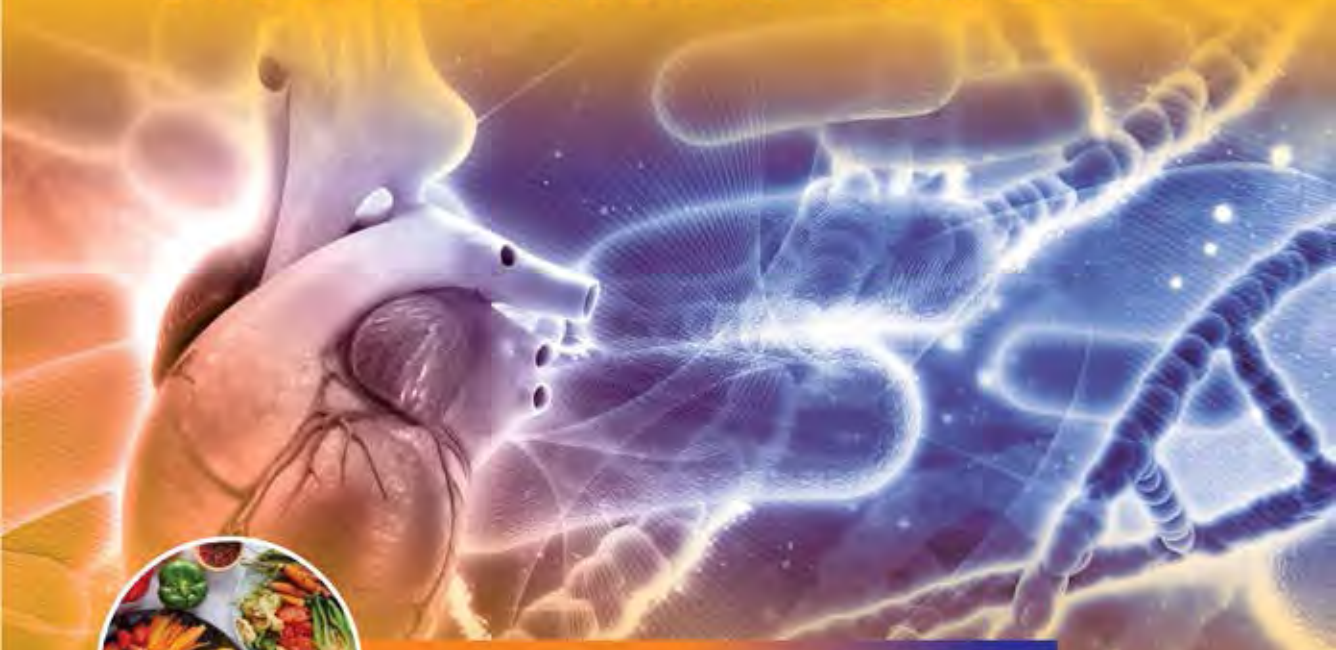
Integrated Society of CDEE & CC

Cardiometabolic Medicine 2022



Editor-in-Chief
PC Manoria

Forewords
Navin C Nanda
Enas A Enas
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Evangel

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CARDIOMETABOLIC MEDICINE

2022

Editor-in-Chief

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Forewords

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New Delhi | Mumbai | Bengaluru | Hyderabad
INDIA

Evangel

Evangel Publishing

277, Second Floor, Aggarwal Millennium Tower II
Netaji Subhash Place, Pitam Pura
New Delhi-110034, India
Phone: +91-11-42637878
Email: info@evangelpublications.com

Website: *www.evangelpublications.com*

ISBN: 978-93-90616-47-3

Printed and distributed by EVANGEL PUBLISHING

Printed in India

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Foreword

The book "Cardiometabolic Medicine 2022" is edited by none other than Dr Prof PC Manoria who is the Director of Manoria Heart and Critical Care Hospital in Bhopal, Madhya Pradesh, India. He has served as the National President of several prestigious medical organizations in India, including the Cardiological Society of India and Association of Physicians of India. He has also been the Dean of the Indian College of Physicians and Indian College of Medical Ultrasound. The book is a part of the Proceedings of the 2nd World Congress on Cardiometabolic Medicine which will be held in India later this year. This Congress will follow the 1st Congress on the same subject which was held in Mumbai in 2019 and was highly successful.

This book is divided into four sections consisting of atherosclerotic cardiovascular disease, cardio-renal continuum, obesity, lipids and diabetes, and hypertension. In the introduction, Dr Manoria expounds on the need for a cohesive approach in the field of cardiometabolic medicine which encompasses several medical specialties including cardiology. The section on atherosclerotic cardiovascular disease covers "malignant" coronary artery disease in young Indians, glucagon-like peptide-1 agonists in type 2 diabetes mellitus and the controversial role of aspirin in heart disease. The second section on heart failure describes newer therapeutic approaches in the management of heart failure. The next section on obesity, lipids and diabetes deals with the role of epicardial fat in cardiometabolic health which has been gaining increasing prominence recently, newer therapeutic options in treating inflammation in diabetes and endoscopic bariatric procedures for treating obesity. The final section on hypertension focuses on blood pressure variability and resting heart rate as an additional therapeutic target for reducing cardiovascular risk in patients with hypertension.

This excellent book is a boon to physicians and other health professionals and uniquely covers a broad range of medical specialties. Dr PC Manoria deserves our congratulations and appreciation for bringing out this book which will become an important addition to our armamentarium in the management of cardiometabolic disorders.

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Foreword

Indians and other South Asians develop accelerated atherosclerotic cardiovascular disease (ASCVD), leading to acute myocardial infarction (AMI) at a younger age (<45 years in men and <55 years in women). The age-standardized mortality from coronary artery disease (CAD) among South Asians is double (212/100,000 vs. 106/100, 000) that of the United States, a country where over 70% of adults are overweight, 42% obese, 35% have prediabetes, 10% have diabetes and 11% have low-density lipoprotein (LDL) >100 mg/dL. They have a high per capita consumption of beef (57 pounds) and eggs (284). The age-standardized CAD mortality rate in the United States has declined by 70% over the past 4 to 5 decades providing strong evidence that CAD had become highly predictable, preventable and treatable.

In the first 3 decades of this decline most of it was due to the control of tobacco use, hypertension and high cholesterol. While control of these major risk factors for ASCVD continues to be of benefit, in the last 2 decades the degree of their contribution to the decline may have become less as obesity and diabetes increased. Concomitantly and thankfully advances in detection and medical treatment has stepped up to decrease the impact of ASCVD.

Epidemiological transition is associated with the increase in obesity, metabolic syndrome, diabetes, hypertension, and atherogenic dyslipidemia all leading to ASCVD. Among Indians, this phenomenon was first observed in the diaspora with a 2-3 fold higher CAD rates compared to whites, Chinese and blacks. Implementation of primordial, primary, and secondary prevention measures led to dramatic decline in CAD in western countries, whereas its neglect led to an escalating epidemic of CAD in India. For example, between 2000 and 2017, the number of CAD deaths increased by 89% and disability-adjusted life years (DALYs) increased by 64% in India. Absence of primordial prevention results in earlier development of ASCVD risk factors in India, whereas its poor control results in Indians developing AMI about 10 years earlier. Ironically risk factor profile of physicians in India is much worse than that of their patients, in contrast Indian physicians in the United States, who have a very low prevalence of risk factors. It is against this background that this important book by Dr Prof PC Manoria should be viewed. During the past 25 years, this scholar and prolific author has published 30 edited books covering a gamut of topics in cardiology.

The four most striking features of CAD in Indians are extreme prematurity, extreme severity, high mortality at a young age and the inability of established risk factors to explain this enigma. CAD mortality in Indians 20–69 years of age is 40% higher than in whites, but the rate increases progressively with decreasing

age, 210% at ages 30–39 and 313% at ages 20–29 years. Besides, Indians have a nearly 2-fold higher incidence and mortality from CAD compared to whites after adjusting for the differences in the prevalence of established risk factors as well as insulin resistance. Metabolic risk factors explain only a third of the excess burden of CAD in Indians. In the lead chapter, Enas A Enas and Basil Varkey espouse the important role of lipoprotein (a) [Lp(a)]–a genetic risk factor found in 25–35% of Indians. Elevated Lp(a) is associated with a 2-3-fold risk of AMI, a risk similar to that of diabetes. But the risk on a population basis is more with elevated Lp(a) as it is 3–4 times more prevalent than diabetes.

The war on heart failure by PC Manoria provides insightful analysis of the newer medications that can substantially reduce mortality in patients with heart failure, the prevalence of which is increasing in patients with chronic coronary syndromes. Two chapters on diabetes underscore the importance of diabetes in India, where only a half of people with diabetes are diagnosed; only 40% of those diagnosed have hemoglobin A1C of <7% and disappointingly most of them do not receive statin therapy. The chapter on glucagon-like peptide-1 receptor agonists (GLP-1 RAs) by PC Manoria highlights the ability of these newer medications to improve ASCVD outcome, in addition to lowering blood sugar. The chapter on new therapeutic options by Anil Pareek highlights the importance of early diagnosis and control of diabetes.

Obesity in Indians is a challenging problem in many respects starting with its definition. The metabolic abnormalities at a body mass index (BMI) of 25 in Indians are similar to whites with a BMI of 30. As such the appropriate classification of BMI in Indians is: <23 optimal, BMI 23–25 overweight, and BMI >25 obese. The chapter on endoscopic bariatric procedures by Mohit Bhandari explores the potential of less invasive procedures in obese people who have appropriate indications.

Approximately one in three Indians has hypertension, but only 10% in rural and 20% Indians have their blood pressure treated to control. The chapter on hypertension by Agrawal spotlights the importance of controlling hypertension.

Aspirin became the drug of choice for primary prevention of AMI in 1988, after the Physicians' Health Study reported a 46% reduction in AMI with low-dose aspirin (325 mg every other day). Of note, this study predated the widespread availability of effective medications to control high blood pressure and high cholesterol. A series of studies done in the contemporary era showed that the harm from major hemorrhagic complications may outweigh the AMI prevented with aspirin in primary prevention. Accordingly, all major national clinical practice guidelines have severely restricted the use of aspirin in primary prevention. For all practical purpose *statin is the new aspirin* for primary prevention. This timely topic is addressed by Pankaj Manoria.

Indians develop ASCVD at a lower level of cholesterol because of enrichment of LDL by lipoprotein(a) and yet, the use of statins that are proven effective and safe, is very low in India. An astonishing 80% of Indians with ASCVD did not receive statin or other secondary prevention medications in one study. In order to reduce the cost of testing as a barrier for statin use, we have recently proposed the initiation of statin therapy without measuring cholesterol based on a risk grading to include people with ASCVD, tobacco use, hypertension, diabetes, or elevated lipoprotein(a).

In order to arrest and reverse the epidemic of CAD and other cardiometabolic disorders in India, greater efforts should be made to implement primordial, primary and secondary prevention directed at the entire population rather a minority that has the wherewithal to access appropriate health-care practitioners and facilities and to afford lifesaving and life prolonging medications. This book, a compilation of important and updated articles, is only a first step. Further, this information should be disseminated and applied to practice with the goal of reducing the burden of cardiometabolic diseases in India.

Enas A Enas
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Foreword

I am happy to write a foreword for the book entitled "Cardiometabolic Medicine 2022" edited by Dr Prof PC Manoria. Cardiometabolic medicine is relatively a new upcoming subspecialty of medicine and it links metabolic diseases with cardiovascular diseases. Dr Manoria deserves special kudos for his untiring efforts to nurture cardiometabolic medicine which is the need of the day.

The book provides current information on diverse aspects of cardiometabolic medicine like obesity, lipids, diabetes, hypertension, heart failure, atherosclerotic cardiovascular disease (ASCVD) particularly malignant coronary artery disease in young Indians and new block buster's, SGLT2 inhibitors and GLP-1 RAs for improving cardiorenal and ASCVD outcomes. A chapter on evaluation of epicardial fat and its role in cardiometabolic health is another highlight of the book.

The time has come when the subspecialty of cardiometabolic medicine should be introduced in the medical curriculum and paid special attention as cardiometabolic diseases are the leading cause of cardiovascular morbidity and mortality. The buildup of this specialty calls for cohesive efforts from diverse specialties like obesity, medicine, lipidology, cardiology, diabetology, hepatology, pulmonary medicine, etc.

I am sure this book on "Cardiometabolic Medicine 2022" with scripts from masters in their own field will not only disseminate the current information, but also contribute towards better patient care of individuals suffering from cardiometabolic diseases.

Partha S Banerjee
Chief Interventional Cardiologist, Columbia Asia Hospital, Kolkata, West Bengal, India
National President Elect, Cardiological Society of India
Former General Secretary and Treasurer, CSI

Foreword

Cardiometabolic diseases, today, are a major concern of society as well as health sector. Various studies have shown that most of them are preventable disorder, or at least, it can be delayed. There are definite risk factors of cardiometabolic diseases and by simple questionnaire, we can identify high-risk population. Prevention of cardiometabolic diseases is a major threat to public health for South Asians, particularly for India.

It is evidently proven that early diagnosis and screening of cardiometabolic diseases help in preventing complications and therefore, the healthcare professionals need to be trained in management and prevention of cardiometabolic disorders.

I congratulate Dr Prof PC Manoria, for his upcoming book entitled "Cardiometabolic Medicine 2022". I am sure it will help healthcare professionals to upgrade their knowledge about prevention and management cardiometabolic diseases as well as their related complications. The contents of the book are aptly designed for the need of the current era and provide information regarding pathophysiology diagnosis, management and prevention.

I have great pleasure in writing the foreword for this book and I am sure it will be a very useful for the readers.

Banshi Saboo
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Dia Care—Diabetes Care and Hormone Clinic
President, RSSDI (Research Society for the Study of Diabetes in India)
Secretary, Diabetes India, Indian Academy of Diabetes, Diabetes in Asia Study Group (DASG)

Preface

Cardiometabolic diseases like obesity, diabetes, hypertension, heart attack, etc. are the leading causes of cardiovascular morbidity and mortality throughout the globe and are reaching pandemic proportions. The idea of this book entitled "Cardiometabolic Medicine 2022" is to curb the growing menace of cardiometabolic diseases by disseminating the current preventing and therapeutic strategies to improve the cardiometabolic outcomes.

Many cardiometabolic diseases commonly coexist and produce multiple comorbidities which are beyond the reach of a physician or single specialist to comprehensively evaluate or treat them. The book begins first chapter laying emphasis on building up this new subspecialty of medicine by a call incorporating cohesive efforts of experts of diverse specialties like cardiology, diabetelogy, hepatology, lipidology, nephrology, obesity medicine, pulmonary medicine, etc.

The first section of the book is dedicated to atherosclerotic cardiovascular disease (ASCVD). A separate chapter is devoted for malignant coronary artery disease in young Indians by a very renowned global expert on the subject. The book also enlightens on new antidiabetic medications like GLP-1 RAs in improving ASCVD outcomes. The changing strategies for use of aspirin for ASCVD are aptly highlighted.

Heart failure is reaching alarming and epidemic proportion and this is focused in the second section of the book. The utility of two new approved weapons for heart failure like sacubitril valsartan and SGLT2 inhibitors is demystified and information is also provided for the two emerging drugs vericiguat and omecamtiv mecarbil. The third section of the book focuses on Obesity, Lipid and Diabetes. Separate chapters are included on endoscopic bariatric procedure inflammation in diabetes and evaluation of epicardial fat. The last section of the Book highlights on two important issues in hypertension i.e. blood pressure variability and resting heart rate.

I am very thankful to my sons, Dr Pankaj Manoria and Dr Piyush Manoria for their never ending support and my daughters-in-laws Smt Anubha Manoria along with her daughters, Renee and Manya and Smt Nirupama Manoria with her son Vardhman Manoria for boosting my motivation in bringing this book. I also owe my thanks to Mr Yogesh Shivhare for his effortless dedication in improving the script of the book. I express our appreciations and gratitude to the efforts of Mr Tarun Duneja, Director, Evangel Publishing, and his team members, especially Miss Heena Gogia, Publishing Manager for printing this book in present shape.

I am sure the book will help all members of the medical fraternity in fighting the menace of cardiometabolic diseases which is rocking the entire universe.

PC Manoria

Plate–1

Fig. 1: Intragastric balloons *(Chapter 6)*

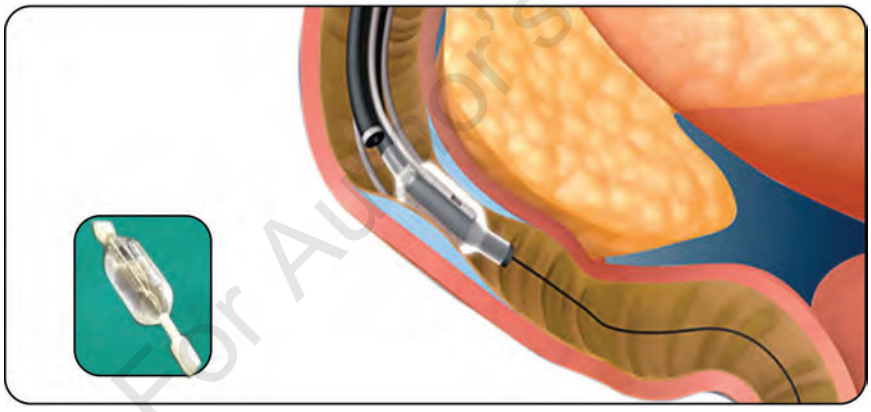

Fig. 4: Mucosal resurfacing *(Chapter 6)*

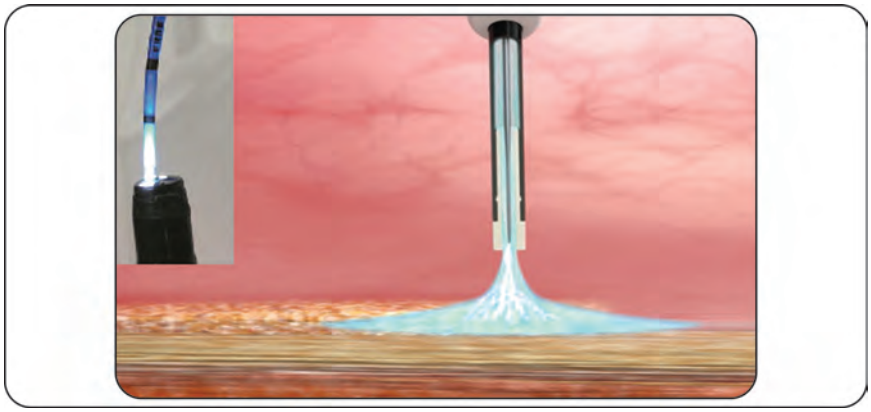

Fig. 5: Argon plasma coagulation *(Chapter 6)*

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Chapter 1

Cardiometabolic Medicine: The Necessity for a Cohesive Approach in the Current Era

PC Manoria

Abstract

Cardiometabolic diseases (CMDs) are rocking the entire universe and creating an ever increasing burden on the healthcare systems both in terms of morbidity and mortality. Although CMD encompasses panoply of diseases, obesity, diabetes, hypertension, and atherosclerotic cardiovascular disease (ASCVD) form the major chunk of CMD. Distressingly enough, most of these diseases, commonly coexist and produce multiple comorbidities which are beyond the reach of a physician or a single specialist to comprehensively evaluate and treat them. Therefore, there is an urgent need to build up this new subspecialty of cardiometabolic medicine to tackle the suffering afflicted population. The fulfillment of this goal requires a cohesive effort of several specialties like cardiology, diabetology, hepatology, pulmonary medicine, etc. The core concepts of cardiometabolic medicine (CMM) must be included in the medical school curriculum for its better growth and implementation in future.

Introduction

Cardiometabolic diseases (CMDs) like obesity, diabetes, hypertension, coronary artery disease (CAD), heart failure, etc. are reaching alarming and pandemic proportions and are the leading cause of cardiovascular morbidity and mortality **(Box 1)**. The key driver for rapid transaction from communicable to noncommunicable diseases is environmental influences like sedentarism, faulty diet, habits like fast food and addiction like smoking and tobacco abuse. In particular, children, adolescents and young adult are being rapidly affected by obesity and even diabetes and distressingly enough they are the forerunner of cardiovascular disease. Chubby children are not healthy children but are the harbingers of atheroma and glycemia and are prime contributors to metabolic syndrome.

Box 1 Cardiometabolic diseases

- Obesity
- Diabetes
- Hypertension
- Atherosclerotic cardiovascular disease
- Obstructive sleep apnea
- NAFLD, NASH
- Fatty Liver
- Cognitive decline and Alzheimer's
- Erectile dysfunction
- Polycystic ovary syndrome
- Osteoporosis

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis

The development of a new subspecialty of cardiometabolic medicine and the availability of newer therapeutic options calls for restructuring of how best we can care for patients with CMDs.

The growing prevalence of CMD is posing a great challenge for the medical fraternity throughout the globe.

Cardiometabolic medicine (CMM) requires cohesive efforts of diverse aspects of medicine like cardiology, diabetology, hepatology, pulmonary medicine, nephrology, bariatric medicine, nutrition and rehabilitation medicine **(Fig. 1)**.

The incidence of cardiovascular disease has been on the decline in the western world during the last few year but the new projections predict an escalation in these disease due to increase prevalence of CMD like obesity, diabetes, hypertension and metabolic syndrome[1,2] but in India the CMD continue to progress in alarming and epidemic proportions.

Obesity is a global health problem and is associated with morbidity and mortality. Life style modification is useful but has poor compliance in the long run. Drug therapy only produces slight decrease in weight.

Endoscopic bariatric procedures have emerged as an exciting therapeutic option for treatment of obesity. Although they are less effective but they are minimally invasive and have better safety and this is increasing acceptability among the patients.

Bariatric surgical procedures are time tested modality of treatment with good result but have substantial risk and less patient's acceptability. However, during the last couple of years endoscopic bariatric procedures[3]

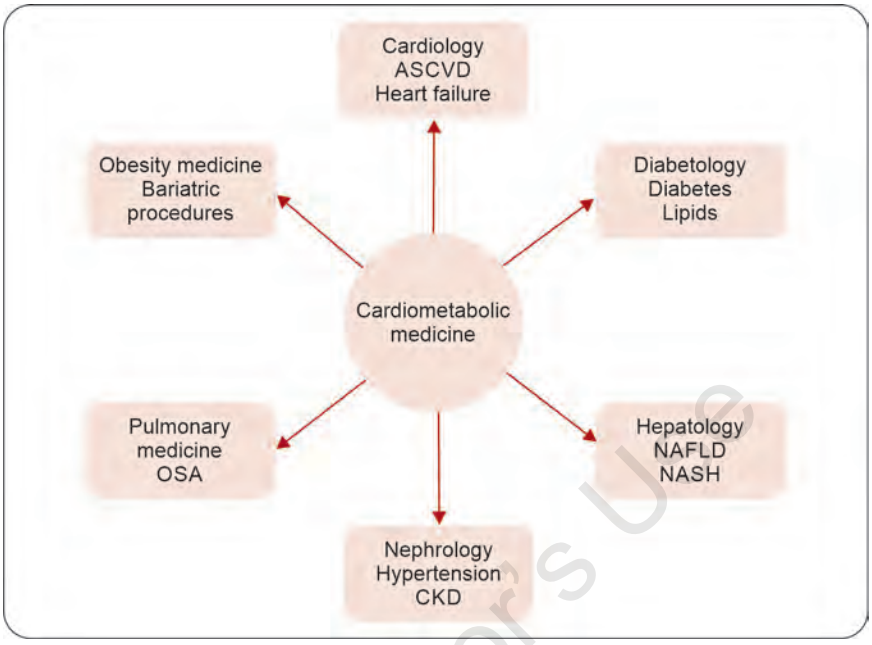

Fig. 1: Conglomeration of specialties required for cardiometabolic medicine

have made great progress and are emerging as the next major breakthrough in the management of obesity. Although they are less effective than bariatric surgery but they are minimally invasive, safe and have good patient acceptability. The therapeutic approaches for obesity treatment are exhibited in **Figure 2**.

The treatment of diabetes during the last couple of years has undergone a sea change. We have moved from glycemic control era and glycemic safety era to the current era of CV risk reduction with the availability of sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs).

The SGLT2 inhibitors like empagliflozin, canagliflozin and dapagliflozin are panacea for heart failure. All three trials, i.e. EMPA-REG OUTCOME[4], CANVAS[4] AND DECLARE TIMI-58[5] have shown decrease in hospitalization for HF both in patients with ASCVD as well as in patients with multiple risk factors. The EMPA REG OUTCOME in addition also showed a decrease in cardiovascular mortality and all cause mortality. Based on these trials the guidelines have approved empagliflozin, canagliflozin or dapagliflozin in patients with type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) or at very high CV risk to reduce cardiovascular events. Empagliflozin has also been recommended for reducing the risk of death in patients of T2DM with CVD. The DAPA HF trial[6] and EMPEROR-Reduced trial[7]

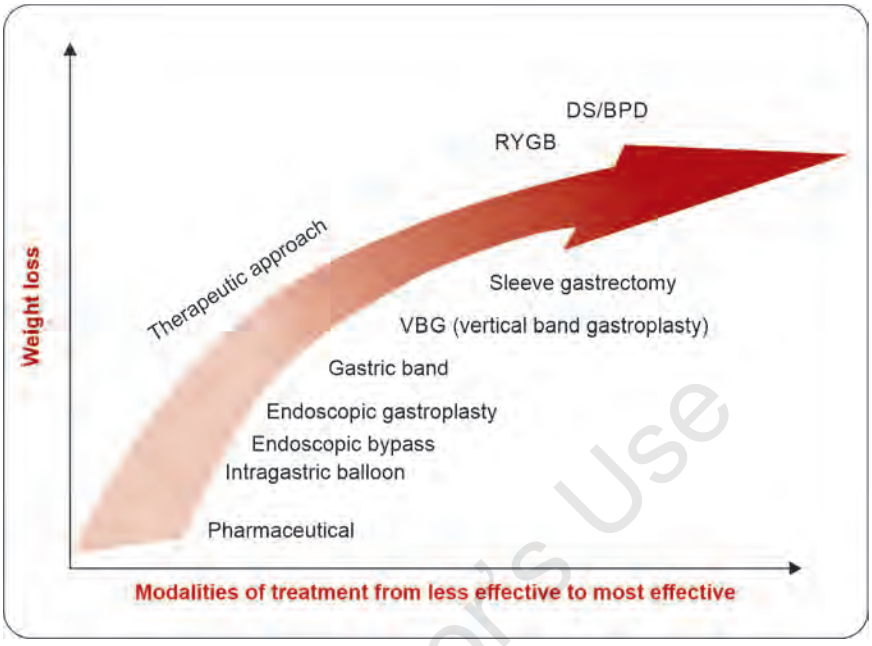

Fig. 2: Therapeutic approaches for obesity management
Abbreviations: VBG, vertical band gastroplasty; RYGB, Roux-en-Y gastric bypass; DS, duodenal switch; BPD, biliopancreatic diversion

have shown improved CV outcome of heart failure with reduced ejection fraction (HFrEF) in diabetics as well as nondiabetics. Dapagliflozin has been approved for treatment of HFrEF and empagliflozin is likely to get approved in future. Trials of SGLT2 inhibitors in heart failure with preserved ejection fraction are ongoing like DELIVER, EMPA PRESERVED and their results are keenly awaited. SGLT2 also slow down the trajectory of chronic kidney disease (CKD) and postpones dialysis by 10 years or so. The CREDENCE trial[8] showed positive results in diabetic CKD and the DAPA CKD trial[9] has shown improved outcome in diabetic as well as nondiabetic CKD. The EMPA CKD trial is ongoing.

