APAC Community Call

March 20, 2025

Agenda

- Study Proposals from OHDSI China

#	Presenter	Title
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2	Jiaqi Liu	Association between fasting plasma glucose levels and annual hospitalization days: a multicenter study using the OHDSI framework
3	Jiaqi Liu	Postoperative LDH levels and their impact on survival in melanoma and other cancer patients: a multicenter study using the OHDSI framework
4	Xiowei Chen	The effect of angiotensin receptor blocker (ARB) on the development of chronic diabetic complications in patients with type 2 diabetes mellitus: a target trial emulation study
5	Yongqi Zheng	Safety outcomes of semaglutide in type 2 diabetes using regional health data: a target trial emulation
6	Xiaowei Liang	Retrospective study on the impact of BMI trajectories on long-term prognosis in CKD patients using electronic health records
7	Sihui Luo	Studying the disease trajectory of type 2 diabetes with a transformer-based model

Zhongshan Hospital Affiliated with Fudan University

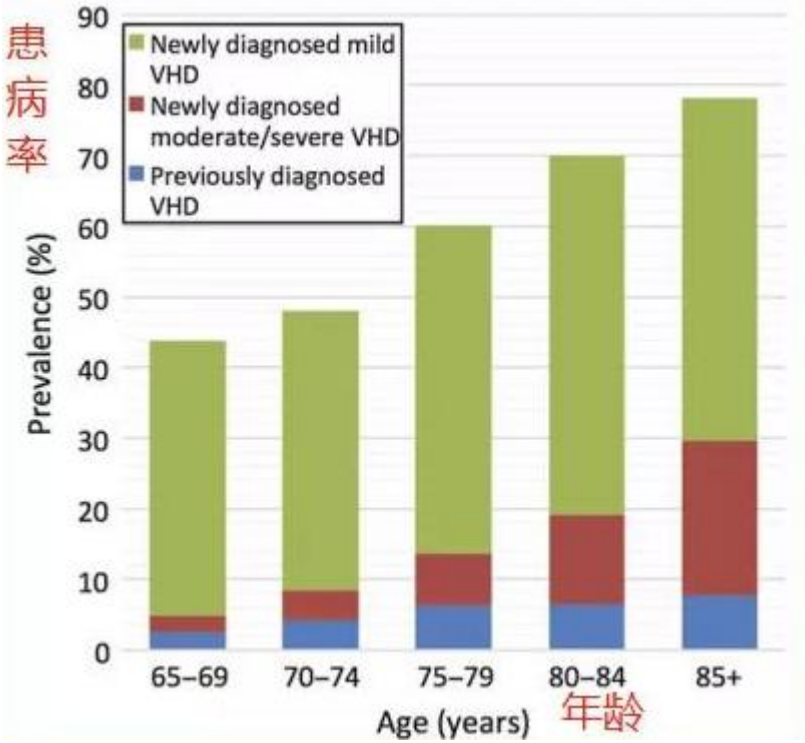
Postoperative Lipid Levels and the Durability of Bioprosthetic Valves

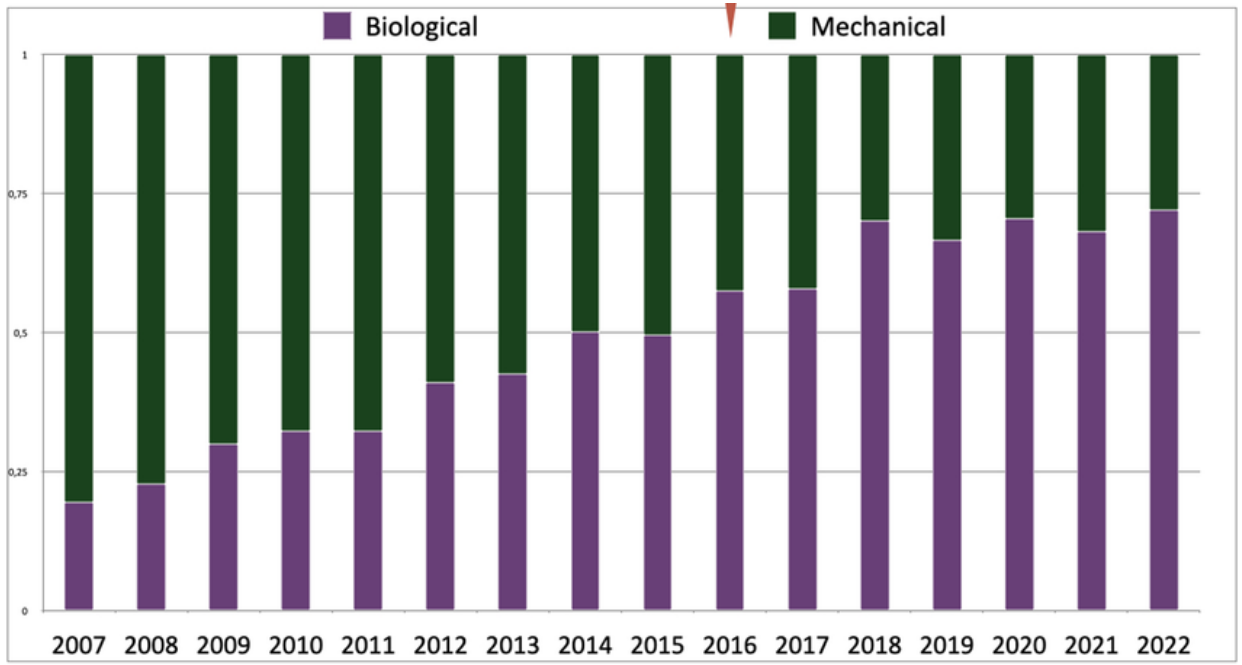
Exploring the Impact of Dyslipidemia on Bioprosthetic Valve Function

Presenter: Dr. Wang

2025.03.20

Valve heart disease(VHD) and Bioprosthetic Valves

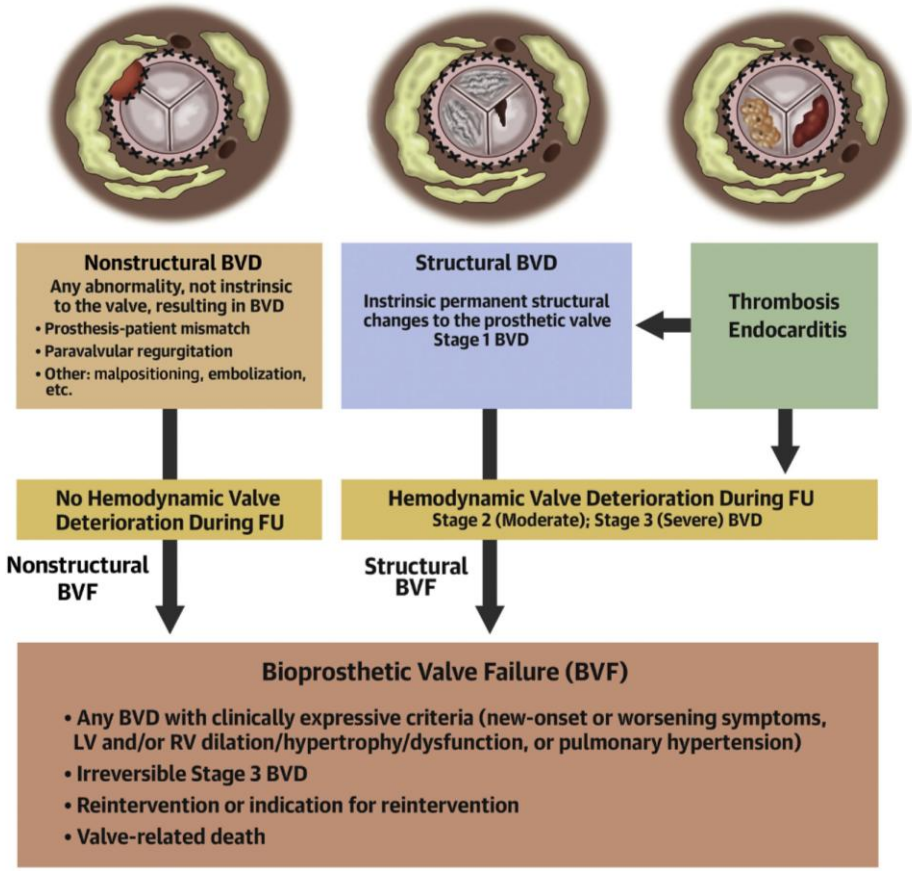




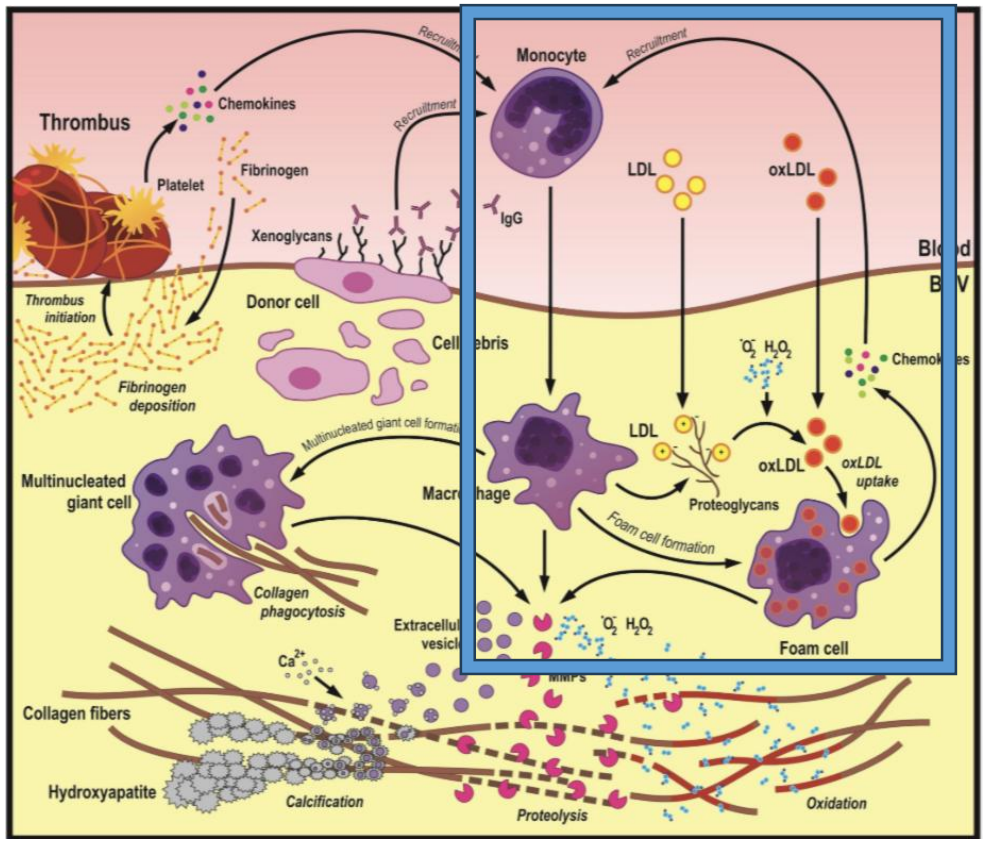
- Over the world, the incidence of valvular heart disease is showing an increasing trend with the aging of the population (left Figure). At the same time, the proportion of patients undergoing replacement with biological valves is also gradually increasing (right Figure).
- In 2019, the clinical application rate of bioprosthetic valves in China was only about 15% (approximately 22,000 units).By 2021, the usage of bioprosthetic valves in China had approached 40,000 units

[1] Peters AS, Duggan JP, Trachiotis GD, Antevil JL. Epidemiology of Valvular Heart Disease. Surg Clin North Am. 2022 Jun;102(3):517-528. doi: 10.1016/j.suc.2022.01.008. PMID: 35671771.
[2] Wang Y, Fu Y, et. Recent advancements in polymeric heart valves: From basic research to clinical trials. Mater Today Bio. 2024 Aug 10;28:101194. doi: 10.1016/j.mtbio.2024.101194..

