Selected Summaries

The use of sodium-glucose cotransporter 2 inhibitor in heart failure: *The rise of the Roman Empire!*

Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators. (Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, USA; Imperial College and Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London; BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow; Department of Cardiovascular Sciences, University of Leicester and National Institute for Health Research Biomedical Research Centre, Glenfield Hospital, Leicester—all in the UK; Department of Cardiology and Berlin Institute of Health Center for Regenerative Therapies, German Center for Cardiovascular Research Partner Site Berlin, Charité Universitätsmedizin, Berlin; Boehringer Ingelheim International, Ingelheim, Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Boehringer Ingelheim Pharma, Biberach, Klinik für Innere Medizin III, Saarland University, Homburg–Saar, and the Department of Medicine, University Hospital of Würzburg, Würzburg—all in Germany; Department of Medicine, University of Mississippi School of Medicine, Jackson, USA; National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, Athens; Washington DC Veterans Affairs Medical Center, Washington DC, USA; the Division of Cardiology, Harvard Medical School and Massachusetts General Hospital, Boston, USA; Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, Toronto; Boehringer Ingelheim Canada, Burlington, ON; and the Division of Cardiology, McGill University and Health Centre, Montreal—all in Canada; Department of Cardiovascular Medicine, Kyushu University, Higashi-ku, Fukuoka, Japan; Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA; Heart Institute, São Paulo University Medical School, São Paulo, Brazil; Department of Medicine, Seoul National University, Seoul, South Korea; Department of Cardiology, Max Super Speciality Hospital, Saket, New Delhi, India; Department of Clinical Cardiology, National Institute of Cardiology, Mexico City, Mexico; Department of Cardiology, University Hospital Gasthuisberg of Leuven, Leuven, Belgium; Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Cardiology Department, University Hospital, Santiago de Compostela, Spain; Department of Cardiology, Cedars–Sinai Medical Center, Los Angeles, USA; Maastricht Heart and Vascular Center, Maastricht, the Netherlands; Heart and Vascular Center, Semmelweis University, Budapest, Hungary; Victorian Heart Institute and Monash University, Melbourne, VIC, Australia; Fleni Institute and Hospital El Cruce–Nestor Kirchner, Buenos Aires, Spain; Department of Medicine, Wayne State and Central Michigan Universities, Detroit, USA; Center for Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; Cardiovascular Department, Papa Giovanni XXIII Hospital, Bergamo, and the Department of Clinical and Experimental Medicine, University of Pisa, Pisa—both in Italy; Department of Cardiology, University Hospital Jean Minjoz, Besançon, Université de Lorraine, INSERM Investigation Network Initiative–Cardiovascular and Renal Clinical Trialists, Centre Hospitalier Régional Universitaire, Nancy—both in France; and Internal Cardiology, University Hospital Brno, Brno, Czech Republic.) Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;**383:**1413–24.

Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La R. Hans-Peter, Choi Dong-Ju, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M, EMPEROR-Preserved Trial Investigators. (Department of Cardiology and the Berlin Institute of Health Center for Regenerative Therapies, German Center for Cardiovascular Research partner site Berlin, Charité Universitätsmedizin Berlin, Berlin, Universitätsklinikum des Saarlandes, Homberg, RWTH Aachen University, Aachen, Boehringer Ingelheim Pharma, Biberach, Boehringer Ingelheim International, Ingelheim; Faculty of Medicine Mannheim, University of Heidelberg, Mannheim—all in Germany; University of Mississippi Medical Center, Jackson, USA; National and Kapodistrian University of Athens School of Medicine, Athens, Greece; Université de Lorraine, INSERM, Centre d'Investigations Cliniques Plurithématique 1433, and INSERM Unité 1116, CHRU, F-CRIN INI-CRCT [Cardiovascular and Renal Clinical Trialists], Université de Lorraine, INSERM INI-CRCT, CHRU—both in Nancy, France; Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto, Portugal; Unidade de Insuficiência Cardíaca, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil; Maastricht University Medical Center and the School for Cardiovascular Disease CARIM—both in Maastricht, the Netherlands; Department of Medicine, Seoul National University Bundang Hospital, Seoul, South Korea; Max Superspeciality Hospital, Saket, New Delhi, India; National Institute of Cardiology, Mexico City, Mexico; McGill University Health Centre, Montreal, and St Michael's Hospital, University of Toronto, Toronto—both in Canada; Cardiology Service, Fundación Valle del Lili, Universidad Icesi, Cali, Colombia; Department of Cardiovascular Diseases, University Hospitals Leuven, Leuven, Belgium; Massachusetts General Hospital and Baim Institute for Clinical Research, Boston, USA; University Hospital, Santiago de Compostela, Spain; Heart and