The SGLT2 inhibitors are a panacea for improving HF and renal outcomes while GLP-1 RA decreases ASCVD events.

A plea is made to combine both these agents for comprehensive cardio-renal outcomes but this will only be possible on a large scale when oral semaglutide is available in India.

The GLP-1 RAs has shown reduction in atherosclerotic cardiovascular disease (ASCVD) in several trials like LEADER,[10] SUSTAIN-6,[11] HARMONY OUTCOME[12] and REWIND[13] trials but have no effect on heart failure. They

however have some beneficial effect on chronic kidney disease (CKD). The GLP-1 RAs has been approved for use in patients with ASCVD or those with multiple risk factors. In patients with ASCVD, the current European guidelines have recommended their use even ahead of metformin. The oral semaglutide is already available in six countries in the world and is likely to be available in India in near future. Following its availability its use and acceptability is likely to increase.

Despite their immense benefits and recommendation by guidelines these agents are highly underutilized in real world scenario. The SGLT2 inhibitors are utilized in 20% of patients while GLP-1 RAs are utilized in 10% of patients in the western world and in the developed country its use is dismal.

The SGLT2 inhibitors improve cardiorenal outcomes while the GLP-1 RAs benefit ASCVD and therefore a plea is made to combine both these agents for improving cardiorenal and ASCVD outcomes. The injectable therapy of GLP-1 RA precludes its use in large number of patients but when oral form is available both these agents will be used in lager number of patients.

Conclusion

Cardiometabolic diseases are posing a great challenge to the medical fraternity throughout the globe. Nurturing this new subspecialty of medicine is an appropriate step in the right direction for providing the best possible holistic care for patients with CMD. The new emerging epidemic of childhood obesity and childhood diabetes is posing a serious threat to the young generation. If appropriate steps for prevention are not taken on an urgent basis throughout the globe it will ruin their future.

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Chapter 2

Malignant Coronary Artery Disease in Young Indians: Unraveling the Enigma

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Abstract

Malignant coronary artery disease is a term introduced by Enas and Mehta to highlight the three most concerning features—early onset, accelerated plaque build-up, and high mortality—of coronary artery disease (CAD) in young Indians. The "malignant" nature of the disease in Indians (in India and in the diaspora) is fully displayed in the following data: three-vessel disease (TVD) is found in nearly half of men and one-third of premenopausal women; acute myocardial infarction (AMI) occurs about 10 years earlier (<45 years in men and <55 in women), and at a higher rate of incidence and mortality (1.5–2 fold) than in the white population. The causative factor(s) for malignant CAD is/are enigmatic as diabetes and other established risk factors are insufficient to explain it. While these (high cholesterol, hypertension, diabetes, tobacco use) and environmental pollution and others attributable largely to "nurture' are risk factors, the role of "nature" is now gaining increased attention. CADI Research Foundation led the way in proposing two factors of nature—ethnicity and elevated lipoprotein (a)—as important in the increased incidence of CAD in Indians and further work by the foundation and other major research groups have validated the role of these two factors. Elevated level of Lp(a) (genetically mediated) is atherogenic and thrombogenic and is to be considered a major factor in the genesis of malignant CAD and in the clinical expressions of AMI and stroke in young Indians. Elevated Lp(a) and malignant CAD are tightly intertwined; both are characterized by extreme prematurity, extreme severity and high mortality at a young age. The risk of AMI from elevated Lp(a) is greater (odds ratio >2) in South Asians than in other ethnic groups. While the risk of AMI from elevated Lp(a) in Indians is similar to that of diabetes, its prevalence is much higher (three-fold) in Indians. It follows that elevated Lp(a) is a major causal or contributing factor for malignant CAD. An one time measurement of Lp(a) level is warranted to assess CAD risk and to plan optimal management. Although a specific drug to lower Lp(a) is not available to most clinical practices there is much that can be done to reduce CAD risk in persons with elevated Lp(a). These include avoidance or reduction of all life-style risk factors and tight control of all established risk factors. In the latter category reducing the level of LDL-C with statin therapy is a prime and proven priority.

Introduction

Annual CAD mortality (years 2000 to 2017) in India increased from 851,000 to reach 1.54 million (+ 81%). The increase was greater in women (+94%) than in men (+ 74%) and most of them were <70 years of age.[1] CAD mortality in the US decreased by 38% during the same period and by 68% during the past 4 decades with Finland reporting >80% decline.[2] Between 2000 and 2017 the DALY in India increased from 22.6 million to 37 million (+ 64%) and India has the highest DALY and second highest number of CAD deaths after China (1.54 vs. 1.75 million).[1] Besides the magnitude of CAD in Indians the most concerning aspects are the early onset, accelerated plaque buildup and high mortality in the young even though the established risk factors are lower than in western countries.[3] As early as 1995, the gravity of this observation led Enas and Mehta to call this "malignant coronary artery disease".[4] The term Indians and South Asian are used interchangeably in this chapter as Indians comprised the majority in most of the CAD studies in South Asians.[5]

CAD mortality has been declining in the US during the last 40 years but in India the rising trend continues unabated.

Malignant Coronary Artery Disease

CAD in Indians commonly starts at a younger age; it is diffuse and multivessel, often presents as AMI, and runs a malignant course with high cardiovascular morbidity and mortality.

We have classified CAD to three types as shown in **Table 1**.[3] The excess burden of the disease in Indians is largely from Type I and to a lesser extent from Type III.[3] The three cardinal features of malignant CAD are extreme prematurity, extreme severity and high mortality.[3] To add to the enigma of this triad, established risk factors for CAD are absent to low in the affected persons (analogous to Type I diabetes in the young).[3] The features that comprise the triad of malignant CAD are further elucidated below.

Extreme Prematurity

CAD is considered premature in men <55 years and women <65 years of age. In the US the average age of first AMI is 66 in men and 72 in women and therefore AMI is considered a disease of older people.[6] Indian men and women experience AMI approximately 10 years earlier than whites.[7] AMI in the young is defined as that occurring in men <45 years of age and women <55 years of age, whereas those occurring in those <35 is defined as AMI in very young.[3] The following published data from different countries lays bare

Table 1 **Classification of coronary artery disease in Indians based on characteristics[3]**

Type I or malignant CAD
• Extremely premature with clinical manifestations <45 years of age in males and <55 years in female • Often presents as acute myocardial infarction rather than as stable angina • Low prevalence of established risk factors: diabetes, hypertension, high cholesterol; but tobacco use often high in men • High prevalence of family history of premature CAD or sudden death • High prevalence of elevated lipoprotein(a), homocysteine, PAI-I and other emerging risk factors • Diffuse and extensive atherosclerosis, often involving the entire length of artery that may masquerade as "small coronary arteries" • Common occurrence of left main and/or three-vessel disease • Seen more frequently in South Asians (10–15%) and less frequently in other populations (2–5%)
Type II or standard CAD
• Standard type of CAD prevalent throughout the world • First manifestation of CAD typically noted after 65 years of age and often presenting as angina rather than ACS • High prevalence of established risk factors • Low prevalence of elevated lipoprotein(a) and other emerging risk factors • Wide range in severity of atherosclerosis from mild to severe disease
Type III or mixed
• Clinical manifestations typically between age 45 and 65 years • Triggered by moderate levels of established and emerging risk factors • Moderate severity of atherosclerosis—intermediate between type I and type II • Seen in 30–40% of South Asian patients

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; PAI-1, plasminogen activator inhibitor-1

the heightened risk in young Indians. 10 to 15% of all AMI in Indians are in the young and very young compared to 2–5% reported in Western populations.[8,9] Littler[10] reported AMI in 4 Indians 18–22 years of age in the UK but he could not find any white person with AMI in that age group. The incidence of AMI among young Indians is 5 times higher than in whites in the UK[9] 4 times higher than in Italy,[11] and 13 times higher than in Chinese in Singapore.[12] Indians accounted for 56% of AMI in the young in Malaysia[13] and 71% in Qatar.[14] In a large study involving over 5000 Bangladeshis with first AMI cases and over 5000 controls, 46% of the AMI occurred in those <50 years; the mean age of AMI was 53 years.[15] In the CADI study the mean age of patients (90% physicians) with CAD was 48 years.[16] In a large single center study of ACS patients (n = 8,268) in India, 820 (10%) were <40 years of age and 611 of the 820 (75%) had STEMI.[17]In another study of 877 patients with angiographically documented CAD in India, more than one-half of patients were <55 years

and one-third <45 years, with a mean age of 48 years.[18] Despite the young age, TVD was found in 55% and MVD in 79%; besides, coronary atherosclerosis was generally diffuse with multiple sites of obstruction in most vessels.[18] In another large Indian study, the median age of CABG surgery was 60 years and 6% of CABG was performed in those <45 years of age.[19] In Kerala, 55–67% of hospitalizations for AMI occur in those <55 years of age.[20] In a Pakistani study of 976 consecutive patients admitted to a single center with AMI, 16% were <45 years of age.[21]

CAD in Indians is categorized as premature if it occurs in men less than 55 years and women less 65 years of age.

AMI in the young denotes occurrence below the age of 45 years and AMI in the very young denotes occurrence below 35 years of age.

Recently further affirmation on the extreme prematurity and severity coupled with relative paucity of established risk factors have come from India in 2 reports. The first was from Gujarat of 787 patients <40 years of age (median age 36), with STEMI who had notably low prevalence of major risk factors (hypertension 12%, diabetes 10%, obesity 5%, family history 13%, and LDL >100 mg/dL 6%), except for smoking (50%). They also noted deficiencies in acute management: only 1% underwent primary angioplasty, 57% received thrombolytic therapy, and 41% did not receive any reperfusion therapy.[22] The second was a study of 102 patients <35 years of age from New Delhi, 93% of whom had STEMI (73% involved the anterior wall). The prevalence of tobacco use was again high (80%) with low rates of diabetes (6%) and hypertension 10%. The report was silent on lipid abnormalities.[23]

Extreme Severity

In Western population CAD in the young is seen mostly among male smokers, and is associated with fewer comorbidities, less severe coronary atherosclerotic disease, better left ventricular function and less in-hospital complications.[8,24-32] Compared to nonsmokers, smokers with AMI are 10–15 years younger and have better short-term and long-term survival, especially if they quit the habit.[33,34] In contrast a high rate of MVD and TVD has been noted in angiographic studies of young Indians in India and in other countries.[3] In a comparative study Bangladeshi immigrants had twice the rate of TVD of non-Bangladeshis (53% vs. 26%) although the former were 6 years younger.[35] In India, TVD has been reported in nearly half of young men and one-third of premenopausal women.[36,37] A large ACS study (n = 2290) in South Africa found TVD in 48% of patients <45 years of age and 14% required CABG.[37,38] Sharma et al,[39] studied 250 Indian CAD patients comparing those ≤40 to those >40 years of age and found no significant difference in the

prevalence of TVD (45% vs. 53%; P = NS), diffuse disease (28% vs. 31% P = NS) and coronary collaterals (33% vs. 45% P = NS).[39] These features of CAD in young Indians may be termed *diabetic-like coronary arteries in the absence of diabetes* as they are reminiscent of CAD in diabetic patients.[3]

Plaques that are extensive and diffuse on angiography may give rise to the wrong notion that Indians have small coronary arteries; coronary artery size index to body surface area is not statistically different in Indians compared to Caucasians.

Contrary to the common notion Indians do not have small coronary arteries, although it appears so; a plausible explanation is that extensive plaques throughout the arteries are misinterpreted as small coronary arteries on angiography.[3] Coronary artery size indexed to body surface area is not statistically different in Indian males and females as compared to Caucasians.[40,41]

High Mortality Rate

The disproportionately high CAD mortality rate in young Indians has been confirmed in multiple studies in different countries.[3] South Asians account for 23% of worldwide deaths due to CAD. Nonetheless, as a result of premature CAD deaths, South Asians have one of the highest rates of age-standardized CAD mortality—double that of North Americans (212 vs. 106/100,000).[42] The high burden of premature CAD in Indians in the US may cause a loss of a decade or more of their lives and almost one-fourth of total years lost to any disease were due to CAD.[43] The relative risk of CAD deaths in Indian-Americans <45 years is higher by 8-fold than whites and 2-fold than blacks in the US.[44] The relative risk of CAD death in Indians <30 years of age is 10-fold higher than Chinese in Singapore.[45] Indian physicians in the UK die of CAD 10 years earlier than white physicians.[46]

South Asians have one of the highest CAD mortality rates and account for 23% of worldwide deaths due to CAD.

Earlier studies from the UK showed a greater proportion of Indians unsuitable for CABG surgery than whites (59% *vs.*47%) because of the severity of coronary atherosclerosis.[47] During a follow-up of 19 months, death rates among these inoperable patients were 4 times higher (25% vs. 6 %) in Indians than in whites.[47]SMR is the optimal method to compare CAD rates of whites and Indians in different age groups. Balarajan et al.[48] applied SMR and found an inverse relationship between increase in relative risk of CAD deaths and decreasing age in Indians. Using the SMR 100 as standard for

Table 2 **Increasing standardized mortality rate ratio (SMR)* with decreasing age in South Asians compared to whites in the United Kingdom[48]**

	SMR white	*SMR South Asians*
SMR ages 20–69	100	136
SMR ages 40–49	100	165
SMR ages 30–39	100	210
SMR ages 20–29	100	313

*The SMR is taken as 100 for whites in the United Kingdom

whites, Indians had an SMR of 136, at ages 20–69 (36% higher CAD mortality). Notably, the SMR increased to as high as 313 in those younger than 30 years as shown in **Table 2**.[48]

Unravelling the Enigma

Ethnicity and elevated levels of lipoprotein(a) are significant contributors to the development of malignant coronary artery disease in Indians.

Established risk factors alone have consistently failed to explain the excess burden of and mortality from CAD in Indians.[16,49-54] What other factor(s) are responsible? The answer to this is the first step to unravel the enigma of malignant CAD in the young. Two landmark studies have provided important leads to this endeavor. The first one, a large prospective study (LOLIPOP) compared CAD factors in 16,774 South Asians to 7,032 Europeans and found a very marked difference in the OR between the two.[53] The OR for CAD in South Asians after adjustment for age, gender was 2.55 (2.26–2.87, P <0.001), which increased to 2.67 (2.33–3.06 P <0.001) after adjustments for cholesterol and smoking. The OR decreased to 2.28 (1.97–2.63 P<0.001, when adjustments were made for obesity, abdominal obesity, hypertension and diabetes. Further adjustments for HOMA–IR (homeostatic model assessment of insulin resistance), triglycerides and HDL decreased the OR to 1.81 (1.54–2.11, P=0.001).[53]Although the role of ethnicity has been long suspected, LOLIPOP study with its prospective design and size established South Asian ethnicity as a risk-enhancer for CAD.[53] The second study, the INTERHEART-Lp(a) study[55] went even further in finding elevated lipoprotein (a) as a likely explanation for the high risk in South Asians. This study found Lp(a) is useful in assessing the risk of AMI in ethnically diverse populations. South Asians had the highest risk. Elevated Lp(a) conferred the highest OR for AMI (2.14) in South Asians compared to the others (P < 0.001).[55] The convincing data from these 2 studies merited designation of both South Asian ethnicity and Lp(a) as ASCVD risk-enhancing factors in the 2018 American Cholesterol Guidelines.[56]

Role of Lp(a) with Focus on Malignant CAD in Young Indians

Of the 4 major classes of lipid disorders, (elevated LDL-C, low HDL-C, elevated triglycerides and elevated Lp(a), the genetic factor Lp(a) has received the least clinically focused attention.

As early as in 1994, Enas et al.[57] reported high levels of Lp(a) in one in four Indians. Lp(a) levels ≥30 mg/dL were found in 25% and >20 mg/dL were found in 44% of Indians.[58,59] Subsequent studies have confirmed higher levels of Lp(a) in South Asians, compared to whites and Chinese, in countries as diverse as US,[59,60] UK,[61] Canada,[58,62] Singapore,[63-65] Australia,[66,67] and India.[55,68-70] Indians in Singapore has had a 3 to 4-fold higher rate of CAD than Chinese for several decades.[69] Indian newborns in Singapore have higher Lp(a) levels than Chinese and ethnic differences in plasma Lp(a) level in the umbilical cord are concordant with adult CAD mortality differences between Indians and Chinese in Singapore.[63] Migrant and resident South Asians have similar levels with a median Lp(a) level of 13 to 14 mg/dL further supporting a genetic origin of Lp(a).[60,61,68]

Atherogenicity and thrombogenicity, the dual pathogenic attributes of Lp(a) play a major role in the development of ASCVD in young Indians.

Epidemiological studies and human genetic analyses have suggested that Lp(a) is causally associated with CAD and AMI in South Asians.[55,70-74] In the PROMIS,[71] a Mendelian randomization study, involving of 9015 patients with AMI and 8629 matched controls, increased lipoprotein(a) concentration was an independent and causal risk factors for AMI after adjusting for age, sex, ethnicity blood pressure, diabetes, tobacco use, LDL-C and HDL-C in South Asians.[71] In 2018, the NHLBI reported an estimated 469 million (25%) of South Asians have Lp(a) >50 mg/dL. This means that the number of South Asians with elevated Lp(a) is much higher than those with diabetes **(Table 3)**.[3,55,70,75] Data from the INTERHEART Lp(a) study, showed not only that South Asians were at the highest risk for AMI (as previously mentioned), but also that their PAR for AMI from high Lp(a) and diabetes were comparable at 10% and 12% respectively.[3,55]

After critical examination of several causation theories [thrifty genotype, dirty genotype, mitochondrial efficiency, adipose tissue distribution, variable disease selection hypothesis, neurobehavioral hypothesis, DOHAD, intergenerational effects, adaptation/dysadaptation, insulin resistance, cooking style (deep frying), transfats, food adulterants and Lp(a)] put forward by 22 experts on CAD and diabetes in South Asians, epidemiologist Bhopal found insufficient credence to all, but left open the possibility for the genetic predisposition mediated by Lp(a).[54]

Table 3 **The prevalence of Lp(a) ≥50 mg/dL and diabetes and odds ratio for acute myocardial infarction from lipoprotein(a) in South Asians compared to other ethnicities**[3,55,70,74]

	Lipoprotein(a)	*Diabetes*
Global total	1,430 million	415 million
South Asians total	469 million	100 million
Global prevalence	10–30%	3–10%
Prevalence in Indians	25% (345 million)	7–8% (71 million)
CAD risk	2–4-fold	2–3-fold
Odds ratio for AMI from Lp(a)	95% CI	
7 largest ethnicities	1.48	1.32–1.67
South Asians	2.14	1.59–2.89

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; Lp(a), lipoprotein(a)

Table 4 **Elevated lipoprotein(a), but not the established risk factors, has all three characteristics of malignant CAD in young Indians**[3,70,74]

	Extreme prematurity	*Extreme severity*	*High mortality rates at a young age*
Elevated Lp(a)	Yes	Yes	Yes
Tobacco use	Yes	No	Yes
Diabetes	Yes	Yes	No
Hypertension	No	No	No
Very high LDL (>190 mg/dL) and familial hypercholesterolemia)	Yes	Yes	Yes

Several lines of evidence support that elevated Lp(a) and malignant CAD are inextricably intertwined.[3,74] Only Lp(a) and none of the established risk factors share all four characteristic features of malignant CAD in young Indians **(Table 4)**.[3,74] The literature on Lp(a) has grown and is voluminous now and therefore for the ease of readers we have listed **(Box 1)**[3,74] the top 10 essential pieces of information on Lp(a). On the treatment front there are some promising developments. The proven benefit of PCSK9 inhibitor therapy for those with high LDL-C extends to those who also have high Lp(a). In the large FOURIER trial the baseline Lp(a) level was a determinant of the ASCVD events (CAD deaths, AMI, urgent revascularization) and its reduction. The median Lp(a) level was 15 mg/dL and PCSK9 inhibitor (evolocumab) reduced Lp(a) by 27%; importantly reduction of ASCVD events were 3 times more (23% vs. 7%) in those with Lp(a) >15 mg/dL than in those with Lp(a) <15 mg/dL.[76] Studies on drugs that lower Lp(a) are currently underway and the results of these large scale trials are expected by the year 2025.

Box 1 **Lipoprotein(a): Top 10 essential bits of information**[3,70,74]

1	Lp(a), a genetic factor is proatherogenic and prothrombogenic and adversely affects endothelial function, fibrinolysis and plaque stability. A high level of Lp(a) leads to accelerated atherothrombosis and premature and severe CAD and high mortality. It also increases the risk of stroke, peripheral arterial disease, chronic kidney disease, aortic stenosis and heart failure
2	Adult level of Lp(a) is reached by 5 years of age and thereafter remains constant. This lifelong exposure to elevated Lp(a) results in early plaque build-up and blockages leading to a heart attack 10–20 years earlier than that occurring from diabetes and high blood pressure. People with markedly elevated Lp(a) develop a heart attack at a very young age—often in their thirties and forties—whereas people with modestly elevated Lp(a) may get heart attack in their fifties and sixties
3	The increased risk of an AMI (2-4-fold risk) from elevated Lp(a) is similar to diabetes but elevated Lp(a) is >3 times common than diabetes (1.43 billion vs. 425 million) globally. Thus, on a prevalence-adjusted basis elevated Lp(a) is likely a stronger contributor to CAD than diabetes. Yet, most people with elevated Lp(a) are undiagnosed and untreated
4	CADI study, a follow-up to the first report by Enas and colleagues on high levels of Lp(a) in Indians, found 25% of Indians had elevated Lp(a) >30 mg/dL and 44% had Lp(a) >20 mg/dL. According to the NHLBI 25% of all South Asians have Lp(a) >50 mg/dL compared to 7–8% having diabetes
5	According to the landmark INTERHEART study, Indians have the highest risk of heart attack from elevated Lp(a) and the second highest level of Lp(a). 10% first heart attacks in Indians is attributable to Lp(a) vs. 12% to diabetes. For Indians, CAD risk is moderate at Lp(a) >30 mg/dL, high at >50 mg/dL and very high at >100 mg/dL. The CAD risk from elevated Lp(a) 50 mg/dL is similar to that of LDL >125 mg/dL
6	Both elevated Lp(a) and South Asian ethnicity are considered ASCVD risk-enhancing factors that should be strongly considered in initiating or intensifying statin therapy, when there is uncertainty in the need for statin therapy in primary prevention
7	Since high Lp(a) is a hereditary condition, whenever one person is diagnosed with high Lp(a), it is important to test all blood-related family members especially, siblings, children, parents, and grandparents. Notably 50% of such relatives are likely to have elevated Lp(a) levels
8	People who benefit the most from knowing their Lp(a) level include those with a personal or family history of one or more cardiovascular events (early heart attack, stroke, sudden death, aortic aneurysm, aortic valve stenosis, carotid artery stenosis) or interventions (coronary angioplasty, stent, bypass surgery, carotid artery stent, carotid endarterectomy or leg amputation). It is also advisable to measure Lp(a) in people with silent heart disease (high coronary artery calcium score on a heart scan)
9	A onetime test for Lp(a) is all that is necessary. A lipid panel [which does not include Lp(a)] may be normal even when Lp(a) is elevated. A separate order for Lp(a) is needed. The cost is comparable to that of a lipid panel and in the US is covered in most insurance plans
10	Considering the 25% prevalence of elevated Lp(a) and the ensuant high CAD risk in Indians it is reasonable to test all for Lp(a). Lifestyle modification, does not affect Lp(a) but is strongly recommended for its significant and favorable effects on all other CAD risk factors. Those with elevated Lp(a) should maintain optimal blood pressure, blood sugar, and cholesterol level. Statins lower ASCVD risk without lowering LP(a) level. However, there are new encouraging developments in treatment (see text)

Lipoprotein(a) level is genetically determined and therefore unaffected by lifestyle modification. However, lifestyle modification is strongly recommended for its important and favorable effect on all modifiable risk factors.

Statins lower ASCVD risk but does not reduce Lp(a). PCSK9 inhibitors markedly decrease LDL-C and also lower Lp(a) and reduce ASCVD events.

Readers who would like to delve deeper should read our 2 comprehensive reviews. The first one is on the role of Lp(a) as a genetic, independent causal factor for CAD while the second one is a reasoned case for considering Lp(a) as a prime causal factor for malignant CAD in young Indians.[3,74]

Nature, Nurture or Both?

