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Our planet - our health

A time for humanity to unite and end all wars and together rescue our planetary home

Editorial

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In this issue a number of review and papers handled various topics of interest to primary care.

Dr. Abdulmohsin, reviewed mental health screening in primary care. This literature review explores the role of mental health screening in primary care settings. It provides an overview of the prevalence and impact of mental health disorders, the importance of early detection and intervention, and the challenges faced by primary care providers in identifying and managing mental health conditions. The review also examines various screening tools and strategies employed in primary care settings, highlighting their effectiveness and limitations. Finally, recommendations for future research and practice are discussed to enhance mental health screening and improve outcomes in primary care

Mansour et al., reviewed the literature relating to the long-term use of PPIs. PPIs are frequently use in hospitals, primary health care centers and private clinics. The adverse effects and interactions are numerous so, physicians' knowledge including accurate indications after confirmations of diagnosis, duration of use and follow-up are essential part of the treatment process. The authors reviewed the available evidence and summarized the long-term use of PPIs as indicated by major clinical guidelines, governmental agencies, and published studies. For instance, United states, Food and Drug Administration, American Gastroenterological Association, American Academy of Family Physicians, British National Formulary, National Institutes of Health, Randomized controlled trials, Systematic review, Meta-analysis and Observational studies. The authors concluded that this review will provide clinical practice with research evidence-based guidelines. Clinicians and physicians should follow the major clinical guidelines and governmental agencies to prescribe PPIs, follow their patients regularly to achieve the goals of treatment, to avoid adverse effects, drug interactions and reduce the costs.

Dr Rahman et al., reviewed the the use of anticoagulation with Direct Oral Anticoagulants (DOACs) for prevention of stroke in patients with Atrial Fibrillation and initiating in Primary care. Anticoagulation with direct oral anticoagulants (DOAC) is becoming increasingly more prominent for stroke prevention in patients with Atrial Fibrillation (AF). Whereas a vitamin k analogue like warfarin would traditionally be used for this; DOACs offer several advantages over warfarin. This review article will provide an overview of the current evidence supporting the use of DOACs for anticoagulation in AF and how a primary care clinician would go about choosing which DOACs to choose and considerations that need to be taken before initiation of the drug.

Helvaci*, et al., looked at Acute chest syndrome and coronavirus disease may actually be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries. Sickle cell diseases (SCD) are severe inflammatory processes on vascular endothelium, particularly at the capillaries since the capillary system is the main distributor of hardened red blood cells into the tissues. Similarly, coronavirus disease (COVID-19) may also be a genetically determined inflammatory process particularly in pulmonary capillaries with much higher mortality rates in some families. All patients with the SCD were studied. The study included 222 males and 212 females with similar mean ages (30.8 versus 30.3 years, $p>0.05$, respectively). Smoking (23.8% versus 6.1%, $p<0.001$), alcohol (4.9% versus 0.4%, $p<0.001$), cirrhosis (8.1% versus 1.8%, $p<0.001$), leg ulcers (19.8% versus 7.0%, $p<0.001$), digital clubbing (14.8% versus 6.6%, $p<0.001$), coronary heart disease (CHD) (18.0% versus 13.2%, $p<0.05$), chronic renal disease (CRD) (9.9% versus 6.1%, $p<0.05$), chronic obstructive pulmonary disease (COPD) (25.2% versus 7.0%, $p<0.001$), and stroke (12.1% versus 7.5%, $p<0.05$) were all higher but not acute chest syndrome (ACS) in males (2.7% versus 3.7%, $p>0.05$). the authors concluded that although smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, COPD, and stroke-like atherosclerotic end-points were all higher in males, prevalences of ACS were similar in both genders. In another definition, ACS and severe COVID-19 may be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries, and immunomodulatory drugs including dexamethasone probably should take the major role in the treatment.

Dr. AlDosari. Presented a case A Case Report of an Unexpected Rare Diagnosis in a Well-Baby Clinic at Primary Care Center in Qatar that is Arterial Tortuosity Syndrome. Arterial Tortuosity Syndrome (ATS) is a rare autosomal recessive genetic disorder characterized by significant alterations in the structure and function of the arterial system. Mutations in the SLC2A10 gene, responsible for encoding the transporter protein GLUT10, lead to the development of ATS. The syndrome is characterized by the elongation, twisting, and increased tortuosity of arteries, predisposing patients to a plethora of vascular complications, including aneurysms, stenosis, and tortuosity [1]. Adding to that, ATS affects connective tissues across various systems, leading to special facial features that can be recognizable at birth or later during early childhood [2]. Being rare and complex disorder signifies the importance of raising awareness among healthcare professionals, particularly in settings where genetic disorders might not be the first consideration such as well baby clinics where the parents bring their kids just for routine well baby follow up and vaccines.

Acute chest syndrome and coronavirus disease may actually be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries

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Abstract

Background: Sickle cell diseases (SCD) are severe inflammatory processes on vascular endothelium, particularly at the capillaries since the capillary system is the main distributor of hardened red blood cells into the tissues. Similarly, coronavirus disease (COVID-19) may also be a genetically determined inflammatory process particularly in pulmonary capillaries with much higher mortality rates in some families.

Methods: All patients with the SCD were studied.

Results: The study included 222 males and 212 females with similar mean ages (30.8 versus 30.3 years, p>0.05, respectively). Smoking (23.8% versus 6.1%, p<0.001), alcohol (4.9% versus 0.4%, p<0.001), disseminated teeth losses (5.4% versus 1.4%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (8.1% versus 1.8%, p<0.001), leg ulcers (19.8% versus 7.0%, p<0.001), digital clubbing (14.8% versus 6.6%, p<0.001), coronary heart disease (CHD) (18.0% versus 13.2%, p<0.05), chronic renal disease (CRD) (9.9% versus 6.1%, p<0.05), chronic obstructive pulmonary disease (COPD) (25.2% versus 7.0%, p<0.001), and stroke (12.1% versus 7.5%, p<0.05) were all higher but not acute chest syndrome (ACS), in males (2.7% versus 3.7%, p>0.05).

Conclusion: Although smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, COPD, and stroke-like atherosclerotic end-points were all higher in males, prevalence of ACS was similar in both genders. In another definition, ACS and severe COVID-19 may be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries, and immunomodulatory drugs including dexamethasone probably should take the major role in the treatment.

Key words: Acute chest syndrome, coronavirus disease, exaggerated immune response syndromes, sickle cell diseases, capillary endothelial inflammation, capillary endothelial edema, tissue hypoxia

Introduction

Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human beings (1). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus the term venosclerosis is not as famous as atherosclerosis in the medical literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature, and they eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, excess weight, animal-rich diet, smoking, alcohol, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, early aging, and premature death (2, 3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and aging, endothelial changes cannot be reversed completely due to their fibrotic nature. The accelerating factors and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the medical literature, extensively (4-6). On the other hand, sickle cell diseases (SCD) are a chronic inflammatory process on vascular endothelium, initiated at birth and terminated with accelerated atherosclerosis induced end-organ failures in both genders (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the major problem since sickling is rare in peripheric blood samples of the patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammation, infection, and various stresses of the body. The hardened RBC induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated tissue hypoxia all over the body (9). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level (10, 11), since the capillary system is the main distributor of the hardened cells into the tissues. The hardened RBC induced chronic endothelial damage builds up an advanced atherosclerosis in early years of life. Vascular narrowing and occlusions induced tissue ischemia and infarctions are the final consequences of the SCD, so the mean life expectancy is decreased by 25 to 30 years in such patients (8). Similarly, coronavirus disease (COVID-19) may actually be a genetically determined inflammatory process, particularly involving the pulmonary capillaries with much higher mortality rates in some families.

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD were included. The SCD were diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, transfused units of RBC in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (12). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since the SCD with associated thalassemia minors show a milder clinical presentation than the sickle cell anemia (SCA) alone (13). Systolic BP of the pulmonary artery of ≥40 mmHg are accepted as PHT (14). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of <70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (16). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a persistent serum creatinine level of ≥1.3 mg/dL in males and ≥1.2 mg/dL in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is >1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is performed

in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, mean age, associated thalassemia minors, smoking, alcohol, painful crises per year, transfused units of RBC in their lives, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, stroke, PHT, autosplenectomy, DVT and/or varices and/or telangiectasias, rheumatic heart disease, avascular necrosis of bones, sickle cell retinopathy, epilepsy, ACS, mortality, and mean age of mortality were detected in both genders, and compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 434 patients with the SCD (222 males and 212 females). Mean ages of the patients were similar in males and females (30.8 versus 30.3 years, $p>0.05$, respectively). Prevalence of associated thalassemia minors were similar in both genders, too (72.5% versus 67.9%, $p>0.05$, respectively). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were higher in males, significantly ($p<0.001$ for both) (Table 1). Similarly, transfused units of RBC in their lives (48.1 versus 28.5, $p=0.000$), disseminated teeth losses (5.4% versus 1.4%, $p<0.001$), ileus (7.2% versus 1.4%, $p<0.001$), cirrhosis (8.1% versus 1.8%, $p<0.001$), leg ulcers (19.8% versus 7.0%, $p<0.001$), digital clubbing (14.8% versus 6.6%, $p<0.001$), CHD (18.0% versus 13.2%, $p<0.05$), CRD (9.9% versus 6.1%, $p<0.05$), COPD (25.2% versus 7.0%, $p<0.001$), and stroke (12.1% versus 7.5%, $p<0.05$) were all higher in males, significantly. On the other hand, prevalence of ACS (2.7% versus 3.7%, $p>0.05$), PHT (12.6% versus 11.7, $p>0.05$), and DVT and/or varices and/or telangiectasias were similar in both genders (9.0% versus 6.6%, $p>0.05$), significantly (Table 2). Beside that when we look at the mean ages of the consequences, they were 30.3 and 34.0 years ($p<0.05$) in the ACS and PHT, respectively (Table 3).

Table 1: Characteristic features of the study cases

Variables	Male patients with SCD*	*p*-value	Female patients with SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated thalassemia minors	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	***<0.001***	***6.1% (13)***
Alcoholism	***4.9% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases †Nonsignificant (p>0.05)

Table 2: Associated pathologies of the study cases

Variables	Male patients with SCD*	*p*-value	Female patients with SCD
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBC‡	***48.1 ± 61.8 (0-434)***	***0.000***	***28.5 ± 35.8 (0-206)***
Disseminated teeth losses (<20 teeth present)	***5.4% (12)***	***<0.001***	***1.4% (3)***
COPD§	***25.2% (56)***	***<0.001***	***7.0% (15)***
Ileus	***7.2% (16)***	***<0.001***	***1.4% (3)***
Cirrhosis	***8.1% (18)***	***<0.001***	***1.8% (4)***
Leg ulcers	***19.8% (44)***	***<0.001***	***7.0% (15)***
Digital clubbing	***14.8% (33)***	***<0.001***	***6.6% (14)***
CHD¶	***18.0% (40)***	***<0.05***	***13.2% (28)***
CRD*	***9.9% (22)***	***<0.05***	***6.1% (13)***
Stroke	***12.1% (27)***	***<0.05***	***7.5% (16)***
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
ACS*****	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Coronary heart disease **Chronic renal disease ***Pulmonary hypertension ****Deep venous thrombosis *****Acute chest syndrome

Table 3: Mean ages of the consequences of the sickle cell diseases

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
ACS*	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth losses (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)
Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	33.5 ± 11.9 (9-58)
COPD†	33.6 ± 9.2 (13-58)
PHT‡	34.0 ± 10.0 (18-56)
Leg ulcers	35.3 ± 8.8 (17-58)
Digital clubbing	35.4 ± 10.7 (18-56)
CHD§	35.7 ± 10.8 (17-59)
DVT¶ and/or varices and/or telangiectasias	37.0 ± 8.4 (17-50)
Cirrhosis	37.0 ± 11.5 (19-56)
CRD**	39.4 ± 9.7 (19-59)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Coronary heart disease **Chronic renal disease ***Pulmonary hypertension ****Deep venous thrombosis *****Acute chest syndrome

Discussion

ACS is a significant cause of mortality in the SCD (19). It occurs most often as a single episode, and a past history is associated with a high mortality rate (19). Similarly, all of 14 cases with the ACS had just a single episode, and two of them were fatal in spite of the rigorous RBC and ventilation supports and antibiotic therapy in the present study. The remaining 12 patients are still alive without a recurrence at the end of the ten-year follow up period. ACS is the most common between the ages of 2 to 4 years, and its incidence decreases with aging (20). As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the present study, too, and the mean ages of the ACS and SCD were similar (30.3 and 30.5 years, $p>0.05$, respectively). The decreased incidence with aging may be due to the high mortality rate during the first episode and/or an acquired immunity against various antigens, and/or decreased strength of immune response. Probably, ACS shows an inborn severity of the SCD, and the incidence of ACS is higher in severe cases such as cases with the SCA or higher white blood cells (WBC) counts (19, 20). According to our experiences, the increased metabolic rate during infections accelerates sickling, thrombocytosis, leukocytosis, and vascular endothelial damage, and terminates with end-organ insufficiencies. ACS may also be a collapse of the lungs during such infections, and an exaggerated immune response syndrome against the abnormal RBC-induced diffuse endothelial damage may be important in the high mortality rate. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCD indicating a significant reduction of episodes of ACS with hydroxyurea therapy suggests that a considerable number of episodes are exaggerated with the increased numbers of WBC and platelets (PLT) (21). Similarly, we strongly recommend hydroxyurea therapy for all patients with the SCD which may also be a cause of the low incidence of ACS among our follow up cases (2.7% in males and 3.7% in females). Additionally, ACS did not show an infectious etiology in 66% of cases (19, 20), and 12 of 27 cases with ACS had evidence of fat embolism in the other study (22). Beside that some authors indicated that antibiotics do not shorten the clinical course (16, 23). Actually, some viral causes as in the COVID-19 may also be important here, and the actual causes of the exaggerated immune response are such viruses, and the anti-inflammatory and immunomodulatory drugs including dexamethasone may be important for the treatment of ACS, too. On the other hand, RBC support must be given early in the course of ACS since it has also prophylactic benefit. RBC support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBC and excessive WBC and PLT. So they prevent further sickling and the exaggerated immune response induced endothelial damage, not in the lungs alone instead all over the body. According to our observations, simple and repeated transfusions are superior to RBC exchange (24, 25). First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their surroundings, since RBC transfusions probably have the strongest analgesic effects during the severe painful crises. Actually, the decreased severity of pain by transfusions may also indicate the decreased inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications, including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange which needs trained staff and additional devices.

