JULY 2024
VOL. 4 / ISSUE 13

Aster Medical Journal

www.theamj.org

Naegleria Fowleri
Brain-Eating Amoeba Claims Lives of Three Children in Kerala

Views & Reviews
The Clinical Translation of Precision Diabetes Medicine

TRANSFORMING DIABETES CARE with **Precision Medicine**

Shaping the future of healthcare

SIEMENS Healthineers

CONTENTS

July 2024

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61

From the scorching streets of Phoenix, Arizona, where temperatures soared to a record-breaking 118°F (48°C), to the sweltering cities of Europe, where thousands succumbed to heat-related illnesses, the impact of rising temperatures on human health is undeniable. In India, a prolonged heat wave claimed the lives of over thousands of people, while in China, emergency services struggled to cope with the influx of heatstroke victims.

While everyone is susceptible to heat-related illness, certain populations are particularly vulnerable. The elderly, with their diminished physiological reserves and often compromised thermoregulatory function, are at heightened risk.

CONTENTS

July 2024

Conversation

" What we know so far is that the mRNA vaccines still appear to be effective against all other variants so far. What we don't know is what is going to show up in the future... So, the concern is that in the future a variant might appear that the vaccine is completely useless against. For mRNA vaccines, it is very simple to make an update—a booster and improvement."

— Dr. Vanessa Kerry

Page 64

Original Research

Views & Reviews

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Features

IN EVERY ISSUE

ON THE COVER

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GO GREEN

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Prologue

Precision Medicine: A New Era in Diabetes Care

When discussing precision medicine, I'm often reminded of the adage attributed to Hippocrates or Sir William Osler: "It is much more important to know what sort of patient has a disease than what sort of disease a patient has." This principle lies at the heart of personalized medicine, which becomes even more powerful when combined with precision. Precision medicine represents the evolution of evidence-based practice, aiming to minimize errors and maximize outcomes. It holds particular significance in the realm of diabetes care.

Diabetes, a global health crisis affecting over half a billion individuals, demands an approach that recognizes its multifaceted nature. Precision medicine offers a transformative solution by acknowledging that diabetes isn't a single entity but a spectrum of conditions with diverse origins and manifestations. This paradigm shift moves us away from generic treatments towards tailored interventions that consider each patient's unique genetic makeup, lifestyle, metabolic profile, and medical history.

Diabetes is a complex disease with multiple pathways leading to its development. Effective management hinges on understanding the specific metabolic dysfunctions involved. A significant step forward is the "Second International Consensus Report on Gaps and Opportunities for the Clinical Translation of Precision Diabetes Medicine," published in Nature Medicine on October 5, 2023. This report, a collaboration of 200 experts from 28 countries and supported by leading diabetes organizations like the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the Novo Nordisk Foundation, underscores the progress made and identifies areas for further research.

Precision medicine could help refine our diagnosis of sub-types of diabetes, predict treatment responses or outcomes, and thereby allow us to better target our clinical management, treatment recommendations, and reduce diabetes-related complications.

The consensus report highlights areas where precision medicine can have a significant impact on clinical practice, providing a framework for future research. Precision medicine stands poised to revolutionize diabetes care. Advancements in genomics, data analytics, and artificial intelligence have equipped us with tools that were once unimaginable. We now have the power to unlock the secrets hidden within our DNA, predict disease progression, and tailor treatments with unprecedented accuracy.

This is a watershed moment in diabetes care. This isn't merely a scientific endeavor; it's a moral imperative to provide our patients with the best possible chance at a healthy, fulfilling life.

Dr Azad Moopen, MD, FRCP
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Aster Medical Journal

www.theamj.org

VOL. 4 | ISSUE 13 | July 2024

PLACE OF PUBLICATION

Aster DM Healthcare Limited
IX/475L, Aster Medcity, Kuttisahib Road,
Near Kothad Bridge, South Chittoor P.O,
Cheranelloor, Kochi, Kerala— 682 027, India
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33rd Floor — Aspect Tower
Business Bay, P.O.Box: 8703
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IMPRINT LINE
Printed and published by Dr Gopakumaran Kartha on behalf of Aster DM Healthcare Limited, IX/475L, Aster Medcity, Kuttisahib Road, Near Kothad Bridge, South Chittoor P.O, Cheranelloor, Kochi, Kerala— 682 027, India and printed at Anaswara Offset Pvt Ltd, Perandoor Junction, Elamakkara, Kochi — 682 026 and published at Aster DM Healthcare Limited, IX/475L, Aster Medcity, Kuttisahib Road, Near Kothad Bridge, South Chittoor P.O, Cheranelloor, Kochi, Kerala— 682 027. Editor: Dr Geetha Philips.

RNI No: **KERENG/2019/77520** | Price: **150 INR**

Case Reports

Editorial

Tailoring Diabetes Treatment: The Precision Medicine Approach

In this issue of AMJ, we delve into the critical importance of precision medicine for diabetes in the context of a consensus report jointly released by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). This report urgently calls for the adoption of precision medicine in diabetes care, urging the medical fraternity to integrate this approach into their practice.

The complexity of diabetes, a heterogeneous disease influenced by intricate metabolic pathways and diverse genetic, environmental, and lifestyle factors, demands a paradigm shift in treatment strategies. Precision medicine offers a tailored approach that considers the unique characteristics of each patient. This methodology extends beyond generalized treatment protocols to incorporate genetic information, biomarkers, and other personal health data. By predicting which treatments will be most effective for which patients, precision medicine aims to optimize outcomes and minimize adverse effects.

A pivotal study conducted in Sweden, known as the ANDIS (All New Diabetics in Scania) study, underscores the necessity of this approach. This research identified five distinct subtypes of diabetes, each with unique genetic and clinical profiles. These subtypes, ranging from severe autoimmune diabetes to mild age-related diabetes, demonstrate why a one-size-fits-all treatment strategy is suboptimal. Each subtype responds differently to treatments, necessitating personalized management plans.

Furthermore, the Swedish study highlighted that approximately 37% of patients were misclassified when relying solely on traditional diagnostic criteria. This misclassification can lead to inappropriate treatment plans and suboptimal patient outcomes.

Our cover story delves deeper into these themes. We also bring a feature story on the pathophysiology of heatwave-related mortality, which swept the world last summer. Additionally, this issue includes a cross-sectional study on sleep patterns and insomnia and a study on risk factors for cardiovascular and metabolic comorbidities in patients with obstructive sleep apnea.

Happy reading!

Dr Geetha Philips, MD, FRCP

Endometriosis: Lack of Care Pathway and Poor Symptom Recognition Hindering Care

Patients with endometriosis are facing significant challenges due to the lack of awareness among healthcare professionals and the absence of a standardized NHS care pathway. A report by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) found that many patients experience delayed investigations and dismissed symptoms. The study reviewed responses from 623 clinicians, 167 hospitals, and 941 patients, revealing that over half of the patients had to repeatedly visit their GP before any investigations were initiated. This highlights a critical need for better recognition and management of endometriosis in the healthcare system.Key findings include:

- The maternal death rate from 2020-22 was 13.41 deaths per 100,000 maternities, a significant increase compared to 8.79 deaths per 100,000 maternities in the previous three-year period (2017-19).
- Excluding COVID-19-related deaths, the maternal death rate for 2020-22 (11.54 deaths per 100,000 maternities) still surpasses that of 2017-19.
- Thrombosis and thromboembolism emerged as the primary cause of maternal deaths, with COVID-19 ranking second, followed by heart disease and mental health-related issues.

Kidney Function in Extreme Heat

Researchers have investigated the impact of extreme heat on kidney function by analyzing blood samples from volunteers exposed to high temperatures and varying humidity levels. In dry heat conditions (47°C, 15% humidity), older volunteers (>65 years) showed significant increases

in blood markers of kidney function (creatinine and cystatin C). However, in humid conditions (40°C, 40% humidity), these markers did not change significantly. This study highlights the potential risks to kidney health during heat waves and suggests that higher humidity may offer some protective effects.

LLMs Not Fit to Practise

A recent diagnostic accuracy study in Nature Medicine has raised serious concerns about the use of large language models (LLMs) as AI diagnosticians. The study found that current state-of-the-art LLMs do not accurately diagnose patients across all pathologies, perform significantly worse than physicians, fail to follow diagnostic or treatment guidelines, and cannot interpret laboratory results. The authors highlight that LLMs pose a serious risk to patient health and are not easily integrated into existing medical workflows due to their frequent failure to follow instructions.

Pfizer Moves Forward with Once-Daily Weight-Loss Pill

Pfizer plans to advance a reworked, once-daily version of its weight-loss pill, danuglipron, into clinical trials later this year. This decision follows the scrapping of a twice-daily version of the drug due to high rates of side effects such as nausea and vomiting. The new formulation is part of the second generation of weight-loss pills, which aim to offer a more convenient alternative to injections. Pfizer will evaluate multiple doses of the reformulated drug in the second half of this year before advancing it into clinical trials. The weight-loss drug market, currently dominated by Novo Nordisk's Wegovy and Eli Lilly's Zepbound, is expected to be worth more than $150 billion in annual sales by the early 2030s.

The brief

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Bird Flu Hits Antarctica's Adélie Colonies

Adélie penguins in Antarctica are testing positive for bird flu without showing outward signs of the disease, according to researchers who journeyed to 13 remote breeding sites aboard an ice-breaking cruise ship. Since bird flu reached the region this year, concerns have grown about the impact on the fragile penguin populations.

In November last year, researchers warned that mass mortality in these colonies could signal one of the largest ecological disasters of modern times. During December 2023 and January 2024, scientists tested 16 Adélie penguins on Beagle Island in the Antarctic Peninsula for H5N1, with seven (43%) testing positive.

Brain-Eating Amoeba Claims Lives of Three Children in Kerala

Naegleria fowleri is a single-celled organism that thrives in warm, freshwater environments such as lakes, rivers, hot springs, and even soil.

In a distressing series of events, an Indian state, Kerala has reported the deaths of three children due to infections caused by the brain-eating amoeba, Naegleria Fowleri. This rare and often fatal organism has raised serious health concerns, prompting a call for increased awareness and preventive measures.

Overview of Naegleria fowleri

Naegleria fowleri is a single-celled organism that thrives in warm, freshwater environments such as lakes, rivers, hot springs, and even soil. It is considered a free-living amoeba because it does not require a host to survive. When it infects humans, it causes primary amoebic meningoencephalitis (PAM), a severe and usually fatal infection of the central nervous system.

How Infection Occurs

The primary mode of infection is through the nasal passages. When individuals swim, dive, or engage in water activities in contaminated water, the amoeba can enter the body through the nose. From there, it travels to the brain, causing severe inflammation and damage. In rare cases, infection can occur from using inadequately chlorinated swimming pool water or contaminated tap water for nasal rinsing. It is important to note that Naegleria fowleri infections do not occur from drinking contaminated water.

Symptoms and Progression

The symptoms of PAM usually appear suddenly and are severe from the outset. Initial signs include:

- High fever
- Severe headache
- Nausea and vomiting
- Stiff neck and photophobia (sensitivity to light)
- Mental confusion

As the infection progresses, patients may experience seizures, hallucinations, and eventually coma. The incubation period ranges from two to 15 days post-exposure. Unfortunately, the fatality rate for PAM exceeds 97%, even with treatment.

Diagnosis

Diagnosing PAM can be challenging due to its rarity and nonspecific symptoms. Healthcare providers typically perform a spinal tap (lumbar puncture) to detect the presence of the amoeba in cerebrospinal fluid (CSF). In some cases, a brain biopsy might be necessary to confirm the diagnosis.

Treatment

There is no definitive treatment for PAM, but the antifungal drug amphotericin B is commonly used. Some patients have shown improvements when treated with a combination of drugs, including amphotericin B, rifampin, fluconazole, and miltefosine. Early diagnosis and prompt initiation of this drug regimen, along with therapeutic hypothermia (cooling the body to reduce brain swelling), have led to successful recoveries in a few cases.

Prevention

Given the high mortality rate and lack of effective treatment, prevention is crucial. Key preventive measures include:

- Avoiding swimming in warm freshwater bodies known to harbor the amoeba.
- Using nose clips when swimming in freshwater to prevent water from entering the nasal passages.
- Using only distilled or sterilized water for nasal rinsing. If using tap water, ensure it is boiled for at least one minute and cooled before use. At altitudes above 6,500 feet, boil for three minutes.
- Ensuring swimming pools are properly chlorinated and maintained.
- The Kerala health department has issued a notification emphasizing the dangers of Naegleria fowleri and the importance of preventive measures.

Transforming Diabetes Care with Precision Medicine

As precision medicine evolves, it transforms how we diagnose, treat, and manage diabetes, heralding a new era in personalized healthcare.

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Diabetes, a complex and multifaceted disease affecting hundreds of millions worldwide, has long been a significant global health challenge. Traditional approaches to diabetes care, which often involve broad, generalized treatment plans, are increasingly being supplemented by precision medicine. This innovative approach tailors interventions to the unique genetic, environmental, and lifestyle factors of individual patients, offering the potential to significantly improve outcomes and quality of life for those living with diabetes. As precision medicine evolves, it transforms how we diagnose, treat, and manage diabetes, heralding a new era in personalized healthcare.

PRECISION MEDICINE TAKES AN INDIVIDUAL APPROACH

Precision medicine represents a logical evolution of evidence-based medicine, aiming to reduce errors and optimize outcomes through individualized care. By recognizing and addressing the heterogeneity in the etiology, clinical presentation, and pathogenesis of diabetes, precision medicine seeks to deliver more effective and targeted interventions. This approach is particularly crucial for diabetes, a disease characterized by its varied forms and diverse patient profiles.

The traditional classification of diabetes into type 1 (T1D) and type 2 (T2D) categories, along with rarer forms such as monogenic diabetes and gestational diabetes mellitus (GDM), does not fully capture the disease's complexity. Precision medicine leverages advances in genomics, proteomics, and other omics technologies to better understand the underlying mechanisms of diabetes and to develop more precise diagnostic and therapeutic strategies.

The Four Pillars of Precision Diabetes Medicine

The Precision Medicine in Diabetes Initiative (PMDI) has identified four key pillars of precision diabetes medicine: prevention, diagnosis, treatment, and prognosis. These pillars provide a framework for translating precision medicine research into clinical practice, with the goal of improving patient outcomes across the spectrum of diabetes types.

PREVENTION

One of the most promising aspects of precision medicine is its potential to prevent diabetes before it develops. By identifying individuals at high risk through genetic testing and other biomarkers, clinicians can implement targeted interventions to delay or prevent the onset of the disease. For instance, genetic risk classification has emerged as a powerful tool for predicting type 1 diabetes. Researchers have identified genetic markers that indicate an increased risk of developing T1D, allowing for early monitoring and intervention.

In type 2 diabetes, precision medicine aims to identify subgroups of patients who will benefit most from specific preventive measures. For example, individuals with certain genetic profiles or lifestyle factors may respond better to interventions such as dietary changes, increased physical activity, or weight loss programs. By tailoring these interventions, precision medicine can more effectively reduce the risk of developing type 2 diabetes.

DIAGNOSIS

Accurate diagnosis is a cornerstone of effective diabetes management. Precision medicine

enhances diagnostic accuracy by integrating genetic, molecular, and clinical data to classify diabetes subtypes more precisely. This approach is particularly valuable for monogenic diabetes, where specific genetic mutations can guide diagnosis and treatment.

For example, glucokinase maturity-onset diabetes of the young (GCK-MODY) is a monogenic form of diabetes caused by mutations in the GCK gene. Patients with GCK-MODY typically have mild, stable hyperglycemia that does not require treatment. Identifying these patients through genetic testing allows for appropriate management without unnecessary interventions. Similarly, patients with HNF1A-MODY, another monogenic diabetes subtype, can often be treated effectively with low doses of sulfonylureas, avoiding the need for insulin therapy.

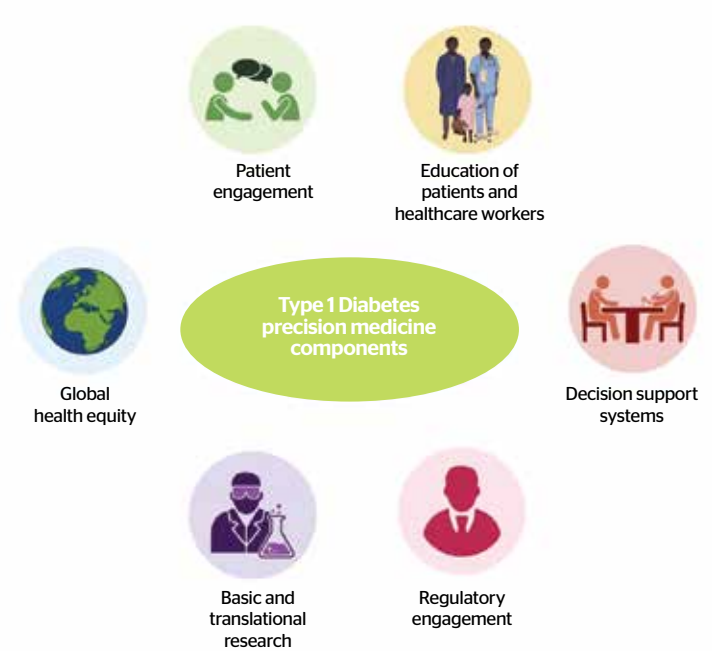
In gestational diabetes, precision medicine can help predict which women are likely to benefit from specific treatments based on their genetic and clinical profiles. By tailoring treatment plans to individual patients, clinicians can improve outcomes for both mothers and their babies.

TREATMENT

Precision medicine revolutionizes diabetes treatment by customizing therapeutic strategies to individual patient profiles. This approach is particularly relevant for type 2 diabetes, where a one-size-fits-all treatment model often falls short. By analyzing genetic, molecular, and clinical data, clinicians can identify which patients are likely to respond to specific medications, thereby optimizing treatment efficacy and minimizing adverse effects.

For instance, some patients with type 2 diabetes have genetic variations that affect their response to metformin, a commonly prescribed first-line medication. Precision medicine can help identify these patients and guide the selection of alternative treatments that may be more effective. Similarly, precision diagnostics can improve cardiovascular risk prediction in diabetes patients, enabling more precise allocation of treatments to prevent cardiovascular events.

In type 1 diabetes, precision medicine holds promise for developing personalized insulin regimens and advanced technologies such as closed-loop insulin delivery systems. These systems continuously monitor blood glucose levels and automatically adjust insulin delivery, providing more precise and effective glucose control.



PROGNOSIS

Predicting disease progression and outcomes is a critical aspect of diabetes management. Precision medicine enhances prognostic accuracy by integrating genetic, molecular, and clinical data to identify patients at higher risk of complications. This information allows for more targeted monitoring and intervention, potentially improving long-term outcomes.

For example, patients with specific genetic markers may be at increased risk of developing diabetic kidney disease, a common and serious complication of diabetes. Early identification of these high-risk individuals enables proactive management, such as more frequent monitoring and early initiation of nephroprotective therapies, to slow disease progression.

AI AND ML IN PRECISION MEDICINE

Artificial intelligence (AI) and machine learning (ML) are rapidly becoming indispensable tools in the translation of precision medicine into clinical

practice. These technologies have the potential to enhance every aspect of diabetes care, from diagnosis and treatment to monitoring and prognosis, by providing data-driven insights and facilitating personalized medical decisions.

ENHANCING DIAGNOSIS AND TREATMENT

AI and ML algorithms can analyze vast amounts of genetic, molecular, and clinical data to identify patterns and correlations that may not be apparent to human clinicians. For instance, AI can help in the early detection of diabetes by analyzing genetic markers and predicting disease onset with high accuracy. This allows for timely intervention and potentially preventing the disease from developing.

In treatment, AI can optimize medication regimens by predicting individual responses to different drugs based on genetic and clinical profiles. For example, AI-driven models can analyze patient data to determine which type 2 diabetes patients will respond best to metformin versus other medications, thereby enhancing treatment efficacy and minimizing adverse effects.

PERSONALIZED MONITORING AND MANAGEMENT

Continuous glucose monitoring systems integrated with AI can provide real-time data analysis and personalized feedback to patients. These systems can predict blood glucose trends and recommend adjustments in diet, exercise, or medication, enabling patients to maintain optimal glucose levels more effectively. Closed-loop insulin delivery systems, also known as artificial pancreas systems, leverage AI to automate insulin delivery based on continuous glucose monitor readings, significantly improving glucose control for type 1 diabetes patients.

In treatment, AI can optimize medication regimens by predicting individual responses to different drugs based on genetic and clinical profiles.

PREDICTIVE ANALYTICS FOR COMPLICATIONS

AI and ML can also play a crucial role in predicting and preventing diabetes-related complications. By analyzing patient data, these technologies can identify individuals at higher risk for complications such as diabetic nephropathy, retinopathy, or cardiovascular diseases. Early detection and proactive management of these risks can significantly improve patient outcomes and reduce healthcare costs.

CASE STUDIES AND GLOBAL INITIATIVES

Several global initiatives and studies are already demonstrating the impact of AI and ML in precision diabetes medicine. For example, the Lund University Diabetes Centre in Sweden utilizes AI to analyze extensive diabetes registries, providing insights into genetic markers and patient outcomes that inform personalized treatment strategies. These efforts have led to better management and reduced complications for diabetes patients in Sweden.

The PMDI is also leveraging AI to foster international collaboration and accelerate the adoption of precision medicine. By sharing data and standardizing practices, the initiative ensures that advancements in AI-driven precision medicine are accessible to all patients, regardless of geographic or socioeconomic status.

THE CONSENSUS REPORT: FROM ASPIRATIONAL TO ACTIONABLE

The second international consensus report on precision diabetes medicine, published by the PMDI, represents a significant milestone in the journey towards personalized diabetes care. This comprehensive report, supported by the Ameri-

can Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the Novo Nordisk Foundation, synthesizes findings from systematic reviews and expert opinions across the key pillars of precision medicine.

The PMDI was established to address the untenable health and economic burdens of diabetes prevention and care. The consensus report underscores the substantial progress made in the field and outlines a clear roadmap for the implementation of precision diabetes medicine in clinical practice. It emphasizes that the era of discussion and theoretical exploration is over; precision medicine is poised to become a reality in diabetes care.

Key milestones highlighted in the report include the development of common standards for clinical readiness, including considerations of cost-effectiveness, health equity, predictive accuracy, liability, and accessibility. These standards are crucial for the broad clinical implementation of precision diabetes medicine within the next decade.

The report also identifies important gaps in knowledge that need to be addressed through further research. These include the need for high-quality evidence on the clinical utility of precision medicine approaches, the development of new diagnostic and therapeutic tools, and the integration of precision medicine into healthcare systems worldwide.

GLOBAL IMPLICATIONS AND FUTURE DIRECTIONS

The implications of precision diabetes medicine are profound, extending beyond high-income countries to benefit populations worldwide. As noted by Dr. Shivani Misra, clinical senior lecturer in Diabetes and Endocrinology at Imperial College London, resource-restricted settings may derive the greatest benefits from precision medicine. By improving the efficiency and effectiveness of diabetes care, precision medicine can help address the growing burden of diabetes in low- and middle-income countries.

A prime example of this is the work being done at Lund University in Sweden. Their extensive diabetes registry and research into genetic markers and patient outcomes have provided invaluable insights that are shaping the future of precision diabetes medicine. Studies from the registry have highlighted the benefits of personalized treatment plans, leading to better management and reduced complications for diabetes patients.

Additionally, initiatives like the PMDI are fostering international collaboration to accelerate the adoption of precision medicine. The initiative brings together experts from around the world to share knowledge, standardize practices, and develop innovative solutions. This global approach ensures that advancements in precision medicine are accessible to all patients, regardless of geographic or socioeconomic status.

As we continue to uncover the genetic and molecular underpinnings of diabetes, precision medicine will enable us to tailor interventions to the unique needs of each patient, ultimately improving outcomes and enhancing quality of life for millions of people worldwide.

THE FUTURE OF PRECISION DIABETES MEDICINE

The future of diabetes care lies in the continued integration of precision medicine into clinical practice. This requires a concerted effort from researchers, clinicians, policymakers, and patients to advance the field and overcome existing challenges. By fostering collaboration and leveraging the latest scientific advancements, we can move closer to a world where every diabetes patient receives the right diagnosis, the most effective treatment, and the best possible prognosis.

Precision medicine has the potential to revolutionize diabetes care, transforming it from a reactive, one-size-fits-all approach to a proactive, personalized model. As we continue to uncover the genetic and molecular underpinnings of diabetes, precision medicine will enable us to tailor interventions to the unique needs of each patient, ultimately improving outcomes and enhancing quality of life for millions of people worldwide.

In conclusion, precision medicine represents a paradigm shift in diabetes care, offering the promise of more effective, personalized interventions. By addressing the heterogeneity of diabetes and focusing on the individual, precision medicine can transform the way we prevent, diagnose, treat, and manage this complex disease. The journey towards widespread clinical implementation of precision diabetes medicine is ongoing, but the progress made so far offers a glimpse into a future where diabetes care is truly personalized and optimized for each patient.

As the field continues to evolve, the consensus is clear: precision medicine is not just a theoretical concept but a practical approach that will shape the future of diabetes care. The work done by the PMDI and other global initiatives provides a robust foundation for this transformation, ensuring that the benefits of precision medicine reach patients worldwide. With continued research, collaboration, and innovation, we can look forward to a new era in diabetes care—one where precision medicine fulfills its promise of improving lives and outcomes for millions of people living with diabetes.

Original Study

A Cross-Sectional Study: Sleep Pattern and Insomnia in the Outpatient Clinic of a Multispeciality Hospital in South India

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Abbreviations:
REM: Rapid Eye Movement
NREM: Non Rapid Eye Movement

Abstract

Introduction: Insomnia is one of the major problems that cause accidents in job site and road traffic accidents. Also it is one of the main illnesses that physicians encounter. So it is mandatory to know prevalence of insomnia in out patients.

Aim: To study the prevalence of insomnia and different types of sleep pattern in the outpatient clinic of internal medicine department in a quaternary care hospital in South India.

Methods And Materials: A questionnaire according to Athens insomnia scale will be given to 800 patients in medical OPD of Aster Medcity hospital Kochi, with exclusion criteria. Questionnaires are tabulated and analyzed to reach a possible conclusion.

Results: The prevalence of insomnia in our studied population is 57% (460 members). The patients with more insomnia are seen in the 40-60 age groups. Late nit mobile users had 3 times risk of insomnia compared to normal population. Insomnia increases accidents in worksite. Mean sleep duration is reduced in insomnia. Most of the population have biphasic sleep pattern.

Conclusion: Insomnia is seen nearly equal in both sexes. Late night mobile/computer use and daily smoking have an increased risk of having insomnia than the normal population. So cessation of late night use of mobiles can decrease the incidence of insomnia. Insomnia can cause an increased incidence of work site accidents. So we have to decrease the incidence of insomnia to decrease accidents Road traffic accidents and insomnia is controversial in our study. Most of the people in our study have a monophasic sleep pattern. The duration of sleep in our population is less than that of the recommended duration of sleep.

INTRODUCTION

Disturbed sleep patterns and insomnia are among the most frequent health complaints that physician encounters. Various studies noted that the symptoms of insomnia were present in about 33-50% of the population while higher rates were seen among divorcees or widowed people, older age, female general population and presence of comorbid or psychiatric illness[2]. About 30% of adults complain of acute insomnia and 10% have chronic insomnia. In a study conducted in South India found a prevalence of insomnia as 18.6% among healthy adults [6]. In developed countries like the United States, more than 50% of adults report consistently experience at least intermediate sleep disturbances[1]. Only 30% of the population is obtaining at least a sufficient amount of sleep [1]. The Institute of Medicine has estimated that 50 -70 million Americans suffer from a chronic disorder of sleep and wakefulness which can adversely affect daytime functioning as well as physical & mental health [1].

