Cluster randomized controlled trial of Delayed Educational Reminders for Long-term Medication Adherence in ST-Elevation Myocardial Infarction (DERLA-STEMI)

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Background Discontinuation of guideline-recommended cardiac medications post–ST-elevation myocardial infarction (STEMI) is common and associated with increased mortality. DERLA-STEMI tested an intervention to improve long-term adherence to cardiac medications post-STEMI.

Methods and Results Between September 2011 and December 2012, STEMI patients from one health region in Ontario, who underwent an angiogram during their admission and survived to discharge, were cluster randomized (by primary care provider) to intervention or control. The intervention was an automated system of personalized, educational-reminders sent to the patient and their family physician, urging long-term use of secondary-prevention medications. Interventions were mailed at 1, 2, 5, 8, and 11 months after discharge. A total of 852 eligible participants were randomized to intervention (n = 424, 287 clusters) and control (n = 428, 295 clusters); 87% completed a 12-month follow-up. The *primary outcome*, defined as the proportion of participants taking (persistence) all 4-cardiovascular medication classes (acetylsalicylic acid, angiotensin blockers, statin, and β-blocker) at 12 months, was 58.4% (intervention) and 58.9% (control; adjusted odds ratio 1.03, 95% CI 0.77-1.36). Medication adherence, as assessed by the Morisky Medication Adherence Score, was statistically significantly better in the intervention group as compared with control (65.3% vs 58.0%, adjusted odds ratio 1.35, 95% CI 1.01-1.81).

Conclusion The results suggest suboptimal use of 4 of 4 cardiac medication classes at 12 months. There was no significant difference compared with usual care in the persistence to guideline-recommended medications post-STEMI when participants (and their family physicians) receive repeated postal reminders. (Am Heart J 2015;170:903-13.)

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ST-segment elevation myocardial infarction (STEMI) is a common presentation of acute coronary syndromes, constituting approximately 30% of all cases.[1] Post-STEMI, patients are at high risk for subsequent cardiac events (18% of men and 35% of women will have a repeat MI within 6 years).[2] International guidelines emphasize the initiation and long-term maintenance of evidence-based secondary preventative therapies.[3-5] Despite strong evidence supporting these guidelines, studies show that adherence to evidence-based cardiac therapies begins decreasing at 30 days and falls to as low as 50% adherence at 6 months after discharge.[6-11] Unfortunately, discontinuation (ie, nonpersistence) of evidence-based therapies is associated with increased mortality in patients with coronary artery disease (CAD).[12-15]

A recent study conducted by the authors evaluating adherence to cardiac secondary prevention medications in patients in whom CAD was evident during angiography demonstrated 4 key findings.[11] First, there is poor persistence of cardiac medications among such patients

in the province of Ontario. Despite all patients having a class IA indication for the selected classes of medications (β-blockers [BBs], statins, and angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin receptor blockers [ARBs]), and all patients having full medication coverage for financial costs (all patients ≥65 years old) and medication use steadily declined to approximately 60% by 18 months after coronary angiogram.[11] Second, poor adherence was consistent across all subgroups of patients, highlighting the need for broad, population-based interventions to promote persistence of cardiac secondary prevention medications. Third, there are vulnerable periods, likely coinciding with the need for prescription refills, during which premature medication discontinuation is most likely to occur. Finally, longer initial prescriptions of cardiac medications were associated with greater medication persistence, presumably by obviating barriers to medication refills.

Numerous studies have been published regarding interventions to improve adherence to medications. Two trials evaluated the role of reminder letters to the primary care provider (with or without patient reminders) to improve adherence to evidenced-based cardiovascular therapies[16,17] demonstrating an absolute increase in statin prescribing of 7% to 10%, but were underpowered for effects of that size. One trial demonstrated improved adherence to BB therapy post-MI, with 2 reminders sent to the patient.[18] Recognizing that nonadherence tends to worsen over time, a recent Cochrane review recommended testing a delayed intervention as opposed to the immediate reminders used in similar previous trials, as one would expect a larger effect size in a delayed intervention.[19] This is especially relevant for postcardiac care because most patients receive an initial prescription at the time of their STEMI. Therefore, DERLA-STEMI was designed to evaluate the effects of delayed and repeated educational reminders on the proportion of participants who demonstrate persistence at 12 months to evidence-based secondary prevention medications.

Methods

Study design

DERLA-STEMI is a pragmatic, cluster-randomized controlled trial, conducted at a single tertiary care center that services 22 hospital sites in one health region (population: 1.5 million) in Ontario, Canada. Details of the study protocol have been previously published.[20]

Participants and Setting

Eligible participants included adult participants with a diagnosis of STEMI, who underwent a coronary angiography procedure, with or without percutaneous coronary intervention (PCI), and who were discharged alive.

