A novel comprehensive program combining optimal medical treatment with lifestyle for type 2 diabetes

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Abstract

This article introduces briefly current status in type 2 diabetes (T2D) and an updated classical standardized comprehensive program which combines optimal medical treatment (OMT) with lifestyle modification, that is, intervention of RT-ABCDEFG (iRT-ABCDEFG) for control and prevention of T2D, and discusses its advantages and prospects. Here, G means goals, F follow-up, E examination, D disease & risk factors control, C changing unhealthy lifestyle & Chinese medicine or control the source of infection & cutting genetic or spreading pathways, B biohazard control, and A antagonistic treatment, such as anti-diabetic agents, the glucagon-like peptide-1 receptor (GLPR) agonists, the sodium-glucose cotransporter 2 (SGLT2) inhibitors, and the ultralong-acting, once-daily basal insulin. As an effective comprehensive program and strategy for Interventions of diabetes, this program can be used as a Reverse, Right, and Routine Treatment (iRT). Several pivotal goals which include less major adverse cardiocerebrovascular events (MACCE) and diabetic complications, less medical costs, longer life expectancy, lower morbidity and mortality, and higher quality of life, will be realized by consistently practicing this program due to early diagnosis, OMT, and lifestyle modification for overall prevention. Herein, this iRT-ABCDEFG program is worthy of recommending for clinical professional management and health care of T2D due to better cost-effectiveness.

REVIEW ARTICLE

A novel comprehensive program combining optimal medical treatment with lifestyle for type 2 diabetes

Running title: A novel program for T2D

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Abstract

This article introduces briefly current status in type 2 diabetes (T2D) and an updated classical standardized comprehensive program which combines optimal medical treatment (OMT) with lifestyle modification, that is, intervention of RT-ABCDEFG (iRT-ABCDEFG) for control and prevention of T2D, and discusses its advantages and prospects. Here, G means goals, F follow-up, E examination, D disease & risk factors control, C changing unhealthy lifestyle & Chinese medicine or control the source of infection & cutting genetic or spreading pathways, B biohazard control, and A antagonistic treatment, such as anti-diabetic agents, the glucagon-like peptide-1 receptor (GLPR) agonists, the sodium-glucose cotransporter 2 (SGLT2) inhibitors, and the ultralong-acting, once-daily basal insulin. As an effective comprehensive program and strategy for Interventions of diabetes, this program can be used as a Reverse, Right, and Routine Treatment (iRT). Several pivotal goals which include less major adverse cardiocerebrovascular events (MACCE) and diabetic complications, less medical costs, longer life expectancy, lower morbidity and mortality, and higher quality of life, will be realized by consistently practicing this program due to early diagnosis, OMT, and lifestyle modification for overall prevention. Herein, this iRT-ABCDEFG program is worthy of recommending for clinical professional management and health care of T2D due to better cost-effectiveness.

KEYWORDS

iRT-ABCDEFG, lifestyle, prevention, treatment, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes (T2D) is one of major non-communicable diseases (mNCDs) that requires lifelong treatments and management of high glycemic level. More than 400 million adults worldwide suffer from diabetes [1]. Obesity, physical inactivity, and unhealthy diet are major risk factors in adults diabetes [2], and racial & ethnic groups, maternal obesity have also led to a relative increase in T2D. In fact, the incidences of both type 1 and T2D increase significantly, particularly among minority racial and ethnic groups [3]. Although mortality and fatal outcomes declined in individuals with T2D in some developed countries [4], for example, in Sweden from 1998 through 2014, it's still a big challenge and a heavy burden in developing countries.

Since high-quality care for individuals with T2D could decrease unnecessary emergency visits [5], for example, urine glucose screening within community and schools may help to detect early asymptomatic T2D [6], and individuals with T2D need to exercise more often (at least meeting physical activity guidelines) for reduction of mortality [7]. However, considerable proportion of T2D patients in some Asian countries and regions, for example, South Korea, were not adequately managed and lack of high-quality care due to no reliable comprehensive program [8]. In addition, a large-scale international study showed that subjects with T2D frequently have depression and psychological and psychiatric problems [9]. Thus, there is arising evidence for better management of T2D, since it is an independent predictor of revascularization and long-term mortality [10].

Currently, treatment of T2D focuses on glucose-lowering medication and non-pharmacological treatment. The former includes oral hypoglycemic agents, insulin pump or injection therapy; The later includes surgical treatment, for example, bariatric surgery for markedly obese individuals with T2D, modification of unhealthy lifestyle. However, most patients with T2D have not achieved optimal glycemic control with mono-therapies. Moreover, some treatments may have side-effects [11]. Although current guidelines for T2D are suitable for clinical doctors to use, it isn't for individuals' self-management of T2D. Of course, there is still a need for self-control of glucose levels in a new era of personnel medicine.

2 | An updated standardized comprehensive program

How can an individual control and prevent T2D with a simple and effective method? We strongly recommend an updated classical standardized comprehensive iRT-ABCDEFG program (Figure 1) for clinical professional management and family health care of T2D. Here, G means goals; F means follow-up; E means examination; D means disease & risk factors control; C means changing unhealthy "environment-sleep-emotion-exercise-diet" intervention [E(e)SEEDi] lifestyle & Chinese medicine or control the source of infection & cutting genetic or spreading pathways during the COVID-19 pandemic; B means biohazard control; And A means antagonistic treatment, such as optimal anti-diabetic agents, which include traditional agents (for example, metformin and others), and novel chemical agents, such as [the glucagon-like peptide-1 receptor (GLPR) agonists, the sodium-glucose cotransporter 2 (SGLT2) inhibitors, the ultralong-acting, once-daily basal insulin, and others]. As a novel strategy for Intervention of diabetes, this program can be used as a Reverse, Right, and Routine Treatment in clinical practice. The detailed tips are as follows (Table 1).

This iRT-ABCDEFG program is very suitable for not only control of risk factors and cardiovascular disease (CVD), eg., hypertension [12], AMI [13], CHF [14], and arrhythmogenic right ventricular cardiomyopathy [15] as well as cancer [16] and major virus-communicable diseases [17], but also T2D. Firstly, good goals help to work better. Moreover, as an updated classical, individualized, and concise "guideline", if treated as "a law" in clinical practice, the vital goals which include less MACCE and diabetic complications, less medical costs, longer life expectancy, lower morbidity and mortality, and higher quality of life, will be realized by consistently practicing this iRT-ABCDEFG program due to early diagnosis, OMT, and overall prevention by healthy E(e)SEEDi lifestyle.

On the one hand, follow-up of both doctors with patients and patients with doctors will improve outcomes. For example, follow-up found that intensive glucose control reduces MACCE [18], but bariatric surgery plus intensive medical therapy is more effective for control hyperglycemia than intensive medical therapy alone [19]. Individuals' comprehensive or targeted examinations or population-based large-scale screening (e.g., urinary glucose screening) will help the early diagnosis of both symptomatic and asymptomatic T2D [6,20]. For example, there are only 10% undiagnosed cases of diabetes in the United States due to large-scale screening, and diagnoses by the criteria of elevated levels of fasting glucose ([?]7.0 mmol/L) and hemoglobin A1c (HbA1c, [?]6.5%) [21].