Normal nocturnal sleep in adults displays a consistent organization from night tonight. After sleep onset, sleep usually progresses through NREM stages N1–N3 sleep within 45–60 min. NREM stage N3 sleep (also known as slow-wave sleep) predominates in the first third of the night and comprises 15–25% of total nocturnal sleep time in young adults. Sleep deprivation increases the rapidity of sleep onset and both the intensity and amount of slow-wave sleep. The first REM sleep episode usually occurs in the second hour of sleep. NREM and REM sleep alternate through the night with an ave age period of 90–110 min (the "ultradian" sleep cycle). Overall, in a healthy young adult, REM sleep constitutes 20–25% of total sleep, and NREM stages N1 and N2 constitute 50–60%. Age has a profound impact on sleep state organization. N3 sleep is most intense and prominent during childhood, decreasing with puberty and across the second and third decades of life. N3 sleep declines during adulthood to the point where it may be completely absent in older adults. The remaining NREM sleep becomes more fragmented, with many more frequent awakenings from NREM sleep. It is the increased frequency of awakenings, rather than a decreased ability to fall back asleep, that accounts for the increased wakefulness during the sleep episode in older people. While REM sleep may account for 50% of total sleep time in infancy, the percentage falls off sharply over the first postnatal year as a mature REM-NREM cycle develops; thereafter, REM sleep occupies about 25% of total sleep time. Sleep deprivation degrades cognitive performance, particularly on tests that require continual vigilance. Paradoxically, older people are less vulnerable to the neurobehavioral performance impairment induced by acute sleep deprivation than young adults, maintaining their reaction time and sustaining vigilance with fewer lapses of attention.

INSOMNIA

The word insomnia originates from Latin words 'in'(no) and 'somnus'(sleep)[2]. The international classification of sleep disorders defines insomnia as difficulty with initiation, maintenance, duration or quality of sleep that results in the impairment of day time function, despite adequate opportunity and circumstances for sleep [3]. It is a sleep disorder that occurs acutely and may become chronic if not treated in time. The presenting complaints are often that of difficulty in falling asleep in the bed, waking up during the night and having trouble in going back to sleep, waking up too early in the morning and or not having a fresh sleep[2].

According to the National Sleep Foundation, insomnia can be categorized into many types.

1) Acute insomnia: It is a brief episode of difficulty in sleeping caused by a stressful life event, such as hearing a bad news. Here insomnia resolves without any treatment
2) Chronic insomnia: If a person has trouble falling asleep or staying asleep at least 3 nights/ week for three months or longer
3) Onset insomnia: It is the difficulty in falling asleep at the beginning of the night
4) Maintenance insomnia: People with maintenance insomnia wake up during the night and have difficulty in returning to sleep
5) Comorbid insomnia: Insomnia associated with comorbid conditions[4]

Chronic insomnia represents a more complex condition than acute which accompanies day time impairment of cognition, mood, performance with impact on the patient, family, coworkers[2]. They also make errors and accidents at work and fatal road traffic accidents. 20% of all accidents that cause deaths are due to drowsy drivers[1]. Chronic

insomnia has a risk to develop medical and psychiatric comorbidities. So it is mandatory to evaluate sleep pattern and insomnia in outpatients.

SLEEP PATTERN

A healthy young adult has to sleep 7-8 hours/night[1]. Timing, duration and internal structure of sleep vary among individuals. Sleep patterns can be mainly divided into three types.

1) Monophasic: In this kind of sleep pattern person has one episode of sleep per 24 hours which is mostly at night.

2) Biphasic: Here a person has two episodes of sleep, one in the afternoon and another at night

3) Multiphasic: Here person has more than two episodes of sleep[14].

In some persons, it may be early night sleeping with early morning awakening (go to bed at 8-9pm and awakens at 4-5pm). Some others are more nocturnal, seen in urban areas, which go to bed at late night (11pm-12am) and late morning (6-8am). The pattern of sleep considerably changes over the life span as infants and young have a longer duration of sleep than the older one. So it is mandatory to assess the sleep pattern of the patient.

AIM AND OBJECTIVES

Aim:

To study the prevalence of insomnia and different types of sleep pattern in the outpatient clinic of internal medicine department in a quaternary care hospital in South India.

Objectives:

1) To find out the relationship between age and insomnia.
2) To find out the relationship between gender and insomnia.
3) To categorize sleep patterns of the patients.
4) To assess the effect of technologies in causing insomnia.
5) To find out the consequence of insomnia in worksite.

MATERIALS AND METHODS

1) **Study area:** Outpatient clinic of the Internal Medicine Department Of Aster Medcity Hospital, Kochi, Kerala
2) **Study Population:** Inclusion criteria includes all outpatients who come in the internal medicine department of Aster Medcity Hospital more than 18 years of age

Figure 1. The prevalence of insomnia

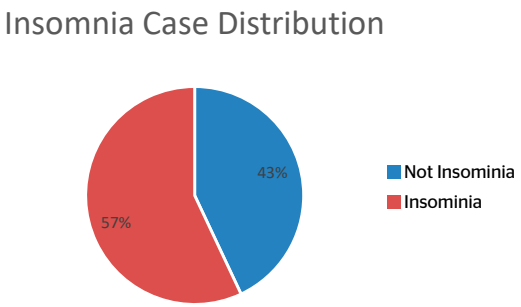
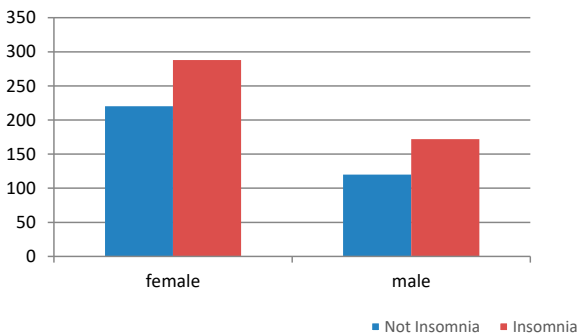


Figure 2. The prevalence of insomnia in male and female



Exclusion criteria:

a) Patients on long term psychiatric medications
b) Patient with COPD and history of orthopnea
c) Patients with diagnosed sleep apnea syndrome
d) Patients on major depression
e) Patients who have night shifts
f) Lactating patients
g) Patients with diagnosed cirrhosis of the liver
h) Patients diagnosed with chronic kidney disease on dialysis
i) Patients on thyroid medication

3) **Sample size:** 800 outpatients
4) **Study design:** It is a type of descriptive study to know the prevalence of insomnia in an unknown population. It is a cross-sectional descriptive study were we are taking a snapshot of the study population for the prescribed time period.[5]

Table 1

		Age Class			Total
		<40	40 to 60	>60	
Not Insomnia	Count	98	140	102	340
	%	28.8%	41.2%	30%	100.0%
Insomnia	Count	167	176	117	460
	%	36.3%	38.3%	25.4%	100.0%
Total	Count	265	316	219	800
	%	33.1%	39.5%	27.4%	100.0%

P value:0.07 (Not significant)

5) **Study duration:** 15 months

6) **Methods of measurement:**

This is a descriptive cross-sectional study in which the method going to use is by preparing a questionnaire including personal details of the patient, the questions revealing sleep pattern of the patients, then the questions about insomnia, to categorize insomnia and consequences of insomnia and other factors that affect insomnia. The questions for exclusion criteria will be present in a questionnaire to exclude them

7) **Data collection Method:**

A questionnaire based on sleep pattern and the Athens insomnia scale in English and Malayalam will be given to the outpatients who are more than 18 years old coming in the internal medicine outpatient department. Questions in the questionnaire can be divided into 4 categories.

1) Personal details and questions about exclusion criteria
2) Questions about sleep pattern
3) Questions based on Athens insomnia scale
4) Questions based on usage of technologies

According to the Athens insomnia scale, if the patient had Athens insomnia score more than or equal to 6, he had insomnia. Thus we can classify patients with insomnia from the patients without insomnia.

STATISTICAL METHODS

Sample size: The sample size is calculated using formula

n= z2pq/d2

Where n is sample size, z = 1.96, p is prevalence in previous studies, q is 1-p and d is sampling error which is considered as 3%.

Here the prevalence from previous south Indian study was 33%[13]. By using this formula, the sample size will be nearly 800.

Other statistical methods: The information from the questionnaire were be tabulated and analyzed by using Microsoft Excel and IBM SPSS Statistics 2d version. According to Athens criteria, the classification between the patient with insomnia and the patient without insomnia was made. All categorical variables are described as frequency and percentage. All continues variable is described as mean and standard deviation and compared using independent sample t-test. The Pearson Chi-square test is used to find the association between the categorical variable. P value <0.05 was considered to be statistically significant.

REVIEW OF LITERATURE

The present study reveals the prevalence of insomnia in the adult population in an outpatient clinic of internal medicine department in a multispecialty hospital. A similar study conducted in South India had found a prevalence of 18.6% among healthy adults[6].In another study on the Indian population in West Bengal, it was found that 43.2% of patients who had insomnia never seek medical advice for insomnia and only 15.3% consulted a doctor for their sleep problem.[8]

Another international survey of sleep disorders in the general population found that many individuals with insomnia (47%–67%) did not seek medical attention for their sleep difficulties. Among those who sought medical help, 50%–90% received treatment. Thus, insomnia remains largely underdiagnosed and undertreated problem.[7]

Another study done in Latin American countries using Athens Insomnia Scale in middle-aged women showed 56.6% of surveyed women suffered from either insomnia, poor sleep quality, or both.[9]

A study done in the US showed that, in patients attending primary care clinics, more than 50% complained of insomnia, only if specifically asked about it. 30% visit their general practitioners on their own initiative, and only 5% go to consultation with the main objective of receiving treatment to solve their problem.[11]

A study on Malaysian patients attending primary care clinics showed that 38.9% of patients had frequent insomnia symptoms (>3 times/week), 30.7% had chronic insomnia without daytime consequences, and 28.6% had chronic insomnia with daytime dysfunction. Indian ethnicity, age ≥50, anxiety symptoms, and depression symptoms

Table 2

			Group		Total
			Not Insomnia	Insomnia	
Mobile	NO	Count	267	267	534
		% within MOBILE	50%	50%	100%
	YES	Count	63	193	266
		% within MOBILE	27.4%	72.6%	100%
Total		Count	340	460	800
		% within MOBILE	42.5%	57.5%	100%

p value< 0.05

Table 3

			Group		Group
			Not Insom-nia	Insom-nia	
Accidents at work site	NO	Count	325	431	756
		% within accidents at work site	43%	57%	100.0%
	YES	Count	15	29	44
		% within accidents at work site	34.1%	65.9%	100.0%
Total		Count	340	460	800
		% within accidents at work site	42.5%	57.5%	100.0%

P value:,<0.05(Significant)

were risk factors for chronic insomnia with daytime dysfunction.[11]

A survey among the adult French population in 2001–2002 regarding insomnia found that 25% of randomly selected respondents were dissatisfied with their sleep and only 13% had consulted a health-care provider, especially for insomnia.[12]

In another study conducted in South India, the prevalence of chronic insomnia was found to be 33% with a statically significant correlation with increasing age and diabetes.[13]

In a study conducted among adolescents in Hong Kong, long hours of mobile phone use were correlated with short sleep duration, poor sleep quality, and excessive daytime sleepiness.[15] Another study in Japanese high school students reported that long hours of mobile phone use was associated with short sleep time and fatigue.[16]

The association between insomnia symptoms or syndromes and accidents is still controversial[17], and is often limited to the debate concerning the potential side effects of hypnotics on driving ability. Some other studies showed an association of insomnia in accidents

In our study also we are including a patient with acute illness and excluded patients with a chronic disorder that causes insomnia. So the prevalence of the study will be a reflection of the prevalence of insomnia in a normal population.

Also, no recent studies are done in Kerala for the prevalence of insomnia. So this study reflects the prevalence of insomnia of Kerala state.

RESULTS

According to our study, there are 800 patients as sample size. Out of them, 508 members were female and 292 were male (Fig. 1). The prevalence of insomnia in our studied population is 57% (460 members).

The prevalence of insomnia in the female population is 56.7% and of the male population is 58.9 %. and the p-value is 0.553 which is not significant (Fig. 2).

Age Groups vs insomnia:

The study population is divided into 3 age groups.

1) below 40 years

2) 40- 60 years

Figure 3. Insomnia in late night mobile users

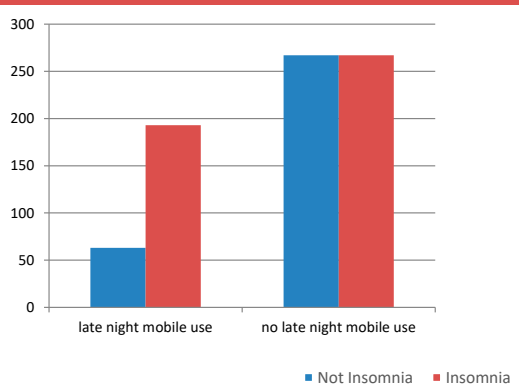


Figure 4. insomnia in patients who had accidents at the worksite

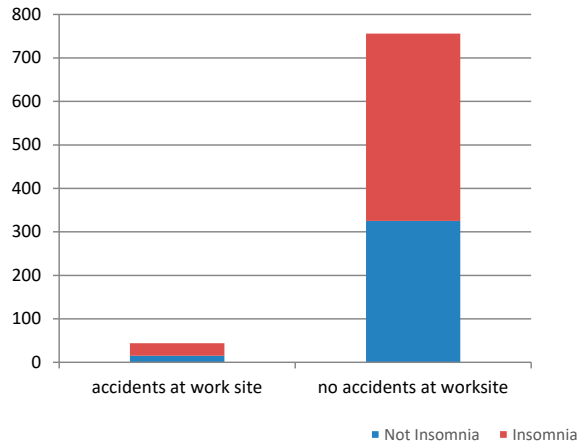
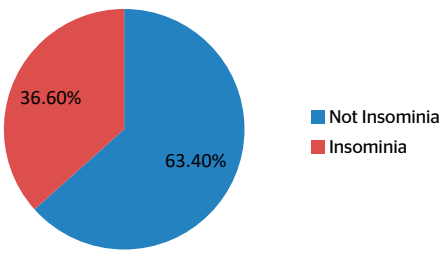


Figure 5. Percentage of people with insomnia in total no. of Road traffic accidents happened



3) above 60 years

Out of 265 members in below 40 years of age group, 167 patients have insomnia and it is about 36. 3 % of total insomnia patients.

Out of 316 members in 40-60 years age group, 176 patient have insomnia and it is about 38.3% of total insomnia patients

Out of 219 members in the above 60 year age group, 117 patients had insomnia and it is about 25.4 % of insomnia.

From the above analysis, the patient with more insomnia is seen in the 40-60 age group (Table 1).

Late night Mobile/ computer use VS Insomnia:

Out of 266 people who use mobile at night, 72.6 % of people have insomnia. This study is significant with P value of less than 0.05. So late night mobile use is a cause for insomnia according to our study.

The odds ratio is 3.06

According to our study, late night use of mobiles can cause 3 times more risk of having insomnia comparing to others (Table 2, Fig. 3).

Accident at worksite VS Insomnia:

In the members who had an accident in worksite due to sleepiness(44 members), 65.9% of patients have insomnia. This analysis has a p-value of less than 0.05, which is significant. So insomnia can increase accidents in worksite (Table 3, Fig. 4).

Road Traffic Accidents and Insomnia:

In patients who had Road traffic accidents, only 36.7 % of patients have insomnia. So in our study insomnia is not a risk for road traffic accidents (Fig. 5).

Duration of sleep and Insomnia:

In our population average duration of sleep in people without insomnia is 6.53±0.79. The average duration of sleep in people with insomnia is 5.56±0.78. This study is statistically significant with p value<0.001 (Fig. 6).

Duration of sleep and Age group:

By analyzing duration in sleep in different age groups, Average sleeping hour of patients with age less than 40 years is 5.83 hours and that off patients with age between 40-60 is 5.92 hours. Patients with age more than 60 have more sleeping hours than others with 6.22 hours. This study is statistically significant with P value of less than 0.05 (Fig. 7).

Sleep Patterns:

Out of 800 patients, 705 patients are following a monophasic pattern. Only 95 patients following a biphasic pattern of sleep. None of them is following a multiphasic pattern. So most of them are following a monophasic pattern of sleep. Mostly job and work in the house attributed to monophasic pattern of sleep (Fig. 8).

DISCUSSION

The prevalence of insomnia in our study is 57%. A similar study conducted in South India had found the prevalence of 18.6% among healthy adults [6] and another study on the Indian population in West Bengal, it was found that 43.2% of patients who had insomnia never seek medical advice for insomnia. Another south Indian study showed a prevalence of 33% among the normal population[13].

But international studies almost correlate with the prevalence of our study. A study done in Latin American countries using Athens Insomnia Scale and other sleep scales in middle-aged females

Figure 6. Mean sleep durations

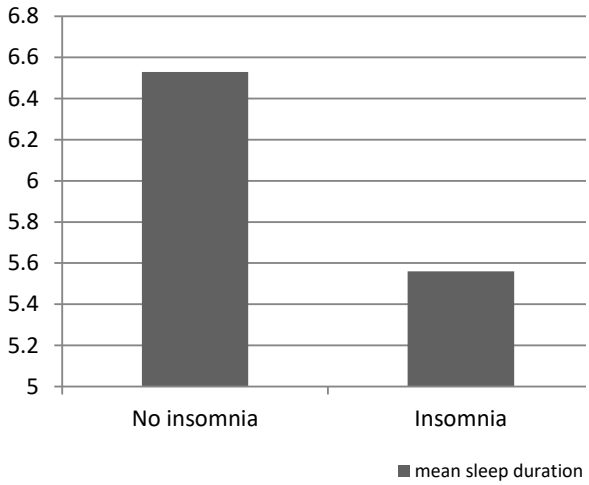
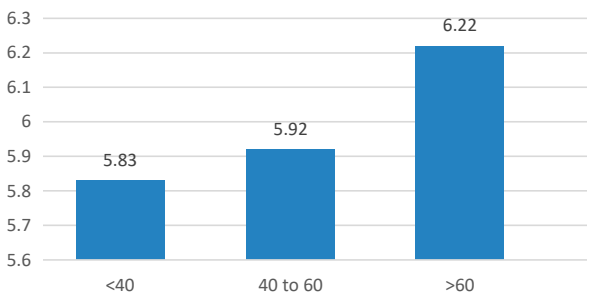


Figure 7. Average sleeping hours in different age groups

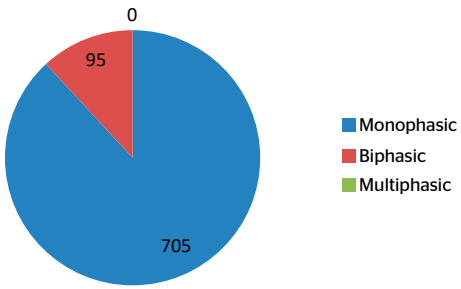


showed 56.6% of surveyed women suffered from insomnia [9]. In our study also, the prevalence of insomnia in women is 56.7% which is correlating with the above study. A study done in the US showed that, in patients attending primary care clinics, more than 50% complained of insomnia, only if specifically asked about it[11].

Age group and Insomnia

In our study, the prevalence of insomnia is more in the middle age group comparing to the younger and older age group. In our study, 38.3 % of total insomnia is falling under the age group 40-60 years. Work stress and family stress may be the reason for insomnia in this age group. In other studies, in-

Figure 8. Sleep patterns



somnia increases as age advances[1]. So in the Indian population, Expenditure of a family increases as the children in the family grew up for education, food, clothes, and every commodity. So there is a chance of getting mental stress thinking about expenditure for both father and mother who can lead to insomnia in this age group.

Mobile / Computer use and Insomnia

In our study, the use of late-night mobile/ computer use can attribute to increasing the incidence of insomnia. In our study persons who are using a mobile phone in the late night had a 3 fold risk of getting insomnia than the normal population. In a study conducted among adolescents in Hong Kong, long hours of mobile phone use were correlated with short sleep duration, poor sleep quality, and excessive daytime sleepiness[15]. Another study in Japanese high school students reported that long hours of mobile phone use was associated with short sleep time and fatigue[16]. Our study is also correlating with other studies in the case of mobile use. So, to avoid late night mobile use is a good practice to get good sleep and to decrease the incidence of insomnia.

Accident at the worksite, Road traffic accident, and Insomnia

In our study, In patients who had an accident at work site 63% had insomnia, which is statistically significant. So insomnia can cause an increase in accidents at the worksite. But road traffic accidents are not correlating with insomnia in our population. In other studies also, the association between insomnia symptoms or syndromes and accidents is still controversial[17], and is often limited to the debate concerning the potential side effects of hypnotics on driving ability. Some other studies showed an association of insomnia in accidents.

Duration of Sleep

In our study, the mean duration of sleep in the normal population is 6.53 hours and that of people with insomnia is 5.56 hours. The duration of sleep needed for a normal man is 7-8 hours[1]. So the mean duration of sleep in our normal population is less than that of the normal duration of sleep advised. When the age increases the duration of sleep will decrease in the normal population[1]. Surprisingly, in our population duration of sleep increases while aging increases.

LIMITATIONS OF THE STUDY

Athens Insomnia scale is a subjective scale. So here the definition of insomnia is taken on a subjective basis. Since other confirmatory sleep studies will increase the cost and time to be spent by the patient, this is the most acceptable tool. Patient to patient variability will be present.

The method we adopted is a questionnaire method. so there can be errors while answering questionnaire.

Many patients would not be ready to correctly answer the question since it includes details about addictions and mobile use. Not many studies were done to correlate mobile use and accidents.

Advantages

Since it is a questionnaire method, a large sample size is obtained It is a cost-effective method. We will get an idea of prevalence in Kerala population.

CONCLUSIONS OF THE STUDY

The prevalence of insomnia in our studying population is 57% is more than half the population. These are the cases that came to the Outpatient clinic for other acute illnesses. So prevalence will be more than what we see above. The problem is most of them are not taking medical attention for insomnia.

- Insomnia is seen nearly equal in both sexes.
- Late night mobile/ computer use and daily smoking have an increased risk of having insomnia than the normal population. So cessation of late night use of mobiles can decrease the incidence of insomnia.
- Insomnia can cause an increased incidence of work site accidents. So we have to decrease the incidence of insomnia to decrease accidents.
- Road traffic accidents and insomnia is controversial in our study.
- Most of the people in our study have a monophasic sleep pattern.
- The duration of sleep in our population is less than that of the recommended duration of sleep.

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Original Study

A Study of Risk Factors for Cardiovascular and Metabolic Comorbidities in Patients with Obstructive Sleep Apnoea Syndrome

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Keywords:
Obstructive sleep apnoea syndrome; lowest desaturation; AHI; BMI; comorbidities; endoscopy; sleep study

Abstract
Obstructive sleep apnoea syndrome (OSAS) is characterized by partial or complete recurrent upper airway obstruction during sleep, resulting in periods of apnoea, oxyhaemoglobin desaturation, and frequent night awakenings with excessive daytime sleepiness therby reducing performance at work and in social activities in many cases. The identification of co-morbidities in OSAS patients is necessary to define the clinical picture and consequently to find the more adequate treatment. However, as the onset of co-morbidities is influenced by the level of OSAS severity and duration, this relationship needs to be well defined. This study addresses the association between OSAS and co-morbidities as a function of OSAS severity and duration, considering it as factors that could influence the morbid condition.
The study will help in providing individualised care to OSA patients with due importance to early identification and treatment of OSAS, thereby preventing the occurrence and reducing the severity of associated comorbidities. Knowledge about the sites of collapse will help in making tailor made approaches for the effective management of obstructive sleep apnoea.

INTRODUCTION

Obstructive sleep apnoea syndrome (OSAS) is a sleep disorder characterised by intermittent, complete and partial airway collapse resulting in frequent episodes of apnoea and hypopnoea. Association of OSA with serious morbidities have shown that untreated OSA is a substantial but underappreciated public health threat. Population based epidemiological studies have uncovered the high prevalence and wide severity spectrum of undiagnosed OSA and have consistently found that even mild OSA is associated with significant morbidity. The factors affecting severity of OSA include endoscopic characteristics of different sites of airway, age, sex, BMI,

thyroid disorder, alcoholism, smoking etc.

About 1 billion people out of the total world adult population of 7.3 billion is estimated to be suffering from OSAS. However, there is gross disparity in the diagnosis and treatment of OSAS. Untreated OSAS can result in significant morbidity and mortality in the long run. It is associated with significantly reduced quality of life (QoL) and depression. There is also an increased need for clinical consultations and health care services. The increased day time sleepiness and compromised vigilance leads to reduced work performance, decreased productivity, absenteeism and workplace and motor vehicle accidents, resulting in unemployment and underemployment.

The identification of comorbidities in OSAS patients is necessary to define the clinical picture and consequently to find the more adequate treatment. However, as the onset of comorbidities is influenced by the level of OSAS severity and duration, this relationship needs to be well defined.

OBJECTIVES

Primary Objective

To determine if the severity of OSA (determined by AHI and lowest desaturation) along with its duration (years), has any role in the development of comorbidities-hypertension, diabetes mellitus, dyslipidemia and stroke (number of comorbidities in a person).

Secondary Objective

Correlation of flexible endoscopic evaluation of sites of collapse at nose, palate, tongue base and larynx (number of sites and pattern of collapse) on the severity of OSA (AHI and lowest desaturation).

MATERIALS AND METHODS

The study was conducted in the ENT department of Aster Medcity, Kochi. Patients aged 18 and above reporting to ENT OP with complaints of snoring and increased day time sleepiness satisfying Epworth Sleepiness Score > 10 and polysomnographic finding of AHI greater than 5 were considered under inclusion criteria. The study was designed to be a prospective study and was conducted for a duration of 8 months from May 2023 to December 2023. with 95% confidence level and 10% allowable error (precision) the minimum sample size required for the present study was calculated to be 87. All the patients underwent sleep study and flexible fibreoptic nasopharyngo-laryngo-scopic examination and the findings were noted.

Descriptive statistics was used to assess the baseline characteristics of the data obtained from a questionnaire. All quantitative variables presented as mean and standard deviation and qualitative variables in frequency and percentages with diagrams and graphs. The association of severity of OSAS with comorbidities was evaluated using Chi-square test, point biserial and Pearson correlation test using SPSS tool.

Table 1. Statistical details of age of participants

Mean	Std. Deviation	Range	Minimum	Maximum
46.29	13.49	66	19	85

Table 2. Distribution of BMI

BMI	Defined range	Frequency
Normal	18.5–24.9	10
Overweight	25.0–29.9	45
Obese-1	30.0–34.9	30
Obese-2	35.0–39.9	13
Extreme Obesity	> 40.0	2
Total		**100**

Table 3. Correlation for cumulative number of comorbidities

Parameter	No. of comorbidities	Pearson Correlation
AHI	Significant	0.480
Lowest Desaturation	Significant	-0.278
Duration of Snoring	Significant	0.318
BMI	Significant	0.292

RESULTS

Analysis of age

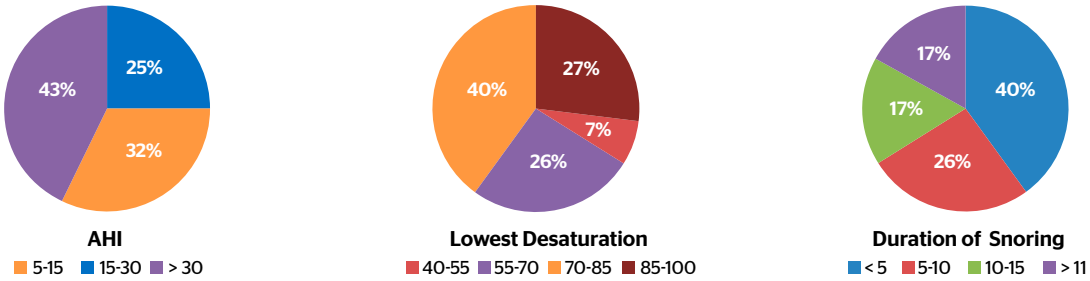
Out of 100 patients enrolled in the study, 15 patients were above the age of 61, 75 patients were between the age of 31-60 and the remaining 10 were below the age of 30.

The youngest patient was 19 years old and the oldest patient was 85 years old. The Mean age was 46.29 years with Standard Deviation (SD) of 13.49.

AHI, Lowest Desaturation and Duration of snoring and BMI Distribution

Out of 100 patients, 32 patients (32%) reported to have Mild: AHI (5-15 per hour), 25 patients (25%) reported to have Moderate: AHI (15-30 per hour), and 43 patients (43%) reported to have Severe: AHI (> 30 per hour). 7 patients were reported to have lowest desaturation

Figure 1. Distribution of AHI, lowest desaturation and duration of snoring



between 40-55%, whereas majority of the patients (40%) of the patients were reported to have lowest desaturation in range of 70-85%.

Majority of patients (40) were reported to have duration of snoring less than 5 years whereas the number of patients who are reported to have duration of snoring between 5 – 10 years is 26 and the number of patients who are reported to have duration of snoring between both 10 to 15 years and greater than 15 years are 17 respectively.

