氧化物酶体增殖物激活受体γ共激活因子 1α（peroxisome proliferator-activated receptor-gamma coactivator-1alpha, PGC-1α）及其下游分子蛋白表达，促进线粒体生物合成与氧化磷酸化功能；通过抑制哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin, mTOR）、激活结节性硬化症复合体 1（tuberous sclerosis complex 1, TSC1）和 II 型微管相关蛋白 1 轻链 3（microtubule-associated protein 1 light chain 3, LC3-II），诱导细胞自噬，清除多余脂质，进一步改善代谢微环境。

在胰岛素信号转导方面，津力达协同激活磷脂酰肌醇 3 激酶（phosphatidylinositol 3-kinase, PI3K)/蛋白激酶 B(protein kinase B, Akt)通路，上调胰岛素受体(insulin receptor, IR）、胰岛素受体底物-1（insulin receptor substrate-1, IRS-1）和葡萄糖转运蛋白（glucose transporter type 4, GLUT4）的表达，增强细胞对胰岛素的响应和葡萄糖摄取能力。同时，其通过抑制 c-Jun 氨基末端激酶（c-Jun N-terminal kinase, JNK）/p38 丝裂原活化蛋白激酶（p38 mitogen-activated protein kinase, p38MAPK）等负调控信号的活化，避免信号通路受阻，从而全面提升胰岛素作用效率。

4.2.2.4 改善微循环

丁英钧等研究表明[46,47]，津力达联合通心络可显著改善高糖条件下肾脏微血管内皮细胞的活力，减少细胞凋亡，降低 ROS 水平；可显著抑制磷酸化 Smad2/3 的表达，并上调 Smad7 的表达。此外，联合干预可有效减少Ⅳ型胶原的生成，缓解肾组织的纤维化程度；显著下调 p-Akt 与 p-mTOR 的表达水平，抑制 mTOR 通路介导的血管内皮生长因子（vascular endothelial growth factor, VEGF）过度表达，改善肾脏组织的血管异常增殖状态；抑制

Akt/mTOR 通路亦有助于调节机体组织的代谢应激，减轻糖尿病相关代谢紊乱的肾脏损害。

4.2.3 津力达在 2 型糖尿病及糖尿病前期中的循证证据

4.2.3.1 糖尿病前期

FOCUS 研究[48]为多中心、随机、双盲、安慰剂对照临床试验，共纳入 889 例糖耐量异常合并多重代谢异常的个体，随机给予津力达（9g/次，每日三次[ter in die, TID]，口服）或安慰剂治疗，主要结局为糖尿病发生率（通过连续 2 次口服葡萄糖耐量试验确诊）。结果显示：①中位观察 2.2 年后，津力达组糖尿病发生风险显著低于安慰剂组（风险比[Hazard Ratio, HR]=0.59, 95%置信区间[confidence interval, CI]: 0.46-0.74；*P*<0.001）。②在代谢指标方面，与安慰剂组相比，津力达组腰围减小 0.95 cm（95%CI: 0.36-1.55）、空腹血糖降低 3.8 mg/dL（95%CI: 2.2-5.6）、餐后 2 小时血糖降低 9.2 mg/dL（95%CI: 5.4-13.0）、糖化血红蛋白（glycated hemoglobin, HbA1c）降低 0.20%（95%CI: 0.13%-0.27%）、胰岛素抵抗指数（homeostatic model assessment of insulin resistance , HOMA-IR）改善 0.47（95%CI: 0.12-0.83）。③在血脂方面，与安慰剂组相比，津力达组总胆固醇、低密度脂蛋白胆固醇、甘油三酯水平均显著下降，高密度脂蛋白胆固醇（high density lipoprotein cholesterol, HDL-C）水平有所上升。④随访 24 个月后，津力达组踝肱指数与腰围较安慰剂组均显著改善。

4.2.3.2 新诊断 2 型糖尿病

一项为期 16 周的双盲随机对照临床试验[49]，评估津力达对新诊断 2 型糖尿病（type 2 diabetes mellitus, T2DM）患者血糖波动的影响（包括单用及联合二甲双胍治疗）。入组患者随机分为四组：对照组、津力达组、二甲双胍组和津力达联合二甲双胍治疗组。采用回顾性持续葡萄糖监测（continuous glucose monitoring, CGM）系统进行连续 3 天的皮下组织间液葡萄糖监测，并在试验前后评估 HbA1c、中医证候积分及 CGM 参数（包括血糖变异系数、血糖标准差和 3.9-10.0 mmol/L 目标范围内时间）。最终 138 名受试者完成全程研究。结果显示：与干预前相比，四组患者的空腹血糖、餐后 2 小时血糖、HbA1c 和中医证候积分均有所下降，其中联合治疗组降幅最为显著。在 CGM 参数方面，津力达组和二甲双胍组的目标范围内时间较基线显著改善（津力达组：78.68±26.15 vs 55.47±33.29；二甲双胍组：87.29±12.21 vs 75.44±25.42；*P*<0.01）。值得注意的是，仅津力达组干预后的血糖标准差显著降低（1.57±0.61 vs 1.96±0.95；*P*<0.01）。研究表明，津力达可有效改善新诊断 T2DM 患者的血糖控制及血糖波动性。

4.2.3.3 血糖控制不佳的 2 型糖尿病

一项随机、双盲、安慰剂对照、多中心临床研究[50]，纳入 186 例 T2DM 患者。受试者被随机分配接受津力达（9g/次，TID，口服）或安慰剂治疗，连续 12 周。两组均继续服用原有剂量二甲双胍且剂量保持不变。在 12 周治疗期间，评估 HbA1c、空腹血糖、餐后 2 小时血糖、体重和体重指数（body mass index, BMI）变化，同时计算 HOMA-IR 和β细胞功能指数（homeostasis model assessment-β, HOMA-β）。结果：治疗 12 周后，津力达组 HbA1c 较基线降低 0.92±1.09%，安慰剂组降低 0.53±0.94%（津力达组 95%CI: 0.69-1.14；安慰剂组

95%CI: 0.34-0.72）。两组间 HbA1c 降幅差异具有显著统计学意义（*P*<0.01）。津力达和安慰剂组的空腹血糖和餐后 2 小时血糖均较基线下降，且两组间差异均具有显著统计学意义（均 *P*<0.01）。津力达组还显示出β细胞功能改善，HOMA-β指数显著增加（*P*<0.05）。体重和 BMI 变化无统计学意义。

4.2.3.4 2 型糖尿病患者的胰岛素抵抗

一项纳入 15 项随机对照临床研究的荟萃分析[51]显示，津力达联合其他降糖药物治疗 2 型糖尿病持续治疗至少 12 周。治疗组和对照组相比，治疗组能显著降低 2 型糖尿病患者的 HbA1c（*P*<0.001）、空腹血糖（*P*<0.001）、餐后 2 小时血糖（*P*<0.001）；同时显示治疗组更具有调节 HOMA-IR 和 HOMA-β的能力。从而增加胰岛素敏感性，改善胰岛素抵抗。

表 1 津力达颗粒治疗糖尿病及糖尿病前期的建议

建议	推荐类别	证据等级
建议对糖耐量异常患者，在生活方式干预基础上加用津力达，降低新发糖尿病发生风险，同时改善糖脂代谢（包括降低空腹及餐后血糖、HbA1c、升高 HDL-C 水平、降低 TG 水平），并可以减小腰围和 BMI，降低颈动脉内膜中层厚度	IIa	A
建议对新诊断的 T2DM 患者，可单用津力达或与二甲双胍联合，以改善患者血糖波动，增加血糖目标范围内时间	IIa	B
对二甲双胍单药或其他口服降糖药治疗不达标的 T2DM 患者，建议加用津力达以进一步下降 HbA1c，同时改善患者的空腹及餐后血糖	IIa	A
建议对 T2DM 患者，津力达可单用或者联合其他降糖药物，以改善 2 型糖尿病患者的体重，增加胰岛素敏感性，改善胰岛素抵抗	IIa	A

注：HbA1c，糖化血红蛋白；HDL-C，高密度脂蛋白胆固醇；TG，甘油三酯；BMI，身体质量指数；T2DM，2 型糖尿病。

4.2.4 津力达的安全性

根据中国国家药品不良反应监测系统[52]，截至 2025 年 3 月，收到津力达药品不良反应报告共计 848 件，报告率约 2.61‰，其不良反应发生率属于罕见级别。不良反应表现主要为腹泻、恶心、呕吐、腹胀、皮疹等。

4.3 通络药物与缺血性心脑血管疾病

4.3.1 通心络“搜剔疏通”的组方特色

基于“壅”——冠状动脉易损斑块和“塞”——急性心肌梗死和脑梗死阶段证候特征和临床表现，确立“搜剔疏通”治法药物通心络作为干预药物。针对该阶段共性病机络气虚滞，通心络以人参、降香补虚通滞、疏畅络气，针对脉络瘀阻以水蛭、土鳖虫剔除络瘀，针对脉络绌急以全蝎、蜈蚣、蝉蜕搜风通络，体现了“搜剔疏通”的组方用药特色，为其防治冠心病心绞痛、急性心肌梗死和脑梗死实现全程干预提供了组方依据[12]。

4.3.2 通心络防治缺血性心脑血管疾病的作用机制

4.3.2.1 保护内皮改善微循环

通心络通过多靶点协同作用实现内皮保护与微循环改善。Wu 等多项研究表明[53,54]，通心络通过激活环磷酸腺苷（cyclic adenosine monophosphate, cAMP）/蛋白激酶 A（protein kinase A, PKA）通路促进内皮型一氧化氮合酶（endothelial nitric oxide synthase, eNOS）在 Ser1179 和 Ser635 位点磷酸化，增强 eNOS 活性，进而上调血管内皮钙粘蛋白（vascular endothelial cadherin, VE-cadherin）和β连环蛋白表达，有效保护心肌微血管内皮结构。Chen 等[55]在缺血再灌注大鼠模型中发现，通心络通过外泌体介导的长链非编码 RNA-重编码调控因子（long intergenic non-protein coding RNA, regulator of reprogramming, Linc-ROR）/p70 核糖体蛋白 S6 激酶（p70 ribosomal protein S6 kinase, p70S6K）/eNOS 通路减轻内皮细胞损伤，改善心脏微循环，减少心肌梗死面积。Li 等人的基础研究证实[56,57]，通心络可显著降低髓过氧化物酶活性及炎症因子水平，降低微血管渗透性和心肌、线粒体水肿，从而改善冠状动脉微循环灌注和促进左心室功能恢复。在脑缺血模型中，通心络还可促进微血管新生、降低血脑屏障通透性[58,59]，增加缺血区血流量[60]，展现多维度改善微循环障碍的作用特点。

4.3.2.2 稳定斑块、抗动脉粥样硬化

Chen 等研究表明[58,61-63]，通心络能显著降低新西兰兔动脉粥样硬化模型的血脂及单核细胞趋化蛋白-1（monocyte chemoattractant protein-1, MCP-1）、超敏 C 反应蛋白（hypersensitive C-reactive protein, hs-CRP）、基质金属蛋白酶 1（matrix metalloproteinase-1, MMP-1）等炎症因子水平，同时通过增加斑块纤维帽厚度提升斑块稳定性。在分子调控层面，通心络通过非受体酪氨酸激酶（bone marrow X-linked kinase, Bmx）/NF-κB/MAPK 通路抑制斑块内炎性血管生成，调节斑块成分构成，显著降低斑块易损指数[64]。Qi 等研究[65]发现通心络在调节动脉硬化粥样斑块时调节肠道菌群，具体表现为增加 indistinctus 菌群丰度及反式阿魏酸含量，进而抑制巨噬细胞核苷酸结合寡聚化结构域样受体蛋白 3（nucleotide-binding oligomerization domain-like receptor protein 3, NLRP3）炎症通路。Zhang 等临床研究[66]显示常规抗血小板治疗基础上加用通心络可进一步降低血小板高反应性和 hs-CRP 水平来预防动脉粥样硬化。此外通心络可激活过氧化物酶体增殖物激活受体γ（peroxisome proliferative activated receptor gamma, PPARγ）通路抑制氧化低密度脂蛋白诱导的树突状细胞成熟及促炎因子分泌，以调控免疫炎症反应延缓动脉粥样硬化进展[67]。

4.3.2.3 保护心肌细胞，促进心肌血管生成

凋亡和自噬是维持心肌细胞存活和死亡的重要途径。Li 等研究发现[56]，通心络预处理可抑制缺血再灌注小型猪模型的心肌凋亡蛋白表达以减少心肌细胞凋亡，此外，通心络提前 1 小时预处理可上调 Ser1179 和 Ser635 的磷酸化 eNOS 表达以减少心肌无复流和缺血再灌注损伤，PKA 通道部分介导心肌保护效应。在急性心肌梗死大鼠模型中，通心络治疗可减轻梗死面积、促进梗死周围区血管生成，发挥心脏保护作用；机制上，通心络激活 AMPK 信号通路，增加心肌自噬蛋白 LC3 表达、降低凋亡蛋白 Bax 水平，促进自噬并抑制心肌细胞凋亡，从而保护心肌细胞、促进心肌修复[68]。Bai 等[69]在心肌梗死小鼠模型中证实，通心络

通过增加 Akt 及细胞外调节蛋白激酶（extracellular regulated protein kinases, ERK）磷酸化，促进 VEGF 及 p-eNOS 蛋白表达来促进心肌新生血管生成，从而改善梗死后心脏功能及心室重塑。

4.3.2.4 解除血管痉挛

通心络通过多靶点调控发挥解除血管痉挛效应，作用机制涉及关键信号通路的调控。Guan 等研究表明[70,71]，通心络可显著改善颈动脉血管外膜慢性损伤模型大鼠的血管收缩功能，降低管腔狭窄程度（8.2%±1.0% vs 20.1%±3.3%）、改善管腔横截面积及血流；通过抑制 RAS 同源基因家族成员 A（RAS homologous gene family member A, RhoA）/Rho 激酶通路，显著下调 Rho 激酶 mRNA 及磷酸化肌球蛋白磷酸酶靶亚基 1（myosin phosphatase target subunit 1, MYPT1）蛋白表达，从而减弱血管对 5-羟色胺收缩反应的敏感性，其效应机制与尼可地尔相似。进一步研究发现，通心络通过激活 ERK1/2-神经型一氧化氮合酶（neuronal nitric oxide synthase, nNOS）信号轴，促进 ERK1/2 磷酸化介导的 nNOS 表达，改善血管收缩、解除血管痉挛、降低血管对收缩因子的超敏反应，发挥抗血管痉挛的保护作用[72]。

4.3.2.5 促进神经功能恢复

针对脑缺血损伤，通心络可增强和延长缺血区脑源性神经营养因子（brain-derived neurotrophic facto, BDNF）和 VEGF 高表达，发挥对脑缺血的神经保护作用[73,74]。在大脑中动脉闭塞型大鼠模型实验中，给予通心络治疗后，在电镜下可观察到缺血后脑皮质微血管超微结构显著改善[75]。通心络还可能通过激活丝裂原活化的细胞外信号调节激酶（mitogen-activated extracellular signal-regulated kinase, MEK1/2）/ERK/p90 核糖体 S6 激酶（p90 ribosomal S6 kinase, p90RSK）、PI3K/Akt 或抑制低密度脂蛋白受体相关蛋白 1（low density lipoprotein receptor related protein 1, LRP1）等途径，改善缺血/再灌注损伤、神经功能损伤和血脑屏障破坏，促进运动神经纤维的轴突重建和突触形成，改善缺血部位微小血管血液循环及新生血管形成，从而改善神经功能[59,76-82]。

4.3.3 通心络在缺血性心脑血管疾病中的循证证据

4.3.3.1 冠心病

4.3.3.1.1 稳定型心绞痛

Feng 等一项纳入了 26 篇随机对照试验（randomized controlled trial, RCT）的 meta 分析[83]显示，稳定型心绞痛患者在冠心病二级预防的基础上，联合应用通心络 4 周以上，可使心绞痛发作频率降低 0.91 次/周、心绞痛持续时间缩短 1.71 min/次，硝酸甘油使用量每周减少 2.22 mg、6 分钟步行试验距离可增加 27.86 m。

4.3.3.1.2 不稳定型心绞痛

Meta 分析[84-98]显示，不稳定型心绞痛患者在冠心病二级预防基础上联合通心络应用 2 周以上，可使心绞痛发作减少 2.32 次/周、心绞痛持续时间缩短 1.74 min/次、心电图 ST 段压低恢复率提高 27%。持续服用 1~6 个月，心肌梗死发生风险下降 65%。

