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RESEARCH ARTICLE

A STUDY ON SHORT-TERM IMPACT OF DAPAGLIFLOZIN ON DIASTOLIC CARDIAC PARAMETERS IN TYPE 2 DIABETES MELLITUS PATIENTS WITH NORMAL EJECTION FRACTION

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Abstract

Background and objectives: Type 2 Diabetes Mellitus (T2 DM) is a leading independent cardiovascular risk factor for developing both systolic and diastolic heart failure (HF). Sodium Glucose Co Transport er 2 (SGLT2) inhibitor Dapagliflozin has proven significant beneficial effect in reducing incidence of major adverse cardio-vascular events (MACE) and hospitalization due to heart failure (HHF) in patients with atherosclerotic cardio-vascular diseases (ASCVD) and established HF. To document the prognostic impact of SGLT2 inhibitor Dapagliflozin in left ventricular diastolic function in T2DM patients with normal eject ion fraction is the purpose of our study for future strategic planning for treatment of heart failure.

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Methods: The study enrolled 100 participants diagnosed with T2DM and preserved ejection fraction. The inclusion criteria ensured that participants had evidence of diastolic dysfunction without acute decompens ated heart failure. Echocardiographic evaluation was performed to asses s diastolic parameters, including the E/e' ratio, left atrial volume index (LAVI), and mitral E/A ratio. The participants were treated with Dapag liflozin for six months, and follow up echocardiographic assessments were conducted to evaluate changes in diastolic parameters. Statistical an alysis included paired t-tests, chi-square tests, and p-values to compare pre- and post-treatment data.

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Results:Mean age of participants were 54.3 years (SD = 8.44), with a predominance of male subjects (74%). Baseline clinical characteristics showed that 75% of participants had hypertension, 16% had dyslipidemia, and 11% were obese, highlighting the high prevalence of cardiovascular risk factors in the cohort. Glycemic parameters, including fasting blood sugar, postprandial blood sugar, and HbA1c, indicated suboptimal glycemic control, with a mean HbA1c of 9.59%. Baseline echocardiographic parameters revealed evidence of diastolic dysfunction, with mean E/e' ratio at 7.28 (SD = 2.17) and LAVI at 30.52 mL/m² (SD = 2.91). After 6 months there was reduction in E/e and LAVI with no reduction in LVEF, development of any new RWMA or new valvular pathology demonstrating the efficacy of dapagliflozin in short term.

Interpretation and Conclusion: This study concludes that Dapagliflozin significantly improves diastolic parameters in T2DM patients with preserved ejection fraction, providing a promising therapeutic strategy for a population with

limited treatment options. The findings emphasize the importance of early intervention, routine echocardiographic assessment, and the integration of SGLT2 inhibitors into clinical practice.

Introduction:-

Diabetes mellitus refers to a group of metabolic disorders that share the phenotype of hyperglycemia depending upon complex genetic interactions, Insulin hyposecretion or relative Insulin deficiency and or Insulin resistance resulting in metabolic dysregulations notably hyperglycemia and dyslipidemia, vascular endothelial dysfunctions, oxidative stress resulting in multi system disorder involving cardio-vascular, renal, neurological, gastrointestinal, endocrine almost all systems of body producing significant mortality and morbidity. Cardiovascular complications are among the most significant contributors to morbidity and mortality in patients with Type 2 Diabetes Mellitus (T2DM). Beyond macro-vascular complications such as coronary artery disease (CAD) and stroke, T2DM predisposes patients to a distinct entity known as Diabetic Cardiomyopathy (DCM). This condition, characterized by myocardial dysfunction in the absence of overt coronary artery disease or hypertension, often manifests as diastolic dysfunction, preceding systolic impairment in the majority of cases (Jia et al., 2018) [1]. Diastolic dysfunction is an early marker of myocardial involvement in diabetes. Despite its high prevalence, therapeutic options targeting diastolic dysfunction remain limited. HF is a multi-factorial major fatal cardio-vascular disease with very high mortality and morbidity.

