

# Unchanged Arterial Stiffness for Long in Diabetic Patient with Low LDL/HDL Ratio Treated by Equmet (Vildagliptin/Metformin) And Twymeeeg (Imeglimin)

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## Abstract

This case is 76-year-old female patient with T2D and hypertension for 12 years. HbA1c increased to 7.7% in January 2022, and decreased to 7.0% by vildagliptin/metformin (EquMet) for 9 months. However, it increased to 7.5% in Jan 2023 again. Providing imeglimin (Twymeeeg) showed effect for reduction to 6.7% for 4 months. Her lipid profile showed HDL 94 mg/dL, LDL 69 mg/dL, TG 30 mg/dL, T-Cho 169 mg/dL with remarkable low arterial stiffness index (ASI) 0.8. For plethysmography, cardio-ankle vascular index (CAVI) showed stable for 10 years. These two factors are likely close-related to each other, preventing exacerbating arteriosclerosis.

**Keywords:** Arterial Stiffness Index (ASI); Cardio-Ankle Vascular Index (CAVI); Atherosclerotic Cardiovascular Accident (ASCVD); Japan LCD Promotion Association (JLCDPA); Vildagliptin Efficacy in Combination with Metformin for Early Treatment of Type 2 Diabetes (VERIFY)

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## Introduction

For decades, atherosclerotic cardiovascular disease (ASCVD) has been in focus for adequate management and protection across the world [1]. ASCVD includes hypertension, type 2 diabetes (T2D), dyslipidemia, cerebral vascular accident (CVA), ischemic heart disease (IHD), peripheral artery disease (PAD) and others. These pathologies include the development of macroangiopathy due to the exacerbation of T2D and hypertensive situations [2]. As the marker of ASCVD, arterial stiffness index (ASI) has been known and estimated for useful measure [3]. In the light of relationships of some markers, ASI has been independently associated with IHD, hypertension, blood pressure (BP), and so on epidemiologically [4]. Aortic stiffness has been a marker for vascular aging, and it may influence the occurrence of CVDs. Further, aortic pulse wave velocity (PWV) has been a biomarker of aortic stiffness, and it may provide useful information for cardiovascular pathology [5].

Among ASCVD, crucial disease in recent clinical practice would be T2D. The standard guideline was announced from American Diabetes Association (ADA) in 2023 [6]. T2D requires three basic treatment axes, which are diet, exercise and medicine. For nutritional therapy, low carbohydrate diet (LCD) has been more prevalent with beneficial effect rather than calorie restriction (CR) [7]. As to pharmacological development, several novel oral hypoglycemic agents (OHAs) and combined OHAs have been

introduced [8]. They include the combined agents of vildagliptin and metformin (EquMet) which shows clinical beneficial effects [9]. It was supported by large medical studies, that was vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY) [10].

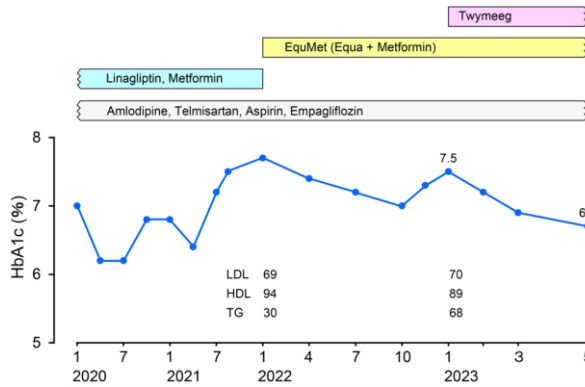
Authors and our clinical group have continued medical research and practice for long. The area includes T2D, ASCVD, hypertension, dyslipidemia, chronic kidney disease (CKD) and others [11]. We have developed LCD medically and socially through Japan LCD promotion association (JLCDPA) [12]. For T2D patients, seasonal HbA1c changes were studied for several years [13]. In addition, clinical effects of imeglimin as novel OHA were reported in early period [14]. Recently, our medical team experienced a characteristic female case who showed unchanged arterial stiffness for 10 years associated with lower ASI value. Her general clinical situation and some perspectives are presented in this article.

## Case Presentation

### Medical History

This case is 76-year-old female patient with T2D and hypertension. Her medical history showed about 10 years for T2D and 12 years for hypertension. She did not have remarkable past history of other diseases. Recently, her diabetic variability has not been satisfactory

level, keeping 7%< of HbA1c (Figure 1). She had provided amlodipine and telmisartan for hypertension, and linagliptin and metformin, empagliflozin for T2D until January 2022. However, HbA1c value was increased to 7.7%, and then she received further evaluation.



**Figure 1:** Clinical progress of the case.

### Physical Examination

Her physical examination in January 2022 revealed in the following: Consciousness and conversation were normal. Vitals signs were in the normal ranges as pulse 72/min, BP 132/72 mmHg, SpO<sub>2</sub> 98%. Her head, neck, lung, heart and abdomen showed unremarkable findings. Neurological exams showed intact. Her physique was 144.2cm, 51.6kg, BMI 24.8 kg/m<sup>2</sup>.

