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Literature Research

A Summary and Evaluation of Current Evidence for Myocardial Infarction with Chinese Medicine*

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ABSTRACT **Objective**: To provide evidence-based recommendations for clinical application and provoke thoughts for future researchers by conducting a comprehensive summary and evaluation of the current evidence profile for the role of Chinese medicine (CM) in treating myocardial infarction (MI). **Methods**: Online databases including PubMed, EMBase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Medicine (CBM), VIP Journal Integration Platform, and Wanfang database were systematically searched for literatures on CM in treating MI. After screening, studies were categorized into 5 types, i.e. systematic review (SR), randomized controlled trial (RCT), observational study, case report and basic research. General information was abstracted, and the quality levels of these studies and their conclusions were summarized and assessed. **Results**: A total of 452 studies including 10 SRs, 123 RCTs, 47 observational studies, 28 case reports, and 244 basic researches were selected. Clinical studies centered primarily on herbal decoction and mostly were not rigorously performed. High-quality studies were predominantly on Chinese patent medicines (CPMs) such as Danshen Injection (丹参注射液), Shenmai Injection (参麦注射液), Shengmai Injection (生脉注射液) and Qishen Yiqi Dripping Pills (芪参益气滴丸). The most frequently observed pattern of drug combination was decoction plus injection. Results of SRs and clinical studies showed that CM may reduce mortality, decrease risk of complication, reduce myocardial injury, improve cardiac function and inhibit ventricular remodeling. Findings from basic researches also supported the positive role of CM in reducing infarct size and myocardial injury, promoting angiogenesis, preventing ventricular remodeling and improving cardiac function. According to the current evidence body, CM has proven effects in the prevention and treatment of MI. It is also found that the effects of CPMs vary with indications. For instance, Shenmai Injection has been found to be especially effective for reducing the incidence of acute clinical events, while CPMs with qi-nourishing and blood-circulating properties have been proven to be effective in inhibiting ventricular remodeling. High quality evidence supports the use of CM injection for acute MI and CPM for secondary prevention. Reports on adverse events and other safety outcomes associated with CM for MI are scarce. **Conclusions**: Sufficient evidence supported the use of CM as an adjuvant to Western medicine for preventing and treating MI. The choice of drug use varies with disease stage and treatment objective. However, the quality of the evidence body remains to be enhanced.

KEYWORDS Chinese medicine, myocardial infarction, clinical evidence

Myocardial infarction (MI) is a common clinical cause of death with 500,000 new cases being diagnosed annually in China.[1] In the United States nearly 900,000 more patients suffer from the disease each year.[2] MI belongs to the category of chest stuffiness and pain in terms of Chinese medicine (CM).

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CM is effective in the prevention and treatment of MI, especially in reducing mortality and complications, and improving quality of life.[3] Scientific management of disease requires that clinical decisions are made considering the doctors' skills, the patients' will and the best clinical evidence.[4] Among these bases, clinical evidence is the most essential.[5-7] Evidence for the efficacy and safety of drugs comes from existing studies. Despite the huge amount of literature published on CM for MI, a systematic categorization and evaluation is lacking. As a result, their value as guidance for clinical decision-making and application is limited. In the present study, a comprehensive summary and evaluation of the current evidence for CM for MI is conducted to generate recommendations for clinical practice.

METHODS

Inclusion and Exclusion Criteria

(1) Participants: patients or animals with MI were included. (2) Intervention: CMs including oral and injection dosage forms were included; acupuncture, massage, qigong and other forms of CM were excluded. (3) Type of Literature: systematic review (SRs), randomized controlled trials (RCTs), observational studies, case reports and basic researches were included; abstracts, editorials, letters and expert opinions were excluded. (4) Language: all studies were published in English or Chinese.

Literature Search Strategy

The following electronic databases were searched from inception until November 2011: PubMed, EMBase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Medicine (CBM), VIP Journal Integration Platform, and Wanfang Database. The reference lists of all retrieved studies were manually searched for further identification of potentially relevant studies.

Selection of Studies

Mu W and Zhang S independently reviewed the title of each article and the full text if necessary. All articles were selected according to predefined inclusion and exclusion criteria. Disagreements between the two reviewers were resolved by discussion.

