Aspects of Multicomponent Integrated Care Promote Sustained Improvement in Surrogate Clinical Outcomes: A Systematic Review and Meta-analysis

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Diabetes Care 2018;41:1312–1320 | https://doi.org/10.2337/dc17-2010

META-ANALYSIS

OBJECTIVE

The implementation of the Chronic Care Model (CCM) improves health care quality. We examined the sustained effectiveness of multicomponent integrated care in type 2 diabetes.

RESEARCH DESIGN AND METHODS

We searched PubMed and Ovid MEDLINE (January 2000–August 2016) and identified randomized controlled trials comprising two or more quality improvement strategies from two or more domains (health system, health care providers, or patients) lasting ≥12 months with one or more clinical outcomes. Two reviewers extracted data and appraised the reporting quality.

RESULTS

In a meta-analysis of 181 trials (N = 135,112), random-effects modeling revealed pooled mean differences in HbA_{1c} of −0.28% (95% CI −0.35 to −0.21) (−3.1 mmol/mol [−3.9 to −2.3]), in systolic blood pressure (SBP) of −2.3 mmHg (−3.1 to −1.4), in diastolic blood pressure (DBP) of −1.1 mmHg (−1.5 to −0.6), and in LDL cholesterol (LDL-C) of −0.14 mmol/L (−0.21 to −0.07), with greater effects in patients with LDL-C ≥3.4 mmol/L (−0.31 vs. −0.10 mmol/L for <3.4 mmol/L; $P_{difference}$ = 0.013), studies from Asia (HbA_{1c} −0.51% vs. −0.23% for North America [−5.5 vs. −2.5 mmol/mol]; $P_{difference}$ = 0.046), and studies lasting >12 months (SBP −3.4 vs. −1.4 mmHg, $P_{difference}$ = 0.034; DBP −1.7 vs. −0.7 mmHg, $P_{difference}$ = 0.047; LDL-C −0.21 vs. −0.07 mmol/L for 12-month studies, $P_{difference}$ = 0.049). Patients with median age <60 years had greater HbA_{1c} reduction (−0.35% vs. −0.18% for ≥60 years [−3.8 vs. −2.0 mmol/mol]; $P_{difference}$ = 0.029). Team change, patient education/self-management, and improved patient-provider communication had the largest effect sizes (0.28–0.36% [3.0–3.9 mmol/mol]).

CONCLUSIONS

Despite the small effect size of multicomponent integrated care (in part attenuated by good background care), team-based care with better information flow may improve patient-provider communication and self-management in patients who are young, with suboptimal control, and in low-resource settings.

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Urgent measures are needed to reduce the growing burden of diabetes, especially in low- and middle-income countries (LMICs) (1,2). The aging population and rising prevalence of young-onset diabetes carry onerous implications on health care expenditure and societal productivity (1,3). The complex clinical course and pluralistic needs of people with diabetes call for an integrated care approach to identify needs and implement timely solutions (4,5). In controlled settings, type 2 diabetes is preventable and treatable, although in real-world practice, fewer than one in four adults underwent annual complication screening or attained composite cardiometabolic targets especially in LMICs (6,7). Insufficient care coordination and lack of communication between patients and health care providers (HCPs) can lead to delayed intervention, psychosocial stress, treatment nonadherence, and poor clinical outcomes (8,9). Here, quality improvement (QI) programs contain multiple components targeting patients, HCPs, or systems to enable periodic evaluation, identify treatment gaps, and promote information sharing for decision making (10,11). Previous meta-analyses concluded that team change, case management, and promotion of self-management had the largest effect sizes in reducing HbA_{1c} (12,13). In this meta-analysis, we included only type 2 diabetes studies lasting at least 12 months in order to examine the sustained effects of multicomponent integrated care on surrogate clinical outcomes in different populations and settings.

RESEARCH DESIGN AND METHODS

Data Sources and Searches

We performed literature searches of PubMed and Ovid MEDLINE for randomized controlled trials (RCTs) published between January 2000 and August 2016 that examined the effects of multicomponent integrated care in type 2 diabetes. The PubMed and Ovid MEDLINE search terms using Medical Subject Headings and text words are listed in Supplementary Table 1. We also searched references from original articles, clinical guidelines, narrative reviews, and previous systematic reviews/meta-analyses to identify additional eligible trials. We followed the PRISMA guidelines for conducting and reporting meta-analyses of RCTs.

Study Selection

Eligible studies were English-language peer-reviewed RCTs and their companion prospective follow-up studies. The 12 existing QI strategies were categorized into three domains, i.e., health system, HCPs, and patients (12,13). We updated their definitions and included electronic health (e-health) under the health system domain, bringing the total to 13 QI strategies (Supplementary Table 2) (14). We defined multicomponent integrated care models as those comprising at least two QI strategies from two of the three domains lasting at least 12 months and reporting at least one cardiometabolic or care process outcome (Supplementary Table 3). Trials with intervention(s) in a single domain or with fewer than 100 patients were excluded.

