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ESC Congress 2022 Barcelona

Presents

DAILY COVERAGE OF

EUROPEAN SOCIETY OF CARDIOLOGY CONGRESS

August 26 – 29, 2022

TOP 7 SESSIONS
DAILY COVERAGE
DAY-1

TOPIC OF CONTENT

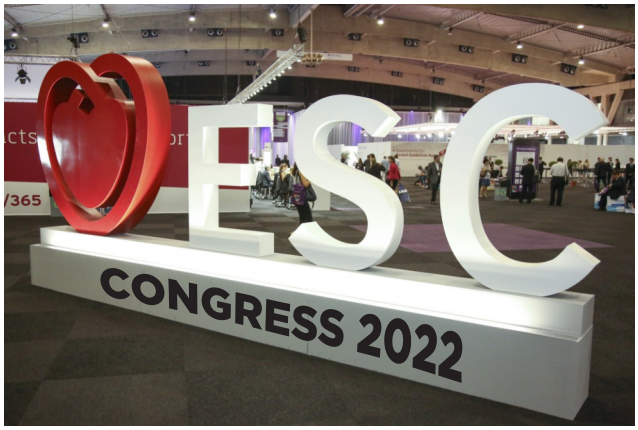
WELCOME TO ESC CONGRESS 2022

Barcelona Friday, August 26th, 2022

The European Society of Cardiology Annual Congress began in Barcelona on August 26th 2022. In the inaugural address "ESC Congress is a great opportunity to share the 'Magic of Cardiology' together," says ESC President, Professor Stephan Achenbach. "Whether it's the sense of excitement as we learn about advances in cardiovascular therapies or the feeling of being part of the ESC community, ESC Congress is an experience like no other. And with the spotlight on cardiac imaging, we will highlight the contributions of modern visualisation techniques to our understanding of the cardiovascular system, towards refined diagnosis and highly personalised therapy."

At the ESC, diversity is the strength, and Professor Stephan Windecker, ESC Congress Programme Committee Chair, is keen to point out the far-reaching nature of this year's sessions: "ESC Congress has evolved into a global event and we have harnessed the power of international representation across our vast programme and activities." He notes, "In terms of new science and education, it is the collective wisdom that comes from all our global contributors, which makes such a great difference."

"The programme has been designed to facilitate sharing of knowledge, learning and interaction for everyone, whether participating in Barcelona or online. The most innovative scientific updates from late-breaking clinical trials and groundbreaking studies will be featured in 10 Hot Line sessions, which will be streamed live. In addition, four new ESC Clinical Practice Guidelines will be presented and discussed, with additional sessions focussing on the use of previous years' guidelines in clinical practice. In the Hubs (Channel 2), you can meet the Guidelines Task Forces and also take part in great debates on important questions that



healthcare professionals working in cardiology face routinely. International specialists will provide cutting-edge insights in nine topic-based lecture rooms, with an emphasis on panel discussions and audience participation." Explained Prof. Windecker.

Diversity is clearly on display on the Global Stage, at the heart of the Global Community area. A series of international joint sessions will take place and insights on hot topics, with a local flavour, will be offered by ESC Member Cardiac Societies in the Daily Highlights programme.

The Research Gateway will showcase more than 3,700 abstracts and over 100 clinical cases in the Clinical Case Corner, Science Boxes and via ePosters. Notably, for the first time, all posters will be moderated by experts at 10 topic-based stations to drive learning and exchange. The online audience will be able to follow abstract presentation sessions via Zoom and will have access to all ePosters via the online Research Gateway.

"For this special return to a face-to-face congress, there are some exciting new features in the Lounge & Exchange Area for everyone to enjoy," says Prof. Achenbach. "Read about them in the Congress News and make sure to drop by to see for yourself."

And a final thought from Prof. Windecker before the congress begins: "Since 1952, ESC Congress has been uniting experts and expanding knowledge. As we celebrate 70 years of ESC Congresses, let's drive forward the scientific exchange that allows cardiology to progress – let's keep the magic flowing!"

NO HINTS OF COGNITIVE DEFECTS WITH ARNIs IN HFpEF: PERSPECTIVE

Barcelona Friday, August 26th, 2022

The PERSPECTIVE study was presented on the first day of the ESC Congress 2022 at Barcelona on August 26th 2022. There are no signs that sacubitril/valsartan (Entresto; Novartis) has any negative impact on cognitive function in people who have heart failure with preserved ejection fraction (HFpEF), at least over a 3-year period, when compared with HFpEF patients taking valsartan alone.

That's the key takeaway from PERSPECTIVE, a randomized, controlled trial that subjected participants to a battery of tests to assess the three main cognitive domains: attention, episodic memory, and executive function. It showed no more hints of cognitive deterioration among patients randomized to the angiotensin receptor-neprilysin inhibitor (ARNI) than to those randomized to the ARB alone. Serial PET imaging in a subset of patients actually revealed a trend towards less amyloid β deposition in the ARNI-treated patients.

"This study, I think, should remove any concern about the safety of neprilysin inhibition related to cognition," presenter John McMurray, MD (University of Glasgow, Scotland), said here at the European Society of Cardiology Congress 2022. "It's questionable whether there really ever was a safety concern, but it had been raised and I believe that we've addressed it. I hope that means that more people with heart failure can be treated with sacubitril/valsartan because it has many benefits, and in patients with heart failure with reduced ejection fraction, that includes an improvement in survival."

This trial, McMurray noted, studied patients with midrange and preserved ejection fraction-it wouldn't have been ethical to randomize heart failure patients with reduced ejection fraction to valsartan, he said-but there is no reason to think that the lack of cognitive side effects would be any different across the spectrum of heart failure.

Indeed, he said, "these results may also open new avenues for use of sacubitril/valsartan. It is a very potent blood pressure-lowering drug, and it might be useful in hypertension. It's use in hypertension really hasn't been developed because of this cloud about potential cognitive problems. Hypertensive treatments are given for a very long time; you would never want to give treatment that might cause cognitive dysfunction.

In a more-sobering takeaway from the study, however, McMurray noted that subtle cognitive dysfunction was "remarkably common" among the patients in PERSPECTIVE-affecting almost two-thirds of patients in the trial. "We really don't know why it occurs, [and] we need to find out," he said.

Required by Regulators

At the time sacubitril/valsartan was approved for use in HFrEF, regulatory bodies, including the US Food and Drug Administration, requested a randomized study checking for any neurocognitive signals. The impetus, McMurray explained, stems from the fact that sacubitril inhibits neprilysin, which is one of a host of enzymes involved in the degradation of amyloid β peptides, one of which (Aβ 1-42) has been linked to Alzheimer-type dementia. Sustained neprilysin inhibition increases concerns that amyloid β peptides might accumulate, he said.

