CCS HEART FAILURE GUIDELINES RAPID REVIEW: HF UPDATE

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April 18, 2020

Disclosures

- **Michael McDonald**
  - Honoraria: Novartis, Servier, Astra Zenica
  - Clinical Trials: Novartis
  - Unrestricted Educational Grant: Abbot, Medtronic

- **Sean Virani**
  - Honoraria: Abbott, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Medtronic, Merck, Novartis, BMS/Pfizer, Servier, Takeda
  - Research: Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Medtronic, Novartis, Pfizer

2019 HF Guideline Development

- New evidence from randomized controlled trials published after the 2017 Update on key topics

- 4 topics of high relevance in terms evolution in the care of patients with HF:
  - Transcatheter mitral valve repair
  - New treatments for ATTR cardiac amyloidosis
  - Prevention/management of HF in patients with type 2 diabetes
  - Clinical trial update in HFpEF

Case

- 60 F, (non-ischemic) heart failure, NYHA III symptoms
- Bp 108/60, HR 66bpm (sinus rhythm), narrow complex QRS, creatinine 120
- Echo shows LVEF 30%, severe mitral regurgitation

  - Sacubitril Valsartan 100mg bid
  - Carvedilol 25mg bid
  - Eplerenone 25mg/d
  - Furosemide 20mg/d

  - Metformin for DM2

  - Prophylactic ICD in situ

What else could be considered to improve this patient's symptoms and prognosis?

Percutaneous Mitral Valve Repair

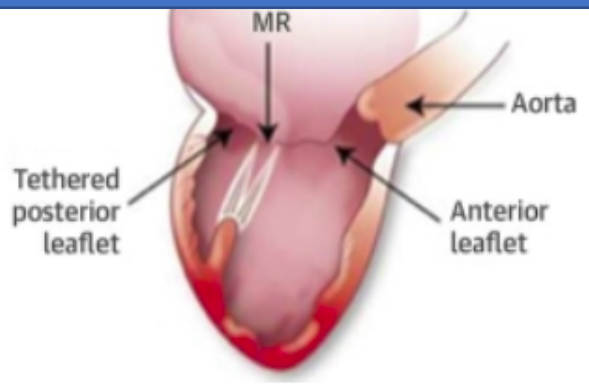
SECONDARY (FUNCTIONAL) MR

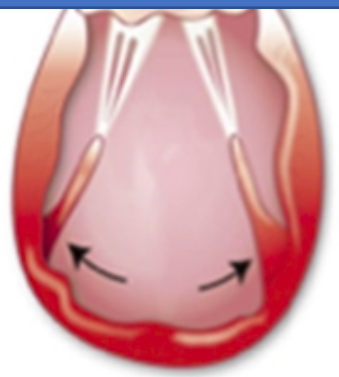
PATHOPHYSIOLOGY

Secondary MR

Ischemic CM **Dilated CM**

Whether interventions to reduce secondary MR improve prognosis ?





- Papillary muscle displacement
- Tethered Chordae
- Restricted leaflet closure
- Annular dilation