Data Extraction and Quality Assessment

Two independent reviewers (L.L.L. and E.S.H.L.) extracted data using standard templates, including authors, year of publication, geographic regions, national income levels, study settings, sample size, participants' characteristics (age, sex, ethnicity, and duration of type 2 diabetes), QI strategies implemented, duration of intervention, and pre- and postinterventional cardiometabolic and care process outcomes. We appraised the quality of reporting using the Cochrane Effective Practice and Organisation of Care (EPOC) risk-of-bias tool (15,16). Each trial was assessed based on seven categories of biases, which were selection bias, attrition bias, performance bias, detection bias, reporting bias, contamination bias, and other risk of bias. Each bias was classified into "high risk," "low risk," or "unclear risk." Trial authors were contacted for clarifications if required. Any disagreement between the two reviewers was resolved by senior investigators (A.P.S.K. and J.C.N.C.).

Data Synthesis and Analysis

We used random-effects modeling to pool the mean postinterventional differences in HbA_{1c}, LDL cholesterol (LDL-C), systolic blood pressure (SBP), and diastolic blood pressure (DBP) levels between the intervention and control (usual care) groups. In some studies, some QI strategies were already part of usual care. Thus, the postinterventional estimates of individual QI strategies were the net differences of the number and total effects of QI strategies between the two groups. As these RCTs had different combinations of QI strategies and there were few trials with similar combinations for direct comparisons, we performed a mixed-effects meta-regression model to control for the confounding effects of cointerventions, adjusted for age, sex, and baseline cardiometabolic risk factors. Financial incentives strategies were excluded from the analysis as only two trials were involved.

In this meta-analysis, 28 RCTs adopted a trial design involving more than two arms. With these studies, we included data from the intervention arm with the largest number of QI strategies. We also compared the effects of these QI strategies stratified by geographic regions (North America, Europe, and Asia), national income levels (high vs. middle income), duration of intervention ($>$12 months vs. 12 months only), median age ($<$60 vs. $\geq$60 years), and cardiometabolic control at baseline, i.e., HbA_{1c} ($\geq$8% [$\geq$64 mmol/mol] vs. $<$8% [$<$64 mmol/mol]), SBP ($\geq$140 vs. $<$140 mmHg), DBP ($\geq$80 vs. $<$80 mmHg), and LDL-C ($\geq$3.4 vs. $<$3.4 mmol/L; to convert to mg/dL, multiply by 38.67). Subgroup analyses for SBP and LDL-C using 130 mmHg and 2.6 mmol/L, respectively, were not performed due to limited extractable data. Heterogeneity and publication bias were assessed by I^2 statistic and funnel plots. All

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Received 26 September 2017 and accepted 5 March 2018.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-2010/-/DC1.

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

statistical analyses were performed using R software version 3.3.1 (17). A two-tailed $P < 0.05$ denoted statistical significance without multiplicity correction in all exploratory analyses.

RESULTS

Study Characteristics

The search strategy yielded 15,458 citations, of which 972 full-text articles were assessed for eligibility. A total of 181 trials (including 12 companion prospective follow-up studies) involving 135,112 participants were included. The PRISMA flow diagram depicts the study selection (Supplementary Fig. 1). Most trials were conducted in high-income nations with only 10 from upper- and lower-middle income countries. The mean (SE) age was 59.6 (0.6) years and median (interquartile range) duration of intervention was 12 (12–24) months. The median (interquartile range) number of QI strategies in these multicomponent integrated care models was 4.5 (3–6), with patient education (91.2%), team change (56.9%), and clinician reminder/decision support (69.6%) as the top QI strategies targeted at patients, system, and HCPs, respectively, in addition to usual care (Supplementary Table 4).

The quality of reporting assessment is summarized in Supplementary Fig. 2. It was not feasible to blind the personnel/participants in 159 (88%) of these pragmatic RCTs. Their internal validity was mainly compromised by contamination bias (90 [50%]), lack of random sequence generation (94 [52%]), inadequate allocation concealment (98 [55%]), and attrition bias (77 [43%]).

Effects of Multicomponent Integrated Care on Cardiometabolic Outcomes

Supplementary Figs. 3–7 show the pooled mean differences of HbA_{1c}, SBP, DBP, and LDL-C levels in all RCTs. Figure 1 summarizes the results of subgroup analyses stratified by different levels of baseline cardiometabolic control and geographic regions. Compared with usual care (e.g., clinical procedures, medical visits, and medications), multicomponent integrated care reduced HbA_{1c} by 0.28% (3.1 mmol/mol) (95% CI −0.35 to −0.21 [−3.9 to −2.3]), with larger effect size in *1*) patients with baseline HbA_{1c} ≥8% (≥64 mmol/mol) (−0.38% [−4.2 mmol/mol] vs. −0.22% [−2.4 mmol/mol] for those with <8% [<64 mmol/mol]; $P_{difference}$ = 0.058); *2*) studies in Asia (−0.51% [−5.5 mmol/mol] vs. −0.23% [−2.5 mmol/mol] in North America, $P_{difference}$ = 0.046, vs. −0.29% [−3.2 mmol/mol] in Europe, $P_{difference}$ = 0.100); *3*) middle-income (−0.53% [95% CI −1.18 to 0.13], −5.8 mmol/mol [−12.9 to 1.4]; 3 trials) vs. high-income countries (−0.28% [−0.35 to −0.21], −3.1 mmol/mol [−3.9 to −2.3], 96 trials) ($P_{difference}$ = 0.275); and *4*) studies lasting >12 months (−0.39% [−0.54 to −0.24], −4.3 mmol/mol [−5.9

