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Digital Health Interventions in Patient Management Following Acute Coronary Syndrome: A Meta-Analysis of the Literature

ABSTRACT

Objective: Acute coronary syndrome patients should be closely followed-up to maintain optimal adherence to medical treatments and to reduce adverse events. Digital health interventions might provide improved outcomes for patient care by providing closer follow-up, compared to standard care. Thus, in this meta-analysis, we aimed to evaluate the effect of digital health interventions on follow-up in acute coronary syndrome patients.

Methods: We searched medical databases to obtain all relevant studies comparing digital health interventions with standard care in acute coronary syndrome patients. After reviewing all eligible studies, a meta-analysis was conducted with the remaining 11 randomized controlled studies and 2 non-randomized controlled studies. A modified Jadad scale and Newcastle-Ottawa scale were used to assess the quality of the publications for randomized controlled studies and non-randomized controlled studies, respectively.

Results: This meta-analysis consisted of 7657 patients. The all-cause mortality rate was 49% lower in the digital health intervention cases, compared to those who received standard care [relative risk (RR) = 0.51 (0.37; 0.70), $P < .01$]. There was a significant decrease in systolic blood pressure in the digital health interventions group, compared to the standard care group [mean difference = -5.28 (-9.47; -1.08), $P = .01$]. The rate of nonadherence to anti-aggregant drugs was 69% lower in the digital health interventions than in the standard care group [RR = 0.31 (0.20; 0.46), $P < .01$]. Also, nonadherence rates for statin and beta-blockers were lower in the digital health interventions group. The risk of rehospitalization was observed to be 55% less in the digital health interventions patients, compared to the standard care group [RR = 0.45 (0.30; 0.67), $P < .01$].

Conclusion: Digital health interventions can be effective in follow-up for secondary prevention in acute coronary syndrome patients.

Keywords: Acute coronary syndrome, digital health intervention, meta-analysis, standard care

META-ANALYSIS

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. Acute coronary syndrome (ACS) is the life-threatening clinical manifestation of CVD, accounting for more than one-third of all deaths in developed countries each year.[1] In addition to invasive medical treatments performed during hospital stays, ACS patients should be closely followed-up because of an increased risk of morbidity and mortality during long-term follow-up. Remarkably, almost half of these deaths might be prevented by implementing appropriate strategies, such as predischarge management, counseling, and adherence assistance.

Digital health interventions (DHIs) have attracted the attention of researchers to improve the quality of patient care, particularly due to the extensive use of telemedicine during the COVID-19 pandemic, which began in 2019.[2] Mobile text message, voice messages, video clips, telephone calls, video conference, mobile applications, and smartwatches were used as DHIs in ACS patients; smartwatches

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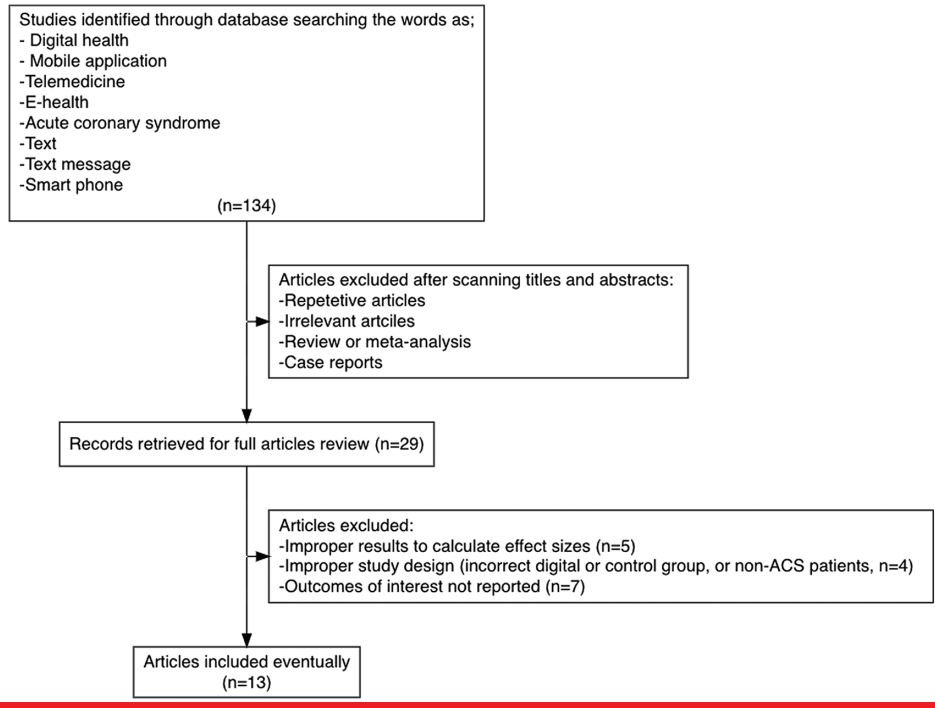

Figure 1. Flowchart of study selection for meta-analysis.

were used to get information via digital compatible devices of blood pressure monitor, heart rate recorder, devices that measure blood glucose or lipid levels, and mobile electrocardiography recorder. Previous studies found that text messaging improved compliance with guideline-based pharmacologic and non-pharmacologic recommendations in CVD patients.[2,3] Even though some studies have indicated that DHIs are associated with positive outcomes, such as improved all-cause mortality in ACS patients, there is no convincing evidence that DHIs are effective in this population.[1,3] As a consequence, a meta-analysis that included all studies was conducted to evaluate whether DHIs have beneficial effects on all-cause mortality, decreasing blood pressure, rehospitalization rates, adherence to medical treatment recommendations, and target vessel revascularization in ACS patients.