Most of the patients (45) were reported to have overweight whereas the number of patients were obese were totally 43 with 30 patients classified as Obese-1 and 13 patients as Obese-2. The number of patients who are extremely obese are 2 patients.

Only one person presented with stroke and the patient had other comorbidities of hypertension, diabetes mellitus and dyslipidemia also.

Prevalence of comorbidities in study population

The most common comorbidity is hypertension occurring in 60% of the patients, followed by dyslipidemia in 50% and diabetes mellitus in 31%. The percentage of patients with both hypertension and diabetes mellitus is 3%, diabetes mellitus & dyslipidemia is 5% whereas percentage of patients with hypertension & dyslipidemia is 18%. The percentage of patients with all three comorbidities of hypertension, diabetes mellitus and dyslipidemia are 18%.

Statistical analyses

Correlation with respect to cumulative number of comorbidities: The direction of the relationship between AHI, lowest desaturation, duration of snoring BMI with the number of comorbidities were analysed using Pearson correlation

Correlation of BMI with various comorbidities

The evaluation of correlation with cumulative number of comorbidities with hypertension, diabetes mellitus, dyslipidemia was conducted using Pearson correlation.

It is observed that there is significant association between BMI with hypertension, and dyslipidemia. Hence, a multivariate analysis is conducted to ascertain the most significant correlation. It is seen that BMI has the strongest influence on the development of dyslipidemia.

Association with respect to presence of comorbidities using Chi-square test

The evaluation of association with AHI, lowest desaturation, duration of snoring and cumulative number of comorbidities using Chi-square test was conducted.

A multivariate analysis is conducted to ascertain the most significant association between the various risk factors to the development of comorbidities The strongest variable determining the development of comorbidity is duration of snoring.

Distribution of sites of obstruction according to flexible endoscopy evaluation

The most common site of obstruction is at the level of palate – circumferential, followed by obstruction

Table 4. Correlation for cumulative number of comorbidities

Parameter	BMI	Pearson Correlation
Hypertension	Significant	0.253
Diabetes Mellitus	Insignificant	0.042
Dyslipidemia	Significant	0.420

Table 5. Association for presence of comorbidities using Chi-square test

Parameter	No. of comorbidities	Chi-Square
AHI	Significant	7.420
Lowest desaturation	Insignificant	4.205
Duration of snoring	Insignificant	5.830

Figure 2. Venn diagram depicting comorbidities of participants.

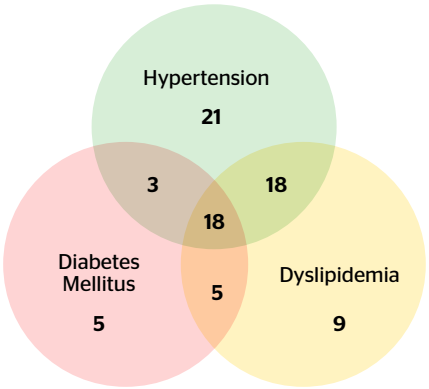


Table 6. Association for presence of comorbidities using Chi-square test

Site of obstruction	Association	Chi-Square
Nose	Insignificant	6.871
Palate-circum-ferential	Significant	14.655
Palate-lateral	Significant	10.026
Palate-antero-posterior	Insignificant	4.468
Tongue	Insignificant	7.098
Larynx	Insignificant	7.852

Table 7. Correlation between sites and lowest desaturation

Site of obstruction	Significance	Coefficient
Nose	Insignificant	-0.154
Palate-circum-ferential	Insignificant	0.074
Palate-lateral	Significant	0.246
Palate-antero-posterior	Significant	-0.218
Tongue	Insignificant	-0.012
Larynx	Insignificant	-0.099

at the level of larynx and then in the tongue base. The most common direction of obstruction in the palate is circumferential, followed by lateral, followed by anteroposterior.

Association Between the levels of obstruction and AHI

The association between the levels of collapse viz. nose, palate-circumferential, palate-lateral, palate anteroposterior, tongue base and larynx evaluated using Chi-square test using univariate analysis.

Significant association was found between levels of collapse in palate-circumferential, palate-lateral and AHI. Hence multivariate analysis using binary logistics was done and the most significant site of collapse affecting AHI was determined to be circumferential collapse at the level of palate.

Correlation between sites of collapse and lowest desaturation

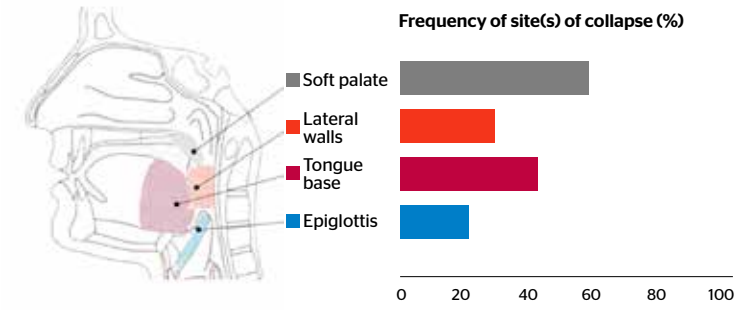
A significant correlation was found between levels of collapse in palate-anteroposterior and palate-lateral and lowest desaturation. Hence multivariate analysis using binary logistics was conducted and the most significant site of collapse affecting lowest desaturation was determined to be at lateral collapse at level of palate.

DISCUSSION

The primary objective of the study was to determine if the severity of OSAS (as determined by AHI and lowest desaturation) along with its duration (years), has any role in the development of comorbidities- hypertension, diabetes, dyslipidemia and stroke (number of comorbidities in a person). It is found that 61% of population with obstructive sleep apnoea had at least one comorbidity. Out of 32 patients with mild OSA, 65% had comorbidities, out of 25 patients with moderate OSA, 76% had comorbidities and out of 43 patients with severe OSA, 93% had comorbidities. This is comparable to the study by Luis Silva, Daniela Cunha et al. wherein of a total of 128 patients with OSA,75% had comorbidities. The percentage of comorbidities in severely apnoeic patients in the current study are higher than that found in the study of Luis Silva et al. where, out of the 39 patients with severe OSA, 31 implying 79.5% had comorbidities.

The present study of positive correlation between AHI and hypertension is further corroborated by the data from the ESADA study in which 4372 subjects with mild OSA were found to have an independent association with hypertension. As per the study by Meslier et al., 494 patients with sleep apnoea were evaluated and diabetes was present in 30.1% patients. This is comparable to present study where the prevalence of diabetes is about 48%. As per the study by Yu -Ting Chou et al. on 236 patients with OSA, the overall prevalence of hypercholesterolaemia was 61.1% and hypertriglyceridemia was 55.3%. Desaturation index was a significant independent risk factor for the de-

Figure 3. Distribution of sites of obstruction.



velopment of dyslipidemia in OSA patients which was also found in the present study.

Hyo Yeol Kim et al. recruited 33 patients with sleep disordered breathing and did flexible fibreoptic endoscopic evaluation with Mullers manouever and found that retroglossal collapse correlated significantly with AHI. But, in the present study, larynx and anteroposterior collapse correlates significantly with AHI. As per the study by Miljeteig et al., in which patients were classified based on their nasal resistance, no significant correlation could be found. In the present study, a positive significant correlation was found between obstruction at the level of nose and AHI.

CONCLUSIONS

The maximum number of comorbidities are in patients with severe OSA. A significant positive correlation was observed to be present between AHI, BMI and duration of snoring with the cumulative number of comorbidities. There also is a significant negative correlation between the lowest desaturation and cumulative number of comorbidities.

Comorbidities evaluated individually implies there is a positive significant correlation between AHI and duration of snoring on duration of hypertension. A positive significant correlation exists between AHI and diabetes and between AHI with dyslipidemia and a significant negative correlation between lowest desaturation and dyslipidemia. BMI is significantly correlated with development of hypertension, diabetes and dyslipidemia; with the strongest association with dyslipidemia. The strongest risk factor contributing to development of comorbidities is dyslipidemia.

With respect to flexible endoscopy findings, the most common site of collapse is at the level of palate at circumferential, followed by collapse at the level of tongue, nose and subsequently larynx. The collapse at the level of palate (anteroposterior) and nose shows a positively significant association with AHI. Tongue collapse also shows a positive correlation with AHI and the most significant effect on AHI is by the collapse at the level of palate (circumferential). Similarly, there is a significant negative correlation between lowest desaturation and palatal (anteroposterior and lateral) collapse.

The comorbidities studies showed a positive association with OSA with significant associations between severity of OSA and duration of snoring in the development of comorbidities hypertension and dyslipidemia. Obesity is a risk factor in the development of comorbidities in patients with OSA. Lowest desaturation is also a determinant in the development of comorbidities with maximum effects on development of hypertension and dyslipidemia. The strongest risk factor determining the development of comorbidity is the duration of snoring. The most common level of collapse is palatal collapse circumferential. There is significant correlation between collapse at the level of nose, anteroposterior palatal collapse and AHI. Anteroposterior and lateral collapse show negative correlation with lowest desaturation.

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Antithrombotic Therapy after Acute Coronary Syndrome or PCI in a Trial Fibrillation — Augustus Trial: A Journal Review

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Atrial fibrillation (AF) has strong associations with other cardiovascular diseases, such as heart failure, coronary artery disease (CAD), valvular heart disease, diabetes mellitus, and hypertension. Whether a person has , Paroxysmal , persistent , long standing or permanent atrial fibrillation , select patients require a an anticoagulation regimen in order to prevent cardioembolic consequences .Choosing antithrombotic therapy for patients with atrial fibrillation who have an acute coronary syndrome or have undergone percutaneous coronary intervention (PCI) is challenging. Dual antiplatelet therapy is proven to reduce the incidence of recurrent ischemic events and stent thrombosis but is less effective in reducing the incidence of cardioembolic stroke associated with atrial fibrillation. Regimens including non–vitamin K antagonist oral anticoagulants appear to offer a number of advantages over vitamin K antagonists, including the potential for less bleeding.

The Augustus trial (a two-by-two factorial, randomized, controlled clinical trial) to assess the safety and efficacy of standard-dose apixaban as compared with a vitamin K antagonist and of low-dose aspirin as compared with placebo, on a background of concomitant P2Y12 inhibitor therapy for 6 months in patients with atrial fibrillation and recent acute coronary syndrome or PCI.

METHODS

The trial was designed and led by an academic steering committee whose members were responsible for the conduct of the trial and the Duke Clinical Research Institute (DCRI, Durham, NC) was the academic coordinating center.

TRIAL DESIGN AND REGIMEN

AUGUSTUS was a prospective, multicenter, two-by-two factorial, randomized clinical trial comparing apixaban with a vitamin K antagonist and comparing aspirin with placebo in patients with atrial fibrillation who had

a recent acute coronary syndrome or underwent PCI (or both). The 2 x 2 factorial design calls for randomizing each participant to treatment A or B to address one question and further assignment at random within each group to treatment C or D to examine a second issue, permitting the simultaneous test of two different hypotheses.

Patients underwent randomization within 14 days after having an acute coronary syndrome or undergoing PCI, with explicit guidance provided to enroll eligible patients and start the trial regimen as soon as possible after the index event once parenteral anticoagulation had been stopped. To be eligible, patients were required to be planning to use an approved P2Y12 inhibitor for at least 6 months. The choice of P2Y12 inhibitor was left to the discretion of the treating physician.

Patients were randomly assigned by means of an interactive voice-response system to receive apixaban or a vitamin K antagonist and to receive aspirin or matching placebo. The treatment regimen comparing apixaban with a vitamin K antagonist was open-label; however, the regimen comparing aspirin with matching placebo was double-blind. The dose of Apixaban was fixed based on patient factors like Age , creatinine , and weight . The dose of Vitamin K antagonist was optimised to achieve a target PTINR between 2-3 . Aspirin dosing was set at 81 mg for those receiving aspirin instead of the placebo.

TRIAL POPULATION

Patients eligible for inclusion:

1. An age of at least 18 years; previous, persistent, permanent, or paroxysmal atrial fibrillation and planned long-term use of an oral anticoagulant
2. Recent acute coronary syndrome or PCI; and planned use of a P2Y12 inhibitor for at least 6 months.

Exclusion criteria:

1. Patients who were using anticoagulation for other conditions (e.g., prosthetic valves, venous thromboembolism, and mitral stenosis) were not eligible).
2. Severe renal insufficiency,
3. History of intracranial hemorrhage
4. Recent or planned coronary-artery bypass graft surgery, coagulopathy or ongoing bleeding, and contraindication to a vitamin K antagonist, apixaban, all P2Y12 inhibitors, or aspirin

	ASPIRIN(A)	PLACEBO(P)
APIXABAN(X)	XA	XP
VITAMIN K ANTAGONIST(V)	VA	VP

2X2 Factorial Study
This study for combinations of patient groups – Aspirin+Apixaban, Aspirin + Placebo, Vitamin K Antagonist + Aspirin, Vitamin K antagonist + Olacebo.

Stroke and bleeding risks were assessed with the use of two scores:

CHA2DS2-VASc scores reflect the risk of stroke among patients with atrial fibrillation who are not receiving anticoagulant therapy; scores range from 0 to 9, with higher scores indicating greater risk.

HAS-BLED scores reflect the risk of bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy; scores range from 0 to 9, with higher scores indicating greater risk.

PRIMARY OUTCOMES

The primary outcome for both factorial comparisons was major or clinically relevant nonmajor bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH). ISTH major bleeding was defined as bleeding that resulted in death, occurred in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome, or pericardial), or was associated with either a decrease in the hemoglobin level of at least 2 g per deciliter or a transfusion of at least 2 units of packed red cells.12 Clinically relevant nonmajor bleeding was defined as bleeding that resulted in hospitalization, medical or surgical intervention for bleeding, an unscheduled clinic visit, or a change in physician-directed antithrombotic therapy. Bleeding was also classified according to the Global Use of Strategies to Open Occluded Arteries (GUSTO) and Thrombolysis in Myocardial.

SECONDARY OUTCOMES

Included the composite of death or hospitalization and the composite of death or ischemic events (stroke, myocardial infarction, stent thrombosis [definite or probable], or urgent revascularization).

RESULTS

From September 2015 through April 2018, a total of 4614 patients from 492 sites in 33 countries were randomly assigned to receive open-label apixaban

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Apixaban (N=2306)	Vitamin K Antagonist (N=2308)	Aspirin (N=2307)	Aspirin-Matched Placebo (N=2307)	Total (N=4614)
Age — yr					
Median	70.4	70.9	70.8	70.6	70.7
Interquartile range	64.1–77.2	64.3–77.2	64.4–77.3	63.8–77.2	64.2–77.2
Female sex — no. (%)	670 (29.1)	667 (28.9)	696 (30.2)	641 (27.8)	1337 (29.0)
Race or ethnic group — no./total no. (%)†					
White	2097/2282 (91.9)	2087/2275 (91.7)	2082/2276 (91.5)	2102/2281 (92.2)	4184/4557 (91.8)
Black	29/2282 (1.3)	30/2275 (1.3)	29/2276 (1.3)	30/2281 (1.3)	59/4557 (1.3)
Asian	70/2282 (3.1)	70/2275 (3.1)	74/2276 (3.3)	66/2281 (2.9)	140/4557 (3.1)
Native American	10/2282 (0.4)	6/2275 (0.3)	6/2276 (0.3)	10/2281 (0.4)	16/4557 (0.4)
Other	76/2282 (3.3)	82/2275 (3.6)	85/2276 (3.7)	73/2281 (3.2)	158/4557 (3.5)
Serum creatinine — no./total no. (%)‡					
<1.5 mg/dl	2101/2274 (92.4)	2051/2258 (90.8)	2078/2260 (91.9)	2074/2272 (91.3)	4152/4532 (91.6)
≥1.5 mg/dl	173/2274 (7.6)	207/2258 (9.2)	182/2260 (8.1)	198/2272 (8.7)	380/4532 (8.4)
CHA_2DS_2-VASc score§	3.9±1.6	4.0±1.6	3.9±1.6	3.9±1.6	3.9±1.6
HAS-BLED score¶	2.9±1.0	2.9±0.9	2.8±0.9	2.9±1.0	2.9±0.9
Hypertension leading to medication use — no. (%)	2042 (88.6)	2031 (88.0)	2031 (88.0)	2042 (88.5)	4073 (88.3)
Heart failure — no. (%)	975 (42.3)	998 (43.2)	982 (42.6)	991 (43.0)	1973 (42.8)
Diabetes mellitus — no. (%)	842 (36.5)	836 (36.2)	842 (36.5)	836 (36.2)	1678 (36.4)
Stroke, TIA, or thromboembolism — no./total no. (%)	326/2289 (14.2)	307/2292 (13.4)	297/2289 (13.0)	336/2292 (14.7)	633/4581 (13.8)
Concomitant $P2Y_{12}$ inhibitor at randomization — no./total no. (%)					
Clopidogrel	2105/2253 (93.4)	2060/2243 (91.8)	2075/2253 (92.1)	2090/2243 (93.2)	4165/4496 (92.6)
Prasugrel	27/2253 (1.2)	24/2243 (1.1)	31/2253 (1.4)	20/2243 (0.9)	51/4496 (1.1)
Ticagrelor	121/2253 (5.4)	159/2243 (7.1)	147/2253 (6.5)	133/2243 (5.9)	280/4496 (6.2)
Previous use of oral anticoagulant — no. (%)‖	1192 (51.7)	1070 (46.4)	1132 (49.1)	1130 (49.0)	2262 (49.0)
Qualifying index event — no./total no. (%)					
Acute coronary syndrome and PCI	873/2297 (38.0)	841/2298 (36.6)	844/2293 (36.8)	870/2302 (37.8)	1714/4595 (37.3)
Medically managed acute coronary syndrome	547/2297 (23.8)	550/2298 (23.9)	547/2293 (23.9)	550/2302 (23.9)	1097/4595 (23.9)
Elective PCI	877/2297 (38.2)	907/2298 (39.5)	902/2293 (39.3)	882/2302 (38.3)	1784/4595 (38.8)
No. of days from acute coronary syndrome or PCI to randomization**	6.7±4.2	6.6±4.2	6.7±4.3	6.5±4.1	6.6±4.2

* Plus–minus values are means ±SD. The characteristics of the patients at baseline were well balanced among the trial groups. PCI denotes percutaneous coronary intervention, and TIA transient ischemic attack.
† Race or ethnic group was determined by the investigator and recorded on the case-report form.
‡ To convert the values for creatinine to micromoles per liter, multiply by 88.4.
§ CHA_2DS_2-VASc scores reflect the risk of stroke, with values ranging from 0 to 9 and with higher scores indicating greater risk (Table S1 in the Supplementary Appendix).
¶ HAS-BLED scores reflect the risk of major bleeding, with values ranging from 0 to 9 and with higher scores indicating greater risk (Table S1 in the Supplementary Appendix).
‖ Shown are the numbers of patients who discontinued use of any oral anticoagulant on or before the date of randomization.
** If the patient both had acute coronary syndrome and underwent PCI within 14 days before randomization, the date of acute coronary syndrome was used.

or a vitamin K antagonist and to receive double-blind aspirin or matching placebo.

The median age among all the patients was 70.7 years, and 29.0% of the patients were women. Among the patients who underwent randomization, 1714 of 4595 (37.3%) had acute coronary syndrome and underwent PCI, 1097 (23.9%) had medically managed acute coronary syndrome, and 1784 (38.8%) underwent elective PCI.

Clopidogrel was the P2Y12 inhibitor used in 92.6% of the patients. A total of 229 of 2290 patients (10.0%) who had been randomly assigned to receive apixaban received the dose of 2.5 mg twice daily.

The median percentage of time in the therapeutic range, as calculated by the Rosendaal method,15 was 59% among patients assigned to receive a vitamin K antagonist . The median percentage of time that patients assigned to a vitamin K antagonist had an INR above 3.0 was 3%, and the median percentage of time with an INR below 2.0 was 23%.

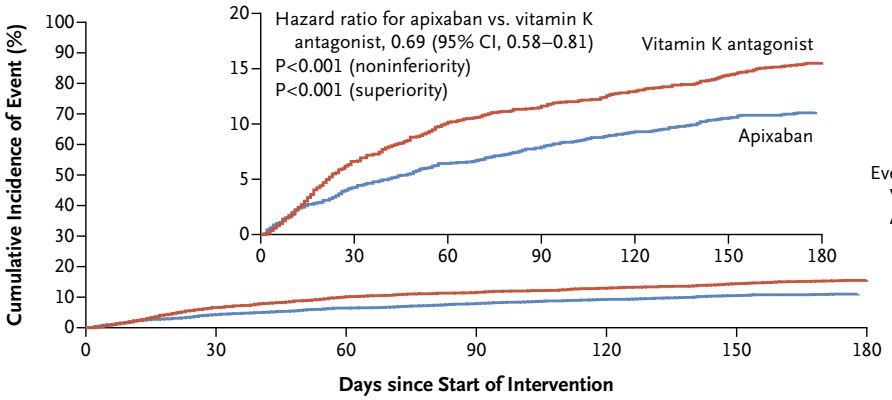
BLEEDING OUTCOME

No significant interaction was noted between the two randomization factors with regard to the primary outcome (P=0.64 for interaction).This can be understood from the Cox proportional plot below . As the p values are far greater than 0.05 , this disproves the hypothesis of interaction between apixaban and aspirin or Vitamin K Antagonist and aspirin for the primary and secondary outcomes .

At 6 months, 241 of 2290 patients (10.5%) receiving apixaban had an ISTH major or clinically relevant nonmajor bleeding event, as compared with 332 of 2259 (14.7%) receiving a vitamin K antagonist, resulting in an event rate per 100 patient-years that was significantly lower among patients receiving apixaban than among those receiving a vitamin K antagonist (hazard ratio, 0.69; 95% confidence interval [CI], 0.58 to 0.81), which met the prespecified criteria for both noninferiority

Figure. Kaplan–Meier Curves for Primary Outcome of Major or Clinically Relevant Nonmajor Bleeding.
The primary outcome was major or clinically relevant nonmajor bleeding as defined by the International Society on Thrombosis and Haemostasis. Insets show the same data on an enlarged y axis.

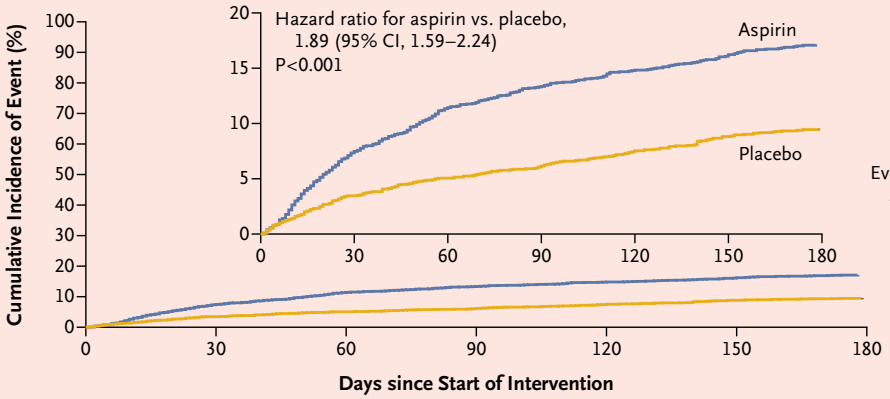
A Primary Outcome — Apixaban vs. Vitamin K Antagonist



Event rate per 100 patient-yr:
Vitamin K antagonist, 35.8
Apixaban, 24.7

No. at Risk							
Vitamin K antagonist	2259	1984	1861	1795	1736	1686	1079
Apixaban	2290	2110	2019	1957	1902	1858	1037

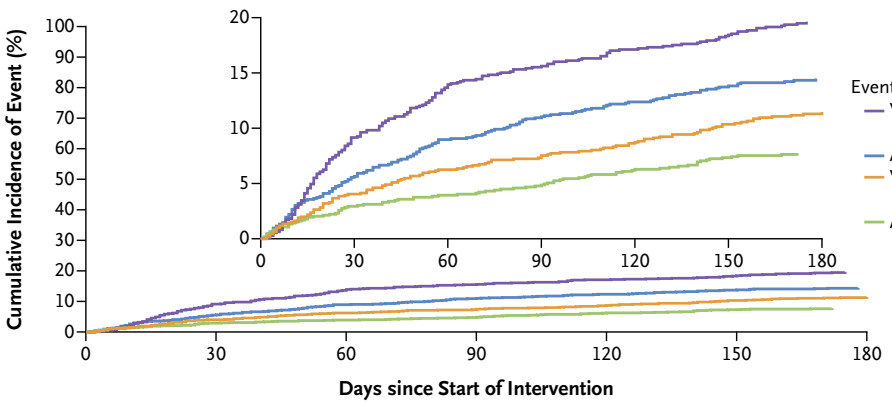
B Primary Outcome — Aspirin vs. Placebo



Event rate per 100 patient-yr:
Aspirin, 40.5
Placebo, 21.0

No. at Risk							
Aspirin	2277	2003	1863	1789	1717	1674	962
Placebo	2279	2095	2006	1941	1880	1824	1079

C Primary Outcome, According to Intervention Combination



Event rate per 100 patient-yr:
Vitamin K antagonist and aspirin, 49.1
Apixaban and aspirin, 33.6
Vitamin K antagonist and placebo, 26.7
Apixaban and placebo, 16.8

No. at Risk							
Vitamin K antagonist and aspirin	1123	962	881	838	800	776	467
Apixaban and aspirin	1145	1036	975	937	903	880	485
Vitamin K antagonist and placebo	1126	1007	947	917	883	851	528
Apixaban and placebo	1143	1075	1044	1007	975	947	536

Table. Time in therapeutic range among patients assigned to VKA

Time in target INR range (Rosendaal Method)	1977
n	58.57% (33.31%, 81.03%)
Median (25th, 75th)	55.95% (30.586%)
Mean (SD)	0.0%, 100.0%
Min, Max	
Time below INR range 2.0	1977
n	22.86% (4.82%, 50.29%)
Median (25th, 75th)	32.03% (31.273%)
Mean (SD)	0.0%, 100.0%
Min, Max	
Time above INR range 3.0	1977
n	2.96% (0.00%, 17.55%)
Median (25th, 75th)	12.02% (18.819%)
Mean (SD)	0.0%, 100.0%
Min, Max	

INR indicates international normalized ratio; SD, standard deviation.

(P<0.001) and superiority (P<0.001). The number needed to treat over a period of 6 months to avoid one ISTH major or clinically relevant nonmajor bleeding event with apixaban instead of a vitamin K antagonist was 24. The Kaplan Meier curves highlight the same .

In the antiplatelet-regimen comparison, 367 of 2277 patients (16.1%) receiving aspirin had an ISTH major or clinically relevant nonmajor bleeding event, as compared with 204 of 2279 (9.0%) receiving placebo. The event rate was significantly higher among those receiving aspirin than among those receiving placebo (hazard ratio, 1.89; 95% CI, 1.59 to 2.24; P<0.001) .The number needed to harm over a period of 6 months to cause one ISTH major or clinically relevant nonmajor bleeding event with aspirin instead of placebo was 14. The percentage of patients with a primary bleeding outcome event was highest among those receiving a vitamin K antagonist and aspirin (18.7%) and lowest among those receiving apixaban and placebo (7.3%).

DEATH AND HOSPITALISATION

No significant interaction was noted between the two randomization factors with regard to the secondary outcome (P=0.64 for interaction) . At 6 months, 541 patients (23.5%) who had been assigned to receive apixaban had died or had been hospitalized, as compared with 632 (27.4%) who had been assigned to receive a vitamin K antagonist . The event rate per 100 patient-years for death or hospitalization at 6 months was lower among patients assigned to receive apixaban than among those assigned to receive a vitamin K antagonist (hazard ratio, 0.83; 95% CI, 0.74 to 0.93; P=0.002). The difference between groups was driven by a lower incidence of hospitalization (518 patients [22.5%] in the apixaban group vs. 607 [26.3%] in the vitamin K antagonist group) since the frequencies of death were similar. The number needed to treat over a period of 6 months to avoid one death or hospitalization with apixaban instead of a vitamin K antagonist was 26.