Data Extraction

Data was independently extracted by Xiao L and Yu HL using a previously designed information table. The extracted data were cross-checked by Wang Y.

Data Processing

Quality Evaluation

The methodological quality of the studies was evaluated as prescribed in the Cochrane Reviewer's Handbook. But the quality of studies lacking authoritatively recognized evaluation criteria was not evaluated.

Summary and Evaluation

The characteristics of the included studies were described in proportions, which included the distribution of disease stage, usage of CM, sample size, and course of treatment, etc. In order to find out any relation between the efficacy and safety of CM and the course of disease, the result and conclusion of each study was emphatically summarized.

RESULTS

In total, 452 reports were retrieved, including 10 SRs, 198 clinical studies, and 244 basic researches. The biggest proportion of clinical studies was taken by RCTs (62.12%). There were 2 RCTs with large sample (the number of samples were 3,500 and 4,870), 121 RCTs with a sample ⩽500, 47 observational studies and 28 case reports. Details about these 5 types of studies are listed below.

SRs

General Characteristics of the Included Reports

Ten SRs[8-17] on the prevention and treatment of MI by CM were published between 2006 and 2011. One[13] of them is a Cochrane SR, and 3[9,11,15] included more than 10 trials. These trials involved 207—2,822 participants. Four reports[9,11,14,15] involved more than 1,700 subjects. Seven SRs[8-10,13,15-17] studied patients in the acute stage (within 28 days of MI onset) and the other 3[11,12,14] included patients both in the acute and recovery stage. The most frequently studied form of CM was injection. Injection was the only study subject in 5 SRs, which were Shengmai Injection (生脉注射液) in 2 SRs,[10,16] Shenmai Injection (参麦注射液) in 2 SRs,[13,15] and Danshen Injection (丹参注射液) in 1 SR.[14] The other CMs being studied were Yiqihuoxue (YQHX, qi-nourishing and blood-circulating) herbs.[11,12] Decoction, Chinese patent medicine (CPM) and injection were the dosage forms of CM (Table 1).

Methodological Quality of Included Reports

These reports were evaluated based on different evaluation systems. In general the SRs were low in quality (Table 1).

Main Results

Because of clinical heterogeneity one report[11] performed only descriptive analysis, and the others adopted quantitative analysis.

Fatality Rate

One SR[8] found that CM made no difference in reducing fatality rate compared with control; 6 SRs[9,10,13-15,17] concluded that CM reduced fatality rate. One[13] of them showed *Salvia miltiorrhiza* preparations had advantage in reducing fatality rate, but the only RCT that the SR included came to inconsistent conclusions. One article[10] concluded that CM could do better in reducing fatality rate when there was no vasoactive agent being used.

Re-infarction Rate

One SR[8] found that CM could reduce infarction

Table 1. SRs of CM on Prevention and Treatment of MI

Research	Number of included studies	Number of subject	Quality evaluation	Course of the disease	Intervention	Efficacy		Safety	
						Better than control	No difference from control	Observation rate	Adverse effect
Lin, et al 2006[8]	8	738	High quality for 1, low quality for 8 studies	Within 28 days	E group use CM	Re-infarction rate, heart failure rate, EF	Fatality rate, arrhythmia, effective rate	37.5%	#1
Zheng, et al 2007[9]	15	1732	D level	Acute phase	Intravenous infusion of CM + WM pills *vs*. WM pills	Fatality rate, recanalization rate, cardiac insufficiency rate in 7 days	Re-infarction rate	20%	#2
Gao, et al 2008[10]	4	376	C level	Within 28 days	Shengmai Injection + routine WM *vs*. routine WM	Fatality rate (absent of vasoactive drugs)	Fatality rate (in presence of vasoactive drugs)	Unknown	No
Zhang, et al 2008[11]	28	2822	C level	Acute or recovery phase	YQHX herbs for more than 7 days	PVC, VT	Re-infarction rate, revascularization, V-fib, bradycardia, atrioventricular block	25%	#3
Song, et al 2008[12]	3	207	All RCTs, unknown if there is defulvium or not	Acute and recovery phase	YQHX herbs + routine WM *vs*. routine WM for more than 21 days	LVEDV, LVESV	None	Unknown	None
Huang, et al 2009[13]	7	901	C level	Within 28 days	Shenmai Injection + routine WM *vs*. routine WM for more than 7 days	Fatality rate, heart failure rate, arrhythmia (reperfusion, secondary to AMI)	Angina rate, re-infarction rate	14.29%	None
Wu, et al 2009[14]	6	2368	One real RCT	Acute or recovery phase	Danshen Injection + other CM *vs*. routine CM / other CM / placebo	Fatality rate, severe heart failure rate	None	Unknown	No final conclusion
Zeng, et al 2010[15]	13	1707	C level	Within 28 days	Shenmai Injection for more than 7 days	Fatality rate	None	Unknown	#4
Jiang, et al 2011[16]	5	266	<3 Jadad points	Within 28 days	Shengmai Injection for more than 7 days	Systolic on the 2nd and 3rd day of treatment, diatolic pressure on the first two days of treatment	Diastolic pressure on the 3rd day of treatment	0	—
Zhang, et al 2011[17]	7	635	>2 Jadad points	Acute phase	CM only or with WM pills	Fibrinolytic complications, fatality rate, clinical curative effect	Fibrinolytic rate	57.14%	#5