HIGHLIGHTS

- This meta-analysis consisted of 7657 acute coronary syndrome patients.
- The all-cause mortality rate and risk of rehospitalization were lower in the digital health interventions group compared with the standard care group.
- The rates of nonadherence with anti-aggregant drugs, statins, and beta-blockers were lower in the digital health interventions group, compared with the standard care group.
- This is the largest meta-analysis to date showing that digital health interventions can be effective in follow-up for secondary prevention in acute coronary syndrome patients.

METHODS

Data Collection

Our meta-analysis was performed in accordance with the guidelines of the Cochrane Collaboration. We conducted a detailed search of the PubMed, Google Scholar, EMBASE, Scopus, and Cochrane library databases using keywords such as "digital health," "mobile application," "telemedicine," "e-health," "acute coronary syndrome," "text," "text message," and "smart phone" to obtain all relevant papers. Out of 134 papers returned, 29 were selected for review, after excluding repetitive and irrelevant studies, review articles, case reports, and duplicate investigations. After reviewing the full texts of these publications, 16 were eliminated from the meta-analysis, due to improper results and research designs (Figure 1). Finally, a total of 13 studies were included in the meta-analysis (Table 1).[3-15]

Study Evaluation

Two authors independently assessed the search results and identified papers that fulfilled the following inclusion criteria: (1) studies comparing DHIs to conventional therapy in ACS patients; (2) at least one endpoint of interest, such as all-cause mortality, blood pressure, rehospitalization, adherence to medical treatment, and target vessel revascularization. There were no restrictions on sample size, follow-up duration, or language.

Quality Assessment and Data Extraction

Two reviewers independently evaluated full-text papers, performed quality assessments, and retrieved and verified the data. A third reviewer resolved any disagreements between the 2 investigators. Each study provided the following information: study design, patient demographics, and key findings. The Cochrane Collaboration guidelines' median

Table 1. All Studies Included in the Meta-Analysis

Study	Year	Study Design	DHI Sample Size	Control Sample Size	Age (DHI)	Age (Control)	Male, n (%) (DHI)	Male, n (%) (control)	Follow-Up Time	DHI Methods	Control Group	Quality Scale*
Roth et al	2009	Non-RCT	699	3899	69 (11)	63 (13)	496 (71)	2963 (76)	12 months	-Phone call -Cardio beeper -ECG transmitter	Usual care	6
Blasco et al	2012	RCT	102	101	60.6 (11.5)	61 (12.1)	83 (81.4)	80 (79.2)	12 months	-Mobile text message -Mobile app.	Usual care	5.5
Quilici et al	2013	RCT	250	249	64 (14)	64 (10)	195 (78)	187 (75.1)	3 months	-Mobile text message	Usual care	2
Rinfret et al	2013	RCT	150	150	63.4 (10)	64.3 (10)	107 (71.3)	112 (74.7)	12 months	-Phone call	Usual care	5
Ho et al	2014	RCT	122	119	63.8 (9.3)	64 (8.6)	120 (98.4)	116 (97.5)	12 months	-Phone call -Mobile text message -Voice message	Usual care	5
Khonsari et al	2015	RCT	31	31	56 (11.3)	59 (13.9)	27 (87)	26 (83.9)	30 days	-Mobile text message	Usual care	5
Pandey et al	2017	RCT	17	16	64.6 (11.5)	62.1 (11)	6 (35.3)	14 (87.5)	12 months	-Mobile text message	Usual care	6
Kamel et al	2021	RCT	100	100	56.2 (9.3)	55.8 (11.2)	73 (73)	70 (70)	3 months	-Video conference	Usual care	5
Varnfield et al	2014	RCT	53	41	54.9 (9.6)	56.2 (10.1)	48 (91)	34 (82.9)	6 months	-Video conference -Mobile text message -Video clips	Usual care	5
Wolf et al	2016	RCT	37	57	59.8 (10.1)	60.9 (8.7)	30 (81)	41 (71.9)	6 months	-Mobile app.	Usual care	3
Marvel et al	2021	Non-RCT	200	864	59.2 (11.5)	65.4 (14.1)	142 (71)	528 (61.1)	30 days	-Mobile app. -Smartwatch app.	Usual care	5
Ross et al	2021	RCT	32	37	59.5 (9.1)	61.1 (9.6)	27 (84.3)	28 (75.7)	60 days	-Mobile text message	Usual care	6.5
Treskes et al	2020	RCT	100	100	59.7 (10)	59 (8.8)	81 (81)	75 (75)	12 months	-Mobile app. -Video conference -Smartphone compatible devices	Usual care	6.5

*Modified Jadad scale was used for RCTs and Newcastle-Ottawa scale was used for non-RCTs.
DHI, digital health intervention; RCT, randomized controlled trial, ECG, electrocardiography.

and interquartile ranges or CIs were used to calculate the mean and standard deviations for the variables of interest. The quality of the randomized controlled trials (RCTs) was assessed using a modified Jadad scale. The Newcastle-Ottawa standard evaluation scale was used to assess the quality of the observational cohort studies included in this review. Studies could be assigned up to 9 points on that scale, based on their participants, consistency, and results of interest. A Newcastle-Ottawa scale score of 0 to 5 indicated poor quality, whereas a score of 6 to 9 suggested high quality. A modified Jadad scale was calculated to assess the quality of RCTs in this meta-analysis. To assess the bias risks of RCTs and non-randomized studies, the RoB2 and ROBINS-I risk of bias tools, as described in the *Cochrane Handbook for Systematic Reviews*, were, respectively, applied (Figure 2).