4.3.3.1.3 变异型心绞痛

随机对照研究[99,100]提示变异型心绞痛患者在西医常规药物治疗基础上联合应用通心络，可有效降低心绞痛持续时间（P<0.05），改善心绞痛症状。

4.3.3.1.4 非阻塞性冠脉缺血相关的冠脉微血管疾病

Meta 分析[101-103]显示，非阻塞性冠脉缺血相关的冠脉微血管疾病（coronary microvascular disease, CMVD）患者常规治疗联合通心络应用 1 个月后，可使心绞痛发作频率减少 3.74 次/周、运动心电图 ST 段压低时间延迟 64.51s；服用 3 月后，靶血管校正 TIMI（thrombolysis in myocardial infarction）帧数降低 11.63 帧。

4.3.3.1.5 ST 段抬高型心肌梗死

ENLEAT 研究[117]共纳入 219 例 ST 段抬高型心肌梗死（ST-segment elevation myocardial infarction, STEMI）患者，急诊 PCI 术前在常规治疗的基础上分别给予通心络或安慰剂负荷剂量 2.08 g（8 粒），术后按照每次 4 粒，每天 3 次服用，疗程 6 月。分别在住院时和冠状动脉球囊扩张后 1、2、6、12、24h 通过心电图记录 ST 段抬高幅度，以评估心肌无复流。结果显示，通心络给药后第 6 小时，ST 段回落幅度显著优于对照组；给药后第 24h，通心络组显著降低无复流发生率达 36.6%（34.3% vs 54.1%, P=0.0031）；明显降低 ST 段抬高幅度、加速 ST 段回落幅度；改善心肌血流灌注，缩小心肌梗死面积；减少节段性室壁运动异常，改善再灌注后心功能。

CTS-AMI 研究[118]共纳入 3797 例 STEMI 患者，在双联抗血小板治疗基础上，随机给予通心络或安慰剂负荷剂量 2.08 g（8 粒）治疗，随后两组分别在二级预防治疗基础上每天 3 次，每次 4 粒服用，治疗 12 个月。结果显示：①通心络组的 30 天主要不良心脑血管事件（major adverse cardiovascular and cerebrovascular events, MACCE）（包括心源性死亡、心肌再梗死、急诊血运重建和脑卒中）风险较安慰剂组降低 36%（3.39% vs 5.24%, 相对危险度[Risk Ratio, RR]=0.64, P=0.006），心源性死亡风险下降 30%、心肌再梗死风险下降 65%、恶性心律失常发生率降低 23%；②患者持续服用通心络 1 年，MACCE 风险较安慰剂组下降 36%（5.3% vs 8.3%, RR=0.64, P<0.001），心源性死亡风险降低 27%、心肌再梗死风险降低 74%、卒中风险降低 56%、因心衰再住院风险降低 52%；③通心络组在给药第 24h 的 ST 段回落幅度显著优于安慰剂组。

Chen 等一项纳入了 10 篇 RCT 的 meta 分析[119]研究提示，STEMI 患者在冠心病二级预防基础上联合应用通心络，MACCE 风险可降低 39%（P<0.001）。

4.3.3.2 颈动脉硬化

CAPITAL 研究[120]共纳入 1212 例非钙化颈动脉斑块患者，分别接受通心络或安慰剂治疗 24 个月（每次 6 粒、每日 2 次）。结果显示，通心络显著降低平均颈动脉内中膜增厚年化变化值（–0.00095mm vs 0.01312mm, P<0.001）、缩小斑块体积，改善血管重构指数，减少主要心血管事件发生率。

4.3.3.3 缺血性脑卒中

TISS 研究[121]是一项多中心、随机、双盲、安慰剂对照临床试验，共纳入 2007 名急性缺血性脑卒中（acute ischemic stroke, AIS）患者，在标准治疗基础上，随机给予通心络或安慰剂（TID，每次 4 粒），治疗 90 天。结果显示：①与安慰剂相比，通心络显著提高了 AIS 患者 90 天独立生活（改良 Rankin 量表[modified Rankin Scale, mRS]评分≤1 分）的比例（65.8% vs 59.1%，比值比[Odds Ratio, OR]=1.33, *P*=0.002）；②通心络组 mRS 评分 0~2 分、美国国立卫生院卒中量表（National Institute of Health stroke scale, NIHSS）评分为 0~1 分或降低≥4 分、日常生活活动能力（barthel index, BI）评分≥85 的患者比例均高于安慰剂组。预先设定的亚组分析表明，年龄<60 岁、症状发作 48h 内、合并糖尿病、大动脉粥样硬化型的卒中患者，更有可能从通心络治疗中受益。通心络治疗发病 72h 内 AIS 患者更有可能获得良好的功能预后，安全性良好。

鄢波等研究[122]将 360 例急性/亚急性期缺血性脑卒中患者随机分为两组，通心络组在常规治疗基础上加用通心络，治疗 14 天后，虽然两组患者的 BI 评分和神经功能缺损评分在 28 天无统计学差异，但在治疗 3、6 和 12 个月时，差异具有统计学差异。治疗 12 个月后，治疗组的心脑血管事件复发率低于对照组。

针对卒中恢复期患者，吴以岭等[123]通过评价超微粉碎工艺的通心络与普通粉碎工艺的通心络，发现使用超微粉碎工艺的通心络对于气虚血瘀络阻型中风病患者疗效确切，与普通粉碎工艺的通心络疗效相当，且服用安全。

周红青等[124]对 39 项通心络应用于脑卒中相关 RCT 研究进行分析发现，通心络组神经功能评分改善显著优于对照组；治疗结束时通心络组的有效率显著高于对照组。从伶男等[125]对 14 项通心络用于脑卒中相关 RCT 进行分析发现，在常规疗法基础上联合使用通心络，在改善神经功能缺损包括降低缺损程度评分及提高神经功能改善率、提高生活能力、降低 NIHSS 评分上，均优于单用常规疗法；不良事件发生率，组间比较差异无统计学意义。

表 2 通心络胶囊治疗缺血性心脑血管疾病的建议

建议	推荐类别	证据等级
在冠心病二级预防的基础上联合通心络，有助于进一步改善稳定型心绞痛患者心绞痛症状，提高运动耐量	I	A
在冠心病二级预防的基础上联合通心络，有助于进一步降低不稳定型心绞痛患者心肌梗死发生率，改善心绞痛症状	I	A
在冠心病二级预防的基础上联合通心络，有助于进一步减少 PCI 术后患者的主要心血管事件，降低 PCI 术后支架内再狭窄率	I	A
在冠心病二级预防的基础上联合通心络，有助于进一步减少 STEMI 患者的主要心血管事件风险	I	A
在常规治疗的基础上联合通心络，有助于进一步降低非阻塞性冠脉缺血相关 CMVD 患者的心绞痛发作频率，改善冠脉血流，提高运动耐量	IIa	A
在西医常规治疗基础上联合通心络，有助于进一步改善变异型心绞痛患者心绞痛症状	IIa	B
急诊 PCI 术前，在常规治疗的基础上给予通心络负荷剂量（8 粒），以后 4 粒 TID 持续 1 年方案，有助于降低 STEMI 患者 PCI 术后 24 小时的无复流发生率、30-	IIa	A

天和 1-年的心脑血管事件（MACCE）发生率和病死率		
在常规治疗的基础上联合通心络，可以延缓颈动脉内中膜增厚，缩小颈动脉斑块患者的斑块体积	IIa	A
对于急性缺血性脑卒中患者，在发病 72 小时内，建议在常规治疗基础上，加用通心络，以改善患者的神经功能缺损症状，有助于改善患者 90 天神经功能缺损程度和日常生活活动能力，提高 90 天良好功能结局的比例	IIa	B
对于轻型卒中（如 NIHSS 评分 4 - 7 分）、合并糖尿病、大动脉粥样硬化型脑卒中或在急性期 48 小时内开始用药的患者，通心络对于改善 90 天功能结局的治疗效果可能更为显著，可优先考虑使用	IIa	B
对于缺血性脑卒中患者，在常规治疗的基础上联合通心络，可能降低长期脑血管事件复发率	IIa	B
针对卒中恢复期患者，与普通粉碎工艺的通心络相比，使用超微粉碎工艺的通心络对于气虚血瘀络阻型中风病患者有效且安全	IIa	B

注：PCI，经皮冠状动脉介入术；STEMI，ST 段抬高型心肌梗死；CMVD，冠状动脉微血管疾病。

4.3.4 通心络的安全性

根据中国国家药品不良反应监测系统[52]，截至 2025 年 3 月，收到通心络药品不良反应报告共计 9598 件，报告率约 0.82‰，其不良反应发生率属于非常罕见级别。不良反应表现主要为恶心、腹部不适、腹痛、呕吐、腹胀、头晕等。如服用通心络引起恶心、腹部不适、腹痛、呕吐、腹胀及腹泻等消化道不良反应，减少用药剂量或改为饭后服用可减轻消化道不良反应。

CTS-AMI 研究[118]显示，通心络不增加出血风险，严重不良事件发生率与安慰剂组相似（2.2% vs 2.8%, *P*=0.25）。TISS 研究[121]显示，通心络和安慰剂组不良事件（38.6% vs 38.4%, *P*=0.95）和严重不良事件（2.2% vs 1.9%, *P*=0.64）发生率相似。出血性疾患及妇女经期禁用。

4.4 通络药物与心律失常

4.4.1 参松养心“温清补通”的组方特色

基于“不通”—心律失常阶段证候特征和临床表现，确立“温清补通”治法代表药物参松养心作为干预药物。方中人参、酸枣仁、山茱萸、麦冬等益气养阴安神，黄连、甘松、丹参、土鳖虫等清火理气通络，发挥“整合调节、快慢兼治”的功效，为其防治心律失常实现全程干预提供了组方依据[12]。

4.4.2 参松养心防治心律失常的作用机制

4.4.2.1 多离子通道阻滞作用

电压门控钠通道（I_{Na}）形成快反应动作电位 0 相。Li 等研究发现[126,127]，在豚鼠心室肌细胞中，参松养心抑制 I_{Na} 峰值电流，通过阻滞 Na^+ 通道发挥 I 类抗心律失常作用。

K^+ 通道对维持静息膜电位及动作电位复极至关重要。瞬时外向钾电流（I_{to}）在心外膜表达较强，参松养心显著抑制心外膜 I_{to}，降低复极离散度，延长心房和心室肌动作电位时程（action potential durations, APD）和有效不应期（effective refractory period, ERP），降低

心房颤动（以下简称房颤）或折返、尖端扭转型室速的发生[128,129]。参松养心主要抑制延迟整流钾电流（I_k）中的缓慢激活成分（I_{ks}），减少快速性心律失常发生[126,130]。参松养心可阻滞内向整流钾电流（I_{k1}）的内向成分、略增大外向成分，抑制早期后除极和触发机制引起的心律失常[126,130]。参松养心对 K^+的多通道阻滞作用与 III 类抗心律失常药物胺碘酮相似。

Zhao 等人在心肌缺血动物模型中发现，参松养心抑制 I_{to} 和 I_{k1}，延长心室肌细胞 APD 和 ERP，但不触发细胞内 Ca^{2+}超载，抑制延迟后除极[121]。参松养心体外可降低心室肌细胞 Ca^{2+}超载，并抑制 L 型钙通道（$I_{Ca\text{-}L}$），使电流密度-电压曲线上移，延长 $I_{Ca\text{-}L}$ 失活后恢复时间[126,131,132]。参松养心通过阻滞 $I_{Ca\text{-}L}$ 通道并减少 Ca^{2+}超载发挥 IV 类抗心律失常和缺血心肌保护的双重作用。

Sun 等研究表明[133]，在转染超极化激活阳离子通道（hHCN4）的人胚肾 293（KEF293）细胞中，参松养心干粉溶液可逆性抑制 hHCN4，且不改变通道激活动力学参数。抑制 hHCN4 起搏电流可能是参松养心治疗室性早搏的电生理机制之一。此外，参松养心对 Kv1.4 钾通道电流也有一定的阻滞作用[134]。

4.4.2.2 改善心肌电生理重构

电生理重构主要包括心肌细胞传导性和自律性的改变、膜离子通道改变、间隙连接异常等。在多种心律失常易感的动物模型中，参松养心可改善心房和心室肌细胞 APD 及 ERP，减小心房心室间 APD 离散程度，降低心肌细胞自律性，降低房颤和室性心律失常易感性[135,136]。间隙连接负责心肌细胞间动作电位的快速传递，参松养心可增加糖尿病大鼠心房肌细胞间隙连接蛋白（Connexin, Cx）40 表达，通过 Toll 样受体 4（toll-like receptor 4, TLR4）/髓样分化因子 88（Myeloid differentiation primary response gene 88, MyD88）/钙-钙调蛋白依赖性蛋白激酶 II（Calcium-calmodulin dependent protein kinase II, CaMKII）CaMKII 信号通路增加代谢综合征大鼠心室肌细胞 Cx43 蛋白表达，改善间隙连接重塑[137,138]。参松养心可上调心肌离子通道蛋白 Kv4.2、Kv4.3 及 Cav1.2 表达，改善离子通道重塑[138]；降低心肌细胞间心电传导异质性，改善电信号传导方向和时间[139]。

4.4.2.3 改善心肌结构重构、抑制纤维化

Liu 等研究提示[140]，参松养心可减轻血管紧张素 II（Angiotensin, Ang II）诱导的心肌细胞肥大，改善心肌细胞形态结构，抑制心肌细胞凋亡。在心肌梗死大鼠及家兔模型中，参松养心提高左室射血分数（left ventricular ejection fraction, LVEF）及短轴缩短率（fractional shortening, FS），增强心肌收缩力，提高心功能；降低 Collagen I/III 蛋白水平，减少胶原蛋白沉积；下调转化生长因子-β1（transforming growth factor beta-1, TGF-β1）、MMP-2、MMP-9、基质金属蛋白酶抑制剂 1（tissue inhibitor of metal protease 1, TIMP-1）等纤维化基因及蛋白表达，抑制心脏成纤维细胞向肌成纤维分化，延缓心房及心室纤维化进程[139,141]。Shen 等研究发现[142]，参松养心通过抑制 TGF-β1/Smad 通路减轻糖尿病心肌病小鼠的心脏纤维化。

4.4.2.4 心脏自主神经功能的双向调节

Zhao 等在犬房颤模型中发现[143]，参松养心升高迷走神经高频成分（high-frequency,

HF）、降低交感神经低频成分（low-frequency, LF）及 LF/HF，抑制心房交感神经过度支配、增加迷走神经功能，调节自主神经活动平衡，减慢快心率。参松养心通过调节交感神经功能，抑制全身或局部肾素-血管紧张素-醛固酮系统（renin-angiotensin-aldosterone system, RAAS）活性，降低 Ang II 水平及生物活性，改善心房基质、减轻纤维化，降低房颤风险并维持窦性心律[128]。参松养心还增加乙酰胆碱和α7 烟碱型乙酰胆碱受体（α7 nicotinic acetylcholine receptor, α7nAChR）表达，从而增强胆碱能抗炎途径，降低肿瘤坏死因子α（tumor necrosis factor-α, TNF-α）、IL-6 等炎性因子水平[143]。参松养心通过调节自主神经活动平衡、抑制交感神经功能、增加迷走神经功能、增强胆碱能抗炎途径，发挥抗心律失常作用。

在缓慢性心律失常微型猪模型中，参松养心可提高心率，促进窦房结及房室结电信号传播，这种作用不受自主神经系统抑制的影响；Feng 等通过体外实验发现，参松养心均匀地缩短 APD 及 ERP，但未致心律失常[144]。

4.4.2.5 抑制炎症、改善代谢及心肌微循环

Zhang 等研究表明[145]，参松养心降低 db/db 小鼠细胞间黏附分子（intercellular cell adhesion molecule-1, ICAM-1）、血管细胞黏附分子（vascular cell adhesion molecule-1, VACM-1）等炎症蛋白表达，减少内皮素-1（endothelin-1, ET-1）、TNF-α、IL-6、MCP-1 等炎性因子水平；抑制 M1 型巨噬细胞的浸润极化，减轻心肌炎症反应。参松养心上调铁转运蛋白，抑制心肌细胞铁过载引起的氧化应激及 ROS 水平[146]；增加心肌细胞线粒体密度、激活 AMPK、上调 PGC-1α改善细胞线粒体能量代谢；增加肉碱棕榈酰转移酶-1 （carnitine palmitoyltransferase I, CPT-1）和 GLUT-4 表达促进脂肪酸和葡萄糖氧化[140]。在多种心律失常易感动物模型中，参松养心改善心脏微血管内皮细胞结构，促进心肌内皮细胞间紧密连接形成增加微血管密度；通过上调 VEGF/eNOS 途径提高一氧化氮（nitric oxide, NO）水平，调节缩血管因子与扩血管因子间的平衡，保护微血管内皮细胞，改善心肌微循环[145,147]。