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Most patients will experience mild to moderate respiratory disease, and recover without a need for special treatment. However, some cases become seriously sick. Older individuals and those with underlying diseases such as SCD, HT, DM, PAD, COPD, CHD, CRD, cirrhosis, stroke, rheumatological disorders, or cancers are more likely to develop serious illness. But actually anyone can get the disease with COVID-19 and become seriously ill or die at any age even in the absence of the above predisposing factors. Genetic susceptibility may be one of the major risk factors to have the severe form of the disease since the COVID-19 mortality rates may be much higher in some families. And probably a genetically determined exaggerated immune response syndrome against the virus may be the chief underlying cause of the severity as in the ACS and rheumatic disorders. As in the ACS, probably the disease keeps whole body circulation but the respiratory capillaries are involved, particularly due to the highest viral load in them. This mechanism may also explain the pathophysiology of ACS, and there may be a superimposed viral infection involving the respiratory system. On the other hand, the capillary system of the respiratory tract may be the most sensitive capillaries against the immune damage in the body. The highest prevalence of lung cancers in both genders among all of the other cancers may also support the hypothesis. So both the ACS and severe COVID-19 may prominently be a vasculitis, and the anti-inflammatory and immunomodulatory drugs including dexamethasone probably should take the major role in the treatment. On the other hand, since the virus is changing its genetic codes continuously, probably all people will get the disease several times with different severity in their lives. Thus the chance of getting a severe form of the disease is always present for all individuals in the world. Even such an infection superimposed on aging or several predisposing factors induced atherosclerotic end-points may be the terminal drop of life for all individuals.

PHT is a condition of increased BP within the arteries of the lungs. Shortness of breath, fatigue, chest pain, palpitation, swelling of legs and ankles, and cyanosis are common symptoms of PHT. Actually, it is not a diagnosis itself, instead solely a hemodynamic state characterized by resting mean pulmonary artery pressure of ≥25 mmHg. An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with PHT (26). The cause is often unknown. The underlying mechanism typically involves inflammation, fibrosis, and subsequent remodelling of the arteries. PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years (27). Onset is typically seen between 20 and 60 years of age (28). The most common causes are left heart diseases and chronic inflammatory pathologies of the lung, particularly CHD and COPD (28, 29). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (30). But the pulmonary vascular remodeling in the COPD may have a much more complex mechanism than just being the medial hypertrophy secondary to the long-lasting hypoxic vasoconstriction alone (30). In fact, all layers of the vessel wall appear to be involved with prominent intimal changes (30). The specific pathological picture could be explained by the combined effects of hypoxia, prolonged stretching of hyperinflated lungs-induced mechanical stress and inflammatory reaction, and the toxic effects of cigarette smoke (30). According to World Health Organization, there are five groups of PHT including pulmonary arterial hypertension, PHT secondary to left heart diseases, PHT secondary to lung diseases, chronic thromboembolic PHT, and PHT with unknown mechanisms (28). On the other hand, PHT is also a common consequence of the SCD (31), and its prevalence was detected between 20% and 40% in the SCD (32), whereas we detected the ratio as 12.2% in the present study. Although the higher prevalence of smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic events in males, and the male gender alone is a risk factor for the systemic atherosclerosis, the similar prevalence of PHT and ACS in both genders also support their nonatherosclerotic nature in the SCD, here. Additionally, as a risk factor for pulmonary thromboembolic events, frequencies of DVT and/or varices and/or telangiectasias were similar in males and females (9.0% versus 6.6%, p>0.05, respectively), parallel to ACS and PHT. Similarly, CHD is the other most common cause of PHT in society (33), and although the higher prevalence of CHD in males in the present study (18.0% versus 13.2%, p<0.05), PHT was not higher in them again. In another definition, PHT may have a hardened RBC-induced chronic, whereas ACS an acute thromboembolic background in the SCD (34, 35) since the mean age of ACS is much lower (30.3 and 34.0 years, p<0.05), and its mortality is much higher than the PHT (19, 20, 28).

COPD is the third leading cause of death with various causes all over the world (36, 37). Male gender, aging, smoking, and excess weight may be the major underlying etiologies. As also observed in the present study, regular alcohol consumption may also be important in the pulmonary and systemic inflammatory process. For example, COPD was one of the most common diagnoses in alcohol dependence (38). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (39). Probably an accelerated atherosclerotic process is the main structural background of functional changes, characteristic of COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced atherosclerosis, fibrosis, and pulmonary losses. COPD may actually be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body (40, 41). For example, there may be close relationships between COPD, CHD, PAD, and stroke (42). Furthermore, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5,887 smokers (43). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (43). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (44). In another definition, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBC in the SCD (36).

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (45). Although the exact cause and significance is unknown, chronic tissue hypoxia is highly suspected (46). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But, according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, or hepatic diseases or smoking, all of which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs and their functions are affected in a short period of time. On the other hand, digital clubbing is also common in patients with the SCD, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% versus 6.6%, p<0.001) may also show some additional role of male gender on the systemic atherosclerotic process.

Leg ulcers are seen in 10% to 20% of the SCD (47), and the ratio was 13.5%, here. Its prevalence increases with aging, male gender, and SCA (48). Similarly, its ratio was higher in males (19.8% versus 7.0%, p<0.001), and mean age of the leg ulcer cases was higher than the others (35.3 versus 29.8 years, p<0.000) in the present study. The leg ulcers have an intractable nature, and around 97% of them

relapse in a period of one year (47). As evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (47). The hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major cause in the SCD (48). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, probably pooling of blood is the cause of delayed wound and fracture healings in the lower extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (49). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (11). Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD (50). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (51). According to our experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts induced exaggerated endothelial inflammation, edema, and fibrosis at the capillary level.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (6). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it became the most common cause of chronic liver disease even in childhood nowadays (52). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (52). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalence of cardiovascular diseases (53). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (54). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCD (9, 55). Probably smoking also takes a role in the endothelial inflammatory process of the liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (56). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol are prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious and inflammatory processes may also terminate with an accelerated atherosclerosis all over the body (57). For example, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (57, 58). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may also be found among the systemic atherosclerotic consequences of the SCD.

The increased frequency of CRD may be explained by aging of the human being as well as increased prevalence of excess weight, all over the world (59, 60). Aging, physical inactivity, excess weight, smoking, alcohol, and inflammatory or infectious processes may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged renal tissues, especially endothelial cells of the renal arterioles. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis and tissue hypoxia and infarcts. Excess weight induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause tissue inflammation and immune cell activation (61). For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (60). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess weight (62). Excess weight also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (62). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in the long term that causes chronic endothelial damage (63). With prolonged weight excess, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess weight, CRD progresses much more easily (62). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (64). The inflammatory and atherosclerotic effects of smoking are much more prominent in the respiratory endothelium due to the highest concentrations of its metabolites there. Although some authors reported that alcohol was not related with the CRD (64), various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis on the renal

endothelium (57). Although CRD is mainly an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (65). For example, the most common cause of death was the cardiovascular diseases in the CRD (66). In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD too (67).

Stroke is an important cause of death, and an acute thromboembolic event on the atherosclerotic background is the most common cause. Male gender, aging, smoking, alcohol, and excess weight and its consequences may be the major triggering causes. Stroke is also a common complication of the SCD (68, 69). Similar to the leg ulcers, stroke is particularly higher in the SCA and cases with higher WBC counts (50, 70). Sickling induced endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic endothelial inflammation, edema, and fibrosis (71). Probably, stroke is a terminal event in the SCD, and it may not have a macrovascular origin, instead disseminated capillary inflammation, edema, and fibrosis may be much more important. Infections and other stresses may precipitate the stroke, since increased metabolic rate during such events may accelerate sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases develop secondary to the increased WBC and PLT induced exaggerated capillary inflammation, edema, and fibrosis (21).

The venous endothelium is also involved in the SCD (72). For example, varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Normally, leg muscles pump veins against gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. DVT may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus physical examination must be performed in upright position. Although the younger mean ages of the patients of the present study (30.8 and 30.3 years in males and females, respectively), and significantly lower body mass index of the SCD patients in the literature (10), DVT and/or varices and/or telangiectasias of the lower limbs were higher in the study cases (9.0% versus 6.6% in males and females, p>0.05, respectively), indicating an additional venous involvement in the SCD. Similarly, priapism is the painful erection of penis that cannot return to its flaccid state within four hours in the absence of any stimulation (73). It is an emergency since damage to the blood vessels may terminate with a long-lasting fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis (73). It is seen with hematological and neurological disorders including SCD, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (74, 75). Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types of priapism (76). Ninety-five percent of clinically presented priapisms are the ischemic (veno-occlusive) disorders in which blood cannot return adequately from the penis as in the SCD, and they are very painful (73, 76). The other 5% are nonischemic (arterial) type usually caused by a blunt perineal trauma in which there is a short circuit of the vascular system (73). Treatment of arterial type is not as urgent as the veno-occlusive type due to the absence of risk of ischemia (73). RBC support is the treatment of choice in acute phase in the SCD (77). Whereas in chronic phase, hydroxyurea should be the treatment of choice. According to experiences, hydroxyurea is an effective drug for prevention of attacks and consequences of priapism if iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls if initiated later in life.

Conclusion

Although smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, COPD, and stroke-like atherosclerotic end-points were all higher in males, prevalence of ACS was similar in both genders. In another definition, ACS and severe COVID-19 may be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries, and immunomodulatory drugs including dexamethasone probably should take the major role in the treatment.

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Review of the use of anticoagulation with Direct Oral Anticoagulants (DOACs) for prevention of stroke in patients with Atrial Fibrillation and initiating in Primary care

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Abstract

Anticoagulation with direct oral anticoagulants (DOAC) is becoming increasingly more prominent for stroke prevention in patients with Atrial Fibrillation (AF). Whereas a vitamin k analogue like warfarin would traditionally be used for this; DOACs offer several advantages over warfarin.

This review article will provide an overview of the current evidence supporting the use of DOACs for anticoagulation in AF and how a primary care clinician would go about choosing which DOACs to choose and considerations that need to be taken before initiation of the drug.

Keywords:
Direct Oral Anticoagulants, atrial fibrillation, stroke, primary care, anticoagulation, warfarin

Introduction

Atrial Fibrillation is a common cardiac arrhythmia characterised by irregular and rapid heartbeats. Patients with AF face an increased risk of stroke compared to those without this cardiac arrhythmia. AF disrupts the normal rhythm of the heart, leading to ineffective blood pumping and potential blood pooling in the atria. This stasis can contribute to the formation of blood clots, particularly in the left atrial appendage. If these clots travel to the brain, they can cause a stroke. Due to the high risk of stroke, anticoagulation is commonly prescribed in patients with AF.

DOACs have quickly become a very popular choice when it comes to anticoagulation as an alternative to the long standard use of warfarin . This review article will only focus on the use of DOACs for stroke prevention in AF, however, they are also increasingly being used in venous thromboembolism (VTE) prophylaxis and treatment.

Mechanism of action of DOACs

Direct oral anticoagulants (DOACs) are a class of anticoagulant medications that act by directly inhibiting specific coagulation factors. There are four DOACs approved for use: dabigatran, rivaroxaban, apixaban, and edoxaban. A brief overview of their mechanisms of action can be seen below

1. Dabigatran - Dabigatran is a direct thrombin inhibitor. It binds directly to thrombin (also known as factor IIa), inhibiting its activity. Thrombin is a key enzyme in the coagulation cascade, converting fibrinogen into fibrin, and promoting platelet activation. By inhibiting thrombin, dabigatran prevents the formation of fibrin clots (1).

2. Rivaroxaban and Apixaban- Rivaroxaban and Apixaban are factor Xa inhibitors. They specifically target factor Xa, which plays a crucial role in the coagulation cascade by facilitating the conversion of prothrombin to thrombin. By inhibiting factor Xa, these medications prevent the formation of thrombin and subsequent blood clotting (2)(3).

3. Edoxaban - Edoxaban is another factor Xa inhibitor. Similar to rivaroxaban and apixaban, it acts by inhibiting factor Xa to interfere with the coagulation process and prevent blood clot formation (4).

Review of clinical trials

Several large randomized controlled trials (RCTs) have evaluated the efficacy and safety of anticoagulation with DOACs in AF patients.

• **The RE-LY trial** compared *Dabigatran*, a direct thrombin inhibitor, to warfarin in over 18,000 patients with AF. Dabigatran was found to be non-inferior to warfarin in preventing stroke or systemic embolism and had a lower risk of major bleeding. Dabigatran 150mg BD demonstrated superiority over warfarin in reducing risk of stroke and systemic embolism (5).

• **The ROCKET-AF** trial compared *Rivaroxaban,* a factor Xa inhibitor, to warfarin in over 14,000 patients with AF. Rivaroxaban was found to be non-inferior to warfarin in preventing stroke or systemic embolism and had a similar risk of major bleeding (6).

• **The ARISTOTLE trial** compared *Apixaban*, another factor Xa inhibitor, to warfarin in over 18,000 patients with AF. Apixaban was found to be superior to warfarin in preventing stroke or systemic embolism and had a lower risk of major bleeding (7).

• **The ENGAGE-AF-TIMI 48 trial** compared *Edoxaban*, another factor Xa inhibitor, to warfarin in over 21,000 patients with AF. Edoxaban was found to be non-inferior to warfarin in preventing stroke or systemic embolism and had a lower risk of major bleeding (8).

Advantages of DOACs over warfarin

• **Predictable pharmacokinetics -** DOACs exhibit more predictable pharmacokinetics compared to warfarin, leading to a more stable anticoagulant effect (5).

