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Regulation and Guideline

Clinical Practice Guideline of Integrative Chinese and Western Medicine for Acute Myocardial Infarction*

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ABSTRACT With increasing morbidity and mortality, acute myocardial infarction (AMI) has become one of the major causes of human death, leading to heavy burdens to individuals, families and society. Previous researches have found that though large amount of resources and great effort were devoted, no significant improvements were achieved in reducing the in-hospital mortality of AMI patients. Meanwhile, extensive studies about Chinese medicine (CM) have found that CM has special advantages in treating AMI patients. However, there is no standardized and unified clinical practice guideline (CPG) of CM for AMI. Therefore, a CPG with strict standard and generally acknowledgement is urgent to be established. This guideline was developed following the methodological process established by the World Health Organization Handbook for Guideline Development. Extensive search on clinical evidences including systematic review (SR), randomized controlled trial (RCT), observational study and case reports was launched, covering evidence of CM for AMI on several aspects, such as diagnosis, CM patterns, CM interventions on AMI and complications, cardiac rehabilitation and clinical pathway management. Besides, the application of Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach enabled the evaluation of evidence and formulation of grade of recommendation (GOR) and level of evidence (LOE). With the help of GOR and LOE, this CPG recommends the integrative CM and WM treatment method in AMI patients and provides useful information on medical decision for clinical physicians.

KEYWORDS acute myocardial infarction, integrative Chinese and Western medicine, clinical practice guideline

Acute myocardial infarction (AMI) occurs when coronary artery is occluded, due to thrombosis or erosion of the coronary atherosclerotic plaque, leading to severe and persistent acute myocardium ischemia.[1] AMI is a major disease that threatens human health and the leading causes of death worldwide. In recent years, with the extensive development of the Cholesterol Education Program in the United States (US) and the active promotion of the AMI treatment guidelines, the prevalence and mortality of AMI in the US have been effectively decreased year after year.[2,3] However, according to the famous Chinese PEACE research, results indicated that from 2001 to 2011, no significant improvements were achieved in reducing AMI patients' in-hospital mortality in China.[4] Besides, based on the estimation of Markov model, China will have 21 million new onsets acute coronary events and 7 million new onsets of cardiac deaths in the next 20 years.[5] Compared with US, the situation of AMI treatment in China was manifested as higher morbidity, lower propotion of in-hospital reperfusion therapy, longer duration from onset to reperfusion and worsen prognosis. Improving AMI patients' survival and long-term prognosis has become an intractable problem and arouses more and more attention.

Originated from the pre-Qin period, Chinese medicine (CM) has accumulated vast experience and treatments in AMI. Most of those experiences were recorded on different monographs, such as *The Yellow Emperor's Classic of Internal Medicine* (Huang Di Nei Jing), and *Essentials from the Golden Cabinet* (Jin Gui Yao Lue). In CM theory, the basic mechanism of AMI can be mainly explained as

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insufficiency of yang and endogenous excess of yin (Yangwei Yinxian). Under the guidance of these CM theory and through thousands years of clinic use and adjustment, many CM herbal formulae were created and applied in the treatment of AMI, achieving satisfactory clinical effects and safety.

Since the foundation of the People's Republic of China, with the country's strong support, plenty of CM clinical and related basic researches in AMI have been implemented.[6] On the basis of previous achievements, in 1980, the Standard of Coronary Heart Disease Syndrome Differentiation, which turned to be the cornerstone of many clinical trials of CM in AMI treatment, was established at the China National Coronary Heart Disease Syndrome Differentiation Congress.[7] After years of studies, based on the principle of promoting blood circulation and removing blood stasis, Academician CHEN Ke-ji and his team developed several CM drugs in treating AMI and verified their therapeutic efficacy and safety via clinical trials.[8] As a precursor, these clinical trials have inaugurated a new era of randomized controlled trials (RCTs) for CM and integrative medicine.

Since the end of last century, the widely development of coronary intervention technology such as percutaneous coronary intervention (PCI) in China has also promoted the further CM research in this field.[9] A clinical trial, held by Xiyuan Hospital of China Acadamy of Chinese Medical Sciences, Beijing Anzhen Hospital and Guangdong Provincial Hospital of Chinese Medicine, has confirmed that Xiongshao Capsule (芎芍胶囊, XSC), a CM patent medicine, could reduce the incidence of coronary restenosis after coronary intervention.[10] In 2011, Guangdong Provincial Hospital of Chinese Medicine formulated the clinical pathway of AMI integrative medicine, and implemented the efficacy evaluation research. Results showed that clinical pathway based on integrative medicine, including CM and Western medicine (WM), could standardize diagnosis and treatment, shorten hospital stays, reduce hospitalization expenses and incidence of major cardiovascular events, indicating that standardize integrative treatment was helpful to improve the prognosis of AMI.[11] In 2014, the Society of Integrative Medicine Doctor, Chinese Medical Doctor Association collaborated with Cardiovascular Disease Professional Committee of Chinese Association of Integrative Medicine and other famous organizations to establish and publish the first "Expert Consensus of Diagnosis and Treatment on Integrative Chinese and Western Medicine for Acute Myocardial Infarction", further affirmating the unique role and special advantangs of CM in the prevention and treatment of AMI.[12]