Nature includes the ethnicity we were born into and the gene we inherited, neither of which can be changed. This might lead to a sense of nihilism in combating malignant CAD and CAD in general in South Asians. However, nihilism is unwarranted as there is much we can do in the "nurture" part. Both the risk factors and risk-enhancing factors of CAD that are most pertinent to Indians are part of "nurture". Examples include cessation of smoking, early identification and control of high cholesterol, diabetes, hypertension, and addressing the deficiencies in the environmental, sociocultural and dietary factors listed in **Table 5**.[3,56,74,77-92] CACS, a risk marker that measures the total burden of calcium in coronary artery plaques is of particular importance in detecting silent heart disease.[91,92]

Call for Expanded Use of Statins

The relationship between cholesterol and atherosclerosis was known for more than a century and the first statin that reduces LDL-C became available in 1987.[93] However, the positive impact of stain on CAD and AMI became convincing only with the 4S (1996) that showed simvastatin reduced AMI by 42% and all-cause death by 30%.[94] A lesser known fact is that Lp(a) was a major determinant of death in this study.[95] Death was reduced by 14% in those with the highest quartile of Lp(a) level and a remarkable 58% in those with the lowest quartile.[95] "Statin provides the biggest bang for the buck" as it is the best drug available in our therapeutic armamentarium to combat CAD.[96] The efficacy and side effects profile of statins in South Asians are similar to Caucasians with 10 mg/day rosuvastatin or 20 mg/day atorvastatin lowering LDL by 41 to 44%.[97]

In a recent editorial, building on the American guidelines, we proposed the expanded use of statins in Indians[96] as the benefit extends far beyond

Table 5 **CAD: Risk factors (established and less well established), risk-enhancing factors and other risk factors of added importance to Indians*[3,70,74-92]**

Risk factor category	***Risk factors***
Major established factors[57, 75]	Smoking, high cholesterol, diabetes, hypertension
Less well established risk factors[77,88]	South Asian phenotype, abdominal obesity (waist circumference >80 cm in women and >90 cm in men); generalized obesity (body mass index >25); South Asian dyslipidemia including low HDL, smokeless tobacco use
Risk-enhancing factors[57,87]	South Asian ethnicity, lipoprotein (a), family history of premature CVD, high triglycerides, high Apo B, high C-reactive protein, metabolic syndrome, chronic kidney disease, ankle brachial index <0.9; chronic inflammatory conditions (psoriasis, rheumatoid arthritis, chronic HIV infection, etc.); premature menopause <40 years, eclampsia and adverse pregnancy outcome
Category	***Risk factors of added importance to Indians****
Genetic factor[3,40,]	Lipoprotein (a)
Thrombogenic factors[76, 77,78]	• Accelerated platelet activation • Fibrinogen • Plasminogen activator inhibitor-1 • High homocysteine
Environmental factors[77,88,89]	• Air pollution (indoor and outdoor) • Urbanization
Socio cultural factors[77, 85,86]	• Low health literacy • Deficiencies in CVD care at all levels [87] (primary prevention, recognition and treatment of risk factors, acute disease management and secondary prevention) • Low vitamin D • Low physical activity • Low adherence to medication for blood pressure, diabetes, and cholesterol • Endogamy and consanguinity • Binge drinking and alcohol abuse
Dietary factors[83-86]	• High intake of low quality (refined) carbohydrates • High intake of saturated fat (coconut oil, palm oil, butter, ghee) • High intake of oxidized fats (natural ghee) • High intake of trans fat from *vanaspati (vegetable ghee) and* fried food including vegetables • Penchant for Indian sweets high in sugar and butter and often fried in ghee or unhealthy cooking oils • Food pollutants and preservatives • Contaminated vegetarianism • Low intake of fruits and vegetables (one of its effects is high homocysteine) • Low intake of fish and omega 3 fats
Other factors[81, 82]	Gestational diabetes

those with ASCVD and those with established risk factors. Thus, we recommend statins for Indians with any of the established risk factors—diabetes, hypertension, smoking (cholesterol measurement is not necessary) or cholesterol >170 mg/dL). Additionally, we also recommend statin treatment for those with LDL-C > 70 mg/dL or cholesterol >140 mg/dL if they have one or more of many risk-enhancing factors that include elevated Lp(a), elevated triglycerides, metabolic syndrome, etc. (full list in our editorial).[96] Intensification of treatment is needed if LDL-C continues to be >70 mg/dL. This expanded use of statins has the potential to save millions of lives over the years.

Abbreviations: 4S, Scandinavian Simvastatin Survival Study; ACS, acute coronary syndrome; AMI, acute myocardial infarction; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; CABG, coronary artery bypass graft; CACS, coronary artery calcium score; CADI study, coronary artery disease in Indians study; CARP, coronary artery revascularization procedures; DALY, disability-adjusted life years; DOHAD, developmental origin of health and disease; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; HDL-C, high-density lipoprotein cholesterol; HOMA–IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LOLIPOP, Lessons from the London Life Sciences Population; MVD, multivessel disease; NS, not significant; OR, odds ratio; PAR, population attributable risk; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; PROMIS, Pakistan Risk of Myocardial Infarction Study; SMR, standardized mortality ratios; STEMI, ST segment elevation myocardial infarction; SVD, single-vessel disease; TVD, three vessel disease; UK, United Kingdom; US, United States

Conclusion

Malignant CAD in young Indian is characterized by extreme prematurity, extreme severity, and high mortality at a young age (defined as age <50 years). Many young Indians with AMI have clinically aggressive, diffuse, severe, and extensive atherosclerotic process, often masquerading as *small coronary arteries*. New data that became available after submitting the book chapter further support and solidify the high mortality at a young age in India. Globally, 624,715 CAD deaths occurred under age 50 years in 2019 that included 185,195 deaths in India. The fact that India, with 18% of the global population accounts for 30% of global CAD deaths at age <50 years compared to 2% in the US, 14% China and 8% globally, is a national urgency that requires concerted proactive measures earlier in life than in other populations.

Indians and other South Asians have double the risk of CAD events, but this heightened risk is not captured by ASCVD risk prediction algorithms that utilizes established risk factors. The condition is analogous to type 1 diabetes occurring in young individuals without the usual risk factors for diabetes in contradistinction to type 2 diabetes occurring in older individuals with well-known risk factors for diabetes (abdominal obesity, physical inactivity, high glycemic load, family history of diabetes etc). LP(a)–an inherited genetic variant of LDL and found in 25–44% of Indians (3–4 times more common than diabetes) is now widely recognized as the foremost risk factor for malignant CAD, leading to extremely premature deaths at <50 years.

The best strategy to reduce the toll of extremely premature death from threatening the economic well-being of one's family and society, is optimization of diet and life style with Life's simple 7 for Indians. The profound safety and benefits of extremely low LDL has led to the current understanding that optimal LDL level is in high risk persons is in the 25 and 50 mg/dL range. Lower is better throughout life and not just after massive heart attack. This level seems reasonable for very high risk individuals (e.g. those with heart disease/stroke with multiple risk factors like diabetes or elevated lipoprotein(a). Most Indians may also require statin therapy–the most effective weapon against CAD to maintain LDL <70 years throughout life. Poly pill therapy with a statin, aspirin, and 2 BP lowering medications that has been shown to reduce CVD events by nearly 50% offers another choice for a large segment of the Indian society among whom the control of high blood pressure, high cholesterol and diabetes is dismally poor.

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Chapter

3

Glucagon-like Peptide-1 Receptor Agonists in T2DM: Impact on Cardiovascular Disease

PC Manoria

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a new block buster to target atherosclerotic cardiovascular disease (ASCVD) in type 2 diabetes (T2D). They have been endorsed by all guidelines across the globe. They produce glucose-dependent increase in insulin secretion and glucose-dependent suppression of glucagon with little or no hypoglycemia. Besides glycemic benefits, it also improves metabolic profile of the patient by decreasing weight. It targets ASCVD by control of risk factors like blood pressure and lipids, improvement in endothelial function coupled with anti-inflammatory, antiatherosclerotic and antithrombotic actions. Cardiovascular outcome trials with GLP-1 RAs has shown a statistically significant reduction in three-point major adverse cardiovascular event (MACE), i.e. a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. Overall, GLP-1 RAs have a good tolerance and safety profile with daily/weekly formulations in appropriate doses.

Introduction

Type 2 diabetes mellitus (T2DM) is a major healthcare and economic burden in India comprising approximately 8.8% of the adult population.[1,2] In the South Asian population, T2DM is significantly associated with a higher risk of microvascular and macrovascular complications.[3-5]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are the only approved antihyperglycemic agents that reduce atherosclerotic cardiovascular disease (ASCVD) in patients with T2DM.[6] They produce good glycemic control with little or no hypoglycemia,[7] improve cardiometabolic profile by decreasing weight and blood pressure, improve dyslipidemia, have anti-inflammatory action and also improve endothelial function. They are particularly useful in patients of T2DM with ASCVD.[7] Cardiovascular Outcome Trials (CVOTs) conducted with GLP-1 RAs like liraglutide, semaglutide,

albiglutide and dulaglutide have shown improved cardiovascular (CV) outcomes during the last couple of years.

ASCVD is common in diabetics. GLP-1 RAs with CV benefit are guideline-based recommendations in individuals with established ASCVD or with multiple ASCVD risk factors.

GLP-1 RAs Landscape

GLP-1 RAs are used for the treatment of T2DM in adult and adolescent patients, especially those with established CVD or in those with high CV risk.[8] It includes several long-acting and short-acting treatment agents like liraglutide, semaglutide, dulaglutide, exenatide and lixisenatide.[8]

GLP-1 RAs like liraglutide, semaglutide, albiglutide and dulaglutide have shown a statistically significant reduction in three-point major adverse cardiovascular event (MACE) of cardiovascular death, nonfatal MI and nonfatal stroke.

Liraglutide is the most common GLP-1 RA that is used for the management of T2DM. The clinical trials under the Liraglutide Effect and Action in Diabetes (LEAD) clinical program as well as the Japanese trial studies have demonstrated that liraglutide helps in achieving HbA1c levels below 7% in a higher proportion of patients when compared with other therapies such as metformin and sulfonylureas.[8] Its weight benefits, higher tolerance and safety profile along with a lower risk of hypoglycemia in T2DM patients support its clinical use.[3]

Oral semaglutide in the PIONEER 6 trial has shown noninferiority to placebo for the primary composite outcome of cardiovascular death, nonfatal myocardial infarction (MI) and nonfatal stroke. The CV outcome trial soul is ongoing

Oral semaglutide is an oral formulation of GLP-1 RA, which has been approved by Food and Drug Administration (FDA) as well as Drugs Controller General of India (DCGI). Its safety has been demonstrated in the PIONEER-6 study.[9] In a trial of 3297 patients, once weekly formulations of s.c. semaglutide administered at a dosage of 0.5 mg or 1.0 mg also helped in reducing the risk of myocardial infarction and stroke in individuals with T2DM.[10]

Mechanism of Action of GLP-1 RAs

GLP-1 RAs increase the secretion of glucagon-like peptide-1, which is an incretin hormone produced in the intestine and brainstem.[11] This hormone

activates the GLP-1 receptors in the pancreas, which leads to glucose-dependent increased levels of insulin secretion from the beta cells and glucose-dependent reduced levels of glucagon from the alpha cells of the pancreas that reduces the overall blood glucose levels.[11] Further, it also delays gastric emptying, which delays glucose absorption.[11]

GLP-1 RAs reduce ASCVD by multiple mechanisms. It controls risk factors like obesity, dyslipidemia, diabetes, hypertension and also has anti-inflammatory, antiatherosclerotic, antithrombotic actions.

GLP-1 RAs upregulate insulin biosynthesis and promote its secretion by inhibiting beta-cell apoptosis and inducing their proliferation.[12,13] This proliferation of the beta cell mass leads to the expansion of beta cell mass, which helps to meet the metabolic demands of insulin in patients with T2DM.[12-14]

GLP-1 RAs reduce the intestinal absorption of dietary lipids and enhance the oxidation of hepatic fatty acids having a weight loss effect.[15] The anti-inflammatory effect of GLP-1 RA on the islet cells of the pancreas as well as the adipose tissue is another underlying mechanism for its glucose-lowering effect[16] **(Fig. 1)**.

The dosages and frequency of administration of different GLP-1 RAs are outlined in **Table 1**.

Glycemic Efficacy of GLP-1 RAs

GLP-1 RAs have demonstrated significant reductions in HbA1c and fasting blood glucose levels in patients with T2DM.[17] They have been successful when used as monotherapy or when administered in the form of combination therapy with first and second-line diabetic agents including metformin, sulfonylureas, thiazolidinediones and insulin.[17] Liraglutide facilitates greater glycemic control when compared with other types of GLP-1 RAs and is well tolerated in patients.[17]

In a retrospective study of 7389 individuals with T2DM who had visited the Cleveland Clinic between the years 2005 and 2016, GLP-1 RA therapy was found to improve the probability of HbA1c goal attainment when compared with other oral antidiabetic (OAD) therapy.[18] The use of injectable GLP-1 RAs such as liraglutide was associated with a two-fold increase in the probability of attaining the target HbA1c goal of patients (7.0–7.9%) when compared with other diabetic therapies.[18] Despite the rigorous improvement of blood glucose levels in individuals with T2DM, the use of GLP-1 RAs is associated with a low risk of hypoglycemia.[18] In another study of 38 individuals with T2DM, in obese insulin-resistant cases, no major hypoglycemic events were observed with the use of GLP-1 RAs.[19]

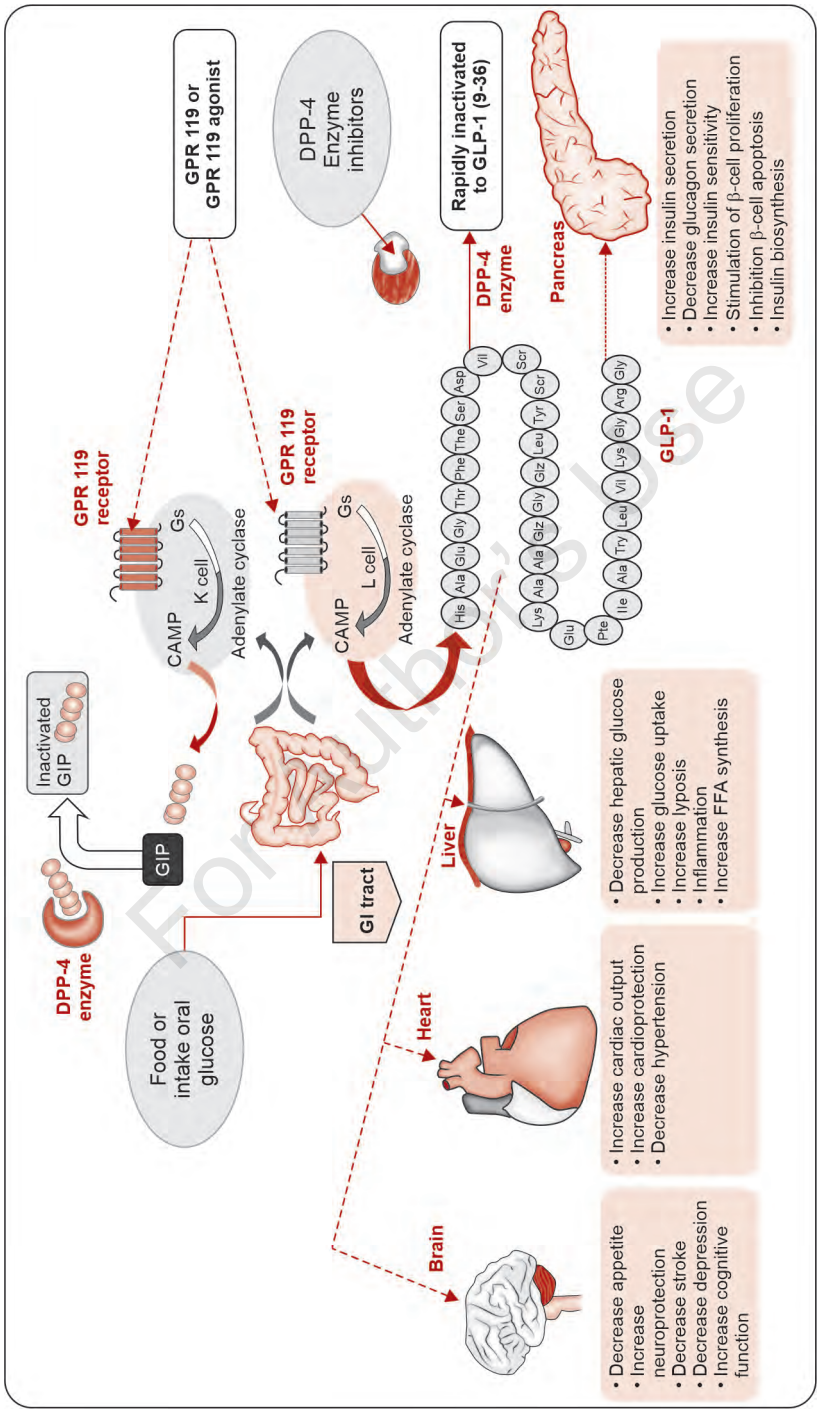

Fig. 1: Mechanism of action of GLP-1 on the target tissues and organs

Table 1 **Dosages and frequency of administration of different GLP-1 RAs**

Drug	*Frequency*	*Properties and dosing*	*CVOT, results*
Albiglutide	Weekly	GLP-1-albumin protein, 30–50 mg	HARMONY, outcomes NR
Dulaglutide	Weekly	GLP-1-Fc conjugate, 0.75–1.5 mg	REWIND, R
Exenatide	Twice daily	Peptide 39 aa, 5–10 µg	ND
Exenatide OW	Weekly	Microsphere peptide suspension, 2 mg	EXSCEL, neutral
Liraglutide	Daily	Acylated peptide, 0.6–1.8 mg, T2D	LEADER, reduced MACEs
Liraglutide	Daily	Acylated peptide, 3 mg, obesity	ND
Lixisenatide	Daily	Peptide 44 aa, 10–20 mg	ELIXA, neutral
Semaglutide	Weekly	Acylated peptide, 0.5–1 mg	SUSTAIN-6, reduced MACEs
Efpeglenatide	Weekly	Exenatide-4-non-glycosylated Fc	Investigational, ND
ITCA650	3–6 months	Exenatide osmotic minipump	Investigational, FREEDOM-CVO, NR

Abbreviations: NR, not repeated; ND, not done; aa, amino acid; T2D, type 2 diabetes; MACEs, major adverse cardiovascular events

Weight Benefits of GLP-1 RAs

Treatment with GLP-1 facilitates weight loss by having a gastrointestinal and neurologic pathway.[20,21] In the gastrointestinal system, treatment with GLP-1 RAs delays gastric emptying, helping to reduce the overall food intake of the patients. Over a period of 6 weeks, individuals receiving GLP-1 treatment demonstrated a significant weight loss of 1.9 kg because of reduced appetite achieved through the use of GLP-1 when compared with placebo. In some individuals, higher weight loss of over 5.3 kg has also been observed. GLP-1 acts on the receptors present in the nucleus tractus solitarius (NTS) of the brain stem, thereby reducing appetite and increasing satiety and also through the metabolism of glucose and lipids. NTS induction also affects cognitive functions for the control of stress and emotional responses, which further help in regulating the eating patterns of the patients. Overall, GLP-1 RAs increase satiety and reduces appetite which facilitates weight reduction.

Cardiovascular Impacts of GLP-1 RAs

Treatment with GLP-1 RAs has shown improvement in left ventricular ejection fraction, myocardial contractility, coronary blood flow, cardiac

output, and endothelial function.[14] At the same time, it helps in reducing the size of infarctions and modulating the overall risks for a cardiovascular event.[18]

The GLP-1 RAs has shown improved CV outcomes in four major trials, i.e. LEADER,[22] SUSTAIN 6,[23] HARMONY and REWIND.[24] The ELIXA[25] and EXSCEL[26] has not shown benefit in ASCVD outcomes.

Amongst GLP-1 RAs liraglutide is usually preferred because in the LEADER trial it showed a 13% reduction in three-point MACE along with 22% reduction in cardiovascular death and 15% reduction in all-cause mortality.

In the LEADER trial,[22] which was a double-blind randomized trial of 9,340 participants showed that liraglutide helped in reducing the risk of CV death, nonfatal myocardial infarction and nonfatal stroke, also termed as three-point MACE, in patients with T2DM. Compared with placebo, liraglutide also lowered the rate of the first occurrence of death from cardiovascular causes among the participants.

In SUSTAIN-6, another randomized, double-blinded, placebo-controlled, multicenter clinical trial of 3297 patients with T2DM, s.c. semaglutide also lowered the risk of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke.

The SUSTAIN 6 trial showed a 26% reduction in three-point MACE driven mainly by reduction in stroke. Albiglutide showed a 22% reduction in three-point MACE driven by reduction in MI but it not available for commercial use.

Dulaglutide in the REWIND trial showed a 12% reduction in three-point MACE and also showed benefit in the primary prevention group.

The salient features of important CVOTs conducted with GLP-1 RAs are outlined in **Table 2**.

Based on the data from published CVOT trials, injectable liraglutide, semaglutide, albiglutide and dulaglutide are the major types of GLP-1 RAs which have depicted superiority in reducing three-point MACE.[28]

In the PIONEER 6 CV safety study, it was found that oral semaglutide corresponded with lower rates of CV mortality (15 out of 1591 with oral semaglutide versus 30 out of 1592 with placebo) as well as all-cause mortality (23 versus 45 in oral semaglutide and placebo groups respectively).[9] The CV mortality was reduced by 51% and all cause mortality by 49%. Since 84.7% of the participants in the PIONEER 6 trial were older than 50 years and had existing CVDs or chronic kidney disorders, a high safety profile of GLP-1 in elderly patients and those with comorbid conditions can be stated. The

Table 2 Salient features of important CVOTs conducted with GLP-1 RAs

CVOT study	*Number of participants*	*Established CVD (%)*	*Follow-up period*	*Summary of the trial*
LEADER trial[20]	9340	81%	42–60 months	The MACE decreased by 13% HR = 0.87, 95% CI = 0.78–0.97, P = 0.01. CV decreased death by 22%. HR = 0.78; 95% CI, 0.66 to 0.93; P = 0.007. All case mortality decreased by 15% HR 0.85; 95% CI, 0.74 to 0.97; P = 0.02
ELIXA trial[24]	6068	100%	25 months	Lixisenatide demonstrated noninferiority in reduction of MACE compared to placebo in patients with T2DM
SUSTAIN-6 trial[21]	2375	58.8%	2.1 years	The MACE decreased by 26% HR = 0.74, 95% CI = 0.58–0.95, P = 0.02. The nonfatal stroke decreased by 39% HR=0.61, 95% CI = 0.38–0.99
HARMONY trial	00, 000	100%	000 years	The MACE decreased by 22% HR = 0.78, 95% CI = 0.69–0.90, P = 0.0006. The nonfatal myocardial infarction were reduced by 25% HR 0.75, CI = 0.61–0.0, P = 0.003
EXSCEL trial[25]	14752	73.1%	3.2 years	The MACE did not differ between the placebo group and patients receiving exenatide
REWIND trial[26]	9901	31%	6 months	The MACE decreased by 12% HR = 0.88, 95% CI = 0.79–0.99, P = 0.026. The primary prevention group also showed significant reduction in MACE
PIONEER 6 trial[27]	3183	85%	15.9 months	In patients with T2DM, the use of oral semaglutide helped in reducing the risk of cardiovascular death (15 in the treatment group vs 30 in placebo). It demonstrated noninferiority in the reduction of risk of nonfatal myocardial infarction and nonfatal stroke. However, the risk of gastrointestinal events was slightly higher in the oral semaglutide group when compared with placebo

PIONEER 6[27] trial was a safety trial with oral semaglutide and it showed non-inferiority in the composite end point of cardiovascular death, nonfatal MI and nonfatal stroke. It showed a 51% reduction in cardiovascular death and 49% reduction in all-cause mortality.

GLP-1 RAs facilitate a significant reduction in the risk of CV death, atherosclerotic cardiovascular disease, and all-cause mortality through an improvement in the overall clinical profile of the patient.[29] In patients with T2DM, these drugs help to reduce several cardiovascular risk factors including systolic blood pressure, hypercholesterolemia, and dyslipidemia by normalizing the serum lipid levels.[29] This effect is achieved through the direct effect of the drug on cardiac myocytes and the endothelium in addition to the weight benefits of GLP-1 RAs.[29,30]

Cardiorenal Benefits of GLP-1 RAs

Meta-analysis reports presenting data from 7 CVOTs depicted that GLP-1 RAs reduced the risk of CV death and all-cause mortality by 12% and 11% respectively.[31] Concerning the cardiorenal benefits, GLP-1 RAs reduced the risk of heart failure by 9%, nonfatal stroke by 16% and kidney outcome by 17% when compared with the placebo.[31]

GLP-1 RAs trials have also shown renal benefits but SGLT2 inhibitors have a better data. Unlike SGLT2 inhibitors GLP-1 RA can be used safely in CKD even upto eGFR 15 mL/min/m^2.

Consensus recommendations from South Asian Taskforce including expert panelists from South East Asian countries like India, Pakistan, Bangladesh, Nepal, Sri Lanka, Afghanistan and Maldives have supported the use of GLP-1 RAs in special populations at high risk of CVDs.[32] According to their guidelines, GLP-1 RAs are suitable for elderly patients since treatment with GLP-1 is associated with a low risk of hypoglycemia and lower glycemic variability.[32] They were considered to be better treatment agents than insulin in the times of fasting such as Ramadan because they do not require major dose adjustments.[32] There is a recommendation advocating the use of GLP-1 RAs in patients with polycystic ovarian disease owing to its weight benefits in addition to its glycemic control and anti-inflammatory effects.[32]

Indications for GLP-1 RAs

GLP-1 RAs are indicated in patients with HbA1c levels 1.5% above the target and those who do not achieve target A1c levels following 3 months of treatment with metformin.[20-29] They are preferred treatment agents in individuals with ASCVD and those with multiple risk factors. They also have renoprotective effect in chronic kidney disease.[20-29]

A high dose of liraglutide is an FDA-approved indication for the management of obesity and associated comorbid conditions. Liraglutide is also the only approved GLP-1 drug for the treatment of adolescents and children above 10 years of age with T2DM. In India, the use of liraglutide and dulaglutide is more common. Drugs such as semaglutide are not available in India but are currently being explored for the management of obesity.

Dosage of GLP-1 RAs

Liraglutide is recommended to be administered at a dose of 0.6 mg subcutaneously once daily for 1 week, following which, a dosage of 1.2 mg is suggested for uptitration based on tolerability of the patient.[33] After a week, this dose can be further up titrated to an optimal dosage of 1.8 mg if no adverse effects like nausea or vomiting are observed.[33] Dulaglutide is used in doses of 0.75 to 1.5 mg SC per week. Injectable semaglutide is used in doses of 0.25 mg to 1 mg SC weekly but is not available in India.

Liraglutide is the most commonly used GLP-1 RA in our country for ASCVD reduction. Oral semaglutide is likely to be available in India in near future.

Oral semaglutide needs to be started in consideration of the blood glucose levels of the patient. Initially, a dosage of 3 mg once daily is recommended, which can be up titrated to 7 mg or 14 mg once daily dosage depending on the glycemic levels of the patient. The once-weekly formulations of subcutaneous semaglutide are also given in a fixed dosage depending on the glycemic profile of the patient.[33]

When oral semaglutide is available in India, it will be easier to use a combination of SGLT-2 inhibitors and semaglutide for providing comprehensive cardiorenal protection.

A dose-response relationship between GLP-1 administration and risk reduction of CVDs has been established.[30] However, there needs to be an individual consideration of the clinical profile and the treatment goals of the patient before deciding the dosage of liraglutide or semaglutide. The cardiovascular benefit of GLP-1 RAs is more profound in obese individuals (BMI above 30 kg/m^2) when compared with nonobese subjects.[30] Safety considerations and tolerance profile of the patient must also be considered before dosage prescription.[34]

Anti-inflammatory Effects of GLP-1 RAs

The anti-inflammatory actions of GLP-1 RAs are prominent on the vascular system including the endothelial cells and the arteries which help in reducing

the risk of atherosclerotic cardiovascular disease.[16,35] These effects have also been observed on other major organs like the liver, brain, kidney, lungs, testis and the skin.[16] GLP-1 RAs act on the smooth muscle cells by inhibiting the over expression of cytokines and reducing the infiltration of immune cells in the tissues facilitating the reduction of comorbid conditions in patients with T2DM.[16,34]

Side Effects of GLP-1 RAs and Practical Considerations for Their Management

Liraglutide is the only approved GLP-1 drug for treatment in adults as well as adolescents with T2DM because of its high safety profile. However, it can lead to mild gastrointestinal side effects including stomach upset, fullness, nausea, vomiting and diarrhea observed in 35–44% of the patients.[28] However, similar side effects including diarrhea, nausea, flatulence, indigestion, vomiting, and abdominal discomfort are also common with the use of first-line antidiabetic agents such as metformin, thereby no particular safety concern associated with the use of GLP-1 RAs has been deduced.[36] Further, the gastrointestinal side effects caused by GLP-1 RAs are mostly dose-dependent and can be reduced through suitable dose adjustments.[29] Reducing the initial dosage of liraglutide for patients exhibiting gastrointestinal side effects is recommended. Along with this, it is recommended to switch to weekly administrations instead of daily dosage in patients with major gastrointestinal complaints.[30] Dietary changes such as the intake of lighter, low fat meals can also help in overcoming gastrointestinal concerns such as nausea.[29]

Gastrointestinal manifestations are the most common side effect of GLP-1 RAs but they can be minimized by prior administration of proton pump inhibitor and taking the injection in fasting stage.

