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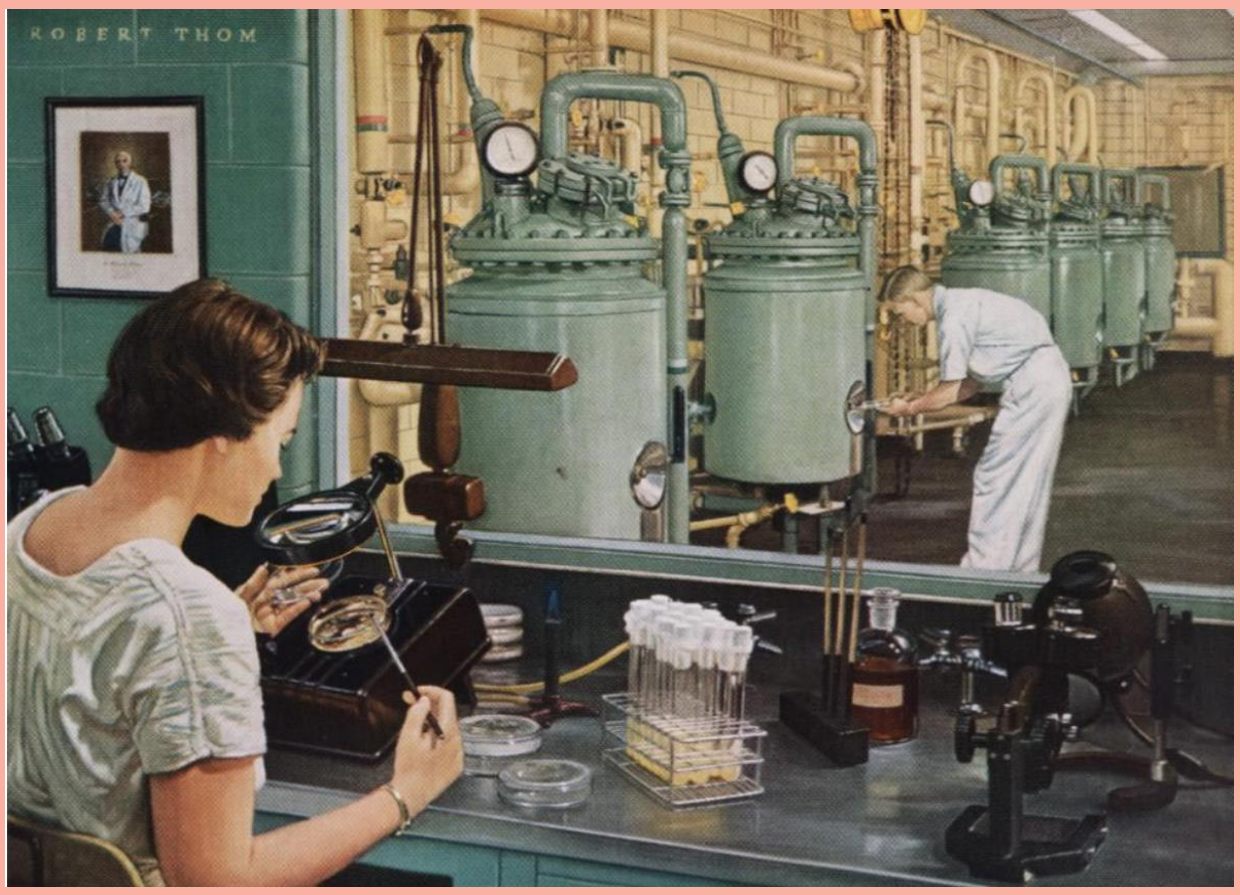

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Cover picture

The era of antibiotics

The development of penicillin in the 1940s brought new and dramatic methods of producing disease-fighting drugs, called antibiotics. Intensive research continues to find antibiotics that will conquer more of man's microbial enemies.

One of a series: A History of Pharmacy in Pictures, presented by Parke, Davis & Company.

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The Sri Lanka Prescriber

Management of Chronic Obstructive Pulmonary Disease (COPD)

Summary

- COPD causes chronic airway limitation which is not fully reversible.
- Patients with chronic stable COPD could present with acute exacerbations.
- Cessation of smoking plays a key role in the reduction of disease progression.
- Pharmacotherapy needs to be individualised, based on disease severity and frequency of exacerbations.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major health challenge worldwide, accounting for a disease burden of 11.7% (1). The prevalence of COPD in South Asia is 6.7% (1). A Sri Lankan study estimated the COPD disease burden to be in par with these global and regional values (1).

COPD is characterized by marked airflow limitation as a result of abnormalities that occur in the airways and alveoli (2). These changes are secondary to inhalation of noxious substances, smoking being the commonest contributor. Genetic and inherited lung abnormalities could also play a role in the pathogenesis of COPD (3).