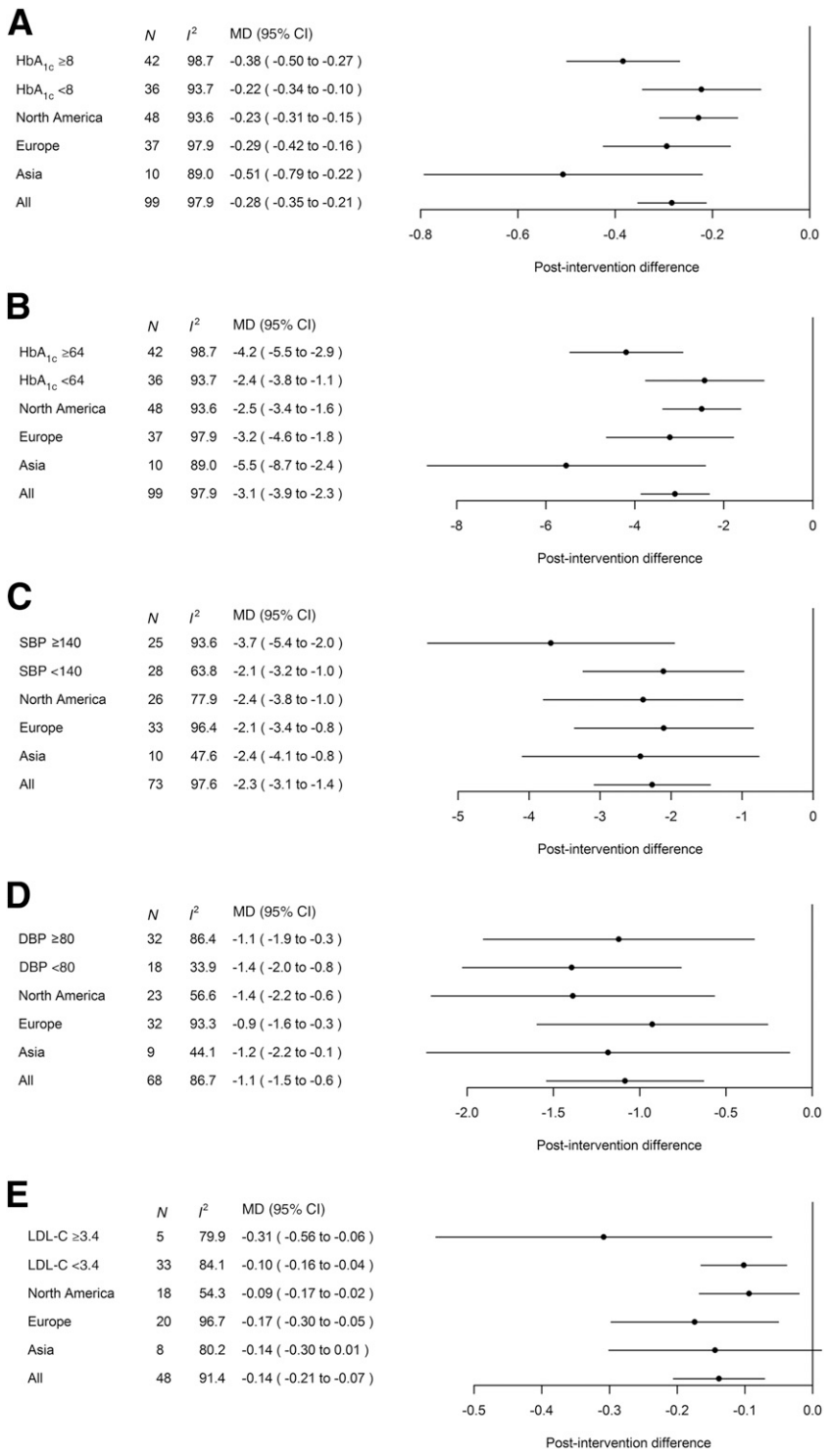

Figure 1—Meta-analyses results of the effects of multicomponent integrated care on HbA_{1c} (%) (*A*), HbA_{1c} (mmol/mol) (*B*), SBP (mmHg) (*C*), DBP (mmHg) (*D*), and LDL-C (mmol/L) (*E*), stratified by different levels of baseline cardiometabolic control and geographic regions. To convert LDL-C to mg/dL, multiply by 38.67. MD, mean difference; *N*, number of trials with analyzable data.

to −2.6], 36 trials) vs. only 12 months (−0.22% [−0.30 to −0.15], −2.4 mmol/mol [−3.3 to −1.6], 62 trials) ($P_{difference}$ = 0.062) (data not shown).