Vascular Center, Semmelweiss University, Budapest, Hungary; Victorian Heart Institute, Monash University, Melbourne, VIC, Australia; Argentine Catholic University, and Medical Advisor in Heart Failure, Pulmonary Hypertension and Intrathoracic Transplant at FLENI and IADT Institute—both in Buenos Aires, Spain; Central Michigan University, Mount Pleasant, USA; Wroclaw Medical University, Wroclaw, Poland; Cardiovascular Department, Cardiology Division, Papa Giovanni XXIII Hospital, Bergamo, and Università di Pisa, Pisa—both in Italy; National Heart Centre Singapore, Singapore; Internal Cardiology Department, St Ann University Hospital and Masaryk University, Brno, Czech Republic; University of Leicester, Glenfield General Hospital, Leicester, University of Glasgow, Glasgow, London School of Hygiene and Tropical Medicine, and Imperial College, London—all in the UK; Kyushu University, Fukuoka, Japan; University of Medicine and Pharmacy, Carol Davila University and Emergency Hospital, Bucharest, Romania; Heart Failure Center, Fuwai Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China; Veterans Affairs Medical Center, Washington, DC, USA; National Heart Centre Singapore, Duke-National University of Singapore, Singapore; Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT and Baylor Heart and Vascular Institute, Dallas—both in the USA.) Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;**385:**1451–61.

SUMMARY

The EMPEROR-Reduced trial pitted empagliflozin (10 mg) versus placebo in patients of heart failure with reduced ejection fraction (HFrEF) with or without diabetes mellitus. Stable outpatients with left ventricular ejection fraction (LVEF) <40% with New York Heart Association (NYHA) functional class II–IV who were already on guideline-directed medical therapy (GDMT) were considered for enrolment if they had either elevated NT-pro-BNP or had history of admission for HF in the past 12 months. Patients who had a recent myocardial infarction or stroke, were recipients of heart transplant, had infiltrative cardiomyopathies, peripartum cardiomyopathy, severe valvular heart disease, device implantation within 3 months and acute heart failure were excluded. The trial enrolled 5988 patients over 3 years across 23 countries. The primary outcome was a combination of cardiovascular (CV) death or hospitalization for heart failure (HHF). At follow-up of 16 months, primary outcome occurred in 19.4% in the empagliflozin group and 24.7% in the placebo group (hazard ratio [HR] 0.75; 95% CI 0.65–0.86; p<0.001] resulting in a 25% relative risk reduction. The total HHF were lower in the empagliflozin group than in the placebo group—13.2% *v*. 18.3% (HR 0.70; 95% CI 0.58–0.85; p<0.001). The number of CV deaths were slightly lower with empagliflozin therapy though it did not reach statistical significance (10% *v*.11%; HR 0.92; 95% CI 0.75–1.12; p>0.05). The improved primary outcome was observed irrespective of diabetes status, age, sex, race, cause of HF, use of other GDMT, baseline estimated glomerular filtration rate (eGFR) and geographical region. Interestingly, the HR for primary events were lowest for Australia and India though the number of participants were less. The rate of decline of eGFR was also lower in the empagliflozin group than in the placebo group (–0.55 *v*.–2.28 ml per minute per 1.73 m² body surface area/year; p<0.001). Composite of renal outcomes (defined by investigators as time to occurrence of need for chronic dialysis orneed for renal transplant or fall of eGFR by >40% or severe reduction of eGFR <15 ml/minute) was also reduced by 50% with empagliflozin. The rates of hospitalization for any cause were lower with empagliflozin while the improvement in Kansas City Cardiomyopathy Questionnaire Quality of life score was higher. The side-effect profile was similar to placebo except for uncomplicated genital tract infections, which were more common in the empagliflozin group.