4.4.3 参松养心在心律失常中的循证证据

4.4.3.1 室性早搏（室性期前收缩）

在一项多中心、随机、双盲对照临床试验[148]中，共纳入 859 例频发室性早搏患者。其中 188 例受试者未合并器质性心脏病（organic heart disease, OHD），给予参松养心或安慰剂（TID，每次 4 粒）治疗；671 例受试者合并 OHD，接受参松养心（TID，每次 4 粒）或美西律片（TID，每次 150mg）治疗，疗程均为 8 周。结果显示，非 OHD 室性早搏试验组，参松养心和安慰剂均减少室性早搏次数，参松养心总有效率显著优于安慰剂（74.2% vs 28.9%, P<0.001）；在 OHD 室性早搏试验组，参松养心和美西律均减少室性早搏次数，参松养心总有效率显著优于美西律（65.8% vs 50.7%, P<0.001）。此外，参松养心还显著改善室性早搏相关的心慌、胸闷等临床症状。

SS-HFVPT 研究[149]为一项多中心、随机、双盲、安慰剂对照临床试验，纳入 465 例心衰合并频发室性早搏患者，在西药标化治疗基础上联合参松养心或安慰剂（TID，每次 4 粒）治疗 12 周。结果显示，参松养心组 24h 室性早搏总次数较安慰剂组明显减少（–2145±2848

vs –841±3411, *P*<0.05），提高 LVEF、降低血浆氨基末端 B 型利钠肽前体（N-terminal pro-brain natriuretic peptide, NT-proBNP）水平。

一项针对室性早搏伴窦性心动过缓的多中心、随机、双盲、安慰剂平行对照临床研究[150]纳入 333 名患者，166 人接受参松养心治疗（TID，每次 4 粒），167 人接受安慰剂治疗，疗程 8 周。结果显示，参松养心显著降低了 24h 室性早搏次数，早搏数下降率优于安慰剂组（68.2% vs 32.2%, *P*<0.001）；同时，参松养心使平均心室率提高 10.9%，显著优于安慰剂组 4.7%（*P*<0.001）。

Meta 分析[148-162]显示，室性早搏患者服用参松养心 4 周以上，室性早搏次数平均降低 867.41 次/24h（*P*<0.001），临床总有效率及临床症状改善优于对照组（*P*<0.001）。

一项随机、双盲、多中心安慰剂对照的研究[163]，对参松养心治疗心动过缓的安全性和有效性进行了评估。共纳入心动过缓患有 115 例，对照组 104 例，接受参松养心治疗 4 周（TID，每次 4 粒）。结果发现，参松养心治疗的患者的平均心率、最快心率及最慢心率均显著上升，症状评分显著改善（均 *P*<0.05 或 0.01）。

4.4.3.2 阵发性房颤

一项多中心、随机、双盲、双模拟、对照临床试验[164]共纳入 349 例症状性阵发房颤患者，分别给予参松养心（TID，每次 4 粒）+普罗帕酮模拟剂（TID，每次 150mg）、普罗帕酮+参松养心模拟剂、参松养心+普罗帕酮，疗程 8 周。结果显示：房颤总体疗效三组比较差异无统计学意义（62.3% vs 58.6% vs 58.5%, *P*>0.05）；单独应用参松养心或参松养心与普罗帕酮联合应用，均可有效降低房颤平均发作频率、缩短房颤发作持续时间（均 *P*<0.01）。

Meta 分析[165-172]结果显示，症状性阵发房颤患者，在抗心律失常药物（antiarrhythmic drugs, AAD）基础上联合参松养心服用 2 月以上，房颤平均发作频率降低 2.23 次/周（*P*=0.002）、房颤发作持续时间缩短 1.64h/次（*P*=0.02）、提高窦律维持有效率（*P*=0.039）。

一项 RCT 显示[173]，阵发性房颤患者行导管消融术后，参松养心联合决奈达隆应用，可降低术后早期复发及房性快速性心律失常发生率（6.6% vs 20%, *P*=0.03）。

4.4.3.3 持续性房颤导管消融术后

SS-AFRF 研究为多中心、随机、双盲、安慰剂对照临床试验[174]，共纳入 920 例首次行导管消融术的持续性房颤患者。所有患者在导管消融术空白期后尽量停用 AAD 基础上，分别给予参松养心或安慰剂（TID，每次 4 粒），随访观察时间 1 年，主要终点为在空白期后，持续≥30s 的复发性房性快速性心律失常的发生率。1 年随访结果显示，与安慰剂组相比，参松养心显著降低持续性房颤患者消融术后房颤复发率（14.5% vs 22.3%, *P*=0.001），降低复发风险 40%（HR=0.6, 95%CI: 0.4-0.8）。此外，参松养心在术后 3 个月和 6 个月显著降低了房颤负荷（分别为 2.8% vs 7.6%, *P*=0.002 和 3.3% vs 7.7%, *P*=0.025），提高患者生活质量。

荟萃分析[174-178]显示，持续性房颤患者行导管消融术后，参松养心联合 AAD 或单独应用 3 月以上，可使房性快速性心律失常发生风险降低 43%（*P*<0.001）。

表 3 参松养心胶囊治疗心律失常的建议

建议	推荐类别	证据等级
对于症状性室性早搏患者，无论是否合并结构性心脏病，参松养心均可减少室性早搏次数，改善心慌、胸闷等临床症状	I	A
对于室性早搏合并左心室收缩功能不全的患者，参松养心可减少室性早搏次数，改善左心功能，无致心律失常的副作用	IIa	B
对于窦性心动过缓、或室性早搏合并窦性心动过缓的患者，参松养心可提高窦性心律、减少室性早搏次数，改善生活质量	IIa	B
对于阵发性房颤患者，参松养心单独使用或联合 AAD，可降低房颤发作频率、缩短房颤持续时间	IIa	B
对于持续性房颤导管消融术后，参松养心单独使用、或联合 AAD，可降低术后房颤早期复发率及/或房性快速性心律失常发生率	IIa	B

注：AAD，抗心律失常药物。

4.4.4 参松养心的安全性

根据中国国家药品不良反应监测系统[52]，截至 2025 年 3 月，收到参松养心药品不良反应报告共计 9835 件，报告率约 0.75‰，其不良反应发生率属于非常罕见级别。不良反应表现主要为腹胀、恶心、肠胃气胀、腹部不适、呕吐、皮疹等。

SS-AFRF 研究[174]显示，参松养心与安慰剂组的不良事件（67.4% vs 67.0%, P=0.94）、严重不良事件（8.5% vs 11.5%, P=0.15）及肝肾功能水平（P>0.05）均无显著差异。

4.5 通络药物与慢性心力衰竭

4.5.1 芪苈强心“气血水同治分消”的组方特色

基于“不通”—心衰阶段证候特征和临床表现，确立“气血水同治分消”治法代表药物芪苈强心作为干预药物。方中以黄芪、附子、人参、桂枝等益气温阳，丹参、红花活血通络，葶苈子、泽泻、香加皮等利水消肿，体现“气血水同治分消”组方特点，为其全方位整体治疗慢性心衰提供了组方依据[12]。

4.5.2 芪苈强心治疗慢性心衰的作用机制

4.5.2.1 改善心衰血流动力学

强心：芪苈强心通过抑制心肌细胞膜 Na^+/K^+-ATP 酶活性，增强副交感神经张力并延缓房室传导[179]。Liang 等研究发现[180,181]，在多种心衰动物模型中，芪苈强心显著提高 LVEF、FS、左室压力最大上升速率及左室心肌收缩力，降低左室舒张末压，改善心功能。

利尿：芪苈强心显著增加心衰模型大鼠肾血流量，降低尿渗量，其调控精氨酸加压素（arginine vasopressin, AVP）水平的作用优于传统利尿剂呋塞米；下调肾集合管上皮细胞 2 型 AVP 受体及水通道蛋白 2（aquaporin 2, AQP2）表达，降低组织对 AVP 的敏感性；双重调节血浆 AVP 水平及其受体通路，有效减少肾小管水重吸收[182,183]。

扩血管：芪苈强心明显增加血浆及主动脉降钙素基因相关肽表达水平，激活 NO-环磷酸鸟苷（cyclic guanosinc monophosphate, cGMP）-蛋白激酶信号级联反应发挥血管舒张效应[182]。

4.5.2.2 拮抗神经内分泌系统过度激活

抑制 RAAS 系统激活：芪苈强心可降低 Ang II、血浆肾素活性及醛固酮水平，下调血管紧张素转换酶及血管紧张素 I 型受体表达，抑制心室重构，改善心功能[184]。

抑制交感神经过度激活：芪苈强心能有效降低心衰动物血浆去甲肾上腺素、促肾上腺皮质激素、前列腺素 E2 及 NT-proBNP 等神经内分泌因子水平，降低交感神经兴奋性，改善心功能，延缓心衰进程，其降低 BNP 水平优于美托洛尔[181,185,186]；通过中枢调控机制改善交感神经过度激活状态，阻抑心室重构进程[187]。

4.5.2.3 调节免疫、抑制氧化应激和心肌纤维化

调节免疫炎症反应：在急性心肌梗死大鼠模型及扩张型心肌病患者中，芪苈强心表现出显著的炎症免疫调节作用，降低促炎因子 TNF-α水平，提升抗炎因子 IL-10 表达，重建促炎/抗炎平衡[188-190]；抑制 NF-κB 及 NLRP3 炎症小体活化，减少 T 淋巴细胞浸润及活化[189-193]，从而发挥抗炎和改善心室重构的作用。

抑制氧化应激及心肌纤维化：芪苈强心通过激活 PI3K/Akt 等信号通路，降低 ROS 水平，上调 SOD 表达，减轻氧化应激[194]；芪苈强心可减少心肌梗死大鼠的心肌胶原沉积，调节基质金属蛋白酶/基质金属蛋白酶抑制剂的平衡，抑制心肌纤维化、延缓心室重构[195-197]，其作用与血管紧张素受体脑啡肽酶抑制剂相当[192]；改善心衰大鼠全心质量指数优于美托洛尔[186]。

4.5.2.4 改善心肌代谢

芪苈强心可激活 PPARγ/PGC-1α信号轴，促进脂肪酸β氧化[198-200]；调控葡萄糖转运系统（GLUT1/GLUT4），增强葡萄糖摄取及氧化磷酸化[201,202]，促进葡萄糖摄取和利用，且疗效与曲美他嗪相当[201]；激活 AMPK/PGC-1α通路，抑制病理性无氧糖酵解[199-202]；保护线粒体结构完整性，改善电子传递链功能[203,204]。

4.5.2.5 保护心肌微血管和心肌细胞

微血管内皮保护：芪苈强心能抑制 VCAM-1、ICAM-1 及心肌营养因子表达，改善心肌微血管内皮结构与功能[205]；激活神经调节蛋白 1（neuregulin-1, NRG-1）/表皮生长因子受体（epidermal growth factor receptor，EGFR）-PI3K/Akt/mTOR 自噬通路，促进缺氧条件下血管新生并减少微血管内皮细胞凋亡[206-209]。

心肌细胞保护：芪苈强心通过调控 Bcl-2/Bax 表达平衡，抑制 caspase 级联反应，发挥抗心肌凋亡作用[181,194,210-213]；通过 PTEN 诱导激酶 1（PTEN-induced kinase 1, PINK1）/泛素蛋白连接酶（parkin）通路促进受损线粒体清除[214]；调控 PI3K/糖原合成激酶 3β（glycogen synthase kinase-3β, GSK-3β）及 mTOR 信号网络，维持自噬稳态，保护心肌细胞[215-218]。

4.5.3 芪苈强心在慢性心衰中的循证证据

4.5.3.1 射血分数降低的心衰

QUEST 研究[219]为多中心、双盲、安慰剂、随机对照临床试验，共纳入 3110 例射血分数降低的心衰（heart failure with reduced ejection fraction, HFrEF）患者，在标准心衰治疗基础上分别给予芪苈强心或安慰剂（TID，每次 4 粒）。结果显示，中位随访时间 18.3 个月，与安慰剂相比，芪苈强心组心血管死亡或心衰再入院的复合心血管事件风险降低 22%（*P*<0.001）、心衰再入院风险降低 24%（*P*=0.002）、心血管死亡风险降低 17%（*P*=0.045）。随访 3 个月时，芪苈强心组 NT-proBNP 水平下降>30%的比例明显高于安慰剂组（56.54% vs 49.86%，*P*=0.002）。此外，与安慰剂组相比，芪苈强心组心血管死亡和心衰再入院的复合终点事件风险在心衰合并冠心病亚组（1156 例 vs 1165 例）下降 24%和心衰合并高血压亚组（708 例 vs 741 例）下降 31%。

QLQX-DCM 研究[190]为多中心、双盲、安慰剂、随机对照临床试验，共纳入 345 例扩张型心肌病患者，在指南指导下的最佳药物治疗（guideline-directed management and therapy, GDMT）基础上分别接受芪苈强心或安慰剂（TID，每次 4 粒）治疗。结果显示，随访 12 个月，两组与基线比较，芪苈强心降低干扰素-γ、IL-17、TNF-α和 IL-4、升高 IL-10（均 *P*<0.001），调节炎性因子失衡；芪苈强心组扩张型心肌病患者全因死亡率（–2.17%）和心衰再入院率（–2.28%）较对照组呈下降趋势。

在一项多中心、双盲、安慰剂、随机对照临床试验[220]中，共纳入 512 例 HFrEF 患者，在标准心衰治疗基础上分别给予芪苈强心或安慰剂（TID，每次 4 粒）12 周。结果显示，芪苈强心组 NT-proBNP 水平下降>30%的比例显著高于安慰剂组（47.95% vs 31.98%, *P*<0.001），芪苈强心组患者复合心脏事件（包括心血管死亡、心衰再入院、心脏骤停后复苏、心衰恶化静脉药物治疗及卒中）发生率较对照组显著降低（4.51% vs 10.93%, *P*=0.008）。

毛天诗等发表的一项纳入上述 3 篇研究的荟萃分析[221]显示，芪苈强心使慢性心衰患者的心血管死亡或心衰再入院组成的复合心血管事件风险降低 18%（*P*=0.0005），心血管死亡风险降低 17%（*P*=0.03），心衰再入院风险降低 18%（*P*=0.004），全因死亡风险降低 16%（*P*=0.03）。芪苈强心服用 4 周以上，LVEF 提高 6.04%（*P*<0.001）、左室舒张末期内径减小 3.66 mm（*P*<0.001）、纽约心功能分级明显改善（P<0.001）、6 分钟步行试验距离增加 51.27 m（*P*<0.001）、明尼苏达生活质量评分降低 8.97 分（*P*<0.001）。服用 3 个月后，NT-proBNP 水平下降 276.78 pg/mL（*P*<0.001）。

4.5.3.2 射血分数保留的心衰

随机对照研究提示射血分数保留的心衰（heart failure with preserved ejection fraction, HFpEF）患者在 GDMT 基础上应用芪苈强心 6 个月，E/A、LVEF、6 分钟步行试验距离水平较治疗前提高，且提升幅度显著高于对照组（*P*<0.05）；左房容积指数、左室舒张末期内径、明尼苏达心衰患者生活质量量表评分、CRP、NT-proBNP 水平降低幅度显著低于对照组（*P*<0.05）；多项临床研究显示，HFpEF 患者服用芪苈强心 1 个月以上，左室舒张功能（如 E/A、E/e’）明显改善[222-225]。

表 4 芪苈强心胶囊治疗慢性心力衰竭的建议

建议	推荐类别	证据等级
HFrEF 患者，在 GDMT 基础上联合芪苈强心，可以进一步降低心衰再入院率及心血管死亡率	I	A
芪苈强心可改善慢性心衰患者心功能及心室重构指标，提高运动耐量、改善生活质量	I	A

注：HFrEF，射血分数降低的心力衰竭；GDMT，指南指导下的最佳药物治疗。

4.5.4 芪苈强心的安全性

根据国家药品不良反应监测系统[52]，截至 2025 年 3 月，收到芪苈强心药品不良反应报告共计 4777 件，报告率约 2.34‰，其不良反应发生率属于罕见级别。不良反应表现主要为恶心、腹泻、腹部不适、呕吐、腹痛、皮疹等。