Definition and Causes of Bioprosthetic Valve Dysfunction(BVD)



BVD = bioprosthetic valve dysfunction;
BVF = bioprosthetic valve failure;
FU = follow-up.



Lipids deposition and lipid-mediated inflammation

[6] Pibarot P, Herrmann HC; Heart Valve Collaboratory. Standardized Definitions for Bioprosthetic Valve Dysfunction Following Aortic or Mitral Valve Replacement: JACC State-of-the-Art Review. J Am Coll Cardiol. 2022 Aug 2;80(5):545-561. doi: 10.1016/j.jacc.2022.06.002. PMID: 35902178.

The existing research results are controversial

REVIEW ARTICLE | Originally Published 21 September 2020 | Check for updates

Degeneration of Bioprosthetic Heart Valves: Update 2020

Alexander E. Kostyunin, PhD, Arseniy E. Yuzhalin, DPhil, Maria A. Rezvova, MSc, Evgeniy A. Ovcharenko, PhD, Tatiana V. Glushkova, PhD, and Anton G. Kutikhin, MD, PhD | AUTHOR INFO & AFFILIATIONS

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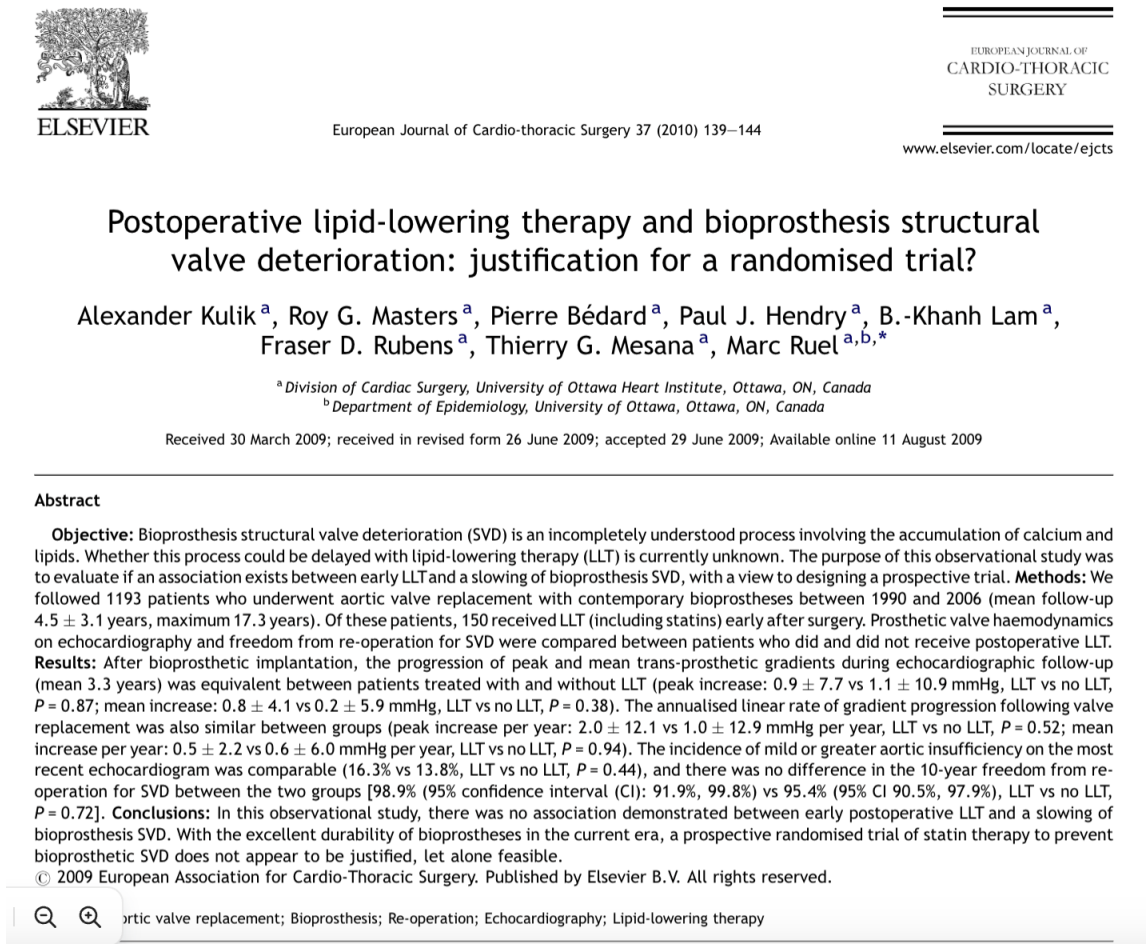
Native Valve Calcification, Atherosclerosis, and SVD: Are There Common Mechanisms?

SVD shares some risk factors with atherosclerosis and calcific aortic stenosis, including the metabolic syndrome, diabetes mellitus, smoking, and hyperlipidemia.[6] Therefore, common mechanisms are conceivable for these diseases. Both calcific aortic stenosis and atherosclerosis are characterized by endothelial dysfunction, lipid deposition in the subendothelial layer, and intense lipid-driven inflammatory reaction, all leading to the activation of resident cells (eg, VICs or smooth muscle cells), and their fibroproliferative response with ultimate tissue mineralization. Dysfunctional BHVs display a considerable lipid deposition and contain foam cells, an atherosclerosis-specific cell type.[73] More important, these lipid deposits primarily consist of oxidized low-density lipoprotein (LDL), another characteristic marker of atherosclerosis.[72] Oxidized LDL is recognized for the stimulation of macrophages and foam cells to secrete MMPs. In agreement, immunohistochemistry studies of explanted BHVs revealed that macrophages and

Hyperlipidemia is an risk factor for bioprosthesis SVD



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EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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Postoperative lipid-lowering therapy and bioprosthesis structural valve deterioration: justification for a randomised trial?

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Abstract

Objective: Bioprosthesis structural valve deterioration (SVD) is an incompletely understood process involving the accumulation of calcium and lipids. Whether this process could be delayed with lipid-lowering therapy (LLT) is currently unknown. The purpose of this observational study was to evaluate if an association exists between early LLT and a slowing of bioprosthesis SVD, with a view to designing a prospective trial. **Methods:** We followed 1193 patients who underwent aortic valve replacement with contemporary bioprostheses between 1990 and 2006 (mean follow-up 4.5 ± 3.1 years, maximum 17.3 years). Of these patients, 150 received LLT (including statins) early after surgery. Prosthetic valve haemodynamics on echocardiography and freedom from re-operation for SVD were compared between patients who did and did not receive postoperative LLT. **Results:** After bioprosthetic implantation, the progression of peak and mean trans-prosthetic gradients during echocardiographic follow-up (mean 3.3 years) was equivalent between patients treated with and without LLT (peak increase: 0.9 ± 7.7 vs 1.1 ± 10.9 mmHg, LLT vs no LLT, $P = 0.87$; mean increase: 0.8 ± 4.1 vs 0.2 ± 5.9 mmHg, LLT vs no LLT, $P = 0.38$). The annualised linear rate of gradient progression following valve replacement was also similar between groups (peak increase per year: 2.0 ± 12.1 vs 1.0 ± 12.9 mmHg per year, LLT vs no LLT, $P = 0.52$; mean increase per year: 0.5 ± 2.2 vs 0.6 ± 6.0 mmHg per year, LLT vs no LLT, $P = 0.94$). The incidence of mild or greater aortic insufficiency on the most recent echocardiogram was comparable (16.3% vs 13.8%, LLT vs no LLT, $P = 0.44$), and there was no difference in the 10-year freedom from re-operation for SVD between the two groups [98.9% (95% confidence interval (CI): 91.9%, 99.8%) vs 95.4% (95% CI 90.5%, 97.9%), LLT vs no LLT, $P = 0.72$]. **Conclusions:** In this observational study, there was no association demonstrated between early postoperative LLT and a slowing of bioprosthesis SVD. With the excellent durability of bioprostheses in the current era, a prospective randomised trial of statin therapy to prevent bioprosthetic SVD does not appear to be justified, let alone feasible.

ortic valve replacement; Bioprosthesis; Re-operation; Echocardiography; Lipid-lowering therapy

Lipid-lowering therapy cannot slow bioprosthesis SVD

Research Objectives

- To investigate **the impact** of different postoperative lipid levels on the deterioration process of bioprosthetic valve function, and to determine which specific subtype of hyperlipidemia accelerates the deterioration of bioprosthetic valves.
- To establish **a model to describe the relationship** between lipid levels and indicators related to the deterioration of bioprosthetic valves (such as transvalvular pressure gradient and degree of valve calcification), providing a basis for clinical monitoring and intervention.
- To evaluate the potential impact of postoperative **lipid control** at different levels on the durability of bioprosthetic valves, offering references for formulating individualized lipid management strategies.