Since postpartum follow-up and screening of oral glucose tolerance test (OGTT) during the delivery hospitalization is helpful to control maternal T2D, follow-up of women after delivery and scheduled screening for preventing T2D is very important for against this public health issue. Whatever, early examination and screening will help the management of T2D and decreasing its complications. Some serum biomarkers are helpful to determine its severity and complications, such as fibroblast growth factor 21 (FGF21) [22], the receptor for advanced glycation end products (RAGE) [23], and salusin-α and salusin-β levels [24]. In addition, albuminuria level is also associated with higher risk of MACCE (AMI, stroke) in patients with T2D [25].

On the other hand, this program helps to control T2D-related complications and major risk factors by cutting genetic pathways and changing unhealthy lifestyles, which can also decrease diabetic gene mutation. Studies have already shown that intensive lifestyle intervention in patients with T2D is beneficial to control individuals' glycemic levels [26], e.g. intensive body weight management [2]. Moreover, healthy lifestyle included five core elements — "environment-sleep-emotion-exercise-diet" intervention [E(e)SEEDi] [27,28] may achieve better goals in control and prevention of T2D (Table 2) [29-43].

As we already known, CVD and T2D are more common in some populations (such as taxi drivers) due to unhealthy lifestyle [44]. However, healthy lifestyle is associated with a lower risk of CVD incidence and mortality among adults with T2D [45], it plays a key role in risk factor management for primary prevention of CVD [46]. In fact, lifestyle modification can reduce risk factors in both CVD and T2D [47]. However, current lifestyle modification is still low among US adults with chronic conditions [48]. Therefore, healthy E(e)SEEDi lifestyle should be recommended to all individuals in the globe.

Previous studies showed that exercises were associated with significantly lower HbA1c and fasting blood

glucose [49], and plant-based diets which include legumes, whole grains, vegetables, fruits, nuts, and seeds, not only reduce the risk of T2D but also help to prevent T2D [50]. However, there are no significant difference in MACCE from n-3 fatty acid supplementation among T2D patients without CVD [51], Vitamin D_3 supplementation did not result in a significantly lower risk of T2D [52]. Without a doubt, individualized biohazard control and antagonistic treatment are necessary according to "5P" medical model [53], because T2D can easily result in injury of organs and a series of complications without long-term optimal glycemic control, for example, erectile dysfunction, lipoprotein (a) and microalbuminuria are predictors of vascular complications [54-56]. The EUCLID Trial showed that every 1% increase in HbA_{1c} was associated with a 14.2% increased relative risk for MACCE in patients with diabetes and peripheral artery disease [57]. There are less costs and better quality of life among patients with individualized glycemic control than uniform intensive control (HbA1c level <7%) [58].

On antidiabetic medical treatment, clinical studies already showed that the GLPR agonists, semaglutide [59] and liraglutide [60-62] the SGLT2 inhibitors [63], canagliflozin [64,65] and empagliflozin [66-68], and an ultralong-acting, once-daily basal insulin degludec [69], are not only helpful to glycemic control but also reduce MACCE including cardiovascular death or hospitalization for heart failure (HHH) in subjects with T2D and/or slower progression of diabetic chronic kidney disease (CKD). Since both were not associated with high rates of venous thromboembolism [70], the SGLT2 inhibitors and the GLPR agonists had already been recommended by the 2019 guidelines of American Diabetes Association (ADA) [71]. It can be said that 2 new classes of antihyperglycemic agents [72], the GLPR agonists and the SGLT2 inhibitors, have indeed led to a paradigm shift of T2D treatment. However, a study found that, a selective SGLT2 inhibitor dapagliflozin [73], not result in a higher or lower rate of MACCE, but in a lower rate of cardiovascular death or HHH.

In addition, the nonsteroidal, selective mineralocorticoid receptor antagonist (MRA) finerenone can reduce the risk of new-onset atrial fibrillation or flutter (AF/AFL) in patients with T2D and CKD [74]. Of course, there is still improper use of aspirin for primary and secondary prevention of CVD in T2D [75]. According to its cost and safety profile, metformin should be the first line drug therapy for patients with newly diagnosed T2D [76]. Due to cardiovascular benefit and lower achieved LDL-C levels associated with lower risk of MACCE [77], statin therapy should be recommended for primary prevention in the elderly with or without T2D [78]. In fact, it is also easy to understand the treatment of T2D and its complications from other systematic reviews, including relatively complete existing drugs, therapeutic effects, adverse events, and other aspects. Therefore, we will not list and summarize here.

3 | Its advantages

Since T2D is as dangerous as coronary heart disease and associates with higher MACCE, which include cardiovascular and non-cardiovascular hospitalizations, AMI, CHF, ischemic stroke/TIA recurrence, and death [79], abnormal glycemic levels link to high mortality and morbidity. For example, on the one hand, maternal T2D highly links to arterial stiffness, cardiac hypertrophy, and congenital heart defects; On the other hand, there is increasing T2D in offspring in late adult life due to maternal gestational hypertension. Thus, we think that there are obvious advantages of this iRT-ABCDEFG for T2D, which will help to realize the European Society of Cardiology's ambitious mission "to reduce the burden of CVD" in countries worldwide [80].

Most cases of new onset T1D in China occurred among adults [81], this iRT-ABCDEFG program is suitable for not only T2D but also T1D because it can help to decrease and delay onset of T1D by healthy E(e)SEEDi lifestyle and cutting a genetic pathway in the early stage of one's lifetime due to control of maternal risks. Thus, this iRT-ABCDEFG program is worthy of conducting in the globe. In addition, since T2D is surprisingly closely linked to AMI, CHF, and stroke, diabetic chronic kidney disease (CKD), maximum effort must be made to control the prevalence of T2D so as to halt CVD and its costs increasing. Since policy initiatives can help controlling increases in health care spending [82], it's time for not only *Health in All Policies*but also *Health in All Laws* [16,83].

With the further studies on mechanisms and the continuing development of new drugs and novel technologies for T2D, more precise and effective management or self-management of T2D with this iRT-ABCDEFG program is possible due to the role of structure-editing on unhealthy lifestyle [84], and long-term trends in mortality and the incidence of MACCE will also decline. For example, a clinical trial confirmed that oral insulin 338 can safely improve glycaemic control in insulin-naive patients with T2D, although it isn't in place of subcutaneous insulin glargine yet due to being not commercially viable at current stage [85].

In short, since some cardiovascular metabolic factors of T2D, such as obesity, physical inactivity, obstructive sleep apnea (OSA), hypertension, and other modifiable unhealthy E(e)SEEDi lifestyle-related factors, may induce MACCE (AF, AMI, CHF, Stroke) and reduce health span and life span[86,87], control and prevention of these risk factors according to this iRT-ABCDEFG program will get more clinical benefit and improve cardiovascular outcomes. The SGLT2 inhibitors and GLP-1 receptor agonists, the newer classes of antihyperglycemic agents with the cardiorenal protective effects [88], will add distinctly clinical benefit. The MRA finerenone also reduces the composite kidney and cardiovascular outcomes [89].