Clinical Outcomes

This meta-analysis focused on all-cause mortality, decreased blood pressure, rehospitalization, adherence to medical therapy, and target vessel revascularization in ACS patients receiving either DHIs or standard treatment.

Statistical Analysis

All statistics were calculated using R software v.3.6.3 (R Statistical Program, Institute for Statistics and Mathematics, Vienna, Austria). The "metabin" and "metacont" functions in the "meta" package were used to evaluate pooled risk ratios and mean differences between the comparison groups with 95% CIs. To assess each study's heterogeneity, the Higgins I^2 and Cochran's Q tests were performed. In the event of moderate to high heterogeneity ($I^2 > 25\%$), the pooled effect size was calculated using the random effect model, and in the case of low heterogeneity ($I^2 < 25\%$), the fixed-effect model was applied. Due to the presence of fewer than 10 studies for each outcome, Egger's regression test and the Funnel plot were not used to assess potential publication bias. Subgroup analyses were used to compare the effect differences between follow-up times and the studies that used older or newer technologies. A 2-tailed *P*-value of $< .05$ was accepted as an indicator of statistical significance.

RESULTS

Studies' Baseline Characteristics

The meta-analysis included a total of 13 studies [2 cohorts[4,13] and 11 RCTs[3,5-12,14,15]] comparing digital and standard follow-up of patients after ACS. The total number of patients was 7657, with male predominance (5709, 74.6%). There were 1893 patients in the digital group and 5764 patients in the standard group. The mean age in the digital group was 63.3 (11.9), whereas it was 63 (12.8) in the standard group. In the digital group, 34.4% had diabetes mellitus (DM), 64.7% had hypertension (HT), 13.2% had heart failure (HF), 43% had hyperlipidemia, 36.3% had previous coronary artery disease (CAD), 9% had a past cerebrovascular event (CVE), and 41.8% were current smokers. In the standard group, 33% had DM, 57.7% had HT, 12.8% had HF, 51.9% had hyperlipidemia, 25.3% had previous CAD, 6.8% had a past CVE, and 35% were current smokers.

Figure 2. Risk-of-bias assessment for studies in the meta-analysis: RoB-2 (A) and ROBINS-I (B) tools.

Quality and Risk of Bias

In general, the quality of the studies was at an acceptable level. There were 2 RCTs with a modified Jadad score lower than 5 points, indicating poor quality (Table 1).[6,12] The RoB2 tool demonstrated that 9 of 11 RCTs had some concerns, due to bias arising from the randomization process and the lack of blinding in those studies[1,5-7,9,10,12,14,15] (Figure 2A). The ROBINS-I tool showed that the study conducted by Marvel et al might have had a serious risk of bias, due to the occurrence of a confounding risk (Figure 2B).[13]

Outcomes

The all-cause mortality rate was 49% lower in the digital follow-up patients, compared to the standard follow-up group (RR = 0.51 [0.37; 0.70], $P < .01$). There was a significant decrease in systolic blood pressure in the digital group, compared to the standard group (mean difference = -5.28 [-9.47; -1.08], $P = .01$). However, a similar difference was not observed for diastolic blood pressure ($P = .63$) (Figure 3). The rate of nonadherence to antiaggregant drugs was 69% lower in the digital group than in

