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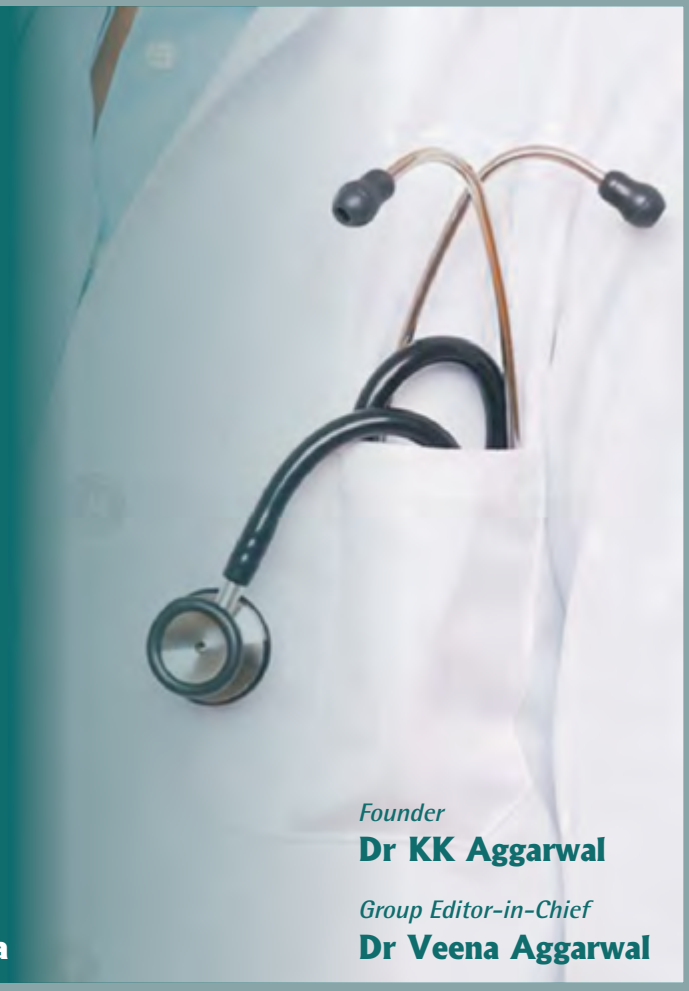

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Impact of PCOS Morphology on Long-Term Risk of Type 2 Diabetes

Women with "string-of-pearls" (SOP) pattern of follicular distribution in polycystic ovary syndrome (PCOS) are at a higher risk of type 2 diabetes compared to women with other patterns of follicular distribution, according to a study presented at the Scientific Congress & Expo of the American Society for Reproductive Medicine (ASRM), held in Denver from October 19 to 23, 2024[1].

This study aimed to investigate the correlation between polycystic ovarian morphology with long-term morbidity and mortality rates in patients with PCOS. Women who enrolled between 1987 and 2005 for long-term health monitoring at a university center were recruited for the study, with follow-up extending to the year 2024. Patients with the "SOP" follicular distribution pattern, defined as presence of 12 or more follicles in the periphery of at least one ovary measuring 2 to 9 mm, were compared with women without this pattern categorized as nonperipheral clustering (NPC). Demographics, serum hormone levels, and cardiovascular risk factors were collected at enrollment for all the participants. The primary outcomes were all-cause mortality and chronic morbidity across a range of health conditions, which included metabolic, cardiovascular, neurological, respiratory, autoimmune, and mental health disorders, as well as specific cancers. Both groups were followed for over three decades.

Out of the initial 1,089 women with PCOS enrolled, 340 had sonographic information available. Of these, 189 had the SOP follicular distribution and 151 had a more random multifollicular distribution.

At the start of the study, patients with SOP follicular distribution were younger with median age of 28.0 years (vs. 32.6 years); they had higher body mass index (BMI) (mean 27.2 vs. 25.3 kg/m^2), and also had higher serum luteinizing hormone, follicle-stimulating hormone, androgens, fasting insulin, total cholesterol, and triglycerides compared to the group with NPC follicular distribution. Seven deaths (3.7%) occurred among patients with the SOP ovarian morphology versus 9 deaths (6.0%) in the NPC group. The SOP group had a significantly younger age of death than the NPC group; 54.3 years versus 70.8 years, respectively.

The prevalence of noninsulin-dependent diabetes mellitus (NIDDM) was significantly higher in patients with the SOP ovarian appearance (23.8%) versus only 9.2% in those with NPC pattern. Women in the SOP group also had a numerically higher rate of hypertension; 34.3% for SOP group versus 25.1% for NPC group; however, this difference failed to reach statistical significance. The prevalence of other medical conditions evaluated did not differ significantly between the two groups.

After adjusting for confounding variables, only NIDDM was found to be associated with the SOP follicular distribution pattern; this group had an almost threefold increased risk of developing NIDDM with adjusted odds ratio of 2.92. However, no other disease state showed

significant between-group difference in the prevalence after controlling for confounders.

This long-term, single-center study confirms that ovarian morphology in PCOS patients is associated with elevated androgen levels and increased metabolic disturbances. However, apart from NIDDM and premature mortality in the SOP group, ovarian morphology had little impact on the development of other chronic diseases later in life in women with PCOS. "Longer follow-up will further delineate how disease states are altered in these groups", conclude the authors.

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Obesitas

The state of having excess fat, or having obesity, is termed, in Latin, as obesitas[1]. Obesitas is used as a noun, as a state of being, and can also be utilized as an adjective to explain the qualities of a person, community, or nation as a non-judgmental, non-sarcastic method of explanation. We use obesitas to describe today's state of affairs, in which obesity has become a pandemic.

The word 'obesity' is used to define a chronic metabolic disorder associated with stigma and ostracization[2]. Various other terms and phrases, such as adiposity and chronic weight management, have been proposed to reduce the negativity linked with obesity and its care. Indeed, there has been a growing concern about body shaming and stigmatization, which, to an extent, has centered around the word "obesity". At the same time, we must not ignore the prevention and treatment of obesity at both a clinical and public health level[3].

Obesity seems to have become endemic. Hot spots exist in the Pacific Islands, the Middle East, North America, and the Caribbean[4]. Obesity rates seem to be plateauing in these areas, as is evidenced by recent data from USA. Results from the National Health and Nutritional Epidemiological Survey suggest that the prevalence of obesity has not grown for the past 4 years[5]. This can also be understood from obesity endemicity indices, which use the prevalence of overweight and obesity or of childhood and adult obesity to predict the future burden of obesity. Thus, there is a probable need for a better term that encompasses the national, regional, and global scale of the epidemic of weight gain, rather than referring to it simply as "obesity".

The word "obesitas" gives an 'Old World' feeling of nostalgia. At the same time, it encourages a proactive approach in fighting the obesity pandemic. Thus, it allows attention and action to address the illness, without encouraging sarcasm or stigmatization of the syndrome. Obesitas can be used as a noun, as in "*She lives with obesitas*", or "*His barophenotype is that of generalized obesitas*", and as an adjective, as follows: "*Obesitas is the flavor of the modern world*".

The word may be rearranged and modified to read *obesisat*, which can refer to a weight tracking device, or clinical evaluation tool; *obesistat*, referring to the hypothalamic set point that prevents change in weight, *obestasis*, which describes the mild venous and lymphatic edema that may accompany obesity, and *obesitus*, a word that may signify a person living with overweight or obesity. Obesitas can be used to issue a clarion call for action at a micro (individual), meso (group), or macro (national) level: "*Let's overcome obesitas*".

Obesitas is similar to Maturitas[6], a respected journal that deals with menopause. It may perhaps be an apt title for a future journal or newsletter on obesity. Until that happens, this editorial's title should suffice to spearhead its use in clinical communication, as well as lay language.

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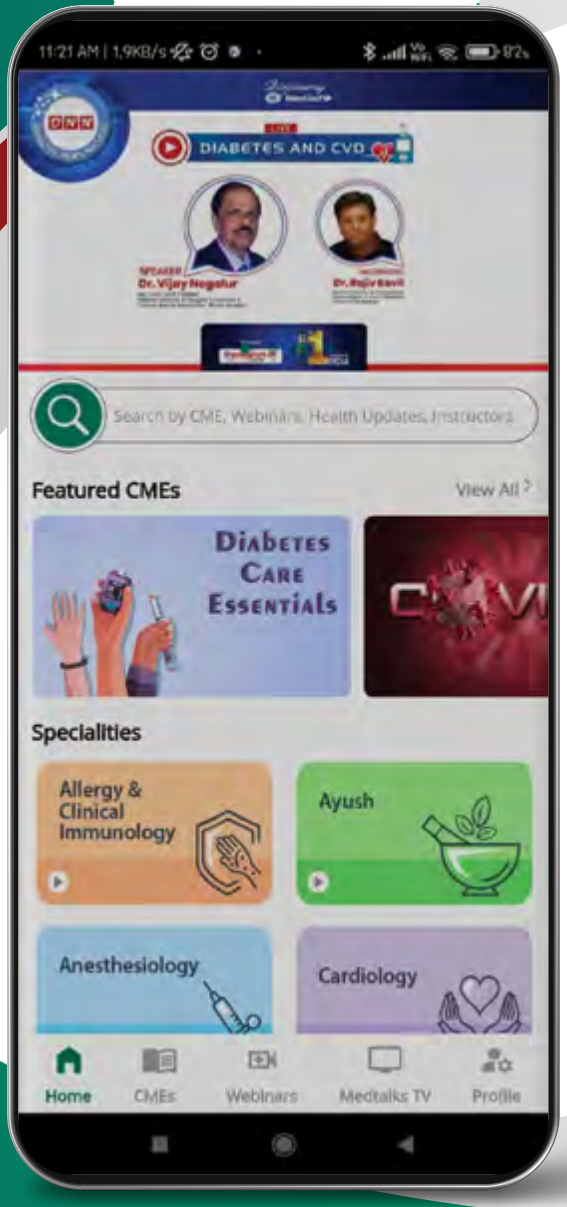

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REVIEW ARTICLE

Challenges and Solutions for Dialysis in Sickle Cell Nephropathy

SOTUBO SOTOMIWA*, SOURABH SHARMA†, AMISU MUMUNI*, ODEYEMI AYOOLA*, BANJOKO OLUWOLE‡, ADEKOYA ADEBOWALE#, AWOBUSUYI OLUGBENGA#

ABSTRACT

Sickle cell disease (SCD) is a hereditary condition characterized by abnormal hemoglobin S (HbS) and intermittent vaso-occlusive crises. Patients with SCD often develop sickle cell nephropathy (SCN), a significant cause of end-stage kidney disease (ESKD) that requires dialysis as a preferred mode of renal replacement therapy. These patients experience higher mortality rates than those with ESKD from other causes due to the unique challenges dialysis physicians face in managing SCN cases. This review discusses these challenges and proposes potential solutions.

Keywords: Sickle cell disease, sickle cell nephropathy, sickle cell crisis, end-stage kidney disease, dialysis, hemodialysis, peritoneal dialysis

Sickle cell nephropathy (SCN) is a crucial contributor to chronic kidney disease (CKD), which, despite its silent progression, significantly impacts survival. Toward the later stages of life, most individuals with sickle cell disease (SCD) require kidney replacement therapy. Although native kidney function is often preserved, kidney disease may go unrecognized, or the need for replacement therapy might be delayed.

SCD is a genetic disorder characterized by the presence of abnormal hemoglobin S (HbS) and recurrent vaso-occlusive crises (VOC). In SCD, the renal medulla is particularly vulnerable to damage when renal blood flow decreases, especially during dehydration, hypovolemia, and chronic anemia. Such events result in specific renal structural changes associated with SCD. CKD occurs in 5% to 18% of the general SCD population, increasing to nearly 30% in patients over 40 years of age[1]. SCN contributes substantially to premature mortality, accounting for 16% to 18% of deaths[2,3].

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Studies indicate a higher 1-year mortality rate following dialysis initiation in SCD patients, though early nephrology care can help reduce this mortality[2]. Rates of CKD and progression to end-stage kidney disease (ESKD) have risen significantly over the past decade, particularly among African American patients. Although CKD is prevalent in SCD and associated with high mortality[3], dialysis treatment for CKD in these patients remains under-examined. Here, we present the dialysis management challenges specific to this patient population.

CHALLENGES IN DIALYSIS FOR SICKLE CELL NEPHROPATHY

The authors, with experience in managing SCN, face various dialysis-related challenges in ESKD cases. These challenges are outlined in Table 1, emphasizing the need to raise awareness among nephrologists and dialysis physicians regarding the elevated mortality risk in SCN-ESKD patients compared to non-SCD patients on dialysis[4].

- **Hemodynamic instability:** Individuals with SCN-ESKD on dialysis have a heightened risk of hypotension due to relatively low blood pressure and anemia, possibly linked to salt-losing tubulopathy[5]. This condition limits blood flow during dialysis, often resulting in inadequate treatment. Extending dialysis duration can improve adequacy[6,7]. Hemoglobin levels must be optimized but should not exceed 10 g/dL to minimize the risk of sickle cell

crises[8]. Conditions like sickle cell cardiomyopathy and anemia-related heart failure also contribute to hemodynamic instability[9]. Sustained low efficiency dialysis (SLED) and peritoneal dialysis may serve as an optimal alternative for such cases[8].

- **Vascular access:** SCN-ESKD patients often exhibit poor compliance with arteriovenous fistula (AVF) creation and have high rates of primary AVF failure. Studies show better survival outcomes in patients using AVF or grafts for dialysis[10]. However, AVF can exacerbate hemodynamic instability, particularly in patients with pulmonary hypertension[11]. AVF use also increases the risks of stenosis, thrombosis, and infection[11]. In cases of access failure, peritoneal dialysis is a viable alternative with less hemodynamic instability[8].
- **Anemia:** Managing anemia in SCN-ESKD presents significant challenges due to resistance to erythropoietin (EPO) therapy, with unachievable targets even at high doses. High EPO doses are linked to elevated mortality and hospitalization risks in SCD[4] and may increase the frequency of VOC[8,12]. Most patients require repeated blood transfusions to reach target hemoglobin levels, posing additional risks of infection and iron overload[13].
- **Sickle cell crisis:** SCN is associated with an elevated risk of VOC[8]. Table 2 outlines the various

Table 1. Challenges of SCN-ESKD on Dialysis and Possible Solutions

Challenges in SCN-ESKD	Underlying mechanism	Possible solutions
Hemodynamic instability	Relative hypotension due to salt-losing tubulopathies, anemia	• Low blood flow rate with longer duration of dialysis to improve dialysis adequacy • Optimize hemoglobin • SLED • Peritoneal dialysis can be adopted for patients with significant residual kidney function
Poor vascular access	Atherosclerosis due to endothelial dysfunction, chronic inflammation, and platelet activation	• Hydroxyurea to increase HbF and nitric oxide • Antiplatelet can be considered if there is significant cardiovascular risk • Consider peritoneal dialysis is vascular access is a challenge
Anemia	• Reduced EPO • Reduce red cell lifespan • Uremic toxins	• High-dose EPO • Exchange blood transfusion
Increase risk of sickle cell crisis	Refer to Table 2	• Refer to Table 2
Poor transplantation outcome	• High sensitization • Comorbidities (e.g., pulmonary hypertension, cardiomyopathy) • Increased thrombotic risk	• Careful patient selection and addressing comorbidities • Transfuse only when necessary, using leukocyte filter

SLED = Sustained low efficiency dialysis; HbF = Fetal hemoglobin; EPO = Erythropoietin.

Table 2. Factors that can Precipitate Sickle Cell Crisis in SCN-ESKD on Dialysis and Possible Solutions[14-21]

Factors precipitating sickle cell crisis	Challenges in sickle cell nephropathy	Possible solutions
Cold weather	Dialysate temperature	• Keep dialysate temperature above 36.5°C • Do not use cool dialysate in intradialytic hypotension
Physical and psychological stress	Exertion, Depression	• Keep stress-free environment • Start antidepressants if needed

Table 2. Factors that can Precipitate Sickle Cell Crisis in SCN-ESKD on Dialysis and Possible Solutions[14-21]

Factors precipitating sickle cell crisis	Challenges in sickle cell nephropathy	Possible solutions
Infections • Atypical bacteria (Chlamydia/ Mycoplasma) • Viruses (RSV/Parvovirus B19) • Encapsulated bacteria	High risk of infections in CKD (dialysis catheters, blood-borne infections, decreased immunity, etc.)	• Strict aseptic precautions • Timely vaccination against Pneumococcus and influenza
Dehydration	Higher risk of dehydration (restricted fluid intake/heat stress/high target ultrafiltration)	• Bioimpedance analysis for dry weight • Avoid heat stress • Weight charting
Low oxygen tension	Respiratory failure (diffusion failure in pulmonary edema and pneumonia or hypoventilation in uremic encephalopathy)	• Strict thrice weekly hemodialysis • Maintain dry weight • Avoid chest infections by applying precautions like face mask, etc.
Acidosis	Metabolic acidosis	• Regular monitoring of bicarbonate levels • Early dialysis initiation • Maintain [HCO_3^-] >23 mEq/L
Pregnancy	Most patients counseled to avoid pregnancy	• Regular counseling • Contraceptive use
Alcohol and Smoking	Most patients counseled to avoid substance abuse	• Regular counseling • Quit smoking and alcohol
Shock	Hypovolemic and cardiogenic shock	• Regular follow-up • Regular cardiology referral • Avoid intradialytic hypotension
Folic acid deficiency	Common in strict vegetarians Dietary restrictions	• Avoid strict dietary restrictions • Regular monitoring of serum folate levels

RSV = Respiratory seasonal virus; CKD = Chronic kidney disease; HCO_3^- = Bicarbonate.

factors contributing to this increased risk, alongside suggested solutions[14-21].

- **Transplantation:** Transplant rates among SCN-ESKD patients are lower, despite the significant survival benefits[4,22]. One-year post-transplant survival is lower in SCN-ESKD compared to non-SCN populations but remains significantly better than in those on dialysis[23]. Increased post-transplant risks, including thrombosis and infection, affect both graft and patient survival[24]. Perioperative blood transfusions to maintain hemoglobin above 10 g/dL and HbS below 30% are recommended to improve post-transplant outcomes[24].

CONCLUSION

In conclusion, dialysis physicians must be aware of the specific challenges in managing SCD-ESKD patients and recognize the factors that can precipitate sickle cell crises in these cases. An in-depth understanding of these conditions and appropriate management strategies are essential for early diagnosis, prompt treatment, and improved mortality and health outcomes in this ESKD population.

