ur website **www.jaypeebrothers.com,** for detailed information on medicine books, visit our website **www.jaypeebrothers.com**

Celebrating 50 YEARS
Passion, Quality and Innovation in Healthcare Publishing

Year Book of MEDICINE 2018

Chief Editor

Gurpreet S Wander

Section Editors

Siddharth N Shah
Surinder K Jindal
Vivekanand Jha
Rohini Handa
Ajay Kumar
K Sarat Chandra
R Rajasekar
Gagandeep Singh
Jyotirmoy Pal

JAYPEE

CONTENTS

Editors Choice

Nations within a Nation: Variations in Epidemiological Transition across the States of India, 1990–2016 in the Global Burden of Disease Study 1

Section 1: Cardiology
Section Editor: K Sarat Chandra

Associate Editors: Tiny Nair, Gurpreet S Wander

1. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease 5
2. System of Care for Patients with ST-segment Elevation Myocardial Infarction in India: The Tamil Nadu–ST-segment Elevation Myocardial Infarction Program 6
3. Predictors of Death in Contemporary Adult Patients with Eisenmenger Syndrome: A Multicenter Study 8
4. Midterm Results of Tetralogy of Fallot with Absent Pulmonary Valve 9
5. Meta-analysis of the Impact of Intervention versus Symptom-driven Management in Asymptomatic Severe Aortic Stenosis 10
6. Prevalence and Clinical Manifestations of Primary Aldosteronism Encountered in Primary Care Practice 12
7. Heart Failure with Preserved, Borderline, and Reduced Ejection Fraction—5-year Outcomes 13
8. Angiotensin-converting Enzyme Inhibitors and Angiotensin Receptor Blockers in High Vascular Risk 14
9. Trends in Use of High-intensity Statin Therapy after Myocardial Infarction, 2011 to 2014 16
10. Trend in Prevalence of Coronary Artery Disease and Risk Factors Over Two Decades in Rural Punjab 18
11. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation 19
12. Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: The EFFORTLESS Study 20
13. Maternal and Fetal Outcomes of Anticoagulation in Pregnant Women with Mechanical Heart Valves 22
14. Diuretic Treatment in Heart Failure 23
15. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease 25
16. Oxygen Therapy in Suspected Myocardial Infarction 26
17. Optimal Timing of an Invasive Strategy in Patients with Non-ST Elevation Acute Coronary Syndrome: A Meta-analysis of Randomized Trials 27

18. Fruits, Vegetables, and Legume Intake and Cardiovascular Disease and Deaths in 18 Countries (PURE): A Prospective Cohort Study 28
19. Global Mortality Variations in Patients with Heart Failure: Results from the International Congestive Heart Failure (INTER-CHF) Prospective Cohort Study 30
20. 3-Year Clinical Outcomes with Everolimus-eluting Bioresorbable Coronary Scaffolds—The ABSORB III Trial 31

Section 2: Chest and Critical Care
Section Editor: Surinder K Jindal

Associate Editors: Sahajal Dhooria, Inder Paul S Sehgal

1. The Effects of Atorvastatin on Inflammatory Responses and Mortality in Septic Shock: A Single-center, Randomized Controlled Trial 33
2. Prevalence and Etiological Profile of Chronic Obstructive Pulmonary Disease in Nonsmokers 34
3. Pulmonary Rehabilitation in Patients with Interstitial Lung Diseases in an Outpatient Setting: A Randomized Controlled Trial 36
4. Correlation of Cutaneous Sensitivity and Cytokine Response in Children with Asthma 37
5. Clinical Profile and Treatment Outcome of Drug-resistant Tuberculosis Patients of Western Maharashtra, India 38
6. Prevalence of Aspergillus Hypersensitivity and Allergic Bronchopulmonary Aspergillosis in Patients with Bronchial Asthma at a Tertiary Care Center in North India 40
7. The Effect of Diabetes Control Status on Treatment Response in Pulmonary Tuberculosis: A Prospective Study 41
8. Efficacy and Safety of Glycopyrrolate/Formoterol Metered Dose Inhaler Formulated Using Co-Suspension Delivery Technology in Patients With COPD 43
9. Use of Mycophenolate Mofetil or Azathioprine for the Management of Chronic Hypersensitivity Pneumonitis 44
10. Early Computed Tomography Modifications Following Bronchial Thermoplasty in Patients with Severe Asthma 46
11. Nintedanib in Patients with Idiopathic Pulmonary Fibrosis and Preserved Lung Volume 47
12. Severe and Difficult-to-treat Asthma in Adults 48
13. Acute Respiratory Distress Syndrome 50
14. Evaluation of a Rapid Molecular Drug-susceptibility Test for Tuberculosis 51
15. Effect of Azithromycin on Asthma Exacerbations and Quality of Life in Adults with Persistent Uncontrolled Asthma (AMAZES): A Randomised, Double-blind, Placebo-controlled Trial 53
16. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease 55
17. Tiotropium in Early-stage Chronic Obstructive Pulmonary Disease 56
18. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism 58

19. Should Recommendations about Starting Inhaled Corticosteroid Treatment for Mild Asthma Be Based on Symptom Frequency: A *Post-hoc* Efficacy Analysis of the START Study 59

Section 3: Diabetes and Metabolic Disorders
Section Editor: Siddharth N Shah

Associate Editors: Mangesh Tiwaskar, Naveen Mittal, Ragini M Rohatgi

1. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum 62
2. A Systematic Review of Known Interventions for the Treatment of Chronic Non-hypovolaemic Hypotonic Hyponatraemia and a Meta-analysis of the Vaptans 63
3. Bariatric Surgery versus Intensive Medical Therapy for Diabetes—5-year Outcomes 65
4. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes 67
5. Clinical Efficacy and Safety of Achieving Very Low LDL-cholesterol Concentrations with the PCSK9 Inhibitor Evolocumab: A Prespecified Secondary Analysis of the FOURIER trial 69
6. Clinical Outcomes of Metformin Use in Populations with Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review 70
7. Cardiovascular Mortality and Morbidity in Patients with Type 2 Diabetes following Initiation of Sodium-glucose Co-transporter-2 Inhibitors versus Other Glucose-lowering Drugs (CVD-REAL Nordic): A Multinational Observational Analysis 72
8. Diabetic Foot Ulcers and Their Recurrence 73
9. Primary Care-led Weight Management for Remission of Type 2 Diabetes (DiRECT): An Open-label, Cluster-randomised Trial 75
10. Effect of Oral versus Intramuscular Vitamin D Replacement in Apparently Healthy Adults with Vitamin D Deficiency 76
11. Electrolyte Disturbances in Patients with Chronic Alcohol-use Disorder 78
12. Hashimoto's Thyroiditis: Relative Recurrence Risk Ratio and Implications for Screening of First Degree Relatives 80
13. High Prevalence of Hypovitaminosis D in Patients Presenting with Proximal Muscle Weakness: A Sub-Himalayan Study 81
14. Liraglutide and Renal Outcomes in Type 2 Diabetes 83
15. Mortality Rates are Lower in SIAD, than in Hypervolemic or Hypovolemic Hyponatremia: Results of a Prospective Observational Study 85
16. Myopathy in Patients Taking Atorvastatin: A Pilot Study 86
17. Prevalence of Diabetes and Prediabetes in 15 States of India: Results from the ICMR–INDIAB Population-based Cross-sectional Study 87
18. Serum Vitamin B12 Levels in Type 2 Diabetes Patients on Metformin Compared to those Never on Metformin: A Cross-sectional Study 89
19. Sheehan's Syndrome—The Most Common Cause of Panhypopituitarism at Moderate Altitude: A Sub-Himalayan Study 90