Diagnosis of COPD

COPD should be suspected in patients with a history of difficulty in breathing, chronic cough and prolonged exposure to cigarette smoke or other noxious gases. Clinical examination may reveal presence of nicotine stains, a barrel shaped chest, tracheal tug and use of accessory muscles when breathing. Confirmation of the diagnosis requires spirometry, indicating a reduced FEV_1/FVC ratio <0.70, suggestive of an obstructive airway disease with persistent airflow limitation (2).

Severity assessment

Severity of COPD is assessed based on how the daytime and night-time symptoms, and exacerbations affect the patient's daily activities, spirometry values and the presence of co-morbidities.

According to the GOLD (global initiative for chronic obstructive lung disease) guidelines there are four stages of disease severity classified based on FEV_1/FVC ratio, correlated with patient's symptoms (Table 1). The treatment modalities depend on these stages.

Principles in management of COPD

Pharmacological methods combined with non-pharmacological methods play a vital role in disease control and prevention of acute exacerbations.

Non-pharmacological methods

Smoking cessation and nicotine replacement therapy have a major impact on reducing progression, morbidity and mortality (4).

Table 1: Assessment of disease severity according to spirometry (FEV_1) and severity of symptoms, compiled according to GOLD guideline 2018

Category	Level of risk	FEV_1 predicted	Symptoms
GOLD 1	Low	≥ 80%	Breathless on walking fast or climbing uphill
GOLD 2	Low	≤ 50%	Have to pause walking due to breathlessness
GOLD 3	High	≤ 30%	Difficulty in continuing walking after 100 meters due to breathlessness
GOLD 4	High	< 30%	Breathless while carrying out household chores

Counselling should be done by a physician and counselling sessions should be individualized. Influenza and pneumococcal vaccinations also reduce the frequency of exacerbations. Reduction in body weight and muscle mass are noted in patients with COPD secondary to the negative energy balance (5). Therefore advice on adapting a healthy dietary intake and dietary supplements are important. Psychological support plays a key role as many patients are prone to anxiety and depression (6). Cognitive behavioural therapy and psycho-therapy are beneficial to patient's quality of life.

Pulmonary rehabilitation

Pulmonary rehabilitation is the most effective treatment modality in management of COPD. Exercise training in the form of endurance and strength training added to aerobic exercise, especially of the upper limbs, improves upper body strength (2). Rehabilitation improves symptoms and exercise tolerance, while reducing frequency of exacerbations and hospitalisation.

Interventional therapy

Interventional procedures such as lung volume reduction surgery, bullectomy and broncho-scopic endobronchial valve placement operates on the principle of reducing lung hyperinflation, making respiratory muscles mechanically more effective (2).

Oxygen therapy

Long-term oxygen therapy is indicated for stable COPD patients who have PaO_2 at or below 55mmHg or SaO_2 at or below 88%, with or without hypercapnia, or a PaO_2 between 55–60mmHg or SaO_2 of 88% if there is evidence of pulmonary hypertension, peripheral oedema suggestive of congestive cardiac failure or polycythaemia (hematocrit >55%) (2). Patients on long-term oxygen therapy need to be evaluated at 2 to 3 monthly intervals.

Principles in pharmacological management

Pharmacological agents reduce disease severity, but are not effective in reducing disease progression (7). A summary of Pharmacotherapy for COPD in accordance with GOLD guidelines 2018 is provided in Table 2.

Inhaler use and technique

An inhaler device is chosen based on the symptomatology of individual patients, availability, cost and patient preference. Inhaler technique is important, since drug delivery is highly dependent on technique. Therefore, it is important to ensure that the patient is able to demonstrate correct inhaler technique. Furthermore, patient's inhaler technique should be re-assessed, before changing medications.

Bronchodilators

Bronchodilators are medications used to increase the forced expiratory volume in one second (FEV_1). $Beta_2$ agonists stimulate the $beta_2$ adrenergic receptors, resulting in bronchodilatation. Short acting $beta_2$ agonists such as salbutamol are only recommended in frequent exacerbations. Treatment should commence with a single or a dual long acting bronchodilator depending on the disease severity. Formoterol and salmeterol are long acting $beta_2$ agonists recommended for long-term symptomatic relief. Antimuscarinic drugs act on M_3 muscarinic receptors in smooth muscles of the airways, causing bronchodilation. Adverse effects of these drugs are dose-dependent. Therefore, using low doses of bronchodilators in combination will enhance the degree of bronchodilation whilst minimising adverse effects (8). Tiotropium is a long-acting, anticholinergic drug which improves resting inspiratory capacity and FEV_1, whilst reducing hyperinflation of the lungs (9). This drug is widely used at present, because of its greater bronchodilator efficacy in COPD patients, with good safety profile (9).

