Epilogue

REFLECTIONS ON 50 YEARS OF RESEARCH

My journey exploring coronary artery disease (CAD) within the Indian community took a troubling turn in the early 1970s. I witnessed an alarming surge in heart attacks among young Indian physicians, including resident physicians from Kerala, India. This unsettling trend, particularly given their lack of traditional risk factors, deeply concerned me and ignited a dedicated pursuit to understand this phenomenon.

My concern deepened during my 3-year tenure as president of the Association of Kerala Medical Graduates (AKMG) in North America. This organization of physicians with roots in Kerala, India, provided a unique vantage point. Among the AKMG members, I observed a surprisingly high prevalence of heart bypass surgery scars—a mark of membership in what was then known as the "Zipper Club". This striking observation further fueled my resolve to investigate this phenomenon, despite the absence of existing research on the topic. This pursuit ultimately culminated in the establishment of the Coronary Artery Disease in Indians (CADI) Research Foundation in 1987.

The AKMG proved to be a stepping stone for national study, providing a crucial link to the vibrant community from Kerala, a state nestled along India's tropical Malabar Coast. Kerala holds the distinction of having the highest literacy rate and lowest infant mortality rate among Indian states, coupled with the highest level of epidemiological transition. Inspired by the support from AKMG and the collaborative spirit of Chicago cardiologists Michael Davidson and Isaac Thomas, I focused on identifying a representative sample of Indian Americans for a comprehensive study. Lacking a university affiliation, I sought advice and guidance from renowned cardiovascular (CV) researchers, Jeremiah Stamler (Northwestern University at Chicago, IL) and Salim Yusuf [National Institutes of Health (NIH), Bethesda, MD] on navigating this initial step.

Salim Yusuf graciously welcomed me into his home and provided invaluable advice. He facilitated connections with William Harlan, head of the noncommunicable disease (NCD) section at NIH, and Thomas Pearson, a visiting consultant with expertise in population health. Dr Harlan was vaguely aware of a study showing higher heart disease rates in Indians in Singapore. Their collective recommendation to broaden the scope of research across multiple Indian states beyond AKMG significantly influenced my research direction. As a 3-year president of AKMG and AAPI governing body member, I gained valuable insights into the diverse AAPI membership, representing Indian physicians from various regions.

THE CORONARY ARTERY DISEASE IN INDIANS STUDY UNMASKING HEART DISEASE RISK IN INDIANS

My 1985–1988 AKMG presidency was pivotal, revitalizing the organization through

membership growth and large conventions, raising its profile among Indian American physician associations. This led to my election as AAPI Treasurer (representing nearly 50,000, now 100,000, Indian American physicians). Recognizing AAPI's potential for research, I prioritized heart disease research among Indian Americans over personal advancement within the organization. Leveraging connections, I secured seed money for the CADI study.

The groundbreaking CADI study, conducted at the 1990 AAPI/AKMG conventions with nearly 2,000 Indian American physicians and families, revealed a fourfold higher heart disease rate compared to the general US general population (Framingham Offspring Study). Notably, the prevalence of traditional risk factors (obesity, hypertension, cholesterol, smoking) were similar or lower. This led me to coin the term "Indian Paradox"—high heart disease rates despite lower rates of traditional risk factors.

While diabetes was more prevalent among Indian Americans, it didn't fully explain their fourfold higher heart disease rate. This contrasted with the "Caribbean Paradox" observed in the UK, where Caribbean populations, despite having three times the diabetes rate of Whites (similar to Indians), exhibited substantially lower heart disease rates. This disparity between Indians and Caribbeans, both with similarly elevated diabetes rates but drastically different heart disease outcomes, challenged the prevailing assumption that diabetes was the overarching driver of heightened heart disease in Indians.

While CADI provided valuable insights, further research exploring the interplay of genetics, lifestyle, and socioeconomic factors is crucial. Ongoing studies like the Mediators of Atherosclerosis in South Asians Living in America (MASALA; US) and the London Life Sciences Population study (LOLIPOP; UK), investigating sociocultural and dietary influences, offer hope for targeted interventions to reduce this disproportionate burden in South Asians.

A QUESTION OF IDENTITY: FROM "EAST INDIAN" TO "INDIAN"

Presenting the CADI study results brought unexpected challenges regarding terminology. Many US professors objected to the term "Indian", associating it exclusively with Native Americans, while journal editors insisted on "East Indian", a term laden with colonial baggage. This confusion stems from Christopher Columbus's misidentification of the Caribbean inhabitants as "Indians" and the subsequent colonial terms "East Indies" and "West Indies".