However, no standardized and unified clinical practice guideline (CPG) of CM for AMI has been enacted. Therefore, a CPG with strict standard and generally acknowledgement is urgent to be established. The aim of this study is to recommend the treatment method and provide useful medical decision. The design and development of this CPG is strictly followed the method used in the development of international guidelines that recommended by World Health Organization Handbook for Guideline Development (2014) and the Appraisal of Guidelines for Research and Evaluation (AGREE Ⅱ).[13,14] Clinical questions was obtained through the first round of national questionnaire survey among famous physicians and methodologists of CM and WM. Afterwards, search terms and keywords based on the results of the clinical questions were applied in comprehensive literature retrieve of several electronic databases (PubMed, EMBASE, Cochrane Library, Chinese VIP Information, China National Knowledge Infrastructure, and Wanfang Databases), without restriction on language, race, gender, and age. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was applied to evaluate the body of evidence and formulate level of evidence (LOE).[15-17] Since then, the second round of national questionnaire survey and several expert conferences were launched to discuss and formulate the CM patterns and grade of recommendations (GOR) by combining the quality of evidence, patient preferences and values, and other risk factors. Finally, the detailed definition about LOE for each recommendation and the grades of recommendation of each therapy are shown in Tables 1 and 2.

Table 1. Levels and Definitions of Evidence

Levels	Definition
High	Very confident of the observed value being close to the true one.
Moderate	Moderate confidence in the observed value: the observed value may be close to the true one, but may be in big difference.
Low	Limited confidence in the observed value: the observed value may be greatly different from the true one.
Very low	Little confidence in the observed value: the observed value may be extremely different from the true one.

Table 2. Grades and Definitions of Recommendations

Strength	Definitions
Strong	Clearly show that the benefits of intervention outweigh the harms or more harms than benefits.
Weak	Uncertain about the benefits and harms or the benefits and harms are tantamount regardless of the quality of evidence.

Clinical Characteristics

Clinical Classification

According to the famous study "Third Universal Definition of Myocardial Infarction" published in 2012,[18] AMI can be divided into 5 types. (1) Type 1 is spontaneous

myocardial infarction (MI): ischemic MI caused by coronary plaque rupture, thrombus or dissection. (2) Type 2 is secondary MI: secondary to myocardial oxygen supply and demand imbalance (such as coronary spasm, arrhythmia, anemia, respiratory failure, hypertension or hypotension). (3) Type 3 refers to sudden cardiac death: suspected to be caused by myocardial ischemia, or suspected to be caused by new electrocardiography (ECG) ischemia changes or new left bundle branch block (LBBB) cardiogenic death. (4) Type 4 refers to the MI caused by PCI or stent thrombosis, including balloon dilatation and stent implantation. (5) Type 5 is coronary artery bypass grafting (CABG) related MI.

Based on whether there is ST-segment elevation, AMI could also be classified as ST-segment elevted MI (STEMI) and non-ST-segment elevted MI (NSTEMI). This guideline mainly describes the diagnosis and treatment of type 1 MI, regardless of STEMI or NSTEMI.

Risk and Inducing Factors

AMI patients generally have history of atherosclerosis and have one or more of the following risk factors: hypertension, diabetes, abnormal glucose tolerance, dyslipidemia, smoking, obesity, lack of exercise, hyperuricemia, hyperhomocysteinemia, older age and family history of early onset of cardiovascular disease.[19]

AMI could occur in all seasons of the year, with high incidence in winter and spring, which is related to cold climate and temperature change. Strenuous exercise, fatigue, trauma, emotional tension, feast, acute bleeding, fever, tachycardia, myocardial oxygen consumption increased by septic shock can all be cause of AMI.

Clinical Manifestations

The clinical symptoms of AMI are various, with different manifestations based on the size and location of the infarction area, disease progression and basic cardiac function. The most typical and common symptom is retrosternal pain or intense crushing pain in the anterior cardiac region, which might radiate to the left arm, neck or jaw. This pain usually lasts more than 10–20 min, without obvious alleviation after rest or oral taking nitroglycerin, often accompanied with dysphoria, sweatiness, fear, or even near death experience. Some patients might have atypical pain sites or absent of chest pain symptoms, while some patients might present with other clinical manifestations, such as respiratory difficulties, arrhythmias, shock or acute heart failure (HF).[20]

Physical examination might reveal with early hemodynamic disorder such as skin dampness, coldness, pale complexion and restlessness. Attention should be paid to cardiac and pulmonary auscultation, seeking for lung rales, increase or decrease of heart rates; weakness of first cardiac tone in apical area, appearance of third (S3) or fourth heart sound (S4). The Killip Classification is recommended for further evaluation of cardiac function in AMI patients (Table 3).

