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A SELECTION OF TEN READINGS ON TOPICS RELATED TO CHRONIC DISEASE MANAGEMENT 2024

Some are available as free full text, and in some payment is required

Selection of readings made by A/Prof Goh Lee Gan

READING 1 – FINERENONE-INDUCED ALBUMINURIA REDUCTION IN CKD OUTCOMES IN T2DM

Agarwal R,[1] Tu W,[2] Farjat AE,[3] Farag YMK,[4] Toto R,[5] Kaul S,[6] Lawatscheck R,[7] Rohwedder K,[8] Ruilope LM,[9] Rossing P,[10] Pitt B,[11] Filippatos G,[12] Anker SD,[13] Bakris GL[14]; FIDELIO-DKD and FIGARO-DKD Investigators. Impact of Finerenone-Induced Albuminuria Reduction on Chronic Kidney Disease Outcomes in Type 2 Diabetes: A Mediation Analysis. Ann Intern Med. 2023 Dec;176(12):1606-1616.

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Author information:
[1]Richard L Roudebush VA Medical Center and Indiana University, Indianapolis, IN (R.A.)
[2]Department of Biostatistics and Health Data Science, Indiana University, Indianapolis, IN (W.T.)
[3]Data Science and Analytics, Bayer PLC, Reading, United Kingdom (A.E.F.)
[4]Bayer U.S. LLC, Cambridge, MA (Y.M.K.F.)
[5]Department of Internal Medicine, University of Texas Southwestern Medicine, Dallas, TX (R.T.)
[6]Department of Cardiology, Cedars-Sinai Medical Center, Los Angeles, CA (S.K.)
[7]Cardiology and Nephrology Clinical Development, Bayer AG, Berlin, Germany (R.L.)
[8]Cardio-Renal Medical Affairs Department, Bayer AG, Berlin, Germany (K.R.)
[9]Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12, CIBER-CV, Hospital Universitario 12 de Octubre, and Faculty of Sport Sciences, European University of Madrid, Madrid, Spain (L.M.R.)
[10]Steno Diabetes Center Copenhagen, Herlev, and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark (P.R.)
[11]Department of Medicine, University of Michigan School of Medicine, Ann Arbor, MI (B.P.)
[12]National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Athens, Greece (G.F.)
[13]Department of Cardiology (CVK) of German Heart Center Charité, Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany, and Institute of Heart Diseases, Wrocław Medical University, Wrocław, Poland (S.D.A.)
[14]Department of Medicine, University of Chicago Medicine, Chicago, IL (G.L.B.)

ABSTRACT

BACKGROUND: In patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), finerenone, a nonsteroidal mineralocorticoid receptor antagonist, reduces cardiovascular and kidney failure outcomes. Finerenone also lowers the urine albumin-to-creatinine ratio (UACR). Whether finerenone-induced change in UACR mediates cardiovascular and kidney failure outcomes is unknown.

OBJECTIVE: To quantify the proportion of kidney and cardiovascular risk reductions seen over a 4-year period mediated by a change in kidney injury, as measured by the change in log UACR between baseline and month 4.

DESIGN: Post hoc mediation analysis using pooled data from 2 phase 3, double-blind trials of finerenone. (ClinicalTrials.gov: NCT02540993 and NCT02545049)

SETTING: Several clinical sites in 48 countries.

PATIENTS: 12,512 patients with CKD and T2D.

INTERVENTION: Finerenone and placebo (1:1).

MEASUREMENTS: Separate mediation analyses were done for the composite kidney (kidney failure, sustained ≥57% decrease in estimated glomerular filtration rate from baseline [approximately a doubling of serum creatinine], or kidney disease death) and cardiovascular (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for heart failure) outcomes.

RESULTS: At baseline, median UACR was 514 mg/g. A 30% or greater reduction in UACR was seen in 3,338 (53.2%) patients in the finerenone group and 1,684 (27.0%) patients in the placebo group. Reduction in UACR (analysed as a continuous variable) mediated 84% and 37% of the treatment effect on the kidney and cardiovascular outcomes, respectively. When change in UACR was analysed as a binary variable (that is, whether the guideline-recommended 30% reduction threshold was met), the proportions mediated for each outcome were 64% and 26%, respectively.

LIMITATION: The current findings are not readily extendable to other drugs.