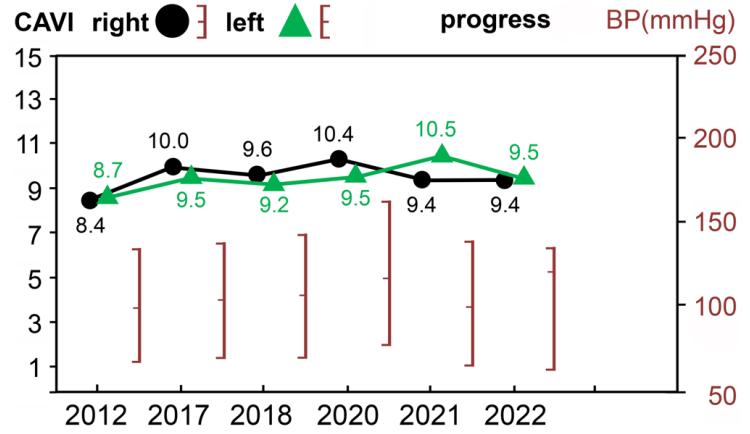
### Laboratory Exams

Results of laboratory tests in Jan 2022 were as follows: T-Bil 0.3 mg/dL, AST 23 U/L, ALT 22 U/L, ALP 89 U/L(38-113), LDH 235 U/L (124-222), GGT 13 U/L, CPK 72 U/L, BUN 19 mg/dL, Cre 0.5 mg/dL, Na 137 mEq/L, Cl 98 mEq/L, K 4.3 mEq/L, WBC 4300/μL, RBC 4.37 x 10<sup>6</sup> /μL, Hb 12.4 g/dL, Ht 43.5 %, MCV 87.9 fL (80-98), MCH 28.3 pg (27-33), MCHC 32.2 g/dL (31-36), Plt 33.9x 10<sup>4</sup> /μL, HDL 94 mg/dL, LDL 69 mg/dL, TG 30 mg/dL, T-Cho 169 mg/dL, arterial stiffness index (ASI) 0.8. The equation of ASI is T-Cho – HDL/HDL = 169-94/94 = 0.8. Another equation would be the calculation of LDL/HDL ratio = 69/94 = 0.73.

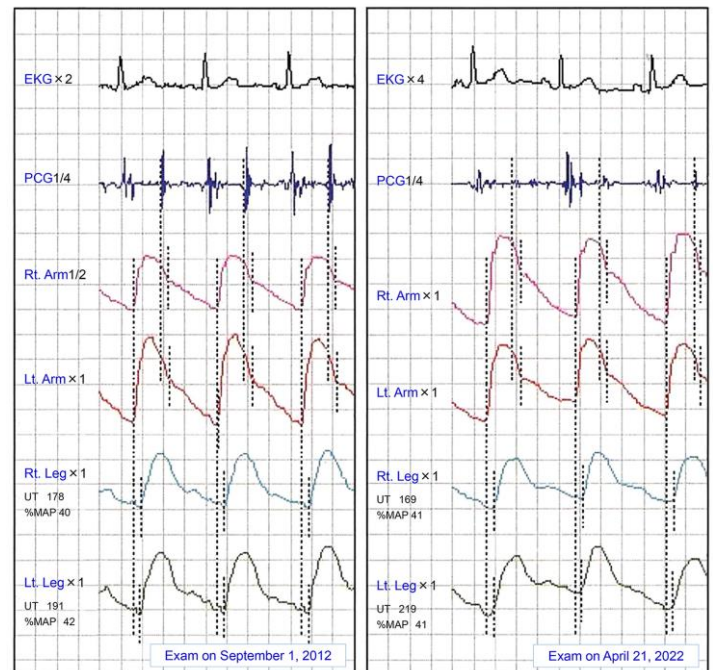
### Physiological Exams

For the physiological tests, chest X-ray revealed negative findings. Electrocardiogram (ECG) showed normal axis, pulse 72/min, ordinary sinus rhythm (OSR), and no remarkable ST-T changes. She received the exam of blood pressure plethysmography regularly for 10 years from 2012 to 2022. The cardio-ankle vascular index (CAVI) showed stable from 8.4 to 10.5 for long period (Figure 2). It also showed almost same blood pressure. Concerning her stature, her BMI was almost the same as 24.0 kg/m<sup>2</sup> in 2012, 24.8 kg/m<sup>2</sup> in 2020 and 22.6 kg/m<sup>2</sup> in 2022. The latter data of 22.6 kg/m<sup>2</sup> was observed after the administration of starting empagliflozin. The detail wave situation of plethysmography in 2012 and 2022 was shown in Figure 3. It shows unremarkable

changes for the long period of 10 years, which are for ECG, PCG, bilateral arms and feet. The value of ABI was 1.00/0.91 and 0.89/0.95 in 2012 and 2022, respectively, without remarkable changes for 10 years.



