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A "New Era" in Therapy of Type 2 Diabetes? A Balanced View

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After publication of the favourable cardiovascular (CV) results with empagliflozin in the EMPA-REG OUTCOME Study [1,2] and with liraglutide in the LEADER Study [3,4], several diabetologists announced the begin of a "new era" for therapy of type 2 diabetes: Metformin should remain the first drug, but then, for escalation of therapy, one of these two drugs should be added instead of other antidiabetics. There was even the proposal to start pharmacotherapy of type 2 diabetes with a combination of liraglutide and empagliflozin, irrespective of the high price, especially since they exert their beneficial CV actions on different points of pathogenetic pathways which are, however, not fully understood.

Such claims seem to be not yet justified and inclusion into guidelines is unwarranted at present. The results of the two studies were obtained in patients with diabetes and CV events or at a very high CV risk and thus cannot be automatically extrapolated for all type-2 diabetes patients. They were designed as CV safety trials. According to a scientific principle they have to be confirmed in at least one or two other studies. The EMPA-REG and LEADER CV results should not be compared with the benefits seen with statins as this has been shown in about 30 other studies [5]. With Lixisenatide, another GLP-1 agonist, no cardiovascular benefit was found [6]. At the 52th Congress of the European Association for the Study of Diabetes (EASD) in Munich on September 16th, 2016, however, positive CV results of the SUSTAIN 6 study have been presented for semaglutide, also a glucagon-like peptide-1 analogon [7-9]. On the other hand, a significant deterioration of diabetic retinopathy was observed with semaglutide; a similar tendency was found also with liraglutide in the LEADER study.

Initiated by Steven Nissen and based on results with rosiglitazone the CV safety of new antidiabetic drugs has to be shown according to

Trial Name	Agent/comparator	n	Primary Endpoint	Follow-Up	HbA1c (%) at the End of Trial	Primary Outcome HR (95% CI)
ORIGIN	Insulin glargine/ conventional	12,537	3-point MACE	6.2 years	Insulin 6.2% Control 6.5%	**Neutral** HR 1.02 (0.94 to 1.11)
SAVOR- TIMI 53	Saxagliptin/placebo	16,492	3-point MACE	24 months	Saxagliptin 7.7% Placebo 7.9%	**Neutral** HR 1.00 (0.89 to 1.12)
EXAMINE	Alogliptin/placebo	5380	3-point MACE	18 months	Alogliptin 7.7% Placebo 8.0%	**Neutral** HR 0.96 (-1.16)
TECOS	Sitagliptin/placebo	14,671	4-point MACE	36 months	Sitagliptin 7.1% Placebo 7.4%%	**Neutral** HR 0.98 (0.99 to 1.08)
ELIXA	Lixisenatide/placebo	6068	4-point MACE	25 months	Lixisenatide 7.4% Placebo 7.6%	**Neutral** HR 1.02 (0.89 to 1.17)
EMPA-REG OUTCOME	Empagliflozin/placebo	7020	3-point MACE	37 months	Empagliflozin 7.8% Placebo 8.2%	**Superior** to placebo HR 0.86 (0.74 to 0.99)
LEADER	Liraglutide/placebo	9340	3-point MACE	46 months	Liraglutide 7.7% Placebo 8.1%	**Superior** to placebo HR 0.87 (0.78 to 0.97)
SUSTAIN-6	Semaglutide/placebo	2735	3-point MACE	24 months	Semaglutide 7.6% and 7.3% Placebo 8.3%	**Superior** to Placebo HR 0.74 (0.58-0-95) (for primary endpoint, but not for CV death)

Table 1: CV Outcome Trials with Antidiabetic Agents in Patients with T2DM at High CV Risk
3-point MACE: Composite of CV death and nonfatal MI or stroke; 4-point MACE: Composite of CV death, nonfatal MI or stroke and hospitalization for unstable angina; CI: Confidence interval; CV: Cardiovascular; HbA1c: Glycated hemoglobin; HR: Hazard ratio; MI: Myocardial infarction; T2DM: Type 2 diabetes mellitus
Table actualized by Helmut Schatz after the 52nd EASD Congress Munich 2016, based on data from Ryden, Sattar and Marso.

FDA regulations since 2008. Heart failure also has to be included now. Therefore, the pharmaceutic companies perform "non-inferiority" studies, and, concomitantly, try to find "superiority" with much financial support by increasing the number of patients to reach necessary statistical power. Many studies find a "non-inferiority" and also "no superiority" for their drug, e.g. for sitagliptin in the TECOS study [10]. Some diabetologists have already questioned the sense of the FDA´s requirement in its present form for expensive non-inferiority studies, and also their extension by the pharmaceutic companies for finding "superiority" which make them still more costly.

After many neutral or even negative CV outcome studies with hypoglycaemic agents , the beneficial CV results with empagliflozin and liraglutide, and now also semaglutide, are highly welcome and give hope for further prolongation of life span and improvement of quality of life for patients with type 2 diabetes (Table 1). However, long-term effects on outcome including side effects have yet to be evaluated. Of special interest will be the findings in the ongoing CAROLINA study which compares the outcomes with the DPP4-inhibitor linagliptin and sulphonylureas. This study will be finished in September 2018 and will substantially contribute to the still ongoing discussion whether sulphonylureas are outdated or not [10].

Treatment of type 2 diabetes is becoming more complicated and personalized. Every patient should be treated not only based on study results but also on the individual characteristics e.g. age, body weight, age at manifestation, disease duration, blood pressure, CV events and renal status, and also the patient's preferences, e.g. for oral or injectable therapy.

Finally, it should be stressed that with every new drug the advantages can be mostly seen quite early. The long-term efficacy and safety including unwarranted adverse events can be judged only later, after years or even decades. They are, however, well documented for the old antidiabetics e.g. insulin and sulphonylureas. Their positive and negative effects - weight gain and hypoglycemia - are well known and they should be to handle by experienced physicians together with their educated patients.

Insulin remains "das kleine Schwarze" (the little black dress, suitable for all occasions) as it has been called in German commentaries. Insulin fits as combination partner to every antidiabetic drug. The author would call insulin rather the "big evening dress", after the ORIGIN and other studies, compared to all other oral and injectable forms of therapy. It has the strongest antihyperglycemic potential of all. One has to wait and see, if, or to which extent the various extrahypoglycemic beneficial CV actions of the new drugs compensate, or hopefully overcome the weaker glucose-lowering effects over longer time periods. They should also become cheaper.

At the moment, the present algorithms for treatment of type-2 diabetes should not yet be changed.

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