Multicomponent integrated care reduced SBP and DBP by 2.3 mmHg (95% CI −3.1 to −1.4) and 1.1 mmHg (−1.5 to −0.6), respectively (Fig. 1*C* and 1*D*). Patients with baseline SBP ≥140 mmHg tended to have greater reduction than those with <140 mmHg (−3.7 mmHg [−5.4 to −2.0] vs. −2.1 mmHg [−3.2 to −1.0]; $P_{difference}$ = 0.198), with similar effect sizes across the three regions. Studies from middle-income countries tended to have greater SBP (−4.4 mmHg [−6.4 to −2.4], 4 trials) and DBP (−2.2 mmHg [−3.7 to −0.8], 4 trials) reductions than high-income countries (−2.2 mmHg [−3.0 to −1.3], 69 trials; $P_{difference}$ = 0.319, and −1.0 mmHg [−1.5 to −0.6], 64 trials; $P_{difference}$ = 0.321, respectively). Studies lasting >12 months had greater improvement in SBP (−3.4 mmHg [−4.9 to −1.9], 29 trials) than 12-month trials (−1.4 mmHg [−2.2 to −0.6], 43 trials; $P_{difference}$ = 0.034). The corresponding data for DBP were −1.7 mmHg (−2.4 to −1.0, 27 trials) and −0.7 mmHg (−1.3 to −0.2, 40 trials) ($P_{difference}$ = 0.047).

Across 48 trials, multicomponent integrated care lowered LDL-C by 0.14 mmol/L (95% CI −0.21 to −0.07) compared with usual care, with greater effect size in patients with LDL-C ≥3.4 mmol/L (−0.31 mmol/L) versus those with <3.4 mmol/L (−0.10 mmol/L); $P_{difference}$ = 0.013 (Fig. 1*E*). Significant LDL-C reductions were reported in Europe and North America (−0.17 mmol/L vs. −0.09 mmol/L, respectively; $P_{difference}$ = 0.342) but not in Asia. The only trial from a middle-income country with analyzable LDL-C data showed a 0.18 mmol/L (−0.31 to −0.05) reduction compared with a 0.14 mmol/L reduction (−0.21 to −0.07, 47 trials) in high-income countries. Sustained LDL-C reduction was more likely in studies lasting >12 months (−0.21 mmol/L [−0.32 to −0.09], 21 trials) than those with only a 12-month duration (−0.07 mmol/L [−0.13 to 0.00], 26 trials) ($P_{difference}$ = 0.049).

When we stratified the analysis by median age at baseline (<60 vs. ≥60 years), improvement in HbA_{1c} with multicomponent integrated care was greater in younger patients (−0.35% [−0.45 to −0.25], −3.8 mmol/mol [−4.9 to −2.8], 50 trials) than in older patients (−0.18% [−0.43 to 0.07], −2.0 mmol/mol [−4.7 to 0.7], 35 trials) ($P_{difference}$ = 0.029). There were no significant between-group differences for other cardiometabolic outcomes (Table 1). The majority of trials reported increased usage of organ-protective agents and uptake of complications screening with multicomponent integrated care (Supplementary Table 5). In 12 trials, hypoglycemia, either self-reported or objective measurements using glucometer/continuous glucose monitoring, was a study outcome. Nine trials indicated no between-group difference and two trials reported reduction in hypoglycemia with multicomponent integrated care. One trial reported increased nonsevere hypoglycemic events with intervention, albeit the rate was very low with no severe hypoglycemia. One sulfonylurea-treated patient in the control group had two severe hypoglycemia episodes (18).

Effects of Individual QI Strategy on Cardiometabolic Outcomes

Most QI strategies were effective in improving cardiometabolic outcomes (Fig. 2 and Supplementary Table 6). System-targeted initiatives, e.g., team change and facilitated patient-provider relay, were most effective in reducing the respective HbA_{1c} and LDL-C by 0.28–0.36% (3.0–3.9 mmol/mol) and 0.14–0.20 mmol/L, respectively, whereas electronic patient registry was the top QI strategy in lowering S/DBP (4/3 mmHg). Patient education and promotion of self-management were the most effective patient-targeted strategies. Other QI strategies targeted at HCPs, such as clinician reminder/decision support and audit and feedback, also improved all cardiometabolic risk factors, although the effect sizes were smaller compared with the aforementioned system- and patient-level interventions. Subgroup analyses indicated greater benefits of individual QI strategies in groups with suboptimal control, i.e., 0.29–0.50% (3.2–5.5 mmol/mol) for HbA_{1c} ≥8% (≥64 mmol/mol) (vs. 0.07–0.37% for <8% [0.8–4.0 mmol/mol for <64 mmol/mol]), 2.6–5.2 mmHg for SBP ≥140 mmHg (vs. 2.3–4.5 mmHg for <140 mmHg), 1.3–3.3 mmHg for DBP ≥80 mmHg (vs. 1.1–2.8 mmHg for <80 mmHg), and 0.20–0.39 mmol/L for LDL-C ≥3.4 mmol/L (vs. 0.07–0.15 mmol/L for <3.4 mmol/L) (Table 2).