QUEST 研究[219]及 QLQX-DCM 研究[190]均显示，芪苈强心与安慰剂组的胃肠道症状发生率无统计学差异。如服用芪苈强心引起恶心、腹部不适、腹痛、呕吐、腹胀及腹泻等消化道不良反应，建议减少用药剂量或改为饭后服用，可减轻相关症状，不建议与地高辛联用。

QUEST 研究[219]显示，在 GDMT 基础上加用芪苈强心，对慢性心衰患者的血压、心率无显著影响；与安慰剂组相比，芪苈强心未引起肾功能恶化（3.79% vs 4.50%）及肝酶水平增加（2.57% vs 3.09%）的风险；该研究排除血肌酐>176.82umol/L 的患者。

QLQX-DCM 研究[190]显示，芪苈强心组患者出现地高辛血液浓度过量的比例与安慰剂组相当（1.17% vs 1.17%）。

5 总结

心血管疾病是全球死亡的主要原因。心血管事件链反映心血管疾病整体性、复杂性的系统特性，与中医整体观高度契合，带来了疾病干预理念的思维转变。脉络学说指导下的通络药物，津力达“健脾运津”、通心络“搜剔疏通”、参松养心“温清补通”、芪苈强心“气血水同治分消”，覆盖心血管事件链不同阶段，达到精准干预，为防治心血管事件链提供具有中国特色的中西医结合临床药物治疗方案。本共识描述了心血管事件链及脉络学说的重要价值，针对糖尿病及糖尿病前期、缺血性心脑血管疾病、心律失常、慢性心衰等，分别介绍了津力达、通心络、参松养心、芪苈强心各个通络药物的组方特色、阐明了相关的药理作用机制、总结了各个药物的主要循证临床证据及用药安全性。此外，汇总专家临床经验，结合循证证据，根据 ESC 标准，针对心血管事件链各个关键环节的中西医结合治疗给予了推荐建议和临床证据等级，供广大临床医生在临床实践中参考与应用。

附录 A
（规范性）
研究方法与技术路线

共识制定流程与方法，参考中华中医药学会发布的《中医临床实践指南制修订中专家共识技术规范》（编号 T/CACM1049-2017），制定流程如图 A.1 所示。

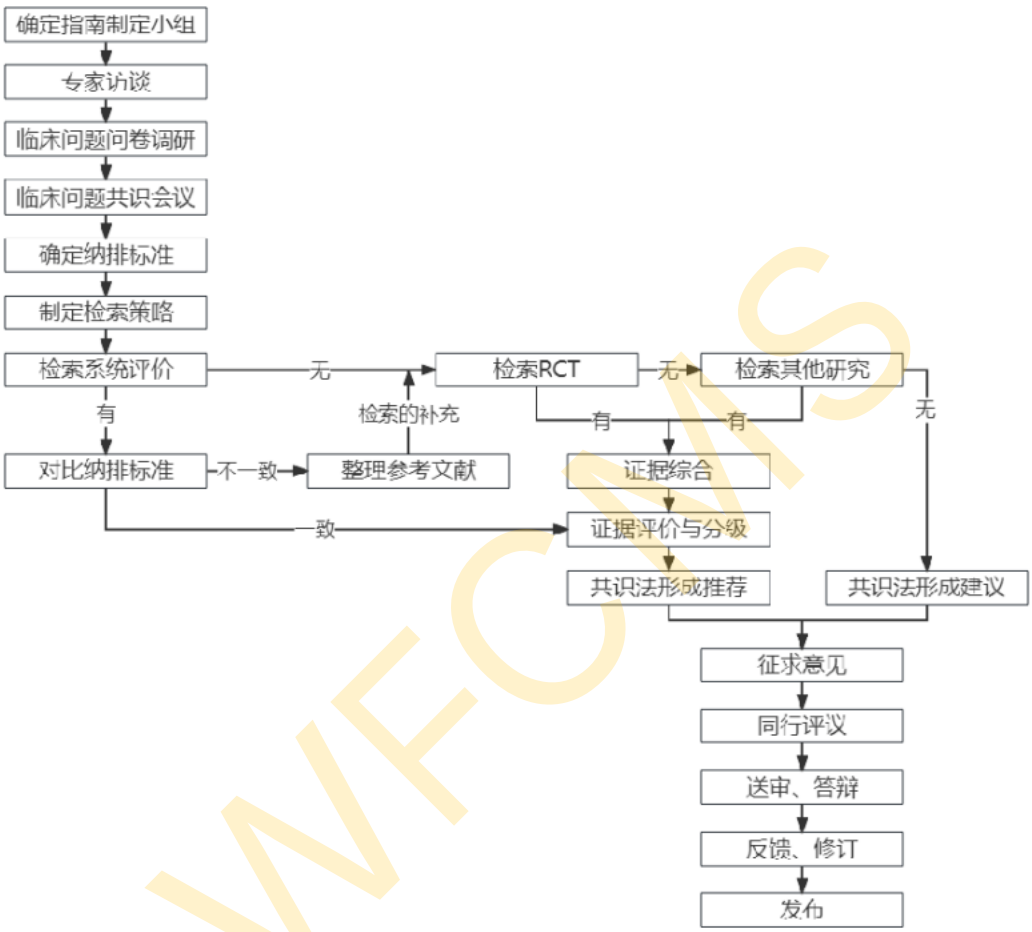

图 A. 1 专家共识制定流程图

附录 B

（资料性）

临床研究文献筛选标准及证据级别

本共识的推荐标准及证据质量评价标准参考欧洲心脏病学会（ESC）指南（表 B.1、表 B.2）。通络药物系统干预心血管事件链常用药物可见表 B.3。

表 1 推荐级别的定义

级别	含义
I 类	已证实和（或）一致公认有益、有用和有效的操作或治疗
II a 类	有关证据/观点倾向于有用和（或）有效，应用这些操作或治疗是合理的
II b 类	有关证据/观点尚不能被充分证明有用和（或）有效，可考虑应用
III 类	已证实和（或）一致公认无用和（或）无效，并对一些病例可能有害的操作或治疗，不推荐使用

表 2 证据级别的定义

级别	含义
A	资料来源于多项随机对照临床试验或荟萃分析
B	资料来源于单项随机对照临床试验或多项非随机对照研究
C	仅为专家共识意见和（或）小型临床试验、回顾性研究或注册登记研究

表 3 通络药物系统干预心血管事件链常用药物

通络药物	常用口服剂量
津力达颗粒	9g/次，每日 3 次
通心络胶囊	颈动脉硬化：6 粒/次，每日 2 次 冠心病：4 粒/次，每日 3 次 STEMI：急诊 PCI 术前负荷剂量 8 粒，术后 4 粒/次，每日 3 次 脑卒中：4 粒/次，每日 3 次
参松养心胶囊	4 粒/次，每日 3 次
芪苈强心胶囊	4 粒/次，每日 3 次

注：STEMI，ST 段抬高型心肌梗死；PCI，经皮冠状动脉介入术。

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Preface

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Introduction

Over the past 30 years, cardiovascular diseases (CVDs) have remained a major global cause of death, posing a significant public health challenge [1,2]。 The "Healthy China 2030" initiative [3] sets a goal to reduce premature mortality from major chronic diseases, including CVDs. Achieving this goal requires the collaboration of multiple disciplines, including Western medicine and traditional Chinese medicine (TCM), to maximally curb the onset and progression of CVDs. In the 1990s, American cardiologist Professor Braunwald and Professor Dzau introduced the concept of the "cardiovascular continuum"[4], which brought a paradigm shift in the approach to comprehensive CVD intervention and challenged the traditional single-target, single-factor, and single-mechanistic drug treatments[5-9]. This concept aligns well with the holistic and systemic theoretical characteristics of TCM. In recent years, significant breakthroughs have been made in the prevention and treatment of CVDs using TCM-based Luobing theory and its guiding principles for promoting blood circulation and removing stasis[10]. To further promote the integration and innovation of TCM and modern/Western medicine, and to provide a clinical management with TCM characteristics for systematically intervening in the cardiovascular continuum. This expert consensus aim to review the systematic intervention of the cardiovascular continuum using Luobing theory-based Chinese medicine formula.

0.1 The Concept of the Cardiovascular Continuum and Its Significance in Disease Prevention and Treatment

"Cardiovascular continuum"[4] refers to the entire process of CVDs, starting from the accumulation of high-risk factors leading to atherosclerosis, vulnerable plaque rupture causing myocardial infarction, arrhythmias, heart failure (HF), and ultimately death. This process is characterized by multiple factors, interconnected links, progressive development, sudden events, and severe consequences [5-9]. The introduction of this concept reflects the systemic nature and complexity of CVDs, shifting the focus from single-factor, single-approach, and single-target interventions to a holistic, continuous, dynamic, and comprehensive intervention strategy. By targeting key pathological links in the cardiovascular continuum, such as high-risk factors, vulnerable coronary plaques, myocardial protection after reperfusion therapy for acute myocardial infarction, arrhythmias, and chronic HF, this approach aims to address current therapeutic

bottlenecks, control upstream risk factors, and prevent the progression of disease downstream. This forms a systematic intervention strategy that integrates prevention with treatment, fundamentally blocking the cardiovascular continuum and reducing the incidence and mortality of CVDs.

0.2 The Proposal of the *Mai Luo Theory* and Its Significance in Preventing the Cardiovascular Continuum

The *Mai Luo Theory* is an original theory established by inheriting and developing the TCM theory of blood vessels. Although TCM has documented theories related to vascular diseases over its 2,000-year history, the lack of systematic development of the blood vessel and *Mai Luo Theory* has hindered their potential in guiding the prevention and treatment of vascular diseases. Under the guidance of the holistic view of TCM, Academician Wu Yiling further developed the *Mai Luo Theory*. This theory emphasizes that from the early stages of the cardiovascular continuum to the occurrence of severe cerebral-cardiovascular events, microcirculation dysfunction plays a critical role.

From a TCM perspective, the *Mai Luo Theory* not only focuses on the surface symptoms but also addresses the underlying microcirculation dysfunction and endothelial dysfunction, thereby alleviating issues in medium and large vessels as well as the myocardium. The *Mai Luo Theory* advocates for improving microcirculation at its source, aligning with the concept of the cardiovascular continuum. The research scope of the *Mai Luo Theory* includes chest pain, stroke, palpitations, and heart edema from the prospective of TCM, covering major diseases in the cardiovascular continuum such as cardiovascular and cerebrovascular diseases, arrhythmias, and HF. Guided by the *Mai Luo Theory*, the holistic and systemic characteristics of TCM can be fully utilized to achieve systematic intervention in the cardiovascular continuum [11,12].

0.3 The Theoretical Basis of Mai Luo Theory-Guided Drugs in Preventing the Cardiovascular Continuum

0.3.1 The Core Concept of Nutrient and Defense (Ying-Wei, 营卫) in Mai Luo Theory Reveals the Development and Medication Mechanism of the Cardiovascular Continuum

Based on the core content of the *Mai Luo Theory*—the Nutrient and Defense Concept—the development of the cardiovascular continuum, characterized by "Coagulation (凝)" → "Obstruction (壅)" → "Blockage (塞)" → "Non-circulation (不通)" is highly correlated with key pathological links such as the accumulation

of high-risk factors, vulnerable arterial plaques, acute myocardial infarction, arrhythmias, and chronic HF. Through data mining of ancient and modern medical records, the characteristics of the cardiovascular continuum are revealed: abnormalities in the "collateral circulation and biochemical interactions" of Nutrient and Defense are the initiating factors and persist throughout the process, leading to abnormal distribution and metabolism of body fluids and blood, and the mutual influence of dampness, phlegm, stasis, and water. This forms the developmental process and constituting a continuous pathological process from collateral dysfunction to structural damage and from primary lesions to secondary myocardial damage in the cardiovascular continuum.

Based on the symptom types, pathogenesis, and medication rules of "regulating Ying-Wei and body fluids" identified through data mining, a medication plan for systematically intervening in the cardiovascular continuum using collateral drugs has been established: the "strengthening the spleen and transporting body fluids (健脾运津)" treatment method and its representative drug, Jinlida Granules, are used to intervene in the "coagulation" stage—the accumulation of high-risk factors leading to blood coagulation; the "searching and dredging (搜剔疏通)" treatment method and its representative drug, Tongxinluo Capsules, are used to intervene in the "Obstruction" stage—vulnerable coronary plaques and the "Blockage" stage—acute myocardial infarction and cerebral infarction; the "warming, clearing, tonifying, and dredging (温清补通)" treatment method and its representative drug, Shensong Yangxin Capsules, are used to intervene in the "Non-circulation" stage—arrhythmias; and the "simultaneous regulation of Qi, blood, and water (气血水同治分消)" treatment method and its representative drug, Qiliqiangxin Capsules, are used to intervene in the "Non-circulation" stage—chronic HF.

This forms a set of intervention drugs targeting the core pathogenesis of the TCM transmission pattern of "Coagulation (凝)" → "Obstruction (壅)" → "Blockage (塞)" → "Non-circulation (不通)" in the cardiovascular continuum [13-15].

0.3.2 The Nutrient and Defense Concept in Mai Luo Theory Guides the Proposal of a Systematic Intervention Strategy for the Cardiovascular Continuum

The proposal of this new systematic intervention strategy draws on the TCM concept of "preventive treatment of disease (治未病)." *The Yellow Emperor's Classic of Internal Medicine* first introduced the concept of "preventive treatment of disease," and Zhang Zhongjing of the Eastern Han Dynasty further developed this concept, emphasizing "preventing disease progression (防传变)." Based on

the TCM concepts of "preventive treatment of disease" and "preventing disease progression," a new perspective of "treating the current disease and preventing future disease (治本病、防未病)"—preventing upstream factors, treating current diseases, and controlling downstream progression—has been proposed for the systematic intervention of the cardiovascular continuum. In-depth research on the "regulating Nutrient and Defense" treatment method and Luobing-based medicines demonstrate their role this procerss. This has significant theoretical value in guiding the holistic, continuous, dynamic, and comprehensive intervention of the cardiovascular continuum [14].

In the past three decades of clinical practice, the primary, secondary, and tertiary prevention concepts and measures proposed by modern/Western medicine have played a significant role in the prevention and treatment of CVDs. However, due to the systemic nature and complexity of CVDs, single-factor, single-mechanistic, and single-target interventions face challenges.

- High-risk factors for CVDs often cluster in individuals and involve multiple metabolic abnormalities, significantly increasing the risk of atherosclerosis [16].
- The residual inflammatory risk of vulnerable plaques significantly increases cardiovascular events, and lipid-lowering combined with anti-inflammatory therapy provides greater benefits for high-risk patients with coronary artery disease (CAD) [17-19]. In the era of reperfusion therapy, no-reflow/slow-flow and ischemia-reperfusion injury in acute myocardial infarction severely affect prognosis [20,21].
- Compared to the rapid progress in catheter ablation, antiarrhythmic drug therapy, which emphasizes suppression and counteraction, has not seen significant breakthroughs, with a recurrence rate of up to 30% after catheter ablation for persistent atrial fibrillation [22-24].
- The 5-year mortality rate for chronic HF remains nearly 50% despite guideline-directed medical treatment, facing the need for further updates in treatment concepts over the past century [25,26].

The concept of the "cardiovascular continuum" suggests that solving these issues requires a shift toward holistic and systemic thinking, which aligns with the theoretical characteristics of the *Mai Luo Theory* systematically constructed based on the inheritance of TCM blood vessel theory over 2,000 years. This also lays the theoretical foundation for the collateral drugs developed under the guidance of the collateral disease theory to address these bottleneck issues and achieve systematic intervention.

The research methods and technical roadmap of this document are detailed in **Annex A**, and the clinical research literature screening criteria and evidence

levels are provided in **Annex B**.

The issuing organization of this document draws attention to the fact that compliance with this document may involve the use of patents related to *Luobing theory*-based drug/formula.

The issuing organization takes no position on the authenticity, validity, or scope of these patents.

The patent holder has committed to the issuing organization that they are willing to negotiate patent licensing agreements with any applicant under reasonable and non-discriminatory terms and conditions.

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Please note that, in addition to the aforementioned patent, certain contents of this document may still involve patents. The issuing organization does not assume responsibility for identifying patents.

Expert consensus on the intervention of the cardiovascular continuum by Luobing theory-based Chinese medicine formula

1 Scope

This document describes the mechanism of action and clinical application recommendations for a series of Luobing theory-based drugs (including Jinlida Granules, Tongxinluo Capsules, Shensong Yangxin Capsules, and Qiliqiangxin Capsules) for systemic intervention in cardiovascular continuum (such as diabetes, stroke, CAD, arrhythmias, and HF).