Table 2: Pharmacotherapy for COPD in accordance with GOLD guidelines 2018

GOLD 1	GOLD 2	GOLD 3	GOLD 4
Preventive: counselling on smoking cessation, vaccination, balanced nutritious diet			
Add as required: SABA ± SAMA			
	LABA ± LAMA	ICS + LABA ± LAMA or LABA + PDE_4 –I	ICS + LABA ± LAMA or LABA + LAMA + PDE_4-I

ICS: inhaled corticosteroid, LABA: long-acting $Beta_2$ agonist, LAMA: long-acting anti-muscarinic, PDE_4-I: phosphodiesterase-4 inhibitor, SABA: short-acting $Beta_2$ agonist, SAMA: short-acting antimuscarinic

Corticosteroids

Corticosteroids have anti-inflammatory properties that induce reduction of mucus production (10). As a result, airway obstruction is reduced. Inhaled corticosteroids are preferred to systemic steroids to reduce adverse effects of the later. Oral steroid use is not recommended in long term management. Long term inhaled corticosteroids are recommended in combination with long acting bronchodilators for those who have frequent exacerbations.

Phosphodiesterase$_4$ inhibitor (PDE_4I) Roflumilast is recommended for those who do not respond to the combination of long term bronchodilators and corticosteroids (2). The most commonly used pharmacotherapy combination for long term management is ICS and LABA combination. ICS/LABA combination should not be paired with PDE_4 inhibitors.

Managing an acute exacerbation of COPD

The goal is to minimize the negative impact of the current exacerbation on overall lung health and prevent the development of further exacerbations. Treatment will depend on the severity of the exacerbation and underlying disease. A quick and comprehensive assessment on presentation to emergency unit will help to decide severity and further care; either in-ward, high dependency unit or intensive care. This should be done while patient is being monitored and on supplemental oxygen (2).

Oxygen should be delivered using a venturi mask to maintain FiO_2 (fraction of inspired oxygen) between 28% to 35% or via a nasal cannula at 2-4 L/min (2). Short acting beta$_2$ agonists with or without a short acting anticholinergic should be used for the initial bronchodilation (11). Oral corticosteroids improve FEV_1 and oxygenation of alveoli. This will also help in reducing the duration of hospital stay. Antibiotics are indicated only if there is evidence suggestive of an underlying infection, such as increased sputum volume and purulence. Both systemic steroid and antibiotic use should be limited to 5 to 7 days (2). Non-invasive ventilation is preferred unless there is evidence of persistent hypoxia (2).

Discharge and Follow up

Prior to discharge it is important to optimise medications and provide adequate advice for the patient and caregiver. Furthermore, supervision and correction of inhaler technique, assessment and optimal management of co-morbidities is also important. Follow up includes an assessment of symptom severity, checking on the adherence to maintenance therapy, and planning rehabilitation programmes. Follow up should commence within one month of discharge, with careful review of discharge medication, and the need for continuing any long term oxygen therapy by assessment of blood gases and disease control.

Additional follow up at three months is recommended to ensure return to a stable clinical state, review of medications, evaluation of lung function (by spirometry), and assessment of prognosis (2). Computed Tomography (CT) assessment should be done in patients with recurrent exacerbations to determine the presence of bronchiectasis and emphysema (2).

Conflicts of interests: All authors declare no conflicts of interests

References

1. Amarasiri L, Gunasinghe W, Sadikeen A, Fernando A, Madegedara D, Wickramasinghe R, Gunasekera K. The prevalence of Chronic Obstructive Pulmonary Disease (COPD) in Sri Lanka: outcome of the BOLD study. Eur Respir J 2017, 50 (suppl 61) PA1212

2. Global Initiative for Chronic Obstructive Lung Disease. Pocket Guide to COPD Diagnosis Management and Prevention 2018. https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf

3. Molfino NA. Genetics of COPD. Chest 2004;125:1929-40

4. Tønnesen P. Smoking cessation and COPD. Eur Respir Rev 2013;22:37-43

5. Schols AM, Brug J. Efficacy of nutritional intervention in chronic obstructive pulmonary disease. Eur Respir Monogr 2003;8:142-52

6. Smith SM, Sonego S, Ketcheson L, Larson JL. A review of the effectiveness of psychological interventions used for anxiety and depression in chronic obstructive pulmonary disease. BMJ open respiratory research 2014;1:e000042

7. Alsaeedi A, Sin DD, McAlister FA. The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials. Am J Medicine 2002;113:59-65

8. Cazzola M, Molimard M. The scientific rationale for combining long-acting β2-agonists and muscarinic antagonists in COPD. Pulm Pharmacol Ther 2010;23:257-67

9. Rice KL, Kunisaki KM, Niewoehner DE. Role of tiotropium in the treatment of COPD. Int J Chron Obstruct Pulmon Dis 2007;2:95.