changes in LV geometry and function

PROGNOSIS

Sannino et al *JAMA Cardiol.2017 Oct 1;2(10):1130-1139*

Meta-analysis of 17 studies, 26,359 patients

Source	Log Risk Ratio (SE)	Risk Ratio (SE)	Weight, %
SMR Present vs Absent at Echocardiography			
Agricola et al,[26] 2011	0.8538 (0.3182)	2.35 (1.26-4.38)	4.8
Aronson et al,[8] 2006	1.0188 (0.1977)	2.77 (1.88-4.08)	6.7
Barra et al,[27] 2012	0.3507 (0.1638)	1.42 (1.03-1.96)	7.2
Calafiore et al,[7] 2008	0.0296 (0.1226)	1.03 (0.81-1.31)	7.9
Engström et al,[30] 2010	0.5365 (0.2636)	1.71 (1.02-2.87)	5.6
Faris et al,[31] 2002	0.5878 (0.2513)	1.80 (1.10-2.95)	5.8
Trichon et al,[53] 2003	0.2070 (0.0433)	1.23 (1.13-1.34)	8.7
Upadhyay et al,[55] 2015	0.2852 (0.1404)	1.33 (1.01-1.75)	7.6
Subtotal (95% CI)		**1.56 (1.31-1.85)**	70.7
Heterogeneity: $\tau^2=0.05$; $\chi^2=33.07$; ($P<.001$); $I^2=67$%			
Test for overall effect: $Z=5.08$, ($P<.001$)			
SMR Present vs Absent at Ventriculography			
Hickey et al,[36] 1988	0.2231 (0.0746)	1.25 (1.08-1.45)	8.5
Lehmann et al,[41] 1992	1.3083 (0.6189)	3.70 (1.10-12.45)	2.1
Mallidi et al,[9] 2004	−0.0429 (0.1420)	0.96 (0.73-1.27)	7.6
Pellizzon et al,[3] 2004	1.7297 (0.2303)	5.64 (3.59-8.86)	6.1
Tcheng et al,[52] 1992	1.8160 (0.2947)	6.15 (3.45-10.95)	5.1
Subtotal (95% CI)		**2.58 (1.29-5.17)**	29.3
Heterogeneity: $\tau^2=0.54$; $\chi^2=73.55$; ($P<.001$); $I^2=95$%			
Test for overall effect: $Z=2.67$, ($P=.008$)			
Total (95% CI)		**1.79 (1.47-2.18)**	100.0
Heterogeneity: $\tau^2=0.12$; $\chi^2=107.97$; ($P=.001$); $I^2=85$			
Test for overall effect: $Z=5.71$, ($P<.001$)			
Test for subgroup differences: $\chi^2=1.89$; ($P=.17$); $I^2=4$			

Favors No SMR | Favors Any SMR

RR for all-cause death 1.79 (95% CI 1.47-2.18, p<0.001)

Risk Ratio (95% CI)

Transcatheter Mitral Repair

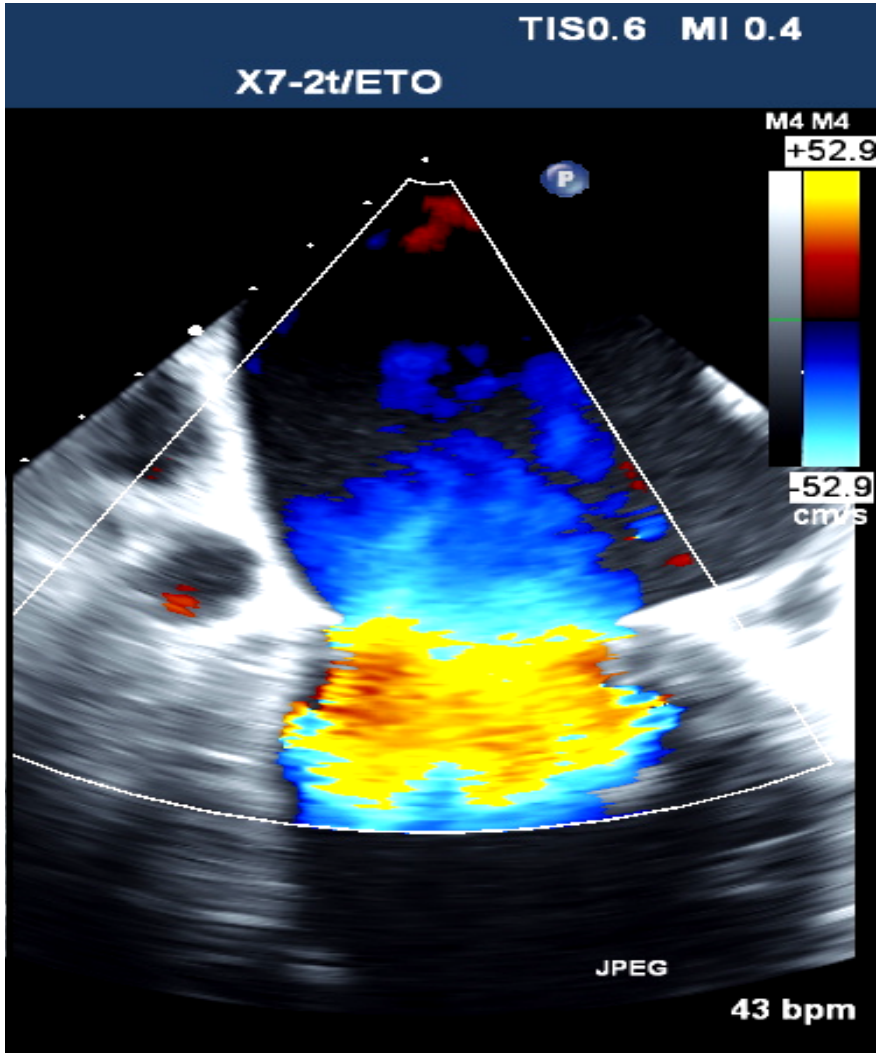
- The **MitraClip** is a transcatheter leaflet repair device for the treatment of degenerative and functional mitral regurgitation.

