Executive Summary

A Health Technology Evaluation Study for Reviewing Possibility of Data Linkage

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▢ Introduction

The public data of Koreans under universal health coverage can be utilized for medical research, enabling the timely production of economic and clinical evidence. The National Evidence-based Healthcare Collaborating Agency (NECA) has a legal basis for accessing public data from different organizations. This study aimed to integrate Korean public data, focusing on healthcare technology assessment.

▢ Healthcare technology assessment to determine the feasibility of public health data linkage

The NECA has identified the need to link different data sources and therefore studied the use of oral hypoglycemic agents and the relationship between cardiovascular risk and cancer survival.

This study required health insurance claims data, cancer statistics in Korea, and data on cause of death. The Korea Central Cancer Registry authorized

and provided National Health Insurance Service (NHIS) data including personal identifiable information. The NHIS extracted the health insurance claims data. Personal identifiable information was subsequently deleted. The NHIS confirmed study participant deaths, and Statistics Korea (KOSTAT) deleted personal identifiable information and constructed an integrated database.

▢ Relationship between oral hypoglycemic drug use and cardiovascular disease risk in diabetics patients

Ⅰ. Methods

In order to identify the risk of major cardiovascular disease associated with therapeutic drugs for diabetes in adult patients, the following data sources were used in a retrospective cohort study: NHIS health insurance claims data, beneficiary enrollment and demographic data, National Health Screening Program data, and data on cause of death. New diabetes patients were defined as adults prescribed at least 6 months (180 days) of oral hypoglycemic agents and were successively prescribed the same medicine for at least 3 months (90 days) between January 1, 2005 and December 31, 2011.

Oral hypoglycemic agents were classified as standard metformin, sulfonylurea, thiazolidinedione (TZD), DPP-4 inhibitors, and others. The first-line drug was defined as the first drug prescribed for more than 90 consecutive days; patients were further divided into the metformin and non-metformin groups. The second-line drug was defined as a drug prescribed for more than 90 consecutive days, including sulfonylurea, TZD, and DPP-4 inhibitors.

The primary outcome was major cardiovascular disease development (including death due to cardiovascular disease, hospitalization for myocardial infarction, and hospitalization for stroke). The secondary outcome was all-cause mortality, death due to cardiovascular disease, hospitalization for myocardial infarction, and hospitalization for stroke and hospitalization for congestive heart failure. Covariates selected to identify the effects of oral hypoglycemic agents on the occurrence of major cardiovascular disease were sex, age, hypertension, hyperlipidemia, smoking, coronary artery bypass

surgery (CABG) or consideration of coronary artery angioplasty, and the Charlson comorbidity index. The Cox proportional hazards model was used to evaluate the risk of major cardiovascular disease in association with oral hypoglycemic agent use.

Ⅱ. Results and conclusions

1. Relationship between metformin use and occurrence of major cardiovascular disease.

Of 1,035,824 patients prescribed oral hypoglycemic agents during the study period, 432,081 patients met the inclusion criteria. The metformin group consisted of 208,990 patients (49.4%). Baseline demographic characteristics were similar between the metformin and non-metformin groups.

The risk of cardiovascular disease occurrence (i.e., death due to cardiovascular disease, hospitalization for myocardial infarction, or hospitalization for stroke) was 14% lower in the metformin group than the non-metformin group (hazard ratio [HR]: 0.86, 95% confidence interval [CI]: 0.83–0.88, p<0.0018).The trend was similar after adjusting for covariates; the risk of cardiovascular disease occurrence was 6% lower in the metformin group (HR: 0.94, 95% CI: 0.91–0.97, p<0.001).

The risk of secondary outcomes was significantly lower in the metformin group. The trend remained similar after adjusting for non-cardiovascular death (HR: 0.95, 95% CI: 0.91–1.00, p: 0.05), myocardial infarction (HR: 0.86, 95% CI: 0.81–0.91, p<0.001), and congestive heart failure (HR: 0.93, 95% CI: 0.88–0.99, p: 0.02).

2. Relationship between secondary drug use and occurrence of major cardiovascular disease.

Among 208,990 patients newly diagnosed with type 2 diabetes, 157,509 were prescribed a second-line drug; sulfonylurea, TZD, and DPP-4 inhibitors were prescribed for 123,830 (78.6%), 9,848 (6.3%), and 23,831 (15.1%) patients, respectively. The baseline characteristics were similar among all groups.

