The effect of text message reminders on medication adherence among patients with coronary heart disease

A systematic review and meta-analysis

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Abstract

Background: To determine the effectiveness of text message reminders (TMR) on medication adherence (MA) and to investigate the effects of TMR on clinical outcomes.

Methods: The PubMed, Cochrane library, EMbase, and China Biology Medicine databases were searched for randomized-controlled trials with TMR as the intervention for patients with coronary heart disease. Two reviewers independently extracted data and assessed the risk of bias. Meta-analysis was conducted using Stata 15.0 software.

Results: In total, 1678 patients in 6 trials were included. Compared with the control group, the MA was 2.85 times greater among the intervention group (RR [relative risk] 2.85; 95% confidence interval [CI] 1.07–7.58). TMR reduced systolic blood pressure (BP) (weighted mean difference) = −6.51; 95% CI −9.79 to -3.23), cholesterol (standard mean difference = −0.26; 95% CI −0.4 to -0.12) and increased the number of patients with BP <140/90 mm Hg (RR 1.39; 95% CI 1.26–1.54).

Conclusion: TMR significantly promoted MA and reduced systolic BP, cholesterol level, and body mass index, but had no effect on mortality, diastolic BP, or lipoproteins. However, substantial heterogeneity existed in our analyses.

Abbreviations: BP = blood pressure, CHD = coronary heart disease, CI = confidence intervals, DBP = diastolic blood pressure, MA = medication adherence, RCT = randomized clinical trial, RR = relative risk, SBP = systolic blood pressure, SMD = standard mean difference, TMR = text message reminders, WMD = weighted mean difference.

Keywords: coronary heart disease, efficacy, medication adherence, text message reminder

1. Introduction

Coronary heart disease (CHD) has become the leading cause of premature death and disease globally, accounting for more than 8 million deaths in 2015.[1–2] About half of the patients with CHD will be readmitted to hospital owing to a variety of recurrent events.[3] Medication adherence (MA) is the basis of

CHD management and a modifiable behavioral risk factor.[4] Low MA can lead to the adverse clinical outcomes in patients with CHD.[5,6] However, current studies show that only 3-quarters of all hospitalized patients take all medications within 120 days after discharge,[7–9] thus limiting the efficacy of treatment and leading to poorer outcomes with a substantial economic burden for patients and the healthcare system as a whole.[10] Therefore, there is an urgent need for innovative and cost-effective interventions to improve MA.

Text message reminders (TMR) are available on any existing mobile device and can be used by all socio-economic groups and ages. The number of mobile phone users reached 4.77 billion in 2017.[11] Text message-based interventions are widely used to arrange medication warnings and reminders to improve MA.[12,13] As a potential low-cost method, this approach provides self-management support for patients seeking to change health behaviors,[14–19] including secondary prevention of CHD, which has gained increasing recognition.[20]

Some systematic reviews and meta-analyses have evaluated the effectiveness of TMR in improving MA among patients receiving treatment for human immunodeficiency virus (antiretroviral therapy) and Type 2 diabetes, but not for CHD.[21–23] At present, only narrative reviews without meta-analysis show the beneficial effects of TMR on secondary prevention of cardiovascular disease.[24,25] However, there is currently no meta-analysis or systematic review of the effectiveness of TMR as an intervention for MA in patients with CHD, especially patients with acute coronary syndrome. In this study, we investigated the

effectiveness of TMR as an intervention for MA as well as the effects of TMR on clinical outcomes.

2. Methods

This meta-analysis was performed according to the preferred reporting items for systematic reviews and meta-analyses statement[26] and the Cochrane collaboration reporting project.[27] As the present meta-analysis is performed based on previous published studies, thus no ethical approval and patient consent are required.

2.1. Search strategy

One author performed a systematic search of the PubMed, Cochrane library, EMbase, and China biology medicine databases using a combination of medical subject headings and keywords. The main search terms were as follows: "coronary heart disease," "medication adherence," and "text messaging." At the same time, we manually searched the reference lists to identify other relevant studies. (The PubMed strategy is available as Supplementary Material, http://links.lww.com/MD/D535.)