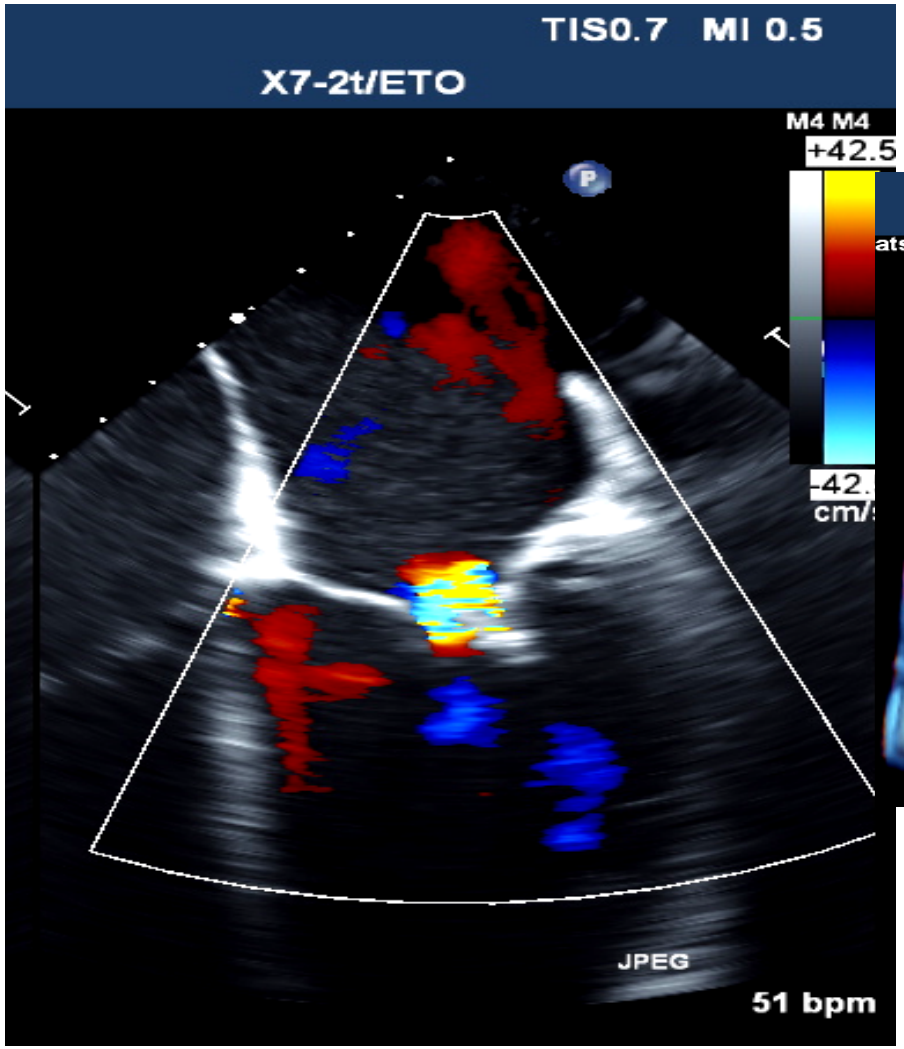
- Use of the device in patients with end-stage heart failure has demonstrated a reduction in mitral regurgitation and improved QOL.