For the second-line drug added on to metformin; compared to the sulfonylurea group, the risk of cardiovascular disease was lower by 42% in both the TZD group (HR: 0.58, 95% CI: 0.51–0.66, p<0.001) and the DPP-4

inhibitor group (HR: 0.58, 95% CI: 0.52-0.65, p<0.001). After adjusting for covariates, the TZD and DPP-4 inhibitor groups had a significantly lower risk of cardiovascular disease than the sulfonylurea group (TZD group HR: 0.65, 95% CI: 0.47-0.90, p: 0.009; DPP-4 inhibitor group HR: 0.65, 95% CI: 0.54-0.78, p<0.001).

The risks of secondary outcomes were significantly lower in the TZD and DPP-4 inhibitor groups than the sulfonylurea group. The trends were similar after adjusting for covariates. Compared to the sulfonylurea group, all-cause mortality and stroke risk were significantly lower in the TZD group, while all-cause mortality, cardiovascular and non-cardiovascular death, and risk of stroke were significantly lower in the DPP-4 inhibitor group.

▢ Comparative Effectiveness of metformin on the mortality of Cancer Patients with Type 2 Diabetes

Ⅰ. Methods

In order to determine the effect of metformin in cancer patients with diabetes, the cancer survival data registry, cancer statistics in Korea, health insurance claims data, and data on cause of death were linked. Patients who underwent curative resection between 2005 and 2011 were included. The liver cancer (C22), pancreatic cancer (C25), colon cancer (C18, C19), and rectal cancer (C20) registry data were used for analysis.

The exclusion criteria were based on cancer etiology according to age, specific procedure, stage, medical history, complications, point of follow-up, and follow-up duration. New diabetic patients were defined as adults prescribed at least 6 months (180 days) of oral hypoglycemic agents.

Oral hypoglycemic agents were classified as standard metformin, sulfonylurea, TZD, DPP-4 inhibitors, and others. The metformin group was defined as patients prescribed metformin for more than 90 consecutive days. Drug adherence to metformin was defined by the medication possession ratio (MPR), which was calculated by dividing the time metformin was prescribed by the time any oral hypoglycemic drug was prescribed. Outcomes included were mortality; death from cancer; and relapse rate identified in liver, colon, and rectal cancer. The common covariates were sex, age, and Charlson comorbidity index. Covariates related to the type of cancer were hepatitis (B

or C) and the use of antivirals in liver cancer, cancer stage and adjuvant chemotherapy in colon cancer, and pre- and postoperative chemotherapy in rectal cancer.

The Kaplan-Meier method and Cox proportional hazard model were used to compare the mortality and cancer relapse with respect to metformin use. The hazard ratios (HRs) were calculated after adjusting for clinically and statistically significant baseline characteristics. Sensitivity analysis was performed. The diagnosis date of cancer and metformin administration period were varied to determine the influence of immortal time bias. The analysis was performed only for subjects with complete data.

Ⅱ. Results

1. Liver Cancer

Of 5,494 early liver cancer patients undergoing surgery, 4,743 were excluded because they did not have type 2 diabetes. The final analysis included 533 and 218 patients in the metformin and non-metformin groups, respectively.

The overall mortality rates in the metformin and non-metformin groups were 36.6% and 56.9%, respectively. Mortality rates due to liver cancer in the metformin and non-metformin groups were 31.7% and 50.9%, respectively; the relapse rates were 41.3% and 66.8%, respectively. All outcome indicators had a lower incidence in the metformin group. After adjusting for baseline characteristics, the Cox proportional hazards model revealed that the risks of overall mortality (HR: 0.39, 95% CI: 0.311-0.493, $p<0.001$), liver-related mortality (HR: 0.38, 95% CI: 0.301-0.491, $p<0.001$), and relapse (HR: 0.41, 95% CI: 0.332-0.517, $p<0.001$) were lower in the metformin group than the non-metformin group.

Patients in the metformin group with high medication adherence (MPR ≥ 80%) had lower all-cause mortality risk (HR: 0.53, 95% CI: 0.389-0.711, $p<0.001$) and liver-related mortality risk (HR:0.57, 95% CI: 0.410-0.777, $p<0.001$) than groups with lower adherence.

2. Pancreatic Cancer

Of 1,919 pancreatic cancer patients who received surgery, 1,155 were excluded because they did not have diabetes. The analysis included 530 and

234 patients in the metformin and non-metformin groups, respectively.