• **Reduced risk of major bleeding -** Clinical trials have shown that DOACs are associated with a lower risk of major bleeding, particularly intracranial haemorrhage, compared to warfarin in patients with atrial fibrillation (7)(9).

• **No routine monitoring -** Unlike warfarin, DOACs do not require routine monitoring of international normalized ratio (INR), simplifying the management of anticoagulation therapy (10).

• **Fixed dosing-** DOACs are typically administered in fixed doses, eliminating the need for frequent dose adjustments based on INR values, which is necessary with warfarin (11).

• **Few drug and food interactions -** DOACs have fewer interactions with other drugs and foods compared to warfarin, reducing the complexity of managing coexisting conditions (12).

• **Rapid onset and offset of action -** DOACs have a faster onset of action and a shorter half-life compared to warfarin, allowing for quicker achievement of therapeutic levels and a more rapid offset when discontinuing treatment (6).

• **Similar or improved efficacy in stroke prevention -** DOACs have demonstrated similar or improved efficacy in preventing stroke and systemic embolism compared to warfarin in patients with atrial fibrillation (8)(13).

• **Improved patient adherence -** The simplified dosing regimens and lack of routine monitoring with DOACs may contribute to better patient adherence compared to warfarin (14).

• **Easier to initiate in primary care –** DOACs are far easier to initiate in primary care due to their reduced monitoring needs.

Review of clinical trials

Determining risk of stroke and bleeding risk

Once AF has been diagnosed in a patient – the clinician will need to work out the patients' risk of stroke and counter this against the risk of bleeding.

CHA2DS2-VASc score is a tool used to assess stroke risk.

HAS- BLED or ORBIT is a tool used to work out the bleeding risk. NICE guidelines recommend the use of ORBIT as a bleeding risk tool (21).

The tables below show how the scores can be calculated using the above-mentioned tools.

CHA_2DS_2-VASc	Risk of stroke/TIA/systemic embolism (%/year)
0	0.3%
1	0.9%
2	2.9%
3	4.6%
4	6.7%
5	10%
6	13.6%
9	17.4%

Tool to assess stroke risk (19)

- CHA2DS2-VASc score- 0 if male or 1 if female- No anticoagulation treatment required
- CHA2DS2-VASc score- 1 if male- Consider Anticoagulation
- CHA2DS2-VASc score ≥2 in any patient- Offer anticoagulation

CHA_2DS_2-VASc	Score
Congestive heart failure	1
Hypertension	1
Age>75	1
Diabetes Mellitus history	1
Stroke/TIA/Systemic arterial embolism	1
Vascular disease (previous MI, peripheral arterial disease, aortic plaque)	1
Age 65 to 74	1
Sex	1
Total score (maximum score 9)	

Bleeding risk tools

HAS-BLED	Score
Hypertension (uncontrolled, >160mmHg systolic)	1
Chronic liver disease or bilirubin 2 x upper limit normal(ULN) with AST/ALT/ALP 3x ULN	1
Abnormal U+Es (creatinine ≥200µmol/L. CrCl <50ml/min, renal transplant or chronic dialysis)	1
Ischaemic or haemorrhagic stroke	1
History of major bleeding or predisposition	1
Labile INRs, time in range of 2-3 less than 60%	1
Elderly (age≥65 or frail condition)	1
Drugs (concomitant antiplatelet, NSAIDs), or alcohol of ≥8 units/week (1 point each)	1 or 2
Total score (maximum score 9)	

HAS-BLED	Major bleed per 100 patient years	Risk group
0	1.13	Relatively low
1	1.02	
2	1.8	Moderate
3	3.74	High
4	8.7	
5	12.5	
6-9	Insufficient data	Very high

ORBIT	Score
Men: Haemoglobin <13g/L or heamatocrit<40% Women: Haemoglobin <12g/L or haematocrit <36%	2
Age > 74 years	1
Bleeding history (Any history of GI bleeding, intracranial bleeding, or haemorrhagic stroke)	2
GFR<60ml/min/1.73m²	1
Treatment with antiplatelet agents	1
Total Score (maximum score 7)	

ORBIT score	Major bleed per 100 patient years	Risk group
0-2	2.4	Low
3	4.7	Medium
4-7	8.1	High

(19)

For most patients, the benefit of anticoagulation will outweigh the bleeding risk. For people with an increased risk of bleeding, the benefit of anticoagulation may not always outweigh bleeding risk, and careful monitoring of bleeding risk is important.

People with a higher bleeding risk can have some of their modifiable risk factors addressed first and thereafter their suitability for anticoagulation can be reassessed. For example, a patient with uncontrolled hypertension can have their medications optimised, NSAIDS can be stopped for alternatives, reversible causes of anaemia can be treated, and harmful alcohol consumption can be reduced.

Contraindications for using DOACs in AF in primary care

There are instances where the use of DOACs are not suitable for the following patients with AF, and alternative anticoagulation like warfarin should be considered (15).

- Those with a prosthetic mechanical heart valve
- With moderate to severe mitral stenosis
- With antiphospholipid syndrome
- Those who are pregnant, breastfeeding or planning a pregnancy
- With severe renal impairment- Creatinine clearance (CrCl) <15ml/min
- Requirement for triple therapy (dual antiplatelet plus oral anticoagulant or those requiring a higher INR than the standard INR range of 2.0-3.0 without appropriate discussion with an anticoagulant specialist/cardiologist)
- With active malignancy/chemotherapy (unless advised by a specialist)
- Prescribed interacting drugs - common examples include: (16)

1) Strong inhibitors of P-glycoprotein and CYP3A4- e.g. azole antifungals, HIV protease inhibitors
2) Strong inducers of P- glycoprotein – eg carbamazepine, phenobarbital, phenytoin, rifampicin, St John's Wort
3) Inhibitors of P- glycoprotein and/or CYP3A4 (to use with caution)– e.g. amiodarone, diltiazem, verapamil, ticagrelor, Azithromycin, erythromycin, clarithromycin. Tamoxifen, grapefruit

- If patient has a lesion or condition considered a significant risk for major bleeding, including current or recent gastrointestinal ulceration, recent brain or spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities- seek specialist advice.

Initiating the correct DOAC for the individual patient

As already discussed there are 4 DOACs that can be used for anticoagulation in AF patients.

Considering contraindications as discussed already we can now move on to determine how to choose the right DOAC for each patient.

Initially a full blood screening should be done for the patient including – Full blood count, clotting screen (including INR), LFTs, U+Es, TFTs. (If patient's platelets are <100 x 109/L, unstable haemoglobin or INR>1.3 then discussion with haematologist should be had before initiating DOACs).

The weight of the patient should also be taken at this stage.

The next step would then be to work out the creatinine clearance (CrCl) for the patient using the Cockcroft-Gault equation. Studies have demonstrated that using this equation allows for more appropriate dosing of DOACs and minimises the risk of over anticoagulation (18).

Cockcroft-Gault Equation

$$\text{Creatinine Clearance (ml/min)} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}^{*} \times \text{constant}}{\text{Serum Creatinine } (\mu\text{mol/L})}$$

Constant = 1.23 for male and 1.04 for female

Once a creatinine clearance has been worked out appropriate dosing can then be done for the patients as can be seen in the following table.

	Standard dose for AF	Reduced dose for AF	Reasons for dose reduction	Contraindications
Apixaban	5mg Twice daily	2.5mg twice daily	2 or more of the following: • Age≥80 years • Body weight ≤60kg • Creatinine≥133µmol/L Or CrCl 15-29ml/min	CrCl <15ml/min
Dabigatran	150mg twice daily	110mg twice daily	• Age≥80 years • On verapamil • Consider reduced dose for: i) Reflux/gastritis ii) Age 75-80 years iii) CrCl 30-50ml/min iv) Bleed risk	CrCl<30ml/min
Edoxaban	60mg once daily	30mg once daily	1 or more of the following: • CrCl 15-50ml/min • Body weight ≤60kg • On medications including: ciclosporin. Dronedarone, erythromycin, ketoconazole	CrCl <15ml/min
Rivaroxaban	20mg once daily	15mg once daily	CrCl 15-49ml/min	CrCl<15ml

Monitoring patients on DOACs

Once the appropriate DOAC has been initiated for the patient, there are certain things that need to be monitored in order to ensure safe prescribing for the patient. This is however, significantly less monitoring required compared to warfarin.

The follow up and monitoring requirements can be seen as below
1 month and then on each visit - the patient should be instructed to come back for a review in which case the following should be looked at.
• check adherence to medication.
• any thromboembolism that has occurred- e.g. TIA, stroke, peripheral
• bleeding that may have occurred for the patient and if there are any preventative measures possible like ppi
• side effects
• co-medication- this is to review any possible interactions with any other medications (prescribed or over the counter medication)

Parameters needed for monitoring patients on DOAC

Patient demographics	Monitoring interval	Parameters
All patients on DOACs	Annually	FBC, U+Es, LFTs, weight, and calculate CrCl
Patients over 75 years and/or frail	6 monthly	FBC, U+Es, LFTs, weight
CrCl 30-60mL/min	6 monthly	U+Es
CrCl 15-30mL/ml	3 monthly	U+Es
Any patients with intercurrent illness that could affect hepatic or renal function	Individually agreed	U+Es, LFTs +/- FBC

(19)

NICE CKS guidance also states that patients should be checked X- monthly[1]- if impaired renal function and CrCl <60ml/min. X months can be worked out using the following formula

[1]X months = CrCl ÷ 10
e.g. Patient with a CrCl of 40 would need monitoring every (40/10) = 4 monthly

Switching from warfarin to DOAC

There are many situations where patients are already taking warfarin as anticoagulation for AF. Some of these patients can be considered to switch to DOACs.

The following process should be considered for switching from warfarin to DOAC as seen below (20)
1. Ensure no contraindications to DOACs
2. Involve patient in a shared decision-making process with consent to switch
3. Check bloods for recent FBC, U+Es and LFTs within the last 3 months and calculation of CrCl.
4. Check INR

If INR ≤ 2	Stop warfarin and commence DOAC on same day
If INR 2-2.5	No warfarin that day and commence DOAC the next day
If INR 2.5-3	Miss 2 or 3 doses of warfarin and start DOAC
If INR ≥3	Recheck INR and then as above

Conclusion

DOACs are increasingly used now as the anticoagulation agent of choice for patients with AF. As discussed earlier there are many advantages to this but most importantly for primary care physicians; it is the fact that it is a lot easier to initiate in primary care that makes it so useful. Traditionally patients who were diagnosed in primary care with AF would need to be referred to an anticoagulation clinic to initiate warfarin due to the rigid monitoring requirements including regular INR checking. This would then cause a delay in initiating anticoagulation for the patient which in the interim could ultimately increase the risk of stroke in these patients.

Starting anticoagulation in primary care is a relatively new management option, therefore not all primary care physicians are confident in doing so. This review article should act as a basic guide for primary care physicians in initiating DOACs.

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The Wise Long-Term Use of Proton Pump Inhibitors PPIs among Adults in Hospitals, Health Centers and Clinics

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Abstract

Background: PPIs are frequently used in hospitals, primary health care centers and private clinics. The adverse effects and interactions are numerous so, physicians' knowledge including accurate indications after confirmations of diagnosis, duration of use and follow-up are an essential part of the treatment process.

Aim: The purpose of this review tis o help health care professionals to prescribe the PPIs wisely and appropriately.

Objective: To undertake a review of the literature relating to the long-term use of PPIs

Data Sources: United States, Food and Drug Administration [FDA], PubMed, Scopus, Science Direct, Wiley, Google Scholar, major clinical guidelines, and governmental agencies.

Data Extraction: The 2 reviewers Musa Basheer Mansour and Sara Ahmedana [MBM and SEA] independently assessed the qualities of the extracted studies and summarized data of the studies for outcomes of interest and performed quality assessments based on review of published articles and the data sources.

Results: We reviewed the available evidence and summarized the long-term use of PPIs as indicated by major clinical guidelines, governmental agencies, and published studies. For instance, United States, Food and Drug Administration, American Gastroenterological Association, American Academy of Family Physicians, British National Formulary, National Institutes of Health, Randomized controlled trials, Systematic review, Meta-analysis and Observational studies.

Conclusion: This review will provide clinical practice with research evidence-based guidelines. Clinicians and physicians should follow the major clinical guidelines and governmental agencies to prescribe PPIs, follow their patients regularly to achieve the goals of treatment, to avoid adverse effects, drug interactions and reduce the costs.

Keywords: Proton Pump Inhibitors, Food and Drug Administration, Gastrointestinal Acid Disorders, Gastro-Esophageal Reflux Disorder, and peptic ulcer disease

Introduction

Proton Pump Inhibitors (PPIs) are most prescribed and used medications worldwide, since 1989 in both primary health care and in hospitals accounting for over $11 billion in expenditures annually [1,2. These drugs have enabled improved treatment of many gastrointestinal acid disorders [GIAD] and ulceration such as, Gastro-Esophageal Reflux Disorder [GERD], dyspepsia, and peptic ulcer disease [PUD] in more than 25% of the population and prevention of gastrointestinal bleeding for those who used Non-Steroid Anti-Inflammatory Drugs [NSAIDs], Aspirin or antiplatelets [3]. With an estimated 113 million PPIs prescriptions yearly, they remain one of the top-selling drug classes in United State of America [USA] [4]. The side effects and drug interactions of these drugs are reported to be enormous if used for more than 12 weeks. Therefore, the physicians should be aware about PPIs and how to use them wisely according to major guidelines and recommendations considering the patients' safety. It was observed that many patients attending hospital, private clinics, and health centers with peptic acid related health problems have been prescribed PPIs for longer duration contrary to the evidence from international best practice guidelines which suggest that these drugs should be prescribed for a definitive time depending upon the confirmed diagnoses. The PPIs have been reported to be more efficient in gastric acid suppression than the H2-receptot blockers[5]. However, evidence has shown that their long-time use has caused many side effects [6]. The first-generation PPIs (omeprazole, Pantoprazole and lansoprazole) are degraded by hepatic enzymes CYP2C19 and second-generation PPIs (esomeprazole and rabeprazole) are more stable and their plasma concentration is not strongly influenced by different CYP2C19 hepatic enzyme activities [7,8] although their plasma half-life is only 2-3 hours.