2.2. Study eligibility

We included trials based on the following criteria:

(1) study participants (≥18 years) with CHD,
(2) participants received TMR to promote MA,
(3) randomized clinical trial (RCT) design with at least 1 month of follow-up,
(4) a quantitative measure of the impact of TMR on MA was reported.

We excluded studies based on the following criteria:

(1) web-based interventions without the use of TMR by mobile phone.
(2) TMR used only for disease management or health education and not to improve MA.

2.3. Data extraction

Two authors independently extracted data from each eligible study. We resolved any disagreements through discussion and reached a consensus with the third reviewer. Data extraction included:

(1) basic information: first author, publication year, country, sample size, mean age, male-to-female ratio;
(2) interventions: text messaging;
(3) outcome: MA, cholesterol, blood pressure (BP);
(4) the key elements of risk assessment of bias.

2.4. Assessment of study quality

Two authors independently assessed the risk of bias of included studies. The methodological risk of bias of included studies was assessed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0,[27] in which the following elements were reported for RCTs: random sequence generation (selection bias), allocation concealment, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting, (reporting bias), and other bias. These items were evaluated as being high, low, or unclear risk of bias (Table 1). Studies with a high or unclear risk of bias in terms of random sequence generation and allocation concealment were considered to be higher risk of bias (Fig. 1).

2.5. Statistical analysis

All analyses were conducted using Stata 15.0 software. Data were pooled using a fixed-effects model or a random-effects model in Stata 15.0 software regardless of the presence or absence of significant heterogeneity. For the binary variable, relative risk (RR) was used as the effect indicator, while for the continuous variable, the mean difference was used as the effect indicator, with each effect size presented in terms of a point estimate with 95% confidence intervals (CIs). The heterogeneity between the results of the studies was analyzed using Chi-square tests, with a test level of $? = 0.1$, and the heterogeneity was quantified using the I^2 statistic and the corresponding P-value. An I^2 statistic exceeding 50% with $P < .05$ was interpreted as representing substantial heterogeneity.[27] In the absence of statistical heterogeneity between the results of the studies, a fixed-effects model was used; otherwise, a random-effects model was used after excluding the influence of clinical heterogeneity. Descriptive analysis of studies with significant clinical heterogeneity was performed.

Table 1

Study quality assessment (according to Cochrane guidelines).

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Quilici J (2013)	Unclear	Low	Unclear	Unclear	Low (4.2%)	Low	Unclear
Park L G (2014)	Random allocation sequence using blocks	Low	Double blinding	Low	Low (6.7%)	Low	Unclear
Khonsari S (2015)	Unclear	Low	Single blinding	Unclear	Low (3.2%)	Low	Unclear
Ho P M (2014)	Blocked randomization stratified by study site in a 1:1 ratio	Low	Double blinding	Low	Low (4.7%)	Low	Unclear
Redfern J (2015)	in a uniform 1:1 allocation ratio with a block size of 8	Low	Double blinding	Low	Low (1.5%)	Low	Unclear
Liu YS (2015)	Random number table	Low	Single blinding	Low	High (10.9%)	Low	Unclear