Notes: E: experimental; EF: ejection fraction; CM: Chinese medicine; WM: Western medicine; YQHX: qi-nourishing and blood-circulating; PVC: premature ventricualr contraction; VT: ventricualr tachycardia; V-fib: ventricualr fibrillation; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; AMI: acute myocardial infarction. Observation rate = the number of reports mentioned side effects/all reports included × 100%. #1: One study reported no side effects, and the other 2 reported headache and gastrointestinal reactions, but no severe response. #2: Mailuoning showed no evident side effects within 7 days. Two patients in the Shenmai Injection group and 3 in the control group had chills and rashes. One patient receiving Lulutong Injection and 3 receiving control had chills and rashes. #3: Five studies reported the main side effect of thrombolytic therapy was hemorrhage. One of the 33 patients taking Naoxintong Capsules experienced stomach discomforts. Three of the 30 patients taking Tongxinluo experienced abdominal distention. #4: One study reported 2 cases of palpation and flash, which disappeared after slowing down the dripping speed. #5: Only one report mentioned slight gastrointestinal discomfort. — means it was unable to assess safety because no single trial reported on safety outcomes.

rate, but 2 SRs[9,11] found no support for that conclusion.

Re-canalization Rate

One SR[9] revealed that CM could improve re-canalization rate while 3 SRs[11,13,17] found CMs made no difference compared with control.

Complications Rate

Four SRs[8,9,13,14] showed that CM could reduce the rate of heart failure. One SR[13] confirmed that CM had better performance in reducing arrhythmia incidence than the control group, but the other one[8] showed no difference. In one study[11] CM showed selective effects on arrhythmia. Specifically, CM was more effective than control in controlling premature ventricular contraction and ventricular tachycardia, but showed no difference than control in reducing ventricular fibrillation, bradyarrhythmia and atrioventricular block. One SR supported that CM had advantages in reducing thrombolysis complications,[17] improving the ejection fraction,[8] inhibiting ventricular remodeling (both systole and diastole)[12] and improving blood pressure.[16] One SR[13] found CM in reducing angina incidence compared with control. One SR[11] which made exclusive descriptive analysis came to no affirmative conclusion about the performance of YQHX CPMs in reducing combined heart failure incidence and combined shock due to disagreements among results. One SR[17] proved that CM had advantages in improving the total effective rate and another one[8] showed no difference compared with control.

Side Effects

Ten SRs reported safety outcomes. Three[10,12,13] reported no side effects, and 5[8-10,15,17] reported responses such as gastrointestinal discomforts. Responses such as chill,[9] rash,[9] thrombolysis bleeding,[11] palpation and flash[15] were presumed to have been caused by combined use of CMs with Western medicines (WMs). As a result, it is uncertain if these effects were in any way related to CM. One report[14] came to no conclusion. In one report[16] it was unable to be assess safety (all trials did not report on safety outcomes).