Mindful of these issues, I opted for "Asian Indian", which gained wider acceptance. However, with the growing number and prominence of Indian Americans (surpassing 5 million), the term "Indian" has increasingly become synonymous with people from India. Recognizing this shift, I've embraced using "Indian" in my scientific work, acknowledging its evolving acceptance and clear connection to the population. This highlights the importance of precise terminology in research. While acknowledging the shared "South Asian" heritage, it is important to recognize the distinct identity of Indians. Just as we would not group all North Americans together in research, studying Indians distinctly is essential. Understanding their unique genetic, environmental, and dietary factors is key to developing effective interventions for this vast and diverse community, especially given their high heart disease rates despite being predominantly vegetarian.

PUBLICATIONS AND EDUCATIONAL INITIATIVES

My 1990 *AAPI Journal* article with Isaac Thomas, "Immigrant Indian Men: Sitting Ducks for Heart Attack?", aimed to raise awareness about heart disease in Indian immigrants. While reaching 50,000 AAPI members, the initial response was mixed, with some cardiology leaders dismissive and others concerned about life insurance implications. However, as data accumulated, a 1992 *American Journal of Cardiology* editorial with Salim Yusuf and Jawahar Mehta, "Prevalence of Coronary Artery Disease in Asian Indians", highlighted the earlier onset and severity of heart disease in Indians, serving as a wake-up call.

POWER OF COLLABORATION

To further foster international collaboration, I organized three meetings of the International Working Group on CADI between 1996 and 1998. These meetings brought together experts from the US, UK, Canada, Singapore, and India, leading to published proceedings in the Indian Heart Journal and fostering a strong collaborative network. Many participants, including Salim Yusuf, Jawahar Mehta, Michael Davidson, Viswanath Mohan, Rajeev Gupta, CS Pitchumoni, Basil Varkey, TS Dharmarajan, Sonia Anand, Guillaume Pare, and others, became valued collaborators and co-authors in my subsequent research and publications, solidifying the lasting impact of these international efforts. I also had the honor of chairing the first two Indo-US Health Summits held in New Delhi, further contributing to this critical dialogue, and fostering continued collaboration in CV research.

A PARADIGM SHIFT FROM HIGH RATES TO HIGH RISK OF HEART DISEASE IN INDIANS

The UK Biobank study (nearly 500,000 participants) showed South Asians have double the CV event rate of Whites, even accounting for diabetes. Critically, standard atherosclerotic cardiovascular disease (ASCVD) risk tools *underestimated* this risk, with South Asians experiencing double the predicted events. This highlighted the need to recognize South Asians' inherently higher *risk*, not just *rates*, of heart disease, demanding deeper investigation beyond traditional risk factors and equations. "South Asians" here refers to those of Indian subcontinent origin (India, Pakistan, Bangladesh, Nepal, Bhutan, Sri Lanka), with Indians comprising 70–75%.

PERSISTING HIGH INCIDENCE OF HEART DISEASE IN YOUNG INDIANS

Despite decades of research, heart disease incidence remains alarmingly high in young Indians. Balarajan's 1991 work showed a 313% higher heart disease mortality rate in Indians under 30 years compared to Whites, a trend confirmed by the recent LOLIPOP study (2024). This 20-year study of 17,606 South Asians and 7,766 White Europeans (35–75 years old) found: (1) South Asian women's CAD incidence was much higher than White women's and nearly equal to White men's; (2) South Asian men had the highest heart attack risk across all ages; and (3) the highest relative risk was in South Asians under 45 years (88% higher), decreasing to 67% higher in those over 65 years. Professor Bhopal's 50-year analysis further supports this, finding no single explanation for the

elevated risk, disproving many existing hypotheses.

MY EUREKA MOMENT IN CADI RESEARCH

In May 1990, I encountered a patient that would dramatically alter the course of my research. Dr X, the principal of a major medical school in South India, suffered a severe heart attack while visiting Chicago. Despite adhering to a strict vegetarian diet and maintaining a healthy lifestyle, he presented with no discernible risk factors. However, his coronary angiogram revealed extensive and severe heart disease **(Fig. 1)**, necessitating emergency quadruple coronary bypass surgery.

