

# OSTIUM 365

*Annual Medical Updates*

## INTERNAL MEDICINE 2020



## Internal Medicine 2020

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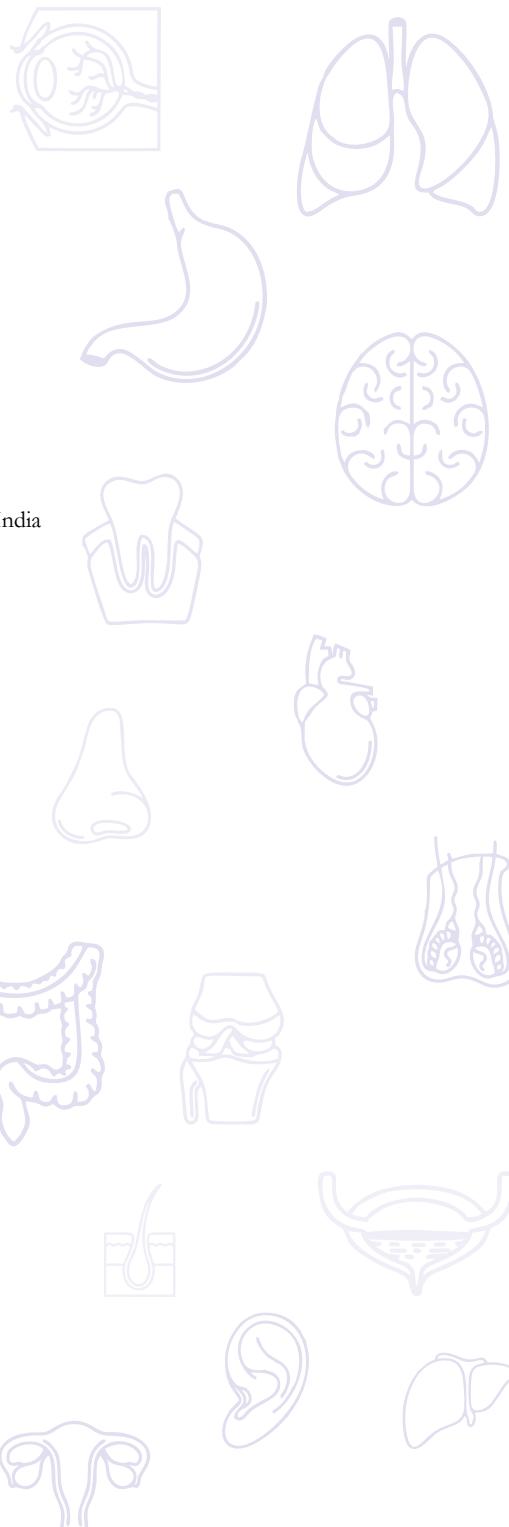
**OSTIUM**  
The Right Brain Scientists

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# PREFACE

"The doctor of the future will give no medication, but will interest his patients in the care of the human frame, diet and in the cause and prevention of disease."

~ Thomas A. Edison, 1903.

Like all great men, Edison's wordings are increasingly being relevant with time. From the times of industrial revolution, the epidemics of infectious diseases are more-or-less within our control owing to magic bullets (antibiotics) and the advances in medical microbiology. At the same time, non-communicable diseases (NCDs) have become a major contributor of health-care burden. This is perhaps true at individual, social, national, and global levels.



Global burden of disease 2018, released by CDC, USA, listed top 10 causes of death in Indian sub-continent. Out of 10, eight causes are NCDs or so-called lifestyle disorders. Three quarter of NCD deaths occur in low-to-middle income countries and based on statistics the global burden of NCDs is expected to rise disproportionately with population explosion and demographic shifts. 73% of global deaths are caused by NCDs and can be explicitly termed as a "global emergency". It is time to reinterpret,

reinvent and reactivate the strategies and practices in the context of lifestyle disorders. This has prompted us to develop a dedicated compendium of major events and buzzing topics in 2019. We have limited to eight significant lifestyle disorders which are of high concern in Asian and African communities.

Ostium365, Internal Medicine 2020, covers annual updates on eight preventable lifestyle disorders under five categories namely, Fact sheet, What's new in guidelines?, Conference snapshots, Hot topics, and EBM updates, to summarize 2019 especially for general physicians. We have taken special attention in ensuring that everything you read here will be relevant, valid and practice-influencing.

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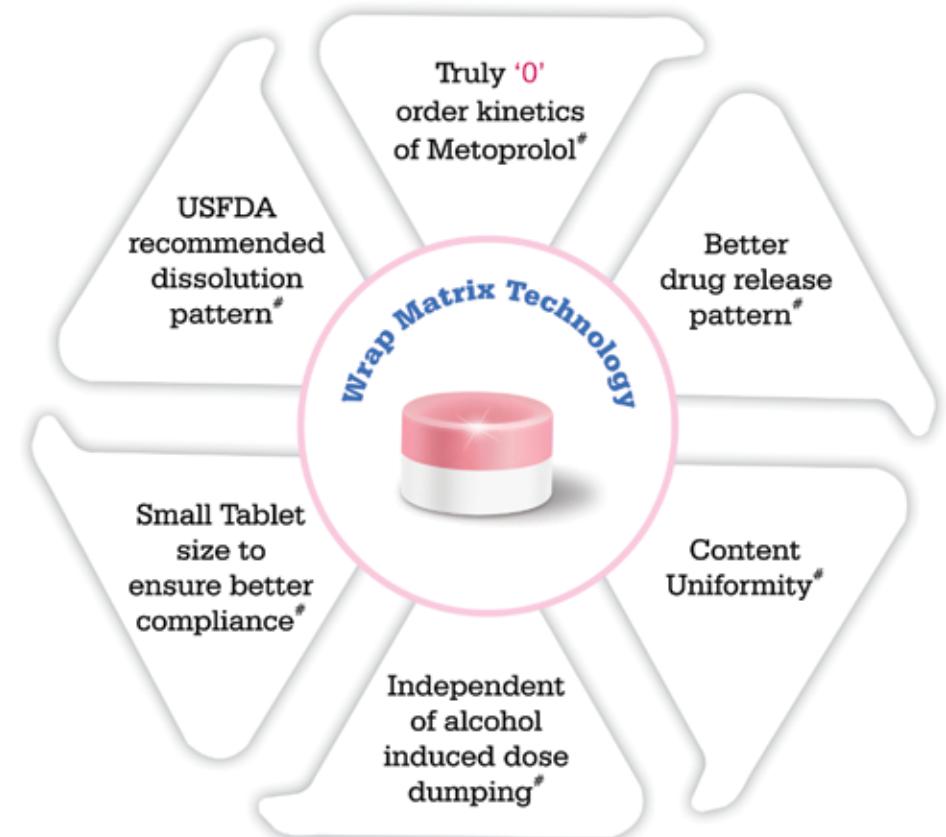
## 2020 Conference Calendar

## 2020 Healthday Calendar



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## Indications:

- Hypertension with IHD\*
- Moderate-to Severe Hypertension
- Hypertension with Diabetes

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# CARDIOVASCULAR DISEASE

- Fact Sheet
- What's New In Guidelines?
- Conference Snapshot
- Hot Topics
- EBM Updates

## Fact Sheet

- The prevalence of ischaemic heart disease (IHD) increased by about 2 times, from 10·2 million to 23·8 million between 1990 and 2016<sup>1</sup>
- The prevalence of stroke has more than doubled, from 2·8 million to 6·5 million between 1990 and 2016<sup>1</sup>
- About 25% of the adult population in India has hypertension which would be about 207 million population<sup>2</sup>
- About 30% of urban population and 20% of the rural India population have hypercholesterolemia<sup>3</sup>
- One in every four deaths** in India is because of cardiovascular diseases<sup>4</sup>
- IHD and stroke are responsible for >80% of all deaths due to vascular diseases<sup>1</sup>
- Deaths due to CVD** in India have **doubled**, from 1.3 million in 1990 to 2.8 million in 2016 with a 34% increase in death rate<sup>1</sup>
- More than **50%** of all the **CVDs** deaths in India were in people **younger than 70 years**<sup>1</sup>
- CVD contributed to 14% of the total disability adjusted life years lost in India in 2016<sup>1</sup>
- The number of **deaths due to high systolic blood pressure (SBP)** have **doubled** in a span of two decades<sup>2</sup>
- A 36% increase in the death rate due to high systolic BP was reported from 1990 to 2016<sup>2</sup>
- Disability adjusted life years lost due to hypertension increased by 88.9% from 1990 to 2016<sup>2</sup>
- Risk factors contributing to disability to CVD are ranked in following order:<sup>1,5</sup>

1. Diet-related riskfactors; 2. High SBP; 3. Air pollution;4. High cholesterol; 5. Tobacco use; 6. High fasting glucose; 7. High body mass index (BMI)

### References

- India State-Level Disease Burden Initiative CVD Collaborator. Lancet Glob Health 2018; 6: e1339–51; 2. Gupta R, et al. J Hum Hypertens. 2019; 33: 575–87; 3. Gupta R, et al. Indian Heart J. 2017; 69(3):382-92; 4. Abdul-Aziz AA, et al. Circ Cardiovasc Qual Outcomes. 2019 Apr;12(4):e005195; 5. Prabhakaran D, et al. Circulation. 2016;133:1605–1620



## ACC/AHA Guideline on the primary prevention of CVD, 2019

The 2019 American College of Cardiology/American Heart Association (ACC/AHA) guideline on the Primary Prevention of CVD was published online on March 17, 2019 in the Journal of the American College of Cardiology and Circulation and was presented at the ACC 68<sup>th</sup> Annual Scientific Session 2019. New recommendations on aspirin use, exercise and physical activity, and tobacco use were included in the current guideline. Recommendations related to team-based care, shared decision-making, and assessment of social determinants of health also found a place in the new guideline.

### Key differences

- Aspirin use:** Routine use of low-dose aspirin is no more recommended for primary prevention in all cases. However, aspirin is recommended for adults (40 to 70 years of age) who are at high CVD risk, but not at increased bleeding risk
- Tobacco use:** Assessment of tobacco use in all adults is recommended at every healthcare visit. Pharmacotherapy and behavioural interventions are recommended to maximize quit-rates
- Exercise and Physical Activity:** At least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity are recommended to reduce CV risk
- Diabetes and ASCVD risk:** Addition of sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to metformin therapy is recommended to reduce or prevent CV risk in patients with diabetes and CV risk

Reference: Arnett DK, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

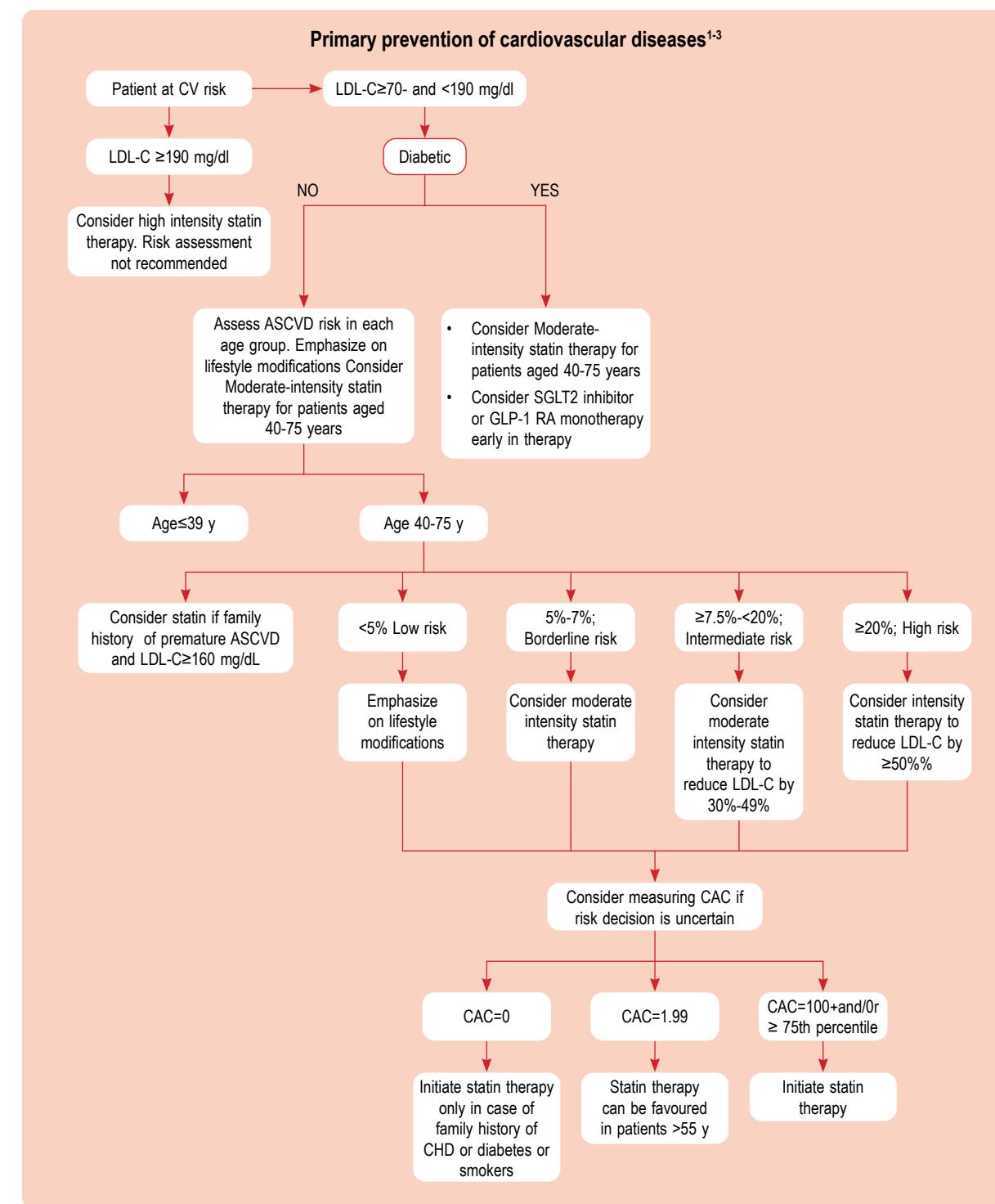
## AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation, 2019

The ACC, AHA and Heart Rhythm Society (AHA/ACC/HRS) has updated key aspects of the 2014 atrial fibrillation (AF) guideline, especially with regards to new data on direct-acting anticoagulants. Important changes include the preference of non-vitamin K oral anticoagulants (NOACs) to warfarin, clarifications to triple therapy in patients undergoing PCI, and recommendations for percutaneous left atrial appendage (LAA) occlusion devices, and catheter ablation in patients with ejection fraction.

### Key differences

- Oral anticoagulants:** NOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban are recommended over warfarin in patients with AF except with moderate-to-severe mitral stenosis or a mechanical heart valve
- Interruption and bridging anticoagulation:** Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure. Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding
- Percutaneous approaches to occlude the LAA:** Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation
- Catheter ablation in HF:** AF catheter ablation can be preferred for selected patients with symptomatic AF and HF with reduced left ventricular (LV) ejection fraction (HFrEF) to potentially lower mortality rate and reduce hospitalization for HF
- Triple therapy:** Clopidogrel is preferred over prasugrel when triple therapy (oral anticoagulant, aspirin, and P2Y12 inhibitor) is prescribed for patients with AF

Reference: January CT, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019 Jul 9;74(1):104-132.



Abbreviations: ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: Atherosclerotic cardiovascular disease; CAC: Coronary artery calcium; CHD: Coronary heart disease; GLP1 RA: Glucagon-like peptide-1 receptor agonists; LDL-C: Low-density lipoprotein cholesterol; SGLT2: Sodium-glucose transport protein 2

### References

- Arnett DK, et al. 2019 Circulation. 2019 Sep 10;140(11):e596-e646; 2. Francesco Cosentino, et al. European Heart Journal. 2019;00:1-69; 3. Piepoli MF, et al. European Heart Journal. 2016;37:2315–2381



## ESC Congress 2019

**When and where:** European Society of Cardiology (ESC) congress was held between 4-8 September 2019, at Paris, France

**Theme:** “Global Health”

**Scientific sessions:** Findings from some of the most awaited clinical trials including DAPA-HF, COMPLETE, THEMIS, PARAGON HF, and HOPE 4 were presented in the scientific sessions.

**New releases:** Guidelines for the diagnosis and management of chronic coronary syndromes and guidelines for the management of dyslipidemia were released

Clinical Trials presented at ESC Congress 2019	
Clinical Trial	What is it about?
DAPA- HF	Effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction and with or without diabetes
COMPLETE	Complete revascularization strategy vs. a culprit-only revascularization strategy among patients with STEMI and multivessel coronary disease
THEMIS	Effect of ticagrelor in patients with stable coronary disease and diabetes
PARAGON-HF	Angiotensin–Neprilysin inhibition in heart failure with preserved ejection fraction
HOPE 4	A comprehensive care model, including non-physician healthcare workers, primary care physicians and close supporters vs. standard care in managing new or poorly controlled hypertension

DAPA-HF: Dapagliflozin in patients with heart failure and reduced ejection fraction; HOPE: Heart Outcomes Prevention and Evaluation; PARAGON-HF: Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction; THEMIS: Ticagrelor Versus Placebo in Patients With Type 2 Diabetes Mellitus

## Awards and honours

### ESC Gold Medals:

Three ESC Gold Medals were awarded to exceptional cardiologists for their contribution to medicine

- Prof. Mariell Jessup for her contribution in establishing the recognition of advanced heart failure and transplant as a cardiology subspecialty
- Prof. Hugo Katus for his outstanding work on gene therapy and identification of biomarkers
- Prof. Christine Seidman for her groundbreaking work leading to the identification of the genetic basis of cardiac diseases

**Reference:** Abdellatif M, et al. Highlights of ESC Congress 2019: a report from the ESC Scientists of Tomorrow. *Cardiorasc Res.* 2019 Nov 1;15(13):e151-e154. doi: 10.1093/cvr/cvz266.

## American College of Cardiology -Scientific session 2019

**When and where:** 68<sup>th</sup> Annual Scientific Session of American College of Cardiology (ACC) was held between March 16-18, 2019 at New Orleans, Louisiana, USA

**Scientific sessions:** Data from DECLARE TIMI-58, PIONEER-HF, AUGUSTUS, REDUCE IT, SMART CHOICE, and other ground-breaking trials were presented in the scientific sessions.

**New release:** ACC/AHA 2019 Guideline on the Primary Prevention of Cardiovascular Disease

Clinical Trials presented at ACC-2019	
Clinical Trial	What is it about?
DECLARE TIMI-58	Dapagliflozin and outcomes in patients with PAD
PIONEER-HF	Initiation of Angiotensin-Neprilysin inhibition after acute decompensated heart failure
AUGUSTUS	Apixaban vs. Vitamin K Antagonist, and Aspirin vs. Placebo in patients with AF and ACS and/or PCI
REDUCE-IT	Reduction in total ischemic events with icosapecten ethyl
SMART CHOICE	P2Y12 Inhibitor monotherapy vs. dual antiplatelet therapy in patients undergoing implantation of coronary drug-eluting stents

ACC: American College of Cardiology; ACS: Acute coronary syndrome; AF: Atrial fibrillation; AUGUSTUS: Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; DECLARE TIMI: The Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction; PIONEER-HF: Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode; REDUCE-IT: Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial; SMART CHOICE: The Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents

## Awards and honours

### Douglas P. Zipes Distinguished Young Scientist Award-2019

Dr. Amit Khera, MD; Massachusetts General Hospital, Boston, Massachusetts

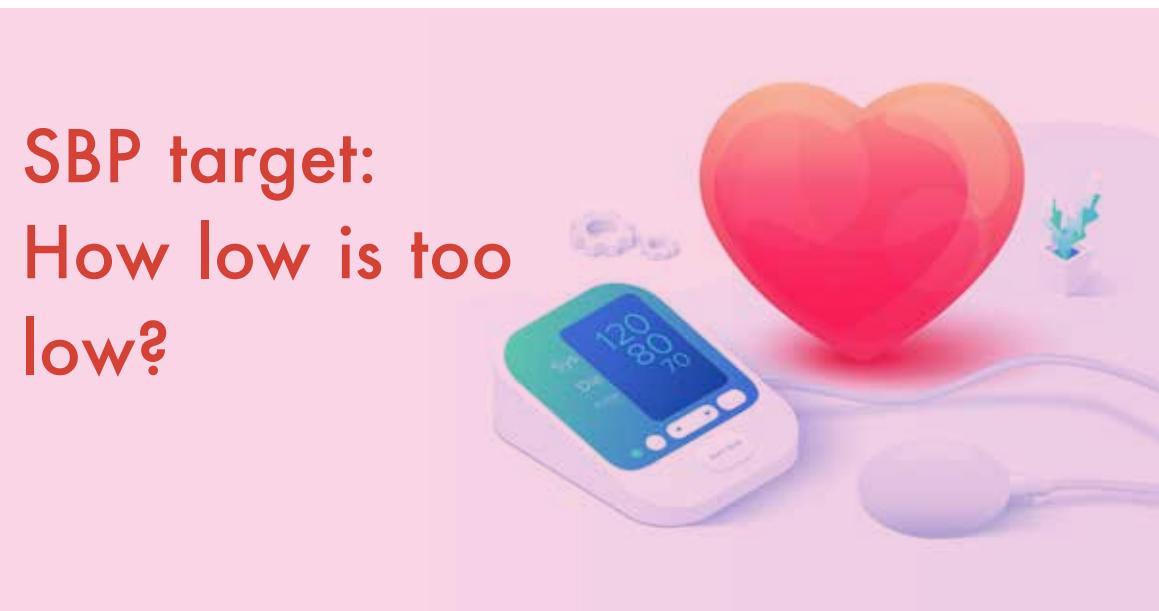
### Lifetime Achievement Award-2019

Dr. Martin B. Leon, MD, FACC; Cardiovascular Research Foundation, New York

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## SBP target: How low is too low?

### BP target: Is there an end to the debate?

To date, there have been many debates regarding the correct definition of hypertension and what are ideal blood pressure (BP) targets. Until 2017, the target BP for adults with hypertension was 140/90 mmHg in most of the guidelines.<sup>2</sup> The scenario has changed with the releases of the 2017 ACC/AHA guidelines which classified hypertension as BP  $\geq 130/80$  mmHg and recommended BP target to be  $< 130/80$  mmHg in all regardless of age and comorbidity. Nearly 50% of adults fall under hypertension category and all such patients require antihypertensive medications, based on 2017 ACC/AHA guideline. On the contrary, the more recent 2019 ESC/ESH guidelines as well as the American Diabetes Association (ADA) guidelines, recommended a target BP of  $< 140/90$  mmHg for everyone and  $< 130/80$  mmHg for those with high CV risk only.<sup>1-3</sup> The discrepancy in recommendations from three elite medical associations stirred a major controversy worldwide regarding intensive BP control and optimal BP targets.

The controversy that arose with the release of 2017 ACC/AHA guidelines which recommended tight BP targets in all patients with hypertension is yet to abate. Intensive blood pressure lowering ( $< 130/80$  mmHg) is associated with decreased cardiovascular events and mortality risk. However, data from some clinical studies suggest that excessive BP lowering can be harmful.<sup>1-4</sup>

### SBP target: How low is too low?

Following the landmark Systolic Blood Pressure Intervention Trial (SPRINT), there is a growing body of evidence that intensive lowering of SBP was beneficial in reducing CV events. SPRINT study compared an intensive SBP target of 120 mmHg to the current standard target of 140 mmHg in individuals at high cardiovascular risk and without diabetes. SPRINT study indicated that targeting SBP  $< 120$  mmHg resulted in lower rates of fatal and nonfatal cardiovascular events and death from any cause compared to achieving SBP  $< 140$  mmHg. However, there is ample evidence suggesting that intensive SBP lowering is

associated with: 1. Increase in polypharmacy-related adverse effects 2. Increase in CVD risk by simultaneous lowering diastolic BP, especially in the elderly.<sup>5,6</sup>

### Is tight BP control appropriate for all patients?

Although results of SPRINT trial cannot be denied, it is equally important to understand that treatment is about balancing benefits and risk. While setting BP target, the age of the patient, comorbidities, and baseline BP should be considered. Evidence from clinical trials suggest that younger patients with high risk may benefit from intensive lowering of SBP. ESC/ESH (2018) guideline introduced the concept of “BP target range” with safety boundaries that can be considered for different age groups (Table 1).<sup>3</sup>

Table 1: BP target range in different age groups<sup>3</sup>

Age group	BP target range
18-65 years	First $< 140/90$ , Aim for 130/80 or lower if tolerated but, SBP not usually $< 120$
65-80 years	First $< 140/90$ , Aim for 130- $< 140$ if tolerated DBP $< 80-70$ SBP not usually $< 130$
$> 80$ years	First $< 140/90$ , Aim for 130- $< 140$ if tolerated DBP $< 80-70$ SBP not usually $< 130$

On the otherhand, the applicability of these guidelines to Asian population is debatable. Asian population tend to have a higher salt intake and higher salt sensitivity which is linked to nocturnal hypertension and high morning BP surge, compared to westerners. Therefore, reductions in salt intake is a more effective intervention, especially in the Asian population.<sup>2</sup>

### Clinical implications

Although benefits of intensive BP lowering are evident, there is an increased risk of adverse events. Therefore, clinicians should assess the balance between efficacy and safety of intensive BP control. Tight BP control may benefit younger patients with high risk. In case of Asians, dietary interventions like low-salt intake may still be the foremost strategy to achieve optimal BP targets. Patient-specific factors (e.g. Age and comorbidities) must be considered while opting for pharmacotherapy.

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## The Aspirin controversy

**L**ow-dose maintenance treatment with aspirin is a common practice to prevent recurrent CVD. Evidence suggests that aspirin use may reduce first heart attack and stroke in selected patients. Should this reason justify aspirin prescription to all patients for primary prevention? Aspirin-for-primary-prevention has been one of the choicest debates among physicians, which was refueled owing to few major guidelines providing conflicting recommendations.

The USPSTF guidelines (2016) recommended aspirin for primary prevention in elderly at CVD risk, but the ESC/ESVS guidelines on peripheral arterial disease (2017) and the new ACC/AHA (2019) guidelines and ESC guidelines (2019) on diabetes, prediabetes, and cardiovascular diseases have recommended against the use of aspirin for primary prevention in most of the patient sub-groups.<sup>1-5</sup>

Aspirin is one of the frontline treatments for antithrombotic management in patients with established cardiovascular diseases. However, Aspirin use for primary prevention, though not uncommon, has long been a topic of debate. Newer data prompted a questionable efficacy and increased risk of bleeding when used for primary prevention in certain patients, forcing recommendations against the common practice

### Is it a doubt about efficacy or concern about safety?

The answer is not so straightforward. However, according to latest and robust results till date, questionable efficacy in certain patients is also a reason for recommendation against the use of aspirin for primary prevention. This evidence is majorly contributed by three clinical trials, namely ARRIVE (Aspirin to reduce risk of initial vascular events), ASCEND (Study of cardiovascular events in diabetes), and ASPREE (Aspirin in reducing events in the elderly).<sup>2</sup> ARRIVE, ASCEND, and ASPREE studies have also revealed that positive effects of aspirin on cardiovascular events were counterbalanced by clinically relevant bleeding complications.<sup>1,2,5</sup>

### Summary of ARRIVE, ASCEND, and ASPREE trials

In patients with multiple CVD risk factors, aspirin therapy (ARRIVE):

- Doubled the risk of GI bleeding events (HR: 2.11, p=0.0007)
- Did not reduce the risk of myocardial infarction (MI), unstable angina, stroke, transient ischemic attack, or death due to CVD

In patients with diabetes, aspirin therapy (ASCEND):

- Increased the risk of major bleeding events (gastrointestinal and extracranial bleeding events) by 29% (rate ratio, 1.29; P=0.003)
- Led to 62% and 33% higher incidence of upper and lower gastrointestinal tract bleeding respectively compared to placebo
- Decreased the risk of serious vascular events (nonfatal MI, nonfatal stroke, or transient ischemic attack) by 12% (RR, 0.88; P=0.01)
- Did not affect on the all-cause mortality or death due to vascular events

In healthy elderly individuals (>70 years), aspirin therapy (ASPREE):

- Increased the risk of:
  - » Major bleeding events by 38% (HR: 1.38; p<0.001)
  - » Upper gastrointestinal bleeding by 87% (HR: 1.87)
  - » Any intracranial bleeding by 50% (HR: 1.50)
  - » All-cause mortality by 14 % (HR: 1.14)
- Had no significant effect on death, dementia, or persistent physical disability

### Clinical implications

While there may be a limited role for aspirin in primary prevention, there are many other strategies that can help reduce CVD risk. Physicians should encourage lifestyle modifications such as physical activity, smoking cessation, low-sodium diet, and weight management which are recommended by the guidelines and found to have positive impact on cardiovascular risk. Aspirin use may be restricted to selected patients with clear indications.

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## Overtreatment of Hypothyroidism and Atrial Fibrillation

Levothyroxine is the first-line treatment option for hypothyroidism.<sup>1</sup> A tendency to up-dose levothyroxine based on symptoms and patient preferences is not uncommon in general practice, which may lead to overtreatment.<sup>2</sup> Both low thyroid stimulating hormone (TSH) levels and elevated free thyroxine (T<sub>4</sub>) levels that result from the overtreatment are associated with a significantly increased risk of atrial fibrillation (AF) and stroke.<sup>1,3</sup>

While hypothyroidism is linked to atherosclerosis and hypertension, hyperthyroidism is linked to atrial fibrillation and stroke. Besides, subclinical thyroid dysfunction is an emerging risk factor for CVD. There seems to exist a fine balance between thyroid biomarkers and the CV risk, as both low and high levels of different markers are linked to different health risks. Often, this confuses the physician, whether to treat or not to treat. Perhaps, the answer still remains to be "treat the patient, not the disease", especially in the case of thyroid dysfunction.

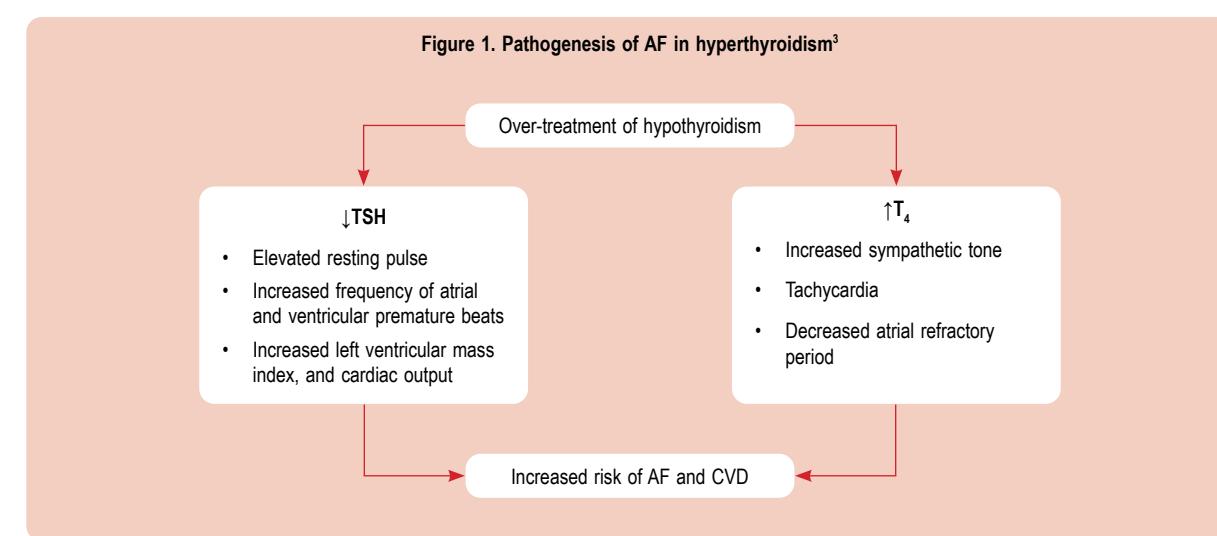
### New warning signals

Papaleontiou et al, presented the results of a large population-based study on thyroid hormone users at 89<sup>th</sup> Annual Meeting of the American Thyroid Association. Out of 7,56,555 patients assessed, 31.3% of patients had at least one TSH<0.5 mIU/L (Suggestive of over-replacement), 17.81% patients developed atrial fibrillation, and 3.7% developed stroke. Lower TSH levels were correlated with both AF and stroke.<sup>2</sup> Similarly, Thayakaran et al. reported that hypothyroidism was not associated with any adverse health outcomes when TSH levels are within normal range, however the same was not the case when TSH levels are outside the normal range.<sup>1</sup> Although, these studies are from USA and UK respectively, mere volume of numbers cannot be ignored especially in resource-limited, data-scarce, poorly-organized settings like poor and developing countries.