Purposes of the Review

Aim: The purpose of this review is to help health care professionals to prescribe the PPIs wisely and appropriately and, to undertake a review of the literature relating to the long-term use of PPIs

Objective: This review was designed for health care professionals to prescribe the PPIs wisely and appropriately, to follow their patients regularly to achieve the goals of treatment, to avoid adverse effects, drug interactions and reduce the costs.

Abbreviations

ACS Acute Coronary Syndrome
AIN Acute Interstitial Nephritis
CAP Community-Acquired Pneumonia
CI Confidence Interval
ECL Enterochromaffin-like
FDA Food and Drug Administration
GI Gastro-intestinal
GIT Gastro-intestinal Tract
GERD Gastroesophageal Reflux Disease
GIAD Gastrointestinal Acid Disorders
HR Hazard Ratio
HC Health Center
ICUs Intensive-care Units
N/A Not Applicable
NSAIDs Non-Steroids Anti-Inflammatory Drugs
OR Odds Ratio
PHCC Primary Health Care Corporation
PPIs Proton Pump Inhibitors
PUD Peptic Ulcer Disease
RCTs Randomized Controlled/Clinical Trials
SIBO Small Intestinal Bacterial Overgrowth
SLE Subcutaneous lupus erythematosus
SUP Stress Ulcer Prophylaxis
USA United State of America
ZES Zollinger-Ellison syndrome

Target

In the medical field: all physicians with specialty in family medicine, general practice, general medicine, gastroenterology, and general surgery.

The users of PPIs: all patients who are presenting with one of the following medical problems; GIAD, GERD, PUD, long term users of NSAIDs.

Indications and Standards

FDA release numerous safety statements and publish recommendations for PPIs use for the following areas only, either as short-term use or long-term therapy. PPIs are prescribed to the patients at appropriate dose for the right duration based on their specific diagnosis as listed below [9].

- Treatment of gastroesophageal reflux disease.
- Healing of erosive esophagitis.
- Maintenance treatment for healed erosive esophagitis.
- Treatment of gastric and duodenal ulcers.
- Treatment and prophylaxis for NSAID-induced ulcers.
- Management of pathologic hypersecretory conditions (including Zollinger-Ellison syndrome).

FDA-approved indications and doses for PPIs therapy. [1,6,9,10] [Tables 1, 2 and 3]

Table 1. FDA-Approved Indications and Doses for PPI Therapy [9]

FDA-Approved Indications	Omeprazole	Esomeprazole	Pantoprazole	Lansoprazole	Dexlansoprazole	Rabeprazole
Duodenal ulcer (treatment)	20 mg once a day	Not Applicable [N/A]	N/A	15 mg once a day for 4 weeks	N/A	20 mg once a day for 4 weeks
Duodenal ulcer (maintenance)	N/A	N/A	N/A	15 mg once a day	N/A	N/A
H pylori eradication (duodenal ulcer, reduce risk of recurrence)	Triple therapy: 20 mg bid for 10 days Dual therapy: 40 mg once a day for 14 days	Triple therapy: 40 mg once a day for 10 days	N/A	Triple therapy: 30 mg bid for 10–14 days Dual therapy: 30 mg tid for 14 days	N/A	Triple therapy: 20 mg bid for 7 days
Erosive esophagitis (treatment)	20 mg once a day for 4–8 weeks	20 mg or 40 mg once a day for 4–8 weeks, longer course may be warranted	40 mg once a day for up to 8 weeks	30 mg once a day for up to 8 weeks	60 mg once a day for up to 8 weeks	N/A
Erosive esophagitis (maintenance)	20 mg once a day	20 mg once a day	40 mg once a day	15 mg once a day	30 mg once a day	N/A
GERD (healing of erosive or ulcerative)	N/A	N/A	N/A	N/A	N/A	20 mg once a day for 4–8 weeks
GERD (maintenance of healing for erosive or ulcerative)	N/A	N/A	N/A	N/A	N/A	20 mg once a day
GERD (non-erosive symptomatic)	20 mg once a day for up to 4 weeks	20 mg once a day for longer course may be warranted	N/A	15 mg once a day for up to 8 weeks	30 mg once a day for 4 weeks	20 mg once for 4 weeks
Gastric ulcer (benign short-term treatment)	40 mg once a day for 4–8 weeks	N/A	N/A	30 mg once a day for up to 8 weeks	N/A	N/A
Gastric ulcer (NSAID-associated)	N/A	N/A	N/A	30 mg once a day for up to 8 weeks	N/A	N/A
Gastric ulcer (risk reduction of NSAID-associated)	N/A	20 mg or 40 mg once a day for up to 6 months	N/A	15 mg once a day for up to 12 weeks	N/A	N/A
Heartburn OTC treatment	20 mg once a day for 14 days, may repeat every 4 months	N/A	N/A	15 mg once a day for 14 days	N/A	N/A
Pathological hypersecretory conditions	60 mg once a day, may adjust to patient needs	N/A	40 mg bid, may increase up to 240 mg	60 mg once a day, may adjust to patient needs	N/A	60 mg once a day, may adjust

Table 2: Appropriateness of Long and Short term PPIs Therapy in 13 Clinical Scenarios of Uncertainty and Common Misuse [10]

Long term PPIs therapy appropriate > 12 weeks	Barrett's esophagus. Healing and maintenance of healed Los Angeles grade C or D erosive esophagitis. PPI-responsive esophageal eosinophilia. Idiopathic (H. pylori and NSAID/aspirin negative) peptic ulcer disease. Zollinger–Ellison disease. PPI-responsive GERD/non-erosive reflux disease. Long-term non-selective NSAID users at high-risk for upper GI complications or long-term cox-2 inhibitor users with a prior episode of GI bleeding. Anti-platelet therapy in patients at high-risk for upper GI complications (age > 65 years or concomitant use of corticosteroids or anticoagulants or history of peptic ulcer disease). Steatorrhea refractory to enzyme replacement therapy in chronic pancreatitis.
Short-term PPIs therapy appropriate (4- to 12-week course)	Healing of Los Angeles grade, A or B erosive esophagitis. Eosinophilic esophagitis. H. pylori eradication (in combination with antibiotics). Stress ulcer prophylaxis in high-risk patients (i.e., critically ill patients with respiratory failure or coagulopathy). Functional dyspepsia. Treatment and maintenance of peptic ulcer disease. Prior to endoscopy for acute upper GI bleeding. Following endoscopic treatment of a high-risk ulcer GI bleed.
PPI use not appropriate for	Corticosteroid users without concomitant NSAID therapy. To prevent bleeding from hypertensive gastropathy in cirrhotic patients. Acute pancreatitis. Stress ulcer prophylaxis in non-critically ill hospitalized patients who are not at high-risk for ulcer formation and GI bleeding
PPIs use of uncertain benefit	• PPI non-responsive GERD • Extra-digestive GERD

Table 3: Current Indications of PPIs [6]

Clinical setting	PPIs duration and dose
GERD	
1-Erosive Esophagitis (A/B)	Standard dose PPI therapy for 8-12 weeks
2-Erosive Esophagitis (C/D)	Double dose PPI therapy for 8-12 weeks
3-NERD	Standard dose PPI therapy for 4-8 weeks
4-Long-term Management (both GERD and NERD)	Standard (or half) dose PPI maintenance (continuous, intermittent or on-demand, depending on clinical characteristics of the patient)
5-Barrett's Esophagus	Long-term individually tailored PPI therapy
6- Extra-digestive GERD	Standard or double-dose PPI therapy for at least 12 weeks
Eosinophilic Esophagitis	Standard or double-dose PPI therapy for 8-12 weeks
H. pylori Eradication	Double dose, twice daily, PPI therapy for 7-14 days (in combination with antimicrobials)
Non-H. pylori-related PU disease	Standard dose PPI therapy for 4-8 weeks
Zollinger-Ellison Syndrome	High-dose (eventually twice daily) long-term PPI therapy
Stress Ulcer Prophylaxis in patients with risk factors	Standard PPI therapy by intravenous route only during ICU stay
Dyspepsia	
1.Uninvestigated Dyspepsia in Patients younger than 45 years	Standard or half-dose empiric PPI therapy for 4 weeks
2.Functional Dyspepsia (EPS phenotype)	Standard or half dose PPI therapy for 4-8 weeks
NSAID-gastropathy Prevention of gastroduodenal lesions and events	Standard or half-dose PPI therapy, starting from the very first dose of NSAID in patients at GI risk
Treatment of gastro-duodenal lesions	Standard dose PPI therapy for 8 weeks
Steroid therapy	No need for gastroprotection unless used in combination with NSAIDs
Anti-Platelet Therapy	Standard dose PPI therapy, starting from the very first dose of antiplatelet agent in patients at GI risk
Anti-Coagulant Therapy	No need for gastroprotection unless used in combination with antiplatelet therapy
PU Bleeding	Intravenous bolus of 80 mg of the available injectable PPIs, followed by 8 mg/h for 72 hours
Cirrhosis	
Hypertensive gastropathy Prevention or/and treatment of	No need for acid suppression.
esophageal ulcers after sclerotherapy or variceal band ligation	Standard dose PPI therapy for 10 days (longer treatment should be avoided taking into account the risk of spontaneous bacterial peritonitis).
Pancreatic Diseases	
Acute pancreatitis	No benefits from acid suppression
Chronic pancreatitis	Standard PPI therapy only in patients with steatorrhea, refractory to enzyme replacement therapy

The Pros of Long-Term use of PPIs

Peptic Ulcer Disease (PUD): PUD is a peptic acid injury of the stomach and duodenum [11]. This can be further categorized into a gastric or duodenal ulcer based upon the location. Helicobacter pylori and NSAIDs are main cause of PUD approximately 10-20%. Also, stress and/or dietary factors are considered [12].

GERD: long-term and maintenance of GERD and its complications. A meta-analysis that included seventeen randomized controlled trials [RCTs] including a total of 6,072 patients found that GERD treatment with PPIs was more superior than H2 inhibitor [13]. Many factors influence response to and effectiveness of treatment such as accuracy of diagnosis, access to treatment, adherence to treatment and poor compliance. One major step in optimizing PPIs treatment for GERD is educating the patient on proper timing of PPIs medication consumption as one study found that 100% of patients in the study who had refractory GERD were consuming PPI inappropriately – an hour before a meal, during a meal and at bedtime instead of the recommended 30 minutes prior to meal [14].

Prophylaxis for NSAIDs-induced Ulcers: PPIs are effective in preventing recurrence of NSAIDs-induced ulcer recurrence. Other studies also indicate that co-administration of NSAIDs and PPIs reduces the risk of gastro-intestinal tract [GIT] bleeding [15]. NSAIDs-induced gastroduodenal ulcers are estimated to account for thousands of GI complications each year, including GI bleeds, gastric pain, or even death [11]. Currently, PPIs are recommended and FDA-approved as chronic prophylaxis in individuals with high risk due to concurrent and planned long-term NSAID use, as well as acutely for the treatment and healing of active ulcers, with most cases resolving with 6 to 8 weeks of therapy [12, 16].

Barrett's Esophagus: PPIs may also have a chemo-preventive effect on Barrett's esophagus by reducing the risk of progression to esophageal adenocarcinoma. In the systemic review cited to support the assertion, none of the included studies was RCT, hence the low-level evidence. [17].

Zollinger-Ellison Syndrome [ZES] and Pathological Hypersecretory Conditions: ZES is an acid hyper-secretory condition caused by a gastrin-secreting tumor [18]. PPIs are the FDA-approved drug of choice for management and must be given chronically to control acid secretion and prevent or reduce complications and symptoms in most patients with ZES [18].

Stress Ulcer Prophylaxis: Although not FDA-approved, numerous guidelines recommend PPIs use as prophylaxis therapy in hospitalized patients. Stress ulcers may occur in patients admitted to intensive-care units (ICUs), and inappropriate management or prophylaxis treatment may lead to severe events such as GI bleeding or ulcer formation [19]. Events such as GI bleeds may occur in up to 15% of patients not on stress ulcer prophylaxis (SUP) [19,20]. Although SUP is critical to improve hospitalized patient outcomes, it should be stressed that PPIs are only approved for SUP in high-risk patients, defined as those who are critically ill and on mechanical ventilation for more than 48 hours, or those on anti-coagulation [19]. PPIs use in these patients should be limited to short-term therapy as appropriate. PPIs should not be used as prophylaxis in low-risk or non-critically ill hospitalized patients.

Other Indications: PPIs are commonly used for a variety of other indications that do not carry an FDA approval. These include as add-on therapy for patients on antiplatelet therapy with high risk of GI bleed; functional dyspepsia; and prior to or following an endoscopy associated with an acute or high risk of bleeding [21].

The Cons/Adverse Effects of PPIs

The potential AEs of PPIs classify into adverse events related to acid inhibition and adverse events unrelated to acid inhibition as represented in Table 4. Overall, the safety of PPIs remains controversial [22].