This study, I think, should remove any concern about the safety of neprilysin inhibition related to cognition.

PERSPECTIVE enrolled just under 600 patients, randomized equally to the ARNI or the ARB. Anyone with prior known cognitive deficits was excluded from the trial.

At 36 months, results on the CogState global composite score capturing all three cognitive domains were no different between groups, which mirrored each other at time points throughout the 3-year follow-up. In a subgroup of 491 patients who underwent amyloid imaging, patients taking sacubitril/valsartan actually had less evidence of amyloid β deposition compared with those on valsartan alone.

This might just be the play of chance, McMurray noted, adding that he hopes the findings, taken together, will alleviate any concerns physicians might have about starting a patient on these agents, which have proved lifesaving in HFrEF patients.

McMurray noted that prior studies have established that valsartan alone has no cognitive side effects and in fact might even be neuroprotective, so for sacubitril/valsartan to match this comparator is reassuring. What's less clear, he said, is whether a 3-year follow-up period would be enough to detect any cognitive decline.

"We chose 3 years because in the lifetime of the patient with heart failure, that's a very large proportion of the remainder of their life," he said, "and it was a balance between the feasibility of doing a study like this."

Biykem Bozkurt, MD, PhD (Baylor College of Medicine, Houston TX), the scheduled discussant in the Hot Line session, congratulated the authors for completing the only randomized, controlled trial addressing cognitive dysfunction in this setting, calling the results "very reassuring.

"There are open questions, she continued-some of which additional analyses of PERSPECTIVE could address-including any differences in sacubitril/valsartan effects between midrange and preserved ejection fraction patients, or any signal of harm among carriers of the APOE4 gene, known to increase the risk of Alzheimer's.

Indeed, Bozkurt said, while it was totally reasonable of PERSPECTIVE investigators to exclude patients with known cognitive problems or cerebrovascular disease, not knowing how these patients fare on an ARNI leaves open the possibility that those with higher baseline risk might be more susceptible to amyloid β deposition.

"In Alzheimer's disease, very subtle and small changes in cognitive dysfunction and amyloid β become detectable over decades, usually preceding a diagnosis: whether 3 years is adequate to detect these changes and rule out the long-term effects is debatable," she commented.

Beyond ARNIs

McMurray called PERSPECTIVE the "hardest trial we've ever had to do." Investigators did 1,200 brain scans to screen patients for entry, then performed serial scans at baseline and at 18 and 36 months-no mean feat in a heart failure population.

The "high prevalence of subtle cognitive dysfunction in patients with heart failure detected with a comprehensive battery of tests is notable and deserves further investigation," McMurray concluded. Speculating during a press conference as to what might be driving this decline, he noted that it might just be a factor of aging-more than a third of patients in PERSPECTIVE were over age 75 (average age 72.4 years; 46.8% women).

"Of course, those are patients who are more susceptible to declines in cognitive function over time: they have more comorbidity, especially atrial fibrillation, and that's a particularly strong predictor of cognitive dysfunction," McMurray said. Other possible contributing factors are reduced cerebral blood flow, inflammation, or hospitalizations. This last is one that McMurray said he finds particularly intriguing, pointing to

studies documenting the cognitive decline seen in hospitalized patients. Cognitive function can take a long time to recover-if at all-once patients are discharged home.

Bozkurt, also highlighting the high proportion of heart failure patients found to have signs of cognitive deterioration, called for longer trials, but also, perhaps, "characterization of what happens to the brains of heart failure patients, regardless of the treatment."

FIRST CARDIO-ONCOLOGY GUIDELINES FROM ESC COVER 'TREMENDOUS' TERRITORY

Barcelona **Friday, August 26th, 2022**

For the first time, the European Society of Cardiology (ESC) has released a guideline aimed at physicians involved in the care of cancer patients and survivors that is focused on CV health and wellness before, during, and after treatment.

Cardio-oncology, a growing field, in the last few years has been the subject of a consensus statement from the Society for Cardiovascular Angiography and Interventions (SCAI) on managing cancer patients in the cath lab, as well as a practice guideline from the American Society of Clinical Oncology (ASCO) on cardiac dysfunction in survivors.

Details of the new guideline were presented today at the European Society of Cardiology Congress 2022 in conjunction with its publication online in the European Heart Journal. The ESC developed the document in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO), and the International CardioOncology Society (IC-OS).

"This is an authoritative document, and it covers a tremendous amount of territory," Daniel J. Lenihan, MD (Saint Francis Medical Center, Cape Girardeau, MO), one of the document's authors and the president of IC-OS, spoke of the 133-page document that the committee spent more than 2 years creating. He added that among the goals they set were to broaden the scope of what those prior cardio-oncology documents had been able to accomplish.

"Over the last few years, the depth and breadth of important developments in the field has been very large, and this is an area with a high level of interest [as evidenced by] it now having its own journal, JACC: CardioOncology," Lenihan added. While the size of the guideline might seem daunting at first, he said the committee will hold upcoming webinars to help physicians utilize it as an educational resource, with an eye toward helping those who "have patients in front of them who have cancer and are trying to figure out how to effectively manage some of these problems."

Delving Into the Guideline

Written by a committee chaired by Alexander R. Lyon, MD (National Heart and Lung Institute, Imperial College London, England), the guideline contains guidance on definitions, diagnosis, treatment, and prevention of cancer therapy-related cardiovascular toxicity (CTR-CVT), and the management of CV disease caused directly or indirectly by cancer. "This area of medicine has limited trials and evidence on which to base decision-making and, where evidence is limited, this guideline provides the consensus of expert opinion to guide healthcare professionals," the authors write.

Throughout the guideline, the authors stress that decision-making is dependent on "the risk/benefit balance of oncology treatment efficacy and the severity and impact of CTR-CVT." Managing CTR-CVT is important, they add,

since it impacts both therapeutic decision-making and long-term morbidity and mortality. An important reference in the guideline is the care pathways, which begin with baseline CV toxicity risk assessment that stratifies patients into low, moderate, and high or very high risk. A risk-assessment checklist is also included, with explanations about recommended examinations, cardiac imaging modalities, and other testing. The guidelines recommend cardiology referral for patients who are moderate risk or above, followed by the type and duration of recommended assessment. The referral should be done urgently, the document states, to minimize delays in starting cancer treatment.