### Hypothyroidism over-treatment and AF: Mechanism

Over-treatment of hypothyroidism may lead to low TSH levels and high free T<sub>4</sub> levels. Low TSH level is associated with

Figure 1. Pathogenesis of AF in hyperthyroidism<sup>3</sup>



elevated resting pulse, increased frequency of atrial and ventricular premature beats, increased left ventricular mass index, and cardiac output.<sup>4</sup> On other hand, elevated levels of thyroid hormone result in shorter action potential, alteration of adrenergic and muscarinic receptors of the heart, increased sympathetic tone, decreased heart-rate variability and atrial refractory period (Figure 1).<sup>3</sup> These changes contribute to the risk of AF.

### Variations within the T4 reference range linked to AF

Findings from the prospective Rotterdam Study and a subsequent analysis showed that elevated free T<sub>4</sub> levels, but not TSH, still within the normal reference range were linked to an increased risk of atrial fibrillation prevalence and incidence. These findings were replicated in a study by Anderson et al. in a much larger population. A 40% higher risk of AF in patients with highest quartile of T<sub>4</sub> levels compared to patients in the lowest quartile was reported. This translated into a 16% increase in newly developing AF during long-term follow-up which averaged 6.3 years. An increasing gradient of the prevalence of atrial fibrillation was observed within the normal range quartiles (T<sub>4</sub> levels 0.91 to 1.54 ng/dL).<sup>5-6</sup>

### The way forward

The above findings clearly demand a need to relook at the definition of the normal reference range of T<sub>4</sub> and determine the intensity of the treatment. Further research is needed to evaluate whether targeting a lower versus a higher upper range of free T<sub>4</sub> in hypothyroidism leads to a lower risk of atrial fibrillation. Meanwhile, overt hypo- or hyperthyroidism should not be ignored. Close monitoring of thyroid function and cardiovascular symptoms in patients receiving thyroid hormone replacement therapy is important.

**References** 1. Thayakaran R et al., BMJ 2019;366:i4892. 2. Papaleontiou, M. Oral Abstract 12. 89th Annual Meeting of the American Thyroid Association Abstracts. Thyroid. 2019; 29 (Suppl.1): A5. 3. Reddy V, et al. Indian Heart Journal. 2017;69(4):545–50. 4. Christian Selmer, et al. BMJ 2012;345:e7895. 5. Chaker L, et al. The Journal of Clinical Endocrinology & Metabolism. 2015;100(10):3718–24. 6. Overtreating Hypothyroidism: Link to Atrial Fibrillation [Internet]. Available from [https://www.medscape.com/viewarticle/904785#p\\_2](https://www.medscape.com/viewarticle/904785#p_2) Last accessed on 10-Dec-2019



### Carvedilol is beneficial in patients with dilated cardiomyopathy

A recent metanalysis reported that carvedilol, a third-generation non-selective beta-blocker, significantly improved cardiac function in patients with dilated cardiomyopathy (DCM), a common cause of heart failure and sudden cardiac death. Clinical trials assessing therapeutic benefits of carvedilol in DCM have reported inconsistent results. However, a metanalysis (RCTs=21; N=1146) by Tao et al., reported a significant functional improvement in DCM in terms of left ventricular (LV) ejection fraction, LV systolic and diastolic volume and dimensions, heart rate, and blood pressure.

Reference: Tao Li, et al. *Medicine (Baltimore)*. 2019; 98(18):1–10.

Weblink: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6504318/>

### Statins reduce vascular events in all age groups, including older adults

Statin therapy produces significant reductions in major vascular events in all age groups including people >75 years old, reported a metanalysis. Although statins are recommended for primary and secondary prevention in people aged <65 years, there is inconsistent evidence to support their use for primary prevention in older adults. This issue was addressed by a metanalysis conducted by Cholesterol Treatment Trialists Collaboration. The study demonstrated that statin therapy yielded a 24%, 24%, 16%, and 12% reduction in the risk of major coronary events, coronary revascularization, stroke of any type, and vascular mortality respectively, per 1·0 mmol/L reduction in LDL cholesterol

Reference: Fulcher, et al. *Lancet*. 2019; 393(10170): 407–15

Weblink: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429627/>

### SGLT2 inhibitors confer renal and cardiovascular protection in T2DM

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduced the risk of hospitalization due to heart failure and progression of renal disease in patients with type 2 diabetes (T2DM) regardless of existing atherosclerotic CVD (ASCVD) or a history of heart failure. Cardioprotective effects of SGLT2i was apparent in patients with established ASCVD. However, evidence for the same in patients with multiple risk factors and no-ASCVD is vague. To address this issue, Zelniker et al conducted a systematic review and meta-analysis. The authors reported a 23% and 45% reduction in risk of hospitalization due to heart failure and progression of renal disease respectively in no-ASCVD subgroup. However, SGLT2i reduced major adverse cardiovascular events by 11% only in patients with ASCVD.

Reference: Zelniker TA, et al. *Lancet*. 2019 Jan 5;393(10166):31–39.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30424892>

### Folic acid supplements reduce the risk of stroke in patients with CVD

Folic acid therapy had significantly decreased risk of stroke in patients with cardiovascular diseases, reported a metanalysis. Mild-to-moderate elevations in homocysteine is associated with increased cardiovascular risk. Data to-date suggest that folic acid supplementation (0.5 to 5.0 mg/day) lowers plasma homocysteine levels by approximately 25% which may indirectly influence CV outcomes. However, previous data about cardioprotective effects of folic acid supplementation are inconclusive and conflicting. Wang et al., conducted a systematic review and meta-analysis to assess the effect of folic acid supplementation in CVD. The study reported a 15% reduction in risk of stroke with folic acid supplementation. However, folic acid supplementation had no effect on all-cause mortality, cardiovascular mortality, or coronary heart disease.

Reference: Wang Y, et al. *Medicine (Baltimore)*. 2019 Sep;98(37):e17095.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/31517834>

### Lycopene and tomato may help in preventing CVD and early death

Higher intake or serum concentration of lycopene was associated with significant reductions in stroke, mortality and CVDs. Several studies have found a positive association between higher intake of lycopene or tomatoes and reduced CV risk. A recent metanalysis by Cheng et al. has found comprehensive evidence for this association. The study reported a 26% reduction in stroke and 14% reduction in CV risk in people with high intake of or high serum lycopene concentrations.

Reference: Cheng HM, et al. *Crit Rev Food Sci Nutr*. 2019;59(1):141–158.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/28799780>



# A SOLID BEGINNING ASSURES LONG JOURNEY

Provide Early Intensification in Management of T2DM

**Gemer**

Glimepiride 0.5mg/1mg/2mg/3mg/4mg + Metformin 500mg ER

**Gemer DS**

Glimepiride 1mg/2mg/3mg/4mg + Metformin 1000mg ER

**Gemer Forte**

Glimepiride 1mg/2mg + Metformin 850mg ER

**Gemer-P**

Glimepiride 1mg/2mg + Metformin 500mg ER + Pioglitazone 15mg



# DIABETES MELLITUS

- Fact Sheet
- What's New In Guidelines?
- Conference Snapshot
- Hot Topics
- EBM Updates

## Fact Sheet

### Diabetes—A huge problem in India

- About **8.7% of adult Indians** have diabetes and about 50% of those are undiagnosed<sup>1,2</sup>
- The **prevalence of diabetes** increased by 3 times, from 26 to 65 million between 1990 and 2016<sup>2</sup>
- An **8-fold increase in percentage prevalence** of diabetes was reported in adults (>20 years) between 1990 and 2016 (From 5.5% to 39.4%)<sup>2</sup>

### Diabetes—Co-morbidities and risk factors

- In South Asians, diabetes increases the risk of hospitalization for heart failure by 50%<sup>4</sup>
- In South Asians, diabetes increases the risk of all-cause death by 29%<sup>4</sup>
- Diabetes increases the risk of any cardiovascular risk by 32%<sup>5</sup>
- Deaths due to diabetes accounted for 3% of all deaths in 2016<sup>2</sup>
- 43% of all deaths due to diabetes in 2016 were in people younger than 70 years<sup>2</sup>
- High fasting plasma glucose was responsible for 64% of all deaths due to CKD and 23% of all deaths due to peripheral artery disease<sup>1</sup>
- 45% of people with diabetes mellitus had vision loss when they first presented to eye care facility<sup>6</sup>
- Overweight, dietary risks, tobacco use, occupational exposure to second-hand smoke, low physical activity, and alcohol use are the main risk factors contributing to diabetes<sup>2</sup>
- About 4 out of 10 people who are overweight had diabetes<sup>2</sup>
- Obesity increases the risk of diabetes by 14%<sup>3</sup>

### References

1. Tripathy JP. *Diabetes Metab Syndr Obes*. 2018; 11: 381–387; 2. India State-Level Disease Burden Initiative Diabetes Collaborators. *Lancet Glob Health* 2018; 6: e1352–62; 3. Babu GR, et al. *World J Diabetes*. 2018;9(1):40–52; 4. Chawla R, et al. *J Diabetol* 2019; 10:57-61; 5. International diabetes federation. *Diabetes Atlas*. 9th Edition, 2019. Available at [https://www.diabetesatlas.org/upload/resources/2019/IDF\\_Atlas\\_9th\\_Edition\\_2019.pdf](https://www.diabetesatlas.org/upload/resources/2019/IDF_Atlas_9th_Edition_2019.pdf) last accessed on 19-Nov-2019; 6. Rani PK, et al. *Indian J Ophthalmol* 2018; 66: 916-20.



## 2019— ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases

The European Society of Cardiology (ESC) in collaboration with the European Association for the Study of Diabetes (EASD) has recently released new guidelines on the management and prevention of CVD in patients with prediabetes and diabetes.

### Key changes

- New treatment algorithm for patients with diabetes and ASCVD or high/very high CV risk was recommended
- Sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide receptor agonists (GLP-1RAs) are recommended as the first-line therapy in treatment-naïve and metformin-treated patients with ASCVD or at high or very risk of CVD
- Aspirin is not recommended for primary prevention in patients with diabetes at moderate cardiovascular risk
- Non-vitamin K antagonist oral anticoagulants are preferred over vitamin K antagonists
- When considering antihypertensives in patients with pre-diabetes, it should be noted that the risk of new-onset diabetes is lower with renin-angiotensin-aldosterone system blockers compared to beta-blockers/diuretics

*Reference:* Francesco Cosentino, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. European Heart Journal. 2019; 00: 1-69

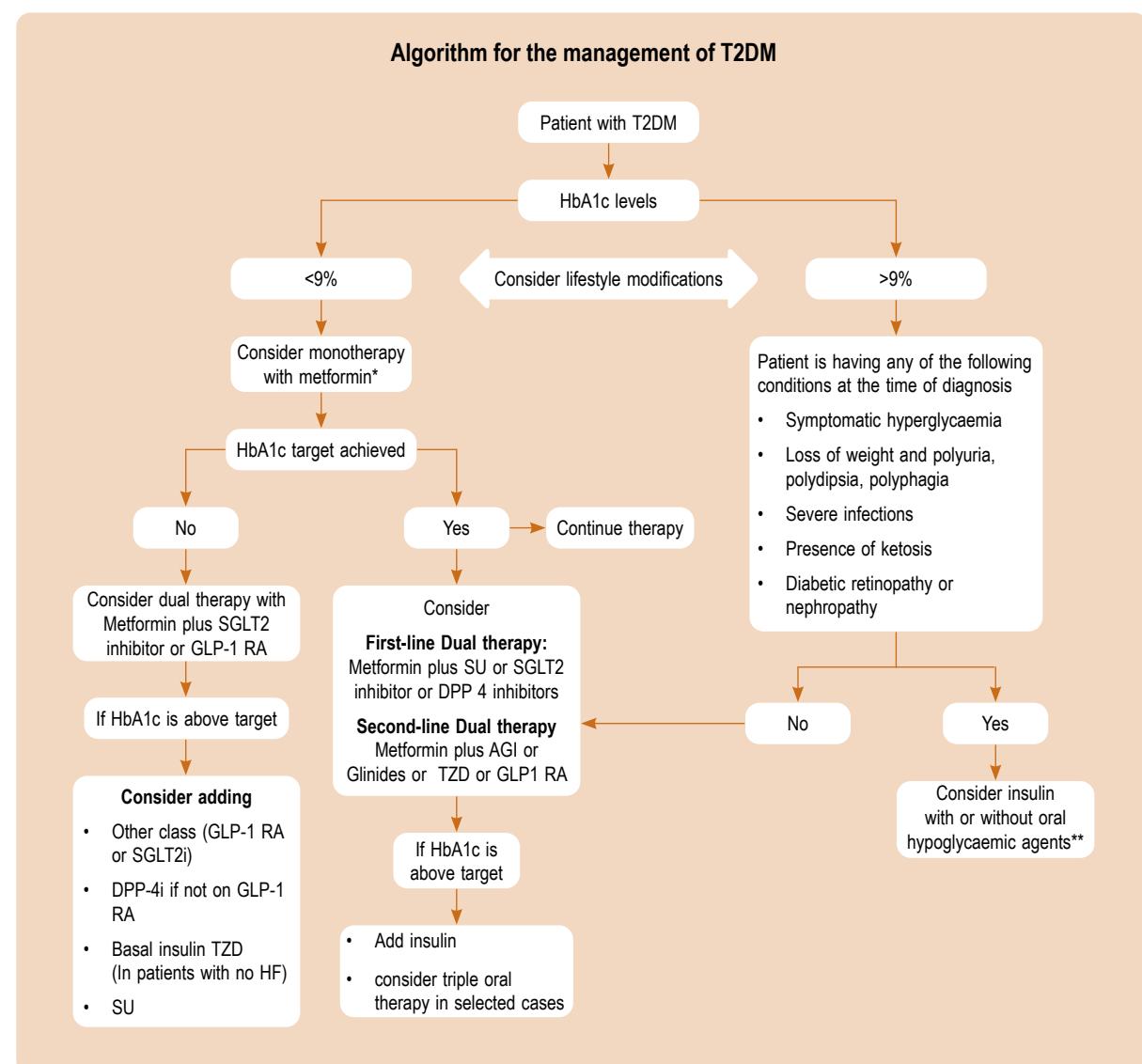
### Standards of Medical Care in Diabetes—2019

The American Diabetes Association (ADA) has released 2019 Standards of Medical Care in Diabetes.

### Key changes

- **Diagnosis:** The criteria for diagnosis of diabetes was changed to include two abnormal test results from the same sample (i.e., fasting plasma glucose and A1c from same sample) rather from samples taken a week or two apart.
- **Diabetes technology:** For the first time, a new section entirely dedicated to diabetes technology was included.
- **Cardiovascular disease and risk management:** Recommendation regarding the use of aspirin in primary prevention was updated with new data. SGLT2 inhibitors and GLP-1RAs were recommended for patients with diabetes and CVD
- **Pharmacotherapy:** A GLP-1RA is recommended as the first choice before prescribing insulin in patients with T2D who need additional glucose-lowering effects. A new section was added on insulin injection technique, emphasizing the importance of techniques for appropriate insulin dosing and the avoidance of complications
- **Microvascular Complications and Foot Care:** Gabapentin was added to the list of agents to be considered for the treatment of neuropathic pain in people with diabetes

*Reference:* Summary of Revisions: Standards of Medical Care in Diabetes—2019. Diabetes Care 2019; 42(Supplement 1): S4-S6.



\*In case of contradictions to metformin, monotherapy can be initiated with any of the other classes of oral agents

\*\*Insulin is indicated in patients with no response to optimal doses of OAH alone or in combination or acute hyperglycaemia, diabetic ketoacidosis / hyperglycemic-hyperosmolar state / lactic acidosis or acute myocardial infarction, stroke, acute infections, or trauma or pregnancy or lactation or Peri-operative state or Intolerance / contraindications to OHA

Abbreviations: ASCVD: Atherosclerotic cardiovascular disease; AGI: Alpha-glucosidase inhibitor; CV: Cardiovascular risk; DPP4i: Dipeptidyl peptidase-4 inhibitors (Gliptins); HbA1c: Glycated haemoglobin; GLP-1RA: Glucagonlike peptide-1 receptor agonists; Glinide: Non-sulphonylurea insulin secretagogue (Repaglinide and Nateglinide); OAH: Oral anti-hyperglycaemic agents; SGLT2i: Sodiumglucose cotransporter-2 inhibitor; SU: Sulphonylureas' TZD: Thiazolidinediones (Glitzazones); T2DM: Type 2 diabetes.

References: 1. ICMR guidelines for management of type 2 diabetes 2018. Available at <https://medibulletin.com/wp-content/uploads/2018/05/ICMR.diabetesGuidelines.2018.pdf>. Last accessed on 21-Nov-2018. 2. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. European Heart Journal (2019) 00, 1-69; Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2018. American Diabetes Association Diabetes Care 2018 ; 41(Supplement 1): S73-S85.



## 79<sup>th</sup> Scientific Sessions—American Diabetes Association

### When and where

The 79th Scientific Sessions (ADA2019) was held between 7-11 June 2019, at the Moscone Centre in San Francisco, California.

### Theme

“Bridging diabetes research with ground-breaking discoveries”

### New release

A consensus report was released on evidence-based guidance about individualizing nutrition therapy for adults with diabetes or prediabetes.

### List of clinical trials discussed

Findings from some of the most awaited clinical trials including DiRECT, DECLARE-TIMI 58, REWIND, CAROLINA, CREDENCE, CARMELINA, D2d, TODAY2, PREVIEW, and RISE were presented in the scientific sessions.

Clinical Trials presented at 79th Scientific Sessions of American Diabetes Association-2019	
Clinical Trial	What is it about?
DiRECT	Remission of T2DM with intensive weight management
REWIND	CV risk reduction with dulaglutide T2DM
DECLARE-TIMI 58	CV risk reduction with dapagliflozin in T2DM
CREDENCE	Improvement in renal outcomes with canagliflozin in T2DM
CAROLINA	Linagliptin vs. glimepiride in reducing CV outcomes in T2DM
CARMELINA	Linagliptin vs placebo in reducing CV outcomes in T2DM

CARMELINA: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; CAROLINA: CARDiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes; CREDENCE: Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DiRECT: The Diabetes Remission Clinical Trial; REWIND: Researching Cardiovascular Events With a Weekly Incretin in Diabetes; D2d: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; TODAY2: Dapagliflozin Efficacy in combination with metformin For early treatment of T2DM; EASD: European Association for the Study of Diabetes; T2DM: Type 2 diabetes

### Awards and honours

#### The Banting medal for Scientific Achievement, 2019

Prof. Sir Stephen O’Rahilly for his pioneering work on the causes of obesity and type 2 diabetes.

#### The outstanding scientific award for the year 2019

Dr. Sadaf Farooqi for her ground-breaking work on tracking down the genetic drivers and molecular signals that regulate body weight.

References: Scientific session recap report. Available at [https://professional.diabetes.org/sites/professional.diabetes.org/files/media/2019\\_scientific\\_sessions\\_recap\\_report.pdf](https://professional.diabetes.org/sites/professional.diabetes.org/files/media/2019_scientific_sessions_recap_report.pdf). Last accessed on 26-Nov-2019

## 55<sup>th</sup> Annual meeting of the EASD

### When and where

The 55th annual European Association for the Study of Diabetes (EASD) meeting convened in Barcelona from 16 to 20 September, 2019.

### New release

Three new EASD e-Learning modules were launched and presented during live demonstrations.

### List of clinical trials discussed

Data from CREDENCE, DECLARE, VERIFY, DAPA-HF, CONCLUDE and other ground-breaking trials were presented in the scientific sessions.

Clinical Trials presented at 55 <sup>th</sup> Annual meeting of EASD, 2019	
Clinical Trial	What is it about?
DiRECT	Remission of T2DM with intensive weight management
VERIFY	Glycaemic control with Vildagliptin plus metformin vs. metformin in T2DM
DECLARE-TIMI 58	CV risk reduction with dapagliflozin in T2DM
CREDENCE	Improvement in renal outcomes with canagliflozin in T2DM
DAPA-HF	Effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction
CONCLUDE	Comparison of insulin degLUDEc and insulin glargine 300 units/mL

CREDENCE: Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; CONCLUDE: Comparing the Efficacy and Safety of Insulin Degludec and Insulin Glargine 300 units/mL in Subjects with T2D Inadequately Treated With Basal Insulin and Oral Antidiabetic Drugs; DiRECT: The Diabetes Remission Clinical Trial; REWIND: Researching Cardiovascular Events With a Weekly Incretin in Diabetes; DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; VERIFY: Vildagliptin Efficacy in combination with metformin For early treatment of T2DM; EASD: European Association for the Study of Diabetes; T2DM: Type 2 diabetes

### Awards and honours

#### The EASD Camillo Golgi Prize, 2019

Dr. R. A. Malik for his outstanding contributions in the field of histopathology, pathogenesis, assessment and treatment of diabetic and other peripheral neuropathies and central neurodegenerative disorders.

#### The Albert Renold lecture award, 2019

Dr. Timo Otonkoski for his breakthrough work on the growth and development of the pancreatic islets.

Reference: Scientific programme, EASD. Available at [https://www.easd.org/sites/default/files/EASD\\_FP\\_19\\_Gesamt\\_Internet.pdf](https://www.easd.org/sites/default/files/EASD_FP_19_Gesamt_Internet.pdf). Last accessed on 26-Nov-2019





## Intensive glycaemic targets: New controversy

For years, most guidelines across the globe have recommended HbA1c target of <7% including the latest ICMR guidelines.<sup>1-3</sup> However, current guidelines from the American College of Physicians (ACP) about glycemic control targets recommended HbA1c level between 7% and 8% in most adults with T2DM.<sup>4</sup> The HbA1c target set by the ACP which is against the traditional target of <7% has sparked controversy and led to an uproar among the medical fraternity across the globe, particularly in the Indian sub-continent.<sup>5,6</sup>

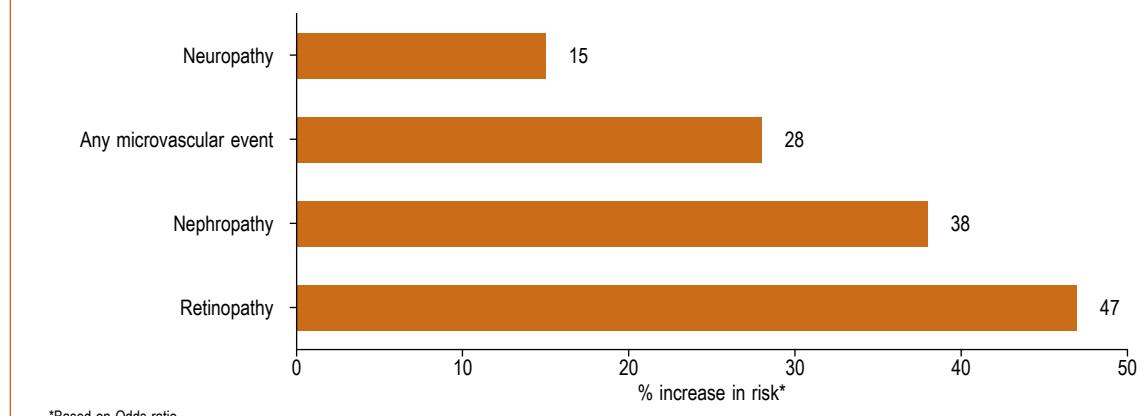
Indians with T2DM differ significantly from westerners in terms of presentation, entry HbA1c level, and duration of disease before diagnosis.<sup>7</sup> Clinical inertia, poor drug adherence, and low disease awareness are crucial challenges for achieving glycemic targets in the real-world. Further, extent of guideline-adherence is unknown in real-life scenario.<sup>8</sup> A Cross-sectional survey among Indian physicians reported that only 41% of the physicians selected HbA1c level 7.0-7.4% to start monotherapy.<sup>7</sup> Therefore, it is crucial to analyse pros and cons of setting tight HbA1c targets.

### Intensive glycaemic control is the best strategy: True or false?

**While several guidelines recommend tight glycaemic control (HbA1c ≤7%) in patients with diabetes, the current ACP guidelines have recommended higher HbA1c targets (7% to 8%) as ideal which sparked a controversy among clinicians worldwide. The recommendation lead to conflicting views. There is an ongoing debate among medical fraternity about relevance and real-world implementation of the current ACP guidelines.**

**HbA1c <7% might be ideal for optimal management of T2DM**, especially in adult Indians. Indians have a tendency for early-onset T2DM, which may lead to accelerated risk of developing micro- and macrovascular diseases. However, patients often present late to the clinic and as a result diabetes is diagnosed only after the disease has progressed to an advanced stage with microvascular complications. The TIGHT study reported that about 76% of Indians with diabetes have poor glycaemic control (HbA1c>7%). Interestingly, uncontrolled

**Figure 1. Among Indian adults with T2DM, the risk for microvascular complications is higher in patients with uncontrolled HbA1c ( $\geq 7\%$ ) compared to patients with HbA1c<7%<sup>8</sup>**



HbA1c ( $\geq 7\%$ ) increased the risk of any microvascular complications by 28% (Odds Ratio: 1.28; P< <0.0001; Figure 1) despite on oral hypoglycaemic agents (OHAs) with or without insulin.<sup>7,8</sup> Hence, it may be essential to achieve a target glycaemic control in a reasonable time frame to reduce vascular complications in patients with T2DM.<sup>8</sup> The UK Prospective Diabetes Study (UKPDS) demonstrated that a 1% reduction in HbA1c with intensive hypoglycaemic therapy is associated with a 37% decrease in risk for microvascular complications.<sup>8,9</sup> Intensive glycaemic control (HbA1c>7%), thus, remains crucial for the prevention of long-term microvascular complications in patients with T2DM.<sup>8</sup> However, tight glycaemic control is not advisable in older adults or patients at increased risk of hypoglycaemia or has cardiovascular comorbidities. Guidelines recommend individualized HbA1c targets in such patient population.<sup>1,10</sup>

### Benefits with intensive glycaemic control are evident only in the long-term

Although studies confirm that intense glycemic control is beneficial in reducing the risk of micro-and macrovascular complications, there is considerable debate regarding how quickly such benefits are realized.<sup>1</sup> According to UKPDS 33 & 34 studies, **mortality-risk-reduction with intensive glycaemic control using metformin or sulphonylureas or insulin can be expected at five to eight years.**<sup>1,11,12</sup> For practicing doctors, this translates to early and tight control may benefit patients in the long-term.

### Clinical implications

Most guidelines recommend HbA1c targets between 6.5% to 7% with allowance for higher levels in appropriate circumstances. Setting up stringent HbA1c (<7%) is beneficial in most cases, especially in the Indian context. If easily attained, there is no reason to modify HbA1c target levels for individuals who are at the normal range or close to it. Nevertheless, setting up higher HbA1c targets in the older adults and individualizing HbA1c targets in patients at higher risk of hypoglycaemia or with cardiovascular diseases are advocated.

**References:** 1. Philip Home. *Diabetes Care* 2019 Jun; *doi*:190002. 2. Sarmah D, et al. *Asian Journal of Biomedical and Pharmaceutical Sciences*. 2012; 2(12): 01-10. 3. ICMR guidelines for management of type 2 diabetes 2018. Available at <https://medibulletin.com/wp-content/uploads/2018/05/ICMR.diabetesGuidelines.2018.pdf>. Last accessed on 21-Nov-2018. 4. The American College of Physicians. *Ann Intern Med*. 2018; 168:569-576. 5. Hirsch IB, et al. *Ann Intern Med*. 2018; 169:253. 6. Indian doctors oppose new diabetes norms. Available at <https://timesofindia.indiatimes.com/city/mumbai/indiandocs-oppose-new-diabetes-normsnew-diabetes-normsnot-mean-for-indians/articleshow/63372962.cms>. Last. 7. Das AK, et al. *JAPI*. 2019; 67:18-21. 8. Borgarkar SS, et al *BMJ Open Diab Res Care* 2019;7:e000654. 9. Stratton IM, et al. *BMJ*. 2000; 321:405-12. 10. HbA1c target goal: individualization vs recommended guidelines?. Available at <https://www.medicographia.com/2017/10/hb-a1c-target-goal-individualization-vsrecommended-guidelines/>. Last accessed on 21-Nov-2019. 11. UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998; 352:837-853. 12. UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998; 352:854-865.





