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Boehringer Ingelheim

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1. LIST OF ABBREVIATIONS

ACEI	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin Receptor Blocker
BI	Boehringer Ingelheim
CCB	Calcium Channel Blockers
CHD	Coronary heart disease
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DMRP	Data management and review plan
eGFR	Estimated glomerular filtration rate
EMR	Electronic medical records
ENCEPP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
ESRD	End stage renal disease
GPP	Good Pharmacoepidemiology Practice
HDL	High-density lipoprotein
ICD	International classification of disease
IDF	International Diabetes Federation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	Low-density lipoprotein
LOS	Length of stay
MALB	Microalbumin
MI	Myocardial infarction
NIS	Non-interventional Study
OHA	Oral hypoglycemic agent
PI	Principal Investigator
SEAP	Statistical and epidemiological analysis plan
SOP	Standard Operating Procedures
TC	Total cholesterol
TG	Triglyceride

2. RESPONSIBLE PARTIES

SEAP author is:

- [redacted]

SEAP reviewers are:

- BI NIS [redacted]
- NIS Data [redacted]
- RWE CoE [redacted]
  or [redacted]
- TM Epi [redacted]
- NIS Statistician [redacted]

3. PURPOSE AND SCOPE

The research question and objectives, study design, data source, study size, data analysis will be clarified as in the NIS protocol; detailed primary outcomes, secondary outcomes and further outcomes will be shown as tables; software applied in this study will be described for each procedure; Rules handling outliers, inconsistencies and missing values are described in SEAP.

4. AMENDMENTS AND UPDATES

None

5. RESEARCH QUESTION AND OBJECTIVE

The study aimed to investigate the clinical characteristics, treatment, and economic burden of disease of Chinese diabetic/non-diabetic patients with/without established cardiovascular disease, chronic kidney disease, or at high cardiovascular risk, including:

- Primary objectives: describe the proportion of Chinese diabetic/non-diabetic patients with established cardiovascular disease, CKD, or at high cardiovascular risk including hypertension and hyperlipidemia;
- Secondary objectives: describe the demographic characteristics of the last visit for all patients, and the demographic characteristics of inpatients over time; investigate the clinical characteristic for all patients;
- Further objectives: examine economic burden of disease of Chinese diabetic/non-diabetic patients with/without established cardiovascular disease, CKD, or at high cardiovascular risk; explore the trends of clinical characteristics, treatment pattern, economic burden of inpatients over time.

6. RESEARCH METHODS

6.1 STUDY DESIGN

This study is an observational, cross-sectional study based on a routinely collected database. We constructed four groups for comparison: the group A and group B included all diabetic patients with/without established CV disease, CKD, or at high CV risk, respectively. The group C included all non-diabetic patients with established cardiovascular disease, chronic kidney disease, or at high cardiovascular risk. The group D will be constructed to match group A, non-diabetic patients will be included without established cardiovascular disease, chronic kidney disease, and not at high cardiovascular risk. For group D, we will randomly sample study populations to acquire a 1:1 sample of non-diabetic patients without disease by matching on age and gender with group A.

6.2 SETTING

After considering the availability, feasibility, coverage, number of included population and data integrity, this study is based on Tianjin regional medical database from 01/01/2015 to 31/12/2019.

6.3 STUDY POPULATION

Diabetic/non-diabetic patients with/without established cardiovascular disease, chronic kidney disease, or at high cardiovascular risk.

Inclusion Criteria:

1) Patients in the Tianjin regional database from 01/01/2015 to 31/12/2019.
2) Group A: patients with diagnosis of diabetes, and with diagnosis of cardiovascular disease, heart failure, chronic kidney disease or at high cardiovascular risk;
3) Group B: patients with diagnosis of diabetes, but not with diagnosis of cardiovascular disease, heart failure, chronic kidney disease or at high cardiovascular risk;
4) Group C: patients with diagnosis of cardiovascular disease, heart failure, chronic kidney disease or at high cardiovascular risk, but not with diagnosis of diabetes;
5) Group D: patients without diagnosis of cardiovascular disease, heart failure, chronic kidney disease or at high cardiovascular risk, and without diagnosis of diabetes. We will randomly select a group of non-diabetic patients without any of the above diseases by matching on age and gender.