After the significantly better outcomes seen in HFrEF patients, empagliflozin was studied in the EMPEROR-Preserved trial to look for cardiovascular outcome benefits in heart failure with preserved ejection fraction (HFpEF) patients, where around 6000 patients with NYHA class II–IV HF and LVEF ≥40% received empagliflozin 10 mg or placebo in addition to GDMT. The primary outcome studied was the same as in EMPEROR-Reduced trial. Over a follow-up period of 26 months, CV death and HHF occurred in 13.8% in the empagliflozin group and 17.1% in the placebo group (HR 0.79; 95% CI 0.69–0.90; p<0.001). The 21% reduction in primary outcome was driven principally by attenuation in HHF, which occurred in 8.6% in the empagliflozin group *v*. 11.8% in the placebo group (HR 0.73; 95% CI 0.61–0.88; p<0.001). Interestingly, the empagliflozin arm had a lower total HHF (summation of first and subsequent HHF) and a longer time to first HHF. The rate of CV death was lower in the empagliflozin group (7.3%) than in the placebo group (8.2%); however, it did not reach statistical significance, mirroring results from the previous study in patients with reduced EF. The fall in eGFR was lower in the empagliflozin group than in the placebo group (–1.25 versus –2.62 ml per minute per 1.73 m² body surface area per year, p<0.001). The improved outcome inthe empagliflozin group was irrespective of the status of diabetes, age, sex, race, eGFR at baseline, LVEF at baseline, baseline systolic blood pressure and presence of atrial fibrillation. However, uncomplicated genital and urinary tract infections and hypotension were reported more commonly in the empagliflozin group.

These trials have shown a significant reduction in relative risk of the combined outcome of CV death and HHF. This was mainly attributed to lower rates of HHF. In the EMPEROR-Reduced trial, the risk of combined CV death and HHF was 25% less among patients taking empagliflozin versus placebo, which was mainly because of 30% lower HHF in patients taking empagliflozin. In the EMPEROR-Preserved trial, the relative risk of CV death and HHF was 21% lower, which was mainly attributed to the 29% lower risk of HHF in the empagliflozin group. The number needed-to-treat for preventing one primary outcome event in these studies was 19 and 31, respectively. Almost parallel results obtained with empagliflozin in the two contrasting phenotypes of HF make the drug unique in its efficacy across the spectrum of HF. Among the hitherto available armamentarium for HF, the SGLT-2 inhibitors appear to be a cut above the rest.

COMMENT

HF is a chronic condition with huge morbidity and mortality affecting >26 million people globally.[1] In India, the prevalence is 2.0–4.5 million by conservative estimates.[2] However, despite optimal medical therapy, patients of HF continue to have high mortality and readmission rates.[3] Hence, there is a clear unmet need in pharmacotherapy for HF. Moreover, majority of the drugs for HF are approved for patients with reduced EF (LVEF<50%) while therapeutic options for those with preserved EF (LVEF>50%) are limited.[4] Unfortunately, HF with preserved EF now accounts for up to 50% of HF burden with similar morbidity and mortality.