## Deprescribing antidiabetic drugs in elderly

Antihyperglycemic medications are prescribed for managing existing symptoms and more importantly to prevent long-term complications of diabetes. Therefore, patients usually will be taking them for many years. Usually, physicians opt for deprescription when switching to other medications which may cause more harm than benefit or providing no benefit. Benefit-to-risk ratio can be unfavourable in elderly patients who are expected to be on multiple medications and are at risk of falls and a high risk of hypoglycaemia.<sup>1,2</sup>

### Factors to consider while deprescribing antidiabetic drugs in elderly

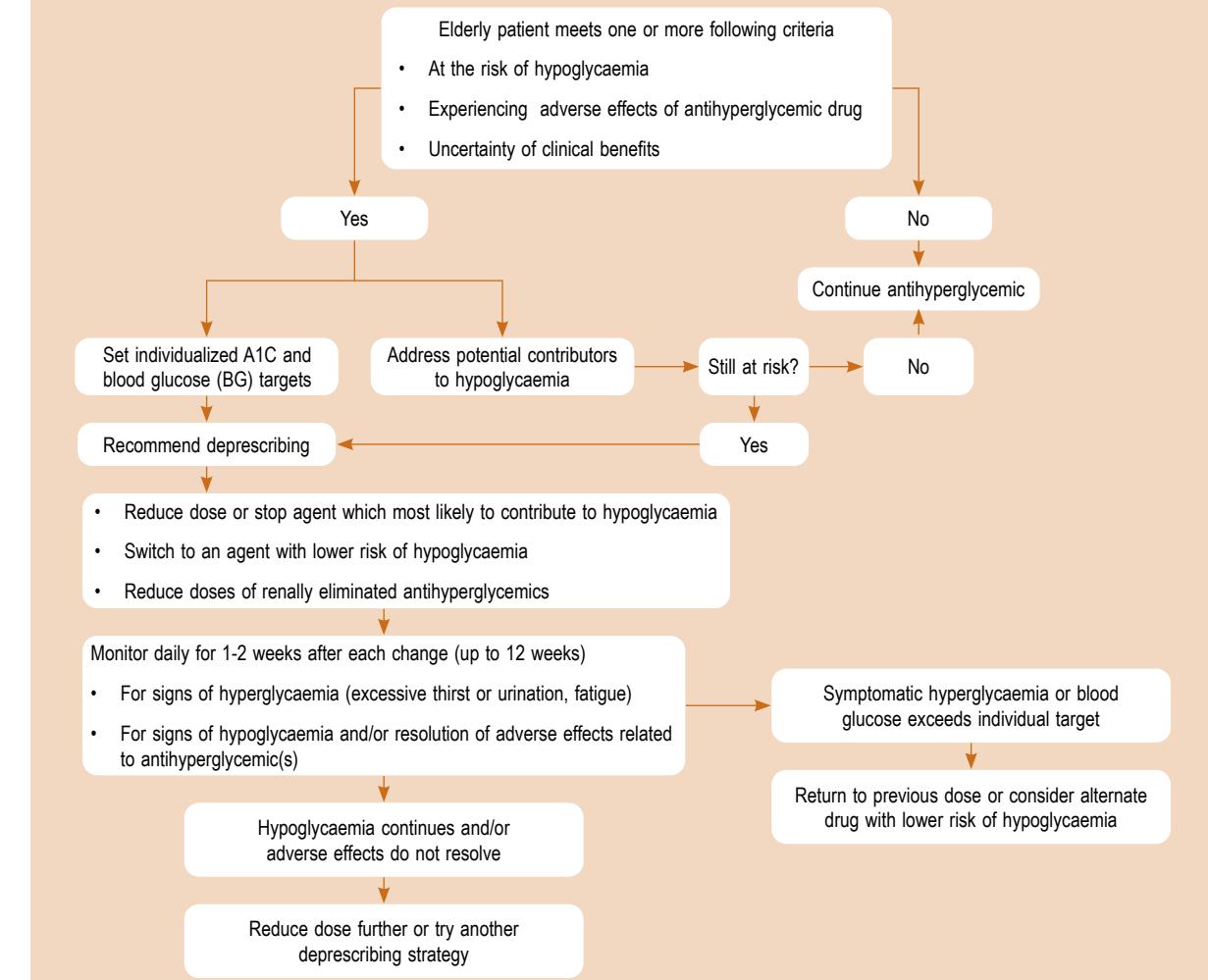
- To check risk factors of hypoglycemia i.e. advancing age, tight glycaemic control, multiple comorbidities, drug interactions, history of hypoglycemia or lacking awareness, impaired renal function, and drug-induced hypoglycemia.<sup>1,2</sup>
- To monitor risk factors of hypoglycemia (e.g. not eating, drug interactions such as trimethoprim/sulfamethoxazole and sulfonylurea, recent cessation of drugs causing hyperglycemia)<sup>1,2</sup>
- Elderly patients experiencing, or at risk of, an adverse effect from antihyperglycemic agents<sup>1,2</sup>
- Uncertainty of clinical benefit (due to frailty, dementia or limited life-expectancy)

While considering the deprescribing in elderly patients, individualized approach to targeting HbA1c level and blood glucose level can be followed (Table 1). The algorithm for deprescribing of antidiabetic is given in Figure 1.<sup>1,2</sup>

Deprescribing antidiabetic drugs is important for elderly patients since they are more vulnerable to adverse effects associated with antidiabetics such as hypoglycemia. However, deprescribing antihyperglycemic agents is challenging as it is necessary to maintain the balance between risk and benefit during deprescribing.<sup>1-3</sup>

Table 1. Individualized A1C and blood glucose (BG) targets <sup>1,2</sup>	
Patient characteristics	Acceptable target
Healthy with 10+ years life expectancy	A1C < 7%
Considering frailty, co-morbidity and advanced age	A1C < 8.5% and BG < 12mmol/L
At end-of life	A1C < 8.5% and BG < 15mmol/L
BG: Blood glucose level A1C	

Figure 1. Algorithm for deprescribing antidiabetics in elderly patients<sup>1,2</sup>



### Clinical implications

Deprescribing of antidiabetics is important in elderly patients. The deprescribing recommendation should be based on risk factors and individualized A1c and blood glucose (BG) targets to ensure patient safety.<sup>1-3</sup>

#### References

- Farrell B, et al. Deprescribing antihyperglycemic agents in older persons: Evidence-based clinical practice guideline. *Can Fam Physician*. 2017;63(11):832-43.
- Penny P, et al. A guide to deprescribe antihyperglycemic agents. 2019;1-6
- Deprescribing Is an Essential Part of Good Prescribing. Available from <https://www.aafp.org/afp/2019/0101/p7.html>. Last accessed on 11-Dec-2019



### Low-dose aspirin reduces CVD risk, however increases the bleeding risk in diabetes

The absolute benefits conferred by low-dose aspirin are largely counterbalanced by the bleeding hazard concluded the ASCEND (A Study of Cardiovascular Events in Diabetes) study. The study was aimed at evaluating the benefits and hazards of low-dose aspirin therapy for primary prevention in patients with diabetes. Low-dose aspirin (100 mg/day) reduced the CVD risk by 12% during mean follow-up of 7.4 years. However, it also increased the risk of major bleeding by 29% compared to placebo.

Reference: The ASCEND Study Collaborative Group. *N Engl J Med* 2018; 379:1529-39.

Weblink: <https://www.nejm.org/doi/full/10.1056/NEJMoa1804988>

### Omega-3 fatty acid supplementation is not effective for primary prevention of CVD in diabetes

Omega-3 fatty acid supplementation conferred no cardiovascular protection in patients with type 2 diabetes and no ASCVD. Although some observational studies have reported positive link between intake of Omega-3 fatty acids and reduction in CVD risk, a comprehensive evidence was lacking. The issue was addressed in the ASCEND trial. In this study, patients with diabetes but no history of CVD were randomized to 1g-capsules containing omega-3 (n-3) fatty acids or placebo. There was no significant difference in the incidence of serious vascular events and mortality outcomes between the fatty acid and placebo groups. The authors concluded that the available evidence does not support the current recommendations for routine dietary supplementation with omega-3 fatty acids to prevent CVD events in diabetes.

Reference: The ASCEND Study Collaborative Group. *N Engl J Med* 2018; 379:1540-50.

Weblink: <https://www.nejm.org/doi/full/10.1056/NEJMoa1804989>

### Viscous fiber supplementation improves glycaemic control in patients with diabetes

Supplementation with viscous fibers (>10 g/day for ~ 8 weeks) such as guar gum or psyllium produced an absolute reduction of 0.58% in HbA1c, 0.82 mmol/L in fasting blood glucose, and 1.89 in HOMA-IR reported a systematic review and meta-analysis. The review quantified the effect of viscous fiber supplementation on indices of glycemic control in patients with type 2 diabetes. The authors concluded that viscous fiber supplements improved conventional markers of glycemic control beyond usual care and could be considered in the management of diabetes.

Reference: Pittas AG, et al. *N Engl J Med*. 2019 Aug 8;381(6):520-30.

Weblink: <https://care.diabetesjournals.org/content/42/5/755.long>

### Pioglitazone prevents stroke recurrence in patients with prediabetes

The Insulin Resistance Intervention After Stroke (IRIS) randomized clinical trial evaluated the efficacy of pioglitazone for secondary prevention in patients with insulin resistance and prior stroke or transient ischemic attack. A post-hoc analysis of IRIS reported that in patients with prediabetes and good adherence, pioglitazone reduced stroke/MI by 40%, stroke by 33%, acute coronary syndrome by 52%, and new-onset diabetes by 80% over a median follow-up of 4.8 years. The authors concluded that pioglitazone may be an effective therapy for secondary stroke prevention in patients with prediabetes and benefits appear to outweigh the risks of fracture and fluid retention.

Definitions: Prediabetes: HbA1c level of 6% to 6.4% or fasting glucose level of 110mg/dL to 125mg/dL; Good adherence: Taking 80% or more of the protocol dose over the duration of the study as measured by pill counts on returned bottles

Reference: Spence JD, et al. *JAMA Neurol*. 2019 May 1;76(5):526-35.

Weblink: <https://jamanetwork.com/journals/jamaneurology/article-abstract/2723653>

### Vitamin D supplementation did not prevent diabetes in people at high risk for diabetes

Vitamin D supplementation has no effect on prevention of Type 2 Diabetes reported the Vitamin D and Type 2 Diabetes (D2d) trial. Although data-to-date support an association between low blood Vitamin D level and the risk of type 2 diabetes, evidence to support that Vitamin D supplementation reduces risk of diabetes is scarce. To address this, a multicentre, randomized, placebo-controlled trial was conducted to evaluate the effect of vitamin D supplementation for preventing the risk of type 2 diabetes (D2d) among adults at high risk for diabetes. The authors reported that Vitamin D3 supplementation at a daily dose of 4000 IU did not produce any a significant reduction in the risk of diabetes compared to placebo after a median follow-up of 2.5 years.

Reference: Pittas AG, et al. *N Engl J Med*. 2019 Aug 8;381(6):520-30.

Weblink: [https://www.nejm.org/doi/full/10.1056/NEJMoa1900906?url\\_ver=Z39.88-2003&rfr\\_id=ori:rid:crossref.org&rfr\\_dat=or\\_pub%3dpubmed](https://www.nejm.org/doi/full/10.1056/NEJMoa1900906?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=or_pub%3dpubmed)



Allergens may trigger  
nocturnal asthma attack<sup>1,2</sup>

In allergic asthma,

Deriphyllin® M

Theophylline SR 69 mg + Etofylline SR 231 mg + Montelukast 10 mg Tablets

@ 8PiM for a Good night to Good morning



(PIM-pH Independent Matrix Technology)\*  
Patent No. 212955 granted under Patents Act 1970



1. Accessed on <https://www.aafa.org/allergic-asthma/> dated 31/01/20

2. Martin RJ et al, Clin Exp Allergy. 1998 Aug;28(3):64-70.

3. Bush RK et al, Postgrad Med J. 1991;67 (4):S20-4.

4. Wang G et al., Allergy Asthma Proc. 2014 Jul-Aug;35(4):278-87

\*Data on file

ZHUOaster4-PharmaDeriphyllin01-2020/004

  
**German Remedies**  
A Division of Zydus Healthcare Limited

# CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- Fact Sheet
- Hot Topics
- What's New In Guidelines?
- EBM Updates
- Conference Snapshot

## Fact Sheet

### About 4% of Indians have COPD

- The prevalence of COPD in India was 1.5 times the global average prevalence in 2016<sup>1</sup>
- The number of people with COPD doubled between 1990 and 2016, i.e. 28·1 million in 1990 to 55.3 million in 2016<sup>1</sup>
- The prevalence of CVD increased by 29% between 1990 and 2016<sup>1</sup>

### Burden of COPD: Key facts

- The disability-adjusted life-years lost per person with COPD were 1.7 times the global average<sup>1</sup>
- COPD is among the top eight leading causes of disabilities in India<sup>1</sup>
- In India, COPD contributed to 75.6% of the disability-adjusted life-years lost due to chronic respiratory diseases<sup>1</sup>
- COPD is currently the fourth leading cause of deaths globally<sup>2</sup>
- Currently, COPD is the second biggest cause of deaths in India<sup>3</sup>
- COPD is projected to be the 3<sup>rd</sup> leading cause of death by 2020<sup>2</sup>

### Risk factors contributing to the burden of COPD

- Among patients with COPD, around 25%–45% are non-smokers<sup>4</sup>
- Risk factors for COPD in non-smokers: Air pollution, occupational and house-hold exposure to smoke, Exposure to smoke from burning of waste, biomass exposure, and exposure to mosquito coil<sup>1,3</sup>

### References

1. India State-Level Disease Burden Initiative CRD Collaborators. Lancet Glob Health 2018; 6: e1363–74; 2. Data available at [https://www.nhp.gov.in/world-copd-day-2018\\_pg](https://www.nhp.gov.in/world-copd-day-2018_pg). Last accessed on 27-Nov-2018; 3. Mabbub Hossain Md, et al. Int J Pul & Res Sci. 2018; 2(5): IJOPRS.MS.ID.555599; 4. Arjun P, et al. J Family Med Prim Care. 2019;8:2714-9.



## The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019

The 2019 version of GOLD guidelines was released recently with some substantial changes from the previous version with regards to assessment, initiation and maintenance of pharmacotherapy, and prophylaxis for prevention of exacerbations.

### Key differences

**COPD assessment:** The revised assessment strategy for ABCD grouping is based on spirometric grading, mMRC or CAT scores, and history of moderate-to-severe exacerbations

**Pharmacotherapy:** The updated version provided new algorithm for the initiation and maintenance of pharmacotherapy based on exacerbation risk and symptom scores following the revised assessment strategy

**ICS therapy:** Inhaled corticosteroids (ICS) are no longer recommended for Group C patients

**Blood eosinophil counts (EOS):** The revised guideline included new evidence to incorporate the use of peripheral blood eosinophil counts to estimate the efficacy of inhaled corticosteroids for exacerbation prevention

Reference: Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2019 report. Available at <https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf>. Last accessed on 03-Dec-2019

## Chronic obstructive pulmonary disease in over 16s—NICE 2018

The National Institute for Health and Care Excellence (NICE) published its long-awaited update to the 2010 guideline on chronic obstructive pulmonary disease (COPD) in over 16-year-olds in December 2018.

### Key differences

**Diagnosis:** The updated version emphasizes on considering primary care respiratory review and spirometry for people with emphysema or signs of chronic airways disease on a chest X-ray or CT scan

**Prognosis:** The use of a multidimensional index (such as BODE) to assess prognosis in people with stable COPD is no longer recommended

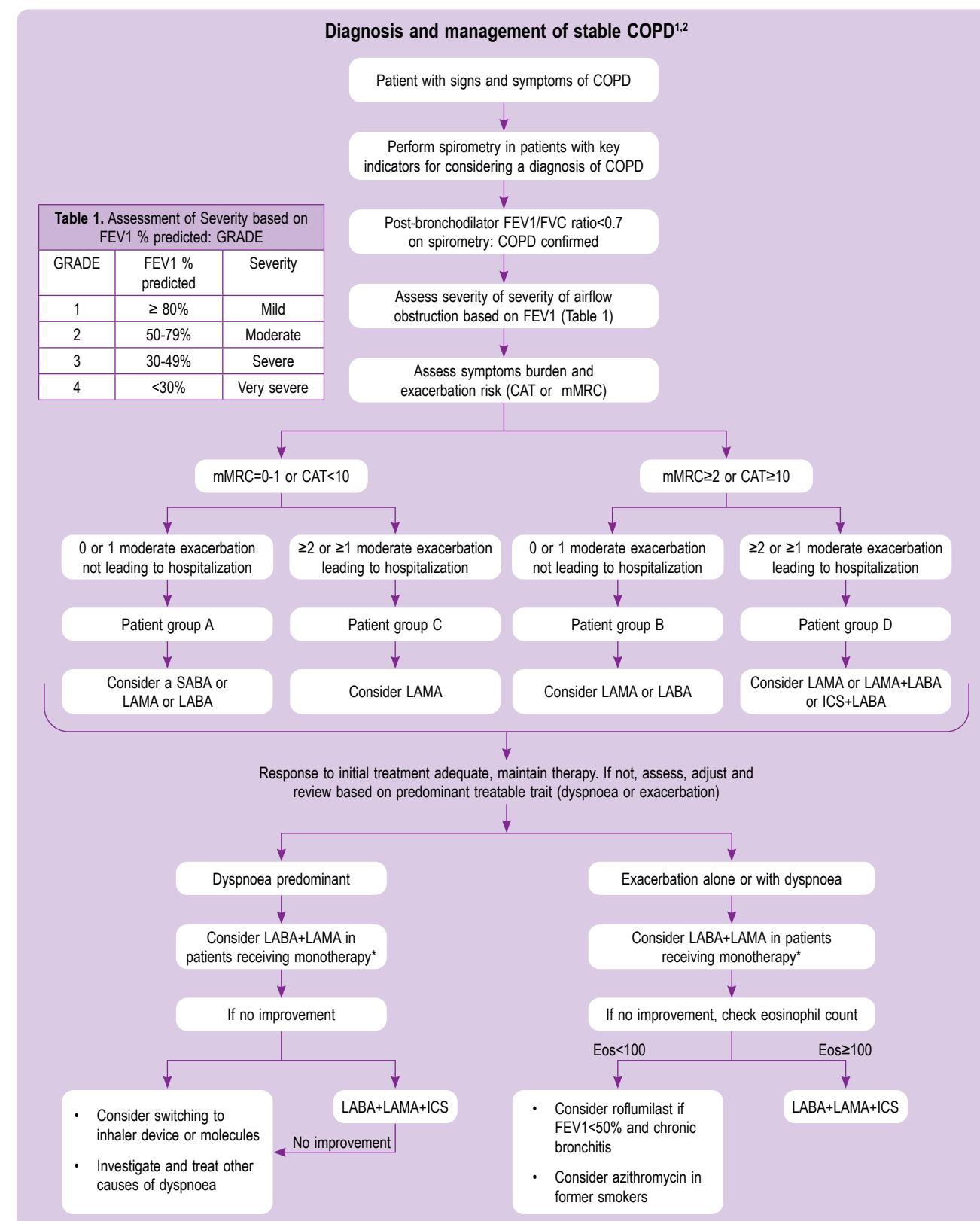
**Inhaled therapies:** The risk of side effects (including pneumonia) with the use of inhaled corticosteroids should be discussed with patients. Number of inhalers and the number of different types of inhaler used by each patient should be minimized as far as possible

**Prophylactic antibiotics:** A CT scan of the thorax to rule out bronchiectasis and other lung pathologies should be considered before offering prophylactic antibiotic therapy

**Pharmacotherapy:** Dual LAMA+LABA therapy is now recommended as first line long-acting bronchodilator therapy for people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators. LAMA monotherapy is no longer recommended in this patient population

**Patient with asthmatic features:** Addition of LAMA to LABA+ ICS was recommended for patients with COPD with asthmatic features or features suggesting steroid responsiveness who remain breathless or have exacerbations despite taking LABA+ICS

Reference: Chronic obstructive pulmonary disease in over 16s: Diagnosis and management. National Institute for Health and Care Excellence (NICE) Guideline-2018. Available at <https://www.nice.org.uk/guidance/ng115/documents/short-version-of-draft-guideline>. Last accessed on 03-Dec-2019



Abbreviations: CAT: COPD Assessment Test; COPD: Chronic obstructive pulmonary disease; Eos: Blood eosinophil count; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; mMRC: Medical Research Council dyspnoea questionnaire; LABA: Long-acting beta2 agonist; LAMA: Long-acting muscarinic 5 antagonists; ICS: Inhaled corticosteroid

References: 1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2019 report. Available at <https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf>. Last accessed on 08-Dec-2019 2. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management Guideline. Available at <https://www.nice.org.uk/guidance/ng115/documents/short-version-of-draft-guideline>. Last accessed on 08-Dec-2019



## European Respiratory Society Congress, 2019

### When and where

European Respiratory Society congress was held between 28 September to 2 October 2019, in Madrid, Spain

### New releases

- European guidelines for malignant pleural mesothelioma management in 2019
- New guidelines for treatment of nontuberculous mycobacterial pulmonary disease
- Guidelines for long-term management of bronchopulmonary dysplasia in children
- New clinical practice guidelines for chronic cough
- Guidelines for long-term non-invasive ventilation in COPD
- Managing drug-resistant tuberculosis: From new guidelines to clinical practice ATS/ERS/IDSA/CDC MDR-TB guideline

### Scientific sessions

List of clinical trials presented in the sessions are given below

- Identification of patients with COPD who benefit from benralizumab
- High-Flow Oxygen Therapy (HFOT) during training in COPD with chronic respiratory failure (CRF): A multicentre randomized controlled trial
- Home initiation of chronic high intensity noninvasive ventilation in COPD patients with chronic hypercapnic respiratory failure: The RECONSIDER trial

### Awards and honours

**ERS Presidential Award:** Professor Jean-Louis Vincent for his outstanding contribution to the strengthening of respiratory medicine worldwide

**ERS Gold Medal in COPD:** Professor Ian Adcock for his outstanding contribution in the field of COPD

**ERS Jean-Claude Yernault Lecture Award:** Professor Gernot Rohde for his exceptional contribution to education in respiratory medicine or the allied

### References

Congress guide. ERS International Congress 2019. Available at <https://erscongress.org/programme-2019/access-the-programme.html>. Last accessed on 05-Dec-2019

ERS Award Winners 2019. Available at <https://erscongress.org/funding-awards-2019/gold-medals-main-awards.html>. Last accessed on 05-Dec-2019

## American Thoracic Society (ATS) Conference, 2019

### When and where

The 104<sup>th</sup> American Thoracic Society international congress was held in Dallas, Texas, United States from 17–22 May 2019

### Scientific sessions

Data from GALATHEA, TERRANOVA, CORTICO-COP and other ground-breaking trials were presented in the scientific sessions.

### New releases

ACC/AHA 2019 Guideline on the Primary Prevention of Cardiovascular Disease

Clinical Trials presented at ATS-2019: Focus on COPD	
Clinical Trial	What is it about?
TERRANOVA	A dose-ranging study of benralizumab for moderate-to- severe COPD
GALATHEA	Benralizumab for COPD
CORTICO-COP	Eosinophil-guided corticosteroid-sparing therapy in hospitalized patients with exacerbated COPD
ATS: American Thoracic Society; COPD: Chronic obstructive pulmonary disease	

### Awards and honours

- **Trudeau Medal:** Dr. Jacob I. Sznajder for his major contributions to prevention, diagnosis, and treatment of lung diseases
- **Distinguished Achievement award:** Dr. John Hansen-Flaschen for his outstanding contributions to fighting respiratory disease through research

### References

ATS 2019 International conference. Available at <https://conference.thoracic.org/program/resources/2019/virtual-final-program-2019.pdf>. Last accessed on 05-Dec-2019.





## Biomass-smoke exposure and the risk of COPD

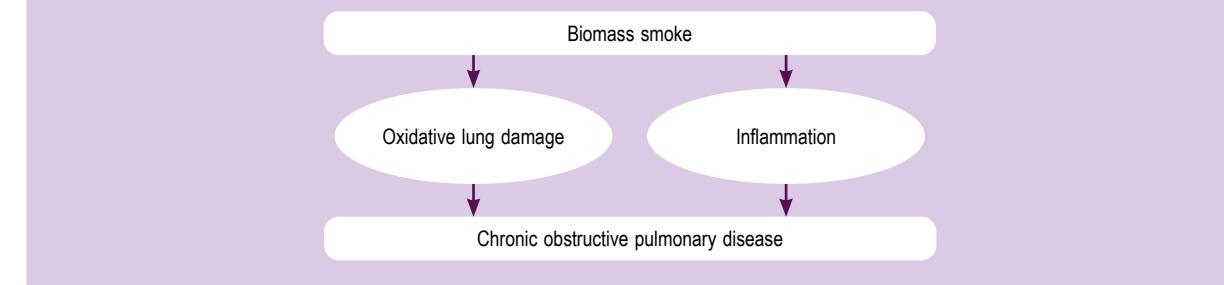
Cigarette smoking, undoubtedly, is a major risk factor for COPD.<sup>1</sup> However, three facts draw great attention in this context. Firstly, smoking as a risk factor for COPD is accountable for <80% in population-based studies.<sup>2</sup> Secondly, three billion people are exposed to biomass smoke exposure especially in developing countries.<sup>3</sup> Thirdly, there exists a wide variation (9.4–68.6%) in the proportion of COPD in non-smokers among total COPD cases in India.<sup>1</sup> This necessitates the need to re-look at association between conventional risk factors and COPD.

### Biomass-smoke exposure: The biggest risk factor for COPD?

Biomass fuels, generally used for cooking in under-developed and developing countries, contain more than 200 chemicals. >90% of these chemicals are in the inhalable size range and harmful to lungs. Considering almost 50% of homes worldwide depend on biomass-fuel, biomass-smoke exposure is a significant public health hazard especially in-terms of causing respiratory disorders which is often ignored

In developing countries where the smoking prevalence is low and biomass is mainly burnt for fuel, biomass-smoke (Solid-fuel smoke) exposure can be considered as a risk factor for COPD other than cigarette smoking.<sup>2,4,5</sup> Nearly 3 billion people are exposed to biomass smoke compared to only 1.1 billion smokers globally.<sup>3</sup> Reports from a meta-analysis concluded that, **population exposed to biomass-smoke have double the risk of getting COPD compared to non-exposed.**<sup>3,4</sup> In addition, the association between biomass-exposure and COPD is stronger than the association between passive cigarette smoking and COPD and similar as that of active cigarette smoking.<sup>3</sup> Both, exposure to cigarette smoke and biomass-smoke will cause significant damage to lungs.<sup>3</sup> Biomass-smoke exposure can be expected as the biggest risk factor for COPD in near future. Therefore, COPD can be presented as two distinct phenotypes based on its major risk factors.

Figure 1. Biomass-smoke causes oxidative lung damage and inflammation which leads to COPD<sup>4</sup>



### Who are at higher risk of biomass smoke exposure?

Majority of COPD cases in a developing country occur in never-smokers especially women (cooking in open-stove in unventilated kitchens), young girls and children.<sup>3</sup> According to a calculation, a girl who starts cooking from the age of 15 years and spending nearly 4-6 hours/day in the kitchen is expected to have a life-time exposure to biomass-smoke accounting for approximately 60,000 hours. The risk of COPD potentially increases in such cases.<sup>3</sup>

Chronic exposure to biomass-smoke leads to:

- Presence of multiple dark anthracotic pigmentations in the large airway mucosa<sup>3</sup>
- Chronic inflammatory and destructive changes in the airways and alveoli<sup>3</sup>
- Low birth-weight, and increased risk of ear and lower respiratory tract infections in children<sup>3</sup>
- Oxidative lung damage and inflammation, which may lead to COPD (Figure 1)

### Time to think beyond cigarette smoking as major risk factor

Interventions that reduce the burden of biomass smoke exposure is an urgent requirement and should be practiced.<sup>3</sup> The possible actions that can be suggested to patients can be:

- Cooking outside or in proper ventilated kitchen<sup>3</sup>
- Keep children away from cooking<sup>3</sup>
- Improve stove construction<sup>3</sup>
- Encourage low smoke fuel<sup>3</sup>

### Clinical implications

People should be educated about the possible adverse effects of inhaling biomass-smoke for better prevention and management of COPD.

#### References

1. Mahmood T, et al. Prevalence and etiological profile of chronic obstructive pulmonary disease in nonsmokers. *Lung India*. 2017;34(2):122–26.
2. Montes de Oca M, et al. Smoke, Biomass Exposure, and COPD Risk in the Primary Care Setting: The PUMA Study. *Respir Care*. 2017;62(8):1058–66.
3. Salvi S, et al. Is Exposure to Biomass Smoke the Biggest Risk Factor for COPD Globally? *Chest*. 2010;138(1):3–6.
4. Capistrano S, et al. Evidence of Biomass Smoke Exposure as a Causative Factor for the Development of COPD. *Toxics*. 2017;5(4):1–16.
5. Eisner MD, et al. An Official American Thoracic Society Public Policy Statement: Novel Risk Factors and the Global Burden of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2010;182(5):693–718.





## Triple therapy for COPD: Why and when?

### Does triple therapy outperform other therapies?

**T**riple therapy lowered the rate of moderate-to-severe exacerbation by 15%-25% when compared to dual therapy<sup>2</sup>. Dual therapies were associated with early higher incidence of exacerbation when compared with triple therapy in all the trials.<sup>2</sup> Single inhalation of triple therapy effectively addresses patient adherence, which otherwise would result in exacerbation, symptom persistence and unfair economic outcomes.<sup>4</sup> The results of various clinical trials assessing the annual exacerbation rate with triple and dual therapy are given in Table 1.<sup>4</sup>

**Table 1:** Annual exacerbation rate with triple and dual therapies in clinical trials

Study	Treatment	Annual Exacerbation rate
FULFIL	Dual therapy (ICS/LAMA)	0.36
	<b>Triple therapy (ICS/LABA/LAMA)</b>	<b>0.20</b>
IMPACT	Dual therapy (ICS/LABA)	1.07
	<b>Triple therapy (ICS/LABA/LAMA)</b>	<b>0.91</b>
TRIBUTE	Dual therapy (LABA/LAMA)	0.59
	Triple therapy (ICS/LABA/LAMA)	0.50
TRILOGY	Dual therapy (ICS/LABA)	0.53
	<b>Triple therapy (ICS/LABA/LAMA)</b>	<b>0.41</b>

Data from several clinical studies suggest that “triple therapy (ICS/LAMA/LABA) in COPD improves symptom in patients who are at moderate-to-severe risk of exacerbation with severe symptoms.”<sup>1,2</sup> In addition, the recent GOLD guidelines (2019) also recommended triple therapy as a step-up therapy, in patients with high risk of exacerbation and severe symptoms<sup>3</sup>.

**FULFIL:** Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy; **IMPACT:** The Informing the Pathway of COPD Treatment; **TRIBUTE:** Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary

**Table 1.** Initiation of triple therapy in patients with COPD<sup>2,3,6</sup>

TRIPLE THERAPY	
<b>When to consider</b>	<b>When not to consider</b>
<ol style="list-style-type: none"> <li>1. Highly symptomatic patients with moderate-to-severe risk of exacerbation<sup>2,3</sup></li> <li>2. Patients with rapid decline in lung function<sup>6</sup></li> <li>3. Symptomatic COPD patients with a history of asthma and/or current asthma<sup>6</sup></li> </ol>	<ol style="list-style-type: none"> <li>1. Asymptomatic patients<sup>6</sup></li> <li>2. Symptomatic patients without airflow limitation<sup>6</sup></li> <li>3. Patients without a history of exacerbations in the previous year<sup>6</sup></li> </ol>

disease; **TRILOGY:** Single inhaler triple therapy versus inhaled corticosteroid plus long-acting  $\beta$ 2-agonist therapy for chronic obstructive pulmonary disease

### Triple therapy: One-size-fits-all?

Triple therapy should be considered as a tailored-dose approach and therefore, it is not a one-size-fits-all therapy.<sup>5</sup> Triple therapy is recommended in highly symptomatic patients with moderate-to-severe risk of exacerbation, patients with rapid decline of lung function, and patients with COPD and history of asthma (Table 1).<sup>2,3,6</sup>

### Considering triple therapy as first choice: What are the issues?

Currently, two issues need to be addressed 1. Whether triple therapy should be the first choice of treatment or a step-up therapy? 2. How efficacious is inhaled corticosteroid (ICS) treatment?

The efficacy of ICS is monitored using blood eosinophilic count, which acts as a biomarker.<sup>3,4</sup> For the first time, GOLD 2019 addressed the role of eosinophils. The guideline stated that ICS therapy is ineffective in patients with blood eosinophilic count <100 cells/ $\mu$ L.<sup>3,5</sup> Nevertheless, it can be considered as the first choice in:

- Patients discharged from the hospital after an acute exacerbation of COPD, and in whom COPD is diagnosed for the first time because of the severe exacerbation<sup>6</sup>
- Patients who present for the first time with COPD, and are diagnosed with severe airway obstruction<sup>6</sup>

### Clinical implications

Consideration of triple therapy with ICS/LAMA/LABA for COPD is common in current clinical practice. Triple therapy can be an appropriate regimen in patients with moderate-to-high risk exacerbations and severe symptoms, persistent accelerated decline in lung function, and patients with chronic airway obstruction at the time of diagnosis of COPD. However, it is best to avoid triple therapy in most patients with COPD who have low symptoms and low risk of exacerbation.

#### References

1. Zheng Y, et al. *Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis*. BMJ. 2018; 363: k4388
2. Suisa S, et al. *Triple therapy trials in COPD: a precision medicine opportunity*. Eur Respir J. 2018;52(6):1801–848.
3. GOLD-2019-POCKET-GUIDE-FINAL\_WMS.pdf. Available at [https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-POCKET-GUIDE-FINAL\\_WMS.pdf](https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-POCKET-GUIDE-FINAL_WMS.pdf). Last accessed on 11-DEC-2019
4. Gaduzo S, et al. *When to use single-inhaler triple therapy in COPD: a practical approach for primary care health care professionals*. COPD. 2019; 14:391–401.
5. Cazzola M, et al. *Pharmacological treatment and current controversies in COPD*. F1000Res. 2019; 8:1–9.
6. Vansteeren LEGW, et al. *Triple therapy (ICS/LABA/LAMA) in COPD: thinking out of the box*. ERJ Open Res. 2019;5(1):1–6.



### Phosphodiesterase-4 inhibitors improve survival rate in COPD

A phenotype/endotype guided therapy with roflumilast has the potential to improve overall survival by reducing the number of exacerbations and increase the life span in patients with COPD, reported Alexa and colleagues. Roflumilast, a selective phosphodiesterase-4 inhibitor, targets the systemic inflammation associated with COPD and is used as part of a combination regimen with long-acting bronchodilators. Identifying the predictors for maximal efficacy of roflumilast in different patient populations can help with a more targeted therapy in COPD. To understand and identified the predictors, the authors conducted a post hoc analysis of pooled data derived from two large-scale randomized controlled trials. The authors concluded that roflumilast can be considered in patients with chronic bronchitis and frequent exacerbators (phenotype) and increased blood eosinophilia (endotype features).

Reference: Alexa I, et al. *Expert Opin Pharmacother.* 2011;20(1):91–3.

