Accepted Manuscript

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PII: S1109-9666(16)30082-3

DOI: 10.1016/j.hjc.2016.07.002

Reference: HJC 28

To appear in: *Hellenic Journal of Cardiology*

Received Date: 21 June 2016

Revised Date: 13 July 2016

Accepted Date: 14 July 2016

Please cite this article as: Skliros NP, Vlachopoulos C, Tousoulis D, Treatment of Diabetes: Crossing to the other side, *Hellenic Journal of Cardiology* (2016), doi: 10.1016/j.hjc.2016.07.002.

Treatment of Diabetes: Crossing* to the other side

*Diabetes is a Greek word that is derived from the verb *diavaino that means "walk/cross"*.

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Abstract

Type 2 diabetes mellitus affects nearly four hundred million people worldwide and one of its major complications is cardiovascular disease. Evaluation of effectiveness and safety of antidiabetic medication has been a challenging issue. Large outcome trials of new anti-diabetic medications have used the non-inferiority approach to ensure primarily safety before incorporation of the drug in clinical practice. This has been gradually changing with superiority being the current trend –that is to prove that the new drug has additional beneficial effect on top of standard medication.

In this review we present the results of recent trials on type 2 diabetes mellitus medications and outline what can be anticipated from the currently ongoing.

Keywords: Type 2 diabetes mellitus, Antidiabetic drugs, Cardiovascular safety, Cardiovascular disease, Cardiovascular outcome trials

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*"Medicine is a **science** of uncertainty and an **art** of probability*"[1] (William Osler) and as such it had and it will always change dynamically. The first incorporation of probability in medicine appears in the Old Testament (605-562 b.c.) where King Nebuchadnezzar II ran the first ever written trial on dietary habits and the effects on human health.[2] The Greek physician and philosopher Galen (129-216 a.d.), who was known for his exploratory spirit, described and used different mixtures of various minerals and herbs on his patients evaluating their positive or negative effects.[3] Avicenna in *The Canon of Medicine* (1025 a.d.), formed the basis of modern clinical trials, introducing seven practical rules for the experimental use and testing of medicines.[4] In 1537, Ambroise Pare, known Renaissance surgeon, unintentionally carried out a trial while changing the standard treatment for open wounds because he ran out of boiling oil and had the first ever non-inferiority results.[5] Since then, innumerable trials showing evidence-based results are providing health-care professionals with reasoning and confidence in everyday practice. Such a continuously

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Abbreviations: A1C: glycated A1c hemoglobin, ACEi: angiotensin converting enzyme inhibitor, ACS: acute coronary syndrome, AHA: American heart association, ARB: angiotensin receptor blockers, CANVAS: canagliflozin cardiovascular assessment study, CAROLINA: cardiovascular outcome study of linagliptin versus glimepiride in patients with type 2 diabetes, CARMELINA: cardiovascular safety and renal microvascular outcome with linagliptin in patients with type 2 diabetes mellitus, CI: confidence interval,CKD: chronic kidney disease, CV: cardiovascular, CVD: cardiovascular disease, CVOT: cardiovascular outcomes trials, DECLARE-TIMI: dapagliflozin effect on cardiovascular events - thrombolysis in myocardial infarction study group, DPP-4i: dipeptidyl-peptidase-4 inhibitors, eGFR: estimated glomerular filtration rate, ELIXA: evaluation of lixisenatide in acute coronary syndrome, EMA: european medicines agency, EMPA-REG OUTCOME: empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients, EXAMINE: examination of cardiovascular outcomes with alogliptin versus standard of care, EXSCEL: exenatide study of cardiovascular event lowering, FDA: U.S. food & drug administration, GLP-1: Glucagon-like peptide-1, HF: Heart Failure, HFH: Heart Failure Hospitalization, HR: hazard ratio, MACE: Major Adverse Cardiac Events, NNT: number needed to treat, NT-proBNP: N-terminal pro brain natriuretic peptide, PROactive: the prospective pioglitazone clinical trial in macrovascular events, RECORD: rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes, SAVOR-TIMI: saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus - thrombolysis in myocardial infarction study group, SGLT2i: sodium glucose co-transporter 2 inhibitor, SoC: Standard of Care, T2DM: type 2 diabetes mellitus, TECOS: trial evaluating cardiovascular outcomes with sitagliptin, TOSCA.IT: thiazolidinediones or sulphonylureas and cardiovascular accidents intervention trial, TZD: thiazolidinediones