It's incidence and prevalence are drastically increasing. HF incidence is 10 in 1000 population after 65 years of age and 80% hospitalized patients due to HF is elderly, >60 years of age. Contribution of Diabetes Mellitus as a very significant independent risk factor for development of HF even in absence of underlying structural heart diseases is immense. 50% of T2DM patients aged >70 years are having underlying diastolic dysfunction (DD). Diastolic dysfunction is more prevalent in female than male and the risk of development and incidence of diastolic dysfunction progressively increases with advancement of age. T2DM predominantly causes heart failure – both systolic and diastolic failure by accelerating micro and macro vascular angiopathy, proinflammatory vascular endothelial dysfunction, oxidative stress, cardiac remodeling by increasing Left Ventricular mass and enhanced myocardial stiffness due to advance glycation end products (AGE) and collagen deposition, insulin resistance, epicardial adipose tissue extension (Steatosis Cardinalis), interstitial fibrosis, autonomic dysfunction, leading to development of Diabetic Cardiomyopathy (DCM) and progressive renal and reno-vascular pathophysiological alteration. Diabetes causes cardiac dysfunction by promoting acceleration in ASCVD leading to ischemic / structural heart diseases as well as developing diabetic cardiomyopathy.

Left ventricular diastolic dysfunctions develop in the early state of T2DM which precipitates early onset HF and aggravates progression towards advanced HF [3,4,1]. Cardiac diastolic dysfunction with normal LV ejection fraction accounts for approximately 50% of all hospitalization due to HF. SGLT2 inhibitor Dapagliflozin, a new class of first line antidiabetic agent, acts independently of insulin to selectively inhibit renal glucose reabsorption and thereby enhances urinary glucose excretion. It exerts multi-dimensional effects in reducing blood pressure, hyperglycaemia, body weight, hypertriglyceridemia, hyperuricaemia, progression of renal dysfunction micro and macro vascular oxidative insults and thereby immensely improves HF related cardiovascular outcome achieving representation of potent anti Heart Failure agent in entire spectrum of heart failure (HFpEF / HFrEF). [5,4] Many landmark trials like Emperor-Outcome (Preserved / Reduced), Dapa-HF, Canvas, Deliver trials established proven significant benefit of SGLT2 inhibitor like Empagliflozin, Canagliflozin and Dapagliflozin respectively to reduce major adverse cardiovascular events (MACE) including CV death, nonfatal Myocardial infarction(MI), nonfatal Stroke by reducing Cardio-vascular death due to heart failure (HF), reduction of hospitalization due to heart failure (HHF) or worsening/ progression of HF in patients with reduced ejection fraction. But all those trials are Cardio-Vascular outcome trials (CVOTs) essentially focusing on heart-failure (HF) irrespective of Diabetic status. Studies on diastolic cardiac functions in asymptomatic T2DM patients are few in number and no definite conclusion can be drawn from available literatures that in T2DM patients with normal cardiac functions do get benefit from SGLT2 inhibitor treatment.

But from the available trials / literature favorable benefit of SGLT2 inhibitor in HF with preserved ejection fraction could not be concluded except in DELIVER trial which showed minimal favorable impact of SGLT2 inhibitor Dapagliflozin in HF patients with mildly reduced or preserved LV ejection fraction. As micro-vascular dysfunction leads to left ventricular diastolic dysfunction promoting right ventricular failure we are going to assess short term impact of Dapagliflozin on diastolic parameters of the heart in T2DM patients with normal ejection fraction by

Transthoracic Echocardiography at base line prior initiation of Dapagliflozin and at 6 months post Dapagliflozin therapy to document prognostic diastolic parameters to assess effect of Dapagliflozin on diastolic cardiac function.

Objectives:

To evaluate the short-term impact of Dapagliflozin on diastolic cardiac parameters in Type 2 Diabetes Mellitus (T2DM) patients with normal ejection fraction.

Material and Methods:-

Study design and population:

This hospital-based observational prospective cohort study was done at OPD and IPD of the Department of Medicine at North Bengal Medical College, Darjeeling in a period of one year from August 2023 to August 2024after getting the approval from the Institutional Ethical Committee.