Weblink: <https://www.tandfonline.com/doi/abs/10.1080/14656566.2018.1544244?journalCode=ieop20>

### Vitamin D supplementation found beneficial in patients with COPD who have low vitamin D levels

Vitamin D supplementation substantially reduced the rate of moderate/severe COPD exacerbations in patients with 25-hydroxyvitamin D levels <25 nmol/L, but not in those with higher levels reported a metaanalysis. Randomized controlled trials (RCTs) evaluating vitamin D efficacy to prevent COPD exacerbations have yielded conflicting results. To address, David and colleagues conducted a metaanalysis to determine whether vitamin D supplementation reduces COPD exacerbation rate. In patients with Vitamin D deficiency, a 45% reduction in the incidence rate of moderate or severe COPD exacerbations with vitamin D supplementation was reported. The authors concluded that in patients experiencing COPD exacerbations routine testing of vitamin D status and offering supplementation to those with deficiency should be encouraged.

Reference: Jolliffe DA, et al. *Thorax.* 2019;74(4):337-45.

Weblink: <https://thorax.bmjjournals.org/content/74/4/337.long>

### Single inhaler LABA/LAMA combination improves QoL in COPD

People who took once daily LABA/LAMA using a single inhaler showed a greater improvement in lung function and quality of life than those taking placebo in a dummy inhaler, reported a meta-analysis. Fixed-dose combination of LABA/LAMA are recommended for the management of COPD. However, it is unclear whether clinical benefits with fixed-dose combination of LABA/LAMA is meaningful. Maqsood et al conducted a systematic review and metanalysis to address this concern. The authors concluded that compared with placebo, once-daily LABA/LAMA via a combination inhaler is associated with a clinically significant improvement in lung function and health-related quality of life in patients with mild-to-moderate COPD.

Reference: Maqsood U, et al. *Cochrane Database Syst Rev.* 2019;6:CD012930.

Weblink: <https://www.cochranelibrary.com/cdr/doi/10.1002/14651858.CD012930.pub2/full>

### Cardiovascular biomarkers capture systemic problems of COPD

The conventional measures to evaluate the systemic problems associated with COPD are the least effective. A metanalysis of 32 studies examined the association of cardiovascular and musculoskeletal biomarkers with clinical outcomes in COPD. Cardiovascular biomarkers such as 6MWD, resting heart rate, fibrinogen, CRP, WCC, and IL-6 were associated with clinical outcomes in COPD whereas, association of musculoskeletal biomarkers needs further investigation. Cardiovascular biomarkers can be used as an effective measure the clinical outcomes in patients with COPD.

Reference: Ferriant JM, et al. *Thorax.* 2019;74(5):439-46.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30617161>

### Bronchodilator combination is superior to monotherapy in symptomatic COPD

The effect of long-acting bronchodilator combination therapy in reducing COPD exacerbation risk compared to monotherapy is inconsistent in patients with symptomatic COPD. The result of post-hoc analysis reported an improvement of trough FEV<sub>1</sub> with a reduced risk of first exacerbation with combination therapy compared to monotherapy in patients with symptomatic COPD with or without exacerbation history. Combination therapy is suggested in symptomatic low-risk patients who are not under maintenance therapy.

Reference: Naya I, et al. *Respir Res.* 2019;20:60.

Weblink: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6434823/>





Abbott

# For your Allergic Rhinitis<sup>1</sup> patients with Unified Airway Disease (UAD)<sup>2,3</sup>



**References:**  
1. Elliott M. Preventing refection.  
2. John E. The Distal Airway Hypothesis. *Univ Dentistry* 2004; 26:1-26.  
3. Weiss J. Liposomal Allergic Inflammation is the unified theory: how both the new Th10 and Th17 paradigms are.

Логотипы и товарные знаки являются  
правственными знаками – символами – коммуникации

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QUALITATIVE AND QUANTITATIVE METHODS

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# ASTHMA

- Fact Sheet
  - What's New In Guidelines?
  - Conference Snapshot
  - Hot Topics
  - EBM Updates

About 10% of the total asthmatics in the world live in India<sup>1</sup>

- The prevalence of asthma increased by 9% from 1990 to 2016<sup>2</sup>
  - The prevalence of asthma was 2. 9% in India in 2016 which translates to 37. 9 million cases<sup>2</sup>
  - The number of asthma cases in India increased by 1.5 times from 1990 to 2016<sup>2</sup>
  - The prevalence of asthma in children varied from 3% to 18% across different states of India<sup>3</sup>
  - The prevalence of asthma in India was 0·7 times the global average in 2016<sup>2</sup>

## Asthma: Burden and Risk factors

- Disability-adjusted life-years per person with asthma were 2.4 times the global average in 2016<sup>2</sup>
  - About 82,000 deaths of asthma were estimated for the year 2015 in India<sup>4</sup>
  - Asthma deaths accounted for nearly one percent of the total deaths in India in 2015<sup>4</sup>
  - Patients with uncontrolled asthma had up to 4.6-fold greater frequency of hospitalizations compared to those without asthma<sup>1</sup>
  - More than 70% of children with troublesome asthma continue to have symptoms in mid-adult life<sup>3</sup>
  - In India, almost 80% of expenditure on a sick patient is on buying medicine from personal savings<sup>4</sup>
  - Paternal smoking doubles the risk of asthma in children<sup>3</sup>
  - Street near house increases the risk of asthma by 1.7 times<sup>3</sup>
  - Children living in households using solid or unclean fuels are at 21% higher risk of having asthma<sup>4</sup>
  - Each additional hour of using traditional stove increases odds of reporting asthma by nearly 4%<sup>4</sup>

## References

1. Koul PA, et al. Lung India 2018;35:281-3; 2. The Global Burden of Disease Study 1990–2016. Lancet Glob Health 2018;6: e1363–74; 3. Kumar V, et al. Indian J Allergy Asthma Immunol 2019;33:45-50; 4. Kumar P, et al. PLoS ONE. 2017; 12(10): e0185938; 5. Global asthma report 2018. Available at <http://www.globalasthmareport.org/Global%20Asthma%20Report%202018.pdf>. Last accessed on 29-Nov-2019

## Global strategy for asthma management and prevention guidelines (GINA), 2019

The Global Initiative for Asthma (GINA) published new recommendations in April 2019 following the routine twice-yearly review of the literature by the GINA scientific committee.

### Key differences

#### Treatment of asthma in adolescents and adults

- Treatment with short-acting bronchodilators (SABA) alone is no longer recommended
- Daily therapy with a corticosteroid-containing inhaler or as needed (in mild asthma) is recommended in all adolescents and adults to reduce risk of severe exacerbations
- Add-on, off-label therapy with azithromycin is recommended as an option in adults with persistent asthma despite treatment with moderate-high dose ICS-LABA
- The step-up treatment approach has been revised. The high-dose ICS-LABA therapy is now recommended in step-5 of the treatment algorithm and maintenance oral corticosteroids (OCS) are no longer preferred in step-5 owing to adverse effects
- Dupilumab is recommended as an additional treatment option for patients  $\geq 12$  years with severe type 2 asthma or OCS-dependent asthma

#### Treatment of asthma in children 6-11 years

- A separate treatment algorithm was incorporated for management of asthma in children aged 6-11 years
- As in adults, SABA- alone therapy is no longer recommended and instead, a corticosteroid-containing inhaler daily or as needed (in mild asthma) is recommended
- In the Step-3 of treatment algorithm, maintenance therapy with low dose ICS-LABA, or medium dose ICS along with as needed SABA is recommended
- Add-on tiotropium by mist-inhaler is now recommended for patients with persistent asthma despite treatment with ICS-LABA

*Reference:* Global strategy for asthma management and prevention-2019. Available at <https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf>. Last accessed on 03-Dec-2019.

## BTS/SIGN national Guideline on the management of asthma, 2019

The British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN) have updated guidance on the management of asthma. The current guideline is an update on 2014 version and provides recommendations based on current evidence for best practice in the management of asthma in adults, including pregnant women, and adolescents and children with asthma.

### Key differences

#### Asthma monitoring

- Routine use of FeNO testing in adults or children except in specialist asthma clinics is not recommended
- Routine use of a sputum eosinophilia test is not recommended

### Pharmacotherapy

Increasing the dose of inhaled corticosteroids (ICS) is recommended in patients with persistent asthma despite treatment with ICS plus LABA. If asthma control remains inadequate, add-on therapy with any of the following is recommended

- Leukotriene receptor antagonist (if not already trialled)
- Tiotropium (adults)
- Theophylline

Single combination inhaler for maintenance and reliever therapy (MART) is considered as an option in adult patients who have a history of asthma attacks on medium dose ICS or ICS/LABA

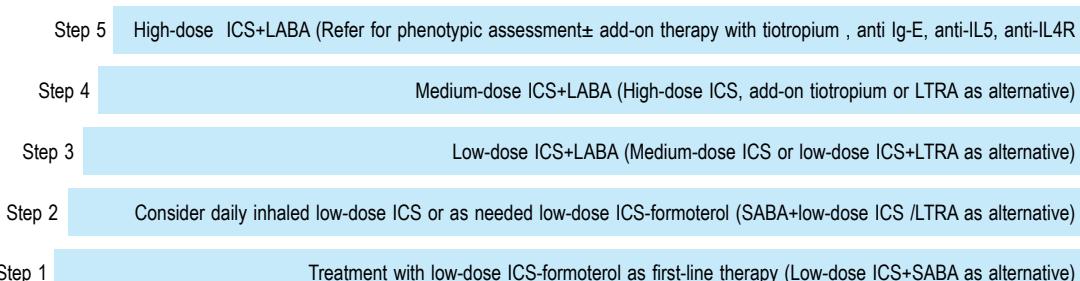
### Specialist care

- The current guideline recommends that all patients whose asthma is not adequately controlled on recommended initial or additional controller therapies should be referred for specialist care

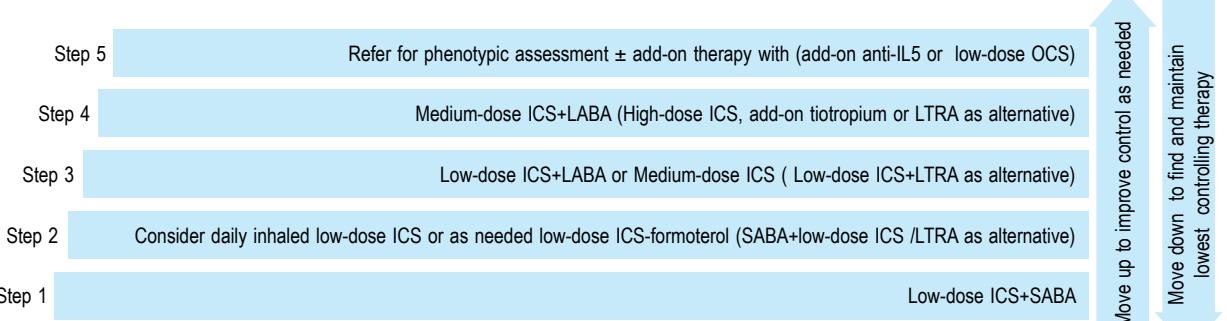
*Reference:* SIGN158-British guideline on the management of asthma-2019. Available at <https://www.sign.ac.uk/assets/sign158.pdf>. Last accessed on 03-Dec-2019

### Management of Asthma in patients $\geq 12$ years<sup>1,2</sup>

Suspected case of Asthma	Asthma diagnosed
Diagnosis and assessment	Evaluation: Assess symptoms, measure lung function, check inhaler technique and adherence; Assess, adjust and review



### Management of Asthma in children (6-11 years)



Abbreviations: FEV: Forced expiratory volume; ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonist; LTRA: Leukotriene receptor antagonist; SABA: Short-acting beta agonist

#### Reference:

- GINA-2019 guidelines. Available at <https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf>. Last accessed on 08-Dec-2019.
- British Guideline on the Management of Asthma. Available at <https://www.sign.ac.uk/assets/sign158.pdf>. Last accessed on 08-Dec-2019.



## ICAAICON – 2019

### When and where:

- The 3<sup>rd</sup> Indian College of Allergy, Asthma Applied Immunology Conference was held in New Delhi on 07<sup>th</sup> and 10<sup>th</sup> November 2019

### Scientific sessions:

- Discussions and presentations on newer topics and latest updates in the field of allergy and asthma were covered in the conference. Keynote presentations are listed below
  - Biomarkers and biologicals in asthma
  - Current concepts in the management of severe asthma
  - Update on paediatric asthma
  - Asthma variables (occupational asthma, thunderstorm asthma, asthma and pregnancy)
  - Use of xanthine in asthma in Indian setting
  - Food allergy in bronchial asthma: Diagnosis and management
  - Stem cell therapy in asthma
  - Link between environmental tobacco smoke and asthma in children

### Awards and honours

#### UCB ICAAI Award

- Dr. Kamal Singh for oral presentation on environmental tobacco smoke and asthma in children in rural area of Delhi-NCR
- Dr. Anjali Mishra for oral presentation on evaluation of potential content and profile of allergic extracts: Mandatory guidelines towards quality control of allergens

#### Reference

ICAAICON 2019 Programme. Available at <http://www.icaaicon2019.in/scientific-program/>. Last accessed on 07-Dec-2019

## ERS Congress-2019

### When and where:

- European Respiratory Society congress was held between 28 September to 2 October 2019, in Madrid, Spain

### Scientific sessions:

- List of clinical trials presented in the sessions are given below**
  - The use of a direct bronchial challenge test in primary care to diagnose asthma
  - Spirometry, FeNO, and asthma control in children managed for asthma in primary care
  - Person-centred approaches to COPD and asthma care
  - Vitamin D status during pregnancy and wheezing and asthma during childhood
  - Dynamics of blood and sputum eosinophils in asthma patients with cold airway hyperresponsiveness during cold air provocation
  - Asthma control and quality of life one year after pulmonary rehabilitation
  - Probiotic treatment and aerobic physical activity effects on visceral fat and posture in overweight patients with asthma
  - Dupilumab efficacy in patients with uncontrolled, moderate-to-severe asthma by immunoglobin E levels at baseline
  - Efficacy of dupilumab in asthma patients with FEV1 60–80% predicted on medium-dose ICS

### New release

- ERS/ATS Severe asthma guidelines: update 2019

### Awards and honours

#### ERS Gold Medal in Asthma:

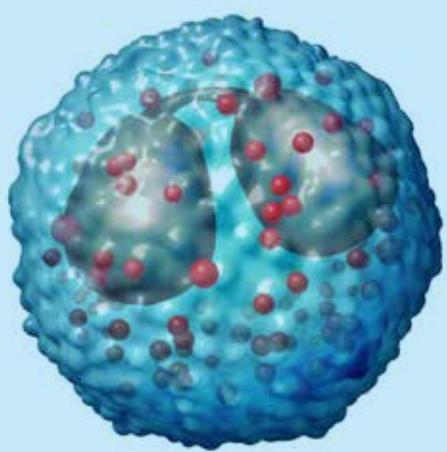
- Professor John Fahy for his outstanding contribution in the field of asthma

#### References

- Congress guide. ERS International Congress 2019. Available at <https://erscongress.org/programme-2019/access-the-programme.html>. Last accessed on 05-Dec-2019
- ERS Award Winners 2019. Available at <https://erscongress.org/funding-awards-2019/gold-medals-main-awards.html>. Last accessed on 05-Dec-2019



## Anti-IL-5 agents: New hope in severe eosinophilic asthma?



**C**urrently, three anti-interleukins (IL)-5 agents (benralizumab, mepolizumab, reslizumab) are approved by the US FDA for the treatment of severe eosinophilic asthma. These three anti-IL-5 biologics are now available in the Indian market.<sup>1-3</sup> The efficacy and safety of the three anti-IL-5 drugs was proven in clinical trials which reported favorable results regarding exacerbation rate, sparing of systemic steroid use, and improvement in lung function with anti-IL-5 therapy in patients with severe eosinophilic asthma. Anti-IL-5 therapy had a mention in the **GINA guidelines, 2019** which **recommended anti-IL-5 as an add-on option for patients with severe eosinophilic asthma that is uncontrolled on high dose ICS/LABA.**<sup>4</sup> However, we need to have a clear understanding about the rationale behind the use of anti-IL-5 agents to optimize the therapy.<sup>14</sup>

### Anti-IL-5 in severe eosinophilic asthma: The rationale

Benralizumab, mepolizumab, reslizumab are the three anti-IL-5 agents currently available in India. Anti-IL-5 agents are proven to be efficacious in severe eosinophilic asthma and are recommended for the same by 2019 GINA guidelines. However, current challenges in using anti-IL-5 in severe eosinophilic asthma are high cost, lack of evidence regarding long-term safety, lack of biomarkers to predict clinical response

Eosinophilic asthma is a subtype of asthma that is often severe and difficult to control, and is characterized by increased eosinophil counts in blood, lung tissue, and sputum. Accumulation of eosinophils leads to potentiated airway inflammation and tissue remodeling which increases mucus secretion and bronchial wall thickening. Interleukin-5, a mediator of the eosinophil pathway, plays an important role in the formation of eosinophils in the bone marrow, as well as in their maturation, migration, and activation. IL-5 also inhibits apoptosis, thus promoting the survival of eosinophils. The anti-IL-5 agents mepolizumab and reslizumab act by blocking IL-5 whereas benralizumab targets the IL-5 receptor and elicits an NK cell-mediated antibody-dependent cellular cytotoxicity against eosinophils.

### When to initiate anti-IL-5 therapy?

The lack of biomarkers predicting the good clinical response of

biologic drugs is a key challenge for initiating the anti-IL-5 in patients with severe eosinophilic asthma. However, clinical studies identified some baseline clinical features associated with a better clinical response to anti-IL-5 in patients with severe eosinophilic asthma, which are:<sup>3</sup>

- Blood eosinophils level  $\geq 300$  cells/ $\mu$ l
- Oral corticosteroid use
- History of nasal polyposis
- Forced vital capacity  $< 65\%$

Head to head comparison between the available three anti-IL-5 is very difficult. However, choice of anti-IL-5 can be made based on the clinical characteristics of patients and pharmacological properties of the drugs (Table 1).<sup>2,3</sup>

Table 1. Clinical characteristics of available anti-IL-5 <sup>2,3</sup>					
Sl.no	Drug	Administration route	Regimen	Target population	Main clinical features
1	Benralizumab	Subcutaneous	30 mg every 4 weeks for the first 3 doses, then every 8 weeks	Eosinophilic asthma $\geq 300$ cells/ $\mu$ L, CRSwNP	High affinity for IL-5 receptor, eosinophils sustained tissue depletion, improvement of pulmonary function even in patients with FAO, steroid-sparing effect
2	Mepolizumab	Subcutaneous	100 mg every 4 weeks	Eosinophilic asthma $\geq 300$ cells/ $\mu$ L	Excellent safety profile, steroid-sparing effect

CRSwNP: Chronic sinusitis with nasal polyposis; FAO: Fixed airway obstruction

### Anti-IL-5 therapy: Some bottlenecks

Therapy with anti-IL-5 agents, like any other therapy, has some limitations such as high cost, lack of evidence for long-term safety, and lack of biomarkers to predict clinical response.<sup>1,3</sup> Further, accurate phenotyping is important for initiating anti-IL-5 therapy to achieve optimal disease control. The purpose of phenotyping is to provide an insight into the mechanism driving the disease and direct treatment accordingly. In Indian patients with asthma, Dasgupta et al. reported a higher prevalence of eosinophil phenotype when a blood eosinophil count of  $>300$  cells/ $\mu$ l was used as the cutoff than when sputum eosinophil count was considered for phenotyping. This indicates that mere finding of eosinophils in blood may not be reflective of the presence of activated eosinophils in the airways. Moreover, India has a higher prevalence of parasitic infections compared to most other countries which might necessitate using a greater cutoff for blood eosinophils. Given the recent availability of specific anti-eosinophil agents, these factors need urgent attention.<sup>5</sup>

### Clinical implications

The introduction of anti-IL-5 agents represents a major advance in asthma care. The anti-IL-5 therapy can be used as add-on therapy in patients with severe eosinophilic asthma after considering patient's baseline clinical characteristics. However, there is an emerging need to have better understanding of the clinical relevance of phenotypes and role of biomarkers which are helpful and necessary to identify patients likely to respond and benefit from anti-IL-5 therapy. Also, cost of therapy will be a major deterrent in poor and developing countries.

- References**
1. Caminati M, et al. New horizons for the treatment of severe, eosinophilic asthma: benralizumab, a novel precision biologic. *Biologics. 2019; 13:89–95.*
  2. Busse W. Biological treatments for severe asthma: A major advance in asthma care. *Allergol Int. 2019;68(2):158–66.*
  3. Pavord I, et al. Severe T2-high asthma in the biologics era: European experts' opinion. *Eur Respir Rev. 2019;28(152).1–11.*
  4. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention. 2019. Available from <https://ginasthma.org/>. Last accessed on 12-Dec-2019.*
  5. Dasgupta A, et al. Inflammatory phenotypes of severe asthma in India. *Lung India : Official Organ of Indian Chest Society. 2019;36(3):267–268HOT TOPIC-2*



## Treating mild asthma: A paradigm shift



Global initiative for asthma (GINA), 2019 recommendations have revised the long-standing clinical practice in the management of mild asthma. The most fundamental change was the recommendation against short-acting beta-agonists (SABA)-only treatment, which has been the cornerstone of asthma management for almost 50 years. Besides, the guideline recommended inhaled corticosteroids (ICS)-containing controller treatment for all adults and adolescents with mild asthma for effective control of symptoms and to reduce the risk of serious exacerbations (Figure 1). These new recommendations are no doubt a paradigm shift from decades-old clinical practice mandating the use of symptom-driven SABA treatment alone in those with mild asthma.<sup>1-4</sup>

### SABA-only treatment: There are some concerns indeed!

Short-acting beta-agonists (SABA) have been the go-to medications for treating mild asthma for almost five decades. Owing to higher recurrence of exacerbations in SABA-only treated patients with asthma and availability of other options (ICS and LTRAs) to cover broader pathophysiological changes, switch from SABA-only strategy may be rationale in mild asthma at least in persistent cases.

### Are new recommendations evidence-based?

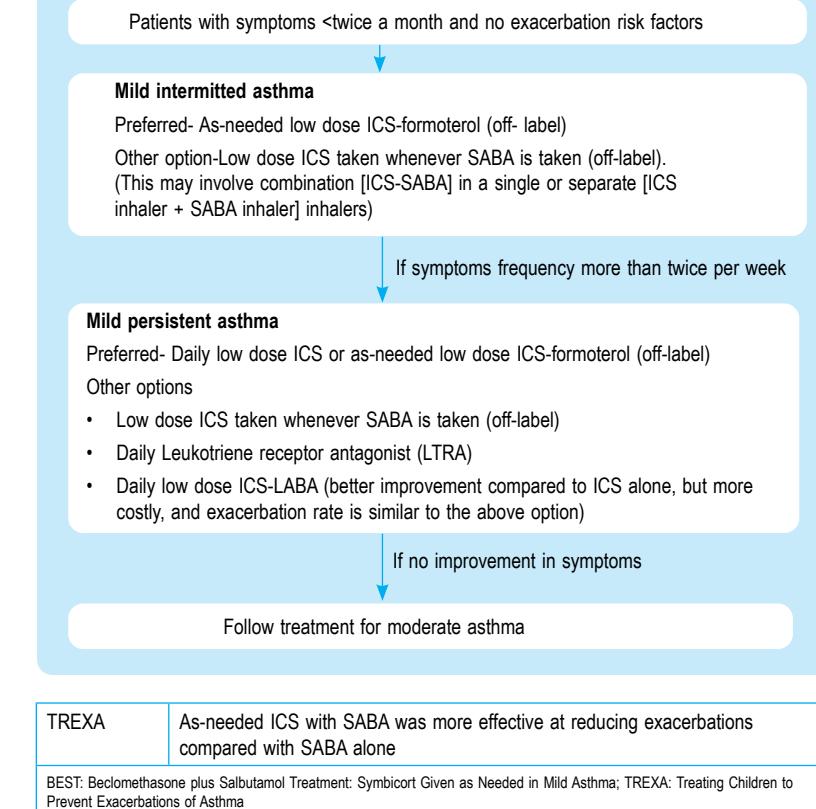
The new GINA recommendations were based on data from clinical trials which raised an alarm that using SABA-only treatment might do more harm than good for people with mild asthma. Besides, ample evidence was observed in several recent

trials supporting the use of as-needed ICS along with as-needed SABA in patients with mild asthma (Table 1).<sup>3,4</sup>

**Table 1.** Clinical trial supporting the GINA-2019 recommendation<sup>3,4</sup>

Clinical trial	Outcomes
SYGMA 1	<ul style="list-style-type: none"> <li>As-needed inhaled budesonide-formoterol provided superior asthma-symptom control to as-needed terbutaline in patients with mild asthma</li> <li>Budesonide-formoterol used as needed resulted in a 64% lower rate of severe exacerbations than terbutaline used as needed</li> </ul>
SYGMA 2	As-needed use of inhaled budesonide-formoterol was non-inferior to budesonide maintenance therapy concerning the annualized rate of severe asthma exacerbations
BEST	Symptom-driven use of ICS with SABA in a single inhaler is as effective as ICS maintenance therapy and is associated with a lower cumulative dose of the ICS

**Figure 1.** Algorithm for the management of mild asthma<sup>1</sup>



### Clinical implications

New recommendations for mild asthma management have considered underlying pathophysiology and evidence from multiple clinical trials. Therefore, it may be prudent to switch from SABA-only strategy for treating milder forms of asthma at least in persistent cases.

**References** 1. Global Strategy for Asthma Management and Prevention. 2019. Available at <https://ginasthma.org/>. Last accessed on 12-Dec-2019. 2. Valero A, et al. J Investig Allergol Clin Immunol. 2019;29(1):15–23. 3. Muneswarao, et al. Respir Res 20, 183 (2019). 1–6. 4. Tang W, et al. J Thorac Dis. 2018;10(10):5655–58. 6. Abramson MJ, et al. Am J Respir Crit Care Med. 2001;163:12–18



### Tiotropium in treating mild-to-moderate asthma: Requires stronger evidence

Although tiotropium is an approved treatment for COPD, there are concerns about its clinical efficacy in moderate-to-severe asthma. In a recent systemic review, treatment with tiotropium was significantly associated with improved morning PEF, evening PEF, peak FEV<sub>1</sub>, and trough FEV<sub>1</sub>. However, when these results were compared with standard therapy with or ICS or LABA, the improvement was not significant. Refractory asthma necessitates the need for an alternative drug other than ICS and β-agonist. High-quality, larger-sample clinical trials are warranted to gather more solid evidence on the safety profile of tiotropium in clinical practice.

Reference: Jian-Feng, et al. *Medicine*. 2019;98(33):1-10. doi: 10.1097/MD.00000000000016637

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/31415357>

### ICS can cause URTIs in patients with Asthma

ICS is recommended as the maintenance therapy for asthma. However, treatment is associated with risk of upper respiratory tract infections (URTIs). A 24% increased risk of URTI (independent of ICS dose) was associated with long-term use of ICS in patients with mild-to-moderate asthma. Both high and low doses of ICS were associated with high risk of URTIs. Clinicians are advised to monitor patients on long-term ICS therapy.

Reference: Yang, et al. *Infection*. 2019;47(3):377-85.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30298471>

### Vitamin D supplements prevent acute respiratory infections

There is an evident link between Vitamin D deficiency and acute respiratory infection (ARI). Vitamin D supplementation reduced the risk of ARI by 12% in patients with asthma or COPD. The clinical benefits were more evident in people with Vitamin D deficiency and in those receiving daily doses or weekly vitamin D without additional bolus doses. The risk of ARIs decreased by 70% in patients with deficiency. Steps to improve vitamin D status should be considered in these patients.

Reference: Martineau AR, et al. *Health Technol Assess*. 2019;23(2):1-44.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30675873>

### ICS+LABA better than SABA or ICS+SABA in mild asthma exacerbation

Mild asthma imposes a substantial burden with respect to risk of exacerbations. Inhaled corticosteroids (ICS) maintenance therapy or ICS+SABA therapy on as-needed basis as reliever therapy is recommended to prevent this risk. ICS therapy is associated with poor adherence and there is insufficient evidence for ICS+SABA therapy. ICS+LABA combination (budesonide-formoterol), on the other hand, was associated with lower risk of severe exacerbations compared to SABA (Salbutamol) alone or ICS+SABA (Budesonide+Salbutamol). The risk was 60% and 56% lower with ICS+LABA compared to SABA alone or ICS+SABA respectively. Annualized exacerbation rate was also lower with ICS+LABA compared to other therapies. ICS+LBA can be considered for the prevention of asthma exacerbations.

Reference: The Novel START study team. *N Engl J Med* 2019; 380:2020-2030.

Weblink: <https://www.nejm.org/doi/full/10.1056/NEJMoa1901963>

### Add-on therapy of azithromycin in asthma improves FEV1

There is a need for additional treatment options in patients with persistent asthma to control exacerbations. The widespread use of monoclonal antibodies and anti-interleukin-5 as add-on therapy is limited by the facts they are effective only in eosinophilic asthma and are not affordable. Airway inflammation and chronic infection of the lower respiratory tract may contribute for the risk of acute exacerbations. Azithromycin, a broad-spectrum antibiotic, can be considered in such conditions owing to its anti-inflammatory and immunomodulatory properties. Azithromycin was not associated with gastric side effects when compared to placebo and improved FEV1 ( $P=0.02$ ) and Fractional Nitric Oxide levels ( $P=0.0009$ ). Short-term azithromycin therapy can be considered as a safe, economic and effective add-on therapy in uncontrolled persistent asthma but its effectiveness in long term therapy needs to be evaluated.

Reference: Wang, et al. *Medicine*. 2019;98(38):1-8

Weblink: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6756741/>



In NSAID-induced gastritis

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**FAST**<sup>3-4</sup>



**SUSTAINED**<sup>2</sup>



**PREDICTABLE**<sup>5-7</sup>

**References:** 1. <https://www.mayoclinic.org/drugs-supplements/rabeprazole-oral-route/proper-use/drug-20066981> (Accessed on 01 Apr 2019). 2. Baldwin CM and Keam SJ. Rabeprazole - A Review of its Use in the Management of Gastric Acid-Related Diseases in Adults. *Drugs*. 2009;69(10):1373-1401. 3. Khan R, Ashraf MS, Afzal M, et al. Formulation and evaluation of sustained release matrix tablet of rabeprazole using wet granulation technique. *J Pharm Biomed Sci*. 2014;6(3):180-4. 4. Marelli S, Pace F. Rabeprazole for the treatment of acid-related disorders. *Expert Rev Gastroenterol Hepatol*. 2012;6(4):423-35. 5. Kinoshita Y, et al. Randomised clinical trial: a multicentre, double-blind, placebo-controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. *Aliment Pharmacol Ther*. 2011;33(2):213-24. 6. Sheu BS, et al. Body mass index can determine the healing of reflux esophagitis with Los Angeles Grades C and D by esomeprazole. *Am J Gastroenterol*. 2008;103(9):2209-14. 7. Swan SK, et al. Review article: the pharmacokinetics of rabeprazole in health and disease. *Aliment Pharmacol Ther*. 1999;13(3):11-7.

# GASTROESOPHAGEAL REFLUX DISEASE

• Fact Sheet

• What's New In Guidelines?