We performed meta-regression analysis to control for confounding effects among the 12 QI strategies with adjustment for age, sex, and baseline cardiometabolic risk factors (Supplementary Table 7). Using analyzable HbA_{1c} data from 75 trials, patient education remained independently associated with HbA_{1c} reduction (−0.15% [−0.28 to −0.02], −1.6 mmol/mol [−3.1 to −0.2]; *P* = 0.019) whereas team change (−0.12% [−0.25 to 0.02], −1.3 mmol/mol [−2.7 to 0.2]; *P* = 0.083) and facilitated patient-provider relay (−0.14% [−0.28 to 0.01], −1.5 mmol/mol [−3.1 to 0.1]; *P* = 0.059) tended toward significance. Other independent predictors included electronic patient registry for SBP (−4.4 mmHg [−8.0 to −0.8]; *P* = 0.016) and DBP reductions (−2.7 mmHg [−4.5 to −0.8]; *P* = 0.004) whereas the corresponding changes for promotion of self-management were −4.7 mmHg (−7.8 to −1.6) (*P* = 0.003) and −2.2 mmHg (−3.8 to −0.7) (*P* = 0.004). Overall, integrated care reduced HbA_{1c} by 0.13% (−0.21 to −0.04) (1.4 mmol/mol [−2.3 to −0.4]) per 1% (11 mmol/mol) increase in baseline HbA_{1c}. There was a significant trend of larger blood pressure reduction with an increasing number of QI strategies (P_{trend} for SBP = 0.025 and for DBP = 0.007) but not for HbA_{1c} and LDL-C changes.

Table 1—Effects of multicomponent integrated care on cardiometabolic outcomes, stratified by median age at baseline

	Age <60 years (*N* = 65)		Age ≥60 years (*N* = 54)		
	N	MD (95% CI)	*N*	MD (95% CI)	$P_{difference}$
HbA_{1c} (%)	50	−0.35 (−0.45 to −0.25)	35	−0.18 (−0.43 to 0.07)	0.029
HbA_{1c} (mmol/mol)	50	−3.8 (−4.9 to −2.8)	35	−2.0 (−4.7 to 0.7)	0.029
SBP (mmHg)	32	−2.8 (−4.1 to −1.4)	32	−2.4 (−5.6 to 0.7)	0.728
DBP (mmHg)	30	−1.4 (−2.2 to −0.7)	30	−1.1 (−2.8 to 0.7)	0.461
LDL-C (mmol/L)	25	−0.16 (−0.26 to −0.06)	19	−0.13 (−0.37 to 0.12)	0.639

MD, mean difference; *N*, number of trials with analyzable data.