20. The Association between Subclinical Thyroid Dysfunction and Dementia: The Health, Aging, and Body Composition (Health ABC) Study 92
21. The Lipid-lowering Effect of Levothyroxine in Patients with Subclinical Hypothyroidism: A Systematic Review and Meta-analysis of Randomized Controlled Trials 93

Section 4: Gastroenterology/Hepatology
Section Editor: Ajay Kumar

Associate Editors: Manav Wadhawan, Praneet Wander

1. A Comparison of the Rate of Gastrointestinal Bleeding in Patients Taking Non-vitamin K Antagonist Oral Anticoagulants or Warfarin 96
2. Comparing Intravenous and Oral Proton Pump Inhibitor Therapy for Bleeding Peptic Ulcers Following Endoscopic Management: A Systematic Review and Meta-analysis 97
3. Complications of Proton Pump Inhibitor Therapy 98
4. Single Center Experience of a New Endoscopic Clip in Managing Nonvariceal Upper Gastrointestinal Bleeding 99
5. ACG and CAG Clinical Guideline: Management of Dyspepsia 100
6. A Randomised Trial of Endoscopic Submucosal Dissection Versus Endoscopic Mucosal Resection for Early Barrett's Neoplasia 102
7. Peroral Endoscopic Myotomy in Treatment-naïve Achalasia Patients Versus Prior Treatment Failure Cases 103
8. Endoscopic "Step-up Approach" Using a Dedicated Biflanged Metal Stent Reduces the Need for Direct Necrosectomy in Walled-off Necrosis (with Videos) 104
9. Association between Screen-Detected Gallstone Disease and Cancer in a Cohort Study 106
10. Efficacy of Pancreatic Enzyme Replacement Therapy in Chronic Pancreatitis: Systematic Review and Meta-analysis 107
11. Endoscopic and Clinical Responses to Antitubercular Therapy Can Differentiate Intestinal Tuberculosis from Crohn's Disease 108
12. Risk of Colorectal cancer in Asian Patients with Ulcerative Colitis: A Systemic Review and Meta-analysis 110
13. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis 111
14. Targeting the Gut-liver Axis in Liver Disease 113
15. Healthy Donor Fecal Microbiota Transplantation in Steroid-ineligible Severe Alcoholic Hepatitis: A Pilot Study 114
16. Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis 116
17. Long-term Outcomes of Entecavir Monotherapy for Chronic Hepatitis B after Liver Transplantation: Results Up to 8 Years 117
18. Liver Transplantation in the Most Severely Ill Cirrhotic Patients: A Multicenter Study in Acute-on-chronic Liver Failure Grade 3 118
19. Successful Treatment of Chronic Hepatitis C Infection with Directly Acting Antivirals in Renal Transplant Recipients 120
20. L-ornithine L-aspartate in Bouts of Overt Hepatic Encephalopathy 121

Section 5: Infectious Diseases, HIV, and TB
Section Editor: R Rajasekar

Associate Editors: N Jeyalakshmidevi, M Nataraj

1. New Drugs and Perspectives for New Antituberculosis Regimens 123
2. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) 125
3. Point of care Diagnostics for Tuberculosis 126
4. Index-TB Guidelines: Guidelines on Extrapulmonary Tuberculosis for India 128
5. Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management 130
6. Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa 132
7. HIV-TB Coinfection among 57 Million Pregnant Women, Obstetric Complications, Alcohol Use, Drug Abuse, and Depression 133
8. Survival of HIV-positive Patients Starting Antiretroviral Therapy between 1996 and 2013: A Collaborative Analysis of Cohort Studies 134
9. Prevalence of Opportunistic Infections and Causes of Death among Hospitalized HIV-infected Patients in Sichuan, China 136
10. An Overview of New Delhi Metallo-beta Lactamase-1 and Extended Spectrum Beta Lactamase Producing Bacteria: Need for an Alternate 137
11. The Antibiotic Resistance Crisis, with a Focus on the United States 139
12. Cardiovascular Complications and Short-term Mortality Risk in Community-acquired Pneumonia 140
13. Tropical Fevers in Indian Intensive Care Units: A Prospective Multicenter Study 141
14. Zika Virus Infection and Associated Neurologic Disorders in Brazil 143
15. Post-Babesiosis Warm Autoimmune Hemolytic Anemia 144

16A. Recognizing Sepsis as a Global Health Priority—A WHO Resolution 145

16B. A CRISPR Way to Diagnose Infectious Diseases 146

17. Typhoid Fever: A Review 147

Section 6: Miscellaneous (Geriatrics, genetics, and pregnancy related)
Section Editor: Jyotirmoy Pal

Associate Editors: Dwijen Das, Pradip K Chowdhury

1. Associations of Fat and Muscle Tissue with Cognitive Status in Older Adults: The AGES-Reykjavik Study 149
2. Frailty Status at Admission to Hospital Predicts Multiple Adverse Outcomes 151
3. Metabolic Syndrome and Insulin Resistance are Associated with Frailty in Older Adults: A Prospective Cohort Study 153
4. Coexistence of Metallo-beta-lactamase-encoding Genes in *Pseudomonas aeruginosa* 155

5. Genetic Diversity Study of Various β-lactamase-producing Multidrug-resistant *Escherichia coli* Isolates from a Tertiary Care Hospital Using ERIC-PCR 157
6. Characterization of Antimicrobial Resistance Markers and Their Stability in *Salmonella enterica* Serovar Typhi 158
7. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease 159
8. Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease 161
9. Asymptomatic Osteoporosis in Indian Geriatric Population 162
10. Current Scenario of Geriatric Fungal Infections: A Prevalence Study from a Tertiary Care Hospital 164
11. SOFA Score and Critically Ill Elderly Patients 165
12. Continuous Glucose Monitoring in Pregnant Women with Type 1 Diabetes (CONCEPTT): A Multicentre International Randomized Controlled Trial 166
13. Obesity and Gynaecological and Obstetric Conditions: Umbrella Review of the Literature 169
14. Statistical Considerations for Randomized Controlled Trials [RCTs]—Understanding Superiority, Equivalence and Non-inferiority Designs 170
15. Molecular Minimal Residual Disease in Acute Myeloid Leukemia 172
16. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis 174
17. Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease 176
18. Why Geriatric Medicine? A Survey of UK Specialist Trainees in Geriatric Medicine 178
19. Will Maintenance of Oral Hygiene in Nursing Home Residents Prevent Pneumonia? 180
20. Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection Compared With Reverse Transcriptase Polymerase Chain Reaction: A Systematic Review and Meta-analysis 182
21. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism 183
22. The Relationship between Neutrophil to Lymphocyte Ratio and Metabolic Syndrome in Patients with Type 2 Diabetes 185

Section 7: Nephrology and Hypertension
Section Editor: Vivekanand Jha

Associate Editors: Arpana Iyengar, Gopesh K Modi

1. Prophylactic Hydration to Protect Renal Function from Intravascular Iodinated Contrast Material in Patients at High Risk of Contrast-induced Nephropathy (AMACING): A Prospective, Randomised, Phase 3, Controlled, Open-label, Non-inferiority Trial 192
2. Quantifying Postdonation Risk of ESRD in Living Kidney Donors 193
3. Kidney Outcomes Three Years after Bariatric Surgery in Severely Obese Adolescents 195
4. Food Insecurity, CKD, and Subsequent ESRD in US Adults 196
5. The Genetic Landscape of Renal Complications in Type 1 Diabetes 198
6. IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation 199
7. Novel Treatment Protocol for Ameliorating Refractory, Chronic Pain in Patients with Autosomal Dominant Polycystic Kidney Disease 200