• Conference Snapshot

• Hot Topics

• EBM Updates

Fact Sheet

- About 7.6% of adults in India have GERD<sup>1</sup>
- Among Indians, the prevalence of GERD is higher among urban dwellers<sup>1</sup>

#### Risk factors contributing to burden of GERD

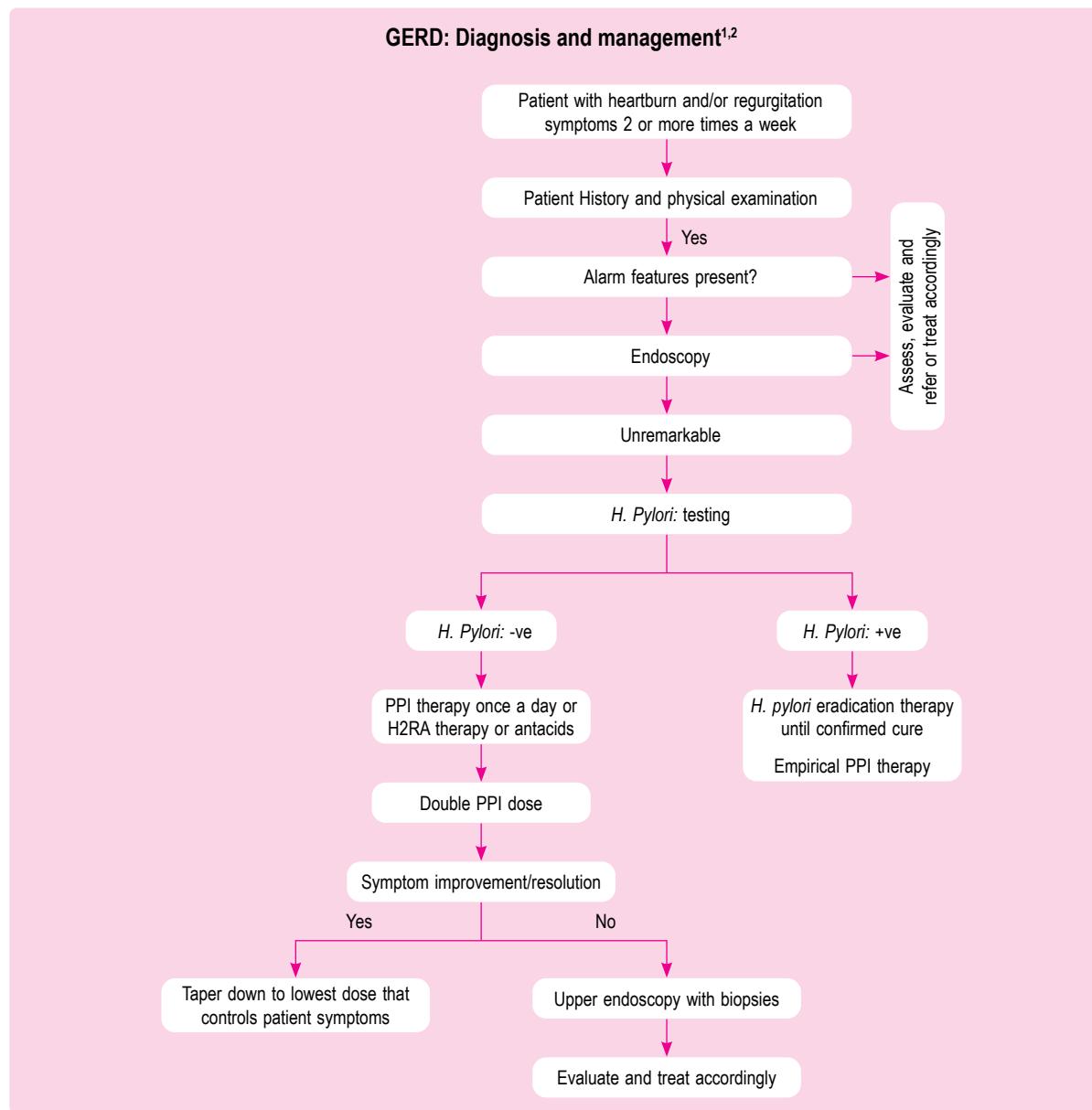
- Women are 30% more likely to have GERD than men<sup>1</sup>
- People living in urban areas are Twice more likely to have GERD compared to those living in rural areas<sup>2</sup>
- Age>30 years increases the risk of GERD by 90%<sup>1</sup>
- Being overweight ( $BMI \geq 25 \text{ kg/m}^2$ ) increases the risk of GERD by 30%<sup>1</sup>
- Infrequent milk intake (< 3 times per week) is associated with 60% higher risk of having GERD<sup>1</sup>
- Drinking >3 cups of tea or coffee per day increases the risk of GERD by 4 times<sup>3</sup>

#### References

1. Chowdhury SD, et al. Prevalence and factors associated with gastroesophageal reflux disease in southern India: A community-based study. *Indian J Gastroenterol*. 2019 Feb;38(1):77-82.
2. Yamasaki T, et al. The Changing Epidemiology of Gastroesophageal Reflux Disease: Are Patients Getting Younger? *J Neurogastroenterol Motil*. 2018;24(4):559-569.
3. Ramachandran Arivan, et al. Prevalence and risk factors of gastro-esophageal reflux disease among undergraduate medical students from a southern Indian medical school: a cross-sectional study. *BMC Res Notes*. 2018; 11: 448.



In 2019, there were no new specific guidelines on GERD from any international committees. Currently, widely accepted management algorithm is given below.



#### References:

1. Hunt R, et al. World Gastroenterology Organisation Global Guidelines: GERD Global Perspective on Gastroesophageal Reflux Disease. *J Clin Gastroenterol.* 2017;51(6):467-478.
2. Sandhu DS, et al. Current Trends in the Management of Gastroesophageal Reflux Disease. *Gut Liver.* 2018;12(1): 7-16.

#### GERD symptoms and causes: New insights and future implications

- GERD, as per 2006 Montreal Consensus, is defined as “a condition that develops when the reflux of stomach contents into the esophagus causes troublesome symptoms and/or complications”. This definition of GERD provides a rationale for initiating acid-suppressive therapy and allows effective management of the substantial symptom burden in patients without the need for complicated evaluation of symptom etiology. However, it is evident that reflux contents other than acid can cause symptoms. Moreover, many times it is difficult to distinguish between GERD and other functional esophageal disorders. Although PPI-response test is used to diagnose GERD,

the results may not be accurate. This was evident from the results of a study which found that esomeprazole use was neither sensitive nor specific for the diagnosis of GERD.

- A recent multicentric study conducted across UK, USA, Brazil, and Russia in patients with GERD reported that heartburn (as interpreted by clinicians) may encompass at least two distinct symptoms, potentially with different aetiologies. Further, about 80% of patients on PPI therapy experience reflux symptoms associated with non-acid reflux. Similar results were reported in patients taking double-dose PPI.
- Impaired mucosal barrier function because of dilated intercellular spaces (DIS) formation due to acid reflux or bile acid, psychological factors such as stress, sleep impairment, peripheral and central hypersensitivity, and obesity can cause reflux hypersensitivity. Patients with reflux hypersensitivity experience heartburn and other symptoms despite treatment with PPI.
- Although PPIs remain the best initial management for patients with suspected GERD, it is important to investigate the heterogeneous causes of suspected GERD symptoms in PPI-resistant cases. A broad understanding of symptoms based on patients’ description is needed to provide better treatment. New diagnostic tools to distinguish GERD from other reflux conditions and functional oesophageal disorders are warranted.

#### References:

1. Hungin APS, et al. Revisiting Montreal: New Insights into Symptoms and Their Causes, and Implications for the Future of GERD. *Am J Gastroenterol.* 2019 Mar;114(3):414-21.
2. Sandhu DS, et al. Current Trends in the Management of Gastroesophageal Reflux Disease. *Gut Liver.* 2018;12(1):7-16.

#### GERD: Current advances and new hopes!

- **Management of refractory GERD:** Double-dose PPI therapy is usually considered for refractory GERD. However, taking PPI twice-daily is associated with poor adherence and high discontinuation rates compared to once-daily PPI therapy. A Dual Delayed-Release PPI can be used to improve compliance and prolonged and effective control of symptoms. A Dual Delayed-Release capsule contains two types of granules, with each having a coating that dissolves at different pH levels and protects the drug from acid-induced degradation. The formulation provides two pulsatile releases, one in the upper and the other in the lower small intestine, giving a prolonged plasma exposure<sup>1-3</sup>
- **Laparoscopic surgical fundoplication:** It is presently the most common technique performed in GERD patients. However, studies comparing laparoscopic surgical fundoplication and medical management reported conflicting results<sup>1</sup>
- **Linx™ reflux management system:** The device consists of a series of titanium beads with a magnetic core connected with titanium wires to form a ring which is placed around the lower end of the distal esophagus by laparoscopy. It helps to augment the lower esophageal sphincter and thus prevent gastroesophageal reflux. A reduction in PPI usage and overall improvement in quality of life was reported in >90% of patients who were treated with Linx reflux management system<sup>1</sup>
- **Transoral incisionless fundoplication (TIF):** It is used to restore the angle of His by creating a valve at the esophagogastric junction (EGJ). This is achieved by delivering multiple full thickness, nonabsorbable fasteners at the EGJ. The TIF procedure achieved a long-lasting elimination of daily dependence on PPI treatment in 75% to 80% of the patients. Ideal candidates for the TIF procedure are patients with chronic GERD (abnormal pH test or low grade EE) who have absent or small hiatal hernia (<2 cm)<sup>1</sup>

#### References:

1. Sandhu DS, et al. Current Trends in the Management of Gastroesophageal Reflux Disease. *Gut Liver.* 2018;12(1):7-16.
2. Grady H, et al. Development of Dexlansoprazole Delayed-Release Capsules, a Dual Delayed-Release Proton Pump Inhibitor. *J Pharm Sci.* 2019;108(11):3496-3501.
3. Skrzypko-Radomańska B, et al. Dexlansoprazole - a new-generation proton pump inhibitor. *Prz Gastroenterol.* 2015;10(4):191-96



## ESPGHAN Annual Meeting, 2019

### When and where

European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) organised its 52<sup>nd</sup> annual meeting in Glasgow, Scotland from 05–08 June 2019

### Scientific sessions

Data from clinical trials in the fields of hepatology, gastroenterology, and nutrition were discussed in scientific sessions. Some of the clinical trials are listed below.

- CD-TREAT a novel dietary therapy of active Crohn's disease
- Exclusive enteral nutrition versus corticosteroid induction therapy for new onset paediatric Crohn's disease
- Safety and efficacy of teduglutide in paediatric patients with short bowel syndrome-associated intestinal failure (SBS-IF)
- Faecal microbiota transplantation – beyond *Clostridium difficile*
- *Helicobacter pylori* infection in children with concomitant coeliac disease and type 1 diabetes mellitus

### New release

2019 ESPGHAN guidelines for coeliac disease: Consolidation of the no-biopsy approach

### Awards and honours

- **John Harries Prize:** Dr. Daniel Kotlarz for the best presentation in gastroenterology at the annual conference (Topic: Human RIPK1 Deficiency - Molecular insights from Children with IBD)
- **Alex Mowat Prize:** Dr. Dominique Lenz for the best presentation in the field of hepatology at the annual conference (Topic: Biallelic mutations in RINT1 - a new cause of recurrent acute liver failure with onset in infancy and dysostosis multiplex)
- **The Annual Jean Rey Prize:** Dr. Katarzyna Miroslawa Boradyn for the best presentation on Nutrition (Topic: Low FODMAP diet is not effective in reducing symptoms of functional abdominal pain in children: a randomised double-blind study)

### References

1. 2019 ESPGHAN Programme book. Available at [https://www.esphancongress.org/fileadmin/user\\_upload/downloads/Scientific\\_Programme/ESPGHAN2019\\_Programme\\_Book.pdf](https://www.esphancongress.org/fileadmin/user_upload/downloads/Scientific_Programme/ESPGHAN2019_Programme_Book.pdf). Last accessed on 06-Dec-2019
2. Prizes. Available at <http://www.esphghan.org/grants-and-awards/funding-opportunities/prizes/>. Last accessed on 06-Dec-2019



## ACG-Annual Scientific Meeting, 2019

### When and where

The 84th Annual Scientific Meeting of the American College of Gastroenterology (ACG) was held in San Antonio, Texas from October 25-30, 2019

### Scientific sessions

More than 5,500 gastroenterologists and other health care professionals convened to review the latest scientific advances in gastrointestinal research, treatment of digestive diseases, and clinical practice management. There were several exciting research posters presented throughout the meeting.

Presentations nominated by the ACG Public Relations Committee	
Topic	Poster presentation
Risks of acute pancreatitis among cannabis users	Association Between Acute Pancreatitis and Cannabis Use – A U.S. Population-Based Study
Protective role statins against developing liver cancer	Statin Use Reduces the Risk of Hepatocellular Carcinoma: An Updated Meta-analysis and Systematic Review
Maintenance of healthy weight and risk of colorectal cancer survival	Impact of Weight Parameters on Colorectal Cancer Survival: A Systematic Review and Meta-Analysis;
The link between chronic opioid use and difficulty in swallowing and esophagus problems	Opioids Interfere with Deglutitive Inhibition Assessed by Response to Multiple Rapid Swallows During High
Patients population that require anesthesia-assisted sedation during endoscopy	Developing and Validating a Prediction Model to Identify Patients at High Risk for Failing Standard Sedation for Routine GI Endoscopy
Impact of caffeine consumption on gut-microbiota	Caffeine Consumption and the Colonic Mucosa-Associated Gut Microbiota
Budesonide oral suspension for Eosinophilic Esophagitis	Efficacy of Budesonide Oral Suspension for Eosinophilic Esophagitis in Adolescents and Adults: Results From a Phase 3, Randomized, Placebo-Controlled Trial

### Awards and honours

- **Berk/Fise Clinical Achievement Award:** Dr. Stephen B. Hanauer for his distinguished contributions to clinical gastroenterology
- **The Samuel S. Weiss Award:** Dr. Alvin M. Zfass for his outstanding service to the American college of gastroenterology

### References

1. ACG-2019, Final program. Available at [https://acgmeetings.gi.org/wp-content/uploads/2019/10/ACG2019\\_Final-Program.pdf](https://acgmeetings.gi.org/wp-content/uploads/2019/10/ACG2019_Final-Program.pdf). Last accessed on 06-Dec-2019
2. Featured Abstracts and Author Insights, ACG-2019. Available at <https://gi.org/media/press-info/scientific-meeting/featured-science/>. Last accessed on 06-Dec-2019



## Chronic Cough and GERD in Children

**C**hronic cough (>4 weeks duration) in children is associated with impaired quality of life and treatment-burden. Gastroesophageal reflux disease (GERD) has long been postulated as one of the several etiologies linked to chronic cough in children. Although the association between cough and GERD is well established in adults, there is uncertainty and controversy regarding their association in the pediatric population. The absence of gold-standard diagnostic tool for the diagnosis of GERD in children is one of the major reasons behind this uncertainty. Moreover, several treatment modalities are available for GERD some of which may cause more harm than good. These observations warrant the need for addressing some key questions to determine the role of empirical therapy for children with GERD and chronic cough.<sup>1,2</sup>

### Should empirical therapy for GERD be used in children with chronic cough?

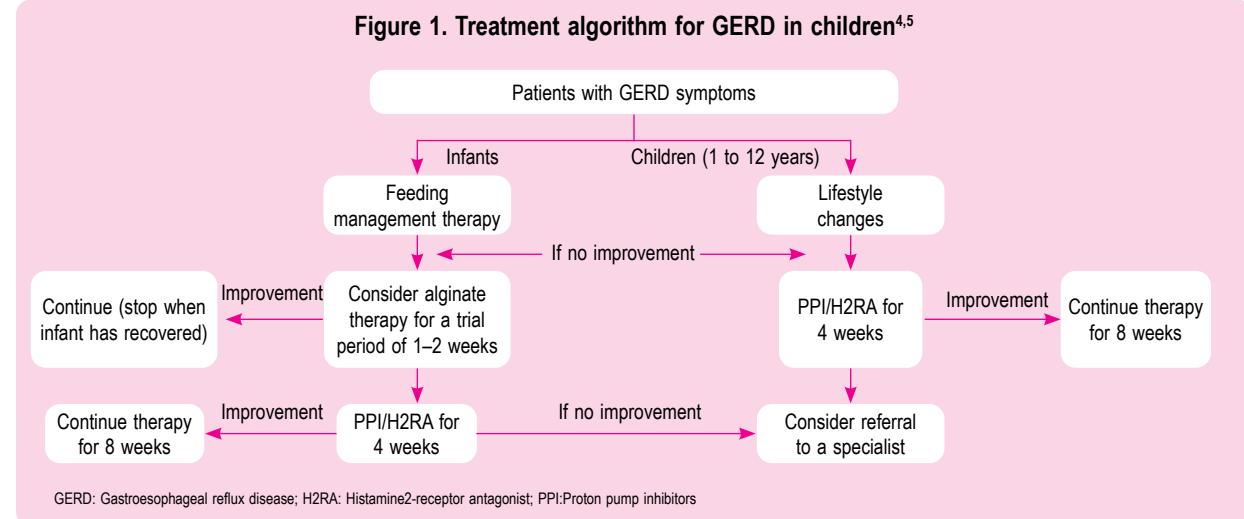
Evidence to date and current guidelines do not support empirical therapy for GERD in children.<sup>1-3</sup> Treatment for GERD is **not recommended** when there are no clinical features of gastroesophageal reflux such as recurrent regurgitation, dystonic neck posturing in infants or heartburn in children with chronic cough.<sup>1</sup>

### Does the treatment for GERD resolve the cough in children, who have gastrointestinal GERD symptoms?

Based on current evidence, it is difficult to establish a causal relationship between chronic cough and GERD and its response to GERD-treatment. Besides, data from randomized clinical trials suggested that empirical therapy is not effective for patients

Chronic cough and GERD association in children is still a vague topic. Empiric treatment of GERD in suspected cases of children with chronic cough is precluded by lack of confirmatory diagnostic tests, lack of evidence for efficacy of GERD-related treatments, and potential harm outweighing the benefit of GERD treatment.

This article describes the latest evidence, guidelines, and treatment approach of suspected GERD in children with chronic cough.



with chronic cough. These observations were supported by a Cochrane review stating that there is lack of strong data supporting the practice of empiric PPI therapy for patients with chronic cough. Moreover, prolonged empirical therapy with PPIs was observed to cause serious adverse events. Therefore, it remains unclear whether treatments for GERD resolve chronic cough in children.<sup>1-3</sup>

### What GERD diagnostic criteria should be followed in children with chronic cough?

Several “symptom association scores” between cough and GERD are available to investigate the coexistence of these two diseases, but these scales were not evaluated systematically for cough with reflux events. Moreover, there are no specific recommended criteria for diagnosis of GERD in children.<sup>1-3</sup> The current guideline recommended that pediatric GERD guidelines should be used to guide treatment and investigations in suspected cases only.<sup>1</sup>

### Can GERD-related therapies be used in children with chronic cough?

At present, there is insufficient evidence to provide specific recommendations for GERD-based therapies in children with chronic cough.<sup>1-3</sup> However, recent guidelines recommended that **treatment for GERD should be in accordance with “evidence-based GERD-specific guidelines” for children with symptoms and signs or tests consistent with gastroesophageal pathological reflux, but no underlying lung disease**. At the same time, the guideline recommended against using acid-suppressive therapy solely for chronic cough in these patients (Figure 1).<sup>1</sup>

### Clinical implications

The association between GERD and chronic cough is uncertain and complicated. At present, there are **no definitive diagnostic criteria for diagnosing GERD in children**. Further, evidence supporting empirical therapy for GERD in children with chronic cough is inconclusive. Therefore, empirical therapy with acid-suppressants solely for chronic cough is not recommended for children with clinical features of GERD and treatment for GERD should not be used when there are no clinical features of GERD.<sup>1-3</sup>

#### References

1. Chang AB, et al. Chronic Cough and Gastroesophageal Reflux in Children: CHEST Guideline and Expert Panel Report. *Chest*. 2019 Jul;156(1):131–140.
2. Fogelman CD, et al. GERD treatment for chronic nonspecific cough in children and adults. *Am Fam Physician*. 2011;84(5):502-4.
3. Cash H, et al. Chronic Cough in Children. *JAMA Otolaryngol Head Neck Surg*. 2015;141(5):417–423.
4. NICE guideline. *Gastro-oesophageal reflux disease in children and young people: diagnosis and management*. Available at <https://www.nice.org.uk/>. Last accessed on Dec 4, 2019.
5. Rybak, et al. *Gastro-Esophageal Reflux in Children*. *Int J Mol Sci*. 2017;18(8):1671.





## Refractory GERD: New insights on mechanisms

**R**ecognition of the underlying cause in patients with refractory GERD is important to optimize the therapy.<sup>1,2</sup> The underlying causes for refractory GERD are numerous and diverse, which include patient compliance, non-acid reflux, PPI bioavailability, heartburn, delayed gastric emptying, nocturnal acid breakthrough, and reflux hypersensitivity. Reflux hypersensitivity and functional heartburn are thought to account for most pain-related symptoms that persist despite PPI therapy.<sup>1,2</sup>

### Refractory GERD: Underlying mechanisms

#### Impaired esophageal mucosal barrier function

- Chronic exposure of the esophageal mucosa to reflux components impair the mucosal integrity that leads to greater exposure of peripheral receptors to reflux components.<sup>1,3</sup>

#### Immune-mediated injury

- Pro-inflammatory cytokines are released from the epithelial cells during initial event of GERD. Activation of proteinase-activated receptor 2 (PAR2) induces neuroinflammatory effects leading to visceral hypersensitivity. PAR2 activation is associated with IL-8 expression, dilatation of the intracellular spaces, papillary hyperplasia, and intraepithelial lymphocyte density. The above findings support the hypothesis that an immune mediated neuroinflammatory cascade may lead to GERD symptoms. This could explain all GERD symptoms are not resolved solely by acid suppression (Figure 1).<sup>4</sup>

Proton pump inhibitors (PPIs) are the most effective and are among the first-line agents for the management of GERD. However, 40% of patients who use standard PPI therapy have refractory symptoms.<sup>1,2</sup> Reasons for refractoriness can be patient-related or drug-related. Identifying possible reasons may drive right approach to treatment. Here, we discuss mechanisms of refractoriness and treatment approach to according latest understandings.

#### Reflux hypersensitivity

- Reflux hypersensitivity is a heightened perception of physiological reflux which results in persistent GERD symptoms despite PPI therapy. Both peripheral and central sensitization are implicated as underlying causes of reflux hypersensitivity.<sup>4</sup>

#### Psychiatric comorbidity

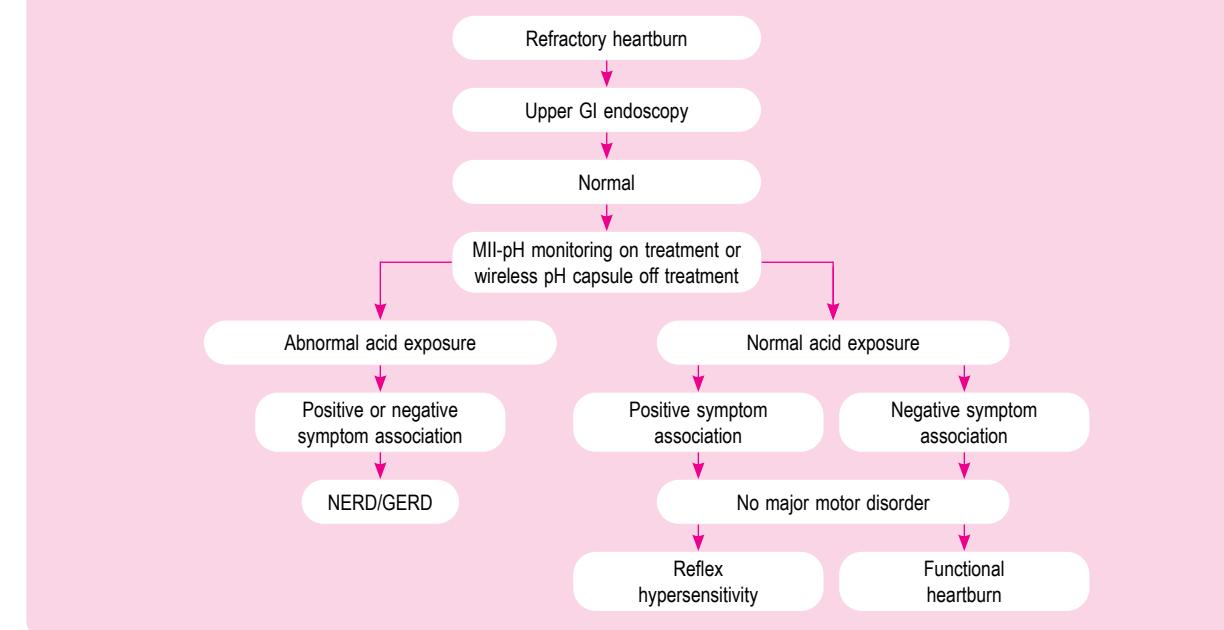
- Psychological distress, anxiety, depression, poor sleep quality, decreased general well-being, and environmental stress could amplify peripheral and central sensitization and cause PPI-refractory GERD.<sup>4</sup>

### Treatment approaches for refractory GERD

Several potential therapies that target one or more of the underlying mechanisms are available for treating refractory GERD. Treatment approaches may vary according to the underlying cause of refractory GERD (Table 1; Figure 1).<sup>1,2</sup>

Table 1. Treatment approaches in refractory GERD <sup>1,3</sup>	
Underlying cause	Potential treatment approaches
Reflux hypersensitivity and functional heartburn	Selective serotonin reuptake inhibitor; Tricyclic anti-depressant; Histamine-2 receptor antagonists (H2RAs)
Non-acid GERD	Alginate; Baclofen
Other causes	<ul style="list-style-type: none"> <li>If once-daily standard PPI therapy fails, double the dose of PPI to twice-daily dosing before breakfast and dinner</li> <li>Histamine-2 receptor antagonists (H2RAs); Sucralfate; Cisapride; PPI + prokinetic</li> </ul>

Figure 1. Diagnostic algorithm reflux hypersensitivity and functional heartburn in refractory heartburn patients<sup>\*3,5</sup>



### Clinical implication

Pathophysiology-based investigation is important in refractory GERD. Such an understanding can direct more precise management

#### References

- Mermelstein J, et al. *Clin Exp Gastroenterol*. 2018; 11:119–34.
- Hungin AP, et al. *Am J Gastroenterol*. 2019;114(3):414–21.
- Yamasaki TT, et al. *J Neurogastroenterol Motil*. 2017;23(4):495–503.
- Vandenplas Y, et al. *Expert Opin Med Diagn*. 2013;7(3):289–98.
- Yamasaki T, et al. *Gastroenterol Hepatol (N Y)*. 2017;13(12): 725–34.



### **Patients with atrial fibrillation are at high risk of GERD**

Atrial fibrillation is a risk factor for GERD and there is no bidirectional association between AF and GERD, reported a metanalysis. Several studies have reported an inconclusive result regarding the association between atrial fibrillation and GERD. A metanalysis of seven studies was conducted to evaluate the bi-directional association between AF and GERD. The study reported that AF increased the risk of GERD by 54% and the bi-directional association was not significant.

Reference: Xu L, et al. Rev Esp Enferm Dig. 2019 Nov;111(11):874-9.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/31617365>

### **Increased risk of GERD reported in patients with NAFLD**

Evidence suggests that nonalcoholic fatty liver disease (NAFLD) is associated with increased risk of extra-hepatic condition. However, its association with GERD is not certain. The metaanalysis of nine observational studies (1,85,118 subjects) evaluated the risk of developing GERD in patients with NAFLD. The study reported the NAFLD increased the risk of GERD by 28%. There is a significant association between NAFLD and risk of GERD, but causal relationship needs further evaluation.

Reference: Xue J, et al. Eur J Clin Invest. 2019;49(9): e13158.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/31338830>

### **Patients with LPR are likely to benefit from PPI therapy**

The clinical practice of managing Laryngopharyngeal reflux (LPR) with PPI therapy was supported by a recent metaanalysis. To date, there is no consistent evidence regarding the benefit of this practice as the efficacy of PPIs in LPR was controversial. Lechien et al., conducted a systematic review to address this issue. The authors reported a mild superiority of PPIs over placebo in symptomatic improvement.<sup>1</sup> However, another metaanalysis that addressed the same issue reported that the existing evidence to support the efficacy of PPIs in LPR is weak. These contradictory data warrants further evaluation and until then it is suggested to follow the current clinical guidelines.<sup>2</sup>

References: 1. Lechien JR, et al. Laryngoscope. 2019;129(5):1174-87. Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30597577>; 2.

Spantideas N, et al. J Voice. 2019. Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/31160182>

### **Vonoprazan can be a potential alternative to PPIs in GERD**

The maintenance effect of vonoprazan for GERD is likely to be higher than that of some PPIs, reported a metaanalysis. Vonoprazan, a novel potassium-competitive acid blocker (P-CAB), is recommended as the first-line agent for GERD. Several studies have reported its superior efficacy over other first-line agents for GERD like PPIs. The same was evaluated in systematic review and network meta-analysis conducted by Miwa et al. The study reported that maintenance effect of vonoprazan in GERD was higher when compared to PPIs (vonoprazan:esomeprazole [OR: 13.92]) and (vonoprazan:omeprazole [OR: 9.32]). The authors concluded that these results would be useful in selecting a more effective treatment for patients with GERD in future. Nevertheless, head-to-head comparison trials of vonoprazan with other PPIs are warranted.

Reference: Miwa, et al. Systematic review with network meta-analysis: indirect comparison of the efficacy of vonoprazan and proton-pump inhibitors for maintenance treatment of gastroesophageal reflux disease. J Gastroenterol. 2019; 54(8): 718–29.

Weblink: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6647489/>

### **Excessive tea consumption is a risk factor for GERD**

Lifestyle modifications are recommended for patients with GERD. It is a known fact that social habits and dietary patterns (like alcohol and coffee drinking) are associated with the risk of GERD. Results from a meta-analysis by Pan et al reported that alcohol consumption increased the risk of GERD by 48%. Findings from another metaanalysis by Cao et al reported that in east-asian population tea consumption increased the risk of GERD by 27%. These findings are important especially for cultures where tea consumption is excessive.<sup>1,2</sup>

References: 1. Pan J, et al. Alkohol Alcoholism. 2019;54(1):62-69. Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30184159/>; 2. Hongying Cao, et al. Medicine. 2019;98(4): e14173. Weblink: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6358326/>



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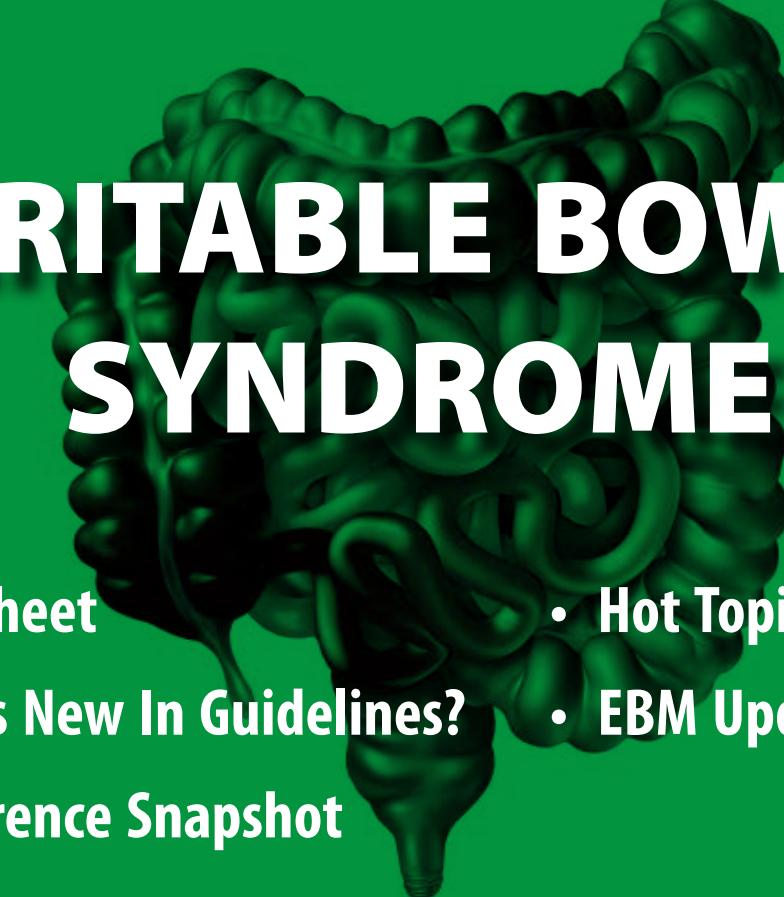
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# IRRITABLE BOWEL SYNDROME



- Fact Sheet
- Hot Topics
- What's New In Guidelines?
- EBM Updates
- Conference Snapshot

## Fact Sheet

- Irritable bowel syndrome (IBS) is the most prevalent functional gastrointestinal disorder with a worldwide prevalence of >10%<sup>1</sup>
- IBS prevalence is less likely to be influenced by socio-economic status<sup>1</sup>
- In India, IBS is equally prevalent in both urban and rural population
- The prevalence of IBS varies from 4.2% to 7.5% in India<sup>3</sup>
- About 3 out of 10 patients with gastroenteritis develop post-infection IBS (PI-IBS)<sup>3</sup>
- Acute gastroenteritis was associated with a 7-fold increase in risk of development of PI-IBS<sup>3</sup>
- Duration of acute gastroenteritis was associated with 8-fold increase in risk of development of PI-IBS<sup>3</sup>
- Presence of abdominal cramps doubles the risk of developing PI-IBS<sup>3</sup>

## References

- Canavan C et al. The Epidemiology of Irritable Bowel Syndrome. *Clin Epidemiol.* 2014;6: 71-80 2014
- Rahman MM, et al. Epidemiological and clinical perspectives on irritable bowel syndrome in India, Bangladesh and Malaysia: A review. *World J Gastroenterol.* 2017; 23(37): 6788-801.
- Parida PK, et al. A prospective study on incidence, risk factors, and validation of a risk score for post-infection irritable bowel syndrome in coastal eastern India. *Indian J Gastroenterol.* 2019;38(2):134-42.