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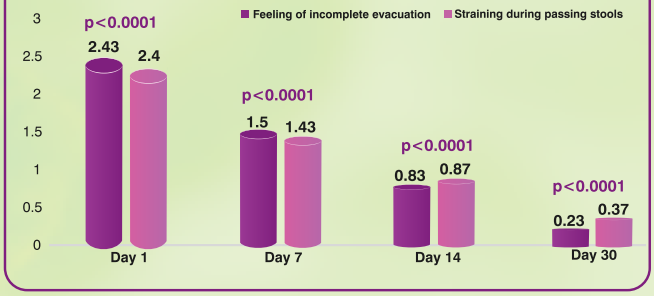

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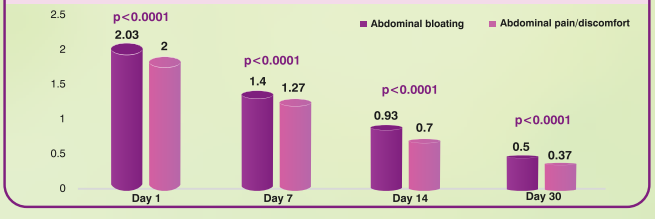

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CLINICAL STUDY

A Controlled Clinical Study to Evaluate the Comparative Effect of Anuloma DS Tablet and Lactitol + Ispaghula Powder in Functional Constipation

RAKESH*, LAKSHMIPRASAD L JADHAV†, YADU GOPAN*, GIRISH KJ†, TOTAD MUTTAPPA‡, VASANTHA B‡

ABSTRACT

Background: The International Classification of Diseases (ICD) has described constipation as decrease in normal frequency of defecation accompanied by difficult or incomplete passage of stool and/or passage of excessively hard, dry stool (ICD10-CM-K59). Overall, the average prevalence of constipation in adults has been estimated as 16% worldwide (varies between 0.7% and 79%); in adults aged 60 to 110 years, the prevalence has been estimated to be 33.5%. **Objective:** To evaluate and compare the efficacy of tablet Anuloma DS and lactitol + ispaghula powder in constipation. **Materials and methods:** Sixty-two subjects with constipation were divided into two groups: Group A with 32 subjects and Group B with 30 subjects. Group A received 1 Anuloma DS tablet at bedtime and Group B received lactitol + ispaghula powder 5 g at bedtime for 15 days. **Results:** Twenty-eight patients in Group A showed significant improvement in stool consistency of stool, whereas just 8 patients showed improvement in consistency of stool in Group B. Twenty patients showed improvement in frequency of stool in Group A, whereas only 3 patients showed this improvement in Group B. Twenty-nine patients in Group A reported good improvement in feeling after defecation compared to 9 patients in Group B. Pain in abdomen improved in 21 patients in Group A versus 9 patients in Group B. Improvements were also seen in scores on the Constipation Assessment Scale, Patient Assessment Scale, and Quality of Life Questionnaire. **Conclusion:** Anuloma DS showed significant clinical benefits in the treatment of constipation compared to lactitol + ispaghula powder.

Keywords: Anuloma DS, constipation, Constipation Assessment Scale, ispaghula, lactitol

The fast-paced, lifestyle adopted by many individuals in today's competitive society has had a significant impact on the health of the gastrointestinal tract resulting in a rising prevalence of gastrointestinal disorders.

Constipation, or *Vibandha*, is one such outcome. *Vibandha* is not mentioned in Ayurvedic texts as a specific disease but has been mentioned as a *Nidana* (causative factor), *Lakshana* (symptoms), and *Upadrava* (complications) of several diseases. It can be considered as a *Lakshana* in *Udavarta* (retention of feces, flatus, and urine) like *Anaha* (obstruction), *Adhmana* (distension), *Malaavastamba* (hardness of feces) due to the *Pratiloma Gati* (reverse flow) of *Apana Vayu*[1].

Vibandha (constipation) is the obstruction of the *Purisha* (feces) in the *Purishavaha Srotas* (excretory system). Constipation is a warning sign for many current or imminent disorders.

The International Classification of Diseases, (ICD10-CM-K59), defines constipation as the decrease in normal frequency of defecation accompanied by difficult or incomplete passage of stool and or passage of excessively hard and dry stool. The prevalence of constipation in India is estimated to be 16.8% and that of self-reported constipation is 24.8%[2]. Overall, the average prevalence of constipation in adults has been estimated to be 16% worldwide (varies between 0.7% and 79%), whereas the prevalence in adults aged 60 to

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110 years was 33.5%[3]. Epidemiological studies show that the prevalence of constipation increases with the age and is more common in women than in men[4].

Various pharmacological agents such as bulk laxatives, stimulant laxatives, stool softeners, osmotic agents, lubricant laxatives, suppositories, and enema are used in clinical practice to treat constipation. However, their long-term use may cause electrolyte disturbance, dehydration and mineral deficiencies, and may even produce drug dependency.

Hence, there is a need for an alternative therapeutic approach, which not only manages the condition, but also minimizes the recurrence of symptoms.

Anuloma DS is an Ayurvedic proprietary medicine that contains different medicinal plants such as *Cassia lanceolata* (Senna), *Apium leptophyllum* (Ajamoda), *Cuminum cyminum* (Cumin or Jeeraka), *Terminalia chebula* (Haritaki), *Glycyrrhiza glabra* (Liquorice), *Zingiber officinale* (Ginger or Shunti), and Halite (Rock salt). These drugs are *Agnideepaka* (increase the digestive fire), *Katu Rasa* (pungent taste), *Ushna Veerya* (hot potency), and *Katu Vipaka*[5].

The primary objective of this comparative study was to evaluate the efficacy of Anuloma DS tablet and lactitol + ispaghula powder in relieving constipation. Improvements in the Quality of Life Questionnaire, Constipation Assessment Scale, and Patient Assessment Scale were the secondary objectives of the study.

METHODS

The study designed as an open-label comparative double arm clinical study enrolled 62 subjects visiting medicine OPDs of our hospital for the treatment of constipation. After screening, eligible subjects were instructed to take either Anuloma DS 1 tablet at bedtime with warm water or lactitol + ispaghula powder 5 g at bedtime with warm milk for a period of 15 days.

The inclusion criteria were male and female adults aged 18 to 70 years, who were suffering from functional constipation, were willing to sign consent form and were able to present for follow-ups.

The primary study objective assessed changes in symptoms of constipation such as consistency of stool, frequency of stool, nature of evacuation, pain in abdomen, generalized weakness, headache, body ache, and muscle cramps. Secondary end points were changes in the Constipation Assessment Scale, which evaluates 8 domains such as abdominal distension, change in amount of gas pass rectally, less frequent bowel movement, oozing of liquid stool, rectal fullness, rectal pain, small stool size, and urge but inability to pass stool. Patient assessment of constipation contain 12 domains such as discomfort- pain-bloating in abdomen, stomach cramp, painful bowel movement, rectal burning, rectal bleeding, incomplete bowel movement, hard bowel movement, small bowel movement, straining to pass bowel movement, and false alarm. And the Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire is a brief but comprehensive tool, which evaluates constipation through daily individual health assessment and functioning.

Constipation was diagnosed based on the Rome IV criteria[6] as follows:

- Fewer than 3 spontaneous bowel movements per week.
- Straining for more than 25% of defecation attempts.
- Lumpy or hard stools for more than 25% defecation attempts.
- Sensation of anorectal obstruction or blockage for more than 25% of defecation attempts.
- Sensation of incomplete defecation for more than 25% of defecation attempts.
- Manual maneuvering required to defecate for more than 25% of defection attempts.

Exclusion criteria were the presence of irritable bowel syndrome, inflammatory bowel disorder, colon carcinoma, medication known to cause constipation (opioid analgesics, antidepressants, anticonvulsants, amitriptyline), uncontrolled systemic ailments or neurological illness, pregnancy and lactation.

The study participants were evaluated at baseline and two assessment points (Visit 1- Day 1 and Visit 2- Day 15). Patients underwent history and physical examination at all assessments points. They were also enquired about constipation signs and symptoms and evaluated with the Constipation Assessment Scale, Patient Assessment Scale, and Quality of Life Questionnaire. Concomitant medication and adverse events were also assessed.

Data comparison between baseline and follow-up visit was performed using a Friedman test, Wilcoxon signed rank test, Mann-Whitney test, unpaired and paired *t*-tests. A p value of 0.05 was considered statistically significant. Statistical analysis was done using statistical software SPSS 21.0.

RESULTS

A total of 62 subjects were enrolled in the study. Two subjects were dropped as they did not come for

follow-up. Hence, 60 subjects were included in the final analysis. Age-wise distribution of subject shows that 28 subjects belong to the age group 18 to 27 years, while 10 subjects belonged to 48 to 57 years. Out of 60 subjects, 34 were females and 26 were males. Thirty-eight subjects belonged to middle class and the diet-wise distribution showed equal number in both vegetarian and mixed diet. Table 1 describes the demographic characteristics of the participants.

Assessment of Signs and Symptoms of Constipation

Constipation symptoms such as reduced appetite, distension of abdomen, pain in abdomen, general weakness, headache, body ache, muscle cramps, consistency of stool, frequency of stool, nature of evacuation, feeling after defecation were assessed on a 4-point scale. The mean symptom scores were significantly improved in Group A compared to Group B as shown in Tables 2 & 3 and Figure 1.

Constipation Assessment Scale and Patient Assessment Scale

Significant improvements were observed in the Constipation Assessment Scale and Patient Assessment Scale in Group A (Anuloma DS) ($p < 0.00$) (Table 4 and Fig. 2).

Assessment of Quality of Life

Group A had significantly greater improvement in quality of life than Group B as assessed via the Quality of Life Questionnaire (Table 5).

DISCUSSION

Constipation is a common condition that affects people of all ages. It is often erroneously attributed to the natural aging process. Although aging is associated with changes in the gastrointestinal tract and may predispose one to develop constipation, the disorder usually has a multifactorial etiology.

Etiologically, constipation can be broadly divided into two main groups: primary and secondary[7]. Primary or functional constipation is defined as constipation for more than 6 months[8], which is not due to any underlying cause such as medication side effect or an underlying medical condition. It can be distinguished from irritable bowel syndrome based on the absence of abdominal pain. It is the most prevalent type of constipation and frequently has multiple causes. Diets, such as consuming too little fiber or water, or behaviors such as engaging in less physical activity are the main culprits[9].

Table 1. Demographic Data of the Enrolled Subjects (n = 60)

Age (years)	Group A (Anuloma DS)	Group B (Lactitol + Ispaghula)
18-27	15	13
28-37	2	4
38-47	3	4
48-57	3	7
58-67	7	2
Gender	**Group A**	**Group B**
Male	13	13
Female	17	17
Diet	**Group A**	**Group B**
Mixed	15	18
Vegetarian	15	12

The incidence of gastrointestinal diseases had an unprecedented hike in recent years. This is mainly due to changes in lifestyle, food habits, behavioral changes, etc. *Annavaha Sroto dushti Vikaras* (disease of gastrointestinal system) explained in Ayurveda classics share similarity with gastrointestinal disorders in terms of etiopathogenesis and symptomatology. *Vibandha* (constipation) is a disease of *Annavaha Srotas* (gastrointestinal system) caused by disturbances of *Agni* (digestive fire). Irregular dietary habits, behavioral changes, stress, etc. lead to *Agnimandya* (weakened digestive fire), which causes *Ajeerna* (indigestion) and then constipation.

Abnormalities of *Samana* (kindling *vata*) – *Apana Vayu* (descending *vata*), *Pachaka Pitta* (digesting *pitta*), and *Kledaka Kapha* (moistening *kapha*) also play significant roles in causing constipation. Along with the difficulty in passing stools, other symptoms like pain in abdomen, flatulence, rectal pain, hemorrhoids, headache can also be associated with constipation. Chronic uncontrolled cases of constipation can lead to complications like *Udavarta*, *Vataja* gulma, *Vatodara*.

Management of constipation includes correction of *Agni*, movement of *Apana Vata* and normalizing the vitiated *Pachaka Pitta* and *Kledaka Kapha*. Different formulations like *Churna*, *Kashaya*, *Arishta*, *Ghrita* are indicated in the management of *Vibandha.*

Management of constipation in contemporary medicine includes lifestyle modifications such as introduction of high-fiber diet, plenty of water intake, physical exercise, and good bowel habits. Various classes of

Table 2. Comparison of Mean Changes in Symptom Score from V1 and V2 (n = 60)

Parameters	Group A (Study Group)			Group B (Control Group)		
	Visit	Mean score (Mean ± SD)	P value	Visit	Mean score (Mean ± SD)	P value
Reduced appetite	V1	1.40 ± 0.724	0.00	V1	1.17 ± 0.747	0.317
	V2	0.47 ± 0.507		V2	1.13 ± 0.730	
Distension of abdomen	V1	1.43 ± 0.626	0.00	V1	1.33 ± 0.711	0.01
	V2	0.40 ± 0.498		V2	1.10 ± 0.712	
Pain in abdomen	V1	0.93 ± 0.785	0.00	V1	0.70 ± 0.750	0.003
	V2	0.20 ± 0.484		V2	0.40 ± 0.498	
Generalized weakness	V1	1.03 ± 0.850	0.00	V1	0.90 ± 0.885	0.002
	V2	0.23 ± 0.430		V2	0.57 ± 0.679	
Headache	V1	0.57 ± 0.858	0.00	V1	0.50 ± 0.777	0.03
	V2	0.10 ± 0.403		V2	0.33 ± 0.606	
Body ache	V1	0.60 ± 0.770	0.00	V1	0.53 ± 0.937	0.03
	V2	0.10 ± 0.305		V2	0.37 ± 0.669	
Muscle cramps	V1	0.57 ± 0.898	0.00	V1	0.80 ± 1.031	0.01
	V2	0.17 ± 0.461		V2	0.60 ± 0.814	
Stool consistency	V1	2.27 ± 0.583	0.00	V1	2.17 ± 0.531	0.01
	V2	1.10 ± 0.305		V2	1.90 ± 0.607	
Stool frequency	V1	1.37 ± 0.556	0.00	V1	1.20 ± 0.407	0.08
	V2	1.00 ± 0.00		V2	1.10 ± 0.305	
Nature of evacuation	V1	2.33 ± 0.479	0.00	V1	2.30 ± 0.535	0.01
	V2	1.27 ± 0.450		V2	2.07 ± 0.640	
Feeling after defecation	V1	2.30 ± 0.466	0.00	V1	2.30 ± 0.596	0.01
	V2	1.20 ± 0.407		V2	2.00 ± 0.695	

Table 3. Comparison of Mean Changes in Symptom Score (n = 60)

	Reduced appetite		Distension of abdomen		Pain in abdomen		Generalized weakness		Headache	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
MR	23.2	37.8	22.7	38.3	27.2	33.8	26.65	34.35	27.5	33.4
SR	695.0	1135.0	681.0	1149.0	816.0	1014.0	799.5	1030.0	827.0	1003.0
P	0.0		0.00		0.06		0.04		0.05	

	Body ache		Muscle cramps		Stool consistency		Stool frequency		Nature of evacuation		Feeling of defecation	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
MR	27.8	33.1	26.3	34.7	20.3	40.7	29.0	32.0	21.1	39.9	21.3	39.3
SR	835.5	994.5	789.0	1041.0	609.0	1221.0	870.0	960.0	632.0	1198.0	639.0	1191.0
P	0.08		0.02		0.00		0.08		0.00		0.00	

MR = Mean Rank; SR = Sum Rank; P = P value

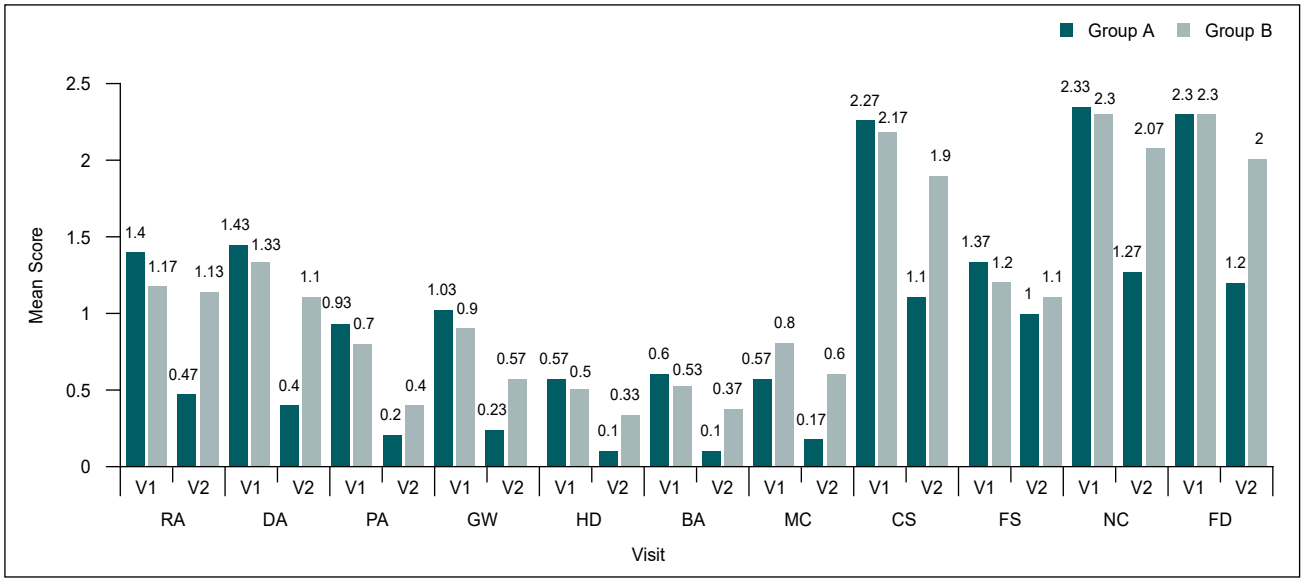

Figure 1. Comparison of mean changes in symptom score from V1 to V2 (n = 60).

RA = Reduced appetite; DA = Distension of abdomen; PA = Pain in abdomen; GW = Generalized weakness; HD = Headache; BA = Body ache; MC: Muscle cramps; CS = Stool consistency; FS = Stool frequency; NC = Nature of evacuation; FD = Feeling after defecation.

Table 4. Comparison of Mean Changes in Constipation Assessment Scale and Patient Assessment Scale from V1 to V2 (n = 60)

Parameters	Group A				Group B			
	Visit	Mean ± SD	SE	P value	Visit	Mean ± SD	SE	P value
Constipation Assessment Scale	V1	5.03 ± 2.13	0.388	<0.00	V1	5.77 ± 2.72	0.498	0.02
	V2	1.73 ± 1.20	0.225		V2	5.60 ± 2.64	0.483	
Patient Assessment Scale	V1	11.8 ± 6.08	1.110	<0.00	V1	12.3 ± 5.37	0.981	0.002
	V2	6.0 ± 3.37	0.061		V2	11.9 ± 5.10	0.931	

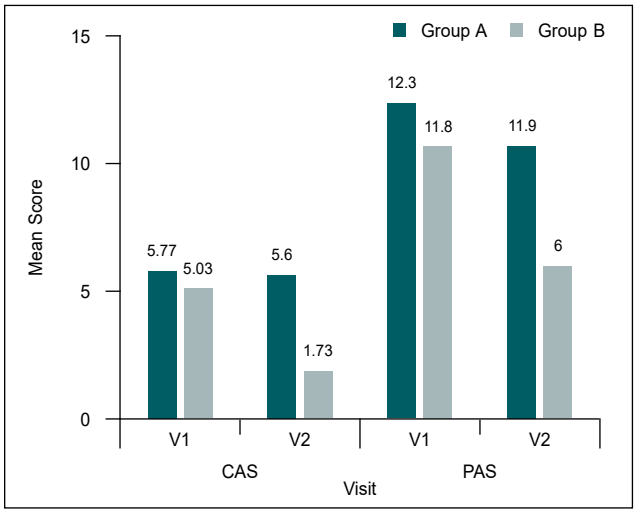

Figure 2. Comparison of mean changes in Constipation Assessment Scale and Patient Assessment Scale from V1 to V2 (n = 60).