4 | Future prospects

It can be easily found that this comprehensive program will help to translate new technologies and research into clinical practice and reverse T2D due to strengthening prevention and management or self-management as well as personalized services. It will meet not only Healthy China 2030 Plan but also updated the National Health Service (NHS) Long Term Plan in the UK [90]. In short, this program can help to achieve global health goals.

In fact, this program has already been used for CVD and cancer in daily clinical practice, but there are more detailed on changing unhealthy lifestyle for T2D (Table 1). If there is a national registered centre for T2D which just likes major virus-communicable diseases, e.g. SARS and COVID-19 [17,91], more satisfactory effects will be got after reliable national clinical trials with this innovative classical comprehensive program, since it combines anti-diabetic agents, insulin use, metabolic surgery with mental health screenings and healthy E(e)SEEDi lifestyle [27,92,93], which includes plant-based dietary patterns, and will get better control of population-level HbA1c and cardiovascular risk among individuals with T2D.

With a better understanding in the pathophysiological mechanisms at the molecular level and the discovery of new targets for metabolism[94,95], the implications for existing guidelines and therapeutic options, as well combination with this iRT-ABCDEFG program and effective lifestyle interventions for T2D, for example, a precision dietary management and scientific dietary recommendations with respect to carbohydrate, fat and dietary fibre, and increases in physical activity and fitness, calorie restriction and weight loss [96,97], these individuals will improve greatly glycaemic control and better prevent its complications [98], such as CVD and neurodegenarative diseases (Alzheimer's disease and Parkinson's disease) [99]. In addition, the prevalence of both depression and thyroid abnormalities is high among individuals with T2D [100,101]. and coronary plaques [102], abnormal gene expression and serum biomarker levels in these patients mean higher risk and adverse clinical outcomes [103-105], hence, we should control and prevent these risk factors so as to reduce cardiovascular mortality.

Theoretically, this iRT-ABCDEFG program is more plausible for better management and self-management of T2D due to truly individualized glycaemic goals. It is helpful to individuals with T2D for early detection of ischemic heart disease, unrecognized CHF, and early statins and SGLT2 inhibitors treatment safely for improvement of lipids and endothelial function and lowering MACCE [106]. In fact, a biomarker score is helpful to stratify T2D and pre-diabetes related CHF risks [107]. Healthy E(e)SEEDi lifestyle may help to reduce these risks and improve clinical outcomes [108]. In addition, clinical trials already confirmed benefits of selective nonsteroidal MRA eplerenone [109] and finerenone [110] in CHF prevention and cardiovascular outcomes improvement. Obviously, a combination of these strategies in this novel comprehensive program is helpful to healthcare of individuals with T2D. Of course, both drug and non-drug management of T2D require more solid evidence-based studies [111].

Since there are more cardiovascular benefits in SGLT2 inhibitors, such as dapagliflozin [112], and new ani-

mal models and clinical trials had already confirmed the glucose-lowering potential of glucokinase activators [113], and there are more and better choices for T2D treatment, but we should pay more attention to both safety and efficacy of these novel hypoglycaemic drugs [114]. Because T2D links to significant abnormalities in cardiocerebrovascular system [115], such as atherosclerotic CVD, diabetic cardiomyopathy, CHF, stroke, CKD, peripheral neuropathy [116], our program may have a role of risk-reduction of MACCE and improvement of clinical outcomes. Herein, this program can be adopted as "a concise guideline" in clinical practice due to OMT and healthy E(e)SEEDi lifestyle.

Both T2D (diagnosed and undiagnosed) and IGT are important CVD risk factors [117] and have higher risk of coronary stenosis and coronary atherosclerotic plaques burden [118]. When there is fragmented QRS, it may predict complex VAs and the risk of sudden cardiac death [119], and LVDD is common [120] in T2D patients, it may also be detected by 3D speckle tracking echocardiography [121]. However, current SGLT2-inhibition remains to be at an underused status in these HF-population [122]. A combination of agents high-intensity statins (rosuvastatin) and more often with ezetimibe [123] and intensifying lifestyle measures is needed for stricter LDL-C and non-HDL-C targets.

Because good clinical investigations or programs could inform future diagnostic and therapeutic strategies, and enhance the understanding of a disease, just like myocardial infarction with nonobstructive coronary arteries (MINOCA) [124] and this iRT-ABCDEFG program. When combined with novel tools [125], new agents [126], fresh preventive and interventional strategies [127,128], it will help us to get better effects on management or self-management of T2D. However, "advances in science are not linear, they are zigzag" [129].[129] Thus, we should keep enough patience and confidence from papers publication to practical application and try to expand related clinical coverage.

In fact, during the pandemic and post-COVID-19 era [130], as major OMT and particularly when combined with healthy E(e)SEEDi lifestyle, both GLP-1 receptor agonists and SGLT2 inhibitors are good choices for prevention of related complications in T2D (CHF, CKD, and AF/AFL-reduction benefit) and MACCE due to direct and favorable cardioprotective and nephroprotective effects [131-134], even if SGLT2 inhibitors have no significant effects on ischemic events stemming from atherosclerotic CVD in T2D [135]. With the development of new drug delivery systems [136-138] and novel technologies [139,140], it's promising in applications for T2D and its complications.

5 | CONCLUSION AND PERSPECTIVES

This iRT-ABCDEFG program combining OMT and healthy E(e)SEEDi lifestyle for T2D is very suitable for healthcare among clinical doctors, patients, and healthy individuals. This program is helpful to access clinical vital goals, which include less MACCE and diabetic complications, less medical costs, longer life expectancy, lower morbidity and mortality, and higher quality of life due to early diagnosis, OMT, and overall prevention by healthy E(e)SEEDi lifestyle. Moreover, this program is not only effective but also not complicated, and easy to perform in primary care centers. In addition, training the professional members and individuals to carry out this program is so easy. In fact, this program can also be developed as a mobile APP for wide use among T2D individuals and general population. Herein, we highly recommend this iRT-ABCDEFG program due to a good expected cost-effective relationship and clinical outcomes, since T2D highly links to CVD (AMI, CHF, and stroke) and cancer, as well as other MACCE and the CDC strips.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

C. H, T.T. and Q.W. have contributed to the development and review of the manuscript and approved the final version of the manuscript for submission.

ETH ICS STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

The data included in this study are available upon request from the corresponding author.

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REFERENCES

1. Lu J, Xia Q, Zhou Q. How to make insulin-producing pancreatic β cells for diabetes treatment. Sci China Life Sci 2017;60:239-48.

2. Lean MEJ, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018;391:541-51.

3. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. SEARCH for Diabetes in Youth Study. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012. N Engl J Med 2017;376:1419-29.

4. Rawshani A, Rawshani A, Franzén S, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. N Engl J Med 2017;376:1407-18.