Research Workflow

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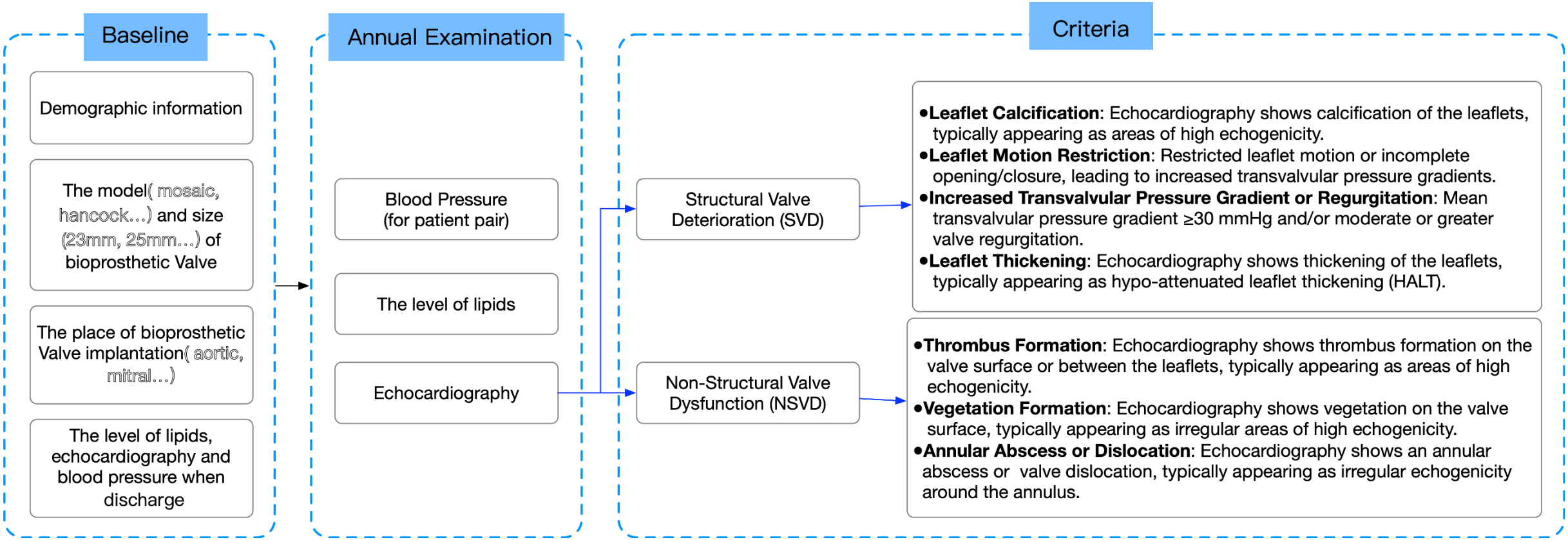


Data Requirement

Zhongshan Hospital Affiliated with Fudan University

ID	Name	Domain	ID	Name	Domain
3046965	Sex	Observation	4205523	Biological atrioventricular valve replacement	Procedure
4265453	Age	Observation	4326744	Blood pressure	Measurement
4013886	Race	Observation	44809580	Total cholesterol level	Observation
4255407	Cardiac surgery	Observation	4055695	Plasma triglyceride measurement	Measurement
4327260	Intraoperative echocardiography	Procedure	4101713	High density lipoprotein cholesterol measurement	Measurement
21494247	Date and time of surgery	Observation	4012479	Low density lipoprotein cholesterol measurement	Measurement
4230911	Echocardiography	Procedure	37170638	Apolipoprotein A1 mass concentration in plasma	Measurement
4019824	Transesophageal echocardiography	Procedure	4193714	Plasma apolipoprotein B measurement	Measurement
764010	Porcine cardiac valve replacement	Procedure	4007663	Lipoprotein (a) measurement	Measurement
4145119	Heart valve replacement	Procedure	44789304	Very low density lipoprotein triglyceride measurement	Measurement

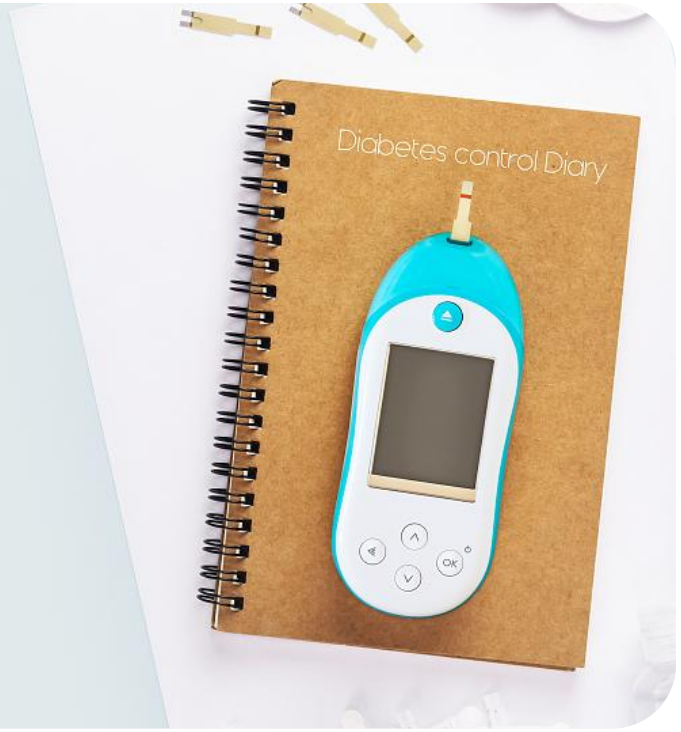
Thanks for listening!

Association Between Fasting Plasma Glucose Levels and Annual Hospitalization Days: A Multicenter Study Using the OHDSI Framework

Dr. Jiaqi Liu
Department of Plastic Surgery
Zhongshan Hospital Affiliated to Fudan University

CONTENTS

Background——Fasting Plasma Glucose Levels



Abnormal FPG levels relate to metabolic health, diabetes, and increased healthcare resource use. High levels can cause disorders, inflammation, and exacerbate chronic diseases, potentially leading to longer hospital stays

Background——OHDSI Framework about FPG

Investigates association between FPG levels and annual hospitalization days using OHDSI framework, to inform glucose management and resource allocation strategies

China Situation——Diagnosis and Metric

CONCEPT_ID	NAME	DOMAIN
201820	Diabetes mellitus	Condition
4099214	Type 1 diabetes mellitus with ulcer	
4227657	Skin ulcer due to diabetes mellitus	
4099651	Type 2 diabetes mellitus with ulcer	
4063569	Ischemic ulcer of foot due to diabetes mellitus	
4159742	Diabetic foot ulcer	
43530690	Foot ulcer due to type 2 diabetes mellitus	
192279	Disorder of kidney due to diabetes mellitus	
4266041	Visually threatening diabetic retinopathy	

CONCEPT_ID	NAME	DOMAIN
4156660	Fasting blood glucose measurement	Measurement
44811255	Blood glucose level after breakfast	
44811253	Blood glucose level after lunch	
44811256	Blood glucose level before breakfast	
44811254	Blood glucose level before lunch	
45770632	Blood glucose level during night	
4235110	Total glycosylated hemoglobin level	

China Situation——Treatments and Outcomes

CONCEPT_ID	NAME	DOMAIN
1361259	Insulin, regular, human Injection	Drug
45884746	Hospitalization	Meas Value
44790591	Patient transfer to outpatient department	Observation
32253	Outpatient Laboratory Visit	Visit
9202	Outpatient Visit	Observation
44792364	Hospital based outpatient care	Observation
42537845	Outpatient care management	Procedure
36713731	Management of outpatient discharge	Observation
4129946	Duration of treatment	Meas Value
4061268	Death in hospital	Observation

Problem statement——Exploring the Relationship FPG Levels and Hospitalization

- Evaluating how glucose abnormalities affect hospitalization rates, aiming to quantify their impact on healthcare resources

- Standard multicenter data in OHDSI to understand the relationship between plasma glucose levels and hospitalization days. This uses OHDSI's multicenter data to study how plasma glucose levels relate to the length of hospital stays, identifying trends for better care planning

Definition of HPG Levels——Criteria and Variables

Inclusion / Exclusion Criteria

- ✓ Age ≥ 18 years, regardless of gender
- ✓ At least two fasting blood glucose test records during the study period
- ✓ Complete hospitalization records (including annual hospitalization days)
- ✗ Patients with incomplete blood glucose test data or hospitalization records

Study Variables

- Exposure variable: Fasting blood glucose levels (continuous variable, stratified into normal, hyperglycemia, and hypoglycemia)
- Outcome variables: Annual hospitalization days (continuous variable, aggregated from all hospitalization records)

Definition of HPG Levels——Statistical Analysis

- **Descriptive Analysis:** Summarize baseline characteristics and annual hospitalization days distribution across different blood glucose level groups.
- **Univariate Analysis:** Compare differences in annual hospitalization days among blood glucose level groups using ANOVA or non-parametric tests.
- **Multivariate Analysis:** Use linear regression models to assess the independent impact of fasting blood glucose levels on annual hospitalization days,
- adjusting for covariates.
- **Subgroup Analysis:** Stratify by age (<65 vs. ≥65 years),
- gender, and chronic medical history to evaluate differential
- effects of fasting blood glucose levels on hospitalization days.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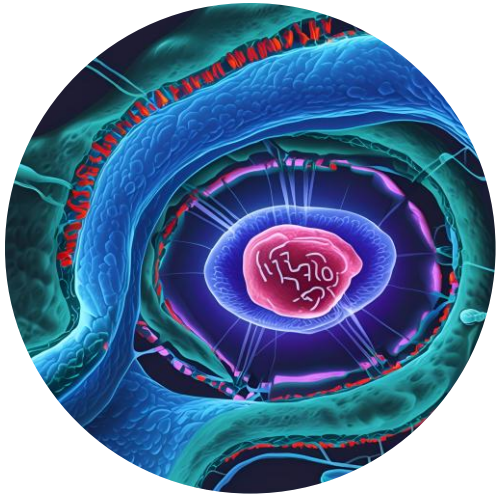
Postoperative LDH Levels and Their Impact on Survival in Melanoma and Other Cancer Patients: A Multicenter Study Using the OHDSI Framework

Dr. Jiaqi Liu
Department of Plastic Surgery
Zhongshan Hospital Affiliated to Fudan University