CAS = Constipation Assessment Scale; PAS = Patient Assessment Scale.

laxative medications include fiber supplements, osmotic laxatives, stimulant laxatives, lubricants, stool softeners, etc. Enemas and suppositories are used when the above treatments yield no result[10].

Various studies report that women are more than twice as likely to develop constipation as men. This is attributed to the slower gut transit in women due to the changing levels of progesterone and estrogen or damage to the pelvic floor in a women's obstetric history.

Considering the socioeconomical background and dietary habits of the locality, it is not possible to draw any conclusions. Out of 60 subjects, 22 were of *Vata-Kapha Prakriti* and 16 were of *Vata-Pitta Prakriti*. *Vibandha* (constipation) is a *Vata-Dosha Pradhana Vyadhi* (main disease), which may be common among people with *Vata*-predominant *Prakriti*.

In this study, patients in Group A (Anuloma DS tablet) showed significant improvement in primary and

Table 5. Comparison of Mean Changes in Quality of Life (PAC-QOL) from V1 to V2 (n = 60)

Parameters	Group A				Group B			
	Visit	Mean ± SD	SE	P value	Visit	Mean ± SD	SE	P value
Quality of life	V1	50.6 ± 13.2	2.404	<0.00	V1	49.5 ± 12.4	2.235	0.001
	V2	29.9 ± 10.3	1.886		V2	33.8 ± 11.4	2.083	

SD = Standard deviation; SE = Standard error.

secondary outcome measures compared to Group B (lactitol + ispaghula powder) after 15 days of intervention.

Appetite was improved in 26 subjects of the study group and remained same in 4 subjects. In the control group, appetite improved in 1 subject, but remained same in 29 subjects of the control group. Anuloma DS contains *Agnideepaka* herbs like *Ajamoda*, *Shunti* and *Jeeraka, Katu Rasa, Ushna Veerya*, and *Katu Vipaka*, which help in improving the appetite.

Distention of abdomen was found to be reduced in 28 subjects of study group and 7 subjects in control group after intervention. This can be attributed to the *Vata Anulomana* property of Haritaki, which properly digests the *Mala* and facilitates the passage of *Apana Vata*.

Pain in abdomen was reduced in 21 subjects and remained same in 9 subjects of study group and 9 subjects showed reduced symptoms and remained same in 21 subjects in control group. *Shunti* and *Ajamoda* possess *Shoolaghna* property, which helped reduced the abdominal pain.

Generalized weakness was reduced in 20 subjects and remained same in 10 patients. *Agnideepaka* drugs helped in normalizing the *Agni* thereby facilitating digestion and absorption. This might have helped in reducing the generalized weakness. Reduction in generalized weakness is also attributed to *Yashtimadhu*, which is a *Jeevaniya dravya* having *Balya, Glanihara*, and *Kshayahara* properties. Headache was reduced in 11 subjects, but remained the same in 19 subjects in Group A. Body ache was reduced in 13 subjects and remained same in 17 subjects. Muscle cramp was reduced in 8 subjects and remained same in 22 subjects.

Consistency of stool was improved in 28 subjects and remained same only in 2 subjects and 8 subjects improved and 22 subjects remained in control group. Haritaki is *Anulomana dravya*, which does the *Malapaka* resulting in improved consistency of stool.

Frequency of stool was improved in 20 subjects and remained same in 10 subjects and 3 subjects showed improvement and 27 subjects remain in control group. Sonamukhi is *Adhoshodhaka* (laxative) dravya and *Saindhava Lavana* is *Vibandha Hara dravya*. Both helped in improving the stool frequency.

Nature of evacuation was improved in 27 subjects and 7 subjects in study and control group, respectively. Feeling after defecation was improved in 29 subjects and 9 subjects in study group and control, respectively. This was due to the improvements observed in appetite, digestion, consistency, and frequency of stool. Ingredients of tablet Anuloma DS were not only effective in facilitating defecation, but also helped in increasing appetite and digestion. This helped in proper absorption, formation and elimination of stools. This was significantly evident in secondary outcome measures such as Constipation Assessment Scale, Patient Assessment Scale of constipation and Quality of Life Scale.

CONCLUSION

Functional constipation refers to a condition where individuals experience hard, infrequent bowel movements that are often difficult or painful to pass. It is not caused by any apparent physical abnormalities or specific diseases; instead, it is diagnosed by ruling out other potential causes.

The current study as demonstrated significant improvement in signs and symptom of constipation such as stool consistency and frequency, nature of evacuation, feeling of defecation, reduced appetite, pain and distention of abdomen, general weakness, headache, body ache, and muscle cramps with Anuloma DS tablets compared to the lactitol + ispaghula powder in patients with functional constipation. The improvement observed in PAC-QOL, Constipation Assessment Scale, Patient Assessment Scale show that Anuloma DS was highly effective for the treatment in functional constipation vis-à-vis lactitol + ispaghula powder. It was also safe as no treatment-related adverse effects were reported by any of the study participants. This beneficial effect can be attributed to the synergistic therapeutic action of its constituent herbs.

Ethics Approval

The study was undertaken after approval by the Institutional Ethics Committee.

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CLINICAL STUDY

Sequential Administration of Abbreviated Dual Antiplatelet Therapy and Ticagrelor Monotherapy versus Standard Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: A Meta-Analysis

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ABSTRACT

Background: Dual antiplatelet therapy (DAPT), consisting of aspirin, and a P2Y12 inhibitor, has been crucial for reducing ischemic events following percutaneous coronary intervention (PCI). However, the optimal duration of DAPT remains under investigation. **Objective:** This meta-analysis aims to compare the efficacy and safety of an abbreviated-duration DAPT (Abv-DAPT) regimen (ticagrelor plus aspirin for 1 month or less, followed by ticagrelor monotherapy) with a conventional long-term duration DAPT (L-DAPT) regimen (ticagrelor plus aspirin for 12 months) in patients who have undergone PCI. **Methods:** We systematically searched PubMed-MEDLINE, EMBASE, Scopus, and the Cochrane Central Registry of Controlled Trials for studies with cohorts of patients who had undergone PCI and received DAPT with ticagrelor and aspirin. We analyzed data from the ULTIMATE-DAPT, T-PASS, and GLOBAL-LEADERS trials. Efficacy outcomes for this analysis were all-cause mortality, myocardial infarction, stent thrombosis, and stroke. Safety outcomes were major bleeding. The efficacy and safety events in patients of the Abv-DAPT arm were compared with those of L-DAPT arms. **Results:** The consolidated population from three major trials included in the meta-analysis was 22,218, with a nearly equal distribution between the Abv-DAPT arm (N = 11,106) and L-DAPT arms (N = 11,112). Our analysis found no significant difference in the incidence of stroke (RR = 0.95 [0.70-1.29]; p = 0.76), myocardial infarction (RR = 1.15 [0.94-1.4]; p = 0.18), thrombosis (RR = 1.25 [0.86-1.83]; p = 0.25), and all-cause mortality (RR = 0.85 [0.68-1.07]; p = 0.16) between two arms. However, major bleeding events were less (RR = 0.52 [0.27-1.0]; p = 0.05) in the Abv-DAPT arm than in the L-DAPT arm. **Conclusion:** Ticagrelor-based monotherapy after 1 month of ticagrelor-based DAPT could reduce bleeding complications without compromising ischemic protection. PROSPERO Registration: (CRD42024536139 - https://www.crd.york.ac.uk/PROSPEROFILES/536139_STRATEGY_20240726.pdf)

Keywords: Dual antiplatelet therapy, ticagrelor, risk of bleeding, stroke, thrombosis, myocardial infarction, all-cause mortality

Percutaneous coronary intervention (PCI) is a widely performed procedure for treating coronary artery disease, with its success rate heavily reliant on the use of dual antiplatelet therapy (DAPT) to prevent thrombotic complications such as stent thrombosis[1]. DAPT, typically consisting of aspirin and a P2Y12 inhibitor, has been the cornerstone of post-PCI management, particularly in reducing ischemic events during the critical period following stent implantation. Traditionally, DAPT has been continued for 12 months or longer, especially in patients at higher risk of ischemic events[2-5]. Since prolonged use of DAPT could increase the risk of bleeding, particularly in patients with a high bleeding risk (HBR) the optimal duration of DAPT before transitioning to P2Y12 inhibitor monotherapy remains under active investigation[1,3]. Balancing the benefits of ischemic protection against the risks of bleeding is crucial in tailoring DAPT duration,

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necessitating strategies that mitigate bleeding risk while maintaining therapeutic efficacy[1,3,4].

Several clinical trials have evaluated the safety and efficacy of limiting DAPT to 1-3 months, followed by P2Y12 inhibitor monotherapy in patients who have undergone PCI[1,4-6]. Notably, trials such as the MASTER DAPT have demonstrated that abbreviated DAPT regimens can reduce bleeding complications without increasing ischemic events, suggesting that this strategy may be particularly beneficial for patients with HBR[3].

Furthermore, studies have indicated that ticagrelor-based monotherapy following a short course of DAPT, even a 1-month DAPT duration, followed by monotherapy, offers favorable outcomes, including reduced all-cause and cardiovascular mortality[1,4].

This meta-analysis aims to evaluate the safety and efficacy of ticagrelor and aspirin therapy for 1 month or less, followed by ticagrelor monotherapy for 12 months or more in patients undergoing PCI. By synthesizing data from multiple trials, this study seeks to clarify whether a shorter DAPT regimen can provide comparable protection against ischemic events while reducing bleeding risk, thus potentially offering a safer and more effective treatment strategy for post-PCI patients.

METHODOLOGY

We aimed to evaluate the efficacy and safety of ticagrelor monotherapy after abbreviated exposure (1 month or less) to DAPT composed of ticagrelor and aspirin. We analyzed data from ULTIMATE-DAPT[7], T-PASS[8], and GLOBAL-LEADERS[9] trials (Table 1). We systematically

Table 1. Details of the Studies Included

	ULTIMATE-DAPT (2024)[7]	T-PASS (2024)[8]	GLOBAL-LEADERS (2018)[9]
Study Design	Randomized, placebo-controlled, double-blind clinical trial	Randomized, multicenter, open-label	Randomized, parallel, stratified, concealed
Key Inclusion Criteria	Adults (≥18 years of age) who tested positive for NSTEMI or STEMI or tested negative for unstable angina. The individual should not have any reported events after their PCI with DES within 1 month of DAPT.	Adults (>18 years) implanted with bioresorbable polymer sirolimus-eluting stent for ACS.	Patients with an implant of a biolimus-eluting stent for ACS and undergoing PCI.
Key Exclusion Criteria	Patients with a history of stroke (within last 3 months), CABG, or require a surgery within the 12 months.	Individuals with increased bleeding risk, pregnant women or who are expecting to get pregnant and those with a life expectancy <1 year.	Individuals with a contraindication/poor tolerance to aspirin or ticagrelor, history of use of a CYP3A4 inhibitor, fibrinolytic therapy (within 24 hours of PCI). Patients with hepatic disease, history of stroke, risk of bleeding, CABG, or requiring any other surgery within the next 12 months.
DAPT Strategy	***Ticagrelor plus Aspirin*** ***Duration:*** Experimental arm: 1 month in (IVUS-ACS) and 1 month from the time of enrollment Control arm: 12 months	***Ticagrelor plus Aspirin*** ***Duration:*** Experimental arm: Less than 1 month (Media DAPT duration in the group) Control arm: 12 months	Experimental arm: Aspirin + ticagrelor in the experimental arm (1 month) Control arm: Aspirin + clopidogrel or ticagrelor for stable or unstable coronary disease, respectively (12 months).
Outcome Measures	Types of bleeding based on BARC (2, 3, or 5) Adverse cardiovascular and cerebrovascular events.	Bleeding events based on BARC (3 or 5) at 12 months and major adverse cardiovascular events.	All-cause mortality or nonfatal myocardial infarction and bleeding events based on BARC (3 or 5).
Median Duration of Follow-up	1 Year	1 Year	2 Years
Trial Registration	NCT03971500	NCT03797651	NCT01813435

NSTEMI = Non-ST-elevated myocardial infarction; STEMI = ST-elevated myocardial infarction; PCI = Percutaneous coronary intervention; DES = Drug-eluting stent; DAPT = Dual antiplatelet therapy; ACS = Acute coronary syndrome; CYP3A4 = Cytochrome P450 3A4; CABG = Coronary artery bypass graft; IVUS = Intravascular ultrasound; BARC = Bleeding Academic Research Consortium.

searched PubMed-MEDLINE, EMBASE, Scopus, and the Cochrane Central Registry of Controlled Trials database to ensure we had caught all the important trials (Fig. 1). Predefined keywords were short-term Dual antiplatelet therapy OR ("Dual Antiplatelet Therapy/adverse effects" [MeSH] OR "Dual Antiplatelet Therapy/mortality" [MeSH]) AND Percutaneous coronary intervention OR Coronary intervention OR Coronary Revascularization OR ("Percutaneous Coronary Intervention/adverse effects" [MeSH] OR "Percutaneous Coronary Intervention/mortality" [MeSH] OR "Percutaneous Coronary Intervention/standards" [MeSH]) AND Ticagrelor OR P2Y12 inhibitors OR ("Ticagrelor/administration and dosage" [MeSH] OR "Ticagrelor/adverse effects" [MeSH] OR "Ticagrelor/blood" [MeSH] OR "Ticagrelor/metabolism" [MeSH] OR "Ticagrelor/pharmacology" [MeSH] OR "Ticagrelor/therapeutic use" [MeSH]). The detailed search strategy can be found in the link listed below. No language and publication period restrictions were applied. Further reference lists of eligible studies, key journals, trial registers, and internet resources were also searched. Only randomized control trials were included in the analysis. The current meta-analysis is registered in PROSPERO (CRD42024536139 - https://www.crd.york.ac.uk/PROSPEROFILES/536139_STRATEGY_20240726.pdf)

Inclusion Criteria

The search included studies with cohorts of patients who had undergone PCI and had received DAPT with ticagrelor and aspirin.

Exclusion Criteria

Studies with a nonrandomized trial design, a follow-up duration of less than 12 months, and unclear safety and efficacy points were excluded from the study. Further studies with monotherapy with an antiplatelet agent other than ticagrelor were also excluded from the study.

Comparator Groups in the Included Studies

The experimental group consisted of patients who received DAPT with ticagrelor and aspirin for 1 month or less (Abbreviated DAPT: Abv-DAPT), followed by ticagrelor monotherapy. In contrast, the control group included patients who had received DAPT for 12 months or more (Long-term DAPT: L-DAPT). Both groups had received antiplatelet therapy as part of their standard post-PCI treatment.

The intervention involved administering DAPT with ticagrelor (a loading dose of 180 mg, followed by 90 mg twice daily) plus aspirin (a loading dose of 160-500 mg, followed by 100 mg once daily) for 1 month or less (Abv-DAPT). This was followed by ticagrelor monotherapy (90 mg twice daily) for 12 months or more after the index PCI.

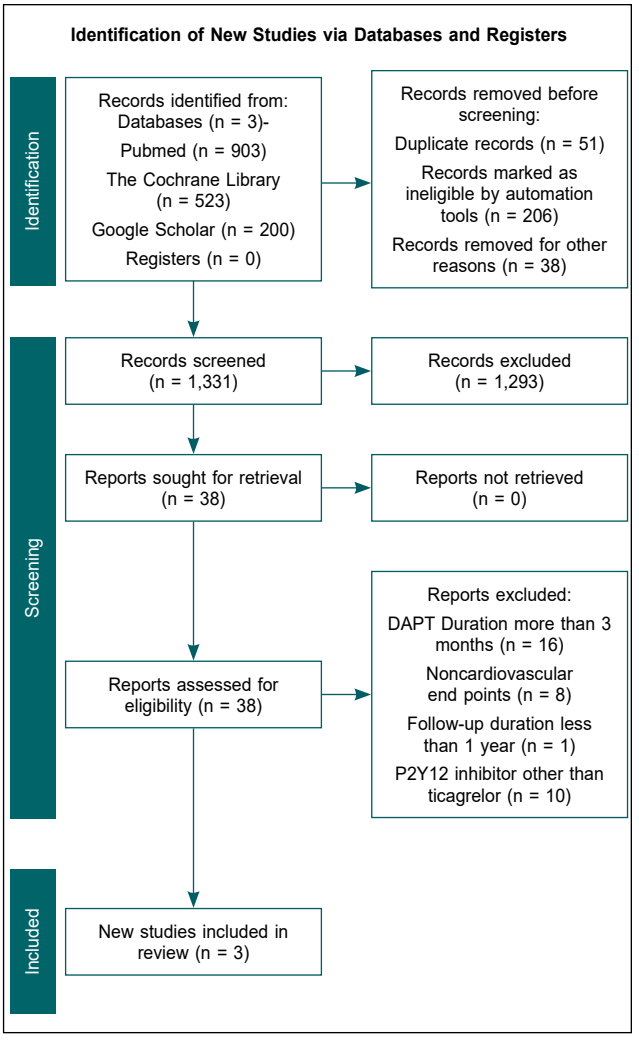


Figure 1. Provides the approach to obtain the studies that fit within the inclusion criteria based on the PICOS strategy.

The comparator was DAPT with any P2Y12 inhibitor (loading dose followed by the standard daily dose) plus aspirin (loading dose of 160-500 mg, followed by 100 mg once daily) for 12 months or more (L-DAPT) after the index PCI.

Similar to the intervention group, antiplatelet therapy in the control group was part of the standard post-PCI treatment. Table 1 provides the characteristics of the included studies.

Outcome Measures

The primary outcome was to assess the efficacy and safety outcomes of interventions. Efficacy outcomes

included all-cause death, cardiovascular death, myocardial infarction, stroke, stent thrombosis, and urgent target vessel revascularization. Safety outcomes focused on major and minor bleeding events.

Measures of Effect

Outcomes for continuous variables were expressed as mean differences (MD) using conventional units. For studies that report results in SI units, conversions to conventional units were performed before analysis. Results were expressed as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes, such as treatment success. Absolute risk differences were calculated for adverse events following treatment. RevMan Web 5.3 was utilized to compare the MDs of the primary and secondary outcomes between the Abv-DAPT and L-DAPT groups.

Data Extraction (Selection and Coding)

Two authors independently extracted data using standardized forms. If multiple publications from the same study group were identified, the results were consolidated, and relevant data from each report was included in the analysis. As mentioned, data on primary and secondary outcomes was extracted. Patient characteristics, including demographic information and comorbidities, were documented in a tabular format from the included and excluded studies. Any disagreements between the authors were resolved by consensus.

Risk of Bias (Quality) Assessment

Three authors independently assessed the risk of bias using the Review Manager (RevMan) web software. The evaluation considered several factors, including adequate sequence generation to avoid selection bias, proper allocation concealment, and measures to prevent knowledge of allocated interventions during the study. Additionally, the blinding of participants, personnel, and outcome assessors was assessed to minimize performance and detection bias. The assessment ensured that incomplete outcome data had been appropriately addressed and the study reports were free from selective outcome reporting. Finally, the study was evaluated for any other potential sources of bias. A fourth author resolved any disagreements among the authors.

A random effect model was used for data analysis, with outcomes expressed as 95% CI. Results were reported as RR with 95% CI for dichotomous outcomes, such as treatment success. Absolute risk differences were calculated for adverse events post-treatment. Forest plots were generated using RevMan software, with the left side of the graph favoring Abv-DAPT and the right side favouring L-DAPT. A p-value of <0.05 was considered statistically significant.