CONCLUSION: In patients with CKD and T2D, early albuminuria reduction accounted for a large proportion of the treatment effect against CKD progression and a modest proportion of the effect against cardiovascular outcomes.

READING 2 – PROGRESSION TO INSULIN THERAPY IN PATIENTS WITH T2DM

Kokkinos P,[1] Nylen E,[2] Faselis C,[2] Pittaras A,[2] Samuel IBH,[3] Lavie C,[4] Doumas M,[5] Heimall MS,[6] Murphy R,[6] Myers J.[7] Progression to Insulin Therapy in Patients With Type 2 Diabetes According to Cardiorespiratory Fitness, Body Mass Index, and Statin Therapy. Mayo Clin Proc. 2023 Jun 29:S0025-6196(23)00201-X.

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Author information:
[1]Veterans Affairs Medical Center, Washington, DC; Department of Kinesiology and Health, Rutgers University, New Brunswick, NJ; George Washington University School of Medicine and Health Sciences, Washington, DC. Electronic address: peter.kokkinos@va.gov
[2]Veterans Affairs Medical Center, Washington, DC; George Washington University School of Medicine and Health Sciences, Washington, DC
[3]Veterans Affairs Medical Center, Washington, DC; Henry M Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD
[4]John Ochsner Heart and Vascular Institute, Ochsner Clinical School-The University of Queensland School of Medicine, New Orleans, LA
[5]Veterans Affairs Medical Center, Washington, DC; Aristotle University of Thessaloniki, Thessaloniki, Greece
[6]Veterans Affairs Medical Center, Washington, DC
[7]Cardiology Division, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA; Department of Cardiology, Stanford University, Stanford, CA

ABSTRACT
OBJECTIVE: To evaluate the association between statin therapy, cardiorespiratory fitness (CRF), body mass index (BMI), and progression to insulin therapy in type 2 diabetes mellitus (T2DM).

METHODS: Participants were patients with T2DM (mean age, 62.7±8.4 years; men, 178,992; women, 8,360) not treated with insulin, with no evidence of uncontrolled cardiovascular disease, who completed an exercise treadmill test between 1 October 1999, and 3 September 2020. Of these, 158,578 were treated with statins and 28,774 were not. We established five age-specific CRF categories according to peak metabolic equivalents of task achieved during an exercise treadmill test.

RESULTS: During a median follow-up period of 9.0 years, 51,182 patients progressed to insulin therapy with an average annual incidence rate of 28.4 events/1,000 person-years. The adjusted progression rate was 27% higher in statin-treated patients (hazard ratio [HR], 1.27; 95% CI, 1.24 to 1.31), related directly to BMI and inversely related to CRF. A progressively higher rate was noted in statin-treated vs non-statin-treated patients within all BMI categories, ranging from 23% for normal weight to 90% for those with BMI of 35 kg/m^2 and higher. The statin-CRF interaction revealed 43% higher rate in the least-fit statin-treated patients (HR, 1.43; 95% CI, 1.35 to 1.51) and a progressive decline with increased CRF to 30% lower risk in highly fit statin-treated patients (HR, 0.70; 95% CI, 0.66 to 0.75).

CONCLUSION: In patients with T2DM, the statin-related progression to insulin therapy was associated with relatively low CRF and high BMI levels. The progression rate was mitigated by increased CRF regardless of BMI. Clinicians should foster regular exercise for patients with T2DM to enhance CRF and to lessen the rate of progression to insulin therapy.

READING 3 – OBESITY AND T2DM

Xu Q,[1,2] Ruze R,[1,2,3] Song J,[1,2,3] Chen Y,[1,2,3] Xu R,[1,2,3] Yin X,[1,2,3] Zou X,[2,3] Liu T.[2,4] Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Front Endocrinol (Lausanne). 2023 Apr 21;14:1161521.

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Author information:
[1]Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[2]Key Laboratory of Research in Pancreatic Tumor, Chinese Academy of Medical Sciences, Beijing, China
[3]Graduate School, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[4]School of Medicine, Tsinghua University, Beijing, China

ABSTRACT
The prevalence of obesity and diabetes mellitus (DM) has been consistently increasing worldwide. Sharing powerful genetic and environmental features in their pathogenesis, obesity amplifies the impact of genetic susceptibility and environmental factors on DM.