Definition of diabetes, cardiovascular disease, chronic kidney disease and high cardiovascular risk

- Diabetes: patients with at least 1 discharged diagnosis or 2 outpatient diagnosis of diabetes (ICD-10 E10-E14)
- Cardiovascular disease: patients with at least 1 discharged diagnosis or 2 outpatient diagnosis of ischemic heart diseases (ICD-10 I20~I25); or patients with at least 1 discharged diagnosis or 2 outpatient diagnosis of cerebrovascular diseases (ICD-10 I60~I69); or patients with at least 1 discharged diagnosis or 2 outpatient diagnosis of ischemic peripheral artery disease (ICD-10 E10.501, E11.603, E14.501, E14.606, E14.503, I73.9, I99.03, I99.04);
- Heart failure: patients with at least 1 discharged diagnosis or 2 outpatient diagnosis of heart failure (ICD-10 I50);
- Chronic kidney disease: inpatients with at least once 1 discharged diagnosis CKD (ICD-10 N18), or inpatients with the last estimated glomerular filtration rate (eGFR, calculated by CKD-EPI equation) <60 mL/min/1.73 m2 or prescription of dialysis, but not with the diagnosis of acute kidney injury (ICD-10 N17); or outpatients with at least 2 diagnosis of CKD or with two consecutive eGFR (calculated by CKD-EPI equation) <60 mL/min/1.73 m2 by 90 days or more.
- High cardiovascular risk: patients with at least 1 discharged diagnosis or 2 outpatient diagnosis of hypertension (ICD-10 I10~I15); or at least 1 discharged diagnosis or 2 outpatient diagnosis of hyperlipidemia (ICD-10 E78.001-E78.003, E78.101, E78.203, E78.301-E78.304, E78.306, E78.401, E78.501, E78.902)

Exclusion Criteria:

1) Patients with non-Chinese nationalities;
2) Duplicated storage (records with same inpatient code).

6.4 STUDY VISITS

Not applicable, this study is based on routinely collected database.

7. VARIABLES

7.1 Exposures

Not applicable. Four groups will be defined according to the diagnosis and laboratory measurements. Diagnosis of diabetes and high-cardiovascular risk differ among groups.

7.2 Outcomes

Our primary outcomes will be the proportion of diabetic/non-diabetic patients with disease/risk Secondary outcomes include demographic characteristics (e.g. age, gender, insurance payment) and clinical characteristics (e.g. HbA1c, random blood glucose, serum creatine) of patients.. Further outcomes include economic burden of disease of diabetic/non-diabetic patients with or without disease/risk (e.g. length of stay, hospital cost).

7.2.1 Primary outcomes

1) The proportion of diabetic/non-diabetic patients with established cardiovascular disease, chronic kidney disease, or at high cardiovascular risk.
2) The proportion of diabetic patients with established cardiovascular disease, chronic kidney disease, or at high cardiovascular risk among all patients with diabetes;
3) The proportion of non-diabetic patients with established cardiovascular disease, chronic kidney disease, or at high cardiovascular risk among patients without diabetes;

Table 1. The proportion of patients with disease or risk among diabetic or non-diabetic patients

	2015		2016		…	2019		Overall	
	Outpatients n (%)	Inpatients n (%)	Outpatients n (%)	Inpatients n (%)		Outpatients n (%)	Inpatients n (%)	Outpatients n (%)	Inpatients n (%)
Patients diagnosed with diabetes									
Group A (n, %)									
with cardiovascular disease									
with chronic kidney disease									
at high cardiovascular risk									
Patients diagnosed without diabetes									
Group C (n, %)									
with cardiovascular disease									
with chronic kidney disease									
at high cardiovascular risk									

Note: Group A: Diabetes with cardiovascular disease, chronic kidney disease or at high cardiovascular risk; Group B: Diabetes without cardiovascular disease, chronic kidney disease or at high cardiovascular risk; Group C: Non-diabetes with cardiovascular disease, chronic kidney disease or at high cardiovascular risk; Group D: Non-diabetes without cardiovascular disease, chronic kidney disease or at high cardiovascular risk;

7.2.2 Secondary outcomes

1) The demographic characteristics of the latest visit for all patients, as well as the trends for inpatients over time (2015, 2017, and 2019 respectively). Clinical characteristics of outpatients and hospitalized patients will be described respectively.

