Health Information Exchange between Specialists and General Practitioners Benefits Rural Patients

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Abstract

Background Health information exchange (HIE) may improve diagnostic accuracy, treatment efficacy, and safety by providing treating physicians with expert advice. However, most previous studies on HIE have been observational in nature.

Objectives To examine whether collaboration between specialists and general practitioners (GPs) in rural areas via HIE can improve outcomes among patients at low-to-moderate risk of cardiovascular disease, kidney disease, and stroke.

Methods In this randomized controlled trial, the Miyagi Medical and Welfare Information Network was used for HIE. We evaluated the clinical data of 1,092 patients aged ≥65 years living in the rural areas of the Miyagi Prefecture and receiving care from GPs only. High-risk patients were immediately referred to specialists, whereas low-to-moderate risk patients were randomly assigned to an intervention group in which GPs were advised by specialists through HIE ($n = 518$, 38% male, mean age = 76 ± 7 years) or a control group in which GPs received no advice by specialists ($n = 521$, 39% male, mean age = 75 ± 7 years).

Results In the intention-to-treat analysis, all-cause mortality and cumulative incidence of serious adverse events (e.g., hospital admission or unexpected referral to specialists) did not differ between the groups. However, per-protocol analysis controlling for GP adherence with specialist recommendations revealed significantly reduced all-cause mortality ($p = 0.04$) and cumulative serious adverse event incidence ($p = 0.04$) in the intervention group compared with the control group.

Conclusion HIE systems may improve outcomes among low-to-moderate risk patients by promoting greater collaboration between specialists and GPs, particularly in rural areas with few local specialists.

Keywords
- cardiovascular disease
- health information exchange
- kidney disease
- stroke

Background and Significance

Health information exchange (HIE) among clinicians is expanding due to the increasing use of digital medical records and the greater availability, higher transmission capacity, and lower cost of communication and storage platforms such as broadband internet and cloud storage.[1,2] HIE enables the sharing of clinical data among facilities virtually anywhere in the world, potentially providing local practitioners and institutions with the latest information

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and expert advice for enhanced diagnostic accuracy and treatment efficacy. Moreover, the ready availability of patient records can help prevent side effects and allergic reactions to drugs as well as decrease the likelihood of redundant examinations, duplicate prescriptions, and drug interactions.[3,4] However, there is still little quantitative evidence that HIE can improve patient outcomes or lower medical costs,[5,6] mainly because most studies on HIE systems are observational in nature. Although such studies highlight the promise of HIE, only a few randomized controlled trials (RCTs) have demonstrated clear benefits on patient outcome.[5,7]

In 2011, the Great East Japan Earthquake and the associated tsunami destroyed or heavily damaged approximately 600 hospitals and clinics within Miyagi Prefecture, Japan, resulting in a massive loss of patient medical records.[8] Launched in 2012, the Miyagi Medical and Welfare Information Network (MMWIN) serves as a backup system for clinical information obtained from medical facilities, including hospitals, clinics, pharmacies, and nursing homes.[9] Moreover, the MMWIN is now used to share clinical information, such as patients' basic information, history of diagnosis, prescription data, laboratory test data, and hospitalization data among >900 facilities in Miyagi Prefecture using a Standardized Structured Medical Information exchange version 2 storage,[10] which enables the collection of clinical information from different vendor systems. The total number of patients with backup data now exceeds 15 million, and almost 100,000 patients have provided consent to share their clinical information.[11] This HIE system may help bridge the care gap between urban and rural areas as the latter usually have fewer specialists available despite a more rapidly aging population. The MMWIN and other such HIE platforms may thus facilitate collaboration between urban specialists and general practitioners (GPs) in medically underserved rural areas.[12,13]

Objectives

The aim of the present RCT was to examine whether advice and guidance from specialists in urban areas transmitted via the MMWIN can assist GPs and improve prognosis among rural patients at low-to-moderate risk of cardiovascular disease, kidney disease, and stroke.

Methods

This prospective RCT was conducted at six clinics and one small hospital in rural areas within Miyagi Prefecture. All patients provided written informed consent following a complete explanation of the study by the medical staff and research coordinators.