The risk of hypoglycemia is significantly lower with the use of GLP-1 RAs when compared with other treatment agents like insulin and metformin.[28] No treatment modifications are thereby necessary for patients prescribed with GLP-1 therapies. Other adjunct drug doses are usually reduced post addition of Liraglutide and also from the perspective of hypoglycemia as Lira doesn't cause severe hypoglycemia.[29] In patients close to their target HbA1c values, a lower dose of GLP-1 RA is recommended.[29]

In the SUSTAIN 6 trial, the risk of retinopathy in patients with T2DM can be attributed to a faster reduction of HbA1c levels. In these patients, long-term improvement of the degree of retinopathy was observed after immediate deterioration, which indicates that these side effects are temporary and can be managed with the help of preventive measures.[21]

The use of GLP-1 RAs such as injectable liraglutide, s.c. semaglutide, dulaglutide and oral semaglutide has been supported by international guidelines such as the WHO and the American Diabetes Association for the management of T2DM in individuals with comorbid conditions.[32]

Safety Profile of GLP-1 RAs

GLP-1 RAs significantly reduce HbA1c levels in patients within the first year of treatment. In a retrospective analysis of 131 patients, it was observed that 47% of patients with T2DM were able to maintain their HbA1c levels close to 7.5% through the long-term use of GLP-1 over 1 year.[37] Over a period of 4 years, it was observed that the HbA1c levels of the patients were maintained.[37] Even after a follow-up of 7 years, no major adverse events were reported with the use of GLP-1 RAs in the patients.[38] However, a regular follow-up of blood glucose levels is recommended for patients with T2DM on the GLP-1 regimen for suitable dose adjustments.[38]

The safety profile of GLP-1 RAs has not yet been established in pregnant and lactating women.[32] South Asian consensus guidelines thereby recommend discontinuation of GLP-1 RAs 2 months before pregnancy.[32] It is also suggested to be avoided during the period of lactation. However, in non-pregnant women of the reproductive age group, oral semaglutide, injectable liraglutide and semaglutide can be safely administered.[32] It does not have any toxic impact on the reproductive system, and is in fact, a suitable treatment for diabetic patients with polycystic ovary syndrome (PCOS).[32]

Future Prospects of GLP-1 RAs

Exciting preliminary data is emerging with GLP-1 RAs in NASH, diabetic retinopathy Alzheimer's disease, Parkinson's disease

In the future, it is expected that GLP-1 RAs will be successfully used for the management of obesity in individuals with T2DM or prediabetes.[39] Through its anti-inflammatory effect, GLP-1 therapy has been suggested as an anti-diabetic agent in ASCVD patients and has a potential for use in patients with other comorbid conditions such as nonalcoholic steatohepatitis, endothelial dysfunction, neurodegenerative disorders like Alzheimer's, diabetic nephropathy, asthma, and psoriasis.[16,35]

Acknowledgment

I would like to thank Dr Vijaya Vasanthakumar, Dr Kunal Srivastava and Dr Ritwik Banerjee from the medical team of Novo Nordisk for the information provided.

Conclusion

GLP-1 RAs such as injectable liraglutide, semaglutide and dulaglutide are effective for reducing the risk of cardiovascular events in individuals with T2DM through glycemic control, cardioprotective benefits and weight reduction. CVOT studies have demonstrated the superiority of these agents when compared with placebo. Oral semaglutide is going to be available in India in near future and its availability will kick off its use with SGLT-2 inhibitors for comprehensive cardiorenal risk reduction. Treatment with GLP-1 RAs has the lowest adverse events' profile when compared with other antidiabetic agents including OADs and insulin. Due to its lower risk of hypoglycemia, it does not require frequent dose adjustments and thus has a higher rate of treatment compliance. Follow-up studies have demonstrated that treatment with GLP-1 RAs helps in maintaining blood glucose levels close to the target range (7.0 to 7.9 %). Practical recommendations for its use include administration of a lower starting dosage to reduce the risk of gastrointestinal events. It also helps in lowering the dosage of other oral antihyperglycemic drugs when used concomitantly over a period of time.

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Chapter

4

When to Say Bye-Bye to Aspirin?

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Abstract

Aspirin is the oldest and most commonly used antithrombotic drug, but the new evidences have made us all to say bye-bye to aspirin. The recent three trial ASCEND, ASPREE, and ARRIVE have put an end to the road of aspirin for primary prevention. In patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI), newer oral anticoagulant drugs trials specially AUGUSTUS have almost closed the door for aspirin as a part of triple antithrombotic therapy in this subset of patients except for an initial use for a very brief period of a week or so. Aspirin can still be used for secondary prevention but new suggests that it can be stopped after 1–3 months.

Introduction

Aspirin was discovered by Bayer's in 1898, was considered as a miraculous drug for thrombotic conditions. It is one of the mainstays of antithrombotic treatment in patients with atherosclerotic cardiovascular disease (ASCVD).[1] Aspirin has starting falling into disrepute due to emerging recent evidences through various trials (ARRIVE, ASPIRE, ASCEND trial), first as a therapy for primary prevention and secondly as a part of triple therapy in atrial fibrillation (AF) with primary coronary intervention (PCI) (AUGUSTUS trial). It has also failed in secondary prevention too (TWILIGHT trial). So, the drug which was once considered a wonder drug, now it's time to withdraw it from the treatment.

The use of aspirin for primary prevention has become dubious because the decrease in ischemic events is offset by increase in bleeding.

Controversies on Relevance of Aspirin Use in Primary Prevention

After initial upsurge, studies after 2005 have revealed negative results with respect to use of aspirin in primary prevention. POPADAD and JPAD studies determined effects of aspirin in diabetic patients,[2,3] which showed that aspirin did not lower the risk of cardiovascular events in diabetic patients. Three large randomized trials *ASCEND, ASPREE, and ARRIVE* were conducted including patients with diabetes but without any grave cardiovascular disease (CVD) to confirm the contradictory opinions about aspirin.

The ASCEND Trial: Moderate Benefit in Patients with Diabetes

The efficacy and safety of aspirin (100 mg daily, oral) versus placebo in patients with diabetes without established ASCVD was studied in the ASCEND trial, in which 15,480 patients were enrolled.[4] Eligible patients were adults ≥40 years of age with diabetes mellitus of any type. The primary endpoint was the first serious vascular event defined as myocardial infarction, stroke or transient ischemic attack or death from any vascular cause apart from intracranial hemorrhage. The primary safety outcome was considered as the first major bleeding event, defined as intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal (GI) bleeding, or other serious bleeding. During the follow-up period of 7.4 years, low-dose aspirin therapy consumed daily resulted in a 12% reduction in primary efficacy endpoint compared with placebo (8.5% vs. 9.6%; RR 0.88; 95% CI: 0.79, 0.97; P = .01). The incidence of major bleeding in the aspirin group was higher, compared with the placebo group (4.1% vs. 3.2%; RR 1.29; 95% CI: 1.09, 1.52; P = .003).[4] The most common major bleeding event in the aspirin group was GI bleeding. It was concluded that though aspirin lowers the risk of serious vascular events in patients with diabetes without established ASCVD, but the benefits of daily low-dose aspirin were negated by the increased risk of major bleeding.

The ASPREE Trial: Aspirin was Proved Harmful in the Elderly[5]

The ASPREE trial was to assess the efficacy and safety of aspirin (100 mg daily, oral) versus placebo for primary prevention of ASCVD in older patients in which total of 19,114 patients were enrolled. Eligible patients were adults ≥70 years in females or ≥65 years in males. The primary endpoint was death, dementia, or persistent physical disability. The secondary endpoints were considered as major hemorrhage and cardiovascular disease (i.e., fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure). During the period of 4.7 years of follow-up, the rate of cardiovascular disease was lower per 1000 person-

years in the aspirin group compared with the placebo group (10.7 events vs. 11.3 events; HR 0.95; 95% CI: 0.83, 1.08). Rates of major bleeding events were higher in the aspirin group compared with the placebo group (8.6 vs. 6.2 events per 100 person-years; HR 1.38; 95% CI: 1.18, 1.62; P < .001), with GI bleeding accounting for the most of the major bleeding events in the aspirin group. The study concluded that daily, low-dose aspirin did not significantly reduce the risk of ASCVD in older patients, rather aspirin therapy resulted in a significantly higher risk of major bleeding in these patients.

The evidence from ASCEND, ASPREE and ARRIVE has paved the way for exit of aspirin for primary prevention.

The ARRIVE Trial: No Use in Patients at Low Risk[6]

The primary goal of the ARRIVE trial was to check the efficacy and safety of aspirin (100 mg daily, oral) versus placebo for primary prevention of ASCVD in patients with a moderate risk of a primary cardiovascular event in which 12,546 patients were enrolled. This was a randomized, double-blind, placebo-controlled multicenter study. Eligible patients were ≥55 years (men) or ≥60 years of age (women) with three or more of the following risk factors: elevated total cholesterol or low-density lipoprotein (LDL) cholesterol or low high-density lipoprotein (HDL) cholesterol irrespective of treatment, past history of cigarette smoking prior to enrolling in the study, hypertension, receiving medication to treat hypertension, and a positive family history of cardiovascular disease. Patients with diabetes were excluded from the study. The primary efficacy end points was the time to first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, or other transient ischemic attack. The safety endpoints of the study were considered as hemorrhagic events and incidence of other adverse events. During the follow-up of 5 years, the primary endpoint was seen in 4.29% versus 4.48% of patients in the aspirin versus placebo group (HR 0.96; 95% CI: 0.81, 1.13; P = .60). The events of GI bleeding were mild and happened in 0.97% of patients in the aspirin group versus 0.46% in the placebo group (HR 2.11; 95% CI: 1.36, 3.28; P = .0007).

Based on these recent evidences, we can say bye-bye to aspirin for primary prevention in every scenario except for a small group of patients who are young (50–70 years) and who have multiple CV risk factors with a 10-year CV risk of >20% and with no bleeding risk or bleeding diathesis **(Table 1)**. There is growing evidence which suggest that calcium score may be taken as a tool to decide whether to start aspirin or not. Those with a calcium score of >100 may be benefited than those with calcium score of <100.[7]

Table 1 Guidelines for primary prevention with aspirin

2016 ESC guidelines for cardiovascular disease (CVD) prevention	*Class*	*Level*
Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding	III	B
2019 ESC guidelines on diabetes, prediabetes and CVD		
In patients with diabetes mellitus (DM) at high/very high risk, aspirin (75–100 mg/day) may be considered in primary prevention in the absence of clear contraindications	IIb	A
In patients with DM at moderate cardiovascular (CV) risk, aspirin for primary prevention is not recommended	III	B
2019 ESC guidelines for CVD prevention		
Low-dose aspirin (75–100 mg orally daily) might be considered for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) among select adults 40–70 years of age who are at higher ASCVD risk but not at increased bleeding risk	IIb	A
Low dose aspirin (75–100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adult >70 years of age	III	B
Low dose aspirin (75–100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding	III	C

Aspirin as a Part of Triple Therapy in Patients with ACS and AF

Patient with atrial fibrillation (AF) undergoing PCI needs both anticoagulant to reduce the incidence of stroke and a strong dual antiplatelet therapy (DAPT) to reduce chance of stent thrombosis and major cardiovascular event (MACE). The triple therapy is known to increase the risk of bleeding three times. The WOEST trial showed that stopping aspirin from the triple antithrombotic regime reduces bleeding by 64%. The series of trials have been conducted with NOAC in this subset of patients.

PIONEER AF-PCI trial[8], where patients with AF and primary coronary intervention with stenting, the administration of low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with a lesser rate of significant bleeding than standard therapy with a vitamin K antagonist plus DAPT for 1, 6, or 12 months.

The RE-DUAL PCI trial[9] compared two antithrombotic regimens, using approved doses of dabigatran (150 mg twice daily or 110 mg twice daily) with a P2Y12 inhibitor, with warfarin and a DAPT. In this trial too, the amount of bleeding was significantly lower with each of the dabigatran-based regimens than with warfarin plus DAPT, and risk of ischemic events was also not higher.

Stopping aspirin early from triple therapy for subset of patients of atrial fibrillation with ACS undergoing PCI and stenting decreases bleeding without any effect on ischemic events.

In AUGUSTUS international trial[10], patients with AF were randomly assigned to two groups, one who had an acute coronary syndrome or undergone PCI and planning to take apixaban or a vitamin K antagonist and to receive aspirin or matching placebo for 6 months. The primary outcome was major or clinically significant nonmajor bleeding. Secondary outcomes were considered as death or hospitalization and a composite of ischemic events. It was concluded that in patients with AF and a recent acute coronary syndrome or PCI treated with a P2Y12 inhibitor, an antithrombotic regimen consisting of apixaban, without aspirin, resulted in less bleeding and lesser hospitalizations without significant differences in the occurrence of ischemic events than regimens that included a vitamin K antagonist, aspirin, or both.

The trial showed that NOAC along with single P2Y12 inhibitor is sufficient to prevent ischemic events and aspirin can be omitted in this subset of patient.

According to the recent ESC NSTEMI guidelines in patients with AF undergoing PCI, aspirin can be used only for 1 week after the first event and then continue only with clopidogrel and a NOAC for 12 months and after 12 months only NOAC is sufficient.[11]

Evidence of Aspirin in Secondary Prevention

According to the ACC/AHA ESC guidelines, it is recommended that aspirin should be continued indefinitely in patients with ASCVD whether it is ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) or stable coronary artery disease (CAD). Recently emerging data showed that aspirin can be stopped usually after 1–3 months, especially in this subset of patients. Reducing duration of DAPT did not increase the number of ischemic events and have reduced the incidence of stent thrombosis without increasing bleeding events.

In the TWILIGHT trial,[12] 9006 patients were randomized undergoing PCI at 3 months into ticagrelor monotherapy versus standard DAPT for 12 months. It was concluded that in high-risk patients who had PCI and completed 3 months of dual antiplatelet therapy, ticagrelor monotherapy without aspirin was associated with reduced incidence of clinically significant bleeding than ticagrelor plus aspirin, without higher risk of death, myocardial infarction, or stroke.

Likewise, TICO trial, TICO STEMI trial, STOP DAPT, SMART CHOICE trial also produced similar results that even if aspirin is omitted after 3 months in

patients undergoing PCI, there is no rise in ischemic events but incidence of bleeding is significantly reduced.[13]

Similarly at 1 year of secondary prevention, aspirin monotherapy may be replaced by either clopidogrel or ticagrelor monotherapy. (A recent meta-analysis has shown that P2Y12 monotherapy is better than aspirin monotherapy in terms of reducing MI at the same time without increasing any extra bleeding risk when given for secondary prevention.[14] The guidelines still recommend aspirin lifelong for secondary prevention but recent data recommends that aspirin can be omitted after 3 months of the index event particularly in high bleeding subgroups and this has been incorporated in the recent ESC 2020 guidelines with a class IIa recommendation.

Evidence of Aspirin in Stroke Prevention in AF

No role of aspirin in stroke prevention in AF (Class III recommendation).

Evidence of Aspirin in Secondary Ischemic Stroke Prevention

Aspirin has a role in this subset and it can be used alone or in combination with Rivaroxaban low dose (COMPASS trial)[15] or in combination with Ticagrelor for TIA and mild stroke (THALES trial)[16] or in combination with clopidogrel (CHANCE or POINT trial).[17]

The subset in which we need to say bye-bye to aspirin is highlighted in **Table 2**.

We know that statins have proved themselves as a good agent for primary prevention. It has been speculated that if person is already taking statin for primary prevention then any further advantage of aspirin may be attenuated by statins. The upcoming acetylsalicylic acid (ASA) and Simvastatin Combination for Cardiovascular Events Prevention Trial (ACCEPT-D) is set to evaluate the strongly suspected attenuation effect of statins on the aspirin benefit. This trial may turn out to be the last nail in the coffin for aspirin for primary prevention.

Table 2 When to say bye-bye to aspirin

Subset	*Response to Aspirin*
Primary prevention	Bye-bye except for a small group of young population with multiple CV risk factors and low bleeding risk
Stroke prevention in AF	Bye-bye
Triple antithrombotic therapy (AF patients undergoing PCI)	Bye-bye except only for first week of index event
Secondary prevention of CAD	Probably no (But in future P2Y12 inhibitors mono-therapy may replace aspirin monotherapy)

Abbreviations: AF, atrial fibrillation; PCI, percutaneous coronary intervention; CAD, coronary artery disease; CV, cardiovascular

Conclusion

Aspirin therapy reduces cardiovascular morbidity and mortality in patients with ASCVD. The bleeding risks can counterbalance the cardioprotective benefits of low-dose aspirin therapy in some cases without ASCVD. Further, aspirin use is associated with increased bleeding. Current evidence says that the low-dose aspirin therapy should be used for primary prevention in patients with high ASCVD risk. Regular and long-term low-dose aspirin should not be started in patients with low-ASCVD risk, patients at higher risk for bleeding, and adults >70 years. The low-dose aspirin therapy should be based on individual patient factors. Before initiating aspirin therapy, benefits and risks of treatment should be discussed with the patients.

The failure of recent trials of aspirin for primary prevention to show a benefit for nonfatal and fatal cardiovascular disease outcomes should also lead to reassessment of its role in secondary prevention, especially in the postacute setting (i.e.,>1 year after myocardial infarction, stroke or revascularization).[18] Intensive therapy for cardiovascular disease risk factors might also have led to the diminished benefit of aspirin for secondary prevention among people with stable cardiovascular disease. The guidelines continue to recommend life-long aspirin for secondary prevention.

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Chapter 5

War against Heart Failure: The New Weapons in the Armory

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Abstract

Heart failure (HF) once sets in runs a malignant progression with a very high morbidity and mortality. The conventional drugs no doubt decreases mortality but the residual mortality is a substantial, the 5-year mortality is 50%. Therefore, there has always been an ongoing search to have newer and newer weapons in the armory to fight the devil of stroke. But curiously enough all new drugs like the old drugs only target heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) is still in search of a therapy which could improve its outcome. The angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB). Beta-blockers and mineralocorticoid receptor antagonist constitute guideline recommended triple foundation therapy for HFrEF. The PARADIGM trial with Sacubitril valsartan was presented in 2014 and was approved for treatment of chronic HFrEF in 2016 and after the PIONNER HF trial it was approved for acute decompensated heart failure (ADHF). The DAPA HF trial presented in 2019 showed improved CV outcome in HFrEF and has been approved for treatment by all guidelines. The two other weapons vericiguat, a direct stimulator of soluble guanylate cyclase has shown positive results in the VICTORIA trial and the selective cardiac myosin activator omecamtiv mecarbil has shown positive results in GALACTIC HF trial but both these new weapons are still in the process of evolution and are not yet approved by the guidelines.

Introduction

The last couple of years have witnessed spectacular advances in the field of heart failure (HF) both in the terms of enhanced understanding and in the availability of a panoply of therapeutic options. HF once sets in, runs a malignant progression with a very high morbidity and mortality. The conventional drugs no doubt blunts this malignant progression but the residual mortality remain substantial, 5-year mortality being 50%. Curiously

enough, all new weapons in the armory targets only heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) is still in search of a drug which could improve its outcome.

HF once set seen runs a malignant progression with a high morbidity and mortality. The conventional drugs no doubt blunts this malignant progression but the residual risk is substantial, 50% at the end of 5 years.

Neurohormonal activation plays a very important role in initiation and perpetuation of heart failure. There are two types of neurohormonal system, the maladaptive which comprises of sympathetic, renin angiotensin and aldosterone system and the vasculoprotective natriuretic peptide system. We have strong blockers to all the maladaptive neurohormonal system, i.e. beta-blockers for sympathetic, angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) for rennin angiotensin system (RAS) and mineralocorticoid receptor antagonists (MRAs) for aldosterone. All these three drugs have laid the base line foundation stone of tripe therapy for treatment of HFrE. All these three drugs became the first three pillars of HFrEF.

Curiously enough all old and new drugs only targets HFrEF and HFpEF is still in search of a new drug with could improve its outcome.

MRAs were approved in 2003 and it took 11 years to target the natriuretic peptide system and the PARADIGM trial[1] with sacubitril valsartan was presented in European Society of Cardiology (ESC) meeting in 2014 and the drug was approved for HFrEF in 2016. After the PIONEER HF[2] trial for acute decompensated heart failure (ADHF) the drug was approved for it in 2019. Sacubitril valsartan became the fourth pillar of HFrEF.

Sacubitril valsartan evoked a new concept of multisystem neurohormonal modulation never utilized before. It has unique distinction of getting a class I recommendation to replace a class IA drug (ACEI/ARB)

2019 initiated dawn of a new era when sodium-glucose cotransporter-2 (SGLT2) inhibitor dapagliflozin (DAPA) in DAPA HF trial[3] in HFrEF showed improved outcomes. The trial included diabetics as well nondiabetic patients and both benefited with DAPA. The drug was approved for treatment of HFrEF by the Canadian guidelines in the same year and by all other guidelines in 2020. After this trial DAPA became the fifth pillar of HFrEF.

In 2020, itself we had the VICTORIA trial[4] with vericiguat which showed positive outcome. The vericiguat is a stimulator of soluble guanylate cyclase

(sGC) which results in increased levels of cGMP which produces cardio-protective and vascular protective benefits. Recently GALACTIC HF trial[5] with selective cardiac myosine activator omecamtiv mecarbil presented at American Heart Association (AHA) 2020 has shown positive results. Therefore, we have two new weapons approved for clinical use for HFrEF, i.e. sacubitril valsartan and dapagliflozin and vericiguat and omecamtiv macarbil are still in the process of evolution and may be approved in future and will further add to therapeutic armamentarium of HFrEF.

Sacubitril Valsartan in HFrEF

Sacubitril valsartan has evoked a new concept of multisystem neurohormonal modulation never heard before. It has the unique distinction of acquiring class I indication to replace a class IA drug, i.e. ACEI/ARB. Usually when a new drug is approved for clinical use it is often given an add on recommendation. The drug has shown a 20% reduction in the primary end point of cardiovascular death and hospitalization for HF in the landmark PARADIGM trial. Both the individual components of the primary end point also showed statistically significant reduction. The cardiovascular death (CVD) was decreased by 20%. The drug decreased all types of mortality, i.e. CV mortality, mortality due to sudden cardiac death (SCD), mortality due to worsening HF and all-cause mortality. The hospitalization for HF was also decreased by 21%. It also decreased multiple hospitalization for HF and also decreased the stay in intensive coronary unit (ICU).

SGLT2 Inhibitors

SGLT2 inhibitors are the molecule of the decade. All three front line SGLT2 inhibitors, i.e. empagliflozin, dapagliflozin and canagliflozin were approved for decreasing hHF in patients at risk after the three landmark trials.[6-8] Empagliflozin, in addition was also approved for reduction in cardiovascular death due to positive data from the EMPA-REG OUTCOME trial.

Dapagliflozin after the DAPA HF trial laid the first foundation milestone of improving CV outcome in HFrEF, both diabetics and nondiabetics patients.

The DAPA HF trial which randomized 4744 patients with New York Heart Association class II, III or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) in addition to the standard of care therapy over a median follow-up of 18.4 months showed a statistically significant relative risk reduction of 26% (hazard ratio, 0.74% 95% confidence interval (CI), 0.65 to 0.85; P<0.001).

The cardiovascular death showed a relative risk reduction of 18% (hazard ratio, 0.82; 95% CI, 0.69 to 0.98). The worsening heart failure event showed a reduction of 30% compared to placebo (hazard ratio, 0.70; 95% CI, 0.59 to 0.83). The trial included diabetics as well as nondiabetic patients and the benefits were similar in both the groups and there is no risk of hypoglycemia associated with the use of this drug in nondiabetic patient. About 11% of the patients were on sacubitril valsartan and showed a statistically significant risk reduction in diabetic as well nondiabetic patients, 25% relative risk reduction in diabetic patients and 26% relative risk reduction in nondiabetic patients.

DAPA also showed incremental benefit on top of ARNI and became a new pillar for treatment of HFrEF.

The drug also showed incremental benefit on top of sacubitril valsartan. The EMPEROR REDUCED[9] randomized assigned 3730 patients with class II, III or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to standard of care therapy. Compare to the DAPA HF trial the EMPERIOR REDUCED trial included more sicker patients in terms of lower ejection fraction and greater values of NT-pro-BNP. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure. After a median follow-up of 16 months the primary end point of cardiovascular death or hospitalization of HF reduced by 25% (hazard ratio for cardiovascular death or hospitalization for heart failure 0.75; 95% confidence interval (CI), 0.65 to 0.86; P<0.001). The benefit was same in diabetic as well as nondiabetic patient. The EMPEROR REDUCED trial enrolled greater number of patients on sacubitril valsartan, about 18% and this subset also showed incremental benefit with empagliflozin.

The EMPERIOR REDUCED trial showed similar reduction like DAPA HF trial but failed to show statistically significant reduction in all CV mortality and all-cause mortality.

The hospitalization for HF was reduced by 30% (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; P<0.001). Thus, both trials showed similar reduction in hospitalization for heart failure but unlike the DAPA HF trial, the EMPERIOR reduce trial failed to show statistically significant reduction in cardiovascular mortality and all-cause mortality.

Vericiguat

It is a novel oral soluble guanylate cyclase (sGC) stimulator and results in increased production of cyclic guanosine monophosphate (cGMP) which

Table 1 **Beneficial effects of cGMP on heart and vasculature**

Heart
• Decreases progressive myocardial thickening • Decreases myocardial thickening • Decreases ventricular remodeling • Decreases fibrosis
Vasculature
• Decreases arterial constriction • Decreases vascular stiffness

produces beneficial effects on the heart and vasculature **(Table 1)**. It also increases sensitivity of nitrous oxide to stimulate sGC.