8A. Effects of Empagliflozin on the Urinary Albumin-to-creatinine Ratio in Patients with Type 2 Diabetes and Established Cardiovascular Disease: An Exploratory Analysis from the EMPA-REG OUTCOME Randomised, Placebo-controlled Trial 202

8B. Canagliflozin Slows Progression of Renal Function Decline Independently of Glycemic Effects 203

9. Single-nephron Glomerular Filtration Rate in Healthy Adults 205

10. Effects of Intensive BP Control in CKD 206

11. Intensified Multifactorial Intervention in Type 2 Diabetics with Microalbuminuria Leads to Long-term Renal Benefits 207

12. Tolvaptan in Later-stage Autosomal Dominant Polycystic Kidney Disease 209

13A. A Randomized Trial of Vitamin D Supplementation on Vascular Function in CKD 210

13B. Effects of Vitamin D Receptor Activation and Dietary Sodium Restriction on Residual Albuminuria in CKD: The ViRTUE-CKD Trial 211

14A. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients with IgA Nephropathy: The TESTING Randomized Clinical Trial 212

14B. Targeted-release Budesonide versus Placebo in Patients with IgA Nephropathy (NEFIGAN): A Double-blind, Randomised, Placebo-controlled Phase 2b Trial 213

15A. Multitarget Therapy for Maintenance Treatment of Lupus Nephritis 216

15B. Induction and Maintenance Immunosuppression Treatment of Proliferative Lupus Nephritis: A Network Meta-analysis of Randomized Trials 216

16. Rituximab for Childhood-onset Refractory Nephrotic Syndrome (RCRNS) Study Group. Long-term Outcome of Childhood-onset Complicated Nephrotic Syndrome after a Multicenter, Double-blind, Randomized, Placebo-controlled Trial of Rituximab 219

17. Antibiotic Prophylaxis for Urinary Tract Infection-related Renal Scarring: A Systematic Review 220

18. Effect of Human Leukocyte Antigen Mismatching on the Outcomes of Pediatric Kidney Transplantation: A Systematic Review and Meta-analysis 221

19. Perinatal Diagnosis, Management, and Follow-up of Cystic Renal Diseases: A Clinical Practice Recommendation with Systematic Literature Reviews 223

20. Mycophenolate Mofetil Is Inferior to Tacrolimus in Sustaining Remission in Children with Idiopathic Steroid-resistant Nephrotic Syndrome 224

Section 8: Neurology
Section Editor: Gagandeep Singh

Associate Editors: PN Sylaja, Jayantee Kalita

1. Global, Regional, and National Burden of Neurological Disorders During 1990-2015: A Systematic Analysis for the Global Burden of Disease Study 2015 226

2. ILAE Classification of the Epilepsies: Position Paper of the ILAE Commission for Classification and Terminology 227

3. Trial of Cannabidiol for Drug-resistant Seizures in the Dravet Syndrome 229

4. Bioequivalence between Generic and Branded Lamotrigine in People with Epilepsy: The EQUIGEN Randomized Clinical Trial 230

5A. Investigations in $GABA_A$ Receptor Antibody-associated Encephalitis 232
5B. DPPX Antibody-associated Encephalitis: Main Syndrome and Antibody Effects 232
6. Safety and Efficacy of Erenumab for Preventive Treatment of Chronic Migraine: A Randomized, Double-Blind, Placebo-controlled Phase 2 Trial 233
7. Referral Practice, Reporting Standards, and the Impact of Dopamine Transporter Scans Done in a Tertiary Hospital 235
8. Risk Factors for Early Psychosis in PD: Insights from the Parkinson's Progression Markers Initiative 237
9. Cluster-randomized, Crossover Trial of Head Positioning in Acute Stroke 239
10. Family-led Rehabilitation after Stroke in India (ATTEND): A Randomized Controlled Trial 240
11. Predictors of Good Outcome after Endovascular Therapy for Vertebrobasilar Occlusion Stroke 242
12. Risk Factors, Vascular Lesion Distribution, Outcome and Recurrence of Strokes Due to Intracranial Atherosclerosis: One Year Data from Hyderabad Stroke Registry 243
13. Prevalence and Risk Factors of Asymptomatic Carotid Artery Stenosis in Indian Population: An 8-year Follow-up Study 245
14. Rapid Clinical Score for the Diagnosis of Tuberculous Meningitis: A Retrospective Cohort Study 246
15. Low-dose Aspirin and Risk of Intracranial Bleeds 247
16. Trial of Pregabalin for Acute and Chronic Sciatica 248
17. Characteristics of Nerve Conduction Studies in Carpal Tunnel Syndrome 250
18. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis 252
19. High-dose Immunosuppressive Therapy and Autologous HCT for Relapsing-remitting MS 253

Section 9: Rheumatology and Immunology
Section Editor: Rohini Handa

Associate Editors: Aman Sharma, Durga Prasanna Misra

1. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease 258
2. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis 259
3. Efficacy and Safety of Tofacitinib Monotherapy, Tofacitinib with Methotrexate, and Adalimumab with Methotrexate in Patients with Rheumatoid Arthritis (ORAL Strategy): A Phase 3b/4, Double-blind, Head-to-head, Randomised Controlled Trial 261
4A. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis 262
4B. Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors 263
5. Trial of Tocilizumab in Giant-cell Arteritis 264
6. Incident Myocardial Infarction Associated with Major Types of Arthritis in the General Population: A Systematic Review and Meta-analysis 266
7A. Rheumatoid Arthritis Triple Therapy Compared with Etanercept: Difference in Infectious and Gastrointestinal Adverse Events 267

7B. Rheumatoid Arthritis Patients with Continued Low Disease Activity have Similar Outcomes Over 10 Years, Regardless of Initial Therapy 268

8. Patients with Seronegative RA Have More Inflammatory Activity Compared with Patients with Seropositive RA in an Inception Cohort of DMARD-naive Patients Classified According to the 2010 ACR/EULAR Criteria 270

9. EULAR Definition of Arthralgia Suspicious for Progression to Rheumatoid Arthritis 271

10. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II 272

11. Co-occurrence and Characteristics of Patients with Axial Spondyloarthritis Who Meet Criteria for Fibromyalgia: Results from a UK National Register 274

12. A Cross-sectional Study of Cardiovascular Involvement in Systemic Lupus Erythematosus in an Urban Indian Tertiary Care Centre with Emphasis on 2-D Echocardiography 275

13. Pulmonary and Ear, Nose and Throat (ENT) Involvement in ANCA-associated Vasculitis at Diagnosis-Experience from a Tertiary Care Centre in North India 276

14. Etiology and Outcomes of Lower Limb Ulcers in Non-diabetic Patients, An Experience from Government Hospital in Western India 278

15. Effect of Disease-modifying Antirheumatic Drug Therapy on Immune Response to Trivalent Influenza Vaccine in Rheumatoid Arthritis 279

16. Clinical Experience with Two Etanercept Biosimilars in Indian Patients with Spondyloarthritis 280

17. Assessment of Extent of Skin Involvement in Scleroderma using Shear Wave Elastography 281

Index *287*

Section 3: Diabetes and Metabolic Disorders

Section Editor: Siddharth N Shah

Associate Editors: Mangesh Tiwaskar, Naveen Mittal, Ragini M Rohatgi

ARTICLE 1

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum

Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum.
Thyroid. 2017;27(3):315-89.

Abstract*

Background and Methods: Thyroid disease is common during pregnancy. The American Thyroid Association (ATA) published the first guidelines in 2011 regarding the management of these patients. Ever since significant changes in the approach to management and diagnosis have happened and so these new ATA 2017 guidelines are being published.