The rate of drop-out above greater than 10% is considered as the high risk of bias.
High: represents high risk of bias; Low: represents low risk of bias.
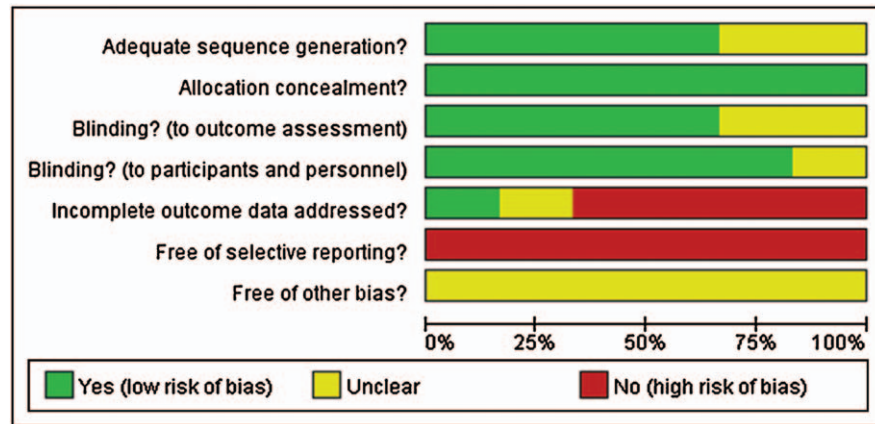
Figure 1. The evaluation result of the included studies. The words on the left represent the content of the evaluation, and the long strips on the right represents the evaluation result, where red indicates high bias, and green indicates low bias and yellow indicates unclear bias.

3. Results

3.1. Study characteristics

We identified 6 RCTs[14,28,29,30,31,32] (Fig. 2) from the 13 studies that met our inclusion criteria. Excluded studies and the detailed reasons of exclusion are presented in Supplementary Table 1, http://links.lww.com/MD/D534. In total, 1678 patients were involved, and 75.6% (1268 of 1678) were male. The mean age of participants was 60.44 years (57.5–64 years). The sample size ranged from 62 to 710 patients.

3.2. TMR characteristics

Detailed features of the TMRs used in the 6 studies are shown in Table 2. In 4 studies[28,29,30,31] personalized TMRs were sent daily before every medication intake, which was generally correlated with patients' medication prescription and was relatively fixed. Medication reminder was the primary purpose of the TMR content. For example, the content used in the study by Khonsari was as follows: "[Mr/Ms] [patient's name], please take [medication quantity] tablet of [medication name] at [time]."[30] The medication reminder in the study by Park was
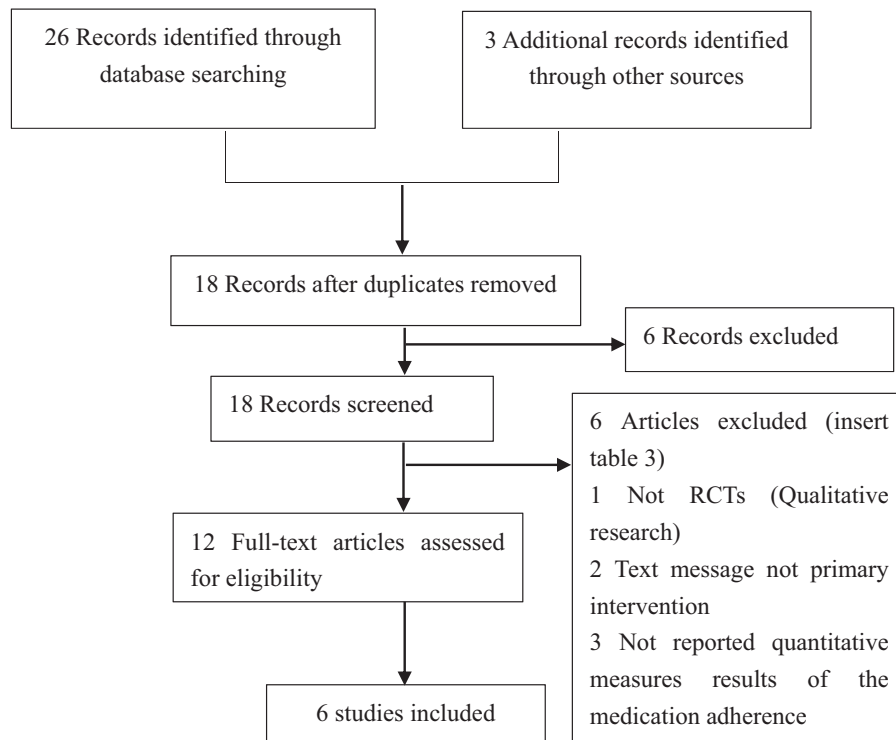
Figure 2. The selection process of included studies. The pointing of the arrow indicates the steps of filtering.