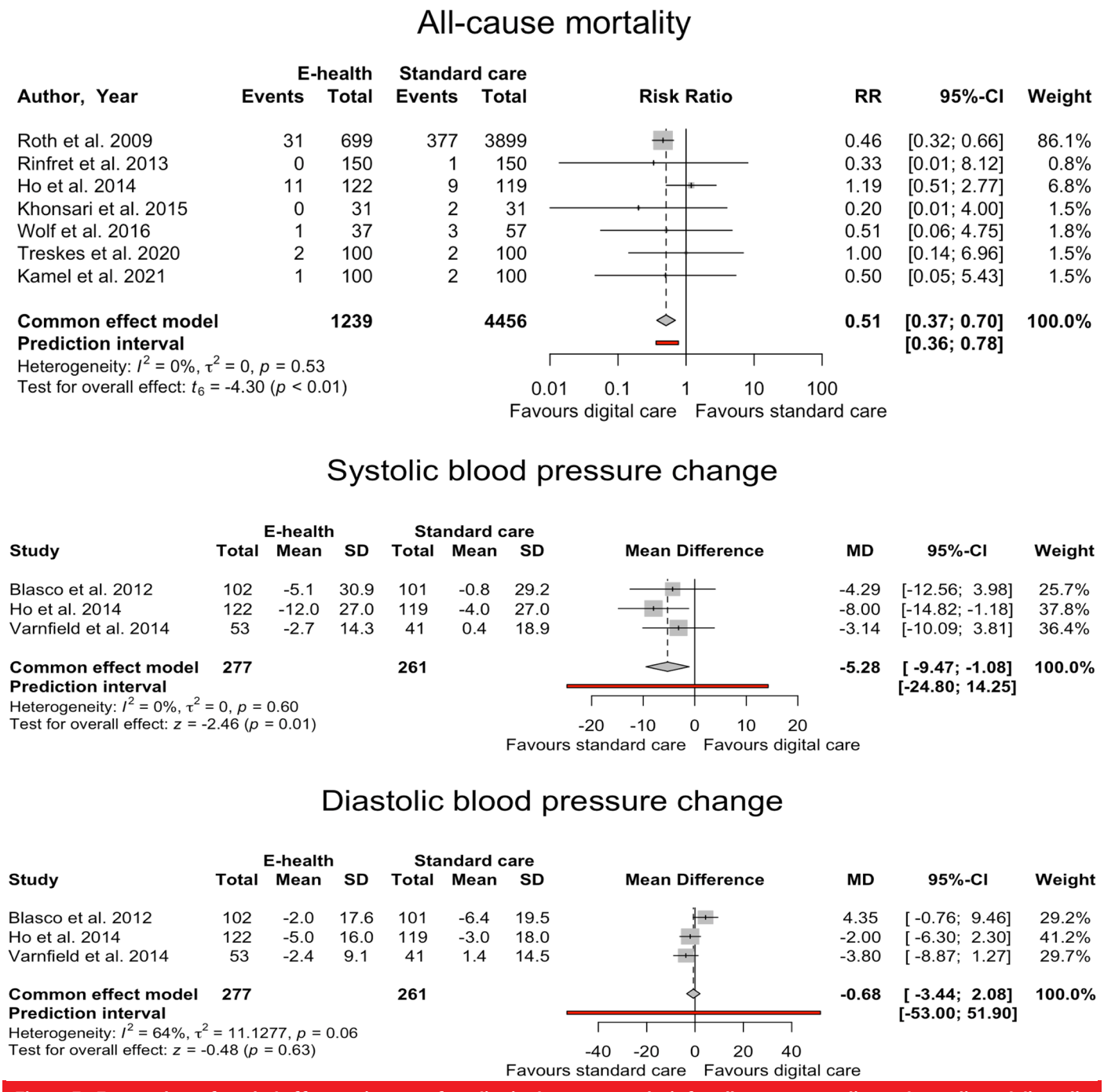

Figure 3. Forest plots of pooled effect estimates of studies in the meta-analysis for all-cause mortality and systolic and diastolic blood pressure changes.

the standard group (RR = 0.31 [0.20; 0.46], $P < .01$). The nonadherence rate for statin therapy was 63% lower in the digital group, compared to the standard group (RR = 0.37 [0.26; 0.83], $P < .001$, $I^2 = 51\%$). The digital group had a 51% lower risk of nonadherence for statin therapy than the standard group (RR = 0.49 [0.31; 0.79], $P = .004$, $I^2 = 57\%$). The risk of rehospitalization was observed to be 55% less in the digital group, compared to the standard group (RR = 0.45 [0.30; 0.67], $P < .01$). Finally, there was no significant difference between the 2 groups in terms of target vessel revascularization ($P = .14$) (Figure 4). Subgroup analyses showed no differences between follow-up times for all-cause mortality, rehospitalization, target vessel revascularization, and drug nonadherence (Supplementary Figures 1-4). When the studies using older and newer technologies of DHIs were compared, there were no differences between subgroups with respect to the above-mentioned outcomes (Supplementary Figures 5-8).