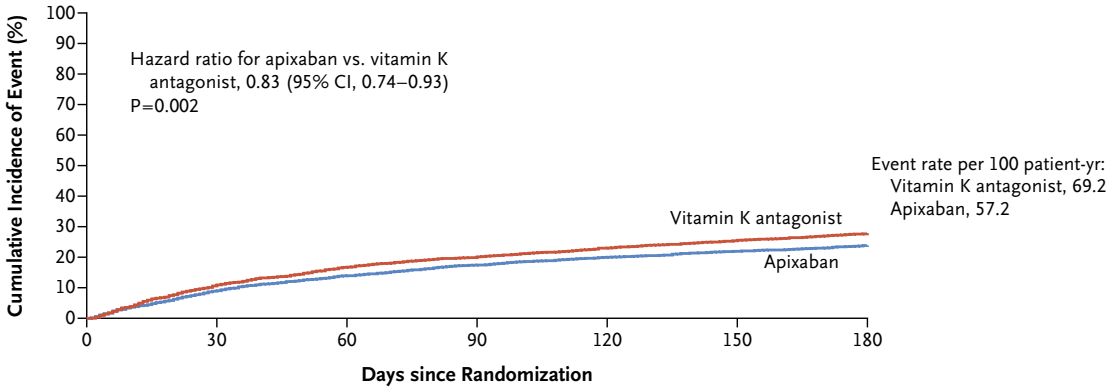
In the antiplatelet-regimen comparison, 604 patients (26.2%) who had been assigned to receive aspirin died or were hospitalized, as compared with 569 (24.7%) who had been assigned to receive placebo . Patients who had been assigned to receive aspirin had an incidence of death or hospitalization at 6 months that was similar to that among patients assigned to receive placebo (hazard ratio, 1.08; 95% CI, 0.96 to 1.21). The cumulative incidence of death or hospitalization at 6 months was highest among patients who had been assigned to receive a vitamin K antagonist and aspirin (27.5%) and lowest among those assigned to receive apixaban and placebo (22.0%).

No significant interaction was found between the two randomization factors with regard to death or ischemic events (P=0.28 for interaction) .At 6 months, 154 patients (6.7%) who had been assigned to receive apixaban had died or had had an ischemic event — including myocardial infarction, definite or probable stent thrombosis, stroke, or urgent revascularization — as compared with 163 (7.1%) who had been assigned to receive a vitamin K antagonist .In the antiplatelet-regimen comparison, 149 patients (6.5%) who had been assigned to receive aspirin died or had an ischemic event, as compared with 168 (7.3%) who had been assigned to receive placebo This difference was not significant, but more ischemic events occurred in the placebo group.

The overall event rates per 100 patient-years for death or ischemic events were similar in the anticoagulant-regimen and antiplatelet-regimen comparisons. The event rate per 100 patient-years for stroke was lower among patients receiving apixaban than among those receiving a vitamin K antagonist (hazard ratio, 0.50; 95% CI, 0.26 to 0.97).

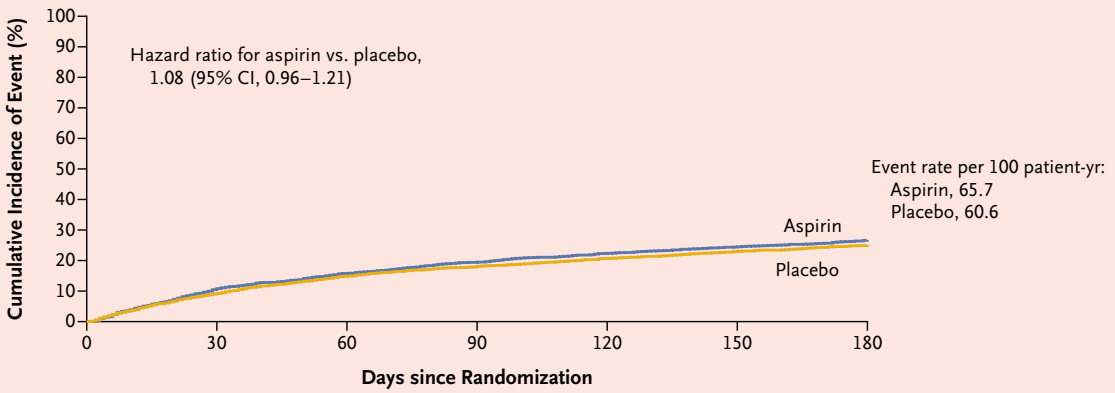
Figure. Kaplan–Meier Curves for the Composite of Death or Hospitalization.

A Death or Hospitalization — Apixaban vs. Vitamin K Antagonist



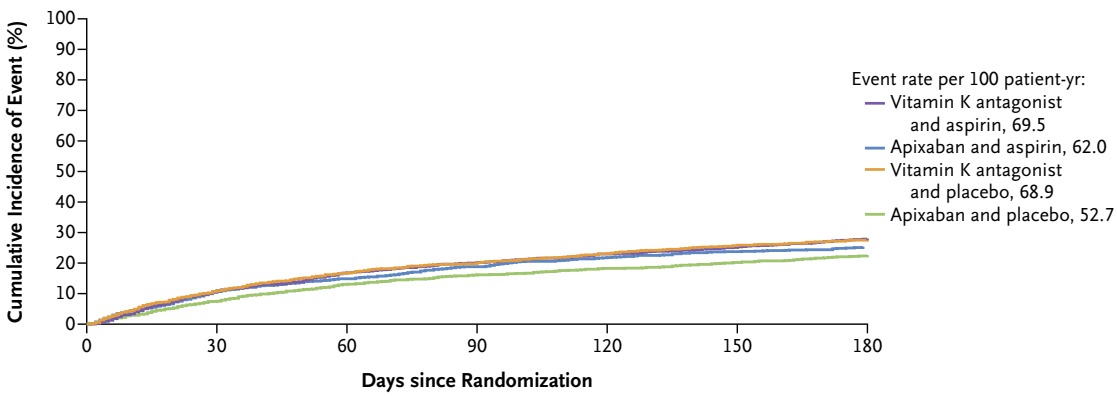
No. at Risk							
Vitamin K antagonist	2308	2035	1885	1805	1732	1673	1001
Apixaban	2306	2090	1965	1881	1821	1772	947

B Death or Hospitalization — Aspirin vs. Placebo



No. at Risk							
Aspirin	2307	2042	1909	1822	1752	1699	951
Placebo	2307	2083	1941	1864	1801	1746	997

C Death or Hospitalization, According to Intervention Combination



No. at Risk							
Vitamin K antagonist and aspirin	1154	1016	939	899	864	836	492
Apixaban and aspirin	1153	1026	970	923	888	863	459
Vitamin K antagonist and placebo	1154	1019	946	906	868	837	509
Apixaban and placebo	1153	1064	995	958	933	909	488

Table. Randomization factors (oral anticoagulant and aspirin) interaction parameters for the primary and secondary outcomes

	Coeffi-cient	Std. Error	HR (95% CI)*	2-Sided p-Value for Superiority Test
ISTH major or CRNN bleeding Interaction: Apixaban/VKA and Aspirin	0.08	0.18	1.09 (0.77, 1.54)	0.64
Death or hospitalization Interaction: Apixaban/VKA and Aspirin	0.15	0.12	1.16 (0.92, 1.46)	0.21
Death or ischemic events Interaction: Apixaban/VKA and Aspirin	0.24	0.23	1.28 (0.82, 1.99)	0.28

* Cox Proportional Hazards Model for time to first event stratified by enrollment indication. CI indicates confidence interval; CRNM, clinically relevent nonmajor, HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis.

DISCUSSION

1. The study was conducted without bias at all levels . An independent data and safety monitoring board reviewed unblinded patient-level data at regular intervals during the trial. Although Bristol-Myers Squibb assisted with data management, all the statistical analyses were performed independently at the DCRI.(The Duke Clinical Research Institute). All bleeding and ischemic events (except for urgent revascularization) were independently adjudicated by the clinical-events classification committee at the DCRI, whose members were unaware of the trial-group assignments.

2. Use of Apixaban led to a lower incidence of both bleeding and the composite of death or hospitalization than did a vitamin K antagonist; the latter result was driven by a lower incidence of hospitalization.

3. Aspirin led to a higher incidence of bleeding than placebo, and the rates of death or hospitalization and of ischemic events were similar in the two groups.

4. Trial showed a significantly lower rate of death or hospitalization, driven by the incidence of hospitalization, and a 50% lower incidence of stroke than were observed with a vitamin K antagonist

5. Avoiding aspirin resulted in a 47% lower risk of bleeding than using aspirin and in a nonsignificantly higher incidence of coronary ischemic events. This finding suggests that the price for a significantly lower incidence of bleeding events without aspirin may be a modestly higher risk of coronary ischemic events

LIMITATIONS

1.The time in the therapeutic range for the patients who received a vitamin K antagonist was modestly lower than in some previous randomized trials of stroke prevention involving patients with atrial fibrillation. The median percentage of time that patients assigned to a vitamin K antagonist had an INR above 3.0 was 3%, and the median percentage of time with an INR below 2.0 was 23%

2.The trial wasn't designed to be large enough to detect small but potentially meaningful differences in the incidence of ischemic event.

3.The trial period was only for 6 months . A longer trial period might have given more insight into certain clinical aspects especially in case of the anticoagulant comparison.

4.29% of the patients included were women . More equal representation may have been warranted .

CONCLUSION

The Author concludes that in patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a P2Y12 inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in ischemic events than regimens that included a vitamin K antagonist, aspirin, or both.

References:

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Second International Consensus Report on Gaps and Opportunities for the Clinical Translation of Precision Diabetes Medicine

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Abstract
Precision medicine is part of the logical evolution of contemporary evidence-based medicine that seeks to reduce errors and optimize outcomes when making medical decisions and health recommendations. Diabetes affects hundreds of millions of people worldwide, many of whom will develop life-threatening complications and die prematurely. Precision medicine can potentially address this enormous problem by accounting for heterogeneity in the etiology, clinical presentation and pathogenesis of common forms of diabetes and risks of complications. This second international consensus report on precision diabetes medicine summarizes the findings from a systematic evidence review across the key pillars of precision medicine (prevention, diagnosis, treatment, prognosis) in four recognized forms of diabetes (monogenic, gestational, type 1, type 2). These reviews address key questions about the translation of precision medicine research into practice. Although not complete, owing to the vast literature on this topic, they revealed opportunities for the immediate or near-term clinical implementation of precision diabetes medicine; furthermore, we expose important gaps in knowledge, focusing on the need to obtain new clinically relevant evidence. Gaps include the need for common standards for clinical readiness, including consideration of cost-effectiveness, health equity, predictive accuracy, liability and accessibility. Key milestones are outlined for the broad clinical implementation of precision diabetes medicine.

Diabetes is a major global problem, with many hundreds of millions of people affected by the disease, many of whom are undiagnosed. The major burden of diabetes is exerted through the development of life-threatening complications, often involving damage to large and small blood vessels. The disease is currently classified into several types of diabetes. The two most common forms are type 1 diabetes (T1D), an autoimmune disease accounting for ~2% of all forms of diabetes worldwide[1], and type 2 diabetes (T2D), which accounts for most of the remaining cases. Rare 'monogenic' forms

of diabetes also exist, with gestational diabetes mellitus (GDM) being an additional category (Box 1). A major challenge with most diabetes is that it is heterogeneous in etiology, clinical presentation and prognosis. Understanding and leveraging this heterogeneity is a core objective of precision diabetes medicine (Fig. 1).

This second international consensus report from the Precision Medicine in Diabetes Initiative (PMDI) summarizes the comprehensive systematic reviews and resulting consensus among the PMDI consortium for the pillars of precision medicine prevention, diagnosis, treatment and prognosis[2] across monogenic diabetes mellitus (MDM), GDM, T1D and T2D[3-16] (Fig. 2). The objectives of the PMDI consortium were to identify (1) where current evidence supports the application of precision approaches in diabetes prevention and care, and (2) key gaps where additional and/or higher quality evidence is needed before precision medicine can be implemented. Areas of consensus for these objectives are reflected in key milestones put forth to support the evidence-based and scalable implementation of precision diabetes medicine within the next decade.

The PMDI was established in 2018 by the American Diabetes Association (ADA) in partnership with the European Association for the Study of Diabetes to address the untenable health and economic burdens of diabetes prevention and care[17]. The first consensus report on precision medicine in diabetes published in 2020 (ref. 2) highlighted that precision medicine involves tailored diagnostics or therapeutics (for prevention or treatment) applied to population subgroups sharing similar characteristics, thereby minimizing error and risk while maximizing efficacy (Box 2). Four key pillars of precision medicine were also defined: prevention, diagnosis, treatment and prognosis, which can be applied throughout the life course (Fig. 3).

The data inputs, technologies and tools for subgroup characterization are incredibly diverse and readiness for valid and cost-effective implementation in diabetes medicine varies widely. The first consensus report concluded with a call for a rigorous review elucidating effective precision medicine strategies, areas of promise and notable gaps across MDM, GDM, T1D and T2D to inform an evidence-based road map to optimize the integration of precision medicine into the global response to the diabetes crisis.

The key findings of this second consensus report are that, within the areas examined, several actionable and near-actionable examples of precision diabetes medicine exist. However, the quality of data is generally low, and few studies have been explicitly designed to test precision medicine hypotheses. There is also a dearth of relevant, high-quality research in people of non-European ancestry, hindering the development and implementation of precision diabetes medicine in many of the most heavily burdened populations worldwide.

Evidence evaluation process

After the first consensus report in 2020 (ref. 2), the PMDI executive committee established the PMDI consortium to represent each of the precision medicine pillars within the four types of diabetes across 15 working groups. The consortium comprises >200 clinical and research investigators across all career stages and domains of diabetes expertise, residing in 28 countries across four continents (see author list). A separate cross-cutting methodology working group provided critical training and guidance and the executive committee provided strategic direction and administrative oversight. The working groups were supported by administrative staff (C.G., E.M., P.S.) and medical librarians (M.B., K.A.).

Working groups were tasked with defining the key research questions that would need to be addressed for precision diabetes medicine to be implemented into practice by 2030. The first consensus report opted for this specific timeline to instill a sense of urgency while allowing time for proof-of-conduct research to be undertaken.

Systematic literature review protocols were developed by the working groups for the priority research questions, with principles for procedure, synthesis and consensus reporting outlined by the methodology working group to ensure a rigorous and consistent process. Working groups were permitted to generate expert opinion statements for hypotheses that did not reach the level of priority for a full systematic review. All systematic review protocols were prospectively registered on the PROSPERO database[18,19]. The full methods, results and working group conclusions are described in the individual systematic reviews[3-16].

Synthesis of evidence

The following summarizes the results and synthesis reported in the supporting series of systematic evidence reviews from the PMDI consortium for the second consensus report[3-16].

MDM

MDM results from a mutation in a single gene[20]. It can be diagnosed in the neonatal period (neonatal diabetes) or typically, but not exclusively, before the age of 45 years. MDM diagnosed outside the neonatal period has historically been known as maturity-onset diabetes of the young. There are autosomal dominant, recessive and maternally inherited forms as well as varieties that arise from de novo mutations and chromosome abnormalities[20]. Although MDM is rare, collectively it accounts for up to 5% of diabetes and presents opportunities for precision medicine[20]. Despite the clinical benefits of making a diagnosis of MDM, many patients are misdiagnosed with T1D or T2D owing to overlapping clinical features.

Precision diagnosis

We systematically reviewed the evidence underpinning two priority questions for precision diagnosis of MDM[7]: (1) who should be tested, and (2) how should they be tested? Our eligible literature review included 98 studies among pediatric or adult populations of testing criteria and 32 studies of testing methods among individuals with suspected neonatal diabetes mellitus or MDM.

Based on our evidence synthesis, the data support precision diagnostics testing for (1) neonatal diabetes in all infants aged <1 year diagnosed with diabetes, (2) MDM in individuals aged <30 years without obesity who are islet cell autoantibody-negative with detectable C-peptide, (3) *GCK*-related hyperglycemia in women with GDM without overweight or obesity and fasting glucose >5.5 mmol l^{-1} and (4) *GCK*-related hyperglycemia in young individuals without obesity with persistent mild fasting hyperglycemia regardless of family history. Ethnic-specific body mass index (BMI) thresholds should be used to determine overweight and obesity.

Testing modalities include the use of (1) targeted next-generation sequencing for neonatal diabetes and MDM, (2) targeted genetic panels with all known causes of MDM, including mitochondrial diabetes, detection of known noncoding mutations, and copy-number variants, (3) a comprehensive panel that includes all recessively inherited genes, particularly in populations with high rates of consanguinity, (4) a separate multiplex ligation-dependent probe amplification assay for copy-number variants detection or genotyping assay (such as pyrosequencing) for detection of m.3243A>G, (5) a methylation-based assay, such as methylation-specific multiplex ligation-dependent probe amplification for neonatal diabetes testing, since 6q24 imprinting defects are a common cause of transient neonatal diabetes mellitus, and (6) rapid Sanger sequencing of *GCK* in suspected *GCK*-related hyperglycemia, and the *KCNJ11, ABCC8* and *INS* genes in suspected neonatal diabetes.

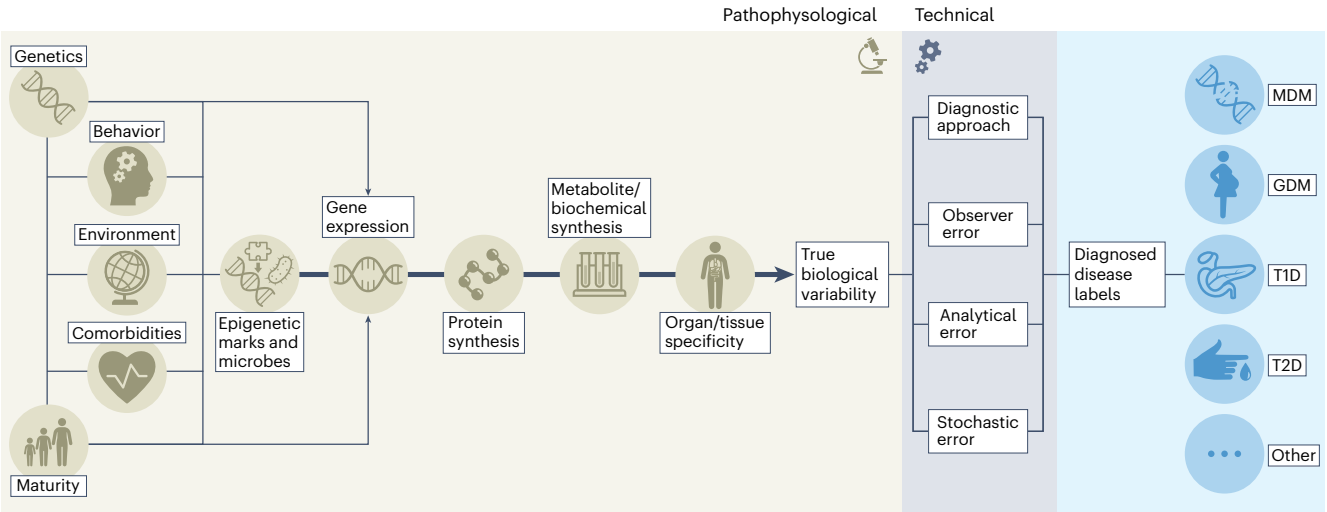
Additional considerations for causality, penetrance, reporting, disparities in testing access and barriers to genetic testing and follow-up of causal variant reporting were qualitatively reviewed. We noted a critical gap across the literature addressing access to genetic testing for MDM to mitigate health disparities, including concerns with replication and external validation in non-European ancestry populations. There was inconsistent measurement of islet autoantibodies and C-peptide diabetes diagnosis under the age of 45 years with ancestry-appropriate T1D genetic risk score data. We encourage the development of guidelines tailored to additional MDM types and genes, de-identified case-sharing platforms to gather the evidence to evaluate pathogenicity and deep mutational scanning maps of MDM genes for variant classification. The clinical guidance for genetic counseling, subsequent referrals and family testing, as well as research on the outcomes of implementation will also be essential to maximize precision diagnostic approaches for monogenic forms of diabetes.

Precision treatment

Precision treatment of MDM is potentially optimized by characterizing an individual's molecular genetic subtype and pathophysiology; thus, we reviewed the evidence for comparative effectiveness of therapies among populations with specific monogenic subtypes of β-cell diabetes and severe insulin resistance[6].

Most diabetes that occurs at ages <6 months is monogenic neonatal diabetes. Sulfonylureas were recently established as the most effective treatment for neonatal diabetes due to a potassium channel mutation[21]. Our systematic review for

Figure 1: Sources of heterogeneity in diabetes.



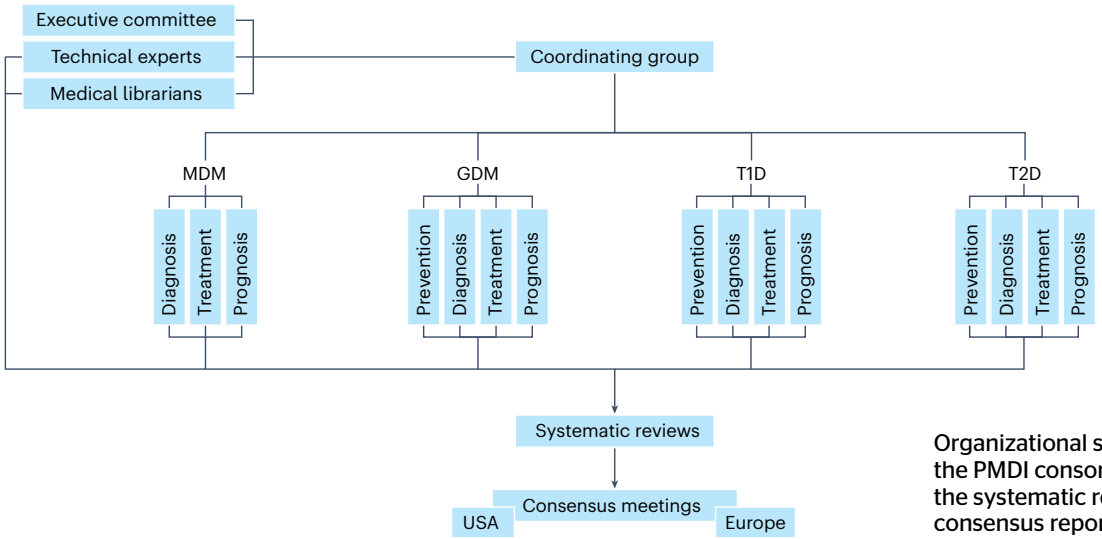
The success of precision diabetes medicine will be enhanced by successfully leveraging heterogeneity in diabetes. To do so will require parsing 'signal' from 'noise'; the figure illustrates the key sources of heterogeneity within each of these domains.

the effects of noninsulin treatments included 19 studies in individuals with 6q24-related transient neonatal diabetes4; all studies graded as having moderate or serious risk of bias. In some, but not all, studies, sulfonylurea use during the neonatal period improved diabetes outcomes, allowing cessation of insulin, and was well tolerated. Evidence for the efficacy of a variety of noninsulin therapies was more consistent later in life during a relapse phase. We reviewed 32 studies in individuals with *SLC19A2*-related neonatal diabetes, also known as thiamine-responsive megaloblastic anemia, all with moderate or serious risk of bias. Most studies described some potential benefits of thiamine, such as reduction or cessation of insulin use and/or improved glycemic control, with no reports of adverse effects. We concluded that the current evidence is low quality for clinical guidance on use of noninsulin therapy with 6q24-related diabetes or thiamine in thiamine-responsive megaloblastic anemia.

We evaluated the effects of therapies for *HNF1A* diabetes, *HNF4A* diabetes and *GCK*-related hyperglycemia reported in 34 studies, including four randomized controlled trials (RCTs). Sulfonylureas are effective specifically in *HNF1A* diabetes for glycemic control, more so than in individuals with T2D. For *HNF1A* and *HNF4A* diabetes, transitioning from insulin or other noninsulin therapies to sulfonylureas may improve glycemic control. Some experimental studies demonstrate glinides and glucagon-like peptide-1 receptor agonists (GLP1-RAs) may be alternatives to sulfonylureas for *HNF1A* diabetes, as well as dipeptidyl peptidase 4 inhibitors as augmentative therapy. For *GCK*-related hyperglycemia, published case series indicate that treatment should not be given and can be discontinued.

Monogenic disorders of severe insulin resistance include generalized lipodystrophy caused by mutations in *AGPAT2* and *BSCL2*, partial lipodystrophy with mutations in *LMNA* and *PPARG*, and pathogenic variants in the *INSR* gene. Safety and efficacy of recombinant human leptin (metreleptin) and thiazolidinediones were analyzed in populations with lipodystrophy syndromes and recombinant insulin-like growth factor-1 in *INSR* mutation carriers. Of 43 nonrandomized experiments and cause series included for review, most individuals had partial lipodystrophy, some had generalized lipodystrophy and few carried *INSR* mutations. This evidence had moderate or serious risk of bias. Response to metreleptin was described in subgroups with familial partial lipodystrophy and congenital generalized lipodystrophy, where treatment was related to lower triglycerides in aggregated lipodystrophy, partial lipodystrophy and generalized lipodystrophy, as well as those with *LMNA*, *PPARG*, *AGPAT2* or *BSCL2* mutations. HbA1c levels decreased in all but *AGPAT2*. Thiazolidinediones lowered triglycerides and HbA1c levels in aggregated lipodystrophy, and

Figure 2: Organogram of the PMDI consortium and workflow.



Organizational structure of the PMDI consortium during the systematic review and consensus report processes.

triglycerides in *LMNA* but not *PPARG*. Response to insulin-like growth factor-1, alone or in combination with *IGFBP3*, lowered HbA1c levels. There were very few adverse events reported for any therapies, possibly due to small samples sizes and underreporting.

Precision prognosis

We reviewed evidence describing the incidence and severity of diabetes-related microvascular and macrovascular complications in populations with permanent neonatal diabetes due to pathogenic variants in *KCNJ11* and *ABCC8*, and MDM due to pathogenic variants in *HNF1A*, *HNF4A* and *GCK*[6]. Extra-pancreatic complications (for example, hepatic adenomas in *HNF1A* diabetes, developmental delay, epilepsy and neonatal diabetes syndrome) were beyond the scope of the review.

Individuals with most forms of MDM are at high risk of microvascular and macrovascular complications, impacted by poor glycemic control. Many studies focused on younger populations diagnosed with neonatal diabetes, where rates of severe microvascular complications were low. Their risk may be in part mitigated by improved glycemic control in neonatal diabetes related to pathogenic variants in the *KCNJ11* and *ABCC8* genes and *HNF1A* diabetes and *HNF4A* diabetes, where precision therapy with sulfonylureas is available. Additional long-term follow-up studies will be important to understand the natural progression of microvascular and macrovascular complications in permanent neonatal diabetes mellitus from mutations in *KCNJ11* and *ABCC8*.

From 78 articles, retinopathy and microalbuminuria were reported in cases with neonatal diabetes mellitus, but progressive retinopathy and severe renal disease were uncommon. Populations with isolated *GCK*-related hyperglycemia have overall very low rates of diabetes-related complications. Indeed, microvascular complications were very rare in cohort studies of populations with *GCK*-related hyperglycemia and prolonged disease duration (>50 years).

Recent studies of *HNF1A* diabetes reported lower rates of complications compared to those published earlier (for example, for retinopathy, 17% in recent versus 47% earlier; for cardiovascular disease (CVD), 7% in recent years versus 16% earlier). In recent studies, rates of microangiopathic complications observed were less than in T1D, although rates were similar or higher among these populations in older studies. More recent studies of patients with *HNF1A* diabetes and *HNF4A* diabetes show improved prognosis of diabetes microvascular and macrovascular complications, likely reflecting an earlier molecular diagnosis, tighter treatment targets and higher rates of precision therapy.

GDM

GDM is abnormal glucose tolerance with onset or first recognition during pregnancy. GDM is the

most common metabolic complication of pregnancy. Unlike most other forms of diabetes, the onset of GDM is rapid and typically resolves after delivery. Nevertheless, the short- and long-term health risks that GDM poses to the mother and offspring can be substantial, underscoring the importance of widely available screening, diagnosis and effective treatment.

Precision prevention

We systematically reviewed results of 116 interventions on GDM prevention, including diet and/or exercise (diet $n = 16$; exercise $n = 17$; diet and exercise combined $n = 59$), metformin ($n = 13$) and supplements such as myoinositol/inositol, probiotics and fish oil ($n = 12$)[9]. We considered interventions initiated in the preconception or antenatal period and reporting GDM among its outcomes for prevention efficacy.