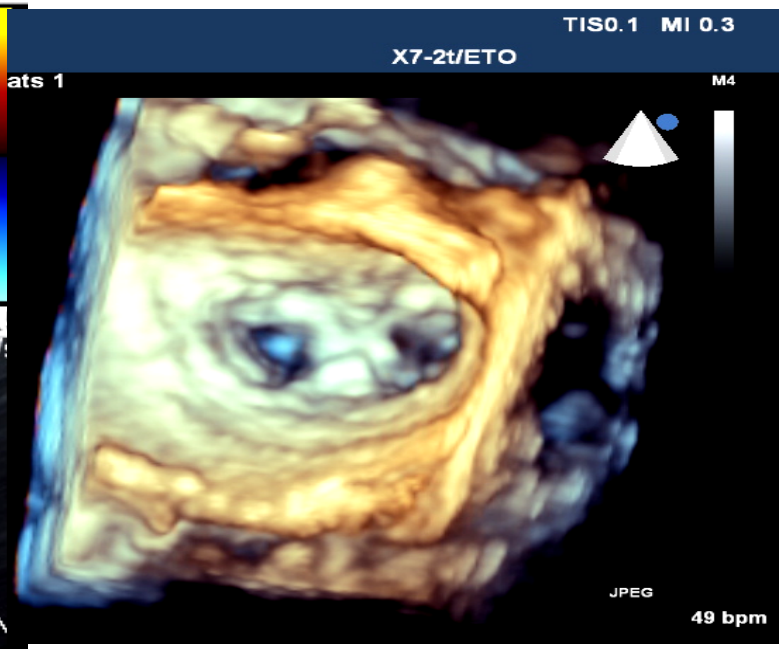
$ 35 000 intervention

Franzen O et al. Eur J Heart Fail 2011;13:569-76.