Vericiguat was evaluated in the VICTORIA trial.[4] Tested in phase 3 randomized, double blind, placebo controlled trial. The trial included 5050 patient with chronic heart failure (New York Heart Association Class II, III or IV) and an ejection fraction of <45% with a recent worsening HF event like recent HF hospitalization or IV diuretic use or elevated NT proBNP >1000 pg/mL and if AF >1600 or BNP >300 pg/mL or if atrial fibrillation >500 and vericiguat 10 mg once daily was compared to placebo on top of guideline-based medical therapy. The primary outcome was a composite of death from cardiovascular causes or first hospitalization for HF. Over a median follow-up 10.8 months the trial showed a statistically significant reduction of 10% in the primary end point (HR 0.90; 95% CI, 0.82 to 0.98, P = 0.02) driven primarily by reduction in hospitalization for HF (HR 0.90; 95% CI, 0.81 to 1.00). The absolute benefit in primary event reduction was 4.2/100 patients years and the NNT for 1 year was only 24. Symptomatic hypotension is a side effect and was seen in 9% in the vericiguat group and 7.9% in placebo group which was not statistically significant. It is once daily medicine, easy to titrate, generally safe and well tolerated, without the need for monitoring renal function or electrolytes.

Vericiguat in the VICTORIA trial and omecamtiv mecarbil in the GALACTIC HF trial has shown positive result but both these molecules have not yet been approved for clinical use.

Omecamtiv Mecarbil

It is novel selective cardiac myosin activator. It increase the entry rate of myosin into the tightly–bound, force-producing state with actin like more hands pulling on the rope. It does not produce increases in myocyte calcium and there is no change in dP/dt and myocardial oxygen consumption (MVO_2).

It was tested in the GALACTIC-HF study[5] which enrolled 8256 patients 18–85 years of age with chronic HFrEF (EF 35% or less) NYHA class II, III or IV symptoms, NT-proBNP >400 pg/mL and BNP ≥125 pg/mL.

The primary outcome was a composite of cardiovascular death of HF event. Over a median follow-up of 21.8 months, the primary end point showed a statistically significant relative risk reduction of 8% (HR 0.92; 95% CL 0.86-0.99; P = 0.03). Among the secondary end points, the first hospitalization for HF showed a numerical decrease of 5% (HR 0.95; 95% CI 0.87–1.03) and there was no decrease in cardiovascular death (HR 1.01; 95% CI 0.92–1.11; 0.86). The METEORIC HF a phase three trial is ongoing to assess the effect of drug on exercise capacity compared to placebo.

HF is always a part of cardiorenal continuum and both HF and CKD should always be treated conjointly and not in isolation in fact targeting CKD triggers benefit for HF.

Cardiorenal Continuum

Heart failure and chronic kidney disease (CKD) commonly coexist and there is an intimate bidirectional interplay between HF and CKD. Worsening HF worsens CKD and deterioration in renal function worsen HF. Both these conditions should never be treated in isolation and the whole cardiorenal continuum should be targeted for optimum results. Infact targeting CKD in HF triggers benefit for HF and this was the missing link which we have ignored for several years. Inherently SGLT2i target cardiorenal continuum as a whole. There are seven reasons why the focus should also be on kidneys in HF **(Box 1)**.

Should all Four Drugs be used in Patients of HFrEF ?

All fours drugs, i.e. beta-blockers, ACEI/ARB/sacubitril valsartan, SGLT2 i have shown incremental benefit on top of other drug. Therefore, as far

Box 1 **Seven reasons why the focus should also be on kidneys in HF**

1. CKD is easy to detect
2. Proteinuria and eGFR are easy to obtain
3. The trajectory of CKD can be slowed down by RAASi & SGLT2i
4. SGLT2i has great efficacy on top of RASS blocker
5. Works just as well in the real world
6. SGLT2i is not just for individuals with complications
7. CKD detection and treatment saves the heart

as possible all four drugs should be utilized although the sequence of initiation may vary depending on the subset of patient. The three important sectors which determine the initiation of drugs are eGFR, blood pressure and potassium levels. If the blood pressure is not low potassium level is normal and eGFR above 30 ARNI can be initiated but if the eGFR is near 30, blood pressure is systolic 90–100 and potassium level is at upper level of normal. SGLT2i should be initiated and when the heart is unloaded and hemodynamics improve ARNI can be initiated.

All four drugs, i.e. beta-blockers, ACEI/ARB/sacubitril valsartan, SGLT2i must be utilized in all patients of HFrEF if the patient tolerates it, although the sequence of initiation may vary from patient to patient. Preferably all four drugs must be on board within 4–6 weeks.

Should We De-escalate Therapy if the Patient become Less Symptomatic?

Heart failure runs malignant progression and should never be considered a stable disease even if the patient has less symptoms. In fact stable heart failure is a myth. Therefore, one should never think of de-escalating pharmacotherapy if the patient is tolerating it.

How Much Time is Required to Put All Four Drugs on Board?

There is no randomized control trial for it but it is agreed that all four drugs should be on board within a period of 4 weeks or so.

Conclusion

The new weapons in the armory for HFrEF, i.e. sacubitril valsartan and SGLT2i dapagliflozin has been approved for clinical use across the globe. Both these drugs provide incremental benefit on top of conventional guideline recommended therapy. Both these drugs are safe if due precautions are taken during their utilization. Time has come when all four drugs, i.e. betablockers, ACEI/ARB/sacubitril valsartan, SGLT2i should be on board with in a period of 4–6 weeks if the patient is tolerating these drugs. Vericiguat and omecamtive are two other new weapons positive results in trials but are still in the process of evolution and not yet approved for clinical use.

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Chapter 6

Will Endoscopic Bariatric Procedures for Obesity Make Bariatric Surgery Redundant in Future?

Mohit Bhandari, Manoj Reddy, Susmit Kosta, Winni Mathur

Abstract

Obesity is a global health problem and is associated with morbidity and mortality. Life style modification is useful but has poor compliance in the long run. Drug therapy only produces slight decrease in weight. Bariatric surgical procedures are time tested modalities of treatment with good results but has substantial risks and less patient acceptability. However, during the last couple of years endoscopic bariatric procedures have made great progress and are emerging as the next major breakthrough in the management of obesity. They are less effective than bariatric surgery but are safer.

Introduction

Obesity is a worldwide health problem associated with substantial morbidity, and cost.[1] Lifestyle modification and pharmacotherapy for obesity have not shown any long-term clinical benefits.[2,3] Bariatric surgery is effective but is associated with substantial risks, and has limited patient acceptability. According to a meta-analysis study, only 1% undergo surgery. Potential reasons for this include fear of complications, irreversibility of the procedure, cost, and lack of widespread accessibility to it.[4,5] Endoscopic approach to obesity has evolved as a result of an attempt to replicate some of the anatomical manipulations and the physiological effects of the traditional weight loss surgery in a minimally invasive manner. Endoscopic interventions such as balloon, aspire assist, endoscopic sleeve gastroplasty (ESG) performed entirely through the *gastrointestinal* (GI) tract offer the potential weight loss that is more cost-effective compared with current surgical approaches.[6] The effect of endoscopic bariatric treatment for weight loss is greater than that of drugs but lower than that of bariatric surgery,[7] but endoscopic bariatric treatment has fewer complications than bariatric surgery.[6,7]

Obesity is rampant throughout the globe. The long-term compliance to life style modification is poor and drug therapy only produces slight decrease in weight.

The development of new endoscopic bariatric procedures allows the endoscopist to play an increasingly significant role in the management of obesity. There is also hope that endoscopic technological advancements will lead to an effective and safer therapy to help the millions of people currently afflicted with metabolic obesity worldwide.

Bariatric surgery produces good results but lacks patient's acceptability. Currently, endoscopic bariatric procedures are emerging as a good option for obesity but are less effective than bariatric surgery but are safer.

Research on endoscopic treatment of obesity treatment is ongoing and the subset of patients to which they are applied is also increasing, and a variety of procedures are being evaluated. The available primary endoscopic bariatric options include:

- Intragastric balloons
- Tissue apposition techniques
- Nutrient diverting therapies

Intragastric Balloons

Intragastric balloon placement is a simple procedure, does not even require endoscopy but fails to achieve long-term results.

Endoscopic placement of intragastric balloon is quite popular but fails to achieve long-term results.[8] With the modern innovations, with introduction of self-inflating balloon, the placement of intragastric balloon has become very simple, with no need of endoscope or anesthesia.[9] Moderately obese patients and those who are too ill to undergo surgery can opt for the self-inflating intragastric balloon **(Fig. 1)**.

Tissue Apposition Technique

Tissue apposition techniques like ESG has proven its stand as primary procedure, revision procedure and bridging procedure.

Nutrient Diverting Therapies

Endo-barrier

It is a malabsorptive procedure first described by Milone in animal models in 2006 which basically involves placing an impermeable barrier between the

Fig. 1: Intragastric balloons
(*For color version see Plate 1*)

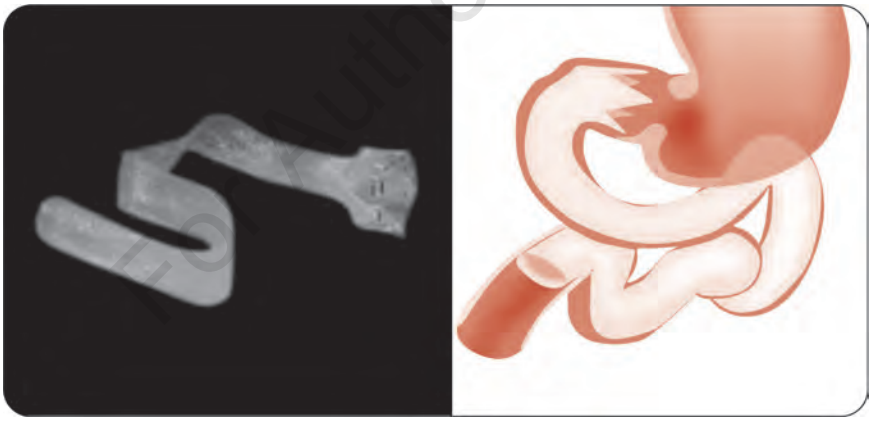


Fig. 2: Endo-barrier

food and the absorptive mucosa within the foregut.[10] Although reversible, the less morbidity of the procedure, long-term use of the device is yet to be determined based on evidence **(Fig. 2)**.

Magnet Anastomosis

Magnetic compression anastomosis (magnamosis) uses a pair of self-centering magnetic "Harrison Rings" to create an intestinal anastomosis without

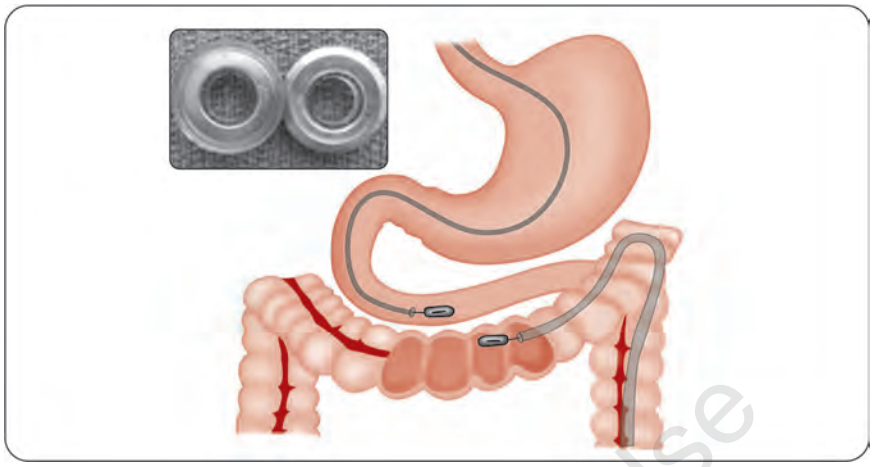


Fig. 3: Magnet anastomosis

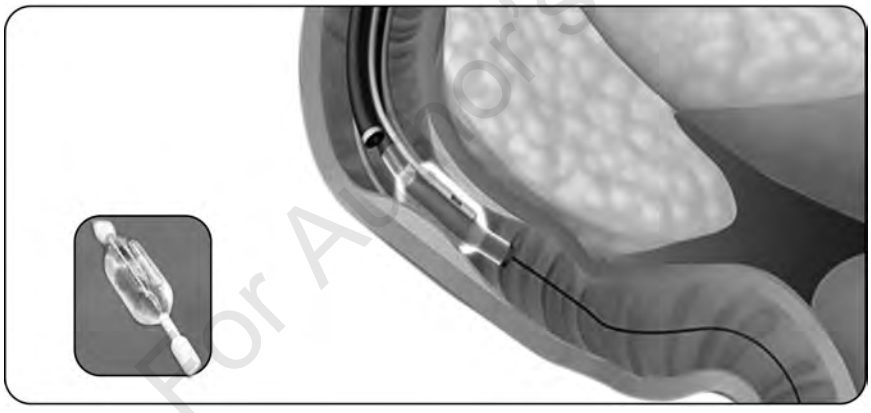


Fig. 4: Mucosal resurfacing
(*For color version see Plate 1*)

sutures or staples. Each magnet is placed within the lumen of a desired segment of the intestine and brought together, or "mated." The magnets then pass through the bowel **(Fig. 3)**.[12]

Mucosal Resurfacing

Duodenal mucosal resurfacing (DMR) is a single, minimally invasive endoscopic procedure that involves circumferential hydrothermal ablation of the duodenal mucosa resulting in subsequent regeneration of the mucosa. Before ablation, the mucosa is lifted with saline to protect the outer layers of the duodenum **(Fig. 4)**.[13,14]

Argon Plasma Coagulation

Argon plasma coagulation (APC) is an application of gas discharges in argon in electrosurgery, which is increasingly used especially in endoscopy. The major application fields are hemostasis, tissue devitalization and tissue reduction.[15] Used with 65 to 75 W and 2–3 L/m flow can be used on the mucosa in the gastrojejunostomy (GJ) anastomosis which leads to fibrosis of gastric mucosa and subsequent reduction of the GJ stoma. Long-term complication of symptomatic stenosis may require sequential balloon dilatation **(Fig. 5)**.[15,16]

Endoscopic Sleeve Gastroplasty Procedure[17]

Out of all the endoscopic bariatric procedure, endoscopic sleeve gastroplasty (ESG) is one of the most studied and reliable procedure which can be used as primary and revision procedure.

ESG is completely nonsurgical. There are no external incisions. The entire procedure is performed through the mouth using a flexible endoscope. All procedures are performed by a single operator using carbon dioxide insufflation. Patients are kept in supine position under general anesthesia. All procedures are performed in a similar fashion using the Apollo OverStitch™ device (Apollo Endosurgery, Austin, TX), placing full thickness sutures to invaginate the greater curvature of the stomach, thus creating a narrow luminal sleeve with a small fundal pouch. After placement of an esophageal length over tube, the endoscopic suturing device mounted on a double channel gastroscope (GIF2T 180 series, Olympus Medical, Tokyo, Japan) is advanced to the gastric antrum. The tissue helix device (Helix, Apollo endosurgery) is used to ensure that sequential full thickness bites were taken.

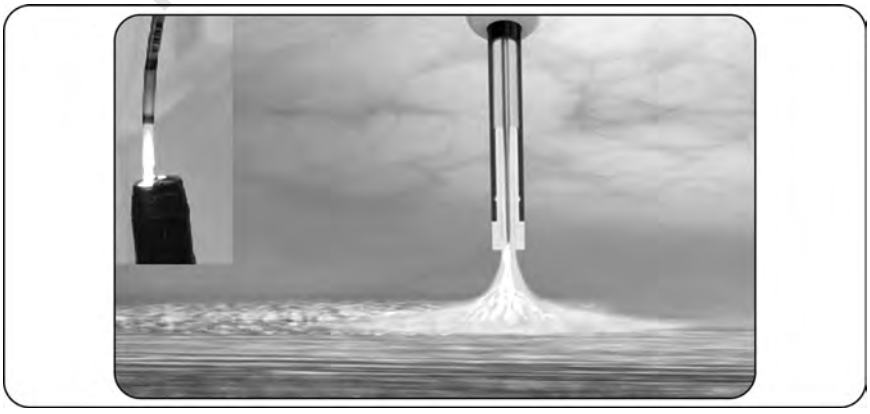
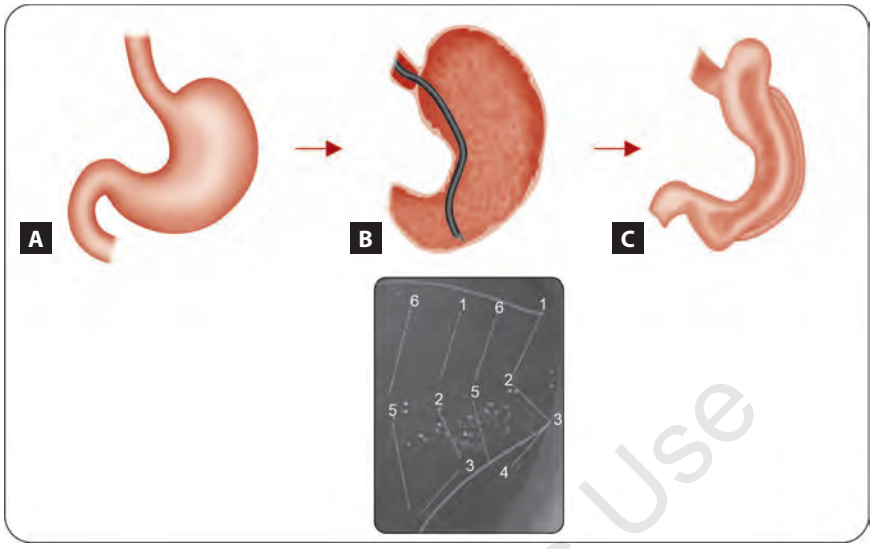


Fig. 5: Argon plasma coagulation
(*For color version see Plate 1*)



Figs. 6A to C: Schematic images of endoscopic sleeve gastroplasty (ESG) procedure. (A) Normal stomach; (B) ESG using U-shaped suture starting at anterior wall moving from greater curvature to posterior wall and returning to anterior wall to reduce body of stomach; (C) Stomach after procedure

Multiple full thickness running sutures (U-shaped) are endoluminally placed from the level of the gastric angular incisura to the gastroesophageal junction to create the ESG **(Fig. 6)**.

Out of all the endoscopic bariatric procedures, ESG is one of the most studied and reliable procedures which can be used as primary and revision procedure. The patient is hospitalized only for a day and then discharged.

Patients are hospitalized for 1 day as per protocol for observation and management of postprocedural symptoms. In comparison the surgical sleeve gastrectomy is typically performed laparoscopically, which means several incisions are made through the abdominal wall, allowing surgical instruments to enter the abdomen. The recovery is a bit longer, usually 1–2 days in the hospital, then 1–2 weeks before returning to work. All patients are given a short course of single dose of IV antibiotics, oral antiemetics as needed, and proton pump inhibitor daily for 1 month. Postprocedure, the diet consisted of 2–3 weeks of liquid protein shakes, followed by 2 weeks of processed diet, and then transitioning to a regular diet. The postprocedural diet was designed to provide 1000 cal/day, delivering 70 g. of protein. In addition, subjects were encouraged to drink 2 liters of noncaloric fluids per day.

The mechanisms by which ESG works includes:

- Contact restriction of ingested food
- Activating stretch receptors of stomach
- Limiting capacity

Our Data on ESG

A total 143 consecutive patients have undergone ESG from March 2017 to January 2020. Out of 143 procedures, 100 cases were operated at Mohak bariatric and robotic research centre (MBRRC), Indore, and other 43 cases were operated outside. Out of total 143 cases, 101 patients were primarily operated for ESG. The mean percentage of total weight loss (%TWL) was followed up at 1,3,6 and 12 months, which showed 7.2±4.4, 10.5±5.9, 16.5±8.7 and 18.9±9.7% TWL respectively, in primary ESG group **(Table 1)**.

The endoscopic bariatric procedures besides producing significant weight loss also resulted in resolution of comorbidities like T2D, hypertension, OSA, etc. in substantial percentage of cases.

Immediate postoperative minor adverse events include 47.9% had epigastric pain, 35.9% patients had nausea, 17.9% had vomiting, 10.1% had bloating, and 2.2% had generalized weakness which resolved on day 2 with conservative treatment. Long-term postoperative complications include weight regain or insufficient weight loss in 42 patients, of them 3 underwent RE-ESG and rest 22 patients underwent sleeve gastrectomy (SG), 9 patients underwent one anastomosis gastric bypass (OAGB) and 8 underwent Roux-en-Y gastric bypass (RYGB). The comorbidities like type 2 diabetes (T2DM) were 21.4%, hypertension (HTN) 22.5% and obstructive sleep apnea (OSA) 10.1% found respectively and after 12 months resolution of comorbidities were T2DM 76.4%, HTN 91.3% and OSA was 100% resolved.

Other 42 cases were operated as revision cases, in those patients who had complaint of weight regain after primary bariatric procedure. In this revision group, primary bariatric procedure performed were SG (n = 22), RYGB (n = 8), OAGB (n = 9) and ESG (n = 3).

The follow-up was taken in all subgroups of revision endoscopic procedure at 1,3,6 and 12 months. The longest possible follow-up was in SG subgroup **(Table 2)**. There was significant %TWL was observed in all sub

Table 1 **Percentage of total weight loss after primary-ESG**

Primary-ESG	*1 m*	*3 m*	*6 m*	*12 m*
%TWL	7.2±4.4	10.5±5.9	16.5±8.7	18.9±9.7

Table 2 Percentage of total weight loss after revision-ESG in subgroups

Revision ESG	*GBP*		*OAGB*			*SG*				*ESG*		
Follow-up	*1 m*	*3 m*	*1 m*	*3 m*	*6 m*	*1 m*	*3 m*	*6 m*	*12 m*	*1 m*	*3 m*	*6m*
%TWL	4.56	7.27	7.44	8.87	15.34	7.94	13.98	16	13.66	7.48	4.76	4.31

groups but in Re-ESG group the %TWL observed was less between 3-month and 6-month interval when compared with other subgroup.

Comparative Effectiveness Studies

Endoscopic bariatric procedures hold the promise of providing the next major breakthrough in the management of obesity. Currently investigated devices have established promising outcomes in short-term weight loss and in control of the metabolic and other medical adverse events of obesity. ESG is a novel and innovative procedure which can be used as primary procedure in patients with body mass index (BMI) less than 35 and in patients in whom surgery is not possible due to severe adhesions or as bridging procedure in high BMI patients or as revisional procedure in patients whom primary bariatric surgery failed with very less to no complications in comparison to revisional surgery.

Our primary ESG results show %TWL of 7.2% at 1 month, 10.5% at 3 months, 16.5% at 6 months and 18.9% at 1 year comparable with data published by Natoetal[18] which shows %TWL of 7.4%,12.9%,17.8% and 18.7% respectively at 1,3,6 and 12 months respectively. Study published by alqahtani et al.[19] shows %TWL of 15% and 14.8% at 12 months and 18 months respectively which is lower than ours. A meta-analysis of twelve studies with 1149 patients also shows %TWL at 6 and 12 months with ESG were 16.01% and 17.41%, respectively.[20]

We had a failure rate in 42 cases of which three patients underwent ESG (n=3), SG (n=22), RYGB (n=8) and OAGB (n=9). When endoscopic suturing techniques were used in failed primary bariatric surgery patients they have yielded very good results with no major complications such as leak or bleeding. Postsleeve endoscopic suturing gave impressive 13.6% TWL.

The advances in endoscopic bariatric procedure hold the promise of providing the next major breakthrough in the management of obesity.

Post-RYGB and OAGB stoma reduction with APC and full thickness bites with endoscopic suturing system gave %TWL of 7.27% and 8.87% at

3 months respectively. Thompson et al.[21] published encouraging results after endoscopic stomal reduction like in our study. ESG when compared to sleeve gastrectomy in our series has shown 19.94% and 30.2% TWL at 1 year respectively. However, mean preoperative BMI for the patients chosen for sleeve gastrectomy is higher than those for ESG and major postoperative complications such as leak and bleeding are literally null in ESG. Long-term complications such GERD and Barrett's esophagus are rare after ESG, whereas sleeve has reported incidence of Barrett's esophagus as high as 17.2%.[22]

Conclusion

Endoscopic bariatric treatment options, although relatively novel, has shown efficacy in the treatment of obesity. There has been a true revolution in gastrointestinal endoscopy with the evolution of endoscopic suturing. Surgeon should be equipped with both the techniques as ESG can be used as primary, bridging or revisional technique postfailed primary surgery, at the same time surgery comes as a saviour for failed ESG. Endoscopic suturing can also be used to close leaks and fistulas post-primary surgery with very less complications compared to surgery. The bariatric endoscopy doesn't make surgery redundant indeed it goes hand in hand with surgery to manage pandemic of obesity better with lowest complication rates and better long-term results. It has potential to become more popular in near future considering being less invasive and having a more favorable side effect profile compared to surgery. Long-term efficacy is not well known at this time but should be available in a few years as more studies are being reported. Additional studies must also include comparison of different modalities and outcomes on obesity-related illnesses (cardiovascular disease, diabetes, hyperlipidemia, etc.). The future of this developing arena will also depend upon training future gastroenterologists in the technical and medical aspects of this field. To date, there is no formalized bariatric endoscopic training amongst gastroenterology fellowship programs. Primary care, bariatric medicine physicians, and bariatric surgeons must incorporate and determine appropriateness of bariatric endoscopy when evaluating patients. Given the promise of this new modality, the authors of this chapter believe that endoscopic bariatric procedures for obesity may make bariatric surgery redundant in future and will make endoscopic interventions as a major tool in its armamentarium.

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Chapter

7

Evaluation of Epicardial Fat and Its Role in Cardiometabolic Health

Yaman Alali, Muhannad Aboud Abbasi, Kashif Shaikh, Alok Saurav, Navin C Nanda, Aiman Smer

Abstract

Epicardial adipose tissue is being recognized as a new risk factor for cardiovascular diseases. It can be measured by echocardiography, magnetic resonance imaging and cardiac computed tomography. It secretes proinflammatory cytokines and is also a storage site for oxidized low-density lipoprotein (LDL). It is emerging as a potential therapeutic target. The role of drugs in targeting epicardial adipose tissue is being evaluated and surgical removal during open heart surgery has shown decrease in recurrence of atrial fibrillation.

Introduction

It is well-known that cardiovascular disease (CVD) is a major cause of morbidity and mortality, worldwide.[1] It is well-established that early detection and treatment of risk factors is crucial for prevention and slowing the progression of atherosclerosis. Over the last few decades, there has been a significant progress in identifying individuals at risk for developing CVD by using cardiovascular risk scores, biomarkers and imaging modalities, yet a significant residual risk persists.[1] Therefore, it is important to identify other risk markers for CVD. Recently, epicardial fat, also known as epicardial adipose tissue (EAT), has been increasingly recognized as a major risk factor for CVD such as coronary artery disease (CAD), atrial fibrillation (AF), and heart failure.[2,3] This chapter will review the standard imaging techniques for evaluation of epicardial fat and its role in cardioembolic health.

Epicardial adipose tissue is being increasingly recognized as a new risk factor for cardiovascular diseases like coronary artery disease, atrial fibrillation and heart failure.