CONTENTS

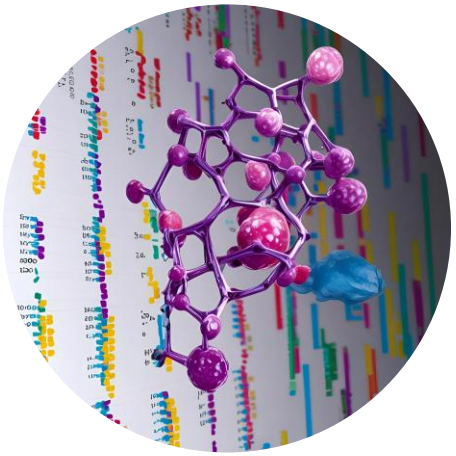
Background——LDH in Tumor Metabolism

LDH Function

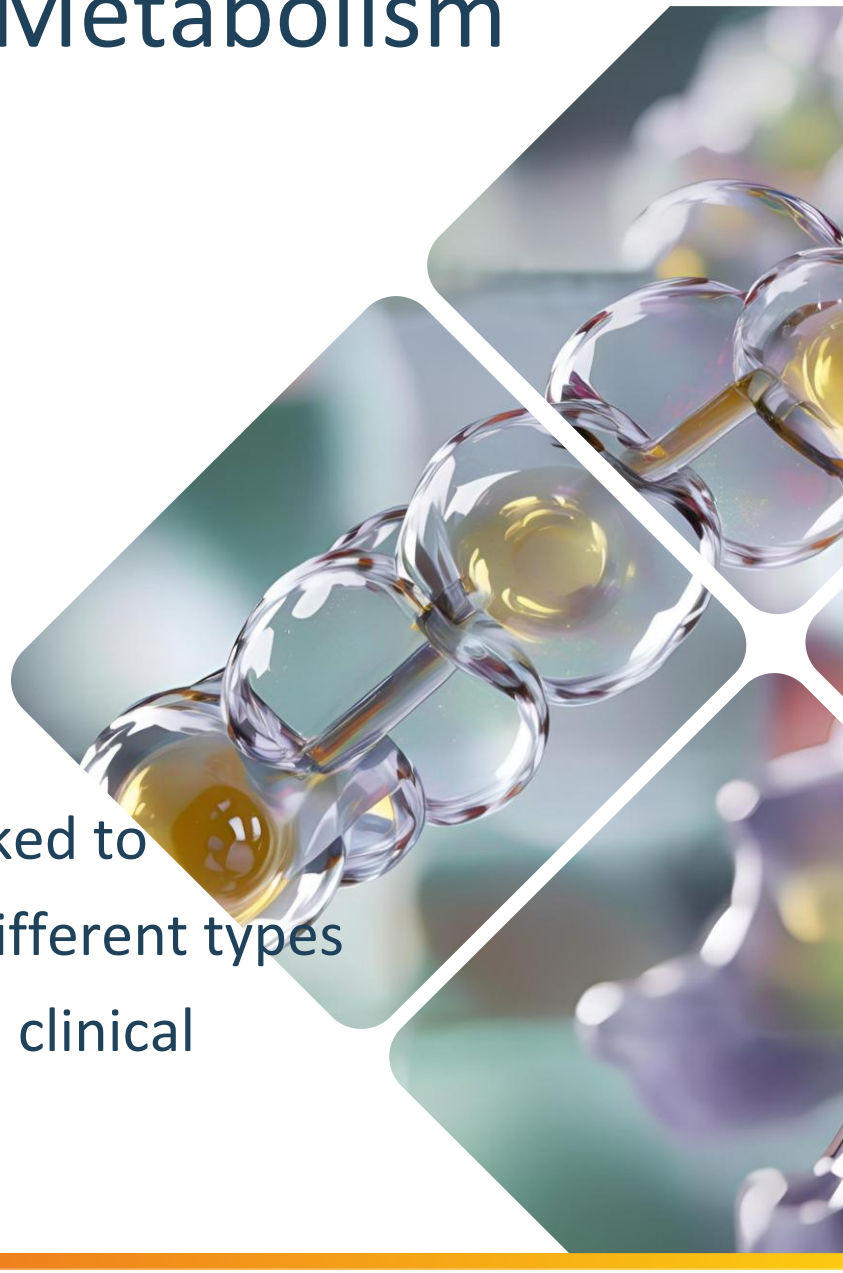


It plays a central role in tumor metabolism, indicating anaerobic glycolysis and is a marker of poor prognosis in multiple cancers

Elevated LDH Levels



High LDH levels are linked to adverse outcomes in different types of cancers, serving as a clinical predictor



Background——LDH and Cancer Prognosis

- **Melanoma**

High LDH levels indicate advanced disease and are associated with reduced survival rates

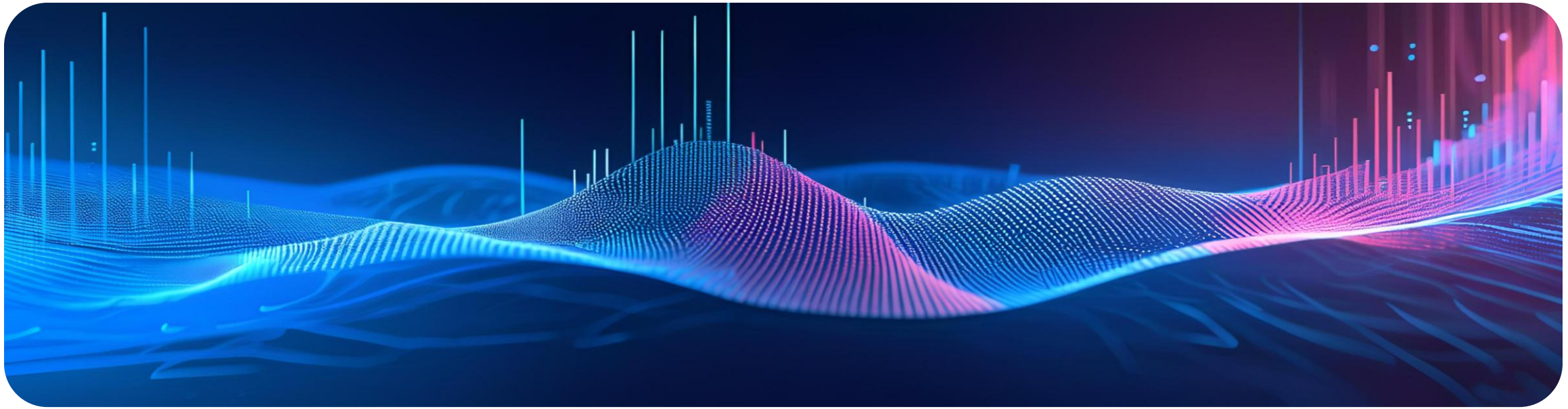
- **Gastric Cancer**

Overexpression of LDH-5 is associated with tumor progression and angiogenesis

- **Pancreatic Cancer**

High LDH-A expression is correlated with malignant tumor characteristics in pancreatic cancer

Background——Multicenter Evidence on LDH



Limited data is available for conducting systematic comparisons of the role of LDH across various cancer types, underscoring the urgent need for further comprehensive, multicenter research studies to elucidate its clinical significance and impact in the field of oncology

China Situation——Basic Information

CONCEPT_ID	NAME	DOMAIN
45883441	Melanoma	Meas Value
44791012	Suspected pancreatic cancer	Observation
45880474	Gastric Cancer	Meas Value
4248802	Adenocarcinoma of stomach	Condition
35624315	Squamous cell carcinoma of stomach	Condition
37311469	Pancreatic ductal adenocarcinoma	Condition
36532491	Follicular dendritic cell sarcoma of pancreatic duct	Condition

CONCEPT_ID	NAME	DOMAIN
4121177	TNM tumor staging classifications	Measurement
37398207	Serum alpha foetoprotein level	
44811957	Serum CEA (carcinoembryonic antigen) measurement	
4197913	CA 125 measurement	
4013180	Cancer antigen 15-3 measurement	
4098519	LDH blood measurement	
4030871	Red blood cell count	
4298431	White blood cell count	

China Situation——Treatments and Effects

CONCEPT_ID	NAME	DOMAIN
4273629	Chemotherapy	Procedure
35803674	Radiation therapy	Regimen
3655897	Immune checkpoint inhibitor therapy	Procedure
1397599	Cisplatin	Drug
1378382	Paclitaxel	
1319193	Gefitinib	
1397141	Bevacizumab	
45775965	Pembrolizumab	
1356009	Ravulizumab	

CONCEPT_ID	NAME	DOMAIN
45884383	Adverse event	Meas Value
1633705	PERCIST: complete response	Measurement
1634681	PERCIST: partial response	
1634497	PERCIST: stable disease	
1634248	PERCIST: progressive disease	

China Situation——Follow-up and Outcomes

CONCEPT_ID	NAME	DOMAIN
1633705	PERCIST: complete response	Measurement
1634681	PERCIST: partial response	
1634497	PERCIST: stable disease	
4168352	Tumor progression	Condition
4061268	Death in hospital	Observation
763388	Death in home	Observation

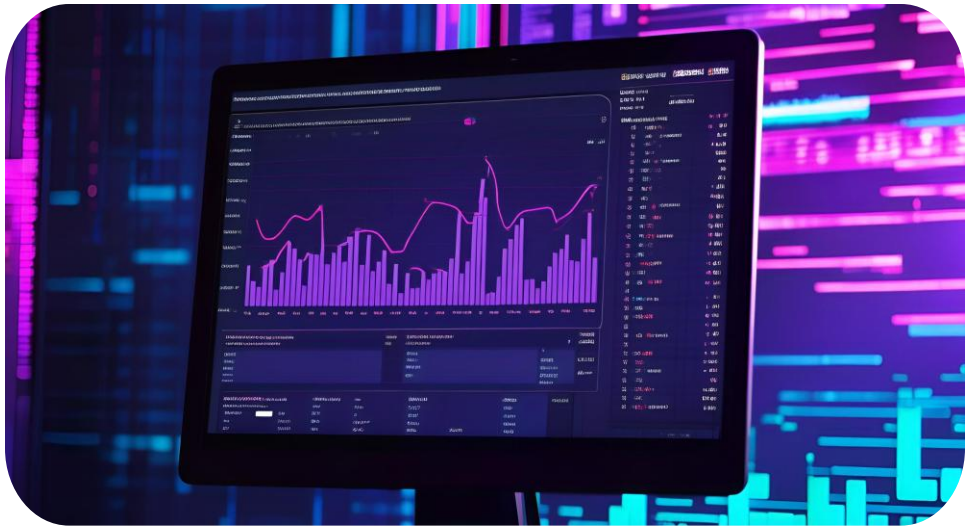
Definition of LDH Levels——Criteria and Variables

Inclusion Criteria

- Age ≥ 18 years
- Diagnosed with melanoma, gastric cancer, or pancreatic cancer
- ≥1 year of follow-up with complete LDH and survival data

Exclusion Criteria

- Metabolic diseases or infections affecting LDH levels
- Missing data or incomplete follow-up



Study Variables

- Exposure variable: Postoperative LDH levels (continuous variable)
- Outcome variables: Overall survival (OS) and progression-free survival (PFS)

Definition of LDH Levels——Statistical Analysis

- **Descriptive analysis:** Summarize baseline characteristics and LDH level distribution among patients with different cancer types
- **Survival analysis:** Evaluate the impact of LDH on OS and PFS using Kaplan-Meier survival curves and Cox regression models
- **Comparative analysis:** Conduct heterogeneity analysis to assess the effect of LDH levels on survival across different cancer types

Definition of LDH Levels——Exploration

Gastric Cancer

Assess the expression levels of LDH-5 in gastric cancer patients and its relationship with pathological findings such as vascular invasion and survival rates

Pancreatic Cancer

Investigate the role of LDH-A levels in pancreatic cancer patients and validate its potential as a marker of invasiveness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THANKS

The effect of angiotensin-receptor blocker (ARB) on the development of chronic diabetic complications in patients with type 2 diabetes mellitus: a target trial emulation study

Xiaowei Chen
Feng Sun*

Peking University

北京大学
PEKING UNIVERSITY

CONTENT

- **Background**
- **Objectives**
- **Methods**
- **Anticipated Results**

PART 01

Background

Background

ARB and chronic diabetic complications

Randomized controlled trials (RCT) have indicated **angiotensin-receptor blocker (ARB)** is the anti-hypertensive agent that may limit the onset and progression of **nephropathy and retinopathy** in subjects with type 2 diabetes mellitus (T2DM). Trials suggest that high-dose Olmesartan in diabetic patients may lead to an increased **cardiovascular (CV) risk**

TTE study framework

However, the findings remain **inconsistent**, and there is a lack of population-based studies using real-world data (RWD). Unlike traditional real-world studies (RWS), employing the **target trial emulation (TTE) study** framework can reduce potential bias and enhance the credibility of causal inference

Do D V, Han G, Abariga S A, et al. Blood pressure control for diabetic retinopathy[J]. Cochrane Database Syst Rev, 2023, 3(3): CD006127.
Wang B, Wang F, Zhang Y, et al. Effects of RAS inhibitors on diabetic retinopathy: a systematic review and meta-analysis[J]. Lancet Diabetes Endocrinol, 2015, 3(4): 263-74.
Haller H, Ito S, Izzo J L, Jr., et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes[J]. N Engl J Med, 2011, 364(10): 907-17.