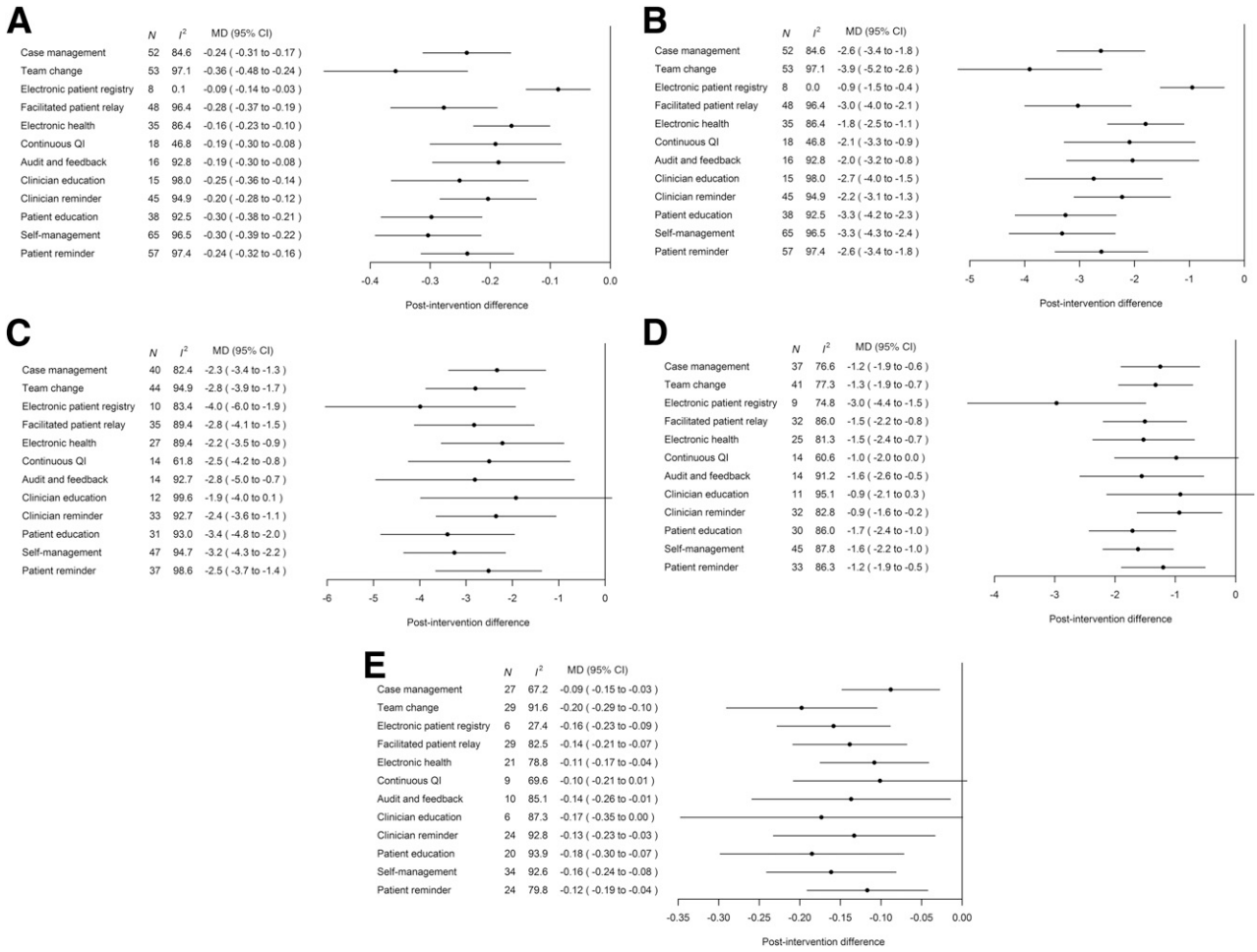

Figure 2—Meta-analyses results of the effects of individual QI strategies on HbA_{1c} (%) (*A*), HbA_{1c} (mmol/mol) (*B*), SBP (mmHg) (*C*), DBP (mmHg) (*D*), and LDL-C (mmol/L) (*E*). To convert LDL-C to mg/dL, multiply by 38.67. MD, mean difference; *N*, number of trials with analyzable data.

CONCLUSIONS

In this meta-analysis, multicomponent integrated care lasting at least 12 months reduced HbA_{1c}, SBP, DBP, and LDL-C levels by 0.28% (3.1 mmol/mol), 2.3 mmHg, 1.1 mmHg, and 0.14 mmol/L, respectively, on top of usual care (clinical procedures, medical visits, and drug therapy). Among the various QI strategies, team change, patient education, patient self-management, electronic registry, and using relay to promote patient-provider communication (e.g., personal reports, trained peers) had the largest independent effect sizes. These results extended that of a previous meta-analysis of 142 studies (12) to a diversity of settings and populations, with greater effect sizes in younger patients and those with suboptimal control and coming from Asia and middle-income countries.

Due to their phenotypic heterogeneity, patients with type 2 diabetes require individualized biomedical, cognitive, psychosocial, and behavioral interventions (19). However, effective delivery of personalized care requires a favorable practicing environment to nurture patient-provider relationship with adequate contact time in order to define unmet needs, reduce clinical inertia, and promote self-management. The use of a team to change workflow will enable HCPs to collect data, stratify risk, relay information, and improve patient-provider communication that will address these interlinking challenges (10).

Effective Patient-Provider Communication

In support of this notion, our analysis indicated that better information flow (e.g., issue of personal reports with treatment targets and decision support, e-health, trained peers, or community health workers) enabled treatment intensification, improved control of cardiometabolic risk factors, promoted self-care behaviors, and reduced hospitalizations, especially in individuals with suboptimal control (20,21). Similarly, interactive telemedicine enhanced patient-provider communication and problem-solving through facilitated learning and self-care monitoring with reduced health care utilization (22–24).

Approximately 20–30% of patients with type 2 diabetes had coexistent distress, anxiety, and/or depression (25), which could lead to suboptimal self-care (26), treatment nonadherence (27), and premature death (28,29). In several studies, trained peers and/or community health workers were used to support these difficult-to-treat or hard-to-reach patients, especially in low-resource settings. These trained nonclinical assistants could overcome the language and cultural communication barriers, alleviate negative emotions, exchange complex health information, and engage patients with linkage to the health care system, especially

Table 2—Effects of individual QI strategies by HbA_{1c}, blood pressure, and LDL-C subgroups

	HbA_{1c} (NGSP)				HbA_{1c} (IFCC)			
	≥8%		<8%		≥64 mmol/mol		<64 mmol/mol	
QI strategy	*N*	MD (95% CI)	*N*	MD (95% CI)	*N*	MD (95% CI)	*N*	MD (95% CI)
Health system								
Case management	23	−0.40 (−0.54 to −0.26)	21	−0.08 (−0.13 to −0.03)	23	−4.4 (−5.9 to −2.8)	21	−0.9 (−1.4 to −0.3)
Team change	24	−0.46 (−0.63 to −0.29)	20	−0.37 (−0.59 to −0.15)	24	−5.0 (−6.9 to −3.2)	20	−4.0 (−6.4 to −1.6)
Electronic patient registry	2	−0.43 (−0.68 to −0.19)	5	−0.07 (−0.13 to −0.02)	2	−4.7 (−7.4 to −2.1)	5	−0.8 (−1.4 to −0.2)
Facilitated relay	23	−0.36 (−0.53 to −0.20)	13	−0.12 (−0.18 to −0.06)	23	−3.9 (−5.8 to −2.2)	13	−1.3 (−2.0 to −0.7)
E-health	17	−0.29 (−0.41 to −0.17)	12	−0.06 (−0.12 to 0.00)	17	−3.2 (−4.5 to −1.9)	12	−0.7 (−1.3 to 0.0)
Continuous QI	10	−0.36 (−0.56 to −0.15)	5	−0.09 (−0.14 to −0.03)	10	−3.9 (−6.1 to −1.6)	5	−1.0 (−1.5 to −0.3)
HCPs								
Audit and feedback	4	−0.50 (−0.51 to −0.49)	10	−0.04 (−0.10 to 0.02)	4	−5.5 (−5.6 to −5.4)	10	−0.4 (−1.1 to −0.2)
Clinician education	6	−0.32 (−0.51 to −0.13)	6	−0.15 (−0.28 to −0.02)	6	−3.5 (−5.6 to −1.4)	6	−1.6 (−3.1 to −0.2)
Clinician reminder	22	−0.31 (−0.46 to −0.17)	14	−0.07 (−0.14 to 0.00)	22	−3.4 (−5.0 to −1.9)	14	−0.8 (−1.5 to 0.0)
Patients								
Patient education	16	−0.46 (−0.60 to −0.32)	13	−0.12 (−0.18 to −0.07)	16	−5.0 (−6.6 to −3.5)	13	−1.3 (−2.0 to −0.8)
Promotion of self-management	32	−0.39 (−0.51 to −0.26)	20	−0.22 (−0.39 to −0.05)	32	−4.3 (−5.6 to −2.8)	20	−2.4 (−4.3 to −0.5)
Patient reminder system	29	−0.36 (−0.50 to −0.22)	16	−0.08 (−0.14 to −0.02)	29	−3.9 (−5.5 to −2.4)	16	−0.9 (−1.5 to −0.2)