The ectopic expansion of adipose tissue and excessive accumulation of certain nutrients and metabolites sabotage the metabolic balance via insulin resistance, dysfunctional autophagy, and microbiome-gut-brain axis, further exacerbating the dysregulation of immunometabolism through low-grade systemic inflammation, leading to an accelerated loss of functional β-cells and gradual elevation of blood glucose.

Given these intricate connections, most available treatments of obesity and type 2 DM (T2DM) have a mutual effect on each other. For example, anti-obesity drugs can be anti-diabetic to some extent, and some anti-diabetic medicines, in contrast, have been shown to increase body weight, such as insulin.

Meanwhile, surgical procedures, especially bariatric surgery, are more effective for both obesity and T2DM. Besides guaranteeing the availability and accessibility of all the available diagnostic and therapeutic tools, more clinical and experimental investigations on the pathogenesis of these two diseases are warranted to improve the efficacy and safety of the available and newly developed treatments.

READING 4 – DRUG THERAPIES FOR DIABETES MELLITUS

Weinberg Sibony R,[1] Dor S,[1] Segev O,[2] Raz I.[3,4] Drug Therapies for Diabetes. Int J Mol Sci. 2023 Dec 5;24(24):17147.

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Author information:
[1]Faculty of Medicine, Ben-Gurion University, Beer Sheva 8443944, Israel
[2]Faculty of Medicine, Tel Aviv University, Tel Aviv 69978, Israel
[3]Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem 9112001, Israel
[4]Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem 91240, Israel

ABSTRACT
The treatment of type 2 diabetes (T2D) necessitates a multifaceted approach that combines behavioural and pharmacological interventions to mitigate complications and sustain a high quality of life. Treatment encompasses the management of glucose levels, weight, cardiovascular risk factors, comorbidities, and associated complications through medication and lifestyle adjustments. Metformin, a standard in diabetes management, continues to serve as the primary, first-line oral treatment across all age groups due to its efficacy, versatility in combination therapy, and cost-effectiveness. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) offer notable benefits for HbA1c and weight reduction, with significant cardiovascular benefits. Sodium-glucose cotransporter inhibitors (SGLT-2i) lower glucose levels independently of insulin while conferring notable benefits for cardiovascular, renal, and heart-failure outcomes. Combined therapies emphasising early and sustained glycaemic control are promising options for diabetes management. As insulin therapy remains pivotal, metformin and non-insulin agents such as GLP-1 RA and SGLT-2i offer compelling options. Notably, exciting novel treatments like

the dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonist show promise for substantially reducing glycated haemoglobin and body weight. This comprehensive review highlights the evolving landscape of pharmacotherapy in diabetes, the drugs currently available for treating diabetes, their effectiveness and efficacy, the impact on target organs, and side effects. This work also provides insights that can support the customisation of treatment strategies.

READING 5 – EFFICACY OF FASTING IN TYPE 1 AND TYPE 2 DIABETES MELLITUS

Herz D,[1] Haupt S,[1] Zimmer RT,[1] Wachsmuth NB,[1] Schierbauer J,[1] Voit T,[1] Thurm U,[1] Zimmermann P,[1,2,3] Rilstone S,[1,5] Moser O,[1,6] Khoramipour K.[4] Efficacy of Fasting in Type 1 and Type 2 Diabetes Mellitus: A Narrative Review. Nutrients. 2023 Aug 10;15(16):3525.

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Author information:
[1]Division of Exercise Physiology and Metabolism, BaySpo-Bayreuth Center of Sport Science, University of Bayreuth, 95447 Bayreuth, Germany
[2]Department of Cardiology, Klinikum Bamberg, 96049 Bamberg, Germany
[3]Interdisciplinary Center of Sportsmedicine Bamberg, Klinikum Bamberg, 96049 Bamberg, Germany
[4]Department of Physiology and Pharmacology, Afzalipour School of Medicine, Kerman University of Medical Sciences, Blvd. 22 Bahman, Kerman 7616914115, Iran
[5]Department of Metabolism, Digestion and Reproduction, Imperial College London, London SW7 2BX, UK
[6]Interdisciplinary Metabolic Medicine Trials Unit, Department of Internal Medicine, Division of Endocrinology and Diabetology, Medical University of Graz, 8036 Graz, Austria

ABSTRACT
Over the last decade, studies suggested that dietary behaviour modification, including fasting, can improve metabolic and cardiovascular markers as well as body composition.