RESULTS

Our search strategy identified three clinical trials that compared the efficacy of DAPT consisting of ticagrelor plus aspirin or clopidogrel plus aspirin for 1 month or less, followed by ticagrelor monotherapy for 12 months or more in patients undergoing PCI. The total population for the meta-analysis was 22,218, with a nearly equal distribution between the experimental (N = 11,106) and control arms (N = 11,112). Baseline characteristics are as per Table 2. The random-effects model was used to analyze five critical outcomes: incidence of stroke, major bleeding, myocardial infarction, stent thrombosis, and all-cause mortality (Fig. 2).

The incidence of stroke was similar between the control group (n/N = 84/11,112 [0.75%]) and the experimental group (n/N = 80/11,106 [0.7%]). The overall RR was 0.95 (95% CI: 0.70-1.29), with no significant difference between the groups (p = 0.76).

The risk of major bleeding events was also comparable between the control group (n/N = 214/11,112 [1.9%]) and the experimental group (n/N = 145/11,106 [1.3%]). The overall RR for bleeding events was 0.52 (95% CI: 0.27-1.00), which was not statistically significant (p = 0.05). Participant characteristics-based subgroup analysis showed higher bleeding in male patients and those with acute coronary syndrome (ACS). However, the analysis was limited by significant heterogeneity (Fig. 3).

Similarly, the incidence of myocardial infarction was comparable between the control group (n/N = 277/11,112 [2.5%]) and the experimental group (n/N = 203/11,106 [1.8%]). The overall RR for myocardial infarction was 1.15 (95% CI: 0.94-1.40), with no significant difference between the groups (p = 0.18).

The incidence of thrombosis was comparable between the control group (n/N = 48/11,112 [0.4%]) and the experimental group (n/N = 60/11,106 [0.5%]). The RR for thrombosis was 1.25 (95% CI: 0.86-1.83), with no statistically significant differences between the groups (p = 0.25).

The incidence of all-cause mortality was also similar between the control group (n/N = 158/11,112 [1.4%]) and the experimental group (n/N = 134/11,106 [1.2%]). The overall RR for all-cause mortality was 0.85 (95%

Table 2. Baseline Characteristics of Patients

Parameters	ULTIMATE-DAPT[7]		T-PASS[8]		GLOBAL-LEADERS[9]	
	Abv-DAPT (n = 1,700)	L-DAPT (n = 1,700)	Abv-DAPT (n = 1,426)	L-DAPT (n = 1,424)	Abv-DAPT (n = 7,980)	L-DAPT (n = 7,988)
Age, years (mean ± SD)	62 (21.3%)	62.6 (18.9%)	61 (10%)	61 (10%)	64.5 (10.3%)	64.6 (10.3%)
Female (%)	436 (25.7%)	443 (26.1%)	233 (16%)	243 (17%)	1,865 (23.4%)	1,849 (23.1%)
BMI (kg/m^2) mean ± SD	-	-	25.1 (3.6%)	25.0 (3.5%)	28.2 (4-6)	28.2 (4-6)
Initial presentation						
Stable CAD (%)	0	0	0	0	4,230 (53.0%)	4,251 (53.2%)
Unstable angina (%)	668 (39.3%)	708 (41.7%)	347 (24%)	361 (25%)	1,004 (12.6%)	1,018 (12.7%)
NSTEMI (%)	545 (32.1%)	531 (31.2%)	507 (36%)	485 (34%)	1,684 (21.1%)	1,689 (21.1%)
STEMI (%)	487 (28.7%)	461 (27.1%)	572 (40%)	578 (41%)	1,062 (13.3%)	1,030 (12.9%)
Medical history						
Diabetes mellitus (%)	540 (31.8%)	535 (31.5%)	422 (30%)	408 (29%)	2,049 (25.7%)	1,989 (24.9%)
Hypertension (%)	1,058 (62.2%)	1,063 (62.5%)	669 (47%)	679 (48%)	5,882 (74.0%)	5,833 (73.3%)
Dyslipidemia (%)	1,178 (69.3%)	1,157 (68.1%)	1,048 (74%)	1,058 (74%)	5,345 (69.3%)	5,423 (70.0%)
Current smoking (%)	486 (28.6%)	482 (28.4%)	557 (39%)	537 (38%)	2,066 (25.9%)	2,103 (26.3%)
Chronic renal insufficiency (%)	119 (7.0%)	129 (7.6%)	118 (8%)	104 (7%)	1,099 (13.9%)	1,072 (13.5%)
Previous myocardial infarction (%)	143 (8.4%)	156 (9.2%)	27 (2%)	25 (2%)	1,831 (23.0%)	1,879 (23.6%)
Previous PCI (%)	171 (10.1%)	174 (10.2%)	92 (7%)	92 (7%)	2,609 (32.7%)	2,612 (32.7%)
Previous CABG (%)	2 (0.1%)	4 (0.2%)	4 (0.28%)	2 (0.14%)	448 (5.6%)	495 (6.2%)
Stroke history (%)	154 (9.1%)	147 (8.7%)	43 (3%)	49 (3%)	210 (2.6%)	211 (2.6%)

Abv-DAPT = Abbreviated dual antiplatelet therapy; L-DAPT = Long-term dual antiplatelet therapy; SD = Standard deviation; BMI = Body mass index; CAD = Coronary artery disease; NSTEMI = Non-ST-elevated myocardial infarction; STEMI = ST-elevated myocardial infarction; PCI = Percutaneous coronary intervention; CABG = Coronary artery bypass graft.

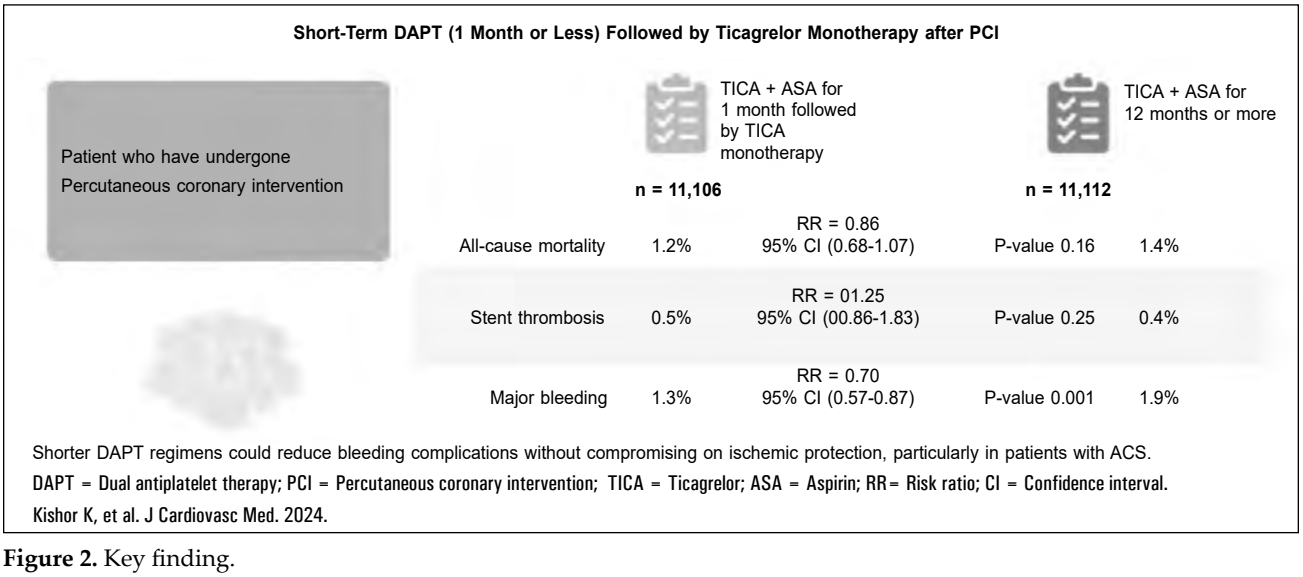


Figure 2. Key finding.

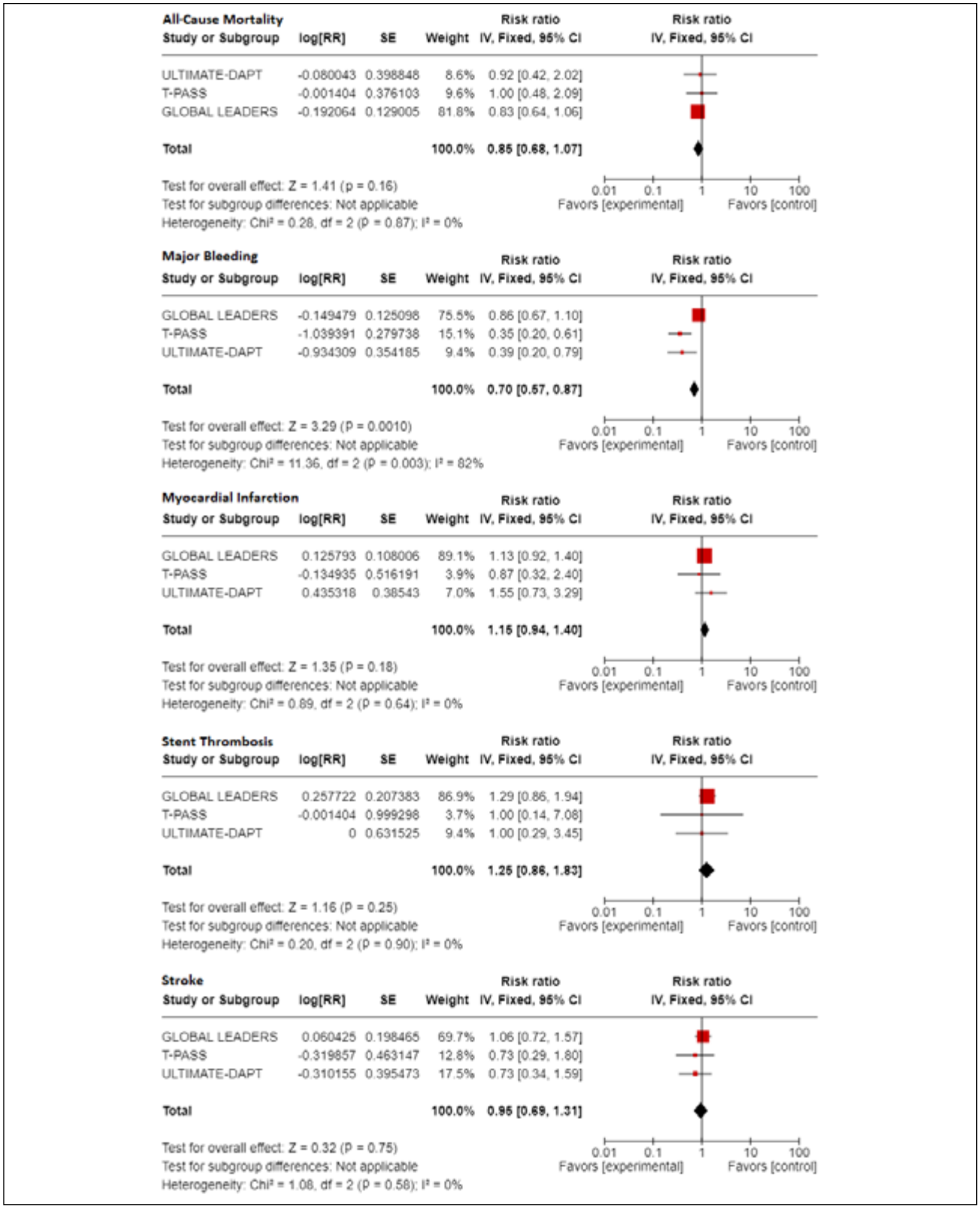
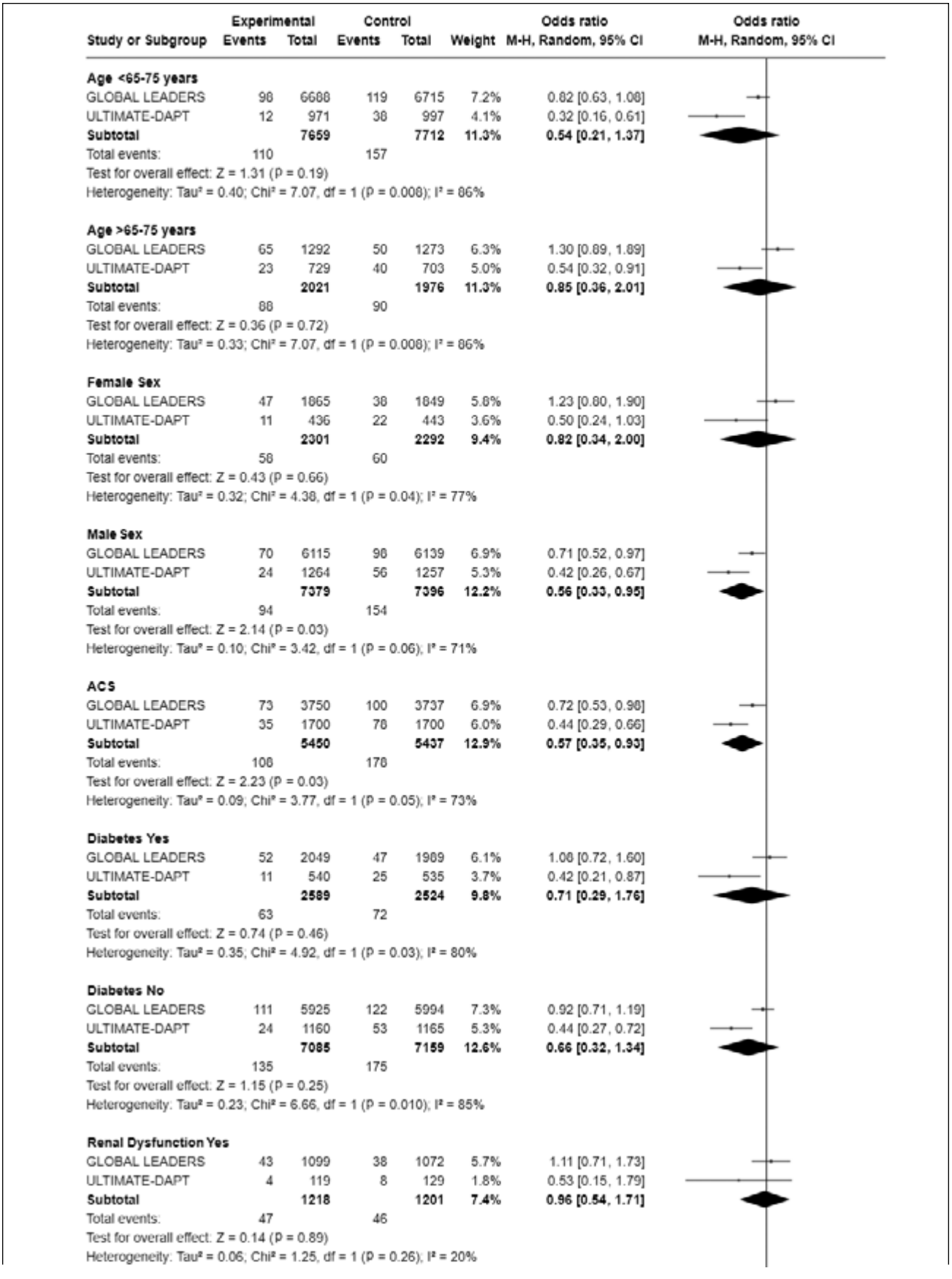


Figure 3. Comparison of the incidence of all-cause mortality, major bleeding, myocardial infarction, stent thrombosis, and stroke between the two groups.

Forrest plots representation of the risk ratio (with 95% CI) of the incidence of all-cause mortality; major bleeding, myocardial infarction, stent thrombosis, and stroke between experimental (Abv-DAPT) vs. control (L-DAPT) groups.


Experimental
Control
Odds ratio
Odds ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Age <65-75 years
GLOBAL LEADERS 98 6688 119 6715 7.2% 0.82 [0.63, 1.08]
ULTIMATE-DAPT 12 971 38 997 4.1% 0.32 [0.16, 0.61]
Subtotal 7659 7712 11.3% 0.54 [0.21, 1.37]
Total events: 110 157
Test for overall effect: Z = 1.31 (P = 0.19)
Heterogeneity: Tau² = 0.40; Chi² = 7.07, df = 1 (P = 0.008); I² = 86%
Age >65-75 years
GLOBAL LEADERS 65 1292 50 1273 6.3% 1.30 [0.89, 1.89]
ULTIMATE-DAPT 23 729 40 703 5.0% 0.54 [0.32, 0.91]
Subtotal 2021 1976 11.3% 0.85 [0.36, 2.01]
Total events: 88 90
Test for overall effect: Z = 0.36 (P = 0.72)
Heterogeneity: Tau² = 0.33; Chi² = 7.07, df = 1 (P = 0.008); I² = 86%
Female Sex
GLOBAL LEADERS 47 1865 38 1849 5.8% 1.23 [0.80, 1.90]
ULTIMATE-DAPT 11 436 22 443 3.6% 0.50 [0.24, 1.03]
Subtotal 2301 2292 9.4% 0.82 [0.34, 2.00]
Total events: 58 60
Test for overall effect: Z = 0.43 (P = 0.66)
Heterogeneity: Tau² = 0.32; Chi² = 4.38, df = 1 (P = 0.04); I² = 77%
Male Sex
GLOBAL LEADERS 70 6115 98 6139 6.9% 0.71 [0.52, 0.97]
ULTIMATE-DAPT 24 1264 56 1257 5.3% 0.42 [0.26, 0.67]
Subtotal 7379 7396 12.2% 0.56 [0.33, 0.95]
Total events: 94 154
Test for overall effect: Z = 2.14 (P = 0.03)
Heterogeneity: Tau² = 0.10; Chi² = 3.42, df = 1 (P = 0.06); I² = 71%
ACS
GLOBAL LEADERS 73 3750 100 3737 6.9% 0.72 [0.53, 0.98]
ULTIMATE-DAPT 35 1700 78 1700 6.0% 0.44 [0.29, 0.66]
Subtotal 5450 5437 12.9% 0.57 [0.35, 0.93]
Total events: 108 178
Test for overall effect: Z = 2.23 (P = 0.03)
Heterogeneity: Tau² = 0.09; Chi² = 3.77, df = 1 (P = 0.05); I² = 73%
Diabetes Yes
GLOBAL LEADERS 52 2049 47 1989 6.1% 1.08 [0.72, 1.60]
ULTIMATE-DAPT 11 540 25 535 3.7% 0.42 [0.21, 0.87]
Subtotal 2589 2524 9.8% 0.71 [0.29, 1.76]
Total events: 63 72
Test for overall effect: Z = 0.74 (P = 0.46)
Heterogeneity: Tau² = 0.35; Chi² = 4.92, df = 1 (P = 0.03); I² = 80%
Diabetes No
GLOBAL LEADERS 111 5925 122 5994 7.3% 0.92 [0.71, 1.19]
ULTIMATE-DAPT 24 1160 53 1165 5.3% 0.44 [0.27, 0.72]
Subtotal 7085 7159 12.6% 0.66 [0.32, 1.34]
Total events: 135 175
Test for overall effect: Z = 1.15 (P = 0.25)
Heterogeneity: Tau² = 0.23; Chi² = 6.66, df = 1 (P = 0.010); I² = 85%
Renal Dysfunction Yes
GLOBAL LEADERS 43 1099 38 1072 5.7% 1.11 [0.71, 1.73]
ULTIMATE-DAPT 4 119 8 129 1.8% 0.53 [0.15, 1.79]
Subtotal 1218 1201 7.4% 0.96 [0.54, 1.71]
Total events: 47 46
Test for overall effect: Z = 0.14 (P = 0.89)
Heterogeneity: Tau² = 0.06; Chi² = 1.25, df = 1 (P = 0.26); I² = 20%

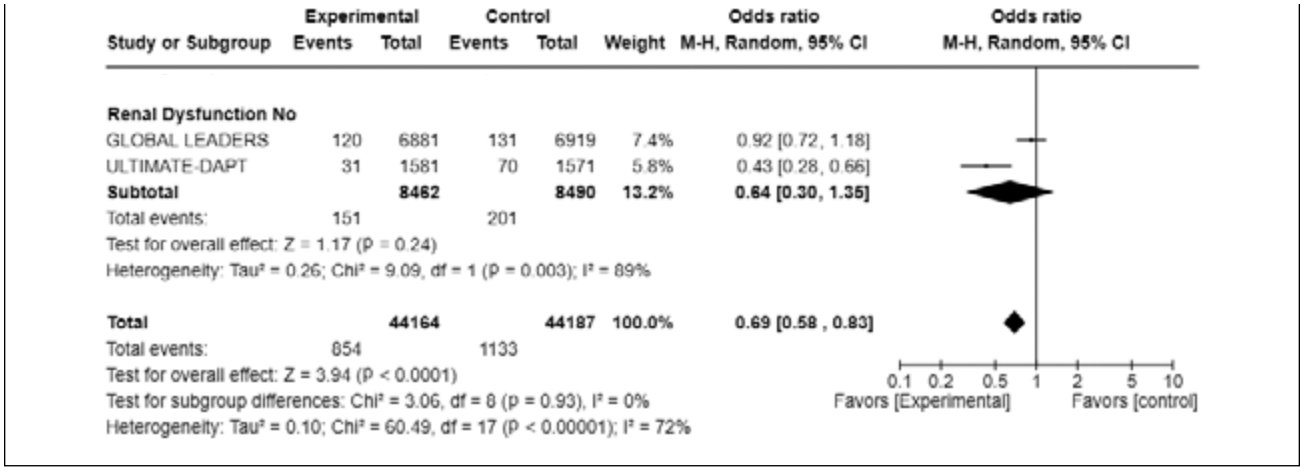


Figure 4. Participant characteristics based subgroup analysis.