Table 4: Potential AEs [9,23]

A=Adverse events unrelated to acid inhibition	B=Adverse events related to acid inhibition
Allergic reaction to drug chemicals	Pneumonia
Collagenous colitis	Gastrointestinal infection
Acute interstitial nephritis	Gastric carcinoid tumor
Chronic kidney disease	Gastric fundic mucosal hypertrophy
Drug interaction	Changes in the gut microbiome
Dementia	Small intestinal bacterial overgrowth
Cerebral ischemic diseases	Iron deficiency
Ischemic cardiac diseases	Bone fracture
	Vitamin B12 deficiency
	Hypomagnesemia
	Gastric fundic gland polyps
	Gastric cancer
	Colon cancer
	Spontaneous bacterial peritonitis
	Hepatic encephalopathy
	Drug interaction

Adverse Events Unrelated to Acid Inhibition

- **Allergic reactions to the chemicals in PPIs:** The allergic reactions to PPIs, including anaphylaxis, pancytopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, acute liver damage, Lyell syndrome, Stevens-Johnson syndrome, interstitial nephritis, and rhabdomyolysis. Hypercreativity reactions, especially anaphylactic reactions, due to PPIs are well documented. A recent multicenter study that included chart reviews of patients with PPI-induced immediate hypersensitivity found that lansoprazole accounted for most reactions (68.3%) and PPI-induced hypersensitivity frequently manifested as anaphylaxis [24].
- **Collagenous colitis:** Collagenous colitis is complicated diarrhea characterized by diarrhea and histopathological identification of thick collagen bands beneath the colonial epithelium [25,26].
- **Increased Risk of Acute Interstitial Nephritis and Chronic Kidney Disease:** Cell- and humoral-mediated drug hypersensitivity [18]. PPIs use causes acute interstitial nephritis (ANI) and was linked to 14% of 70% of clinical cases of ANI (New Zealand). 572,661 patients without a history of ANI or other renal disease reported an increased risk of AIN with PPI use. The case-control analysis indicated that the current use of PPI increased ANI risk when compared with past use (OR=5.16 after controlling for confounding factors) [27].
- **Subcutaneous lupus Erythematosus:** Subcutaneous lupus erythematosus (SLE) has been reported in patients taking PPIs. Drug-induced SLE can occur weeks, months or even years after exposure to the drug [18].
- **Cardiovascular disease and reduced effectiveness of clopidogrel:** Some evidence suggesting that concomitant use of PPIs and clopidogrel may reduce the anti-thrombotic activity of clopidogrel and increase the risk of cardiovascular events. Clopidogrel and the Optimization of Gastrointestinal Events Trial [COGENT]: Individuals with acute coronary syndrome (ACS) who have undergone percutaneous coronary intervention are commonly prescribed antiplatelet therapy to reduce and prevent further cardiovascular complications. PPIs may be prescribed in conjunction with antiplatelet therapy to reduce risk of GI bleeding. In addition, as mentioned, PPIs are used commonly by the general populace for other acid-related disorders [28]. In 2009, the FDA issued a statement warning against the combination of the antiplatelet agent clopidogrel and PPIs due to potential drug interactions between the two [29]. Mechanistically, clopidogrel is metabolized to its active form through the same liver enzymes that metabolize PPIs,

raising concern of a potential diminished antiplatelet effect and therefore an increase in cardiovascular events [30]. Currently, data surrounding the clinical significance of this event are mixed. A 2015 meta-analysis of 31 observational studies found that individuals on PPI therapy and clopidogrel had a 30% increased risk of cardiovascular events as compared to nonusers of PPI therapy [31]. However, the four RCTs included in the review found there was no increased risk of events identified [31]. In addition, another 2015 systematic review that explored the use of PPIs and the risk of myocardial infarction found a 16% increased risk associated with use. This was found to be regardless of clopidogrel use and was not seen with H2 blocker therapy [4].

- **Potential Dementia Risk:** Increased production and degradation of amyloid and binding to tau. Decreased availability of other nutrients PPIs use increased risk of dementia in elderly persons. The evidence is supplied by two retrospective studies on a German database [18].

PPIs adverse events related to acid inhibition

- **Small Intestinal Bacterial Overgrowth (SIBO):** PPIs are a risk factor for SIBO, which is the increase in the bacterial counts in the jejunum and duodenum because of reduced gastric acid which is bactericidal. In one study, Alteration of gut microbiome, Pereira et al. (1998) reported that PPIs increased the duodenal bacterial load, but participants remained asymptomatic [32] whereas Lewis et al. (1996) reported both that PPIs caused SIBO and symptoms, including diarrhea [33]. Other studies have also reported that PPIs aggravate dysbiosis of normal flora in the small intestines, which worsens NSAIDs-related small intestinal injury [34].
- **GI Infection:** PPIs use enhanced susceptibility to infections caused by Salmonella, Campylobacter and C. difficile (OR=4.2-8.3, 3.5-11.7, and 1.2-5.0 respectively) [35]. More recent studies corroborate these findings e.g. a case-control study found an increased risk of hospital-acquired C. difficile infection in critically ill patients (OR=2.03 and CI =1.23-3.36) [36]. A recent meta-analysis of observational studies reported similar results (OR=1.81 95% CI, 1.52–2.14). Furthermore, a recent update to a cumulative meta-analysis strengthens the evidence as a significant association between PPIs use and C. difficile infection risk was demonstrated (OR= 1.26; 95% CI: 1.12-1.39). A population-based case-control study associated PPIs with an increased risk of C. difficile in infants and children [37]. In 2015, the FDA issued a public safety alert regarding increased Clostridium difficile infections associated with PPI use. This was primarily based upon a 2012 systematic review and meta-analysis study that included over 30 studies and 300,000 patients, which concluded that PPI users had a 74% higher risk of developing a C diff infection, as well as a 2.5-fold higher risk of recurrent infections, as compared with nonusers [38].
- **Respiratory Infection:** PPIs use may also lead to increased rates of pneumonia. A meta-analysis performed in 2011 showed that the risk of community-acquired pneumonia (CAP) was 34% higher in patients on PPIs, which increased with higher dosing [39]. For both C diff and CAP, it is generally hypothesized to be due to decreased gastric acidity caused by long-term PPI use and a subsequent increase in bacterial colonization [39] [40].
- **The potential risk of Gastric Neuroendocrine Tumor:** PPIs use increase the intragastric pH, plasma gastrin concentration is increased, and gastrin stimulates the proliferation of enterochromaffin-like (ECL) cells and gastric neuroendocrine tumors [41].
- **Thickening of the gastric fundic mucosa:** Increased proliferation of gastric mucosal stem cells is what causes the thickening of the gastric fundic mucosa [42].
- **Impaired absorption of micronutrients:**
  - **Magnesium** is absorbed in the small intestine and the micronutrient is important for regulation of neuromuscular activity as well as various enzymatic activities. Increased gastric pH alters Mg transport and absorption. Some cases of hypomagnesemia associated with chronic PPI use were shown in systemic review of observational studies that report a modest positive association between PPI use and hypomagnesemia (HR=1.43). In 2011, the FDA issued a warning that long-term PPI use may lower serum magnesium levels that supplementation alone may not correct unless the PPI was discontinued [43]. When severe, hypomagnesemia may present in the form of muscle weakness, tetany, seizures, cardiac arrhythmias, and hypotension, with the potential to be life-threatening [30]. The risk of hypomagnesemia was further studied by a 2015 systematic review and meta-analysis that included over 100,000 patients and assessed the risk of hypomagnesemia in patients with PPI as compared with non-PPI users. This study ultimately concluded approximately a 40% increased risk of hypomagnesemia with PPI use as compared with non-PPI therapy [44].
  - **Iron deficiency:** Evidence showed the long-term PPI use in patients with hereditary hemochromatosis result in significantly reduced iron absorption [45].
  - **Calcium:** The long use of PPIs can decrease calcium absorption because gastric acid plays an important role in the process [46]. Fractures and osteoporosis are due to reduction in calcium absorption because of increased gastric pH [47]. In May of 2010, the FDA issued a public safety statement alert regarding potential increased risk of fractures associated with PPI use [48]. Since then, numerous studies exploring the relationship between PPI use and fracture risk have been examined. A 2016 meta-analysis reviewing over 200,000 fracture cases reported a 26% higher risk of hip fracture, 58% higher risk of spine fracture, and a 33% risk of fracture at any site in individuals who used PPI as compared with those who have not, even at a duration of less than 1 year [47].
  - **Vitamin B12**, increased gastric pH alters absorption, potential for microbial overgrowth that utilizes cobalamin. There is association between PPIs and vitamin B12 absorption which depends on protein digestion **[18,46,49].**

- **Gastric Cancer:** PPIs may "play dual role" in gastric carcinogenesis and treatment of gastric cancer [50].
- **Gastrointestinal Malignancies:** High-doses of PPIs in refractory gastro-intestinal cancer because hypergastrinemia associated with PPI would stimulate the proliferation of neoplastic colonic cells and increase the risk of colon cancers [51].
- **Drug-Drug Interactions [9]:** Omeprazole have included prolonged elimination of diazepam, warfarin, and phenytoin. Isolated reports of changes in elimination have been reported with cyclosporine, disulfiram, and other benzodiazepines. No drug-drug interactions were found between esomeprazole and phenytoin, R-warfarin, quinidine, amoxicillin, oral contraceptives, and clarithromycin. Esomeprazole may interfere with the elimination of other drugs metabolized by CYP2C19. Co-administration of esomeprazole and diazepam results in a 45% reduction in diazepam clearance and increased plasma diazepam levels. Changes in gastric pH can affect the bioavailability of some medications. Examples of medications where the bioavailability of the medication may be decreased with profound and long-lasting inhibition of gastric acid secretion are ketoconazole and iron salts.

Monitoring requirements

Document the medical indication, non-pharmacological measure, duration of PPIs uses and stepping if needed. Serum magnesium checkup during the prolonged use [52]. Vit B12 and Calcium. To reduce PPIs use, stewardship program, managed by pharmacists is highly recommended to determine if use is necessary, educate patients on the proper administration, and discuss whether deprescribing is warranted. Involving patients in the decision to de-prescribe PPIs is vital for patient success. Patients who are educated on the risks associated with long-term therapy and possible side effects associated with PPIs are more likely to understand the reasoning for deprescribing and may experience better long-term outcomes [53].

Prescribing, Deprescribing & Dispensing Information

PPIs should be prescribed appropriately at the lowest effective dose for the shortest period and those who use PPIs for a long time should be checked regularly [52]. In 2017, guidelines for deprescribing PPIs were published in Canadian Family Physician. A team of healthcare professionals, including three pharmacists, collaborated to establish the evidence-based clinical practice guideline [53]. Deprescribing is reducing the dose, stopping, or using "on-demand" dosing. The guideline recommends deprescribing PPIs in adults who suffer from heartburn and who have completed a minimum treatment of 4 weeks in which symptoms are relieved. These recommendations do not apply to patients with Barrett's esophagus, severe esophagitis, or patients with a history of bleeding gastrointestinal ulcers [11]. Per the published guidelines, an algorithm can be used in determining when and how PPIs should safely be deprescribed. For patients needing occasional symptom relief, OTC antacids or H2 receptor antagonists (H2RAs) may be used on an as-needed basis. H2RAs may be used on a daily basis, although the recommendation only proves to have moderate-quality evidence. Patients should also be educated on the nonpharmacologic approaches to minimize symptoms of heartburn, dyspepsia, regurgitation, and epigastric pain. Patients should be counseled to avoid meals 2 to 3 hours before bedtime, avoid dietary triggers, and address whether weight loss is required [53].

PPIs Use after the Discharge of the Patients from the Hospital [6]

Studies in primary care and emergency offer that PPIs are extremely prescribed for inconvenient indications or offers some advantages. Hospitalized patients considerably often started PPIs inappropriately and continued, following discharge, by primary care physicians. Unsuitable recommendations for PPIs with the discharge are completely repeated and persistent. This prescription habit may lead to a continuation of PPI therapy in primary care, thereby unnecessarily increasing polypharmacy and the risk of adverse events as well as burdening the public health budget. An Italian study found that the persistence rate of PPI therapy is high, after both appropriate and inappropriate prescriptions (62 % and 71 %, respectively). The general practitioners' attitude to continuing or discontinuing PPIs depends on their level of knowledge and their perceptions of hospital physicians' competence as well as the threshold to prescribing in hospitals.

Points to be Focused on and Considered

- Confirmed diagnosis prior to prescribing PPIs and enable mandatory indication per medication.
- PPIs therapy should be evidence based.
- Practice of giving PPIs with drugs as a poly pharmacy is not a good practice.
- Physicians and clinicians must consider and know the risk of long-term PPIs use in clinical practice.
- Be aware about adverse effects, drug interactions, and adverse drug reactions reports (ADRS).
- Refill or repetition should be done on a clinical base.
- Decisions on whether to initiate or continue PPIs therapy should be sound and PPIs should only be prescribed when there is an appropriate clinical indication.
- Pharmacists should help in alerting physicians especially with long term administration and any other drug related problems (labs interpretation, discontinuation, drug interactions etc.)
- Encourage non-pharmacological approach and dietary assessment.
- Implement "deprescribing" concept including discontinuing medications, tapering the dose, reducing the dose.
- Follow up patients after deprescribing or discontinuation of therapy.

Impact in Clinical Practice

This review may guide policymakers and physicians in designing future clinical guidelines and or clinical audit programs. The findings will inform national health planning strategies by identifying the pros and cons of the use of PPIs. The physicians should follow the major clinical guidelines and governmental agencies for the best health services outcomes.

Recommendations for Research

This research will provide clinical practice with research evidence-based guidelines. In addition to that, conducting future research such as a systematic review, meta-analysis systematic, and longitudinal Cohort studies are very important in clinical practice to manage the gaps in knowledge identified from the results of this review.

Conclusion

We have presented the most current research outlining and we conclude that the use of PPIs provide benefits if prescribed appropriately. This review found a significant level of risks of long-term use of PPIs. The periodic follow-up and assessment of risks in PPIs users is very helpful. In addition to that, physicians should follow the guidelines when prescribing PPIs and must consider the advantages and disadvantages for patients.

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ANNEXES

Annex 1 ; PPIs doses: National Institutes of Health, U.S. National Library of Medicine, DailyMed Database. Provides access to the latest drug monographs submitted to the FDA. https://globalrph.com/drugs/proton-pump-inhibitors-ppis/# (54)

Esomeprazole dosing:

- Healing of erosive esophagitis: Oral: Initial: 20-40 mg once daily for 4-8 weeks. If incomplete healing, may continue for an additional 4-8 weeks. Maintenance: 20 mg once daily.
- Symptomatic gastroesophageal reflux: Oral: 20 mg once daily for 4 weeks.
- Pathological hypersecretory conditions (Zollinger-Ellison syndrome): 40 mg twice daily; adjust regimen to individual patient needs; doses up to 240 mg/day have been administered.