RCTs

Large Sample, Multi-Center and High Quality RCTs

Two high-quality RCTs[18,19] were retrieved, which both focused on secondary prevention of MI, and included 8,370 subjects altogether. The average follow-up period lasted for 3.5 years. Both were multi-center, large-scale, randomized, double-blind, and strictly controlled high quality research. Drugs for the experimental groups were Qishen Yiqi Dripping Pills (芪参益气滴丸, QYDP) and Xuezhikang Capsule (血脂康胶囊), their respective controls were aspirin and placebo. The results showed that in reducing the incidence rates of primary endpoints (cardiovascular death, nonfatal recurrence of infarction and nonfatal stroke), the difference between QYDP and aspirin were not statistically significant, but the former had a better safety profile. In reducing the incidence of nonfatal MI and of coronary heart diseases, the needs for percutaneous coronary intervention/coronary artery bypass grafting (PCI/CABG) and deaths due to various reasons, Xuezhikang Capsule was better than placebo and the difference between them on safety outcomes were not statistically significant.

General RCTs

All 121 RCTs had the following characteristics. (1) The smallest sample size was 22[20] while the biggest was 500.[21] (2) The most frequently investigated dosage forms of CM were decoction, CPM and CM injection (Table 2). And 90.08% RCTs compared CM combined with WMs to WMs only. (3) Various formulations of CPMs were studied, including 29 kinds of oral liquids and 19 kinds of injections (Appendix 1). The most frequently investigated injections were Danshen Injection, Shenmai Injection, Shengmai Injection, Compound Danshen Injection (复方丹参注射液), Wenxin Granule (稳心颗粒), and Ligustrazine Injection. (4) The quality of research methodology was generally low (Appendixes 2 and 3). (5) The results suggested that treating MI with WM and CM combination was better than routine WM only in terms of lowering fatality rate, reducing complications, increasing effective rate, reducing myocardial damages, and improving heart function, etc. (Appendix 2). Certain Chinese herbs had the same curative effects as WMs or were even more effective (Appendix 3).[22-33] (6) Twenty-seven reports mentioned safety issues. No adverse events were reported in 13 studies investigating decoctions and QYDP. Tongxinluo (通心络), Wenxin Granule, Shenmai Injection and other drugs used in the other 14 studies reported adverse events such as slight gastrointestinal reactions and dizziness.

Observational Studies

A total of 47 studies had the following

Table 2. Dosage From of CMs Used in Clinical Studies

CM dosage form	RCT	Observational study	Case report	Total number
Decoction	47	21	15	83
CPM	36	2	0	38
Injection	28	8	6	42
Injection+decoction	6	12	3	21
Injection+CPM	3	0	1	4
Decoction+CPM	1	1	1	3
Injection+decoction+CPM	0	3	1	4
Powder	0	0	1	1
Total number	121	47	28	196

characteristics. (1) The sample size ranged from 5 to 124.[34,35] (2) There were 63.83% studies used combined CM and WM therapy. (3) The most commonly used types of CM interventions were decoction, decoction plus CM injection and CM injection (Table 2). Typically, CM injection was applied to patients with acute myocardial infarction (AMI), whereas decoction and CPM were used for sub-acute or chronic MI patients (Appendix 4). (4) Various types of CMs were used, including 7 kinds of oral CPMs and 11 kinds of CM injections, in which Danshen Injection, Shenmai Injection and Shengmai Injection are the most frequently used (Appendix 1). The number of decoction is hard to count due to variation. (5) The results showed that in the treatment of MI based on pattern differentiation CM had certain effects in treating acute and long-term MI, as well as its complications (Appendix 4). (6) In 80.85% studies safety outcomes were not mentioned. Safety outcomes were mentioned in 9 studies, in which 7 reported no adverse reactions. The CMs used were self-designed decoction, Shenfu Injection (参附注射液), Shenfu Decoction (参附汤), Shengmai Injection, Danshen Powder Injection (丹参粉针注射剂) and Jianxin Decoction (健心汤). One study reported 1 case of mild loose stool, and this symptom disappeared after adjustment of the constituents of the decoction. One study reported nausea, thirst and stretching head after administering Shenmai Injection in the right atrium, however, these symptoms disappeared without disposal.

