Hellenic Journal of Cardiology (2016) 57, 304–310

Available online at www.sciencedirect.com

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journal homepage: http://www.journals.elsevier.com/hellenic-journal-of-cardiology/

REVIEW ARTICLE

Treatment of diabetes: Crossing to the other side☆

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Received 21 June 2016; received in revised form 13 July 2016; accepted 14 July 2016
Available online 25 July 2016

KEYWORDS
Type 2 diabetes mellitus;
Antidiabetic drugs;
Cardiovascular safety;
Cardiovascular disease;
Cardiovascular outcome trials

Abstract Type 2 diabetes mellitus affects nearly four hundred million people worldwide, and one of its major complications is cardiovascular disease. The evaluation of the effectiveness and safety of antidiabetic medication has been a challenging issue. Large clinical trials of new antidiabetic medications have used the non-inferiority approach to ensure primary safety of the drug before its incorporation into clinical practice. Currently, the trend is to prove superiority, that is, to prove that the new drug has additional beneficial effects to those of standard medications.

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

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 sulfonylureas and cardiovascular accidents intervention trial; TZD, thiazolidinediones.

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

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Peer review under responsibility of Hellenic Cardiological Society.

http://dx.doi.org/10.1016/j.hjc.2016.07.002

*"Medicine is a **science** of uncertainty and an **art** of probability"*[1] (William Osler). As such, it has changed and will continue to 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 written trial on dietary habits and its 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 and 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, a known Renaissance surgeon, unintentionally carried out a trial when he ran out of boiling oil and changed the standard treatment for open wounds and recorded the first non-inferiority results.[5] Since then, numerous evidence-based trials have provided health-care professionals with reasoning and confidence in everyday practice. The effects of oral antidiabetic drugs for type 2 diabetes mellitus (T2DM) on cardiovascular (CV) risk is a continuously evolving matter that needs multiple confirmations from trials because of its multifactorial and complex nature.

According to the World Health Organization (WHO), in 1985, there were 30 million people who had diabetes worldwide, and by 1995, there were 135 million.[6] The number is presently at 387 million, and by the year 2035, it is estimated to reach at least 592 million people worldwide.[7,8] Type 2 diabetes mellitus, which affects more than 90% of diabetic patients, is a metabolic disorder with a progressive decline of pancreatic β-cell function and a biochemical presentation of impaired fasting and/or post-prandial blood glucose levels.

One of the major complications of T2DM is cardiovascular (CV) disease, and at least 68% of people >65 years with diabetes die of heart disease.[9,10] The etiology of diabetes-derived CV complications is not clear yet, but the underlying mechanisms are based on a complex and multifactorial pathophysiology that includes macrovascular, epigenetic and intracellular metabolic changes.[11—14]

While a variety of categories of antidiabetic drugs (Table 1) are available to help clinicians fight the disease, the mechanism of action and effect on end-points of the specific drug must be elucidated to decide on the appropriate choice for a specific patient profile (Figure 1). The blood glucose and glycated A1C hemoglobin (A1C) levels are routinely used to monitor the effectiveness of the antidiabetic medication and patient compliance. The target A1C levels have been set from the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation to a range between 6.5% and 7%. Reaching this target is difficult to achieve in everyday clinical practice. However, what is most important is whether A1C can be used as a surrogate for CV end-points. Because the latest trials do not confirm

Table 1 Types of antidiabetic drugs and mechanism of action.

Class	Substance	Mechanism of Action	Weight	Known Side-Effects
Sulfonylureas	Gliclazide Glimepiride Glibenclamide	Stimulate the pancreas to produce more insulin	Increase	Allergy Risk for hypoglycemia and weight gain
Meglitinide	Nateglinide Repaglinde	Stimulate the pancreas to produce more insulin	Increase	Frequent dosing Risk for hypoglycemia
Biguanides	Metformin	Reduce the production of glucose by the liver	Neutral / loss	Gastrointestinal side-effects, lactic acidosis (disputed), B12 deficiency. Contraindications, low eGFR, hypoxia, dehydration
Thiazolidinediones (TZD)	Pioglitazone Rosiglitazone	Increase insulin sensitivity of the body cells and reduce the production of glucose by the liver	Increase	Heart failure, edema, fractures, urinary bladder cancer (disputed)
Alpha-glucosidases inhibitors	Acarbose	Slow the absorption of carbohydrates (sugar) ingested	Neutral	Gastrointestinal side-effects Frequent dosing
Dipeptidyl- peptidase-4 (DPP-4) inhibitors	Linagliptin Saxagliptin Sitagliptin Alogliptin	Intensify the effect of intestinal hormones (incretins) involved in the control of blood sugar	Neutral	Pancreatitis
Glucagon-like peptide-1 (GLP-1) agonist	Exenatide Liraglutide	Mimic the effect of certain intestinal hormones (incretins) involved in the control of blood sugar	Decrease	Gastrointestinal side-effects Pancreatitis Injectable
Sodium glucose co-transporter 2 inhibitors (SGLT2)	Canagliflozin Empagliflozin Dapagliflozin	Help eliminate glucose in the urine	Decrease	Urinary tract infections