Lansoprazole dosing: the strength we have is only 30 mg but, if 15 mg will be added to HMC in the future.

- Duodenal ulcer: Oral: Short-term treatment: 15 mg once daily for 4 weeks. Maintenance therapy: 15 mg once daily. Gastric ulcer: Oral: Short-term treatment: 30 mg once daily for up to 8 weeks.
- Symptomatic GERD: Oral: Short-term treatment: 15 mg once daily for up to 8 weeks.
- Erosive esophagitis: Oral: Short-term treatment: 30 mg once daily for up to 8 weeks. Maintenance therapy: 15 mg once daily.
- Hypersecretory conditions: Oral: Initial: 60 mg once daily; adjust dose based upon patient response and to reduce acid secretion to <10 mEq/hour (5 mEq/hour in patients with prior gastric surgery). Doses of 90 mg twice daily have been used... administer doses >120 mg/day in divided doses

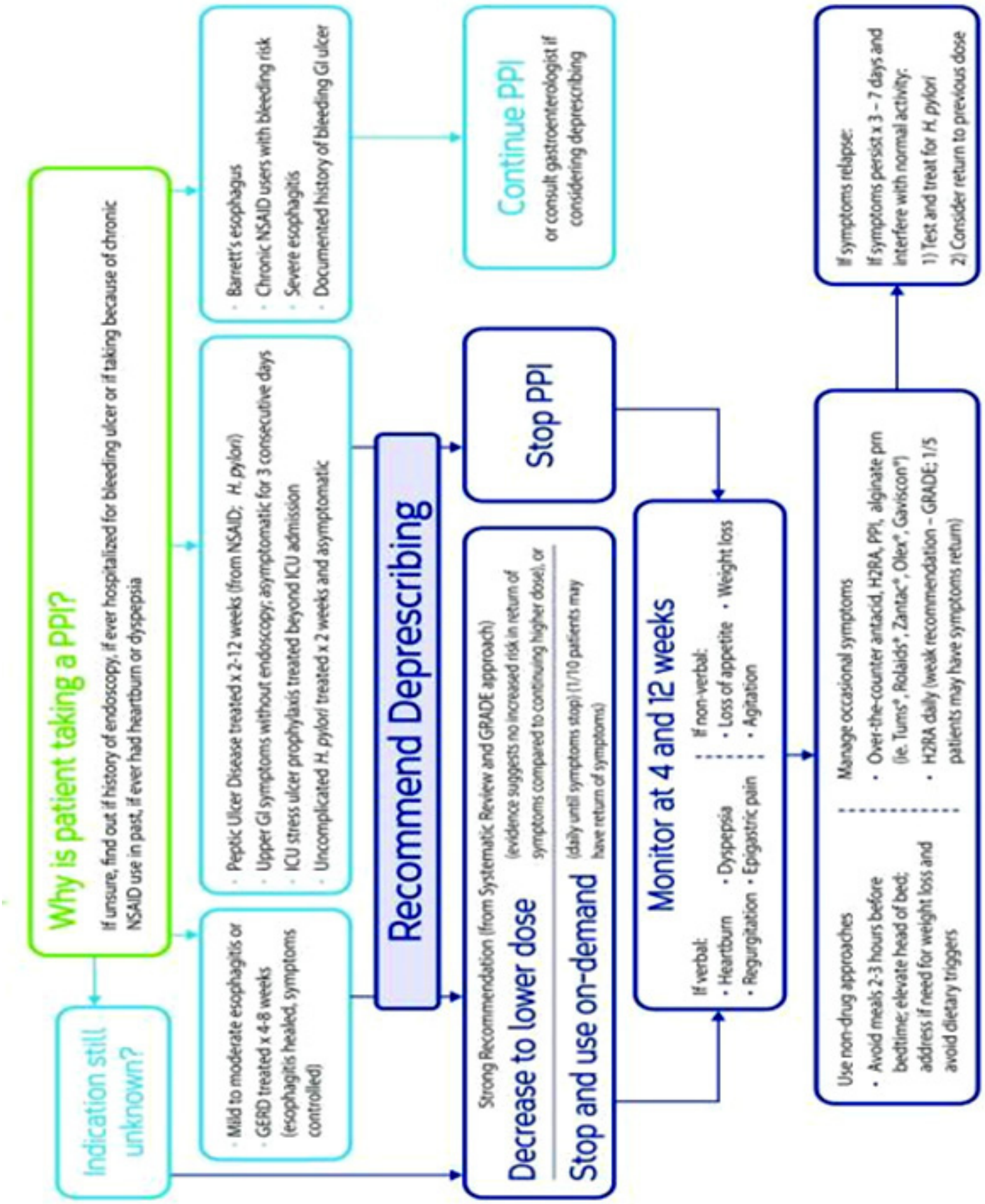
Pantoprazole dosing:

- Erosive esophagitis associated with GERD: Oral: Treatment: 40 mg once daily for up to 8 weeks. An additional 8 weeks may be used in patients who have not healed after an 8-week course. Maintenance of healing: 40 mg once daily. I.V.: 40 mg once daily for 7-10 days.
- Hypersecretory disorders (including Zollinger-Ellison): Oral: Initial: 40 mg twice daily. Adjust dose based on patient needs. Doses up to 240 mg/day have been administered.

Rabeprazole Dosing:

- Duodenal ulcer: Oral: 20 mg/day before breakfast for 4 weeks.
- GERD: Oral: 20 mg once daily for 4-8 weeks; maintenance: 20 mg once daily.
- Hypersecretory conditions: Oral: 60 mg once daily. Dose may need to be adjusted as necessary. Doses as high as 100 mg once daily and 60 mg twice daily have been used.

Annex 2; Algorithm on PPIs use (55)
PPIs Algorithm



Mental Health Screening in Primary Care: A Literature Review

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Abstract

This literature review explores the role of mental health screening in primary care settings. It provides an overview of the prevalence and impact of mental health disorders, the importance of early detection and intervention, and the challenges faced by primary care providers in identifying and managing mental health conditions. The review also examines various screening tools and strategies employed in primary care settings, highlighting their effectiveness and limitations. Finally, recommendations for future research and practice are discussed to enhance mental health screening and improve outcomes in primary care.

Keywords: mental health screening, primary care

Introduction

Mental health disorders are a significant public health concern with profound impacts on individuals, families, and communities. Primary care settings play a crucial role in detecting and managing mental health conditions due to their accessibility and the frequent contact between patients and healthcare providers. This literature review aims to explore the effectiveness of mental health screening in primary care, focusing on the identification and early intervention of mental health disorders.

Prevaleice and Impact of Mental Health Disorders

Major depressive disorder (MDD), a common mental disorder in the US, can have a substantial impact on the lives of affected.individuals (1,2).

If left untreated, MDD can interfere with daily functioning and can be associated with an increased risk of cardiovascular events, exacerbation of comorbid conditions, or increased mortality (1).

Depression is common in postpartum and pregnant persons and affects both the parent and infant. Depression during pregnancy increases the risk of preterm birth and low birth weight or small-for-gestational age (1).

Postpartum depression may interfere with parent-infant bonding(1).

Anxiety disorders are often unrecognized in primary care settings and substantial delays in treatment initiation occur (2). anxiety disorder can be chronic conditions characterized by periods of remission and recurrence. However, full recovery may occur (2).

This regular attendance suggests that primary care practitioners are in the unique position to deliver opportunistic screening for mental health and health compromising behaviors as part of young people's routine health care, providing early intervention and referrals where necessary. (3).

The review begins by examining the prevalence and impact of mental health disorders in the general population, emphasizing the burden they pose in terms of disability, morbidity, and mortality. Studies consistently demonstrate high rates of mental health disorders among primary care patients, underscoring the need for routine screening to ensure timely identification and appropriate management.

Importance of Early Detection and Intervention

The USPSTF concludes with moderate certainty that screening for MDD in adults, including pregnant and postpartum persons, as well as older adults, **has a moderate net benefit** (1).

The USPSTF concludes with moderate certainty that screening for anxiety disorders in adults, including pregnant and postpartum persons, has a moderate net benefit.

Studies of psychological interventions showed a small but statistically significant reduction in anxiety symptom severity in primary care patients with anxiety disorders (2).

Financial benefits of such interventions result in part from decreases in overall healthcare costs and increased rates of workforce participation (4).

The World Economic Forum estimates the global cost of chronic diseases at over USD 47 trillion between 2010 and 2030, of which USD 16 trillion is attributed to mental health problems (4,5).

Perinatal depression, which is the occurrence of a depressive disorder during pregnancy or following childbirth, affects as many as 1 in 7 women and is one of the most common complications of pregnancy and the postpartum period (6).

The USPSTF recommends that clinicians provide or refer pregnant and postpartum persons who are at increased risk of perinatal depression to counseling interventions (B recommendation) (6).

The USPSTF also recommends screening for depression in adolescents aged 12 to 18 years (B recommendation) and found insufficient evidence to recommend for or against screening in children 11 years or younger (I statement) (6).

Early detection and intervention are crucial in improving mental health outcomes. Untreated mental health conditions can lead to worsening symptoms, functional impairment, increased healthcare utilization, and reduced quality of life. The review explores the benefits of early detection and intervention, highlighting the potential for improved prognosis, reduced healthcare costs, and increased patient satisfaction.

Challenges in Mental Health Screening in Primary Care

Although many health care experts agree that there is a need for improved mental health screening in primary care, mental health case-finding tools are not widely used in primary care settings (7). The need to integrate mental health into primary care is justified and relevant to contemporary needs in the APEC. economies. In order to achieve effective integration, conceptual principles need to be translated into operational models, implementation steps and strategies (4).

Primary care providers face several challenges in effectively screening for mental health disorders. Time constraints, limited resources and lack of training in mental health assessment can hinder accurate identification. This section of the review examines these challenges and emphasizes the need for integrated care models, enhanced provider education, and improved support systems to facilitate mental health screening in primary care settings.

Screening Tools and Strategies

Commonly used depression screening instruments include the Patient Health Questionnaire (PHQ) in various forms in adults, the Center for Epidemiologic Studies Depression Scale (CES-D), the Geriatric Depression Scale (GDS) in older adults, and the Edinburgh Post-natal Depression Scale (EPDS) in postpartum and pregnant persons (1).

Screening instruments for suicide risk include the Beck Hopelessness Scale, the SAD PERSONS Scale (Sex, Age, Depression, Previous attempt, Ethanol abuse, Rational thinking loss, social supports lacking, Organized plan, No spouse, Sickness), and the SAFE-T (Suicide Assessment Five-step Evaluation and (Triage) (1). Some depression screening instruments, such as the PHQ-9, incorporate questions that ask about suicidal ideation (1).

Selected screening tools widely used in the US include versions of the Generalized Anxiety Disorder (GAD) scale, Edinburgh Postnatal Depression Scale (EPDS) anxiety subscale, Geriatric Anxiety Scale (GAS), and the Geriatric Anxiety Inventory (GAI) (2).

A comprehensive review of screening tools and strategies commonly used in primary care is presented in this section. Various validated instruments, such as the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7), are discussed, highlighting their utility in identifying common mental health disorders. The review also explores collaborative care models, stepped-care approaches, and the integration of technology to enhance screening effectiveness.

Effectiveness and Limitations of Mental Health Screening

For patients to benefit from screening, positive screening results should be confirmed by diagnostic assessment and patients should be provided with, or referred to, evidence-based care, which should be accessible to all populations (2).

Potential barriers to screening include clinician knowledge and comfort level with screening, inadequate systems to support screening or to manage positive screening results, and impact on care flow, given the time constraints faced by primary care clinicians (2).

Systemic barriers, such as lack of connection between mental health and primary care settings, patient hesitation to initiate treatment, and nonadherence to medication and therapy, also exist (2).

For major depression, sensitivity and specificity is 81% and 96%, respectively. For other disorders, sensitivities ranged from 69% to 98%, and specificities ranged from 90% to 97% (7).

The efficacy and limitations of mental health screening in primary care are critically evaluated in this section. The review examines the evidence supporting the effectiveness of screening in improving detection rates, treatment initiation, and patient outcomes. It also discusses the potential for false positives, limited follow-up resources, and the stigma associated with mental health screening.

Implementation and integration of mental health in primary care

The recommendations for implementation of strategies to promote the integration of mental health into primary care are aligned with the APEC Digital Hub and WONCA collaborative framework (Engage, Enable, Empower). These recommendations include identifying relevant stakeholders involved in implementation, improving mental health awareness, ensuring the infrastructure and resources needed to facilitate implementation are in place, and identifying clear indicators for monitoring and evaluating implementation (4). The gold- standard criterion was nurse-initiated assessment using the Adult Primary Care (APC) guidelines (8). The criterion standard for establishing the validity of screening tools would typically use another accepted standard of the construct under consideration, usually a clinician-initiated diagnostic interview. As diagnostic assessments are done by the PHC nurse using the APC guidelines, each of the three scales were compared with an independent assessment done by a professional PHC nurse who had received advanced training in the use of the mental health APC guidelines (8).

Recommendations for Future Research and Practice

The USPSTF has recommendations on other mental health topics pertaining to adults, including screening for anxiety, preventive counseling interventions for perinatal depression, screenings for unhealthy drug use, and screening and behavioral counseling for alcohol use .(1)

Whether more individuals with screen-detected suicidal ideation could be helped before they act (1).

Based on the findings of the literature review, this section provides recommendations for future research and practice. Suggestions include developing standardized screening protocols, integrating mental health services within primary care settings, enhancing provider training in mental health assessment, and exploring innovative approaches, such as telehealth and digital interventions, to improve screening accessibility and follow-up care.

Conclusion

In light of its validity and its practicality in primary care settings, the QPD (Quick psychodiagnostics) Panel may make routine mental health screening feasible for many more physicians. Such routine screening would benefit the many patients who currently go undiagnosed and untreated (7).

This literature review highlights the importance of mental health screening in primary care and its potential to improve patient outcomes. It underscores the need for comprehensive screening tools, provider education, and enhanced support systems to overcome existing challenges. By implementing evidence-based screening practices and integrating mental health services within primary care, healthcare systems can effectively address mental health needs and promote overall well-being.