Case Reports

A total of 28 reports of 39 cases were included. They had the following characteristics. (1) Publication year ranged from 1984 to 2001 for 16 articles, and 9 of them used only CM (decoction, CPM or injection) to treat MI. Patients in the other 5 studies were given CM and WM therapy considering their severe condition. Twelve reports were published from 2002 to 2011. The patients in 8 reports were given CM and WM therapy. Three reported on the use of CM only for complications after interventional operation for MI. (2) CMs used were in various forms. The most frequently used were decoction, CM injection, and decoction combined with CM injection (Table 2). In 15 reports (53.57%) the patients were given combined CM and WM therapy. (3) Decoction (20 reports) was the most commonly used drug type. They were the mostly self-designed decoction or the adjustment of an existing decoction. There were 1 kind of powder, 3 kinds of oral CPMs and 11 kinds of CM injections. Danshen Injection, Shenmai Injection and Shengmai Injection are quite widely used. (4) It was summarized that CM played a positive role in the treatment of AMI, remission of MI, coronary revascularization and complications happening after MI (Appendix 5).

Basic Researches

A total of 244 studies had the following characteristics. (1) A total of 220 (90.16%) were published in Chinese and 24 in English articles. Twelve were *in vitro* experiments. (2) Most frequently used animal models were rats (81.33%), followed by rabbits, pigs, dogs, cats, and mice (Appendix 6). (3) Basic researches were classified into 5 categories, and covered altogether 123 types of CM (Table 3). The most commonly investigated were self-designed

Table 3. Basic Researches on Usage of CM

Type of CM formulation	Number of studies	Account of type	Example
Self-designed decoction	113	53	Xinfukang, Xinshuaikang, YQHX herbs
Monome of Chinese herb*	56	34	Salvianolic acid B, notoginseng triterpenes, Rhodiola rosea
CM Injection	40	20	Danshen Injection, Huangqi Injection
CPM	32	13	Tongxinluo, Qili Qiangxin, Shexiang Baoxin Pill
Classic recipe	3	3	Buying Huanwu Decoction, Taohong Siwu Decoction, Shengmai Powders
Total	244	123	——

Note: *includes single herb and its extracts.

decoctions (46.31%) and single CM (22.95%). Classic decoctions (1.23%) were the least used. (4) The results of basic researches indicated that the mechanism involved many aspects (Appendix 6). Most CMs could control ventricular remodeling, reduce the area of damaged heart tissue, improve the cardiac function, promote angiogenesis and reduce infarction size, etc. *Salvia miltiorrhiza* agents have the widest range of mechanisms, followed by the bioactive components in *Panax notoginseng* and YQHX herbs.

DISCUSSION

In this research, it was found that only 10 SRs and 2 high-quality of RCTs provided high quality evidence. It was concluded that intravenous infusion of Chinese herbs had advantages in treating AMI and the deficiency syndrome associated with death. Despite that the evidence from SRs proved limited effects of CM injection on AMI, they were representative of drug choices for patients in the acute stage. The results showed that CMs had great advantages in reducing mortality, decreasing heart failure rate, reducing thrombolysis complications, improving ejection fraction and inhibiting ventricular remodeling. However, these findings should be interpreted with caution due to the low quality of individual trials included in the SRs. It was also found that CMs had a better safety profile. This finding was less than conclusive because of the limited number of studies reporting on safety. Two high-quality RCTs focused on the secondary prevention of old MI. The results suggest that preventing MI with CMs effectively reduced the incidence rate of many primary endpoints and were safer, and that different CMs treat and prevent MI in various ways.

A total of 196 common RCTs, observational studies and case reports were included. The results of RCTs confirmed that compared to routine WMs, WMs combined with CMs had better therapeutic effects and reduced more complications. Each drug had its own unique indication. For example, Shenmai Injection, CM decoctions and Danshen Injection were better at reducing the incidence of clinical events. As shown in case reports that CM injections were typically used for AMI, whereas decoctions and CPMs were used for the subacute stage of MI and old MI. Furthermore, combined therapy of CMs and WMs had greater performance on short- and long-term outcomes. Decoctions were most commonly used in single case reports. It was largely due to the flexibility of decoction, which was also a strength of CM, and reflected the diagnostic method of syndrome differentiation characteristic of CM. However the inherent limitations of decoction have restricted its application. Twenty-eight case reports suggested that CM had supplementary role in the treatment of thrombolytic therapy and of MI complications and post-operation prognosis. According to the few observational studies having reported on safety outcomes CM was safe to use.