5. Lee C, Sung NJ, Lim HS, Lee JH. Emergency Department Visits Can Be Reduced by Having a Regular Doctor for Adults with Diabetes Mellitus: Secondary Analysis of 2013 Korea Health Panel Data. J Korean Med Sci 2017;32:1921-30.

6. Kim MS, Lee DY. Urinary Glucose Screening for Early Detection of Asymptomatic Type 2 Diabetes in Jeonbuk Province Korean Schoolchildren. J Korean Med Sci 2017;32:985-91.

7. Shin WY, Lee T, Jeon DH, Kim HC. Diabetes, Frequency of Exercise, and Mortality Over 12 Years: Analysis of the National Health Insurance Service-Health Screening (NHIS-HEALS) Database. J Korean Med Sci 2018;33:e60.

8. Cho S, Shin JY, Kim HJ, et al. Chasms in Achievement of Recommended Diabetes Care among Geographic Regions in Korea. J Korean Med Sci 2019;34:e190.

9. Lloyd CE, Nouwen A, Sartorius N, et al. Prevalence and correlates of depressive disorders in people with Type 2 diabetes: results from the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study, a collaborative study carried out in 14 countries. Diabet Med 2018;35:760-9.

10. Wang JL, Qin Z, Wang ZJ, et al. New predictors of in-stent restenosis in patients withdiabetes mellitusundergoing percutaneous coronary intervention with drug-eluting stent. J Geriatr Cardiol 2018;15:137-45.

11. Jakobsen GS, Småstuen MC, Sandbu R, et al. Association of Bariatric Surgery vs Medical Obesity Treatment With Long-term Medical Complications and Obesity-Related Comorbidities. JAMA 2018;319:291-301.

12. Hu CS, Han YL, Ge JB, et al. A novel management program for hypertension. Cardiovasc Diagn Ther 2015;5:316-22.

13. Hu C, Tkebuchava T, Hu D. Managing acute myocardial infarction in China. Eur Heart J 2019;40:1179-81.

14. Hu CS, Wu QH, Hu DY, Tkebuchava T. Treatment of chronic heart failure in the 21st century: A new era of biomedical engineering has come. Chronic Dis Transl Med 2019;5:75-88.

15. Hu CS. A comprehensive strategy for managing arrhythmogenic right ventricular cardiomyopathy. Turk Kardiyol Dern Ars 2020;48:88-95.

16. Hu CS. Intervention of RT-ABCDEF for cancer. Croat Med J 2019;60:55-7.

17. Hu CS, Tkebuchava T. SARS and its treatment strategies. Asian Pac J Trop Med 2019;12:95-7.

18. Reaven PD, Emanuele NV, Wiitala WL, et al. VADT Investigators. Intensive Glucose Control in Patients with Type 2 Diabetes - 15-Year Follow-up. N Engl J Med 2019;380:2215-24.

19. Schauer PR, Bhatt DL, Kirwan JP, et al. STAMPEDE Investigators. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. N Engl J Med 2017;376:641-51.

20. Gong L, Li R, Ren W, et al. The FOXO1 Gene-Obesity Interaction Increases the Risk of Type 2 Diabetes Mellitus in a Chinese Han Population. J Korean Med Sci 2017;32:264-71.

21. Selvin E, Wang D, Lee AK, Bergenstal RM, Coresh J. Identifying Trends in Undiagnosed Diabetes in U.S. Adults by Using a Confirmatory Definition: A Cross-sectional Study. Ann Intern Med 2017;167:769-76.

22. Esteghamati A, Khandan A, Momeni A, et al. Circulating levels of fibroblast growth factor 21 in early-stage diabetic kidney disease. Ir J Med Sci 2017;186: 785-94.

23. Liu B, Ye X, Zhao G, Jin L, Shi J. Association of RAGE with acute ischemic stroke prognosis in type 2 diabetes. Ir J Med Sci 2021;190:625-30.

24. Argun D, Argun F, Borku Uysal B. Evaluation of salusin-alpha and salusin-beta levels in patients with type 2 diabetes mellitus and determination of the impact of severity of hyperglycemia on salusin levels. Ir J Med Sci 2021;190:1403-11.

25. Fangel MV, Nielsen PB, Kristensen JK, et al. Albuminuria and Risk of Cardiovascular Events and Mortality in a General Population of Patients with Type 2 Diabetes Without Cardiovascular Disease: A Danish Cohort Study. Am J Med 2020;133:e269-79.

26. Johansen MY, MacDonald CS, Hansen KB, et al. Effect of an Intensive Lifestyle Intervention on Glycemic Control in Patients With Type 2 Diabetes A Randomized Clinical Trial. JAMA 2017;318:637-46.

27. Hu C. Grants supporting research in China. Eur Heart J 2018;39:2342-4.

28. Hu CS, Tkebuchava T. SEEDi$^{1.0\text{-}3.0}$ strategies for major noncommunicable diseases in China. J Integr Med 2017;15:265-9.

29. Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 2007;356: 447-58.

30. Coogan PF, White LF, Jerrett M, et al. Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. Circulation 2012;125:767-72.

31. Yang BY, Qian ZM, Li S, et al. Ambient air pollution in relation to diabetes and glucose-homoeostasis markers in China: a cross-sectional study with findings from the 33 Communities Chinese Health Study. Lancet Planet Health 2018;2: e64-73.

32. Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z. The 2016 global and national burden of diabetes mellitus attributable to PM(25) air pollution. Lancet Planet Health 2018;2:e301-12.

33. Zhang S, Mwiberi S, Pickford R, et al. Longitudinal associations between ambient air pollution and insulin sensitivity: results from the KORA cohort study. Lancet Planet Health 2021;5:e39-49.

34. Liu L, Wang F, Lu H, et al. Effects of Noise Exposure on Systemic and Tissue-Level Markers of Glucose Homeostasis and Insulin Resistance in Male Mice. Environ Health Perspect 2016;124:1390-8.

35. Hu CS, Tkebuchava T. E-noise: An increasingly relevant health risk. J Integr Med 2019;17:311-4.

36. Osborne MT, Naddaf N, Abohashem S, et al. A neurobiological link between transportation noise exposure and metabolic disease in humans. Psychoneuroendocrinology 2021;131:105331.

37. Eriksson JG, Kajantie E, Lampl M, Osmond C. Trajectories of body mass index amongst children who develop type 2 diabetes as adults. J Intern Med 2015;278: 219-26.

38. Elmasry A, Lindberg E, Berne C, et al. Sleep-disordered breathing and glucose metabolism in hypertensive men: a population-based study. J Intern Med 2001; 249:153-61.

39. Pan KY, Xu W, Mangialasche F, Fratiglioni L, Wang HX. Work-related psychosocial stress and the risk of type 2 diabetes in later life. J Intern Med 2017;281:601-10.

40. Giovannucci EL, Rezende LFM, Lee DH. Muscle-strengthening activities and risk of cardiovascular disease, type 2 diabetes, cancer and mortality: A review of prospective cohort studies. J Intern Med 2021;290:789-805.

41. Wang Y, Lee DC, Brellenthin AG, et al. Leisure-Time Running Reduces the Risk of Incident Type 2 Diabetes. Am J Med 2019;132:1225-32.