In our meta-analyses, lifestyle interventions led to lower incidence of GDM compared with control care: diet only by 25%, exercise only by 31%, and combined diet and exercise by 18% (moderate-to-low-quality evidence). Metformin reduced GDM by 34%, and myoinositol/inositol supplements by 61%; however, this evidence was rated very low quality. Only seven trials initiated interventions in the preconception period. Metformin interventions implemented in the preconception period had better GDM risk reduction when compared to those initiated during pregnancy. For exercise-only interventions, greater risk reduction for GDM was seen in studies enrolling women with a BMI in the normal range. Combined diet and exercise interventions were more effective in GDM reduction among women with overweight or obesity, without polycystic ovary syndrome, without history of prior GDM and with advanced maternal age at pregnancy. Metformin was relatively more effective in preventing GDM among women with a history of polycystic ovary syndrome, with older maternal age and with higher fasting blood glucose at enrollment. Parity, education and employment status, race and history of having a large for gestational age infant did not appreciably impact the effectiveness of interventions. These findings came primarily from comparing effect estimates across trials with different participant characteristics rather than from within-study analyses stratified by participant characteristics. Overall, the strength of evidence for GDM risk reduction with the use of lifestyle modification, metformin and myoinositol/inositol is moderate to very low. Moreover, few data were available to determine which individual characteristics might predict who would benefit most from a given type of intervention.

Future research should include interventions in early pregnancy with sufficient sample size to assess GDM as a primary outcome as well as to provide results stratified by pertinent participant characteristics, including social and environmental factors, clinical traits and other novel risk factors to predict the effectiveness of GDM prevention programs.

Precision diagnosis

The overarching goal of the GDM precision diagnosis working group was to review evidence of precision markers beyond glycemic level (that is, information about a person's pathophysiology, environment and/or context) that might help refine the diagnosis of GDM. Through the lens of clinical translation, we investigated the evidence supporting GDM subtypes and etiologic or pathologic heterogeneity, as well as associations with adverse perinatal outcomes[14]. The systematic review and meta-analysis focused on observational studies evaluating maternal and fetal anthropometry, clinical and sociocultural/environmental risk factors, genetics, omics and nonglycemic biomarkers that could identify subgroups of individuals with diagnosed GDM at differentially higher risk of adverse pregnancy outcomes. Of 137 studies included, 68 studies evaluated maternal anthropometry as a potential modifier or precision marker related to pregnancy outcomes. The meta-analysis among a subset of studies reporting on maternal BMI in relation to risk for neonatal large for gestational age and/or macrosomia. Forty-nine studies evaluated maternal clinical or sociocultural factors, and 30 studies evaluated nonglycemic biomarkers, lipids and insulin sensitivity/secretion indices. Few studies incorporated fetal anthropometry (11 studies), risk-prediction models with multiple variables (six studies) or genetics/genomics and other omics (five studies).

Anthropometry measures were the most analyzed risk factor with outcomes among pregnancies complicated by GDM. Meta-analyses demonstrated that women with GDM and overweight/obesity have two to three higher risk for neonatal macrosomia or neonatal large for gestational

Box 1

Contemporary diagnostic definitions of the established forms of diabetes

Based on the ADA Standards of Care 2022, diabetes can be classified into the following general categories:

(1) T1D is a disease caused by autoimmune damage of the insulin-producing β-cells of the pancreatic islets, usually leading to absolute endogenous insulin deficiency, including latent autoimmune diabetes of adulthood.
(2) T2D is a disease characterized by a progressive loss of adequate β-cell insulin secretion frequently in the presence of excess adiposity and insulin resistance.
(3) GDM is a disease characterized by persistent hyperglycemia, often diagnosed in the second or third trimester of pregnancy, which was not determined to be prepregnancy diabetes.

Other rarer types of diabetes include:
(1) MDM, which represents a rare form of diabetes due to specific genetic defects that cause β-cell dysfunction with minimal or no defects in insulin action and include neonatal diabetes and maturity-onset diabetes of the young.
(2) Secondary forms of diabetes, such as diabetes due to other causes such as the exocrine pancreas (for example, cystic fibrosis) and pancreatitis and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS or after organ transplantation).

age. Larger birth size is the leading risk factor for birth trauma (shoulder dystocia) and emergency C-section. Regarding nonglycemic biochemical markers ($n = 33$ studies), lipids and insulin resistance or secretion indices were the most studied, with elevated maternal triglycerides and insulin resistance generally associated with greater risk of neonatal large for gestational age and macrosomia; study findings were inconsistent. Studies reporting on genetics and omics were scarce. Few studies described risk-prediction models with multiple variables. Traditional GDM risk factors, such as advanced maternal age, parity, prior history of GDM or family history of diabetes, were not consistent markers of adverse perinatal outcomes in women with GDM. There was sparse evidence to support conclusions for the role of race, ethnicity or country of origin as precision markers, given high heterogeneity across studies, and that data interpretation is dependent on sociocultural context. Very few studies investigated diet, physical activity or psychological health as precision markers for diagnosis of GDM.

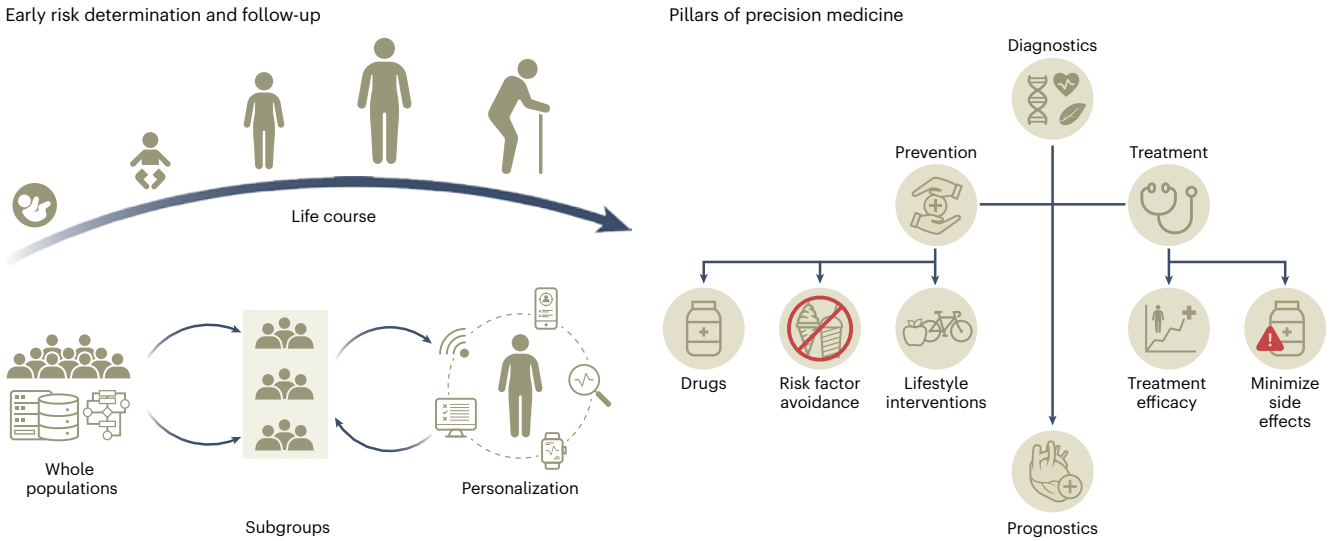
For most of the precision markers (other than BMI), it will be necessary to conduct validation and replication studies in adequately powered studies of people representing the diversity of target populations. For precision biomarkers, validated, standardized and affordable assays are required for broad adoption by clinical laboratories. There is a need to identify and test different clinical decision and management strategies if a precision diagnostic identifies a woman at high risk of perinatal complications. Finally, for modifiable precision markers (for example, lipid levels, insulin sensitivity), novel interventions should be developed and validated that specifically target these markers during pregnancy.

Precision treatment

It is unknown whether precision treatment of GDM could improve maternal and/or offspring outcomes. We conducted a systematic review of evidence for precision markers of GDM treatment success to determine (1) which precision approaches in addition to standard of care can enable achievement of glucose targets with lifestyle measures alone, and (2) which characteristics predict whether glucose targets can be achieved in women treated with diet and lifestyle alone, and in women receiving oral agents[10].

Only two studies reporting personalized approaches of tailoring lifestyle-based treatments in GDM met the inclusion criteria for review, with variable findings for prepregnancy BMI or excessive gestational weight gain as precision markers for intervention efficacy and implementation. For predictors of escalation with the need for pharmacological interventions, 48 studies were included, and 34 studies were included in meta-analyses. Precision markers for successful GDM management with lifestyle measures without the need for additional pharmacological therapy (insulin, metformin and/or glyburide; 34 studies) were (1) younger maternal age, (2) nulliparity, (3) lower BMI, (4) no previous history of GDM, (5) lower levels of HbA1c, fasting glucose and postchallenge glucose concentrations (at 1, 2 and 3 h), (6) no family history of diabetes, (7) later gestation of diagnosis of GDM, and (8) no previous macrosomia. Similar precision markers for successful treatment with metformin and/or glyburide without requiring supplementary insulin were found with the addition of later gestation of initiation of the oral agent (12 studies). Data were lacking to identify precision markers of responses to one agent versus another. Only two studies included genetics or omics as potential markers for

Figure 3: Precision medicine across the life course and the role of precision diabetes medicine.



The collection of deep phenotypic, environmental and social data through the life course will allow the generation of prediction algorithms to identify individuals with shared characteristics that are more likely to benefit from targeted screening and preventive and treatment strategies for the prevention, diagnosis and management of diabetes.

treatment escalation. The studies were limited by the predominant focus on high-income settings and the small sample sizes.

Overall, based on findings from moderate-to-good quality, key maternal characteristics were identified that may be used to build prediction models for pharmacological GDM treatment. Precision markers for GDM treatment are usually available from routine clinical measures; however, it is unknown whether other precision markers could be identified (for example, genetics or omics) or whether these can be implemented in clinical practice. Future studies should be appropriately powered and designed to assess individual precision markers or algorithms incorporating multiple precision markers. Validation and replication in diverse populations are lacking and are also needed.

Precision prognosis

GDM incurs health risks to both a mother and her offspring, not only during pregnancy and at delivery but also over the longer term. The systematic evidence evaluation focused on studies describing predictors of postpartum and long-term cardiometabolic outcomes in women with GDM and their offspring[5]. The evidence synthesis focused on prognostic endpoints of T2D and CVD for women with prior GDM, as well as anthropometric features and preclinical cardiometabolic biomarkers among offspring exposed to GDM in utero. We included 89 studies of which 55 reported on maternal outcomes (52 observational, three RCTs) and 45 reported on offspring outcomes (37 observational, eight RCTs).

Collectively, studies reported that women with a history of GDM are at higher risk of T2D and CVD, with a dose-dependent relationship between degree of pregnancy hyperglycemia and these outcomes. Similarly, offspring born to women with more severe GDM had more adiposity and higher risk of being overweight or of obesity across the life span. GDM severity was also associated with greater risk of incident T2D and CVD among women and with an unfavorable cardiometabolic profile in offspring later in life. Broadly, the relationships between GDM severity and the maternal/offspring outcomes were robust to adjustment for gestational week at diagnosis, offspring birth size and family-level socioeconomic status; however, failing to adjust for maternal BMI and lifestyle factors was a concerning source of bias for the relationships of GDM with offspring outcomes.

Some studies considered whether the type of treatment needed to achieve glycemic targets in women with GDM is a precision marker for long-term outcomes. Treatment with insulin, but not

lifestyle, had a worse prognosis for both mothers and offspring; however, this apparent effect could be due to the prescription of insulin when GDM is 'more severe', which may be partly due to confounding by indication. Unfavorable maternal and child outcomes associated with GDM history (exposure) were modified by lifestyle. For maternal outcomes, the primary risk mitigators were healthy diet and regular moderate-to-vigorous physical activity. For offspring outcomes, the offspring's diet and physical activity modified cardiometabolic risk. Greater exclusivity and longer duration of breastfeeding attenuated cardiometabolic risk among GDM-exposed offspring, although this literature was less robust than that for reduction of the risk for T2D in breastfeeding women with prior GDM. There is presently very limited evidence about the role of omics biomarkers and polygenic scores (for T2D or CVD) in women with prior GDM.

Despite the above insights, studies regarding GDM prognostic factors indicative of future maternal and offspring cardiometabolic health are generally low quality. Most current literature describes retrospective studies leveraging registry data and observational cohort studies; inferring causal relationships from these data about prognostic factors is hampered by risk of confounding and reverse causation (attributable, for example, to preexisting conditions and other pregnancy characteristics).

T1D

T1D results from autoimmune-induced destruction of the pancreatic β-cells, requiring insulin treatment for survival. While representing ~2% of all forms of diabetes worldwide[1], T1D has a large healthcare cost owing to the early age at onset for many affected, the high cost of insulin and related technologies (insulin infusion pumps, continuous glucose monitors (CGM), hybrid closed loop systems) and elevated risk of both microvascular and macrovascular complications. Growing insights into the pathogenesis of T1D motivated the classification of the disease in different stages, with stage 0 being presence of 1 autoantibody in people at high genetic risk, stage 1 and 2 being the presence of two or more islet autoantibodies in normo- (stage 1) or dysglycemia (stage 2) and clinical diabetes (stage 3). Etiologic heterogeneity is recognized in both children and adults.

Precision prevention

A key question in T1D is whether individual characteristics or biomarkers can be used to identify those most likely to respond to disease-modifying therapy before clinical T1D onset (stage 3). We conducted a systematic review of RCTs focused on the identification of features associated with treatment response published over the past 25 years[13]. Multiple trials were identified that compared disease-modifying agents, mostly immunotherapies, to placebo. A formal meta-analysis was not conducted given the heterogeneity of interventions and approaches. Of 75 manuscripts extracted for review, 15 described prevention trials with the remainder focused on treatment in the recent- or stage 3-onset period.

Prevention trials generally enrolled individuals at elevated genetic risk, typically based on the presence of a first-degree relative with T1D and/or with islet autoimmunity, with or without changes in β-cell function (stages 0 to 3). Studies commonly used time-to-diabetes as an outcome. Stage 3 studies used more consistent eligibility criteria and frequently tested C-peptide area under the curve as a primary outcome. Fifty-seven studies, including primary trials and longitudinal follow-up of trials, performed precision analyses, specifically testing features associated with treatment response. Analyses tested the associations of many features with treatment response, most commonly age, measures of β-cell function and/or an immune phenotype.

Overall, the RCTs received high-quality ratings and were graded to have a low risk of bias; however, precision prevention analyses had lower quality rankings. Reasons for this were that studies typically did not prespecify an analytic plan, had inconsistent reporting of key methodologic details (for example, sample size or a correction for multiple comparisons) and tended to report only positive (that is, statistically significant) findings. There is large interest in precision features associated with treatment response to disease-modifying therapy in T1D; however, most analyses were exploratory without follow-up with prespecified prospective analyses.

We recommend that future studies are powered to undertake multiple prespecified analyses to permit statistically robust testing of features associated with treatment response (for example, through stratified effects or biomarker–treatment

interactions). These data will be required for the effective identification and implementation of precision approaches to disease-modifying therapies.

Precision diagnosis

Islet autoantibodies are validated predictors of disease progression and are being incorporated into clinical practice. We focused this systematic evidence review[13] on determining whether autoantibodies help stratify subgroups across four settings: (1) disease progression before stage 3 diagnosis, (2) disease presentation/stage 3 diagnosis, (3) disease progression after stage 3 diagnosis and (4) response to disease-modifying interventions.

We identified 151 publications, 90 relevant to progression before stage 3, 44 for heterogeneity at stage 3, 11 for progression after stage 3 and 13 for interventions. While insulin autoantibodies are commonly the first to appear before diagnosis in younger children, the presence of IA-2 autoantibodies corresponds with faster disease progression. Interactions between high-risk HLA alleles (for example, HLA-DRB1*03:01 and HLA-DRB1*04:01), the number and types of islet autoantibodies, and age at seroconversion are most often used in models (or added to existing models) to predict disease. The replacement of traditional radio-binding assays with electrochemiluminescent assays improved the sensitivity of some autoantibody testing and identified high-risk subgroups (individuals with two or more autoantibodies) who were previously low risk (positive for a single autoantibody).

At stage 3 diagnosis, the presence of specific autoantibodies correlated with age, suggesting that the inciting antigens are different in younger, compared to older, individuals. The primary antibodies at seroconversion often disappeared at the time of stage 3 diagnosis. There was weak evidence that declining islet autoantibody titers and the number of autoantibodies after stage 3 diagnosis corresponded to preserved residual C-peptide level, thereby not supporting the use of islet autoantibodies to define heterogeneity in metabolic outcomes. Evidence of islet autoantibody features to predict response to disease-modifying therapies was modest, making the impact of a specific antigen (and its corresponding autoantibody) less significant. For clinical implementation, the grade of evidence is limited by the reports (1) being mainly from European ancestry populations, (2) rarely correcting analyses for multiple comparisons, (3) consisting of observational measurements from RCTs limited to observational endpoints and (4) inconsistently reporting on assay methods and validation.

These results suggest that islet autoantibodies are useful to define heterogeneity in T1D before stage 3 diagnosis, and that benefit will be gained by incorporating age and genetics into risk scores. Thoughtfully designed, prospective trials are needed to apply these observations and develop precision medicine approaches to diagnosis and treatment. In a corresponding paper[13], a methods checklist is proposed to ensure reproducibility and applicability of islet autoantibody-based research.

Box 2

Revisions to definitions described in the first PMDI consensus report

Several definitions used in the first consensus report on precision diabetes medicine2 are revised here to (1) highlight key benchmarks used to determine the success of precision diabetes medicine in practice and (2) distinguish individual-level processes that can be objectively quantified and incorporated into prediction models from those that cannot, yet are integral to the transfer of medical or health recommendations to recipients.
The following terms are revised:

Precision medicine:

From: "Precision (or stratified) medicine emphasizes tailoring diagnostics or therapeutics (prevention or treatment) to subgroups of populations sharing similar characteristics, thereby minimizing error and risk while maximizing efficacy"2

To: "Precision medicine focuses on minimizing errors and improving accuracy in medical decisions and health recommendations. It seeks to maximize efficacy, cost-effectiveness, safety, access for those in need and compliance compared with contemporary evidence-based medicine. Precision medicine emphasizes tailoring diagnostics or therapeutics (prevention or treatment) to subgroups of populations sharing similar characteristics."

Personalized and individualized medicine:

From: both terms are used interchangeably, defined as: "the final step in the process of translating knowledge into practice"2

To: "The use of a person's own data to objectively gauge the efficacy, safety, and tolerability of therapeutics, and, subjectively, to tailor health recommendations and/or medical decisions to the individual's preferences, circumstances, and capabilities"61.

Precision treatment

Treatment of clinical, stage 3 T1D includes insulin therapy, adjunctive agents, nutrition, exercise, behavioral health, glycemic targets and transitions of care; however, in the last decade, the major development for people living with T1D has been in technology. This systematic evidence review focused on whether diabetes management technologies impact clinically relevant outcomes, based on differences between subpopulations[11].

A systematic review of 71 peer-reviewed RCTs and related secondary/extension studies with at least 50 participants from the past 10 years concluded that novel technologies (ranging from isolated CGM, decision-support tools, continuous subcutaneous insulin infusion pumps, to advanced hybrid closed loop systems) have resulted in lower HbA1c levels, increased CGM-defined time-in-range glucose between 70–180 mg dl^{-1}, reduced hypoglycemia risk and improved person-reported outcomes. The broad array of technologies permits the application of individualized treatment plans for people living with T1D but limits cross-trial comparisons or meta-analyses. CGM use among very young children reduced the risk of hypoglycemia and lowered parental distress while having minimal impact on HbA1c level and time-in-range when compared to self-monitoring of blood glucose. Technologies that include sensor-augmented pump therapy, predictive low glucose suspend pumps and automated insulin-delivery systems improved hypoglycemia, time-in-range and HbA1c levels across all age groups. Age of the individual should be considered in clinical decisions related to technology use. Variation in baseline glycemic status (for example, suboptimal versus targeted HbA1c level) did not consistently impact these outcomes.

Important limitations of published trials were identified. There is limited availability of pre-planned or well-powered analyses in subgroups (for example, children, older adults or people with advanced complications). While the quality of evaluated RCTs is high with a low risk of bias, high-quality data related to these subpopulations is needed, and results are considered exploratory until appropriately powered studies are conducted and findings are adjusted for multiple comparisons. Confounding variables, including (1) access to technologies, (2) education with device initiation, (3) concomitant behavioral modifications and (4) frequent contact with the healthcare team are rarely described in enough detail to assess their impact.

Precision prognosis

The landmark Diabetes Control and Complications Trial demonstrated that intensive glucose control effectively prevents microvascular complications in individuals with uncomplicated and recent-onset T1D (<5 years), as well as those with more than 5 years since diagnosis and mild nonproliferative diabetic retinopathy[22,23]. However, glucose control accounts for only 50% of T1D complication risk[24-27]. Moreover, certain subgroups, including the elderly, young children and people with hypoglycemia unawareness or autonomic neuropathy, may be harmed from severe hypoglycemia resulting from tight glucose control[28]. This highlights the importance of identifying additional nonglycemic interventions to mitigate complication risk for all people living with T1D.

Epidemiological studies have identified additional (epi-)genetic, biological and phenotypic traits in people with T1D at higher risk for kidney, eye and neurological complications and a worse prognosis. Presence of risk factors traditionally associated with CVD and T2D such as overweight, dyslipidemia, hypertension and smoking also contribute to the development of advanced stages of kidney disease, peripheral neuropathy, retinopathy and CVD in T1D[25,29-31]. Although cholesterol and blood pressure levels outside of current clinical targets increase complication risk in T1D[32,33], T1D-specific recommendations are lacking.

Recent evidence has identified distinct changes in lipid and amino acid metabolism that predict earlier, more rapid kidney function decline in T1D[34]. Additionally, socioeconomic and psychological factors play a role in microvascular complications[35-38]. Although evidence from RCTs is absent, blood pressure control with renin-angiotensin-aldosterone system (RAAS) inhibition and the use of statins for hyperlipidemia are promising therapies against progression to hard endpoints (for example, end-stage renal disease or CVD); however, there is a scarcity of evidence that precision medicine alters prognosis in T1D.

A rare example of precision prognosis in T1D relates to the haptoglobin (*HP*) genotype. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and

Table 1: Recommendations for future impact in precision diabetes medicine.

Domain	Milestones/priorities	Stakeholders
Benchmarking and technology	Establishing mechanisms of research to identify novel and improved risk markers to form the basis for future clinical guidelines	Research to translation (researchers, healthcare providers)
	Developing and testing new assays for commonly used analytes with respect to sensitivity, specificity, the cost for implementation, cost of the assay to patient/practice	Research to translation (researchers)
	Standardization and sharing of laboratory technologies, assays and pipelines for biomarker assessment and quantification within healthcare systems and in point-of-care settings	Research to translation (researchers, healthcare providers)
	Standard reporting definitions and transparency in computational algorithms and artificial intelligence approaches to enhance access, reproducibility and transparency	Research to translation (researchers)
	Creating systems for routine assessment of heterogeneity in diabetes and revision to the current classification of diabetes across the life course concerning diagnosis, treatment, prognosis and prevention	Research to translation (researchers, healthcare providers)
	Improved estimation of the costs and benefits above current practice to translate precision medicine into approaches consistent with 'simple clinical measures'	Translation to implementation (healthcare providers, regulators, policymakers)
Policy, implementation and liabilities	A framework optimized to the target population will be necessary for moving precision diabetes research from evidence generation to clinical implementation	Research to translation to implementation (all stakeholders)
	Decision-support systems for healthcare practitioners will need to be developed, specifically for those making first contact with patients, likely in the setting of primary care	Translation to implementation (healthcare providers, regulators, policymakers)
	Forging alliances with regulatory and healthcare agencies to facilitate the coverage of precision medicine tools and decision-support aids, making them accessible and affordable, ideally with free global access	Translation to implementation (healthcare providers, regulators, policymakers, patients/relatives)
	Learning precision diabetes medicine from the MDM perspective, where rare forms may be most clinically ready but not yet widely implemented	Translation to implementation (healthcare providers, regulators, policymakers, the public, patients/relatives)
Equity and community engagement	Increase ethnic, geographic and sociodemographic diversity in biomedical research and healthcare access by addressing language barriers, cultural biases and geographical constraints	Research to translation (researchers, clinicians, the public, patients/relatives)
	Defining context-specific surveillance programs, systems and strategies to identify vulnerable and minority groups experiencing the highest burden of diabetes and related complications	Research to translation to implementation (all stakeholders)
	Evaluation of the impact of precision diabetes medicine approaches should involve patient advisory groups for impact and utility	Translation to implementation (healthcare providers, regulators, policymakers, the public, patients/relatives)
	National and international societies and advocacy groups should play an increasing and supportive role in the promotion, educational and research approaches to increase the implementation of 'standards of care' and access to precision medicine tools	Translation to implementation (healthcare providers, regulators, policymakers, the public, patients/relatives)
Commercialization and access	Generate a therapeutical framework optimized to the target populations, accessible to those in need, cost-effective and safe	Research to translation to implementation (all stakeholders)
	Recognition of the impact of precision diabetes from a 'patient journey' perspective, especially the impact of research on people living with diabetes	Translation to implementation (healthcare providers, regulators, policymakers, patients/relatives)
	Establishing open lines of communication, involving community stakeholders in decision-making processes and ensuring data privacy and security are crucial to building trust and maintaining engagement	Research to translation to implementation (all stakeholders)
Education	Establish programs to ensure that individuals are equipped with the knowledge and education to understand their personal risk factors, make informed decisions about preventive measures and actively engage in appropriate interventions for effective diabetes management	Translation to implementation (healthcare providers, regulators, policymakers, the public, patients/relatives)
	Combating digital health illiteracy. Efforts should be made to bridge the digital divide by providing resources, training and infrastructure to underserved populations, ensuring access to telemedicine, digital health tools and genetic testing services	Translation to implementation (healthcare providers, regulators, policymakers, the public, patients/relatives)
	Develop training programs for healthcare providers to equip them with the knowledge and skills necessary to effectively implement precision diabetes medicine approaches	Translation to implementation (healthcare providers, regulators, policymakers)

Complications study, coronary artery disease (CAD) risk was comparable between the intensive and conventional therapy groups with the *HP* 2-2 genotype[39]. CAD risk was greatly reduced with intensive therapy in noncarriers of *HP* 2-2. Similarly, although better glycemic control was associated with lower CAD incidence in the EDC study, a residual risk related to *HP* 2-2 was observed[39,40].

After the Diabetes Control and Complications Trial, there has been little evidence from RCTs for evaluating the impact of tight glycemic control in specific subgroups with respect to complications; however, clinical precision medicine is utilized in the prognosis and choice of therapy for people with T1D. More sophisticated decision tools, based on deeper genetic and phenotypic profiling in multi-ethnic cohorts are needed to improve personalized prognosis in T1D.

T2D

Approximately 500 million people worldwide are estimated to have T2D[41], which is predicted to rise to 1.3 billion by 2050 (ref. 42). A diagnosis of T2D is one of exclusion, occurring when other plausible explanations for chronically elevated blood glucose have been considered and dismissed. This high degree of uncertainty and potential heterogeneity presents major challenges for the prevention and treatment of T2D.

Precision prevention

Large-scale RCTs demonstrate that dietary or lifestyle interventions can delay the progression to T2D. However, there is large interindividual variability in response to preventive interventions[43]. Identifying predictors of response to interventions and the characteristics of people who would be most likely to benefit remain high priorities and are key focus areas for precision prevention in T2D[15]. This systematic review identified 33 trials focused on lifestyle interventions (n = 24 studies), dietary modification (n = 4 studies) and dietary supplementation (n = 5 studies). From the 33 trials, there were 80 post hoc stratified analyses based on demographic, clinical, social or molecular factors.

Sociodemographic characteristics such as age, sex, race/ethnicity or socioeconomic status were not found to significantly affect response to intervention. We found evidence, albeit of low quality, that individuals with poorer health status at baseline, in particular prediabetes, tend to benefit more from lifestyle and dietary interventions than healthier individuals. Studies that stratified on body size at baseline reported inconsistent observations, with some showing that those with a lower BMI benefited more from intervention, whereas other studies found no difference according to body size. There was suggestive evidence that individuals who smoke and those with lower levels of physical activity at baseline benefited less from a lifestyle program, whereas no such interactions were reported for dietary or supplement interventions. There was little evidence that genetic factors or biomarkers attenuated or exacerbated the effects of these interventions.