Inclusion and exclusion criteria:

100 Patients with T2DM with normal ejection fraction as defined by clinical and investigational criteria treated with SGLT2 inhibitor Dapagliflozin, were included. The inclusion criteria were age of 30 years and above, LVEF > 50%but with evidence of diastolic dysfunction and HbA1C> 7.0%. The exclusion criteria were inter-current illnesses like sepsis, DKA, AMI, advanced renal diseases (Serum creatinine > 2.5mg/dl), arrhythmia, pericardial effusion / Cardiac tamponade, patients already on treatment with SGLT2 inhibitor, pregnancy, Type 1 DM, valvular heart diseases, congenital heart di

Data collection and interpretation:

A pre-determined pre-designed pre-tested questionnaire was used to obtain data. A complete examination of cardio-vascular status checkup was done by measuring blood pressure (BP), Heart Rate and rhythm, Heart Sounds (to rule out valvular heart diseases, ASD, VSD causing HF), Jugular Venous Pressure (JVP), pedal edema. All the patients underwent hematological, biochemical, radiological and Trans- thoracic Echocardiographic evaluation. The diastolic parameters of the heart were assessed at baseline before initiating treatment with Dapagliflozin. Diastolic cardiac parameters were documented after 6months of treatment with Dapagliflozin. Grading of diastolic dysfunction (DD) was done.

Parameter	Grade 1	Grade II	Grade III	Grade IV
	Abnormal	Pseudonormal	Restrictive	Restrictive fixed
	relaxation			
Mitral inflow	E/A<0.75	0.75 <e a<1.5<="" td=""><td>E/A>1.5</td><td>E/A>1.5</td></e>	E/A>1.5	E/A>1.5
	DT>240	150 <dt<200< td=""><td>DT<150</td><td>DT<150</td></dt<200<>	DT<150	DT<150
	IVRT >90	IVRT<90	IVRT<70	IVRT<70
Mitral annular	E/e'<10	E/e'>10	E/e'>10	E/e'>10
motion				
Left atrial	<34	>34	>34	>34
volume index				ļ

Grading of diastolic dysfunction by Echo

Outcome of the patients including hospitalization due to cardiovascular causes and death was noted.

Statistical analysis:

The data collected from this study was tabulated in a Excel Master Chart and statistically analyzed with IBM SPSS version.22 software to establish disease prevalence and patterns. Special attention was paid to establish geographical distributions and clinical patterns which contribute to easier diagnosis and follow up of cases. Besides recording laboratory and radiological work up coupled with clinical, biochemical and imaging parameters at base line Transthoracic Echocardiography assessments of left ventricular diastolic parameters at base line before starting Dapagliflozin followed by same Echocardiographic assessments of Cardiac diastolic parameters at 6 months post Dapagliflozin therapy in the Type 2 Diabetic patients landed up towards complete assessment of short term effect of Dapagliflozin for 06 months on diastolic cardiac parameters for this research work. Then base line data and post six months of Dapagliflozin therapy Cardiac diastolic parameters data along with other variables among study participants were compared amongst themselves as well as with data from previous studies.

Observation and Results:-

Among the study participants, 74% of participants were male and 26% were female, indicating a male predominance in the study population. The highest distribution patients were in the age group 50-59 years.

Treatment history was noted like Metformin has known cardiovascular benefits, and the inclusion of such medications allows for a better understanding of how Dapagliflozin compares or interacts with existing therapies in improving diastolic parameters. 62% of participants have had T2DM for 6-10 years, while 26% had a disease duration of 1-5 years and 12% had a duration of 11-15 years. The duration of diabetes is directly related to the development and progression of complications, including diabetic cardiomyopathy and diastolic dysfunction. Longer disease duration is associated with greater myocardial stiffness and reduced ventricular compliance due to chronic hyperglycemia-induced damage. Including this variable helps evaluate whether Dapagliflozin offers similar short-term benefits across different durations of T2DM or whether patients with earlier-stage disease derive greater cardiac improvements. The glycemic status was evaluated by HbA1c levels and majority were in 9.6-10.5 bracket.