Table 2

Characteristics of trials (studies) using TMR to promote medication adherence.

Study	Sample size (E/C)	Country	Age (mean) (E/C)	Gender (M/F)	Experiment arms vs control arms	Follow-up	Patient characteristics
Quilici J (2013)	250/249	France	Mean ± SD 64 ± 14/64 ± 10	382/117	TMR versus usual care	1 mo	The CHD patients of Receiving aspirin after coronary stenting.
Park L G (2014)	28/28/28	USA	Mean ± SD 58.2 ± 10.6/ 58.3 ± 8.5/61.1 ± 9.1	68/32	TMR versus usual care	1 mo	The CHD patients of Receiving Antiplateletmedication
Khonsari S (2015)	31/31	Malaysia	59/56	51/9	TMR versus usual care	2 mo	Inpatientsin a teaching hospital for CHD.
Ho P M (2014)	122/119	USA	63.8/64	236/5	TMR versus usual care	12 mo	CHD patients taking statin, ACEI/ARB, β-Blocker, clopidogrel
Redfern J (2015)	352/358	Australia	57.9/57.3	582/134	TMR versus usual care	6 mo	CHD patients in a referral center of teaching hospital.
Liu YS (2015)	41/41	China	NR	NR	TMR versus usual care	1 mo	patients with CHD taken PCI therapy

C = control group, CHD = coronary heart disease, E = experiment group, F = female, M = male, Mo = month, NR = not reported in study, PCI = percutaneous coronary intervention, TMR = text short message reminder.

2-way, requiring patients to respond and confirm receipt. For example, "John, take Plavix 75 mg at 9:00 AM. Respond with 1." Furthermore, 2 studies[14,32] also included assessments of secondary interventions for the prevention of CHD, such as dietary changes, sport, cholesterol reduction, and smoking cessation. Self-reporting was the most common method used for assessment of MA.[14,28,29,30,32] One of the studies[28] defined good adherence as >95% of prescribed doses, followed by the corresponding medication auto-monitoring system.[28,29] Two studies,[14,31] in which cost was reported, suggested that TMR improved MA without increasing costs.

Both self-reporting and testing were used in 2 studies of MA.[28,29] Within those studies, a variety of specific self-report measures were used including questionnaire by telephone, fax and mail,[14] Morisky medication adherence scale,[29,30,32] management of disease in general scale, and self-efficacy for appropriate medication use scale.[32] Only 1 study did not use self-reported methods to measure MA; instead MA was calculated based on the proportion of days covered during the 365-day follow-up.[31]

3.3. Primary outcomes

3.3.1. MA. Due to the different methods for evaluation of MA used in each study, fewer studies were included in the data merger. High MA (RR 2.85; 95% CI 1.07– 7.58) was reported in 2 studies involving 144 patients (Fig. 3), showing that TMR significantly improved MA.[30,32] Park[29] and Ho[31] both reported the MA for various types of CHD medication, including statins, Ace inhibitor (ACEI)/ARB, β-blockers, and Clopidogrel.[31] A greater proportion of patients who received TMR adhered to treatment with Clopidogrel (86.8% vs 70.7%; P = .03), statins (93.2% vs 71.3%; P < 0.001), and ACEI/ARB (93.1% vs 81.7%; P = .03) but not to treatment with β-blockers (88.1% vs 84.8%; P = .59). There were no statistically significant differences in the proportion of self-reported MA (97.2% vs 92.3%; P = .691) and tested MA (94.8% vs 88.8%; P = .611). A random-effects model was used when heterogeneity measured by the I^2 statistic exceeded 50% for the high MA (I^2 = 73.9%).