Participants

We recruited patients aged ≥65 years living in rural areas within Miyagi Prefecture who received care from GPs only. Those receiving routine care from any specialists such as cardiologists, nephrologists, and neurologists were excluded. The risks of cardiovascular disease, kidney disease, and stroke were assessed in all patients by specialists based on Japanese guidelines.[14–18] The following factors were measured and considered in risk evaluation: blood pressure, pulse, smoking history, current disease, and blood test results, including hemoglobin level; white blood cell count; serum alanine aminotransferase, aspartate aminotransferase, uric acid, blood urea nitrogen (BUN), creatinine, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, fasting blood sugar, hemoglobin A1c (HbA1c), and B-type natriuretic peptide (BNP) levels; and $CHADS_2$ score. When the necessary data were insufficient (0.5–6.7%), the GPs were asked to conduct the test for evaluation or use surrogate data, such as fasting blood glucose for HbA1c. After 1 month, two patients had withdrawn from the study before risk evaluation. Finally, a total of 1,090 patients were enrolled from November 2015 to September 2016 (39% men, mean age = 76 ± 7 years, range = 65–94 years). Fifty-one high-risk patients were immediately referred to specialists based on the following criteria: current cardiovascular disease (myocardial infarction, angina pectoris requiring coronary artery bypass graft surgery, congestive heart failure with serum BNP level >200 pg/mL or New York Heart Association Classification >Class II, or untreated atrial fibrillation with eligibility for anticoagulation therapy), signs of stroke or cerebral/subarachnoid hemorrhage, renal dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m^2 or uric albumin/creatinine >300 mg), or the GP's judgment. Simple randomization was used to assign low-to-moderate risk patients to either the intervention group or control group. The assignment was disclosed to the enrolled patients. The 1,039 patients with low-to-moderate risk were then randomly assigned to an intervention group ($n = 518$, 38% men, mean age = 76 ± 7 years) or a usual care (control) group ($n = 521$, 39% men, mean age = 75 ± 7 years). In the intervention group, specialists evaluated each participant's risk and provided recommendations to the GP, who then decided whether to alter the treatment strategy. However, 6 months after the first recommendation, specialists provided additional comments to the GPs via MMWIN as well as on paper. We conducted follow-up assessments at 6 months and 1 year to evaluate GP's adherence to recommendations and current risks among patients.

Main Outcome Measures

Patient outcomes were compared between the intervention and control groups 6 months and 1 year after the initial recommendation by the specialist. All-cause mortality and serious adverse events such as hospital admission or unexpected referral to specialists were regarded as primary outcomes. We first performed an intention-to-treat analysis according to the intervention or control group, followed by a per-protocol analysis based on whether GPs strictly adhered to the specialist's recommendations (adherence group) or not (nonadherence group).

Statistical Analysis

Data are presented as mean ± standard deviation (SD). The Kolmogorov–Smirnov test was used to examine the

normality of each distribution. Normally distributed variables were compared by using the independent samples Student's *t*-test, and non-normally distributed variables were compared by using the Mann–Whitney U test. Kaplan–Meier analyses were used to evaluate all-cause mortality and cumulative incidence of serious adverse events. Log-rank tests were used to compare survival time between the intervention and control groups. All analyses were performed by using R version 3.6.0 (http://www.R-project.org/). Two-sided *p*-values of <0.05 were considered significant.

To assure confidentiality, identifying information was removed before analysis. Due to the nature of the intervention, neither the patients nor the physicians were blinded to group assignment. However, outcome assessors and data analysts were blinded.

Results

Recommendations for advanced treatment were provided to GPs by specialists for 51 high-risk patients from among registered 1,090 patients. ►Table 1 compares the clinical and demographic characteristics of high- and low-to-moderate risk groups, revealing significant differences in serum creatinine, BUN, BNP, and HbA1c levels, as well as in the use of anticoagulants. ►Table 2 shows that there were no significant differences in demographic or baseline clinical parameters between the intervention group and control group among 1,039 patients with low-to-moderate risk.

Five deaths occurred in the intervention group and nine in the control group during the follow-up period. Furthermore, 40 serious adverse events occurred in the intervention group, whereas 43 occurred in the control group. There was no significant difference in all-cause mortality or cumulative incidence of serious adverse events between the groups ($p = 0.4$ and $p = 1.0$, respectively; ►Fig. 1).