"We wanted to get across the idea that that there is an important way of assessing a patient before they start therapy to get an idea how much risk for cardiovascular toxicity they may have," Lenihan said.

That's part of what these guidelines are intended to do: make you think in the [context of] the individual patient's history, how important those treatments are from a cardiovascular point of view.

CTR-CVT severity is broken down into mild, moderate, and severe/very severe, and definitions are provided for its various types, including myocarditis, vascular toxicity, arterial hypertension, and cardiac arrhythmias. Another important section of the guidelines addresses primary and secondary CTR-CVT prevention strategies, recognizing that some patients may be referred for a second cancer treatment requiring more exposure to cardiotoxic chemotherapy and/or radiation.

Yet another section describes recommended anthracycline and HER2-targeted therapy surveillance protocols from baseline through 12 months after cancer therapy. Other therapeutic areas covered include: fluoropyrimidines, vascular endothelial growth factor inhibitors, various kinase inhibitor-related CV toxicities, multiple myeloma therapies and risk factors for venous thromboembolism, proteasome inhibitor surveillance, immune checkpoint inhibitors, androgen deprivation and endocrine therapies, and hematopoietic stem cell transplantation.

Ongoing Surveillance and Considerations

The section on diagnosis and management of acute and subacute CV toxicity covers various forms of direct toxicity to the heart and other organs, cancer-associated thrombosis, bleeding complications, and PAD, among others.

The guideline also addresses the timing of when the first CV assessment should occur after cancer treatment is completed and discusses the recommended education, support, and ongoing surveillance of these patients.

"The time after their cancer treatment is done is when we can anticipate that those who had radiation therapy to any vascular beds may be more likely to develop atherosclerosis, something that is not really on many cardiologists' radars," Lenihan added.

"If you are asked to see a patient in the emergency room for chest pain, you're going to go look at their EKG and look at their blood tests and try to decide whether this is coronary artery disease or not, but you're not really going to explore their history for an important event from 10 or 15 or 20 years ago. But, if you know that they had a cancer history and radiation . . . this is where that historical event can change your decision-making," he explained. "So, that's part of what these guidelines are intended to do: make you think in the [context of] the individual patient's history, how important those treatments are from a cardiovascular point of view."

SESSION-1 :
Heart Failure in Women: Causes, Consequences, and Treatment

SEX-BASED DIFFERENCES IN TREATMENT OUTCOMES IN HFpEF: A SYSTEMATIC REVIEW

Barcelona Friday, August 26th, 2022

This paper was presented as a part of the session "Heart Failure in Women: Causes, Consequences, and Treatment on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Drs Moore and Lang from the, University of Dundee United Kingdom. Heart failure with preserved ejection fraction (HFpEF) is the prevailing heart failure phenotype among women. Disease-modifying treatment in HFpEF has proved a challenge and little is known on sex-based differences in treatment outcomes in HFpEF.

This systematic review aimed to identify drug and non-drug exercise randomized controlled trials that stratified treatment outcome by sex. A systematic literature search of PubMed for randomised controlled trials that assessed treatment outcomes by sex (pre-specified, secondary, post-hoc analysis) for HFpEF was performed until January 2021. This systematic review included 36 drug and 2 exercise RCTs. There was an increased benefit in reducing the composite outcome of first and recurrent HF hospitalisation and cardiovascular death among women (HR 0.73, 95% CI 0.59-0.90) compared to men (HR 1.03, 95% CI, 0.84-1.25, p-interaction = 0.017) treated with sacubitril-valsartan. However, women (HR 1.41, 95% CI 1.02-1.97) had higher risk of new-onset AF compared to men (HR 0.79, 95% CI 0.55,1.14, p-interaction = 0.019) taking sacubitril-valsartan, and men (Δ2.8, 95% CI 1.3-4.3) were more likely to show improvements in the KCCQ-CSS compared to women (Δ-0.6, 95% CI -2.1,0.8, p-interaction=0.003). There may be benefit among women treated with sacubitril-valsartan in lowering blood pressure and characteristic impedance. A superior risk reduction in all-cause mortality was reported in women treated with spironolactone (HR 0.66, 95% CI 0.48-0.90) when compared with men (HR 1.06, 95% CI 0.81-1.39, p-interaction=0.024). No differences in treatment outcomes by sex were reported with SGLT2 inhibitors or with exercise interventions in HFpEF.

Conclusions: Women may respond to HFpEF treatment differently than men. Identifying sex-based differences in treatment outcomes should be prioritised in future research and taken into consideration in the development of guidelines for the management of HFpEF.

DETRIMENTAL EFFECTS OF INTENSE VASODILATION IN WOMEN WITH ACUTE HEART FAILURE: NOVEL INSIGHTS FROM A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

Barcelona Friday, August 26th, 2022

This paper was presented as a part of the session "Heart Failure in Women: Causes, Consequences, and Treatment on August 26th 2022 at the ESC Congress 2022 held in Barcelona by

Dr. D Wussler from the University Hospital Basel, Department of Cardiology - Basel – Switzerland.

Guidelines recommend evaluating the risk/benefit ratio of novel therapies individually in women and men, as the pathophysiology and the response to treatment may differ according to sex. Among patients with acute heart failure (AHF), a strategy of intensive vasodilation, compared with usual care, overall did provide comparable outcomes. However, sex-specific differences in heart failure pathophysiology and the effect of the strategy in women with AHF remained unclear.

The purpose of this study was to characterize sex-specific differences in heart failure patho-physiology and to evaluate the effect of a strategy that emphasized early intensive and sustained vasodilation in women with AHF.

In a randomized, open-label blinded-end-point trial patients hospitalized for AHF were enrolled in 10 hospitals in Switzerland, Bulgaria, Germany, Brazil, and Spain. Inclusion criteria were AHF expressed by acute dyspnea and increased plasma concentrations of natriuretic peptides, systolic blood pressure ≥100 mmHg, and a plan for treatment in a general ward. Patients were randomized 1:1 to a strategy of early intensive and sustained vasodilation throughout the hospitalization or usual care. The primary end point was a composite of all-cause mortality or rehospitalization for AHF at 180 days. The subgroup analysis according to sex was predefined.

Among 781 patients who completed the trial, 288 (36.9%) were women. Women were significantly older, had a higher systolic blood pressure at presentation and a more common history of diastolic dysfunction (all ps <0.05), whereas men had a significantly higher body surface area, a more common history of ischemic heart disease and a significant lower left ventricular ejection fraction (all ps <0.05). The primary end point, a composite of all-cause mortality or rehospitalization for AHF at 180 days, occurred in 53 female patients (37.9%) in the intervention group (including 28 deaths [20.0%]) and in 35 female patients (23.6%) in the usual care group (including 22 deaths [14.9%]) (absolute difference for the primary end point, 14.3%; adjusted hazard ratio, 1.62 [95%CI, 1.05-2.50]; p = .03).