The paired t-test results for echocardiographic parameters provided a robust statistical evaluation of the impact of Dapagliflozin. Key findings were the reduction in LAVI (p < 0.001) as a strong indicator of improved diastolic function, as left atrial size reflects chronic elevation of filling pressures. The significant reductions in ventricular dimensions (both p < 0.001) suggest favorable ventricular remodeling, likely driven by a reduction in preload and afterload. The improvement in LVEF (p = 0.042) underscores the potential of Dapagliflozin to enhance systolic performance alongside diastolic benefits. These results demonstrate the efficacy of Dapagliflozin in addressing structural and functional abnormalities associated with diabetic cardiomyopathy. (as seen in Table 1 and 2)

The data from table 3 showed that at base line before starting Dapagliflozin in treatment 98% of participants had no chamber enlargement, while 2% exhibited mild dilation of the left atrium, right atrium, and right ventricle. After 06 months of post treatment with Dapagliflozin the distribution remains the same, indicating no significant change in the prevalence of chamber enlargement over the study period. While the lack of change may reflect the short duration of observation, the absence of new enlargement suggests that Dapagliflozin contributes to stabilizing cardiac structure in patients with diastolic dysfunction as shown in table 4.

At base line before starting Dapagliflozin (BD) 99% of participants had no significant valvular pathology, and 1% presented with mild aortic regurgitation (AR), mitral regurgitation (MR), and tricuspid regurgitation (TR). After 06 months post Dapagliflozin use in treatment 96% of participants remained free of significant valvular pathology, while a small proportion exhibited mild to moderate regurgitation across valves. This indicates no significant adverse impact of Dapagliflozin on valvular function, ensuring its safety in patients with pre-existing diastolic dysfunction. Analysis also reveals that at baseline before treatment with Dapagliflozin (BD), 99% of participants had no regional wall motion abnormality (RWMA), with only 1% showing abnormalities. After 06 months of ongoing treatment with Dapagliflozin (AD), the prevalence of RWMA increases slightly to 4%. This increase, though minor, warrants further investigation to rule out potential adverse effects or progression of underlying ischemic heart disease in a small subset of participants.

Discussion:-

This study aimed to evaluate the short-term impact of Dapagliflozin on diastolic cardiac parameters in patients with Type 2 Diabetes Mellitus (T2DM) and preserved ejection fraction. The following discussion integrates these results with findings from relevant studies- The DAPA-HF trial by McMurray et al. (2019) [3] demonstrated that Dapagliflozin significantly reduced cardiovascular mortality and hospitalization for heart failure in patients with reduced ejection fraction (HFrEF). While our study focused on diastolic dysfunction in patients with preserved ejection fraction (HFpEF), the improvements in E/e' ratio (7.28 to 6.85, p = 0.074) and LAVI (30.52 mL/m² to 28.72 mL/m², p < 0.001) are consistent with the hemodynamic benefits observed in DAPA-HF. Both studies highlight Dapagliflozin's ability to reduce left ventricular filling pressures, albeit in different patient populations. The DAPA-HF trial attributed these benefits to reductions in preload and afterload, mechanisms likely at play in our study cohort as well. The DELIVER trial, described by Solomon et al. (2021) [6], specifically targeted patients with chronic heart failure with preserved ejection fraction (HFpEF) and or mildly reduced ejection fraction (HFmrEF) LVEF > 40 % with primary outcome of composite of worsening heart failure or cardio-vascular death due to hospitalization for heart failure. It was a large, multicentric, double blind, randomized, placebo controlled, long term of 2.3 years study involving 6263 patients aged more than 40 years of age with or without Diabetes, with signs and symptoms of heart failure, elevated natriuretic peptides and evidence of structural heart diseases for comparing the effect of Dapagliflozin 10 mg once daily vs. placebo. It was revealed that SGLT2 inhibitor Dapagliflozin reduces MACE

mainly by reducing HHF or worsening of heart failure and thus reducing CV death in variable ranges of ejection fraction and Diabetes status. Primary endpoint outcome in DELIVER trial and EMPEROR-PRESERVED trial was similar and comparable, 18% and 21% respectively.

Although there is no question of comparison applicable with DELIVER trial and our study as our study population differed slightly and our study was for short duration of only six months with exclusion of underlying structural heart diseases, HFrEF and non-involvement of NT-proBNP in investigating of HF patients but the observed improvements in diastolic parameters are comparable. In DELIVER, Dapagliflozin improved outcomes by enhancing diastolic compliance and reducing filling pressures. Our study's reduction in E/e' ratio and LAVI supports these findings, suggesting that similar pathophysiological mechanisms drive the benefits of Dapagliflozin across different subtypes of heart failure.