Table 3. Killip Classification

Class	Manifestation
Ⅰ	No clinical signs of HF.
Ⅱ	Rales or crackles less than 50% area of the lungs , an S3 gallop, and elevated jugular venous pressure.
Ⅲ	Extensive acute pulmonary edema.
Ⅳ	Cardiogenic shock or hypotension (measured as systolic blood pressure lower than 90 mm Hg), and evidence of peripheral vasoconstriction (oliguria, cyanosis or sweating).

Laboratory Examination

Conventional 12 leads ECG is a useful and convenience method for AMI diagnosis; 18 leads ECG is recommended in suspected inferior wall and/or posterior wall AMI patients. Typical ECG manifestation of STEMI could be unusually high and asymmetrical T waves, ST-segment elevation, and pathologic Q wave, which are helpful in locating infracted area and coronary artery. In contrast, no ST-segment elevation would appear in NSTEMI ECG, but present as more than 0.1 mV ST segment descent and/or symmetric T wave inversion. Cardiac troponin (cTn) T or I, biomarker that is very sensitive to myocardial injury in early stage of AMI, is strongly recommended in sespueted AMI patients as soon as possible.[21] Echocardiography can detect abnormal ventricular segment movement and make judgment on the area of myocardial ischemia. Besides, echocardiography can also evaluate the overall and local cardiac function, papillary muscle function, aortic dissection, ventricular aneurysm, ventricular wall thrombus, ventricular septal perforation and pericardial effusion. Coronary computed tomography can show coronary artery stenosis and calcification, and identify the coronary lesions, which is of high value for diagnosis and excluding coronary heart disease.

Diagnostic Criteria

Detection of a rise of cardiac biomarker values (preferably cTn) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischaemia;
- New or presumed new significant ST-segment-T wave (ST-T) changes or new LBBB;
- Development of pathological Q waves in ECG;

• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;

• Identification of an intracoronary thrombus by angiography or autopsy.

WM Interventions

Complete and systematic WM interventions are recommended by relative AMI guidelines that published and continuously updated by the American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC). Therefore, strategies and princeples of WM intervention would be shown in this integrative CPG, detailed imformation please refer to related WM guidelines.

Risk Stratification

Preliminary risk stratification should be conducted according to AMI patient's ST-segement in ECG. STEMI patients are of very high risk. Therefore, reperfusion therapy and revascularization to the infarct-related coronary artery as early as possible is recommended. For NSTEMI patients, GRACE risk score and TIMI risk score are commonly used to further evaluate the risk of ischemia. Early reperfusion therapy should also be considered in high-risk NSTEMI patients.[21-23] (GOR: strong, LOE: high)

Monitoring and Oxygen Therapy

AMI patient should be monitored immediately for ECG, blood pressure, respiration and blood oxygen saturation (SaO_2). (GOR: strong, LOE: high)

Studies have shown that routine oxygen therapy is not beneficial to AMI patients; on the contrary it would increases the myocardial injury and MI area after 6 months.[24,25] Therfore, in accordance with 2017 ESC guideline, routine oxygen therapy is not recommended, only patients with hypoxemia (SaO_2<90% or blood partial oxygen pressure < 60 mm Hg) are suitatble.[26] (GOR: strong, LOE: moderate)

Nitrates

Studies found that routine use of nitrates in STEMI was of no benefit and so it is not recommended.[27] In NSTEMI patients, nitrates would be useful to alleviate chest pain and discontinued after symptom control.[28] (GOR: strong, LOE: moderate)

Beta-Blockers

Studies have found the benefit of beta-blockers to AMI patients. Therefore, beta-blockers are suggested as early as possible within 24 h, starting from a small dose and gradually increasing to the maximum tolerated dose of the patient.[29,30] (GOR: strong, LOE: high)

Calcium Antagonists

Routine use of calcium antagonists in STEMI patients is not recommended, for researches have indicated that no benefit was obtained.[31,32] Non-dihydropyridine calcium antagonists would be useful to NSTEMI patients with contraindications to beta-blockers.[33] (GOR: weak, LOE: moderate)

Reperfusion Therapy

Previous evidence has found that the efficacy of fibrinolytic treatment was similar to PCI in STEMI patients within onset of 3 h.[34] Based on risk stratification, STEMI and high risk NSTEMI patients are recommended to receive primary PCI within 120 min of first medical contact. If primary PCI is unavailable in 120 min, fibrinolysis strategy is strongly recommended.[21,28,33] (GOR: strong, LOE: high). Routine PCI should be performed within 72 h in moderate or low risk of NSTEMI patients.[33] (GOR: strong, LOE: high).

