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Future individualization medicine in diabetes with different responsive subtypes

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Abstract

Action to Control Cardiovascular Risk in Diabetes (ACCORD) has been diabetic mega study and analyzed cardiovascular disease (CVD) and major adverse cardiovascular events (MACE). Recently, subgroup analyses have showed heterogeneous treatment effects (HTE). Using genome-wide association study (GWAS) and modified dynamic time-warping approach (etwDTW), presence of subgroups (C1-4) was suggested. Four-month strict treatment resulted in HbA1c 6.7%, 7.0%, 7.7% and 6.2%, respectively. The hazard ratio (HR) for C4/C3 showed: MACE 0.27/1.60, total mortality 0.33/2.52, hypoglycemia 0.33/1.66, and microvascular outcome 0.86/1.30. C4 showed suggestive significance of single-nucleotide polymorphism (SNP) for rs220732, in MAS1. Future diabetology may proceed to individualization medicine.

Keywords: Action to Control Cardiovascular Risk in Diabetes (ACCORD); major adverse cardiovascular events (MACE); heterogeneous treatment effects (HTE) ; genome-wide association study (GWAS) ; modified dynamic time-warping approach (etwDTW)

Editorial

For decades, non-communicable disease (NCD) has been gradually increasing, and type 2 diabetes (T2D) has become crucial NCD from social, medical and economic points of view [1]. T2D is already prevalent for more than 450 million people across the world [2]. In the US, T2D is found in 10% of adults with medical cost for 327 billion dollars [3]. Latest diabetic guideline has been presented adequate treatment from American Diabetes Association (ADA) [4]. However, various situations for actual risks exist in the different subgroups for T2D patients [5]. From real-world data, clinical inertia for diabetes care has been recognized for indicating certain evidence leading to treatment individualization [6]. Leading cause of mortality for T2D is from cardiovascular disease (CVD). For reducing risk of CVD, intensive glycemic control would be required with research for individualization data [7].

As clinical diabetic mega study, Action to Control Cardiovascular Risk in Diabetes (ACCORD) was one of the important landmarks. It was to investigate the efficacy of strict glucose control for <6% of HbA1c vs moderate treatment 7.0-7.9% of HbA1c. This study was performed for T2D patients on high CV risk at high cardiovascular risk with major adverse cardiovascular events (MACE) [8]. The results of ACCORD showed the crucial implications concerning guidelines for adequate glycemic management [9,10]. Although a significant higher mortality was observed for the intensive glycemia arm, the presence of heterogeneity was found [11]. Furthermore, several beneficial tendency of retinopathy, neuropathy and nephropathy were reported [12]. From ACCORD results, cases with high mortality and MACE were those who were treated intensively with failing to reach the target HbA1c [13].

As former diabetic mega studies, the ACCORD and the Veterans Affairs Diabetes Trial (VADT) study have been well-known with significant results. They could not show the associations of intensive glycemic control with MACE [14]. However, the trials of subgroup analyses for both ACCORD and VADT may present probable heterogeneous treatment effects (HTE). Recent analyses have revealed machine learning method, in which hypothesis-free approach method was used for evaluating subgroups from combinations of variables [11]. Successively, causal forests machine learning method was applied for the evidence gaps for T2D individualization for mitigating CVD risk [15,16]. For the previous data of ACCORD and VADT trials, the methods can bring the identification of HTE of intensive glycemic control on MACE [15].

In the ACCORD trial, 4946 patients were assigned to the intensive therapy group [8]. These cases were classified into 4 groups according to similar HbA1c change course using the modified dynamic time-warping approach (etwDTW) [17]. In these 4 groups, the analyses were performed and compared based on the standard therapy group. As a result, after 4 months of treatment, HbA1c was 7.6% in the standard group. On the other hand, the HbA1c values of C1,2,3,4 was 6.7%, 7.0%, 7.7%, 6.2%, respectively. Furthermore,

the data comparing the C4 group and the C3 group are shown as follows. Hazard Ratio (HR) of C4 vs C3 showed the following results: MACE 0.27 vs 1.60, total mortality 0.33 vs 2.52, hypoglycemia episodes 0.33 vs 1.66, and microvascular outcome 0.86 vs 1.30, respectively. The impressive results showed that C4 revealed fewer CVD (HR 0.34), outcome of microvascular complication (HR 0.86). For group C4, suggestive significance showed rs220732, in MAS1 for a single-nucleotide polymorphism (SNP). C4 group displayed lower CVD risk compared to standard treatment as HR 0.53, but not lower risk for microvascular outcomes.

From ACCORD results, two genetic variants were detected that could predict modified risk of CV mortality with significant interaction for glycemic variability [18]. Based on these data, risk score method was developed, and investigated the relationship with MACE, mortality and other CVD outcomes. Moreover, a genome-wide association study (GWAS) was conducted in order to identify genetic variants for lower risk group [19]. Successively, machine learning method was performed for constructing a polygenic score (PS) in order to predict adequate patients that seem to receive beneficial response from ACCORD-like strict glucose control [20]. This study may generate new hypothesis in which such case of lower risk group will have significantly lower CVD outcomes in comparison with other cases. Similar studies may generate novel hypotheses with precision medicine for T2D, and propose crucial landmark for clinical trial in the future.

Recent report has been observed in this area of research [21]. For identifying HTE of intensive vs standard glycemic control, causal forests machine learning analysis was conducted. The subjects included 12,042 cases, and the biomarkers included HbA1c, blood glucose, eGFR, age, BMI, and so on. As a result, risk differences for MACE have ranged from -5.1% to 3.1%. Intensive glycemic control showed lower MACE in 3 subgroups, in which -4.2% for low, -5.1% for intermediate and -4.3% for high result, respectively. Thus, MACE showed lower consistent efficacy directions for ACCORD and VADT.

Some latest reports are found. As perspective for diabetes typology and precision diabetology, the approach will be considered to the subtypes of the diabetes [22]. They include mild age-related diabetes and mild obesity-related diabetes for T2D, and severe insulin-resistant diabetes, severe insulin-deficient diabetes and severe autoimmune diabetes for T1D. Diabetes has been one of the representative NCVs and it is often accompanied with other diseases. They always have complicated interrelationships each other with dyslipidemia, atherosclerotic cardiovascular disease (ASCVD), hypertension, cerebral vascular accident (CVA), and others [23]. These pathologies have to be always considered from general point of view. As to future diabetic therapy, the important issues would be the choice of antidiabetic agents (ADA) and also other required factors. They include the management of lipid, blood pressure, antiplatelet agents associated with considering the status of the cardiovascular system [24]. Consequently, diabetic patients will be managed and in the light of individualization aspects.

In summary, the management of diabetes would be changed associated with novel perspectives. They include categorization of diabetic subgroups, individualization, gene analysis and interrelationships with CVD and macro-/micro- angiopathic complications. This article becomes hopefully useful reference for future clinical research.

Conflict of interest

The authors declare no conflict of interest.

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