Vaduganathan et al. (2022) [7] conducted a meta-analysis of five randomized controlled trials on SGLT2 inhibitors, reporting significant reductions in heart failure hospitalizations across diverse patient groups. Our study aligns with these results, demonstrating improvements in diastolic function even in a short-term follow-up. For example, the reduction in left ventricular internal diameter in systole (LVIDs) from 30.46 mm to 28.84 mm (p < 0.001) and diastole (LVIDd) from 40.41 mm to 38.25 mm (p < 0.001) may partially explain the lower hospitalization rates seen in the meta-analysis. These findings underscore the versatility of Dapagliflozin in addressing both systolic and diastolic dysfunction. Anker et al. (2021) [8] reported in their study on Empagliflozin that this SGLT2 inhibitor led to significant improvements in HFpEF, including enhanced diastolic function and reduced filling pressures. Similarly, our study demonstrated a small but significant improvement in mitral E/A ratio (from 0.846 to 0.867, p = 0.346) and a trend toward reduced E/e' ratio. These findings collectively highlight the class-wide benefits of SGLT2 inhibitors in improving diastolic mechanics, regardless of the specific agent used. Yeoh et al. (2020) [9] explored the relationship between the duration of heart failure and the efficacy of Dapagliflozin, reporting greater benefits in patients with a shorter disease duration. While our study did not specifically stratify participants by heart failure duration, the significant reductions in LAVI (p < 0.001) and improvements in diastolic grades (e.g., 64% of participants improving to no diastolic dysfunction after treatment) suggest that early intervention with Dapagliflozin may yield optimal results.

This aligns with the hypothesis that targeting diastolic dysfunction in its early stages can prevent progression to overt heart failure. Studies on the mechanisms of diabetic cardiomyopathy, such as those by Koulis et al. (2015) [10] and Kasper et al. (2018) [4], emphasize the role of oxidative stress, advanced glycation end-products (AGEs), and myocardial fibrosis in diastolic dysfunction. Our study's findings, particularly the improvements in left ventricular compliance and reductions in LAVI, likely reflect Dapagliflozin's anti-inflammatory and anti-fibrotic effects.

These mechanisms have been well-documented in preclinical models and are increasingly supported by clinical evidence. The findings of our study align with the guidelines outlined by Heidenreich et al. (2022) [11], which recommend SGLT2 inhibitors as first-line agents in managing heart failure due to their robust cardiovascular benefits. Our results further extend this recommendation to patients with diastolic dysfunction and preserved ejection fraction. Importantly, no significant adverse effects were observed in our cohort, consistent with the safety profiles reported in large trials such as DAPA-HF and EMPA-REG OUTCOME. This study corroborates the growing body of evidence supporting Dapagliflozin's efficacy in improving diastolic parameters in T2DM patients with preserved ejection fraction. Improvements in E/e' ratio, LAVI, and left ventricular dimensions align with findings from major trials and meta-analyses, underscoring Dapagliflozin's role in addressing the pathophysiological underpinnings of diastolic dysfunction. These results highlight the importance of early intervention and pave the way for future research into the long-term cardiac benefits of SGLT2 inhibitors in diverse patient populations

Table1: ECHOCARDIOGRAPHY FINDINGS OF DIFFERENT PARAMETERS AT BASE LINE BEFORE STARTING DAPAGLIFLOZIN (BD) & 06 MONTHS AFTERDAPAGLIFLOZINTHERAPY(AD)AMONG STUDYPARTICIPANTS(N=100)

