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http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **20**(4):361-367
doi: 10.2478/rjdnmd-2013-0035

Editorial
SAILING ACROSS THE SEA OF GUIDELINES

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According to our current knowledge, diabetes mellitus is an incurable disease. After years of evolution, the patients develop chronic complications, the cardiovascular ones being extremely frequent and severe. It is estimated that the incidence of coronary artery disease, cerebrovascular disease and peripheral artery disease is at least two times higher in diabetic patients as compared to non-diabetic subjects [1]. Furthermore, these cardiovascular diseases cause almost half of the deaths of patients with diabetes mellitus [2].

The prevention of cardiovascular events represents a priority of diabetes mellitus therapy. The patients have frequently a cluster of risk factors for atherosclerosis: high blood pressure, lipid disorders, obesity, sedentary lifestyle, smoking etc. In order to improve the prognosis, the correction of all these abnormalities is needed. An important number of interventional clinical trials, of good scientific quality, conducted in the last decades in patients with diabetes mellitus (especially type 2) or in larger populations (but having important subgroups of diabetics), have proven the utility of these interventions. The studies analyzed the effects on hard endpoints of lowering glucose levels, lipid values, blood pressure or all of these parameters together [3-22].

The interpretation of the scientific information derived from these studies is provided by the clinical practice guidelines, established by various scientific societies. Their recommendations constitute important working tools for practitioners, due to several reasons (or, at least, this should be the case). First, they represent a pertinent synthesis, performed by experts in a domain (in our case, diabetes mellitus), of a huge amount of scientific information, that otherwise may be difficult to digest by the majority of the physicians (due to its impressive volume, lack of accessibility, heterogeneity etc.). Second, the guidelines summarize the information in treatment targets (expressed as figures), that have to be reached during the management of a certain patient. Third, the guidelines are an "umbrella" for the physician, by conferring legitimacy to a therapy that, besides its benefits, may lead to the occurrence of side effects that sometimes might be severe. Last but not least, the health insurance companies reimburse the expenses related to a patient if they are supported by guidelines.

Regarding diabetes mellitus, several guidelines have been elaborated in the past years, all of them by worldwide recognized experts [23-41]. There are guidelines dedicated to diabetes patients but, due to its important risk for cardiovascular and renal complications, diabetes mellitus also represents a special section in the cardiologists' and nephrologists'

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guidelines. The recommendations have changed over the time as a consequence of the evolution of medical knowledge about the disease. Anyhow, even guidelines published in the same year are not identical with regard to the targets. This leads to the impression that the scientific information that supports them is interpretable, so that the conclusions of different experts do not entirely overlap.

Data derived from large clinical trials conducted in patients with type 2 diabetes mellitus have shown that the incidence of cardiovascular diseases parallels the level of HbA_{1c}. For example, UKPD Study [42] demonstrated that, for each 1% increase in HbA_{1c}, there is an elevation in the incidence of myocardial infarction with 14%, of stroke with 12%, of heart failure with 16%, and of amputation or death from peripheral artery disease with 43%. Another study showed that the relative risk of death by any cause raises with 26-31% for each increase in HbA_{1c} with 1% [43].

UKPD Study, a reference trial for subjects with newly diagnosed type 2 diabetes mellitus, showed that a therapeutic intervention, performed with insulin or sulphonylureas, that reduced with 0.9% the HbA_{1c} level, did not diminish significantly the occurrence of cardiovascular outcomes over a 10-years interval [7]. The results were somehow different in overweight patients in whom metformin was used: for these, the risk of death was significantly diminished compared to lifestyle management alone [6]. Other clinical interventional trials [16,17,21] could not demonstrate a reduction in major cardiovascular events and mortality by intensive glycemic control over a follow-up period of 3.5-5.6 years. Moreover, in one of them [16] mortality even increased in the intensively-treated group. But it must be noted that two meta-analyses of the aforementioned trials have demonstrated an improvement of the coronary prognosis by intensive glycemic control [44,45]. The 10-year follow-up of the cases from UKPD Study showed that the patients treated conventionally in the first 10 years presented, on the long term, a significantly higher risk of myocardial infarction or death than those treated intensively from the beginning, even if all subjects had the same glycemic control during follow-up. A legacy effect of glucose control has thus been demonstrated [19].

The recommendations regarding glucose targets varied during time, depending on the current guidelines of that time [25,28,31,33]. Nowadays, a consensus seems to be reached: the glycemic control of the patients has to be tailored according to the clinical context. The general target for HbA_{1c} is 7%, but it is recommended that the control should be tighter in patients that are young, highly compliant, newly diagnosed, without comorbidities and risks related to hypoglycemia and with long life expectancy, and, on the contrary, less stringent in subjects who are old, not compliant, with long disease duration, severe comorbidities, short life expectancy and high risk in case of hypoglycemia [36,39,40].

The prevalence of arterial hypertension is very high in patients with diabetes mellitus, being about 60% in type 2 cases [46]. It is even higher in elderly, obese subjects and in case of kidney involvement. Its co-existence multiplies the cardiovascular risk by four [47].