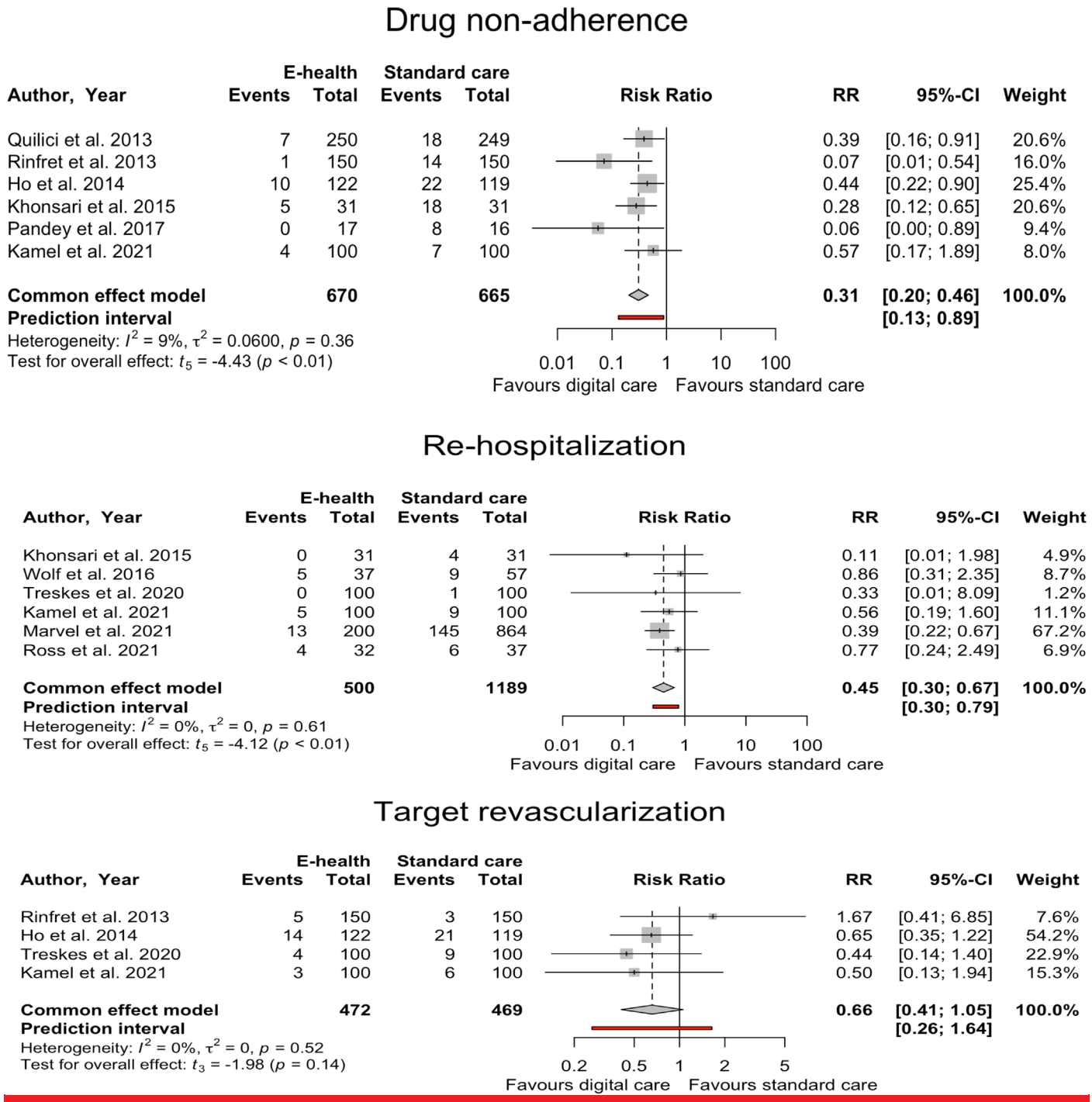

Figure 4. Forest plots of pooled effect estimates of studies in the meta-analysis for drug nonadherence, rehospitalization, and target revascularization.

DISCUSSION

In this meta-analysis, DHIs were demonstrated to be effective for reducing all-cause mortality, systolic blood pressure, drug nonadherence, and rehospitalization following ACS, when compared to conventional follow-up methods. However, no statistical difference was detected between conventional follow-up and DHIs in terms of diastolic blood pressure change and the frequency of target vessel revascularization.

Digital health interventions have already presented important contributions to healthcare system regarding primary prevention.[16,17] In particular, smartphone applications have shown promising effects on daily life by simultaneously reducing different types of cardiovascular risk factors in large cohorts.[17,18] Digital health interventions have also been proven to be game changers in the secondary prevention of CVDs, which was as expected, given that primary prevention always appears to be more challenging, compared to secondary prevention, in the management of CVDs.[19] The endpoints, such as all-cause mortality and rehospitalization, can be more achievable in RCTs of secondary prevention; thus, the effect of DHIs in patients with ACS is easily testable. Therefore, meta-analyses addressing the effects of DHIs in patients with ACS may provide a pathfinder effect on the routine use of DHIs in CVD management.

Different DHI methods were used in the studies included in this meta-analysis. A phone call method was used in 3 of 13 studies providing counseling in terms of drug adherence, medication problems, or adverse events of drugs.[4,7,8] A mobile text message strategy was used in 7 of 13 studies presenting the records of patients regarding the blood pressure, heart rate, serum glucose and lipid levels, step counts, and weight scale to cardiologists or healthcare professionals (HCPs). Additionally, it enabled patients to take their medications and exercise regularly by sending remainder messages or informing the risk factors of heart attack in a systematic way[3,5-9,11,14] Video conferences were arranged with patients to determine plans and goals, check for symptoms of patients and drug adherence, and control the need of laboratory analysis in 3 of 13 studies.[10,11,15] Lastly, a mobile application was used in 4 of 13 studies and it gathered the data of the physical activity, blood pressure measurements, heart rate, electrocardiograms, body weight, self-rating scale of symptom for HCPs, and helped patients to manage their medications, gave information about the risk factors of ischemic heart diseases via a telephone or a smartwatch.[5,12-15] The recent studies were designed with more updated technologies, such as digital recorders, video conferences, mobile applications, and smartwatches instead of mobile text message or telephone calls. However, we could not find any differences in endpoints between studies using older or newer DHI technologies.

Decreases in systolic blood pressure measurements, drug nonadherence, and rehospitalization are strictly connected factors that impact all-cause mortality.[20,21] There are 2 important points that potentially address the positive effects of DHIs in the follow-up patients with ACS. Systolic blood pressure and drug adherence are modifiable variables in patient follow-up; however, the sustainability of this modification affects the durability of the positive effects of DHIs.[22] The emotional power of DHIs on patient motivation and the curiosity arousal among patients using DHIs may be the underlying reasons that play a role in affecting the aforementioned factors, according to the results of our meta-analysis.[23] It can also be interpreted that long-term follow-up of ACS patients with DHIs has also provided significant data about the sustainability of the positive effects of DHIs. However, the studies reported by Roth et al[4] and Marvel et al[13] had a higher influence in the pooled effect sizes for all-cause mortality and rehospitalization in this meta-analysis, respectively. Due to the inclusion of relatively higher population in these 2 studies compared to others, the results were mainly driven by these 2 studies for the outcomes, which could be determined by weights. Thus, more RCTs with a larger sample size could give more precise results in further investigations.