42. Carlsson S, Andersson T, Araghi M, et al. Smokeless tobacco (snus) is associated with an increased risk of type 2 diabetes: results from five pooled cohorts. J Intern Med 2017;281:398-406.

43. Shi L, Brunius C, Johansson I, et al. Plasma metabolite biomarkers of boiled and filtered coffee intake and their association with type 2 diabetes risk. J Intern Med 2020;287:405-21.

44. Martin WP, Sharif F, Flaherty G. Lifestyle risk factors for cardiovascular disease and diabetic risk in a sedentary occupational group: the Galway taxi driver study. Ir J Med Sci 2016;185:403-12.

45. Liu G, Li Y, Hu Y, et al. Influence of Lifestyle on Incident Cardiovascular Disease and Mortality in Patients With Diabetes Mellitus. J Am Coll Cardiol 2018;71:2867-76.

46. Newman JD, Schwartzbard AZ, Weintraub HS, Goldberg IJ, Berger JS. Primary Prevention of Cardiovascular Disease in Diabetes Mellitus. J Am Coll Cardiol 2017;70:883-93.

47. Unick JL, Beavers D, Bond DS, et al. Look AHEAD Research Group. The long-term effectiveness of a lifestyle intervention in severely obese individuals. Am J Med 2013;126:236-42;242.e1-2.

48. Grabovac I, Smith L, Stefanac S, et al. Health Care Providers' Advice on Lifestyle Modification in the US Population: Results from the NHANES 2011-2016. Am J Med 2019;132: 489-97.e1.

49. Song G, Chen C, Zhang J, Chang L, Zhu D, Wang X. Association of traditional Chinese exercises with glycemic responses in people with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. J Sport Health Sci 2018;7:442-52.

50. McMacken M, Shah S. A plant-based diet for the prevention and treatment of type 2diabetes. J Geriatr Cardiol 2017;14:342-54.

51. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, et al. Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus. N Engl J Med 2018;379:1540-50.

52. Pittas AG, Dawson-Hughes B, Sheehan P, et al. D2d Research Group. Vitamin D Supplementation and Prevention of Type 2 Diabetes. N Engl J Med 2019;381: 520-30.

53. Hu CS, Tkebuchava T. New "P" in Medical Model. Chin Med J (Engl) 2016;129: 492-3.

54. Gazzaruso C, Coppola A, Pujia A, et al. Erectile dysfunction as a predictor of asymptomatic coronary artery disease in elderly men with type 2diabetes. J Geriatr Cardiol 2016;13:552-6.

55. Gudbjartsson DF, Thorgeirsson G, Sulem P, et al. Lipoprotein(a) Concentration and Risks of Cardiovascular Disease and Diabetes. J Am Coll Cardiol 2019;74: 2982-94.

56. Rutter MK, Wahid ST, McComb JM, Marshall SM. Significance of silent ischemia and microalbuminuria in predicting coronary events in asymptomatic patients with type 2 diabetes. J Am Coll Cardiol 2002;40:56-61.

57. Low Wang CC, Blomster JI, Heizer G, et al. EUCLID Trial Executive Committee and Investigators. Cardiovascular and Limb Outcomes in Patients With Diabetes and Peripheral Artery Disease: The EUCLID Trial. J Am Coll Cardiol 2018;72:3274-84.

58. Laiteerapong N, Cooper JM, Skandari MR, et al. Individualized Glycemic Control for U.S. Adults With Type 2 Diabetes: A Cost-Effectiveness Analysis. Ann Intern Med 2018;168:170-8.

59. Husain M, Birkenfeld AL, Donsmark M, et al. PIONEER 6 Investigators. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2019;381:841-51.

60. Tamborlane WV, Barrientos-Pérez M, Fainberg U, et al. Ellipse Trial Investigators. Liraglutide in Children and Adolescents with Type 2 Diabetes. N Engl J Med 2019;381:637-46.

61. Marso SP, Baeres FMM, Bain SC, et al. LEADER Trial Investigators. Effects of Liraglutide on Cardiovascular Outcomes in Patients With Diabetes With or Without Heart Failure. J Am Coll Cardiol 2020;75:1128-41.

62. Mann JFE, Ørsted DD, Brown-Frandsen K, et al. LEADER Steering Committee and Investigators. Liraglutide and Renal Outcomes in Type 2 Diabetes. N Engl J Med 2017;377:839-48.

63. Kosiborod M, Lam CSP, Kohsaka S, et al. CVD-REAL Investigators and Study Group. Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL 2 Study. J Am Coll Cardiol 2018;71:2628-39.

64. Neal B, Perkovic V, Mahaffey KW, et al. CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017;377:644-57.

65. Perkovic V, Jardine MJ, Neal B, et al. CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 2019;380:2295-306.

66. Wanner C, Inzucchi SE, Lachin JM, et al. EMPA-REG OUTCOME Investigators. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med 2016;375:323-34.

67. Sharma A, Ofstad AP, Ahmad T, et al. Patient Phenotypes and SGLT-2 Inhibition in Type 2 Diabetes: Insights From the EMPA-REG OUTCOME Trial. JACC Heart Fail 2021;9:568-77.

68. Bilgin S, Kurtkulagi O, Duman TT, et al. Sodium glucose co-transporter-2 inhibitor, Empagliflozin, is associated with significant reduction in weight, body mass index, fasting glucose, and A1c levels in Type 2 diabetic patients with established coronary heart disease: the SUPER GATE study. Ir J Med Sci 2021;1-6.

69. Marso SP, McGuire DK, Zinman B, et al. DEVOTE Study Group. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. N Engl J Med 2017;377: 723-32.

70. Schmedt N, Enders D, Walker J, Garbe E, Douros A. Sodium-Glucose Co-Transporter 2 Inhibitors and the Risk of Venous Thromboembolism in Patients with Type 2 Diabetes: A Cohort Study. Am J Med 2021;134: 606-13.e6.

71. Ferraro RA, Nass CM, Dudum R, Blumenthal RS, Sarkar S. What Clinicians Need to Know About the Cardiovascular Effects of the Most Recent Classes of Drugs Used for Type 2 Diabetes. Am J Med 2019;132:1027-31.

72. Newman JD, Vani AK, Aleman JO, Weintraub HS, Berger JS, Schwartzbard AZ. The Changing Landscape of Diabetes Therapy for Cardiovascular Risk Reduction: JACC State-of-the-Art Review. J Am Coll Cardiol 2018;72:1856-69.

73. Wiviott SD, Raz I, Bonaca MP, et al. DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019;380:347-57.

74. Filippatos G, Bakris GL, Pitt B, et al. FIDELIO-DKD Investigators. Finerenone Reduces New-Onset Atrial Fibrillation in Patients With Chronic Kidney Disease and Type 2 Diabetes. J Am Coll Cardiol 2021;78:142-52.

75. Tan SY, Cronin H, Byrne S, O'Donovan A, Tuthill A. Appropriateness of aspirin prescribing for primary and secondary prevention of cardiovascular disease in type 2 diabetes in different care settings. Ir J Med Sci 2021; doi: 10.1007/s11845-021-02649-5.