Among women with AHF, a strategy of early intensive and sustained vasodilation, compared with usual care, had a detrimental effect on a composite outcome of all-cause mortality and AHF rehospitalization at 180 days.

SESSION-2 :
New Challenges and Strategies in Cardiac Rehabilitation

SUSTAINED USAGE OF AN APP-BASED CLINICAL-DECISION MAKING AID FOR THE MANAGEMENT OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Barcelona Friday, August 26th, 2022

This paper was presented as a part of the session "New Challenges and Strategies in Cardiac Rehabilitation" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. A Pandey et al. from the University of Ottawa, Canada.

Complexity of therapies for atherosclerotic cardiovascular disease (ASCVD) risk reduction represents a challenge for clinicians and may lead to poor uptake of these therapies.

The goal of this project was to design an easy-to-use, point-of-care tool to risk stratify ASCVD patients and provide individualized guidance for clinicians to incorporate these agents. Based on the REACH registry trial and predictive modeling (including 49,689 patients with ASCVD in 44 countries), we designed and implemented an app for secondary risk assessment. Using demographic and comorbidity profiles, this tool was used to calculate an individual's 20-month risk of cardiovascular events and mortality. It also provided graphical comparison to an age-matched control with optimized cardiovascular risk profile to illustrate the modifiable residual risk. The app then utilized the patient's risk profile to provide specific guidance for possible therapeutic interventions SGLT2-inhibitors, GLP1-agonists, PCSK9-inhibitors, Vascular-dose Rivaroxaban, and Icosapent Ethyl. Additionally, it identified individuals who qualified for cardiac rehabilitation or may benefit from smoking cessation interventions, including counselling or pharmacological therapies.

"We launched a pilot test of the "Residual Cardiovascular Risk: Assessment and Management Guide" app at a regional cardiac center. 240 referring physicians (including family doctors, emergency physicians, internists, and cardiologists) were invited by email or fax to utilize the app. Feedback was solicited from all users three months into the test period. Following this, no further marketing of the app was performed for all users. Usage data was recorded using Google Analytics over a 12-month period and analyzed in 4-month increments." Explained Dr. Pandey.

From January to December 2021, our app was used to risk stratify 1576 patients. A total of 47 individual users utilized the app over this period. From January to April, the app was used on average 160 times monthly. From May to August, it was used 115 times monthly. From September to December, it was used 118 times monthly. Twenty-four physicians provided feedback; 100% affirmed the functionality, ease of use, and utility of the tool. The app was described as "useful for discussions with patients", "helpful to optimize patients" and "similar to a mini-cardiology consult". User suggestions resulted in further improvements to the app, including integration of reports into Electronic Medical Records. The early success of this app demonstrates a need for simple, accessible, and individualized guidance for management of ASCVD patients to improve uptake of guideline-based medical therapies. This tool demonstrates sustained usage among clinicians, as well as subjective utility in aiding thera-

peutic decision making. Future clinical research will focus on the ability of this tool to impact physician prescribing patterns and clinical outcomes.

FACTORS ASSOCIATED WITH EARLY CATHETERIZATION IN PATIENTS RANDOMIZED TO THE CONSERVATIVE STRATEGY IN THE ISCHEMIA TRIAL

Barcelona **Friday, August 26th, 2022**

This paper was presented as a part of the session "New Challenges and Strategies in Cardiac Rehabilitation" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. R Pacron et al. from the National Institute of Cardiology - Warsaw – Poland.

In the ISCHEMIA trial, individuals randomized to the conservative strategy (CON) could undergo coronary catheterization (cath) for suspicion of an endpoint event, persistent symptoms despite optimal medical therapy, or through protocol non-adherence. Understanding the reasons for cath in CON participants can aid in ISCHEMIA results interpretation. The purpose of this study was to describe the frequency of and factors associated with early cath in ISCHEMIA CON participants.

A prespecified, post-hoc analysis of the 2591 CON participants was performed with multivariable analyses to identify independent factors associated with cath within 6 months of randomization ("early cath"). Overall, 8.7% (225/2591) of CON participants underwent an early cath: with 4.6% (119/2591) for a suspected endpoint, 1.6% (41/2591) for medical treatment failure, and 2.6% (67/2591) for protocol non-adherence; 67% of all these caths (151/225) occurred within the first 3 months from randomization. Independent factors associated with cath among CON participants included daily (HR=5.84, CI=2.73-12.47, p<0.01) and weekly (HR=2.64, CI=1.52-4.58, p<0.01) baseline angina vs no angina, severe (HR=2.02, CI=1.03-3.95, p=0.04) and moderate baseline quality of life impairment vs no impairment (HR=2.03, CI=1.24-3.33, p=0.01), randomization in Europe vs Asia (HR=1.83, CI=1.15-2.9, p=0.01), with the proviso that all these characteristics were associated with cath occurring within the first 3 months of follow-up (very early cath), but not those between 3 and 6 months (proportional hazard assumption violation). Other factors independently associated with early cath were new or increasing angina pattern over 3 months pre-randomization (HR=1.79, CI=1.33-2.39, p<.0001) and increases in anti-anginal medication use during follow-up (HR=1.45, CI=1.06-1.98, p=0.02). Baseline LDL-C <70mg/dL (HR=0.65 CI=0.46-0.91, p=0.01) and a subsiding angina pattern during follow-up (HR=0.65, CI=0.6-0.71, p<0.01) were independently associated with a reduced hazard of early cath. Neither ischemia severity nor extent of atherosclerosis on coronary imaging showed association with cath in CON participants at 6 months.

The rate of early cath in the ISCHEMIA CON strategy was low and driven mainly by a suspected endpoint event. Severe/moderate baseline angina and quality of life impairment were independently associated with very early cath. Chances of early cath were greater with worsening pre-randomization angina and need for additional antianginal medication, and less with well controlled LDL-C and decreasing angina pattern. The baseline severity of ischemia or extent of disease on coronary imaging were not related to early cath. These results give important insight into the coronary disease treatment trajectory in the conservative strategy of the ISCHEMIA trial, further inform real-life decision making and point to the efficacy of optimal medical therapy in reducing the need for cath.