Mitral Regurgitation : Before & After Mitraclip



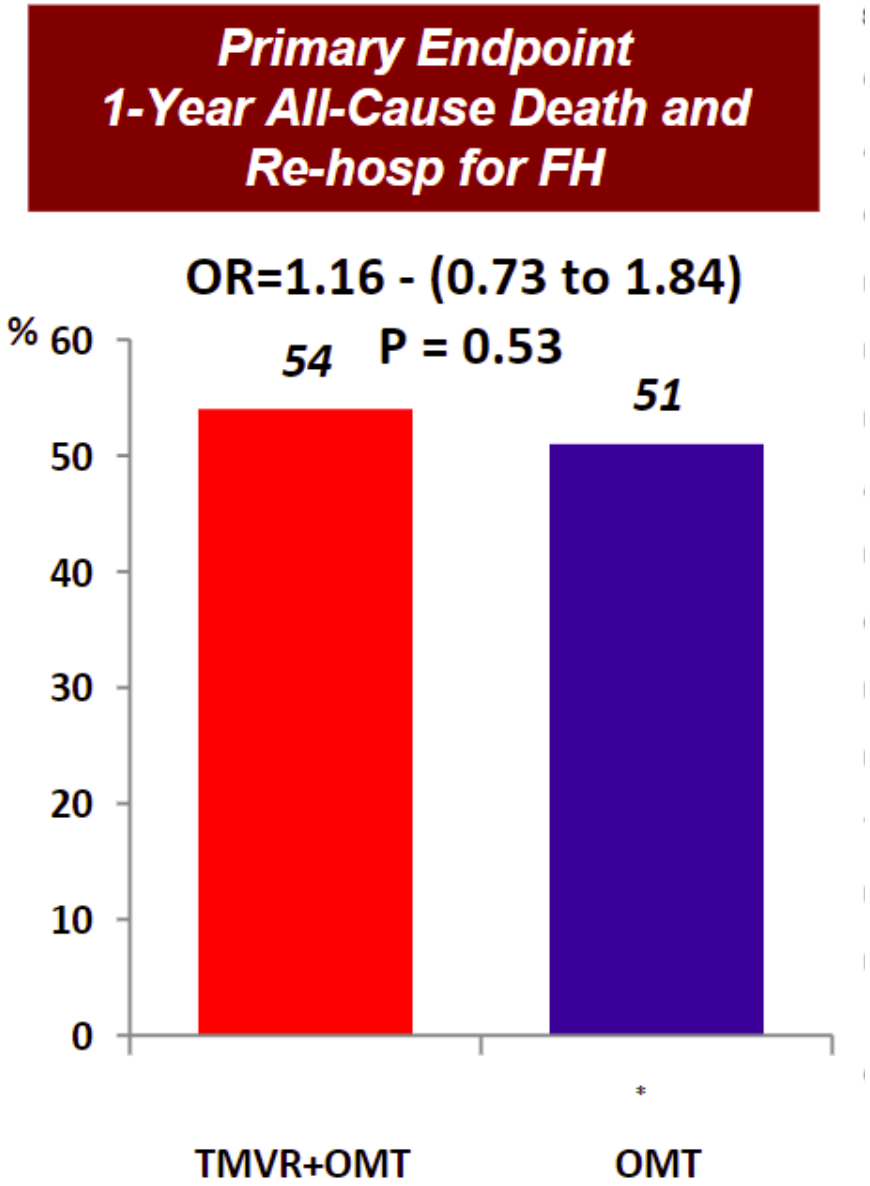




Percutaneous Mitral Valve Repair for Patients with HFrEF and Severe Functional MR - The Data:

- In 2018, two RCTs comparing the efficacy of MitraClip in addition to Guideline-Directed Medical Therapy (GDMT) compared with GDMT alone in patients with Functional MR for whom mitral valve surgery was not deemed appropriate were published

MITRA-FR Primary Endpoints and Subgroups

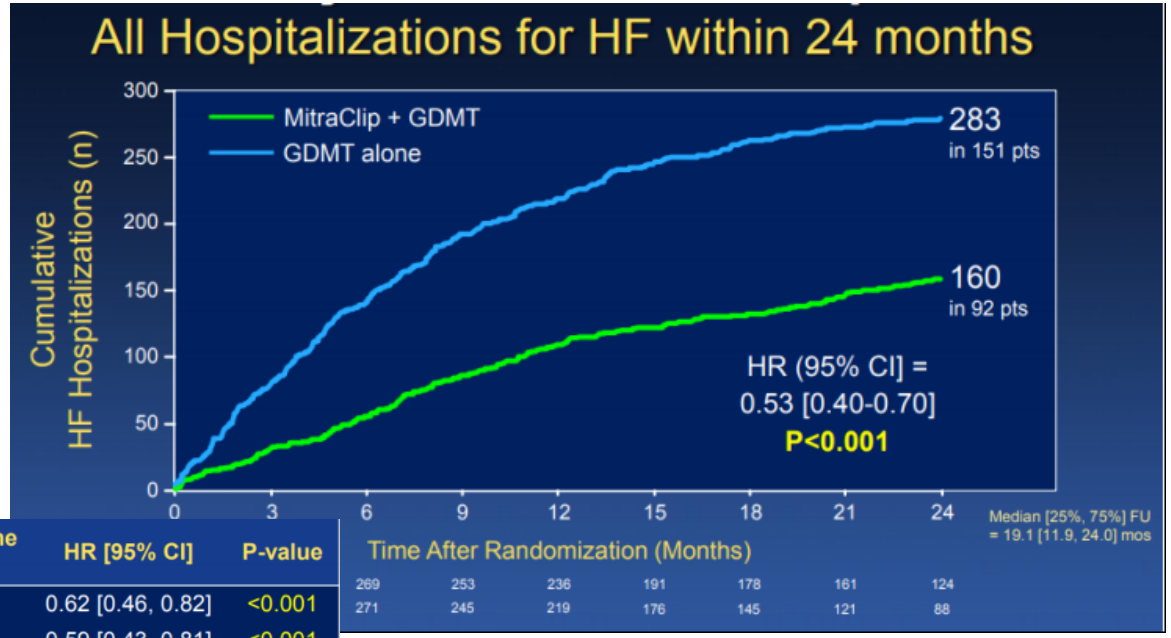


MITRA-FR

304 patients
1 year follow up
Very dilated LV
Mod-Severe MR

Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation: The COAPT Trial

- 614 patients ***after optimization*** of GDMT
  - 1/3 of the screened patients randomized
- 2 year follow-up