Approved first by the US Food and Drug Administration (FDA) in 2013, sodium-glucose cotransporter 2 (SGLT-2) inhibitors are a class of drugs approved to lower blood sugar in type 2 diabetes mellitus. They can be used as monotherapy or in combination with other anti-diabetic drugs.[5] They reduce blood sugar by inhibiting the reabsorption of glucose in the kidney by inhibiting SGLT-2. The FDA-approved SGLT-2 inhibitors canagliflozin, dapagliflozin, empagliflozin and

ertugliflozin. With the emergence of large cardiovascular outcome trials—EMPA-REG OUTCOME (2015), CANVAS (2017), CREDENCE (2019) DECLARE-TIMI 58 (2019), the CV safety of SGLT-2 inhibitors was established.[6] It was shown that SGLT-2 inhibitors when used as in people with diabetes as a hypoglycaemic agent reduced CV death, HHF and renal events.[7] The reduction of HHF was impressive and was comparable to that achieved by ivabradine (in SHIFT trial) and angiotensin receptor blocker-neprilysin inhibitor (in PARADIGM-HF trial). Multiple mechanisms have been proposed to explain these outstanding CV and renal benefits.[8] However, these trials did not include patients of HF *per se* and there was lack of clarity on echocardiographic EF details in many patients.

The subsequent trials of SGLT-2 inhibitors are of pivotal importance as they have enrolled HF patients *per se* with or without diabetes mellitus. Three agents, i.e. dapagliflozin, empagliflozin and sotagliflozin, have been tested in HF with reduced EF while only empagliflozin has been used in HF with preserved EF. The DAPA-HF trial was the first to report the use of SGLT-2 inhibitors in heart failure *per se*. In the DAPA-HF trial, 4744 patients of HF (defined by EF <40%) and NYHA class II–IV who were already on GDMT were randomized to dapagliflozin 10 mg or placebo. The primary outcome was a composite of CV death and HHF similar to the EMPEROR trials. At a follow-up of 18.2 months, the primary outcome occurred in 16.3% patients in the dapagliflozin group and in 21.2% in the placebo group—a significant 26% risk reduction (p<0.001). HHF occurred in 10% in the dapagliflozin group and 13.7% in the placebo group translating into significant 30% relative risk reduction in HHF with dapagliflozin (HR 0.70; 95% CI 0.59–0.83). Simultaneously, CV death occurred in 9.6% in the dapagliflozin group and 11.5% in the placebo group (HR 0.82; 95% CI 0.69–0.98). Death from any cause was also lower by 17% in the dapagliflozin arm (HR 0.83; 95% CI 0.71–0.97). A better primary outcome was observed irrespective of the status of diabetes. The number needed-to-treat to prevent one primary outcome event was 21, which is comparable to empagliflozin. The adverse events of renal dysfunction, hypotension and hypoglycaemia were similar in the two groups.[9] Then came EMPEROR-Reduced study with results described above. Though both these trials were comparable, EMPEROR-Reduced enrolled more advanced HF patients based on NT-pro-BNP levels and had higher occurrence of primary outcome events. The effect on CV deaths was more pronounced and significant with dapagliflozin than with empagliflozin (18% reduction *v.* 8% reduction). Additionally, dapagliflozin is now off patent and hence cheaper in comparison to empagliflozin. Nevertheless, based on positive outcome both drugs have obtained FDA approval as well as an approval from the Drug Controller General of India for use in HF with reduced EF. However, from a public health perspective, dapagliflozin appears more appealing and cost-effective.

One important caveat is that both studies enrolled chronic HF patients in the outpatient setting, hence empagliflozin therapy should be contemplated in similar settings. Positive data have emerged from SGLT-2 inhibitor use in acute HF setting from the SOLOIST-WHF study.[10] The SOLOIST-WHF trial has shown that sotagliflozin improves composite end-point of CV death and HHF in people with diabetes with recent worsening of HF when it is started before or early after discharge. A total of 1222 patients were enrolled in the study and followed for 9 months. Sotagliflozin or placebo was started before discharge in 48.8% of patients and shortly after discharge, at a median of 2 days, in 51.2% of patients. The primary end-point occurred in 51% in the sotagliflozin group and 76.3% in the placebo group (HR 0.67; 95% CI 0.52–0.85; p<0.001). CV death occurred in 10.6% in the sotagliflozin group and 12.5% in the placebo group (HR 0.84; 95% CI 0.58–1.22). The death rate from any cause was 13.5% in the sotagliflozin group and 16.3% in the placebo group (HR 0.82; 95% CI 0.59–1.14). The adverse drug effects of hypotension and acute kidney injury were similar in both groups, but diarrhoea and severe hypoglycaemia were more common in the sotagliflozin group than in the placebo group (6.1% *v.* 3.4% and 4.1% *v.* 4.4%, respectively)