SESSION-3 :
Advances in Echocardiography Technology

MITRAL ANNULUS STRAIN BY 3D ECHO REVEALS REGIONAL ANNULAR DYSFUNCTION IN BARLOW'S DISEASE

Barcelona Friday, August 26th, 2022

This paper was presented as a part of the session "Advances in Echocardiography Technology" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. HM Aguilera et al. from the Norwegian University of Science and Technology, Barlow's disease (BD) provides both diagnostic and therapeutic challenges. Annular dilation is typically seen in BD, however, data on regional deformation is lacking.

"We hypothesized that mitral annulus dilates non-homogenously during ventricular systole in BD. A method to calculate annular regional strain was developed and applied in a subset of BD patients and healthy controls."

Ten patients with BD and late systolic mitral regurgitation and nine healthy controls were studied. For each subject, the mitral annulus was segmented throughout the cardiac cycle using 3D echocardiography. Twelve evenly distributed geometrical points were annotated along the annular perimeter, enabling the creation of periodic degree-3 spline curves parameterized by arc length at each discrete time-frame. The motion of the mitral annulus was then acquired by assuming that heterogeneity in annular strain is small and finding the point-wise map that minimized the total displacement between the consecutive curves. Then, the end-diastolic annular curve was divided into 200 evenly distributed points around the annular perimeter, and the point-wise mapping was implemented to create a continuous movement of the discretized annulus throughout the cycle. Annular strain was then calculated for each individual line segment. The method presented herein is validated by comparing the strain between sonomicrometric crystals in pigs and the method described above. The timescale was normalized from ED (end-diastole) to mitral valve opening for each individual. The regional strains of the annulus were calculated with the ED configuration as reference.

In BD annulus area increased from 16.6 ± 3.2 to 21.7 ± 4.2 cm^2 at end-diastole and peak systole, respectively ($p<0.001$). In controls, annulus area at end-diastole and end-systole was 9.6 ± 2.2 cm^2 and 9.2 ± 1.8 cm^2, respectively (NS). In healthy controls, peak systolic strain was similar in all segments. In the present study, we have applied a novel non-invasive method to demonstrate non-homogenous deformation of the mitral annulus in Barlow patients. On average, the most severe deformation was seen in the posteromedial region. This finding may reveal further insight into the mechanisms of late systolic mitral regurgitation in BD as well as the design of annuloplasty in the future.

3D ATRIAL STRAIN FOR PREDICTION OF ATRIAL FIBRILLATION RECURRENCE

Barcelona Friday, August 26th, 2022

This paper was presented as a part of the session "Advances in Echocardiography Technology" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. I Krizanovic-Grgic et al. from the University Hospital Zurich.

Atrial fibrillation (AF) is one of the most common supraventricular arrhythmias. Treatment options apart from medication include interventional catheter-guided pulmonary vein isolation (PVI). However, there is limited knowledge about factors predicting arrhythmia recurrence after PVI.

The aim of this paper was to study the association of 3-dimensional (3D) left atrial (LA) strain (LAS) and 3D electro-anatomical voltage mapping (EAVM) with early recurrence of AF after PVI.

In this prospective single center study, 93 patients undergoing PVI were enrolled between December 2018 and October 2021. All patients underwent an echocardiographic examination within two weeks before PVI using the Canon Aplio i900 system to analyse LAS from 3D LA volume. A 3D EAVM was obtained using high-density mapping catheters during PVI. The CARTO 3 system (Version V6-V7) was used for determining LA scar area by low voltage mapping (local amplitude <0.5 mV) indicated as percentage (EAVM-%). Follow-up time points were set at 2, 3, 6 and 12 months to investigate recurrence of AF, with exclusion of events occurring during the first two months (blanking phase).

During follow-up, 12 out of 93 patients experienced recurrence of AF (12.9%; AF-Group). Baseline characteristics did not differ between AF-Group and Non-AF-Group. In contrast, LAS was significantly impaired in the AF-Group (median -4.6, IQR [-5.6 to -3.6]) when compared to the Non-AF-Group (-6.2 [-8.3 to -4.5]; p=0.009). The EAVM-% did not differ between the groups (AF-Group: 5.0 [1.5 to 21.5]; Non-AF-Group: 4.4 [1.5 to 15.9]; p=0.710). No significant correlations were found between LAS and EAVM-% (r=0.03, p=0.812). A cut-off value of -5.89% for LAS had a sensitivity of 100% and a specificity of 57% for AF recurrence (AUC=70%; p<0.001). Kaplan Meier curves for event-free survival were generated based on the LAS cut-off demonstrating excellent differentiation of those with and without AF recurrence (p<0.001. Furthermore, LAS was associated with an increased risk of early AF recurrence (HR 1.40, IQR [1.02-1.92], p=0.040), while EAVM-% was not (HR 0.99 [0.95-1.04], p=0.787).

3D LAS was associated with an increased risk of early AF recurrence after PVI, while EAVM-% was not. 3D LAS might be used for identifying patients who would benefit from PVI.

SESSION-4 :
Risk Stratification with Echocardiographic Parameters

A STREAMLINED, MACHINE LEARNING-DERIVED APPROACH TO RISK-STRATIFICATION IN HEART FAILURE PATIENTS WITH SECONDARY TRICUSPID REGURGITATION

Barcelona Friday, August 26th, 2022

This paper was presented as a part of the session "Risk Stratification with Echocardiographic Parameters" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. Gregor Heitzinger et al., from the Medical University of Vienna, Austria.

Secondary tricuspid regurgitation (sTR) is the most frequent valvular heart disease and has significant impact on mortality. A high burden of comorbidities often worsens the already dismal prognosis of sTR, while tricuspid interventions remain underused and initiated too late.

The objectives of this study are to examine the most powerful predictors of all-cause mortality in moderate and severe sTR using machine learning techniques and to provide a streamlined approach to risk-stratification using readily available clinical, echocardiographic and laboratory parameters. This large-scale, long-term observational study included 3359 moderate and 1509 severe sTR patients encompassing the entire heart failure spectrum (preserved, mid-range and reduced ejection fraction). A random survival forest was applied to investigate the most important predictors and group patients according to their number of adverse features. The identified predictors and thresholds, that were associated with significantly worse mortality were higher age (≥75 in moderate and ≥ 70 years in moderate and severe sTR respectively), higher NT-proBNP (≥4000 pg/ml), increased high sensitivity C-reactive protein (≥ 1.0 mg/dl), serum albumin < 40 g/L and hemoglobin < 13 g/dL. Additionally, grouping patients according to the number of adverse features yielded important prognostic information, as patients with 4 or 5 adverse features had a sevenfold risk increase in moderate sTR (7.11 [2.27- 4.30] HR 95%CI, P < 0.001) and fivefold risk increase in severe sTR (5.08 [3.13-8.24] HR 95%CI, P < 0.001).