76. Liao EP. Patterns of medication initiation in newly diagnosed diabetes mellitus: quality and cost implications. Am J Med 2012;125:S1-2.

77. Rana JS, Liu JY, Moffet HH, Sanchez RJ, Khan I, Karter AJ. Risk of Cardiovascular Events in Patients With Type 2 Diabetes and Metabolic Dyslipidemia Without Prevalent Atherosclerotic Cardiovascular Disease. Am J Med 2020;133:200-6.

78. Lavie G, Hoshen M, Leibowitz M, et al. Statin Therapy for Primary Prevention in the Elderly and Its Association with New-Onset Diabetes, Cardiovascular Events, and All-Cause Mortality. Am J Med 2021;134:643-52.

79. Echouffo-Tcheugui JB, Xu H, Matsouaka RA, et al. Diabetes and long-term outcomes of ischaemic stroke: findings from Get With The Guidelines-Stroke. Eur Heart J 2018;39:2376-86.

80. Atlas Writing Group, Timmis A, Townsend N, Gale C, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2017. Eur Heart J 2018;39:508-79.

81. Weng J, Zhou Z, Guo L, et al. T1D China Study Group. Incidence of type 1 diabetes in China, 2010-13: population based study. BMJ 2018;360:j5295.

82. Dieleman JL, Squires E, Bui AL, et al. Factors Associated With Increases in US Health Care Spending, 1996-2013. JAMA 2017;318:1668-78.

83. Hu C, Tkebuchava T. Health in All Laws: a better strategy for global health. J Evid Based Med 2022;15:10-4.

84. Hu CS, Tkebuchava T. Structure-Editing: A New Branch? Chin Med J (Engl) 2016; 129:1629-30.

85. Halberg IB, Lyby K, Wassermann K, Heise T, Zijlstra E, Plum-Mörschel L. Efficacy and safety of oral basal insulin versus subcutaneous insulin glargine in type 2 diabetes: a randomised, double-blind, phase 2 trial. Lancet Diabetes Endocrinol 2019;7:179-88.

86. Ruiz HH, López Díez R, Arivazahagan L, Ramasamy R, Schmidt AM. Metabolism, Obesity, and Diabetes Mellitus. Arterioscler Thromb Vasc Biol 2019;39:e166-74.

87. Chung MK, Eckhardt LL, Chen LY, et al; American Heart Association Electrocardiography and Arrhythmias Committee and Exercise, Cardiac Rehabilitation, and Secondary Prevention Committee of the Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and Council on Lifestyle and Cardiometabolic Health. Lifestyle and Risk Factor Modification for Reduction of Atrial Fibrillation: A Scientific Statement From the American Heart Association. Circulation 2020;141:e750-72.

88. Rangaswami J, Bhalla V, de Boer IH, et al; American Heart Association Council on the Kidney in Cardiovascular Disease; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Lifestyle and Cardiometabolic Health. Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease: A Scientific Statement From the American Heart Association. Circulation 2020;142: e265-86.

89. Filippatos G, Anker SD, Agarwal R, et al; FIDELIO-DKD Investigators. Finerenone and Cardiovascular Outcomes in Patients With Chronic Kidney Disease and Type 2 Diabetes. Circulation 2021;143:540-52.

90. The Lancet. Modernising the NHS: leading the way with diabetes. Lancet 2019;393:200.

91. Hu CS. Analysis of COVID-19 Cases and Public Measures in China. SN Compr Clin Med 2020;2:1306-12.

92. Qian F, Liu G, Hu FB, Bhupathiraju SN, Sun Q. Association Between Plant-Based Dietary Patterns and Risk of Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA Intern Med 2019;179:1335-44.

93. Owens-Gary MD, Zhang X, Jawanda S, Bullard KM, Allweiss P, Smith BD. The Importance of Addressing Depression and Diabetes Distress in Adults withType 2 Diabetes. J Gen Intern Med 2019;34:320-4.

94. Vergari E, Denwood G, Salehi A, et al. Somatostatin secretion by Na(+)-dependent Ca(2+)-induced Ca(2+) release in pancreatic delta-cells. Nat Metab 2020;2:32-40.

95. De Jesus DF, Zhang Z, Kahraman S, et al. m(6)A mRNA Methylation Regulates Human β-Cell Biology in Physiological States and in Type 2 Diabetes. Nat Metab 2019;1:765-74.

96. Campbell MD, Sathish T, Zimmet PZ, et al. Benefit of lifestyle-based T2DM prevention is influenced by prediabetes phenotype. Nat Rev Endocrino 2020;16: 395-400.

97. Magkos F, Hjorth MF, Astrup A. Diet and exercise in the prevention and treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2020;16:545-55.

98. Perreault L, Skyler JS, Rosenstock J. Novel therapies with precision mechanisms for type 2 diabetes mellitus. Nat Rev Endocrinol 2021;17:364-77.

99. Caputo V, Termine A, Strafella C, Giardina E, Cascella R. Shared (epi)genomic background connecting neurodegenerative diseases and type 2 diabetes. World J Diabetes 2020;11:155-64.

100. Foran E, Hannigan A, Glynn L. Prevalence of depression in patients with type 2 diabetes mellitus in Irish primary care and the impact of depression on the control of diabetes. Ir J Med Sci 2015;184:319-22.

101. Tudor RM, Garrahy A, Woods CP, et al. The prevalence and incidence of thyroid dysfunction in patients with diabetes - a longitudinal follow-up study. Ir J Med Sci 2020;189:171-5.

102. Manfrini O, Russo V, Ciavarella A, Ceroni L, Montalti M, Fattori R. Coronary plaque quantification and composition in asymptomatic patients with type II diabetes mellitus. J Cardiovasc Med (Hagerstown) 2012;13: 423-31.

103. Stoynev N, Dimova I, Rukova B, et al. Gene expression in peripheral blood of patients with hypertension and patients with type 2 diabetes. J Cardiovasc Med (Hagerstown) 2014;15:702-9.

104. Ruocco G, Evangelista I, Franci B, et al. Combination of ST2 and B-type natriuretic peptide in diabetic patients with acute heart failure: relation with ventricular stiffness and outcome. J Cardiovasc Med (Hagerstown) 2019;20:81-90.

105. De Luca G, Verdoia M, Savonitto S, et al. Elderly ACS 2 Investigators. Impact of diabetes on clinical outcome among elderly patients with acute coronary syndrome treated with percutaneous coronary intervention: insights from the ELDERLY ACS 2 trial. J Cardiovasc Med (Hagerstown) 2020;21:453-9.

106. Zwart K, Velthuis S, Polyukhovych YV, et al. Sodium-glucose cotransporter 2 inhibitors: a practical guide for the Dutch cardiologist based on real-world experience. Neth Heart J 2021;29:490-9.

107. Pandey A, Vaduganathan M, Patel KV, et al. Biomarker-Based Risk Prediction of Incident Heart Failure in Pre-Diabetes and Diabetes. JACC Heart Fai 2021;9: 215-23.