Given the increasing prevalence of people with type 1 (T1DM) and type 2 diabetes mellitus (T2DM) and the increasing obesity (also in combination with diabetes), nutritional therapies are gaining importance, besides pharmaceutical interventions.

Fasting has demonstrated beneficial effects for both healthy individuals and those with metabolic diseases, leading to increased research interest in its impact on glycaemia and associated short- and long-term complications. Therefore, this review aimed to investigate whether fasting can be used safely and effectively in addition to medications to support the therapy in T1DM and T2DM.

A literature search on fasting and its interaction with diabetes was conducted via PubMed in September 2022. Fasting has the potential to minimise the risk of hypoglycaemia in T1DM, lower glycaemic variability, and improve fat metabolism in T1DM and T2DM. It also increases insulin sensitivity, reduces endogenous glucose production in diabetes, lowers body weight, and improves body composition.

To conclude, fasting is efficient for therapy management for both people with T1DM and T2DM and can be safely performed, when necessary, with the support of healthcare professionals.

READING 6 – ARE YOUR PATIENTS AT RISK OF NASH?

Flamm SL. Clinical Consult in NASH: Are Your Patients at Risk? Based on a Medscape Education Online Activity. J Fam Pract. 2023 Nov;72(9 Suppl):S3-S8.

doi: 10.12788/JFP.0677 (Payment is required).

ABSTRACT

Nonalcoholic steatohepatitis, or NASH, is the most severe form of nonalcoholic fatty liver disease (NAFLD).

If left untreated, NASH can develop into advanced liver disease, such as cirrhosis. Moreover, patients with NASH and cirrhosis are also at increased risk of developing hepatocellular carcinoma.

Therefore, early detection and intervention are key components to prevent disease progression, particularly in the primary care setting where many patients with NASH are typically encountered.

READING 7 – NUTRITION AND NAFLD

Romero-Gómez M,[1,2,3] Zelber-Sagi S,[4,5] Martín F,[6,7] Bugianesi E,[8,9] Soria B.[10] Nutrition could prevent or promote non-alcoholic fatty liver disease: an opportunity for intervention. BMJ. 2023 Oct 9;383:e075179.

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Author information:
[1]UCM Digestive Diseases and Ciberehd. Virgen del Rocío University Hospital, Spain mromerogomez@us.es
[2]Institute of Biomedicine of Seville (HUVR/CSIC/US), Spain
[3]Department of Medicine, University of Seville, Seville, Spain
[4]School of Public Health, University of Haifa, Haifa, Israel
[5]Department of Gastroenterology, Tel-Aviv Medical Center, Tel-Aviv, Israel
[6]Andalusian Center of Molecular Biology and Regenerative Medicine (CABIMER), Pablo de Olavide University, University of Seville, Spain
[7]Biomedical Research Network on Diabetes and Related Metabolic Diseases (CIBERDEM), Instituto de Salud Carlos III, Madrid, Spain
[8]Department of Medical Sciences, University of Turin, Turin, Italy
[9]Division of Gastroenterology, Città Della Salute e Della Scienza University-Hospital, Turin, Italy
[10]Unit of Advanced Therapies and Regenerative Medicine, Health Research Institute of the Dr Balmis University Hospital of Alicante (ISABIAL), Institute of Bioengineering University Miguel Hernández, CIBERDEM, Instituto de Salud Carlos III, Madrid, Spain

ABSTRACT

Manuel Romero-Gómez and colleagues discuss how diet and modifiable factors can help prevent non-alcoholic fatty liver disease and the importance of engaging all society through awareness, education, and policy change

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READING 8 – COMPARATIVE EFFECTIVENESS OF SGLT2I FOR RECURRENT GOUT FLARES

McCormick N,[1] Choi HK,[1] Yokose C,[2] Zhang Y,[2] Wei J,[3] Lu N,[4] Wexler DJ,[5] Aviña-Zubieta JA,[6] De Vera MA.[7] Comparative Effectiveness of Sodium-Glucose Cotransporter-2 Inhibitors for Recurrent Gout Flares and Gout-Primary Emergency Department Visits and Hospitalizations: A General Population Cohort Study. Ann Intern Med. 2023 Aug;176(8):1067-1080.

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Author information:
[1]Clinical Epidemiology Program, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Boston, Massachusetts; The Mongan Institute, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; Department of Medicine, Harvard Medical School, Boston, Massachusetts; and Arthritis Research Canada, Vancouver, British Columbia, Canada (N.M., H.K.C.)