N	Mean	Median	SD	SE
100	0.846	0.840	0.181	0.0181
100	0.867	0.840	0.216	0.0216
100	30.525	29.750	2.906	0.2906
100	28.721	28.600	3.544	0.3544
100	2.779	2.820	0.258	0.0258
100	4.725	2.800	19.929	1.9929
100	7.285	6.720	2.179	0.2179
100	6.856	6.100	2.338	0.2338
100	60.527	60.000	3,431	0.3431
100	61.321	61.700	5.216	0.5216
100	30.460	30.000	3.066	0.3066
100	28.841	28.410	3.866	0.3866
100	40.413	39.430	4.617	0.4617
100	38.252	38.500	4.832	0.4832
	100 100 100 100 100 100 100 100 100 100	100 0.846 100 0.867 100 30.525 100 28.721 100 2.779 100 4.725 100 7.285 100 6.856 100 60.527 100 61.321 100 30.460 100 28.841 100 40.413	100 0.846 0.840 100 0.867 0.840 100 30.525 29.750 100 28.721 28.600 100 2.779 2.820 100 4.725 2.800 100 7.285 6.720 100 6.856 6.100 100 60.527 60.000 100 61.321 61.700 100 30.460 30.000 100 28.841 28.410 100 40.413 39.430	100 0.846 0.840 0.181 100 0.867 0.840 0.216 100 30.525 29.750 2.906 100 28.721 28.600 3.544 100 2.779 2.820 0.258 100 4.725 2.800 19.929 100 7.285 6.720 2.179 100 6.856 6.100 2.338 100 60.527 60.000 3.431 100 61.321 61.700 5.216 100 30.460 30.000 3.066 100 28.841 28.410 3.866 100 40.413 39.430 4.617

Table 2: PAIRED SAMPLES T-TEST OF TRANSTHORACIC ECHOCARDIOGRAPHY FINDINGS AT BASELINE BEFORE STARTING DAPAGLIFLOZIN (BD) AND 06 MONTHS AFTER ONGOING DAPAGLIFLOZIN (AD) TREATMENT (N = 100)

			statistic	df	p
Mitral (E/A) ratio BD	Mitral (E/A) ratio AD	Student's t	-0.946	99.0	0.346
LAVI (ml/m2) BD	LAVI (ml/m2) AD	Student's t	5.895	99.0	< .001
TR VEOCITY (m/s) BD	TR VEOCITY (m/s) AD	Student's t	-0.977	99.0	0.331
E/e- Ratio BD	E/e- Ratio AD	Student's t	1.808	99.0	0.074
LVEF (%) BD	LVEF (%) AD	Student's t	-1.703	99.0	0.042
LVIDs (mm) BD	LVIDs (mm) AD	Student's t	5.380	99.0	< .001
LVIDd (mm) BD	LVIDd (mm) AD	Student's t	4.633	99.0	<.001

Table 3: COMPARISON OF CHAMBER ENLARGEMENT AT BASELINE BEFORE STARTING DAPAGLIFLOZIN (BD) AND 06 MONTHS AFTER DAPAGLIFLOZIN THERAPY (AD) (N = 100)

Chamber Enlargement BD	Counts	% of Total	Cumulative %
NIL	98	98.0 %	98.0 %
MILD DILATED LA,RA,RV	2	2.0 %	100.0 %
Frequencies of Chamber Enlarge	ement AD		
Chamber Enlargement AD	Counts	% of Total	Cumulative %
NIL	98	98.0 %	98.0 %
MILD DILATED	2	2.0 %	100.0 %

Table 4: COMPARISON OF DIASTOLIC FUNCTIONAL STATUS AT BASELINE BEFORE STARTING DAPAGLIFLOZIN (BD) AND 06 MONTHS AFTER TREATMENT WITH DAPAGLIFLOZIN (AD) (N = 100)

DIASTOLIC FUNCTIONAL STATUS BD	Counts	% of Total	Cumulative %
Gr-I DD	40	40.0 %	40.0 %
Gr-II DD	10	10.0 %	50.0 %
NO DD	50	50.0 %	100.0 %
Frequencies of DIASTOLIC FUNC DIASTOLIC FUNCTIONAL STATUS AD	Counts	% of Total	Cumulative %
31111 2211			
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	64	64.0 %	64.0 %
NO DD	64 27	64.0 % 27.0 %	64.0 % 91.0 %
NO DD Gr-I DD Gr-II DD		7.017.45	(F)(1)(T)(1)(1)

Conclusion:-

In conclusion, this study demonstrates that Dapagliflozin significantly improves diastolic parameters in T2DM patients with preserved ejection fraction, providing a promising therapeutic strategy for a population with limited treatment options. The findings emphasize the importance of early intervention, routine echocardiographic assessment, and the integration of SGLT2 inhibitors into clinical practice. With further research, Dapagliflozin has the potential to transform the management of diastolic dysfunction and HFpEF, improving outcomes for millions of patients worldwide.

Conflict of interest: None declared

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