For HF with preserved EF, the dismal performance of standard HF therapies, namely angiotension converting enzyme inhibitors/angiotension receptor blockers, beta blockers and mineralocorticoid receptor antagonists has been a cause of concern.[4] Even angiotension receptor neprilysin inhibitor therapy failed to show any difference in the primary end-point compared to placebo in the PARAGON-HF trial in this subset.[11] The success of empagliflozin in the EMPEROR-Preserved study comes as a shot in the arm for pharmacotherapy for HF. Practically, it is the only therapy in HF with preserved EF with unequivocal benefits on CV outcomes. Some positive data with dapagliflozin in patients of HF with preserved EF have also emerged from the PRESERVED-HF trial.[12] In this study, 342 patients of HF with preserved EF were enrolled for 12 weeks. Improvement in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CS) was the primary end-point. Not only dapagliflozin improved the primary end-point by 5.8 points, but it also improved many secondary end-points such as KCCQ-total score, KCCQ-physical limitation score, KCCQ-overall score and 6-minute walk distance. The benefits were present irrespective of the status of diabetes and range of EF. A large randomized trial (*n*=6263) of dapagliflozin in patients diagnosed with HF with preserved EF has already completed enrolment (DELIVER-NCT03619213) and is expected to present results next year. Interestingly, 21% of patients in the SOLOIST-WHF had EF >50%. There was no heterogeneity in treatment effect in the pre-specified analysis based on EF cut-off of 50%.[10] A pooled analysis of two sotaglifloz in trials revealed that the drug was beneficial across the spectrum of EF.[13] The effect of HF with preserved EF also appears to be a class effect like that in HF with reduced EF.

SGLT-2 inhibitors are now recommended as first-line therapy for HF at par with other established therapy in the recent 2021 version of HF guidelines of the European Society of Cardiology.[14] As these drugs do not need any dose up-titration and benefits have been evident in the trial as early as first month after initiation, some authors initiate them at the earliest after a diagnosis of *de novo* HF is made.[15] More importantly impressive benefits in renal outcomes are also observed simultaneously.

To conclude, SGLT-2 inhibitor are a new class of drugs initially approved for glycaemic control in type 2 diabetes. However, the CV outcome trials revealed impressive benefits in HHF and CV death in primary prevention. Four large randomized trials (three in reduced EF and one in preserved EF) have shown improved CV outcomes in HF patients *per se*. Simultaneously, improved kidney outcomes augur well for HF patients too. These drugs herald a new era in HF pharmacotherapy acting across the spectrum of disease—acute or chronic, preserved EF or reduced EF.