The American College of Physicians guideline grading system was used for collection of evidence and for making recommendations. The task force was not influenced by the ATA and had complete independence. The conflict of interest of task force was regularly monitored. The members of the panel thoroughly went through electronic database searching and review techniques, selection of citations and critical evaluation of the studies published in Indian literature. Thus all due precautions were taken.

Results: Guidelines give recommendations about how to interpret thyroid function tests during pregnancy, issues of thyroid disease infertile women and during pregnancy. Role of iodine in diet is mentioned. Significance of thyroid antibodies, thyroid nodules is mentioned. They also address issues of thyroid nodules, thyrotoxicosis and cancer during pregnancy. Effect of thyroid disease on fetal and neonatal outcomes and on lactation are discussed.

Conclusion: Evidence-based recommendations have been made regarding thyroid disorders during pregnancy and postpartum period. They provide general guidelines although care will have to be individualized for each patient.

"Pregnancy with thyroid dysfunction: At what level of thyroid stimulating hormone (TSH) should thyroxin be started and what should be target TSH?"

COMMENT

The aim of these guidelines is to inform clinicians, patients, researchers, and health policy makers on published evidence relating to the diagnosis and management of thyroid disease in women during pregnancy, preconception and the postpartum period.

Salient Features of These Guidelines

There is a downward shift of the thyroid-stimulating hormone (TSH) reference range during pregnancy, due to elevated levels of serum human chorionic gonadotropin (hCG), which stimulates TSH receptor directly, and hence increases thyroid

*Redrafted abstract

JAYPEE BROTHERS

hormone production. In the first trimester, the lower reference range of TSH can be reduced by approximately 0.4 mU/L, while the upper reference range is reduced by approximately 0.5 mU/L. For the typical patient in early pregnancy, this corresponds to a TSH upper reference limit of 4.0 mU/L.

Euthyroid but antithyroid peroxidase (anti-TPO) antibody, or thyroglobulin (TG) antibody positive pregnant women, should get serum TSH at the time of pregnancy confirmation, and every 4 weeks throughout mid-pregnancy.

Subclinical hypothyroidism in pregnancy should be approached as follows:

- Levothyroxine (LT4) treatment is recommended for:
  - TSH >4.0 mU/L
  - TSH between 2.5 and 4.0, but anti-TPO positive.
- Levothyroxine therapy is not recommended for:
  - TPO antibody negative women with normal TSH (TSH <4.0 mU/L)
- While treating hypothyroidism in pregnant patients, target TSH should be maintained below 2.5 mU/L
- During monitoring the therapy, serum TSH should be measured every 4 weeks until mid-gestation and at least once near 30 weeks of gestation.

A nonpregnant, hypothyroid patient receiving LT4 treatment with a suspected or confirmed pregnancy (e.g., positive home pregnancy test) should herself increase the dose of LT4 by 20–30%. One means of doing this is to administer 2 additional tablets weekly of patient's current daily LT4 dosage.

After delivery, dose of LT4 should be reduced to preconceptional level. Additional thyroid function should be performed at 6 weeks post-partum.

For hyperthyroidism in pregnancy, propylthiouracil (PTU) should be used in first trimester. After 16 weeks, either PTU or methamizole may be used. Antithyroid medicines should be administered at the lowest effective dose, targeting maternal serum free T4 or total T4 at or moderately above the reference range.

Radionucleotide scanning is absolutely contraindicated during pregnancy.

During lactation, both LT4 and antithyroid drugs if required can be used safely.

In summary, these guidelines are really helpful in managing the patient of thyroid disorder during pregnancy.

Key Messages

- ***Levothyroxine (LT4) treatment is recommended for:***
  - ***TSH >4.0 mU/L***
  - ***TSH between 2.5 and 4.0, but anti-TPO positive***
- ***Target TSH should be below 2.5 mU/L while treating hypothyroidism.***

ARTICLE 2

A Systematic Review of Known Interventions for the Treatment of Chronic Non-hypovolaemic Hypotonic Hyponatraemia and a Meta-analysis of the Vaptans

Bhandari S, Peri A, Cranston I, et al. A systematic review of known interventions for the treatment of chronic nonhypovolaemic hypotonic hyponatraemia and a meta-analysis of the vaptans.
Clin Endocrinol (Oxf). 2017;86(6):761-71.

Abstract

International and national guidelines on the treatment of chronic nonhypovolemic hypotonic hyponatremia differ; therefore, we have undertaken this systematic review and meta-analysis to investigate the efficacy and

JAYPEE BROTHERS

safety of interventions for the treatment of chronic nonhypovolemic hypotonic hyponatremia. Following registration of the review protocol with PROSPERO, systematic literature searches were conducted to identify randomized and quasi-randomized controlled trials (RCTs) assessing any degree of fluid restriction or any drug treatment with the aim of increasing serum sodium concentration in patients with chronic nonhypovolemic hypotonic hyponatremia. Where appropriate, outcome data were synthesized in a meta-analysis. 45,716 bibliographic records were identified from the searches and 18 trials (assessing conivaptan, lixivaptan, tolvaptan and satavaptan) met the eligibility criteria. Results suggest that all four vasopressin receptor agonists ("vaptans"), significantly improve serum sodium concentration. Lixivaptan, satavaptan and tolvaptan were associated with greater rates of response versus placebo. There was no evidence of a difference between each of the vaptans compared with placebo for mortality, discontinuation and rates of hypernatremia.

No RCT evidence of treatments other than the vaptans for hyponatremia such as oral urea, salt tablets, mannitol, loop diuretics demeclocycline or lithium was identified. Vaptans demonstrated superiority over placebo for outcomes relating to serum sodium correction. Few trials documented the potential benefit of vaptans on change in health-related quality of life as a result of treatment. There was also a lack of high-quality RCT evidence on the comparative efficacy of the vaptans and other treatment strategies for the treatment of chronic nonhypovolemic hypotonic hyponatremia.

Conclusion: Atorvastatin-induced changes in inflammatory biomarkers did not confer mortality benefit in septic shock.

"What is the best treatment for chronic nonhypovolemic hyponatremia?"

COMMENT

Hyponatremia, i.e., serum sodium (S. Na^+) concentration <135 mmol/L, is the most common disorder of fluid and electrolyte imbalance. It could be iatrogenic or noniatrogenic. The most common noniatrogenic cause of nonhypovolemic hypotonic hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Nonhypovolemic hyponatremia is not a single diagnosis but, a combination of a very heterogeneous group of clinical circumstances with variable clinical outcome depending on the etiology. Chronic nonhypovolemic hypotonic hyponatremia was defined as the presence of three criteria:

- Hyponatremia >48 hours
- Serum osmolality <280 mOsm/kg
- Serum sodium concentration <135 mmol/L.

Chronic nonhypovolemic hypotonic hyponatremia is a frequent critical clinical scenario in hospitalized patients. But international and national guidelines differ on the treatment algorithms. Generally fluid restriction is a reflex action as a primary step in management, but in milieu of poor indication of fluid restriction, guidelines diverge on optimal second line therapeutic option. Hence this peer reviewed unpublished article attempted this systematic review and meta-analysis to investigate and scrutinize the efficacy and safety of interventions for the treatment of chronic nonhypovolemic hypotonic hyponatremia. Systematic literature searches were conducted to identify randomized and quasi-randomized controlled trials (RCTs) assessing any degree of fluid restriction or any drug treatment with the aim of increasing serum sodium concentration in patients with chronic nonhypovolemic hypotonic hyponatremia. 45,716 bibliographic records and 18 vaptan trials (assessing conivaptan, lixivaptan, tolvaptan, and satavaptan) met the eligibility criteria. Searches were conducted in MEDLINE, Embase, PubMed, Cochrane Library, Science Citation Index, World Health Organization International Clinical Trials Registry Platform, Selected Conference proceedings and website clinicaltrials.gov.