Forrest plots representation of the odds ratio (with 95% CI) for the incidence of major bleeding across different participant characteristics between experimental (Abv-DAPT) vs. control (L-DAPT) groups.

CI: 0.68-1.07), with no statistically significant difference between the comparator groups (p = 0.16).

Efficacy outcomes as per age (<65-75 years and >65-75 years), gender, diabetes, and renal dysfunction subgroups is shown in Figure 4.

DISCUSSION

Dual antiplatelet therapy is a crucial component of post-PCI care to minimize ischemic events. Considering the benefit-to-risk ratio, there is a need to optimize the duration of the DAPT regimen to the shortest yet most effective way of reducing ischemic events, especially in HBR cohorts. This meta-analysis identified three trials that administered DAPT for up to 1-month (experimental group) compared to the traditional 12-month period in the control group. Our results from the meta-analysis found no significant difference in the incidence of stroke (RR = 0.95 [0.70-1.29]; p = 0.76), major bleeding events (RR = 0.52 [0.27-1.0]; p = 0.05), incidence of myocardial infarction (RR = 1.15 [0.94-1.4]; p = 0.18), incidence of thrombosis (RR = 1.25 [0.86-1.83]; p = 0.25), and incidence of all-cause mortality (RR = 0.85 [0.68-1.07]; p = 0.16), between the two arms.

The ULTIMATE-DAPT (2024) randomized, double-blind, placebo-controlled trial consisted of diverse patient profiles, including those tested biomarker-positive and biomarker-negative for ACS. The rigorous design of the study and broad inclusion criteria allowed for a comprehensive assessment of DAPT duration across different clinical scenarios, ensuring the findings apply to a wide range of patients[7]. Similarly, the T-PASS (2024) trial, which focused on patients with ACS undergoing bioresorbable polymer sirolimus-eluting stent implantation, provides crucial data on the impact of significantly shortening DAPT duration. This study compared a median DAPT duration of less than 1 month with the standard 12-month regimen, assessing a composite outcome of death, myocardial infarction, thrombosis, stroke, and incidence of any major bleeding events. A key finding from the T-PASS trial was that stopping aspirin within 1 month and transitioning to ticagrelor monotherapy was noninferior and may be superior to the 12-month DAPT regimen for the 1-year composite outcome[8]. This superiority was reflected by a significant reduction in major bleeding events, highlighting the potential benefits of a shorter DAPT duration in this patient population.

Interestingly, the results of the T-PASS trial contrast with those of the GLOBAL-LEADERS (2018) trial, where a 1-month DAPT regimen followed by ticagrelor monotherapy did not demonstrate superiority over the 12-month DAPT regimen in terms of ischemic outcomes[8,9]. The primary factor driving the noninferiority in T-PASS was the significantly lower bleeding rate (1.2% in T-PASS vs. 3.4% in GLOBAL-LEADERS), underscoring the critical role of bleeding risk in determining the optimal duration of DAPT[8]. The findings from ULTIMATE-DAPT and T-PASS are consistent in showing that ticagrelor monotherapy following a shortened DAPT regimen results in a lower rate of clinically relevant bleeding while maintaining similar rates of major adverse cardiovascular and cerebrovascular events compared to more extended DAPT regimens. Both trials focused on populations with ACS, a group at higher risk for both ischemic and bleeding complications, making the balancing of these risks particularly challenging.

Recently, a patient-level meta-analysis concluded that stopping aspirin 1 to 3 months after PCI followed by ticagrelor monotherapy is safer and equally effective as standard DAPT[4]. Unlike clopidogrel, ticagrelor monotherapy significantly reduced major bleeding events (53% reduction in major bleeding), while offering comparable protection against ischemic events[10,11]. Notably, the use of clopidogrel-based monotherapy may pose a considerable challenge in patients with high platelet reactivity[12,13]. While on clopidogrel-based DAPT, the probability of ischemic events in such patients increases as soon as the aspirin is discontinued. The discontinuation of aspirin leaves clopidogrel with suboptimal platelet inhibition and minimal antiplatelet effect due to high platelet reactivity. In contrast, ticagrelor offers more consistent and profound P2Y12 receptor inhibition, thereby substantially reducing ischemic events compared to clopidogrel monotherapy[9]. The analysis has strengths in combining patient-level data from three large trials to quantify the risks and benefits associated with P2Y12 inhibitor monotherapy compared to DAPT continuation after PCI. It also allows for a detailed assessment of the efficacy and safety of ticagrelor and clopidogrel monotherapy across different clinical settings.

Additionally, the analysis captures diverse patient populations and treatment scenarios, enhancing the reliability and applicability of the findings to routine clinical practice. These results and the current meta-analysis suggest that an Abv-DAPT duration, especially with potent P2Y12 inhibitor monotherapy, may effectively balance ischemic risk without significantly increasing bleeding risk. The evidence supports the hypothesis that ticagrelor monotherapy could replace aspirin in DAPT regimens, offering similar protection against ischemic events while reducing the risk of major bleeding.

However, several critical questions remain unanswered, such as determining the best molecule for monotherapy to optimally balance ischemic and bleeding risks, defining the optimal duration of DAPT, and standardizing the factors that should guide DAPT duration in various patient subgroups, such as those who have undergone coronary artery bypass grafting or those at higher risk for bleeding or ischemic events.

The ongoing exploration of these aspects, from complete aspirin elimination to prolonged DAPT regimens, reflects the complexity of managing patients' post-PCI and highlights the need for continued research to refine DAPT strategies further.

CONCLUSION

In conclusion, this systemic literature review and meta-analysis contributes valuable evidence to the growing literature advocating a more personalized approach to DAPT duration. These studies highlight the potential of shorter DAPT regimens in reducing bleeding complications without compromising ischemic protection, particularly in patients with ACS. Future research should address the unresolved issues related to optimizing DAPT strategies and improve patient outcomes following PCI.

LIMITATIONS

This study has several limitations. First, although data from three large trials were combined, the overall sample size may still limit the ability to detect rare safety events and outcomes.

Second, the heterogeneity of the included trials, such as variations in patient populations, procedural techniques, and duration of follow-up, may introduce bias and affect the generalizability of the findings. Additionally, this analysis relies on post-hoc data, which inherently carries the risk of confounding factors that must be fully accounted for. The limitation of long-term follow-up hinders the ability to assess the sustained effects of the intervention strategy.

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CASE REPORT

Refractory Anemia in a Patient with Sickle Cell Nephropathy on Dialysis

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ABSTRACT

This case highlights a middle-aged female with sickle cell nephropathy (SCN) on maintenance hemodialysis who presented with refractory anemia despite initial erythropoiesis-stimulating agent therapy and dialysis. Intensifying dialysis frequency to alternate-day sessions and switching from erythropoietin to darbepoetin significantly improved the patient's management. This report underscores the critical role of adequate dialysis and optimized anemia management in SCN patients.

Keywords: Sickle cell disease, sickle cell nephropathy, refractory anemia, end-stage kidney disease, erythropoiesis-stimulating agents

Sickle cell nephropathy (SCN) is a progressive complication of sickle cell disease (SCD) that often leads to end-stage kidney disease (ESKD)[1,2]. Anemia in SCN patients is multifactorial, driven by chronic inflammation, hemolysis, and erythropoietin (EPO) resistance[3,4]. Adequate dialysis plays a pivotal role in addressing these contributing factors by improving uremia, reducing inflammation, and stabilizing fluid and metabolic imbalances.

Inadequate dialysis can exacerbate anemia, increasing reliance on erythropoiesis-stimulating agents (ESAs) and blood transfusions[5]. This case report describes the management of a patient with SCN and refractory anemia, emphasizing the impact of increased dialysis frequency and the replacement of EPO with darbepoetin in improving anemia control.

CASE REPORT

A 41-year-old female teacher with a history of SCD diagnosed at the age of 3 years and hypertension for 5 years became dialysis-dependent 2 years ago. Initially, she received once-weekly hemodialysis, which was progressively increased to thrice-weekly sessions over the last 6 months.

In the past year, the patient developed bilateral leg swelling, uncontrolled hypertension, and a progressive decline in hematocrit levels, which ranged between 14% and 18%. She reported no bleeding from any orifice, melena, dark-colored urine, jaundice, recurrent fever, weight loss, or night sweats. However, she experienced easy fatigability and palpitations without associated chest pain, dizziness, syncope, orthopnea, or paroxysmal nocturnal dyspnea. There was no abdominal swelling or facial puffiness, but her urine output had significantly decreased.

On examination, the patient had a blood pressure of 180/100 mmHg, bilateral basal crepitations, and bilateral lower limb edema extending to the distal third of the legs. Initial investigations revealed the hemoglobin 6.2 gm%, packed cell volume (PCV) 14%, white blood cell count 9,700 cells/mm^3, platelet count 2,50,000 cells/mm^3, erythrocyte sedimentation rate 46 mm/hr, C-reactive protein (CRP) 7 mg/L, and reticulocyte count 2.2%. Peripheral blood smear showed a reduced number of red cells, numerous sickle cells, and target cells. Biochemistry evaluation revealed serum lactate dehydrogenase (LDH) 496.8 U/L (normal: 130-300 U/L),

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urea 181 mg/dL, creatinine 9.1 mg/dL, total bilirubin 22 μmol/L, conjugated bilirubin 2.8 μmol/L, serum albumin 32.5 g/L, alanine transaminase 25 U/L, aspartate transaminase 45 U/L, serum β_2-microglobulin 12.4 mg/L (<3 mg/L), serum folic acid 24 ng/mL (4.8-37 ng/mL), and vitamin B12 1,357.5 pg/mL (211-911 pg/mL). Direct and indirect Coombs tests were negative. Urinalysis showed traces of protein; serum protein electrophoresis was normal. Iron studies revealed serum iron 20.6 μmol/L, transferrin saturation 71.03%, transferrin 115.48 μmol/L, total iron-binding capacity 29 μmol/L (normal: 42.9-80.5 μmol/L). Extensive investigations ruled out other causes of anemia, including nutritional deficiencies, chronic inflammation, and infection.

The patient was co-managed by a nephrologist and a clinical hematologist. Treatment modifications included continuing dialysis as alternate-day sessions, adjustments in antihypertensive medications- losartan 100 mg daily, atenolol 25 mg daily, torsemide 60 mg daily, and nifedipine XL 60 mg daily, and increasing EPO dose from 4,000 unit twice weekly to 6,000 units and further increase to 10,000 units (twice weekly) after 1 month.

Despite 2 months of ESA therapy, the patient's PCV remained between 14% and 16%. Hemoglobin level stayed around 6.5 gm%. She required occasional intradialytic blood transfusions for symptomatic anemia. Anti-EPO levels were also checked which were found to be within normal range.

To address persistent anemia, EPO was replaced with subcutaneous darbepoetin alfa 40 μg weekly and dose further increased to 60 μg weekly after 1 month. Patient's PCV and hemoglobin levels started rising after 2 months and during last follow-up, patient was asymptomatic with hemoglobin level of 8.9 gm% without requirement of blood transfusion in past 2 months.

DISCUSSION

Anemia management in SCN patients requires a multifaceted approach, with adequate dialysis being a cornerstone of therapy[6]. In this case, the patient's initial once-weekly dialysis regimen was inadequate to address her metabolic and inflammatory burden. Transitioning to alternate-day dialysis improved uremic clearance, reduced inflammation, and stabilized fluid and metabolic imbalances, creating a more favorable environment for erythropoiesis.

Replacing EPO with darbepoetin alfa was the next step in management. Darbepoetin's longer half-life allows for less frequent dosing, improving patient compliance[7].

Moreover, darbepoetin demonstrates superior efficacy in overcoming EPO resistance associated with chronic inflammation and functional iron overload in SCN[8]. Many studies have reported successful conversion of EPO to darbepoetin alfa in cases with EPO resistance[8,9].

Persistent anemia despite optimized dialysis and ESA therapy highlights the multifactorial nature of refractory anemia in SCN[1-4]. Contributing factors in this patient included:

- **Erythropoietin resistance:** As depicted in various studies[10], in our case too, chronic inflammation, as evidenced by elevated β_2-microglobulin and CRP levels, likely reduced ESA responsiveness.
- **Hemolysis:** Elevated LDH levels and peripheral blood smears showing sickle cells indicated ongoing hemolysis.
- **Iron dysregulation:** Functional iron overload, as suggested by a high transferrin saturation, may have further impaired erythropoiesis.

In this patient, the combination of alternate-day dialysis and switched ESA therapy resulted in modest improvements in PCV and reduced the frequency of blood transfusions. However, challenges such as inflammation and hemolysis remain significant barriers to optimal anemia management.

Future strategies could include the use of anti-inflammatory therapies, hydroxyurea optimization to reduce hemolysis, and novel agents targeting the hepcidin pathway to improve iron utilization. This case emphasizes the importance of adequate dialysis in the management of refractory anemia in SCN patients on maintenance dialysis.

CONCLUSION

This case highlights the critical role of adequate dialysis and optimized anemia management in patients with SCN. Intensifying dialysis to alternate-day sessions and transitioning from EPO to darbepoetin significantly improved anemia control.

We want to reiterate the need for individualized management strategies and further exploration of novel therapies for refractory anemia in this challenging patient population.

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CASE REPORT

Echoes of a Hidden Cardiac Tumor: Case Report of a Left Atrial Myxoma

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ABSTRACT

Myxomas are the most common primary cardiac tumors, predominantly arising in the left atrium and less frequently in the right atrium or ventricles. Although benign, myxomas can cause significant symptoms and complications due to embolization, obstruction, or vasoactive substance production. This case report describes a 37-year-old male presenting with intermittent palpitations, anxiety, and breathlessness. Clinical examination and routine investigations were unremarkable except for early finger clubbing. Echocardiography revealed a pedunculated left atrial mass, later confirmed as a myxoma via histopathological examination. The patient underwent successful surgical resection of the tumor. This case underscores the diagnostic challenges of myxomas, particularly in asymptomatic individuals, and highlights the importance of echocardiography for detection. Surgical excision remains the definitive treatment, with follow-up to monitor for recurrence. This case report emphasizes the need for awareness of varied presentations of myxoma and the role of comprehensive cardiac evaluation in symptomatic patients.

Keywords: Asymptomatic cardiac tumor, left atrial myxoma, echocardiography, embolism, surgical resection

Myxomas are the most common primary tumors of the heart and are benign in nature. Seventy-five percent of myxomas arise from the left atrium, either at the mitral valve annulus or the fossa ovalis border of the interatrial septum. Twenty percent arise from the right atrium, and the remaining 5% may arise from the atria, ventricles, or elsewhere. The familial variety may arise from multiple sites and is often transmitted as autosomal dominant. Myxomas are polyploid, round or oval, gelatinous, with a white or yellowish-brown color, and with a lobulated or smooth surface. Though mostly benign, recurrence can occur due to inadequate removal. Recurrence is also common with familial myxomas, and distant recurrence has been reported due to embolization[1]. Females are more frequently affected than males[2].

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Symptoms of myxomas could be due to embolization of the tumor, obstruction of valves by the tumor, or vasoactive substances produced by the tumor. Polypoid tumors are more likely to embolize than round ones[3]. Embolization can occur in the systemic or pulmonary circulation depending on the tumor's presence in the left or right atrium, respectively. Embolization to the systemic circulation may cause cerebral, coronary, or peripheral arterial occlusion, producing relevant symptoms[4]. Embolization to the pulmonary circulation may cause pulmonary infarction and recurrent embolization pulmonary hypertension. The tumor can obstruct the mitral or tricuspid valves and precipitate sudden death, most commonly the mitral valve[5]. Systemic symptoms like fever, arthralgia, weight loss, and Raynaud's phenomenon may occur, attributed to interleukin-6 (IL-6) produced by the tumor mass. Patients are often asymptomatic and found to have a cardiac mass when echocardiography is performed for any other purpose.

Physical signs are scanty but signs of left or right heart failure may be observed. Loud and delayed P2 due to pulmonary hypertension, and a systolic murmur due to mitral or tricuspid valve destruction by the tumor may be present. A loud S1 is caused by a delay in the closure of the mitral or tricuspid valve due to obstruction by the tumor. An early diastolic sound called a tumor plop

may be heard. Tumor obstructing the mitral or tricuspid valve may produce a diastolic murmur resembling the murmur of valvular stenosis. Variability of the diastolic murmur with a change of body posture is said to be pathognomonic of myxoma. In a few cases, clubbing has been observed.

There are no specific laboratory diagnostic tests for atrial myxoma. Normocytic normochromic, microcytic, or hemolytic anemia may be found. Leukocytosis, elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and gamma globulin may be observed. Serum levels of IL-6 may be raised and can be used as markers of recurrence[6].