3.4. Secondary outcomes

3.4.1. BP. Three studies[14,29,32] including 876 participants were eligible for meta-analysis and reported the systolic blood pressure
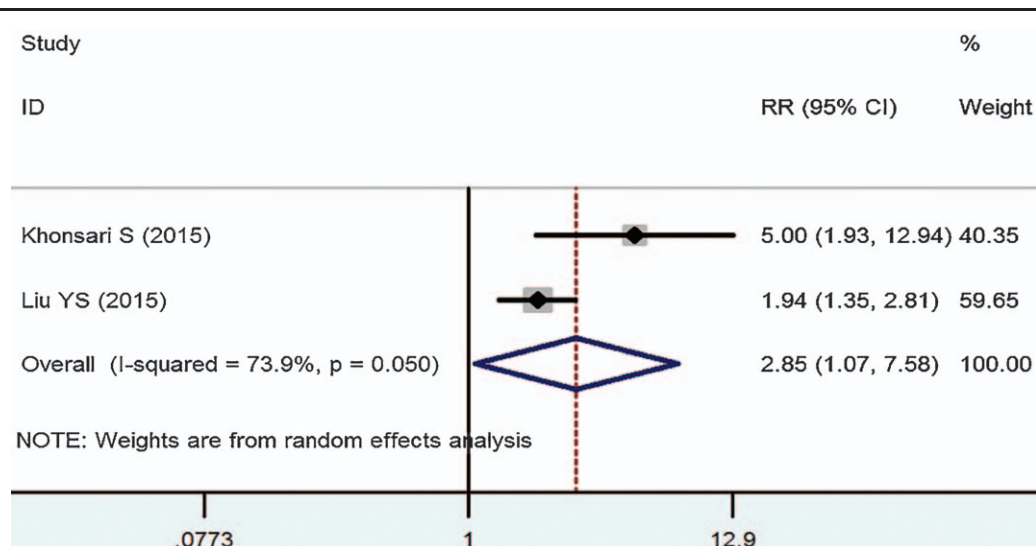
Figure 3. The result of meta-analysis showed that text message reminder significantly improved medication adherence, which did not intersect with X = 1. Red lines represent the total amount of effect. Black lines represent the amount of effect in the 2 studies respectively.

Table 3

Characteristics for the TMR intervention of the included studies.

Study	TMR frequency	TMR content	Adherence measure approach	Patient feedback	Cost effective
Quilici J (2013)	A daily personalized TMR reminding	Aspirin intake, with different formulation every day.	Self-reported and platelet function testing.	92% satisfied and thought the TMR was valuable.	NR
Park L G (2014)	Delivered at times correlated with patients' medication schedule	Take antiplatelet and statin The TMR were 2-way, requiring patients to respond to confirm receipt.	Self-reported and tested medication adherence	Easy (88.6%), technical difficulties (7.6%) with receiving TMR.	NR
Khonsari S (2015)	Daily before every intake and calls per 2 weeks to reassure the delivery of text-messages.	Automatically generated the corresponding TMR by participants' demographics and prescription.	A self-reported of medication adherence (MMAS-8-item).	Useful (93.5%), helped (64.5%). Over 80% requested for the TMR reminders to be continued.	NR
Ho P M (2014)	At regularly scheduled intervals	Medication reminder and medication refill calls.	Calculated based on the proportion of days during the 365-d follow-up.	NR	$360 per patient. Increased medication adherence did not lead to medication costs.
Redfern J (2015)	Four messages per wk and sent on 4 of 5 randomly selected wk days.	Advice, motivation, and information to improve diet, physical activity, and smoking cessation.	Self-reported. With questionnaire by telephone, fax and mail,	Easy to understand (97%), be useful (91%).	US $0.10 per message. Average cost of less than US $10 per patients.
Liu YS (2015)	Every 5 d for a total of 5 TM, 5 topics.	Medication, dietary, sport, cholesterol reduction, drug precautions.	Self-reported adherence, disease relapse.	The satisfaction rate was 95.10%.	NR

NR = not reported in study, TMR = text short message reminder.