Although our systematic review included intervention studies, most of which were RCTs with low risk of confounding, we evaluated certainty of post hoc stratification analyses. This suggested that statistical power was often limited. Further, most did not adjust for individual-level risk factors.

Although T2D can be prevented or delayed in tightly controlled clinical trials, adherence to lifestyle or diet modifications in real-world settings is often suboptimal. Thus, to maximize success of precision prevention interventions it will be important to incorporate methods tailored to the individual that enhance adherence.

Precision diagnosis

In this systematic review[8], evidence was assessed for optimization of T2D diagnosis through subclassification using (1) approaches involving 'simple' categorization of clinical characteristics such as biomarkers, imaging or other routinely available parameters and (2) 'complex' approaches involving machine learning applied to omic and genomic data.

Current data on the clinical value of T2D subclassification come predominantly from populations of European ancestry. Though glycemic measures are used to diagnose T2D, several nonglycemic measures were consistently applied to subclassify disease, including BMI, homeostatic model assessment of insulin resistance, C-peptide and lipid profiles.

Simple T2D subclassification approaches focused on data including pancreatic autoantibodies, BMI, measures related to pancreatic β-cell function, age at diagnosis, lipid profiles, oral glucose tolerance test measures and cardiovascular features. The study designs, specific cutoffs and outcomes were heterogeneous, with no study replicated or meeting high Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality.

Complex approaches yielded some reproducible subtypes of T2D. The most frequently replicated subtypes were the clusters first described by Ahlqvist et al.[44], which were replicated in 22

studies, including people of diverse ancestries. These studies used k-means clustering applied to exposures assessed close to diabetes diagnosis: age, HbA1c, BMI, homeostatic model assessment of β-cell function, homeostatic model assessment (2) of insulin resistance and GAD-65 antibody. The four nonautoimmune diabetes subtypes described were severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes and mild age-related diabetes. Associations of these subtypes with clinical outcomes, including glycaemia, microvascular and macrovascular outcomes and death, were replicated in 12 studies. There was also replication of genetic subtypes of T2D from Udler et al.[45], with associations with clinical features seen in multiple cohorts of European ancestry.

Subclassification strategies for T2D have been associated with meaningful clinical outcomes. However, evidence supporting the clinical application of these subclassification approaches is of moderate quality at best. Further ancestry-inclusive and high-quality evidence is needed. In contrast to simple approaches, the clinical application of machine-learning-derived approaches may require real-time computation of subphenotype classification of an individual with T2D, and necessary computing resources may be unavailable in some settings.

Precision treatment

This systematic evidence review3 focused on two of the most recently introduced antihyperglycemic drug classes, SGLT2 inhibitors (SGLT2i) and GLP1-RAs. These drugs have been shown in RCTs to not only reduce glycemia but also to lower the risk of renal and CVD outcomes among high-risk individuals with T2D. Other therapeutics were not included in this evaluation owing to the complexity and volume of this literature.

The population of those with T2D is heterogenous in its demographics, clinical features and prognosis; thus, there may be differences in response to one or both of these drug classes. A systematic review was conducted to identify individual-level demographic, clinical or biological biomarkers associated with heterogeneous glycemia, CVD and renal outcome in individuals with T2D treated with SLGT2i or GLP1-RA.

For SGLT2i, 339 full-text articles were screened, which yielded 101 studies for evaluation; for GLP1-RA, 161 full-text articles were screened, yielding 75 studies for evaluation. These studies predominantly represent secondary analyses of industry-funded, placebo-controlled trials, or meta-analyses of these trials, with a few observational studies. The most common stratification variables were demographics, baseline HbA1c, obesity and preexisting CVD or nephropathy.

Overall, limited evidence was found for robust modification of the effects of GLP1-RA or SGLT2i on glycemia, renal or CVD outcomes by these features. For SGLT2i, reduced baseline renal function was associated with lesser glycemic response, while a higher baseline HbA1c level was associated with greater glycemic response. For GLP1-RA, a lower β-cell function was associated with a lesser glycemic response. Generally, the strength of evidence was modest, largely reflecting a lack of studies designed and sufficiently powered to address the question of treatment effect heterogeneity.

Precision prognosis

This systematic review included a meta-analysis[16] to combine evidence from longitudinal studies of individuals with T2D for markers predicting CVD and evaluated their predictive utility beyond current practice. After full-text review, 416 studies were analyzed with 77% focusing on nongenetic biomarkers, 12% on genetic biomarkers and 11% on risk scores.

There were 195 novel nongenetic biomarkers for CVD, of which 134 (69%) had a net positive number of studies showing a significant adjusted association. Of these, 12 biomarkers showed improvement in c-statistic, net reclassification index or integrated discrimination index consistently in more than one study. Considering the results of our pooled meta-analyses, nonpooled analyses, evidence for improved prediction performance indicators and risk of bias, we found high predictive utility for N-terminal pro b-type natriuretic peptide (high evidence), troponin T and triglyceride-glucose (moderate evidence), moderate predictive utility for coronary computed tomography angiography and single-photon emission computed tomography (low evidence) and pulse wave velocity (moderate evidence), and low predictive utility for C-reactive protein (moderate evidence), coronary artery calcium score, galectin-3 (Gal-3), troponin I, carotid plaque and growth differentiation factor-15 (low evidence).

Among the 48 genetics studies, 79 genetic biomarkers were evaluated for CVD outcomes,

29 having a net positive number of studies with a significant association. Three genetic biomarkers demonstrated promise: rs10911021 in *GLUL*, genetic risk score (GRS) for CAD and isoform e4 in *APOE*. Only the GRS for CAD showed improvement in all three performance indicators in a single study. A few studies employed different GRSs using up to 204 variants from 160 distinct loci derived from the general population that were externally validated, demonstrating improvements in CVD risk reclassification and significant enhancements in discrimination indices. Most studies, however, were conducted in European ancestry populations, with a few of Asian ancestry and very little or no representation of most other ethnicities. Some studies report a relative integrated discrimination index >6%, suggesting adequate predictive utility for the GRS for CAD, but this will need to be confirmed in appropriately designed ad hoc trials, to confirm clinical utility and transferability to other ancestries.

Risk scores showed overall modest discrimination, and model performance tended to decline when validated in countries that differed from the derivation cohort. Most studies focused on baseline characteristics and did not account for time-varying factors that may modify CVD risk, such as medications.

In summary, the highest predictive utility was found for N-terminal pro b-type natriuretic peptide, troponin T, triglyceride-glucose and GRS for CAD, with NT-proBNP having the highest level of evidence. Prospective studies evaluating prognostic biomarkers and risk scores as clinical decision-support tools in T2D are scarce, as is information on their cost-effectiveness. Our findings illustrate the need for development and validation of prognostic markers for CVD in diverse populations of people with T2D to promote equity in precision diabetes care.

Consensus on implementation of precision diabetes medicine

The PMDI consortium working groups convened over two in-person meetings to deliver consensus across the precision medicine pillars and diabetes domains. Their main objectives were identifying evidence to support immediate clinical applications of precision medicine approaches and the gaps to address otherwise. Although the framework we outlined using the pillars of precision medicine may help structure approaches in research and practice, there will be overlap between pillars in some settings. For example, 'precision diagnostics' may focus on identifying diabetes subtypes that are treatment-dependent, and within 'precision prognostics' there may be elements of 'precision prevention.' Thus, while these pillars may help with implementation of precision medicine in both research and practice settings, they should not be considered monolithic.

Promising applications of precision medicine in diabetes

Through the systematic reviews of prioritized diabetes research questions, we identified cases where the available evidence supports the use of a precision medicine approach. Research for MDM has witnessed progress for precision diagnosis, underscored by major advances in the availability and affordability of next-generation sequencing technologies for genetic testing.

In women with a GDM pregnancy, factors reflecting severity of GDM, including higher serum glucose values or the number of time points with elevated serum glucose at the diagnostic oral glucose tolerance test, earlier gestational age at diagnosis and insulin treatment requirement predicted GDM treatment success and risk of long-term prognostic outcomes for mother[46] and offspring[47]. Precision prevention, diagnosis and treatment research should leverage information provided by readily available clinical measures to support GDM care. Published evidence shows that maternal BMI, insulin sensitivity and secretion and dyslipidemia may enhance precision diagnostic tools[14]. Beyond this, there is a need for further research to develop and validate algorithms predicting GDM treatment success or risk of complications using traditional clinical factors possibly combined with novel markers such as metabolomics, paving the way for precision treatment and prognosis tools.

In T1D, clinical prevention strategies are increasingly informed by the primary etiology and progression in those at elevated genetic risk. Recent approval by the US Food and Drug Administration (FDA) of an anti-CD3 monoclonal compound (teplizumab) for use in stage 2 T1D has provided evidence of slowing, if not blocking, disease progression. Heterogeneity in response to

preventive therapies represents a major opportunity for research and clinical investigation. In T1D, genetic risk has been defined largely using data from pediatric-onset populations of European ancestry individuals, aiding the development of GRS in this group that, when coupled with islet autoantibody testing, predicts disease development and aids diagnosis.

Precision medicine in T2D includes refining the subclassification of diabetes into pathophysiologically and clinically meaningful disease subtypes[44] or the development of probabilistic scoring algorithms to assert likely 'archetypes'[48]. The methods and data inputs to these derivations are diverse, often with machine learning unsupervised clustering methods applied to clinical and genomics or other omic data. The application of such approaches to the clinical setting is likely to require further refinement of classification models, as only about a third of people with diabetes can be reliably subclassified currently, and people tend to drift between diabetes subtypes as their disease progresses[48], making longer-term prognosis challenging. The most promising precision approaches to T2D treatment, however, are to use individual patient-level features to predict differential treatment outcomes[49]. There is now robust evidence that routine clinical features and pharmacogenetic biomarkers alter glycemic response for all major drug classes after metformin, supported by the recent prospective TriMaster trial[50]. Development of treatment decision-support tools prioritizing routine clinical features would provide a low-cost and equitable approach to T2D precision treatment that may be of special utility in global regions where access to essential diabetes medications is very limited.

Research gaps to accelerate precision medicine in diabetes

A key finding of this consensus report is that trials explicitly designed to test precision medicine hypotheses are needed, particularly those that yield clinically translatable findings. Incorporating trials explicitly designed to test precision medicine hypotheses in the drug development pipeline will be important if treatment recommendations for these drugs are to be meaningfully optimized. For this to succeed, engagement with regulatory authorities will be required. These and other supporting studies should consider whether markers of treatment heterogeneity are part of causal process, or noncause predictors of such effects. Although noncausal markers may be adequate for the purpose of prediction, where the marker is the intervention target, it should lie on the causal pathway. Determining causal mechanisms will also be important in research focused on understanding biological heterogeneity and interactions, which may, for example, include novel target discovery efforts.

As much of the current precision diabetes medicine research has been conducted in people of European ancestry living in high-income settings, there is a pressing need to broaden the scope to include other ethnic, geographic and cultural groups, particularly those who are most vulnerable. Correspondingly, there is also a need to better understand the impact of precision medicine on disparities, to help ensure gaps are closed and not inadvertently widened.

Across the pillars of MDM, there is a need to develop improved differential diagnosis of MDM that can masquerade as either T1D or T2D. As MDM encompasses several genetic variants in genes involved in glucose metabolism, it is important to consider complementary approaches for clinical translation, including genetic counseling, cascade testing and open sharing of confirmed mutations in a standardized global platform. More studies are needed to determine the efficacy of treatments for specific monogenic forms of diabetes, with focus on extra-pancreatic effects of MDM.

GDM is heterogeneous in etiology and prognosis, arguing for more precise prevention, diagnosis and treatment, as well as continued investigation of prognostic implications in both women and offspring throughout the life course. The clinical translation of precision medicine in GDM will require new studies that test precision interventions targeting the physiological processes characterized by these biomarkers; such studies will also need to demonstrate improved health outcomes in women and/or their offspring. Dynamic biomarker assessments in pregnancy and postpartum will also be required, ideally with point-of-care testing, since GDM, unlike other types of diabetes, unfolds and exerts its effects rapidly. Many GDM prevention trials have intervened relatively late in pregnancy and reported variable outcomes on maternal and offspring health[51]. Interventions starting in early pregnancy

or preconception may be more impactful; success in identifying who should be the focus of interventions, the specific nature of those interventions and when they should occur may be enhanced by precision prediction models. Because the impact of the intrauterine environment on the fetus is plausibly mediated by epigenetic modifications to fetal deoxyribonucleic acid, the characterization of cell-free fetal deoxyribonucleic acid using maternal plasma[52] may prove useful in the development of precision GDM medicine. This would also facilitate identification of fetal carrier status for pregnant women with MDM, potentially aiding management decisions.

With T1D, there is substantial heterogeneity in age, presence and type of islet autoantibodies, and genetic risk in those who transition to clinical (stage 3) disease, impacting diagnosis and prediction. Critical gaps remain in both non-European ancestry and adult-onset groups. Although improved glycemic control has aided in the reduction of proportion and impact of complications of T1D, evidence suggests that not all groups benefit from tight glycemic control, in part due to the risks associated with hypoglycemia. For T1D, the most promising areas for immediate clinical implementation include genetic risk classification, screening for islet autoantibodies (particularly at an early age and, potentially, later in life) and the ability to detect those at risk of progression, thereby affording the opportunity to utilize an immune intervention to delay or prevent progression to stage 3 T1D, recognizing that such therapies must also be cost-effective. Continued development of pharmacologic agents and technologies to minimize risk of microvascular and macrovascular complications in those living with T1D remains essential. Further, the availability of an effective and cost-effective disease-modifying intervention for early detection and prevention in those at risk, with use of better therapeutics, and recommendations for control of microvascular and macrovascular complications is essential in those living with T1D.

As with many other areas of precision diabetes medicine, much of the evidence for T2D precision medicine is of weak quality, focusing mainly on populations of European ancestry, and with a dearth of adequate validation. Papers reporting studies on precision medicine in T2D that claim translational potential often lack key metrics to allow benchmarking against current standards of care such as measures of predictive accuracy and cost-effective analyses. There is also a need for prospectively designed precision medicine trails that focus on validating key hypotheses pertaining to, for example, a stratified treatment response.

Road map and milestones for global precision medicine in diabetes

Recommendations, derived from the systematic reviews underpinning this consensus report and through two in-person consensus meetings, are shown in Table 1.

Reporting precision medicine research

Barriers to determining the clinical relevance of published research for precision diabetes medicine are that published reports rarely provide key details regarding a priori hypotheses, statistical tests for heterogeneity, number of events observed, statistical power to evaluate interactions, and more. Often these metrics are unclear, leading to misinterpretation of results. This has been the case with some of the diabetes subtyping that relies on hard clustering methods, where the individual-level probabilities of a person having a specific diabetes subtype are often low, such that treating a person based on their 'subtype' would often be ineffective. Nevertheless, much of the popular narrative has focused on using this type of subtyping to transform individual-level treatment.

Information that should be described in precision medicine research publications, particularly when citing evidence said to be of relevance for clinical translation, includes:

(1) Measures of discriminative or predictive accuracy and calibration accuracy (both ideally in independent datasets) of precision medicine models
(2) Measures of variance and central tendency
(3) Effect estimates and risk ratios with 95% confidence intervals (not merely P values)
(4) The units underlying effect estimates and risk ratios (for example, mmol/allele or risk/allele)
(5) For unsupervised clustering, classification probabilities (for example, relative entropy statistic)

The use of machine learning and deep learning is becoming increasingly popular in preci-

sion medicine-facing research. However, as population-specific features (including prevalence of diabetes, risk factors and cultural and lifestyle features) are important in determination of diagnosis, treatment and prognosis, these algorithms need to be tailored to the community being served. In addition, it is often not possible to determine how outputs from such models were derived, which may increase the risk of misinterpretation or inadequate understanding of the potential risks associated with deployment of algorithms in clinical practice. Thus, methods to interpret and validate results from machine-/deep-learning models are likely needed for the safe and meaningful translation of precision medicine research into clinical practice.

Regulatory requirements

The successful deployment of precision medicine may require regulatory bodies to adopt new approaches for product approval. This will entail new guidance about the processes for obtaining approval to commercialize new therapeutics and diagnostics, including when and under what circumstances the use of a new drug must be preceded by and/or accompanied by a diagnostic or screening test. If the healthcare system is to secure the full benefits of precision medicine, it must provide full and fair reimbursement for new technologies, products and services, based on market principles to the extent possible.

Diagnostics include clinical decision-support software. In 2022, the FDA provided updated guidance on the regulation of this type of software[53], which distinguishes between nondevice clinical decision-support software and software as a medical device with more stringent regulatory requirements. Software as a medical device is intended to provide high-level clinical decision-support software, have direct impacts on patient care and typically requires FDA clearance or approval before it can be marketed. On the other hand, nondevice clinical decision-support software does not require clearance; applying the criteria to distinguish between the two can be challenging. A new risk-prediction tool for CVD in people with T2D developed using machine learning in a large electronic health record dataset could qualify as either software as a medical device or nondevice clinical decision-support software. The tool may guide clinical decision-making, which would qualify more as a nondevice clinical decision-support software, but also has the potential to impact patient care by assisting in making treatment decisions for people at risk of developing CVD. If a risk score is considered nondevice clinical decision-support software, it will not require FDA clearance or approval, making the process of bringing it to market easier and faster. However, if it is considered software as a medical device, the regulatory requirements will be more stringent and the development process will likely be more costly and time consuming. Making a clear distinction between nondevice clinical decision-support software and software as a medical device is crucial for precision medicine, as the development and implementation of biomarkers, risk scores and other precision tools rely on the interpretation of the FDA guidance.

Meeting standards of care

Diabetes is a multifaceted disease that is impacted by broad societal issues and has ramifications beyond the affected individual. Consequently, healthcare systems face significant challenges in providing effective and equitable care. While precision medicine promises to provide more personalized care for people at risk of and with diabetes, it requires effective implementation in healthcare systems to enhance disease prevention, management and prognosis. However, healthcare systems are currently struggling to provide care following current practice guidelines in diabetes. Gaps in adherence to current standards of care, which incorporate relatively simplistic personalized approaches, highlight the need for research to understand strategies for deploying precision medicine. While this may introduce additional levels of complexity if poorly managed, precision medicine may reduce complexity by improving or replacing suboptimally functioning processes and improving cost-effectiveness. Nevertheless, healthcare service optimization through precision medicine remains an understudied topic and represents an area in need of investment.

Commercialization versus access

The commercialization of precision medicine through direct-to-consumer platforms or products for diabetes often involves complex trade-offs. Companies investing in precision diabetes medicine need to protect their intellectual property with patents to prevent infringement. However, this can lead to high costs for recipi-

ents, potentially widening healthcare disparities. In addition, companies must ensure the financial viability of their products to continue research and development, which may lead to pricing barriers that restrict access for those most in need. To balance commercialization and accessibility, companies may need to make their products more affordable and accessible through partnerships with healthcare providers, insurers and government funding. Workflow complexity within the clinical environment is a barrier to commercialization; embedding precision medicine decision-support systems within the electronic medical record system may improve adoption by clinicians, but there may be additional proprietary considerations such as the electric medical system record vendor requiring a share of the profits. Ultimately, achieving a balance between commercialization and accessibility is crucial, considering the ethical, social and economic implications of precision diabetes medicine approaches. The balance point will vary depending on the sociocultural setting where the product or service is deployed.

Health equity and mitigating disparities

Precision medicine has the potential to improve health equity if the solutions it provides are optimized to the target populations, accessible to those in need, cost-effective and safe. Precision medicine solutions developed in one population may not transfer adequately to another[54]. Moreover, developing such solutions will require high-quality data for the target populations, as imprecise data are likely to obstruct the development of precision medicine. This is true of many technologies[55] and data of relevance to precision medicine. For example, at present, most genetic data and other omics data used in genome-wide studies of diabetes come from people of European ancestry living in high-income countries[56], yet the burden of diabetes is growing most quickly in other regions and ethnicities[41].

Although genomic medicine is an important component of precision medicine and is relatively easy to deploy owing to the robustness of deoxyribonucleic acid samples and the stability of a person's germline genetic variation across the life course[57], overreliance on this single technology may contribute to inequities in health. This is because not all diabetes subtypes are equally heritable or understood[58]. This may be especially problematic in non-European ancestry populations, where genomics research is less advanced.

The systematic evidence reviews conducted as part of this report reinforce the need for increased ethnic, geographic and sociodemographic diversity in precision medicine research. Nevertheless, there are major genomic and precision medicine initiatives underway in some regions of Asia[59], Africa[60] and the Middle East that will help offset this imbalance. On the other hand, most low- and middle-income countries currently lack adequately resourced and structured efforts to generate such data, despite a compelling rationale to develop precision medicine solutions for these populations. Thus, a key marker of the success of precision diabetes medicine will be its accessibility and cost-effectiveness where it is most needed; given that the burden of diabetes is growing most rapidly in the global south, the development and implementation of precision diabetes medicine in these regions should be prioritized.

Liabilities

A precision medicine approach for diabetes should also consider potential liabilities. Liabilities could relate to both underutilizing recommendations, for example with an omission to assess for MDM in a person with a high-risk score, or potentially restricting access to certain treatments if underpowered subgroup analyses suggest limited utility. As precision medicine approaches should apply to all individuals at risk of, or living with, diabetes, the global implementation of these approaches will need to be shown as economically beneficial to the global community, a task that could be difficult in countries with historically limited resources allocated to healthcare. Further consideration of potential liability remains an area for ongoing evaluation.

Future research priorities

Key future research priorities include (1) meta-analyses of existing clinical trials using individual-level data to ensure adequate power and re-analysis of existing trials with attention placed on determining treatment effect heterogeneity, (2) novel clinical trial designs to test a priori hypotheses regarding treatment heterogeneity, particularly those with two or more active comparators to inform clinically relevant decisions, (3) discovery and evaluation of novel genetic and nonstandard biomarkers and (4) integration of combinations of clinically accessible features to

enhance prediction of response and selection of optimal therapies.

Summary

Precision diabetes medicine is currently largely aspirational. Nevertheless, it is a potentially highly practical and economically viable alternative to current practices for diabetes prevention, diagnosis, treatment and prognostics, encompassing wide-ranging data about exposures and outcomes. In this second international consensus report, we summarize findings of 15 systematic reviews and expert opinions in prioritized areas of precision diabetes medicine. This effort was wide-reaching and multifaceted, yet of necessity not entirely comprehensive given the enormity of the diabetes field. The results show clear progress in the implementation of precision diabetes medicine, while illuminating many knowledge gaps. This review highlights the importance of specific diagnoses, and how etiological complexity and diagnostic uncertainty must be appropriately dealt with as part of this process. While precision diagnoses help determine treatment choices, there remains a great need for additional biomarkers and other signposts to guide precision prevention, therapeutics and prognostics. The dearth of data from non-European ancestry populations will need to be addressed to help ensure equity in precision diabetes medicine.

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Steck[122], Norbert Stefan [52,56,123], Julie Støy[124], Rachael Taylor[125], Sok Cin Tye[126,127], Gebresilasea Gendisha Ukke[61], Marzhan Urazbayeva[65,128], Bart Van der Schueren[107,129], Camille Vatier[130,131], John M. Wentworth[132,133,134], Wesley Hannah[135,136], Sara L. White[77,137], Gechang Yu[38,62], Yingchai Zhang[38,62], Shao J. Zhou[89,138], Jacques Beltrand[139,140], Michel Polak[139,140], Ingvild Aukrust[59,141], Elisa de Franco[12], Sarah E. Flanagan[12], Kristin A. Maloney [142], Andrew McGovern[12], Janne Molnes[59,141], Mariam Nakabuye[3], Pål Rasmus Njølstad [59,60], Hugo Pomares-Millan[6,143], Michele Provenzano[144], Cécile Saint-Martin[145], Cuilin Zhang[146,147], Yeyi Zhu[148,149], Sungyoung Auh[150], Russell de Souza[102,151], Andrea J. Fawcett[152,153], Chandra Gruber[154], Eskedar Getie Mekonnen[155,156], Emily Mixter[157], Diana Sherifali[102,158], Robert H. Eckel[159,] John J. Nolan[160,161], Louis H. Philipson[157], Rebecca J. Brown[150,196], Liana K. 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Feature

Why Heat Waves Kill: A Deep Dive into the Deadly Pathophysiology of Extreme Heat

The summer of 2023 & 2024 has been marked by unprecedented heat waves across the globe, leaving a trail of devastation in their wake.

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From the scorching streets of Phoenix, Arizona, where temperatures soared to a record-breaking 118°F (48°C), to the sweltering cities of Europe, where thousands succumbed to heat-related illnesses, the impact of rising temperatures on human health is undeniable.

In India, a prolonged heat wave claimed the lives of over thousands of people, while in China, emergency services struggled to cope with the influx of heatstroke victims. These incidents are a stark reminder of the growing threat posed by extreme heat, a phenomenon exacerbated by climate change.

The Silent Killer: Heatstroke

While heatstroke remains the most widely recognized and feared consequence of extreme heat, it represents merely the tip of a physiological iceberg. Characterized by a core body temperature exceeding 104°F (40°C), heatstroke is a medical emergency with a high mortality rate. Its symptoms include altered mental status, seizures, coma, and ultimately, multi-organ failure.

At the cellular level, heat stress disrupts protein homeostasis, leading to protein misfolding and aggregation. This impairs cellular function and can trigger apoptosis, or programmed cell death. Heat stress also damages mitochondria, the powerhouses of the cell, leading to energy depletion and further cellular dysfunction. Additionally, heat stress induces oxidative stress, a state of imbalance between reactive oxygen species and antioxidant defenses, which can damage cellular components and exacerbate inflammation.

The central nervous system is particularly vulnerable to heat-induced damage. Neuronal dysfunction and apoptosis can lead to neurological sequelae, including encephalopathy, seizures, and coma. The cardiovascular system also suffers under heat stress, as the body struggles to maintain adequate perfusion to vital organs while simultaneously diverting blood to the skin for cooling. This hemodynamic challenge, coupled with dehydration-induced hemoconcentration, can precipitate myocardial ischemia, arrhythmias, and acute heart failure.

Beyond Heatstroke: A Spectrum of Heat-Related Illness

While heatstroke is the most severe manifestation of heat-related illness, it is crucial to recognize the broad spectrum of conditions that can arise from heat stress. Heat cramps, often affecting skeletal muscles, are thought to arise from electrolyte imbalances due to excessive sweating. Heat exhaustion, a more severe condition, presents with fatigue, dizziness, headache, nausea, and vomiting, and can progress to heatstroke if left untreated.

Beyond these acute conditions, heat stress can also exacerbate chronic diseases. Individuals with pre-existing cardiovascular, respiratory, or renal disease are at increased risk of complications and mortality during heat waves. Heat can worsen heart failure, trigger asthma exacerbations, and accelerate the progression of chronic kidney disease. Moreover, certain medications, such as diuretics and anticholinergics, can impair the body's ability to thermoregulate, increasing vulnerability to heat stress.

Vulnerable Populations: The Young, Old, and Marginalized

While everyone is susceptible to heat-related illness, certain populations are particularly vulnerable. The elderly, with their diminished physiological reserves and often compromised thermoregulatory function, are at heightened

risk. Young children, who have a larger surface area-to-body mass ratio and are less able to regulate their body temperature, are also more susceptible.

Socioeconomic factors also play a significant role in vulnerability. Individuals living in poverty, particularly those without access to air conditioning, are at increased risk. Additionally, outdoor workers, homeless individuals, and those with limited access to healthcare are disproportionately affected by heat waves.

Evidence-Based Medicine: Guiding Clinical Practice

The scientific literature provides a compelling body of evidence linking heat waves to increased morbidity and mortality. A 2021 study published in The *Lancet* found an 85% increase in heat-related deaths among individuals over 65 years of age between 2000-2004 and 2017-2021. Another study, published in *Nature Medicine* in 2023, estimated that over 61,000 excess deaths occurred in Europe during the summer of 2022 alone. These studies, along with numerous others, underscore the urgent need for clinicians to adopt evidence-based practices for the prevention, diagnosis, and management of heat-related illnesses.

At the cellular level, heat stress disrupts protein homeostasis, leading to protein misfolding and aggregation. This impairs cellular function and can trigger apoptosis, or programmed cell death.