Two-dimensional echocardiography is good enough for the diagnosis, although transesophageal echocardiography (TEE) is more sensitive. Left atrial myxoma needs to be differentiated from a left atrial thrombus. A thrombus is usually located in the posterior atrium and has a layered appearance. The presence of a stalk and mobile nature favors left atrial myxoma. Magnetic resonance imaging (MRI) can provide additional information regarding the location of the mass. Preoperative coronary angiography is valuable in evaluating the vascularity of this tumor[7].

Myxomas need to be differentiated from a thrombus, which closely resembles it. Carcinoid heart diseases and valvular heart diseases at times are close contenders. Left atrial myxoma has been wrongly treated as endocarditis[8].

Surgery is the treatment of choice, either by median sternotomy or robotically-assisted minithoracotomy[9].

CASE REPORT

A 37-year-old male patient presented with a history of intermittent palpitations, anxiety, and breathlessness lasting 5 to 10 minutes, not associated with exertion over the past 3 months. These episodes occurred 4 times during this period. He was employed as an engineer in Saudi Arabia. He did not report chest pain, fever, body pains, lethargy, or loss of appetite. There was no history suggestive of rheumatic fever during childhood. He had been undergoing annual health checks as mandated for his parents' employment. While he experienced anxiety about his symptoms, his sleep was not disturbed. He was married with children.

On general examination, he appeared well-built and well-nourished, without anemia or lymphadenopathy. He exhibited early clubbing of the fingers but no cyanosis. No obvious skin abnormalities were noted. Jugular venous pressure was normal and no pedal or sacral edema was detected. Respiratory examination, normal breath sounds were heard. Cardiovascular examination revealed normal heart sounds with no murmurs detected in sitting and supine positions. Abdominal palpation revealed no hepatosplenomegaly, and examination of the central nervous system did not reveal any abnormalities.

Laboratory findings showed a total leukocyte count of 11,400 cells/μL, hemoglobin of 15.8 grams %, platelet count of 4,90,000/μL, and ESR of 12 mm/hour. Creatine phosphokinase, lipid profile, liver function tests, and renal functions were within normal limits. Peripheral smear indicated mild thrombocytosis. Screening tests for hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus (HIV) were negative.

Chest X-ray, electrocardiography, and abdominal ultrasound were normal. Echocardiography revealed a pedunculated left atrial mass measuring 2.53 × 1.76 cm suggestive of myxoma (Fig. 1). TEE confirmed this finding. Coronary angiography showed normal coronary arteries without abnormal tumor circulation.

The patient underwent surgery, during which the left atrial mass along with the fossa ovalis was excised via

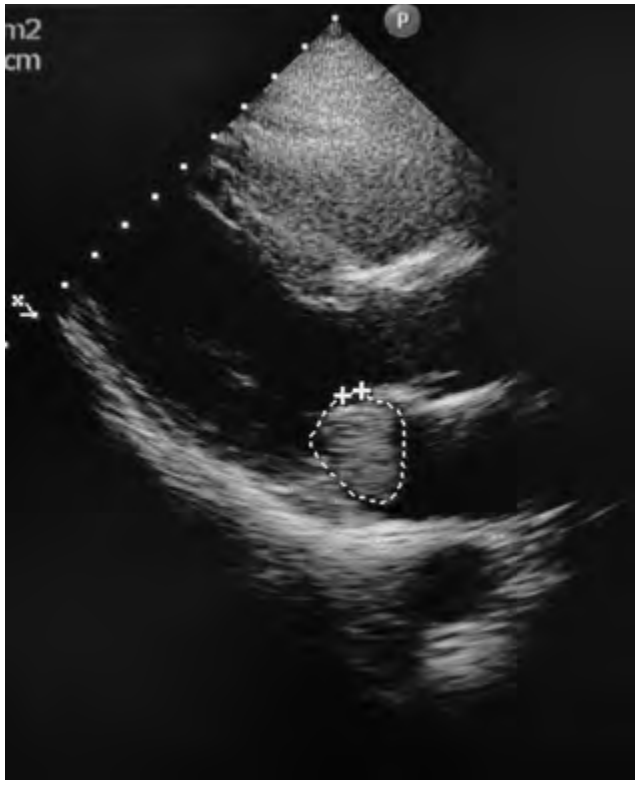

Figure 1. Echocardiography showing a mass of 2.53 × 1.76 cm in the left atrium close to the mitral valve orifice.

a transthoracic approach (Fig. 2). Histopathological examination of the mass revealed stellate, fusiform, and polygonal cells immersed in an amorphous myxoid matrix consistent with myxoma (Fig. 3). Subsequent monthly reviews postoperatively for 1 year showed no signs of recurrence, and the patient remained asymptomatic.

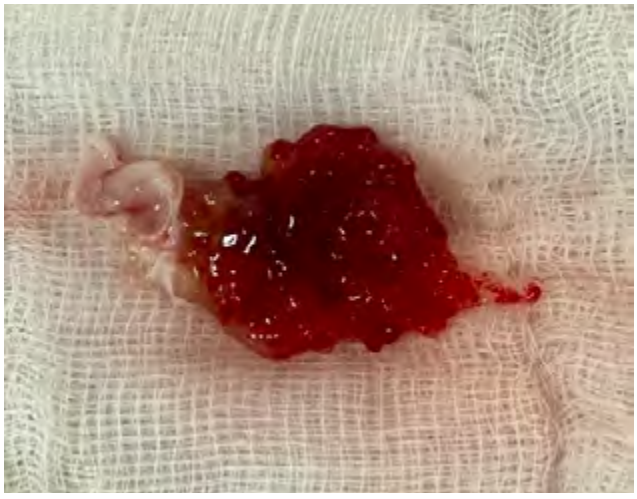

Figure 2. Specimen of left atrial myxoma along with fossa ovalis, surgically excised.

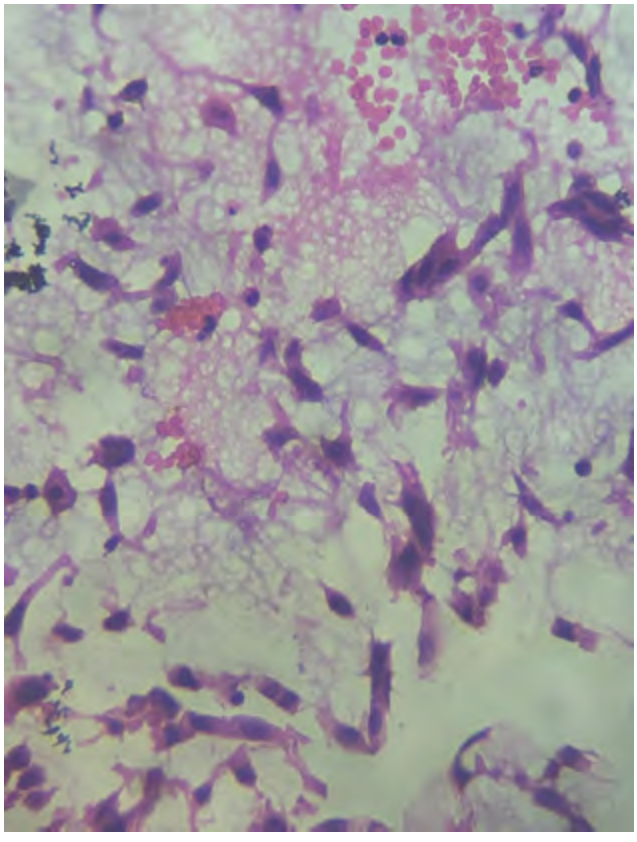

Figure 3. Histopathological examination of the mass revealed stellate, fusiform, and polygonal cells immersed in an amorphous myxoid matrix consistent with myxoma.

DISCUSSION

Our patient presented with episodic palpitations, breathlessness, and transient anxiety. Left atrial myxomas often present with mild symptoms, posing a diagnostic challenge. Conversely, they can lead to sudden death due to cardiac valve obstruction, commonly affecting the mitral valve given that 75% of myxomas originate in the left atrium near the mitral valve annulus or fossa ovalis border of interatrial septum, as observed in this case. A subset of cases involves familial myxomas, which typically exhibit autosomal dominant inheritance and may manifest at multiple cardiac sites.

Symptoms of myxomas vary depending on their effects, whether obstructive, embolic, or through biochemical mechanisms. Our patient did not exhibit systemic symptoms or elevated inflammatory markers suggestive of vasoactive substance secretion by the tumor. There were no syncopal episodes or signs of flash pulmonary edema indicative of significant valvular obstruction, nor symptoms suggestive of systemic or pulmonary embolism. The tumor measured 2.53 × 1.76 cm, with larger tumors (>5 cm) more likely to cause valvular obstruction. It had an oval shape; the polypoid shape increases the likelihood of embolization.

No cardiac murmurs were detectable in either sitting or supine positions, nor were there any additional sounds noted. The absence of clinical signs such as a loud and delayed P2 ruled out pulmonary hypertension and pulmonary embolism from the tumor. Clubbing was the sole clinical sign attributable to the myxoma in our patient, underscoring the diagnostic challenges associated with myxomas.

There are no specific biochemical tests for diagnosing myxomas, although some cases may present with elevated ESR and CRP levels, which were not observed in our case. Reports indicate associations with leukocytosis, anemia, and hemolysis, but our patient exhibited normal leukocyte counts and had no anemia. Thrombocytopenia has been reported in some cases, whereas our patient had thrombocytosis[10].

Echocardiography, performed as part of cardiac screening for symptoms, unexpectedly detected a left atrial mass. It remains the preferred diagnostic modality, with TEE offering higher sensitivity. Cardiac MRI can provide additional details on tumor location but was unnecessary in our case. Coronary angiography ruled out obstructive coronary artery lesions and vascularization abnormalities of the tumor, revealing normal coronary arteries with no aberrant circulation.

Surgical resection of the tumor, including the fossa ovalis attachment, was performed and sent for

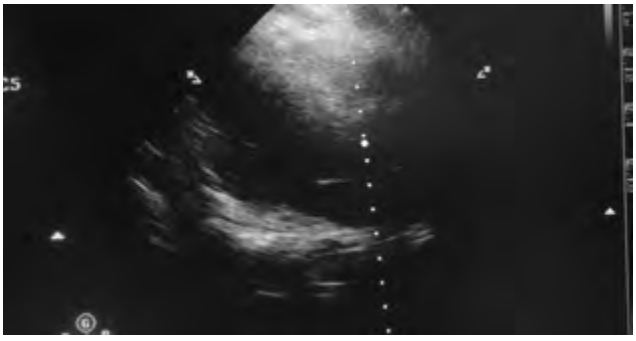

Figure 4. Postoperative Echo showing absence of the tumor in the left atrium.

histopathological examination. This approach minimizes the risk of recurrence. Postoperative echocardiography confirmed the absence of residual tumor mass in the left atrium (Fig. 4).

CONCLUSION

This case highlights the clinical presentation, diagnostic approach, and management of left atrial myxoma in a young male patient. Echocardiography remains pivotal in diagnosis, with surgical excision being curative in most cases. Awareness of familial predisposition and diligent follow-up are crucial for long-term management.

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Declarations

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BRIEF COMMUNICATION

What is Person-Centered Care?

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This question has been asked, and answered by multiple experts, in multiple ways[1-3]. It may be safe to say, in fact, that just as there are 8 billion inhabitants on earth, there may be 8 billion answers to this question. A standard definition of person-centered care, however, continues to be quoted in literature. The Institute of Medicine (IOM), Washington DC, USA defines person-centered care as care that is respectful of, and responsive to, the preferences, needs and values of the individual, and is guided by his or her values[4].

The word 'care' itself, can be used as a noun, or as a verb. 'Careful' is an adjective, which can be used to describe the quality of caring, or of care. The word 'person' refers to the individual who interacts with the health care system, in an effort to promote health, prevent disease, or placate illness.

In this perspective piece, we utilize the preceptive platform of our journal to decipher and describe the peculiar, poly-faceted properties of person-centered care.

Person-centered care, we feel, is much more than a mere provision of care, or even a process of health management. Person-centered care is a philosophy, which must be incorporated and internalized; a pedagogy, which must be taught and shared, and a partnership, which must be established and nurtured. It is a practical and prudent praxis, which ensures optimal prevention of disease at all levels, and allows positive payback or pay off in the form of health.

Person-centered care is a perception as well, for all stakeholders involved in health care, including the person, their peers and caregivers, the public at large, physicians and other health care providers.

Not only this, person-centered care contributes to the personal evolution and growth of the health care professional. It professes patience, persistence, and perseverance, while promoting passion and prurience for our profession. It acts as a protective shield, not only against potential professional mishaps such as litigation, but also against possible psychosocial burnout. In a nutshell, person-centered care is a proactive method of preserving and promoting one's own personal as well as professional health.

Person-centered care is a proceeding in perpetuity, which works as a virtuous chain or cycle of excellence. Enhanced experience and expertise contribute to personality development of engaged personnel. Provision of person-centered care, therefore, should be part and parcel of all health care policy making, planning, and preparation. Table 1 proposes a panorama of person-centered care, which puts all our discussion as a precis.

We understand that every publication is viewed in a person-centered manner by those who read it. Some may consider this poetry; others may label it as prosaic. Our purpose, however, is to stimulate our readers to explore the wide universe of person-centered care, and widen their horizons. This will ensure meaningful growth, not only for the persons and public we care for, but also for us, and for the profession we love so much.

Table 1. The Person-Centered Care Panorama

Person-centered care is a

- Philosophy and part of pedagogy
- Partnership between people and professionals
- Prudent and proactive practice
- Pragmatic and practical prescription
- Preventive and promotive process for health
- Positive payback or pay off
- Psychosocial protective shield
- Personality developer, promoting passion, and prurience
- Platform for patience and perseverance
- Perception of people and professionals
- Part & parcel of policy making and planning
- Proceeding in perpetuity

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Bhagadatta: The First Case Report of Ocular Palsy

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It is often said that the Mahabharata is a complete encyclopedia. In this communication, we explore a case of neuro-ophthalmology, as described in the epic. Bhagadatta, the King of Pragjyotisha, took part in the Mahabharata, fighting on the side of the Kauravas. Riding his war elephant, Supratika, he was one of the most feared generals of the war[1].

Bhagadatta, is described as an old man, with a wrinkled face and drooping eyelids. To prevent these from obstructing his vision, he tied thin folds of a silken handkerchief over his forehead. On the 12th day of the 18-day long Mahabharata war, Bhagadatta fought with Bhima. He had almost defeated him, when Lord Krishna and Arjuna came to support their brother. Arjuna aimed his arrows at the King's handkerchief, tearing it and blinding him successfully. This allowed Arjuna to kill Bhagadatta and Supratika, and contributed to the victory of the Pandavas[1].

This nugget from our history raises significant issues. The author of the Mahabharata, Rishi Ved Vyas, was astute and discerning enough to note the wrinkles and drooping eyelids of one of the characters. He described them accurately, including details about how Bhagadatta managed his limitation.

Did the elderly King have third nerve palsy?[2] Or was it myasthenia gravis? Was it a congenital anomaly, or an event associated with old age? The seemingly bilateral and symmetrical nature of eyelid drooping suggests an ischemic or metabolic etiology, rather than a localized lesion. The commonest cause of eyelid droop is senility[3], also known as senile involution. There is no mention of a diurnal variation in the severity of Bhagadatta's symptoms. However, the explanation that he became almost blind towards the end of the day, suggests that he may have had myasthenia gravis. Table 1 lists other possible differential diagnoses of drooping eyelids.

Table 1. Differentials of Bhagadatta's Condition

Etiology	Bilateral	Eyelid crease margin	Other clinical feature
Congenital abnormality of the levator muscle	Sometimes	Crease often absent	Associated with amblyopia, strabismus
Oculomotor nerve palsy	Rarely	Normal	Impaired extraocular movement in ipsilateral eye; may be due to aneurysm
Myasthenia	Sometimes	Normal	Variable; associated with fatigue
Aponeurotic ptosis	Sometimes	Often increased	Isolated ptosis
Horner's syndrome	Rarely	Normal	Ipsilateral miosis
Myopathy	Yes	Normal	Orbicularis oculi, other extraocular or bulbar muscles may be affected

Epics and classic literatures are a useful platform to explore and learn the complexity of medicine in an interesting and fun-filled manner[4].

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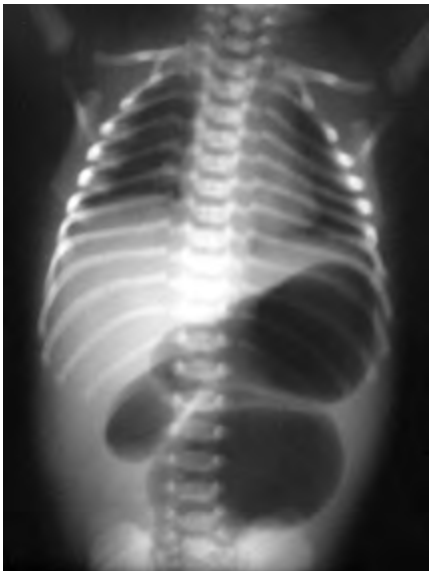
PICTURE QUIZ

What is the Diagnosis?

A preterm baby boy of 34 weeks gestation was born via normal delivery. There was history of polyhydramnios and the antenatal ultrasonography finding was suggestive of upper gut obstruction. Baby weighed 1.9 kg. Abdomen was soft without any distension. Blood reports were normal. Abdominal X-ray revealed three prominent gas shadows in upper abdomen with gasless distal abdomen.



a) Apple peel jejunal atresia

b) Esophageal atresia

c) Pediatric duodenal atresia

d) Biliary atresia

Answer to the Picture Quiz from the Indian Journal of Clinical Practice, Vol. 35, No. 6, November 2024
Answer: (a) Amniotic band syndrome

See Answer in the Next Month's Issue!

Doctor-Patient Relationship

The doctor-patient relationship is central to the practice of medicine and is essential for delivery of high quality health care in the diagnosis and treatment of disease.

The doctor-patient relationship is multilayered, dynamic, and bilateral. It has been defined as "a consensual relationship in which the patient knowingly seeks the physician's assistance and in which the physician knowingly accepts the person as a patient. However, such a contractual definition fails to portray the immense and profound nature of the doctor-patient relationship. Patients sometimes reveal secrets, worries, and fears to physicians that they have not yet disclosed to friends or family members.

The relationship between the doctor and patient is a fiduciary relationship. This bond of trust between the doctor and the patient is essential to begin the process of healing. Doctors must adhere to the principles of medical ethics (autonomy, nonmaleficence, beneficence, and justice), rules (fidelity, confidentiality, privacy, and veracity), and virtues (compassion, kindness, respect, etc.) in their interactions with the patients, which have been laid down by various professional bodies and associations as professional codes of conduct and standards for doctors. The Hippocratic Oath, the oldest of these codes of ethics, still holds true today.

The doctor-patient relationship is in itself therapeutic; a successful consultation with a trusted doctor will have beneficial effects irrespective of any other therapy given. A patient hearing and empathy result in quality care that builds mutual faith, respect, and trust between doctor and patient. Therefore, it is important for physicians to recognize when the relationship is challenged or failing. If the relationship is challenged or failing, physicians should be able to recognize the causes for the disruption in the relationship and implement solutions to improve care.

THE 4 KEY ELEMENTS OF DOCTOR-PATIENT RELATIONSHIP

This unique relationship encompasses 4 key elements: mutual knowledge, trust, loyalty, and regard, which constitute the foundation of the doctor-patient relationship.