(SBP) (Supplementary Fig. 1, http://links.lww.com/MD/D529) and diastolic blood pressure (DBP) (Supplementary Fig. 2, http://links.lww.com/MD/D530). SBP was significantly reduced in the TMR group (weighted mean difference [WMD] = −6.51; 95% CI -9.79 to -3.23, P = .000) and the number of patients with BP <140/90 mm Hg was clearly higher than that in the control group (RR 1.39; 95% CI 1.26–1.54; 2 trials; 951 participants) (Supplementary Fig. 3, http://links.lww.com/MD/D531). TMR did not reduce the DBP (WMD = −0.34; 95% CI −3.72 to 3.05; P = .845; 3 trials; 1033 participants).

3.4.2. Cholesterol levels. There was no significant heterogeneity (I^2 = 0.0%) in cholesterol levels reported in 2 studies[14,32] with 792 patients (Supplementary Fig. 4, http://links.lww.com/MD/D532). Cholesterol levels were significantly reduced in those trials within TMR (standard mean difference [SMD] = −0.26; 95% CI −0.4 to −0.12; P = .000). Low-density lipoprotein was not associated with differences in MA (SMD −0.08; 95% CI −0.31 to 0.15; 3 trials; 1033 participants) (Supplementary Fig. 5, http://links.lww.com/MD/D533). High-density lipoprotein was also not associated with differences in MA (SMD −0.12; 95% CI −0.26 to 0.02; 2 trials; 792 participants).

3.5. Patient feedback

Patient perceptions of TM-based reminder systems were reported in 5 trials (Table 3). More than 90% of patients who received the TMR reported their satisfaction and thought the TMR was valuable; 80.6% requested continuation of the TMR. Park et al[29] reported that only 7.6% of patients experienced technical difficulties with receiving TMRs, while 88.6% strongly or moderately agreed that the text messaging feature on their mobile phone was easy to use and understand. In the study by Redfern et al,[14] 55% of patients shared messages with family, friends, and clinicians, and reported changes in the influence on motivation and behavior, including changed motivation (77.2%), healthier diet (81.1%), and increased exercise (72.6%).

4. Discussion

In this study, 6 RCTs were assessed that investigated the effect of TMR on MA in patients with CHD, demonstrating that TMR increased MA. These trials were conducted in 5 countries, including 2 developing countries. These findings indicated that TMR has great potential as a scalable and convenient tool to improve MA, since it is a primary, inexpensive and quick form of communication.[33,34] Compared with regular care, TMR not only improved MA, but also had an effect in lowering BP and cholesterol. It is worth mentioning that the effect of TMR on MA may also depend on the type of medication. Among them, antiplatelet medications are associated with the highest MA, which may be related to the increased patient awareness of the importance of taking antiplatelet drugs after myocardial infarct and/or percutaneous coronary intervention,[29] followed by statins that are generally taken in the evening instead of the morning, reflecting the pattern of mobile phone use, and finally ACEI/ARB. These findings are in accordance with those of Eagle et al who reported an 8% discontinuation rate at 6 months for aspirin, 13% for statins, and 20% for ACEI after 5 to 10 years of follow-up.[35,36,37] The cost-effectiveness analysis performed in the trials of Redfern and Ho[14,31] suggested that TMR improved MA without increasing costs. The reasons for nonadherence were addressed in 2 trials.[28,30] The factors that influence non-adherence are complex and include patient-centered factors (eg, forgetfulness, carelessness, feeling better, or worse), healthcare system factors, socio-economic factors, and therapy-related

factors. However, substantial heterogeneity existed in our analyses, including clinical heterogeneity determined by the nature of the TMR, and methodological heterogeneity due to differences in the criteria for defining the outcome indicators and the method of measurement used in each study.