Early recognition of heat stress is paramount, as prompt intervention can significantly improve outcomes. Clinicians should be vigilant for the signs and symptoms of heat-related illness, particularly in vulnerable populations. Treatment focuses on rapid cooling, rehydration, and electrolyte replacement, as well as management of any organ-specific complications.

Prevention and Mitigation: A Multi-Pronged Approach

Preventing heat-related illness requires a multi-pronged approach that encompasses individual, community, and public health measures. Clinicians should educate patients about the importance of hydration, avoiding strenuous activity during peak heat hours, and recognizing the early warning signs of heat illness. Community-based interventions, such as cooling centers and public awareness campaigns, can help protect vulnerable populations, including the elderly, children, and those with chronic medical conditions.

Public health initiatives, such as heat wave early warning systems, urban planning strategies to reduce the urban heat island effect, and investments in climate change mitigation, are essential for safeguarding public health in the face of rising global temperatures.

Conclusion

The escalating threat of heat waves, fueled by climate change, demands a concerted effort from the medical community to understand the complex pathophysiology of heat-related illnesses and develop effective strategies for prevention and mitigation. By remaining vigilant, educating ourselves and our patients, and advocating for evidence-based policies, we can help protect vulnerable populations and mitigate the devastating impact of extreme heat on human health. The time for action is now.

Dr Drew Weissman

Interview By **Priya Menon**

"mRNA is going to be turning point in medicine"

Drew Weissman, Nobel laureate shared his journey to creating the mRNA vaccine technology

Photo by Peggy Peterson/Courtesy of Penn Medicine

Dr Drew Weissman had dreamed about the seemingly endless possibilities of treating diseases with custom-made mRNA. However, he didn't expect the mRNA technology he co-created with former colleague Katalin (Kati) Karikó to become critical to some of the Covid-19 mRNA-based vaccines and win them a Nobel Prize.

In an interaction done in the midst of the pandemic, Weissman shared the science behind mRNA and his journey to creating the mRNA vaccine technology that is a critical component of Pfizer-BioNTech's and Moderna's mRNA-based Covid-19 vaccines and others being developed globally. Excerpts:

Before we discuss the vaccines, could you shed some light on what is the role of mRNA and DNA?

Sure. The way our cell and our body works is that our DNA contains all of our genetic information. Every protein in our body is coded for in the DNA. The way the body makes a protein from that DNA is that it uses an mRNA—a messenger RNA. So, an enzyme copies protein off the DNA, the mRNA then travels to a machine called a ribosome. But it is essentially a machine that can read the code in the mRNA and turn that into a protein. So, it is kind of a middleman. It is in between the DNA and the protein. It is responsible for making proteins in a cell. So, the way the mRNA vaccine works is that we encode the spike protein from coronavirus as an mRNA. We give it to a cell and the ribosomes; the cell machines read the mRNA and produce the spike protein. The body then recognises that spike protein as foreign and makes an immune response against it.

You have been working on the mRNA vaccine for a few years. Could you give us a little bit of history of the vaccine journey?

I came to UPenn 23 years ago and met Kati Karikó at a copy machine. I have studied vaccines and she studied mRNA but wasn't getting very far and nobody in the mRNA field was advancing. So, we started to investigate mRNA in the immune system, and we figured out that mRNA was highly inflammatory and that was problematic. Because if you give mRNA to a patient, you don't want to get sick from it. So, we figured out what made it so inflammatory and then we figured out how to avoid that inflammation and that was our breakthrough in 2005. It is called nucleoside modified mRNA. And what we essentially did was we changed the mRNA, so that the immune system in our bodies did not recognise it as foreign. And that is the mRNA that is used in the Moderna and Pfizer-BioNTech vaccines.

Do you think mRNA manipulation is a holy grail for other diseases as well?

I think the therapeutic platform has enormous potential. It has worked unbelievably well for Covid in the hands of two different companies. We are doing clinical trials for five more pathogens right now. BioNTech and Moderna are doing additional clinical trials. mRNA vaccines are in phase 2 clinical trials for cancer as personalised vaccines and have shown great success or better success so far. It has enormous potential and my guess is that it is going to be a turning point in medicine, but you will have to see.

Do you think mRNA vaccines have an advantage over other type of vaccines? If so, what are some of these that we are seeing for Covid-19?

The two mRNA vaccines from Moderna and Pfizer are the first ones licensed. So, this is the first comparison that we have got. It is hard to say whether they are better or have advantages [over other vaccines]. What we do know is one of their advantages is that they are incredibly quick to make. So, if you have to make an inactivated virus vaccine, that is a lot of work. You have to figure out how to grow the virus, how to inactivate it, how to purify it, how to make sure it is safe. With mRNA you only need the sequence of the protein of interest. So for coronavirus, that is the spike protein and we have known for over 20 years that the spike protein is the principal vaccine component. The

day that this sequence was released, we made an mRNA vaccine for it. So it is very quick. It is also very effective. We have seen that in the clinical trials and in the patients—[it had] 90-95 per cent efficacy against any symptoms and 100 per cent efficacy against serious symptoms and death. There are a lot of unknowns still and we will learn those over time.

Is there a difference in the antibody repertoire between mRNA-based vaccines and attenuated virus vaccines?

There are a couple of differences and this has not been investigated well yet. We have investigated in animal models and what we see is that mRNA vaccines give much higher levels. Even in the phase 3 trials, the level of antibodies in vaccinated people were about five times higher than convalescent patients. With other vaccines, the antidotes typically give a level similar to the convalescent patients. So the mRNA vaccines make higher levels of antibodies. As part of that, some of those antibodies neutralise the virus—kill the virus before it can infect a cell—those levels are also higher. We are looking at specificities. So, particular parts of the spike that the vaccines can recognise, and we have identified some that mRNA induces well, that infection doesn't induce and some of those are conserved antigens that may offer broad protection. Those are new and ongoing studies. In general, the mRNA vaccines are better than most other vaccines. They give higher levels of antibodies.

These vaccines are all against the spike protein and when we are using mRNA, you're using a discrete region of the spike protein versus the traditional method where you are using potentially a larger segment. So, are there regions of the spike protein, for instance, which are less subject to mutation, which would be better targets?

“In general, the mRNA vaccines are better than most other vaccines. They give higher levels of antibodies.”

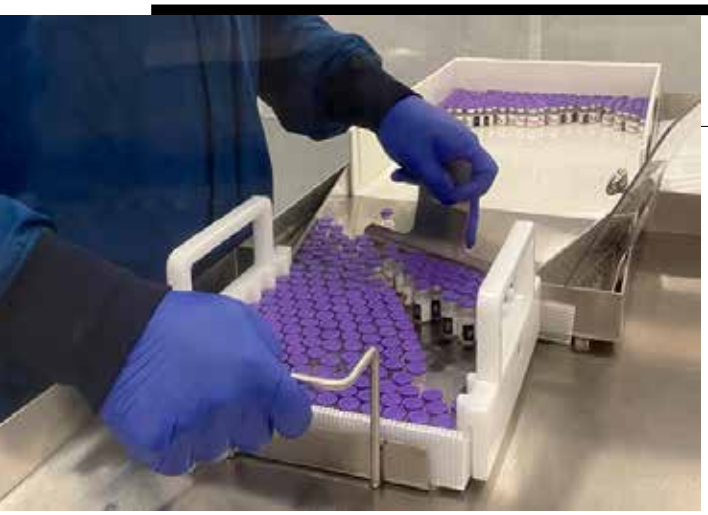
Another thing that my lab is doing is we have been working on a pan-coronavirus vaccine and what that means is that there have been three coronavirus epidemics in the past 20 years. It would be foolish to not think that we are going to have more. We are definitely going to have more coronavirus epidemics and potential pandemics in the future. What we started doing last summer is try to make a vaccine that would prevent or protect against any bad coronaviruses that have the potential to infect humans. The way we are doing that is we are looking at conserved regions of the entire virus as well as conserved regions of the spike protein, and we are trying to make vaccines that induce those responses. We had some success; we have made a vaccine that can prevent SARS, which was the first coronavirus we know about, and Covid-19 as well. So it looks like we have the potential to make a pan-coronavirus vaccine. But you are right—it is identifying the right immunogens, the right regions of the spike protein and the entire virus to use in a vaccine.

What do we know about the duration of action of the immune response?

Right now, Moderna and Pfizer-BioNTech are measuring antibody levels over time. We can predict that in a year, [vaccinated people] will probably be well protected, but we don't know if the vaccine is going to last a year, five years, 10 years. The other issue is that a vaccine does two things—it makes memory and it makes effector, which are active antibodies and T-cells. They are only measuring active antibodies in the blood. There are memory B cells that respond very quickly. And for all we know you could have zero antibodies in your blood. But if you have got good memory cells, you will make a response fast enough and you are completely protected. So, it is really going to be about following people over time and seeing when they start getting the disease again, and that will tell us when the vaccine needs to be boosted.

Why do we need multiple shots to make mRNA vaccines create more antibodies? Why is there a more pronounced reaction after multiple shots? And what is shown about delaying the booster dose?

Those are great questions, but we don't have answers to all of them. We have developed prob-



An employee at the Pfizer manufacturing facility in Kalamazoo, Michigan, during Covid-19

ably over 30 different vaccines using mRNA for everything, from Zika to Ebola to genital herpes, HIV, influenza, hepatitis C. Some of those vaccines work well with a single injection, others require multiple. If you look at the phase 3 trials, both the Moderna and the Pfizer vaccines are 80 per cent effective after a single [dose]. What we don't know and what the concern was was that how durable that response is and that gets into basic immunology. And in basic immunology, the first time you see a pathogen or an antigen, the response is limited and it is usually not very potent and the immune system requires a boost, a second vision of that pathogen to make a better response. And that is why most vaccines are given two, three, four times to boost and to improve the response. We see the same thing with mRNA, the level of antibodies goes up about 10 to 20-fold when somebody gets a booster. And that is why you go from 80 per cent to 95 per cent protection. We are now investigating the effect on longevity. Nobody or very few people got a single vaccine with the mRNA. So, it is going to be hard to know [whether] one vaccine dose will give you years of protection. But people wanted 95 per cent protection and good durability and that is why they get two doses.

What about booster dose side-effects? I felt a little lousy, a couple friends of mine felt terrible. Some others were very sick. Is there any data on these second dose side-effects? Or, is this just a case of immune systems being funny and individualised?

If you look at the side effects, 80 to 90 per cent of people get sore arms, swelling at the site and a smaller percentage gets systemic effects. This is telling us that the vaccines are working. This is the immune system responding to the vaccine. It has nothing to do with manufacturing. It has nothing to do with contaminants or any other problems with the vaccine. They appear to be purely our immune system responding. In my mind, it is a good thing if you have an adverse event because it means the vaccine is doing its job. Having said that, we are working on newer vaccines that have fewer of these adverse events, so that the vaccine is better tolerated.

My friend has some familiar arthritis in his carpometacarpal joints, at the base of his thumb. And he seemed to have gotten some severe arthritic flare-ups within 12 hours of his second shot. Is this the sort of thing that you might expect when the immune system gets amped up from that second/booster shot?

Yeah, we just don't know. I mean look at the vaccines in the phase 3 clinical trials. People with arthritis and autoimmune diseases weren't included in those trials. There is no scientific evidence from any animal studies or earlier human trials that the vaccines will cause a flare up in an autoimmune disease. But that's not to say it may not happen when your immune system is amped up... there is a potential that it will recognise other antigens, autoantigens that it regularly recognises. So this is something that needs to be studied.

As far as we know at this point, are mRNA vaccines less effective on cancer patients or even more specifically blood cancer patients?

Certainly, for anybody with an impaired immune system, the vaccine is not going to work as well. If anybody has had their B-cells depleted with CD19 antibodies or CD19 Car T's, they are not expected to make much of an antibody response. They will still make some T-cell response which offers some protection. We don't have good data yet, but the more immunosuppressed the person is, the less well they are going to respond to a vaccine.

How effective do you think mRNA vaccines would be against newer variants of Covid-19?

What we know so far is that the mRNA vaccines still appear to be effective against all other variants so far. What we don't know is what is going to show up in the future.... So, the concern is that in the future a variant might appear that the vaccine is completely useless against. For mRNA vaccines, it is very simple to make an update—a booster and improvement. I was talking to the person who runs BioNTech who said it would take them six weeks to have a new vaccine in a patient's arms. So mRNA allows you to very quickly update vaccines, which I suspect will be important as new variants appear.

Priya Menon produces and hosts CureTalks, an internet talk show on health care. She works as Vice President, TrialX, a clinical trial solutions company headquartered in New York.

The Dark Web: A Case Report

The inferior vena cava outflow membrane is an unusual, but a potentially treatable cause. We present a case of 4 year old child with IVC membranous web causing venous outflow obstruction and successfully managed with endovascular technique.

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Keywords:
IVC WEB, BUDD CHIARI SYNDROME

ABSTRACT

Budd-Chiari syndrome is defined as a hepatic venous outflow track obstruction of various aetiology, which appears at different levels. The inferior vena cava outflow membrane is an unusual, but a potentially treatable cause. We present a case of 4 year old child with IVC membranous web causing venous outflow obstruction and successfully managed with endovascular technique. The percutaneous treatment has emerged as a very promising management mode for such patients. Follow-up results are favourable for balloon angioplasty and/or stenting, with minimal restenosis rates.

INTRODUCTION

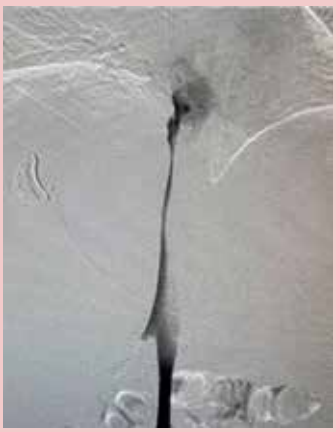
Membranous obstruction of inferior vena cava is one of the causes of Budd-Chiari Syndrome (BCS). These membranes are thought to be a congenital abnormality, but they are more frequently acquired . Inferior Vena Cava (IVC) obstruction is more common in Asian male population, and in western countries BCS is found mostly in women and its predominant cause is hepatic vein obstruction .This syndrome encompasses various hepatic venous outflow blocks, one of which is membranous obstruction of the IVC. In contrast to hepatic vein thrombosis, formation of a membrane may be an outcome of recurrent thrombosis . BCS has been shown by the literature to be associated with pro-thrombotic states .

Diagnosis can be established by clinical examination, Doppler ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and venography.

Obstructive membrane was predominantly treated through surgery but percutaneous transluminal balloon angioplasty is an alternative and effective form of treatment .Balloon dilatation, with or without stenting of hepatic veins and/or IVC has been reported earlier by various authors . Percutaneous transluminal angioplasty for a complete membranous obstruction of the suprahepatic inferior vena cava is safe and effective, and the long-term results are excellent.

CASE REPORT

4 year old child presented to our Paediatric Gastroenterology department with complaints of abdominal distension and mildly altered liver function tests. This boy had a week's



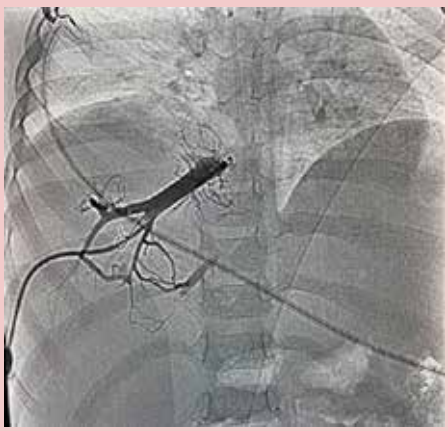


Figure 1. Cavogram from IJV access showing narrowed intrahepatic IVC.

Figure 2. Percutaneous access of RHV and venogram showing sudden cut off at RHV - IVC junction S/o a web

history of abdominal distension without any history of abdominal pain, jaundice, bruising, or acholic stools. No relevant past history. Birth history was uneventful. Parents or elder sibling did not have any relevant medical history.

On examination the boy had abdominal distention with dilated cutaneous veins, hepatomegaly, and ascites:

Laboratory tests revealed minimally abnormal liver enzymes with Bilirubin at 2,SGOT 90, SGPT 124 and INR -1.5. Ultrasound done from outside revealed mild ascites and CT abdomen had shown some parenchymal changes with poor visualization of the hepatic veins.. The patient was referred to Interventional Radiology department suspecting a venous outflow obstruction. A review of the CT showed hepatomegaly with heterogeneous enhancement, giving an appearance of nutmeg liver.The caudate lobe appeared hypertrophied, narrowing the inferior venacava. There was moderate ascites. A repeat USG Doppler of the liver revealed hepatomegaly with normal but sluggish hepatopetal flow. The right hepatic vein showed dampened flow with multiple small collaterals. A diagnosis of Budd-Chiari syndrome was made and endovascular intervention was offered.

Venography via a transjugular approach, showed a paucity of hepatic veins. Percutaneous transhepatic access confirmed patent hepatic veins with central occlusion due to web with intrahepatic collateral vessel formation.

A guidewire was then manipulated through the hepatic vein occlusion and advanced successfully to the IVC and the right jugular vein using a snare technique. Balloon angioplasty of the occlusion with 8- and 10-mm balloons re-established flow.

There was no procedural or late complication. The patient recovered very well, and a permanent anticoagulation therapy with warfarin was introduced. The first follow-up was done three months afterwards. Clinically, the patient felt well, there was no evidence of ascites or peripheral edema. A reduction of collaterals, and only a discrete hepatomegaly was found. A permanent anticoagulation therapy was recommended to the patient and at the 12-month follow up, he was without any problems

DISCUSSION

BCS is defined as a hepatic venous outflow track obstruction at any level: from small hepatic veins to right atrium-IVC junction, regardless of the cause of obstruction .Membrane-like obstruction commonly found in angiography, consist of organized old thrombus, arranged in layers of different ages. The clinical onset is mild and causes liver damage by congestion, as was the case in our patient. A distinct pattern of subcutaneous venous collaterals typically develops together with retroperitoneal collaterals through the ascending lumbar and the iliolumbar veins into the hemiazygos and azygos veins.

The best imaging methods for establishing the diagnosis, are the ultrasound, CT and MRI. Once the diagnosis is established, IVC venography is needed to guide the endovascular techniques. In our patient, the USG abdomen was first misleading, and CT was the key diagnostic tool. In BCS with membranous obstruction of IVC, balloon dilatation with or without stenting should be the treatment of choice with an expected good long-term result. The intervention was chosen as the best therapeutic option in our patient's case. In the absence of any communication through the membrane, a technique similar to trans-septal puncture was applied

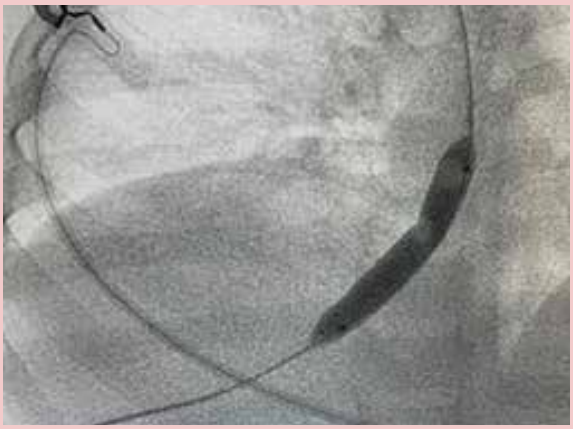


Figure 3. Using a Terumo wire broke the web and was able to navigate the wire into the IVC , then snared the wire into the IJV access.

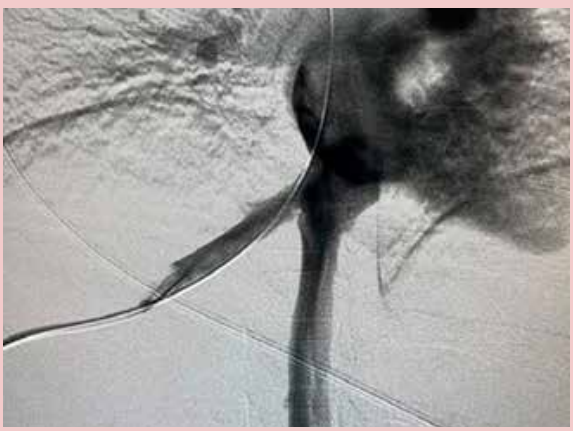


Figure 4. Post plasty venogram showed brisk flow in the hepatic vein.

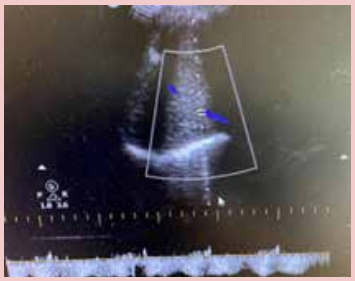


Figure 5. Post procedure doppler

Figure 6. Post procedure doppler showed good flow. after 6 weeks showing good flow.

CONCLUSION

Balloon angioplasty is effective in relieving IVC obstruction with minimal morbidity. Stents should be used whenever there is a residual obstruction or restenosis after balloon angioplasty. Follow-up results are favourable in both balloon angioplasty and/or stenting

Early diagnosis and prompt treatment of IVC web with normalization of hepatic venous outflow will prevent the patient from developing cirrhosis and thereby can avoid the need for future liver transplantation.

Current Practice: The recanalization of a short-segment occluded hepatic vein or the IVC may result in the restoration of the splanchnic and hepatic blood flow and lead to a clinical improvement. In the absence of cirrhosis, the procedure may be potentially curative.

In patients with IVC webs, an angioplasty resulted in one-year primary and long-term secondary patency rates of >90% .In hepatic vein web BCS, primary one-year and secondary long-term patency rates were 78% and 84%, respectively .Complications were rare, appeared predominantly after a transhepatic access, and consisted of intraperitoneal bleeding (2%) and pulmonary embolisms .

As of now the main stay of treatment for IVC web is minimally invasive endovascular recanalisation of IVC

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Case Report

Clinical Research Methodology Series Paper 2: Research Designs

The second paper in the clinical research methodology series focuses on understanding different study designs used in clinical research. The paper provides an overview of how different study designs are derived in clinical research and what a researcher should know before conducting clinical research with the evidence-based questionnaire.

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Keywords:
Study design, observational studies, prospective studies, retrospective studies.

ABSTRACT

The second paper in the clinical research methodology series focuses on understanding different study designs used in clinical research. The paper provides an overview of how different study designs are derived in clinical research and what a researcher should know before conducting clinical research with the evidence-based questionnaire. Study designs are crucial depending on the condition studied, and this paper provides insight into the standard study designs.

INTRODUCTION

Clinical research has various study designs, and this paper provides an overview of these in the clinical research methodology series. It addresses the obstacles the researcher faces in establishing suitable designs and how a researcher should focus their clinical research questions to decide their correct study designs. It is imperative, especially when submitting the project for approvals such as for Institutional Review Boards (IRB) or research funding; if the designs are incorrect, the study will be deemed invalid. This is often a problem with young clinical researchers, and this paper is aimed at a reader who is embarking on their careers during their early research days or at anyone who wishes to refresh their clinical research knowledge.

Studies are either experimental or observational; the easiest way is to look at what the investigators did about the exposures – specifically, whether they assigned exposure or not.

BASIC PRINCIPLES OF STUDY DESIGNS

Fig 1 shows the basic principles of study design[(1)]. The difference in study design is assigned to exposure. Observational studies do not involve any intervention or experiment. Experimental studies entail manipulating the study factor (exposure) and randomising subjects to treatment (exposure) groups.

There are biases in study designs; experimental studies have a lower potential for biases, while obser-

vational studies have a higher potential for biases. Evidence-based medicine categorises levels of evidence, which forms the basis for incorporating evidence into clinical practice. (2) The evidence pyramid in Fig 2 is built based on evidence quality levels. (3) the higher the study, the better the quality of evidence. Therefore, systematic review and meta-analysis are considered to have high levels of evidence, followed by control trials such as randomised control trials. The lower the hierarchy, such as case series, case- reports and expert reviews, are considered with lower quality of evidence.

RESEARCH QUESTION AND TYPE OF STUDY

When we ask a research question in clinical research, it is directed to the type of study.

1. Therapy: Questions of treatment to achieve some outcome may include drugs, surgical intervention, change in diet, counselling, etc.
2. Diagnosis: Questions of identification of a disorder in a patient presenting with specific symptoms. To know if the diagnostic tests are accurate.
3. Prognosis: Questions of the progression of a disease or the likelihood of a disease occurring.
4. Aetiology/ harm: Questions of negative impact from an intervention or an exposure.
5. Screening: Questions related to if early detection is possible.

Therefore, as we discussed in the first series, using the PICO format to ask a clinical question will help us categorise which type of study the question answers and relate to the study design.

There are numerous study designs(4), and some of the common terminologies of study designs are given in Table 1. We will consider some of the designs to understand here in paper 2, and others will be covered in detail in the upcoming series.

Table 1. Study design terms

a) Randomised controlled trial (RCT)	h) Nested case-control study
b) Nonrandomised comparative trial	i) Case-control study
c) Prospective cohort study	j) Interrupted time series (without a comparison group)
d) Retrospective cohort study	k) Before-after study
e) Interrupted time series with comparison group	l) Cross-sectional study
f) Controlled before-after study	m) Noncomparative study
g) Nonconcurrent cohort study	n) Other considerations: Meta-analysis of individual participant data Modeling Additional systematic review

RANDOMISED TRIALS

Study design advantage: A well-designed randomised control trial (RCT) produces the most convincing results and, if inclusion/ exclusion criteria and setting are realistic, should be reasonably generalisable.

Resources: An RCT has to be significant because the question compares active treatments, and the effect size may be small and easily swamped by other courses of mobility and mortality in any population. Duration depends on whether the trial focuses on peri-procedural complications and short-term outcomes or the long-term durability of different treatment options. In either case, the resource requirements will be large or very large, given the effect size between the treatments.

Ethical issues: as long as equipoise exists among the treatment options, ethical issues regarding enrolment should not be present. However, if the study includes patient recruitment issues, such as patients with dementia, consent issues may occur.

OBSERVATIONAL STUDIES

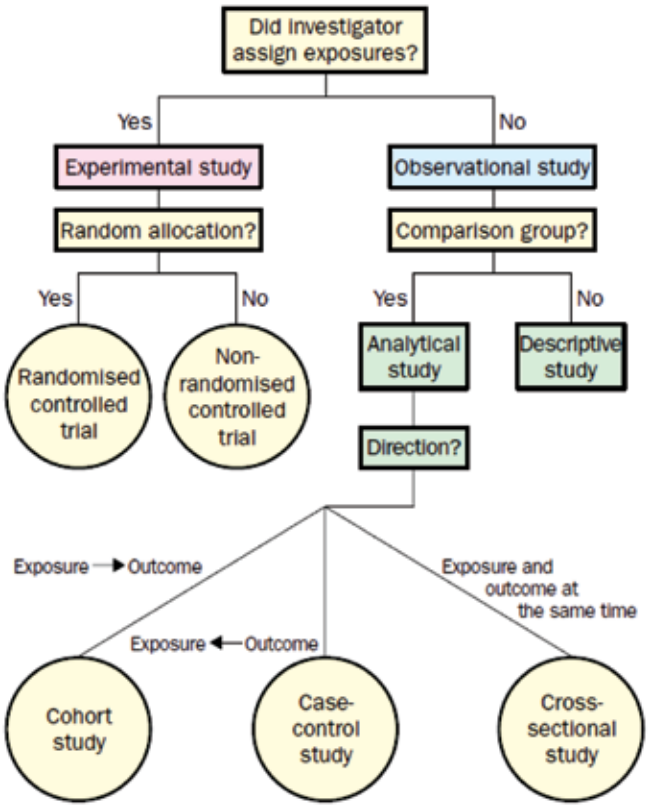
Observational studies dominate the literature. (5) As the name indicates, observational studies merely observe the patients in a non-controlled environment without interfering with or manipulating any study aspects. Observational studies can be grouped differently:

a. Exploratory studies are used when the knowledge about the phenomenon is poor: small scale, of limited duration. They aim to explore an unknown field.
b. Descriptive studies (often surveys) or statistical research describes data and characteristics about the population or phenomenon being studied. However, it does not answer questions about how/when/why the characteristics occurred, which is done under analytic research. Although the data description is factual, accurate and systematic, the research cannot describe what caused a situation. Thus, Descriptive research cannot be used to create a causal relationship where one variable affects another.
c. Analytical Studies were used to test hypotheses on a small/large scale. Examples: case-control, cross-sectional, cohort

Table 2. Qualitative versus Quantitative

Qualitative	Quantitative
Understanding	Prediction
Interview/observation	Survey/questionnaires
Discovering frameworks	Existing frameworks
Textual (words)	Numerical
Theory generating	Theory testing (experimental)
Quality of informant more important than sample size	The sample size is a core issue in the reliability of data
Subjective	Objective
Embedded knowledge	Public
Models of analysis: fidelity to text or words of interviewees	Model of analysis: parametric, nonparametric

Figure 1. Study design based on exposure.