	SBP				DBP			
	≥140 mmHg		<140 mmHg		≥80 mmHg		<80 mmHg	
	N	MD (95% CI)	*N*	MD (95% CI)	*N*	MD (95% CI)	*N*	MD (95% CI)
Health system								
Case management	14	−2.7 (−4.6 to −0.8)	15	−2.9 (−4.7 to −1.0)	15	−1.3 (−2.4 to −0.1)	12	−1.6 (−2.6 to −0.7)
Team change	14	−5.2 (−7.3 to −3.0)	14	−2.3 (−3.6 to −1.0)	23	−1.5 (−2.5 to −0.6)	7	−1.1 (−1.3 to −1.0)
Electronic patient registry	3	−4.9 (−7.6 to −2.2)	4	−4.0 (−7.6 to −0.4)	5	−3.3 (−5.0 to −1.6)	3	−1.9 (−5.8 to 2.1)
Facilitated relay	12	−4.4 (−7.1 to −1.8)	15	−2.7 (−4.4 to −1.0)	11	−1.6 (−3.1 to 0.0)	10	−1.5 (−2.2 to −0.9)
E-health	9	−2.6 (−5.0 to −0.2)	10	−2.0 (−4.4 to 0.4)	10	−1.7 (−3.3 to 0.0)	8	−1.6 (−2.9 to −0.2)
Continuous QI	6	−4.7 (−7.2 to −2.2)	7	−1.1 (−2.8 to 0.6)	5	−1.7 (−3.9 to 0.5)	5	−0.9 (−2.2 to 0.5)
HCPs								
Audit and feedback	9	−3.2 (−6.5 to 0.0)	2	−2.9 (−7.0 to 1.3)	6	−1.9 (−4.2 to 0.3)	6	−1.3 (−1.8 to −0.7)
Clinician education	5	−2.5 (−8.0 to 3.1)	2	−4.5 (−7.4 to −1.5)	6	−0.9 (−2.9 to 1.2)	2	−1.2 (−2.8 to 0.4)
Clinician reminder	12	−2.8 (−5.4 to −0.3)	9	−4.3 (−6.5 to −2.0)	15	−0.7 (−1.9 to 0.4)	8	−1.4 (−3.0 to 0.1)
Patients								
Patient education	15	−5.1 (−7.3 to −3.0)	8	−2.9 (−5.9 to 0.1)	17	−1.8 (−2.9 to −0.8)	5	−2.8 (−4.6 to −0.9)
Promotion of self-management	18	−4.7 (−6.7 to −2.7)	20	−2.4 (−3.9 to −0.9)	23	−1.7 (−2.6 to −0.8)	13	−1.5 (−2.0 to −1.0)
Patient reminder system	14	−3.2 (−5.6 to −0.8)	11	−2.9 (−4.8 to −1.0)	16	−1.5 (−2.8 to −0.3)	9	−1.3 (−1.8 to −0.9)

	LDL-C*			
	≥3.4 mmol/L		<3.4 mmol/L	
	N	MD (95% CI)	*N*	MD (95% CI)
Health system				
Case management	2	−0.20 (−0.27 to −0.14)	21	−0.07 (−0.14 to 0.00)
Team change	4	−0.31 (−0.60 to −0.02)	18	−0.15 (−0.24 to −0.06)
Electronic patient registry	NA	NA	3	−0.13 (−0.26 to 0.01)
Facilitated relay	4	−0.39 (−0.62 to −0.17)	20	−0.12 (−0.19 to −0.04)
E-health	NA	NA	16	−0.10 (−0.18 to −0.02)
Continuous QI	NA	NA	6	−0.10 (−0.25 to 0.04)
HCPs				
Audit and feedback	2	−0.33 (−0.62 to −0.04)	6	−0.06 (−0.22 to 0.09)
Clinician education	NA	NA	5	−0.12 (−0.27 to 0.04)
Clinician reminder	NA	NA	17	−0.08 (−0.16 to 0.00)
Patients				
Patient education	4	−0.23 (−0.48 to 0.01)	10	−0.11 (−0.21 to −0.02)
Promotion of self-management	4	−0.23 (−0.48 to 0.01)	23	−0.13 (−0.20 to −0.06)
Patient reminder system	4	−0.31 (−0.60 to −0.02)	16	−0.06 (−0.14 to 0.01)

IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; MD, mean difference; *N*, number of trials with analyzable data; NA, no available trials for analysis; NGSP, National Glycohemoglobin Standardization Program. *To convert LDL-C to mg/dL, multiply by 38.67.

in those with frequent peer-to-peer contacts (30–33).