Anti-platelet Therapy

Plenty of studies have shown that dual anti-platelet therapy (DAPT), combining aspirin and a P2Y12 inhibitor (i.e. prasugrel, ticagrelor, or clopidogrel), is benefitcial to AMI patients and should be administrated to AMI patients as soon as possible and continue up to 12 months after PCI.[35,36] (GOR: strong, LOE: high)

Anticoagulation

Anticoagulation could prevent thrombosis, which plays a significant role in AMI treatment, especially in NSTEMI. Therefore, anticoagulation drugs (i.e. unfractionated heparin, enoxaparin or or bivalirudin) should be applied to AMI patients along with DAPT and adjust dose according to patients' bleeding risk.[37-39] (GOR: strong, LOE: moderate)

Lipid-lowering Therapy

Researches have indicated that early initiation of statin after AMI could significantly improve the clinical prognosis and reduce the incidence of perioperative MI. Therefore, statin should be early initiated to AMI patients without contraindication in 24 h and maintained for long term after PCI.[40,41] (GOR: strong, LOE: moderate)

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Ⅱ Receptor Blockers

Angiotensin-converting enzyme Inhibitor (ACEI)

is recommended in AMI patients with left ventricular ejection fraction (LVEF) impairement. Treatment with ACEI is recommended in patients with HF, hypertension, diabetes or stable chronic kidney disease.[42-44] (GOR: strong, LOE: high). In patients with ACEI intolerance, angiotensin Ⅱ receptor blockers (ARB) should be given as replacement. Howerer, combination of ACEI and ARB is not suggested for the increased risk of adverse events of both drugs.[45] (GOR: strong, LOE: high)

CM Patterns Diagnosis

In modern clinical practice, CM patterns could be up to 84 kinds, due to absence of uniform standard in CM patterns. Therefore, CPG development panel consulted the patterns classification from "Expert Consensus of Diagnosis and Treatment on Integrative Chinese and Western Medicine for Acute Myocardial Infarction", monographs including "Internal Medicine of Chinese Medicine" and "Chest Stuffiness and Coronary Artery Disease Intervention", based on the data derived from extensive questionnaire of national experts in CM and WM, then determined 6 common CM patterns of AMI (Table 4).

Table 4. Diagnostic Criteria of CM Patterns

Pattern	Diagnostic criteria
Qi deficiency and blood stasis	Chest pricking pain, sense of stuffiness and stagnation with postactive aggravation, mental fatigue, shortness of breath, sweatiness, palpitation, ecchymosis on limb skin, pale or bruising spot tongue with thin white coating, deficient and weak pulse or wiry, thin and weak purlse.
Binding of phlegm and stasis	Intense chest pain, chest tightness as smothering, dizziness, brain swelling sense, heaviness of limbs and body, shortness of breath, cough with large amount of phlegm, loss of appetite, nausea and vomiting, abdominal distension, darkish complexion, cyanosis in tongue and lips, limbs edema, purple dusky or dusky red tongue with stasis macules, blood stasis in sublingual veins, thick greasy coating, slippery or rough pulse.
Qi stagnation and blood stasis	Stuffiness, frequent chest pricking pain with fixed location, constant sigh, induce or aggravate by emotional disorders, blackish complexion, cyanosis in fingernails and lips, skin petechiae, purple dusky tongue with purpura, blood stasis in sublingual veins, thin coating, wiry and rough pulse.
Cold coagulation in heart vessel	Chest pain involving the back aggravated with cold and alleviated with warm, chest distressness and shortness of breath, palpitation, pain complexion, aversion to cold, cold limbs, pale dusky tongue with white coating, deep weak, slow, moderate, knotted or intermittent pulse.
Deficiency of both qi and yin	Chest dull pain, annoyance, palpitation, mental fatigue, limbs lack of strength, night sweat, shortness of breath, dizziness, blushing complexion, low voice, feverish feeling in palms and sole, bright red tongue with teeth-marked, lack of coating or thin white coating, deep thread and weak pulse or slow, moderate, knotted, intermittent pulse.
Healthy qi deficiency and yang collapse	Dull pain and suffocated feeling in chest, panting, fluster, pale complexion, great dripping sweating, vexation, agitation, indifference or coma, counterflow cold of the four limbs (cold distal extremities with cold moving proximally past elbows and knees), eyes closed and mouth open, enuresis, pale tongue, white coating, rapid weak pulse or feeble pulse.

CM Interventions

Chest Pain Symptom Remission

Chest pain is the most common symptom in AMI patients and plays an important role in AMI management. Excessive pain could stimulate sympathetic nerve, exacerbating myocardial oxygen consumption and ischemia. Previous evidence of CM in treating AMI proved that CM achieved satisfactory therapeutic efficacy in chest pain symptoms resmission. CM drugs, most common items including Suxiao Jiuxin Pill (速效救心丸), Compound Danshen Dripping Pill (CDDP, 复方丹参滴丸), Shexiang Baoxin Pill (麝香保心丸), and Kuanxiong Aerosol (宽胸气雾剂), could be administrated to AMI patients that are contraindicated or poor response to analgesic like nitroglycerin and morphine.

