



# Diabetic Patient with Atherosclerosis Treated By Equmet (Vildagliptin/Metformin) and Novel Twymeeg (Imeglimin)

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## Abstract

Diabetes has macroangiopathic complications, such as peripheral artery disease (PAD). Current case is 62-year-old men with type 2 diabetes (T2D) and moderate atherosclerosis, who was treated by EquMet (vildagliptin/metformin) and Twymeeg (imeglimin). Plethysmography showed normal ankle brachial index (ABI) as 1.13/1.12, and rather high brachial ankle pulse wave velocity (baPWV) as 1859/1823. After 5 years, the baPWV value was elevated to 2121/2152, showing significant arterial stiffness. For treatment of T2D, he had Equmet for years. Starting Twymeeg in 2023, HbA1c showed remarkable reduction from 7.6% to 6.5% for 4 months with no gastro-intestinal adverse effects (GIAEs), indicating clinical efficacy.

**Keywords:** Vildagliptin/metformin (EquMet); Imeglimin (Twymeeg); Gastro-intestinal adverse effects (GIAEs); Trials of Imeglimin for Efficacy and Safety (TIMES); Vildagliptin Efficacy in combination with metformin For early treatment of type 2 diabetes (VERIFY)

## Introduction

International Diabetes Federation (IDF) has announced in the latest report that 537 million adults have lived with diabetes in the world [1]. Diabetes has the complication of macroangiopathic and microangiopathic problems. Concerning the former, arterial stiffness has been clinical problems for cerebral vascular accident (CVA), ischemic heart disease (IHD) and peripheral artery disease (PAD) [2]. PAD means the atherosclerosis of lower extremities and it is common angiopathic complication which affects about 20-30% of such diabetic patients [3]. Ankle brachial index (ABI) and brachial-ankle pulse wave velocity (baPWV) has been used for the evaluation of arterial stiffness. In addition, baPWV is obtained by the calculation for the distance between brachial-tibial arteries and pulse wave time, which reveals the impaired degree of atherosclerotic vascular damage [4]. Recent report has showed the evidence for the relationship among ABI, baPWV and diabetes, which leads to the development for diabetic research [5].

For standard guideline treatment for diabetes, American Diabetes Association (ADA) has recently announced the management of Type 2 diabetes (T2D) as "Standards of Care in Diabetes" [6]. Fundamental crucial aspects mean adequate life style habit with meal, exercise and medical agents [7]. Recent oral hypoglycemic agents (OHAs) include sodium-glucose cotransporter 2 inhibitor (SGLT2i), dipeptidyl peptidase-4 inhibitor (DPP-4i), glucagon-like-peptide 1 receptor agonist (GLP1-RA), imeglimin (Twymeeg) and some combined OHA agents [8].

Authors and co-researchers continued clinical research and practice for long [9]. The related areas are T2D, metabolic syndrome (Met-S), cardiovascular disease (CVD), chronic kidney disease (CKD), low carbohydrate diet (LCD), meal tolerance test (MTT) and others [10]. Concerning OHAs, we have reported Twymeeg, EquMet, and other novel agents [11]. Our diabetic team had recently a male diabetic case who showed impressive arterial stiffness. General outline of the patient and some related perspective will be described here.

## Case Presentation

### Medical history

The patient is a 62-year-old male with T2D for about 7 years. He did not have other past history except diabetes. His profession has been a taxi driver for long. In April 2022, HbA1c value increased to 8.2%, and then he started empagliflozin (Figure 1). After that HbA1c decreased remarkably to 6.7% in October 2022. However, he stated the problem during working period as a taxi driver. He often has to urinate many times, which has been annoying for his life style. Consequently, the empagliflozin was taken every other day or was decreased for its dose. Then, HbA1c increased from 6.7 to 7.6% in January 2023. He received further evaluation for general laboratory examination.