Take away points in the above paper:

- Treatment depends on the underlying cause
- Be prudent to avoid too rapid correction of sodium which my lead to osmotic demyelination syndrome or central pontine myelinolysis (CPM) which carries a grave prognosis and is utterly avoidable

JAYPEE BROTHERS

- The main goal of therapy for moderate to severe hyponatremia is to reliably increase the S. Na^+ concentration and safely minimize the risk of CPM
- Fluid restriction generally is a cardinal step
- Vaptans are the recent popular choice of therapy, which endeavor V2 receptor blocked in kidneys culminating facilitated aquaresis restoring Na^+ levels
- RCTs revealed all 4 vasopressin receptor agonists (vaptans) significantly improved S. Na^+ concentration
- Currently only tolvaptan is available for the oral use globally
- National guidelines suggest tolvaptan as second line option; especially in SIADH; after fluid restriction, but many endocrine, nephrology and critical care guidelines differ on this
- Currently, tolvaptan has Eropean approval for the treatment of hyponatremia secondary to SIADH and United States approval for clinically significant nonhypovolemic hyponatremia (S. Na^+ <125 mEq/L or less)
- Rapider increase in serum Na^+ levels was demonstrated in pooled analysis of tolvaptan treated patients – be vigilant for CPM
- Satavaptan was withdrawn from the European Medicines Agency in 2008
- Lixivaptan is not licensed and conivaptan (IV) is approved for the treatment of euvolemic hyponatremia in hospitalized patients only in the United States
- Alternative treatment strategies include oral urea, salt tablets, mannitol, loop diuretics, and lithium, etc.

To wrap up, vaptans have the adequate evidence base for the management of non-hypovolemic hyponatraemia. They have been delineated to improve Na^+ levels in comparison to placebo arm. More RCTs are required to determine the comparative efficacy of vaptans, fluid restriction and the other treatments. Tolvaptan is the only oral therapeutic pharmacological option for treatment of nonhypovolemic hypotonic hyponatremia. Be smartly alert and monitor for complications especially CPM.

Key Messages

- ***Fluid restriction is the cardinal step***
- ***Vaptans (tolvaptan, satavaptan, lixiviptan, conivaptan) have demonstrated superiority over placebo.***

ARTICLE 3

Bariatric Surgery versus Intensive Medical Therapy for Diabetes—5-year Outcomes

Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. ***N Engl J Med. 2017;376(7):641-51.***

Abstract

Background: Long-term results from randomized, controlled trials that compare medical therapy with surgical therapy in patients with type 2 diabetes are limited.

Methods: We assessed outcomes 5 years after 150 patients who had type 2 diabetes and a body mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 27 to 43 were randomly assigned to receive intensive medical therapy alone or intensive medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The primary outcome was a glycosylated hemoglobin level of 6.0% or less with or without the use of diabetes medications.

Results: Of the 150 patients who underwent randomization, 1 patient died during the 5-year follow-up period; 134 of the remaining 149 patients (90%) completed 5 years of follow-up. At baseline, the mean (±SD) age of the 134 patients was 49 ± 8 years, 66% were women, the mean glycosylated hemoglobin level

JAYPEE BROTHERS

was 9.2 ± 1.5%, and the mean BMI was 37 ± 3.5. At 5 years, the criterion for the primary end point was met by 2 of 38 patients (5%) who received medical therapy alone, as compared with 14 of 49 patients (29%) who underwent gastric bypass (unadjusted p = 0.01, adjusted p = 0.03, p = 0.08 in the intention to-treat analysis) and 11 of 47 patients (23%) who underwent sleeve gastrectomy (unadjusted p = 0.03, adjusted P = 0.07, p = 0.17 in the intention-to-treat analysis). Patients who underwent surgical procedures had a greater mean percentage reduction from baseline in glycosylated hemoglobin level than did patients who received medical therapy alone (2.1% vs. 0.3%, p = 0.003). At 5 years, changes from baseline observed in the gastric-bypass and sleeve-gastrectomy groups were superior to the changes seen in the medical-therapy group with respect to body weight (−23%, −19%, and −5% in the gastric-bypass, sleeve gastrectomy, and medical-therapy groups, respectively), triglyceride level (−40%, −29%, and −8%), high-density lipoprotein cholesterol level (32%, 30%, and 7%), use of insulin (−35%, −34%, and −13%), and quality-of-life measures (general health score increases of 17, 16, and 0.3; scores on the RAND 36-Item health survey ranged from 0 to 100, with higher scores indicating better health) (p <0.05 for all comparisons). No major late surgical complications were reported except for one reoperation.

Conclusion: Five-year outcome data showed that, among patients with type 2 diabetes and a BMI of 27 to 43, bariatric surgery plus intensive medical therapy was more effective than intensive medical therapy alone in decreasing, or in some cases resolving, hyperglycemia.

"In obese type 2 diabetes patients which is better: Intensive medical treatment or surgery plus intensive medical treatment?"

COMMENT

The world is confronting with epidemic incidence of obesity and diabetes mellitus—especially type 2 diabetes mellitus (T2DM) encompassing the unsurmountable population and the onslaught is relentlessly increasing. The rise in the prevalence of obesity is associated with increases in the prevalence of obesity comorbidities and increasing morbidity and mortality. These comorbidities are responsible for more than 2.5 million deaths per year worldwide. Bariatric surgery, in recent years, has become a very popular therapeutic intervention along with medical therapy to curb this assault of obesity and T2DM. This article reviews the potency of bariatric surgery against the intensive medical therapy (IMT); over the last 5 years; in achieving the excellent glycemic control.

Observational studies and short term randomized controlled trials (RCTs) have exhibited that bariatric surgery, when used specifically to treat diabetes, significantly ameliorates glycemic control and reduces cardiovascular risk factors. Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial avow gastric bypass (GB) and sleeve gastrectomy were superior to IMT alone in achieving excellent glycemic control (i.e., HbA1c ≤6.0%), reducing cardiovascular (CV) risk, improving quality of life (QoL), and decreasing medication use.

The current article provides results of the final, 5-year follow-up, analyses from that trial and attempts to address questions regarding the relative long-term efficacy and safety of bariatric surgery and its effects on diabetes-related end-organ disease. This trial was a 3-group IMT only, IMT + GB, IMT + SG (sleeve gastrectomy) trial randomized, controlled, nonblinded, single centre study of 150 obese (BMI of 27–43) patients having T2DM. The effects of IMT only were compared with IMT + GB and IMT + SG after 1:1:1 randomization depending on baseline insulin use.

Key observation:

- Sixteen patients could not complete trial (9 dropped out at start, 6 lost follow-ups and 1 died)
- Five percent in IMT arm vs. 29% in IMT + GB vs. 23% IMT + SB achieved HbA1c <6% (bariatric superior)
- Most of the patients in IMT + GB or IMT + SG group were either off antidiabetic medications or on minimum antidiabetics at the end of 5 years (bariatric superior)
- The decreases from baseline in median fasting plasma glucose levels were greater in the

JAYPEE BROTHERS

two surgical groups than in the IMT group (bariatric superior)
- There was rapid, larger and more sustained reduction in glycemic markers (HbA1c and FPG) and BMI in surgical intervention groups versus IMT (bariatric superior)
- Reduction in BMI in surgical intervention groups were similar in patients with BMI <35 or >35
- The use of glucose lowering drugs (GLDs) including insulin and cardiovascular drugs went down significantly in surgical group (required few or no medication) in comparison to IMT group (bariatric superior)
- Percentage of patients NOT taking GLDs was higher in IMT + GB group vs. IMT + SG Group (bariatric-gastric bypass superior)
- 89% in surgical group were off insulin maintaining HbA1c <7% at the end of 5 years (bariatric superior)
- Weight loss was significantly higher and sustained in surgical intervention group (bariatric superior)
- Better lipid profile (low triglycerides and increased HDL from baseline) was observed in surgical group (bariatric superior)
- No difference in blood pressure or LDL levels were observed in all three arms (bariatric neutral)
- Urinary albumin creatinine ratio (UACR) decreased significantly over 5 years in IMT + SG group (bariatric superior)
- Quality of life score was much superior in surgical intervention group vs. IMT only (bariatric superior).