Witnessing the surgeon extract an enormous, 6 cm long plaque **(Fig. 2)** from Dr X's totally occluded right coronary artery, at my behest, proved to be a pivotal moment—a true "Eureka!" moment in my research career. This unexpected finding, unlike anything I had previously encountered, ignited a profound sense of curiosity and a

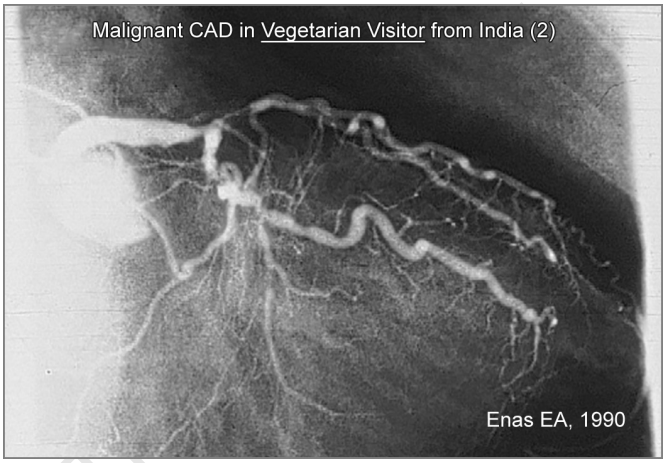

Fig. 1: Severe stenosis of the left main artery and subtotal blockage of left anterior descending artery and multiple stenosis of circumflex arteries.

Fig. 2: An unusually large plaque that was removed from the right coronary artery.

determination to unravel the hidden forces driving heart disease, particularly in individuals like Dr X, who seemingly defied all the known risk factors. I meticulously documented the extracted plaque, capturing every intricate detail; even Dr X, a seasoned pathologist, was stunned by its size and unusual composition.

Dr X's inexplicable case, defying all known risk factors, solidified my conviction: "There's an unrecognized, more common and dangerous genetic risk factor in Indians". Feeling profound responsibility to my community, I vowed, "I won't rest until I find it". I confided in my wife. This wasn't just a medical mystery; it was a call to action, a solemn promise to unravel this hidden danger and challenge conventional wisdom.

A SERENDIPITOUS DISCOVERY: HIGH LIPOPROTEIN(a) AND MALIGNANT HEART DISEASE IN A YOUNG INDIAN PHYSICIAN

Dr Y's case—a heart attack of a 37-year-old physician—with no significant traditional CV risk factors but a strong family history of early heart attacks, became a turning point. Despite his heart attack, his initial workup, including a coronary angiogram and stress test, showed minimal disease **(Fig. 3)**. Nonetheless, his arterial plaque buildup progressed relentlessly, leading to severe heart failure within 10 years. A repeat angiogram revealed extensive blockages **(Fig. 4)**, prompting two surgeons to decline bypass surgery due to high risk and poor prognosis. A third surgeon reluctantly agreed, emphasizing the high mortality and poor long-term outlook. This case starkly illustrated the aggressive and unpredictable nature of heart disease in some young Indians.

A pivotal moment in my research occurred with the discovery of Dr Y's lipoprotein(a) [Lp(a)] level—a staggering 127 mg/dL—four times the normal limit. This pivotal discovery shifted my research trajectory. This missing piece revealed a deeper understanding of heart disease, especially in those defying traditional risk factors. Further confirmation came when his 14-year-old son was found to have an identical very high Lp(a) level of 127 mg/dL. This undeniable evidence of a powerful hereditary link—a genetic thread connecting father and son, both burdened

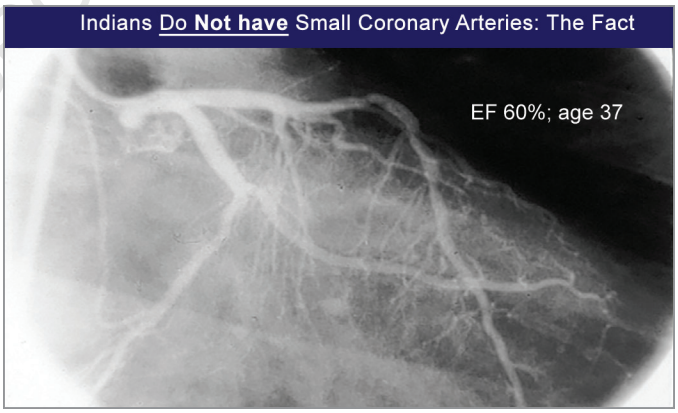

Fig. 3: Dr Y's first angiogram at age 37 years showing large coronary arteries. (EF: ejection fraction)