Adapted from "Diabetes Québec", 2015 and "ESC Guidelines on diabetes, pre-diabetes and CVD", 2013

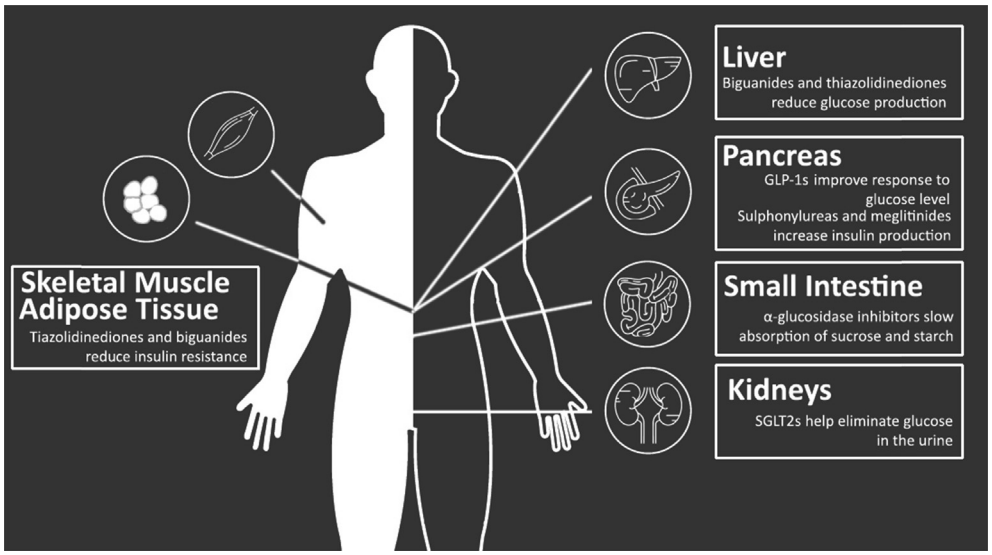

Figure 1 Mechanism of action of T2DM drugs.

that the control of A1C levels in patients with T2DM has been associated with a positive effect on macrovascular complications, its use as a surrogate marker may have to be re-evaluated.[15]

1. To CVOT or not to CVOT?

Cardiovascular outcome trials (CVOT) are the optimal way to evaluate not only the efficacy but also the CV safety of a drug. In past decades, especially in the 1990's, a large number of medical studies addressed the risk of antidiabetic drug-induced CVD.[16–20] In 1999, the American Heart Association (AHA) confirmed, collected and published data from these evidence-based trials in a scientific statement entitled "*Diabetes and Cardiovascular Disease*".[21] Large clinical trials highlighted the positive role of antidiabetic drugs in lowering A1C levels and obtaining optimal glycemic control. However, data from a number of trials showed that antidiabetic drugs provoked heart and vessel disease, dividing the scientific community. The most recent indicative example was with the thiazolidinedione (TZD) drug, rosiglitazone. Initial clinical trials showed that it was positively correlated with CV prevention in diabetic patients, making it one of the top antidiabetic drugs on the market until 2007, when a meta-analysis study[22] linked rosiglitazone to a significant (43%) increase in risk for myocardial infractions and an increasing trend (64%) towards CV death. These data called into question the validity of basing diabetes treatment on a measurable outcome, glycemic control. The European Medicines Agency (EMA) banned the drug, and the US Food and Drug Administration (FDA) forced the company to add a box warning about the potential increased risk for heart attacks. However, post-market studies, albeit years later, did not confirm the results of the meta-analysis for rosiglitazone. In addition, the *RECORD* trial did not show an increase of the overall risk of CV morbidity or mortality compared with standard glucose-lowering drugs (with the exception of an increased risk of heart failure hospitalization HR: 2.10, 95% CI 1.35 to 3.27), indicating how complex the issue of effectiveness and CV safety of an antidiabetic drug is.[23]