- **Knowledge** refers to the doctor's knowledge of the patient as well as the patient's knowledge of the doctor.
- **Trust** involves the patient's faith in the doctor's competence and caring, as well as the doctor's trust in the patient and his or her beliefs and report of symptoms.
- **Loyalty** refers to the patient's willingness to forgive a doctor for any inconvenience or mistake and the doctor's commitment not to abandon a patient.
- **Regard** implies that the patients feel as though the doctor likes them as individuals and is "on their side".

WHAT IS PATIENT SATISFACTION?

Patient satisfaction is defined as "the degree to which the individual regards the health care service or product or the manner in which it is delivered by the provider as useful, effective, or beneficial". All four elements of the doctor-patient relationship impact patient satisfaction.

- **Trust:** Bennett et al found that, among patients with systemic lupus erythematosus, those who trust and "like" their physician had higher levels of satisfaction. In another study, patients' perceptions of their physician's trustworthiness were the drivers of patient satisfaction.
- **Knowledge:** When doctors discovered patient concerns and addressed patient expectations, patient satisfaction increased as it did when doctors allowed a patient to give information.
- **Regard:** Ratings of a physician's friendliness, warmth, emotional support, and caring have been associated with patient satisfaction.
- **Loyalty:** Patients feel more satisfied when doctors offer continued support; continuity of care improves patient satisfaction.

NMC Regulations

24. Confidentiality: Every communication between Registered Medical Practitioner (RMP) and patients shall be kept confidential. Such communication, whether personal, or related to health and treatment, shall not be revealed unless required by the laws of the state, or if non-disclosure may itself be detrimental to the health of the patient or another human being. (L2 and/or L3)

25. Truth-telling: RMP should neither exaggerate nor minimize the gravity of a patient's condition. He/She shall ensure that the patient or legally appointed representative has such knowledge of the patient's condition that can assist in making decisions that will best serve the interests of the patient. (L1)

WHICH FACTORS CAN ADVERSELY INFLUENCE THE DOCTOR-PATIENT RELATIONSHIP?

The following factors can interfere with the doctor-patient relationship.

- **Patient factors:** New patient, poor prognosis, afflicted with a frustrating disease (which is difficult to treat), difficult patient, health literacy, turbulent society.
- **Provider factors:** Physician burnout (state of detachment, emotional exhaustion, and lack of work-related fulfilment), doctors in training or in early career, Conflict on or with the treatment team, poor communication skills, increased specialization.
- **Patient/Provider mismatches:** Language barriers, cultural barriers, locus of control (power struggle).
- **Systemic factors:** Time constraints, space/room (lack of/inadequate privacy), high patient-provider ratio, urgent care setting (e.g., emergency department, clinic), cost, documentation burden.

TYPES OF DOCTOR-PATIENT RELATIONSHIP

Different forms of doctor-patient relationship arise from differences in the relative power and control exercised by doctors and patients. In reality, these different models perhaps do not exist in pure form, but nevertheless most consultations tend towards one type.

- **Paternalistic relationship:** A paternalistic (or guidance-cooperation) relationship, involving high physician control and low patient control, where the doctor is dominant and acts as a 'parent' figure who decides what he or she believes to be in the patient's best interest. This form of relationship traditionally characterized medical consultations and, at some stages of illness, patients derive considerable comfort from being able to rely on the doctor in this way and being relieved of burdens of worry and decision-making. However, medical consultations are now increasingly characterized by greater patient control and relationships based on mutuality.
- **Mutuality relationship:** A relationship of mutuality is characterized by the active involvement of patients as more equal partners in the consultation and has been described as a 'meeting between experts', in which both parties participate as a joint venture and engage in an exchange of ideas and sharing of belief systems. The doctor brings his or her clinical skills and knowledge to the consultation in terms of diagnostic techniques, knowledge of the causes of disease, prognosis, treatment options and preventive strategies, and patients bring their own expertise in terms of their experiences and explanations of their illness, and knowledge of their particular social circumstances, attitudes to risk, values and preferences.
- **Consumerist relationship:** A consumerist relationship describes a situation in which power relationships are reversed; with the patient taking the active role and the doctor adopting a fairly passive role, acceding to the patient's requests for a second opinion, referral to hospital, a sick note, and so on.
- **Default relationship:** A relationship of default can occur if patients continue to adopt a passive role even when the doctor reduces some of his or her control, with the consultation therefore lacking sufficient direction. This can arise if patients are not aware of alternatives to a passive patient role or are timid in adopting a more participative relationship.

Not only has medicine undergone tremendous advancements over the years, the social milieu has changed and the patients have changed as well, which is reflected in the doctor-patient relationship; from "*paternalism*", where doctors were "*parent figures*" taking medical decisions on behalf of their patients to the current "*patient-centric*" where the patient is an "*equal partner*".

Nevertheless, the different types of relationship, and particularly those characterized by paternalism and mutuality, can be viewed as appropriate to different conditions and stages of illness. For example, in emergency situations it is generally necessary for the doctor to be dominant, whereas in other situations patients can be more actively involved in treatment choices and other decisions regarding their care.

DIFFICULTIES IN THE DOCTOR-PATIENT RELATIONSHIP

Regardless of experience and skill, it is inevitable that, at some point in a doctor's career, the doctor-patient relationship will break down. There can be many reasons for this; sometimes, these are beyond the control of the clinician, but often conflict arises when there is a genuine or perceived failure of the doctor to meet one or more of his/her duties. It is important to recognize a breakdown in the relationship quickly and,

whenever possible, identify the reason. If patients are unhappy with an aspect of their care, they are entitled to a prompt, open, constructive, and honest response that includes an explanation and, if appropriate, an apology. It is also important to reassure the patient that the issues raised will not adversely affect their future care. Often, an acknowledgment that something is wrong and demonstration of a desire to put things right are sufficient to rectify any conflict. However, the longer one takes to address a problem, the more difficult it becomes to resolve. The patient may continue to be dissatisfied with the doctor and it may be most appropriate for another colleague to take over their care.

Another contemporary effect on the doctor-patient relationship has been the exponential increase in the use of the internet by the patients. This means that the patients are better informed, especially in the more affluent society, and this has facilitated the patient-centered approach to health care that predominates today. While better patient education has obvious advantages for the doctor-patient relationship, there are concerns that information on the internet might not always be accurate and reliable. This poses a new challenge for the medical professional – that of revising any misinformation the patient has found himself or herself.

It is patients right to know about his disease and management plan. However, most patients expect cure & of the disease and relate outcome to doctors competence and efforts. They do not understand limitations of medical science and that of a doctor who cannot cure every disease even with best of competence and intentions. Earlier generation of patients had full faith in their doctors and they were satisfied with doctor's best efforts irrespective of the outcome. Lack of faith in doctors of present generation of patients is the cause of poor doctor-patient relationship.

DOCTOR-PATIENT COMMUNICATION

Effective communication between doctor and patient is a central clinical function that cannot be delegated. Most of the essential diagnostic information arises from the interview, and the doctor's interpersonal skills also largely determine the patient's satisfaction and positively influence health outcomes. Such skills, including active listening are qualities of a doctor most desired by patients. There is considerable healing power in the doctor-patient alliance. The bond of trust between the patient and the doctor is vital to the diagnostic and therapeutic process. It forms the basis for the doctor-patient relationship.

The primary objective of the doctor is to listen to the patient in order to identify what is the 'real' problem actually is instead of simply eliciting symptoms and signs. Shared decision-making between the doctor and the patient will determine the most appropriate and best course of action for an individual patient.

Some Barriers to Good Communication in Health Care

The Doctor

- Authoritarian or dismissive attitude
- Hurried approach
- Use of jargon
- Inability to speak first language of the patient
- No experience of patient's cultural background

The Patient

- Anxiety
- Reluctance to discuss sensitive or trivial issues
- Misconceptions
- Conducting sources of information
- Cognitive impairment
- Hearing/speech/visual impairment

CONSEQUENCES OF DETERIORATING DOCTOR-PATIENT RELATIONSHIP

Unethical practices by doctors and unrealistic expectations leading to irrational behavior of patients have resulted in erosion of faith, trust, and mutual respects for each other. Present generation of doctors practice defensive medicine that demands large number of tests and interventions with increase in cost of health care. It is a known fact that error of commission is more acceptable and condoned than error of omission that is punished.

Doctors look at every patient as a potential litigant while patients look at the doctor as one who would cheat. This kind of behavior on the part of patients has led to increase in number of legal suits against the doctors and hence doctors justify defensive medicine. Besides doctors have to face danger to their own life and property.

Hence, present generation of doctors have to spend for professional indemnity insurance against such possible events and such extra expenses are indirectly borne by patients. It has further vitiated doctor-patient relationship with disadvantage to both the parties.

DRS-WCPD: 11th World Congress on Prevention of Diabetes and Its Complications

ASSOCIATION OF NUTRITIONAL FACTORS WITH TYPE 2 DIABETES IN INDIA

Dr V Mohan, Chennai

The debate over whether the diabetes epidemic is primarily driven by genetic or environmental factors continues. Three key contributors to diabetes have been identified: high carbohydrate intake leading to increased glycemic load, reduced physical activity, and urbanization-related factors such as air pollution. A multicountry study involving 21 nations revealed that higher white rice consumption is associated with an increased risk of diabetes, particularly in South Asia, while other regions exhibited only a modest, nonsignificant association. Conversely, another study found that increased dairy intake was linked to a modest reduction in the prevalence of metabolic syndrome (MS) and its components, including a lower incidence of hypertension and diabetes over time. In Asian Indians, higher dairy consumption has been shown to mitigate cardiometabolic risk factors such as elevated blood pressure, body mass index, fasting plasma glucose (FPG), and low high-density lipoprotein cholesterol, thereby reducing MS prevalence. At the population level, diabetes reversal may be achievable through diet modifications. Even a 10% reduction in carbohydrate intake, replaced with portion, particularly from plant sources, can prevent or remit type 2 diabetes. Recommendations for macronutrient intake in Indian South Asians emphasize the importance of both the quantity and quality of macronutrients, with strategies encompassing both population-wide and individualized approaches.

It can be concluded that healthier diets with lower carbohydrates along with increased protein and fiber, along with increased physical activity can help prevent and control type 2 diabetes in India.

AMPLIFY TIR – COMPARATIVE ANALYSIS OF SGLT2 + DPP-4 COMBINATION IN INDIAN PATIENTS

Dr Shashank Joshi, Mumbai

Time-in-range (TIR) refers to the duration an individual spends within the target glucose range, typically 70 to 180 mg/dL. Research indicates that a 1% decrease in TIR increases the risk of microalbuminuria, peripheral neuropathy, and cardiopathy by 40%, 25%, and 60%, respectively. Therefore, maintaining glucose levels within the recommended range is crucial to prevent diabetes-related complications.

The Amplify TIR study evaluated the efficacy of a fixed-dose combination (FDC) of dipeptidyl peptidase 4 (DPP-4) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors in improving parameters derived from 24-hour glucose monitoring. The study compared the effects of FDC of teneligliptin 20 mg + dapagliflozin 10 mg (Arm A), sitagliptin 100 mg + dapagliflozin 10 mg (Arm B), and linagliptin 5 mg + empagliflozin 25 mg (Arm C) in Indian patients with type 2 diabetes mellitus using continuous glucose monitoring.

The results demonstrated a significant reduction in TAR (time above range) levels across all three groups from baseline to the end of the study. Comparable efficacy in improving TIR was observed among the study arms, except between Arm A and Arm B. There were no significant changes in TBR (time below range) levels across the groups from baseline to the end of the study.

Additionally, all groups had a significant reduction in HbA1c, FPG, and postprandial glucose (PPG) levels. Arm A showed significantly better FPG control than Arm B in phase II. Significant improvements in estimated glomerular filtration rate, serum creatinine, and blood urea nitrogen levels were observed across all three treatment arms by the end of phase II.

Based on these findings, the following conclusions can be drawn:

- The glycemic variability parameter improved significantly for the teneligliptin + dapagliflozin combination from baseline to the end of treatment.
- Glycemic and renal parameters improved with the teneligliptin + dapagliflozin combination, comparable to the other study arms.
- The FDC of teneligliptin + dapagliflozin was comparable and noninferior to sitagliptin + dapagliflozin and linagliptin + empagliflozin in improving glycemic variability and renal parameters.

THE DIABETIC PANDEMIC: WHERE ARE WE, WHERE ARE WE HEADED AND WHAT CAN POPULATION-BASED INTERVENTIONS ADD IN TURNING THE TIDE

Dr Bruce Duncan, USA

- The type 2 diabetes pandemic continues out of control.
- The main problem is the increasing prevalence.
- To control prevalence, we must decrease incidence.
- To decrease incidence, we must: Not only continue to implement and improve high-risk clinical strategies; But with equal or greater emphasis – Stimulate our societies to implement population-based measures, evaluate the effectiveness of these measures.
- Interventions in nutrition include marketing bans, front-of-pack nutrition labels, taxes on sugar-sweetened beverages and subsidies on fruits and vegetables, and product reformulations.

ORIGIN OF DIABETES – THE GUT FEELING

Dr Alka Gandhi, Mumbai

The gut plays a critical role in regulating glucose and energy homeostasis. Emerging evidence suggests that the gut may also contribute to the pathogenesis of type 2 diabetes, influenced by both intestinal microbiota composition and gut hormone secretion patterns. The gut microbiota may produce molecules that impair insulin secretion and action.

Several studies have demonstrated the following:

- Microbiota dysbiosis is present in both type 1 and type 2 diabetes patients.
- This dysbiosis can contribute to insulin resistance, low-grade inflammation, and fat deposition through various molecular interactions with the host.
- Gut microbiota dysbiosis may lead to increased gut permeability ("leaky gut").
- This, in turn, allows external antigens to enter the circulation unchecked.
- These antigens may trigger islet autoimmunity, directly damage pancreatic beta cells, and cause hormonal imbalances leading to metabolic disorders.

Some antidiabetic interventions targeting gut microbiota include probiotics, prebiotics, traditional Chinese medicine, natural compounds, and non-drug therapies like bariatric surgery, fecal microbiota transplantation, diet, and exercise. Pharmacological treatments include incretin therapy, alpha-glucosidase inhibitors, SGLT2 inhibitors, and metabolic surgery. These strategies aim to improve gut health and mitigate the metabolic disturbances associated with diabetes.

UNIQUE WAYS IN PATIENT COMMUNICATION AND CONNECT: OVERCOMING LIMITATIONS

Dr Amit Rajput, Jalgaon

Effective communication is key to accurate diagnosis, treatment adherence, and patient satisfaction. However, hearing impairment is an often overlooked complication of diabetes. Diabetes-related hearing loss is associated with microangiopathy and damage to the stria vascularis, endolymph, hair cells, and cochlear nerve. Unfortunately, there is currently no cochlear equivalent of a fundus examination, making early detection and treatment of hearing loss vital for preventing cognitive decline, dementia, and depression.

One practical method for communicating with patients experiencing hearing loss is the "Stethospeak" technique. In this approach, the stethoscope is reversed so the patient wears the earpieces while the doctor speaks into the diaphragm, ensuring clear communication.

When patients can hear and understand their doctor's words clearly:

- They no longer feel neglected.
- Complex instructions can be effectively conveyed.
- Regular follow-ups become more likely, resulting in better management of diabetes and related comorbidities.
- Family members can also use the stethoscope at home for communication.
- It encourages the use of hearing aids, breaking the stigma often associated with them.

■■■■

News and Views

Impact of Gastroesophageal Reflux on Chronic Cough and Interstitial Lung Disease

Patients with interstitial lung disease (ILD) and chronic cough have high levels of pepsin in the bronchial lavage fluid suggesting acid reflux as an etiologic factor, according to a study from Turkey published in the November 2024 issue of the journal *Respiratory Medicine*[1].

The study included 52 patients with ILD and 81 patients with chronic cough who underwent bronchoscopy at a tertiary clinic between January 2021 and February 2022. Seventy-nine patients with a prediagnosis of lung cancer, served as the control group. In this study, researchers from Turkey explored the potential link between pepsin and ILD and chronic cough. They also evaluated pepsin levels in bronchial lavage in patients with ILD. The most common symptoms in all the three groups were shortness of breath and cough.

The pepsin levels were 16.71 ng/mL in patients with chronic cough, 15.6 ng/mL in those with ILD and 10.58 ng/mL in the control group. Pepsin levels in the ILD and chronic cough group were statistically significantly higher than in the lung cancer group. The increase in pepsin levels in the ILD and chronic cough groups versus the lung cancer (control) group was statistically significant.

However, the study found no statistical difference in pepsin levels between patients with ILD and chronic cough. Pepsin levels were found to be lower among patients who received anti-reflux treatment in all three groups. There was no difference in pepsin levels among ILD subgroups.

The elevated pepsin levels in bronchial lavage among patients with ILD and chronic cough suggest a potential role of reflux in the etiology of these conditions. The reduction in pepsin levels in patients who received anti-reflux therapy supports the occult reflux as a contributing factor. Hence, incorporating antacid therapy into treatment strategies could help patients with chronic cough and ILD by improving symptom control and disease outcomes.

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1. Ala Çitlak FS, et al. Investigation of pepsin levels in bronchial lavage in patients with interstitial lung disease and chronic cough. Respir Med. 2024;233:107781.

Younger Age at Type 2 Diabetes Diagnosis Linked to Higher Mortality Rates

New research published in *The Lancet Diabetes & Endocrinology* suggests that patients who were newly diagnosed with type 2 diabetes under 40 years of age are at a higher mortality risk, including higher risk of incident diabetes-related complications and poorer glycemic control, compared to those who were diagnosed after 40 years[1].

This study focused on examining differences in complications and mortality rates between those with younger-onset diabetes and those with later-onset diabetes over a follow-up period of 30 years. The study analyzed data of 4,550 participants, aged 25 to 65 years, from the UKPDS trial collected between 1977 and 2007. All the participants tested negative for diabetes autoantibodies. Standardized mortality ratios (SMRs) were evaluated against UK general population data, and incidence rates of outcomes were analyzed by 10-year age intervals at time of diagnosis. The predefined outcomes were diabetes-related end points, diabetes-related death, any-cause death, myocardial infarction, peripheral vascular disease, stroke, and microvascular disease.

Out of the 4,550 participants who tested negative to all measured autoantibodies, nearly 10% (n = 429) had younger-onset type 2 diabetes at an average age of 35.1 years, while the remainder had later-onset type 2 diabetes at an average age of 53.8 years,. Nearly 60% of the participants were male and the mean glycated hemoglobin (HbA1c) was 76 mmol/mol.

At the time of diagnosis of type 2 diabetes, participants with younger-onset type 2 diabetes were more likely to be of Asian or Indian ethnicity. They also had a higher mean body mass index or BMI (30.6 kg/m^2 vs. 29.0 kg/m^2), higher proportion of participants with obesity (50.8% vs. 35.2%), lower mean HbA1c (8.7% vs. 9.2%), and higher median fasting triglycerides (1.85 vs. 1.69 mmol/L) versus those with later-onset type 2 diabetes.