Intervention

The intervention was developed in concert with clinical experts from both primary care and cardiology as well as experts in knowledge translation and medical decision making. It consisted of personalized letters (patient name and place and date of MI) sent via the post to the patient and their family physician at 1, 5, 8, and 11 months after their angiogram, signed by an interventional cardiologist on behalf of all invasive and interventional cardiologists from the PCI center. The patient letter provided a review of the importance and role of each evidence-based cardiac medication and urged long-term adherence (Appendix 4-3). The intervention explicitly encouraged discussion of medication adherence with the family physician by asking participants to take the letter to their family physician. It also asked participants to take the final page of their letter to their pharmacist; this page urged pharmacists to participate in promoting long-term adherence. A brief reminder postcard was also mailed to the patient at 2 months (Appendix 4-2). The patient letter used principles of plain language targeted at a grade 6 reading level. The intervention was developed iteratively, using "think-aloud" interviews with a series of cardiac care inpatients to ensure that the letter was both understandable and acceptable.[21] The letter for the family physician identified the patient and provided brief evidence in support of long-term medication use (Appendix 4-4). This was refined based on discussions with family physicians from a different area of the province.

The timing of the intervention was specifically chosen based on data indicating that discontinuation can occur within 30 days and continues in an almost linear fashion.[11] This may be because the common practice in Ontario is for pharmacists to dispense medications for no more than 3 months at a time (regardless of duration of the prescription ordered by the physician). Therefore, we decided to deliver the intervention at regular intervals (1, 5, 8, and 11 months post-STEMI), ensuring that the participant and physicians will receive the reminders prior to the likely periods that a prescription renewal/refill is required (3, 6, 8, and 12 months). Participants received an added reminder postcard at 2 months, given that the first 3 month period is the most vulnerable time for medication discontinuation.[11]

Control/Usual care

The control group did not receive any intervention. In keeping with the pragmatic nature of the trial, no attempt was made to standardize the usual care arm.

Outcomes

The primary outcome was the proportion of participants who describe taking a statin, BB, angiotensin blocker (ACEI or ARB), *and* acetylsalicylic acid (ASA) at 12 months (4 of 4 medication classes). "Taking" is defined as a participant who reports that he/she has a current prescription for the given cardiac medication and verbally confirms that he/she is actively using the said medication at the time of outcome assessment. This definition does not address day-to-day adherence or

participants who stop and start medications prior to the outcome assessment, but captures nonpersistence or discontinuation of medication, which is the most severe form of nonadherence. We also assessed whether participants were taking these 4 medication classes *plus* a secondary antiplatelet (clopidogrel, prasugrel, or ticagrelor) at 3 months (5 of 5 medication classes). Additional secondary outcomes included a comparison of (1) the proportion of participants who report actively taking each cardiac medication class of interest (item-by-item) at 3 and 12 months, (2) proportion of participants taking high dose statins at 3 and 12 months (defined as rosuvastatin 20-40 mg, atorvastatin 40-80 mg or simvastatin 80 mg), (3) the proportion taking 3 medication classes concurrently at 3 and 12 months (3 of 4 medication classes), (4) the proportion of participants who report stopping medications due to adverse effects at 3 months, (5) the proportion of participants with a perfect Morisky Medication Adherence Score (MMAS) for cardiac medication adherence is at 3 months[22] (a perfect score is a "no" to all 4 items on the MMAS), and (6) whether participants had discussed their medications with their family physician or specialist in the first 3 months after hospital discharge.

Baseline patient characteristics were obtained from standard patient-registry information. Outcomes were assessed through structured telephone calls to the participant by a blinded research coordinator, following a previously published approach.[23]

Allocation and blinding

The randomization schedule was computer generated, using a permuted block design with randomly varying block lengths of 4, 6, or 8. Eligible participants were randomly allocated 1:1 to intervention or control. Randomization was carried out to ensure that once a patient from any family physician was randomized, all future participants seen by that family physician were automatically assigned to the same arm to avoid contamination (with individual family physicians having participants in different arms of the study). Participants without a family physician at the time of randomization were enrolled and evaluated as independent subjects. Randomization was delayed by 1 week after the index angiogram to permit time to identify and exclude patients with early in-hospital death. Randomization continued until the target sample size was achieved. The allocation sequence (individual participants and clusters) was concealed from the investigators and outcome assessors; only the study coordinator who sent out the letters had access to the unblinded allocation list.

Ethics

Local research ethics board approval was received (No. 11-191). Given the low risk nature of the intervention, which falls within the realm of continuity of care and circle of care, the research ethics board agreed that verbal consent at the time of outcome assessment was the most appropriate design to test this pragmatic intervention.