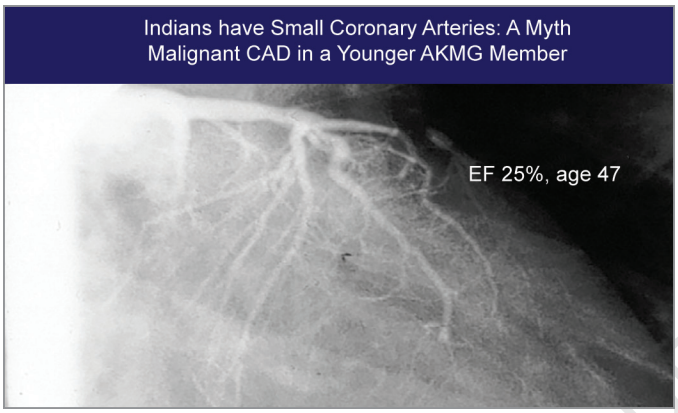

Fig. 4: Apparently small coronary arteries. Compare the size of the arteries of the same patient **(Fig. 3)** 10 years earlier.

with this hidden risk factor, served as a stark reminder that heart disease often defies predictable patterns.

THE "SMALL ARTERIES" MYTH

Dr Y's case challenged the misconception that Indians have inherently smaller coronary arteries. His initial angiograms showed healthy large arteries, but later images revealed seemingly "small arteries" due to extensive plaque buildup **(Figs. 3 and 4)**. This highlights the importance of considering factors beyond artery size, such as Lp(a), when assessing heart disease risk in Indians. Recognizing that extensive plaque can mimic small coronary arteries encourages a more nuanced understanding of heart disease risk in this population.

A BEACON OF HOPE

Dr Y's case, despite its grim initial prognosis, became a beacon of hope. Against all odds, he fought back with unwavering tenacity, defying the initial predictions of a shortened lifespan. Armed with cutting-edge medical therapies and aggressive lipid-lowering treatments, he was able to celebrate his 82nd birthday—a testament to the resilience of the human spirit and the power of medical innovation. We were able to gain 35 additional years of life for him, a far cry from the initial grim prognosis. Dr X's case, rather than a medical tragedy, became a beacon of hope, illuminating a new path in the fight against heart disease, a path I've dedicated my life to exploring.

This realization ignited a fire in me. I felt a renewed sense of urgency, a responsibility to delve deeper into the mysteries of Lp(a) and its role in premature heart disease. Dr Y's case, and the striking parallel with his young son, became a driving force in my research, pushing me to explore new avenues and challenge conventional wisdom.

Years later, Dr X's case provided a contrasting perspective. When he returned from India for a follow-up visit, his Lp(a) level was found to be modestly elevated at 48 mg/dL. This observation highlighted that cumulative lifetime exposure to Lp(a), rather than just a single measurement, significantly contributes to the development of heart disease.

This insight explained the delayed onset of his heart issues at 68 years in Dr X, compared to Dr Y's premature heart attack at 37 years. The contrasting cases of Dr X and Dr Y solidified my understanding of Lp(a)'s crucial role in malignant heart disease, particularly within the Indian population. Early aggressive lipid-lowering therapy in Dr Y's son, diagnosed with high Lp(a) at age 14 years, successfully prevented heart disease in the son as evidenced by consistently zeros scores, in later years including 2024.

Together these cases demonstrated that Lp(a) can be a primary driver of severe heart disease, even when other traditional risk factors are absent. Furthermore, Lp(a) emerged as a powerful predictor of familial risk, enabling early identification and management of individuals at high risk.

UNRAVELING THE INDIAN PARADOX AND HISPANIC PARADOX

In the early 1990s, awareness of Lp(a) was minimal, and research had seemingly stalled, until a landmark report, utilizing a more accurate assay, reignited interest by revealing a strong correlation between Lp(a) and severe heart disease. Individuals with very high Lp(a) exhibited a fourfold increased risk of severe CAD. This risk escalated to 12-fold in individuals with both very high Lp(a) and very high low-density lipoprotein cholesterol (LDL-C), highlighting the synergistic effects of these two risk factors. Leveraging Salim Yusuf's introduction, I collaborated with Thomas Pearson to analyze blood samples from the CADI study in his research laboratory, comparing Lp(a) levels across different ethnicities. Simultaneously, noting Steven Hafner's work on "Hispanic Paradox" (low heart disease rates, despite high traditional risk factors), I hypothesized that high Lp(a) might explain the Indian paradox (high rates of heart disease without high levels of traditional risk factors). This led to collaboration with Dr Steven Haffner's work suggesting that low Lp(a) levels might explain the "Hispanic Paradox". This sparked a question: Could high Lp(a) levels explain the "Indian Paradox"? We subsequently collaborated with Dr Haffner to compare Lp(a) levels in Indians and Hispanics.