10. Cazzola M, Dahl R. Inhaled combination therapy with long-acting β2-agonists and corticosteroids in stable COPD. Chest 2004;126:220-37

11. Bellinger CR, Peters SP. Outpatient chronic obstructive pulmonary disease management: going for the GOLD. J Allergy Clin Immunol Pract 2015;3:471-8

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Self-Assessment Questions – COPD

1. Regarding Chronic Obstructive Pulmonary Disease (COPD)

A. It is characterized by irreversible airway obstruction
B. Genetic factors do not play a role in the disease
C. Inhalation of noxious substances is a known association
D. Is definitively diagnosed using spirometry with bronchodilator reversibility
E. A diurnal variation is noted in symptoms

2. Non-Pharmacological methods of disease control include

A. Reducing calorie intake
B. Cessation of smoking
C. Vaccination against influenza and pneumococcus
D. Endurance and strength training
E. Targeted group therapy

3. Regarding pharmacological methods of management of COPD

A. Pharmacological agents are effective in reducing disease progression
B. Treatment is commenced with a combined Long Acting Beta Agonist/Corticosteroid inhaler
C. Oral or systemic steroids are preferred to inhaled steroids
D. Long acting antimuscarinic agents are commonly used in these patients
E. Short acting beta agonists are recommended for daily use

Self-Assessment Questions – COPD (Answers)

1. T F T T T

Chronic Obstructive Pulmonary Disease (COPD) is an obstructive airways disorder that differs from asthma in that the airways obstruction is poorly responsive to reversal by beta adrenergic agonists. Hence, the term 'irreversible airways obstruction'. The definitive diagnosis is made by spirometry after demonstrating a poor response to inhaled bronchodilator.

An established genetic risk factor for COPD is homozygosity for the Z allele of the alpha1-antitrypsin gene. Heterozygotes for the Z allele may also be at increased risk. Other mutations affecting the structure of alpha1-antitrypsin or the regulation of gene expression have been identified as risk factors. The commonest inhaled noxious substance known to cause COPD is cigarette smoke, closely followed by burning of solid fuels like wood, indoor air pollution and traffic fumes. Symptoms of COPD do exhibit a diurnal variation even though they may be less marked than Asthma.

2. F T T T T

COPD is a wasting disease. Reduction in body weight and muscle mass are noted in patients with COPD secondary to the negative energy balance. A high calorie high protein diet is advised in these patients in the absence of other co-morbidities that may advise against this. Cessation of smoking is the single most effective non-pharmacologic method of disease control and in fact, reversibility of the disease process. It is especially advised in patients who are being considered for long term oxygen therapy (LTOT). As COPD patients are more prone to infectious exacerbations, all possible steps should be taken to minimize the risk of infection. This includes vaccination. Pulmonary rehabilitation is a must in COPD therapy. Exercise training is personalized to the patient and includes aerobic training as well as strength and endurance training. The purpose is to salvage and build up muscle that will assist in breathing. Group therapy is a part of this. COPD is a disease of isolation. Many patients suffer from depression and cognitive behavioral therapy especially in a peer group setting has been found to significantly enhance quality of life.

3. F T F T F

Pharmacological agents reduce disease severity, but are not effective in reducing disease progression. Treatment should commence with a single or a dual long acting bronchodilator (LABA) depending on the disease severity. Formoterol and salmeterol are long acting $beta_2$ agonists recommended for long-term symptomatic relief. These are available in combination inhalers with corticosteroids. Inhaled corticosteroids are preferable to systemic steroids. Oral steroids are not recommended in the treatment of COPD. Long acting antimuscarinic agents (LAMA) like tiotropium have been used with good efficacy in COPD patients. Short acting beta agonist (SABA) inhalers are only recommended in exacerbations.

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Cardiovascular benefits of newer anti-diabetic medicines used in the management of type-2 diabetes

Introduction

Patients with type-2 diabetes are at high risk of developing cardiovascular disease which is the leading cause of death among them. Therefore, it is essential to optimize glycaemic control as well as other cardiovascular risk factors when managing patients with type-2 diabetes mellitus (T2DM). While the benefits of intensive glycaemic control on microvascular risk reduction are well established, data on its effect on macrovascular benefits are somewhat unclear. Therefore, multifactorial risk reduction strategies which include the use of antidiabetic agents with proven cardiovascular risk reduction have been highlighted in the recent guidelines for managing T2DM patients (1,2). In 2008, United States Food and Drug Administration (US FDA) made it mandatory for all new antidiabetic agents to demonstrate their cardiovascular impact evaluated through cardiovascular outcome trials. Data from recent cardiovascular endpoint trials with some of the newer antidiabetic medicines have shed light on this important complication. It is mandatory to choose antidiabetic agents wisely in the context of high cardiovascular risk in patients with T2DM, keeping in mind their high cost compared to the older and more established antidiabetic agents.

Older antidiabetic medicine classes and their cardiovascular effects

Biguanides

Out of several agents in this class, metformin discovered as early as the 1920s, is now the most recommended, and prescribed anti-diabetic medicine worldwide (3). Metformin has not shown cardiovascular safety concerns and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that metformin reduced the risk of fatal macrovascular complications compared with other treatment modalities used in the study (4). Despite its long duration of use, cardiovascular endpoint data mostly come from small studies. A recent meta-analysis showed that metformin reduces the incidence of cardiovascular events compared to no medicine given for diabetes, and compared to sulfonylureas. This data also comes from a limited number of studies (5). The cardio-protective mechanism of metformin is not very clear. Metformin activates AMP-activated protein kinase (AMPK) which will inhibit the mammalian target of rapamycin (mTOR) and inhibit protein synthesis pathways which in turn will inhibit cardiac muscle hypertrophy (6). Additionally, metformin increases myocyte insulin sensitivity, whereas insulin resistance is known to play a role in the development of diabetic cardiomyopathy (7).