Digital health interventions have not been found to reduce the frequency of target vessel revascularization in the follow-up of patients with ACS. Non-modifiable factors, such as variables in the intervention, age, and gender, have been proven effective in predicting target vessel revascularization.[24,25] Digital health interventions have similar results for target vessel revascularization, compared to conventional methods, which also demonstrates the importance of non-modifiable risk factors.

The content and software of DHIs support the collaboration of patients and clinicians, as they allow frequent updates according to the needs of the partners. A well-designed DHI system may help to reduce major adverse cardiac events following ACS according to the results of our meta-analysis. Further randomized studies are warranted to emphasize the role of DHIs in the management of patients with ACS. There is significant potential for the routine use of DHIs in the secondary prevention of CVDs.

Study Limitations

There are several limitations to our meta-analysis. First, there was a limited number of studies comparing DHIs and conventional follow-up in patients with ACS. However, all the reported studies were included in this meta-analysis, in order to reach more precise results. Second, since we were unable to analyze individual-level patient data, neither subgroup analyses nor meta-regressions could be performed to evaluate the impact of potential confounders. Third, there are notably different DHI systems among the reported studies in this issue. Standardizing DHI strategies is a subject of ongoing debate.

CONCLUSION

Digital health interventions might have beneficial effects on follow-up for secondary prevention in ACS patients.

Ethics Committee Approval: Ethics committee approval and informed consent were not needed since this was a meta-analysis of the literature.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.Ş., T.Ç., M.İ.H.; Design – F.Ş., T.Ç., M.İ.H., A.İ.T.; Supervision – M.İ.H., A.İ.T.; Funding – F.Ş., M.İ.H., A.İ.T.; Materials – T.Ç., M.İ.H.; Data Collection and/or Processing – F.Ş., T.Ç.; Analysis and/or Interpretation – F.Ş., T.Ç.; Literature Review – F.Ş., T.Ç.; Writing – F.Ş., T.Ç., M.İ.H.; Critical Review – F.Ş., T.Ç., M.İ.H., A.İ.T.

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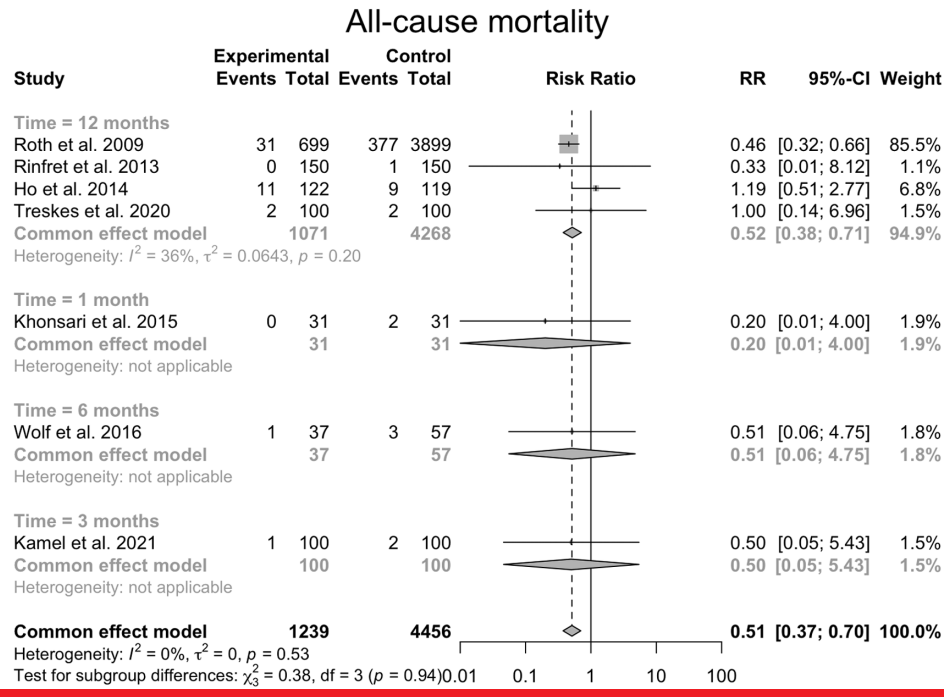
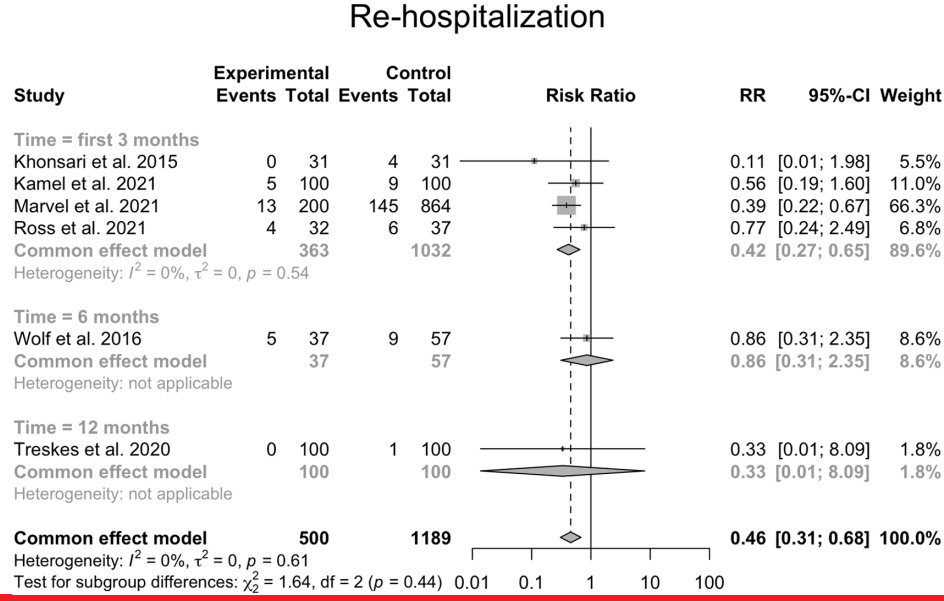
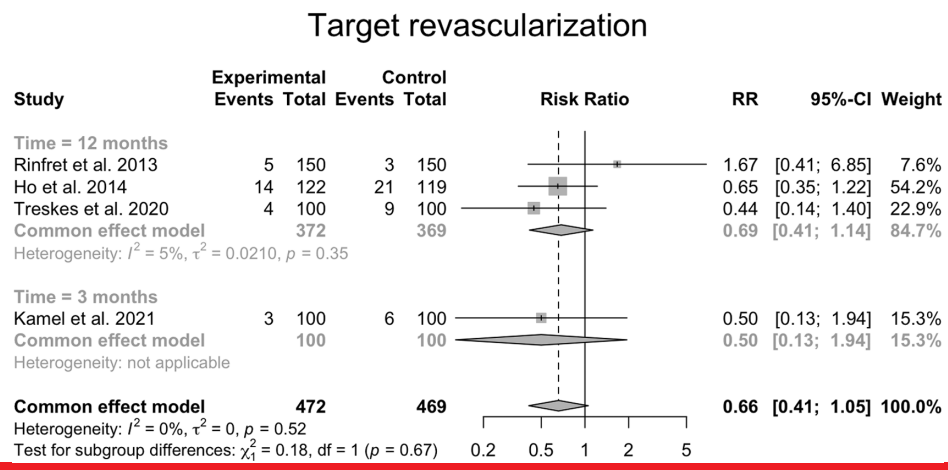