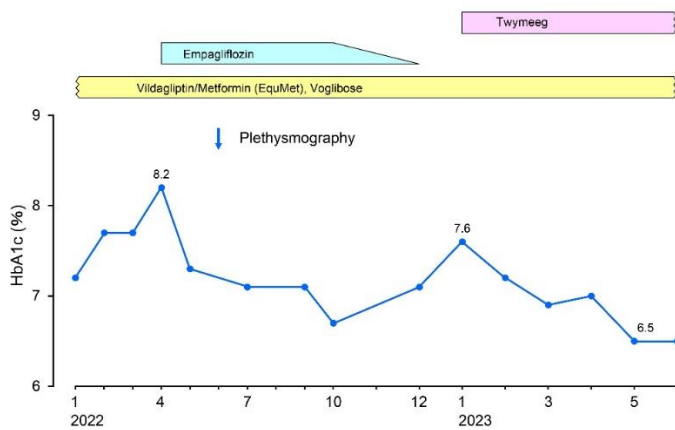


Figure 1: Clinical progress of the case with HbA1c and treatment.

### Physical examination

Consciousness and speech are normal. His vitals are stable as BP 128/74 mmHg, pulse 64 /min, SpO<sub>2</sub> 98%. No remarkable findings are observed for his head, neck, heart and lung. Abdomen showed flat and soft without abnormal signs. Neurological exams showed unremarkable, including motor and sensory disturbance, and other impairments. His physique showed rather slender, associated with stature 166cm, weight 53.2kg and BMI 19.5 kg/m<sup>2</sup>.

### Laboratory examination

The results of laboratory exam in Jan 2023 were as follows: HbA1c 7.6 %, post-prandial blood glucose 203 mg/dL, RBC 4.13 x 10<sup>6</sup> /μL, Hb 13.5 g/dL, Ht 40.6 %, MCV 98.3 fL (80-98), MCH 32.7 pg (27-33), MCHC 33.3 g/dL (31-36), WBC 6400/μL, Plt 25.6 x 10<sup>4</sup> /μL, GOT 20 U/L, GPT 17 U/L, γ-GTP 21 U/L, Uric acid 4.1 mg/dL, BUN 17 mg/dL, Cre 0.71 mg/dL, HDL 66 mg/dL, LDL 119 mg/dL, TG 133 mg/dL. Urinalysis: glucose (+), protein (-), urobilinogen (+/-), pH 6.0, ketone bodies (-). Chest X-ray test showed negative finding. Electrocardiogram (ECG) revealed normal axis, pulse 68/min, ordinary sinus rhythm, and no remarkable ST-T changes. Abdominal CT showed the

presence of gall stone without acoustic shadow, suggesting cholesterol polyps. Otherwise, unremarkable findings are observed for liver, common bile duct, kidney, spleen and pancreas.

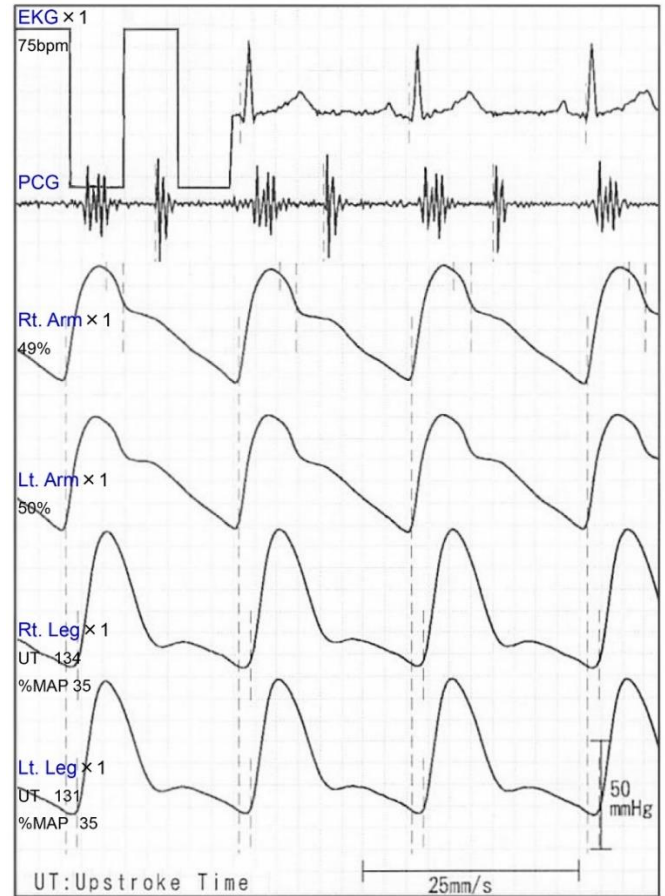


Figure 2: Plethysmography; The ABI value is normal range bilaterally.