REFERENCES

1 Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017;**3:**7–11.
2 Huffman MD, Prabhakaran D. Heart failure: Epidemiology and prevention in India. *Natl Med J India* 2010;**23:**283–8.
3 Harikrishnan S, Jeemon P, Ganapathi S, Agarwal A, Viswanathan S, Sreedharan M, *et al*. Five-year mortality and readmission rates in patients with heart failure in India: Results from the Trivandrum heart failure registry. *Int J Cardiol* 2021; **326:**139–43.
4 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, *et al*.; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18:**891–975.
5 Tat V, Forest CP. The role of SGLT2 inhibitors in managing type 2 diabetes. *JAAPA* 2018;**31:**35–40.
6 Pradhan A, Vohra S, Vishwakarma P, Sethi R. Review on sodium-glucose cotransporter 2 inhibitor (SGLT2i) in diabetes mellitus and heart failure. *J Family Med Prim Care* 2019;**8:**1855–62.
7 McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, *et al*. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: A meta-analysis. *JAMA Cardiol* 2021;**6:**148–58.
8 Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: A state-of-the-art review. *JACC Basic Transl Sci* 2020;**5:**632–44.
9 McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al*. DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381:** 1995–2008.
10 Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, *et al*; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;**384:**117–28.
11 Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, *et al*; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibitor in heart failure with preserved ejection fraction. *N Engl J Med* 2019; **381:**1609–620.
12 Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, *et al*. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: A multicenter randomized trial. *Nat Med* 2021;**27:**1954–60.
13 Koufakis T, Mustafa OG, Tsimihodimis V, Ajjan RA, Kotsa K. Insights into the results of sotagliflozin cardiovascular outcome trials: Is dual inhibition the cherry on the cake of cardiorenal protection? *Drug* 2021;**81:**1365–71.
14 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42:**3599–726.
15 McMurray JJV, Packer M. How should we sequence the treatments for heart failure and a reduced ejection fraction?: A redefinition of evidence-based medicine. *Circulation* 2020;**143:**875–77.

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H2 blockers in the prevention of paclitaxel-related hypersensitivity reaction

Cox JM, van Doorn L, Malmberg R, Oomen-de Hoop E, Bosch TM, van den Bemt PM, Boere IA, Jager A , Mathijssen Ron HJ, van Leeuwen Roelof WF. (Department of Clinical Pharmacy and Maasstad Lab, Maasstad Hospital, Rotterdam; Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam; Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam; Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen; Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam—all in the Netherlands.) The added value of H2 antagonists in premedication regimens during paclitaxel treatment. *Br J Cancer* 2021;**124:**1647–52.

SUMMARY

Dexamethasone and histaminic (H1 and H2) blockers are routinely used as pre-medication drugs for the paclitaxel-related hypersensitivity reaction (HSR). The inclusion of this strategy was more empirical than evidence-based following the initial experience with life-threatening HSR during phase 1 studies done in early 1981.[1] The inclusion was to reciprocate the prevention strategy similar to contrast-induced HSR.[2] People worldwide continued to use the same preventive measures over the past 40 years. Of the three components of a preventive strategy, the most argued one is the role of H2 receptor antagonists.[3] We congratulate Cox *et al*. for raising and successfully testing the research question. However, they selected a pre–post interventional study. A randomized study design is a preferred scheme to get a value close to the true one. In this study, steroids and clemastine (H1 blockers) were given with or without ranitidine (H2 blockers) during October 2018 to April 2019 and April to December 2019. The study design was an open-labelled, non-randomized, non-inferiority trial. The trial enrolled adult patients (18 years or above) who were to receive the first cycle of conventional paclitaxel (weekly or three-weekly, with or without partner drug) for a maximum of six cycles. The primary end-point was the incidence of grade 3 or more HSR. The sample size was 366 with a 6% non-inferiority margin, 90% power and a one-sided alpha error of 0.05. The common tumour type was oesophagus (42%), breast (32%), lung (9%) and gynaecological (14%). In both the arms, an equal proportion of patients received corticosteroids (9.8%) and antihistamines (4.95) for other associated comorbid conditions. In the two study arms with and without ranitidine, the rate of all grades HSR was (20% *v.* 12%), grade 3 or higher HSR (4.4% *v.* 1.6%) and grade 1–2 HSR (16% *v.* 10%).[4] The difference between the two arms was –2.7% (90% CI –6.2% to 0.1%). The present study concluded that ranitidine (H2 blocker) can be safely omitted from the standard paclitaxel pre-medication strategy.

COMMENT

It is good to see a real-life, simple question being addressed, which has remained neglected for the past four decades. Although ranitidine is a cheap drug, its routine use with paclitaxel (one of the most commonly used chemotherapy drugs) adds cost to cancer care. Interestingly, the rate of severe