In any case, the scene for drawing safer conclusions on the CVD safety of antidiabetic drugs had been set. The next step for the FDA was the 2008 publication of "*Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*", that demanded changes in the way T2DM drug trials were conducted. The publication stipulated that trials had to include special populations such as advanced disease patients and multi-national ethnic groups, predetermined subgroup analyses and an in-depth safety review with a specific focus on CVD outcomes, such as stroke, myocardial infraction and CV mortality. Finally, new limits were set on the upper bound of the two-sided 95% confidence interval for the estimated risk ratio to be below 1.3. For instance, it is not reassuring to find an insignificant risk ratio of which the upper boundary of the confidence interval is 1.5. To gain more confidence that an increase in risk does not truly exist, a trial must clearly show that the upper boundary of the two sided 95% confidence interval for the estimated risk ratio is below 1.3.[24]

2. Non-maleficence? No beneficence either

Following the new FDA and EMA requirements for the CV safety of antidiabetic drugs and adhering to the Hippocratic principle "(first) to do no harm", several new trials (Table 2) in the last 5 years used the non-inferiority design, that is, the drug under investigation had to be no less effective and no more harmful than the control before it could be introduced into the drug market. This approach may at first appear cautious and passive. We have to emphasize, however, that in the era of a holistic therapeutic approach, it is difficult to add therapeutic benefit with a new intervention. Across time, in landmark trials including patients with a high CV risk, the number needed to treat (NNT) to prevent one primary event has increased from 30 (for 5.4 years) in the pre-statin era with simvastatin, to 56 (for 5 years) in the

Table 2 General data of CVOT in TD2M.

CVOT	Class	Generic Name	Year	Primary Objective	Enrollment	Population additional characteristics	Primary Outcome	Primary Outcome Confirmation	HFH Confirmation	Non-inferiority	Superiority
	TZD										
RECORD		Rosiglitazone	2008	CV outcome vs. SoC	4447	A1C:7.0%-9.0%, BMI>25 kg/m2	CV death or hospitalization	HR:0.99, CI:0.85-1.16	HR:2.10, CI:1.35-3.27	√	Not evaluated
	DPP4i										
EXAMINE		Alogliptin	2013	MACE vs. SoC	5380	Recent ACS, A1C:6.5%-11.0%	CV death	HR:0.96, CI≤1.16	HR:1.07, CI:0.79-1.45	√	Not evaluated
SAVOR-TIMI 53		Saxagliptin	2013	CV efficacy and safety vs. SoC	18206	CVD, high CV risk	CV death	HR:1.00, CI:0.89-1.12	HR:1.27, CI:1.07-1.51	√	Not proved
TECOS		Sitagliptin	2015	CV outcome vs. SoC	14724	CVD, A1C:6.5%-8.0%	CV death or hospitalization	HR:0.98, CI:0.88-1.09	HR:1.00, CI:0.83-1.20	√	Not evaluated
	GLP-1										
ELIXA		Lixisenatide	2015	CV outcome vs. SoC	6076	ACS, A1C:7.0%-11.0%	CV death or hospitalization	HR:1.02, CI:0.89-1.17	HR:0.96, CI:0.75-1.23	√	Not proved
LEADER		Liraglutide	2015	CV outcome vs. SoC	9341	Vascular disease	Composite of the 1st occurrence of CV death	HR:0.87, CI:0.78-0.97	HR:0.87, CI:0.73-1.05	√	Proved for primary outcome
	SGLT2i										
EMPA-REG OUTCOME		Empagliflozin	2015	CV efficacy and safety vs. SoC	7064	High CV risk	3-point MACE	HR:0.86, CI:0.74- 0.99	HR:0.96, CI:0.75-1.23	√	Proved for CV death, HF hospitalization & all-cause mortality

A1C: Glycated A1c hemoglobin, ACS: acute coronary syndrome, CV: Cardiovascular, CVD: Cardiovascular Disease, HFH: Heart Failure Hospitalization, MACE: Major Adverse Cardiac Events, SoC: Standard of Care, T2DM: Type 2 Diabetes Mellitus

