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# Comparative cost-effectiveness of metformin-based dual therapies associated with risk of cardiovascular diseases among Chinese patients with type 2 diabetes: Evidence from a population-based national cohort in Taiwan

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ABSTRACT

*Objective:* To assess the cost-effectiveness of metformin-based dual therapies associated with cardiovascular disease (CVD) risk in a Chinese population with type 2 diabetes.
*Methods:* We utilized Taiwan's National Health Insurance Research Database (NHIRD) 1997–2011, which is derived from the claims of National Health Insurance, a mandatory-enrollment single-payer system that covers over 99% of Taiwan's population. Four metformin-based dual therapy cohorts were used, namely a reference group of metformin plus sulfonylureas (Metformin–SU) and metformin plus acarbose, metformin plus thiazolidinediones (Metformin–TZD), and metformin plus glinides (Metformin–glinides). Using propensity scores, each subject in a comparison cohort was 1:1 matched to a referent. The effectiveness outcome was CVD risk. Only direct medical costs were included. The Markov chain model was applied to project lifetime outcomes, discounted at 3% per annum. The bootstrapping technique was performed to assess uncertainty in analysis.
*Results:* Metformin–glinides was most cost-effective in the base-case analysis; Metformin–glinides saved $194 USD for one percentage point of reduction in CVD risk, as compared to Metformin–SU. However, for the elderly or those with severe diabetic complications, Metformin–TZD, especially pioglitazone, was more suitable; as compared to Metformin–SU, Metformin–TZD saved $840.1 USD per percentage point of reduction in CVD risk. Among TZDs, Metformin–pioglitazone saved $1831.5 USD per percentage point of associated CVD risk reduction, as compared to Metformin–rosiglitazone.
*Conclusions:* When CVD is considered an important clinical outcome, Metformin–pioglitazone is cost-effective, in particular for the elderly and those with severe diabetic complications.



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## 1. Introduction

An estimated 9% of adults 18 years and older had diabetes mellitus in 2014 and this disease was the direct cause of 1.5 million deaths in 2012 [1]. Type 2 diabetes is most common, with 90–95% of all individuals with diabetes having this type [2]. Patients with diabetes have higher all-cause mortality than those without diabetes; this excess mortality is largely attributable to cardiovascular disease (CVD) [3–5]. When patients with diabetes develop CVD, they have a worse prognosis for survival compared to that of those without CVD [5–8]. In Taiwan, the percentage of adults diagnosed with type 2 diabetes increased from 4.5% in 2000 to 7.6% in 2010 [9]. The prevalence of CVD was about 38.1% in 2000 and 33.4% in 2009 [10]. CVD was one of four major causes of death for patients with diabetes in Taiwan [11]. The mortality rates for Taiwan's patients with diabetes in 2009 were 3.1% and 2.7% for men and women, respectively [11].

Patients with diabetes require more healthcare resource as compared to those of patients without diabetes [1]. Approximately $88.4 billion USD was spent on diabetes in the West Pacific region in 2013, which is projected to increase to $98.4 billion USD by 2035 [12]. The total medical spending per patient with diabetes in Taiwan was about 2.7-fold higher than that for those without diabetes in 2010 [9]. The healthcare costs per patient with type 2 diabetes in Taiwan increased about 18% between 2000 and 2010 [9]. Also, patients with type 2 diabetes that had developed CVD had two times higher medical spending than that for those without CVD [13].

Medication therapies for diabetes are aimed to reduce the impact of diabetes and its associated complications to the healthcare system. Pharmacotherapy for type 2 diabetes is relatively complex, in terms of regimen combination, and accounts for a large proportion of medical spending [14]. Antidiabetic medications for type 2 diabetes consist of oral hypoglycemic agents (OHA) and injectable agents (e.g., insulin). Current algorithms [15] advocate that newly diagnosed patients receive both a lifestyle intervention and metformin, with other drugs (e.g., sulfonylureas; SU) added subsequently in a stepwise fashion if needed to achieve glycemic control. As a result, metformin is the most prescribed drug for type 2 diabetes in practice, with other drugs being subsequent stepwise additions for those failing on metformin alone.

Treatment for diabetes may be an effective and safe option, but it also imposes a tangible cost on the healthcare system. The balance of treatment efficacy and costs should be examined to maximize value for healthcare spending. Pressure to control medical spending has created an interest in "cost-effective" healthcare. Many new treatments are expensive; pharmacoeconomic analysis can help answer whether improved healthcare outcomes justify the expenditures relative to other choices.

As aforementioned, patients with type 2 diabetes typically begin with metformin treatment and most of them have another antidiabetic agent added on when monotherapy fails. However, there is no particular recommendation about which second-line add-on OHA is best for Chinese patients with type 2 diabetes. In addition, the choice of medication may depend on the patient's characteristics or prescriber's preferences. Hence, the clinical effectiveness and economic benefit of alternative OHAs need to be assessed to provide evidence for clinical decision. Therefore, the present analysis focuses on the comparative effectiveness of metformin-based dual-OHA therapies associated with CVD risk, which is one of the leading causes of mortality for type 2 diabetes patients. This study utilized a large population-based national cohort to derive empirical estimates of the effectiveness and costs for pharmacoeconomic analysis.

## 2. Methods

This study utilized pooled data from the years 1997–2011 obtained from Taiwan's National Health Insurance Research Database (NHIRD) – Longitudinal Health Insurance Database (LHID). The NHIRD provides operation procedure codes and diagnosis codes for each patient, using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The LHID, as created by the National Health Insurance Research (NHRI), was derived by randomly sampling 1,000,000 enrollees from the Registry for Beneficiaries of the NHIRD sampling in 2010. The NHRI is the only institute approved, as per local regulations, to conduct a sampling of a representative sample of the whole population. The NHIRD lacks patient or physician identifiers, by authorization from the NHRI, and is retrieved only for academic research. The Institutional Review Board of National Cheng Kung University Hospital approved the study before commencement.

### 2.1. *Study cohort*

The 2000–2005 dataset was used to identify cases with any hospitalized events as diabetes or those with any outpatient visits for diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-9-CM code = 250). We first selected cases aged $\geqslant$20 year old and then patients were classified as having type 2 diabetes if they had at least one hospital admission with a diagnostic code of type 2 diabetes or three or more outpatient visits with a diabetes diagnostic code within 365 calendar days. To avoid accumulation of misdiagnoses, the selection was conducted each year. The first and last outpatient visits within one year had to be >30 days apart to avoid accidental inclusion of miscoded cases. This algorithm was evaluated with the 2009 NHIRD, showing a high level of sensitivity (96.9%) and a high positive predictive value (93.9%) [16]. It has been used in the previous Taiwanese studies on type 2 diabetes based on the NHIRD [17–19]. Women with claims of diabetes within 270 days before parturition were excluded in order to avoid misclassifying those with gestational diabetes that returned to normoglycemia after baby delivery. However, those with 3 or more subsequent visits with a type 2 diabetes diagnosis within 365 days after childbirth were included [20]. Also, potential type 1 diabetes patients were excluded if they (i) had ever been hospitalized because of diabetic ketoacidosis (ICD-9-CM: 250.1x); (ii) had ever had hospital admission with