Table 2. The demographic and clinical characteristics of the latest visit

	Outpatients				Inpatients				Total patients
	Group A	Group B	Group C	Group D	Group A	Group B	Group C	Group D	
Demographic characteristics in 2015									
Age (mean, sd)									
Gender (n, %)									
Insurance payment (n, %)									
Demographic characteristics in 2017									
Age (mean, sd)									
Gender (n, %)									
Insurance payment (n, %)									
Demographic characteristics in 2019									
Age (mean, sd)									
Gender (n, %)									
Insurance payment (n, %)									

Note Group A Diabetes with cardiovascular disease, chronic kidney disease or at high cardiovascular risk; Group B Diabetes without cardiovascular disease, chronic kidney disease or at high cardiovascular risk; Group C Non-diabetes with cardiovascular disease, chronic kidney disease or at high cardiovascular risk; Group D Non-diabetes without cardiovascular disease, chronic kidney disease or at high cardiovascular risk;

2) The clinical characteristics of the studied population of the latest visit for all patients, as well as the trends for inpatients over time (2015, 2017, and 2019 respectively). Clinical characteristics of outpatients and hospitalized patients will be described respectively.

Table 3. The clinical characteristics of the latest visit

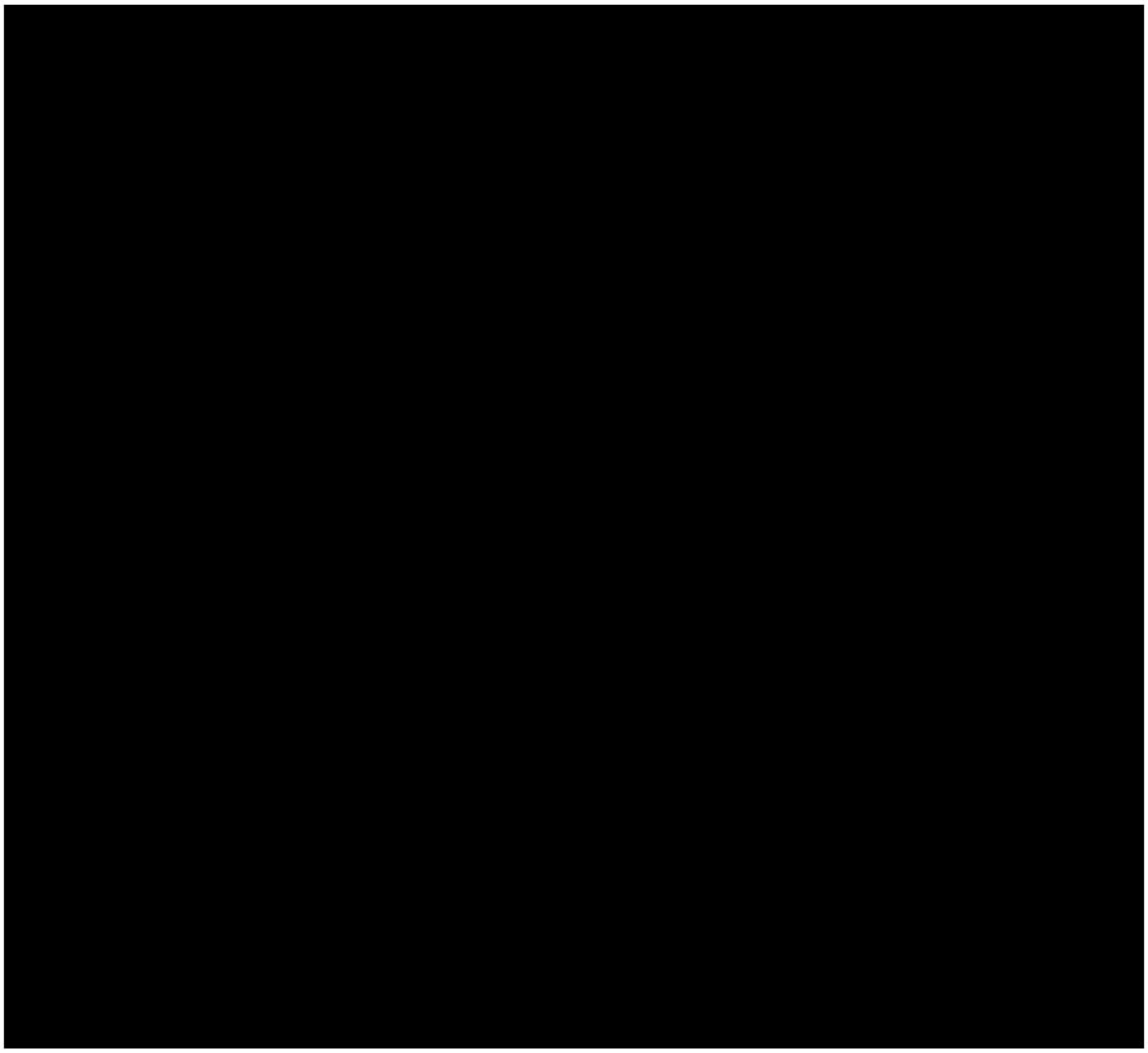
	Outpatients				Inpatients				Total patients
	Group A	Group B	Group C	Group D	Group A	Group B	Group C	Group D	
Clinical characteristics in 2015									
Department of discharge									
Death									
Clinical characteristics in 2017									
Department of discharge									
Death									
Clinical characteristics in 2019									
Department of discharge									
Death									