108. Echouffo-Tcheugui JB, Zhang S, Florido R, et al. Duration of Diabetes and Incident Heart Failure: The ARIC (Atherosclerosis Risk In Communities) Study. JACC Heart Fail 2021;9:594-603.

109. Brandt-Jacobsen NH, Lav Madsen P, Johansen ML, et al. Mineralocorticoid Receptor Antagonist Improves Cardiac Structure in Type 2 Diabetes: Data From the MIRAD Trial. JACC Heart Fail 2021;9:550-8.

110. Pitt B, Filippatos G, Agarwal R, et al. FIGARO-DKD Investigators. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. N Engl J Med 2021;385:2252-63.

111. Hou L, Ge L, Li Y, et al. Physical activity recommendations for patients with type2diabetes: a cross-sectional survey. Acta Diabetol 2020;57:765-77.

112. Phrommintikul A, Wongcharoen W, Kumfu S, et al. Effects of dapagliflozin vs vildagliptin on cardiometabolic parameters in diabetic patients with coronary artery disease: a randomised study. Br J Clin Pharmacol 2019;85:1337-47.

113. Baker DJ, Wilkinson GP, Atkinson AM, et al. Chronic glucokinase activator treatment at clinically translatable exposures gives durable glucose lowering in two animal models of type 2 diabetes. Br J Pharmacol 2014;171:1642-54.

114. Shimazawa R, Ikeda M. Approvals of type 2 diabetes drugs tested in cardiovascular outcome trials: A tripartite comparison. Br J Clin Pharmacol 2021;87:3938-48.

115. Levelt E, Pavlides M, Banerjee R, et al. Ectopic and Visceral Fat Deposition in Lean and Obese Patients With Type 2 Diabetes. J Am Coll Cardiol 2016;68: 53-63.

116. Das SR, Everett BM, Birtcher KK, et al. 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2018;72:3200-23.

117. Enquobahrie DA, Dolidze N, Chapidze G, Vadachkoria S, Soh J, Fitzpatrick A, Williams MA. Type 2 diabetes and impaired glucose tolerance among cardiac patients. Acta Cardiol 2007;62:439-44.

118. Canpolat U, Aytemir K, Yorgun H, Hazirolan T, Kaya EB, Ateş AH, Sunman H, Dural M, Yalçin MU, Tokgözoğlu L, Kabakçi G, Oto A. Association of type 2 diabetes mellitus with coronary atherosclerotic plaque burden and morphology measured by multidetector computed tomography coronary angiography. Acta Cardiol 2012;67:71-7.

119. Eren H, Kaya Ü, Öcal L, Öcal AG, Genç Ö, Genç S, Evlice M. Presence of fragmented QRS may be associated with complex ventricular arrhythmias in patients with type-2 diabetes mellitus. Acta Cardiol 2021;76:67-75.

120. Bayramoğlu A, Taşolar H, Kaya Y, et al. Fragmented QRS complexes are associated with left ventricular dysfunction in patients with type-2 diabetes mellitus: a two-dimensional speckle tracking echocardiography study. Acta Cardiol 2018;73:449-56.

121. Wang Q, Fu C, Xia H, Gao Y. Aggravating effect of obstructive sleep apnoea on left ventricular remodelling and function disorder in patients with type 2 diabetes mellitus: a case-control study by 3D speckle tracking echocardiography. Acta Cardiol 2021:1-10.

122. Martens P, Janssens J, Ramaekers J, Dupont M, Mullens W. Contemporary choice of glucose lowering agents in heart failure patients with type 2 diabetes. Acta Cardiol 2020;75:211-7.

123. Hermans MP, Ahn SA, Rousseau MF. Lipid and cardiometabolic features of T2DM patients achieving stricter LDL-C and non-HDL-C targets in accordance with ESC/EAS 2019 guidelines. Acta Cardiol 2021;76:375-83.

124. Serpytis R, Majauskiene E, Navickas P, et al. Randomized Pilot Trial on Optimal Treatment Strategy, Myocardial Changes, and Prognosis of Patients with Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA). Am J Med 2022;135:103-9.

125. Rauh SP, Rutters F, van der Heijden AAWA, et al. External Validation of a Tool Predicting 7-Year Risk of Developing Cardiovascular Disease, Type 2 Diabetes or Chronic Kidney Disease. J Gen Intern Med 2018;33:182-8.

126. Alexander JT, Staab EM, Wan W, et al. Longer-term Benefits and Risks of Sodium-Glucose Cotransporter-2 Inhibitors in Type 2 Diabetes: a Systematic Review and Meta-analysis. J Gen Intern Med 2021; doi: 10.1007/s11606-021-07227-0.

127. Raghavan S, Pachucki MC, Chang Y, et al. Incident Type 2 Diabetes Risk is Influenced by Obesity and Diabetes in Social Contacts: a Social Network Analysis. J Gen Intern Med 2016;31:1127-33.

128. Kobe EA, Lewinski AA, Jeffreys AS, et al. Implementation of an Intensive Telehealth Intervention for Rural Patients with Clinic-Refractory Diabetes. J Gen Intern Med 2022; :1-9. doi: 10.1007/s11606-021-07281-8.

129. Alpert JS. Advances in Science Are Not Linear; They Are Zigzag. Am J Med 2021;S0002-9343(21)00797-X.

130. Anastasiou G, Hatziagelaki E, Liberopoulos E. Could Dapagliflozin Attenuate COVID-19 Progression in High-Risk Patients With or Without Diabetes? Behind DARE-19 Concept. J Cardiovasc Pharmacol 2021;78:e12-9.

131. Li W, Chen X, Xie X, et al. Comparison of sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide receptor agonists for atrial fibrillation in type 2 diabetes mellitus: systematic review with network meta-analysis of randomised controlled trials. J Cardiovasc Pharmacol 2021; doi: 10.1097/FJC.0000000000001197.

132. Qiu M, Ding LL, Wei XB, Liu SY, Zhou HR. Comparative Efficacy of Glucagon-like Peptide 1 Receptor Agonists and Sodium Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular Events in Type 2 Diabetes: A Network Meta-analysis. J Cardiovasc Pharmacol 2021;77:34-7.

133. Vider E, Sapir R, Mosseri E, Gavioli E. Current perspectives of the use of Sodium Glucose Transport-2 Inhibitors for patients with heart failure and chronic kidney disease. J Cardiovasc Pharmacol 2021; doi: 10.1097/FJC.0000000000001176.

134. Zheng RJ, Wang Y, Tang JN, Duan JY, Yuan MY, Zhang JY. Association of SGLT2 inhibitors with risk of atrial fibrillation and stroke in patients with and without type 2 diabetes: a systemic review and meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol 2021; doi: 10.1097/FJC.0000000000001183.

135. Ye G, Wang S, Peng D. Effects of SGLT2 Inhibitor on Ischemic Events Stemming From Atherosclerotic Coronary Diseases: A Systematic Review and Meta-analysis With Trial Sequential Analysis of Randomized Controlled Trials. J Cardiovasc Pharmacol 2021;77:787-95.