Suxiao Jiuxin Pill, consists of *Rhizoma Chuanxiong* and *Borneolum*, is found to be with ideal effect in alleviating chest pain and with lower occurance of adverse effects.[46] (GOR: strong, LOE: moderate)

Previous studies of CDDP on AMI patients have demonstrated that CDDP could not only relieve chest pain, but also reduce the risk of cardiac death of patients with AMI and improve the patient's heart function and quality of life (QOL).[47] (GOR: strong, LOE: moderate)

Meanwhile, Shexiang Baoxin Pill could alleviate chest pain symptom, inhibit platelet aggregation, reduce serum lipid level and improve endothelial and cardiac function with good safety.[48-51] (GOR: strong, LOE: moderate)

Trials have shown that efficacy of Kuanxiong Aerosol on symptom alleviation, which could be verified by improvement of cardiac ischemia on ECG, is no less than nitroglycerin, but with a significantly lower incidence of adverse events.[52,53] (GOR: strong, LOE: moderate)

CM Patterns Differentiation and Treatments

Pattern differentiation and treatment are the special advantage and characteristic method of CM, and it is also the best embodiment of the combination of the best evidence, doctors' clinical experience and patients' individual willingness. All prescription of drugs and dosage of CM herbal that recommended in this CPG are derived from the 12th "Five-Year Plan" textbook "Chinese Medical Formulae", which is supported by the higher education materials of National Chinese Medicine Industry.[54] In clinical practice, physicians could adjust the composition and dosage of drugs according to their personal experience, but this CPG would not take any relative legal liability.

In modern clinical practice, CM patterns could be up to 84 kinds, due to absence of uniform standard in CM patterns. Therefore, CPG development panel consulted the patterns classification from " Expert Consensus of Diagnosis and Treatment on Integrative Chinese and Western Medicine for Acute Myocardial Infarction", monographs including "Internal Medicine of Chinese Medicine", and "Chest Stuffiness and Coronary Artery Disease Intervention", based on support data derived from extensive questionnaire of experts in CM and WM, then determined 6 common CM patterns and diagnostic criteria (Table 4).[55-59] The treating princeples, recipe and ingredient herbs of each CM patterns are shown in Table 5.

CM Patent Drugs

Pattern of Qi Deficiency and Blood Stasis

Tongxinluo Capsule (通心络胶囊, usage and dosage: oral use, 2–4 capsulses per time, 3 times a day) has accumulated several researches that demonstrated its efficacy on the basis of routine treatment, reducing the risk of cardiac death and major adverse cardiovascular event (MACE) in AMI patients.[60-63] (GOR: strong, LOE: moderate)

Shexiang Tongxin Pill (usage and dosage: oral use, 2 pills per time, 3 times a day) could reduce the frequency of angina pectoris attacks, relieve the intensity of pain, chest tightness, chest pain and shortness of breath and reduce the dosage of nitroglycerin.[64-66] (GOR: weak, LOE: low)

Based on conventional WM therapy, additional use of Danhong Injection [丹红注射液, usage and dosage: intravenous drip, 20–40 mL added to 100–500 mL 5% glucose solution (GS) or 0.9% normal saline (NS), 1–2 times a day] was associated with lower mortality, reduced incidence of complications such as HF, angina and arrhythmia.[67] (GOR: strong, lOE: Low)

Sodium Tanshinone ⅡA Sulfonate Injection (usage and dosage: intravenous drip, 40–80 mL per time added to 250–500 mL 5% GS or 0.9% NS, once a day) could improve AMI patients' cardiac function, reduce occurance of angina pectoris after AMI, and prevent myocardial ischemia reperfusion injury via mechanisms of protection of vascular endothelium and anti-oxygen free radical action.[68-71] (GOR: weak, LOE: moderate)

Safflower Yellow Injection (usage and dosage: intravenous drip, 100 mL per time, once a day) could improve myocardial ischemia, reduce plasma brain natriuretic peptide (BNP) and improve the cardiac function of AMI patients by inhibiting antiplatelet aggregation, eliminating oxygen free radical, restraining intracellular flow of calcium ions and anti-inflammation.[72-75] (GOR: weak, LOE: moderate)

Pattern of Binding of Phlegm and Stasis

Dan Lou Tablet (丹蒌片, usage and dosage: oral use, 5 tablets per time, 3 times a day and taken after meals) could reduce the incidence of MACE and relieve angina pectoris attacks.[76-80] (GOR: weak, LOE: low)