This study presents a streamlined, machine learning-derived and internally validated approach to risk-stratification in patients with moderate and severe sTR, that adds important prognostic information to aid clinical decision making.

A NOVEL ECHOCARDIOGRAPHIC RISK SCORE PREDICTS PROGNOSIS IN AL-AMYLOIDOSIS

Barcelona Friday, August 26th, 2022

This paper was presented as a part of the session "Risk Stratification with Echocardiographic Parameters" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. Paul Geenty et al. from the Westmead Hospital - Sydney – Australia.

Prognosis in light chain (AL) amyloidosis is largely determined by the severity of cardiac involvement. Conventional (Mayo) staging includes 1) hs-Troponin 2) N-terminal pro-beta natriuretic peptide (NT-pro BNP) and 3) free light chain difference. In a retrospective study of 75 AL amyloidosis patients referred to a quaternary amyloid clinic, all patients underwent comprehensive echocardiographic assessment. Echocardio-graphic parameters included left ventricular (LV) ejection fraction, LV mass, diastolic function, global longitudinal strain (GLS) and indexed left atrial volume (LAVI). Mortality was assessed through review of clinical records.

Over a median follow up of 51 months, 29/75 (39%) of patients died. LAVI, E/e', e', LVGLS, were univariate predictors of mortality ($p<0.1$). LAVI was the only independent echocardiographic predictor in a multivariable model. Kaplan Meir analysis evaluated LAVI, LVGLS and E/e' using clinical cutoffs as a predictor of survival; only LAVI and LVGLS were significant. A novel "Echo score" comprising of LAVI (>42ml/m^2) and LVGLS (<-12%) was a predictor of mortality with similar prognostic performance as Mayo stage. (Echo score AUC 0.745, 95% CI 0.64-0.85 vs Mayo score AUC 0.752 95% CI 0.66-0.86, $p=0.9$).

LAVI, a simple, echocardiographic parameter was as an independent predictor of mortality in AL amyloidosis. A composite echocardiographic score combining LAVI and LVGLS stratified AL-amyloidosis patients into 3 distinct groups with similar prognostic power as Mayo stage for all-cause mortality.

SESSION-5 :
Coronary Artery Disease - Different Aspects

CARDIAC RUPTURE AFTER ST ELEVATION MYOCARDIAL INFARCTION - A DECADES EXPERIENCE OF A TERTIARY CARDIOLOGY CENTRE

Barcelona **Friday, August 26th, 2022**

This paper was presented as a part of the session "Coronary Artery Disease- Different Aspects" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. Cornelia Margineanu et al. from the Emergency Institute of Cardiovascular Diseases Prof. Dr. C.C. Iliescu - Bucharest - Romania.

Mechanical complications post ST elevation myocardial infarction (STEMI) are life-threating events, that require rapid recognition and appropriate management. Clinical diagnosis, considering high index of suspicion and bedside echocardiography should be considered in all STEMI patients. Despite the overall decrease of the incidence of cardiac rupture (CR) secondary to STEMI in context of early revascularization and the wide availability of primary PCI, CR has still an unacceptable high mortality. The purpose of this study is to provide demographic, clinical, management and prognostic data associated to cardiac rupture from a tertiary centre of cardiology in Romania and to better describe in-hospital trajectory. The primary endpoint was defined as the incidence of CR and secondary endpoints were rate of surgical interventions, in-hospital mortality rate at 24 hours and after 24 hours during index hospitalization.

The analysis of the electronic medical records retrospectively identified 7703 patients admitted for STEMI between 01 Jan 2011 and 31 Dec 2020. A database consisting of demographic data, medical history, cv and non-cv comorbidities, in-hospital management were recorded using an UiPath robotic process automation (RPA) technology. Characteristics of the patients +/- CR were compared, and data analysis was performed using SPSS 26 Ed. Of a total number of 7703 consecutive STEMI patients, CR has been identified in 185 patients (mean incidence of 2.4%). The annual rates for CR incidence remained stable during the past decade. Patients with CR were older compared with non-CR (71.6 ± 10.2 vs 61.47 ± 12.8 years; $p<0.001$) and more commonly female (3.92 % vs 1.78% males, $p=0.04$). The CR patients had more comorbidities and CV risk factors – HTN, smoker status, DLP, more AF, CKD, obesity and chronic cognitive deficit ($p < 0.05$), but not DM ($p=0.6$).

Among the CR group patients, anterior MI was the frequent localisation (52%), followed by inferior MI (17%), infero-lateral (23%) and RV involvement MI (6.4%). According to the type of the mechanical complication, patients developed free wall rupture (50% of cases), 39% IVS rupture and 11% papillary muscle was involved; A number of 50 patients (27%), benefited from emergent cardiac surgery and 31.3% of CR patients received mechanical circulatory support. The overall STEMI mortality in the first 24-hours was 1.84% and in most of these patients the main cause of death was related to CR (31%). Overall total in-hospital mortality was 8.08% (6.5% non-CR group vs. 70.8% the CR group).

The study presents the epidemiological characteristics of CR complicating STEMI in the largest tertiary cardiovascular hospital in Romania. We have identified a stable trend for the incidence of

CR incidence among patients with STEMI. In spite of the high rate of cardiac surgery and MCS, in-hospital mortality remains very high, particularly in the first 24 h since admission.

BIOMARKER-BASED PREDICTION OF FATAL AND NON-FATAL CARDIOVASCULAR OUTCOMES IN INDIVIDUALS OF THE GENERAL POPULATION WITH AND WITHOUT DIABETES MELLITUS

Barcelona **Friday, August 26th, 2022**

This paper was presented as a part of the session "Coronary Artery Disease- Different Aspects" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. Paul Michael Haller et al. from the University Heart & Vascular Center Hamburg - Hamburg – Germany.

Cardiovascular biomarkers may reflect different aspects of cardiovascular disease, including myocardial tissue damage (high-sensitive cardiac troponin [hs-cTn]), hemodynamic stress (N-terminal prohormone of brain natriuretic peptide [NT-proBNP]), or inflammation (high-sensitivity C-reactive protein [hs-CRP]).