To consummate, STAMPEDE study has stamped the authoritative superiority on the glycemic and nonglycemic outcomes at the end of 5 years over IMT only therapy while managing obese T2DM patients. Bariatric surgery can be considered as an effective option for long term benefits in terms of sustained glycemic control, weight reduction, CV risk reduction, renal well-being, reduced or no need of GLDs and better QoL in comparison with intensive medical therapy only.

Key Message

- ***Bariatric surgery can be considered as an effective option for long-term benefits in terms of sustained glycemic control, weight reduction, CV risk reduction, renal wellbeing, reduced or no need of glucose lowering drugs, and better quality of life in comparison with intensive medical therapy only.***

ARTICLE 4

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. ***N Engl J Med. 2017;377(7):644-57.***

Abstract

Background: Canagliflozin is a sodium–glucose cotransporter 2 inhibitor that reduces glycemia as well as blood pressure, body weight, and albuminuria in people with diabetes. We report the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes.

Methods: The Canagliflozin Cardiovascular Assessment Study (CANVAS) program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

JAYPEE BROTHERS

Results: The mean age of the participants was 63.3 years, 35.8% were women, the mean duration of diabetes was 13.5 years, and 65.6% had a history of cardiovascular disease. The rate of the primary outcome was lower with canagliflozin than with placebo [occurring in 26.9 vs. 31.5 participants per 1,000 patient-years; hazard ratio, 0.86; 95% confidence interval (CI), 0.75–0.97; p <0.001 for noninferiority; p = 0.02 for superiority). Although on the basis of the prespecified hypothesis testing sequence the renal outcomes are not viewed as statistically significant, the results showed a possible benefit of canagliflozin with respect to the progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77). Adverse reactions were consistent with the previously reported risks associated with canagliflozin except for an increased risk of amputation (6.3 vs. 3.4 participants per 1,000 patient-years; hazard ratio, 1.97; 95% CI, 1.41–2.75); amputations were primarily at the level of the toe or metatarsal.

Conclusion: In two trials involving patients with type 2 diabetes and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal.

"What is the effect of canagliflozin on cardiovascular and renal outcome in type 2 diabetes?"

COMMENT

The present trial was conducted on integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. In two trials patients with type 2 diabetes and established cardiovascular disease or at high risk for cardiovascular events who were treated with canagliflozin had significantly lower rates of the primary cardiovascular outcome than patients assigned to placebo. The results also showed that patients treated with canagliflozin had a lower risk of hospitalization for heart failure, progression of albuminuria, and substantive loss of kidney function than patients who received placebo, although on the basis of the prespecified hypothesis testing sequence these findings are not considered statistically significant. The favorable direction of effect with respect to stroke observed in this trial program differs from a previously reported possible adverse effect on stroke risk.[1,2] The adverse effects observed in this program of two integrated trials are generally consistent with the known safety profile of canagliflozin and other sodium–glucose cotransporter 2 inhibitor (SGLT2) inhibitors.[1] The increased rate of amputation is a new finding for which the mechanism is unknown, and care is warranted in the use of canagliflozin in patients at risk for amputation. An increase in bone fractures has been described previously with canagliflozin,[3] but the excess in bone fracture seen in Canagliflozin Cardiovascular Assessment Study (CANVAS) was not observed in CANVAS-R. There is no clear explanation for the difference in fracture risk between the two trials, which included directly comparable patient groups and assessed the same intervention.

In short, the trial program showed that among patients with type 2 diabetes who had an increased risk of cardiovascular disease, patients treated with canagliflozin had a significantly lower risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than those who received placebo but a greater risk of amputation, with unknown mechanism.

Key Message

- ***Patients treated with canagliflozin had a significantly lower risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke but a greater risk of amputation.***

JAYPEE BROTHERS

ARTICLE 5

Clinical Efficacy and Safety of Achieving Very Low LDL-cholesterol Concentrations with the PCSK9 Inhibitor Evolocumab: A Prespecified Secondary Analysis of the FOURIER trial

Li X, Wang Y, Guan Q, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: A prespecified secondary analysis of the FOURIER trial.
Lancet. 2017;390:1962-71.

Abstract

Background: The low-density lipoprotein (LDL) cholesterol is a well-established risk factor for atherosclerotic cardiovascular disease (CVD). How much one should or safely can lower this risk factor remains debated. We aimed to explore the relationship between progressively lower LDL-cholesterol concentrations achieved at 4 weeks and clinical efficacy and safety in the FOURIER trial of evolocumab, a monoclonal antibody to proprotein convertase subtilisin-kexin type 9 (PCSK9).

Methods: In this prespecified secondary analysis of 25,982 patients from the randomized FOURIER trial, the relationship between achieved LDL-cholesterol concentration at 4 weeks and subsequent cardiovascular outcomes (primary endpoint was the composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or unstable angina; key secondary endpoint was the composite of cardiovascular death, myocardial infarction, or stroke) and ten prespecified safety events of interest was examined over a median of 2.2 years of follow-up. We used multivariable modeling to adjust for baseline factors associated with achieved LDL-cholesterol.

Findings: Between February 8, 2013, and June 5, 2015, 27,564 patients were randomly assigned a treatment in the FOURIER study. A total of 1,025 (4%) patients did not have an LDL cholesterol measured at 4 weeks and 557 (2%) had already had a primary endpoint event or one of the ten prespecified safety events before the week-4 visit. From the remaining 25,982 patients (94% of those randomly assigned) 13,013 were assigned evolocumab and 12,969 were assigned placebo. A total of 2,669 (10%) of 25,982 patients achieved LDL-cholesterol concentrations of less than 0.5 mmol/L, 8,003 (31%) patients achieved concentrations between 0.5 and less than 1.3 mmol/L, 3,444 (13%) patients achieved concentrations between 1.3 and less than 1.8 mmol/L, 7,471 (29%) patients achieved concentrations between 1.8 to less than 2.6 mmol/L, and 4,395 (17%) patients achieved concentrations of 2.6 mmol/L or higher. There was a highly significant monotonic relationship between low LDL-cholesterol concentrations and lower risk of the primary and secondary efficacy composite endpoints extending to the bottom first percentile (LDL-cholesterol concentrations of less than 0.2 mmol/L; $p = 0.0012$ for the primary endpoint, $p = 0.0001$ for the secondary endpoint). Conversely, no significant association was observed between achieved LDL cholesterol and safety outcomes, either for all serious adverse events or any of the other nine prespecified safety events.

Interpretation: There was a monotonic relationship between achieved LDL-cholesterol and major cardiovascular outcomes down to LDL-cholesterol concentrations of less than 0.2 mmol/L. Conversely, there were no safety concerns with very low LDL-cholesterol concentrations over a median of 2.2 years. These data support further LDL-cholesterol lowering in patients with CVD to well below current recommendations.

"What is the cardiovascular outcome with lowering of low density lipoprotein to <0.1 mmol/L with PCSK?"