Totally 123 species of CM have been investigated in basic researches including CPMs and decoctions. These studies covered a wide scope and included both *in vitro* and *in vivo* experiments. Many showed that CM prevent and treat MI in different ways while aiming at multiple targets. Some of its mechanisms have been supported by sufficient evidence, such as reducing myocardial injury, improving cardiac function and inhibiting ventricular remodeling. Each CM has its own unique mechanisms. *Salvia miltiorrhiza* preparation, pseudo-ginseng and qi-nourishing and blood-circulating decoctions each have a variety of pharmacological mechanisms.

As observed most (83.67%) studies were focused on one dosage form. The choice of a right study design is made considering factors such as practicality, the characteristics of the dosage form and the study objective. CPM was a constant subject of cohort studies and RCTs, whereas decoction was a typical subject of case reports, case series and observational studies. Combined drug use is more frequently identified in observational studies and case reports than in RCTs. The most commonly studied combination is decoction together with injection. A possible reason is that the onset of effects is fast for injection and slow for decoction. According to the CM therapeutic rules of "alleviate the symptoms if the disease progresses fast and eradicate the cause if the disease develops slowly" such a combination may take the advantage of both. Our study concluded that the intravenous preparation of CM had an advantage in the treatment of MI.[3] In CM theories the basic pathogenesis of MI is qi deficiency and blood stasis. However, no YQHX injection was found in the present study. This question merits further investigation.

As this is a secondary research its reliability is to a great extent determined by the quality of all the included original studies. It was found from this review that the majority of original studies were inadequately conducted. The quality of other types of studies was not evaluated. As a result we were unaware if any

bias exists. Caution should be taken when interpreting the conclusion of this review, and further study is necessary using methods such as meta-analysis or the Grading of Recommendations Assessment, Development and Evaluation system (GRADE).

MI is a common clinical critical disease. Interventional therapy is one of the most effective treatment methods. Our report showed that CM has a great potential in the prevention and treatment of MI, and it can be considered a routine treatment for MI. The combination of CM and WM showed better efficacy. Our review provided the following information for clinical practice: (1) CM injection is suitable for treating AMI. Danshen Injection, Shenmai Injection and Shengmai Injection are some examples. (2) Decoctions and oral CPMs are suitable for treating patients in the remission period of MI. QYDP and Xuezhikang Capsules are 2 representatives. (3) *Salvia miltiorrhiza* can be used to prevent complications such as heart failure. Medicines with qi-nourishing and blood-circulating properties such as QYDP have been proven to be good at inhibiting ventricular remodeling and improving cardiac function.

Proof of drug efficacy and safety requires evidence from animal experiments and clinical trials. The reliability of original study and secondary study are critical in the production of clinical evidence. Multi-disciplinary efforts are required to help transform the potential effects of CMs for MI to clinical evidence. Based on findings from the present study it is recommended that: (1) Expanding research scope. The potential of qi-nourishing and blood-circulating injection in MI prevention and treatment merits investigation. (2) Carrying out in-depth researches focusing on specific topics, for example, the efficacy of CMs combined with vasoactive WMs. (3) Strengthening the evidence body. In this case, large-scale, multi-enter and high quality RCTs and adequately conducted SRs need to be performed. (4) The system for clinical evaluation of CM should be rigorously established to promote the production and transformation of evidence. For example, strict inclusion and exclusion criteria for selecting secondary studies should be formulated, unified quality evaluation standards should be applied, and the methods for quality evaluation of meta-analysis should be developed. (5) Improving the quality of original research. (6) More attention should be paid to the observation and reporting of drug safety. (7) Improving the reporting quality in medical research. The reporting of medical research needs to be truthful, detailed and highly standardized.

Conflict of Interest

The authors declare that they have no conflict of interests.

Author Contributions

Wang Y, Shang HC designed the protocol of this research. Mu W, and Zhang S performed searches, appraised and selected trials. Wang Y, Yu HL and Xiao L extracted data, contacted authors for additional data. Wang Y, Mu W and Yu HL carried out the summary and evaluation of the data. Wang Y drafted this report. Tian GH and Xiao L suggested advice. Shang HC reviewed and critiqued this report and assisted with interpretation of the data. All authors read and approved the final manuscript.

Electronic Supplementary Material

Supplementary materials (Appendixes 1–6) are available in the online version of this article at http://dx.doi.org/10.1007/s11655-017-2824-y

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