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Statistical analysis

Baseline characteristics for participants in the intervention and control arms were described using means and SDs, or frequencies, and percentages as appropriate. Outcomes at discharge, 3 months, and 12 months were analyzed using hierarchical logistic regression analyses accounting for clustering by family physician and correlations due to repeated measures on the same patient over time. Time (measured as a categorical variable) and the interaction between group and time were included as fixed effects, whereas the family physician and the patient were specified as random effects. The intervention effect was estimated as adjusted odds ratios (ORs) with 95% CIs. The following prespecified baseline covariates were included as fixed effects: age <5 years; history of CAD; history of diabetes; medications prior to admission that includes ASA, any secondary antiplatelets (clopidogrel or other antiplatelets), ACEI/ARB, BB, and statins; in-hospital blood transfusion; renal insufficiency, defined as creatinine clearance ≤0 mL/min[24]; and participant enrolment in the TOTAL trial.[25] These covariates were included in the model, regardless of statistical significance, as they were considered to be important predictors of medication use at follow-up. We dichotomized age, as participants 5 years or older in Ontario have full medication insurance, and cost of medications can therefore be a factor in those younger than 65 years. Younger age has also been associated with medication nonadherence, regardless of costs.[26,27] Comorbidities, including a history of CAD and diabetes, as well as prior medication use can influence future medication adherence.[27-29] Peri-ACS blood transfusions and renal dysfunction can limit future use of secondary preventative medications.[30,31] Finally, some DERLA-STEMI participants were also enrolled in the TOTAL trial.[25] The TOTAL trial evaluated the impact of thrombectomy at the time of primary PCI, and the authors were concerned that the close follow-up of participants in TOTAL could have influenced medication use.[25] For hierarchical models that yielded negative

variance estimates for the family physician random effects, the intracluster correlation coefficient was assumed to be 0, and models were reestimated using generalized estimating equations accounting for correlation in repeated measures on the same patient using an unstructured correlation matrix.[32]

Secondary outcomes were analyzed, cross sectionally using generalized estimating equation, accounting for clustering by family physician using an exchangeable correlation structure. Several post hoc subgroup analyses were conducted in an attempt to explore potential mechanisms underlying the trial results relating to 2 intermediate outcomes: attendance to a cardiac rehabilitation program and participant discussion of their medications with a specialist. These postrandomization variables were not included as covariates in the multivariable analysis of the primary outcome as the intervention recommended attendance to cardiac rehabilitation and encouraged discussions regarding their medications with their specialist. As per recommendations for handling postrandomization variables, these variables were treated as outcomes and regressed on baseline covariates to identify potential subgroup analyses for the primary outcome.[33] Each subgroup analysis was conducted by including 2- and 3-way interactions with the subgroup variable terms in the hierarchical model for the primary outcome.

We performed all analyses using SAS, version 9.2 (Cary, NC) for UNIX, and statistical significance was assessed at the 5% level.

Sample size

The sample size required for this trial was 815 participants to achieve 80% power to detect a difference at the 5% significance level between intervention and control arms at 12 months, assuming 80% follow-up, an absolute increase in the proportion of participants taking all 4 cardiovascular medication classes of 11%; an estimated control group proportion of 50%; and a variance inflation factor of 1.02. The variance inflation factor assumed an intracluster correlation coefficient of 0.019, calculated from data in the hospital registry and an average cluster size of 1.2, based on pilot data.[20] Descriptive data were reviewed at 3 months as part of an ongoing STEMI registry that was previously underway.[34]

Validity of outcome assessment

One hundred five consecutive participants 65 years and older underwent assessment of the accuracy of the self-reported primary outcome (persistence with medications). Their medication lists were compared against their prescriptions filled as reported in the Ontario Drug Benefit database. Most patients younger than 65 years are not captured in this provincial drug database, and therefore, the accuracy of the self-reported primary outcome in this population could not be ascertained.

Process evaluation

A 20% random sample of participants in the intervention group was asked a series of additional, structured questions at the time of outcome assessment. This process evaluation was elicited after the outcome data were obtained and was designed to describe the acceptability of the intervention and the reasons for any (lack of) action taken. The answers to these questionnaires were summarized descriptively.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

Between September 2011 and December 2012, 852 participants from 466 family practices were randomized to intervention (n = 424, 287 clusters) and control (n = 428, 295 clusters; mean cluster size 1.49, variance 0.91) (Figure 1). One hundred six participants were randomized without a family physician. Recruitment ceased when the sample size was achieved. A total of 361 (85%) participants in the intervention arm and 380 (89%) in the control arm completed a 12-month follow-up.

Baseline characteristics of participants who underwent randomization are presented in Table I. The 2 groups were well balanced, with a mean age of approximately 63 years, 29% female, 19% with a Killip class 4, and 77% undergoing primary PCI. The intervention group had a higher proportion of diabetic patients (26.4% vs 18.9%), participants with a history of atrial fibrillation (5.9% vs 3.5%), and blood transfusions in hospital (5.2% vs 3.7%).