PART 02

Objectives

Objective

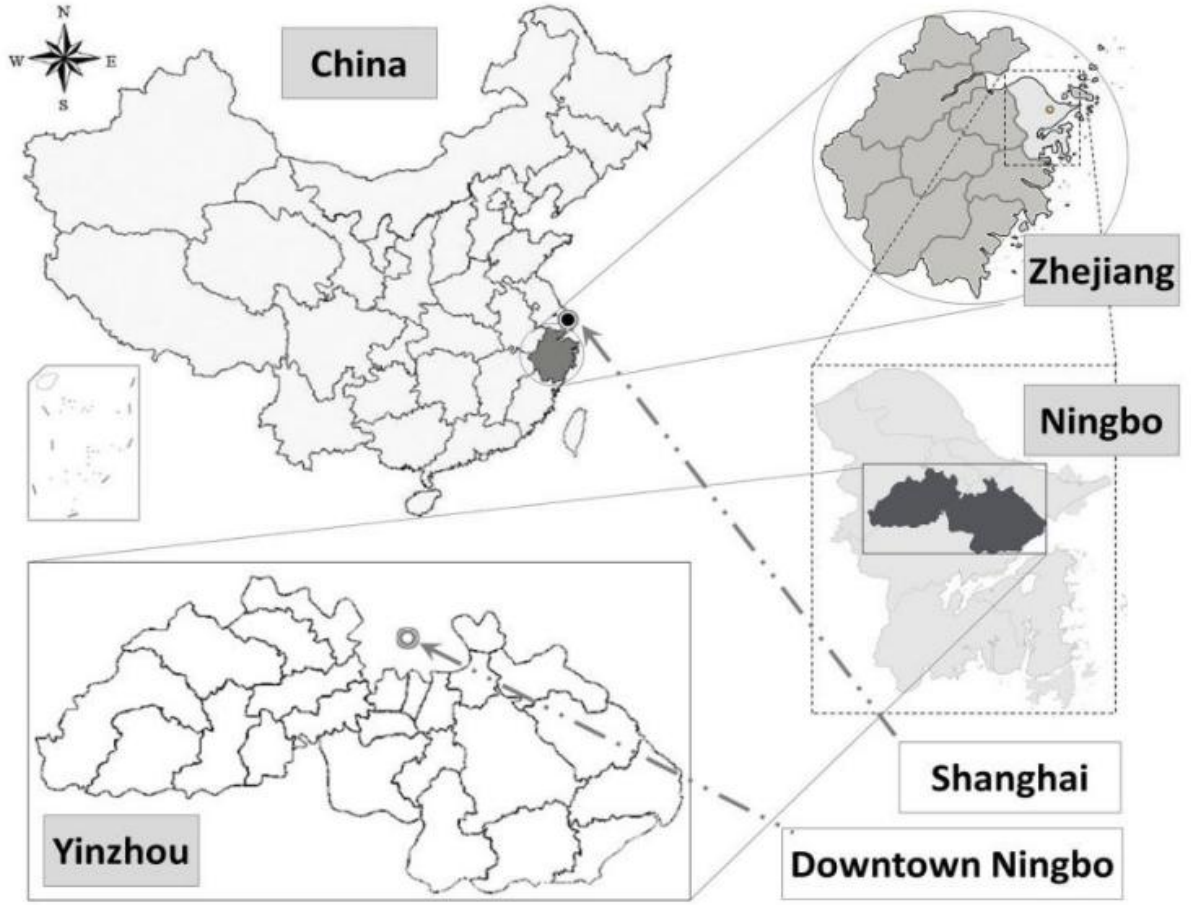
- This study aims to conduct a target trial emulation study utilizing the Yinzhou Regional Health Care Database (YRHCD) Diabetes OMOP CDM to investigate whether the use of ARB (specifically **Olmesartan medoxomil**), can prevent **the occurrence of chronic complications among T2DM patients**

PART 03

Methods

Methods—Data source

Yinzhou Regional Health Care Database (YRHCD)



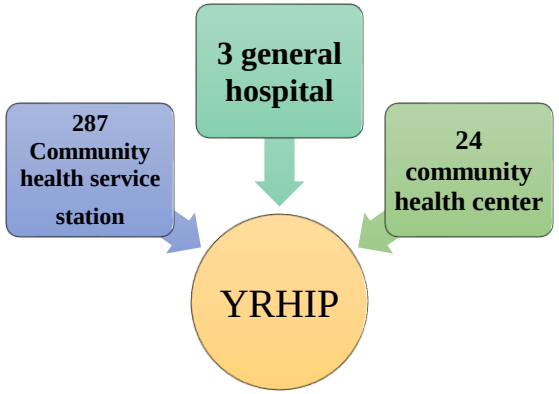
Diabetes OMOP CDM

Figure. Study location for the Chinese Electronic health Records Research in Yinzhou study

Methods—Introduction to database: Yinzhou regional health information platform

Data Source

- ✓ Largest district in Ningbo
- ✓ **Stable** population： More than 98% of the permanent population, covering almost all health activities
- ✓ All Level 1 and above hospitals and their affiliated health service centers in Yinzhou District
- **2005～2025**
- Cover **314** medical institutions
- More than **5TB** of data
- More than **1,000 forms**
- More than **400 millions records**



Data Integration

- ✓ **Owner: Yinzhou Health-Bureau**
- ✓ **Administrator: Yinzhou CDC**

Multiple Dataset

- ◆Electronic Medical Records
- ◆Disease Surveillance and Management System
- ◆Death Registry
- ◆Physical Examination Data
- ◆Public Health Data

OMOP CDM

- ◆Diabetes
- ◆Chronic Obstructive Pulmonary Disease (COPD)
- ◆Hypertension
- .....

Research Achievement

This platform has facilitated numerous studies in areas such as epidemiology, chronic disease management, pharmacoepidemiology, and health informatics

Researchers have utilized its comprehensive datasets to conduct analyses on disease prevalence, treatment outcomes, and public health interventions, leading to many publications in reputable medical and epidemiological journals

Methods—Study protocol

- **TTE study protocol**

➢ **Target trial**: The ROADMAP trial (ClinicalTrials.gov identifier NCT00185159)

➢ Emulating its study design, including **inclusion/exclusion criteria**, **interventions**, **outcomes**, **assignment procedures**, **time zero and follow-up schedules**, **causal contrasts and statistical analysis methods**

Methods—Inclusion/exclusion criteria

	Target trial	TTE
Inclusion criteria		
1	18 years to 75 years (Adult, Older Adult)	18 years to 75 years
2	T2DM, defined as fasting blood glucose of greater than or equal to 126 mg/dL	Diagnosed as T2DM before index date
3	Presence of **at least one of** the following cardiovascular risk factors:	Presence of at least one of the following cardiovascular risk factors:
	Total cholesterol greater than 200 mg/dL or statin treatment	Total cholesterol greater than 200 mg/dL during baseline period or statin treatment before index date
	High density lipoprotein (HDL) less than 40 mg/dL	High density lipoprotein (HDL) less than 40 mg/dL during baseline period
	Triglycerides greater than 150 mg/dL and less than 400 mg/dL	Triglycerides greater than 150 mg/dL and less than 400 mg/dL during baseline period
	Blood pressure greater than or equal to 130/80 mmHg	Blood pressure greater than or equal to 130/80 mmHg during baseline period
	BMI greater than 28 kg/m2	BMI greater than 28 kg/m2 during baseline period
	Waist circumference greater than 102 cm for men and greater than 88 cm for women	***No waist circumference information in database**
	Smoking of more than 5 cigarettes a day	Smoking during baseline period
4	Normoalbuminuria at screening	No albuminuria during baseline period
Exclusion criteria		
1	Severe uncontrolled hyperlipidemia	***Hard to emulate**
2	Documented renal and/or renal-vascular disease	Diagnosed as renal and/or renal-vascular disease before index date
3	Myocardial infarction, stroke or myocardial revascularization within the last 6 months	Myocardial infarction, stroke or myocardial revascularization within 6 months before the index date
4	History of alcohol and/or drug abuse	ICD-10 diagnostic code F10 or T51.0 or F11-F19 before the index date
5	Allergic reaction, lack of response or contraindication to angiotensin receptor blockers (ARBs)	***Hard to emulate**
6	Current treatment with an ARB or angiotensin converting enzyme (ACE) inhibitor	No previous ARB and ACEI prescription record before index date

baseline period: 6 months before the index date

Methods—Intervention

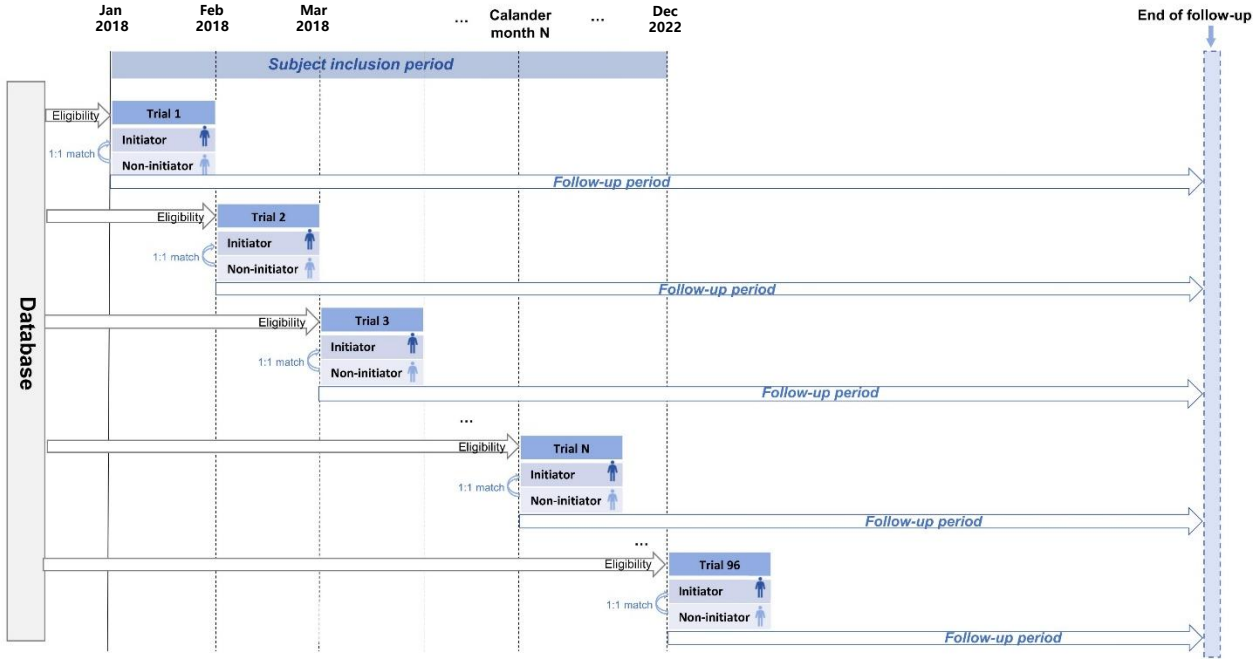
Study type	Group	Interventions
Target trial	Experimental group	**Olmesartan medoxomil** (40mg)
	Control group	Placebo Tablet
TTE	Experimental group	At least one prescription record of **olmesartan medoxomil** during the study period
	Control group	Not initiate olmesartan medoxomil use during the study period