This document is intended for use by clinicians in endocrinology, cardiology, neurology, and related specialties in the treatment of conditions such as diabetes, stroke, CAD, arrhythmias, and HF.

2 Normative References

The contents of the following documents/articles, through normative references, constitute essential provisions of this document. For dated references, only the version corresponding to that date applies to this document. For undated references, the latest version (including all amendments) applies to this document.

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3 Terms and definitions

The following terms and definitions apply to this document.

3.1
Diabetes mellitus

a metabolic disease characterized by elevated blood glucose levels due to

absolute or relative insulin deficiency (insulin secretion defect) and reduced sensitivity of target tissues or organs to insulin (insulin action defect), which may be accompanied by dyslipidemia and other features.

Note: Diabetes mellitus falls under the categories of "Xiaodan " or "Xiaoke" in Chinese medicine.

[Source: SCM 18-2017, 3.3]

3.2

Coronary artery disease (CAD)

a heart disease caused by impaired blood circulation to the heart due to coronary artery atherosclerosis, leading to myocardial ischemia and hypoxia.

3.3

Ischemic stroke

a clinical syndrome characterized by rapid onset of neurological deficits due to ischemic and hypoxic necrosis of brain tissue caused by various cerebrovascular disorders that disrupt blood supply to the brain.

3.4

Atrial fibrillation (AF)

one of the most common arrhythmias, characterized by disordered atrial electrical activity and loss of effective atrial contraction, resulting in irregular ventricular rates and an increased risk of various complications.

3.5

Ventricular premature contraction (VPC)

ventricular pre-excitation

a common arrhythmia referring to a single or paired premature depolarization of the myocardium originating from sites below the bifurcation of the atrioventricular bundle.

3.6

Heart failure (HF)

a complex clinical syndrome caused by abnormal changes in cardiac structure and/or function due to various reasons, leading to impaired ventricular systolic and/or diastolic function.

[Source: SCM/TR 0008-2025, 3.1]

4 Luobing Theory-Based Medicine and Cardiovascular Continuum

4.1 Luobing Theory-Based Medicine

Luobing theory-based medicine developed under the guidance of the *Mai Luo Theory* in TCM include Jinlida Granules (JLD), Tongxinluo Capsules (TXL), Shensong Yangxin Capsules (SSYX), and Qiliqiangxin Capsules (QLQX). These drugs target different stages of the cardiovascular continuum.

JLD, based on the "strengthening the spleen and transporting body fluids (健脾运津)" treatment method, is used to intervene in the "Coagulation (凝)" stage—the accumulation of high-risk factors leading to blood coagulation at the source of the cardiovascular continuum.

TXL, using the "searching and dredging (搜剔疏通)" treatment method, intervenes in the "Obstruction (壅)" stage—vulnerable coronary plaques and the "Blockage (塞)" stage—acute myocardial infarction and cerebral infarction.

SSYX, employing the "warming, clearing, tonifying, and dredging (温清补通)" treatment method, intervenes in the "Non-circulation (不通)" stage—arrhythmias.

QLQX, based on the "simultaneous treatment of Qi, blood, and water (气血水同治分消)" medication principle, intervenes in the "Non-circulation (不通)" stage—chronic heart failure.

Together, these drugs form a set of interventions targeting the core pathogenesis of the TCM transmission pattern of "Coagulation (凝)" → "Obstruction (壅)" → "Blockage (塞)" → "Non-circulation (不通)" in the cardiovascular continuum [13-15].

4.2 Luobing Theory-Based Medicine and Diabetes Mellitus/Prediabetes

4.2.1 Formulation Characteristics of JLD - "Strengthening the Spleen and Transporting Body Fluids"

Based on the symptom characteristics and clinical manifestations of the "Coagulation (凝)" stage—the accumulation of high-risk factors, JLD, the representative drug of the "strengthening the spleen and transporting body fluids (健脾运津)" treatment method, was established as the intervention drug. The formula integrates various TCM spleen-regulating prescriptions: ginseng (人参) for replenishing Qi and strengthening the spleen; Polygonatum (黄精) and Ophiopogon (麦冬) for nourishing spleen Yin; Atractylodes (苍术) and Eupatorium (佩兰) for drying spleen dampness; Litchi seed (荔枝核) for promoting spleen Qi; Sophora flavescens (苦参) and Coptis (黄连) for clearing spleen heat; Epimedium (仙灵脾) for warming spleen Yang; and Pueraria (葛根)

for lifting spleen Qi. Combined with Salvia miltiorrhiza (丹参) to tonify meridians, the formula exerts the effects of "strengthening the spleen and transporting body fluids," providing a formulation basis for its role in the comprehensive intervention of diabetes [12].

4.2.2 Mechanisms of JLD in Improving Type 2 Diabetes Mellitus

4.2.2.1 Improving Insulin Sensitivity

Antioxidant Effects: Studies by Song Guangyao et al. [27-30] suggested that JLD upregulates the expression of silent information regulator 3 (SIRT3), enhances the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), and reduces levels of reactive oxygen species (ROS) and malondialdehyde (MDA), thereby alleviating oxidative stress interference with insulin signaling.

Anti-inflammatory Effects: Research by Tang Yange et al.[31] showed that JLD effectively inhibits the activation of the nuclear factor kappa-B (NF-κB) signaling pathway, reduces the release of pro-inflammatory factors such as interleukin-1β (IL-1β) and IL-6, and alleviates insulin resistance caused by chronic low-grade inflammation, thereby improving insulin sensitivity and regulating blood glucose.

Relieving Lipotoxicity: Studies by Song Guangyao et al. [32] revealed that JLD activates AMP-activated protein kinase (AMPK), promotes the phosphorylation of acetyl-CoA carboxylase (ACC), and enhances the expression of hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), thereby improving fatty acid oxidation efficiency. Research by Zhang Huixin et al. [33] indicated that JLD downregulates the expression of fatty acid translocase (FAT/CD36), reduces the uptake of free fatty acids, and decreases the deposition of triglycerides and non-esterified fatty acids in skeletal muscle, alleviating lipotoxicity and improving insulin sensitivity.

4.2.2.2 Protection of islet β-cell

Anti-β-Cell Apoptosis: Studies by Le Ling et al. [34,35] demonstrated that JLD inhibits Smad2/3 phosphorylation, upregulates the expression of anti-apoptotic proteins such as B-cell lymphoma-2 (Bcl-2), and downregulates pro-apoptotic proteins such as caspase-3 and Bcl-2-associated X protein (Bax), significantly reducing high glucose-induced β-cell apoptosis. Additionally, it improves the function of pancreatic microvascular endothelial cells, optimizes the survival environment of pancreatic β-cells, and protects pancreatic function.

4.2.2.3 Multi-Pathway Synergistic Regulation of Glucose and Lipid Metabolism Network

Research by Gao Huailin et al. [36-45] showed that JLD activates the fibroblast growth factor 21 (FGF21)/AMPK signaling pathway, inhibits the expression of hepatic diacylglycerol acyltransferase 1 (DGAT1), and reduces triglyceride synthesis and accumulation. It also upregulates brown fat thermogenesis-related genes such as uncoupling protein 1 (UCP1) and PR domain-containing 16 (PRDM16), promoting fatty acid oxidation and energy expenditure, and improving the metabolic state of the liver and adipose tissue.

Furthermore, JLD upregulates the expression of peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) and its downstream molecules, promoting mitochondrial biogenesis and oxidative phosphorylation. By inhibiting mammalian target of rapamycin (mTOR), activating tuberous sclerosis complex 1 (TSC1), and upregulating microtubule-associated protein 1 light chain 3 (LC3-II), it induces autophagy, clears excess lipids, and further improves the metabolic microenvironment.

In terms of insulin signaling, JLD synergistically activates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway, upregulates the expression of insulin receptor (IR), insulin receptor substrate-1 (IRS-1), and glucose transporter type 4 (GLUT4), enhancing cellular response to insulin and glucose uptake. It also inhibits the activation of negative regulatory signals such as c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38MAPK), preventing signal pathway blockage and comprehensively improving insulin efficiency.

4.2.2.4 Improving Microcirculation

Studies by Ding Yingjun et al. [46,47] indicated that JLD combined with TXL significantly improves the viability of renal microvascular endothelial cells under high glucose conditions, reduces apoptosis, and lowers ROS levels. It also significantly inhibits the expression of phosphorylated Smad2/3 and upregulates Smad7 expression. Additionally, the combined intervention effectively reduces the generation of type IV collagen, alleviates renal fibrosis, downregulates p-Akt and p-mTOR expression, inhibits mTOR pathway-mediated overexpression of vascular endothelial growth factor (VEGF), and improves abnormal vascular proliferation in renal tissue. Inhibition of the Akt/mTOR pathway also helps regulate metabolic stress in tissues, reducing renal damage associated with diabetes-related metabolic disorders.

4.2.3 Evidence-based practice of JLD in Type 2 Diabetes and Prediabetes

4.2.3.1 Prediabetes

The FOCUS study [48] was a multicenter, randomized, double-blind, placebo-controlled clinical trial involving 889 individuals with impaired glucose tolerance and multiple metabolic abnormalities. Participants were randomly assigned to receive JLD (9 g/dose, three times daily [TID], orally) or placebo. The primary outcome was the incidence of diabetes (diagnosed by two consecutive oral glucose tolerance tests). Results showed:

① After a median follow-up of 2.2 years, the risk of developing diabetes in the JLD group was significantly lower than in the placebo group (Hazard Ratio [HR] = 0.59, 95% Confidence Interval [CI]: 0.46–0.74; $P < 0.001$).

② In terms of metabolic indicators, compared to the placebo group, the JLD group showed a reduction in waist circumference by 0.95 cm (95% CI: 0.36–1.55), fasting blood glucose by 3.8 mg/dL (95% CI: 2.2–5.6), 2-hour postprandial blood glucose by 9.2 mg/dL (95% CI: 5.4–13.0), glycated hemoglobin (HbA1c) by 0.20% (95% CI: 0.13%–0.27%), and improvement in the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) by 0.47 (95% CI: 0.12–0.83).

③ In terms of blood lipids, compared to the placebo group, the JLD group showed significant reductions in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, while high-density lipoprotein cholesterol (HDL-C) levels increased.

④ After 24 months of follow-up, the ankle-brachial index and waist circumference in the JLD group were significantly improved compared to the placebo group.

4.2.3.2 Newly Diagnosed Type 2 Diabetes

A 16-week double-blind randomized controlled trial (RCT) [49] evaluated the effects of JLD on glycemic variability in patients with newly diagnosed type 2 diabetes mellitus (T2DM), including monotherapy and combination therapy with metformin. Participants were randomly divided into four groups: control group, JLD group, metformin group, and JLD combined with metformin group. Retrospective continuous glucose monitoring (CGM) was performed for three consecutive days, and HbA1c, TCM symptom scores, and CGM parameters (including glucose coefficient of variation, glucose standard deviation, and time in range [3.9–10.0 mmol/L]) were assessed before and after the trial. A total of

138 participants completed the study. Results showed: Compared to baseline, fasting blood glucose, 2-hour postprandial blood glucose, HbA1c, and TCM symptom scores decreased in all four groups, with the most significant reduction in the combination therapy group. In terms of CGM parameters, the time in range significantly improved in both the JLD group and metformin group (Jinlida group: 78.68 ± 26.15 vs. 55.47 ± 33.29; metformin group: 87.29 ± 12.21 vs. 75.44 ± 25.42; $P < 0.01$). Notably, only the JLD group showed a significant reduction in glucose standard deviation (1.57 ± 0.61 vs. 1.96 ± 0.95; $P < 0.01$). The study demonstrated that JLD effectively improves glycemic control and variability in newly diagnosed T2DM patients.

4.2.3.3 Poorly Controlled T2DM

A randomized, double-blind, placebo-controlled, multicenter study [50] included 186 T2DM patients. Participants were randomly assigned to receive JLD (9 g/dose, TID, orally) or placebo for 12 weeks. Both groups continued to take their original dose of metformin, which remained unchanged. Changes in HbA1c, fasting blood glucose, 2-hour postprandial blood glucose, weight, and body mass index (BMI) were assessed during the 12-week treatment period, while HOMA-IR and Homeostasis Model Assessment-β (HOMA-β) were calculated. Results: After 12 weeks of treatment, HbA1c decreased by 0.92 ± 1.09% in the JLD group and by 0.53 ± 0.94% in the placebo group (JLD group 95% CI: 0.69–1.14; placebo group 95% CI: 0.34–0.72). The difference in HbA1c reduction between the two groups was statistically significant ($P < 0.01$). Both fasting blood glucose and 2-hour postprandial blood glucose decreased in both groups compared to baseline, with statistically significant differences between the groups (both $P < 0.01$). The JLD group also showed improved β-cell function, with a significant increase in the HOMA-β index ($P < 0.05$). Changes in weight and BMI were not statistically significant.

4.2.3.4 Insulin Resistance in T2DM

A meta-analysis [51] including 15 RCT showed that JLD combined with other hypoglycemic drugs significantly improved glycemic control in T2DM patients after at least 12 weeks of treatment. Compared to the control group, the treatment group significantly reduced HbA1c ($P < 0.001$), fasting blood glucose ($P < 0.001$), and 2-hour postprandial blood glucose ($P < 0.001$). Additionally, the treatment group demonstrated greater ability to regulate HOMA-IR and HOMA-β, thereby increasing insulin sensitivity and improving insulin resistance.

Table 1 - Recommendations for Jinlida Granules (JLD) in the management

of Diabetes and Prediabetes

Recommendation	Class of Recommendation	Level of Evident
For patients with impaired glucose tolerance, JLD is recommended to be added to lifestyle interventions to reduce the risk of new-onset diabetes, improve glucose and lipid metabolism (including lowering fasting and postprandial blood glucose, HbA1c, increasing HDL-C levels, and reducing TG levels), and reduce waist circumference, BMI, and carotid intima-media thickness.	IIa	A
For newly diagnosed T2DM patients, JLD can be used alone or in combination with metformin to improve glycemic variability and increase time in the target glucose range.	IIa	B
For T2DM patients who do not achieve glycemic control with metformin monotherapy or other oral hypoglycemic agents, JLD is recommended to further reduce HbA1c and improve fasting and postprandial blood glucose.	IIa	A
For T2DM patients, JLD can be used alone or in combination with other hypoglycemic agents to improve body weight, increase insulin sensitivity, and alleviate insulin resistance.	IIa	A

Note: JLD, Jinlida granules; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; BMI, body mass index; T2DM, type 2 diabetes mellitus.

4.2.4 Safety of JLD

According to the China National Adverse Drug Reaction Monitoring System [52], as of March 2025, a total of 848 adverse drug reaction (ADR) reports related to JLD have been received, with a reporting rate of approximately 2.61‰ , indicating that the incidence of adverse reactions is rare. The main adverse reactions include diarrhea, nausea, vomiting, abdominal distension, and rash.

4.3 Luobing Theory-Based Medicine and Ischemic Cardiovascular and Cerebrovascular Diseases

4.3.1 Formulation Characteristics of TXL —— The "Searching and Dredging"

Based on the syndrome characteristics and clinical manifestations of "obstruction" (vulnerable coronary plaques) and "blockage" (acute myocardial infarction and cerebral infarction), the therapeutic method of "searching, removing, and dredging" was established, with TXL as the intervention drug.

Targeting the common pathogenesis of qi stagnation, TXL uses ginseng (人参) and dalbergia wood (降香) to tonify deficiency, relieve stagnation, and regulate collateral qi. For blood stasis, it employs leech (水蛭) and ground beetle (土鳖虫) to remove stasis. For relieve vessel spasm, it uses scorpion (全蝎), centipede (蜈蚣), and cicada slough (蝉蜕) to dispelling wind and dredging meridians. This reflects the formulation characteristics of "searching, removing, and dredging," providing a basis for its comprehensive intervention in the prevention and treatment of coronary heart disease, angina pectoris, acute myocardial infarction, and cerebral infarction [12].