We also evaluated the adherence of GPs to recommendations from specialists. Based on this evaluation, we then categorized patients into an adherence group including just those with GPs following specialist's advice, and a non-adherence group including both patients in the intervention group with GPs who did not follow specialist's recommendations as well as all patients in the control group (►Table 3). As shown in ►Fig. 2, significant improvements in survival ($p = 0.04$) and cumulative incidence of serious adverse events ($p = 0.04$) were observed in the adherence group.

Discussion

In this RCT, we examined the potential clinical benefits of collaborative care between specialists and GPs for patients at low-to-moderate risk of cardiovascular disease, kidney disease, and stroke. While our intention-to-treat analysis did not indicate significant improvements in outcomes in the intervention group compared with the control group, a subsequent per-protocol analysis further stratifying the intervention group according to GP adherence with specialist's advice indicated that this collaboration reduced both all-cause death and the cumulative incidence of serious adverse events. To the best of our knowledge, this is the first RCT to show that the use of HIE for collaboration between rural GPs and specialists can significantly improve patient prognosis, although a similar protocol is underway, for which the results are not yet available.[19]

The primary finding of this study is that adherence to recommendations provided by specialists is critical for improving patient care via HIE. The rapid pace of medical advances results in the frequent updating of treatment guidelines, and thus, many potential discrepancies between recommended and current treatment strategies. For instance, Dai et al reported that the overall adherence by GPs to the American Diabetes Association guidelines for monitoring diabetes was less than optimal.[20] Ensuring highest quality of care for chronic diseases such as diabetes, heart failure, renal insufficiency, and stroke may require more frequent communication with specialists in these fields.[21–24] Indeed, the European Society of Cardiology/European Society of Hypertension guidelines recommend close collaboration between GPs and specialists when treating patients with hypertension, as this results in better management of blood pressure.[25–28] In the present study, early recommendations for advanced treatment were provided for six patients in the intervention group, whereas only one patient from the control group was referred for advanced care.

Our results further demonstrate that the clinical information obtained via HIE allows specialists to provide the most current advice to GPs. The MMWIN contains important clinical information such as diagnoses, laboratory data, prescription records, hemodialysis records, and imaging data. While the current study relied mainly on laboratory and prescription data, the MMWIN could also allow other specialists to provide advice on medication dosage and potential contraindications to improve treatment efficacy and safety with more data available.[29] However, it can be costly and time consuming to implement an analysis of complete patient data.[30] Our findings suggest that laboratory and prescription data provide sufficient information for specialists to help GPs in treating patients at risk for cardiovascular disease, kidney disease, and stroke. In addition, factors that promote or hinder GP adherence should be addressed. Based on the results of our questionnaire, the attending GPs preferred the specialists' recommendations. The average evaluation was 7.6 out of 10 (data not shown). They were satisfied with finding cases of asymptomatic heart failure, renal insufficiency, and diabetes, and they gained more confidence regarding the treatment. However, they complained about an increased number of tests and the time required to perform them, which were problematic. These points should be considered to encourage adherence of GPs.

Although our study presented strong evidence for the benefits of HIE in remote regions, several studies have mentioned the importance of communication among clinicians in suburban locations as well. Martin et al investigated the progress of emergency medical service–HIE integration,[31] and Kruse et al highlighted patient handoff among different levels of care.[32] Both studies concluded that there

Table 1 Baseline characteristics of patients in high- and low-to-moderate risk groups