Methods—Outcome

Outcome	Target trial	TTE
Primary Outcome	Time to the first occurrence of microalbuminuria defined as excretion of greater than 35 mg albumin/g urine creatinine for women and greater than 25 mg albumin/g urine creatinine for men in morning spot urine	New onset of **retinopathy**
Secondary Outcome	Incidence of renal disease, such as worsening of renal function as well as end-stage (dialysis)	First occurrence of albuminuria
	Occurrence and progression of retinopathy	Incidence of renal disease, such as worsening of renal function as well as end-stage (dialysis)
	Incidence of cardiovascular mortality and morbidity	Incidence of cardiovascular mortality and morbidity
	Treatment effects on a combined endpoint of cardiovascular mortality and morbidity and renal disease	First occurrence of a combined endpoint of cardiovascular mortality and morbidity and renal disease
Other Outcome	Safety and tolerability	—

Methods—Time zero and follow-up schedule

- **Sequential Trial TTE**
  - The study period is from Jan 2018 to Dec 2022
- **Baseline**
  - **Time zero (index date)**: Defined as the first date of every month at each sequential trial start
  - **Baseline period**: Baseline covariates will be assessed within a 1-month window prior to the time zero
- **Follow-up schedule**
  - Patients will be followed-up from the index date till the occurrence of the primary/secondary outcomes, death, loss to follow-up, or the end of the study period, whichever comes first in each sequential trial after iniation of olmesartan



Methods—Assignment procedure

- **Propensity score matching (PSM)** will be employed to simulate random allocation of RCT and balance baseline characteristics between the Olmesartan initiators and non-initiators in each sequential trial
- The matching method is **1:1 nearest neighbor matching**, with a caliper width set to 0.05
- Propensity scores will be calculated using **logistic regression**, incorporating variables such as **age, sex, duration of diabetes, baseline blood pressure, HbA1c levels, eGFR, lipid profiles, smoking status, drinking status, baseline comorbidities and concomitant medications** etc.
- Patients will be matched using a nearest-neighbor algorithm with a caliper of 0.2 standard deviations of the logit of the propensity score
- **Standardized mean difference (SMD)** will be used to compare baseline characteristics between groups. SMD < 0.1 indicates that baseline covariates are well-balanced and comparable
- If key baseline covariates still have an SMD > 0.1 after matching, further adjustments will be needed in subsequent multivariable models

Methods—Causal contrasts and statistical analysis

Primary analysis

- **Intention-to-treat (ITT) analysis**
- In the descriptive analysis, continuous variables were summarized as mean ± standard deviation (SD), while categorical variables were presented as frequency (percentage) to describe the central tendency and dispersion of the data
- A time-discrete dataset will be constructed by month for each eligible person-trial, where **the marginal structural model (MSM)** is adopted to estimate the causal effect that accounts for the **time-varying information**
- As the typical statistical model in MSM, the pooled logistic model was employed to estimate the association between olmesartan therapy and the incidence of outcomes
- Owing to the outcome of the models may be rare at all times, the odds ratio from the pooled logistic model approximates the hazard ratio (HR)

Secondary analysis

- **Subgroup analyses** will be conducted based on baseline characteristics, such as age, sex, blood pressure, and baseline CV risk
- Analyzing whether there is a dose-response relationship between **the cumulative use of** olmesartan and the incidence of outcomes

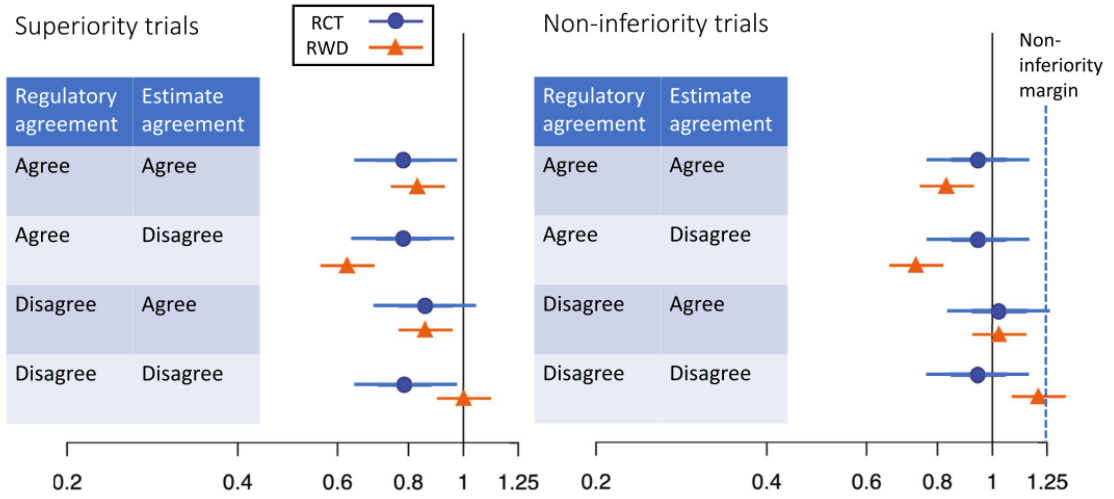
Sensitivity Analyses

- A **per-protocol (PP) analysis** was conducted to assess consistency with the ITT analysis results
- The primary analysis was repeated after **1:2 PS matching**

Agreement Assessment

Efficacy-Effectiveness Agreement Assessment Method

To compare the TTE study results with those from RCTs, the U.S. RCT Duplicate project proposed three agreement assessment indicators:



Regulatory Agreement:
whether the direction and statistical significance of treatment effects observed in RCTs are maintained in real-world studies (RWS)

Estimate Agreement:
whether the effect estimate from the real-world study (RWS) falls within the 95% confidence interval (95% CI) of the RCT results

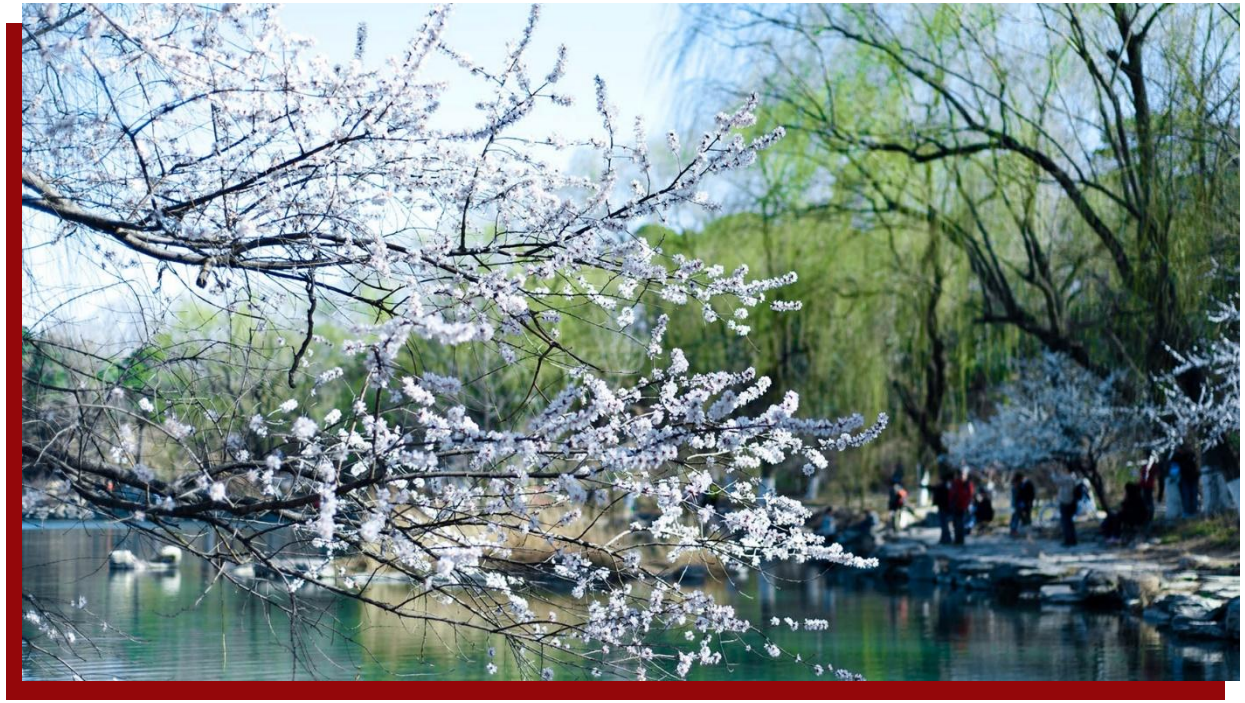
Standardized Difference:

$$Z = \frac{\theta_{RWE} - \theta_{RCT}}{\sqrt{\sigma\hat{}2_{RWE} + \sigma\hat{}2_{RCT}}}$$

PART 04

Anticipated Results

Anticipated Results



- This target trial emulation study aims to provide real-world evidence on the effectiveness and olmesartan medoxomil in preventing chronic complications among T2DM patients
- By using TTE design within a real-world setting, we seek to validate previous findings and address existing uncertainties regarding retinopathy/cardiovascular outcomes associated with Olmesartan use

Next step——Expanding Evidence Beyond Target Trial

➢ To address the limitations of traditional RCTs by providing evidence for populations often underrepresented, including:

- Elderly individuals (those over 75 years old)
- Specific ethnic groups (East Asians)
- Patients with comorbidities (e.g., baseline hypertension, renal disease)

Thanks

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Safety Outcomes of Semaglutide in Type 2 Diabetes Using Regional Health Data : A Target Trial Emulation

Yongqi Zheng
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PART 01

Background & Significance

1.1 Background

Effects of GLP-1 RAs

- Lowering blood glucose
- Reducing body weight
- Regulating metabolic abnormalities

Impact of cardio-vascular outcomes

- **Leading cause of death** in patients with T2DM
- Cardiovascular events have a significant impact on patients' **quality of life and prognosis**