The observation can be prospective, retrospective or current.[6] Depending on the direction of the observation, they are further grouped into cohort studies, case-control studies, and cross-sectional studies.

COHORT STUDIES

In a cohort study, an investigator defines a study population (cohort) of subjects free of the outcome of interest. This study design aims to determine which factors are associated with developing the outcome(s). Depending on the exposure status at the start of the study, subjects are classified as exposed or unexposed (controls). After that, subjects are followed over time to see who will develop the outcome and who will not. Relative risk is the measure of effect in a cohort study. Multiple outcomes can also be studied. [7]

It begins with a group of people who do not have the disease, takes baseline measurements, and then follows them over time to determine whether they use correlations to assess the absolute risk of subject contraction. A cohort is a group of people who share a common characteristic or experience within a defined period (e.g., are born, are exposed to a drug or vaccine or pollutant, or undergo a specific medical procedure). Thus, a group of people born on a day or in a particular period, say 2024, form a birth cohort. The comparison group may be the general population from which the cohort is drawn, or another cohort of persons thought to have had little or no exposure to the substance under investigation but otherwise similar. Alternatively, subgroups within the cohort may be compared with each other.

PROSPECTIVE COHORT STUDY

Study design advantage: Although concerns for selection bias and unmeasured confounders will always exist, the prospective design allows data for the most relevant known confounders to be collected and controlled. Therefore, while the results are not as definite as an RCT, they could be informative.

Resources: this type of study still requires a large size because of potentially small treatment effects, but it would likely be less expensive than an RCT.

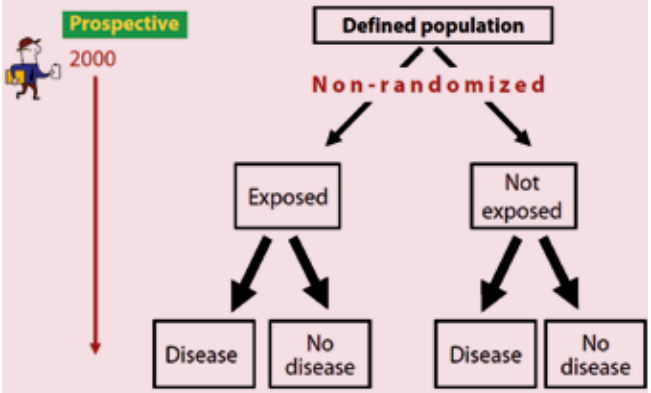
Ethical issues: The ethical issues are similar to those of RCTs when recruiting patients for a prospective cohort study.

RETROSPECTIVE COHORT STUDY

Study design advantage: There is a significant risk of selection bias, and there is less ability to control for confounders than in a prospective cohort study because key variables may not be collected. However, the design could be sufficient for hypothesis generation and could be used to design a more focused RCT.

Figure 2. Levels of evidence pyramid

Figure 3. Prospective Cohort study design



Ethical issues: Confidentiality and health insurance portability and account issues may arise when diverse databases are linked without specific patient consent.

CASE-CONTROL STUDIES

Study design advantage: Case-control studies determine the degree of association between various risk factors and outcomes. Here, the factors that affect the risk factors are the exposures. Case-control can identify beneficial and harmful risk factors. The two groups' cases and controls differ as follows: cases are patients who have a particular disease, condition, or disability. Controls are those patients who do not have the disease, condition, or disability. Typically, we identify appropriate controls for cases we study from the general population. Then, they retrospectively looked for the possible relationship between exposure and the studied risk factor.

Ethical issues: Due to the study's retrospective nature, case-control studies are subject to recall bias. Case-control studies are inexpensive, efficient, and often less time-consuming to conduct. They are also suitable for rare disease studies that have long latency intervals.[8]

CROSS-SECTIONAL STUDIES

Cross-sectional studies are observational in nature and give a snapshot of the study subject at a single point in time. They do not have to follow up time and, therefore, are easy to conduct. As the exposure status or outcome/disease status is often collected in a single moment by surveys, they cannot provide a cause-effect relationship, i.e., whether the exposure preceded or followed the disease, and they are the weakest observational study designs. This design is generally used to study the prevalence of a disease or condition in a population.[9]

QUALITATIVE STUDIES

Qualitative studies explore real problems without numerical data points; this type of research gathers participant's experiences, perceptions, and behaviours. The main differences between qualitative and quantitative are summarised in Table 2.

SYSTEMATIC REVIEWS AND META-ANALYSIS

These studies involve systematic literature searches to identify, appraise, and synthesize all relevant research. They should be conducted no matter the study design, and their justification is based on the scientific principle of replication and simple good academic practice. We will explore further systematic reviews and meta-analyses in the upcoming series.

CONSIDERATIONS FOR RESEARCHERS

There are standardised reporting guidelines to be followed when conducting any study. The equator network provides all reporting guidelines specific to each study design. The critical function of a study design is to enable the researchers to address the clinical research questionnaire with minimal ambiguity. Study design should be well thought out before initiating clinical research. Choosing an inappropriate study design may undermine overall study validity. Therefore, critical

Figure 4. Retrospective Cohort Study Design

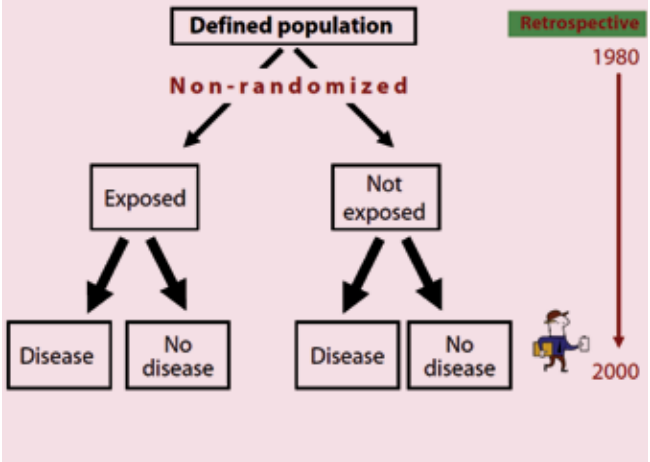
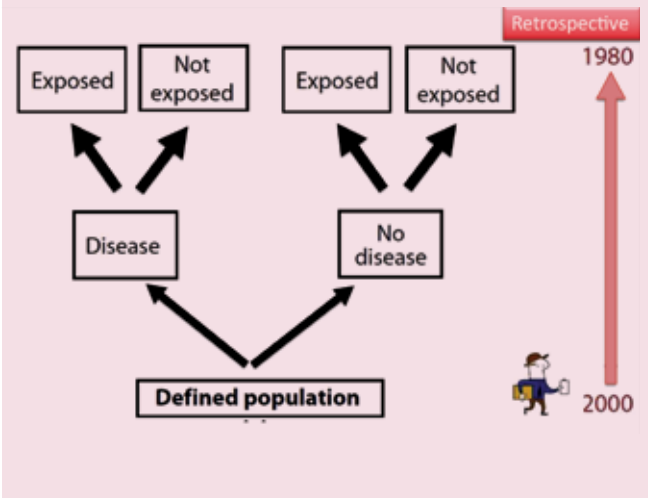


Figure 5. Case-control study



thinking about the possible study design will ensure the research question is answered appropriately. Study design plays a significant role in determining the scientific value of a clinical research study. Understanding the basic study design concepts will aid clinicians in practising evidence-based medicine. Errors in study designs are extremely difficult to correct, especially after study completion. A thorough planning is required to avoid weak conclusions or unconvincing results.

All healthcare professionals, including doctors, nurses, pharmacists, and clinical allied staff, should be well-versed in study design if they plan to do any clinical research.

CONCLUSION

Understanding evidence-based medicine and the study design will assist young clinical researchers and practitioners understand current clinical research study design. An elaborate understanding of key designs will be provided in the upcoming series. Failure to conduct research properly with faulty designs can negatively impact clinical decisions and patient outcomes.

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Neuromyelitis Optica Spectrum Disorder (NMOSD)

Neuromyelitis Optica Spectrum Disorders (NMOSD) represents recurrent autoimmune disease, generally beginning with optic nerve neuritis or acute transverse myelitis.

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ABSTRACT

Neuromyelitis Optica Spectrum Disorders (NMOSD) represents recurrent autoimmune disease, generally beginning with optic nerve neuritis or acute transverse myelitis. 2 cases of Neuromyelitis Optica have been diagnosed in the last 2 years at Aster Sanad hospital. I will present below one of the cases, stating medical history, diagnosis and treatment regimens.

CASE DESCRIPTION

A 41 years old previously healthy woman was seen in neuro clinic of Aster Sanad hospital – Riyadh with visual loss of 4 months duration associated with headache, neck pain, both upper limbs paresthesia of 2 weeks duration.

Neurological examination showed intact cranial nerves, neck rigidity, and vibration hypoesthesia in upper limbs, bilateral negative Babinski signs and normal muscle strength.

On ophthalmologic examination the patient was able to count fingers at three meters.

Ophthalmoscopic examination found pale optic disc's which indicated bilateral optic atrophy and Vital signs were normal.

INVESTIGATION

Routine work up including complete blood cell count, basic metabolic panel and rheumatology panel was normal. Immunology screening (including SLE) were negative.

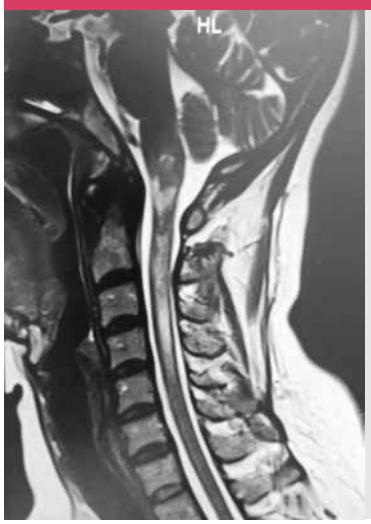
Resonance imaging (MRI) of the brain was unremarkable. Initial lumbar puncture revealed a CSF opening pressure of 140 mm h2o, with normal CSF chemistry and cellularity – oligoclonal band was negative.

Spinal Cord MRI: (figure 1) demonstrated longitudinal intra – medullary segment of t2 / stir hyperintence plaque within spinal cord is seen extending from medulla oblongata to c5 level with bright spot lesions, appears faintly hypointence on t1 weighted images, involving the central aspect and more obvious on the left side and causing mild expansion of the spinal cord, mild faint heterogeneous cloudy enhancement is noted post iv gadolinium administration.

DIAGNOSIS

The diagnosis of opticospinal variant NMOSD (Neuromyeltis Optica Spectrum Disorders) was made using ipnd diagnostic criteria (table 1).

Figure 1. Spinal Cord MRI



Spinal Contrast: enhancement MRI angiography showed no abnormalities.

Neuromyeltis Optica (NMO): aqp4 anti – bodies igg was positive (1: 20)

(Border line range – 1: 10)

Table 1. The 2015 International Panel forNMOSD Diagnostic Criteria forAdult Patients

Diagnostic criteria for NMOSD with AQP4-IgG
I. At least one core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses
Diagnostic criteria for nmosd without aqp4-IgG status
1. At least two core clinical charasteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
a) At least two core clinical charasteristics must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
b) Dissemination in space (two or more different core clinical characteristisc)
c) Fullfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclution of alternative diagnoses

TREATMENT:

The patient was started on intravenous methylprednisolone for 1 week, and changed to prednisone 1 mg /kg daily for one month, to be tapered over three to six months (with improvement of her neurological symptoms)

Treatment to prevent relapse (maintenance therapy) was with immunosuppressive drugs (rituximab = monoclonal anti – cd 20) with initial 1000 mg IV once, the repeat dose in 2 weeks, and then 500 mg IV every 6 months.

BACKGROUND

Neuromyeltis Optica Spectrum Disorder (NMOSD) is an autoimmune astrocytopathie disorder characterized by optic neuritis, transverse myelitis and brain stem lesions.

Autopsied case reports of Neuromyeltis Optica were first reported by Eugene Devic in 1894.

Discovery of aquaporin – 4 antibody, and distinct pathophysiological, clinical and MRI finding of NMOSD have led to it being recognized as a separate disease from multiple sclerosis.

Aquaporin – 4 antibodies is a specific biomarker for NMOSD and is considered as an additional criterion supporting the diagnosis.

Immunosuppressant drugs and immunotherapies are the treatment of choice for NMOSD with variable outcomes.

CONCLUSION

The case emphasizes the existence of Neuromyelitis Optica spectrum disorder in clinical settings of the developing world.

High index of suspicion of this rare disease required to avoid delayed diagnosis and treatment.

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Perforated Marginal Ulcer After OAGB Managed with Conversion to Roux-en-Y Gastric Bypass

This is a case of perforated marginal ulcer in a patient who's undergone one-anastomosis gastric bypass around 2 years prior to presentation, and the laparoscopic approach taken to revise the gastric bypass to Roux-en-Y configuration as a means of treatment.

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Keywords:
OAGB, marginal ulcer, revision gastric bypass, omental patch repair.

Abbreviations:
OAGB: One Anastomosis Gastric Bypass
RYGB: Roux-en-Y Gastric Bypass
NSAIDs: Non-steroidal anti-inflammatory drugs
PMU: Perforated Marginal Ulcer

ABSTRACT

Marginal ulcer is one of the most common complications following gastric bypass. Pathogenesis of PMU is not very well-understood. In this report, we describe a case of perforated marginal ulcer in a patient who's undergone one-anastomosis gastric bypass around 2 years prior to presentation, and the laparoscopic approach taken to revise the gastric bypass to Roux-en-Y configuration as a means of treatment, as well as discuss the previous literature describing the pathogenesis, presentation and management of perforated marginal ulcers.

INTRODUCTION

A marginal, or stomal, ulceration is defined as the development of mucosal erosion at the gastrojejunal anastomosis, typically occurring on the jejunal side.[1,2] Etiology of marginal ulcers is thought to be multifactorial, including exogenous & intrinsic, as well as technical, with smoking and use of NSAIDs regarded among the strongest offenders. Other risk factors include a large or dilated gastric pouch, suture erosion into the mucosa, alcohol use, steroid use, Helicobacter pylori, and chronic anticoagulation.[2,3]

A few mechanisms have been suggested to explain the pathogenesis of marginal ulcers.[2] It's postulated that smoking causes mucosal ischemia, NSAIDs causes mucosal damage, foreign bodies (sutures/staples) can erode through the mucosa and cause ulceration, and a high acid production from a large/dilated gastric pouch can affect the mucosal integrity of the jejunum, making it more susceptible to ulceration.

Presenting symptoms of marginal ulcers include abdominal pain, nausea, vomiting, hematemesis. The diagnostic test of choice is endoscopy. Treatment, involving PPI & sucralfate therapy, begins immediately after diagnosis.

However, intractable ulcers require surgical intervention. Revision of gastrojejunostomy & excision of ulcer have been described in the literature.

A perforated marginal ulcer is a surgical emergency and requires immediate intervention. Omental patch repair has been repeatedly described as an effective method of treatment.4 Here we describe a case of perforated marginal ulcer after OAGB, managed with 1-step revision to Roux-en-Y Gastric Bypass.

CASE REPORT

An 18-year-old male with a surgical history of OAGB in 2021, presented to the ER with complaints of abdominal pain and bilateral shoulder irritation. Further inquiries into the history revealed recent daily use of NSAIDs for pain management after hand orthopedic surgery.

Tests performed by the ER physician revealed a high leukocyte count, high C-reactive protein, free fluid in pelvis on ultrasound, and bilateral air under the diaphragm on erect abdominal x-ray.

Diagnosis of perforated viscus was made and patient was shifted to the operating room for an emergent Diagnostic Laparoscopy.

Upon arriving to the operating theatre, patient was assessed by the anesthesiologist, two 18G IV cannula were inserted to suitable peripheral veins with infusion of pre-warmed lactated Ringers' solutions as per infusion protocol. After 3-5 minutes of preoxygenation utilizing 80% O2, anesthesia was induced with 1% propofol 1–2 mg/kg IV, and IV fentanyl 1–1.5 µg/kg. Tracheal intubation was facilitated with rocuronium 0.6 mg/kg IV followed by insertion of 7.5, cuffed endotracheal tube (ETT).

Surgery revealed a perforated marginal ulcer on the anterior aspect of the gastrojejunostomy of the OAGB [Fig. 1], fibrin bands on the liver and parietal peritoneum covering the anterior abdominal wall. Turbid fluid was seen in the peri-splenic and peri-hepatic areas. A look into the pelvis showed a fluid collection in pelvic cavity.

Using PDS sutures, primary closure of the perforated marginal ulcer, with a plan for omentopexy, was tried. However, the suture cut through the margins of the ulcer and the classic primary closure could not be achieved [Fig. 2].

Decision was made to revise the OAGB to a Roux-en-Y Gastric Bypass; which comprised excising the site of the previous gastrojejunostomy, and thus the site of perforated marginal ulcer, using Purple EndoGIA linear staplers [Fig. 3], then creating a new gastrojejunostomy [Fig. 4], at the previous length of intestines from ligament of Trietz, and finally creating a jeju-jejunostomy, 75 cm away from the new gastrojejunostomy. With a resultant Roux-en-Y Gastric Bypass of a 150-cm biliary limb and a 75-cm alimentary limb, in which the gastrojejunostomy was created with a hand-sewn technique using 2 layers of PDS sutures, and the jeju-jejunostomy created with Gold EndoGIA linear stapler and 2 layers of PDS sutures to close the enterotomy. That was followed by closure of the mesenteric defect resulting from the creation of jeju-jejunostomy, defect was closed using Ethibond sutures.

Thorough irrigation and suction of the peritoneal cavity was done. Drain was placed, with a course tracking from the pelvic cavity to the site of the revised gastrojejunostomy.

When the laparoscope was withdrawn, 4 mg Ondansetron was given for prevention of postoperative nausea and vomiting and IV paracetamol 1 gm. Fentanyl boluses of (30 ug) was used if additional analgesia was required during the surgery. At the end of the surgical procedure, residual neuromuscular blockade was reversed with 100 mg IV Sugammadex, and the patient was extubated smoothly once met the criteria of extubation

Patient was shifted to the general ward after close monitoring for 2 hours in the post-operative recovery area. Patient was encouraged to mobilize on post-operative day #0. He was kept nil per mouth for 24 hours. On post-operative day #2, fluoroscopy image with gastrografin oral contrast was done, revealing no leak, drain was bringing sero-sanguineous fluid, and so clear liquid diet was started as tolerated.

Our patient was discharged in stable condition on post-operative day #4, on clear liquid diet and with drain still in-situ. He came for a follow-up in the outpatient clinic on post-operative day #6 for drain removal, and was advised to progress into a full-liquid diet, with a plan to gradually progress into normal diet over the course of 3 weeks.

DISCUSSION

Marginal ulcer is a recognized late complication of gastric bypass surgery[3,4,5], most occurring within 1 year of surgery.[1] Marginal ulcer is defined as an ulcer on the margins of the gastrojejunal anastomosis, most commonly on the jejunal side.[5] Incidence of marginal

Figure 1. Perforated marginal ulcer

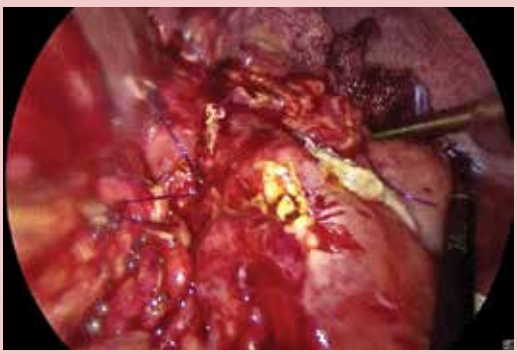

Figure 2. Sutures cutting through the ulcer

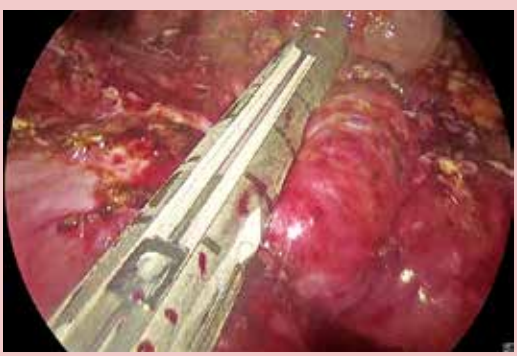

Figure 3. Resection of the marginal ulcer site

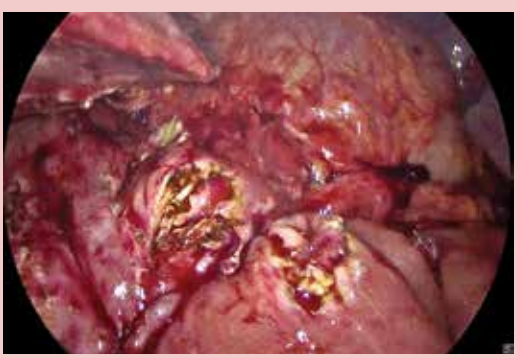

Figure 4. Enterotomies of gastrojejunostomy

ulcer following Roux-en-Y Gastric Bypass goes up to 16%,[4,6] with 1-1.1% of those developing perforation.[3,4]

Roux-en-Y Gastric Bypass and One-Anastomosis Gastric Bypass are the second and third, respectively, most commonly performed bariatric procedures performed worldwide.[3] Incidence of marginal ulcer following One-Anastomosis Gastric Bypass has been reported to be similar to that following Roux-en-Y Gastric Bypass;[3] however, Baksi et al. reported a higher incidence of asymptomatic marginal ulcer after One-Anastomosis Gastric Bypass, with a recommendation of a routine surveillance endoscopy at 1 year for detection & prevention of ulcer-related complications.[7]

Pathogenesis of marginal ulcer is not very well-understood, and is thought to be multifactorial, with tissue ischemia, staples (foreign bodies) and gastric acid, playing a role in the formation of a marginal ulcer. Risk factors include smoking, e-cigarettes, use of NSAIDs, aspirin, steroids, Helicobacter pylori infection, diabetes, and alcohol use, among others.[3]

A study done in Ohio State University concluded that patients should be educated regarding the risk factors of perforation, considering that prolonged PPI use may not be sufficient in preventing this complication in the presence of even one risk factor, specifically smoking, NSAID & steroid use.[4]

Most marginal ulcers respond to proton pump inhibitor therapy, however complicated ones warrant surgical intervention; namely, perforated, obstructing, bleeding and intractable marginal ulcers.[1,5] A perforated marginal ulcer after gastric bypass is a surgical emergency and requires surgical management.[1,3,5]

The Ohio State University study also concluded that omental patch repair of a perforated marginal ulcer was favorable to anastomotic revision in terms of operative time, blood loss and hospital stay.[4]

Moon *et al.* concluded that perforation of a marginal ulcer after Roux-en-Y Gastric Bypass can be effectively managed by oversewing the ulcer,[6] which could not be done in our case of perforated marginal ulcer following one-anastomosis gastric bypass.

Wang *et al.* presented a case of an obstructive marginal ulcer after Roux-en-Y Gastric Bypass managed with revision of anastomosis, following which the ulcer recurred and was complicated by perforation, which, accompanied by septic shock & severe malnutrition, mandated reversal of gastric bypass.[8]

A systematic review published in September 2022 identified 26 articles with a total of 610 patients, who'd suffered a perforated marginal ulcer after gastric bypass surgery. Majority of these patients (59%) underwent a laparoscopic omental patch repair of the perforation, while only 30% (4/13) of patients with perforated marginal ulcer after One-Anastomosis Gastric Bypass underwent a conversion to Roux-en-Y Gastric Bypass. Authors of the systematic review reported that their experience indicates a simple repair of the perforation with an omental patch, avoiding a complex surgery in a sick, septic patient.[7]

CONCLUSION

We presented a case of perforated marginal ulcer in an 18-year-old gentleman, with a surgical history of one-anastomosis gastric bypass, and recent use of NSAIDs. Diagnosis of perforated viscus was made after recognizing air under the diaphragm on an erect abdominal x-ray. Emergent diagnostic laparoscopy revealed a perforated marginal ulcer, for which primary closure was unsuccessful, and conversion of OAGB to RYGB was performed.

We conclude that management of a perforated marginal ulcer should be individualized, taking multiple patient factors into consideration, including operative findings of the size of the ulcer and nature of the tissue, as well as septic & nutritional status of the patient.

Our review of the literature also found a lack of insight into the benefits of eliminating bile reflux into the gastric pouch in cases of perforated marginal ulcer after OAGB, by converting the OAGB to RYGB. We also recommend that further studies should be conducted to determine the role of reversal of gastric bypass in the management of a perforated marginal ulcer.

Statements:

Ethical Approval: This case report was presented to & reviewed by the Ethical Committee, ethical clearance was provided to carry out the study.

Informed Consent & Written Informed Consent: consent & written informed consent for publication of the case details with any accompanying images was taken from the patient involved in this case report. Written consent will be made available to the Editor upon request.

Conflict of Interest Statement: The authors have no conflict of interest to declare.

Funding: This case report was not funded externally.

Author Contributions: Author 1 contributed to the acquisition, analysis and interpretation of the work; Authors 2 & 3 contributed to drafting the case report revising it critically for important intellectual content. All three authors agreed to be accountable for all aspects of the work. Author 1 provided the final approval of the version to be published.

Data Availability Statement: All data generated or analyzed during this case are included in this article. Further enquiries can be directed to the corresponding author.

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The Future of Precision Medicine in Diabetes Treatment

Ideal for clinical endocrinologists and other professionals involved in the management of diabetes and its complications, *Precision Medicine in Diabetes* is first of its kind to address this paradigm-shifting topic in a comprehensive way.

Precision Medicine in Diabetes: A Multidisciplinary Approach to an Emerging Paradigm

Editor:
Rita Basu

Publisher:
Springer Nature

Softcover ISBN:
978-3-030-98929-3

Bringing clarity to the emerging model of precision medicine within the diabetes field, and expanding upon how it will lead to the development of specifically tailored treatment for patients and even macro strategies in public health, this unique book explores the realm of biomarkers in the era of big data. Various experts in their respective areas discuss the current practice to illuminate how creating a more discreet profile of patients and even substratum of populations will lead to more refined therapies targeted towards the phenotype and genotype of the patient.

Embracing a multidisciplinary team science approach, this book demonstrates how precision medicine in diabetes can mine a web of data toward diabetes risk stratification and treatment options. The authors skillfully articulate how the construction of various prediction-based models can revolutionize clinical decision-making, and they examine the challenges and pitfalls of integrating disparate sources of information and how the collection of data and cooperation among stakeholders will be key to the future of precision medicine in diabetes treatment. Topics include personalized approaches to the management of both type 1 and type 2 diabetes, various macro and microvascular complications of diabetes, inpatient management of glycemia, nutrition, exercise, advances in diabetes technology and others.

Ideal for clinical endocrinologists and other professionals involved in the management of diabetes and its complications, *Precision Medicine in Diabetes* is first of its kind to address this paradigm-shifting topic in a comprehensive way.

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Keywords:

- Bioinformatics
- Biomarkers
- Clinical decision-making
- Genomics
- Metabolomics
- Model-based prediction
- Neonatal diabetes
- Nutrition
- Obesity
- Personalized medicine
- Precision medicine
- Proteomics
- Type 1 diabetes
- Type 2 diabetes
- Virtual imaging

Printed and published by Dr Gopakumaran Kartha on behalf of Aster DM Healthcare Limited, IX/475L, Aster Medcity, Kuttisahib Road, Near Kothad Bridge, South Chittoor P.O, Cheranelloor, Kochi, Kerala– 682 027, India and printed at Anaswara Offset Pvt Ltd, Perandoor Junction, Elamakkara, Kochi – 682 026 and published at Aster DM Healthcare Limited, IX/475L, Aster Medcity, Kuttisahib Road, Near Kothad Bridge, South Chittoor P.O, Cheranelloor, Kochi, Kerala– 682 027. Editor: Dr Geetha Philips. RNI No: **KERENG/2019/77520**

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