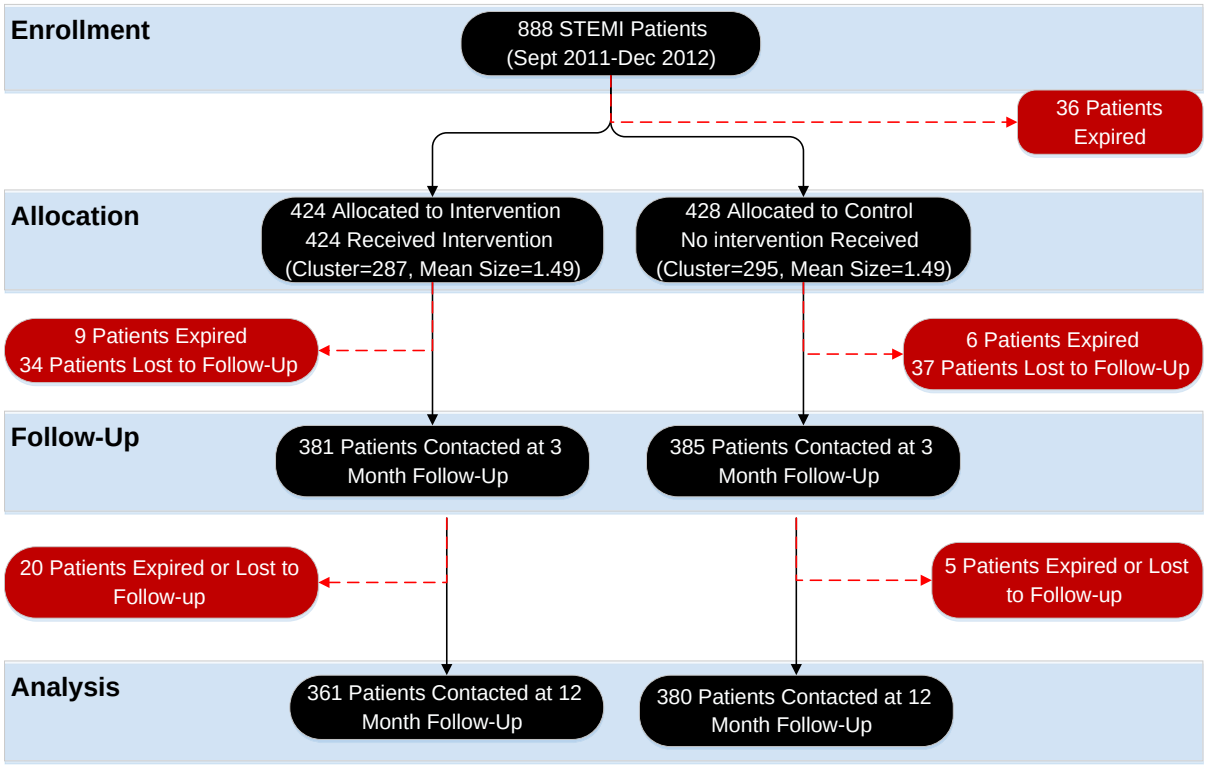
Primary outcome

The proportions taking 4 of 4 medication classes at discharge were 73.6% and 75.5% in intervention and control arms, respectively. At 12 months, observed proportions persistent with 4 of 4 medications were 58.4% and 58.9% in the intervention and control group, respectively (unadjusted ORs 1.01 [95% CI 0.76-1.32] and 1.03 [95% CI 0.77-1.36]) (Table II). In-hospital blood transfusion and renal dysfunction were the only variables found to be statistically significantly associated with discontinuation: both decreasing the odds of persistence. Figure 2 highlights the low baseline use of cardiac medications before their STEMI, despite 84% of the study population having a history of cardiovascular disease or a significant cardiac risk factor. At discharge, there is a marked increase in the prescription of evidence-based cardiac medications in both groups, with declining persistence over time: at 12 months, the odds of persistence to 4 of 4 cardiac medications (ASA, BB, ACEI/ARB, and statin) combined across groups was only 0.47 relative to baseline (95% CI 0.39-0.56).

Secondary outcomes

There were no significant differences between the intervention and control groups with respect to

Figure 1



Flow diagram of progress of clusters and individuals through phases of randomized controlled trial.

the persistence to 5 of 5 medications at 3 and 12 months (Table III). Although there were no statistically differences in the persistence to ASA, BB, ACEI/ARB, or statins (high or low dose) at 12 months, there was an increased trend in the proportion of participants in the intervention group taking a second antiplatelet at 1 year compared with control (68.1% vs 62.1%, OR 1.36, 95% CI 0.99-1.85). Medication adherence, as assessed by the MMAS, was significantly better in the intervention group as compared with control (65.3% vs 58%, adjusted OR 1.35, 95% CI 1.01-1.81).