Anatomy and Definition of Epicardial Fat

Epicardial fat originates from the splanchnopleuric mesoderm and is defined as adipose tissue located between the visceral pericardium and the myocardium.[4] It is important to differentiate between epicardial fat and pericardial fat, which is defined as all adipose tissue (epicardial and paracardial fat) surrounding the heart between the parietal pericardium and myocardium. The exact function of epicardial fat remains unclear. However, possible physiological roles of epicardial fat include thermoregulation, lipid storage, protection of autonomic ganglia and regulation of coronary artery vasomotion. [4,5]

Measurement of Epicardial Fat

Due to the recent advancements in cardiovascular imaging, there are several imaging modalities that allow both anatomic and functional evaluation of epicardial fat. However, there is no consensus on the normal value of epicardial fat thickness or volume. The use of different imaging modalities in epicardial fat assessment remains investigational and for research purposes.

Echocardiographic Imaging of Epicardial Fat

Echocardiography is the most commonly used diagnostic tool for the evaluation of epicardial fat. Several large population-based studies have shown decent interobserver and intraobserver correlation for the echocardiographic measurements of maximum epicardial fat thickness.[6-9] In general, parasternal long- and short-axis views are used to measure the epicardial fat thickness during end-systole. Epicardial fat represents the echo-free distance between the visceral pericardium and the outermost layer of the myocardium **(Fig. 1)**.

Epicardial adipose tissue thickness is measured by echocardiography by the free distance between the visceral pericardium and outermost layer of the myocardium in left parasternal long- and short-axis views.

The use of echocardiography to assess epicardial fat thickness could potentially be helpful in identifying high-risk individuals for CVD. [7] In one study conducted by Erkan et al.,184 patients underwent coronary angiogram and echocardiogram for chest pain evaluation. Interestingly, an increased epicardial fat thickness of >5.75 mm revealed a strong correlation between epicardial fat and the severity and extent of CAD, assessed by Gensini and Syntax scores (r=0.875, P<0.001).[10] Another study by Mahabadi et al., showed that an increased epicardial fat thickness obtained by echocardiogram was associated with worsening severity of aortic stenosis.[11]

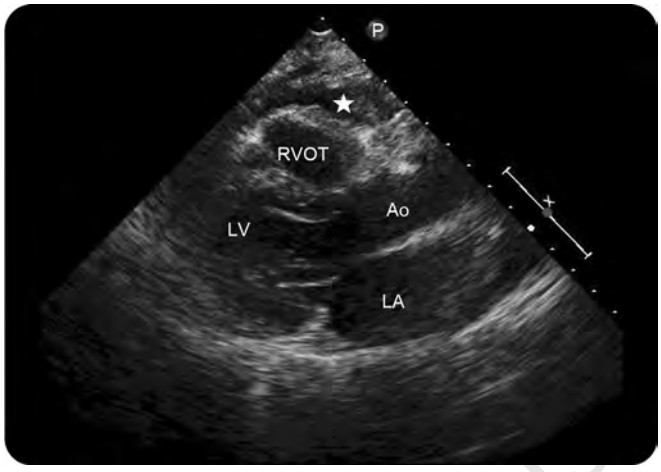

Fig. 1: Transthoracic echocardiography in parasternal long-axis view shows epicardial fat (white asterick) as hypoechoic anterior echo-free space anterior to RVOT
Abbreviations: Ao, aorta; LA, left atrium; LV, left ventricle; RVOT, right ventricular outflow tract

Studies have shown that increased epicardial fat thickness >5.75 mm has good correlation with severity and extent of coronary artery disease.

Cardiovascular Magnetic Resonance Imaging of Epicardial Fat

Cardiac magnetic resonance (CMR) is a powerful noninvasive imaging technique used to assess cardiac structures and function. The ability of CMR to provide tissue characterization and three-dimensional volumetric capability, allows accurate evaluation of epicardial fat in different locations.[12] Epicardial fat tissue characterization is determined through different longitudinal and transverse relaxations times T1 and T2. When compared to a lean tissue, the T1 relaxation time of adipose tissue is quite shorter, approximately 300 ms. This makes adipose tissue appear brighter on T1-weighted spin echo MRI **(Fig. 2)**. Using semiautomated software a region of interest is identified to determine the area of fat around the heart.[13]

Another CMR technique commonly used to assess epicardial fat is steady-state free precession (SSFP) pulse sequences. This technique relies on the differences between tissue T1/T2 signal to produce high quality images. In this setting, CMR can clearly distinguish between myocardium and adipose tissue given that T1 and T2 ratio and relaxation times-quantified in milli-seconds-of adipose tissue is much higher than myocardium.[14,15] Increased epicardial fat volume detected by CMR has been shown to correlate with increased myocardial fibrosis in patients with cardiomyopathy[16-18], and atrial fibrillation.[19]

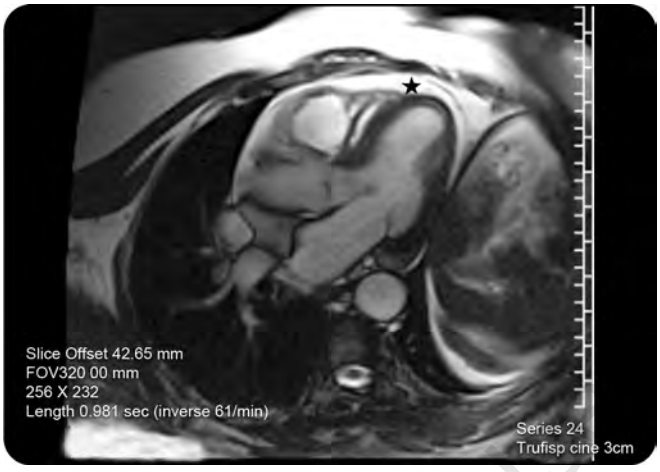

Fig. 2: Visualization of epicardial fat tissue (black asterick) in cardiac magnetic resonance with balanced gradient sequence (T2/T1) with bright blood sequence

CMR is another modality to assess epicardial adipose tissue and increase epicardial fat volume detected by MR correlates with increase myocardial fibrosis in patients with cardiomyopathy and atrial fibrillation.

A newer CMR technique, called hydrogen-1 magnetic resonance spectroscopy (H1-MRS) has shown a strong correlation between epicardial fat volume and myocardial triglycerides concentration.[20,21] An increased level of myocardial triglyceride content on CMR was also shown to directly correlate with reduced left ventricular ejection fraction in patients with heart failure.[22]

Cardiac Computed Tomography Imaging of Epicardial Fat

Cardiac computed tomography (CCT) has been identified as the preferred modality for epicardial fat quantification as it has high spatial resolution and true volumetric coverage of epicardium. Epicardial fat can be reliably measured on electrocardiographic gated noncontrast as well as contrast CCT **(Fig. 3)**.

Epicardial fat is identified using Hounsfield (HU) attenuation values.[23,24] To quantify epicardial fat volume, the upper and lower limits of pericardial sacs are identified and manual or semiautomated contouring is performed via a commercial software. Subsequently, epicardial fat volume is automatically calculated by inclusion of all contiguous 3D voxels with CCT attenuations within a defined threshold of -190 HU units as the lower threshold and -30 HU as the upper threshold.[25–27]

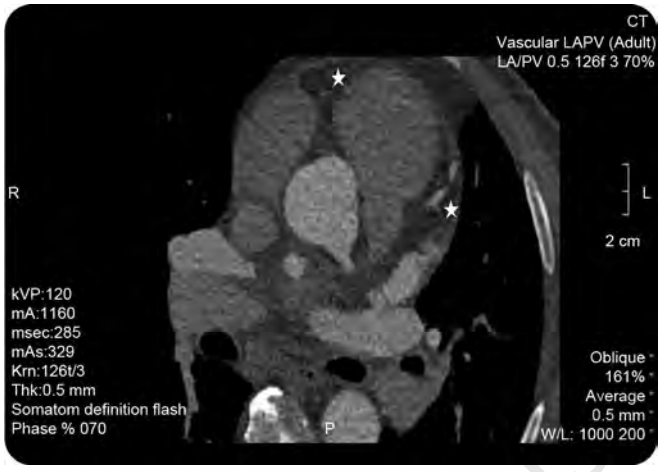

Fig. 3: Axial cardiac computer tomography scan demonstrating prominent epicardial fat (white astericks) in a 65-year-old female with chest pain

Cardiac computed tomography is the preferred method for quantifying epicardial fat and this is expressed in Hounsfield attenuation values. Increased values are associated with coronary calcification, plaque progression and atherosclerosis severity and future cardiovascular events.

Studies with CCT have demonstrated that increased epicardial fat volume is associated with coronary calcification, plaque progression, and atherosclerosis severity.[28-30] Several reports from large population-based studies have shown a strong correlation between epicardial fat deposition detected on CCT and future cardiovascular events. For instance, Mahabadi et al., reported 8-year follow-up of asymptomatic individuals from Heinz Nixdorf Recall (HNR) study conducted in Germany, in which participants within the highest quartile of epicardial fat volume had 5-fold greater risk of cardiovascular events compared to those in the lowest quartile (0.9% vs. 4.7% for 1st and 4 quartile, respectively), even after adjustment of traditional risk factors and coronary artery calcium score.[31]

From another large population-based study named 'Multi-Ethnic Study of Atherosclerosis" (MESA) of 6500 asymptomatic participants, the authors reported that higher pericardial fat was associated with higher cardiovascular events (HR-1.22, P<0.001). They also noted that higher epicardial fat thickness was associated with greater left ventricular mass (P<0.001).[32]

Epicardial Fat and Its Role in the Development of CVD

Several studies have demonstrated significant association between epicardial fat deposition and CVD.[7,25,33-35] Epicardial fat is also associated

with other major cardiovascular risk factors such as age, diabetes mellitus, hypertension, metabolic syndrome, and obesity.[36,37] Although the exact pathophysiologic effects of epicardial fat in CVD is not well understood, it has been proposed that epicardial fat may contribute to the development of CVD via different pathways. Epicardial fat secretes proinflammatory cytokines (adipocytokines, tumor necrotic factor alpha (TNF-α), interleukin; IL-1b, IL-6),which attract inflammatory cells, inducing endothelial dysfunction, and promote vascular inflammation through paracrine and endocrine effects.[29,31,38,39] Epicardial fat may also serve as a storage for oxidized low-density lipoprotein (LDL).[30] Epicardial fat volume has been shown to be directly associated with coronary artery plaque progression.[40] The endocrine activity of epicardial fat (secreting adipocytokines) may explain how it promotes coronary atherosclerosis.[31,34]

Epicardial fat is emerging as a new method to evaluate CVD and it contributes to it by secreting proinflammatory cytokines and is also a storage site for oxidized LDL.

Similar to atherosclerosis, epicardial fat deposition has been linked to the development of AF as well as higher burden of AF.[3,41-45] Epicardial fat could contribute to the etiology of AF through several mechanisms including direct fatty infiltration, fibrosis due to secretion of Activin A and Matrix Metalloproteases, inflammation via secreting IL-6, IL-8 and TNF-α,[41,46,47] oxidative stress (producing reactive oxygen species affecting ion channels), autonomic nervous system dysfunction as pericardial fat contains substantial ganglionic plexi, upregulating pro-inflammatory gene expression, and biventricular diastolic dysfunction.[46-48] Collectively, this inflammatory cascade results in structural and electrical remodeling of the atria acting as a nidus for AF.[46-48]

Epicardial fat is also linked to developing of atrial fibrillation. The inflammatory cascade mediated by proinflammatory cytokines results in structural and electrical remodeling of the atria which acts as a nidus for atrial fibrillation.

Therapeutic Application for Epicardial Fat

Epicardial fat is a emerging as a potential therapeutic target. Weight loss and healthy lifestyle has been shown to be beneficial in preventing and managing AF.

Interestingly, targeting the ganglionated plexi within the epicardial fat by injecting botulinum toxin or surgical removal during open heart surgery has also shown to decrease recurrence of AF.

Epicardial fat may represent a potential therapeutic target as physical activity and other healthy lifestyle patterns have a major impact on epicardial fat. Healthy lifestyle modifications may prevent CVD in subjects with increased epicardial fat volume.[31,49] In addition, statin therapy can decrease the inflammatory state related to epicardial fat, which could explain their ability to reduce CVD risk.[38,49] Interestingly, surgical excision of epicardial fat in animals slowed the progression of coronary atherosclerosis, but data in humans are lacking.[50] Furthermore, understanding how epicardial fat potentially contributes to AF has led to the emergence of potential therapeutic options to target epicardial fat and AF. Weight loss has been shown to be beneficial in preventing and managing patients with AF.[42,45,46,51] Newer antidiabetic medications such as thiazolidinediones (TZD), glucagon-like peptide-1 agonists (GLP-1 RA), dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors (SGLT2i), and statins have been shown to decrease epicardial fat volume.[46,51] Moreover, targeting the ganglionated plexi within the epicardial fat either through injecting botulinum toxin, ablation or surgical removal (during posterior pericardiectomy in open heart surgery) has been shown to decrease the recurrence of AF. [46,51] However, whether targeting epicardial fat by preventive or pharmaceutical measures would be beneficial in cardiometabolic disease is still open to debate.

Statins and several antidiabetic agent like TZD, SGLT2i, GLP-1 RA has shown reduction in epicardial fat but their role in therapeutics requires further evaluation.

Acknowledgment

We gratefully acknowledge the help of Zeyad M Elmarzouky MD and Subash Dulal MBBS, Research Fellows working with Dr Navin C Nanda at the University of Alabama at Birmingham, Birmingham, Alabama USA for their help in searching references for this manuscript.

Conclusion

Epicardial fat is increasingly recognized as a major marker for CVD. Unfortunately, there have been significant variations in cut off values of epicardial fat thickness and volume that signify high-risk value. This mainly relates to different diagnostic techniques used to measure epicardial fat and the heterogeneity of the studied population. Nevertheless, the prognostic value of epicardial fat is evident in multiple studies. The clinical application of epicardial fat as another screening or prognostic tool in daily practice needs further studies and validation.

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Chapter

8

Targeting Inflammation in Diabetes: Newer Therapeutic Options

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Abstract

The role of chronic metabolic inflammation (metaflammation) as an important mediator in initiation and progression of type 2 diabetes (T2D), and its cardiometabolic dysfunctions, is now well established. Multiple pathways have been studied to be involved in the pathogenesis of T2D and its complications. In the last 2–3 decades, many anti-inflammatory drugs have been evaluated in T2D, including established broad-spectrum agents like hydroxychloroquine and salsalate, to the newer targeted therapies like antitumor necrosis factor agents and interleukin-1 antagonists. Hydroxychloroquine is the first anti-inflammatory agent to be approved for management of uncontrolled T2D in India. The mechanisms underlying the beneficial metabolic effects of the anti-inflammatory therapies are still not very clear; and there are concerns, especially with the new drugs, regarding the safety and modest efficacy on HbA1c and glucose control. Further evidence is warranted to strengthen the concept that targeting inflammation pathways may ameliorate glycemic control and reduce cardiovascular complications in type 2 diabetes.

Introduction

Diabetes is one of the largest global health emergencies of this century, with the number of adults living with diabetes having more than tripled over the past 20 years. Today, 9.3% of adults aged 20–79 years, a staggering 463 million people are living with diabetes; with a further 374 million at increased risk of developing type 2 diabetes (T2D). In the year 2016, diabetes resulted in 1.6 million deaths, increasing to 4.2 million deaths by 2019 and predicted to result in nearly 592 million deaths in total by the year 2035.[1] Despite the presence of a plethora of therapeutic options for lowering blood glucose levels, these alarming numbers clearly highlight the need for better understanding of the pathologic processes involved in initiation and progress of T2D leading to therapies targeting the core pathogenic defects.

Besides conventional factors for pathogenesis of diabetes, inflammation is emerging as a new mediator for initiation and perpetuation of type 2 diabetes.

Evolution, Inflammation and Metabolic Diseases

From an evolutionary insight, selective pressures do not favor the development of countermeasures against excess nutrients and energy. Rather, phenotypes that ensure survival in the face of deficiencies are selected. This is signified by the fact that while hyperglycemia is not an immediate threat to survival, hypoglycemia is. Hence, organisms have evolved to develop strong pathways to seek food, favor energy storage, produce glucose and prevent hypoglycemia. While these characteristics provide advantage in the context of limited supplies, with the removal of these selective pressures, they have now become a prominent problem manifested in the form of obesity and related metabolic diseases like T2D. At the same time, there are evolutionary advantages of a strong defence system in protecting against pathogens. As a strong immune response is dependent on energy sources, the integration of these systems, coined as 'immunometabolism', is obvious and advantageous.[2] In metabolic organs including the liver, pancreas and adipose tissue, immune cells sense and react to the excess nutrient availability by altering lipid metabolism or inhibiting glucose uptake. This in turn influences the intrinsic metabolic action within neighboring cells critical for metabolic homeostasis. These tissues and mediators produced from them also cause systemic inflammatory responses and disrupt the metabolic homeostasis. There is no survival advantage to a chronic low-grade inflammatory response incapable of pathogen elimination. Thus, while inflammation is essential for repair and remodeling of tissues, low-grade and chronic inflammatory activation can have adverse consequences for health and function of metabolic tissues (called as '*metaflammation*'), leading to damage and consequently metabolic diseases.

In order to target the chronic inflammation in these metabolic diseases, it is important to understand this crosstalk between the immune and metabolic pathways. These processes have been shown to play central pathogenic role leading to both—insulin resistance and insulin insufficiency, the hallmark features of T2D. The central framework of this relationship is defined by a potent and pleiotropic immune mediator (tumor necrosis factor, TNF), a pathogen sensing system (the toll-like receptors, TLRs), and insulin, a powerful metabolic hormone **(Fig. 1)**.[3] TNF and TLR signaling block insulin signaling or production through JuN N-terminal kinase (JNK) activation. This link is strengthened by findings that macrophages secrete TNF that induces insulin resistance in adipocytes, and that obesity is associated with increased

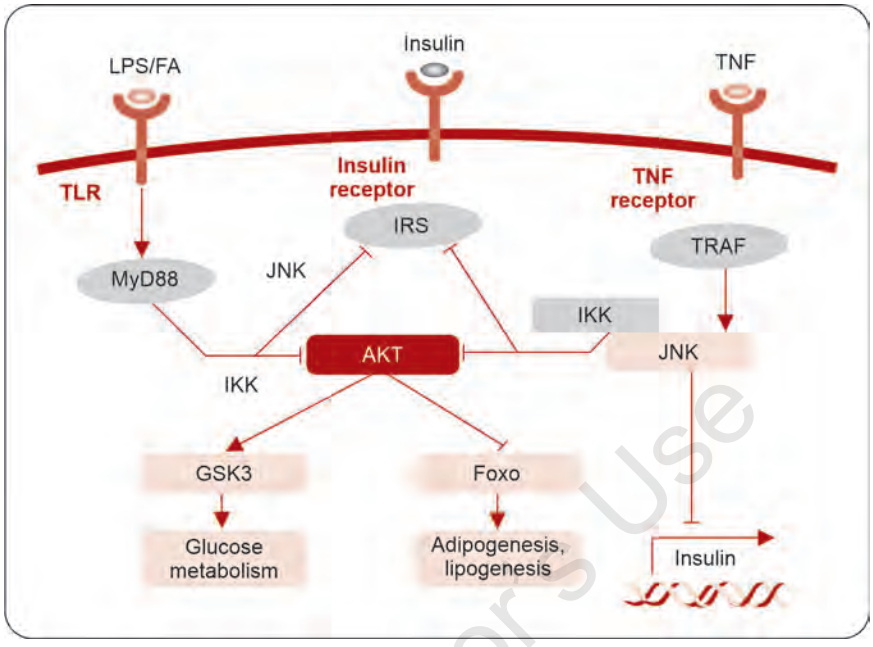

Fig. 1: Crosstalk between immune and metabolic pathways

expression of inflammatory mediators in adipose tissue which interferes with glucose metabolism.[4,5]

Adipose tissue contains multiple sets of immune cells whose primary function appears to be maintenance of the integrity and hormonal sensitivity of the adipose cells. In the metabolically-healthy state, these cells maintain the resident macrophages in an 'alternately activated' (M2) state. Overall, M2 macrophages block the inflammatory response and secrete cytokines including interleukin (IL)-10 and IL-13, that help maintain insulin sensitivity.[6] In obesity, free fatty acid exposure promotes the polarization of adipose tissue resident macrophages towards a proinflammatory ('classically activated' or M1-polarized) phenotype which can block insulin action leading to insulin resistance. The phenotype switching of macrophages from predominantly anti-inflammatory M2-type to the proinflammatory M1-type is a hallmark of metaflammation and has been shown to play a crucial role in the initiation and amplification of islet inflammation leading to β-cell dysfunction and insulin insufficiency.[7]

The cellular and biochemical pathways for inflammation in diabetes are complex and multifaceted and targeting it with pharmacological agents seems to ameliorate glycemic control and reduce cardiovascular complications in diabetes.

Chronic Inflammation: Mechanisms Leading to T2D

Several factors can trigger an inflammatory response in the adipose tissue like endoplasmic reticulum stress and hypertrophy due to storing of excess nutrients (glucotoxicity and lipotoxicity) which leads to production of cytokines and chemokines. The lipid overload resulting in adipocyte death, and local hypoxia caused by the rapid expansion of adipose tissues further elicit the inflammatory response. Finally, increased levels of endotoxins (lipopolysaccharides) as a result of gut leakiness for bacterial products due to altered gut flora, further trigger tissue inflammation. These stresses (glucose, endotoxins, free fatty acids and other lipids) activate TLR2 and TLR4, which in turn, causes direct activation of the nuclear factor-κB (NF-κB), the central modulator of inflammatory responses. It regulates the expression and release of proinflammatory cytokines and chemokines such as TNF, IL-1β, IL-8 and monocyte chemoattractant protein 1 (MCP1).[8] These cytokines then promote the accumulation of various immune cells. In macrophages, hyperglycemia and lipids promote the formation of inflammasomes, particularly NOD-LRR and pyrin domain containing 3 (NLRP-3). This leads to the activation of caspase 1 and the subsequent splicing of pro-interleukin (IL)-1β to active IL-1β.[9] This potent cytokine in turn, dampens insulin sensitivity by inducing JNK-dependent serine phosphorylation of insulin receptor substrate-1 (IRS-1), resulting in the disruption of insulin-induced signaling in insulin-targeted cells. At the same time, IL-1β induces the expression of TNF-α, which can independently impair insulin signaling leading to insulin resistance.[10] Also, another upstream activator kinase of NF-κB is IKK (inhibitor kappa B kinase), which is also reported to phosphorylate IRS-1 at serine residues to block insulin signaling.[11]

An important mediator to be noted here is the endosomal NADPH (nicotinamide adenine dinucleotide phosphate) oxidase (NOX). The NOX is an enzyme complex involved in numerous proinflammatory signaling cascades. Particularly, the signaling of TNF-α via TNF-receptor 1 (TNFR1) and IL-1β via IL-1R are mediated in part by uptake of the ligand-receptor complexes into the endosome. This leads to activation of endosomal NOX and generation of superoxide and subsequently other reactive oxygen species (ROS), further leading to activation of NFκB and its broad downstream effects.[12,13] Inhibition of endosomal NOX massively reduces the downstream activation of NFκB via these pathways. Also, it is important to understand that adipose tissue is not the sole site of metaflammation, this influx of immune cells and inflammatory mediators occurs in many other tissues such as the hypothalamus, liver, muscle, pancreatic islets and the gut[3] leading to a state of systemic low-grade inflammation further contributing to insulin resistance.

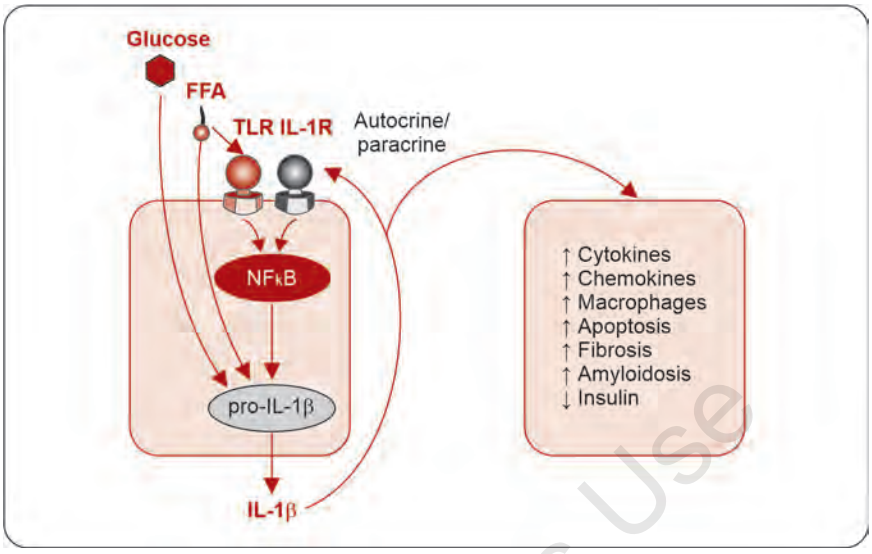

Fig. 2: IL-1β autostimulation by metabolic stress leading to islet inflammation and β-cell dysfunction

In islet cells, high concentrations of glucose and free fatty acids (FFA) elevate the metabolic activity of islet cells, leading to increased formation of reactive oxygen species (ROS). This promotes the activation of the NLRP3 inflammasome and caspase 1, leading to production of mature IL-1β. Furthermore, lipopolysaccharides from bacterial cell walls (endotoxins) or free fatty acids activate TLR2 and TLR4, leading to the translocation of NF-κB and further induction of inflammatory cytokines including IL-1β. In turn, IL-1β induces various cytokines and chemokines-including IL-6, IL-8, TNF and MCP-1 that lead to the attraction of macrophages and other immune cells. These initial mechanisms of IL-1β induction are amplified by a cycle of 'auto-induction' **(Fig. 2)**. This is probably a consequence of the abundant expression of IL-1 receptor type 1 (IL-1R1) by the islet cells, particularly the β-cells. The recruitment of immune cells is enhanced by this vicious cycle of IL-1β autoinduction. Thus, the resident islet macrophages adopt a pro-inflammatory phenotype that impairs β-cell secretory function and survival, ultimately leading to insulin insufficiency.[14,15]

Thus, chronic low-grade inflammatory response induced by metabolic stress becomes deleterious, probably precipitated by genetic predispositions, leading to insulin resistance and beta-cell dysfunction. Eventually, this leads to the development of the chronic inflammatory metabolic disease: type 2 diabetes. The term 'metaflammation' has been coined to define this low-grade, chronic inflammation orchestrated by metabolic cells in response to

excess nutrients and energy in metabolic tissues including adipose, liver, muscle, pancreas, and brain.[16] Accordingly, anti-inflammatory treatment for patients with T2D have the potential to modulate this overstimulation of the immune-metabolic system, and must be explored.

Besides HCQ, several anti-inflammatory agents like TNF inhibitors IL-1 inhibitors, salsalate, low dose methotrexate, etc. have been tried to target inflammation in diabetes like but HCQ is ahead in the race.