HIGH LIPOPROTEIN(a) IN INDIANS

Our studies of nearly 500 individuals revealed that significantly elevated Lp(a) levels in Indians (25%) compared to Whites (17%) and Hispanics (10%) was a key factor in explaining the Indian Paradox. Subsequent US studies from the UK and Singapore have confirmed these findings with the UK Biobank showing 60% higher Lp(a) levels in Indians versus Whites. Similarly, Singaporean Indians, who have threefold higher heart disease rates than other ethnicities, also showed higher cord blood Lp(a) levels further supporting Lp(a)'s role in increased heart disease risk in Indians. The groundbreaking 2019 INTERHEART-Lp(a) study showed that South Asians had the second highest Lp(a) level (after Blacks) and the highest risk of heart attack associated with an elevated Lp(a). The evidence convincingly demonstrates that Lp(a) is a major independent risk factor for heart attacks, particularly in young individuals (<50 years) and very young individuals (<40 years), with approximately double the risk. This risk is further amplified to fourfold among those with other risk factors, particularly diabetes or elevated LDL-C.

THE GLOBAL BURDEN OF ELEVATED LIPOPROTEIN(a) IS THREE TIMES GREATER THAN DIABETES

According to the 2018 special report by the National Heart, Lung, and Blood Institute (NHLBI) elevated Lp(a) affects 1.43 billion individuals worldwide. For comparison, diabetes affects less than 500 million. Lp(a) levels vary by ethnicity: 25% of Indians have high Lp(a) levels, compared to 20% of Whites and 10% of Chinese. The report established the following Lp(a) classifications: <30 mg/dL is normal, 30–50 mg/dL is moderately high, and >50 mg/dL is high (Chapter 8).

LIPOPROTEIN(a), MALIGNANT HEART DISEASE AND RESEARCH PUBLICATIONS

Two striking features of elevated Lp(a) are its association with early heart disease and the severity of outcomes. Impressed by existing research and my own observations, I began routinely screening my patients for Lp(a). This revealed a strong correlation between Lp(a) levels and both the early onset and severity of heart disease in both Indian and White patients. In 1995, I collaborated with Jawahar Mehta on a review article highlighting the potential role of Lp(a) in aggressive heart disease in young Indians. My 2000 article, "Coronary Artery Disease Epidemic in Indians", emphasized the severe and early onset of heart disease in Indians both in India and within the diaspora. To address the misconception that Lp(a) screening should be limited to patients with unexplained heart disease, I authored a monograph in 2006 titled "Elevated Lipoprotein(a)—A Genetic Risk Factor for Premature Vascular Disease in People With and Without Standard Risk Factors: A Review".

Since my earlier work didn't have the intended impact on clinical practice, I wrote two comprehensive articles on Lp(a) for the Indian Heart Journal in 2019. The first focused on the general role of Lp(a) in CV disease, while the second specifically addressed its significance in young Indians with aggressive heart disease. I highly recommend these articles to readers interested in learning more about Lp(a).

AMERICAN GUIDELINES RECOGNIZE ELEVATED LP(a) AND INDIAN ETHNICITY AS ASCVD RISK-ENHANCING FACTORS

The 2018 American College of Cardiology/American Heart Association (ACC/AHA) Clinical Practice Guidelines marked a significant step forward by recognizing South Asian ethnicity and elevated Lp(a) as ASCVD risk-enhancing factors (Chapter 8). This recognition has important implications for treatment, warranting a more proactive approach to prevention, particularly with reference to statin therapy.

I have dedicated my career to raising the awareness about heart disease in Indians, delivering over 1,000 lectures and publishing more than 100 articles in major medical journals. I've strived to share the latest scientific progress with audiences in India and the US. My lecture series, "Heart Disease in Indians—A Global Perspective", presented at prestigious medical institutions in both countries, provided a valuable platform for engaging with leading cardiologists. My first book, "How to Beat the Heart Disease Epidemic Among South Asians", published in 2005, has helped countless individuals in India and the US. This 2025 edition synthesizes the latest scientific knowledge and treatment strategies in a clear and accessible style for

both medical professionals and the general public.