pre-angiotensin converting enzyme inhibitor/angiotensin receptor blockers (ACEi/ARB) era with ramipril[25,26] and remained stable thereafter (NNT 50 for 7 years) with ezetimibe, where over 75% of the patients receive statins and ACEi/ARB.[27] In 2013, the results of two major studies dealing with dipeptidyl-peptidase-4 inhibitor (DPP4i) drugs were simultaneously presented. The EXAMINE trial evaluated the major CV outcomes of treatment with alogliptin versus standard of care in patients with T2DM and recent acute coronary syndrome. The likelihood of the primary end point (composite death from CVD, non-fatal myocardial infraction (MI), non-fatal stroke) was not raised in the investigational drug arm of the trial (HR: 0.96, CI upper boundary of one side repeated 1.16, $p<0.001$ for non-inferiority). However, a trend (HR: 1.07, 95% CI 0.79 to 1.45) towards an increased risk of heart failure (HF) events was shown.[28] The SAVOR-TIMI 53 trial, assessed the CV efficacy and safety of saxagliptin on top of standard treatment in patients with T2DM and showed similar results in the rate of ischemic events (HR: 1.00, 95% CI 0.89 to 1.12, $p<0.001$ for non-inferiority and $p=0.99$ for superiority), with an increase in HFH events (HR: 1.27, 95% CI 1.07 to 1.51, $p<0.007$).[29] As shown later, the HF events occurred in patients with chronic kidney disease (CKD) who had an estimated glomerular filtration rate (eGFR) of <60 ml/min, preexisting HF and an elevated baseline N-terminal pro brain natriuretic peptide (NT-proBNP).[30]

Two years later, data from the TECOS and ELIXA trials were published followed by data from the most recently published EMPA-REG OUTCOME trial. The TECOS trial used a non-inferiority design to assess the CV outcome of long-term treatment with the DPP4i drug, sitagliptin used as part of usual care compared to standard care in patients with T2DM, a history of CVD and an A1C of 6.5% to 8.0%. The sitagliptin-treated group was non-inferior to the control group for primary composite CV outcomes (HR: 0.98, 95% CI 0.88 to 1.09, $p<0.001$). There was no difference in the heart failure hospitalization rate between the two groups (HR: 1.00, 95% CI: 0.83 to 1.20, $p=0.98$).[31] The ELIXA study, on the other hand, evaluated the CV outcomes of the GLP-1 drug, lixisenatide, compared to a placebo in patients with T2DM after an acute coronary syndrome (i.e., MI in the last 180 days as ST-segment elevation myocardial infraction (STEMI), non-STEMI or unstable angina) and A1C values between 7.0%-11.0%. Once again, the drug group was non-inferior in comparison to the control group for the primary outcome of a CV event (HR: 1.02, 95% CI: 0.89 to 1.17) and also for HFH (HR: 0.96, 95% CI: 0.75 to 1.23). No superiority was seen in reducing CV events.[32]

The prioritization that puts emphasis first on non-inferiority and not on superiority started to change with the recent trial, EMPA-REG OUTCOME. This study assessed the safety of the sodium glucose co-transporter 2 inhibitor (SGLT2i) drug, empagliflozin, in addition to the standard of care for patients with T2DM and high CV risk (established CVD). The primary outcome was a 3-point major adverse cardiac event (MACE) and the key secondary outcome was a 4-point MACE, both using the non-inferiority and the superiority design. The empagliflozin-treated group of patients was split into two subgroups: one treated with 10 mg and the other with 25 mg of empagliflozin. Data from both groups showed a great reduction in A1C levels, weight and systolic blood pressure (SBP) and had similar results. They were non-inferior in comparison to the control group for the primary outcome of a 3-point MACE (HR: 0.86, 95% CI 0.74 to 0.99, $p<0.0382$), the secondary outcome of a 4-point MACE (HR: 0.89, 95% CI 0.78 to 1.01) and also for HFH (HR: 0.96, 95% CI 0.75 to 1.23). Superiority of the drug was evidenced by a 38% reduction in CV death (HR: 0.62, 95% CI 0.49 to 0.77, $p<0.0001$), a 35% reduction in HFH (HR: 0.65, 95% CI 0.50 to 0.85, $p<0.0017$) and a 32% reduction in all-cause mortality (HR: 0.68, 95% CI 0.57 to 0.82, $p<0.0001$).[33] Interestingly, the NNT with empagliflozin was just 39 (for 3 years).[25,26]

Superiority seems to be the new trend to T2DM trials fulfilling the demands of the worldwide drug organizations. This seems to be the case with the LEADER trial (results published on July 28, 2016), which evaluates the CV outcome of the glucagon-like peptide-1 (GLP-1) drug liraglutide versus placebo, added to standard of care treatment. The composite outcome of the first occurrence of CV death, non-fatal MI or non-fatal stroke was set as the primary endpoint of the study. Among patients in the liraglutide group, there were significantly lower occurrences of the primary outcome (HR: 0.87, 95% CI 0.78 to 0.97 [$P<0.001$ for non-inferiority and $P=0.01$ for *superiority*]). While there were fewer deaths from CV causes in the liraglutide group (HR: 0.78, 95% CI 0.66 to 0.93), the rates of HFH were not significantly lower in the liraglutide group.[37]