COMMENT

In this prespecified secondary analysis of 25,982 patients from the randomized FOURIER trial, in an analysis of over 25,000 patients with atherosclerotic cardiovascular disease (ASCVD), we found a strong relationship between on-treatment low-density lipoprotein (LDL) cholesterol concentration and

JAYPEE BROTHERS

major cardiovascular outcomes. Conversely, there was no significant association between LDL-cholesterol concentrations and prespecified adverse events in patients followed up for a median of 2.2 years.

First, subgroup analyses from clinical trials have showed consistent benefit with LDL-cholesterol lowering therapy even in subgroups with the lowest baseline concentrations of LDL-cholesterol. Specifically, in the Cholesterol Treatment Trialists Collaboration, the clinical benefit of LDL-cholesterol lowering with statins was consistent even in patients whose baseline LDL-cholesterol concentration was <2 mmol/L, in whom statin therapy lowered LDL-cholesterol concentrations to less than approximately 1.6 mmol/L.[4,5] Likewise, in the JUPITER trial of primary prevention, there was a consistent clinical benefit with rosuvastatin even in patients starting with an LDL-cholesterol concentration of less than 1.6 mmol/L, in whom rosuvastatin lowered LDL-cholesterol concentrations to less than approximately 0.8 mmol/L. After extending the data to unprecedented low concentrations of LDL cholesterol, with the lowest prespecified group (2,669 patients) with an on-treatment LDL-cholesterol concentration of less than 0.5 mmol/L, a median LDL cholesterol of 0.36 mmol/L, and a quarter of that subgroup with an LDL-cholesterol concentration of less than 0.28 mmol/L, and an exploratory subgroup of 504 patients with an on-treatment LDL cholesterol of less than 0.26 mmol/L (median 0.18 mmol/L). The major limitations of this analysis were the absence of randomization to on-treatment LDL-cholesterol concentrations (patients were classified based on postrandomization measurement of LDL cholesterol), a median follow-up of 2.2 years, and low frequency of some safety events.

In summary, LDL-cholesterol can now be reduced to unprecedented low levels with statin + PCSK9i (<1 mM), a strong linear relationship of achieved LDL-cholesterol and CV events seen, down to an LDL and no excess in safety events with very low achieved LDL-cholesterol. Thus, these data suggest that we should target considerably lower LDL-cholesterol than is currently recommended for our patients with ASCVD. Hope the FOURIER trial will pave the way for recommending lower LDL-cholesterol as the target for prevention of ASCVD.

Key Messages

- ***Low-density lipoprotein (LDL)-cholesterol can now be reduced to low levels with statin + PCSK9i (<1 mM), a strong linear relationship of achieved LDL-cholesterol and CV events is seen***
- ***No safety concerns with very low LDL-cholesterol concentration.***

ARTICLE 6

Clinical Outcomes of Metformin Use in Populations with Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review

Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: A systematic review.
Ann Intern Med. 2017;166(3):191-200.

Abstract*

Background and Methods: The study was done to look at use of metformin in patients with type II diabetes and moderate to severe chronic kidney disease (CKD), congestive heart failure (CHF), and chronic liver disease (CLD) due to recent changes in FDA warning for use of metformin which is going to increase its usage.

***Redrafted abstract**

JAYPEE BROTHERS

MEDLINE (via PubMed) search, Cochrane library, EMBASE and international pharmaceutical abstracts were assessed from 1994 to 2015–16. Patients of CKD with eGFR <60 mL/min/1.73 m^2, CHF, CLD who received metformin and those who did not were evaluated for all-cause mortality and major adverse cardiovascular events (MACE) and other outcomes.

Results: 17 observational studies were evaluated and showed that metformin use was associated with reduce all-cause mortality in patients with CKD, CHF, and CLD. Also, there was reduction in admissions for heart failure in patients with CKD and CHF.

Conclusion: Metformin use was associated with improvement in most clinical outcomes in patients with CKD, CHF, and CLD. These findings support the recent change in metformin labeling for indications.

"Can metfromin be used in patients with chronic kidney disease, congestive heart failure, or chronic liver disease?"

COMMENT

Metformin has been recommended as initial treatment for type 2 diabetes mellitus after life style modification all over the world. The FDA applied a boxed warning to metformin concurrent with its approval. This warning cautioned against using metformin in the setting of chronic kidney disease (CKD),which may impair excretion of the drug, and recommended caution in patients with conditions that may promote lactate accumulation [such as congestive heart failure (CHF) and chronic liver disease (CLD)] with impaired hepatic function. In 2006, the Food and Drug Administration (FDA) removed CHF as a contraindication to metformin use, although acute or unstable CHF remains a precaution. In April 2016, the FDA revised its warning regarding metformin use in patients with CKD, switching from a serum creatinine-based definition of renal impairment to more inclusive criteria based on estimated glomerular filtration rate (eGFR). Severe CKD (eGFR, <30 mL/min/1.73 m^2) remains a contraindication for metformin.

This analysis adds to existing knowledge about metformin's effects on mortality outcomes. On the basis of a meta-analysis of 35 randomized, controlled trials (RCTs) reported through October 2009, Lamanna and colleagues concluded that metformin monotherapy is associated with improved survival. In a subsequent analysis of 6 RCTs and 8 observational studies reported between April 2009 and April 2015, Bolen and colleagues found lower cardiovascular mortality with metformin versus sulfonylurea therapy (risk difference, 0.1% to 2.9% in RCTs). In contrast, Palmer et al. conducted a network meta-analysis of 25 comparative monotherapy studies reported through March 2016 and found that cardiovascular mortality did not differ between diabetes medication classes, including metformin and this study analysis included only 67 total cardiovascular deaths. The review differs from these analyses in that they focused on diabetes populations with historical metformin contraindications or precautions. Consequently, they analyzed observational studies with longer follow-ups, which in some ways are better suited for examining outcomes that require long-term observation (such as mortality). The findings are consistent with those of Eurich and colleagues, who found that metformin use is associated with reduced mortality in CHF; their analysis included 3 additional studies (n = 6,514) and excluded another study without an active comparator. Beyond providing information for prescribers, this review may help inform revision of clinical guidelines because diabetes medication classes have varying effects on cardiovascular outcomes. Additional research comparing metformin with specific alternative agents in populations with historical contraindications or precautions would help refine prescribing guidelines. On the basis of limited evidence, metformin is associated with reduced all-cause mortality in patients with moderate CKD, CHF, or CLD with impaired hepatic function. Available data provide no evidence that the risks associated with metformin exceed those of other antihyperglycemic medications in these populations.

In conclusion, metformin remains the drug of choice for reducing the insulin resistance and

JAYPEE BROTHERS

novel properties of avoiding weight gain and hypoglycemia and other pleiotropic effects. The drug has stood the test of time and still remains the first drug of choice and can be combined effectively with all available oral hypoglycemic agents and insulin.

Key Message

- ***Metformin is associated with reduced all-cause mortality in patients with moderate CKD, CHF, or CLD.***

ARTICLE 7

Cardiovascular Mortality and Morbidity in Patients with Type 2 Diabetes following Initiation of Sodium-glucose Co-transporter-2 Inhibitors versus Other Glucose-lowering Drugs (CVD-REAL Nordic): A Multinational Observational Analysis

Birkeland K, Jørgensen ME, Carstensen B, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): A multinational observational analysis.
Lancet Diabetes Endocrinol. 2017;5(9):709-17.

Abstract

Background: In patients with type 2 diabetes and a high cardiovascular risk profile, the sodium–glucose co-transporter-2 (SGLT2) inhibitors empagliflozin and canagliflozin have been shown to lower cardiovascular morbidity and mortality. Using real-world data from clinical practice, we aimed to compare cardiovascular mortality and morbidity in new users of SGLT2 inhibitors versus new users of other glucose-lowering drugs, in a population with a broad cardiovascular risk profile.