The analysis of the clinical trials conducted in patients with type 2 diabetes mellitus, as well as the results from the subgroups of diabetics from larger studies, have confirmed the utility of blood pressure reduction in terms of cardiovascular prevention [5,8,9,15,20]. For many years, clinical guidelines have established as target for blood pressure lowering in patients with diabetes mellitus the value of 130/80 mmHg [24,26-29,34,38]. The guidelines released

during the last year and a half bring a new trend in terms of blood pressure lowering in diabetes mellitus. Now, the target for treating blood pressure is set to <140/80 mmHg by the European Guideline on Cardiovascular Disease Prevention, and by the American Diabetes Association [38,39], <140/85 mmHg by the European Guideline for the Management of Arterial Hypertension, and by the European Guideline on Diabetes, Pre-diabetes, and Cardiovascular Diseases (elaborated by the European Association of Cardiology, and by the European Association for the Study of Diabetes) [40,41], and, finally, <140/90 mmHg by the Kidney Disease Improving Global Outcomes group – KDIGO [37]. These changes are the consequence of a better analysis of the existing interventional studies [5,8,9,15,20]. Even though the proposed targets in the intensive treated groups from these trials were lower, in the majority of the cases they were not achieved. In fact, in patients without kidney or cardiovascular disease, the value of systolic blood pressure that *proved* to offer cardiovascular benefits was 140 mmHg, and that of diastolic blood pressure somewhere between 80 and 90 mmHg. In addition, in some patients, there may be even an increase in the number of cardiovascular events and mortality, due to a too vigorous blood pressure lowering, probably as a consequence of hypotension episodes [41]. There is no change regarding the target for patients with chronic kidney disease [37] and coronary artery disease [40,41], that remains below 130/80 mmHg.

Many patients with type 2 diabetes have dyslipidemia. The characteristic lipid disorder is represented by a combination of high triglycerides and low HDL-cholesterol. Other features are represented by the increase in the number of triglyceride-rich lipoproteins, and the presence of small, dense, LDL particles. These abnormalities contribute to the high cardiovascular risk of patients with diabetes mellitus. Data from a large number of clinical trials [3,4,10,12,14] have clearly shown the utility of lipid lowering, obtained mainly by statin therapy, in primary and secondary cardiovascular prevention. A meta-analysis of 14 such interventional trials demonstrated that for every mmol/L decrease in LDL-cholesterol, there is a 13% reduction in the number of cardiovascular deaths and a 9% diminution of all-cause mortality, over a 4.3 years interval [18]. The benefits of statin therapy in reducing hard cardiovascular endpoints are highest in the subgroup of patients with known cardiovascular diseases, but they are significant in other diabetes patients, as well.

LDL-cholesterol is the main target for lipid lowering therapy. In patients with type 2 diabetes mellitus and cardiovascular disease, clinical trials have demonstrated the benefits of aggressive statin therapy, that reduces this parameter to <70 mg/dL [48,49]. In contrast, trials conducted in patients without cardiovascular disease, which investigated the effects of various types and doses of statins, showed the utility of LDL-cholesterol reduction compared to baseline, but the values obtained in these cases were usually higher than 70 mg/dL.

The target for LDL-cholesterol was different according to various guidelines, developed in the past decade. These differences persist in our days, as well. The Standards of Medical Care in Diabetes, elaborated by American Diabetes Association in 2013, state that LDL-cholesterol should be lowered to <100 mg/dL if the patient has no overt cardiovascular disease and to <70 mg/dL if cardiovascular disease is present. The alternative goal, if target cannot be reached with maximal statin therapy, is a 30-40% LDL-cholesterol reduction from baseline. Statins are recommended in those with history of myocardial infarction or aged >40 years [39]. According to the European opinion, expressed in the professional guidelines [38,40], the majority

of patients with diabetes mellitus (i.e., those with cardiovascular disease, chronic kidney disease, target organ damage or other risk factors) is considered as being at very high cardiovascular risk. Statin therapy is recommended in these cases, and the target for LDL-cholesterol is <70 mg/dL (or at least 50% reduction from baseline, if the proposed level cannot be obtained). Statins are recommended for the rest of the patients, as well, with a LDL-cholesterol target of <100 mg/dL.

As you may have noticed, there are a lot of clinical guidelines "on the market", and their recommendations are somehow different. The question that arises is: What should the practitioner do? Sometimes I get the impression that he or she may experience some uncertainty and emotions, similar to what Christopher Columbus felt when, more than five centuries ago, he started his expedition to discover the Indies. My opinion is that, despite all discussions they may raise, the guidelines that are periodically released have to be read. They inform the physician about the trends in therapy and are meant to help.

However, when facing a particular patient with diabetes mellitus and trying to improve the cardiovascular prognosis, in addition to the concerns regarding the target values for glucose, lipids and blood pressure, there are some issues that lead to a better clinical care and that every practitioner should consider:

1. Use your own judgment to assess the patient, taking into account all the particular aspects that are present. Don't forget that you are treating a human being, not a disease!

2. Even if sometimes time is not enough and a lot of patients are waiting at your door, don't forget to measure systematically blood pressure, HbA_{1c}, and cholesterol levels.

3. Obey the rules for the correct measurement of blood pressure since there are several factors that may influence the result (I won't insist on them, because they are well known).

4. Double check the laboratories you are dealing with and use only those with proven results. Sometimes you may have the surprise to find important differences in lab tests for the same patient (this concerns mainly the HbA_{1c} measurement).

5. Remember that diabetes care means team work, and very often the management of the patient has to be done in collaboration with colleagues from related specialties.

Of course, we are all waiting for new scientific data, for a better analysis of the existing ones and, finally, for unifying, worldwide-accepted therapeutic guidelines for diabetes mellitus. This will clarify many concerns regarding the management of our patients. But until they will be released, I wish you the traditional "Good tailwind!"

Acknowledgements. The author acknowledges the contribution of Dr. Romulus Timar for choosing the topic and of Dr. Mihaela Rosu for language proofing.

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