Table IV highlights that there appears to be increased discussions of their medications with their health care providers in the intervention group (81% vs 78%), but this was not statistically significant (OR 1.60, 95% CI 0.94-2.74). There was a decreased attendance to cardiac rehabilitation in the intervention (36.2%) vs control group (43.5%; OR 0.76, 95% CI 0.56-1.03). The variables age (<65 vs ≥65 years), history of CAD, blood transfusion, and participation in the TOTAL trial were significantly associated with attendance at cardiac rehabilitation, whereas age (<65 vs ≥65 years) alone was associated with participants discussing their medications with their specialist.

Table V presents the results from the subgroup analyses. Although differences were not statistically significant, we found that the treatment effect reversed direction across some subgroups; most notably, among patients younger than 65 years, there was a trend toward increased adherence due to intervention (OR 1.5, 95% CI 0.93-2.41) compared with decreased adherence among those older than age 65 (OR 0.73, 95% CI 0.42-1.28, *P* value for difference = .056).

Participants in both groups reported that discontinuation of medication was most commonly at the direction of the internist/cardiologist (9.5% intervention and 7.4% control, *P* = .29). Medication-related adverse effects was the most common cause for medication discontinuation (9.5% intervention and 6.6 % control, *P* = .83).

Validation of self-reported outcome

Validation of the self-reported primary outcome revealed that 98%, 93%, and 97% of participants that reported they were actively taking a statin, BB, and/or ACEI/ARB at 12 months, respectively, had medication prescriptions filled from their pharmacy at the time of outcome assessment.

Process evaluation

Of the 91 participants surveyed in the intervention group, only 46 (51%) recalled receiving the reminders.

Table I. Baseline characteristics of study participants

	Intervention (n = 424)	Control (n = 428)
Characteristics		
Age (y), mean (SD)	63.3 (12.6)	62.4 (13.2)
Female	133 (31.4)	115 (26.9)
History of CAD	79 (18.6)	83 (19.4)
Previous PCI	41 (9.7)	45 (10.5)
Previous stroke/TIA	22 (5.2)	19 (4.4)
Diabetes	112 (26.4)	81 (18.9)
Hypertension	211 (49.8)	204 (47.7)
Current smoker	181 (42.7)	177 (41.4)
Dyslipidemia	154 (36.3)	157 (36.7)
History of atrial fibrillation	25 (5.9)	15 (3.5)
Any PCI	381 (89.9)	397 (92.8)
Primary PCI	322 (75.9)	335 (78.3)
Rescue PCI	32 (7.5)	33 (7.7)
Worst Killip class 4	82 (19.3)	81 (18.9)
TIMI score for STEMI, mean (SD)	3.8 (2.5)	3.4 (2.3)
Enrolled in TOTAL trial	155 (36.6)	175 (40.9)
In-hospital events		
Re-MI	4 (0.9)	4 (0.9)
PCI	42 (9.9)	35 (8.2)
CABG	21 (5.0)	16 (3.7)
Stroke	2 (0.5)	3 (0.7)
Blood transfusion	22 (5.2)	16 (3.7)
Medications at discharge		
ASA	418 (98.6)	422 (98.6)
Secondary antiplatelet	393 (92.7)	397 (92.8)
ACEI/ARB	362 (85.4)	377 (88.1)
BB	372 (87.7)	372 (86.9)
Statin	403 (95)	408 (95.3)

Table entries are frequency (%) unless otherwise indicated.
Abbreviations: *TIA*, Transient ischemic attack; *TIMI*, Thrombolysis in Myocardial Infarction, *CABG*, coronary artery bypass grafting.

Table II. Longitudinal logistic regression analysis of the primary outcome measure: 4 of 4 cardiac medications

Variable	Adjusted OR	95% CI for OR
Treatment vs control		
3 mo	1.10	0.83-1.45
12 mo	1.03	0.77-1.36
Blood transfusion	0.38	0.22-0.66
Age <65 y	1.12	0.88-1.43
History of CAD	0.80	0.57-1.13
History of DM	0.90	0.67-1.19
Prior ASA	0.89	0.64-1.23
Prior secondary antiplatelet	0.70	0.41-1.19
Prior ACEI/ARB	1.32	0.96-1.81
Prior BB	1.18	0.81-1.72
Prior statin	1.06	0.77-1.45
Renal dysfunction	0.70	0.52-0.94
Enrollment in the TOTAL trial	1.14	0.90-1.45

Abbreviation: *DM*, Diabetes mellitus.