Pattern of Qi Stagnation and Blood Stasis

CDDP (usage and dosage: oral or sublingual use,

Table 5. Treating Principles, Recipe and Ingredient Herbs of CM Patterns

Pattern	Treating principle	Recipe and ingredient herbs
Qi deficiency and blood stasis	Boost qi and invigorate blood, dispel stasis and relieve pain	Recipes: Baoyuan Decoction (保元汤) and Xufu Zhuyu Decoction (血府逐瘀汤) Ingredient Herbs: *Semen Persicae*, *Radix et Rhizoma Ginseng*, *Radix Astragali*, *Flos Carthami*, *Radix Angelicae Sinensis*, *Radix Rehmanniae*, *Radix Achyranthis Bidentatae*, *Radix Paeoniae Rubra*, *Fructus Aurantii*, *Radix Platycodonis*, *Rhizoma Chuanxiong*, *Radix Bupleuri*, *Radix et Rhizoma Glycyrrhizae Praeparata cum Melle*, *Rhizoma Zingiberis Recens*, *Cortex Cinnamomi*
Binding of phlegm and stasis	Invigorate blood anddissolve phlegm, rectify qi and relieve pain	Recipes: Gualou Xiebai Decoction (瓜蒌薤白半夏汤) and Taohong Siwu Decoction (桃红四物汤) Ingredient Herbs: *Fructus Trichosanthis*, *Radix Rehmanniae Praeparata*, *Bulbus Allii Macrostemi, Rhizoma Pinelliae*, *Radix Angelicae Sinensis*, *Radix Paeoniae Alba*, *Semen Persicae*, *Rhizoma Chuanxiong*, *Flos Carthami*
Qi stagnation and blood stasis	Soothe the liver and rectify qi, invigorate blood and unblock the collaterals	Recipes: Chaihu Shugan Powder (柴胡疏肝散) and Shixiao Powder (失笑散) Ingredient Herbs: *Rhizoma Chuanxiong*, *Rhizoma Cyperi*, *Radix Paeoniae Rubra*, *Fructus Aurantii*, *Radix Bupleuri*, *Pericarpium Citri Reticulatae*, *Faeces Trogopterori*, *Pollen Typhae*, *Radix et Rhizoma Glycyrrhizae*
Cold coagulation in heart vessel	Dissipate cold and diffuse impediment, warming and unblocking with aromatic medicinals	Recipe: Danggui Sini Decoction (当归四逆汤) Ingredient Herbs: *Radix Angelicae Sinensis*, *Ramulus Cinnamomi*, *Radix Paeoniae Alba*, *Medulla Tetrapanacis*, *Radix et Rhizoma Glycyrrhizae Praeparata cum Melle*, *Radix et Rhizoma Asari*, *Fructus Jujubae*
Deficiency of both qi and yin	Boost qi and nourish yin	Recipes: Shengmai Powder (生脉散) and Renshen Yangrong Decoction (人参养荣汤) Ingredient herbs: *Radix Paeoniae Alba*, *Radix et Rhizoma Ginseng*, *Radix Astragali*, *Radix Angelicae Sinensis*, *Radix Rehmanniae Praeparata*, *Radix Ophiopogonis*, *Pericarpium Citri Reticulatae*, *Rhizoma Atractylodis Macrocephalae*, *Radix Polygalae*, *Fructus Schisandrae Chinensis*, *Poria*, *Cortex Cinnamomi*, *Radix et Rhizoma Glycyrrhizae*
Healthy qi deficiency and yang collapse	Restore yang to rescue from counterflow, boost qi to rescue from desertion	Recipe: Sini Decoction plus *Radix et Rhizoma Ginseng* (四逆汤加人参) Ingredient herbs: *Radix Aconiti Lateralis Praeparata*, *Rhizoma Zingiberis*, *Radix et Rhizoma Ginseng*, *Radix et Rhizoma Glycyrrhizae Praeparata cum Melle*

10 pills per time, 3 times a day, could reduce patient's risk of cardiac death and improve their cardiac function and QOL.[47,81,82] (GOR: strong, LOE: moderate)

Shexiang Baoxin Pill (usage and dosage: oral use, 1–2 pills per time, 3 times a day) could effectively relieve chest pain symptom, decrease occurance of angina pectoris attacks, restrain platelet aggregation, reduce serum lipid level and improve endothelial and cardiac function with good safety.[48-51] (GOR: strong, LOE: moderate)

Danqi Soft Capsule (丹七软胶囊; usage and dosage: oral use, 4–6 capsules per time, 3 times a day) could regulate blood lipid, prevent atherosclerosis and anti-myocardial ischemia effect through anti-inflammation, anti-oxidation and anti-platelet aggregation mechanisms.[83,84] (GOR: weak, LOE: low)

CM Treatment on Concomitant Diseases and Complications

Previous researches have accumulated a lot of evidence on WM about concomitant diseases and complications of AMI, such as hypertension, dyslipidemia, acute HF and hypertension guidelines that published and continuously updated by ESC, AHA and ACC. Detailed treatment and drugs of WM on concomitant disease prevention and treatment of the complications are manifested in those guidelines. However, few CM therapies on concomitant diseases and complications were reported in WM guidelines. Therfore, this CPG aims to provide CM treatment methods and recommendations in the treating concomitant diseases and complications.