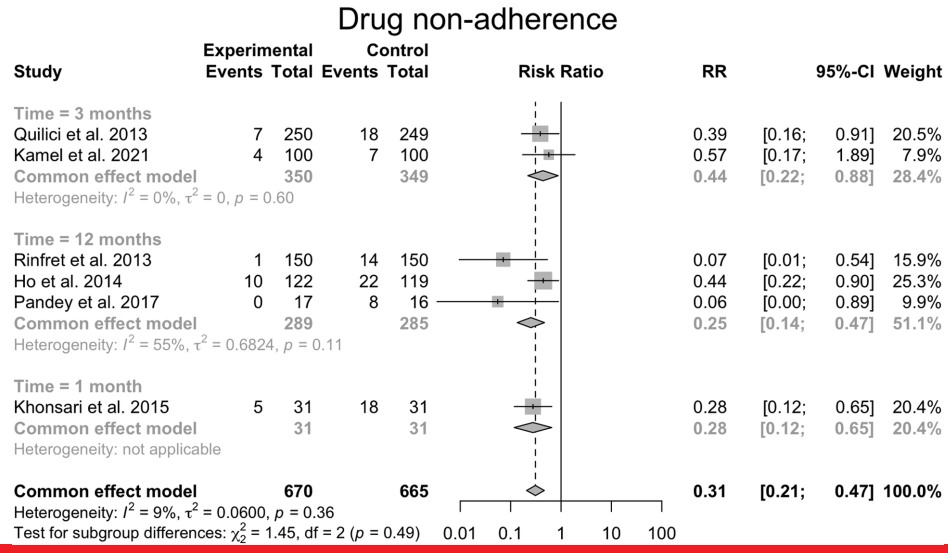
Supplementary Figure 1. Subgroup analysis of all-cause mortality according to follow-up times.



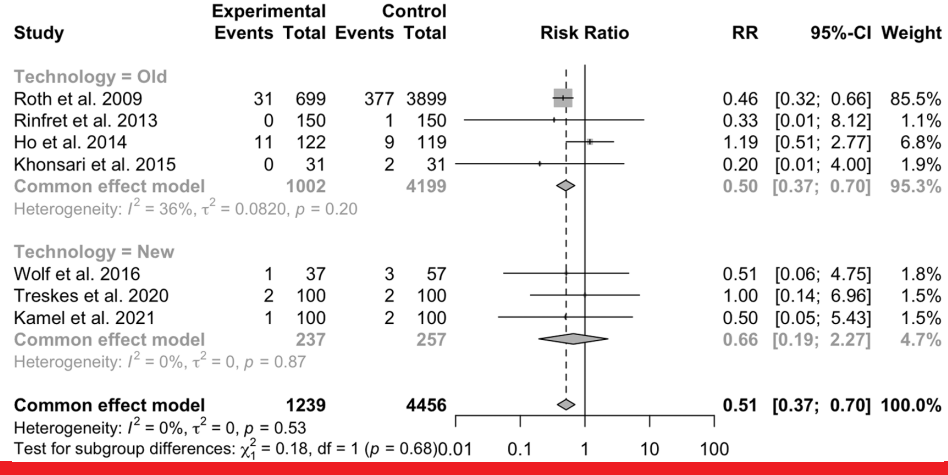
Supplementary Figure 2. Subgroup analysis of re-hospitalization according to follow-up times.