STRATEGIES TO ARREST AND REVERSE HEART DISEASE EPIDEMIC IN INDIANS

The rising heart disease epidemic in India is a complex issue fueled by lifestyle changes, dietary shifts, and the synergistic effects of various risk factors, notably the significant contribution of genetically elevated Lp(a). Urbanization and increased affluence have led to a sedentary lifestyle, a diet high in processed foods, and reduced physical activity, contributing to rising rates of obesity, metabolic syndrome, diabetes, and hypertension. High consumption of saturated and trans fats significantly increase LDL-C levels. Elevated Lp(a) significantly increases the risk of an early heart attack. An estimated 300 million Indians have elevated Lp(a), compared to 70 million with diabetes, highlighting the significant impact of this underappreciated risk factor. This risk is dramatically amplified when elevated Lp(a) coexists with other risk factors such as elevated LDL-C or diabetes, often increasing the risk of heart attack fourfold. Furthermore, the control of LDL-C and diabetes remains suboptimal in India, with only 10–20% of individuals achieving adequate control. This complex interplay of factors necessitates a multipronged approach to address the rising burden of heart disease in India. This approach must prioritize:

- Promoting healthy lifestyles through the early adoption of "Life's Essential 8" with specific targets tailored to the Indian population, including lower thresholds for waist circumference, cholesterol, and LDL-C (Chapter 17)
- Implementing strategies to effectively control LDL-C, diabetes, hypertension, and tobacco use (Chapters 4 to 7)
- Raising awareness about the significance of Lp(a) and developing strategies for universal screening and management of elevated Lp(a) (Chapter 8)
- Raising awareness that the American guidelines have lowered the desirable cholesterol level to 170 mg/dL, and our research suggests a target of 140 mg/dL for Indians (Chapters 7 and 17).
- Early identification of subclinical atherosclerosis, the foremost predictor of clinical heart disease and heart attacks, through coronary artery calcium scoring, also known as a heart scan (Chapter 2)

The PESA (Progression of Early Subclinical Atherosclerosis) study demonstrates that LDL-C levels below 60 mg/dL are needed to halt plaque progression, and levels below 30 mg/dL can induce significant regression. For Indians, achieving and maintaining an LDL-C level of 60–70 mg/dL should be a primary goal. The CV outcomes trial HORIZON, evaluating the Lp(a)-lowering agent pelacarsen, is expected to provide crucial data on the impact of significantly reducing Lp(a) levels on CV events.

By combining these efforts with personalized strategies, significant progress has been made in reducing heart disease rates among South Asians in Canada and the US, achieving near-parity with the dominant White population (personal communications with Salim Yusuf and Sonia Anand). This progress is attributed in part to awareness and educational initiatives championed by organizations like the CADI Research Foundation.

Inspired by these successes, this book provides practical tools to combat the disproportionately high rates of heart disease

in young people. By implementing these strategies and fostering a proactive approach to CV health, we can significantly reduce the burden of heart disease and create a healthier future.

A LIFETIME OF GRATIFYING RESEARCH ON CARDIOVASCULAR DISEASE

It is incredibly rewarding to see the culmination of 50 years of research recognized in the growing understanding of the heightened heart disease risk in Indians and the crucial role of Lp(a). My professional idol, James Herrick, revolutionized our understanding of heart disease by being the first to describe myocardial infarction in living patients, challenging the prevailing belief that it was invariably fatal. Unlike Herrick, who may not have received widespread recognition during his lifetime, I am fortunate to witness my work gain widespread acceptance and be incorporated into national guidelines.

This legacy of knowledge, built upon the shoulders of giants like Jeremiah Stamler, Salim Yusuf, Jawahar Mehta, and Basil Varkey, whose guidance and mentorship were instrumental in my journey, will hopefully inspire continued research and innovation in heart disease prevention and treatment. Driven by a deep sense of compassion and a collaborative spirit, this journey has yielded discoveries with potentially global implications. To witness these findings, translating into improved lives for individuals and families fills me with immense gratitude.

The recognition of our work with the Most Distinguished Physician Award from AAPI and the AKMG Master Award has been a tremendous honor, acknowledging our contributions to the health and well-being of the Indian community. This 2025 book, along with the continued efforts of the CADI Research Foundation, will empower individuals to take control of their heart health by disseminating the latest data and promoting proactive lifestyle changes. I believe this work can serve as a testament to the power of dedicated research, the importance of collaboration, and the profound impact that scientific discovery can have on human health.