Sulfonylureas

Sulfonylureas are another popular group of antidiabetic medicines that is commonly used due to their efficacy in improving glycaemic control as well as due to their lower cost. The controversy of cardiovascular safety of sulfonylureas first came to light when University Group Diabetes Program (UGDP) study showed that patients treated with the sulfonylurea, tolbutamide experienced more cardiac deaths compared to placebo or insulin treatments (8). Although UKPDS did not confirm this finding, some other studies have raised similar concerns. Despite its long duration of use, sulfonylureas also lack dedicated cardiovascular endpoint studies to evaluate cardiovascular benefit. Data from meta-analysis reveals that glimepiride and gliclazide reduced cardiovascular-related mortality compared to glibenclamide (9). All sulfonylureas do not have a similar action on the heart. Cardiovascular effects of sulfonyl-ureas are mediated through sulfonylurea receptor 2A (SUR2A) which leads to inhibition of ATP-dependent potassium channels on cardiac cells, resulting in hyperpolarization and inadequate coronary vasodilation. This may result in inhibition of ischemic preconditioning which is a cardio-protective mechanism. Glimepiride does not cause inhibition of cardiac sulfonylurea receptor and seems to have anti-inflammatory and pro-angiogenic effects (10). Gliclazide exerts some antithrombotic effect by inhibiting platelet aggregation and inducing a fibrinolytic effect. Due to these reasons, it is preferred to choose newer generation sulfonylureas to reduce possible adverse cardiovascular outcomes (11).

Thiazolidinediones (TZDs)

Although TZDs have established efficacy in T2DM treatment, their usage during the past years was questioned following the emergence of some concerning adverse effects including

cardiovascular safety. Currently, they are not the preferred antidiabetic agents in the context of cardiovascular disease especially in the presence of cardiac failure. The ADOPT trial which compared rosiglitazone vs metformin and glibenclamide (12) as well as the DREAM trial which compared rosiglitazone with placebo, demonstrated an increased incidence of heart failure as well as increased use of diuretics among the rosiglitazone users. In the real-world setting, compared to pioglitazone, rosiglitazone was associated with a higher risk of heart failure, myocardial infarction, and death (13). Due to these reasons, rosiglitazone was withdrawn from the market. However, new data on pioglitazone suggest better cardio-vascular outcomes including reduction of incidence of stroke, major vascular events, and reduced rate of coronary atherosclerosis (14).

DPP-4 inhibitors

DPP-4 inhibitors are well known for their weight-neutral effect and reduced incidence of hypoglycaemia. Except for saxagliptin (15), all other DPP-4 inhibitors have shown a cardiovascular neutral effect. Saxagliptin showed increased rates of hospitalization due to heart failure, although there was no increase or decrease in the rates of ischemic events (15). All the studies with DPP-4 inhibitors were done as add-on therapy and further head-to-head comparison studies are required to assess the cardiovascular benefit of these medicines.

Newer antidiabetic medications and their cardiovascular effects

Sodium Glucose Co Transporter 2 inhibitors (SGLT2 inhibitors)

SGLT2 inhibitors lower blood glucose by acting on the SGLT2 receptors of the S1 segment of the proximal convoluted tubule, an action independent of insulin. They may have some degree of SGLT1 inhibition as well, where the effect of SGLT1 inhibitors being mainly on the gut glucose absorption. Canagliflozin, empagliflozin, dapagliflozin, and ertugliflozin are more specific SGLT2 inhibitors while newer dual SGLT1 and SGLT2 inhibitors have been also developed.

SGLT2 inhibitors improve cardiovascular outcomes beyond their effect on glycaemic control. In earlier days, cardiovascular outcomes were mainly measured through the 3-point Major Adverse Cardiovascular Events (MACE) which comprised of non-fatal myo-cardial infarction (MI), non-fatal stroke, and cardiovascular- related death. However, heart failure is one of the important outcomes in atherosclerotic cardiovascular disease which may be independent of coronary artery atherosclerosis in certain populations. In T2DM the risk of heart failure is increased two-fold compared to the normal population (6). Hyperglycemia, hyperinsulinemia, and insulin resistance play a key role in mitochondrial dys-function, renin–angiotensin–aldosterone sys-tem activation, inflammation and oxidative stress, elevated uric acid levels, microvascular dysfunction, autonomic neuropathy, and card-iac myocyte death which will lead to cardiac stiffness, hypertrophy, and impaired cardiac remodeling. These changes result in cardiac diastolic and systolic dysfunction in diabetic cardiomyopathy (7). An increase in HbA1c has a strong relationship with heart failure. The risk of heart failure increased by 8% per each 1% rise in HbA1c (16).