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Unravelling the Mystery of Arterial Tortuosity Syndrome: A Case Report of an Unexpected Rare Diagnosis in a Well-Baby Clinic at a Primary Care Center in Qatar

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Abstract

A case of Arterial Tortuosity Syndrome (ATS) is a rare autosomal recessive genetic disorder characterized by significant alterations in the structure and function of the arterial system. Mutations in the SLC2A10 gene, responsible for encoding the transporter protein GLUT10, lead to the development of ATS.

Keywords:
Arterial Tortuosity Syndrome, case report, well baby clinic, Qatar

Background

Arterial Tortuosity Syndrome (ATS) is a rare autosomal recessive genetic disorder characterized by significant alterations in the structure and function of the arterial system. Mutations in the SLC2A10 gene, responsible for encoding the transporter protein GLUT10, lead to the development of ATS. The syndrome is characterized by the elongation, twisting, and increased tortuosity of arteries, predisposing patients to a plethora of vascular complications, including aneurysms, stenosis, and tortuosity [1]. Adding to that, ATS affects connective tissues across various systems, leading to special facial features that can be recognizable at birth or later during early childhood [2]. Being a rare and complex disorder signifies the importance of raising awareness among healthcare professionals, particularly in settings where genetic disorders might not be the first consideration such as well baby clinics where the parents bring their children just for routine well baby follow up and vaccines.

Rationale

The diagnosis of ATS in a primary care setting is exceptionally rare, given the complex presentation and the need for specialized genetic testing for confirmation. This case report aims to highlight the role primary care physicians can play in the early identification and referral of cases suspected of having rare genetic disorders in general and AST in particular. Sharing experience and insights from this unique case can contribute to the broader medical literature by underlining the necessity for vigilance and a comprehensive approach in the evaluation of infants and young children presenting with nonspecific symptoms and dysmorphic features.

Case presentation

In June 2022, a 2-month-old baby boy was brought by his mother to a well-baby clinic for a routine check-up and vaccination. The boy weighed 5.4 kg and was 61 cm tall. The mother expressed concern over the baby's excessive crying. The maternal history included gestational diabetes mellitus (managed without insulin) and recurrent urinary tract infections. The prenatal history was insignificant; all fetal ultrasounds were normal. The baby, born at a gestational age of 38 weeks to a 31-year-old G5P3 mother via elective caesarean section, did not require resuscitation, with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. The neonatal period was marked by jaundice (2).

The family's social history noted non-smoking, first-degree relative parents with secondary school-level education. The family consisted of the father (32 years old), the mother (31 years old), two girls (aged 10 and 5), and two boys (aged 8 and the 4-year-old patient). The patient's growth and milestones were normal according to the WHO pediatric growth charts. However, examination revealed dysmorphic features such as low-set ears, a high arched palate, and wide epicanthic folds, though these observations were not observed by the mother. The chest examination showed abnormal shape and pectus excavatum but normal heart sounds without murmurs. The abdomen appeared distended during crying, and the neurological examination revealed hypotonia but no limb deformities. The genitourinary examination was normal. A follow-up plan was agreed on with the mother, with a referral to pediatric emergency services for further assessment and possible referral to genetics.

Investigations

No special investigations were done at primary care as possible genetic tests can only be done through the pediatrics department. The referral aimed to exclude serious conditions and initiate further investigations for an accurate diagnosis.

Differential diagnosis

Initial differential diagnoses included diaphragmatic hernia, various connective tissue disorders, Klinefelter syndrome, and Arterial Tortuosity Syndrome.

Treatment

The treatment plan included vitamin D3 supplementation, antipyretics as needed, and comprehensive health advice to the parents which were provided based on age and routine well baby visit, but nothing was prescribed based on the accidental findings for which the baby was referred to pediatrics.

Outcome and Follow-up

The follow-up protocol included well-baby primary health care center visits at 4 months old as per the protocol and referrals to secondary care for genetic studies that reveal gene mutation (SLC2A10 Homozygous state) and pediatric services, like Neurology to follow up the Axial hypotonia , pulmonology to follow up the moderate to severe pectus excavatum and provide the prophylactic medicines, urology to follow up the left proximal hydroureter and pelviectasis, pediatric surgery for the bilateral inguinal hernia and cardiology as risk assessment and follow up. The patient also received rehabilitation services at a child development center and ongoing well baby visits are planned.

Discussion

This case report is an example of the difficulties and possibilities associated with diagnosing uncommon genetic disorders, like ATS, in a primary care setting when the presentation was made for an unrelated reason and the family were not concerned about the disorder's symptoms. Although it is rare, the early identification of ATS highlights the significance of considering a wide variety of differential

diagnoses when dealing with such clinical presentations. In this instance, the multidisciplinary approach combining pediatricians, cardiologists, and geneticists is essential, supporting the need for integrated care for such uncommon genetic disorders. This case does also support the value of genetic testing and the necessity for medical professionals to be competent identifying these features early.

Lastly, this case report highlights the need for primary care practitioners to be aware of and consider rare genetic disorders in their differential diagnosis, facilitating timely referral and appropriate management.

Ethical considerations

PHCC IRB approval was obtained. This case report addresses the principle of beneficence, as outlined in the Belmont Report, by prioritizing the well-being of the patient through early diagnosis and intervention, thus aiming to prevent possible complications. Privacy and autonomy were maintained by ensuring confidentiality and consenting parents.

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Assessing knowledge and preparedness in airway management among senior medical students in Al-Baha University

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Abstract

Background: Airway management is the basis for resuscitation. As such, it is imperative that all physicians become proficient in this critical ability. The purpose of this study was to examine medical students' perceptions, knowledge, and preparedness for airway management.

Method: Our research was a prospective, cross-sectional study. Focused on the clinical years (fourth, fifth, sixth, and internship years) of medical students at the Al-Baha Faculty of Medicine in Al-Baha University, Al-Baha Saudi Arabia. The data processing and analysis was done using SPSS version 24, with the mean ± standard deviation being used for continuous variables and frequency and percentage for categorical variables.

Result: 156 students were involved in our investigation, 63.5% were male. Over 50% of the participants completed all three modules at once. With 51.4 and 59.2%, respectively, the participants who completed the modules in tandem demonstrated the highest degree of good and moderate grade point average. The modality type used, and overall degree of confidence were shown to be significantly correlated (p value 0.002). Additionally, the modality type used, and overall level of preparedness were shown to be significantly correlated (p value 0.016). However, there was no discernible correlation found between the modality type used and overall effectiveness.

Conclusion: Enhancement of the participants' expertise in executing endotracheal intubation and supraglottic airways devices is necessary, in addition to their readiness for both emergency department and elective operating room intubations.

Keywords: airway management, students' knowledge assessment, preparedness

Background

Airway management is a vital clinical skill for any medical student. Severe consequences, including death, are linked to lung ventilation incapacity. During a crisis, physicians should be able to use a variety of procedures to quickly and definitively manage the airway. There are several published evidence-based practice guidelines for airway management that offer suggestions for safe airway management (1–3). All of these recommendations emphasize anticipating difficult airways, maintaining oxygenation, using different airway adjuncts promptly, utilizing supraglottic airway devices as rescue or final measures, surgical airways for complete ventilation failure, and coordinated teamwork, effective communication, even though their methods may vary slightly.

Anesthesia and emergency medicine, among other clinical specialties, have benefited greatly from the extensive **use of simulation based learning in medical education. Inadequate treatment of airways continues to be a major source of morbidity and mortality and has long been seen as one of the most difficult responsibilities facing healthcare professionals. A few studies have been conducted on the application of simulation based learning to train medical students in different facets of airway management (4–6). Notably, a systematic review conducted by Y Sun et al. revealed that SBT was linked to improvements in learner behavior, performance, and an increase in learner interest and satisfaction when compared to non-SBT. However, there was no discernible impact on the acquisition of information for airway management (7).**

From the very beginning of training, it is crucial to provide both normal and difficult airways with sustainable airway management training. In addition to non-simulation-based training techniques like classroom lectures, video demonstrations, problem-based learning, case discussions, and traditional airway training methods involve bedside instruction on patients under supervision. It might not be sufficient, though, as an unexpectedly difficult airway is uncommon.

Objectives

Our study aimed to examine the foundational knowledge, self-assurance, and comfort levels of medical students in airway management, to assess the students' knowledge of different airway tools and procedures and to examine how various learning methods affect students' proficiency with airway management.

Method

Study design
Our study was cross sectional prospective study.

Study area
Al-Baha faculty of medicine, Al-Baha, Saudi Arabia.

Study population.
Our research focused on medical students in their clinical years (fourth, fifth, sixth, and internship year) to guarantee a varied sample that would represent different training stages**.**

Sample size and sampling technique.
We included 156 students who represent all fourth, fifth, sixth year as well as internship students in the training program.

Study period
Study was conducted in March 2024.

Data collection tool
Information was collected using a questionnaire, which was filled in by participants in Google form. The questionnaire contains questions regarding; (Gender; study level; participant GPA; Module taken; knowledge, confidence, preparedness and effectiveness assessment questions).

Statistical consideration
SPSS version 24 was used for data analysis and processing, frequency and percentage were used for categorical variable, while mean ± standard deviation was used for continuous variables. Sum tool in SPSS was used calculate the total levels of knowledge, preparedness, confidence and effectiveness, by calculating mean of the domains of each parameter. Chi squire with Fisher exact test were used to find the relation between the modality taken by participants and total level of knowledge, preparedness, confidence and effectiveness.

Ethical consideration
Ethical approval was obtained from Al-Baha medical faculty, ethical review board with IIRB approval number REC/SUR/BU-FM/2024/23

Expected outcomes
• Determine where medical students' airway management skills need to be improved and where knowledge gaps exist.
• Evaluate how various teaching modalities affect students' readiness and self-assurance.
• Give medical educators advice on how to improve training programmers and curricula for airway management.

Results

In our study we included 156 participants, 63.5% were male. Of the overall participants 43.6% were in the Sixth year medical school, 21.2% in the Fourth year, 18.6% in the Fifth year, and 16.7 in internship (Table 1). Providing that A+ score was the maximum and F was the minimum score (in a scale from 0 to 8), the mean participant GPA was 5.6±1.5. The majority of the participant's score, 44 (28.2%), was B+, while the least score was D (1.3%). More than half of the participants took the 3 modules together (Intensive care module, ENT (otolaryngology) module and emergency medicine module), 19.2% had ENT (otolaryngology) module only, 4.5% had Emergency medicine module and 1.3% had Intensive care and emergency medicine modules together, while no module taken in 19.8% of them.

Table 1: characteristics of included participants

		Frequency	Percent
Gender	Male	99	63.5
	Female	57	36.5
Study level	Fourth year	33	21.2
	Fifth year	29	18.6
	Sixth year	68	43.6
	Intern	26	16.7
Participant GPA	D	2	1.3
	D+	2	1.3
	C	9	5.8
	C+	25	16.0
	B	29	18.6
	B+	44	28.2
	A	23	14.7
	A+	22	14.1
Which Module have you already taken	ENT (otolaryngology) module	30	19.2
	Intensive care module; ENT (otolaryngology) module	2	1.3
	Intensive care module; ENT (otolaryngology) module; emergency medicine module	82	52.6
	Intensive care module; emergency medicine module	2	1.3
	ENT (otolaryngology) module; emergency medicine module	1	.6
	Emergency medicine module	7	4.5
	Intensive care module	1	.6
	No module taken	31	19.87
GPA; grade point average			

Regarding the emergency medicine module which was taken by 100 participants the mean ± SD score was (5.5 ± 1.4), the most prevalent score was B+ (17.9%) and the least one was D (0.6%). Intensive care unit module was taken by 94 participants and its mean score was (5.7±1.5), and the most prevalent score was B+ also. The mean score of ENT module was (7.6±0.7) providing that ENT module got the highest mean score among the others (Table 2).

Table 2: grade of participants in each module

Grade/ Module	Emergency medicine module N (%)	Grade in Intensive Care Module N (%)	ENT (Otolaryngology) Module N (%)
M ± SD	5.5 ± 1.4	5.7±1.5	7.6±0.7
1.00 D	1 (0.6)	1 (0.6)	NA
2.00 D+	4 (2.6)	1 (0.6)	NA
3.00 C	3 (1.9)	7 (45)	NA
4.00 C+	13 (8.3)	10 (6.4)	2 (1.3)
5.00 B	25 (16.0)	20 (12.8)	
6.00 B+	28 (17.9)	25 (16.0)	7 (4.5)
7.00 A	19 (12.2)	18 (11.5)	21 (13.5)
8.00 A+	7 (4.5)	12 (7.7)	92 (59.0)
Module not taken	56 (35.9)	62 (39.7)	34 (21.8)
Abbreviation ; NA; not available, M; mean, SD; standard deviation			

Each of the 4 domains assessed in the questionnaire in a scale was as follows; (very poor, poor, moderate, good, and very good). Table 3 demonstrates the frequency and percentages of questions used to assess the 4 domains.