4.3.2 Mechanisms of TXL in Management of Ischemic Cardiovascular and Cerebrovascular Diseases

4.3.2.1 Protecting Endothelium and Improving Microcirculation

TXL achieves endothelial protection and microcirculation improvement through multi-target synergistic effects. Multiple studies by Wu et al.[53,54] have shown that TXL activates the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway, promoting phosphorylation of endothelial nitric oxide synthase (eNOS) at Ser1179 and Ser635 sites, enhancing eNOS activity, and upregulating vascular endothelial cadherin (VE-cadherin) and β-catenin expression, thereby effectively protecting myocardial microvascular endothelial structure. Chen et al.[55] found in an ischemia-reperfusion rat model that TXL alleviates endothelial cell damage and improves cardiac microcirculation by regulating the exosome-mediated long intergenic non-protein coding RNA (Linc-ROR)/p70 ribosomal protein S6 kinase (p70S6K)/eNOS pathway, reducing myocardial infarction area. Basic research by Li et al.[56,57] confirmed that TXL significantly reduces myeloperoxidase activity and inflammatory factor levels, decreases microvascular permeability and myocardial and mitochondrial edema, thereby improving coronary microcirculation perfusion and promoting left ventricular function recovery. In cerebral ischemia models, TXL also promotes microvascular neovascularization, reduces blood-brain barrier permeability[58,59], and increases blood flow in ischemic areas[60], demonstrating its multi-dimensional role in improving microcirculation disorders.

4.3.2.2 Stabilizing Plaques and Anti-Atherosclerosis

Studies by Chen et al.[58,61-63] showed that TXL significantly reduces lipid levels and inflammatory factors such as monocyte chemoattractant protein-1 (MCP-1), hypersensitive C-reactive protein (hs-CRP), and matrix metalloproteinase-1 (MMP-1) in New Zealand rabbit atherosclerosis models, while increasing plaque

fibrous cap thickness to enhance plaque stability. At the molecular level, TXL inhibits intraplaque inflammatory angiogenesis and regulates plaque composition by modulating the bone marrow X-linked kinase (Bmx)/NF-κB/MAPK pathway, significantly reducing plaque vulnerability index[64]. Qi et al. [65] found that TXL regulates gut microbiota during atherosclerosis, specifically increasing the abundance of indistinctus microbiota and trans-ferulic acid content, thereby inhibiting the macrophage nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammatory pathway. Clinical research by Zhang et al.[66] demonstrated that adding TXL to conventional antiplatelet therapy further reduces platelet hyperreactivity and hs-CRP levels to prevent atherosclerosis. Additionally, TXL activates the peroxisome proliferative activated receptor gamma (PPARγ) pathway to inhibit oxidized low-density lipoprotein-induced dendritic cell maturation and pro-inflammatory factor secretion, regulating immune-inflammatory responses and delaying atherosclerosis progression [67].

4.3.2.3 Protecting Cardiomyocytes and Promoting Myocardial Angiogenesis

Apoptosis and autophagy are critical pathways for cardiomyocyte survival and death. Li et al. [56] found that TXL pretreatment inhibits myocardial apoptosis protein expression in ischemia-reperfusion minipig models to reduce cardiomyocyte apoptosis. Moreover, TXL pretreatment for one hour upregulates phosphorylated eNOS expression at Ser1179 and Ser635 to reduce myocardial no-reflow and ischemia-reperfusion injury, with the PKA pathway partially mediating the cardioprotective effects. In acute myocardial infarction rat models, TXL treatment reduces infarct size and promotes angiogenesis in the peri-infarct zone, exerting cardioprotective effects. Mechanistically, TXL activates the AMPK signaling pathway, increases myocardial autophagy protein LC3 expression, reduces apoptosis protein Bax levels, promotes autophagy, and inhibits cardiomyocyte apoptosis, thereby protecting cardiomyocytes and promoting myocardial repair [68]. Bai et al. [69] confirmed in myocardial infarction mouse models that TXL promotes myocardial neovascularization by increasing Akt and extracellular regulated protein kinases (ERK) phosphorylation, enhancing VEGF and p-eNOS protein expression, thereby improving post-infarction cardiac function and ventricular remodeling.

4.3.2.4 Relieving Vascular Spasm

TXL exerts anti-vasospasm effects through multi-target regulation, involving key signaling pathways. Studies by Guan et al. [70,71] showed that TXL significantly improves vascular contraction function in rat models of chronic carotid artery

adventitial injury, reducing lumen stenosis (8.2% ± 1.0% vs. 20.1% ± 3.3%), improving lumen cross-sectional area and blood flow. By inhibiting the RAS homologous gene family member A (RhoA)/Rho kinase pathway, TXL significantly downregulates Rho kinase mRNA and phosphorylated myosin phosphatase target subunit 1 (MYPT1) protein expression, reducing vascular sensitivity to serotonin-induced contraction, with mechanisms similar to nicorandil. Further research found that TXL activates the ERK1/2-neuronal nitric oxide synthase (nNOS) signaling axis, promoting ERK1/2 phosphorylation-mediated nNOS expression, improving vascular contraction, relieving vasospasm, and reducing vascular hypersensitivity to contractile factors, exerting anti-vasospasm protective effects [72].

4.3.2.5 Promoting Neurological Recovery

For cerebral ischemic injury, TXL enhances and prolongs the high expression of brain-derived neurotrophic factor (BDNF) and VEGF in ischemic areas, exerting neuroprotective effects [73,74]. In middle cerebral artery occlusion rat models, TXL treatment significantly improves the ultrastructure of cerebral cortical microvessels under electron microscopy [75]. TXL may also improve ischemia/reperfusion injury, neurological damage, and blood-brain barrier disruption by activating mitogen-activated extracellular signal-regulated kinase (MEK1/2)/ERK/p90 ribosomal S6 kinase (p90RSK), PI3K/Akt pathways, or inhibiting low-density lipoprotein receptor-related protein 1 (LRP1), promoting axonal reconstruction and synapse formation of motor nerve fibers, improving microvascular circulation and neovascularization in ischemic areas, thereby enhancing neurological function [59,76-82].

4.3.3 Evidence-Based Practice of TXL in Ischemic Cardiovascular and Cerebrovascular Diseases

4.3.3.1 Coronary Artery Disease

4.3.3.1.1 Stable Angina Pectoris

A meta-analysis by Feng et al. [83], which included 26 randomized controlled trials (RCTs), showed that in patients with stable angina, the addition of TXL to secondary prevention of CAD for more than 4 weeks reduced the frequency of angina episode by 0.91 times per week, shortened the duration of angina by 1.71 minutes per episode, decreased nitroglycerin usage by 2.22 mg per week, and increased the 6-minute walk test distance by 27.86 meters.

4.3.3.1.2 Unstable Angina Pectoris

Meta-analyses [84-98] demonstrated that in patients with unstable angina, the addition of TXL to secondary prevention for more than 2 weeks reduced the frequency of angina episode by 2.32 times per week, shortened the duration of angina by 1.74 minutes per episode, and improved the recovery rate of ST-segment depression by 27%. Continuous use for 1–6 months reduced the risk of myocardial infarction by 65%.

4.3.3.1.3 Variant Angina Pectoris

RCTs [99,100] suggested that in patients with variant angina, the addition of TXL to conventional medical treatment effectively reduced the duration of angina ($P < 0.05$) and improved angina symptoms.

4.3.3.1.4 Coronary Microvascular Disease Associated with Non-Obstructive Coronary Ischemia

Meta-analyses [101-103] showed that in patients with coronary microvascular disease (CMVD) associated with non-obstructive coronary ischemia, the addition of TXL to conventional treatment for 1 month reduced the frequency of angina attacks by 3.74 episodes per week and delayed the time of ST-segment depression during exercise electrocardiography by 64.51 seconds. After 3 months of treatment, the corrected TIMI (thrombolysis in myocardial infarction) frame count of the target vessel decreased by 11.63 frames.

4.3.3.1.5 ST-Segment Elevation Myocardial Infarction (STEMI)

The ENLEAT study [117] included 219 patients with STEMI. In addition to conventional treatment, patients were given a loading dose of TXL or placebo (2.08 g, 8 capsules) before emergency percutaneous coronary intervention (PCI). After the procedure, patients took 4 capsules three times daily for 6 months. ST-segment elevation was recorded via electrocardiography (ECG) at hospitalization and 1, 2, 6, 12, and 24 hours after coronary balloon dilation to assess myocardial no-reflow. The results showed that at 6 hours post-administration, the degree of ST-segment resolution was significantly better in the TXL group. At 24 hours post-administration, the TXL group significantly reduced the no-reflow rate by 36.6% (34.3% vs. 54.1%, $P = 0.0031$), decreased ST-segment elevation, accelerated ST-segment resolution, improved myocardial blood perfusion, reduced myocardial infarction area, and improved post-reperfusion cardiac function by reducing segmental wall motion abnormalities.

The CTS-AMI study [118] included 3,797 STEMI patients who, in addition to dual

antiplatelet therapy, were randomly assigned to receive a loading dose of TXL or placebo (2.08 g, 8 capsules). Subsequently, both groups took 4 capsules three times daily for 12 months on top of secondary prevention treatment. The results showed:

①The 30-day risk of major adverse cardiovascular and cerebrovascular events (MACCE) (including cardiac death, myocardial reinfarction, emergency revascularization, and stroke) in the TXL group was 36% lower than in the placebo group (3.39% vs. 5.24%, risk ratio [RR] = 0.64, P = 0.006), with a 30% reduction in cardiac death, a 65% reduction in myocardial reinfarction, and a 23% reduction in malignant arrhythmias.

②After 1 year of continuous TXL use, the MACCE risk was 36% lower than in the placebo group (5.3% vs. 8.3%, RR = 0.64, P < 0.001), with a 27% reduction in cardiac death, a 74% reduction in myocardial reinfarction, a 56% reduction in stroke, and a 52% reduction in heart failure-related rehospitalization.

③The degree of ST-segment resolution at 24 hours post-administration was significantly better in the TXL group.

A meta-analysis by Chen et al. [119], which included 10 RCTs, suggested that in STEMI patients, the addition of TXL to secondary prevention reduced the MACCE risk by 39% (P < 0.001).

4.3.3.2 Carotid Atherosclerosis

The CAPITAL study [120] included 1,212 patients with non-calcified carotid plaques who were treated with TXL or placebo for 24 months (6 capsules twice daily). The results showed that TXL significantly reduced the annualized change in mean carotid intima-media thickness (−0.00095 mm vs. 0.01312 mm, P < 0.001), decreased plaque volume, improved vascular remodeling index, and reduced the incidence of major cardiovascular events.

4.3.3.3 Ischemic Stroke

The TISS study [121] was a multicenter, randomized, double-blind, placebo-controlled clinical trial that included 2,007 patients with acute ischemic stroke (AIS). In addition to standard treatment, patients were randomly assigned to receive TXL or placebo (4 capsules, TID) for 90 days. The results showed:

① Compared to placebo, TXL significantly increased the proportion of AIS patients achieving independent living (modified Rankin Scale [mRS] score ≤ 1) at 90 days (65.8% vs. 59.1%, odds ratio [OR] = 1.33, P = 0.002).

② The proportions of patients with mRS scores of 0–2, National Institute of Health Stroke Scale (NIHSS) scores of 0–1 or a reduction of ≥4, and Barthel Index

(BI) scores ≥85 were higher in the TXL group than in the placebo group. Prespecified subgroup analyses indicated that patients aged <60 years, those with symptom onset within 48 hours, those with diabetes, and those with large artery atherosclerotic stroke were more likely to benefit from TXL treatment. TXL treatment within 72 hours of AIS onset was more likely to result in favorable functional outcomes, with good safety.

A study by Yan Bo et al. [122] randomized 360 patients with acute/subacute ischemic stroke into two groups. The TXL group received TXL in addition to conventional treatment. After 14 days, although there was no statistical difference in BI scores and neurological deficit scores at 28 days, significant differences were observed at 3, 6, and 12 months. After 12 months, the recurrence rate of cardiovascular and cerebrovascular events was lower in the treatment group.

For stroke recovery patients, Wu Yiling et al. [123] evaluated TXL with ultra-fine grinding technology versus conventional grinding technology and found that the ultra-fine version was effective and safe for patients with qi deficiency, blood stasis, and collateral obstruction type stroke, with efficacy comparable to the conventional version.

A meta-analysis by Zhou Hongqing et al. [124] of 39 RCTs related to TXL in stroke treatment found that the TXL group showed significantly better improvement in neurological function scores than the control group, with higher efficacy at the end of treatment. Cong Lingnan et al. [125] analyzed 14 RCTs and found that the addition of TXL to conventional therapy improved neurological deficits (reducing deficit scores and increasing neurological improvement rates), enhanced daily living ability, and lowered NIHSS scores compared to conventional therapy alone, with no significant difference in adverse event rates.

Table 2 - Recommendations for Tongxinluo Capsule (TXL) in the Management of Ischemic Cardiovascular and Cerebrovascular Diseases

Recommendation	Class of Recommendation	Level of Evident
The addition of TXL to secondary prevention of coronary artery disease (CAD) further improves angina symptoms and enhances exercise tolerance in patients with stable angina.	I	A
The addition of TXL to secondary prevention of CAD further reduces the incidence of myocardial infarction and improves angina symptoms in patients with unstable angina.	I	A

The addition of TXL to secondary prevention of CAD further reduces major cardiovascular events and the rate of in-stent restenosis in patients after percutaneous coronary intervention (PCI).	I	A
The addition of TXL to secondary prevention of CAD further reduces the risk of major cardiovascular events in patients with ST-segment elevation myocardial infarction (STEMI).	I	A
The addition of TXL to conventional treatment further reduces the frequency of angina attacks, improves coronary blood flow, and enhances exercise tolerance in patients with coronary microvascular disease (CMVD) associated with non-obstructive coronary ischemia.	IIa	A
The addition of TXL to conventional Western medical treatment further improves angina symptoms in patients with variant angina.	IIa	B
Administering a loading dose of TXL (8 capsules) before emergency PCI, followed by 4 capsules three times daily for 1 year, reduces the no-reflow rate at 24 hours post-PCI, as well as the 30-day and 1-year risk of major adverse cardiovascular and cerebrovascular events (MACCE) and mortality in STEMI patients.	IIa	B
The addition of TXL to conventional treatment slows the progression of carotid intima-media thickening and reduces plaque volume in patients with carotid plaques.	IIa	A
For patients with acute ischemic stroke, the addition of TXL to conventional treatment within 72 hours of onset improves neurological deficit symptoms, enhances 90-day neurological function and daily living ability, and increases the proportion of patients with favorable functional outcomes at 90 days.	IIa	B
For patients with mild stroke (e.g., NIHSS score 4–7), comorbid diabetes, large artery atherosclerotic stroke, or those who start treatment within 48 hours of the acute phase, TXL may have a more significant effect on improving 90-day functional outcomes and should be prioritized.	IIa	B
The addition of TXL to conventional treatment may reduce the long-term recurrence rate of cerebrovascular events in patients with ischemic stroke.	IIa	B
For stroke recovery patients, TXL with ultra-fine grinding technology is effective and safe for patients with qi deficiency, blood stasis, and collateral obstruction type stroke, compared to the conventional grinding version.	IIa	B

Note: TXL, Tongxinluo; CAD, coronary artery disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; CMVD, coronary microvascular disease.

4.3.4 Safety of TXL

According to the China National Adverse Drug Reaction Monitoring System [52], as of March 2025, a total of 9,598 ADR reports related to TXL were received, with a reporting rate of approximately 0.82 per 10,000, indicating that the incidence of adverse reactions is classified as very rare. The main adverse reactions include nausea, abdominal discomfort, abdominal pain, vomiting, bloating, dizziness, and others. If gastrointestinal adverse reactions such as nausea, abdominal discomfort, abdominal pain, vomiting, bloating, or diarrhea occur after taking Tongxinluo, reducing the dosage or taking the medication after meals can alleviate these symptoms.

The CTS-AMI study[118]showed that TXL does not increase the risk of bleeding, and the incidence of serious adverse events was similar to that of the placebo group (2.2% vs. 2.8%, P = 0.25). The TISS study [121] demonstrated that the incidence of adverse events (38.6% vs. 38.4%, P = 0.95) and serious adverse events (2.2% vs. 1.9%, P = 0.64) was similar between the TXL and placebo groups. TXL is contraindicated in patients with hemorrhagic disorders and women during menstruation.

4.4 Luobing Theory-Based Medicine and Arrhythmias

4.4.1 Formula Characteristics of SSYX—— "warming, clearing, tonifying, and dredging"

Based on the syndrome characteristics and clinical manifestations of "Non-circulation" during the arrhythmia stage, the therapeutic principle of "warming, clearing, tonifying, and dredging" was established, with SSYX as the representative intervention drug. The formula includes ingredients such as ginseng (人参), sour jujube seed (酸枣仁), cornus (山茱萸), and Ophiopogon (麦冬) to replenish qi, nourish yin, and calm the mind, as well as coptis (黄连), spikenard (甘松), salvia (丹参), and ground beetle (土鳖虫) to clear heat, regulate qi, and dredge meridians. This combination exerts an "integrated regulatory effect, treating both fast and slow arrhythmias," providing a formula basis for its comprehensive intervention in the prevention and treatment of arrhythmias [12].