## Second Asian Consensus on Irritable Bowel Syndrome, 2019

The Asian Neurogastroenterology and Motility Association (ANMA) has published new consensus on IBS as an update to first Asian consensus published in 2010. A team of 21 key opinion leaders from Asian countries, who were convened by ANMA to review literature published on IBS since 2010, worked together to draft new consensus.

### Key differences

- The section “Symptoms and Diagnosis” was changed to “Symptoms and Epidemiology”
- Definition of IBS symptoms was revised as “Bowel-related symptoms in IBS consist of abdominal pain, bloating, or discomfort that is either improved or aggravated by passing stool or flatus”
- IBS definition: A multi-dimensional disorder with a variable combination of gut dysbiosis, GI low grade inflammation, mucosal immune activation, increased gut permeability, food intolerance, GI dysmotility, visceral hypersensitivity, altered gut-brain interaction, genetic, and psychosocial factors
- Gut microbial dysbiosis is a risk factor for IBS, especially diarrhea-predominant IBS (IBS-D)
- Evidence grade for GI infection as risk factor for IBS was changed from “Moderate” to “High”
- Diagnosis and investigations were included as a separate section
- Thyroid function test and stool examination for parasites and *Clostridium difficile* infection were included as part of investigations in the referral-center setting
- A low-FODMAPs diet is now considered helpful in patients with IBS
- Treatment with 5-HT<sup>3</sup> antagonists and secretagogues received “High” evidence grade
- Treatment with antidiarrheal agents and antidepressants received “Moderate” evidence grade

**References:** Gwee KA, et al. Second Asian Consensus on Irritable Bowel Syndrome. *J Neurogastroenterol Motil.* 2019;25(3):343–62; Gwee KA, et al. Asian consensus on irritable bowel syndrome. *J Gastroenterol Hepatol.* 2010 Jul;25(7):1189–205. doi: 10.1111/j.1440-1746.2010.06353.x.

## Laboratory evaluation of diarrhea in adults with IBS-D (AGA guidelines)

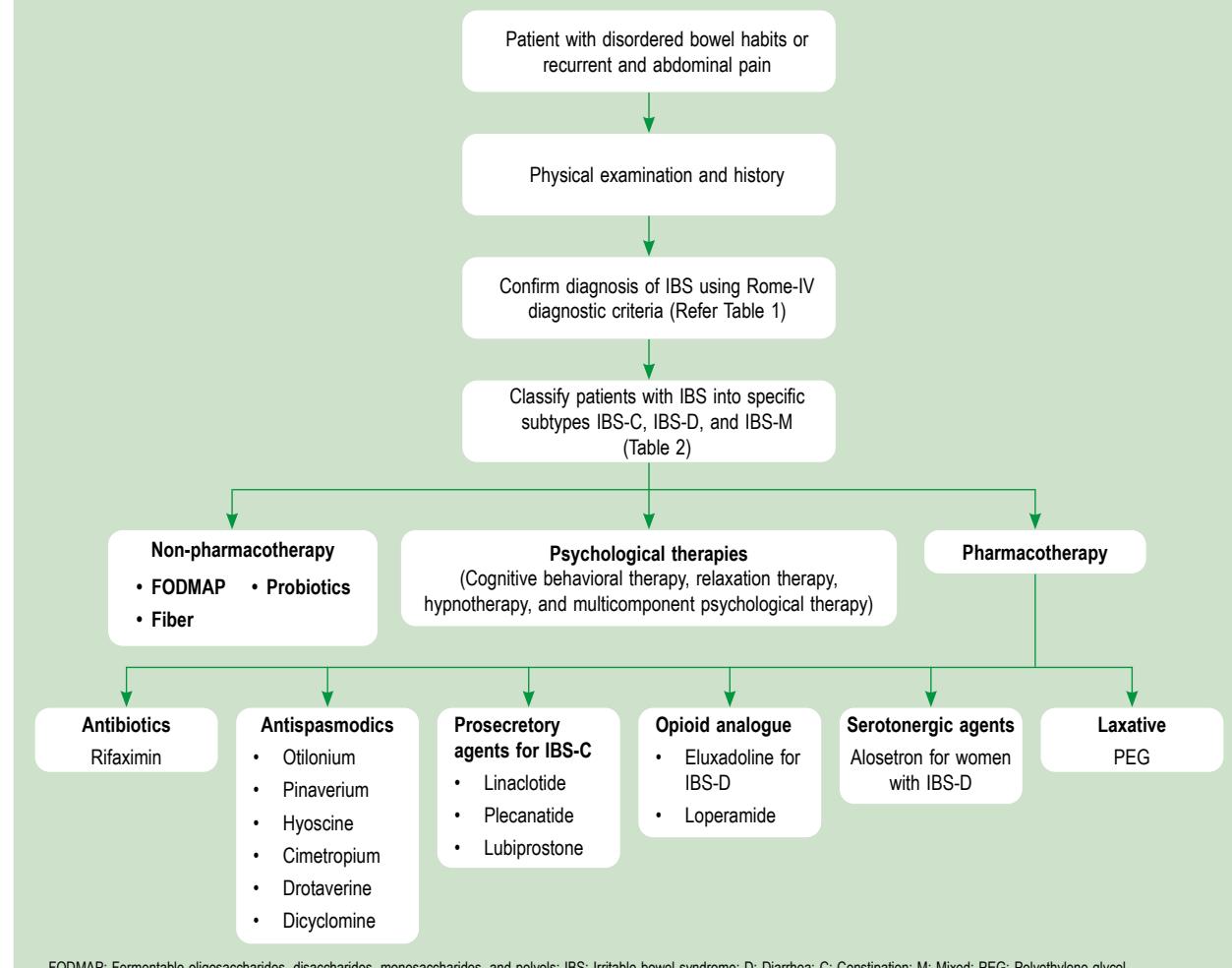
The American Gastroenterological Association (AGA) has released new guidelines on laboratory tests to exclude other diagnoses in the setting of suspected functional diarrhoea or diarrhea-predominant irritable bowel syndrome (IBS-D). The guidelines are applicable for the evaluation of the immunocompetent patients with “watery” diarrhea of at least 4 weeks duration.

### Key recommendations

- AGA suggested estimation of fecal calprotectin or fecal lactoferrin to screen for inflammatory bowel disease (IBD) in patients presenting with chronic diarrhea
- AGA did not recommend estimation of erythrocyte sedimentation rate or C-reactive protein to screen for IBD in patients presenting with chronic diarrhea
- While AGA recommended testing for *Giardia* in most patients with chronic diarrhea, the test is not recommended in patients with no travel history to or recent immigration from high-risk areas
- Testing for celiac disease with IgA tissue transglutaminase and a second test to detect celiac disease in the setting of IgA deficiency were recommended in patients presenting with chronic diarrhea
- Testing for bile acid diarrhoea is considered apt in patients with chronic diarrhoea to confirm if excess bile acids are the cause for diarrhea
- It is important to note that AGA made no recommendation for the use of currently available serologic tests for diagnosis of IBS

**Reference:** Walter Smalley, et al. AGA Clinical Practice Guidelines on the Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D). *Gastroenterology* 2019;157:851–854.

### Diagnosis and management of IBS<sup>1,2</sup>



FODMAP: Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS: Irritable bowel syndrome; D: Diarrhea; C: Constipation; M: Mixed; PEG: Polyethylene glycol

Table 1. Rome IV Diagnostic Criteria for Irritable Bowel Syndrome

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria:

- Related to defecation
- Associated with a change in the frequency of stool
- Associated with a change in the form (appearance) of stool

(These criteria should be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.) \* Modified from Rome IV

Table 2. The Bristol stool form scale

Type 1: Separate hard lumps, like nuts (hard to pass)	IBS-C
Type 2: Sausage-shaped, but lumpy	
Type 3: Like a sausage but with cracks on its surface	IBS-D
Type 4: Like a sausage or snake, smooth and soft	
Type 5: Soft blobs with clear cut edges (passed easily)	IBS-D
Type 6: Fluffy pieces with ragged edges, a mushy stool	
Type 7: Watery, no solid pieces, entirely liquid	

### References

- Lacy BE, Patel NK. Rome Criteria and a Diagnostic Approach to Irritable Bowel Syndrome. *J Clin Med.* 2017;6(11):99.
- Ford AC, et al. American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome. *Am J Gastroenterol.* 2018;113(Suppl 2):1–18.



## ESPGHAN Annual Meeting 2019

### When and where

European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) organised its 52<sup>nd</sup> annual meeting in Glasgow, Scotland from 05–08 June 2019

### Scientific sessions

Data from clinical trials in the fields of hepatology, gastroenterology, and nutrition were discussed in scientific sessions. Some of the clinical trials that focused on IBS are listed below.

- Human milk oligosaccharides improve all the central symptoms of IBS
- Eluxadoline for bowel and abdominal symptoms improvement in patients with IBS-D who report inadequate symptom control with loperamide
- Nutritional deficiencies in IBS
- Is there a link between Irritable Bowel Syndrome and Non-alcoholic liver disease?
- The association of gender and quality of life in patients with IBS
- Plecanatide for patients with chronic idiopathic constipation and IBS-Constipation
- Impact of colonoscopy timing on rifaximin in patients with IBS-D

Reference: 2019 ESPGHAN Programme book. Available at [https://www.esphancongress.org/fileadmin/user\\_upload/downloads/Scientific\\_Programme/ESPGHAN2019\\_Programme\\_Book.pdf](https://www.esphancongress.org/fileadmin/user_upload/downloads/Scientific_Programme/ESPGHAN2019_Programme_Book.pdf). Last accessed on 06-Dec-2019

## Euro Gastroenterology 2019

### When and where

The 4<sup>th</sup> International Conference on Gastroenterology & Hepatology was organised on 25<sup>th</sup> & 26<sup>th</sup> of March 2019, in Amsterdam, Netherlands

**Theme** Exploring Novel Innovations in the field of Gastroenterology and Hepatology

### Scientific sessions

The conference covered several Scientific Sessions and Plenary Lectures, out of which the following few were highlighted as Keynote Presentations and Special Sessions:

- Indicators of metabolic activity of micro biocenosis in patients with stomach cancer
- Novel natural-product-based small molecule as potent anticancer drug target
- Novel natural-product-based small molecule as potent anticancer drug
- Interventional MRI and its role in image-guided therapy
- Primary hepatic neuroendocrine tumors, a rare entity – Multimodal approach for diagnosis and management
- Surgery or upper GI endoscopy in symptomatic gallstones
- Comparison of quantitative hepatitis B virus DNA Real Time PCR (RT-PCR) with reverse transcription PCR (rt-PCR)
- The histopathological study of “horse bone calcium” preparation effect on the acetic acid induced gastric ulcer model
- The hepatoprotective effect’s result of new drug lonal in patient with non-alcoholic fatty liver disease concomitant with chronic hepatitis

Reference: Euro Gastroenterology 2019. Report. Available <http://gastroenterology.alliedacademies.com/2019>. Last accessed on 06-Dec-2019





## Low-FODMAP diet in IBS: Fact or fad?

**L**ow Fermentable Oligo-, Di-, Monosaccharides, and Polyols (Low-FODMAP) diet has recently emerged as an effective intervention for reducing gastrointestinal symptoms in IBS. Concerns were raised regarding efficacy and safety of Low-FODMAP in IBS. There has been a considerable amount of research across the globe to understand the efficacy of Low-FODMAP, comparing its efficacy with other therapeutic approaches, defining predictors and examining risks, and determining the mechanism of action of the diet.<sup>1,2</sup> The mechanisms by which FODMAP-rich diet may induce IBS symptoms overlap disease pathophysiology.<sup>1-4</sup>

- Poorly absorbed FODMAPs exert an osmotic effect, inducing diarrhea<sup>1</sup>
- Bacterial fermentation of the carbohydrates, induce bloating, distension, abdominal pain, and excessive flatulence<sup>1</sup>
- The release of short-chain fatty acids (SCFAs) from fermentation of FODMAPs is also likely to influence motility.<sup>1</sup>

Above mechanisms formed the rationale for considering Low-FODMAP in patients with IBS. Several studies that evaluated the role of FODMAP diet in improving the symptoms of IBS reported a positive outcome. These studies have shown that 50% to 86% of patients have a clinically meaningful response to the low-FODMAP.<sup>4</sup> Food sources of FODMAP are listed in below (Table 1)<sup>3</sup>

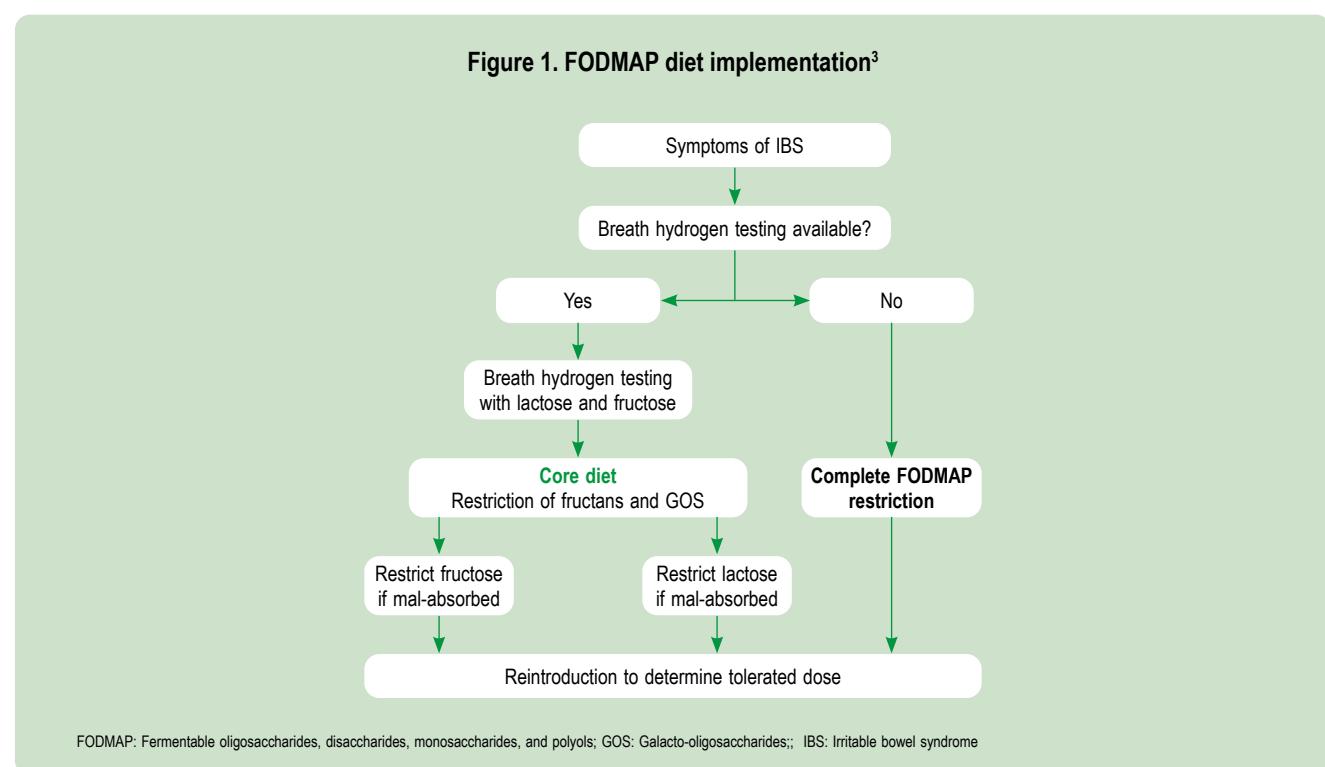
Table 1: List of food sources of FODMAP <sup>3</sup>				
FODMAP content	Oligosaccharides	Disaccharides	Monosaccharides	Polyols
High FODMAP content	<ul style="list-style-type: none"> <li>Cabbage</li> <li>Onion</li> <li>Peas</li> <li>Wheat</li> <li>Watermelon</li> </ul>	<ul style="list-style-type: none"> <li>Milk</li> <li>Ice-cream</li> </ul>	<ul style="list-style-type: none"> <li>Apple</li> <li>Pear</li> <li>Mango</li> <li>Honey</li> </ul>	<ul style="list-style-type: none"> <li>Plum</li> <li>Mushroom</li> <li>Cauliflower</li> </ul>
Low FODMAP content	<ul style="list-style-type: none"> <li>Carrot</li> <li>Tomato</li> <li>Gluten-free bread</li> </ul>	<ul style="list-style-type: none"> <li>Lactose free yogurt</li> </ul>	<ul style="list-style-type: none"> <li>Banana</li> <li>Grape</li> <li>Orange</li> </ul>	<ul style="list-style-type: none"> <li>Lemon</li> <li>Orange</li> <li>Sugar</li> <li>Glucose</li> </ul>

### Low-FODMAP vs. Other diets

A UK based study reported that Low-FODMAP approach was found superior to NICE diet. In contrast, a recent randomized study from Sweden reported similar responses between the low-FODMAP diet and the traditional IBS diet. In another study, Low-FODMAP approach produced superior improvements in abdominal pain and bloating compared to traditional diet in patients with IBS-D. Data from observational studies reported similar response rates with low-FODMAP and Gluten-Free Diet.<sup>4</sup>

### Low-FODMAP diet: Implementation in clinical practice

Low-FODMAP diet, although effective in IBS, not devoid of controversies Careful implementation is key to success of low-FODMAP diet treatment (Figure 1). If implemented correctly, FODMAP re-introduction is possible in 75% patients with adequate symptom control. Disordered eating behavior, altered gut microbiota, and inappropriate use of low-FODMAP diet should be monitored while on therapy.<sup>3-6</sup>



### Clinical implications

Based on moderate-grade evidence low-FODMAP diet can be considered for the management of abdominal symptoms in adult patients with IBS especially as a second line therapy. Low-FODMAP diet should be implemented with proper monitoring and patient education, preferably by involving a trained dietitian.

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## Emerging therapies for IBS

### Treatment of IBS: An overview of established approaches

Irritable bowel syndrome (IBS) is characterized by abdominal pain, bloating, nausea along with bowel function alteration (constipation, diarrhea or both).<sup>1</sup> Even though patients with mild symptoms get adequate relief from the existing therapies, it is not the case with every patient. As the symptoms become severe, it leads to functional impairment affecting the patient's quality of life. There is a need for improved treatment modalities for IBS.<sup>2</sup>

IBS presents with non-specific and diverse symptoms which demand a multifactorial treatment approach.<sup>1</sup> Treatment options available in IBS are tabulated in Table 1.<sup>1,2</sup>

Table 1: Treatment strategies followed in IBS <sup>1,2</sup>	
Non-pharmacological therapy	Pharmacological therapy
Patient education	Antispasmodics and antidiarrheals
Dietary changes	Probiotics
Herbal therapy	Antibiotic (Rifaximin)
Psychological therapy	Secretagogues (lubiprostone, linaclotide, and plecanatide)
Bio-feedback therapy	Antidepressants (SSRIs and TCAs)

### List of emerging therapies for IBS

Newer therapies for management of IBS include agents targeting GI motility and opioid receptors, and targeting gut microbiota, and herbal medicines.<sup>1,2</sup>

#### Herbal therapies

- **Gwakhyangjeonggisan:** A Korean herbal medicine is found to be effective in relieving abdominal pain. Studies are being carried out to evaluate its efficacy with and without probiotics<sup>1</sup>
- **Peppermint oil** showed a significant improvement in pain and global symptoms of IBS<sup>3</sup>

#### Opioid agonists and antagonists

- **Asimadoline:** A k-opioid agonist which improves abdominal pain owing to its peripheral analgesic action.<sup>1</sup>

- **Eluxadoline:** A mixed  $\mu$ -opioid receptor agonist and  $\delta$ -opioid receptor antagonist which improves symptoms in IBS-D by imparting improved bowel movement frequency and urgency, which was found to be effective in loperamide-non responders as well<sup>4</sup>

#### Tenapanor

- **Tenapanor** is an inhibitor of the enterocyte sodium/hydrogen exchanger isoform. It acts by increasing intestinal fluid volume and transit; thereby improving the symptoms of constipation<sup>3,4</sup>

#### Ibudant

- It is a selective neurokinin-2 receptor antagonist. Neurokinins are involved as mediators of gastrointestinal motility and nociception. It is indicated for IBS-D<sup>4</sup>

#### Serotonin receptor antagonists

- **5-HT<sub>3</sub> receptor antagonist:** A newer agent **Ramosetron** is found to have similar properties to alosetron. Ramosetron improves stool consistency, over symptoms and quality of life, as per the findings of a randomized study
- **5-HT<sub>4</sub> receptor agonists:** **Prucalopride**, differs from older non-selective 5-HT<sub>4</sub> receptor agonists. It stimulates gut motility and improves the symptoms in laxative-unresponsive chronic constipation<sup>1,4</sup>

#### Guanylate cyclase C agonists

- **Plecanatide**, a guanylate cyclase C agonist, is currently under evaluation. Already approved drug in this category is linaclotide which acts as a laxative<sup>1,4</sup>

#### Mast cell stabilizers

- Mast cells play an important role in the pathophysiology of IBS. **Disodium cromoglycate**, a mast cell stabilizer is found to improve the symptoms of abdominal pain induced by colorectal distension<sup>1</sup>

#### Luminal adsorbents

- **AST-120:** A luminal adsorbent which binds to the substances (histamine, serotonin, bacterial products, and bile acids) that are raised in the gut lumen of patient with IBS<sup>1</sup>

#### Bile acid binders

- Colonic exposure to bile acids stimulates secretion and motility thereby causing diarrhea. Bile acid sequestrants significantly improved the symptoms and will be a targeted treatment<sup>1,4</sup>

#### Fecal transplantation

- Fecal transplantation resulted in short-term and long-term benefits in patients with IBS, as per studies. Fecal transplantation is an effective treatment option in patients with refractory *Clostridium difficile* colitis<sup>1</sup>

#### Sacral nerve stimulation

- Sacral nerve stimulation deals with the abnormal nerve signaling from the gut, which plays a role in the pathogenesis of IBS<sup>1</sup>

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3. Alammar N, et al. The impact of peppermint oil on the irritable bowel syndrome: A meta-analysis of the pooled clinical data. *BMC Complement Altern Med*. 2019;19(1):1-10.
4. Bharucha AE, et al. Existing and emerging therapies for managing constipation and diarrhea. *Current Opinion in Pharmacology*. 2017; 37:158–66.



### Mesalazine, not suggestive in IBS owing to its poor efficacy and cost burden

Mesalazine is not superior to placebo in relieving clinical symptoms and improving general well-being reported a meta-analysis. Available data for the efficacy of mesalazine in IBS is inconsistent. Zang, et al conducted a meta-analysis to assess the efficacy of mesalazine therapy in IBS. The study reported that, mesalazine therapy showed a statistically non-significant improvement in abdominal pain, bloating ( $p=0.70$ ), defecation frequency/day, and general well-being. The authors concluded that mesalazine might be a cost burden to patients without providing good effectiveness for the treatment of IBS. The authors suggested that more studies with longer treatment duration and adequate dosage are needed to draw robust conclusions.

Reference: Zhang FM, et al. *Medicine (Baltimore)*. 2019;98(28).

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/31305414>

### People with IBS may benefit more from multi-strain probiotics

Multi-strain probiotic treatment was found more beneficial in alleviating IBS symptoms compared to a mono-strain probiotic treatment as reported by systematic review. Probiotic supplements are thought to improve IBS symptoms through manipulation of the gut microbiota. Identification of specific bacterial strains or probiotic supplements with beneficial effects on IBS symptoms may lead to more effective therapeutic strategies. A systematic review conducted to address this issue reported a significant improvement in IBS symptoms with probiotic administration and better results were achieved with longer duration of multi-strain probiotics therapy compared to single-strain probiotic therapy. While emphasizing on the need for further evaluation, the authors concluded that multi-strain probiotic supplements over a period of time have the potential to improve IBS symptoms.

References: Dale H, et al. *Nutrients*. 2019;11(9).

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/31480656>

### Time to reconsider tegaserod for women with IBS-C

Tegaserod, an FDA approved drug for IBS with constipation (IBS-C) was withdrawn from market in 2007 owing to its cerebrovascular and cardiovascular ischemic events. However, tegaserod was recently re-introduced only for use in women  $<65$  years with no history of cardiovascular disease and with only one risk factor for future cardiovascular disease. In light of this, a network meta-analysis was done by Black, et al. to evaluate the relative efficacy of tegaserod with other FDA-approved drugs for IBS-C. The study reported that even though tegaserod was efficacious and superior to placebo it was not superior to other approved drugs. Tegaserod 6 mg twice a day was ranked third in terms of efficacy.

Reference: Black CJ, et al. *Clin Gastroenterol Hepatol*. 2019

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/31302307>

### Peppermint oil may improve pain and global symptoms in IBS

Peppermint oil was found to be a safe and effective therapy for pain and global symptoms in adults with IBS. Peppermint oil may benefit patients with IBS owing to its intrinsic properties. Alammar, et al conducted a systematic review to evaluate the safety and efficacy of peppermint oil in patients with IBS. The authors reported that patients treated with peppermint oil had twice higher improvement in global symptoms compared to treatment with placebo. Further improvement in pain was 78% higher in patients treated with peppermint compared to placebo. The number needed to treat with peppermint oil to prevent one patient from having persistent symptoms was three for global symptoms and four for abdominal pain. The results suggest that enteric-coated peppermint oil can be used for symptomatic improvement in IBS.

References: Alammar N, et al. *BMC Complement Altern Med*. 2019;19(1):21.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30654773>



# **In Management of Acute Painful Conditions**

# *Ultranise*

## *Tramadol 37.5 mg + Paracetamol 325 mg Tablet*

## **EMPOWERED WITH QUALITY BY DESIGN (QBD) MANUFACTURING APPROACH\***



## • Fact Sheet

## • What's New In Guidelines?

## • Conference Snapshot

- Hot Topics
- EBM Update

לענין זיהוי

5 million Indian population has rheumatoid arthritis

- Out of 1.2 billion population, 5 million have rheumatoid arthritis (RA)<sup>1</sup>
  - One in 12 women and one in 20 men develop RA during their lifetime<sup>2</sup>

**Women are likely to be more affected than men**

- RA is more prevalent among the age-group of 20 years–40 years<sup>3</sup>
  - 41.6% patients with RA manifested extra-articular symptoms (Figure 2)<sup>6</sup>
  - Anemia is the most frequently occurring manifestation<sup>4</sup>

Osteoarthritis: 10th leading cause of non-fatal disease burden

- The second most common rheumatological disease in India is osteoarthritis (OA)<sup>5</sup>
  - OA has a prevalence of 22%-39% in India<sup>5</sup>
  - 45% of women over the age of 65 years have symptoms of OA<sup>5</sup>
  - Elderly population has a higher prevalence of OA(<50 years: 19.2%; >70 years: 54.1%)<sup>5</sup>
  - There is a significantly increased prevalence of OA in rural Indian population compared to urban population (56.6% vs.32.6%)<sup>6</sup>

<sup>a</sup>ICH: International Council for Harmonisation    \*Data on file

Abridged prescribing information

*this medicinal product. Preg  
Further information availabl*

Date: 23 September 23, 2019  
For the use of a Registered Medical Practitioner. Hospital or Laboratory only.

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## APLAR recommendations for treatment of rheumatoid arthritis

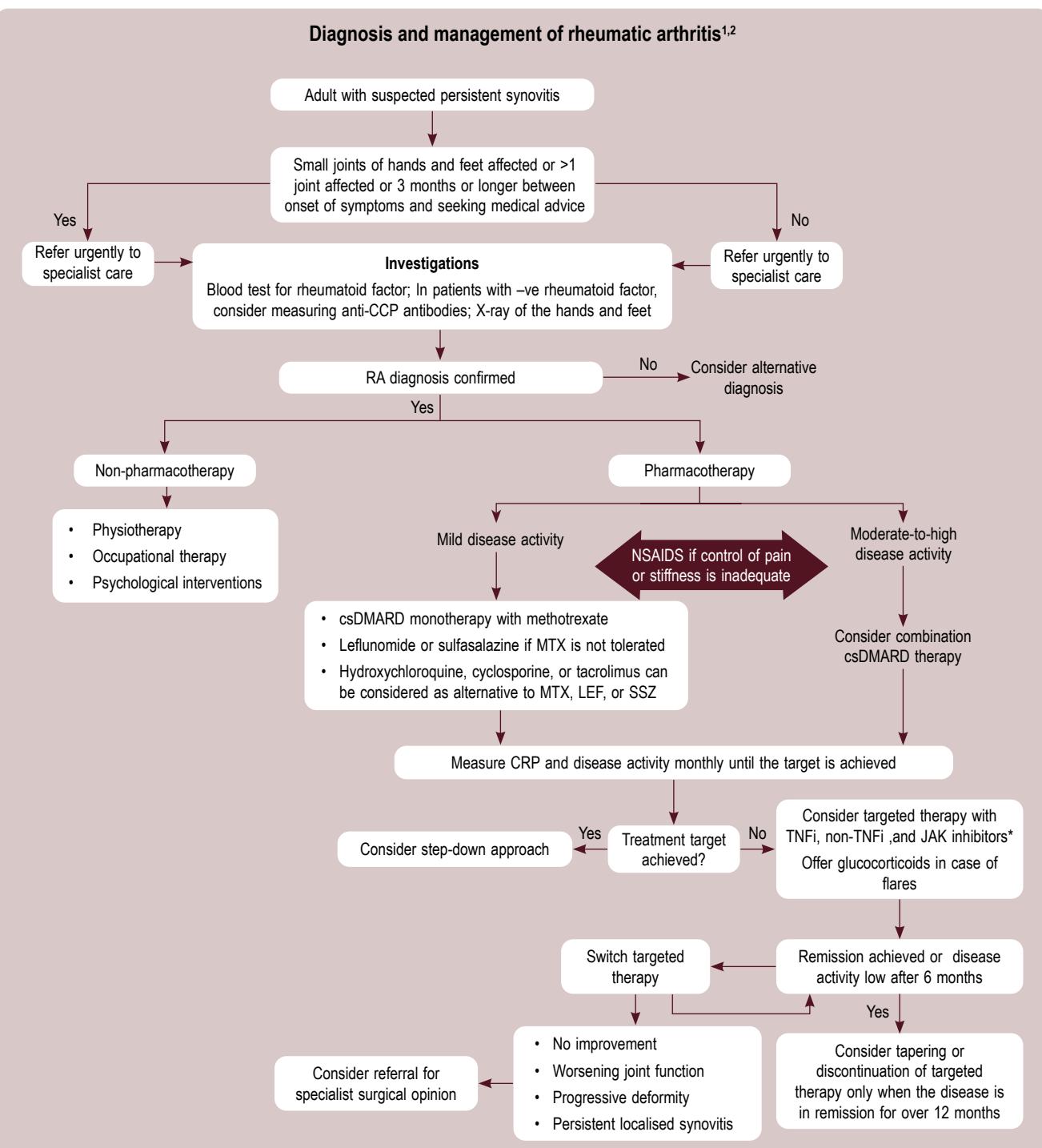
In 2018, the Asia-Pacific League of Associations for Rheumatology (APLAR) convened a Steering Committee to develop recommendations on pharmacological treatment of rheumatoid arthritis (RA) that would serve as a reference for best RA management practices in the region. The guideline was an update on the 2015 version.