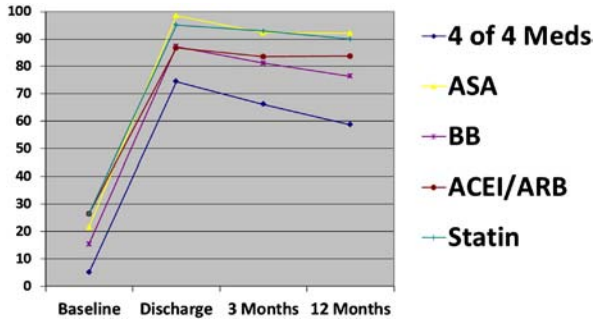
In this sample, 89% understood the contents of the letter, and 50% took them to their health care provider and 43% to their pharmacy. Only 30% agreed that the reminders helped them to take their medications, and only 20% that it prompted them to renew their medications.

Discussion

Our findings show that delayed and repeated educational reminders sent to the patient and family physician did not change the proportion of participants taking guideline-recommended cardiac medications at 12 months post-STEMI. This study was sufficiently powered to rule out clinically important differences in medication persistence at 12 months. However, there was a significant benefit in the intervention group with respect to the secondary outcome, MMAS for medication adherence. This study is novel for 2 key reasons. First, to our knowledge, this is the largest study to assess the impact of delayed and repeated postevent reminders directed at the patient and family physician, with tear-outs for the pharmacist. Second, this trial used a pragmatic design in which every STEMI patient treated in an entire health region that survived to discharge was included. Verbal consent was obtained at the time of outcome assessment and loss-to-follow-up rates were minimal for such a pragmatic design (13% at 12 months). By capturing all possible participants with minimal selection criteria, this pragmatic evaluation of a quality improvement program supports generalizability of the results.

Our team has also conducted a systematic review of postevent automated reminder systems for improving adherence to medical recommendations among chronic disease.[35] This review indicates that automated reminder systems can increase adherence rates to medical recommendations, particularly if the following features are used: (1) the intervention is delivered after hospital contact; (2) the reminders are repeated; (3) primary care physicians are included in the reminders; and (4) the reminders must be specific in reinforcing not only the intended behavior, but also the reasons for taking such action.[35] The DERLA-STEMI intervention captured all 4 of these highlighted features, and yet the study failed to detect an increase in medication persistence. Four key factors in the design, implementation, and results of this study may account for the discrepancy in the DERLA study results as compared with the literature. First, the content and/or the design of the reminders used in this study may not have been adequate. Although the reminders were developed in concert with clinical experts (in both primary care and cardiology), as well as researchers in knowledge translation and medical decision-making, we only tested the comprehensibility and acceptability of the intervention with patients while in hospital, and thus, the content may not have addressed the salient beliefs that affect medication adherence after discharge. Tailoring the message of the intervention to target specific subgroups of patients could also be considered. The letters were not sent directly to the patient's pharmacist or the outpatient cardiologist

Figure 2



Trends in percent of medication use in all DERLA-STEMI patients at baseline, discharge, 3 months, and 12 months. *OR refers to discharge vs 12 months.

because data identifying these care providers were not collected in the registry. Finally, despite the mailing addresses of the participants being confirmed while they were in hospital, only 51% of participants recalled receiving the intervention. We think that it is unlikely that they were mailed to the wrong address, given the mailing addresses were double checked in hospital, but rather, it is more likely that the design and/or content was not salient enough for the patient to remember the receiving the postal intervention, let alone impact medication adherence.

A second factor that may have contributed to the lack of effect of the intervention is the chosen outcome measure. Although self-reported medication nonadherence is associated with adverse cardiac events,[36] the "all or none" definition of persistence as an outcome for medication use at follow-up may not have been sufficiently sensitive to detect an effect of the intervention. Most postevent reminder studies use the proportion of days covered (PDC) or medication possession ratio as a proxy for medication adherence.[26] Unfortunately, this method of outcome assessment was not feasible for this pragmatic trial. A perfect score on the 4-item MMAS is associated with a PDC of >80%,[22,37] which in turn has been shown to be associated with reduced mortality post-MI.[12] There was a significantly greater proportion of participants in the intervention group at 3 months with a perfect score on the MMAS as compared with the control group (OR 1.35, 95% CI 1.01-1.81). This suggests that focusing on adherence rather that discontinuation would be a more sensitive outcome measure and may have detected a difference between the 2 groups.