Methods: CVD-REAL Nordic was an observational analysis of individual patient-level data from the Prescribed Drug Registers, Cause of Death Registers, and National Patient Registers in Denmark, Norway, and Sweden. All patients who filled a prescription for glucose-lowering drugs between 2012 and 2015 were included and followed up until Dec 31, 2015. Patients were divided into new users of SGLT2 inhibitors and new users of other glucose-lowering drugs. Each SGLT2 inhibitor user was matched with three users of other glucose-lowering drugs by use of propensity scores. Hazard ratios (HRs) were estimated by country (Cox survival model) and weighted averages were calculated. Cardiovascular outcomes investigated were cardiovascular mortality, major adverse cardiovascular events (cardiovascular mortality, myocardial infarction, and ischemic or hemorrhagic stroke), hospital events for heart failure (inpatient or outpatient visit with a primary diagnosis of heart failure), nonfatal myocardial infarction, nonfatal stroke, and atrial fibrillation. We also assessed incidence of severe hypoglycemia.

Findings: Matched SGLT2 inhibitor (n = 22,830) and other glucose-lowering drug (n = 68,490) groups were well balanced at baseline, with a mean follow-up of 0.9 (SD 4.1) years (80,669 patient-years) and mean age of 61 (12.0) years; 40% (36,362 of 91,320) were women and prevalence of CVD was 25% (22,686 of 91,320). 94% of the total SGLT2 inhibitor exposure time was for use of dapagliflozin, with 5% for empagliflozin, and 1% for canagliflozin. Compared with other glucose-lowering drugs, use of SGLT2 inhibitors was associated with decreased risk of cardiovascular mortality [HR 0.53 (95% CI 0.40–0.71)], major adverse cardiovascular events [0.78 (0.69–0.87)], and hospital events for heart failure [0.70 (0.61–0.81); p <0.0001 for all). We did not identify significant differences between use of SGLT2 inhibitors and use of other glucose-lowering drugs for nonfatal myocardial infarction, nonfatal stroke, or atrial fibrillation. Compared with other glucose-lowering drugs, use of SGLT2 inhibitors was associated with a decreased risk of severe hypoglycemia (HR 0.76 [0.65–0.90]; p = 0.001). For cardiovascular mortality, the differences were similar for the 25% of individuals with CVD at baseline and those without (HR 0.60 [0.42–0.85] vs. 0.55 [0.34–0.90]), while for major adverse

JAYPEE BROTHERS

cardiovascular events the HR in the group with CVD at baseline was 0.70 (0.59–0.83) versus 0.90 (0.76–1.07) in the group without.

Interpretation: In a population of patients with type 2 diabetes and a broad cardiovascular risk profile, SGLT2 inhibitor use was associated with reduced CVD and cardiovascular mortality compared with use of other glucose-lowering drugs—a finding consistent with the results of clinical trials in patients at high cardiovascular risk.

"In real world (not in randomized controlled trial), what is the effect of SGLT2 inhibitors on cardiovascular morbidity and mortality in type 2 diabetes?"

COMMENT

In patients with type 2 diabetes and a high cardiovascular risk profile, the sodium glucose co-transporter-2 (SGLT2) inhibitors empagliflozin and canagliflozin have been shown to lower cardiovascular mortality and morbidity in new users of SGLT2 inhibitors versus new users of other glucose-lowering drugs, in a population with a broad cardiovascular risk profile.

CVD-REAL, Nordic was an observational analysis of individual patient-level data from the prescribed Drug Registers, Cause of Death Registers, and National Patient Registers in Denmark, Norway, and Sweden. All patients who filled a prescription for glucose-lowering drugs between 2012 and 2015 were included and followed up until December 31, 2015. Cardiovascular outcomes investigated were cardiovascular mortality, major adverse cardiovascular events.

Matched SGLT2 inhibitor and other glucose-lowering drug groups were well balanced at baseline, with a mean follow up of 0.9 years and mean age of 61 years, 40% were women and prevalence of cardiovascular disease was 25%. Ninety four percent of the total SGLT2 inhibitor exposure time was for use of dapagliflozin with 5% for empagliflozin and 1% for canagliflozin. Compared with other glucose lowering drugs use of SGLT2 inhibitors was associated with decreased risk of cardiovascular mortality and severe hypoglycemia.

In a population of patients with type 2 diabetes and a broad cardiovascular risk profile, SGLT2 inhibitor use was associated with reduced cardiovascular disease and cardiovascular mortality compared with use of other glucose-lowering—a finding consistent with the results of clinical trials in patients at high cardiovascular risk.

Key Message

- ***SGLT2 inhibitor use was associated with reduced cardiovascular disease and cardiovascular mortality compared with use of other glucose lowering—a finding consistent with the results of clinical trials in patients at high cardiovascular risk.***

ARTICLE 8

Diabetic Foot Ulcers and Their Recurrence

Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence.
N Engl J Med. 2017;376(24):2367-75.

Abstract*

Diabetic foot ulcers are common and management involves significant cost. Annual incidence was found to be 2.2% in a community study from UK. In others, like US Veterans this is 5% and in the global population

***Redrafted abstract**

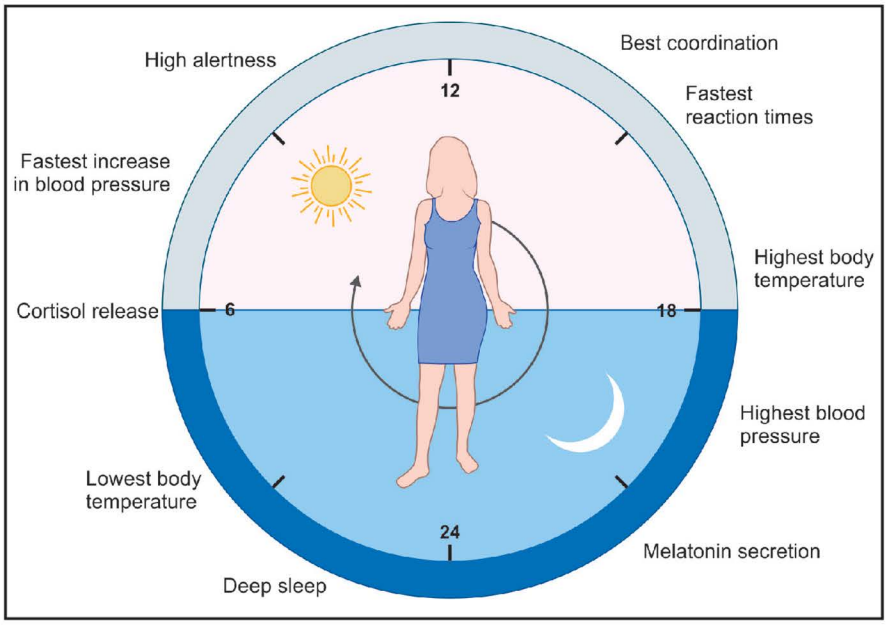
JAYPEE BROTHERS

for detailed information on medicine books, visit our website **www.jaypeebrothers.com,** for detailed information on medicin

Year Book of
MEDICINE 2018

The Nobel Prize in Physiology or Medicine 2017

The Nobel Prize in Physiology or Medicine 2017 was awarded jointly to **Jeffrey C Hall**, New York City, USA; **Michael Rosbash**, Kansas City, Missouri, USA; **Michael W Young**, Miami, Florida, USA, "for their discoveries of molecular mechanisms controlling the circadian rhythm".



The circadian clock anticipates and adapts our physiology to the different phases of the day.

Available at all medical bookstores
or buy online at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com
Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
MEDICINE
ISBN 978-93-5270-511-5