**Figure 2:** Changes in CAVI for 10 years.



**Figure 3:** Stable results of plethysmography in 2012 and 2022.

### Clinical Progress

From the results of Jan 2022, she started vildagliptin/metformin (EquiMet) for combined OHA. Then, HbA1c was decreased from 7.7% to 7.0% for 9 months. After that, HbA1c was increased again to 7.5% to Jan 2023. Consequently, she was provided imeglimin (Twymeeg), and HbA1c was decreased to 6.7% for 4 months. The laboratory data of lipids in Jan 2023 was unchanged to those of 12 months ago, where LDL 70 mg/dL, HDL 89 mg/dL, and triglyceride 68 mg/dL (Figure 1).

## Ethical Standards

This report complies with the ethic guideline of Declaration for Helsinki. In addition, some commentary is based on the regulation of personal information. The related principle is observed in the ethical regulation about the clinical practice and research. The standard guideline is presented from Japanese government. They include Ministry of Education, Culture, Sports, Science Technology and Ministry of Health, Labor and Welfare. The authors and co-researchers have established our ethical committee as to this case. It was present in Sakamoto hospital, Kagawa prefecture, Japan. It included several staffs, such as hospital president, physician, pharmacist, head nurse, dietitian, and legal professional. We have fully discussed on the current protocol and agreed the protocol satisfactory. We have obtained the informed consent by the written document from the case.

## Discussion

In this report, the current case was 74-year-old female patient who has some medical characteristics. She has #1 low value of ASI and low LDL/HDL ratio for long years, #2 stable results of blood pressure plethysmography and #3 T2D, #4 hypertension, #5 clinical efficacy of EquMet and Twymeeg. Some perspectives are described for the current discussion in this order.

Firstly, this case showed stable results of plethysmography for 10 years. It may be from her lipid profile with low ASI and low LDL/HDL ratio. She did not take oral agents for dyslipidemia for long. Probably, she seems to have somewhat hereditary beneficial lipid profile.

From the detail research of arterial stiffness for 132 thousand cases, phenotyping profiles of higher ASI levels were investigated [15]. As a result, threshold values of lipids seem to be 5.409 mmol/L (209.2mg/dL) for T-Chol, and 1.286 mmol/L (113.9 mg/dL) for triglycerides. Arterial stiffness has been influenced not only by lipids, but also by systolic and diastolic blood pressure (SBP, DBP). For 169 thousand of cases, the associations among ASI, SBP, DBP and hypertension were investigated [16]. As a result, ASI could predict the exacerbation of isolated systolic hypertension as odds ratio (OR) 1.30, especially OR 2.20 by the variability adjustment. Further, aortic stiffness has been a marker for vascular aging, and it may influence the occurrence of CVDs. Aortic pulse wave velocity (PWV) for a biomarker of aortic stiffness, may be measured by using applanation tonometry [5]. From 597 cases for 6 years, validation decision model was estimated, associated with the results of sensitivity 70%, specificity 78%, and accuracy values 0.73.

Secondly, this patient had hypertension and diabetes for more than 10 years. She was taking antihypertensives and OHAs. On the other hand, lipid values of LDL, HDL, and TG were originally kept in the normal range. It was probably due to the genetic background, and then agents for dyslipidemia were not administered. In Japan,

we do not give anti-lipidemia agents to such patients. In contrast, lipid medications are usually provided to such patients in the United States, regardless of their LDL level [17]. In the future, standard treatment for diabetes and LDL would be changed [18].

From lifestyle point of view, the case has been working as a hospital assistant. She has kept regular daily life for long years physically and psychologically. Her weight has been unchanged for long. After taking SGLT2-i, she developed slight weight reduction and slight decrease in blood pressure [19]. Renal function has been kept in the normal range. The association of these factors may have contributed to the slow progress of diabetic macroangiopathy over the past decade.

Thirdly, the case was provided EquMet, which revealed efficacy for HbA1c reduction. This agent is the combination of vildagliptin and metformin, as DPP4-i and biguanide. The clinical effect has been presented by investigation of the Vildagliptin Efficacy in combination with metformin for early treatment of type 2 diabetes (VERIFY) studies [10]. VERIFY was conducted for multi-center international studies over 34 countries [20]. When comparing with other OHAs, EquMet contributes benefit for reducing blood glucose fluctuation during daytime and also night period [21]. By the detail analysis, mean amplitude of glycemic excursion (MAGE) was remarkably lowered by EquMet administration. Its characteristics seems to be induced from bid administration (twice intake a day).

Some limitation may exist in this article. Current case showed clinical effect of EquMet and Twymeeg, but other beneficial factors may be involved [22]. Further, she showed lower ASI and LDL/HDL ratio, which may bring unchanged arterial stenosis for long years. Various factors will be followed up with close attention. In summary, 74-year-old T2D patient showed various characteristic aspects. This article becomes hopefully useful reference for clinical research of diabetes and arteriosclerosis.

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