Necessity of Investigating Cardiovascular Safety of GLP-1 RAs

- Large-scale clinical trials and real-world studies are needed
- Optimizing treatment strategies for T2DM patients

T2DM: Type 2 Diabetes Mellitus, GLP-1 RAs: Glucagon-Like Peptide-1 Receptor Agonists

1.1 Background

➢ Current Research Status

International Research

- **RCT:** Semaglutide significantly reduces MACE, mainly lowering risks of **heart attack and stroke** (**SUSTAIN-6, SELECT**)
- **RWD**: Consistent with trials, showing improved **glycemic control, weight loss, and cardiometabolic benefits**

Asia-Pacific Research

- Some regional studies based on single centers or small samples have shown results consistent with international findings
- High-quality RCTs and large-scale real-world studies remain limited in China

RCT: Randomized Controlled Trial, RWD: Real-World Data, MACE: Major Adverse Cardiovascular Events

1.1 Background

➢ Definition and Steps of TTE

- Proposed by Hernán and Robins in 2016, is a causal inference methodology based on counterfactual reasoning
- Aims to emulate this ideal RCT using observational data by explicitly designing observational studies according to the critical design elements of the hypothetical target trial
- Essential components: **Eligibility criteria, Intervention strategies, Assignment procedures , Time zero and follow-up periods, Outcomes, Causal contrasts , Statistical analyses**

➢ Advantages of TTE in this study

- It considers biases existing in RWS and improves the accuracy of drug effect estimation
- **Allows for progressively relaxed inclusion/exclusion criteria to evaluate drug effectiveness in target and broader populations**

TTE: Target Trial Emulation, RCT: Randomized Controlled Trial, RWS: Real-World Study

1.2 Significance

➢ Addressing research gaps in Asia

- Lack of large-scale, population-based studies evaluating the safety of semaglutide among Asian patients with T2DM, particularly within the Chinese population

➢ Expanded Indication

- First application of TTE in Chinese T2DM patients, expanding the population to additional age groups, and incorporating diabetic retinopathy (DR), hypoglycemia and neoplasm as primary outcomes

TTE: Target Trial Emulation, T2DM: Type 2 Diabetes Mellitus

PART 02

Study Design & Methods

Study Design & Methods

➢ Ningbo regional health information platform，NRHIP

➢ Platform Overview

- Established: 2011
- Officially launched: August 2015
- Population coverage: Over 9 million people

➢ Platform Functions

- Enables interconnection and interoperability of residents' electronic health records, vaccination information, hospital electronic medical records, maternal and child healthcare information, and cause-of-death monitoring systems.

➢ OMOP for T2DM patients has been completed

Study Design & Methods

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➢ Eligibility criteria

RCT

- **Diagnosed with type 2 diabetes**
- Glycated hemoglobin (HbA1c) ≥7%
- No prior antihyperglycemic treatment, or limited prior use
- **Age ≥50 years, with established cardiovascular, heart failure or chronic kidney disease**
- **Or age ≥60 years with at least one cardiovascular risk factor**

TTE

- **Consistent with RCT criteria within the limits of database availability**

Study Design & Methods

➢ Intervention strategies

RCT

- Patients randomized in a 1:1:1:1 ratio
- Weekly subcutaneous injections of semaglutide or placebo
- Dose levels: 0.5 mg or 1.0 mg
- Placebo injections matched semaglutide injections.

TTE

- Observation group: **Semaglutide**
- Control group: DPP-4 inhibitors (**DPP-4i**)

Study Design & Methods

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➢ Assignment procedures

RCT

- **Randomized, controlled, double-blind design**
- Randomization conducted across multiple countries and centers
- Stratified randomization to balance key prognostic factors

TTE

- Propensity score (PS) matching (1:1 ratio)
- Nearest-neighbor matching method, caliper width set at 0.05
- Standardized mean difference (SMD) used to assess baseline characteristic balance, SMD < 0.1 indicates adequate matching quality
- **Blinding not feasible in real-world data analysis.**

Study Design & Methods

➢ Time zero and follow-up periods

➢ Active-comparator new-user (ACNU) design

- New-user definition: Patients who have not received GLP-1RAs or DPP-4i treatment during the baseline period (6 months prior to initiation)
- Index date (time zero): The date of the first prescription (2020.01.01-2023.12.31)

➢ Follow-up

- Start of follow-up: One day after the index date
- End of follow-up: The earliest among 52 weeks after the index date, occurrence of an outcome event, death, or end of the study period (Dec 31, 2024)

Study Design & Methods

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➢ Outcomes

RCT

➢ **Primary outcome:**

- Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

➢ **Secondary outcomes:**

- Expanded composite endpoint
- Additional composite endpoint Retinopathy-related events
- Hypoglycemia
- Neoplasm and pancreatitis events

TTE

- **Consistent with RCT criteria within the limits of database availability**
- **Inaccurate determination of cause of death**: Real-world data may not reliably distinguish cardiovascular deaths; all-cause mortality may be used instead

Study Design & Methods

➢ Statistical analyses

- **Primary Analysis**
  - ➢ TTE adopts an **intention-to-treat (ITT) analysis** approach, consistent with the target trial
  - ➢ Missing data are imputed using random forest imputation
  - ➢ Cox proportional hazards model applied for primary analysis
- **Subgroup analysis**
  - ➢ Aligned with RCT as closely as possible
- **Sensitivity analyses**
  - ➢ Aligned with RCT as closely as possible
  - ➢ Adding **per-protocol (PP) analysis**

Study Design & Methods

➢ Effectiveness and Consistency Assessment

To evaluate the consistency between results from TTE studies and RCT findings, the U.S. RCT Duplicate Project proposed three consistency metrics

Regulatory agreement:

Whether the direction and statistical significance of the effect in the RWE are consistent with those of the RCT.

Estimate agreement:

Whether the real-world effect estimate lies within the 95% confidence interval of the RCT result.

Standardized difference: $$Z = \frac{\theta_{RWE} - \theta_{RCT}}{\sqrt{\sigma^2_{RWE} + \sigma^2_{RCT}}}$$

Study Design & Methods

➢ Indication expansion

- Expanding to populations not covered by RCTs, filling the evidence gap.

Expanding age indications:

Filling the evidence gap for the **30-40 and 40-50** age groups to assess the safety of Semaglutide in a broader population

Extending study outcomes:

Elevating **DR, hypoglycemia and neoplasms** to primary outcomes in this study. Utilizing Cox regression models to evaluate the association between Semaglutide and these complications

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Thank you for your attention

Safety Outcomes of Semaglutide in Type 2 Diabetes Using Regional Health Data : A Target Trial Emulation

Yongqi Zheng
Feng Sun*
Peking University

Retrospective Study on the Impact of BMI Trajectories on Long-Term Prognosis in CKD Patients Using Electronic Health Records

Global CKD Burden

CKD affects 697.5 million people globally and 82 million in China, posing a significant public health and economic burden.

The progression of CKD leads to end- stage renal disease, requiring costly treatments like dialysis and transplantation.

Obesity & CKD

Obesity as an Independent Risk Factor

Obesity is a well- established independent risk factor for CKD progression, increasing the risk of renal function decline.

Mechanisms include increased renal blood flow, inflammation, and oxidative stress, which accelerate CKD progression.

Limitations of Single-Timepoint BMI Studies

Previous studies have focused on single- timepoint BMI measurements, neglecting the dynamic nature of BMI trajectories.

Long- term BMI patterns may provide better predictive power for CKD outcomes.

Potential of EHR Data and Advanced Methods

Electronic Health Records (EHR) data offer a wealth of longitudinal patient information.

Advanced methods like Group-Based Trajectory Modeling (GBTM) enable detailed trajectory analysis.

Identify BMI Trajectory Patterns

Timeframes for Trajectory Analysis

Identify distinct BMI trajectory patterns in CKD patients over 3, 5, and 10 years.

Different timeframes may reveal unique insights into short- term and long- term BMI changes.

Investigate Associations with Renal Function Decline

Analyze how BMI trajectories influence renal function decline, including eGFR drop and progression to end-stage renal disease (ESRD).

Identifying protective or detrimental BMI patterns can inform clinical management strategies.

Determine Clinical Intervention Thresholds

Determine critical BMI change thresholds that can serve as indicators for clinical intervention.

These thresholds can help clinicians identify patients at high risk and implement timely interventions.

Investigate Associations with Cardiovascular Events

Examine the relationship between BMI trajectories and cardiovascular events such as myocardial infarction, stroke, and heart failure.

Cardiovascular diseases are major complications in CKD patients, and understanding their link with BMI trajectories is crucial.

Investigate Associations with All-Cause Mortality

Assess the impact of BMI trajectories on all- cause mortality in CKD patients.

Establishing a quantitative link between BMI changes and mortality can guide clinical interventions.

Conduct a retrospective cohort study using EHR data.

Population Selection

Inclusion Criteria

- Include adults (≥18 years) with CKD (KDIGO stages 1–4), with ≥3 BMI measurements (≥6- month intervals) and ≥3 years of follow-up.
  These criteria ensure sufficient data for trajectory analysis and long-term outcome assessment.

Exclusion Criteria

- Exclude patients with severe comorbidities, organ transplants, and incomplete data.
  Excluding these patients reduces confounding factors and ensures data quality.

Trajectory Modeling

GBTM for BMI Pattern Classification

- Use Group- Based Trajectory Modeling (GBTM) to classify BMI patterns into distinct groups such as stable, rising, and fluctuating.

- GBTM allows for the identification of different BMI trajectory patterns within the patient population.

Outcome Analysis

Kaplan-Meier Survival Curves

Employ Kaplan- Meier survival curves to analyze event-free survival across different BMI trajectory groups. Survival curves provide a visual representation of the differences in outcomes between trajectory groups.

Cox Regression

Use Cox regression to calculate adjusted hazard ratios (HRs) for outcomes, accounting for confounders such as age, sex, baseline eGFR, diabetes, and hypertension. Adjusting for these confounders ensures that the results accurately reflect the impact of BMI trajectories on outcomes.

Expected Outcomes

- Distinct BMI Trajectory Groups
- Quantitative Links with Outcomes
- Clinically Actionable Thresholds
- High-Impact Publication

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Studying the Disease Trajectory of Type 2 Diabetes with a Transformer-based Model

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2025.3

Prevalence and Impact of Type 2 Diabetes

Global Burden of Type 2 Diabetes

- The most common chronic metabolic disease worldwide
- Affects patients' quality of life
- leads to complications like cardiovascular diseases, kidney diseases, retinopathy, etc.