Table 3: frequency and percentage of evaluation parameters in knowledge, confidence, preparedness and effectiveness domains

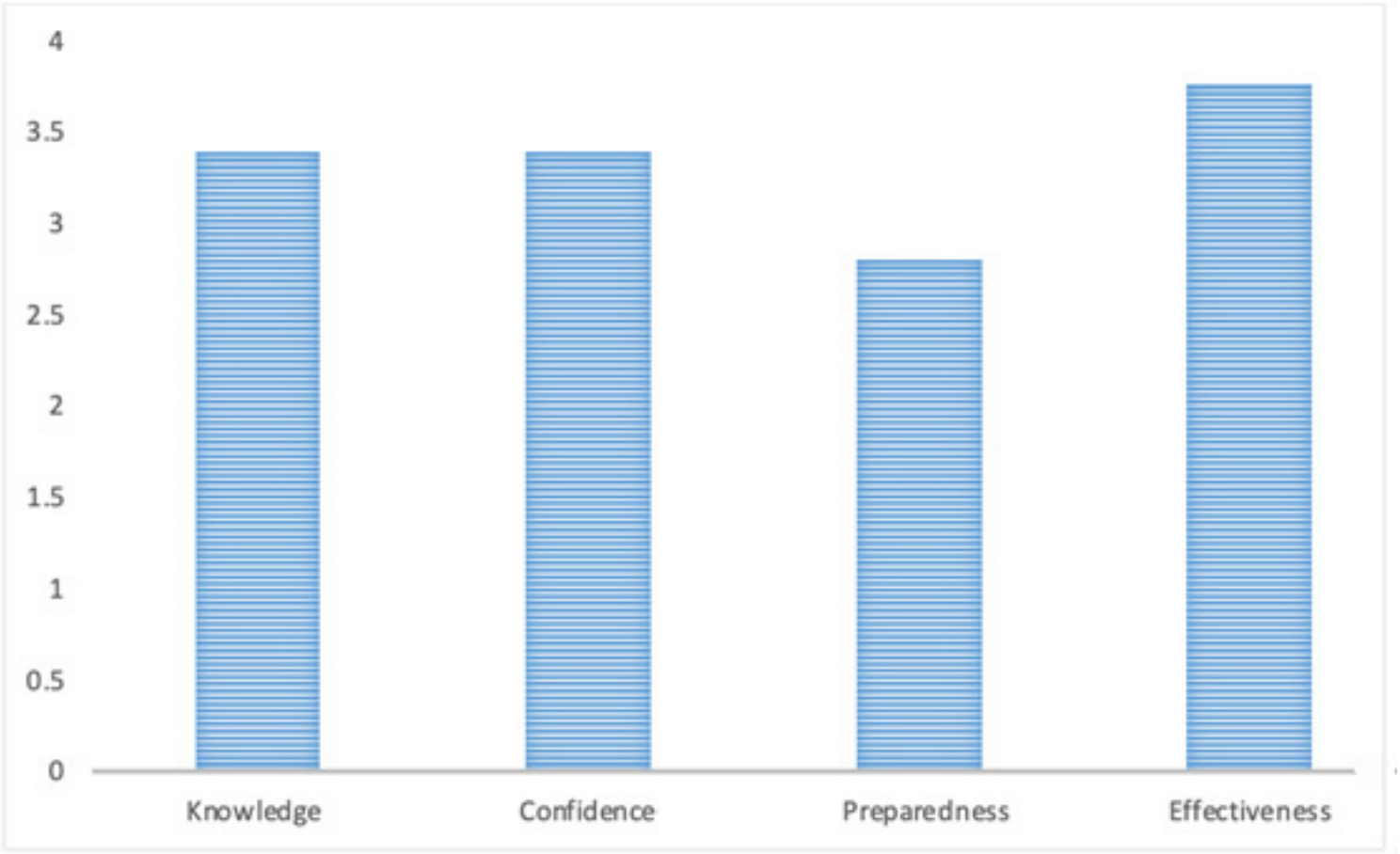
		Very poor	Poor	Moderate	Good	Very good
Confidence to perform Bag-mask ventilation	N	9	16	26	49	56
	%	5.8	10.3	16.7	31.4	35.9
Confidence to perform Endotracheal intubation	N	28	34	40	31	23
	%	17.9	21.8	25.6	19.9	14.7
Confidence to perform supraglottic airway devices	N	25	42	47	27	15
	%	16	26.9	30.1	17.3	9.6
Level of knowledge in Anatomy of the respiratory system	N	2	8	46	67	33
	%	1.28	5.13	29.5	42.95	21.2
Level of knowledge Physiology of respiration	N	3	20	55	50	28
	%	1.92	12.8	35.3	32.05	17.9
Level of knowledge Airway assessment techniques	N	2	7	38	54	55
	%	1.28	4.49	24.4	34.62	35.3
Level of knowledge Techniques for airway management	N	5	27	31	44	49
	%	3.21	17.3	19.9	28.21	31.4
Prepared to perform elective intubation in the operating room	N	37	34	44	24	17
	%	23.7	21.8	28.2	15.38	10.9
Prepared to perform Emergency intubation in the emergency department	N	33	45	41	23	14
	%	21.2	28.8	26.3	14.74	8.97
Prepared for Management of a failed airway situation	N	29	49	45	26	7
	%	18.6	31.4	28.8	16.67	4.49
Effectiveness of Self-directed learning	N	26	25	51	32	22
	%	16.7	16	32.7	20.51	14.1
Effectiveness of Case-based learning	N	15	25	50	33	33
	%	9.62	16	32.1	21.15	21.2
Effectiveness of Clinical sessions	N	7	8	32	36	73
	%	4.49	5.13	20.5	23.08	46.8
Effectiveness of Lectures	N	7	20	51	51	27
	%	4.49	12.8	32.7	32.69	17.3

Total knowledge was obtained by adding all the 4 components of knowledge in the questionnaire (Anatomy of the respiratory system, physiology of respiration, airway assessment techniques, and techniques for airway management) and the mean of total score was calculated and classified into (very poor, poor, moderate, good, very good). Participants who took the modules together had the highest level of good and moderate total knowledge 51.4 and 59.2% respectively (Table 4). Total confidence was obtained by adding all the 3 components of confidence in the questionnaire (confidence to perform Bag-mask ventilation, confidence to perform endotracheal intubation and confidence to perform supraglottic airway devices) and the mean of total score was calculated and classified into (very poor, poor, moderate, good, very good). We found a significant association between the modality type taken and total level of confidence (p value 0.002) (Table 4). Total preparedness was obtained by adding all the 3 components of preparedness in the questionnaire (prepared to do elective intubation in the operating room, prepared to do emergency intubation in the emergency department, and prepared to manage failed airway situation) and the mean of total score was calculated and classified into (very poor, poor, moderate, good, very good). We found a significant association between the modality type taken and total level of preparedness (p value 0.016) (Table 4). Total effectiveness was obtained by adding all the 4 components of effectiveness in the questionnaire (effectiveness of Self-directed learning, effectiveness of Case-based learning, effectiveness of Clinical sessions, effectiveness of Lectures) and the mean of total score was calculated and classified into (very poor, poor, moderate, good, very good). We found no significant association between the modality type taken and total level of effectiveness. Comparison of the mean values for total levels of knowledge, preparedness, confidence and effectiveness is presented in Figure 1.

Table 4: chi square test of (module taken VS total knowledge, preparedness and confidence)

		ENT (otolaryngology) module, n (%)	Intensive care module; ENT (otolaryngology) module, n (%)	Intensive care module; ENT (otolaryngology) module; emergency medicine module, n (%)	Intensive care module; emergency medicine module, n (%)	ENT (otolaryngology) module; emergency medicine module, n (%)	Emergency medicine module, n (%)	Intensive care module, n (%)	No module taken	P value
Total knowledge	Poor	3 (30)	0 (0)	2 (20)	1 (10)	0 (0)	1 (10)	0 (0)	3 (30)	0.291
	Moderate	13 (17.6)	1 (1.4)	38 (51.4)	0 (0)	1 (1.4)	2 (2.7)	1 (1.4)	18 (24.3)	
	Good	14 (19.4)	1 (1.4)	42 (58.3))	1 (1.4)	0 (0)	4 (5.6)	0 (0)	10 (13.9)	
Total confidence	Very poor confidence	1 (25)	0 (0)	0 (0)	00 (0)	0 (0)	00 (0)	0 (0)	3 (75)	0.002
	Poor confidence	9 (33.3)	0 (0)	3 (11.1)	1 (3.7)	0 (0)	3 (11.1)	0(0)	11 (40.7)	
	Moderate	11 (22.4)	0 (0)	22 (44.9)	0 (0)	1 (1.8)	3 (6.1)	1 (2)	12 (24.5)	
	Good confidence	9 (16.4)	0	40 (72.7)	1 (1.8)	0 (0)	1 (1.8)	0 (0)	3 (5.5)	
	Very good confidence	0 (0)	2 (9.5)	17 (81)	0 (0)	0 (0)	0 (0)	0 (0)	2 (9.5)	
Total Preparedness	Very poor preparedness	4 (28.6)	0 (0)	2 (14.3)	0 (0)	0 (0)	1 (7.1)	0 (0)	7 (50)	0.016
	Poor preparedness	9 (20.9)	0 (00	17 (39.5)	0 (0)	0 (0)	2 (4.7)	0 (0)	15 (34.9)	
	Moderate	13 (22)	1 (1.7)	35 (59.3)	0 (0)	00 (0)	4 (6.8)	1 (1.7)	5 (8.5)	
	Good preparedness	4 (13.8)	0 (0)	20 (69)	2 (6.9)	1 (3.4)	00 (0)	0 (0)	2 (6.9)	
	Very good preparedness	0 (0)	1 (9.1)	8 (72.7)	0 (0)	0 (0)	0 (0)	0 (0)	2 (18.2)	
Total effectiveness	Very poor effectiveness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0.352
	Poor effectiveness	3 (30)	0 (0)	3 (30)	0 (0)	0 (0)	2 (20)	0 (0)	2 (20)	
	Moderate	9 (20.5)	0 (0)	19 (43.2)	1 (2.3)	0 (0)	3 (6.8)	1 (2.3)	11 (25)	
	Good effectiveness	14 (19.7)	0 (0)	40 (56.3)	1 (1.4)	1 (1.4)	2 (2.8)	0 (0)	13 (18.3)	
	Very good effectiveness	4 (13.3)	2 (6.7)	20 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	4 (13.3)	

Figure 1: mean scores of total levels of knowledge, preparedness, confidence and effectiveness



Discussion

The knowledge of the participants was evaluated in the following four domains: 1. anatomy of the respiratory system; 2. physiology of respiration; 3. procedures for airway assessment; and 4. techniques for airway management. The majority of participants had a moderate and good level of knowledge, 47.4% and 46.2% respectively. The greatest degree of good and moderate overall knowledge (51.4 and 59.2%, respectively) was attained by participants who completed the 3 modules collectively. In 2021, a study on fifth and sixth grade students at the Faculty of Medicine was carried out to assess the knowledge level regarding airway treatment in maxillofacial injuries. A third of the students reported performing laryngeal mask airway, nasoendotracheal intubation (17%), and orotracheal intubation (61%). Out of the students, thirty-four percent said they didn't use any of these applications. Merely 52% of them reported using a conventional laryngoscope equipped with Macintosh blades. Although 74% of the students believed that a patient with craniofacial injuries lacked the training and expertise to execute intubation comfortably, 81% of the students said they never performed any intubation on a patient with this type of trauma (8). As well as our study, Ömer et al., 2021 study findings show that students' proficiency and understanding of airway management in situations like craniofacial trauma were inadequate.

A patient's airway should be assessed as quickly and accurately as feasible. The patient should be transferred right away to a room with all the necessary equipment when the doctor determines the best course of action for achieving airway control. Physicians should possess not only theoretical knowledge but also the ability to identify and operate tools used in airway care. In our study 35.3% and 34.6% had a very good and good knowledge respectively, regarding Airway assessment techniques.

A number of researchers looking on Turkish doctors' knowledge and proficiency in airway management have been conducted recently. Sixty percent of doctors who serve in ambulances for emergency services in Turkey responded to a poll asking about their training, which included 27 doctors. Furthermore, it was noted that following graduation, none of the doctors had any additional training in airway care (9). More than 80% of participants in a different study that examined research assistants' experiences with airway management during medical specialization training in Turkey said that their first exposure to airway equipment and its use occurred during their internship in anesthesiology and reanimation at the medical faculty. 13.4% of the participants said they had never used the airway, one of the most basic airway devices, whereas 34.3% of them said they had performed their first endotracheal intubation after graduating from medical school (10). In our study only 14.7% had very good confidence in endotracheal intubation.

We evaluated students' confidence in their ability to use supraglottic airway devices, endotracheal intubation, and bag-mask ventilation in our study. 35.9 of the students had very good confidence in Confidence to perform Bag-mask ventilation. 21.8% and 17.9% had poor and very poor Confidence respectively to perform endotracheal intubation. Regarding the performance of supraglottic airway devices 26.9

had poor confidence and only 9.6% had very good confidence to perform. In order to determine how well learning strategies for intubation during the COVID-19 pandemic worked, a study was carried out in 2023, which found that for students at the Faculty of Medicine, the modified and traditional Peyton Four-Step Approach learning technique was equally effective in teaching the fundamentals of endotracheal intubation (11). According to Chugh et al.'s, 2020 study, medical students' information retention was statistically enhanced by spaced instruction combined with extended time learning (12). A study was conducted in 2020 comparing the effectiveness of two widely used supraglottic airway devices, classic LMA and I-gel, in securing airway. Following a brief training period, the study discovered that while overall success was the same, first-attempt success rate was higher than in I-gel's if compared to cLMA's. Most of the participants had the ability to secure airway more quickly and readily with I-gel than cLMA, according to the authors' conclusion, and over 90% of participants preferred I-gel (13).

In the advanced resuscitation, maintaining airway patency during cardiopulmonary resuscitation and implementing optimum ventilation are crucial components. In an earlier study, 52.4% of participants had received practical training on supraglottic airway devices (SADs), compared to 63.4% of participants who had received theoretical instruction on SADs. When performing cardiopulmonary resuscitation on an adult, 81.7% of participants would use a supraglottic breathing device to keep the airway patency open; in the event that a paediatric patient went into cardiac arrest, 71.9% of participants would use the same device (14).

In our study 67.3 of students having either good or very good confidence in performing bag mask ventilation, these findings were similar to a previous study by Lin et al., 2009, where they found the majority of students in the study were aware of the appropriate head placement techniques in both trauma-related and non-trauma-related instances (72% and 93%, respectively) (15).

Conclusion

Participants' confidence in performing endotracheal intubation, supraglottic airways devices once they have to do it, needs to be improved, as well as their preparedness in elective intubation in the operating room and emergency intubation in the emergency department. On the other hand, participants' knowledge in anatomy of the respiratory system, physiology of respiration and airway assessment techniques was good.

More studies and simulated modules improvements in the medical clinical year should be focused on, to ensure graduation of safe efficient students prepared to manage life threatening situations like airway issues.

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