SGLT2 inhibitors induce osmotic diuresis due to glycosuria, which leads to reduced effective intravascular volume as well as improved glycemic control. An initial drop in systolic blood pressure is due to the diuretic effect and later is due to the local inhibition of renin-angiotensin-aldosterone system (17). In addi-tion to glycosuria, they also lead to natriuresis resulting in plasma volume contraction and increased tubuloglomerlular feedback. These effects ultimately lead to a beneficial reduction in blood pressure, sympathetic drive, and finally reduce strain on the heart (18). Chronic elevation of uric acid has been shown to increase risk of hypertension, cardio-vascular disease, and kidney disease. Uricosuria that occurs with SGLT2 inhibitors is sustained for 2 years according to available clinical trial data explaining another possible cardioprotective effect of SGLT2 inhibitors (19).

Cardiovascular benefits of empagliflozin

Empagliflozin is a specific SGLT2 inhibitor and is the first medicine in its class to demonstrate cardiovascular outcome benefit (20). EMPA-REG OUTCOME investigated 7020 patients with T2DM having high cardio-vascular risk. This trial compared empagli-flozin versus placebo and the primary outcome assessed was 3-point MACE. There was no difference between the occurrence of MI or stroke. However, there was a significant reduction in the rates of cardiovascular related

death and hospitalization due to heart failure (20). This study was done over a short period (3.1 years) and demonstrated early cardiovascular benefits suggesting that these benefits are more likely to be due to improvement of the haemodynamic status rather than reduction of atherosclerosis.

These findings led to the evaluation of the effectiveness of empagliflozin in patients with heart failure with reduced ejection fraction (≤40%) who are on optimal medical therapy. EMPEROR REDUCED trial demonstrated that empagliflozin is superior to placebo in improving heart failure outcomes including lower risk of hospitalization due to heart failure and risk of cardiovascular disease related death, even in non-diabetic populations (21). The benefits were shown at a mean follow-up period of 16 months. EMPIRE HF and EMPEROR-Preserved trials would further evaluate these outcomes. In addition to improved heart failure outcomes, EMPEROR REDUCED also demonstrated reduced rates of decline in eGFR and reduced rates of serious renal effects in the population who used empagliflozin (21).

Cardiovascular benefits of dapagliflozin

Dapagliflozin has also demonstrated similar outcomes in its cardiovascular profile. DECLARE TIMI 58 trial assessed a larger population (17160 patients) compared to empagliflozin, over 4.2 years (22). Most of the enrolled population had high cardiovascular risk profiles. Results showed a reduced risk of hospitalization due to heart failure and lower cardiovascular deaths and non-inferiority over placebo for occurrence of 3-point MACE. Like the EMPEROR REDUCED trial, the DAPA HF trial also demonstrated similar benefits of dapagliflozin in those with heart failure in both diabetic and non-diabetic populations within a short follow-up period (23).

Cardiovascular benefits of canagliflozin

The CANVAS program combined two trials assessing cardiovascular outcomes and renal effects of canagliflozin. The primary endpoint assessed was 3-point MACE. This study demonstrated that canagliflozin is superior to placebo when achieving the primary endpoint at the expense of increased risk of amputations, mainly at the level of toes or metatarsals (24). Canagliflozin also showed superiority over placebo for reducing the incidence of hospitalization due to heart failure. CREDENCE which was mainly aimed at assessing renal outcome in patients with T2DM comparing canagliflozin vs placebo also confirmed above finding of cardiovascular benefit, however, there was no increase in risk of amputation or fractures (25).

Cardiovascular benefits of ertugliflozin

Ertugliflozin, a newer SGLT2 inhibitor did not show promising results compared to the above SGLT2 inhibitors during the clinical trials. VERTIS-CV, recruited 8246 T2DM patients who were followed for a mean period of 3.5 years, compared cardiovascular effectiveness of ertugliflozin vs placebo (26). Ertugliflozin was found to be non-inferior to placebo for non-fatal MI, stroke, cardiovascular related death, and hospitalization due to heart failure. However, later analysis revealed that ertugli-flozin resulted in reduced rates of recurrent hospital admissions due to heart failure and subsequent mortality compared to placebo (27).

SGLT1 inhibitors: sotagliflozin

Compared to SGLT2 inhibitors, SGLT1 inhibitors mainly lead to gastrointestinal loss of glucose. SGLT1 is responsible for glucose absorption from the intestine and reabsorption of about 10% of renal glucose from the proximal convoluted tubule, S3 segment. SGLT2 is responsible for 90% of glucose reabsorption from the S1 segment of the proximal renal tubule. The inhibition of glucose absorption from the intestine leads to reduction of postprandial glucose levels and increased GLP-1 release as a consequence of delayed glucose absorption (28). SOLOIST-WHF trial evaluated the effectiveness of sotagliflozin in patients with diabetes and recently worsening heart failure. Sotagliflozin is a dual SGLT1 and SGLT2 inhibitor with more SGLT1 inhibition compared to SGLT2 inhibition. The primary endpoint, death due to cardiovascular related causes and hospitalization due to heart failure were significantly low in sotagliflozin group.