The overall mortality rates in the metformin and non-metformin groups were 72.5% and 81.6%, respectively. The cumulative incidences of pancreatic cancer-related deaths were 70.4% and 79.5% in the metformin and non-metformin groups, respectively. The risks of all outcomes were lower in the metformin group. The Cox proportional hazards model of the mortality risk adjusting for baseline characteristics showed the mortality risk was 27.3% lower in the metformin group than the non-metformin group (HR: 0.727, 95% CI: 0.611–0.866, p: 0.004). In addition, the risk of pancreatic cancer-related death was 27.3% lower in the metformin group than the non-metformin group (HR: 0.727, 95% CI: 0.609–0.868, p: 0.004).

In the metformin group, high medication adherence (MPR ≥ 80%) was associated with a lower all-cause mortality risk (HR: 0.586, 95% CI: 0.462–0.743, p<0.001) and pancreatic cancer-related mortality risk (HR: 0.595, 95% CI: 0.468–0.757, p<0.001) than the other groups.

3. Colon Cancer

Of 45,447 colon cancer patients who received surgery, 36,735 were excluded because they did not have diabetes. The final analysis included 7,091 and 1,621 patients in the metformin and non-metformin groups, respectively.

The overall mortality rates in the metformin and non-metformin groups were 12.8% and 26.9%, respectively. The cumulative incidences of colon cancer-related deaths in the metformin and non-metformin groups were 8.7% and 16.5%, respectively; relapse rates were 11.3% and 17.6%, respectively. The risks of all outcomes were lower in the metformin group.

After adjusting for baseline characteristics, the Cox proportional hazards model showed overall mortality and colon cancer mortality were 48.8% (HR: 0.512, 95% CI: 0.456–0.574, p<0.001) and 43.5% lower (HR: 0.565, 95% CI: 0.489–0.653, p<0.001) in the metformin group than the non-metformin group, respectively. The risk of relapse in the metformin group was 44.8% lower than that the non-metformin group (HR: 0.552, 95% CI: 0.482–0.633, p<0.001).

Patients in the metformin group with high medication adherence (MPR ≥ 80%) had lower all-cause mortality (HR: 0.651, 95% CI: 0.569–0.745, p<0.001)

and colorectal cancer-related mortality (HR: 0.664, 95% CI: 0.564-0.782, p<0.001) than groups with lower adherence.

4. Rectal Cancer

Of 26,410 rectal cancer patients who received surgery, 21,907 were excluded because they did not have diabetes. The final analysis included 3,694 and 809 patients in the metformin and non-metformin groups, respectively.

The overall mortality rates in the metformin and non-metformin groups were 14.6% and 24.2%, respectively. The cumulative incidences of rectal cancer-related deaths in the metformin and non-metformin groups were 9.8% and 15.6%, respectively; the relapse rates were 19.6% and 30.8%, respectively. The risks of all outcomes were lower in the metformin group. After adjusting for baseline characteristics, the Cox proportional hazards model showed the overall mortality risk was 34.7% (HR: 0.653, 95% CI: 0.554-0.770, p<0.001) in the metformin group than the non-metformin group. The risks of rectal cancer-related death and relapse were 33.8% (HR: 0.662, 95% CI: 0.540-0.812, p<0.001) and 44.1% lower (HR: 0.551, 95% CI: 0.483-0.646, p<0.001) in the metformin group, respectively.

Patients in the metformin group with high medication adherence (MPR ≥ 80%) had lower all-cause mortality risk (HR: 0.631, 95% CI: 0.527-0.755, p<0.001) and rectal cancer-related mortality risk (HR: 0.598, 95% CI: 0.479-0.746, p<0.001) than other groups with lower adherence.

▢ Discussion and conclusion

This study linked data from various sources. However, there were difficulties owing to the stringent laws on the use of personal information. Therefore, it may be helpful to establish a legal basis to waive the informed consent process for individual subjects when conducting research for public benefit.

Regarding the cardiovascular disease occurrence in type 2 diabetic patients treated with oral hypoglycemic agents, metformin use significantly reduced cardiovascular risk. In addition, in the context of secondary drugs, the TZD and DPP-4 inhibitor groups had significantly lower risks than the sulfonylurea

group. The results of the present study form a foundation for a future large-scale randomized controlled clinical trial.

Liver, pancreatic, colon, and rectal cancer patients with type 2 diabetes and on metformin (with high medication adherence) who underwent curative resection exhibited a lower all-cause mortality rate than other groups. In liver, colon, and rectal cancer, the relapse rates were lower with metformin use. These findings based on public data in Korea provide valuable epidemiological evidence of the anti-cancer effect of metformin, specifically by reducing mortality and relapse rates.

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▢ Key words

Data integration, diabetes, oral hypoglycemic agents, metformin, cardiovascular disease, liver cancer, pancreatic cancer, colon cancer, rectal cancer