3. Shaping the future

There is still much to be learned and much to be reconsidered. DPP4 inhibitors are gradually being regarded as an important, alternative second line agent to the currently preferred sulfonylurea drugs (SU) for T2DM. The CAROLINA trial is testing the effectiveness and safety of linagliptin, a DPP4 inhibitor drug compared with the SU drug, glimepiride. Because the CAROLINA trial has no placebo group, the CARMELINA trial is simultaneously evaluating the drug versus placebo over standard of care. The CARMELINA trial is investigating the long-term impact of linagliptin treatment on CV morbidity, mortality and renal function in patients with T2DM. The primary objective is to show non-inferiority of linagliptin with respect to time to first occurrence of the primary composite endpoint. If non-inferiority is ultimately shown, then the primary and renal endpoints will be tested for superiority.[35] The CAROLINA trial, on the other hand, is investigating the long-term impact of treatment in patients with T2DM at an elevated CV risk on CV morbidity, mortality, relevant efficacy parameters (e.g., glycemic parameters) and safety (e.g., weight and hypoglycemia). The primary objective is to show non-inferiority of linagliptin in comparison to glimepiride as a monotherapy or as an add-on therapy, with respect to the time to first occurrence of the primary composite endpoint (CV death, non-fatal stroke, non-fatal MI and hospitalization for unstable angina). If non-inferiority with a margin of 1.3 is shown, then the primary composite endpoint will be tested for superiority.[36] Results are to be published after 2018.

In keeping with the growing interest in SGLT2i action, the DECLARE-TIMI 58 and CANVAS trials are also of interest. DECLARE-TIMI 58 is investigating the effect of dapagliflozin

versus placebo in reducing CV events (MI, heart attack, ischemic stroke and CV related death), when added to current anti-diabetes therapy. It has a superiority hypothesis, testing whether it reduces the incidence of the composite endpoint of CV events over the long-term for a median follow-up of 4.5 years. Results will be presented by the fall of 2019.[34] The CANVAS trial is using the non-inferiority hypothesis followed by testing for superiority[38] to assess the effect of canagliflozin versus placebo on the treatment of patients with T2DM by evaluating CV risk for MACE. Results are expected by the end of 2017.

The TOSCA.IT trial, by the Italian Society of Diabetology, is investigating the efficacy and side effects of TZDs over SUs, or vice versa, on reducing CV risk. It is the first study after PROactive, to investigate the CV effects of TZDs. It compares the impact of pioglitazone versus SUs as add-on drugs on CVD in patients inadequately controlled with metformin. The primary outcome is a composite of all-cause mortality, nonfatal MI, nonfatal stroke, and unplanned coronary revascularization, while the main secondary outcome is a composite of sudden death, MI (fatal and nonfatal), stroke (fatal and nonfatal) and vascular interventions. Results are anticipated by 2018.[39]

Finally, regarding GLP-1s, exenatide is being tested in the EXSCEL trial, which is evaluating CV outcomes after treatment in patients with T2DM. Data are expected by the end of 2018. The trial is comparing the effect of once weekly exenatide as an add-on to usual care versus placebo on reducing major CV outcomes (CV related death, nonfatal MI, or nonfatal stroke) in patients with T2DM with a broad range of CV risk and will also provide long-term safety information. The primary efficacy hypothesis is that exenatide once-weekly is superior to usual care with respect to the primary composite CV end point, and the primary safety hypothesis is that exenatide once-weekly is non-inferior to usual care with respect to the primary CV composite end point.[40]

4. Conclusions

Diabetes is a multifactorial, multidimensional disease that affects the entire body. The mechanisms that cause its overall harmful effects, especially in the heart and vessels, remain undiscovered.

Until recently, trials for T2DM drugs were primarily focused on proving no harm before obtaining market approval. The scientific world approached new medications with caution rather than expectation. We are now *crossing* from this necessary era of ensuring the safety of a drug *to the other side*, where proof of positive effects is the mainstay. Ongoing and future trials aim at evaluating the risk ***and*** the benefit of oral agents; they incorporate bigger, heterogeneous, multinational populations and high CV-risk patients, and they take into account comorbidities, demographic and cultural differences. The motto of the new trials is a paraphrase of the Hippocratic dictum: *"do no harm, but also do some good"*.

Recent and ongoing, robustly executed trials will define the optimal drug combinations required to fight the aftermath of diabetes on the heart and its vessels. Individualization of therapy, tailored to the patient's specific profile, may prove to be the ultimate solution.

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