Table 4. The laboratory measurement of the latest visit

	Outpatients				Inpatients				Total patients
	Group A	Group B	Group C	Group D	Group A	Group B	Group C	Group D	

Clinical characteristics in 2015
HbA1c
Random blood glucose
Serum creatinine
Clinical characteristics in 2017
HbA1c
Random blood glucose
Serum creatinine
Clinical characteristics in 2019
HbA1c
Random blood glucose
Serum creatinine

Note Group A Diabetes with cardiovascular disease, chronic kidney disease or at high cardiovascular risk; Group B Diabetes without cardiovascular disease, chronic kidney disease or at high cardiovascular risk; Group C Non-diabetes with cardiovascular disease, chronic kidney disease or at high cardiovascular risk; Group D Non-diabetes without cardiovascular disease, chronic kidney disease or at high cardiovascular risk;



[redacted]

[redacted]

[redacted]

7.3 Covariates

No applicable. This is a cross-sectional study aiming to describe the proportion, clinical characteristics and economic burden.

8. DATA SOURCES

Tianjin regional database covers individual-level health information from hundreds of public hospitals. There were 40 tertiary hospitals, 32 secondary hospitals and 276 community hospitals Tianjin. Through integrating EMR systems of hospitals by patient unique identify code, the database contains comprehensive information regarding clinical care, such as patients' basic information, medical advice, diagnosis, laboratory examination, medical records and medical costs. It could be a valuable big data resource for clinical studies. There were approximately 600,000 patients diagnosed with diabetes in 40 tertiary hospitals from 01/01/2015 to 31/12/2019. Of these, 10,000 patients were with comprehensive information through integrating EMR systems.

9. DATA MANAGEMENT AND SOFTWARE/TOOLS

9.1 Software/Tools

PL/SQL version 13.0.2.1898 for data extraction at first step;
R version 4.0.3 for further data cleaning, transformation and data analysis;
All operation will be carried out on the elastic-compute-services.

9.2 Handling of Missing Values

We will clean data using transparent and prespecified rules, including the development of variable dictionaries, standardization of medical texts, and approaches to inconsistent data and outliers. A multidisciplinary research team will be assembled for developing the rules, including epidemiologists, statisticians, and clinical experts.