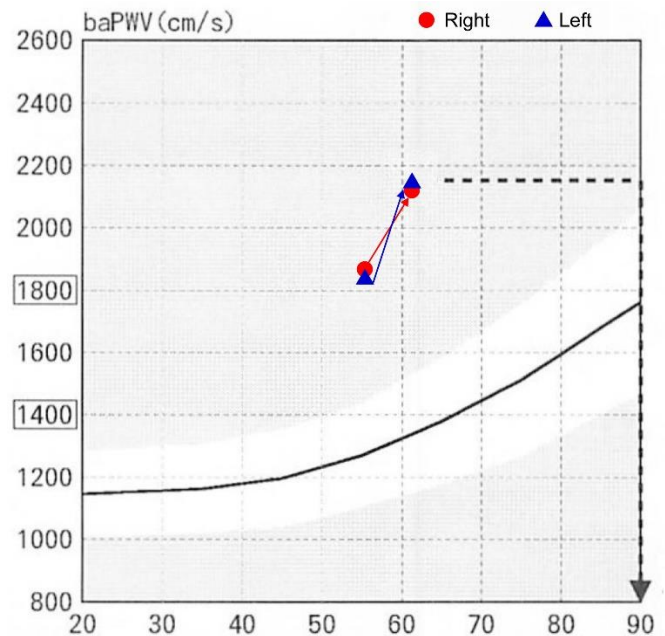


Figure 3: Plethysmography; The baPWV value was elevated for 5 years.

## Plethysmography

This patient underwent blood pressure plethysmography in 2017 and June 2022. In 2017, ankle brachial index (ABI) was in the normal range as 1.13/1.12, but brachial ankle pulse wave velocity (baPWV) was high at 1859/1823 that is above the standard level. The standard range is between 1400-1800 cm/sec [4]. After 5 years, the ABI remained unchanged at 1.12/1.12 (Figure 2). On the other hand, the baPWV was 2121/2152, showing stronger arteriosclerosis than the previous time (Figure 3) [12]. Changes in body weight were observed during this period. Compared for 2017 vs 2022, weight and BMI were 61.1kg and 21.9 kg/m<sup>2</sup> vs 50.3kg and 18.0 kg/m<sup>2</sup>, respectively.

## Clinical progress

The case started to take vildagliptin/metformin (EquMet) from January 2023, which is administered 1000mg for twice per day. After that, HbA1c was decreased from 7.6% to 6.5% in May 2023, which was satisfactory reduction of 1.1% for 4 months. The case has felt no gastro-intestinal adverse effects (GIAEs) by Twymeeeg. From winter 2022 to spring 2023, he did not have any trouble for frequent urination during his work as a taxi driver. He was satisfied with decreased HbA1c and comfortable daily working without worry.

## Ethical consideration

The case complied with the ethical guidelines from the Declaration of Helsinki. In addition, several commentaries were announced from the standard regulation. The latest principle has included the ethical rule concerning the medical research and practice. Some clinical problems of human have been present. The guidelines have been regulated by Japanese government, including 2 ministries that are Ministry of Health, Labor and Welfare and also Ministry of Education, Culture, Sports, Science Technology. The authors and staffs have established the ethical committee for this case study. It exists in Kanaiso hospital, Komatsushima, Tokushima, Japan. The committee includes several members, such as hospital president, physician, registered nurse, pharmacist, dietician and legal professional. The committee members have fully discussed as to this case, and agreed with the current protocol. We have taken the informed consent by the document from the case.

## Discussion

The current case has some characteristic aspects, which are i) atherosclerosis has been developed during his clinical progress, ii) empagliflozin seemed to be effective but inconvenient for urinary incontinence during the work as a taxi driver, iii) the combination of OHAs of EquMet and Twymeeeg seemd to be effective. Some perspectives are described in this order as follows.