The purpose of this paper is to determine the risk for fatal and non-fatal cardiovascular events in patients with diabetes mellitus (DM), a high-risk group for cardiovascular complications, after accounting for these biomarkers and to determine the risk associated with these biomarkers. Harmonized data of population-based studies from the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomaCaRE) and MOnica Risk, Genetics, Archiving and Monograph (MORGAM) consortia were used to calculate hazard ratios (HRs, 95% confidence intervals [CI] per standard deviation) for these biomarkers adjusted for diabetes, patient characteristics and biomarkers for their association with the primary endpoint of fatal and non-fatal cardiovascular events during a median follow-up of 9.6 years (maximum 28 years). Additionally, a years-of-life-lost analysis was conducted stratified by prevalent diabetes and specific biomarker cut-offs known to be associated with increased risk for events (hs-cTnI >5 ng/L, NTproBNP >125 ng/L, hs-CRP >5mg/L).

We included 95,302 individuals, of whom 6,501 had DM (6.8%). Cox-regression analysis revealed DM to be independently associated with the primary endpoint (2.1 [95% CI 1.9, 2.3], $p < 0.001$) despite adjustment for clinical characteristics and biomarkers. Also, all three biomarkers were independent predictors themselves: log-transformed NT-proBNP 1.3 [95% CI 1.3, 1.4] $p < 0.001$; log-transformed hs-CRP 1.2 [95% CI 1.1, 1.2] $p < 0.001$; third-root-transformed hs-cTnI 1.1 [95% CI 1.0, 1.1] $p = 0.0038$). The sex-, age- and cohort-adjusted HR for the primary endpoint according to absolute biomarker concentrations derived by cox-regression models using cubic splines is provided for the three biomarkers. Upon dichotomi-zation of biomarkers, individuals with diabetes and at least one elevated biomarker lost a median of 15.5 healthy years because of the primary endpoint."

"Our findings confirm that diabetes confers a residual cardiovascular risk beyond adjustment for clinical characteristics and cardiovascular biomarker. Furthermore, biomarkers may aid in the identification of patients at highest risk, which should be considered in future models of risk prediction."

SESSION-6 :
Challenges in Invasive Cardiology
Joint with the Great Wall International Congress of Cardiology (GW-ICC)

TAVI VERSUS SAVR IN INTERMEDIATE-RISK PATIENTS WITH SEVERE AORTIC STENOSIS AND CHRONIC KIDNEY DISEASE: A MATCHED COMPARISON IN A SUBCOHORT FROM THE GARY REGISTRY

Barcelona Friday, August 26th, 2022

This paper was presented as a part of the session "Challenges in Invasive Cardiology-Joint with the Great Wall International Congress of Cardiology (GW-ICC)" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. Silva Mas Piero et al. from the University Heart & Vascular Center Hamburg - Hamburg – Germany.

According to American and recent European guidelines, both transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) may be used to treat severe aortic stenosis in a subgroup of patients with intermediate surgical risk, in spite of slight differences in recommended age limits (ACC/AHA: 65-80 years and ESC/EACTS: <75 years). A shared therapeutic decision is made with the patient, based on a heart team assessment. For this, individual factors should be taken into account. Concomitant chronic kidney disease (CKD) is a prognostic factor in such patients, and CKD stage ≥ 3a and ≥ 3b has been shown to be a significant independent risk factor for SAVR and TAVI, respectively.

The purpose of this study is to compare TAVI vs. SAVR outcomes in a subgroup of patients for whom both therapies could possibly be considered according to current guidelines.

The large nation-wide German Aortic Valve Registry (GARY) includes data from patients treated with TAVI or SAVR. A subcohort of patients from GARY with intermediate surgical risk (age ≤80 years, STS-score 4-8) and moderate-to-severe chronic kidney disease (CKD stages 3a, 3b, and 4) was selected. A matched analysis of 704 patients undergoing TAVI and 374 undergoing SAVR was carried out using a propensity score method. Primary endpoint was 1-year survival. Clinical complications and specifically the need for postprocedural new-onset dialysis were secondary endpoints.

TAVI and SAVR showed similar survival results at 1 year in a Kaplan-Meier analysis (HR [95% CI] for TAVI: 1.271 [0.795,2.031], p=0.316). Despite a numerically higher post-procedural short-term survival in TAVI patients and a numerically higher 1-year survival in SAVR patients, such differences did not reach statistical significance (96.4% vs. 94.2%, p=0.199, and 86.2% vs. 81.2%, p=0.316, respectively). In weighted analyses, need for permanent pacemaker, vascular complications, and moderate-to-severe valvular regurgitation were significantly more common with TAVI, whereas patients undergoing SAVR had significantly higher rates of myocardial infarction, and transient ischaemic attack, needed more transfusions for bleeding, and had a significantly longer intensive care unit stay and overall hospital stay. The need for new-onset dialysis for a limited time was more common after SAVR (p <0.0001); however, very few patients required chronic dialysis either after TAVI or after SAVR.

In a matched analysis of intermediate-risk patients with severe aortic stenosis and a concomitant moderate-to-severe CKD, for whom both TAVI and SAVR could possibly be considered, both approaches showed excellent and comparable results.

EVALUATION OF NON-BREATH-HOLD, ULTRA-FAST, LOW-DOSE HIGH-PITCH (FLASH) CT SCAN AS A PRACTICAL ALTERNATIVE TO STANDARD SPIRAL SCAN FOR PRE-TAVI PATIENTS: A REAL-WORLD SINGLE-CENTER EXPERIENCE

Barcelona **Friday, August 26th, 2022**

This paper was presented as a part of the session "Challenges in Invasive Cardiology-Joint with the Great Wall International Congress of Cardiology (GW-ICC)" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. I Vikton Barkey et al. from the Yitzhak Shamir Medical Center - Beer Yakov - Israel.

Aortic annulus dimensions change during the cardiac cycle. A retrospective ECG-gated (Spiral) scan is the default technique for pre TAVR evaluation since it includes systolic phases considered optimal for aortic annulus assessment. Ultra-fast, Low-Dose High-Pitch (FLASH) offers faster, potentially low radiation and low contrast dose scans. However, it lacks the ability to time data acquisition to the systole. Therefore, measurements derived from FLASH scan are considered suboptimal for reporting. The effect of this potential annular measurement difference on procedural success and safety was not evaluated. Therefore, we aimed to assess the feasibility and safety of FLASH vs. Spiral scan before TAVI.

We conducted a retrospective, single-center study. 409 patients underwent CT-TAVI scan with either FLASH or SPIRAL acquisition. Baseline characteristics, CT study, procedural and f/u data were acquired from the EMR. Outcomes defined by Valve Academic Research Consortium 3 (VARC-2) endpoint definitions included in-hospital mortality, bleeding, vascular complications, acute kidney injury (AKI), conduction disorders, mechanical complications, and prosthetic aortic valve regurgitation. Composite endpoints such as device success were also examined.