GLP-1 receptor agonists

GLP-1 receptor agonists (GLP-1 RA) are an important yet expensive group of medicines considered mainly in patients with T2DM, which are recommended treatment options for those expecting weight loss or having cardiac or renal involvement. Glucagon-like peptide 1 (GLP-1) aids in glucose-dependent insulin secretion, increase in glucose uptake from peripheral tissues and delay gastric emptying.

ELIXA was the first cardiovascular outcome study conducted with the GLP-1 receptor agonist, Lixisenatide (30). The follow-up period was short (25 months) and about 25% dropped out due to side effects. It showed non-inferiority over placebo for 3-point MACE in patients with T2DM and recent acute coronary syndrome. However, Liraglutide, the next GLP-1 RA assessed, showed promising results in T2DM patients with high cardiovascular risk. These patients achieved a 2.3kg mean weight loss at the end of 36 months and had significantly reduced cardiovascular cause-related deaths. The rates of non-fatal MI, stroke and hospitalization due to heart failure were non significantly low compared to placebo (31). In a post-hoc analysis the subgroups with established atherosclerotic cardiovascular disease with or without past MI or stroke were to benefit more with reduced MACE compared to those who only had risk factors.

SUSTAIN 6 and PIONEER 6 assessed the effects of subcutaneous and oral semaglutide respectively. Subcutaneous semaglutide treatment did not reduce cardiovascular cause-related deaths, but a significant reduction of non-fatal stroke and nonsignificant reduction of myocardial infarction was noted (32). Oral semaglutide also showed noni-nferiority compared to placebo (33). Once weekly exenatide in the EXSCEL trial did not show cardiovascular superiority compared to placebo (34). Although a large number of patients were enrolled in to this trial, there were also a high rates of dropout due to side effects.

REWIND trial which was designed to assess the superiority of dulaglutide over placebo was carried out over a 5.4 years period. Compared to previous studies this included a lesser number of patients with previous cardiovascular events (31%) yet the primary outcome, which was the first occurrence of 3-point MACE was significantly lower in the dulaglutide group (35).

The GLP-1 receptor agonist class is quite diverse concerning its molecular structure, duration of action and potency. Therefore, it is not surprising that the findings of cardiovascular outcomes trials of these medications have differed. More potent and long-acting agents of this class have consistently shown to reduce 3-point MACE in clinical trials and compared to SGLT2 inhibitors cardiovascular benefits appear to take time, meaning the effects are probably through modification of atherosclerosis rather than haemodynamic changes. In contrast to SGLT-2 inhibitors, trials of GLP-1 receptor agonists have not shown any beneficial effect in heart failure and demonstrated only a neutral effect on rates of heart failure hospitalization.

Conclusion

Some of the newer antidiabetic agents have recently shown promising results in their cardiovascular outcome trials. Nevertheless, except few, the older generation of antidiabetic medicines have not yet proven to be non-beneficial in the context of cardiovascular disease as large-scale cardiovascular trials have not been conducted with these agents. The newer antidiabetic agents are expensive but may yet be cost-effective second line agents if used appropriately in T2DM patients with high cardiovascular disease risk.

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References

1. American Association of Diabetes. ADA standards of diabetes care 2021. Diabetes Care 2021;44:S1-2.
2. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Euro Heart J 2020;41:255-323
3. Bailey CJ. Metformin: historical overview. Diabetologia 2017;60:1566-76
4. UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS). Lancet 1998;352:837-53
5. Han Y, Xie H, Liu Y, et al. Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: A