Anti-inflammatory Therapeutic Options in T2D

Anti-inflammatory drugs can potentially improve glycemic control without causing hypoglycemia. Interventions that address inflammation could have a role in preventing the progressive decline in insulin secretion as well in improving insulin sensitivity. Numerous inflammatory pathways have been identified and consequently, various targets have been recognized that may affect metabolism. Targeting these molecules has potential implications in the management of T2D by improving various markers including inflammatory, glycemic and lipid parameters. Few major anti-inflammatory agents are reviewed here for their effects in T2D (there are numerous others being developed including mTOR inhibitors, SIRT-1 activators, CCR-2 antagonists, MCP-1 inhibitors, histone deacetylase inhibitors, etc.).

TNF-inhibitors

TNF-α was the first inflammatory cytokine implicated in the pathogenesis of insulin resistance and T2D. TNF-α antagonists (infliximab, adalimumab, etanercept) usually used therapeutically in management of inflammatory diseases such as rheumatoid arthritis, psoriasis and Crohn's disease, have been associated with improvement in insulin sensitivity.[17] This signal further strengthens the significant role of TNF in the pathogenesis of T2D. Large cohort studies in patients with rheumatoid arthritis or psoriasis have also linked TNF inhibition with a statistically significant decline in the risk of T2D. However, till date, **(Table 1)** TNF-α antagonism has not demonstrated any clear benefit in T2D in humans. Pioneer human studies using TNF-α blockade, mostly with etanercept, failed to demonstrate beneficial effects on insulin sensitivity or glucose metabolism in various populations with insulin resistance but without overt inflammatory disease. However, most of these studies were limited in sample size and duration; well-designed long-term studies assessing its precise role are warranted.[18] Also, possible cardiometabolic benefits of drugs targeting TNF-α have to be weighed against known adverse effects associated with such approaches (mainly risk of infection) and the cost of therapy.

Table 1 **Major anti-inflammatory therapeutic options for type 2 diabetes-metabolic profile**

Mechanism	*Drug*	*Main metabolic effects*
IL-1 receptor blockade	Anakinra	CRP ↓, insulin secretion ↑, insulin sensitivity
IL-1β antagonism	Canakinumab	CRP and IL-6 ↓, 6 months HbA1c ↓, but not consistent HbA1c ↓ long-term, no ↓ in incident diabetes
TNF-α antagonism	Etanercept	CRP ↓, insulin secretion ↑, no effect on insulin sensitivity, lipids or IL-6
TNF-α antagonism	Infliximab	FBG improvement, ratio of high molecular weight to total adiponectin ↑, no effect on CRP
Multiple pathways	Hydroxychloroquine	HbA1c ↓, FBG ↓, CRP ↓, insulin sensitivity ↑ (?), adiponectin ↑, LDL-C ↓
IKKβ–NFκB inhibition	Salsalate	HbA1c ↓, FBG ↓, CRP ↓, insulin sensitivity ↑, adiponectin ↑, LDL ↑, urinary albumin
Multiple pathways	Low-dose methotrexate	No effects on CRP, IL-1 beta or IL-6

IL-1 Inhibitors

Many reagents that target the inflammasome products IL-1β and IL-18, including the recombinant IL-1RA anakinra, the neutralizing IL-1β antibody canakinumab, the soluble decoy IL-1 receptor rilonacept, IL-18–binding protein, soluble IL-18 receptors and anti–IL-18 receptor monoclonal antibodies, have been developed to treat 'autoinflammatory' diseases such as cryopyrin-associated periodic syndrome (CAPS). Of these, anakinra and canakinumab have also been evaluated for effects on metabolic and cardiovascular diseases in numerous clinical studies. Improved beta-cell secretory function and glycemia, as well as reduced inflammatory biomarkers in people with diabetes and prediabetes have been demonstrated with these agents, demonstrating that IL-1β mediates the deleterious effects of high glucose on human beta cells.[19] However, in a prespecified outcome analysis of the large randomized trial—Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS)—over a median period of 3.7 years, canakinumab did not reduce the incidence of diabetes in patients with prior MI. Also, though canakinumab reduced HbA1c during the first 6–9 months of treatment, no consistent long-term benefits on HbA1c or fasting plasma glucose was observed.[20] Other anti-IL-1β agents including gevokizumab and LY2189102 are also being evaluated to better understand the effects of IL-1 antagonism on glucose control in patients with T2D.

Broad-spectrum Anti-inflammatory Agents

As discussed above, anti-inflammatory agents that are selective in action, i.e. agents which act on and inhibit selective inflammatory mediators [such as anakinra (IL-1 receptor antagonist), etanercept (TNF-α inhibitor), canakinumab (IL-1β antagonist)], have yielded conflicting and often, disappointing effects on glycemic parameters. It is already established that there are multiple inflammatory pathways involved in the pathogenesis of cardiometabolic diseases including type 2 diabetes, obesity and metabolic syndrome (MetS). Hence, it has been postulated that, too selective targeting of the inflammatory processes may not yield the desired results[21], and broad-spectrum anti-inflammatory agents like hydroxychloroquine, salsalate and methotrexate may be better candidates for further development as anti-inflammatory armamentarium against T2D.

Hydroxychloroquine

Hydroxychloroquine (HCQ) is the first anti-inflammatory agent to be approved for management of uncontrolled type 2 diabetes in India.

In 1984, the observation of reduced insulin requirement by chloroquine (CQ) in a patient with severe insulin resistance, suggested that treatment with CQ or its analogs may be a new approach in the management of diabetes.[22] HCQ, an analog with a safer profile than CQ, is an anti-inflammatory agent with immunomodulatory properties. It is widely used across the globe since more than 6 decades for management of autoimmune inflammatory diseases including rheumatoid arthritis and systemic lupus erythematosus. In an observational study of 4,905 patients with rheumatoid arthritis, there was a significantly reduced risk of developing diabetes in patients who used HCQ compared to those who never used HCQ.[23] In RA, HCQ use has been shown to exert positive cardiorenal effects by causing significant reduction in incident CV events[24] as well as incident chronic kidney disease.[25] The antidiabetic and insulin-sparing effect of HCQ were initially highlighted in patients with diabetes by two independent teams in treatment refractory T2D in 1990[26] and 2002.[27] In 2014, HCQ became the first anti-inflammatory agent to be approved in India as an antidiabetic, for management of T2D uncontrolled on metformin-sulfonylurea combination after a phase III double-blind, randomized study found that control of glycemic parameters by HCQ was similar to pioglitazone.[28] Postapproval, numerous real world studies have evaluated use of HCQ in management of T2D for varying durations ranging from 24 weeks (n = 1523)[29] to 72 weeks (n = 498)[30]; and HCQ has shown comparable efficacy against different comparators including vildagliptin (n=100)[31], sitagliptin (n=600)[32], canagliflozin (n = 87).[33]

HCQ has high affinity to the acidic intracellular compartments like lysosomes and endosomes. As a lysosomotropic weak base, HCQ is rapidly protonated after getting internalized, thereby increasing the pH of endolysosomal vesicles. This blocks activation of lysosomal enzymes, including insulin-degrading enzymes, which need an acidic pH to act. As a consequence, there is inhibition of release of various inflammatory cytokines as well as reduced degradation of insulin. Also, it has been reported that HCQ blocks the induction of endosomal NOX, the signaling pathway common to TNF-α and IL-1β, which leads to proinflammatory and procoagulant cellular responses.[34] Since signaling endosomes serve as physical platforms for crosstalk between different signaling pathways, inhibition of endosomal NOX2 can explain reduction of cytokine production and plasma concentrations or inhibition of different immune effector cells by HCQ. This might explain the broad-spectrum anti-inflammatory profile of HCQ while also providing an explanation for its beneficial role in the prevention of thromboembolic events. In a randomized clinical study, HCQ was shown to improve β-cell function, insulin sensitivity and adiponectin levels in nondiabetic, obese individuals, with insulin resistance and impaired fasting glucose. [35] These metabolic effects may explain why HCQ treatment is associated with a lower risk of T2D in at-risk population. Thus, the potential of HCQ in preventing progression of prediabetes to diabetes must be explored further. Overall, HCQ appears to be an effective and well tolerated anti-inflammatory therapeutic option in management of uncontrolled T2D. Further long-term studies are warranted to help understand its effect on complications of diabetes including nephropathy and retinopathy.

Salsalate

Salsalate, a prodrug of salicylate, is a well-studied anti-inflammatory agent in T2D. In fact, salicylates were the first class of drugs reported to improve glycosuria in diabetes, in a paper published in the *Berliner Klinische Wochenschrift* in 1876.[36] Post this, the concept has been validated in animal studies as well as in several clinical trials including multicenter, placebo-controlled studies. Salsalate has been shown to reduce glycemia and improve inflammatory cardiovascular risk indices probably through inhibition of the NF-kB pathway. Limitations associated with salsalate were an increase in LDL cholesterol level and urinary albumin excretion, and no improvement in vascular inflammation.[37] Thus, though salsalate appears to be an effective adjunct to T2D treatment, further studies are needed to confirm its long-term cardiovascular and renal safety.[38]

Low-dose Methotrexate

It is a widely used treatment for patients with chronic inflammatory diseases such as rheumatoid arthritis, psoriasis and psoriatic arthritis. It has been shown to reduce several inflammatory biomarkers including CRP, IL-6 and TNF-α in patients, without affecting lipid levels, blood pressure, platelet function or measures of hemostasis. Based on epidemiological and observational data suggesting CV risk reduction with methotrexate, a large randomized double-blind trial of low-dose methotrexate—Cardiovascular Inflammation Reduction Trial (CIRT)—was conducted in parallel with CANTOS.[39] CIRT evaluated the effect of low-dose methotrexate in secondary prevention of atherothrombotic events among patients with a history of myocardial infarction who additionally had either T2D or metabolic syndrome. The trial was stopped after a median follow-up of 2.3 years. Low-dose methotrexate did not reduce levels of IL-1β, IL-6, or CRP and did not result in fewer CV events than placebo. In this context, certain important differences between CIRT and CANTOS must be understood. CANTOS, by design, included patients with residual inflammatory risk and thus selectively enrolled patients with persistently elevated hsCRP levels, resulting in a median baseline hsCRP level among participants of 4.2 mg/liter. In contrast, CIRT did not screen for hsCRP level but instead required participants to have either diabetes or the metabolic syndrome. This trial design resulted in a median hsCRP level of only 1.6 mg/L at randomization. Thus, CIRT did not include patients with evidence of inflammation or residual inflammatory risk, making it difficult to interpret the anti-inflammatory effect.

Conclusion

Chronic, low-grade inflammatory state originating from metabolic cells in response to excess nutrients, contributes to the development of T2D by increasing insulin resistance in peripheral tissues (mainly in the adipose tissue, liver, muscles) and impairing insulin secretion by targeting pancreatic islets. This metaflammation has been proposed to play central role in converting prediabetes to diabetes, and also in the pathogenesis of the micro- and macrovascular complications of T2D. Diabetes-associated inflammation is multifactorial and the mechanisms involved are not limited to hyperglycemia. This rationalizes the role of anti-inflammatory therapies on glycemia, diabetes progression, and cardiovascular morbidity.

Various anti-inflammatory therapies have been evaluated for management of diabetes as well as atherosclerotic cardiovascular morbidity. Treatments designed to modulate the inflammatory and immune response have been shown to have beneficial metabolic effects, thus opening new avenues for the management of T2D. India is the first country to approve an anti-inflammatory agent—HCQ for management of T2D uncontrolled on metformin-sulfonylurea combination. Based on the multifaceted inflammatory pathways involved in T2D, it appears that

selective targeting of the inflammatory pathways may not be productive, and broad-spectrum anti-inflammatory agents like hydroxychloroquine and salsalate must be developed further as anti-inflammatory armamentarium against T2D. Nonetheless, long-term and larger studies are required to clarify the role of anti-inflammatory therapies in the management of T2D. In conjunction with current pharmacologic and lifestyle interventions, better understanding of the inflammatory processes involved in T2D are essential for providing improved modalities, not just for treatment, but also for prevention of T2D.

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Chapter 9

Blood Pressure Variability: The Missing Link in the Current Treatment of Hypertension-Challenges and Barriers for Modulation

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Abstract

Blood pressure variability (BPV) is the missing link in the current treatment of hypertension. It is associated with increased incidence of cardiovascular events and adverse effect on prognosis of the patient. Calcium channel blocker is superior to other agents in reducing BPV. Amongst this class of agents amlodipine has the highest smoothness index. BPV is poised to make new inroads among physicians and practitioners in the management of hypertension in future .

Introduction

It has been a well-established and accepted fact that elevated blood pressure (BP) leads to target organ damage and antihypertensive therapy can reduce such a risk.[1] BP is a physiologic parameter, variability of it has been well described and noted over ages. Such variability and oscillations are spontaneous and can be seen over short-term ranging from minutes to days and long-term durations over life of individual. These fluctuations are the result of a complex interplay between environmental, physical and emotional factors and cardiovascular regulatory mechanisms aimed at maintaining the so-called BP "homeostasis". The size and patterns characterizing these BP variations define the term BP variability (BPV).[2,3]

Blood pressure variability is a new target in the management of hypertension and it contributes to adverse cardiovascular events in the long run.

From a clinician perspective, BPV could be seen as a source of noise that creates difficulties in assessing the individual's "true" BP level. Excessive

fluctuation in blood pressure in animal models have been shown to be linked to organ damage targeted by hypertension.[4] This was further corroborated by clinical studies in hypertensives where blood pressure variability (BPV) was found to be of clinical and prognostic significance[5] which can enhance complications due to hypertension.

Types of BPV and Measuring BPV

The term BPV encompasses a wide range of BP variations. Such a variation can take many patterns and can be seen over seconds or minutes (very short-term BPV), over 24 hours (short-term BPV), and between days (mid-term or day-to-day BPV). Typically, short-term BPV are noted on ambulatory BP monitoring (ABPM) and day-to-day BPV is assessed with home BP monitoring (HBPM). In addition, there is long-term BPV which encompasses changes between clinic visits over months or years and called as visit-to-visit BPV[3] **(Fig. 1)**.

BP is physiological variable and bound to change over time due to influence of number of factors. These fluctuations can be random or erratic without any regular pattern or can have well-defined patterns over time which can be linked to physiological and circadian rhythms such as rhythmic fluctuations or related to drop in BP in night or during sleep as well as early morning surges and variations during seasons.

The former is usually described using simple measures of dispersion (such as standard deviation [SD]). SD can be of average values over a given time window or estimates that also take into account the sequence of measurements over time (average real variability [ARV], the time rate of variations) **(Table 1)**. Among more sophisticated methods for BPV assessment, spectral analysis techniques are particularly relevant when describing faster BP changes in beat-by-beat recordings, but can also be used for discontinuous 24-hour BP monitoring. Fourier analysis can be used in sophisticated analysis to remove slower cyclic components to obtain "residual" variability of 24-hour BP variation.

Ultra-short-term Blood Pressure Variability

Such a beat-to-beat BP variability is called as ultra-short-term BP variability and it occurs due to called complex interplay of number of factors. These include vasodilatory effect of nitric oxide, myogenic response of blood vessels and effect of the renin-angiotensin system (RAS).[5] As the response times of different neurohormonal systems differ from each other, hence, the analysis of beat-to-beat BPV allows the estimation of the relative contribution of neurohumoral systems.[5]

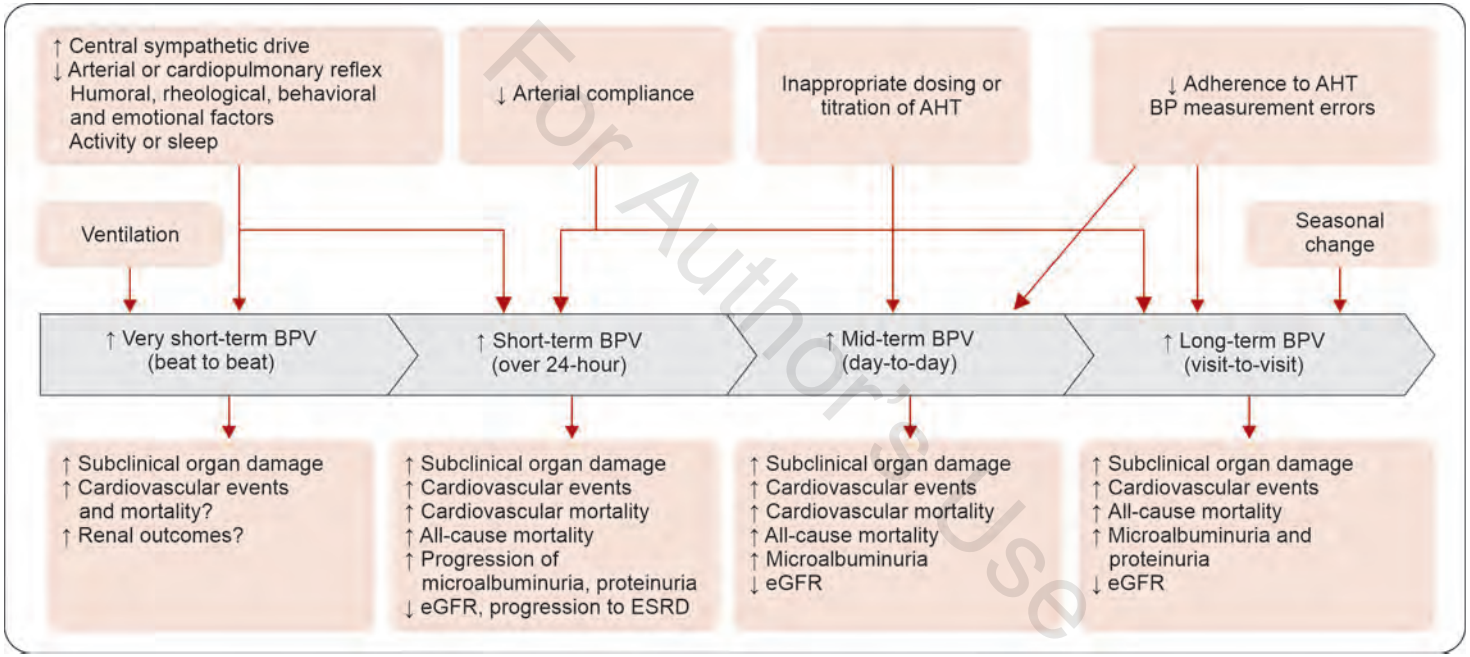

Fig. 1: Various types of BPV, their determinants, and prognostic relevance for cardiovascular and renal outcomes

Table 1 **Summary of principal indices of blood pressure variability**

Type of index	*Type of BPV assessed*
Frequency: • Spectral indices (HF, LF, VLF) • Residual variability	• Short-term BPV • Very short-term BPV (spectral analysis)
Dispersion: • Standard deviation (SD) • Coefficient of variation (CV) • Variability independent of the mean (VIM) • Weighted 24-hour SD (wSD)	• Short-term BPV • Mid-term BPV • Long-term BPV
Sequence: • Average real variability (ARV) • Interval weighted SD (wSD) • Time rate of BP fluctuations	• Short-term BPV • Mid-term BPV • Long-term BPV
Instability: • Range (Maximum-minimum BP) • Peak size (Maximum BP) • Trough size (Mean-minimum BP)	• Short-term BPV • Mid-term BPV
Specific patterns of BPV: • Nocturnal BP fall • Night/day ratio • Morning blood pressure surge (MBPS) • Afternoon siesta dipping • Postprandial blood pressure fall	Short-term BPV

Blood pressure variability may be very short-term, short-term, mid-term and long-term and all these subset have different pathogenetic mechanisms.

Blood pressure shows ultra-short-term or beat-to-beat blood pressure variability due to the interplay of baroreceptor reflex, the renin-angiotensin system (RAS), the vascular myogenic response, and the release of nitric oxide (NO) from the endothelium.[5] The response times at which different neurohormonal systems operate differ considerably and, therefore, the analysis of beat-to-beat BPV allows the estimation of the relative contribution of neurohumoral systems.[5]

Researchers have used the pattern on BPV to study the mechanism and benefit from antihypertensive medications. Bertera et al.[6] showed larger hypotensive response in rats with spontaneous hypertension coupled with significant reduction of low frequency/high frequency ratio suggesting that this to be due to larger vascular sympatholytic activity. The same authors[7] by using spectral analysis of BP measurements in sino-aortic denervated rats were also able to show that third generation beta-blockers (carvedilol and nebivolol) significantly reduced the LF/HF ratio indicating reduced vascular sympathetic activity.

Such an analysis can have therapeutic implications. Hypertensive patients with elevated low frequency BPV may have good response to sympatholytic drugs due to increased sympathetic modulation of vascular tone. This may be not seen in those with impaired cerebrovascular myogenic function, such as CKD on hemodialysis and they can be theoretically identified by reduced very low frequency BPV.

Short-term Blood Pressure Variability

Short-term blood pressure variability is usually defined as the oscillation of blood pressure within 24 hours. This variability is mainly due to stiffening or change in elastic properties of arteries and due to central and autonomic modulation of sympathetic activity.[2]

In clinical trials, short-term BPV has been assessed by using a number of indices. These include 24 hours BPV, standard deviation (SD) of daytime and night-time BP values as well as coefficient of variation (CV) of BP readings, both systolic and diastolic.[3]

A new sophisticated index of short-term BPV has been advocated to improve the significance. It is called as average real variability (ARV) of daytime and night-time BP and is average of the absolute differences of consecutive measurements. This allows it to be less influenced by low sampling frequency of ABPM and more reliant on order of individual BP measurement.[8,9]

Long-term Blood Pressure Variability

Apart from ultra-short term and short-term BPV, there is also long-term BP variability which can have prognostic significance by enhancing the CV risk. This includes day-to-day, visit-to-visit, or seasonal variation in BP. The Multiethnic Study of Atherosclerosis (MESA) showed a reduction in aortic distensibility and arterial elasticity in patients while it increased in hypertensive patients with higher visit-to-visit BPV[10] thereby implicating increased arterial stiffness as a pathological mechanism contributing to long-term BPV.

However, large variation in visit-to-visit BP readings is not uncommonly seen and could be due to multiple reasons. Common causes can include poor or improved BP control in patients on treatment or alternatively technical variables such as improper BP cuff, white coat hypertension, etc. giving rise to inconsistent office BP readings. Hence, it is important to make sure that patient is compliant with his antihypertensive treatment at appropriate dosages at appropriate interval.

ABPM measurements over consecutive days or multiple HBPM recordings can help to define and clarify such day-to-day BPV. Visit-to-

visit BPV can be clarified by clinic-based OBPM done on frequent basis commonly in primary health settings or between-visit ABPM.[8] Certainly, use of 24-hour ABPM is very helpful and useful to overcome such limitations of OBPM by providing extensive readings of on BP levels within a given 24-hour period. However, ABPM due to technical reasons and frequent cuff inflations and multiple variable influencing the readings, cannot be routinely used to assess visit-to-visit BPV.[8]

Clinical Impact of BPV on Target Organ Damage and Cardiovascular Events

Impact of Short-term BPV

Current evidence available in literature has clearly shown the influence of short-term[11] as well as long-term BPV on cardiovascular events and target organ damage patients with hypertension. Further, the magnitude of short-term BPV has been also shown to independently associated with rate of cardiovascular events in general population as well.

Parati et al.[12] in 108 mild-to-severe essentially hypertensive patients could demonstrate for first time an independent association between both 24-hour mean BP and 24-hour BPV with the prevalence and severity of target organ damage. Further, the severity of target organ damage was linearly related short-term BP variability for any given 24-hour mean BP value.

One can also calculate and use "daytime systolic BPV" which is estimated by standard deviation (SD) of 24-hour ABPM. This has been shown in over 700 subjects with normal BP and hypertension of different degrees of severity to be associated with increased vascular damage and left ventricular hypertrophy.[8] In the PAMELA study, authors were able to show an independent relationship between the risk of death and SD of 24-hour, daytime, and night-time BP.[13] In addition, ELSA study (The European Lacidipine Study on Atherosclerosis) has shown that carotid IMT was related with 24-hour systolic BPV assessed by SD. This strongly suggests a relationship between short-term BPV and alterations of large artery structure in hypertension.[14] A recent meta-analysis of observational cohorts and of clinical trials reported significant hazard ratios for cardiovascular events as well as for cardiovascular and all-cause mortality in relation to an increased short-term BPV.[15]

Accumulating evidence suggests that specific patterns of the diurnal BPV may indeed have an important prognostic role. Night-time ambulatory BP carries superior prognostic value. More specifically, a non-dipping BP and, even more so, a pattern of BP rising during night have been shown to be linked with enhanced cardiovascular risk. Recent evidence suggests that it is the night-time average BP level which is of more importance.[16]

Impact of Long-term BPV

Studies showing the impact of long-term BPV on target organ damage and cardiovascular events in patients with hypertension and/or diabetes are shown in **Table 2**.

2455 residents of Ohasama underwent self-measurement of day-by-day variability of BP in Ohasama study.[17] There was an association between systolic and diastolic day-to-day BPV and cardiovascular and stroke mortality. This association was not seen for cardiac mortality. Data from Third National Health and Nutrition Examination Survey was examined by Muntner et al.[18] for relationship between increased visit-to-visit variability in blood pressure and all-cause mortality. Authors could show 57% increase in overall mortality in the general population in those who had SD of visit-to-visit systolic variability greater than 4.8 mm Hg.

Patient with type 2 diabetes also showed an inverse association between long-term BPV and microvascular, and macrovascular complications as well as mortality. A longitudinal cohort study with a mean follow-up period of 5.5 years which included 2161 patients with type 2 diabetes showed that visit-to-visit variability in BP significantly predicts all-cause mortality even after adjusting for confounding variables.[19] Ushigome et al.[20] looked in 858 patients with type 2 diabetes at the association between day-to-day

Table 2 **Long-term blood pressure variability and target organ damage and cardiovascular events in patients**

Study group	*BPV index*	*Results*	*Reference*
General population	BPV systolic day-to-day	Hazard ratios for cardiovascular and stroke mortality increased	Kikuya et al.[17]
General population	BPV systolic visit-to-visit	All-cause mortality increased	Muntner et al.[18]
General population	BPV morning systolic day-to-day	Cardiovascular events increased	Johansson et al.[33]
T2D patients	Systolic and diastolic BPV visit-to-visit	All-cause mortality increased	Hsieh et al.[33]
T2D patients	Systolic and diastolic BPV day-to-day	Macroalbuminuria	Ushigome et al.[20]
T1D patients	Visit-to-visit annual BPV	Progression of nephropathy	Kilpatrick et al.[21]
CKD patients	Visit-to-visit systolic BPV	Death risk increased	Di Iorio et al.[22]
Nondiabetic CKD	Visit-to-visit systolic BPV	Renal function deterioration	Yokota et al.[34]
ESRD patients on dialysis	BPV dialysis-to-dialysis	Cardiovascular mortality increased	

variability in HBPM done for 14 consecutive days and macroalbuminuria. They showed that increase in BPV of morning systolic and diastolic BP to be strongly related to the development of macroalbuminuria.