136. Wang Z, Guo W, Kuang X, Hou S, Liu H. Nanopreparations for mitochondria targeting drug delivery system: Current strategies and future prospective. Asian J Pharm Sci 2017;12:498-508.

137. Yang L, Yang Y, Chen H, Mei L, Zeng X. Polymeric microneedle-mediated sustained release systems: Design strategies and promising applications for drug delivery. Asian J Pharm Sci 2022;17:70-86.

138. Ng LC, Gupta M. Transdermal drug delivery systems in diabetes management: A review. Asian J Pharm Sci 2020;15:13-25.

139. Liu Y, Zhou S, Gao Y, Zhai Y. Electrospun nanofibers as a wound dressing for treating diabetic foot ulcer. Asian J Pharm Sci 2019;14:130-43.

140. Simos YV, Spyrou K, Patila M, Karouta N, Stamatis H, Gournis D, Dounousi E, Peschos D. Trends of nanotechnology in type 2 diabetes mellitus treatment. Asian J Pharm Sci 2021;16:62-76.

Table 1.

iRT-ABCDEFG program as a standardized comprehensive program for T2D.

iRT-ABCDEFG	Tips
G	**Goals** are less MACCE and diabetic complications, less medical costs, longer life expectancy, lower morb
F	**Follow-up** with registered subjects or patients, especially populations with family history, IGT, and an u
E	**Examination** for early diagnosis, treatment, and prevention, which includes large-scale screening and re
D	**Diseases and risk factor control**, which includes prediabetes state or impaired glucose tolerance, hyp
C	**Change unhealthy E(e)SEEDi lifestyle** with SEEDi$^{1.0\text{-}3.0}$ technologies, such as not staying up late, l
B	**Biohazard control**, which includes abnormal symptoms and physiological indexes, HbA1c level of bio-m
A	**Antagonistic treatment,** which includes oral hypoglycemic agents (such as GLPR agonists, SGLT2 inh
iRT	**intervention** with these strategies as **Routine**, **Right** & **Reversible Treatment**.

Notes : SEEDi$^{1.0\text{-}3.0}$ technologies were developed based on core healthy elements; that is, sleep-emotion-exercise-diet (SEED) intervention (SEEDi). When E(e)SEED-BasED healthy lifestyle included external and internal environment combines with RT-ABCDEF and Grade 210 prevention, it's 3.0 version of SEEDi (SEEDi$^{3.0}$) or General Formula (Health & Longevity equality) for major non-communicable diseases (mNCDs). GLPR agonists: glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors: sodium-glucose cotransporter 2 inhibitors.

Table 2.

The effects of healthy or unhealthy E(e)SEEDi lifestyle on T2D: Evidences from PubMed literatures.

E(e)SEEDi (healthy or unhealthy)	Linkage to T2D risk (lower or increase)
Environment (external or self-internal)	Clinical studies confirmed that long-term exposure to air pollution links to the increased risk of both CVD and T2D [29-33].[29-33] And increased transportation noise and e-noise exposures are associated with a greater risk of T2D [34-36]. Early growth status (short length and / or thinness at birth and during infancy) also links to T2D [37].
Sleep	Sleep breathing disorders (severe obstructive sleep apnea, OSA) may add the risk of T2D [38].
Emotion	Work-related psychosocial stress may increase the risk of T2D [39].
Exercise	Aerobic physical activity is associated with reduced risk of T2D and the higher levels of muscle-strengthening activities, the lower risk of T2D [40]. For example, leisure-time running is associated with a lower risk of developing T2D in adults [41].
Diet	Smoking (nicotine intake) increases the risk of T2D, but there is a protective role of habitual intake of filtered coffee on T2D development [42,43].

Notes: If individuals can keep healthy E(e)SEEDi lifestyle, they will basically get away from T2D or at least lower the risk of T2D.

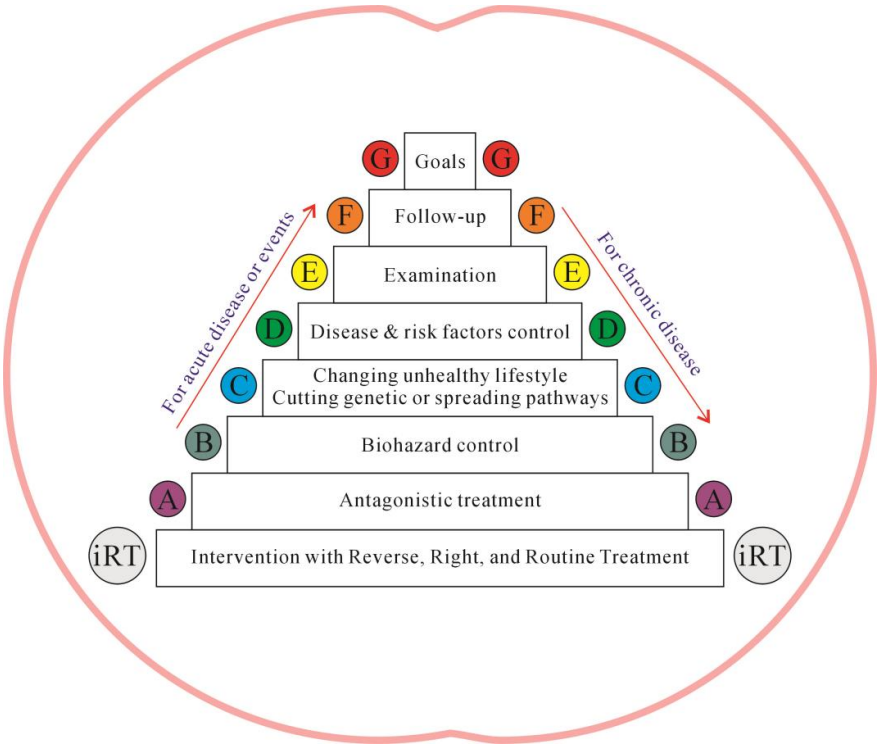

Figure 1 . The iRT-ABCDEFG program for managing type-2 diabetes (T2D).

According to this figure, it's easy to understand that this comprehensive program is very helpful to control and prevent T2D and reach several pivotal goals after consistently practice, which include less major adverse cardiocerebrovascular events (MACCE) and diabetic complications, less medical costs, longer life expectancy, lower morbidity and mortality, and higher quality of life, due to early diagnosis, OMT, and healthy E(e)SEEDi lifestyle for overall prevention. Herein, this iRT-ABCDEFG program is worthy of recommending for clinical professional management and health care of T2D due to better cost-effectiveness. However, it needs to confirm by long-term follow-up and clinical trials. In fact, it is suitable for not only acute diseases or events, such as acute myocardial infarction (AMI), stroke, and COVID-19 infection, but also chronic diseases, such as C-type hypertension (CtH), chronic heart failure (CHF), chronic kidney disease (CKD), neurodegenarative diseases (dementia or Alzheimer's disease and Parkinson's disease), and cancer as well as the cardiovascular, diabetes, and cancer (CDC) strips.