Over a median follow-up of 17.5 years, the excess mortality associated with type 2 diabetes compared with the general population was higher in younger-onset type 2 diabetes; the SMRs for younger-onset diabetes was found to be significantly higher (3.72) than those for later-onset diabetes (1.54). Younger-onset diabetes showed higher incidence rates for microvascular disease

(14.5 vs. 12.1 per 1,000 person-years) and worse glycemic control (elevated annual mean HbA1c levels) compared to later-onset type 2 diabetes over the first 20 years.

For those with younger-onset diabetes, the 5-year incidence of diabetes-related outcomes, all-cause mortality including diabetes-related mortality, microvascular disease, and myocardial infarction was higher at any age compared to later-onset diabetes. In participants assigned to either intensive or conventional glycemic control, "no interactions by subgroup of younger-onset versus later-onset type 2 diabetes for any outcome" were observed.

This study demonstrates that the mortality risk is increased nearly fourfold in patients with younger age of onset of type 2 diabetes compared with people with later-onset disease. This heightened risk together with the higher incidence rates of complications and poorer glycemic control emphasizes the need for identification and effective management of these patients.

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1. Lin B, et al. Younger-onset compared with later-onset type 2 diabetes: an analysis of the UK Prospective Diabetes Study (UKPDS) with up to 30 years of follow-up (UKPDS 92). Lancet Diabetes Endocrinol. 2024;12(12):904-14.

Predicting Gestational Diabetes Using Continuous Glucose Monitoring

The continuous glucose monitoring (CGM) parameters have superior predictive accuracy for incident gestational diabetes mellitus (GDM) in early pregnancy compared to the traditional risk model. Additionally, these CGM parameters effectively predicted the likelihood of cesarean deliveries and large-for-gestational-age infants at birth[1,2].

The objective of this study was to assess the potential role of CGM in predicting GDM and related outcomes in the first trimester of pregnancy. The study included pregnant Asian women of multiple ethnicity with overweight or obesity from a hospital-based, prospective cohort. All the study participants wore CGM devices in early pregnancy at 11 to 15 weeks (baseline). They were later screened for GDM at 24 to 28 weeks. Early pregnancy risk factors and CGM-derived parameters were used for models to evaluate and compare how well each could predict GDM and pregnancy outcomes.

Various CGM parameters analyzed included average glucose and glycemic variability parameters such as liability index, mean amplitude of glycemic excursions, mean of daily differences, J-index, % in coefficient variability (% CV)[2].

Results published in the journal *Diabetes Care* show that there were 18 cases of GDM out of a total of 103 participants. Women with GDM showed significantly higher levels in mean glucose, time-above-range duration, and other glycemic variability parameters compared to the non-GDM group[2]. CGM-derived parameters showed strong predictive performance for incident GDM in the early GDM prediction model compared to the traditional risk model (maternal age, baseline BMI and baseline systolic blood pressure) with area under the curve of 0.953 vs. 0.722. Additionally, CGM data was significantly effective in predicting primary cesarean sections and large-for-gestational-age infants.

This study shows that the use of CGM in early pregnancy could be useful for early prediction of incident GDM and adverse outcomes, particularly among pregnant women with overweight or obesity who are at high risk.

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Risk of Pulmonary Embolism-Related Mortality in Patients with COPD

Patients, aged 65 to 85 years, with chronic obstructive pulmonary disease (COPD) are at a higher risk of developing fatal pulmonary embolism (PE) and may benefit from individualized, targeted thromboprophylaxis strategies, suggests a study published in the journal *Chest*. These findings were also presented at the CHEST 2024 Annual Meeting, which was held in Boston[1].

In this study, researchers analyzed data on deaths with PE due to any underlying cause. Data was sourced from the Centers for Disease Control and Prevention (CDC)'s WONDER database, covering the period from 1999 to 2020. Their aim was to assess the contribution of COPD to PE-related deaths across different age groups. The participants were categorized into two groups (with or without COPD) whose data were included in the multiple causes of death (MCOD) dataset in the age groups ranging from 35 years to over 100 years. The proportional mortality ratios in the non-COPD group were calculated and applied to the COPD-positive group among different age ranges to estimate

the observed versus expected number of deaths. The observed-to-expected mortality ratio was then derived for each age group.

A total of 10,434 individuals who died from PE with COPD listed as one of the causes of death were identified. Of these, 5,181 were females (F:M 1:1). The peak range of deaths occurred among those aged 75 to 84 years. Analysis showed a statistically significant rise in mortality due to PE among COPD patients aged 65 to 85 years. The ratios of observed-to-expected deaths among these patients were "substantially greater than 1". Patients in the age group 75 to 79 years had the highest risk for PE-related death, with an observed-to-expected ratio of 1.443.

Among patients aged 85 to 89 years, the observed number of deaths (1,189) was nearly identical to the expected number (1,170), with the 95% confidence interval for the observed-to-expected ratio including[1]. This suggests that COPD has a limited effect on PE-related mortality risk in persons aged 85 and older. The risk for death from PE among patients aged 35 to 64 years was not significantly higher for any of the 5-year age categories.

These findings therefore highlight the importance of proactive targeted thromboprophylaxis and tailored management strategies for patients with COPD, aged 65 to 85, due to increased PE mortality, particularly in those within the high-risk age group. The researchers further emphasize that "given the observed trend, individualized patient assessments are imperative to optimize preventable measures against PE in the aging COPD population". However, the contribution of confounding comorbid conditions in the heightened risk of PE-related mortality cannot be totally negated.

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Cardiovascular Benefits of GLP-1 Receptor Agonists in High-Risk Type 2 Diabetes

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) significantly lower the risk of cardiovascular events in high-risk type 2 diabetes patients, especially with combination therapy and in those with chronic kidney disease, according to a systematic review and meta-analysis published online October 26, 2024 in the journal *Diabetology & Metabolic Syndrome*[1]. Although the beneficial effects were evident with monotherapy, their impact was stronger when used as combination therapy, which notably reduced all-cause mortality, cardiovascular death, and heart failure-related hospitalization.

A systematic review and meta-analysis of randomized controlled trials was conducted to evaluate the effect of GLP-1RAs on cardiovascular outcomes in patients with high-risk type 2 diabetes. Following a comprehensive search of PubMed, Embase, Web of Science, and The Cochrane Library databases, nine randomized controlled trials with 63,613 participants, focusing on cardiovascular protection accorded by GLP-1RAs were selected for the meta-analysis.

Analysis of cardiovascular outcomes showed that GLP-1RAs significantly reduced risks for major cardiovascular events. The hazard ratio (HR) for the primary composite outcome was 0.86. The HR was 0.85 for cardiovascular death, 0.87 for all-cause death, 0.90 for myocardial infarction, 0.85 for stroke, and 0.90 for hospitalization due to heart failure. However, the reduction in hospitalization for unstable angina was statistically nonsignificant with HR 1.04. The benefits were most pronounced in patients receiving combination therapy, especially among patients with chronic kidney disease. Based on the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) system, the evidence quality was rated as "high" for six outcomes, while for unstable angina hospitalization, it was rated as "moderate".

This study reaffirms the cardioprotective effects of GLP-1RAs, such as semaglutide, in general or low-to-moderate risk patients with type 2 diabetes. At the same time, it provides evidence for cardiovascular benefits and safety in high-risk type 2 diabetes patients, particularly those with a history of cardiovascular events or severe chronic kidney disease. Nonetheless, the authors advocate additional research to confirm the long-term effects of GLP-1RAs.

Reference

1. Chen X, et al. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular outcomes in high-risk type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetol Metab Syndr. 2024;16(1):251.

IMPACT OF PRE-PREGNANCY ENDOMETRIOSIS ON POSTPARTUM MENTAL HEALTH OUTCOMES

Women with endometriosis are at a significantly higher risk of being diagnosed with psychiatric disorders such as postpartum depression, anxiety, mood disturbance, and obsessive-compulsive disorder (OCD) during the postpartum period, according to a study presented

at the American Society for Reproductive Medicine's 2024 Scientific Congress and Expo in Denver, Colorado[1].

This retrospective matched-cohort study investigated the potential link between endometriosis and the risk of postpartum psychiatric disorders. The research used data from the TriNetX US Collaborative cohort, which is a large, diverse dataset of de-identified electronic health records (EHRs) from around 45 million individuals across over 50 health care organizations in the US.

A total of 28,462 women aged ≥18 years (average age 33.0 years) who had been diagnosed with endometriosis prior to becoming pregnant and delivered between January 2005 and October 2023 were eligible for inclusion in the study. They were matched with a similar number of women without pre-pregnancy endometriosis (n = 28,462). Patients were followed from the time of delivery until the development of any postpartum psychiatric disorder, patients who discontinued and were lost to follow-up or the end of the study.

Women with pre-pregnancy endometriosis had a 31% higher risk of developing postpartum depression compared to women without endometriosis with HR of 1.31. The risk of developing OCD postpartum was 86% higher in women with endometriosis (HR 1.86). A 41% increased risk of mood disturbances postpartum among those with endometriosis (HR 1.41). The risk of postpartum anxiety was increased by 45% (HR 1.45). Comparable associations were found in women without pre-existing depression prior to pregnancy.

By demonstrating a significant association between pre-pregnancy endometriosis and an elevated risk for postpartum depression, OCD, mood disturbances, and anxiety, this study suggests endometriosis as an independent risk factor for postpartum psychiatric disorders. Lack of awareness of this association may worsen outcomes for mothers with these conditions. Hence, women with a history of endometriosis but without known psychiatric disorders should be proactively screened for mental health issues after childbirth. This may help to identify and address potential postpartum psychiatric conditions early thereby supporting maternal mental well-being.

Reference

1. Jin Hsieh TY, et al. Associations between pre-pregnancy endometriosis and postpartum psychiatric disorders. Fertil Steril. 2024;122(4 Suppl):e24.

Central Obesity and Risk for Pelvic Organ Prolapse

Women with central obesity are at a higher risk of incident pelvic organ prolapse. This risk is particularly pronounced in those younger than 60 years of age or do not have a history of hysterectomy. These findings were published online October 24, 2024, in the journal *Obstetrics & Gynecology*[1].

This prospective study was conducted to ascertain the association between central and general obesity and the risk of incident pelvic organ prolapse. A total of 2,51,143 participants, aged 39 to 71 years, without a history of pelvic organ prolapse from the UK Biobank were enrolled for the study between 2006 and 2010. Baseline data for waist/height ratio and BMI. Central obesity was defined as waist/height ratio ≥0.5. Nearly 61% were postmenopausal and 17% had undergone hysterectomy prior to their enrollment for the present study.

Results showed 9,781 cases of pelvic organ prolapse (POP) over the median follow-up duration of 13.8 years. The risk of POP was increased by 48% among participants with central obesity, independent of BMI, with a HR of 1.48. Approximately 21.7% of all POP cases were attributable to central obesity. The risk was 23% higher among women with overweight without central obesity (BMI 25-29.9 and waist/height ratio <0.5) with HR of 1.23. This accounted for 2.0% of all POP cases that were identified in the study. The association between risk of POP and central obesity was stronger among subjects younger than 60 years (vs. ≥60 years) (57% vs. 39%) and those without a history of hysterectomy (54% vs. 27%).

These findings therefore suggest that central obesity and overweight without central obesity are risk factors for POP. Combining waist-to-height ratio with BMI provides a more accurate assessment of risk for POP compared with using either alone. Higher waist/height ratio among women with the same BMI face a greater risk of POP than those with a normal ratio.

Reference

1. Si K, et al. Association of central and general obesity measures with pelvic organ prolapse. Obstet Gynecol. 2024 Oct 24.

Pregnancy Outcomes in Women with Coexisting PCOS and GDM

Polycystic ovary syndrome (PCOS) and GDM alone increased the risks for complications like pre-eclampsia and preterm birth, their coexistence did not significantly amplify the risks beyond those associated with GDM alone, according to a study of over 2,80,000 women published in *Acta Obstetricia et Gynecologica Scandinavica*[1].

Ragnheidur Valdimarsdottir from the Dept. of Women's & Children's Health, Uppsala University in Sweden and

coauthors conducted this study to determine if the coexistence of GDM and PCOS affects maternal and neonatal outcomes.

A total of 2,81,806 women from Sweden who had singleton births between 1997 and 2015 were examined in the nationwide register-based historical cohort study. Of these, 40,272 had only PCOS, 2,236 had only GDM, while 1,036 had both PCOS and GDM. The control group included 2,38,262 women without PCOS or GDM. Postpartum hemorrhage, gestational hypertension, pre-eclampsia, and obstetric anal sphincter injury were the maternal adverse outcomes examined. The neonatal outcomes were preterm birth, stillbirth, macrosomia, low Apgar score, shoulder dystocia, born small or large for gestational age, birth trauma, neonatal hypoglycemia, meconium aspiration syndrome and respiratory distress.

The study found no significant interaction between PCOS and GDM regarding maternal and neonatal outcomes. PCOS alone was associated with an 18% higher risk for pre-eclampsia with adjusted odds ratio (aOR) of 1.18; the aOR for pre-eclampsia in women with GDM alone was 1.77, while it was 1.86 among women who had both PCOS and GDM. The study reported aORs for preterm birth in the groups analyzed; 1.34 in PCOS-only group, 1.64 in GDM-only group and 2.08 in the group with both PCOS and GDM. The risk of stillbirth was increased 1.5 times in women with PCOS (aOR 1.52), but no such risk was observed in women with GDM (aOR 0.58).

Based on these findings, the study concluded that although the coexistence of PCOS and GDM does not multiply the risk, nevertheless PCOS is an underrecognized pregnancy risk factor, as demonstrated by its association with an increased risk of stillbirth, a risk that was not observed with GDM alone.

Reference

1. Valdimarsdottir R, et al. Polycystic ovary syndrome and gestational diabetes mellitus association to pregnancy outcomes: A national register-based cohort study. Acta Obstet Gynecol Scand. 2024 Oct 30.

Could Semaglutide be a Game Changer in Managing Obesity and Osteoarthritis?

Treatment with once-weekly subcutaneous semaglutide in the dose of 2.4 mg significantly reduced body weight and osteoarthritis-related pain and improved physical function in patients with obesity and knee osteoarthritis, according to the results of the STEP 9 trial published in *The New England Journal of Medicine*[1].

This multicenter study was conducted over 68 weeks at 61 sites in 11 countries with 407 adults with a BMI of 30 or higher and moderate-to-severe knee osteoarthritis, which was clinically and radiologically diagnosed. Their mean age was 56 years, the mean BMI 40.3, and the mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score 70.9. Over 80% of the study population was female.

The participants were randomized 2:1 to receive either once-weekly subcutaneous semaglutide (2.4 mg) or a placebo, as adjunct to counseling on low-calorie diet and physical activity for 68 weeks. The primary end points were the percentage change in body weight and change in the 100-point scale WOMAC pain score from baseline to week 68.

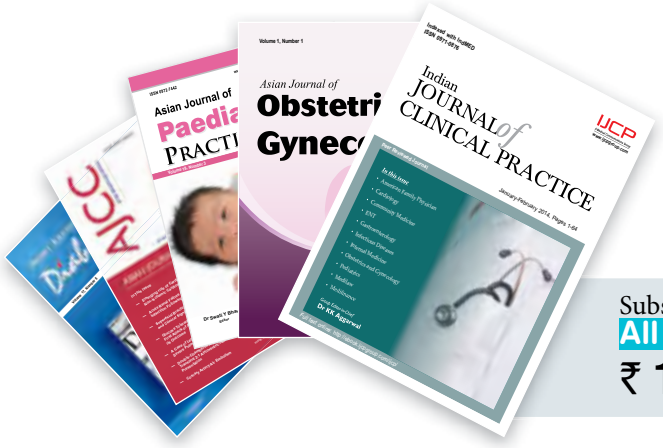
Patients treated with semaglutide had a 13.7% reduction in body weight at week 68 compared to just 3.2% decrease in the placebo group with treatment difference of 10.5. Patients treated with semaglutide had greater reduction in pain. The WOMAC pain score was reduced by an average of 41.7 points with semaglutide compared to a reduction of 27.5 points among the placebo recipients (treatment difference -14.2). Semaglutide also improved physical function as evident by greater improvement in the SF-36 physical-function score, a secondary end point of the study, with an average increase of 12 points compared to 6.5 points with placebo.

Nearly 7% in the semaglutide group (vs. 3% in the placebo group) discontinued the treatment due to adverse events, mainly gastrointestinal. The incidence of serious adverse events was comparable between the two groups.

This trial highlights the role of semaglutide as a promising dual therapy for weight management and alleviating symptoms of osteoarthritis. Semaglutide not only reduced pain, it also improved physical function. Hence, by addressing both obesity and pain, semaglutide may be a potential therapeutic option for patients with obesity and knee osteoarthritis with moderate-to-severe pain.

Reference

1. Bliddal H, et al; STEP 9 Study Group. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. N Engl J Med. 2024;391(17):1573-83.



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Lighter Side of Medicine

HUMOR

WHERE IS THE TOAST?

An elderly husband and wife visit their doctor when they begin forgetting little things. Their doctor tells them that many people find it useful to write themselves little notes.

When they get home, the wife says, "Dear, will you please go to the kitchen and get me a dish of ice cream? And may be write that down so you won't forget?"

"Nonsense," says the husband, "I can remember a dish of ice cream."

"Well," says the wife, "I'd also like some strawberries and whipped cream on it."

"My memory's not all that bad," says the husband. "No problem – a dish of ice cream with strawberries and whipped cream. I don't need to write it down."

He goes into the kitchen; his wife hears pots and pans banging around. The husband finally emerges from the kitchen and presents his wife with a plate of bacon and eggs.

She looks at the plate and asks, "Hey, where's the toast I asked for?"

STOP FOLLOWING ME!

A man was walking home alone one night when he heard a "BUMP…BUMP…BUMP…" behind him. Walking faster, he looked back, making out an image of an upright coffin banging its way down the middle of the street towards him… "BUMP…BUMP…BUMP…"

The man began to run toward his home, and the coffin bounced after him faster…faster…BUMP BUMP BUMP!

He ran up to his door, fumbled with his keys, opened the door, rushed in, and locked it behind him. The coffin crashed through his door, with the lid of the coffin clapping BUMP…BUMP… BUMP… on the heels of the terrified man. The man rushed upstairs to the bathroom and locked himself in, heart pounding.

With a CRASH, the coffin broke down the door, coming slowly toward him. The man while screaming, reached for something, anything…all he can find was a box of cough drops which he hurled at the coffin… and suddenly "the coffin stops!"

TALKING CLOCK

While proudly showing off his new apartment to friends late one night, the drunk led the way to his bedroom where there was a big brass gong.

"What's that big brass gong for?" one of the guests asked.

"Why, that's the talking clock" the man replied. "Watch", the man said, giving the gong an ear-shattering pound with a hammer.

Suddenly, someone on the other side of the wall screamed, "F'gosh sakes, you idiot, its 2 am in the blankety-blank morning!"

Dr. Good and Dr. Bad

SITUATION: An obese type 2 diabetic patient was advised bariatric surgery in the cold-induced activation of brown/beige adipose tissue.

LESSON: According to the findings of an observational study, it has been reported that body mass reduction has a better effect to induce the activation of brown/beige adipose tissue in nondiabetic than in diabetic patients. Moreover, this effect is associated with more pronounced insulin sensitivity and serine 473 phosphorylation of Akt in brown/beige adipose tissue of nondiabetic individuals than in diabetic population.

Int J Obes (Lond). 2017;41(11):1662-8.

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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

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