	High risk	Low-to-moderate risk	*p*-Value
n	51	1,029	
Male (%)	45	36	0.34
Age (y)	76.4 ± 7.8	75.7 ± 6.9	0.62
Current smoker (%)	12	4	0.01
Hypertension (%)	80	86	0.24
Diabetes (%)	43	22	<0.001
Hyperlipidemia (%)	51	40	<0.001
Systolic blood pressure (mmHg)	133.5 ± 16.0	132.3 ± 12.9	0.62
Diastolic blood pressure (mmHg)	77.4 ± 11.9	74.6 ± 9.2	0.10
Pulse (bpm)	73.8 ± 11.6	74.5 ± 12.2	0.94
Body weight (kg)	60.4 ± 11.2	57.9 ± 10.8	0.08
Laboratory parameters			
White blood cell (1,000/mm^3)	6.2 ± 1.7	5.9 ± 3.0	0.24
Hemoglobin (g/dL)	13.0 ± 1.8	13.2 ± 1.5	0.26
Total protein (g/dL)	7.0 ± 0.6	7.2 ± 0.5	0.12
Aspartate aminotransferase (IU/L)	26.0 ± 17.8	25.2 ± 16.2	0.35
Alanine transaminase (IU/L)	23.4 ± 17.8	23.1 ± 23.5	0.72
Creatinine (mg/dL)	1.1 ± 0.8	0.7 ± 0.2	<0.001
Blood urea nitrogen (mg/dL)	21.7 ± 10.5	16.5 ± 4.7	<0.001
Low-density lipoprotein (mg/dL)	108.1 ± 36.3	100.5 ± 39.6	0.86
High-density lipoprotein (mg/dL)	57.1 ± 18.5	60.5 ± 17.7	0.09
Triglycerides (mg/dL)	141.5 ± 138.6	123.7 ± 78.6	1.00
Total cholesterol (mg/dL)	187.2 ± 45.7	183.3 ± 36.2	0.80
Hemoglobin A1c	7.1 ± 1.4	5.9 ± 0.7	<0.001
Na (mEq/L)	142.5 ± 2.8	142.4 ± 2.7	0.55
K (mEq/L)	4.7 ± 0.7	4.4 ± 0.5	0.01
B-type natriuretic peptide (pg/mL)	305.2 ± 229.1	74.4 ± 105.9	0.01
Medications			
Angiotensin-converting enzyme inhibitor (%)	15.7	10.3	0.31
Angiotensin-receptor blocker (%)	54.9	49.8	0.48
Beta-blocker (%)	15.7	5.3	0.05
Calcium blocker (%)	68.6	65.9	0.69
Aldosterone antagonist (%)	3.9	2.6	0.64
Statin (%)	43.1	39.7	0.64
Acetylsalicylic acid (%)	15.7	8.2	0.16
Warfarin (%)	15.7	2.1	0.01
Direct oral anticoagulant (%)	11.8	2.5	0.04
Loop diuretic (%)	13.7	3.2	0.03

Note: Continuous variables are expressed as mean ± standard deviation.

were difficulties in the adoption of HIE systems. Similarly, previous studies have cited several limitations and barriers to implementing and maintaining HIE systems.[33–36] However, most previous HIE studies have been observational, which has the potential to underestimate benefits due to selection bias and confounding influences. Conversely, RCTs have suggested that HIE can improve health care delivery by identifying medication discrepancies, previous test results, and changes in various clinical parameters over time.[37,38] Although our results demonstrate that HIE can improve

Table 2 Baseline characteristics of randomized low-to-moderate risk patients

	Intervention	No intervention	*p*-Value
n	518	521	
Male (%)	38	39	0.61
Age (y)	75.9 ± 6.9	75.4 ± 6.9	0.35
Current smoker	4.2	3.8	0.74
Hypertension (%)	85	87	0.50
Diabetes (%)	22	22	0.91
Hyperlipidemia (%)	38.4	42.0	0.23
Systolic blood pressure (mmHg)	132.7 ± 13.2	132.0 ± 12.6	0.51
Diastolic blood pressure (mmHg)	74.7 ± 9.7	74.4 ± 8.8	0.43
Pulse (bpm)	74.7 ± 12.6	74.2 ± 11.8	0.47
Body weight (kg)	57.4 ± 10.5	58.5 ± 11.1	0.10
Laboratory parameters			
White blood cell (1,000/mm^3)	5.8 ± 1.5	6.0 ± 3.9	0.42
Hemoglobin (g/dL)	13.2 ± 1.5	13.3 ± 1.6	0.44
Total protein (g/dL)	7.1 ± 0.5	7.2 ± 0.5	0.34
Aspartate aminotransferase (IU/L)	24.4 ± 8.8	25.9 ± 21.1	0.78
Alanine transaminase (IU/L)	22.0 ± 12.5	24.1 ± 30.6	0.40
Creatinine (mg/dL)	0.7 ± 0.2	0.7 ± 0.2	0.88
Blood urea nitrogen (mg/dL)	16.6 ± 4.7	6.5 ± 4.6	0.61
Low-density lipoprotein (mg/dL)	102.4 ± 39.2	98.6 ± 39.9	0.08
High-density lipoprotein (mg/dL)	60.4 ± 16.7	60.6 ± 18.6	0.97
Triglycerides (mg/dL)	120.5 ± 67.0	126.8 ± 88.4	0.29
Total cholesterol (mg/dL)	185.0 ± 34.6	181.7 ± 37.6	0.26
Hemoglobin A1c	5.9 ± 0.7	6.0 ± 0.7	0.38
Na (mEq/L)	142.4 ± 2.7	142.3 ± 2.7	0.44
K (mEq/L)	4.4 ± 0.5	4.4 ± 0.5	0.87
B-type natriuretic peptide (pg/mL)	88.3 ± 108	80.7 ± 121	0.25
Medications			
Angiotensin-converting enzyme inhibitor (%)	9.8	10.7	0.63
Angiotensin-receptor blocker (%)	49.6	49.9	0.93
Beta-blocker (%)	5.4	5.2	0.87
Calcium blocker (%)	64.1	67.8	0.21
Aldosterone antagonist (%)	2.7	2.5	0.83
Statin (%)	37.8	41.7	0.21
Acetylsalicylic acid (%)	6.8	9.8	0.08
Warfarin (%)	2.5	1.7	0.38
Direct oral anticoagulant (%)	2.9	2.1	0.42
Loop diuretic (%)	3.1	3.3	0.87

