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Review

Pharmacotherapy of type 2 diabetes: An update

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Abbreviations: T2DM, type 2 diabetes; IR, insulin resistance; HbA1c, glycated hemoglobin A1c; GLUT-4, glucose transporter4; GLP-1, glucagon-like peptide-1; DPP4, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; HF, heart failure; UKPDS, United Kingdom Prospective Diabetes Study; DR, delayed-release; MI, myocardial infarction; SU, sulfonylureas; SUR, sulfonylurea receptor; AMPK, adenosine monophosphate-activated protein kinase; ACCORD, Action to Control Cardiovascular Risk in Diabetes Trial; ADOPT, A Diabetes Outcome Progression Trial; VADT, Veteran Affairs Diabetes Trial; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; RECORD, rosiglitazone evaluated cardiovascular outcomes in oral agent combination therapy for type 2 diabetes; AGS, American Geriatrics Society; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; IGT, impaired glucose tolerance; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; NYHA, New York Heart Association; NASH, nonalcoholic steatohepatitis; CRP, C-reactive protein; PROACTIVE, Prospective Pioglitazone Clinical Trial In Macrovascular Events; ACS, acute coronary syndrome; CVD, cardiovascular disease; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; NPH, protamine Hagedorn; EASD, European Association for the Study of Diabetes; ORIGIN, Outcome Reduction with Initial Glargine Intervention; NPL, protamine lispro; LVEF, left ventricular effective fraction; GLP-1RA, GLP-1 receptor agonists; FDG PET, fluorodeoxyglucose positron emission tomography; fMRI, functional magnetic resonance imaging; PP, pancreatic polypeptide; ACE, angiotensin converting enzyme; HOMA, homeostatic model of assessment; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus –Thrombolysis in Myocardial Infarction; EXAMINE, The Examination of CV Outcomes with Alogliptin vs. Standard of Care; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CAROLINA, Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Patients with T2DM; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with T2DM; SGLT-2, sodium glucose co-transporter 2; ADA, American Diabetes Association; EMA, European Medicine Agency; RCT, randomized controlled trials; AACE, American Association of Clinical Endocrinologists; LEAD, Liraglutide Effect and Action in Diabetes; AWARD-2, Assessment of Weekly Administration of LY2189265 [dulaglutide] in Diabetes-2; ELIXA, The Evaluation of Lixisenatide in Acute Coronary Syndrome; LEADER, The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LYDIA, Effects of Liraglutide in Young Adults With Type 2 DIAbetes; EXSCEL, The EXenatide Study of Cardiovascular Event Lowering; MACE, major adverse cardiovascular events; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; CANVAS, CANagliflozin cardioVascular Assessment Study; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial; (DECLARE TIMI-58, Dapagliflozin Effect on CardiovascuLAR Events; PTP-1B, Protein Tyrosine Phosphatase inhibitors.

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https://doi.org/10.1016/j.metabol.2017.08.010
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ARTICLE INFO

Article history:
Received 9 May 2017
Accepted 26 August 2017

Keywords:
Algorithm
Goals pharmacotherapy
Personalized therapy
Type 2 diabetes

ABSTRACT

Type 2 diabetes (T2DM) is a leading cause of morbidity and mortality worldwide and a major economic burden. The prevalence of T2DM is rising, suggesting more effective prevention and treatment strategies are necessary. The aim of this narrative review is to summarize the pharmacologic treatment options available for patients with T2DM. Each therapeutic class is presented in detail, outlining medication effects, side effects, glycemic control, effect on weight, indications and contraindications, and use in selected populations (heart failure, renal insufficiency, obesity and the elderly). We also present representative cost for each antidiabetic category. Then, we provide an individualized guide for initiation and intensification of treatment and discuss the considerations and rationale for an individualized glycemic goal.

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1. Introduction

Type 2 diabetes (T2DM) is a leading cause of morbidity and mortality worldwide and its prevalence is rising, rendering prevention and treatment of paramount importance. By 2040, the total number of diabetics worldwide is projected to increase to $642 million resulting in an increased economic burden [1]. In 2012, the total cost related to T2DM in United States of America (USA) was $245 billion with direct health care costs of $176 billion and reduced productivity of $69 billion [2]. After adjusting for population age and sex differences, average medical expenditures in individuals with T2DM were 2.3 times higher than those without diabetes, highlighting the need for more cost-effective strategies to prevent and treat diabetes [2].

T2DM is primarily characterized by insulin resistance (IR) and a defect in insulin secretion, the latter regarded as an early abnormality. The interplay between defective insulin secretion and IR initially leads to hyperglycemia, due to increased hepatic glucose production and decreased peripheral uptake of glucose. At a later stage, persistent hyperglycemia causes glucotoxity, increased oxidative stress and lipotoxicity, which causes further [3] reduction in insulin secretion due to progressive beta-cell failure [4]. Death risk in diabetes is about twice compared with non-diabetic individuals of similar age [5]. This proportion is even higher for women and younger individuals, although there is consideration about estimating mortality in T2DM [6]. The target for T2DM aims to reduce the risk of long-term complications and mortality [7–9]. Decrease in glycated hemoglobin A1C (HbA1c), an index for

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