Patient Education and Self-management

The need to change lifestyle, self-manage, and adhere to lifelong treatment requires considerable commitment and self-discipline, especially when the disease is silent. Over 50% of patients with type 2 diabetes had major gaps in knowledge/skills, which could be improved by structured education programs with adequate contact time and reinforcement (34,35). In several studies, culturally relevant and patient-centered education improved negative emotions and health-coping behaviors (35–37). In other studies, if treatment nonadherence and default were reduced, there was also a reduction in cardiovascular events, all-cause death, hospitalizations, and treatment costs (38–41). In the 2016–2017 U.K. National Diabetes Audit Report, structured education was offered to 77% of newly diagnosed patients with type 2 diabetes, but the attendance rate was <10% (42). These low response rates call for more research to evaluate strategies to increase the reach and user-friendliness of these self-management and empowerment programs, especially for patients who cannot attend these sessions for reasons such as busy work schedule, social isolation, or physical disability.

Using Team-Based Integrated Care to Identify Unmet Needs

In clinical trial settings, use of additional nurses to implement protocols under medical supervision ensured care continuity and good clinical practice during the evaluation of novel therapies. In these settings, the event rates were considerably reduced compared with those observed in real-world practice (43). Some examples of multifaceted care such as the Steno-2 study (44–46) and Japan Diabetes Optimal Integrated Treatment Study for 3 Major Risk Factors of Cardiovascular Disease (J-DOIT3) (47) confirmed that optimal control of HbA_{1c}, blood pressure, and LDL-C reduced micro- and macrovascular complications and death.

In the past two decades, the incidences of diabetes-related cardiovascular-renal complications and death have declined in high-income countries (48–51). However, this was less evident in young people (50–52) who often have competing priorities, different social values, and suboptimal psycho-behavioral health (7,53,54). In LMICs, where the health care system is less well developed and expensive treatment for advanced disease is least affordable, these team-based care models may be particularly relevant. Indeed, our results suggested the superior effects of integrated care in young people, those with suboptimal management, and in patients from Asia. Using Hong Kong as an example, the implementation of a structured assessment and education program using doctor-nurse teams in primary care and hospital settings has increased the attainment rate of HbA_{1c}<7% (53 mmol/mol) from 33% to 50% during a 13-year period, with a significant decline in cardiovascular-renal events and death rates in patients with long disease duration (55).

Strengths and Limitations

Compared with a previous review (12) (Supplementary Table 8), we have included more patients who received complex interventions, including peer support and e-health, lasting at least 12 months and demonstrated the sustained effects, especially in patients who are young, with suboptimal control, and in low-resource settings. One of our limitations is that we have used protocols and criteria defined a priori to overcome search bias and to structuralize evaluation of the studies. The funnel plots showed slight asymmetry related to study heterogeneity, which had been adjusted in the random-effects meta-analysis modeling (Supplementary Figs. 8 and 9). Second, classification of these complex QI strategies is challenging and the presence of some QI strategies in usual care have attenuated the effect size of additional interventions. Third, despite our detailed classification of interventions and adjustment for confounding effects (e.g., patient characteristics, study design, settings, and co-interventions), there remained unknown or unmeasured confounders. Fourth, lack of access to patient-level data limited the robustness of our subgroup analyses. Here, socioeconomic/education status, sex, ethnicity, disease duration, health care system (e.g., public, private, subsidized), and access to drugs can all influence the effectiveness of integrated care. Fifth, without access to patient-level data, we could not comment on the measurement variabilities of these trials and the possibility of regression to the mean. However, in these RCTs with low risk of selection bias, the mean differences of both intervention and control groups were equally affected by regression to the mean and thus should represent a true effect of the intervention. Last, although the greatest effects were observed in trials that came from LMICs, there were only 10 of them, which calls for more studies for validation.

Summary

By leveraging existing resources, changing the workflow, and using a team approach, doctors are in a better position to define the phenotypes and clinical needs of the patients for personalizing care that will improve control of cardiometabolic risk factors and clinical outcomes. These multicomponent integrated care models will particularly benefit those who are young, with suboptimal control, and in low-resource settings where patient volume is large and contact time with doctors is short. However, given the diversity of health care providing and financing policies, socioeconomic development, and expectations of payors, patients, providers, and regulators, context-relevant care models will need to be developed with economic analysis to confirm their acceptability and sustainability.

Funding. L.L.L. is partially supported by the University of Malaya for pursuing a postgraduate study at The Chinese University of Hong Kong.
Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Authors' Contributions. L.L.L. A.P.S.K., and J.C.N.C. conceptualized the study design. L.L.L. and E.S.H.L. performed the literature search, appraised the articles, and performed the analysis with support from J.C.N.C. and A.P.S.K. L.L.L. wrote the first draft and J.C.N.C. finalized the manuscript. All authors participated in the research methodology and data interpretation, revised the manuscript critically for important intellectual content, and approved the final version of the manuscript. J.C.N.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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