### Key recommendations

- Methotrexate (MTX) is retained as the first-line therapy in patients diagnosed with RA
- In patients with contradictions to methotrexate, leflunomide and sulfasalazine are still considered as the first-line therapy
- Recommendation regarding targeted therapies, including TNFi, non-TNFi and JAK inhibitors, was revised. Targeted therapies are now recommended for patients who have moderate or high disease activity despite adequate treatment with csDMARD, or in patients with intolerance to csDMARD
- The current guideline did not recommend one targeted therapy over the other as all targeted therapies are equally effective in the treatment of RA when combined with MTX or csDMARDs
- APLAR recommended close monitoring of all patients receiving targeted therapy for therapy-related toxicities
- In patients with a history of TB or latent TB, APLAR recommended targeted therapies other than monoclonal Ab TNFi
- Targeted therapies other than rituximab are preferred in patients at increased risk of HBV reactivation
- For pregnant women with RA in whom disease cannot otherwise be controlled, the guideline recommended that TNFi can be continued throughout pregnancy

### Reference

Chak Sing Lau, et al. 2018 update of the APLAR recommendations for treatment of rheumatoid arthritis. *Int J Rheum Dis.* 2019;1–19.



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## ACR Annual Meeting, 2019

### When and where

The American College of Rheumatology (ACR)/Association of Rheumatology Health Professionals (ARHP) Annual Meeting was organized by ACR from Nov 08-13, 2019 at Atlanta, Georgia, USA

### Scientific sessions

New research and recommendations presented at ACR 2019 are:

Highlights of key presentations from the ACR conference 2019	
Presentation	Key highlight
Intestinal Microbiota & Progression of RA	The intestinal communities of patients at high-risk for RA had a lower diversity than those of healthy controls
High-intensity strength training for knee osteoarthritis	Long-term high-intensity strength training increases knee extensor and flexor strength
Optimal methotrexate dosing for RA	Escalating methotrexate dose to 20-25 mg per week either given subcutaneously or split-dose oral can be considered before adding a biologic or a JAK inhibitor in patients with poor response to usual methotrexate doses
Methotrexate in patients with hand erosive osteoarthritis refractory to usual treatments	Methotrexate reduced progression of joint damage and may facilitate bone remodelling
Prednisolone in patients with painful hand osteoarthritis	Six-week treatment with low-dose prednisolone improved pain and signs of inflammation

### New releases

Previewed draft of updated gout treatment guideline. Drafts of new clinical guidelines for giant cell arteritis (GCA), Takayasu's arteritis (TAK), and polyarteritis nodosa (PAN) were presented

### Awards and honours

- Presidential Gold Medal:** Dr. John Patterson Atkinson for his outstanding achievements in rheumatology
- Distinguished Basic Investigator Award:** Dr. Bruce N. Cronstein for making outstanding contributions to the field of rheumatology
- Paulding Phelps Award:** Dr. Alfred Denio for his outstanding service to patients, community and the practice of medicine

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2. 2019 ACR/ARP Annual Meeting highlights. Available at <https://www.acrdailynewslive.org/in-case-you-missed-it-2019-acr-arp-annual-meeting-highlights/>. Last accessed on 06-Dec-2019
3. American College of Rheumatology Announces 2019 Award Recipients. Available at <https://www.newsweise.com/articles/american-college-of-rheumatology-announces-2019-award-recipients>. Last accessed on 06-Dec-2019.

## The EULAR Congress, 2019

### When and where

The European League Against Rheumatism annual meeting (EULAR) was held from June 12 -15 in Madrid, Spain

### Scientific sessions

New research and recommendations were presented at EULAR 2019. The features below highlight key presentations from the conference.

- Weight loss: A valuable adjunctive strategy for improving outcomes in patients with psoriatic arthritis
- Over-reliance on disease activity scores undermines RA management
- Flu vaccination effective in patients taking TNF inhibitors
- Consensus on routine lung disease screening in systemic sclerosis

### New releases

- Revised guidelines on management of RA
- Recommendations for antiphospholipid syndrome in adults
- Guidelines on managing rheumatic complications of cancer immunotherapies

### Awards and honours

Winners of EULAR Abstract Award 2019

- Dr. Ross Wilkie for his presentation on “Targets for reducing premature mortality in older adults with osteoarthritis: Results from a novel path analysis within a cox proportional hazards model”
- Dr. Else Marit H for her poster on “Does occupational therapy delay or reduce the proportion of patients who receives thumb carpometacarpal surgery? A randomized controlled trial”
- Dr. Lindsay Bearne for her presentation on “The prevalence and impact of fatigue in people with primary antiphospholipid syndrome: A mixed methods study”

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2. Winners of EULAR Abstract Award 2019. Available at [https://www.eular.org/abstract\\_award\\_winners\\_2019.cfm](https://www.eular.org/abstract_award_winners_2019.cfm). Last accessed on 06-Dec-2019





## Revisiting glucocorticoid therapy in RA

Corticosteroids mimic the naturally occurring cortisol and reduce the levels of inflammation that cause joint pain, stiffness, and bone and cartilage deterioration in patients with RA. They also act as immune system inhibitors (or immune modulators) by suppressing antibody formation and subsequent attacks which cause inflammation in RA patients. The emerging evidence also supports the use of glucocorticoids in patients with RA.<sup>3</sup>

### When to use glucocorticoids in RA?

GCs are commonly given along with disease-modifying anti-rheumatic drugs (DMARDs) for patients with RA. DMARDs can take weeks to begin working in a patient with RA, it is important to keep the disease under control during that time. Evidence suggests that GCs are an effective method of reducing inflammation and helping alleviate pain and stiffness in RA (bridge therapy). Guidelines recommended GCs during periods of flare-ups, whereby the disease becomes highly active and severe symptoms appear. Long-term use of GCs is associated with many adverse effects e.g. weight gain, diabetes, osteoporosis, eye and heart disease, however they are used in some cases wherein patients do not respond to DMARDs.<sup>1,4</sup>

Glucocorticoids can be used in three instances in RA<sup>1,4</sup>

1. During initial treatment with conventional DMARDs
2. During flare-ups
3. When no or inadequate response to DMARDs

Despite major therapeutic developments in the treatment of rheumatoid arthritis (RA) in the past 20 years, glucocorticoids (GCs) are still widely used for the symptomatic treatment of RA. In view of potential risks associated with long-term glucocorticoid treatment, we have attempted to review the relevance of GCs in today's context and how to optimize their use in RA.<sup>1,2</sup>

### What should be the initial dose?

The use of GCs at the lowest possible dose for the shortest possible time is the main principle for optimizing GC therapy. Moreover, it is evident that a low dose of GC in early RA doubled the chances of achieving a remission. However, there is an ongoing controversy regarding the initial dose of GC. Based on available evidence, it was found that an initial medium dose (30 mg/day) or low dose (7.5–10 mg/day) glucocorticoid treatment increases the therapeutic response rate in patients with RA.<sup>1</sup>

### How to monitor long-term use of glucocorticoids?

The long-term use of GC is associated with serious adverse events like the risk of infection, cardiovascular morbidity, or osteoporosis. Therefore, it is important to monitor patients on long-term GCs. Parameters including body weight, blood pressure, serum lipids, blood and/or urine glucose, infections, osteoporotic fractures, or eye-related adverse effects should be monitored during the long-term GC treatment period in patients with RA.<sup>1,2</sup> Elderly patients are at a higher risk of adverse events associated with GC such as osteoporosis, cataract or diabetes. Therefore, it is important to monitor older patients more frequently than younger adults.<sup>1,2</sup>

### How to manage “withdrawal symptoms” associated with glucocorticoids?

An important risk associated with GCs is the withdrawal symptoms in patients with RA. According to the guidelines, this risk needs to be considered once the GCs dose surpasses 7.5 mg/d prescribed over three weeks. It is a general understanding that long-term GCs treatment should not be suddenly discontinued, but there is no consensus regarding the best withdrawal regimen to adopt.<sup>1</sup>

### Clinical implications

The use of GCs at the lowest possible dose for the shortest possible duration in patients is the foremost rule that should be followed in patients with RA. Moreover, side effects and withdrawal symptoms should be monitored with caution especially in patients on long-term GC therapy.<sup>1,5</sup>

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## Biosimilars in RA: Where are we?

### To switch or not to switch?

**I**t is important to understand the challenges of using biosimilars when considering switching patients from an originator biological medicine to a biosimilar (Box 1). The concerns currently raised against biosimilar products are immunogenicity, indication extrapolation, interchangeability, and long-term effects.<sup>1-3</sup>

**Box 1.** Concerns raised against biosimilars<sup>1-3</sup>

- Efficacy and safety profile
- Immunogenicity
- Indication extrapolation
- Interchangeability
- Long-term effects

Biosimilars remain a hot topic in rheumatology with many products being introduced and approved and a growing data supporting switching to biosimilars. Biosimilars have demonstrated high efficacy similar to biological at comparatively lower prices which can change the landscape of rheumatic arthritis therapy. However, there is an ongoing debate regarding interchangeability of biologicals and biosimilars.

### Immunogenicity

Immunogenicity is one of the major safety concerns associated with the use of biosimilars. Potential clinical consequences of immunogenicity are loss of response, lack of efficacy, pharmacokinetic alteration, development of antibodies that neutralize the product, hypersensitivity, infusion or injection site reactions. However, a recent study found no difference in the immunological profile of biosimilar infliximab (approved for RA) and the reference compound.<sup>1-3</sup>

### Indication extrapolation

Extrapolation is an important concept of the biosimilar therapy. Extrapolation is the approval of a biosimilar for clinical indications of the reference medicine without the need to compare the biological and biosimilar for those indications in a clinical trial. In plain words, clinical data generated in one

condition are extrapolated to the other indications. Indication exploration will have direct impact on cost of the treatment. Concerns about indication exploration were mainly raised by originator companies. Many of these concerns appear to be hypothetical, are unlikely to be problematic in the long term, and could be solved by some noninferiority clinical studies, which would increase confidence in using biosimilars.<sup>1-3</sup>

### Switching and interchangeability

The most important questions raised regarding switching are loss of efficacy or emergence of a hypersensitivity reaction after switching. However, switching from biologics (infliximab) to biosimilar showed maintenance of efficacy and comparable safety.<sup>1-3</sup>

#### What is the nocebo effect? What is the relevance of the nocebo effect on biosimilars?<sup>1</sup>

- A nocebo effect is said to occur when a patient expects that a given treatment will have no benefit, a nocebo effect, which is the opposite of the placebo effect, can occur in clinical trial and routine care settings
- The potential implications of viewing biosimilars in a negative context are evident in high rates of discontinuation after a switch from the reference compound in recently published clinical studies (BIO-SWITCH and DANBIO). It can happen in the clinical setting also.
- Education and effective communication between healthcare providers and patients are key to dispelling any pre-existing negative perceptions and concerns patients may have about biosimilars, avoiding nocebo effects and facilitating long-term adherence to biosimilars<sup>1</sup>

### Long term safety

Establishing the long-term efficacy and safety of biosimilars is important to examine in clinical settings for the successful long-term switch to biosimilar therapy<sup>1-3</sup>

### Current status of biosimilars in India

Table 1. Biosimilars approved (CDSCO) and marketed in India for rheumatoid arthritis <sup>3-5</sup>		
Product name	Active substance	Year of approval
Adfrar	Adalimumab	2016
Etacept	Etanercept	2013
Exemptia	Adalimumab	2014
Reditux	Rituximab	2007
RituxiRel	Rituximab	2015
Infimab	Infliximab	2014

### Clinical implications

With the availability of a number of biosimilars for the treatment of rheumatic disease, more patients can be switched from expensive reference products to more cost-effective biosimilars. However, there are some concerns regarding the use of biosimilars. Clinicians and patients need to have awareness of the consistent efficacy and safety of biosimilars in relation to reference biologicals.

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### Long-term treatment with bDMARDs improve remission in RA

Biological disease-modifying antirheumatic drugs(bDMARDs), including infliximab, are approved as a first-line treatment in patients with severe, active and progressive rheumatoid arthritis (RA) and who are naïve to methotrexate. However, the cost-effectiveness and long-term safety of bDMARDs is still questionable. The long-term safety and cost-effectiveness of first-line infliximab treatment were evaluated in patients with RA who are naïve to methotrexate in a recent meta-analysis. Treatment with infliximab produced significant improvement in 1-year efficacy outcomes (responses and remission) in patients with MTX-naïve RA. However, cost-effectiveness analyses of first-line biosimilar therapy in RA is warranted.

Reference: Zrubka Z, et al. *Expert Rev Pharmacoecon Outcomes Res.* 2019;19(5):537-49.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/31340686>

### Remission is a reachable target in patients with RA

The primary target (“treat-to-target” strategy) for patients with RA is clinical remission or low disease activity. However, knowledge of how frequently patients achieve remission and whether this target is practical or achievable in real-world circumstances is scarce. These concerns were addressed in a recent meta-analysis by Yu and colleagues. The study reported that the remission rates were 17.2%, 16.3%, 21.5%, and 23.5% at months 3, 6, 12, and 24, respectively. While male gender, higher education level, and lower baseline disease activity were found as positive predictors of remission, initial use of corticosteroids was recognized as a negative predictor. Remission is a reachable target for patients with RA. Attention should be focussed on maintaining remission and achieving sustained remission.

Reference: Yu C, et al. *Clin Rheumatol.* 2019;38(3):727-38.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30341703>

### Biosimilars are a cheaper alternative for biologics with comparable efficacy and safety in RA

Recently, the European Medicines Agency (EMA), approved the use of biosimilars disease-modifying drugs (bsDMARDs) of biologic disease-modifying drugs (boDMARDs) in rheumatoid arthritis. bsDMARDs provide a cheaper alternative to boDMARDs. However, there is limited clinical evidence regarding the safety and efficacy of biosimilars with biologics. Latest systematic studies reported that combinations of boDMARDs/bsDMARDs with csDMARD (conventional disease-modifying drugs) showed superior efficacy compared to single csDMARD and efficacy of boDMARDs and bsDMARDs were comparable. The results suggested that biosimilar can be preferred over biologics for the treatment of RA without any safety concern.<sup>1,2</sup>

References: 1. Bae SC, et al. *Clin J Clin Pharmacol Ther.* 2019;57(4):188-96. Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30574867>; 2. Simpson EL, et al. *Int J Technol Assess Health Care.* 2019;35(1):36-44. Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30722803>

### bDMARDs combination may cause more harm than benefit in RA

Combination therapy with two biologic disease-modifying antirheumatic drugs (bDMARDs) was associated with increased the risk of serious infections and other serious adverse events (SAEs). A meta-analysis reported that patients treated with combination bDMARDs therapy were five times more likely to acquire serious infections compared to monotherapy. The risk of SAEs during the first six to twelve months was twice higher compared to monotherapy, especially in patients receiving full doses of both bDMARDs. Clinicians should assess the risk/benefit ratio before considering combination therapy.

Reference: Boleto G, et al. *Semin Arthritis Rheum.* 2019 Aug;49(1):35-42. Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30638975>

### Biological agents are not safe in older patients with RA

Guidelines recommended the use of biological agents in patients with rheumatoid arthritis (RA). However, the use of biological agents is comparatively low in older patients due to the lack of evidence. Treatment with biologics was found to increase the risk of infection by 59% and other adverse reactions by 40% in older compared to young patients with RA. Treatment with biologicals should be monitored in elderly until further studies provide clear benefit over risk.

Reference: Dalal DS, et al. *Efficacy and safety of biological agents in the older rheumatoid arthritis patients compared to Young: A systematic review and meta-analysis.* *Semin Arthritis Rheum.* 2019;48(5):799-807.

Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30185379>



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# CHRONIC KIDNEY DISEASE

- Fact Sheet
- Hot Topics
- What's New In Guidelines?
- EBM Updates
- Conference Snapshot

## Fact Sheet

### Chronic kidney disease of all causes is a growing problem in India

- About 17% of the Indian population have chronic kidney disease (CKD)<sup>1</sup>
- More than 50% of patients with advanced CKD are first presented to clinic when the eGFR is <15 ml/min per 1.73 square meters<sup>1</sup>
- The prevalence of CKD due to unknown origin (eGFR <60) was found to be 1.6%<sup>2</sup>
- Over 120,000 patients are receiving haemodialysis making it the most common treatment modality for CKD<sup>1</sup>
- Protein energy wasting is present in 68%–93% of patients on dialysis<sup>1</sup>
- Less than 25% of patients with advanced CKD receive hepatitis B vaccine<sup>1</sup>

### Risk factors contributing to burden of CKD: Key facts

- CKD is more prevalent in men compared to women<sup>3</sup>
- Diabetes and hypertension account for 40–60% cases of CKD<sup>4</sup>
- The risk of death due to CKD is twice higher in patients with diabetes (glycaemic control  $\geq 8\%$ )<sup>5</sup>
- Tobacco use is associated with 39% higher risk of CKD of unknown origin<sup>2</sup>
- Alcoholic consumption increases the risk of CKD of unknown origin by 57%<sup>2</sup>

**Abbreviated Prescribing Information:-** **GENERIC NAME:** Rocaltrol 0.25 mcg. **BRAND NAME:** Calcitriol Capsule. **COMPOSITION-** Each capsule contains: Calcitriol 0.25 µg. **Colours:** Canthaxanthin and Titanium Dioxide. **INDICATIONS:** For the treatment of metabolic bone diseases. **DOSAGE AND ADMINISTRATION:** Rocaltrol therapy should always be started at the lowest possible dose (0.25 mcg) and should not be increased without careful monitoring of serum calcium. Postmenopausal osteoporosis: The recommended dosage for Rocaltrol is 0.25 µg twice daily. Renal osteodystrophy (dialysis patients): The initial daily dose is 0.25 µg. In patients with normal or only slightly reduced serum calcium levels, doses of 0.25 µg every other day are sufficient. **CONTRAINDICATIONS:** Hypersensitivity. All diseases associated with hypercalcemia. Vitamin D toxicity. **WARNINGS AND PRECAUTIONS:** Calcium supplements may be necessary but monitor for hypercalcemia. **PREGNANCY AND LACTATION:** Rocaltrol should be used during pregnancy only if the benefits outweigh the potential risk to the fetus. Mothers may breast feed while taking Rocaltrol, provided that the serum calcium levels of the mother and infant are monitored. **ADVERSE REACTIONS:** Anorexia, headache, nausea, vomiting, abdominal pain or stomach ache and constipation, soft-tissue calcification, increase in serum creatinine. **ISSUED ON- SOURCE:** Prepared based on full prescribing information, version 1.0: Dated 16/09/2015. <sup>TM</sup> \* Trademark of the Abbott Group of Companies.

\*\* Data on file.

Please read full prescribing information before usage.

For full prescribing information, please contact:

Abbott Healthcare Private Limited, Floor 18, Godrej BKC, Plot No. C 68, BKC, Near MCA Club, Bandra (E), Mumbai 400 051.

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### References

1. Santosh Varughese, et al. CJASN 2018; 13 (5) 802-804; 2. O'Callaghan-Gordo C, et al. BMJ Open. 2019;9:e023353; 3. Singh A.K, et al. BMC Nephrol.2013;14: 114; 4. Varma PP. Indian J Nephrol. 2015; 25(3): 133–135; 5. Anand Set al. PLOS ONE. 2017; 12(3): e0173554



## Blood pressure in CKD: Conclusions from a KDIGO controversies conference

The Kidney Disease: Improving Global Outcomes (KDIGO) group convened a Controversies Conference titled Blood Pressure in Chronic Kidney Disease (CKD) in September 2017 to figure out which recommendations from the 2012 KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD need to be revised or updated based on new evidence from the recent clinical trials. A multidisciplinary panel of clinical and scientific experts examined current evidence and arrived at consensus. Conclusions from the conference were published recently.

### Key controversies, conclusions, and consensus

- Blood pressure (BP) measurements: There is an ongoing controversy regarding choice of BP measurement method. The expert panel suggested that the future guideline work group should explicitly state which BP measurements should be used to diagnose and manage BP in CKD
- Salt intake: KIDGO-2012 guideline recommended lowering salt intake to <2 g per day. The panel indicated that there is a need to review the recommendation on salt intake identify new evidence specific to people with CKD, as debate about optimal salt intake in the general population is ongoing
- BP targets: Based on current data, the panel suggested revision of each recommendation in the KIDGO-2012 guideline regarding BP diagnosis thresholds and treatment targets.
- Patients with albuminuria or proteinuria: KIDGO-2012 guideline recommended a lower BP target and the use of RAAS inhibitors for people with albuminuria or proteinuria. The panel sought reassessment of these recommendations

*Reference:* Cheung AK, et al. Blood pressure in chronic kidney disease: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney International.* 2019; 95:1027-36; Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int Suppl.* 2012;2:337-414

## Heart failure in chronic kidney disease (KDIGO Controversies Conference)

The Kidney Disease: Improving Global Outcomes (KDIGO) group convened an international, multidisciplinary Controversies Conference titled Heart Failure in CKD to develop optimal strategies detection, prevention, diagnosis, and management of heart failure in patients with CKD.

### Key outcomes

- Echocardiography can support the diagnosis of HF by providing information on chamber volumes, ventricular systolic and diastolic function, wall thickness, valve function, and filling pressures. However, the panel points out that there are no accepted definitions or criteria for HF diagnosis in CKD
- Tight BP control (<120 mm Hg) is recommended to reduces incident HF with LV ejection fraction  $\geq$  35% in the presence of CKD
- Sodium-glucose cotransporter-2 inhibitors can be considered in patients with CKD and diabetes as they were found to slow the progression of CKD and reduce the risk of hospitalizations for HF
- The panel acknowledged that there are proven treatments for HFpEF (Heart failure with preserved ejection fraction), including in the setting of CKD
- Emphasis was laid on determining the optimal timing for initiating dialysis in the setting of HFrEF and HFpEF.
- The panel provided algorithm for the prevention and treatment of heart failure with reduced ejection fraction (HFrEF) in CKD progressing to end-stage kidney disease (ESKD)
- Incidence, prevalence, and management of HF in kidney transplant recipients were discussed

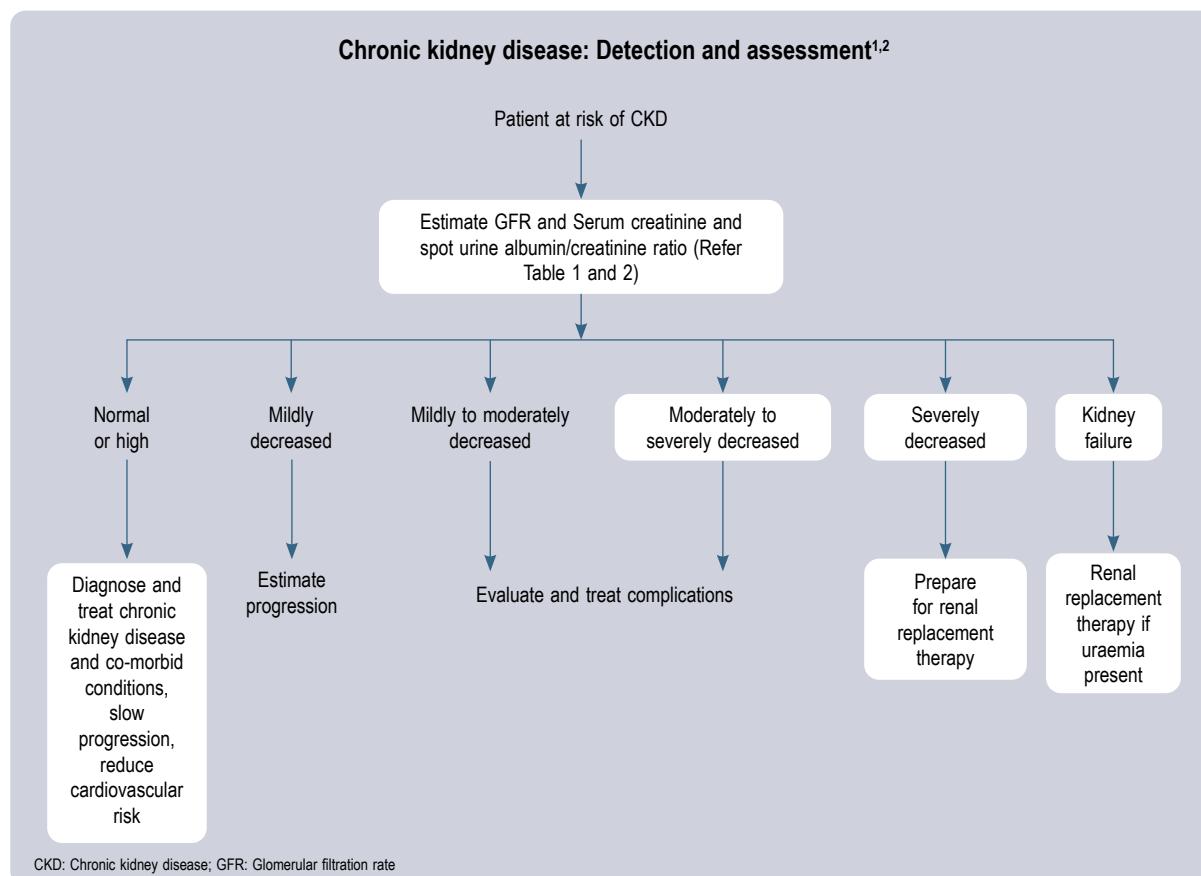


Table 1. Stages of Chronic Kidney Disease based on GFR<sup>1,2</sup>

Grade	Estimated GFR (ml per minute per 1.73 m <sup>2</sup> )	Description
G1	$\geq 90$	Kidney damage with normal or increased
G2	60 to 89	Kidney damage with mildly decreased
G3a	45 to 59	Mildly to moderately decreased
G3b	30 to 44	Moderately to severely decreased
G4	15 to 29	Severely decreased
G5	< 15 (or dialysis)	Kidney failure

Table 2. Stages of Chronic Kidney Disease based on albumin/creatinine ratio<sup>1,2</sup>

Grade	Albumin/creatinine ratio	Description
A1	<30 mg/g < 3 mg/mmol	Normal or to mildly increased
A2	30-300 mg/g 3-30 mg/mmol	Moderately increased
A3	>300 mg/g >30 mg/mmol	Severely increased

### References:

- Gaitonde DY, et al. Chronic kidney disease: Detection and evaluation. *Am Fam Physician.* 2017;96(12):776-783.
- KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International Supplements.* 2013; 1(3):1-150



## World Kidney Congress, 2019

**When and where:** The 4<sup>th</sup> World Kidney Congress was held on 28<sup>th</sup> and 29<sup>th</sup> May 2019 in Istanbul, Turkey

**Theme:** Recent advancements and prospects in nephrology

**Scientific sessions:** The conference highlighted keynote presentations, oral talks, poster presentations, and exhibitions.

- ABO-Incompatible kidney transplantation: Current trends and future perspectives
- Estimation of renal function in elderly diabetic patients
- Heat shock protein 70 gene polymorphism in Egyptian patients type 2 diabetes mellitus with and without nephropathy
- Role of chemical parameters on quality of water treatment for haemodialysis and clinical evaluation results
- Incidence of stroke among diabetic nephropathy patients: A meta-analysis
- Sutures on renal transplantation

*Reference:* 2019 World kidney congress, scientific report. Available at <https://d2cax41o7ahm5l.cloudfront.net/cs/pdfs/kidney-meet-2019-45839-program10582.pdf>. Last accessed on 06-Dec-2019

## ERA-EDTA Congress, 2019

**When and where:** The 56<sup>th</sup> European Renal Association – European Dialysis and Transplant Association congress (ERA-EDTA) was held in Budapest, Hungary, from June 13-16, 2019

**Scientific sessions:** The conference highlights keynote presentations, oral talks, poster presentations, and symposiums

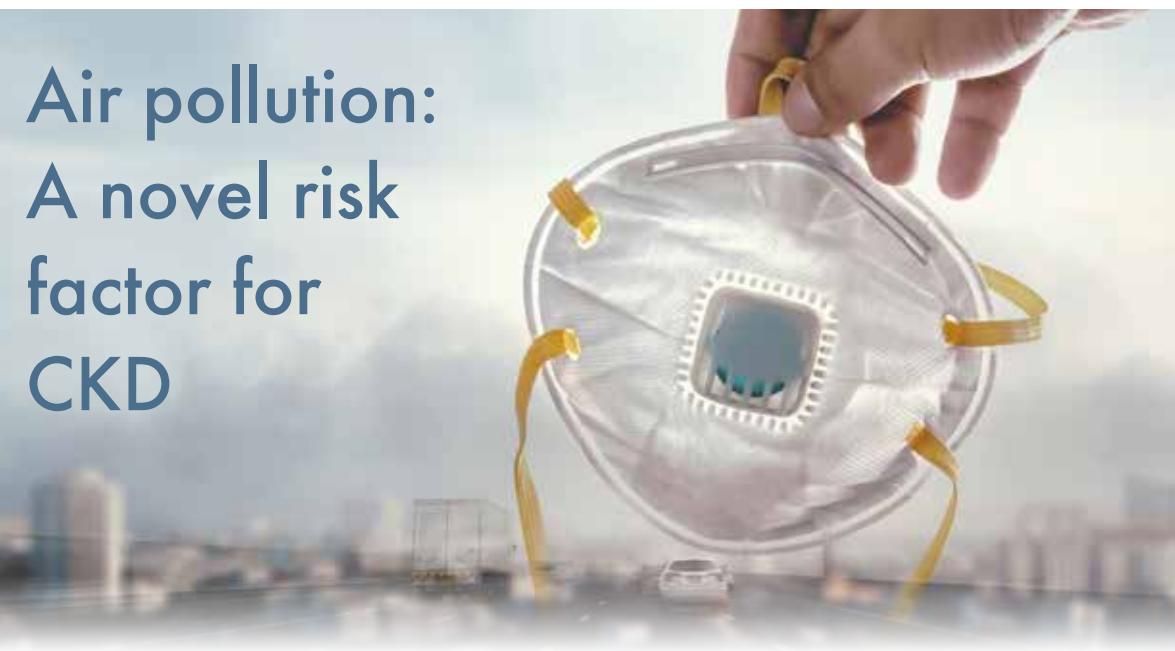
- Vitamin D<sub>3</sub> at doses higher than recommended dose is effective in preventing bone fracture in kidney transplant recipients
- A highly selective potassium-removing agent, sodium zirconium cyclosilicate effectively treats hyperkalaemia in patients with end-stage renal disease
- *Helicobacter pylori* colonization can have a significant effect on duodenal acidity which increases phosphate binder pill burden in dialysis
- Sodium bicarbonate decreases disease progression in patients with CKD
- High preoperative levels of DKK3 (Dickkopf), a novel urinary biomarker, can predict risk for acute kidney injury after cardiac surgery

### Awards and honours

- Professor Claudio Ronco received 2019 ERA-EDTA Award for Outstanding Clinical Contributions to Nephrology
- Dr. Olivier Devuyst was honored with the 2019 ERA-EDTA Award for Outstanding Basic Science Contributions to Nephrology
- Professor Claudio Ronco received the 2019 ERA-EDTA Award for Outstanding Clinical Contributions to Nephrology
- Dr. Rebecca Herzog was the recipient of the 2019 ERA-EDTA Stanley Shaldon Award for Young Investigator

*References:* 1. ERA-EDTA Congress, 2019, Final program. [http://www.era-edta2019.org/Final\\_Programme.pdf](http://www.era-edta2019.org/Final_Programme.pdf). Last accessed on 06-Dec-2019. 2. ERA-EDTA 2019, Daily congress newspaper, issue 2. Available at [http://www.era-edta2019.org/Daily\\_Congress\\_Newspaper2.pdf](http://www.era-edta2019.org/Daily_Congress_Newspaper2.pdf). Last accessed on 06-Dec-2019





## Air pollution: A novel risk factor for CKD

### Air pollution and CKD: Are they linked?

An increasing body of evidence demonstrate that air pollution may be a novel risk factor for CKD. Moreover, in the past two decades, outbreaks of CKD of unknown etiology have been reported in several developing countries like India. Air pollutants such as heavy metals, smoking, particulate matter, are suspected potential causes of CKD of unknown etiology. Therefore, it is necessary to understand which type of air pollutant is primarily responsible for developing CKD and pathogenic mechanisms of environmental pollutants leading to kidney damage, especially in developing countries where which environmental pollution is prevalent.<sup>1,2</sup>