Relatedly, there may be little room to demonstrate a benefit in this STEMI population due to both low rates of unexplained discontinuation of cardiac medications and higher-than-expected cardiac medication use at follow-up. Only 28% of both the intervention (n = 106) and control (n = 100) groups, with complete follow-up at 12 months, potentially had unexplained discontinuation of their 4 cardiac medications. This is assuming that the 31% of participants in both groups with documented atrial fibrillation, renal dysfunction, blood transfusion, allergy, or reported adverse effects had potentially appropriate discontinuation of at least 1 of the 4 cardiac medications. Interestingly, most of the variables included in the primary analysis, except renal dysfunction and in-hospital blood transfusion, were not significantly associated with the primary outcome. It does make clinical sense that participants with renal dysfunction are less likely to be started on an ACEI/ARB and those requiring a blood transfusion are less likely to be continued on antiplatelet agents, including ASA.[30,31]

The higher-than-expected rates of medication use at 1-year follow-up may be another factor contributing to the findings of this trial. It was estimated that 50% of the control group would be taking 4 of 4 cardiac medications at 1 year, but the measured rate was 59%. Furthermore, the use of individual cardiac medications at 12 months post-STEMI was 90% for statins and ASA, >80% for ACEI/ARB, and >75% for BB, all approaching expected benchmarks that take adverse effects and contraindications into consideration.[6] These reasonable rates of evidence-based medication use 1-year post-STEMI may be due to several factors: (1) a combination of full medication coverage for participants older than 65 years in the province of Ontario and lower medication costs for those without insurance (all evidence–based cardiac medications classes are now available in a generic formulation)[38]; (2) the evidence for secondary prevention is well established with guidelines recommending the same classes of medications for more than 8 years[39]; (3) STEMI is the most acute and symptomatic presentation of acute coronary syndromes and thus may promote better medication adherence as compared with unstable angina and non-STEMI[28]; (4) the telephone call follow-up at 3 months in both intervention and control groups, as part of the existing STEMI registry, may have positively influenced medication use at 1 year; and (5) the verbal consent at the time of outcome assessment may have influenced the participants to overreport adherence in both groups. However, this final potential explanation for better than expect medication use is unlikely for 2 reasons. First, the explanation to the participants at the time of outcome assessment did not specifically state that adherence to medications was being measured. Instead, the following general sentence was used to describe the reason for the participant contact, "This phone call is to try to-follow up on the status of our patients so that we can try to improve our services and programs. I was hoping you could take about 2 minutes to answer some health-related questions." Second, the patient-reported medication use correlated very well with the validation substudy using administrative databases, thus rendering overreporting of adherence less likely.

Finally, 7.3% more participants in the control group attended a cardiac rehabilitation program after discharge post-STEMI. It is unlikely that the reminders contributed

Table III. Secondary outcomes for treatment vs control

Variable*	Intervention		Control		Adjusted OR	95% CI for OR
	Frequency	%	Frequency	%		
5/5 Medications at 12 mo	152	42.1	156	41.1	1.12	0.84-1.5
3/4 medications at 12 mo	286	79.2	306	80.5	0.92	0.67-1.26
ASA at 12 mo	334	92.5	349	91.8	1.09	0.63-1.88
2nd antiplatelet at 12 mo	246	68.1	236	62.1	1.36	0.99-1.85
ACEI/ARB at 12 mo	294	81.4	327	86.1	0.71	0.48-1.04
BB at 12 mo	281	77.8	285	75.0	1.14	0.80-1.61
Statin at 12 mo	322	89.2	345	90.8	0.89	0.55-1.45
Perfect MMAS score at 3 mo	247	65.3	220	58.0	1.35	1.01-1.81

*OR refers to intervention vs control.

Table IV. Multivariable analysis of secondary outcomes

Variable*	Attendance at cardiac rehabilitation		Discuss with physician	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Unadjusted				
Treatment vs control	0.73 (0.54-0.98)	.0387	1.60 (0.94-2.74)	.0852
Adjusted				
Treatment vs control	0.76 (0.56-1.03)	.0765	1.92 (1.11-3.35)	.0206
Enrollment in the TOTAL trial	1.37 (1.00-1.89)	.0496	1.12 (0.64-1.97)	.6885
Blood transfusion	2.47 (1.22-5.00)	.0120	0.68 (0.26-1.75)	.4201
Age <65 y	1.86 (1.35-2.57)	.0002	2.28 (1.34-3.86)	.0023
History of CAD	0.57 (0.35-0.92)	.0207	1.10 (0.49-2.43)	.8217
History of DM	0.81 (0.55-1.20)	.2943	0.61 (0.32-1.15)	.1280
Prior ASA	0.94 (0.61-1.47)	.7927	2.17 (0.90-5.28)	.0863
Prior secondary antiplatelet	1.01 (0.44-2.33)	.9850	0.83 (0.25-2.74)	.7615
Prior ACEI/ARB	1.09 (0.73-1.61)	.6830	0.53 (0.27-1.05)	.0679
Prior β-blocker	0.66 (0.39-1.10)	.1071	1.72 (0.72-4.10)	.2182
Prior statin	1.01 (0.68-1.50)	.9630	0.85 (0.43-1.68)	.6466
Renal dysfunction	0.97 (0.64-1.47)	.8837	0.77 (0.41-1.44)	.4080