4.4.2 Mechanisms of SSYX in Preventing and Treating Arrhythmias

4.4.2.1 Multi-Ion Channel Blocking Effects

Voltage-gated sodium channels (I_{Na}) form the rapid depolarization phase (Phase 0) of the action potential. Li et al. found that SSYX inhibits the peak I_{Na} current in guinea pig ventricular myocytes, exerting a Class I antiarrhythmic effect by

blocking Na^+ channels [126,127].

Potassium channels (K^+) are crucial for maintaining the resting membrane potential and repolarization of the action potential. The transient outward potassium current (I_{to}) is strongly expressed in the epicardium. SSYX significantly inhibits epicardial Ito, reduces repolarization dispersion, prolongs the action potential duration (APD) and effective refractory period (ERP) in atrial and ventricular myocytes, and decreases the occurrence of atrial fibrillation (AF), reentry, and torsades de pointes [128,129]. SSYX primarily inhibits the slow component (I_{ks}) of the delayed rectifier potassium current (I_k), reducing the incidence of tachyarrhythmias [126,130]. It also blocks the inward component of the inward rectifier potassium current (I_{k1}) while slightly increasing the outward component, suppressing early afterdepolarizations and triggered arrhythmias [126,130]. Its multi-channel blocking effects on K^+ are similar to those of the Class III antiarrhythmic drug amiodarone.

Zhao et al. found in myocardial ischemia animal models that SSYX inhibits Ito and Ik1, prolongs APD and ERP in ventricular myocytes, but does not trigger intracellular Ca^{2+} overload, suppressing delayed afterdepolarizations [121]. In vitro, SSYX reduces Ca^{2+} overload in ventricular myocytes and inhibits L-type calcium channels ($I_{Ca\text{-}L}$), shifting the current density-voltage curve upward and prolonging the recovery time after $I_{Ca\text{-}L}$ inactivation [126,131,132]. By blocking $I_{Ca\text{-}L}$ channels and reducing Ca^{2+} overload, SSYX exerts dual effects of Class IV antiarrhythmia and ischemic myocardial protection.

Sun et al. demonstrated that in HEK293 cells transfected with hyperpolarization-activated cyclic nucleotide-gated channels (hHCN4), SSYX powder solution reversibly inhibits hHCN4 without altering channel activation kinetics[133]. Inhibiting hHCN4 pacemaker current may be one of the electrophysiological mechanisms of SSYX in treating ventricular premature beats. Additionally, SSYX has a certain blocking effect on Kv1.4 potassium channel current [134].

4.4.2.2 Improvement of Myocardial Electrophysiological Remodeling

Electrophysiological remodeling mainly includes changes in myocardial cell conductivity and automaticity, alterations in membrane ion channels, and abnormal gap junctions. In various arrhythmia-prone animal models, SSYX improves APD and ERP in atrial and ventricular myocytes, reduces APD dispersion, decreases myocardial cell automaticity, and lowers susceptibility to AF and ventricular arrhythmias[135,136]. Gap junctions are responsible for the

rapid transmission of action potentials between myocardial cells. SSYX increases the expression of connexin 40 (Cx40) in atrial myocytes of diabetic rats and enhances connexin 43 (Cx43) protein expression in ventricular myocytes of metabolic syndrome rats through the TLR4 (Toll-like receptor 4)/MyD88 (Myeloid differentiation primary response gene 88)/CaMKII (Calcium-calmodulin dependent protein kinase II) signaling pathway, improving gap junction remodeling [137,138]. It also upregulates myocardial ion channel proteins Kv4.2, Kv4.3, and Cav1.2, improving ion channel remodeling [138], and reduces heterogeneity in intercellular electrical conduction, improving the direction and timing of electrical signal propagation[139].

4.4.2.3 Improvement of Myocardial Structural Remodeling and Inhibition of Fibrosis

Liu et al. suggested that SSYX alleviates angiotensin II (Ang II)-induced myocardial hypertrophy, improves myocardial cell morphology, and inhibits apoptosis[140]. In myocardial infarction rat and rabbit models, SSYX increases left ventricular ejection fraction (LVEF) and fractional shortening (FS), enhances myocardial contractility, improves cardiac function, reduces Collagen I/III protein levels, decreases collagen deposition, and downregulates the expression of fibrosis-related genes and proteins such as transforming growth factor-β1 (TGF-β1), MMP-2, MMP-9, and tissue inhibitor of metalloproteinase 1 (TIMP-1), inhibiting the differentiation of cardiac fibroblasts into myofibroblasts and delaying atrial and ventricular fibrosis [139,141]. Shen et al. found that SSYX alleviates cardiac fibrosis in diabetic cardiomyopathy mice by inhibiting the TGF-β1/Smad pathway [142].

4.4.2.4 Bidirectional Regulation of Cardiac Autonomic Nerve Function

Zhao et al. found in a canine AF model that SSYX increases the high-frequency component of vagal activity, decreases the low-frequency component and LF/HF ratio of sympathetic activity, inhibits atrial sympathetic hyperinnervation, enhances vagal function, and balances autonomic nerve activity, slowing down rapid heart rates [143]. By regulating sympathetic function, SSYX inhibits systemic or local renin-angiotensin-aldosterone system (RAAS) activity, reduces Ang II levels and bioactivity, improves atrial substrate, alleviates fibrosis, lowers AF risk, and maintains sinus rhythm [128]. It also increases acetylcholine and α7 nicotinic acetylcholine receptor (α7nAChR) expression, enhancing the cholinergic anti-inflammatory pathway and reducing levels of inflammatory factors such as tumor necrosis factor-α (TNF-α) and IL-6[143]. Through balancing autonomic nerve activity, inhibiting sympathetic function, enhancing vagal function, and

activating the cholinergic anti-inflammatory pathway, SSYX exerts antiarrhythmic effects.

In a porcine model of bradyarrhythmia, SSYX increases heart rate and promotes electrical signal propagation in the sinoatrial and atrioventricular nodes, an effect not influenced by autonomic nervous system inhibition. Feng et al. found in vitro that SSYX uniformly shortens APD and ERP without inducing arrhythmias[144].

4.4.2.5 Anti-Inflammatory Effects, Metabolic Improvement, and Myocardial Microcirculation Enhancement

Zhang et al. demonstrated that Shensong Yangxin reduces the expression of inflammatory proteins such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), as well as levels of inflammatory factors including endothelin-1 (ET-1), TNF-α, IL-6, and MCP-1 in db/db mice [145]. It inhibits the infiltration and polarization of M1 macrophages, alleviating myocardial inflammation. Shensong Yangxin upregulates iron transport proteins, suppressing oxidative stress and reactive oxygen species (ROS) levels caused by myocardial iron overload [146]. It increases mitochondrial density, activates AMPK, upregulates PGC-1α to improve mitochondrial energy metabolism, and enhances the expression of carnitine palmitoyltransferase I (CPT-1) and GLUT-4 to promote fatty acid and glucose oxidation [140]. In various arrhythmia-prone animal models, Shensong Yangxin improves the structure of cardiac microvascular endothelial cells, promotes the formation of tight junctions between myocardial endothelial cells, increases microvascular density, and enhances nitric oxide (NO) levels by upregulating the VEGF/eNOS pathway, balancing vasoconstrictors and vasodilators, protecting microvascular endothelial cells, and improving myocardial microcirculation [145,147].

4.4.3 Evidence-Based Practice of SSYX in Arrhythmias

4.4.3.1 Premature Ventricular Contractions (PVCs)

In a multicenter, double-blind, RCT [148], 859 patients with frequent PVCs were enrolled. Among them, 188 patients without organic heart disease (OHD) were treated with SSYX or placebo (TID, 4 capsules each), while 671 patients with OHD received SSYX (TID, 4 capsules each) or mexiletine (TID, 150 mg each) for 8 weeks. The results showed that in the non-OHD PVC group, both SSYX and placebo reduced the number of PVCs, with SSYX significantly outperforming placebo in total efficacy (74.2% vs. 28.9%, $P < 0.001$). In the OHD PVC group, both SSYX and mexiletine reduced PVC frequency, with SSYX significantly

outperforming mexiletine in total efficacy (65.8% vs. 50.7%, P < 0.001). Additionally, SSYX significantly improved clinical symptoms such as palpitations and chest tightness associated with PVCs.

The SS-HFVPT study [149]a multicenter, randomized, double-blind, placebo-controlled clinical, included 465 patients with heart failure and frequent PVCs. Patients received standardized Western medicine treatment combined with Shensong Yangxin or placebo (TID, 4 capsules each) for 12 weeks. The results showed that the SSYX group had a significantly greater reduction in 24-hour PVC counts compared to the placebo group (−2145 ± 2848 vs. −841 ± 3411, P < 0.05), along with improved LVEF and reduced plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.

A multicenter, randomized, double-blind, placebo-controlled clinical study [150] enrolled 333 patients with PVCs and sinus bradycardia. Among them, 166 patients received SSYX (TID, 4 capsules each), and 167 received placebo for 8 weeks. The results showed that SSYX significantly reduced 24-hour PVC counts, with a higher reduction rate than the placebo group (68.2% vs. 32.2%, P < 0.001). Additionally, SSYX increased the average ventricular rate by 10.9%, significantly outperforming the placebo group for 4.7% (P < 0.001).

Meta analysis [148-162] indicated that patients with PVCs taking SSYX for over 4 weeks experienced an average reduction of 867.41 PVCs/24h (P < 0.001), with total clinical efficacy and symptom improvement superior to the control group (P < 0.001).

A randomized, double-blind, multicenter, placebo-controlled study [163] evaluated the safety and efficacy of SSYX in treating bradycardia. It included 115 patients with bradycardia, with 104 in the control group receiving SSYX (TID, 4 capsules each) for 4 weeks. The results showed significant increases in average, maximum, and minimum heart rates, along with improved symptom scores in the SSYX group (all P < 0.05 or 0.01).

4.4.3.2 Paroxysmal Atrial Fibrillation (AF)

A multicenter, randomized, double-blind, double-dummy, controlled clinical trial [164] enrolled 349 patients with symptomatic paroxysmal AF. Patients were divided into three groups: SSYX (4 capsules TID) + propafenone placebo, propafenone + SSYX placebo, or SSYX + propafenone, all for 8 weeks. The results showed no significant difference in overall AF efficacy among the three groups (62.3% vs. 58.6% vs. 58.5%, P > 0.05). However, SSYX alone or combined with propafenone effectively reduced the average AF episode frequency and

shortened AF duration (all P < 0.01).

Meta-analyses [165-172] demonstrated that patients with symptomatic paroxysmal AF taking SSYX combined with antiarrhythmic drugs (AAD) for over 2 months experienced a reduction in AF episode frequency by 2.23 times/week (P = 0.002), shortened AF duration by 1.64 hours/episode (P = 0.02), and improved sinus rhythm maintenance efficacy (P = 0.039).

An RCT [173] showed that in patients with paroxysmal AF undergoing catheter ablation, the combination of SSYX and dronedarone reduced early postoperative recurrence and atrial tachyarrhythmia incidence (6.6% vs. 20%, P = 0.03).

4.4.3.3 Persistent AF Post-Catheter Ablation

The SS-AFRF study, a multicenter, randomized, double-blind, placebo-controlled clinical trial [174], enrolled 920 patients with persistent AF undergoing their first catheter ablation. After a blanking period post-ablation, patients were given SSYX or placebo (4 capsules, TID) and followed for 1 year. The primary endpoint was the incidence of recurrent atrial tachyarrhythmias lasting ≥30 seconds after the blanking period. The 1-year follow-up showed that SSYX significantly reduced AF recurrence rates post-ablation compared to placebo (14.5% vs. 22.3%, P = 0.001), lowering the recurrence risk by 40% (HR = 0.6, 95% CI: 0.4–0.8). Additionally, SSYX significantly reduced AF burden at 3 and 6 months post-ablation (2.8% vs. 7.6%, P = 0.002 and 3.3% vs. 7.7%, P = 0.025, respectively) and improved quality of life.

Meta-analyses [174-178] indicated that in patients with persistent AF post-catheter ablation, SSYX combined with AAD or used alone for over 3 months reduced the risk of atrial tachyarrhythmias by 43% (P < 0.001).

Table 3 - Recommendations for Shensong Yangxin Capsules (SSYX) in the Management of Arrhythmias

Recommendation	Class of Recommendation	Level of Evidence
For patients with symptomatic premature ventricular contractions (PVCs), regardless of the presence of structural heart disease, SSYX can reduce PVC frequency and improve clinical symptoms such as palpitations and chest tightness.	I	A
For patients with PVCs and left ventricular systolic dysfunction, SSYX can reduce PVC frequency, improve left ventricular function, and has no proarrhythmic side effects.	IIa	B

For patients with sinus bradycardia or PVCs with sinus bradycardia, SSYX can increase sinus rhythm, reduce PVC frequency, and improve quality of life.	IIa	B
For patients with paroxysmal atrial fibrillation (AF), SSYX, either alone or combined with antiarrhythmic drugs (AAD), can reduce AF episode frequency and shorten AF duration.	IIa	B
For patients with persistent AF post-catheter ablation, SSYX, either alone or combined with AAD, can reduce early postoperative AF recurrence and/or atrial tachyarrhythmia incidence.	IIa	B

Notes: SSYX, Shensong Yangxin; PVC, premature ventricular contraction; AAD, antiarrhythmic drugs.

4.4.4 Safety of SSYX

According to the China National Adverse Drug Reaction Monitoring System[52], as of March 2025, a total of 9,835 adverse drug reaction (ADR) reports related to Shensong Yangxin were received, with a reporting rate of approximately 0.75‰, indicating a very rare level of ADR incidence. The main adverse reactions included abdominal distension, nausea, flatulence, abdominal discomfort, vomiting, and rash.

The SS-AFRF study[174] showed no significant differences in adverse events (67.4% vs. 67.0%, P = 0.94), serious adverse events (8.5% vs. 11.5%, P = 0.15), or liver and kidney function levels (P > 0.05) between the SSYX and placebo groups.

4.5 Luobing Theory-Based Medicine and Chronic Heart Failure

4.5.1 Formulation Characteristics of QLQX —— "Simultaneous Regulation of Qi, Blood, and Water"

Based on the "non circulation" theory and the symptomatic characteristics and clinical manifestations of HF, the therapeutic principle of "simultaneous regulation of Qi, blood, and water" was established, with QLQX as the representative intervention drug. The formulation includes herbs such as Astragalus (黄芪), Aconite (附子), Ginseng (人参), and Cinnamon Twig (桂枝) to tonify Qi and warm Yang; Salvia (丹参) and Safflower (红花) to promoting blood circulation for removing obstruction meridians; and Tinglizi (葶苈子), Alisma (泽泻), and Cortex Periplocae (香加皮) to inducing diuresis for removing edema. This embodies the formulation principle of "simultaneous regulation of Qi, blood, and water," providing a comprehensive basis for the holistic treatment of chronic heart failure [12].

4.5.2 Mechanisms of QLQX in Management Chronic Heart Failure

4.5.2.1 Improvement of Hemodynamics in Heart Failure

Cardiotonic Effects: QLQX enhances cardiac function by inhibiting Na^+/K^+-ATPase activity in myocardial cells, increasing parasympathetic nerve tension, and delaying atrioventricular conduction [179]. Studies by Liang et al. [180,181] demonstrated that in various heart failure animal models, QLQX significantly improved LVEF, FS, maximum left ventricular pressure rise rate, and myocardial contractility, while reducing left ventricular end-diastolic pressure.

Diuretic Effects: QLQX significantly increased renal blood flow and reduced urine osmolality in heart failure model rats. Its regulatory effect on arginine vasopressin (AVP) levels surpassed that of the traditional diuretic furosemide. It downregulated the expression of type 2 AVP receptors and aquaporin 2 (AQP2) in renal collecting duct epithelial cells, reducing tissue sensitivity to AVP. Through dual regulation of plasma AVP levels and its receptor pathway, it effectively reduced renal tubular water reabsorption [182,183].

Vasodilatory Effects: QLQX markedly increased plasma and aortic calcitonin gene-related peptide (CGRP) expression levels, activating the NO-cyclic guanosine monophosphate (cGMP)-protein kinase signaling cascade to exert vasodilatory effects [182].