At present, there are 4 main measures in the prevention of MA in patients with CHD: facilitating provider-patient communication,[38,39] providing patient education in tandem with lifestyle and behavioral management counseling,[40,41,42] providing psychosocial support,[43,44] and mobile health technology. As a potential low-cost, personalized health management system, the use of mobile health technology is receiving attention.[45,46] Mertens reported that the iPad application was more effective than a paper diary for reporting BP values and medication intake. However, it is impossible to achieve in-person home visit intervention in clinical situations.[47,48] Keyserling et al conducted a study in 5 diverse family medicine practices in North Carolina, which indicated that counselor-delivered and web-based medicine reminders improved MA and reduced CHD risk, although cost is an important factor that cannot be ignored.[38] Gallagher et al found that telephone and e-mail communication was not effective for confirming intake of the correct number of pills per dosing and one-third of participants expressed concerns about privacy and security.[49] TMR is a convenient, cost-effective method for promotion of MA, especially in rural populations, by reducing environmental barriers, which increases patient participation in disease management.[2] TMR has a unique advantage over other electronic reminders such as pagers or interactive voice reminders in that provides comparatively private support to patients.[50] Meanwhile, in 6 RCTs, the TMR was sent to the patients by short message service (SMS). However, compared with the WeChat or relative similar phone app, SMS was not so good or fast feedback as social media.

Although accumulating evidence supports the use of TMRs, many issues remain to be explored, such as the advantages of real-time medication monitoring, in which patients are sent a TMR only if they fail to take their medication on time. Fang[42] also found that MA is related to marital status, gender, age, disease history, and educational level. Women are more persistent than men. In addition, marriage has a positive effect on MA. Whether the effect of TMR varies with other participant characteristics, such as the race, insurance (private, Medicare, or others), financial resources (self-sponsored, pensioner, civil servant, recipient of welfare assistance) and remains to be established. This information will aid the development of more personalized TMR for different patients. Moreover, methods to determine whether 2-way personalized TMR is more beneficial than 1-way, and how to measure MA more objectively because subjective and objective measures of MA showed significant differences are issues that require further investigation.[50,51]

There are several limitations of this meta-analysis. First, a small number of RCTs were included and the follow-up time was short (average approximately 4 months). Therefore, long-term adherence trends or clinical outcomes were not reported. However, the risk of early in-stent thrombosis following PCI was assessed since the majority of these events occur in the first month after PCI.[52] Second, 5 trials[28,29,30,31,32] used self-reporting to measure MA, which may increase recall bias. In addition, high MA by different criteria in each study; for example, good adherence was defined as more than 95% of prescribed doses in the study by Quilici et al[28] While Khonsari et al defined it as more than 75%.[30] Finally, the time period of enrolled trials in this meta-analysis

varied substantially. For example, some followed-up 6 or 12 months, but the rest only 1 to 2 month (Table 2), which are perhaps too brief to expect significant changes in MA.

Despite these potential limitations, several strengths of this meta-analysis are notable. First, no meta-analysis of the effects of TMR on MA in patients with CHD has been reported previously. Furthermore, the included studies were conducted in different countries and regions, including Europe, South Asia, and Arab states, which may increase the external validity of the findings. In addition, we analyzed the MA for a range of drugs including statins, ACEI/ARB, β-blockers, and Clopidogrel.

5. Conclusion

This meta-analysis showed that TMR by mobile phone promoted MA for patients with CHD, and was also associated with reductions in SBP (but not DBP), body mass index, and cholesterol. Given the global prevalence of poor MA in patients with CHD, TMR should be considered as an effective method to increase MA and promote secondary prevention of CHD. Further studies with longer follow-up periods and more objective MA measurements are required to assess whether the higher MA in the intervention group translates into better clinical outcomes.

Author contributions

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Writing – original draft: Fang-Ping Dang.
Writing – review and editing: Fang-Ping Dang.

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