9.3 Handling of Inconsistencies in Data and Outliers

We will clean data using transparent and prespecified rules, including the development of variable dictionaries, standardization of medical texts, and approaches to inconsistent data and outliers. A multidisciplinary research team will be assembled for developing the rules, including epidemiologists, statisticians, and clinical experts.

10. DATA ANALYSIS

10.1 Main analysis

The analyses will mainly describe the patient demographic characteristics, comorbidities, complications, treatment pattern and economic burden based on 40 hospitals EMRs of Tianjin regional database.

Characteristics presented as continuous data will be summarized through means, standard deviations, medians, minimum and maximum values; whereas, categorical data will be summarized as counts and proportions.

All tests of statistical significance among different subgroups (age, gender, department, underlying diseases, etc.) will be two-sided unless otherwise specified; any test resulting in $p<0.05$ will be considered statistically significant. Student-t test, analysis of variance, chi-square test and other rank test will be mainly applied for this study.

[redacted]

10.3 Safety Analysis

Not applicable.

11. QUALITY CONTROL

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities.

Before analyses start, 200 randomly selected medical chart will be fully reviewed by well-trained experts to validate the accuracy and sensibility of code used to identify patients with cardiovascular disease or at high cardiovascular risk. This QC procedure for database study would be performed by [redacted].

In the procedure of data extraction, investigators will verify if the extracted data conform to predefined inclusion and exclusion criteria, 1000 records will be sampled randomly from extracted database;

Procedure of cleaning will be conducted according to the predefined reference range, unit, diagnosis code, and other standard;

The quality assurance auditor will have access to all results of the study, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

12. REFERENCES

12.1 PUBLISHED REFERENCES

R Federation ID. IDF Diabetes Atlas. 8th edn ed, 2017.
J-2016-316(24) Dieleman JL, Baral R, Birger M, et al. US Spending on Personal Health Care and Public Health, 1996-2013. JAMA 2016;316(24):2627-46. [published Online First: 2016/12/28]
J-1998-339(4) Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. The New England journal of medicine 1998;339(4):229-34. [published Online First: 1998/07/23]
J-2005-28(12) Juutilainen A, Lehto S, Ronnemaa T, et al. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. Diabetes care 2005;28(12):2901-7. [published Online First: 2005/11/25]
J-2008-358(24) Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. The New England journal of medicine 2008;358(24):2560-72. [published Online First: 2008/06/10]
J-1993-16(1) Nelson RG, Knowler WC, Pettitt DJ, et al. Diabetic kidney disease in Pima Indians. Diabetes care 1993;16(1):335-41. [published Online First: 1993/01/01]
J-2004-364(9438) Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet (London, England) 2004;364(9438):937-52. [published Online First: 2004/09/15]
J-2010-375(9733) Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet (London, England) 2010;375(9733):2215-22. [published Online First: 2010/07/09]
J-1999-100(10) Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1999;100(10):1134-46. [published Online First: 1999/09/08]
J-1973-32(1) Margolis JR, Kannel WS, Feinleib M, et al. Clinical features of unrecognized myocardial infarction--silent and symptomatic. Eighteen year follow-up: the Framingham study. The American journal of cardiology 1973;32(1):1-7. [published Online First: 1973/07/01]
J-2006-47(1) Scognamiglio R, Negut C, Ramondo A, et al. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. Journal of the American College of Cardiology 2006;47(1):65-71. [published Online First: 2006/01/03]

12.2 UNPUBLISHED REFERENCES

ANNEX 1. ADDITIONAL INFORMATION

None

[redacted]

Study Title: Characteristics, treatment, and economic burden of disease of Chinese diabetic/non-diabetic patients with/without established cardiovascular disease, chronic kidney disease, or at high cardiovascular risk

Study Number: 1245-0203

Protocol Version: 2.0

I herewith certify that I agree to the content of the study SEAP and to all documents referenced in the study SEAP.

Position: NIS [redacted] Name/Date: [redacted] Signature:

Position: NIS [redacted] Name/Date: [redacted] Signature:

Position: RWE COE Name/Date: [redacted] Signature:

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[redacted]
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签名原因：我批准此文档
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