4.5.2.2 Antagonism of Neuroendocrine System Overactivation

Inhibition of RAAS Activation: QLQX reduced Ang II, plasma renin activity, and aldosterone levels, downregulated angiotensin-converting enzyme (ACE) and angiotensin type 1 receptor expression, inhibited ventricular remodeling, and improved cardiac function [184]。

Inhibition of Sympathetic Overactivation: Qili Qiangxin effectively reduced plasma levels of norepinephrine, adrenocorticotropic hormone, prostaglandin E2, and NT-proBNP in heart failure animals, lowering sympathetic excitability, improving cardiac function, and delaying heart failure progression. Its reduction of BNP levels surpassed that of metoprolol [181,185,186]. Through central regulatory mechanisms, it improved sympathetic overactivation and inhibited ventricular remodeling [187].

4.5.2.3 Regulation of Immunity, Inhibition of Oxidative Stress, and Myocardial Fibrosis

Regulation of Immune-Inflammatory Responses: In rat models of acute myocardial infarction and patients with dilated cardiomyopathy, QLQX exhibited significant immunomodulatory effects, reducing pro-inflammatory factor TNF-α levels and enhancing anti-inflammatory factor IL-10 expression, thereby

restoring the pro-inflammatory/anti-inflammatory balance [188-190]. It inhibited NF-κB and NLRP3 inflammasome activation, reducing T lymphocyte infiltration and activation [189-193], thereby exerting anti-inflammatory effects and improving ventricular remodeling.

Inhibition of Oxidative Stress and Myocardial Fibrosis: QLQX activated the PI3K/Akt signaling pathway, reduced ROS levels, and upregulated SOD expression to alleviate oxidative stress [194]. It reduced myocardial collagen deposition in myocardial infarction rats, regulated the balance of matrix metalloproteinases (MMPs) and their inhibitors, and inhibited myocardial fibrosis and ventricular remodeling [195-197], with effects comparable to angiotensin receptor-neprilysin inhibitors [192]. Its improvement of the whole heart mass index in heart failure rats surpassed that of metoprolol [186].

4.5.2.4 Improvement of Myocardial Metabolism

QLQX activated the PPARγ/PGC-1α signaling axis to promote fatty acid β-oxidation [198-200]. It regulated the glucose transport system (GLUT1/GLUT4), enhanced glucose uptake and oxidative phosphorylation [201,202], and promoted glucose utilization, with efficacy comparable to trimetazidine [201]. It activated the AMPK/PGC-1α pathway to inhibit pathological anaerobic glycolysis [199-202] and protected mitochondrial structural integrity, improving electron transport chain function [203,204].

4.5.2.5 Protection of Myocardial Microvasculature and Cardiomyocytes

Microvascular Endothelial Protection: QLQX inhibited VCAM-1, ICAM-1, and myocardial nutrient factor expression, improving myocardial microvascular endothelial structure and function [205]. It activated the neuregulin-1 (NRG-1)/epidermal growth factor receptor (EGFR)-PI3K/Akt/mTOR autophagy pathway, promoting angiogenesis under hypoxic conditions and reducing microvascular endothelial cell apoptosis [206-209].

Cardiomyocyte Protection: Qili Qiangxin regulated the Bcl-2/Bax expression balance, inhibited caspase cascade reactions, and exerted anti-apoptotic effects [181,194,210-213]. It promoted the clearance of damaged mitochondria through the PTEN-induced kinase 1 (PINK1)/parkin pathway [214]. It regulated the PI3K/glycogen synthase kinase-3β (GSK-3β) and mTOR signaling networks to maintain autophagy homeostasis and protect cardiomyocytes [215-218].

4.5.3 Evidence-Based Practice of QLQX in Chronic Heart Failure

4.5.3.1 Heart Failure with Reduced Ejection Fraction (HFrEF)

The QUEST study[219], a multicenter, double-blind, placebo-controlled, randomized clinical trial, enrolled 3,110 HFrEF patients. In addition to GDMT, patients were given either QLQX or placebo (4 capsules, TID). Results showed that, after a median follow-up of 18.3 months, the QLQX group experienced a 22% reduction in the composite risk of cardiovascular death or HF hospitalization ($P < 0.001$), a 24% reduction in HF hospitalization risk ($P = 0.002$), and a 17% reduction in cardiovascular death risk ($P = 0.045$) compared to the placebo group. At the 3-month follow-up, the proportion of patients with NT-proBNP levels reduced by >30% was significantly higher in the QLQX group than in the placebo group (56.54% vs. 49.86%, $P = 0.002$). Additionally, compared to the placebo group, the QLQX group showed a 24% reduction in the composite endpoint of cardiovascular death and heart failure rehospitalization in the subgroup of HF with CAD (1,156 vs. 1,165 cases) and a 31% reduction in the subgroup of HF with hypertension (708 vs. 741 cases).

The QLQX-DCM study[190], another multicenter, double-blind, placebo-controlled, randomized clinical trial, enrolled 345 patients with dilated cardiomyopathy. Patients received either QLQX or placebo (4 capsules, TID) on top of GDMT. After 12 months of follow-up, compared to baseline, the QLQX group showed reductions in interferon-γ, IL-17, TNF-α, and IL-4, and an increase in IL-10 (all $P < 0.001$), indicating improved regulation of inflammatory factor imbalance. The QLQX group also exhibited a downward trend in all-cause mortality (−2.17%) and heart failure rehospitalization rates (−2.28%) compared to the control group.

In another multicenter, double-blind, placebo-controlled, randomized clinical trial [220], 512 HFrEF patients were given either QLQX or placebo (4 capsules, TID) on top of standard heart failure treatment for 12 weeks. Results showed that the proportion of patients with NT-proBNP levels reduced by >30% was significantly higher in the QLQX group than in the placebo group (47.95% vs. 31.98%, $P < 0.001$). The QLQX group also had a significantly lower incidence of composite cardiac events (including cardiovascular death, HF hospitalization, resuscitation after cardiac arrest, intravenous therapy for worsening heart failure, and stroke) compared to the control group (4.51% vs. 10.93%, $P = 0.008$).

A meta-analysis by Mao Tianshi et al. [221], which included the above three studies, demonstrated that QLQX reduced the composite risk of cardiovascular death or heart failure rehospitalization by 18% ($P = 0.0005$), cardiovascular death risk by 17% ($P = 0.03$), heart failure rehospitalization risk by 18% ($P = 0.004$), and all-cause mortality risk by 16% ($P = 0.03$) in chronic heart failure patients. After

more than 4 weeks of QLQX treatment, left ventricular ejection fraction (LVEF) increased by 6.04% ($P < 0.001$), left ventricular end-diastolic diameter decreased by 3.66 mm ($P < 0.001$), New York Heart Association (NYHA) functional class significantly improved ($P < 0.001$), 6-minute walk test distance increased by 51.27 meters ($P < 0.001$), and the Minnesota Living with Heart Failure Questionnaire score decreased by 8.97 points ($P < 0.001$). After 3 months of treatment, NT-proBNP levels decreased by 276.78 pg/mL ($P < 0.001$).

4.5.3.2 Heart Failure with Preserved Ejection Fraction (HFpEF)

Randomized controlled studies suggest that HFpEF patients treated with QLQX on top of GDMT for 6 months showed improvements in E/A ratio, LVEF, and 6-minute walk test distance compared to baseline, with significantly greater improvements than the control group ($P < 0.05$). Reductions in left atrial volume index, left ventricular end-diastolic diameter, Minnesota Living with Heart Failure Questionnaire scores, C-reactive protein, and NT-proBNP levels were significantly greater in the QLQX group than in the control group ($P < 0.05$). Multiple clinical studies have shown that HFpEF patients taking QLQX for more than 1 month experienced significant improvements in left ventricular diastolic function (e.g., E/A, E/e') [222-225].

Table 4 - Recommendations for Qiliqiangxin Capsules (QLQX) in the Management of Chronic Heart Failure

Recommendation	Class of Recommendation	Level of Evidence
For HFrEF patients, adding QLQX on top of GDMT can further reduce heart failure rehospitalization and cardiovascular mortality rates.	I	A
QLQX can improve cardiac function and ventricular remodeling indicators, enhance exercise tolerance, and improve quality of life in chronic heart failure patients.	I	A

Note: QLQX, Qiliqiangxin; HFrEF, Heart Failure with Reduced Ejection Fraction; GDMT, Guideline-Directed Management and Therapy.

4.5.4 Safety of QLQX

According to the National Adverse Drug Reaction Monitoring System[52], as of March 2025, a total of 4,777 adverse drug reaction reports related to Qili Qiangxin were received, with a reporting rate of approximately 2.34 per 100,000, classifying its adverse reaction incidence as rare. The main adverse reactions included nausea, diarrhea, abdominal discomfort, vomiting, abdominal pain, and rash.

Both the QUEST study[219] and the QLQX-DCM study[190] showed no statistically significant difference in the incidence of gastrointestinal symptoms between the QLQX and placebo groups. If gastrointestinal adverse reactions such as nausea, abdominal discomfort, abdominal pain, vomiting, bloating, or diarrhea occur while taking QLQX, it is recommended to reduce the dosage or take the medication after meals to alleviate symptoms. Concurrent use with digoxin is not recommended.

The QUEST study [219] also demonstrated that adding QLQX to GDMT did not significantly affect blood pressure or heart rate in chronic heart failure patients. Compared to the placebo group, Qili Qiangxin did not increase the risk of renal function deterioration (3.79% vs. 4.50%) or elevated liver enzyme levels (2.57% vs. 3.09%). The study excluded patients with serum creatinine levels >176.82 μmol/L.

The QLQX-DCM study [190] showed that the proportion of patients with excessive digoxin blood concentrations was similar between the Qili Qiangxin and placebo groups (1.17% vs. 1.17%).

5 Conclusion

Cardiovascular diseases are the leading cause of death globally. The cardiovascular continuum reflects the systemic and complex nature of cardiovascular diseases, aligning closely with the holistic perspective of traditional Chinese medicine (TCM). This has led to a paradigm shift in disease intervention strategies. Under the guidance of the Mai Luo theory, Luobing theory-based medicine such as Jinlida (for “strengthening the spleen and promoting fluid circulation”), Tongxinluo (for “searching and dredging”), Shensong Yangxin (for “warming, clearing, tonifying, and dredging”), and Qiliqiangxin (for “simultaneous regulation of Qi, blood, and water”) cover different stages of the cardiovascular continuum, enabling precise intervention. These therapies provide a clinical treatment approach integrating tradition and modern medicine with distinctive Chinese characteristics for the prevention and management of the cardiovascular continuum.

This consensus describes the significant value of the cardiovascular continuum and the Mai Luo theory. It introduces the formulation characteristics, elucidates the pharmacological mechanisms, and summarizes the main evidence-based clinical evidence and safety profiles of Jinlida, Tongxinluo, Shensong Yangxin, and Qiliqiangxin for conditions such as diabetes and prediabetes, ischemic

cardiovascular and cerebrovascular diseases, arrhythmias, and chronic heart failure. Additionally, by synthesizing expert clinical experience with evidence-based research and adhering to ESC standards, the consensus provides recommendations and clinical evidence levels for integrated Chinese and Western medicine interventions at key stages of the cardiovascular continuum. These recommendations are intended to serve as a reference for clinicians in their practice.

Annex A
(Informative)
Methods and Technical Approach

The process and methods for developing this consensus were based on the Technical Specifications for Expert Consensus in the Development and Revision of Clinical Practice Guidelines for Traditional Chinese Medicine (T/CACM1049-2017) issued by the China Association of Chinese Medicine. The development process is illustrated in Figure A.1.

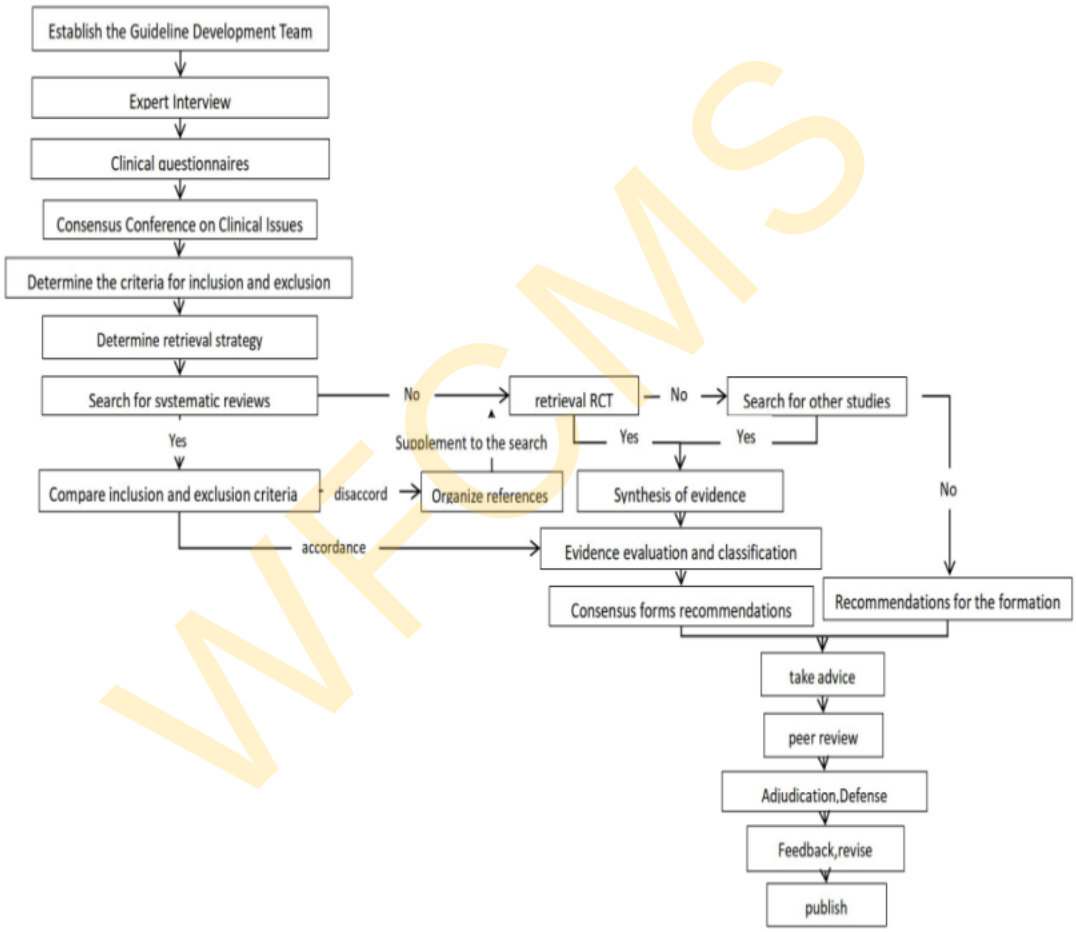

Figure A.1 Flowchart of Expert Consensus Development

Annex B
(Informative)
Literature Screening Criteria and Evidence Levels

The recommendation criteria and evidence quality evaluation standards in this consensus were referenced from the European Society of Cardiology (ESC) guidelines (Tables B.1 and B.2). Commonly used drugs for systematic intervention in the cardiovascular event chain based on collaterals theory are listed in Table B.3.

Table B.1 - Definitions of Recommendation Classes

Class	Definition
I	Procedures or treatments proven and/or unanimously recognized as beneficial, useful, and effective.
IIa	Evidence/opinion favors usefulness and/or effectiveness, and the application of these procedures or treatments is reasonable.
IIb	Evidence/opinion is not yet fully proven to be useful and/or effective, but their application may be considered.
III	Procedures or treatments proven and/or unanimously recognized as useless and/or ineffective, and potentially harmful in some cases; not recommended.

Table B.2 - Definitions of Evidence Levels

Level	Definition
A	Data derived from multiple randomized controlled trials or meta-analyses.
B	Data derived from a single randomized controlled trial or multiple non-randomized studies.
C	Based solely on expert consensus opinions and/or small-scale clinical trials, retrospective studies, or registry studies.

Table B.3 - Usage Indication for Luobing Theory-based Medicine in Systematic Intervention on the Cardiovascular Continuum

Drug	Common Oral Dosage
Jinlida Granules	9 g/dose, 3 times daily
Tongxinluo Capsules	Carotid atherosclerosis: 6 capsules/dose, 2 times daily Coronary heart disease: 4 capsules/dose, 3 times daily STEMI: Loading dose of 8 capsules before emergency PCI, followed by 4 capsules/dose, 3 times daily Stroke: 4 capsules/dose, 3 times daily
Shensong Yangxin Capsules	4 capsules/dose, 3 times daily

Qiliqiangxin Capsules	4 capsules/dose, 3 times daily

Note: STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

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