[2]Clinical Epidemiology Program, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital; The Mongan Institute, Department of Medicine, Massachusetts General Hospital; and Department of Medicine, Harvard Medical School, Boston, MA (C.Y., Y.Z.)
[3]Health Management Center, Department of Orthopaedics, National Clinical Research Center of Geriatric Disorders, and Key Laboratory of Aging-related Bone and Joint Diseases Prevention and Treatment, Ministry of Education, Xiangya Hospital, and Department of Epidemiology and Health Statistics, Xiangya School of Public Health, Central South University, Changsha, China (J.W.)
[4]Arthritis Research Canada, Vancouver, British Columbia, Canada (N.L.)
[5]Department of Medicine, Harvard Medical School, and Diabetes Center, Massachusetts General Hospital, Boston, MA (D.J.W.)
[6]Arthritis Research Canada, and Division of Rheumatology, Faculty of Medicine, The University of British Columbia, Vancouver, British Columbia, Canada (J.A.A.)
[7]Arthritis Research Canada, and Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia, Canada (M.A.D.V.)

ABSTRACT

BACKGROUND: Sodium-glucose cotransporter-2 inhibitors (SGLT2is) decrease serum urate levels, but whether this translates into prevention of recurrent flares among patients with gout and gout-primary emergency department (ED) visits or hospitalisations is unknown.

OBJECTIVE: To compare gout flares and cardiovascular events among patients with gout initiating SGLT2is versus dipeptidyl peptidase 4 inhibitors (DPP-4is), another second-line glucose-lowering agent not associated with serum urate levels or cardiovascular risk.

DESIGN: Propensity score-matched, new-user cohort study.

SETTING: General population database from 1 January 2014 to 30 June 2022.

PARTICIPANTS: Patients with gout and type 2 diabetes.

MEASUREMENTS: The primary outcome was recurrent gout flare counts ascertained by ED, hospitalisation, outpatient, and medication-dispensing records. Secondary outcomes included myocardial infarction and stroke; genital infection (positive control) and osteoarthritis encounter (negative control) were also assessed. Poisson and Cox proportional hazards regressions were used with 1:1 propensity score matching (primary analysis) and overlap weighting (sensitivity analysis).

RESULTS: After propensity score matching, the flare rate was lower among SGLT2i initiators than DPP-4i initiators (52.4 and 79.7 events per 1,000 person-years, respectively), with a rate ratio (RR) of 0.66 (95% CI, 0.57 to 0.75) and a rate difference (RD) of -27.4 (CI, -36.0 to -18.7) per 1,000 person-years. The corresponding RR and RD for gout-primary ED visits and hospitalisations were 0.52 (CI, 0.32 to 0.84) and -3.4 (CI, -5.8 to -0.9) per 1,000 person-years, respectively. The corresponding hazard ratio (HR) and RD for myocardial infarction were 0.69 (CI, 0.54 to 0.88) and -7.6 (CI, -12.4 to -2.8) per 1,000 person-years; the HR for stroke was 0.81 (CI, 0.62 to 1.05). Those who initiated SGLT2is showed higher risk for genital infection (HR, 2.15 [CI, 1.39 to 3.30]) and no altered risk for osteoarthritis encounter (HR, 1.07 [CI, 0.95 to 1.20]). Results were similar when propensity score overlap weighting was applied.

LIMITATION: Participants had concurrent type 2 diabetes.

CONCLUSION: Among patients with gout, SGLT2is may reduce recurrent flares and gout-primary ED visits and hospitalisations and may provide cardiovascular benefits.

READING 9 – PATIENT WITH HFPEF

Smetana GW,[1] Ho JE,[1] Reynolds EE,[1] Orkaby AR.[2] How Would You Manage This Patient With Heart Failure With Preserved Ejection Fraction? Grand Rounds Discussion From Beth Israel Deaconess Medical Center. Ann Intern Med. 2023 Dec;176(12):1656-1665.

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Author information:
[1]Beth Israel Deaconess Medical Center, Boston, MA (G.W.S., J.E.H., E.E.R.)
[2]VA Boston Healthcare System and Brigham & Women's Hospital, Boston, MA (A.R.O.)