Note: Continuous variables expressed as the mean ± standard deviation.

patient care by connecting specialists to GPs, further studies are required to determine whether HIE can ameliorate both the disease burden on patients and the economic burden on society.[33,35,38,39]

The present study has several limitations. First, GPs were not required to adhere to specialists' recommendations for patients in the intervention group. On the contrary, they might have acquired knowledge from specialists' comments that may have affected patients' prescriptions in the control group despite there being no direct recommendation from specialists. This may explain the lack of significant improvement in the intention-to-treat analysis. However, due to

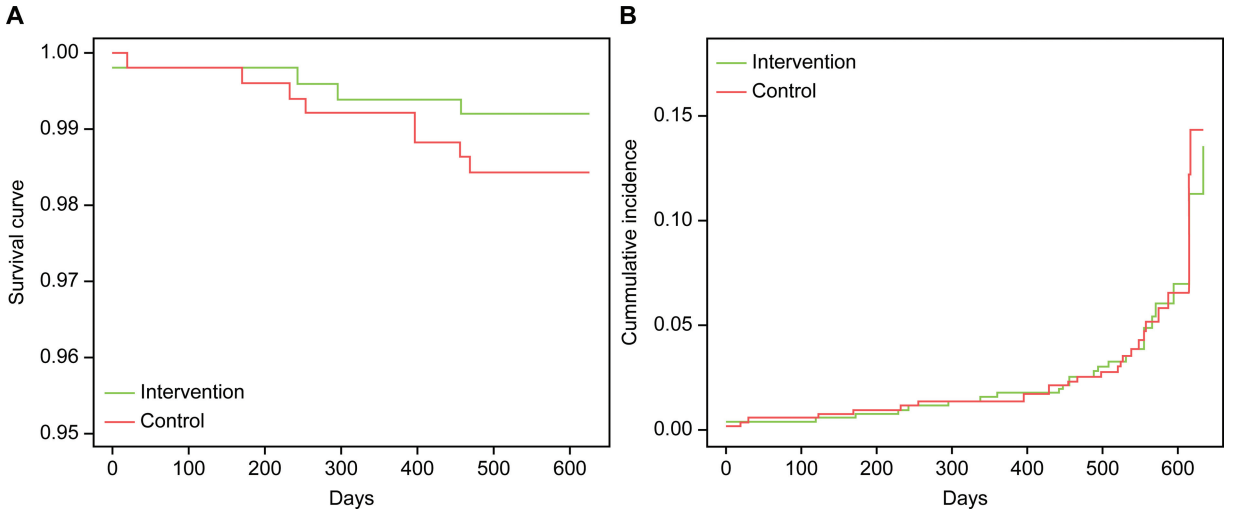

Fig. 1 Survival curves and cumulative incidence of serious adverse events in the intention-to-treat analysis. Kaplan–Meier estimates of all-cause mortality (**A**) and cumulative incidence of serious adverse events (**B**) for all patients grouped according to the intention-to-treat principle.