Hypertension

Songling Xuemaikang Capsule (松龄血脉康胶囊, SLXMKC, usage and dosage: oral use, 3 capsules per time, 3 times a day) is suitable for hypertension patients with ascendant hyperactivity of Gan (Liver) yang pattern. On the basis of conventional WM antihypertensive agents, SLXMK could significantly reduce the patients' diastolic blood pressure, achieving a better control on the blood pressure (BP) of hypertensive patients.[85-87] (GOR: strong, LOE: moderate)

Dyslipidemia

Xuezhikang Capsule (血脂康胶囊, usage and dosage: oral use, 2 capsules per time, 2 times a day after breakfast and dinner) could effectively decrease the serum lipid level and reduce the risk of AMI onset. In elderly patients suffering from hypertension or diabetes, Xuezhikang Capsule can better prevent the occurance and risk of cardiovascular events.[88-91] (GOR: strong, LOE: moderate)

Anti-platelet Aggregation

Qishen Yiqi Dripping Pills (芪参益气滴丸, QSYQ, usage and dosage: oral use, 1 bag per time, 3 times a day, with 30 min after meals) is designed for qi deficiency and blood stasis pattern. Studies have indicated that QSYQ could reduce AMI patients' MACE incidence, without significant difference of curative effect compared with aspirin, but less bleeding events than aspirin. QSYQ is ideally suitable for either aged, high bleeding risk or contraindicated to oral aspirin patients.[92] (GOR: strong, LOE: moderate)

HF

HF is one of the most common complications of AMI. Previous researches have shown that the HF after AMI could significantly increase the risk of death by at least 3- to 4-fold.[94] Efficacy in HF treatment and management plays an important role in patient's clinical symptom alleviation and the long-term QOL. A large number of clinical studies have verified that the combination of CM and WM in the treatment of HF has certain efficacy and safety in improving clinical symptoms, cardiac function and exercise tolerance.[94,95]

Xinmailong Injection (心脉隆胶囊, usage and dosage: intravenous drip, 5 mL/kg per time and added to 200 mL 5% GS or 0.9% NS, 2 times a day and interval between 2 administrations) should be more than 6 h, could improve patients' heart function, ventricular wall motion score, reduce the BNP level, increase LVEF and the distance in 6-min walk trials.[96-98] (GOR: strong, LOE: moderate)

Qili Qiangxin Capsule (芪苈强心胶囊, usage and dosage: oral use, 4 capsules per time, 3 times a day) is ideally suitable for HF patients with deficiency of both qi and yang, stasis in collateral vessel and water amassment pattern. Qili Qiangxin Capsule could effectively improve the cardiac function evaluated by New York Heart Association classification, QOL, reduce the plasma BNP level, and increase LVEF.[99,100] (GOR: Strong, LOE: Moderate)

Shenmai Injection (参脉注射液, usage and dosage: intravenous drip, 20–100 mL per time and added to 250–500 mL 5% GS, once a day) is suitable of patients with deficiency of both qi and yin pattern and capable of reducing BNP level, improving patients' cardiac function and the 6-min walking distance.[101,102] (GOR: weak, LOE: low)

Huangqi Injection (黄芪注射液, usage and dosage:

intravenous drip, 10–20 mL per time, once a day) is suitable for patients with heart blood stasis obstruction and qi deficiency pattern. Relevant studies have shown that Huangqi Injection could effectively alleviate HF symptoms and improve cardiac function.[103] (GOR: weak, LOE: low)

A meta-analysis of several trials has found that QSYQ could also be administrated to AMI-induced HF patients with qi deficiency and blood stasis pattern.[104] (GOR: strong, LOE: moderate)

Cardiac Shock

Cardiac shock (CS) advanced from AMI is a clinically critical and severe disease. Although the widespread of development and application of drugs, equipment support and vascular revascularization technology like PCI, cardiogenic shock is still the main cause of death of AMI patients.[105] Integration of CM and WM have done a plenty of research in this area, accumulated a considerable amount of evidence. The results suggest that CM in treating CS originated from AMI has certain curative effect and safety in raising the blood pressure, stabilizing heart rate and improving cardiac function.

Shenfu Injection (参附注射液, SFI, usage and dosage: intravenous drip, 20–100 mL per time and added to 250–500 mL 5%–10% GS or 0.9% GS, once a day) could be applied in CS patients with qi deficiency and yang deficiency. Trials have proved that, on the basis of conventional anti-shock therapy, additional usage of SFI could further improve blood pressure, stabilize heart rate, enhance cardiac function and reduce the mortality rate.[106,107] (GOR: strong, LOE: low)

Arrhythmia

Due to myocardial ischemia and necrosis, reperfusion injury, electrolyte disturbance, sympathetic nerve excitation and other factors, AMI patients might merge with arrhythmias. CM could effectively reduce the occurrence of arrhythmias and reduce the use of WM against arrhythmias, which has become an important method in clinical treatment.