systematic review and an updated meta-analysis. Cardiovasc Diabetol 2019;18:96

6. Kenny HC and Abel ED. Heart Failure in Type 2 Diabetes Mellitus. Circ Res 2019;124:121-41
7. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: An update of mechanisms contributing to this clinical entity. Circ Res 2018;122:624-38
8. Blackburn H and Jacobs DR. The University Group Diabetes Program 1961-1978: Pioneering randomized controlled trial. Int J Epidemiol 2017;46:1354-64
9. Simpson SH, Lee J, Choi S, et al. Mortality risk among sulfonylureas: A systematic review and network meta-analysis. Lancet Diabetes and Endocrinol 2015;3:43-51
10. Nakamura I, Oyama J, Komoda H, et al. Possible effects of glimepiride beyond glycemic control in patients with type 2 diabetes: A preliminary report. Cardiovasc Diabetol 2014;13:15
11. Kalra S, Aamir AH, Raza A, et al. Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. Indian J Endocrinol Metab 2015;19:577-96
12. Viberti G, Lachin J, Holman R, et al. A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care 2002;25:1737-43
13. Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: Systematic review and meta-analysis of observational studies. BMJ 2011;342:d1309
14. Lebovitz HE. Thiazolidinediones: the Forgotten Diabetes Medications. Curr Diab Rep 2019;19:151
15. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and Cardiovascular Outcomes in Patients with Type-2 Diabetes Mellitus. N Engl J Med 2013;369:1317–43.
16. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, et al. Glycemic control and heart failure among adult patients with diabetes. Circulation 2001;103:2668-73
17. Burns KD and Cherney D. Renal Angiotensinogen and Sodium-Glucose Cotransporter-2 Inhibition: Insights from Experimental Diabetic Kidney Disease. Am J Nephrol 2019;49:328-30
18. Ali A, Bain S, Hicks D, Phillip NJ, et al. SGLT2 Inhibitors: Cardiovascular Benefits Beyond HbA1c—Translating Evidence into Practice. Diabetes Ther 2019;10:1595-622
19. Bailey CJ. Uric acid and the cardio-renal effects of SGLT2 inhibitors. Diabetes Obes Metab 2019;21:1291-8
20. Steiner S. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. Zeitschrift fur Gefassmedizin 2016;13:16-8
21. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 2020;383:1413-24
22. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019;380:347-57
23. Colombo G, Casella R, Cazzaniga A, Casiraghi C. Dapagliflozin in patients with heart failure and reduced ejection fraction. Intern Emerg Med 2020;15:515-7
24. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017;377:644-57
25. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 2019;380:2295-306
26. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med 2020;383:1425-35
27. Cosentino F, Cannon CP, Cherney DZI, et al. Efficacy of Ertugliflozin on Heart Failure-Related Events in Patients with Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease: Results of the VERT CV Trial. Circulation 2020;142:2205-15
28. Cefalo CMA, Cinti F, Moffa S, et al. Sotagliflozin, the first dual SGLT inhibitor: Current outlook and perspectives. Vol. 18, Cardiovas Diabetol 2019;18:20
29. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and

Recent Worsening Heart Failure. N Engl J Med 2021;384:117-28

30. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med 2015;373:2247-57

31. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2016;375:311-22

32. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2016;375:1834-44

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

34. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2017;377:122

35. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121-30

Self-Assessment Questions – Newer antidiabetic medicines

1. A 62-year-old patient with T2DM for 8 years presented with poor glycemic control (HbA1c 8.0%). He was recently diagnosed with inferior ST-elevation myocardial infarction (ejection fraction 40%). With diuretics and other heart failure medications, he is now asymptomatic with no chest pain, shortness of breath or ankle oedema. He is currently on metformin 1g bd, gliclazide 160mg bd for his glycemic control. Which therapeutic options are suitable to improve glycemic control?

   A. Discontinue gliclazide and start on tolbutamide
   B. Add empagliflozin 10mg daily to existing regime
   C. Discontinue gliclazide and start on glibenclamide
   D. Add pioglitazone 30mg mane to existing regime
   E. Discontinue present oral medicines and start on twice daily premixed insulin

2. Which of the following are true about the antidiabetic medications?

   A. All DPP4 inhibitors have shown cardiovascular neutral effect
   B. SUSTAIN-6 study showed cardiovascular benefits of semaglutide
   C. Both SGLT2 and SGLT1 inhibitors have shown cardiovascular benefits
   D. It is mandatory to evaluate cardiovascular benefits of all new antidiabetic medications
   E. There is evidence that metformin may reduce the development of diabetic cardiomyopathy

3. A 48-year-old female with background history of T2DM and hypertension was admitted with symptoms of heart failure. She was started on empagliflozin 10mg daily by the cardiology team. Through which mechanisms does SGLT2 inhibitors reduce cardiovascular disease related risk?

   A. Blood pressure reduction
   B. Improved glycemic control
   C. Reduced serum uric acid concentration
   D. Plasma volume reduction
   E. All of the above

Self-Assessment Questions – Newer antidiabetic medicines (Answers)

1. F T F F T

Gliclazide and glimepiride have been shown to be safer options when it comes to cardiovascular risks compared to other sulfonylureas. Glibenclamide has higher risk of hypoglycaemia SGLT2 inhibitors are recommended by the current guidelines as add on therapy to metformin due to their cardiovascular benefits. Pioglitazone is not recommended in symptomatic heart failure especially in NYHA III or IV heart failure. Insulin can be considered a safe option for improvement of glycemic control if SGLT2 inhibitors are not available.

2. F T T F T

All but saxagliptin have shown cardiovascular benefits as it has shown increased hospitalization due to heart failure (SAVOR TIMI 53 trial). SUSTAIN 6 study has shown cardiovascular benefits for subcutaneous semaglutide. Since 2008, it is mandatory to show cardiovascular safety of any newly introduced antidiabetic medicines to gain FDA approval. Metformin exerts cardiovascular benefits through mTOR pathway and improving insulin sensitivity.

3. Answer - E

SGLT2 inhibitors are known to improve cardiovascular disease related deaths through all the above mentioned mechanisms.

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