T2D

Limitations of Traditional Screening Methods

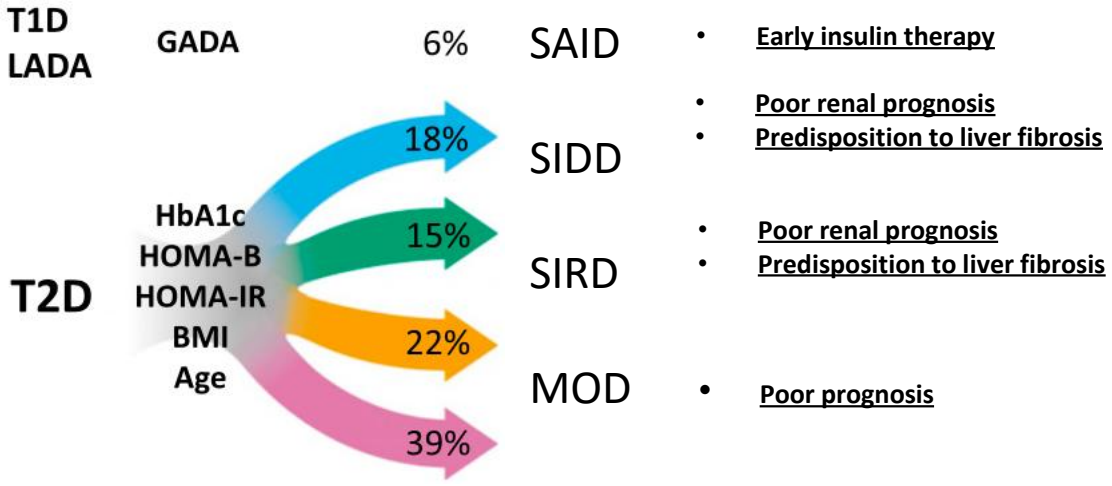
- Costly and have high false-positive rates when applied to large populations
- Difficult for traditional screening to capture high-risk individuals in a timely manner

Potential of Real-World Data and AI

- Risk prediction research based on real- world data (RWD) has become an important means
- long- term clinical data with machine learning (ML) and deep learning (DL)

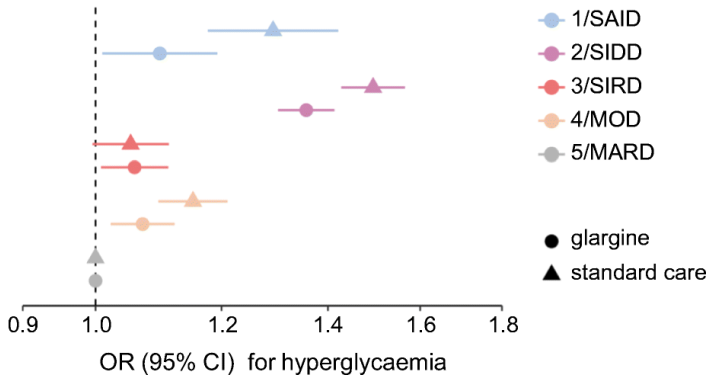
Diabetes & related vascular complications: heterogenous and changeable

In 2018, Prof. Leif Groop re-classified diabetes mellitus into 5 pathophysiological subtypes using 6 clinical parameters.

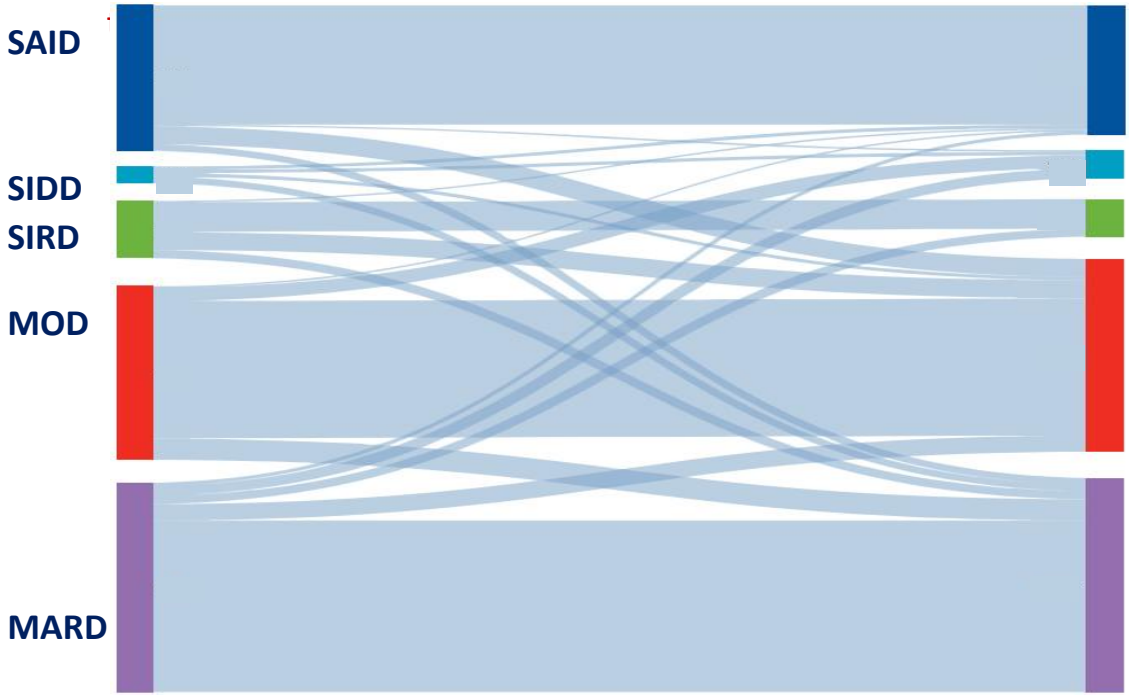


The ORIGIN trial demonstrated differential responses to insulin therapy among these five novel subtypes.

Cluster	Intervention	*n*	Adjusted OR
SAID	standard care	118	1.29 (1.18, 1.42)
	glargine	123	1.10 (1.01, 1.19)
SIDD	standard care	791	1.49 (1.43, 1.57)
	glargine	803	1.36 (1.30, 1.41)
SIRD	standard care	455	1.05 (1.00, 1.11)
	glargine	459	1.06 (1.01, 1.11)
MOD	standard care	833	1.16 (1.10, 1.22)
	glargine	762	1.07 (1.02, 1.12)
MARD	standard care	1323	REF
	glargine	1350	REF



The 5-year follow-up study of the German Diabetes Study (**GDS**) cohort revealed that these novel DM subtypes exhibited dynamic variability, though such changes were confined to specific evolutive



1. Lancet Diabetes Endocrinol 2018; 6: 361-69
2. Diabetes 2020;69:2086–2093
3. Lancet Diabetes Endocrinol.2019;7(9):684-694.
4. Diabetologia. 2022;65(1): 206-215.

Research Gap and Aim

Existing Models' Shortcomings

Current risk prediction models mostly rely on static data and **fail to fully utilize the time- series information of the disease**.

Objective of the Study

This study aims to fill the gap by combining the OHDSI database and DL technology to construct **a precise and dynamic diabetes risk prediction model**, providing support for early screening and personalized intervention.

Study Design Overview

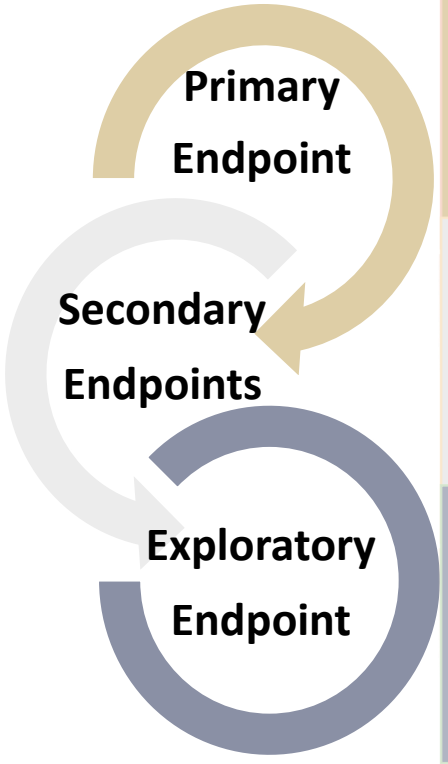
■ Retrospective Cohort Study Design

- Constructing the **disease trajectory** of T2D patients based on real-world data
- Analyzes large- scale patient clinical data with ML and DL techniques to **explore disease progression** at different time points
- Establish a **dynamic disease trajectory model**

■ Patient Inclusion and Exclusion Criteria

- **Inclusion criteria:** Patients aged ≥18 years with a confirmed diagnosis of T2D
- **Exclusion criteria:**
  - Patients diagnosed with type 1 diabetes, gestational diabetes, or other special types of diabetes
  - Diagnosed with rheumatic diseases during the study period
  - Those with missing serum creatinine levels, follow-up time less than 30 days, who received renal replacement therapy before or within 10 days of their first visit.

Study Endpoint

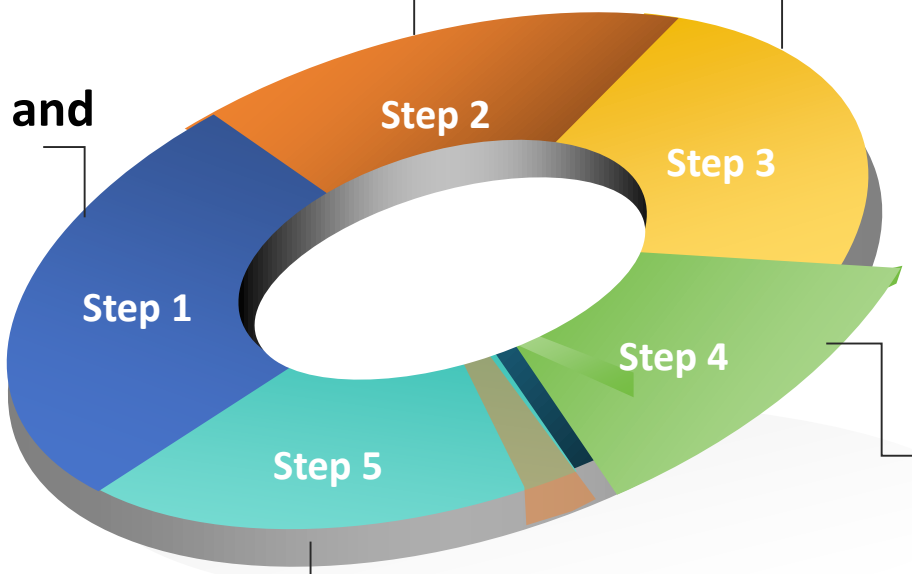


Reclassification and Progression of T2D, including the time nodes of diabetes diagnosis and changes in related disease states, and outcome-based reclassification of T2D.

Incidence and severity of diabetes-related complications such as cardiovascular diseases, kidney diseases, diabetic retinopathy, peripheral vascular diseases, diabetic foot, MASLD, and other significant complications caused by diabetes.

Assessment of drug treatment effects, including the efficacy of various drugs like insulin, SGLT2 inhibitors, and GLP- 1 receptor agonists, as well as predicting the personalized effects and adverse reaction risks of drugs based on patients' disease trajectories.

Data Analysis Methods



Data Preprocessing and Integration

Feature Engineerin and Modeling

Clinical Application of the Model

Model Interpretation and Feature Importance

Multi-Center Validation and Cross-Platform Application

Thank you!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