Abbreviation: *DM*, Diabetes mellitus.
*OR refers to intervention vs control.

to this trend in decreased cardiac rehabilitation attendance in the intervention group, given that it was designed to reinforce attendance. This finding is most likely a play of chance. The multivariable analyses (Table IV) revealed that patients younger than 65 years were substantially more likely to attend cardiac rehabilitation and to have discussion with their physician, whereas subgroup analyses by age (Table V) revealed that there was a trend toward statistically significant improved medication adherence in this younger age group. Although these subgroup effects were not statistically significant (likely as a result of small subgroup sizes), they do shed some light on potential reasons for lack of treatment effect; the imbalance in attendance at cardiac rehabilitation between treatment and control arms could have potentially lessened the effect of the intervention overall, as cardiac rehabilitation attendance has been shown to improve cardiac medication adherence.[40]

Our findings demonstrated that medications were most frequently discontinued by the physician, rather than the patient. The most frequent reason for discontinuation was medication-related adverse effects. Similar findings have been previously reported in "real-world" studies.[41] We did find that medications were more often discontinued by the specialist (cardiologist or internist), rather than the family physician. Given that most participants were being followed up by a specialist post-STEMI, it is hypothesized that the family physician would defer any cardiac medication-related concerns to the specialist involved in their care. It is possible, therefore, that in focusing on patient, family physician, and pharmacist, rather than the specialist, the intervention failed to target a key decision maker in the process.

Limitations

This study does have limitations. First, the results presented are only applicable to the exact interventions

Table V. Subgroup analyses of the primary outcome measure using longitudinal logistic regression: adherence to 4 of 4 cardiac medications at 12 months

	Least square mean adherence† (%), 95% CI		Treatment effect‡	
Variable*	Control arm	Treatment arm	OR (95% CI)	*P*
Age				
<5 y	59.0 (52.3-65.3)	61.8 (54.7-68.5)	1.50 (0.93 to 2.41)	.0932
≥65 y	56.3 (48.3-64.1)	53.6 (45.9-61.3)	0.73 (0.42 to 1.28)	.2781
Subgroup difference			2.04 (0.98 to 4.25)	.0556
History of CAD				
Yes	50.2 (38.1-62.3)	59.9 (47.3-71.4)	1.17 (0.51-2.70)	.7035
No	59.6 (53.9-65.0)	57.7 (51.8-63.3)	1.06 (0.71-1.59)	.7657
Subgroup difference			1.10 (0.44-2.78)	.8325
Blood transfusion				
Yes	44.8 (22.5-69.4)	39.8 (19.4-64.5)	0.34 (0.05-2.51)	.2890
No	58.5 (53.4-63.5)	58.9 (53.6-64.0)	1.14 (0.79-1.64)	.4904
Subgroup difference			0.30 (0.04-2.28)	.2430
Enrollment in the TOTAL trial				
Yes	55.5 (47.8-62.9)	61.3 (53.3-68.8)	1.10 (0.60-2.02)	.7621
No	60.1 (53.4-66.4)	55.9 (49.0-62.6)	0.99 (0.63-1.56)	.9723
Subgroup difference			1.11 (0.52-2.36)	.7917

* OR refers to intervention vs control.
† Model-based mean adherence for an average patient.
‡ Expressed as difference in change from baseline: intervention arm vs control arm.

used in this study. Given significant effects seen in other studies, it would be incorrect to conclude that a set of reminders, varied in design, content, timing, or mode of delivery (text messaging, emails) would not improve medication use in the post-STEMI setting. Second, this study used participant-reported telephone call follow-up as the outcome assessment. As outlined above, PDC or medication possession ratio is a more sensitive measure of adherence.[26] Third, the pragmatic design of this study prohibited the capture of potential contraindications to medications at discharge, thus limiting the findings. Finally, this study did not capture clinical events, including hospital readmission, within the 12-month follow-up, which could have impacted long-term medication adherence.

Conclusion

DERLA-STEMI demonstrates the feasibility of recruiting and randomizing all eligible STEMI patients in a provincial health region into a quality improvement program. The results suggest suboptimal but better than previously reported persistence to all 4 cardiac medication classes at 12 months. There was no significant difference in persistence with guideline-recommended medications post-STEMI between those receiving delayed and repeated reminders vs usual care. The DERLA-STEMI trial results demonstrate that prior to widespread adoption of patient reminders, further rigorous evaluation of "optimized" reminders is warranted. Given the relative low cost and scalable nature of this type of intervention, even a small increase in medication adherence, as demonstrated with the MMAS, might be efficient.

Author contributions

The authors meet all 3 authorship criteria outlined by the International Committee of Medical Journal Editors.

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Disclosures

The authors do not have any conflicts to declare.

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