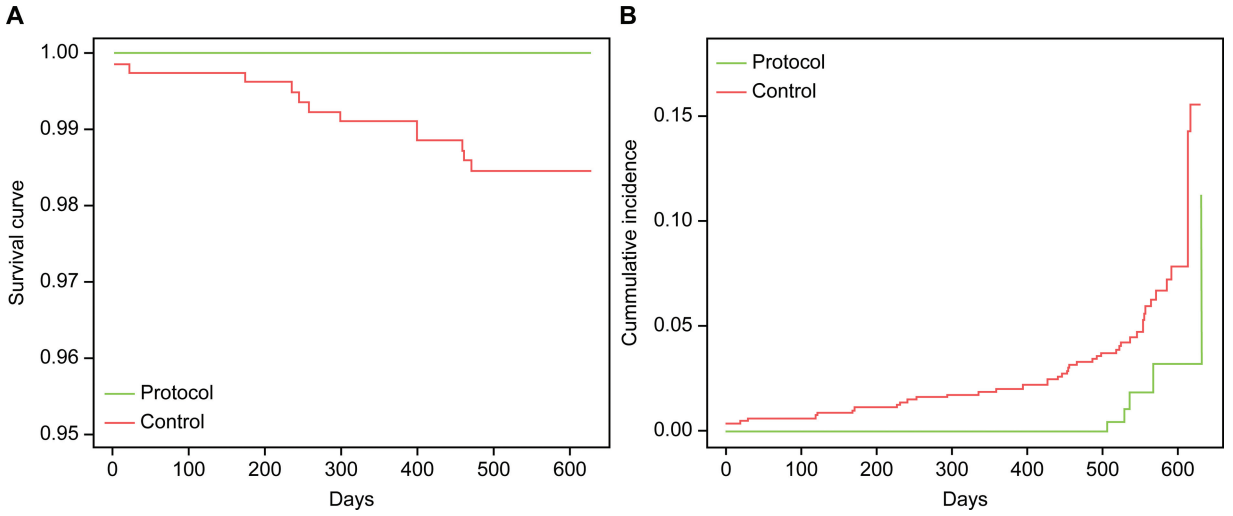

Fig. 2 Survival curves and cumulative incidence of serious adverse events in the per-protocol analysis. Kaplan–Meier estimates of all-cause mortality (**A**) and cumulative incidence of serious adverse events (**B**) for all patients grouped according to whether the treating general practitioner followed the specialist's advice (adherence group). All other patients in both intervention and control groups were included in the nonadherence group.

ethical concerns, we did not prevent GPs from altering treatment strategies in the control group. Alternatively, our per-protocol analysis highlighted the significant benefits of HIE, particularly in cases of early intervention before unexpected aggravation of disease. Second, the lack of significant group difference in intention-to-treat analysis might have resulted from an inadequate sample size, given the low-to-moderate risk for the target diseases and relatively brief study period. However, we calculated the sample size before the study, and the event rates were almost equivalent to our expectations. Therefore, we believe that the similarity between the groups in intention-to-treat analysis was due to a higher than expected rate of nonadherence by the GPs treating intervention group patients. Although the event rate was low, which made it difficult to determine each patient's true level of risk, our objective was improved management of patients with low-to-moderate risk of cardiovascular disease, kidney disease, and stroke rather than precise risk assessment. Third, since clinical notes were not available on MMWIN, we could not verify the reasons why the GPs selected the treatment or whether patients may have rejected the treatment. This failed to reveal the complex decision making-process the GPs underwent despite the specialist's recommendation. This may have resulted in selection bias. Further studies should clarify the critical factors involved in the adherence of GPs. Last, our analysis was limited to clinics and hospitals in Miyagi Prefecture, as the MMWIN includes data for this region only. Given that the benefits of HIE may vary among regions or countries, further studies are required to verify our findings.