Wenxin Granule (稳心颗粒, usage and dosage: oral use, 1 bag per time, 3 times a day) could be used in treating arrhythmia with deficiency of both qi and yin, stasis obstruction in heart vessel pattern. Wenxin Granule combined with conventional WM is more effective in treating arrhythmias, which can not only effectively alleviate symptoms, reduce the occurrence of ventricular premature beats, but also have the effect of treating atrial fibrillation.[108-110] (GOR: strong, LOE: moderate)

Shensong Yangxin Capsule (参松养心胶囊, usage and dosage: oral use, 2–4 capsules per time, 3 times a day) could be applied in arrhythmia with Xn (Heart) yin deficiency and heart blood stasis obstruction pattern, improve the efficacy of anti-arrhythmia treatment.[111-113] (GOR: strong, LOE: moderate)

Complications of Coronary Intervention

In recent years, several researches reported that CM has its unique advantages in treating complications of coronary intervention, offering new challenges and opportunities for the development of enterprise of integrative CM and WM.[114]

Coronary Microcirculation Disorder

The major manifestations of coronary microcirculation disorder (CMD) are no-reflow phenomenon and slow flow of coronary artery after interventional treatment. There is no satisfactory treatment for coronary microcirculation disorder in WM. However, it has been found that some Chinese patent medicines could reduce the incidence of CMD and reduce the area of myocardial necrosis.[115-116]

Tongxinluo Capsule (usage and dosage refer to previous parts) have accumulated a certain amount of evidence, which demonstrated that Tongxinluo Capsule could reduce the incidence of CMD and narrow the infracted area of myocardium.[117-121] (GOR: strong, LOE: moderate)

In-Stent Restenosis

Studies have shown that the coronary artery lumen stenosis could be up to 50% after 6 months of PCI.[122] At present, conventional WM treatment in preventing in-stent restenosis (ISR) and thrombosis after PCI mostly rely on antiplatelet aggregation agents and lipid-lowering drugs. As an alternative medicine, CM has achieved certain accomplishment in treating ISR verified by RCT. However, more strictly designed, high-quality and large sample RCT researches are appealed in the future to further validated CM's curative effect.[122-123]

XSC, with function of invigorating blood and dissolving stasis, could be applied in ISR patients with blood stasis pattern. The results of the national 9th and 10th "Five-Year Plan: Scientific and Technological Breakthrough Projects" showed that XSC could significantly reduce the incidence of ISR by dilating coronary arteries, improving myocardial

ischemia and hypoxia and inhibiting platelet aggregation and thrombosis.[10,125-128]

Tongguan Capsule (通冠胶囊, TGC), with function of boosting qi, invigorating blood and dissolving stasis, is suitable for patients with qi deficiency and blood stasis pattern. Relative laboratory and clinical researched have exhibited that TGC have protective effects against myocardial ischemia reperfusion injury and anti-ventricular remodeling effects.[128,129]

Cardiac Rehabilitation

Evidence-based medicine researched suggests that cardiac rehabilitation could recover AMI patients' physiological, psychological and social functional to a favorable state, so as to improve the QOL of AMI patients and prolong their life expectancy and improve their long-term prognosis.[130,131] CM is going to take a more and more important role in the field of cardiac rehabilitation, because of alleviating AMI patients' clinical symptoms and improving cardiac function, improving QOL and lowering the readmission rate.[132,133]

Baduanjin exercise, with easy learning motions and moderate amount of exercise, has functions of regulating viscera and bowels. Some trials reported that Baduanjin exercise could improve AMI patients' sleep quality, relieve bad emotions, improve QOL and increase cardiac output and stroke output, indicating that Baduanjin exercise would be an ideal rehabilitation method.[134,135]

Tai Chi, an internal Chinese martial art practiced for both its defense training and its health benefits, is not only a low-intensity aerobic exercise, but also can regulate blood pressure, breath and improve cardiopulmonary function, which has its unique advantages for the cardiac rehabilitation of AMI patients.[136]

Acupoint stimulation, like accupuncture and balance needle, could shorten the duration of chest pain and reduce the degree of chest pain in AMI patients. Acupoint stimulation in cardiovascular disease related acupoints, such as Neiguan (PC 6), Jianshi (PC 5) and Shenmen (TF 4), could contribute to the recovery and improvement of cardiac function in AMI patients.[137,138]

Clinical Pathway of Integrative Chinese and Western Medicine

Clinical pathway, a standardized method of diagnosis and treatment, is the best medical and nursing scheme designed for specific disease. The standardized clinical pathway, which plays an important role in building a harmonious doctor-patient relationship, could not only effectively reduce the length and cost of hospitalization, but also significantly improve the quality of medical service. Previous research on clinical pathwat of AMI has demonstrated that it could reduce AMI patients' hospitalization time, costs, and incidence of major cardiovascular events.[11] Therefore, clinical pathway of integrative Chinese and Western Medicine is recommended for the management of the treatment in AMI patients.

Conflict of Interest

All author and members of the Clinical Practice Guideline of Integrative Chinese and Western Medicine for Acute Myocardial Infarction Working Group declared no conflict of interests regarding the publication of this paper.

Author Contributions

Liao PD drafted the manuscript, Ge JB and Chen KJ gave critical review and advice to the manuscript, Zhang MZ supervised and revised the final manuscript.

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