Of the 409 patients, 55.7% underwent FLASH scans. The median age was 80 years, and males accounted for 55%. The FLASH-protocol patients had higher rate of chronic kidney disease, their CT-measured aortic annulus area and diameter were smaller, and they were exposed to a smaller amount of contrast agent and radiation than the SPIRAL group. There was no statistically significant difference in primary clinical and safety endpoints between the two groups, including mechanical complications (such as annular rupture and valve malposition) and conduction disorders.

FLASH CT scan is a pragmatic and safe approach that potentially may replace spiral scan for the evaluation before TAVI procedure in the appropriate patients.

SESSION-7 :
How Do SGLT2 Inhibitors Act in Heart Failure?

PHARMACOLOGICAL SELECTIVITY OF SGLT2 INHIBITORS AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES: A META-ANALYSIS

Barcelona Friday, August 26th, 2022

This paper was presented as a part of the session "How Do SGLT2 Inhibitors Act in Heart Failure?" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. Alex Ali Sayour from the Semmelweis University Heart and Vascular Center - Budapest - Hungary.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. However, SGLT2 inhibitors show great variance in pharmacological selectivity to SGLT2 over SGLT1. Reduced functional capacity of SGLT1 is associated with lower risk of heart failure development and mortality in humans. Yet, the clinical relevance of additional pharmacological SGLT1 inhibition is unclear.

The purpose of this study was to assess whether additional pharmacological SGLT1 blockade adds further benefits to SGLT2 inhibition.

Methods: In this preregistered meta-analysis, we included randomized placebo-controlled cardiovascular outcome trials (CVOTs) of SGLT2 inhibitors assessing MACE (composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in patients with type 2 diabetes. Hazard ratios (HRs) and 95% confidence intervals (CIs) of prespecified clinical endpoints were pooled using a random-effects model. Interactions were assessed according to low versus high pharmacological SGLT2 selectivity of the given medication. Mixed-effects meta-regression analysis was performed to quantify correlation between pharmacological SGLT2: SGLT1 selectivity ratio and clinical outcomes.

A total of 6 independent CVOTs comprising 57553 type 2 diabetic patients (mean age 64.6±7.9 years; 36769 [63.9%] men) were included. Overall, SGLT2 inhibitors significantly reduced risk of adverse cardiovascular and renal outcomes, but had no significant impact on the risk of fatal and nonfatal stroke compared with placebo (HR, 0.92; 95% CI, 0.77-1.10; p=0.36; I^2=63%). Agents with clinically relevant SGLT1 inhibitory effect (sotagliflozin, canagliflozin) significantly reduced the risk of stroke (HR, 0.78; 95% CI, 0.64-0.94) compared with placebo, whereas those with high SGLT2 selectivity did not (HR, 1.06; 95% CI, 0.92-1.22), yielding a significant interaction (p=0.018). The difference was also significant in patients with estimated glomerular filtration rate (eGFR) lower than 60 mL/min/1.73m^2 (p=0.047). Meta-regression indicated that lower SGLT2:SGLT1 pharmacological selectivity ratio was associated with lower risk of stroke (pseudo-R^2=78%; p=0.011), which was evident even after adjusting for baseline eGFR values (p=0.047). Pharmacological selectivity of SGLT2 inhibitors had no significant impact on any other assessed clinical outcomes, including hospitalization for heart failure and all-cause death.

These hypothesis-generating results indicate that targeting SGLT1 in addition to SGLT2 inhibition might constitute a new avenue for stroke risk reduction in patients with type 2 diabetes. Further confirmatory studies are needed.

THE REAL-WORLD SAFETY PROFILE OF SGLT2 INHIBITORS AMONG ADULTS 75 YEARS OR OLDER: A RETROSPECTIVE, PHARMACOVIGILANCE STUDY

Barcelona Friday, August 26th, 2022

This paper was presented as a part of the session "How Do SGLT2 Inhibitors Act in Heart Failure?" on August 26th 2022 at the ESC Congress 2022 held in Barcelona by Dr. Elad Maor from the The Chaim Sheba Medical Center - Tel Hashomer – Israel.

As indications for sodium-glucose co-transporter-2 (SGLT2) inhibitors treatment are expanding, more older adults become candidates for treatment. However, data regarding the treatment's safety profile in the older population are limited.

A retrospective, pharmacovigilance study of the FDA's global database of safety reports (7/1/2014-6/30/2021). To assess reporting of pre-specified adverse events following SGLT2-inhibitors treatment among adults (18≥age<75) and older adults (age≥75), we performed disproportionality analysis using the reporting odds ratio (ROR).

Of 10,526,408 patients in the full database, 279,619 eligible patients with non-insulin-dependent diabetes mellitus were identified (mean age 63.4 [SD 13.0] years, 54,791 [19.6%] aged ≥75 years), among whom 29,431 receiving SGLT-2 inhibitors. Compared to other non-insulin anti-diabetics, SGLT2-inhibitors were significantly associated with amputations (ROR= 127.87 [95% CI: 111.31-146.90] vs ROR = 74.91 [49.99-112.25]), Fournier gangrene (ROR = 53.27 [44.38-63.92] vs ROR = 33.33 [20.33-54.64]), diabetes ketoacidosis (ROR= 39.25 [37.20-41.42] vs ROR = 58.46 [49.41-69.1]), genitourinary infections (ROR = 4.36 [4.12-4.61] vs ROR=5.08 [4.45-5.79]), nocturia (ROR=2.81 [2.13-3.73] vs ROR=3.51 [1.84-6.68]), and dehydration (ROR=2.22 [2.05-2.40] vs ROR = 2.33 [1.93-2.81]) in both adults and older adults, respectively. The relative reporting of these safety signals was consistent between age groups (all P interaction>0.05). Acute kidney injury was associated with SGLT2-inhibitors treatment in adults (ROR=1.47 [1.40-1.54]) but not older adults (ROR=0.84 [0.72-0.98]). No new safety signals were observed in older adults. Falls, fractures, hypotension, and syncope were not associated with SGLT2-inhibitors among either adults or older adults.

In this global post-marketing study, treatment with SGLT-2 inhibitors in older adults was associated with increased reporting of amputations, Fournier gangrene, DKA, genitourinary infections, and dehydration. Nevertheless, the relative reporting was consistent between adults and older adults, and no new safety signals were found in the older population.

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