### Air pollutants causing CKD

#### Heavy metals

Heavy metals are among the best-known environmental pollutants causing kidney disease. They cause nephrotoxicity by various mechanisms (Table 1).<sup>1,2</sup>

Table 1. Effect of heavy metals on kidney<sup>1,2</sup>

Heavy metal	Kidney injury
Cadmium	Proximal tubular dysfunction (glucosuria, aminoaciduria, and low-molecular-weight proteinuria), reduced GFR
Lead	Proximal tubular dysfunction, interstitial fibrosis, tubular atrophy, reduced GFR
Arsenic	Tubular interstitial nephritis, acute tubular necrosis, reduced GFR
Mercury	Secondary membranous nephropathy, interstitial nephritis, acute tubular necrosis, reduced GFR

GFR: Glomerular filtrate rate

#### Particulate matter (PM)

Particulate matter is the major component of air pollution and it mainly comes from road traffic and industrial burning of fossil fuels. Several studies have shown an association with various PM and CKD. Long-term exposure to particulate matter <2.5 µm in mean aerodynamic diameter (PM<sub>2.5</sub>) is associated with an increased risk of membranous nephropathy and a more rapid decline in renal function.<sup>1-3</sup>

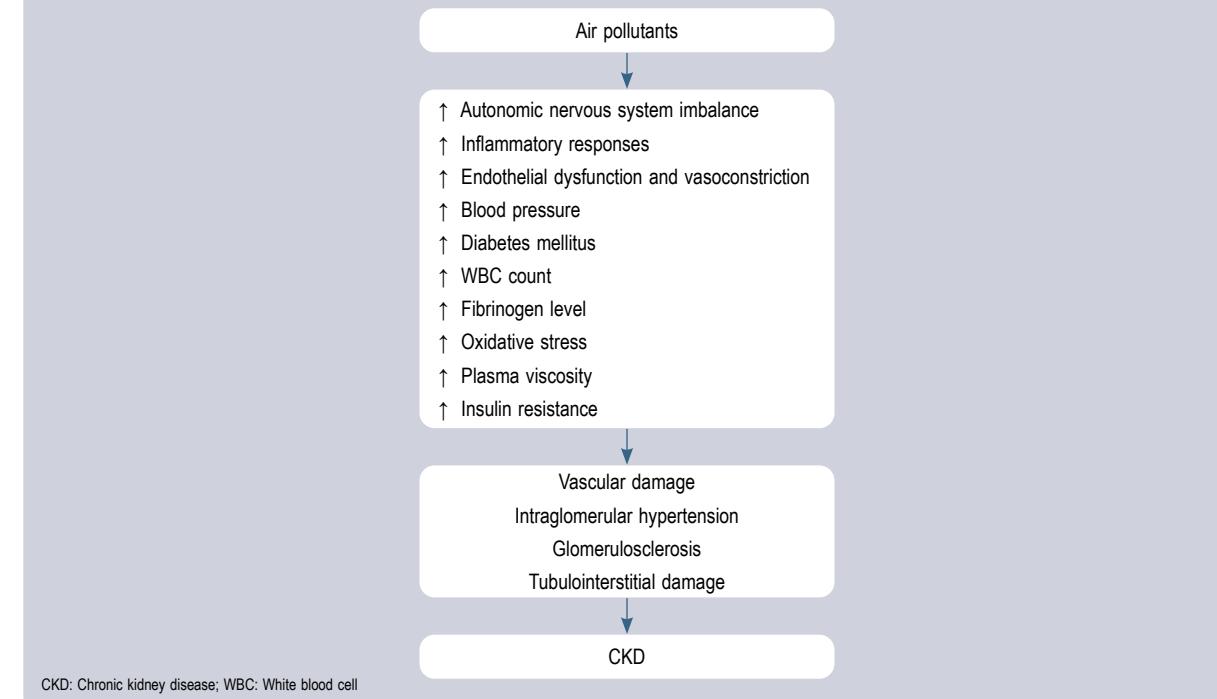
### Smoking

Smoking is also an air pollutant detrimental to kidney health. Both active smoking and second-hand smoking (passive smoking) are associated with a decline in renal function. However, the exact mechanism of this association is still unclear.<sup>1,2</sup>

### What is the pathological link between air pollution and CKD?

Currently, several mechanisms have been proposed to link exposure to air pollution and kidney damage (Figure 1). However, the exact mechanism underlying the association between air pollution and kidney disease remain to be elucidated.<sup>1,2</sup>

Figure 1. Pathogenic mechanisms of environmental pollutants leading to kidney damage<sup>1,2</sup>



### Future research needs<sup>1-3</sup>

- Which air pollutants especially cause kidney damage and to what extent?
- Whether improving air pollution and setting preventive measures for clean air has beneficial effects on a reduction in the incidence of CKD?
- What is the exact underlying mechanism of association between air pollution and CKD?

The detrimental effect of air pollution on kidney function has just begun to be acknowledged. According to currently available evidence air pollutants such as heavy metals, particulate matter and smoking are important risk factors for CKD. As the air quality and extent of environmental pollution are becoming worse in developing countries like India, it is crucial to raise awareness about air pollutants as a public health threat.<sup>1-3</sup>

References 1. Afsar B, et al. Air pollution and kidney disease: a review of current evidence. *Clin Kidney J.* 2019;12(1):19–32. 2. Xu X, et al. Environmental pollution and kidney diseases. *Nat Rev Nephrol.* 2018 May;14(5):313–24. 3. Bowe B et al. Estimates of the 2016 global burden of kidney disease attributable to ambient fine particulate matter air pollution. *BMJ Open.* 2019;9(5):e022450.





## Heat-stress and CKDu

### CKDu due to heat-stress: What is it?

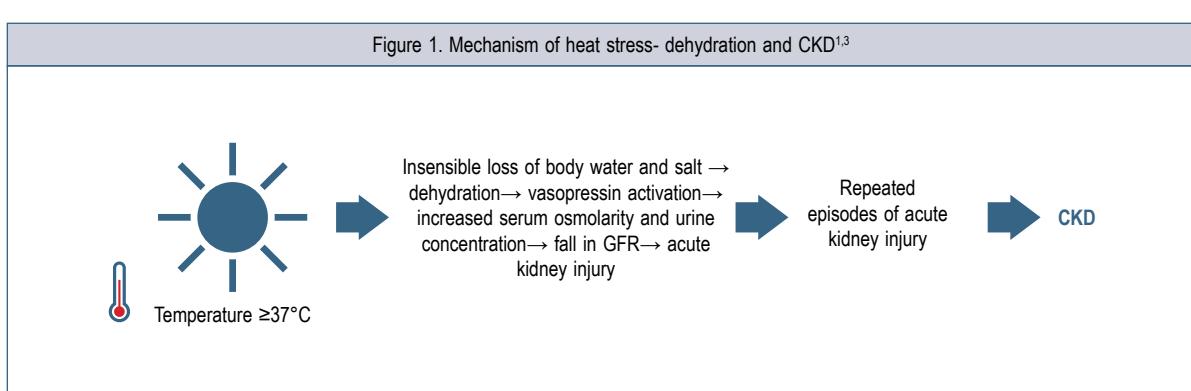
**C**KD prevalence is increasing in young agricultural-workers, in hot regions of Central America and Asia.<sup>1,2</sup> International Society of Nephrology has recently categorized it as chronic kidney disease of unknown (CKDu) etiology.<sup>2</sup> Nearly 40% of the world population resides in areas subjected to excessive heat throughout the year.<sup>1</sup> Although heat-stress and its consequences prevail in developed countries, it is particular to low-to-middle income countries and in tropical regions.<sup>3</sup> As per new evidence “Heat stress nephropathy may represent one of the first epidemics due to global warming” and needs to be dealt efficiently.<sup>4</sup>

### Heat stress-dehydration hypothesis for CKDu

Heat stress is expressed as sum of metabolic heat and environmental heat minus heat loss.<sup>3</sup> Heat stress results in heat strain, wherein the core body temperature increases by losing body's heat balance.<sup>3</sup> Heat stress often occurs in conjunction with dehydration, which explains the relationship between CKD and heat stress.<sup>3</sup>

### Understanding the mechanism

Increase in insensible loss of body water and salt in hot environment leads to substantial dehydration. Dehydration activates vasopressin which leads to increase in serum osmolarity and subsequent increase in urine concentration. Upon prolong volume depletion, GFR falls progressively which progresses to acute kidney injury (AKI). Such repeated episodes of AKI lead to CKD as depicted in Figure 1<sup>1,3</sup>



Heat stress-nephropathy resulting from extreme occupational heat stress and repeated episodes of dehydration is now considered as the central mechanism for CKDu.<sup>3</sup>

### Attention deserving findings

#### Higher prevalence of heat stress dehydration among women

- It may be related to lower fluid intake because female workers prefer drinking less to avoid the need to urinate while working.<sup>1,4</sup> Indoor exposure due to kitchen work with oven is also implicated in CKDu.<sup>1</sup>

#### Greater risk of CKDu is associated with low-income

- Majority of people affected will be working in agriculture sector and instability of seasonal agriculture work may lead to economic insecurity.<sup>4</sup>

#### Local perception of symptoms

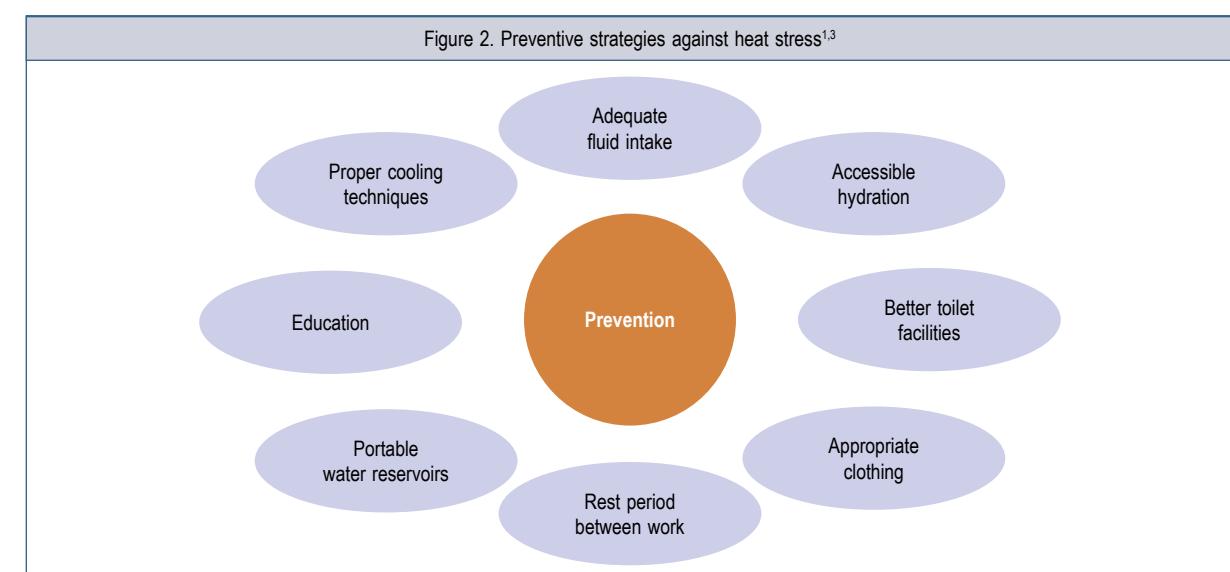
- People often wrongly perceive their symptoms to be of kidney disease without a proper diagnosis. Such cases are more likely to be reported as heat stress-dehydration symptoms.<sup>4</sup>

#### Heat stress-dehydration associated CKD in indoor workers

- The relationship is well established in outdoor workers, not in indoor workers. According to two recent Indian studies, continuous indoor exposure to heat leads to significant alteration in kidney function. In one study 85% had an albumin-to-creatinine ratio >30 mg/dl and in the latter 71% of the workers had exposures above the recommended limit (90% were steel workers).

### Effectively tackling the situation with preventive measures

The best approach to address the situation is to focus on preventive measures (Figure 2)<sup>1,3</sup>



#### References

- Ó Flatharta T, et al. Heat-related chronic kidney disease mortality in the young and old: differing mechanisms, potentially similar solutions? *BMJ EBM*. 2019;24(2):45–7.
- Nerbas FB, et al. Hydration Status and Kidney Health of Factory Workers Exposed to Heat Stress: A Pilot Feasibility Study. *Ann Nutr Metab*. 2019;74(Suppl. 3):30–7.
- Nerbas FB, et al. Occupational Heat Stress and Kidney Health: From Farms to Factories. *Kidney International Reports*. 2017;2(6):998–1008.
- Jayasekara KB, et al. Relevance of heat stress and dehydration to chronic kidney disease (CKDu) in Sri Lanka. *Preventive Medicine Reports*. 2019;15:1009–28.



### Change in proteinuria or albuminuria may not be suitable surrogate marker for CV risk in CKD

Cardiovascular diseases are a leading cause of morbidity and mortality among patients with CKD. The search for surrogates for long-term clinical outcomes including CV events and end-stage renal disease (ESRD) has been a focus in CKD research. Change in proteinuria or albuminuria has been investigated as a potential surrogate outcome. However, there is ongoing controversy around the surrogacy of proteinuria or albuminuria, particularly for cardiovascular. The validity of these markers was checked in a recent meta-analysis. The study raised concerns for the prospect of using changing proteinuria or albuminuria levels as a clinical surrogate for CV events and mortality. Further studies are required to establish clinical validity of these markers.

Reference: Harrison TG, et al. *Can J Cardiol.* 2019;35(1):77-91. Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30595186>

### Parenteral IV vs oral iron in patients with anemia in CKD: Have we reached a conclusion?

The anemia associated with CKD is often exacerbated by iron deficiency. Iron can be provided through different routes, with advantages and drawbacks of each route. There lies certain ambiguity about whether IV iron should be used rather than oral iron. A recent meta-analysis reported that IV iron compared with oral iron increased hemoglobin, ferritin and transferrin levels in patients with CKD participants. The number of participants who achieved target hemoglobin was 71% higher in the IV iron group than in oral iron group. Evidence was insufficient to determine whether IV iron compared with oral iron altered all-cause mortality, CVD-related death, and quality of life. Further studies that focus on patient-centered outcomes with longer follow-up periods are warranted to draw robust conclusions.

Reference: O'Lone EL, et al. *P Cochrane Database Syst Rev.* 2019;21(2):1-12. Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/30790278>

### Metabolic abnormality in normal-weight people is a risk factor for CKD

The major risk factors for the development of CKD are obesity and obesity-related metabolic syndromes. Nevertheless, the role of obesity in kidney insufficiency is controversial. Recently, it was hypothesized that glomerular filtration rate depends on body size phenotypes. This hypothesis was supported by a recent meta-analysis which reported a positive link between body size phenotype and risk of CKD. Individuals with metabolic abnormality, although at normal weight, were at an increased risk for CKD. The risk was higher among overweight and obese individuals. It is essential to consider both BMI and metabolic factors to reliably estimate the risk of incident CKD.

Reference: Shahab Alizade, et al. *Arch. Endocrinol. Metab.* 2019;63(4):427-37. WebLink: [http://www.scielo.br/scielo.php?script=sci\\_arttext&pid=S2359-39972019005006103&lng=en&nrm=iso&tlang=en](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S2359-39972019005006103&lng=en&nrm=iso&tlang=en)

### Patients with CKD are twice more likely to have periodontitis

Patients with CKD are at a higher risk for periodontal disease because of their weakened immune systems. Bacterial spreading and cytokines dissemination from periodontal pocket through blood flow could affect both endothelial and renal functions. The incidence rate of periodontitis was 73% in patients with CKD and the risk of severe periodontitis 2.39 times higher in CKD vs. no CKD. Based on the current evidence periodontitis may be a novel modifiable risk factor as it can be, cost-effectively diagnosed and treated. Thus, periodontal screening, through referral to dentist, may be included in the multidisciplinary management of CKD, or at-risk patients.

Reference: Lenhardt S, et al. *Oral Dis.* 2019;25(2):385-402. Weblink: <https://www.ncbi.nlm.nih.gov/pubmed/29377446>

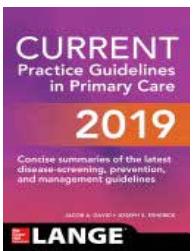
### Febuxostat demonstrated reno-protective effect in patients with CKD

Hyperuricemia is an independent risk factor for CKD, but its association with disease progression is unclear. Febuxostat is used as first-line for hyperuricemias in patients with CKD. In a recent metaanalysis, febuxostat demonstrated a significant reno-protective effect. Serum creatinine levels were significantly lower in patients treated with febuxostat  $\geq 6$  months compared to placebo or other urate-lowering agents. Febuxostat showed a superior urate-lowering effect compared to placebo or other urate-lowering agents. Febuxostat can be used to slow the deterioration of symptoms in CKD

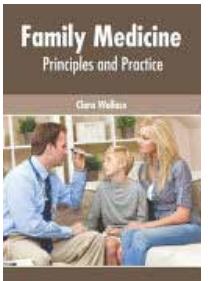
Reference: Tsu-Chen Lin, et al. *Medicine.* (2019);98(29):1-9. Weblink: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6709169>



# Book Releases 2019



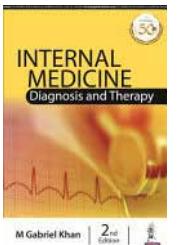
Title	CURRENT Practice Guidelines in Primary Care 2019
Authors/Editors	Joseph S. Esherick, Evan D. Slater, Jacob David(A)
Edition	17
Publisher	McGraw Hill Professional, 2019
About	Current screening, prevention, and management guidelines – compiled from the most authoritative sources.



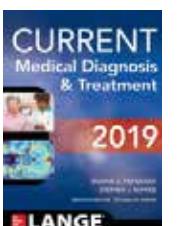
Title	Family Medicine: Principles and Practice
Authors/Editors	Clara Wallace
Edition	NA
Publisher	Foster Academics, 2019
About	This book includes some vital pieces of work being conducted across the world, on various topics related to family medicine. It strives to provide a fair idea about the practice of family medicine and to help develop a better understanding of the latest advances within this field.



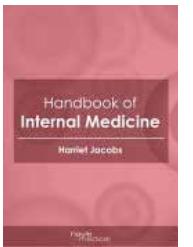
Title	Medicine Update & Progress in Medicine 2019 - Volume 29
Authors/Editors	KK Parek, G Narsimulu (A)
Edition	1
Publisher	JP Medical Ltd, 2019
About	A comprehensive compilation of the current understanding of various aspects in the field of medicine written by leading experts from India and overseas.



Title	Internal Medicine: Diagnosis and Therapy
Authors/Editors	M Gabriel Khan (A)
Edition	2
Publisher	JP Medical Ltd, 2019
About	The book has been fully revised with new topics added to provide the latest advances in the field. Each chapter examines the pathophysiology and techniques for accurate diagnosis and appropriate therapy.



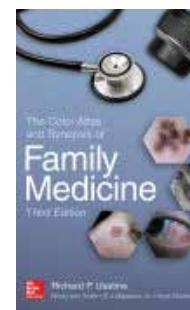
Title	CURRENT Medical Diagnosis and Treatment 2019
Authors/Editors	Maxine A. Papadakis, Stephen J. McPhee, Michael W. Rabow (A)
Edition	58
Publisher	McGraw Hill Professional, 2019
About	The book emphasizes on the practical features of clinical diagnosis and patient management in all fields of internal medicine and in specialties of interest to primary care practitioners and to subspecialists who provide general care.



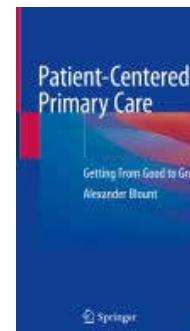
Title	Handbook of Internal Medicine
Authors/Editors	Harriet Jacobs
Edition	NA
Publisher	Hayle medical, 2019
About	This book is a compilation of chapters that discuss the most vital concepts and emerging trends in the field of internal medicine. The various advancements in this field are glanced at and their applications as well as ramifications are looked at in detail. This book includes contributions of experts and doctors, which will provide innovative insights into this medical specialty.



Title	Pocket Medicine: The Massachusetts General Hospital Handbook of Internal Medicine
Authors/Editors	Marc Sabatine (A)
Edition	7
Publisher	Wolters Kluwer Health, 2019
About	This book provides an up-to-date, dependable guidance on the internal medicine information needed to make an accurate diagnosis and develop a treatment plan.



Title	The Color Atlas and Synopsis of Family Medicine, 3rd Edition
Authors/Editors	Richard Usatine, Mindy Ann Smith, E.J. Mayeaux, Heidi Chumley (A)
Edition	3
Publisher	McGraw-Hill Education, 2019
About	This book simplifies and supports visual diagnosis like no other guide. The text is bolstered by more than 2,000 illustrations integrated with evidence-based diagnostic pearls presented in bulleted text and is for time-pressed physicians. New chapters on this edition includes Mental Health, the Opioid Crisis, Dementia, Sports-related Head Injury, LGBT health issues, Zika, Ebola. Addition of dermoscopy chapter and chapters on dermatology terminology, topical and intralesional steroids, and biopsy principles and techniques. Management section is now divided into first- and second-line therapies.



Title	Patient-Centered Primary Care: Getting From Good to Great
Authors/Editors	Alexander Blount (A)
Edition	1
Publisher	Springer Nature, 2019
About	This book offers a summary of the approaches that are currently in growing use, such as health literacy assessment, motivational interviewing, appreciative inquiry, shared decision making, minimally disruptive care, trauma informed care, enfranchisement coaching, relationship-centered care, and family-informed care. Finally, it offers a transformative method, based on familiar elements, that is Transparent, Empowering, Activating, and Mutual: the T.E.A.M. Way.



Title	Asthma, An Issue of Clinics in Chest Medicine
Authors/Editors	Serpil Erzurum, Sumita B Khatri (A)
Edition	1
Publisher	Elsevier Health Sciences, 2019
About	This book is devoted to several key areas of interest related to understanding Asthma and its treatments. Few topics covered in this issue include: Epidemiology of the Asthma Epidemic in the 21st Century; Classification of Asthma; Comorbidities and Non-allergic Triggers in Asthma Exacerbations and Severity; Microbiome in Mechanisms of Asthma; Diet and Metabolism in the Evolution of Asthma and Obesity; Asthma and Corticosteroid Responses in Childhood and Adult Asthma; Immunomodulators and Biologics; Bronchial Thermoplasty; Population Health Models for Asthma; and The Future of Asthma Care: Personalized Asthma Treatment.

# Conference Calendar 2020

## January

### Association of Physicians of India 75<sup>th</sup> Annual Conference

#### 2020 (APICON 2020)

- **Venue:** Agra, UP, India
- **Theme:** Translating expertise to evidence
- **Date:** Jan 6–9, 2020
- **Scientific programme:** Jan 7–9, 2020, CME: Jan 6, 2020
- **Online Registration:** Dec 1–15, 2019 (closed); Spot registration available
- **Website:** <http://www.apicon2020agra.com/>

### 57<sup>th</sup> Annual Conference of the Indian Academy of Pediatrics, 2020 (PEDICON 2020)

- **Venue:** Indore, MP, India
- **Theme:** Quality Child C.A.R.E which denotes: C-Comprehensive, A-Accessible, R-Relevant and E-Economical
- **Date:** Jan 9 and 10, 2020
- **Pre-conference:** Jan 8, 2020
- **Registration:** Jan 9–12, 2020 (Pre-conference registration Jan 8)
- **Website:** <https://pedicon2020.com/>

### Venous Association of India 13<sup>th</sup> Annual Conference 2020

- **Venue:** Mumbai, Maharashtra, India
- **Theme:** Newer initiatives in venous interventions
- **Date:** Jan 16–19, 2020
- **Pre-conference:** Jan 16, 2020
- **Registration:** Regular registration: Jan 21–Oct 15, 2019  
Regular Registration: Oct 16-Dec 31, 2019 and Spot registration: Jan 1, 2020 onwards
- **Website:** <http://www.vaicon2020.com/>

### SwasthyaCON 2020

- **Venue:** Ahmedabad, Gujarat, India
- **Theme:** Be the Leader in Metabolic Disease Management
- **Date:** Jan 10–12, 2020
- **Registration:** 1<sup>st</sup> round: Till Dec 20, 2019, 2<sup>nd</sup> round: Dec 21, 2019 onwards
- **Website:** <https://www.swasthyacon.org/>

### Certificate program in Insulin Management

- **Venue:** Mumbai, Maharashtra, India
- **Date:** Jan 25, 2020
- **Registration:** Early bird registration last date: Jan 5, 2020  
Regular registration last date: Jan 25, 2020
- **Website:** <https://assimilate.creativesprout.com/Diabetes-InsulinManagementMumbai#/tickets?lang=en>

### GP Update Refresher Masterclass

- **Venue:** London, UK
- **Credits:** 30 CME credit hours
- **Date:** Jan 16–19, 2020
- **Registration:** Open
- **Website:** <https://www.cmed.org.uk/>

## The Third Emirates Cardiac Society Heart Failure Conference

### 2020 (EHFC 2020 )

- **Venue:** Dubai, UAE
- **Date:** Jan 23–25, 2020
- **Pre-conference:** Jan 23, Hands-on Echocardiography Applications in HF
- **Registration:** Early Bird registration- July 23–Nov 22, 2019
- **Website:** <http://emirateshf.com/>

## February

### 3<sup>rd</sup> Global Public Health Conference 2020 (GlobeHeal 2020)

- **Venue:** Bangalore, Karnataka, India
- **Theme:** Embracing Community's Responses to Address Global Public Health Issues
- **Date:** Feb 13 and14, 2020
- **Registration:** Last date- Jan 8, 2020
- **Website:** <https://healthconference.co/>

### International conference on obesity, diabetes and cardiology (ICODC-2020)

- **Venue:** Madurai, Tamil nadu, India
- **Theme:** Exploring Advancements to Prevent Endocrine Disorders
- **Date:** Feb 25 and 26, 2020
- **Registration:** Registration opens on: Sept 15, 2019 Early bird registration last date: Oct 10, 2019 Spot registration available
- **Website:** <https://www.endlingconferences.com/ICODC2020/index.php>

### 10<sup>th</sup> World Congress of Diabetes India

- **Venue:** Bangalore, Karnataka, India
- **Date:** Feb 28-Mar 1, 2020
- **Registration:** Early bird registration last date - Jan 1, 2020  
Regular registration - After Jan 1, 2020
- **Website:** <http://diabetesindia2020.in/>

### India EUS Summit 2020

- **Venue:** Hyderabad, Telangana, India
- **Date:** Feb 14–16, 2020
- **Registration:** Through academics@aighospitals.com
- **Website:** <https://icause.com/hyderabad/india-eus-summit-2020/200018496080424>

## March

### 4<sup>th</sup> International Diabetes Summit 2020

- **Venue:** Pune, Maharashtra, India
- **Date:** Mar 6–8, 2020
- **Pre-conference:** Mar 6, 2020, In Hospital Glucose Control: A Simulated Learning Session
- **Registration:** Early bird registration last date: Jan 1, 2020

Regular registration last date: Mar 5, 2020  
Spot Registration available

### 2020 ACG / FGS Annual Spring Symposium

- **Venue:** Naples, Florida, US
- **Credits:** : 13 AMA PRA Category 1 Credits
- **Date:** Mar 13–15, 2020
- **Registration:** Early bird registration last date: Feb 24, 2020
- **Website:** <https://gi.org/2020-acg-fgs-annual-spring-symposium/>

### Primary care challenges for today's practitioner: Practice strategies for internal and family medicine

- **Venue:** SSarasota, Florida, US
- **Credits:** 20 AMA PRA Category 1 Credits 20 CME Credits – AAFP ACEP
- **Date:** Mar 16–20, 2020
- **Website:** <https://www.americanmedicalseminars.com/>

## April

### 2<sup>nd</sup> World Congress on Cardiac Sciences

- **Venue:** Bangalore, Karnataka, India
- **Theme:** Advances in cardiology: Research and innovations
- **Credits:** 6 CME credits
- **Date:** April 16 and 17, 2020
- **Registration:** Early bird registration last date: Dec 10, 2019  
Regular registration last date: Feb 28, 2020
- **Website:** <http://www.cardiacsciencesconference.com/>

### Cardiology for Primary Care and Hospital Medicine

- **Venue:** Srasota, Florida, US
- **Credits:** 20 AMA PRA Category 1 Credit, 20 CME Credits - AAFP ACEP
- **Date:** Apr 20–24, 2020
- **Registration:** Early bird registration last date: Apr 20, 2020
- **Website:** <https://www.americanmedicalseminars.com/events/cardiology-for-primary-care-and-hospital-medicine/>

## May

### 6<sup>th</sup> ANNUAL MAYO CLINIC RHEUMATOLOGY REVIEW FOR PRIMARY CARE

- **Venue:** Orlando, Florida, US
- **Credits:** AAFP, AMA PRA Category 1 Credits, ANCC, AOA Category 2-A
- **Date:** May 7–9, 2020
- **Website:** <https://ce.mayo.edu/family-medicine/content/6th-annual-mayo-clinic-rheumatology-review-primary-care-2020>

## August

### ESC Congress 2020

- **Venue:** Amsterdam, Netherlands
- **Theme:** The Cutting Edge of Cardiology
- **Date:** Aug 29–Sept 2, 2020
- **Registration:** Early bird registration last date: May 31, 2020
- **Website:** <https://www.escardio.org/Congresses-&Events/ESC-Congress>

## September

### 11<sup>th</sup> National Annual Conference of Indian Association of Clinical Cardiologists

- **Venue:** Vadodara, Gujarat, India
- **Credits:** UEMS credits
- **Date:** Sept 4–6, 2020
- **Registration:** Early bird registration last date: October 30, 2019 Normal registration last date: March 31, 2020 Late registration last date: April 1, 2020
- **Website:** <https://www.iacccon.org/>



# 2020 HEALTHDAY CALENDAR

JANUARY	FEBRUARY	MARCH
30 <sup>th</sup> World Leprosy Day 2020	04 <sup>th</sup> World Cancer Day 2020 09 <sup>th</sup> Toothache Day 2020 28 <sup>th</sup> Rare Disease Day 2020	05 <sup>th</sup> Multiple Personality Day 2020 12 <sup>th</sup> World Kidney Day 2020 21 <sup>st</sup> World Down Syndrome Day 2020 24 <sup>th</sup> World Tuberculosis Day 2020
APRIL	MAY	JUNE
02 <sup>nd</sup> World Autism Awareness Day 2020 07 <sup>th</sup> World Health Day 2020 17 <sup>th</sup> World Hemophilia Day 2020 25 <sup>th</sup> DNA day 2020 25 <sup>th</sup> World Malaria Day 2020 28 <sup>th</sup> World Day for Safety and Health at Work 2020	05 <sup>th</sup> World Asthma Day 2020 05 <sup>th</sup> World Hand Hygiene Day 2020 12 <sup>th</sup> Chronic Fatigue Syndrome Day 2020 12 <sup>th</sup> International Nurses Day 2020 31 <sup>st</sup> World No Tobacco Day 2020	08 <sup>th</sup> World Brain Tumor Day 2020 14 <sup>th</sup> World Blood Donor Day 2020 25 <sup>th</sup> World Vitiligo Day 2020
JULY	AUGUST	SEPTEMBER
28 <sup>th</sup> World Hepatitis Day 2020	August 1 <sup>st</sup> - August 7 <sup>th</sup> World Breast Feeding Week 2020	10 <sup>th</sup> World Suicide Prevention Day 2020 28 <sup>th</sup> World Rabies Day 2020
OCTOBER	NOVEMBER	DECEMBER
03 <sup>rd</sup> Virus Appreciation Day 2020 05 <sup>th</sup> Child Health Day 2020 10 <sup>th</sup> World Mental Health Day 2020 20 <sup>th</sup> World Osteoporosis Day 2020	12 <sup>th</sup> World Pneumonia Day 2020 14 <sup>th</sup> World Diabetes Day 2020	01 <sup>st</sup> World AIDS Day 2020