There is impact of BPV on TOD in diabetics and retrospective analysis Diabetes Control and Complications Trial (DCCT) showed that increased systolic and diastolic annual visit-to-visit BPV was related to the risk of the development or progression of nephropathy but not that of retinopathy.[21] A relationship between visit-to-visit variability in systolic BP and change in urinary albumin excretion or development of albuminuria has been found in patients with type 2 diabetes. Therefore, long-term visit-to-visit BPV could be considered a novel risk factor for the development and progression of diabetic nephropathy in patients with diabetes.

Another population which is affected by visit-to-visit BPV are the patients with chronic kidney disease or those under hemodialysis where impact on TOD and cardiovascular events has been shown.

A longitudinal retrospective and multicenter study done in 374 elderly subjects with chronic renal failure has shown an association between systolic BPV, defined as the ratio of the SD to the mean systolic BP of five values recorded during 4–5 months, and the risk of death but not of progression to dialysis.[22] Similarly, results from The Fosinopril in Dialysis Study[23] showed that visit-to-visit BPV is extremely high in hemodialysis patients compared with other populations and a major determinant of cardiovascular events in this setting.

Once again, we need to emphasize that short-term and long-term BPV are both linked to cardiovascular outcomes, TOD and cardiovascular events **(Fig. 2)**. Eguchi et al.[24] demonstrated that both variability of BPV of clinic systolic BP and night-time systolic BPV are independent predictors for cardiovascular events in hypertensive patients.[24] The European Lacidipine Study on Atherosclerosis[14] was able to demonstrate in patients with mild to moderate hypertension, that both carotid IMT and cardiovascular outcomes were related to the mean clinic or systolic BP on ABPM achieved by treatment but not to on-treatment visit-to-visit clinic or 24-hour BPV.

Both short-term and long-term BPV are associated with target organ damage and cardiovascular events in hypertensive patients.

The pathophysiological relationship is not clear and there are many associations seen. Of note is the fact, that BPV (in particular systolic BPV) correlates with arterial stiffness, which in turn is related to aging and increasing SBP levels. When researchers looked deeply and critically at BP variability in large prospective randomized trials,[27] they could note it to be a powerful independent risk factor of all-cause mortality, CVD incidence,

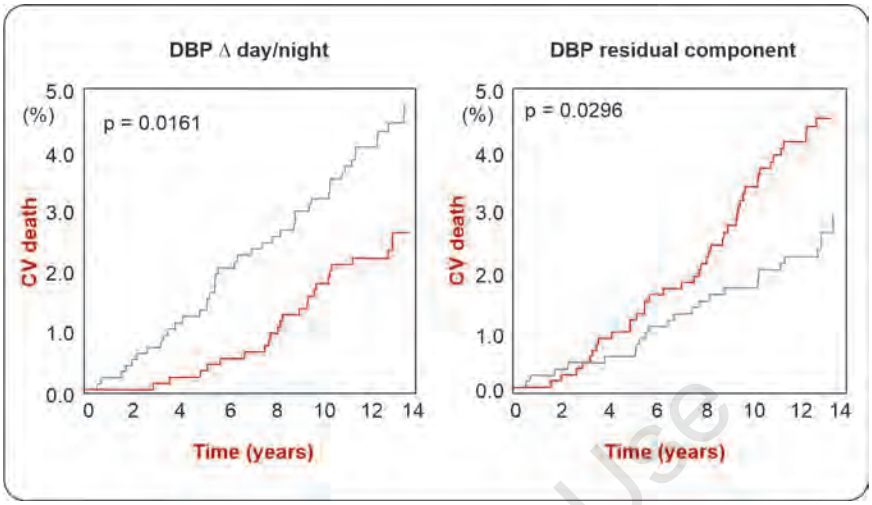

Fig. 2: Opposite impact on cardiovascular mortality of day–night change in diastolic blood pressure (DBP; left) and of "erratic" residual DBP variability (right). Kaplan-Meier curves are shown for subjects with values above (red lines) and below (gray lines) the population median

CVD mortality, CHD incidence, and stroke incidence **(Table 3)**. In fact, a contemporary large study looking at the relationship between BPV and chronic kidney disease showed that with worsening renal function, an increase occurs in systolic BPV, but not in diastolic BPV.[25] This might indicate that systolic BPV reflects primarily vascular stiffness and aging, while diastolic BPV has a different pathophysiological background such as, for instance, impaired autonomic function with increased sympathetic activity, and endothelial dysfunction.[26]

Treatment Effects on BPV

BPV is known to decrease with antihypertensive drug treatment but it is less clear whether classes of antihypertensive drugs differ in their effects. Undoubtedly, long-acting dihydropyridine calcium antagonists (CCB) seem the most promising drugs in this regard. CCBs were indeed found to be more effective in smoothing BPV and the reducing related organ damage in experimental animals. Rothwell et al., in the ASCOT-BPLA trial, found SBP SD to be lower with amlodipine versus those on atenolol at all follow-up visits ($p < 0.0001$). Parati et al.[28] showed that the lercanidipine alone or in combination with the ACE inhibitor enalapril reduced BP variability. On the other hand, monotherapy with enalapril did not lower BP variability, in spite of significantly lowering 24-hour ambulatory BP. Unfortunately, clinical studies showing advantages of CCB in reducing different types of BPV are mainly

Table 3 **BP Variability and Outcome in Randomized Controlled Trials**

Trial	*Number*	*HR for coronary heart disease/ myocardial infarction*	*HR for stroke*	*HR for all-cause mortality*	*HR for heart failure*	*Variability measurement*
ASCOT-BPLA	9,302	3.41	2.97	na	na	CV (SD/mean) of SBP in the amlodipine group
INVEST	22,576	1.42	1.5	na	na	Comparing those in the lowest versus those in highest quartile of visits with BP in control
ALLHAT	25,814	1.30	1.46	1.58	ns	Comparing those in the highest versus those in lowest quintile of SBP SD
LIFE	8,505	Ns	1.02 for SBP 1.06 for DBP	na	na	SD
VALUE	13,803	3.2	1.5	na	3.1	Lowest versus highest quintile of SD of visit-to-visit SBP
STABILITY	15,828	1.20 for SBP 1.28 for DBP	ns	1.12 for SBP 1.26 for DBP	ns	Per 5 mm Hg increase in SD
ONTARGET TRANSCEND	28,790	Ns	ns	1.22	1.30	Quintile 5 vs. 1 SBP CV
SPRINT	8,884	Composite endpoint (acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes)				CVs for DBP

posthoc analyses of trials, with only a few of them adhoc studies.[29] Hence, it is important that antihypertensives used are longer duration with action preferable over 24 hours as short-acting antihypertensive drugs can cause interval increase in BP thereby causing enhanced BPV. In fact, the smoothness index, which includes information on the homogeneity of drug effects over 24 hours, correlates with both a reduction in 24-hour BPV and the regression of organ damage in hypertension.[30]

Long acting calcium channel blocker is the most promising agent for treatment BPV and amlodipine has the highest smoothness index.

Long acting calcium channel blocker are the most promising agents for treatment BPV and amlodipine has the highest smoothness index. However, there are no studies documenting that reduction of such variability per se (independent of BP reduction) improved outcomes.[27]

Clinical Considerations

The possible clinical significance of BPV is science in evolution, but 3 aspects should be considered.

1. BPV by definition introduces uncertainty in assessing subject's BP status, especially when spot clinic measurements are used.
2. Assessment of BPV might be useful in improving cardiovascular risk stratification although the size of its actual independent contribution in this regard remains to be better documented.
3. Increased BPV may be a target for treatment, aiming at improved outcome possibly without generating additional costs.

The choice of long-acting drugs, in particular, dihydropyridine calcium antagonists and the combination of long-lasting compounds, might be indicated in individuals with elevated BPV, although the possible clinical benefits from such an approach have not yet been fully demonstrated.

BPV is poised to make new inroads among physicians and practitioner for improving clinical outcomes in patients with hypertension.

Current antihypertensive treatment often consists of once-daily administration of long-acting antihypertensive drugs upon awakening. Since the vast majority of drugs have a trough-to-peak ratio lower than 100%, it is expected that a diminished effect occurs during night-time and the early morning hours of the next day. This phenomenon may have important implications for subjects with night-time hypertension and/or nondipping profile and/or pronounced morning surge. Preliminary results derived from a single research center in Spain (MAPEC study) appear to support

dosing of at least one of the antihypertensive drugs at bedtime to improve cardiovascular prognosis.[31]

In general, more evidence is needed before recommending BPV as a possible target for treatment and before suggesting selection of any specific treatment in this regard, if not general advice is on use of long-lasting drugs and drug combinations to smooth a 24-hour BP profile.

Conclusion

Increasing values of overall short-term BPV or alterations in different patterns of BPV are associated number of adverse consequences in patient with hypertension. There is development and progression of damage to heart, vascular and kidneys. There is increase in cardiovascular events and cardiovascular and all-cause mortality, supporting the concept that BPV may contribute to cardiovascular risk prediction over and above the impact of recorded BP levels.

Hence, there is possible usefulness of assessing BPV and using it in clinical practice. We may consider an elevated BPV as a possible target for treatment to further improve prognosis. Though, many indices of short-term BPV have been shown to be of prognostic value, no interventional longitudinal outcome study has yet been conducted specifically addressing what short-term BPV levels should be considered as normal, and what level of short-term BPV achieved should be considered as target for antihypertensive treatment. Further studies and robust data are needed to confirm the key question of whether a reduction in short-term BPV by treatment translates into a better outcome.

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Chapter 10

Resting Heart Rate: An Additional Therapeutic Target in Hypertensives for CV Risk Reduction

Jamshed J Dalal, Sachin Suryawanshi

Abstract

Resting heart rate (rHR) has emerged as an independent risk factor for adverse cardiovascular and mortality outcomes in patients of hypertension (HTN) as well as those with coronary artery disease, heart failure, and stroke. Targeting rHR has been suggested as one of the approaches to lower cardiovascular risk. Despite proving its implication in clinical outcomes, the current evidence is limited in considering rHR as a therapeutic target. Large randomized controlled trials are necessary to understand the outcomes of targeting high rHR in patients with HTN and associated comorbidities.

Introduction

Resting heart rate (rHR) and blood pressure (BP) association is complex. Both central, as well as peripheral BP, are strongly related to HR. An increase in rHR is known to increase the peripheral pressure while reducing the central aortic pressure.[1] With regard to cardiovascular (CV) outcomes, the strong heart study demonstrated that the central pulse pressure is more strongly associated with vascular hypertrophy, extent of atherosclerosis, and CV events than peripheral pulse pressure.

Resting heart rate is evolving as an emerging risk factor for cardiovascular disease.

In patients with hypertension (HTN), rHR has a positive correlation with both systolic and diastolic BP. A cross-sectional survey from India—The BEAT survey—performed in 3743 young (18 to 55 years) hypertensive reported average resting heart rate of 82.79±10.41 bpm and BP of 146.82±15.46/89.08±8.8 mm Hg. HR had significant positive correlation with both SBP ($r = 0.247$, $p<0.01$) and DBP ($r = 0.219$, $p<0.01$).[2]

In the Kailuan cohort study, Wang et al. from China studied 31,507 participants with mean age of 46.3±11.5 years having no known HTN. During the mean follow-up of 3.5 years, 39.88% developed HTN. In multivariate analysis, significant increase in new onset HTN with increase in the resting HR ($p<0.0001$) was observed. Further, with increase in the resting HR by 10 bpm, a rise of 8% in HTN was reported.[3] The risk of incident HTN reported being 2–3 times greater in individuals with rHR of ≥90 bpm.[4] Further, such a rise in rHR increases the risk of adverse CV and mortality outcomes in patients of HTN. Thus, a target rHR of <70 bpm in patients of HTN and <65 bpm in those who have associated complications such as ischemic heart disease has been advocated.[5] Selective reduction of rHR with an agent such as ivabradine reduces rehospitalizations and mortality in heart failure (HF) and improves exercise tolerance and reduces anginal attacks in patients with coronary artery disease (CAD). Considering these effects, rHR is now designated as an emerging risk factor in CV disease.[6] In this chapter, we discuss the current evidence on rHR as a CV risk factor and provide perspectives for future research.

Resting Heart Rate: A Cardiovascular Risk Factor

Resting HR is not only a risk factor for CV disease in patients with HTN but also adds to the risk in patients with existing CV disease. The below sections highlight the current evidence for risk attributable to rHR in different clinical scenarios.

Hypertension

Multiple studies have demonstrated the association between rHR and CV outcomes. One of the early evidence is from Levy et al. who showed that in the presence of transient HTN along with transient tachycardia, the risk of development of sustained HTN and enhanced risk of CV deaths was twice as compared to those who did not develop transient tachycardia and HTN.[7]

Resting heart rate is associated with increased incidence of new onset hypertension and adverse CV outcomes.

In analyzing the Framingham data, Gilman et al. reported a nearly twice higher risk of all-cause death and a 1.5 times risk for CV death with each increment in rHR of 40 bpm.[8] The analysis of data from the VALUE trial that involved patients with high-risk HTN indicated a significant association with CV outcomes and HR. Every 10 bpm rise of rHR from baseline increased the risk of composite cardiac outcome (Hazard ratio 1.16), heart failure (hazard ratio 1.24), sudden cardiac death (hazard ratio 1.18), MI (hazard ratio 1.10),

stroke (hazard ratio 1.09), and all-cause death (HR 1.19).[9] In addition, LIFE study data analysis also revealed that a 10 bpm rise in rHR increased risk of CV deaths and all-cause deaths by 25% and 27% respectively. The risk was significantly greater in patients with rHR ≥84 bpm (89% and 97% respectively) and it persisted even in multivariate analysis after adjustment for various factors including treatment with losartan or atenolol.[10] These data establish the role of rHR as an independent CV risk factor in patients with HTN. Not only clinic measured rHR but ambulatory rHR is essential in this context. A study from Japan assessed 1444 people without any CV disease and among them, 27.4% had HTN. Over the 12-year follow-up, a 10-bpm rise in day-time HR or night-time HR predicted non-CV deaths (hazard ratio 1.28 and 1.48, respectively) but no association with CV death. Further, a similar 10 bpm increase in the night-time rHR had an independent association with all-cause death (hazard ratio 1.29).[11] These published data indicate that a 10 bpm rise in rHR from baseline can be considered an independent risk factor for CV outcomes and mortality. Additionally, measuring ambulatory HR can provide further insights into understanding its association with adverse CV outcomes. More research is necessary to establish the role of ambulatory HR in HTN.

Coronary Artery Disease

Evidence indicates that rHR has a significant association with the severity of atherosclerosis in the coronaries of young patients who had a myocardial infarction (MI) as well as with the progression of coronary atherosclerosis.[12,13]

Resting heart rate is a potential risk factor for heart failure in male. Data is also emerging that resting heart rate is associated with higher CV mortality, hospitalization for MI and need for coronary revascularization.

The BEAUTIFUL (Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction) trial included patients of CAD with left ventricular (LV) dysfunction. Compared with ≤70 bpm, a rHR of >70 bpm had a significant association with higher CV mortality, hospitalization for MI and the need for coronary revascularizations.[14] With ivabradine, there was a significant reduction in the need for revascularization and MI in patients who had rHR>70 bpm.[15] A posthoc analysis from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trials showed that rHR had a significant association with CV death, stroke, and HF hospitalization in patients with existing atherosclerotic CV disease (ASCVD). However, the

adjusted analysis revealed the association with MI was not significant.[16] It indicates the association of rHR with CV outcomes may differ among populations of different risk and different antecedent events. In the Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) involved patients with stable CAD without LV systolic dysfunction and without clinical HF. Ivabradine did not reduce a composite endpoint of CV death and nonfatal MI at a rHR of >70 bpm.[17] This is indicative of rHR being a risk indicator rather than a risk factor. In patients of CAD treated for HTN, analysis from the International VErapamil-SR/trandolapril STudy (INVEST) data indicated a linear association of rHR and CV outcomes. The follow-rHR (hazard ratio 1.06, p<0.0001) was independently associated with the adverse outcomes but the risk contribution was much lower than the established risk factors such as diabetes (hazard ratio 1.78, p<0.0001), increase in age by 10 years (hazard ratio 1.54, p<0.0001), smoker (hazard ratio 1.41, p<0.0001), etc. At 24 months, atenolol-based treatment reduced rHR better than verapamil-based treatment (mean HR 69.2 vs 72.8 bpm, respectively). However, there was no difference in the incidence of adverse CV outcomes in two groups (9.88% vs 9.67%, p=0.62). The study concluded that on-treatment HR is a better predictor of outcomes than resting HR.[18]

Heart Failure

Hypertension is one of the commonest factors in the development of heart failure. HR is important element in patients with HF. In a failing heart, HR determines the oxygen consumption, balance of energy demand, and supply and contractility. The rise in rHR can lead to adverse outcomes such as MI, cardiomyopathy.[6]

Increase heart rate in heart failure not only increases oxygen consumption of heart but is also associated with increase CV death and HF hospitalization.

The SHIFT (Systolic Heart Failure Treatment with the I_f-inhibitor Ivabradine trial) study, included patients with heart rates >70 bpm. With an increase was of 1 bpm and 5 bpm in rHR, the risk for the composite of CV death and HF hospitalization increased by 3% and 16% respectively. This clearly establishes the rHR is important risk factor for HF.[19] This observation is also supported by the CHARM (candesartan in heart failure: assessment of reduction in mortality and morbidity) study. In patients of HF, an increase in HR by 5 bpm from preceding visit increased risk of all-cause mortality and the composite endpoint of CV death or hospitalization for HF (adjusted hazard ratio 1.06, p < 0.001).[20] Not only patients of HF but healthy adults with higher

rHR are also at risk of HF. The Rotterdam study analysis included healthy adults (≥55 years) without any HF. It was observed that for each 10 bpm rise in rHR, the multivariable-adjusted hazard ratios in men were 1.16 (p=0.005) in the time-fixed heart rate model and 1.13 (p=0.017) in the time-dependent heart rate model. No effect was reported in females.[21] These data indicate rHR as a potential risk factor for HF in healthy adult males and contribute to increased risk of adverse outcomes in patients with existing HF.

Stroke

Evidence in assessing the impact of HR in patients with stroke is sparse. One of the largest assessments of such association is available from the post-hoc analysis of PRoFESS (the Prevention Regimen For Effectively avoiding Second Stroke) trial that included patients who recently experienced an ischemic stroke or had a recurrent stroke. Results from this analysis, indicate that compared with the lowest quintile, the patients in the two highest quintiles of HR (77–82 and >82 bpm) had a higher risk for all-cause death (hazard ratio 1.42 and 1.74 respectively, p<0.0001), vascular death (hazard ratio 1.39 for 77–82 bpm, p<0.0001) and nonvascular death (hazard ratio 1.66 for >82 bpm, p = 0.0016). No significant association existed for risk of MI (p = 0.7084) and recurrent stroke (p = 0.1379). In addition, the study found that a low HR is associated with a better functional outcome and less cognitive decline after an ischemic stroke.[22] In patients with acute intracerebral hemorrhage, the INTERACT (INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial) study reported a significantly increased risk of mortality and worse modified Rankin Scale score indicating poor functional outcome in patients with admission HR of ≥85 bpm than those with <65 bpm. (adjusted hazard ratio 1.50, p<0.05).[23] With a strong association between hypertension and stroke, control of heart rate would be beneficial on both counts.

Evidence from a Meta-analysis

In a meta-analysis of 45 nonrandomized prospective cohort studies, Zhang et al. demonstrated that increase in rHR by 10 bpm, resulted in a 12% increase in CAD risk, 5% increase in stroke risk, 12% increase in the risk of sudden death, and 16% increase in non-CV disease risk. The risk of these outcomes was linear across the rHR range **(Table 1)**.[24]

An increase in resting heart rate by 10 bpm is associated with increase in risk of CAD, stroke, sudden cardiac death and increase in non-CV disease risk.

Table 1 **Risk ratios for different outcomes according to categories of resting heart rate[24]**

Population	*Relative risk (95% confidence intervals)*				
	Overall	*rHR<60*	*rHR 60–70*	*rHR 70–80*	*rHR>80*
CAD	1.12 (1.09–1.14)	REF	0.99 (0.93–1.04)	1.08 (1.01–1.16)	1.30 (1.19–1.43)
Stroke	1.05 (1.01–1.08)	REF	1.08 (0.98–1.19)	1.11 (0.98–1.25)	1.08 (0.93–1.25)
Sudden death	1.12 (1.02–1.24)	REF	—	—	—
Noncardiovascular disease	1.16 (1.12–1.21)	REF	1.17 (0.94–1.46)	1.31 (1.12–1.54)	1.57 (1.39–1.77)

Abbreviations: rHR, resting heart rate (beats per min); REF, reference category

Resting Heart Rate: A Therapeutic Target

It should be emphasized that despite its recognition as important contributor to the mortality and CV outcomes, treating elevated HR in patients with HTN is debatable. No clear evidence is for the optimal approach to manage HR in HTN. Recently, the European Society of Hypertension suggested the practical approaches in patients of HTN with high rHR.[25] Recently, the European Society of Hypertension suggested the practical approach in patients of HTN with high rHR. This approach suggests reporting of self-measured HR by patients who measure their blood pressure at home. If HR in the doctor's office is high, the ambulatory HR may provide additional useful information in such patients. Improvement of an unhealthy lifestyle is recommended after ruling out secondary causes of tachycardia. Lifestyle modifications such as physical activity, smoking cessation, avoidance of excessive alcohol consumption and heavy coffee use as well as dietary intervention for weight control should be implemented. Cardiac slowing drug such as β-1 selective β-blockers should be considered for treatment of symptomatic patients.[25]

There is no doubt that elevated resting heart rate is a risk factor for cardiovascular disease and 10 bpm rise is associated with adverse clinical outcome but targeting resting heart rate for improving CV outcomes is still in search of randomized controlled trials.

Currently, beta-blockers and ivabradine are two prominent therapies that reduce rHR. In the context of therapeutic benefit reducing rHR is observed in patients with HF. In patients with HTN, Jozwiak et al. demonstrated a 25% reduction in HR (baseline 86±5 bpm) with ivabradine that resulted in significant improvement in LV twist and untwist which occur in systole and

diastole, respectively.[26] Analysis from SHIFT trial showed that in patients with chronic HF having baseline rHR>75 bpm, ivabradine significantly reduced the outcomes. There was 24% risk reduction in primary end point (hazard ratio 0.76, p<0.0001), 17% each risk reduction in all-cause death (hazard ratio 0.83, p=0.0109) and CV death (hazard ratio 0.83, p=0.0166). There was a significant reduction in risk of HF death (hazard ratio 0.61, p<0.0006), and HF hospitalization (hazard ratio 0.70, p<0.0001). The study observed best protection for HR<60 bpm or reductions >10 bpm.[27] In a study of patients developing acute MI without HF, Park et al. demonstrated β-blocker use was associated with 48% reduced risk for 5-year mortality in patients with high heart rates (hazard ratio, 0.52), but not in those with low heart rates (p=0.97).[28] Another analysis from subgroup analysis from BISO-CAD study, patients of CAD with HTN (n=681), the composite outcomes (CV death, non-fatal MI and hospitalization due to unstable angina or for revascularization) was significantly lower with on treatment rHR<65 bpm and <70 bpm compared with rHR ≥65 bpm and ≥75 bpm. This outcome was identified to be independent of BP reduction.[29] These results point towards the beneficial effect of reducing HR especially in patients with HF and MI. However, in patients with HTN, paradoxical finding were reported in a meta-analysis from Bangalore et al. They identified 22 randomized controlled trials that evaluated beta-blockers as first-line therapy for HTN. Of the 22 trials, 9 reported HR data. A lower HR attained with the beta-blocker group was associated with an increased risk of all-cause mortality, CV death, MI, stroke, or HF.[29] Whether this is related to the opposing effects of heart rate on peripheral and central aortic pressure needs to be elucidated. Thus, further large prospective trials are necessary to clearly establish rHR as a therapeutic target in patients with HTN.

Conclusion

Evidence is clear that elevated rHR is a risk factor for CV disease. In evaluating patients with HTN, rHR should be included in overall assessment. A 10 bpm rise in rHR has significant association with adverse clinical outcomes. Experts advised a target rHR of <70 bpm in patients with HTN. The current evidence is limited in drawing any conclusions to consider rHR as therapeutic target. European Society of Hypertension also identifies the need of randomized clinical trials aiming at evaluating the effects of HR reduction in hypertensive patients with high HR.

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Note: Page numbers followed by *f*, *t*, and *b* represent figures, tables, and boxes respectively.

Cardiometabolic Medicine 2022

The book entitled "Cardiometabolic Medicine 2022" is a great step to build up the new upcoming subspecialty of cardiometabolic medicine to tackle the suffering afflicted population with cardiometabolic diseases. Distressingly enough, most of the cardiometabolic diseases like obesity, diabetes, hypertension, atherosclerotic cardiovascular disease etc. commonly co-exists and produces multiple co-morbidities which are beyond the reach of a physician or single specialist to comprehensively evaluate and treat them and therefore requires a cohesive effort of several specialties. The above book will immensely help to fulfill the goal of evaluating and treating cardiometabolic diseases in the current era.

PC Manoria, Director, Manoria Heart and Critical Care Hospital, Bhopal, Madhya Pradesh, India and Former Professor and Head, Department of Cardiology, Gandhi Medical College, Bhopal has a distinguished academic career. He has great clinical acumen and is an unmatched superspecialist with an in-depth knowledge of other subspecialties of medicine too.

He has been bestowed with several awards and orations like Life Time Achievement Award in clinical and preventive cardiology by Hon'ble (Late) Shri APJ Abdul Kalam, Past President of India, Life Time Achievement Award by Indian Federation of Ultrasound in Medicine and Biology, Netaji Oration Award of API, Special Award in Cardiology by AACIO 2011 at New Orleans (USA), Master Teacher Award by Indian College of Physicians 2019, Dhanwantari Award, Award of Excellence in Academics by PGI Chandigarh. He is also Honorary Cardiologist to His Excellency, The Governor of MP. Besides MD, DM he has also received several fellowships like FACC (USA), FESC (Europe), FCAPSC (Asia), FICA (USA), FICP, FCSI, FISE, FCCP, FIAMS, FICMU, FIACM, FICC, FIAE, FISH, etc.

He has been the National President of nearly all prestigious associations, including API and CSI. He is also Past Dean, ICP and ICMU. He was also Past Chairman, Hypertension Council Asian Pacific Society of Cardiology and Past Vice President SAARC Cardiac Society. He has widely traveled abroad, delivered 800 lectures in various national and international conferences and has 75 publications to his credit in various journals. He is on the editorial board of several journals. He has the unparalleled organizing capacity and has been organizing scientific meetings for last 40 years including International Conferences, International Echo Workshops, etc. He has vast experience in editing books and this is his 33rd book entitled "Cardiometabolic Medicine 2022". He has organized the First World Congress on Cardiometabolic Medicine at Mumbai, Maharashtra in 2019 and the second one is scheduled to be held at Mumbai, Maharashtra in 2022.

ISBN:978-93-90616-47-3

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