ABSTRACT

The proportion of patients with new-onset heart failure who have preserved rather than reduced left ventricular ejection fraction (HFpEF and HFrEF) has been increasing over recent decades.

In fact, HFpEF now outweighs HFrEF as the predominant heart failure subtype and likely remains underdiagnosed in the community. This is due in part to an ageing population and a rise in other risk factors for HFpEF, including obesity and associated cardiometabolic disease.

Whereas the diagnosis of HFrEF is relatively straightforward, the diagnosis of HFpEF is often more challenging because there can be other causes for symptoms, including dyspnea and fatigue, and cardinal physical examination findings of elevated jugular venous pressure or pulmonary congestion may not be evident at rest.

In 2022, the American College of Cardiology, the American Heart Association, and the Heart Failure Society of America published a comprehensive guideline on heart failure that included recommendations for the management of HFpEF. The use of diuretics for the management of congestion remained the only class 1 (strong) recommendation. New recommendations included broader use of sodium-glucose cotransporter-2 inhibitors (SGLT2i, class 2a) and angiotensin receptor-neprilysin inhibitors (class 2b). In 2023, the American College of Cardiology published an expert consensus decision pathway for the management of HFpEF that suggests treatment strategies based on sex assigned at birth, ejection fraction, clinical evidence of congestion, and candidacy for SGLT2i therapy.

Here, two experts, a cardiologist and a geriatrician, discuss their approach to the diagnosis and management of HFpEF and how they would apply guidelines to an individual patient.

READING 10 – ASIAN PATIENTS WITH HFPEF

Tay JCK,[1] Chia SY,[1] Sim DKL,[1] Yap J,[1] Koh SHM,[2] Chai P,[3] Loh SY,[4] Jaufeerally FR,[5] Guang Lee SS,[6] Yun Lim PZ.[7] Clinical characteristics and outcomes in Asian patients with heart failure with mildly reduced ejection fraction. Singapore Med J. 2023 May 30.

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Author information:
[1]Department of Cardiology, National Heart Centre Singapore, Singapore
[2]Department of Respiratory Medicine, Singapore General Hospital, Singapore
[3]Department of Cardiology, National University Heart Centre, National University Hospital, Singapore
[4]Department of Cardiology, Tan Tock Seng Hospital, Singapore
[5]Department of Internal Medicine, Singapore General Hospital, Singapore
[6]Department of Cardiology, Changi General Hospital, Singapore
[7]Department of Cardiology, Khoo Teck Puat Hospital, Singapore

ABSTRACT

INTRODUCTION: Data on heart failure (HF) with mildly reduced ejection fraction (HFmrEF) is still emerging, especially in Asian populations. This study aims to compare the clinical characteristics and outcomes of Asian HFmrEF patients with those of HF patients with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF).

METHODS: Patients admitted nationally for HF between 2008 and 2014 were included in the study. They were categorised according to ejection fraction (EF). Patients with EF <40%, EF 40%-49%, and EF ≥50% were categorised into the following groups: HFrEF, HFmrEF, and HFpEF, respectively. All patients were followed up till December 2016. Primary outcome was all-cause mortality. Secondary outcomes included cardiovascular death and/or HF rehospitalisations.

RESULTS: A total of 16,493 patients were included in the study: HFrEF, n=7,341 (44.5%); HFmrEF, n=2,272 (13.8%); and HFpEF, n=6,880 (41.7%). HFmrEF patients were more likely to be gender neutral, of mid-range age, and have concomitant diabetes mellitus, hyperlipidaemia, peripheral vascular disease, and coronary artery disease (P<0.001). The two-year overall mortality rates for HFrEF, HFmrEF, and HFpEF were 32.9%, 31.8%, and 29.1%, respectively. HFmrEF patients had a significantly lower overall mortality rate compared to HFrEF patients (adjusted hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.83-0.95; P<0.001) and a significantly higher overall mortality rate (adjusted HR 1.25, 95% CI 1.17-1.33; P<0.001) compared to HFpEF patients. This was similarly seen with cardiovascular mortality and HF hospitalisations, with the exception of similar HF hospitalisations between HFmrEF and HFpEF patients.

CONCLUSION: HFmrEF patients account for a significant burden of patients with HF. HFmrEF represents a distinct HF phenotype with high atherosclerotic burden and clinical outcomes saddled in between those of HFrEF and HFpEF. Further therapeutic studies to guide management of this challenging group of patients are warranted.