Supplementary Figure 3. Subgroup analysis of target revascularization according to follow-up times.

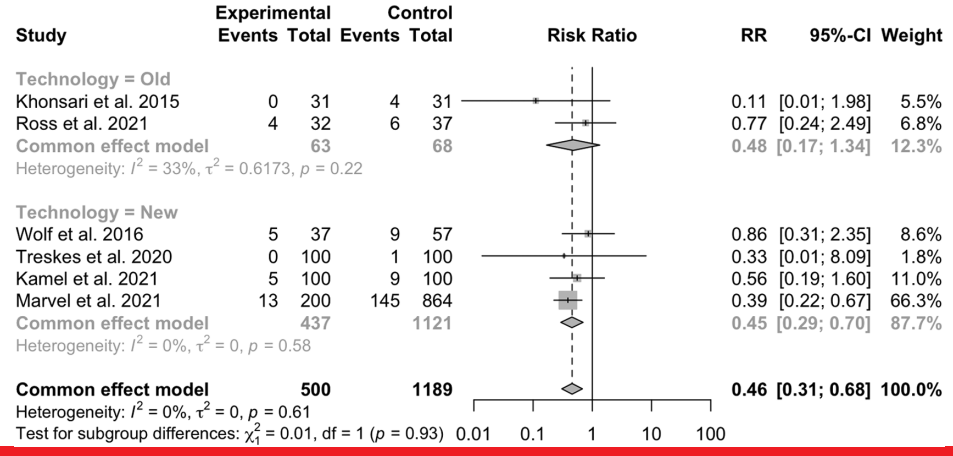


Supplementary Figure 4. Subgroup analysis of drug non-adherence according to follow-up times.



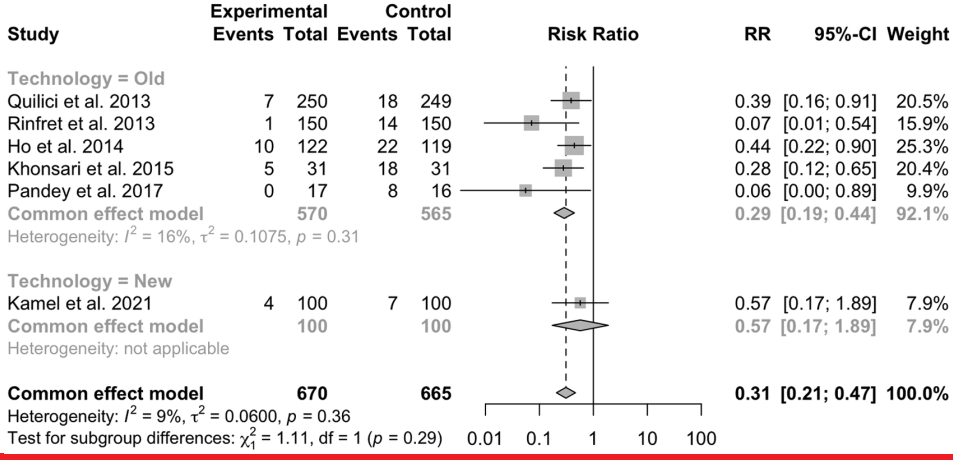
Supplementary Figure 5. Subgroup analysis of all-cause mortality according to technology types.

Re-hospitalization



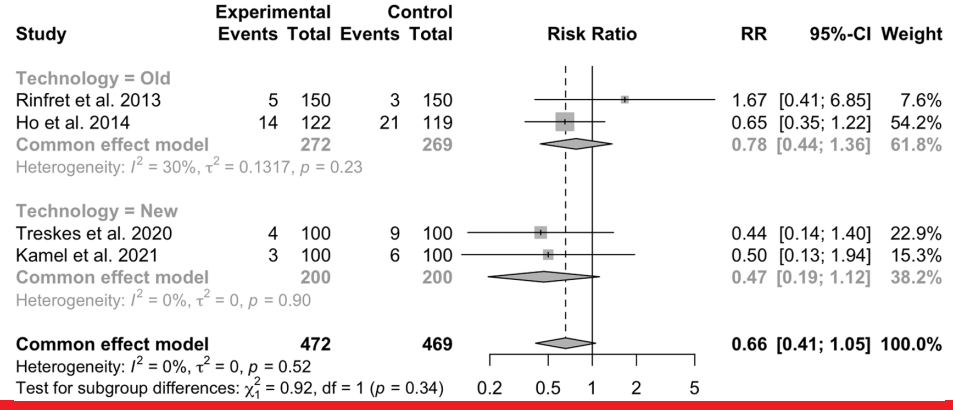
Supplementary Figure 6. Subgroup analysis of re-hospitalization according to technology types.

Drug non-adherence



Supplementary Figure 7. Subgroup analysis of drug non-adherence according to technology types.

Target revascularization



Supplementary Figure 8. Subgroup analysis of target revascularization according to technology types.