First, the case showed aggravation of arterial stiffness for 5 years. During this period, no special changes in symptoms, signs or exacerbation of laboratory data were found. Concerning his daily habit, he has kept muscle training every day, such as push-ups and sit-ups several hundred times a day. His weight reduction was likely to be due to such continuous exercise. For the relationship of ABI, baPWV and T2D, retrospective analysis was conducted for 452 cases [13]. As the protocol, grouping was performed for baPWV (<1,700 cm/s vs. ≥1,700 cm/s) and ABI (<0.9 vs. ≥0.9). As a result, the cases of low ABI and high baPWV showed hazard ratio (HR) 17.01 for all-cause mortality and HR 8.53 for composite events. Furthermore, cases with lower ABI plus lower baPWV or normal ABI showed similar outcomes. Consequently, the ABI plus baPWV can present a better relationship for the future outcomes of T2D.

In order to detect arterial stiffness and atherosclerosis, ABI and baPWV are well-known predictors for mortality in T2D patients. However, two markers show independent relationship with mortality. Then, detail association among ABI, baPWV, all-cause mortality, expanded CVD mortality in T2D patients was analyzed (n=2160) [14]. For mean follow-up for 8.4 years, 268 cases were attributed to CV events. low ABI and high baPWV quartile showed elevated risk for all-cause mortality (HR 1.67), and expanded CVD mortality (ABI 2.21, baPWV 1.75). Combined low ABI and highest PWV quartile showed significant higher risk of all-cause (HR 4.51) and expanded CVD mortality (HR 9.74) in comparison with combined normal ABI and lowest baPWV quartile.

Second, this case began the intake of empagliflozin as SGLT2-i in spring 2022. It was effective for HbA1c reduction for several months. However, he came to complain of urinary incontinence because of working for taxi driver [15]. Then he gradually decreased to take empagliflozin. SGLT2-i has been evaluated to show beneficial effects for diabetes, chronic heart failure (CHF), chronic kidney disease (CKD), and others [16]. On the other hand, other reverse effects or other influence should be considered including water intake, dehydration, polyuria and urinary incontinence. Among them, life style of the patient should be taken into account from bio-psycho-social points of view [17].

Third, this case was administered both of EquMet and Twymeeeg for T2D, which was clinically effective. For detail analysis of EquMet, VERIFY studies were known [18]. For diabetic macrovascular events, risk reduction by EquMet was proved to be 0.71 of hazard ratio (HR) [18,19]. The comparison of early combination of vildagliptin/metformin vs monotherapy of metformin was conducted, where two categories were prepared. When the cases were late-onset (more than 40 years), combined treatment showed 46% risk reduction for cardiovascular events [20].

Further, this case had add-on therapy of Twymeeq on EquMet. HbA1c reduction was remarkable by 1.1% for only 4 months. Thus, previous treatment included DPP4-i and biguanide, and after that imeglimin was added. From the investigation of Trials of IMeglimin for Efficacy and Safety (TIMES) 1, 2, 3, the result of add-on treatment of Twymeeq was reported. They showed that 0.92% for DPP4-i, 0.67% for biguanides, 0.46% for monotherapy, 0.85% for alfa-GI, 0.57% for SGLT2-I, and 0.56% for sulfonyl urea agents [21]. According to these data, equa plus metformin (vildagliptin plus biguanide) are equivalent to 0.92% plus 0.67% [22]. Consequently, combination of two OHAs would be expected to show beneficial efficacy [23]. Twymeeq can possess several possible mechanisms in the mitochondrial function [24]. Then, further function research will be expected for the apparent pharmaco-physiological aspect.

Some limitation may be found in this report. Clinical efficacy of HbA1c decrease would be at least in part, from the combined administration of some OHAs. They cannot be clarified for each medical effect. In addition, this case felt inconvenient urinary symptom during the course. Diabetic team should consider multiple aspects for the patient. Follow up the clinical progress will be required.

In summary, 62-year-old male patient with T2D and higher atherosclerosis was shown, who was treated by Equmet and Twymeeq with 1.1% HbA1c reduction. Follow up the clinical progress will be required. This case presentation is hopefully a useful reference for future clinical research.

## Conflict of interest

The authors declare no conflict of interest.

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