Table 3 Baseline characteristics of patients in the adherence and nonadherence groups

	Adherence	Nonadherence	*p*-Value
n	234	805	
Male (%)	34	40	0.15
Age (y)	75.4 ± 6.8	75.7 ± 7.0	0.46
Current smoker (%)	4.3	4.0	0.83
Hypertension (%)	87	86	0.78
Diabetes (%)	24	21	0.46
Hyperlipidemia (%)	41	40	0.90
Systolic blood pressure (mmHg)	132.3 ± 12.1	131.9 ± 15.3	0.88
Diastolic blood pressure (mmHg)	74.4 ± 9.0	74.3 ± 10.3	0.44
Pulse (bpm)	74.7 ± 12.1	73.8 ± 13.8	0.47
Body weight (kg)	56.9 ± 10.0	58.1 ± 11.2	0.13
Laboratory data			
White blood cell (1,000/mm^3)	5.8 ± 1.4	5.8 ± 1.8	0.54
Hemoglobin (g/dL)	13.2 ± 1.4	13.2 ± 1.5	0.57
Total protein (g/dL)	7.1 ± 0.4	7.2 ± 0.5	0.29
Aspartate aminotransferase (IU/L)	24.2 ± 8.6	25.5 ± 10.3	0.67
Alanine transaminase (IU/L)	22.6 ± 14.0	22.4 ± 13.7	0.74
Creatinine (mg/dL)	0.7 ± 0.2	0.7 ± 0.2	0.20
Blood urea nitrogen (mg/dL)	15.9 ± 3.8	16.7 ± 4.8	0.19
Low-density lipoprotein (mg/dL)	111.7 ± 28.7	107.7 ± 26.1	0.04
High-density lipoprotein (mg/dL)	60.6 ± 17.4	60.4 ± 17.7	0.96
Triglycerides (mg/dL)	123.7 ± 69.5	123.6 ± 81.1	0.67
Total cholesterol (mg/dL)	184.7 ± 31.6	183.0 ± 37.1	0.43
Hemoglobin A1c	5.9 ± 0.6	6.0 ± 0.7	0.40
Na (mEq/L)	142.7 ± 2.5	142.3 ± 2.7	0.04
K (mEq/L)	4.4 ± 0.4	4.4 ± 0.5	0.52
B-type natriuretic peptide (pg/mL)	84.1 ± 122.1	71.8 ± 101.0	0.55
Medications			
Angiotensin-converting enzyme inhibitor (%)	7.2	11.3	0.07
Angiotensin-receptor blocker (%)	48.3	50.1	0.61
Beta-blocker (%)	4.7	5.5	0.65
Calcium blocker (%)	66.7	65.7	0.79
Aldosterone antagonist (%)	1.7	2.9	0.33
Statin (%)	40.1	39.6	0.88
Acetylsalicylic acid (%)	4.3	9.4	0.01
Warfarin (%)	3.0	1.9	0.29
Direct oral anticoagulant (%)	3.0	2.4	0.59
Loop diuretic (%)	3.0	3.2	0.86

Note: Patients of general practitioners not following specialist's recommendations and all control group patients were included in the nonadherence group. Continuous variables are expressed as the mean ± standard deviation.

Conclusion

Our findings support the utility of HIE for promoting collaboration between specialists and GPs, which may in turn improve the clinical care of patients at risk of cardiovascular disease, kidney disease, and stroke in rural areas.

Clinical Relevance Statement

This controlled clinical trial highlights the potential of health information exchange to promote collaboration between specialists and GPs, particularly in rural areas. Both all-cause death and cumulative adverse event frequency were lower among patients of GPs following the advice provided by specialists than patients of GPs not implementing specialist advice. Nation-wide studies are warranted to confirm and extend these findings.

Multiple Choice Questions

1. How were subjects with high risk treated in this study?
   a. Randomized
   b. Treated with medication
   c. Excluded from this study
   d. Hospitalized

   Correct Answer: The correct answer is option c. High-risk patients were excluded from this study and immediately referred to specialists.

2. Which protocol in this study showed a significant improvement in outcomes among low-to-moderate risk patients by collaboration between specialists and general practitioners in rural areas?
   a. Intention-to-treat analysis
   b. Per-protocol analysis
   c. Both of intention-to-treat and per-protocol analyses
   d. Interim analysis

   Correct Answer: The correct answer is option b. Per-protocol analysis showed significant improvement in outcomes. This suggested that adherence of general practitioners to specialists' comment seemed to be critical for improving the patients' outcomes.

Protection of Human and Animal Subjects

The study was performed in compliance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and was reviewed by Tohoku University Ethics Committee and registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000018552).

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Conflict of Interest

None declared.

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