	MitraClip + GDMT (n=302)	GDMT alone (n=312)	HR [95% CI]	P-value
Death, all-cause	29.1%	46.1%	0.62 [0.46, 0.82]	<0.001
- CV	23.5%	38.2%	0.59 [0.43, 0.81]	<0.001
- HF-related	12.0%	25.9%	0.43 [0.27, 0.67]	<0.001
- Non-HF-related	13.1%	16.6%	0.86 [0.54, 1.38]	0.53
- Non-CV	7.3%	12.7%	0.73 [0.40, 1.34]	0.31
Hospitalization, all-cause	69.6%	81.8%	0.77 [0.64, 0.93]	0.01
- CV	51.9%	66.5%	0.68 [0.54, 0.85]	<0.001
- HF-related	35.7%	56.7%	0.52 [0.40, 0.67]	<0.001
- Non-HF-related	29.4%	31.0%	0.98 [0.71, 1.36]	0.92
- Non-CV	48.2%	52.9%	0.91 [0.71, 1.17]	0.47
Death or HF hospitalization	45.7%	67.9%	0.57 [0.45, 0.71]	<0.001

Comparison of Trial Patients and Outcomes in the MITRA-FR and COAPT Studies

Trial and Patient Characteristics	MITRA-FR	COAPT
Comparison	MitraClip vs GDMT	MitraClip vs GDMT
Heart team evaluation and GDMT	Heart team evaluation, GDMT not described over time	Heart team evaluation, ***GDMT described over time***
Study period	2013-2017	2012-2017
Follow-up period, year	***1***	***2***
Patients enrolled/Patients considered for trial (%)	307/452 (67.9)	665/1576 (42.2)
LVEDVI, mean (SD), mL/m^2	***135 (35)***	***101 (34)***
Baseline EROA, mm^2, mean (SD)	***31 (10)***	***41 (15)***
LVEF, mean (SD), %	33 (7)	31 (9)
Outcomes		
Procedural complications*	21/144 ***(14.6)***	25/293 (8.5)
MR grade ≥ 2 at discharge	30/123 ***(24.4%)***	46/260 (17.7)
MR grade ≥ 2 at 1-year	48/97 (49.5)	65/210 (31.0)
All-cause mortality/ HF hospitalization at 1 year No/Total (%)		
MitraClip arm	83/151 (54.6)	102/302 (33.9)
GDMT arm	78/152 (51.3)	145/312 (46.5)
p value	0.53	***<0.001***

Modified from: GHL Tang, et al. JAMA Cardiology 2019;4:307-308.

Comparison of Trial Patients and Outcomes in the MITRA-FR and COAPT Studies

Trial and Patient Characteristics	MITRA-FR	COAPT
Follow-up perio		
Patients enrolled		
LVEDVI, mean		
Baseline EROA,		
Outcomes		
Procedural comp		

Positive Clinical Trial Outcomes Associated With:

- Longer follow –up
- Highly selected, medically optimized patients
- Less dilated ventricles
- Proportionally more MR
- Better procedural success

* Mitraclip group only

Modified from: GHL Tang, et al. JAMA Cardiology 2019;4:307-308.

CCS HF Guidelines 2019: Recommendations

1. We recommend that maximally tolerated GDMT, including CRT and revascularization where appropriate, be implemented before consideration of percutaneous mitral valve repair for patients with HFrEF and severe functional MR
   (**Strong Recommendation; High-Quality Evidence**).

2. We recommend that a multidisciplinary dedicated heart-team (including interventionalists, cardiac surgeons, imaging specialists, and HF specialists) perform the evaluation and care of potential candidates for percutaneous mitral valve repair
   (**Strong Recommendation; Low-Quality Evidence**).

CCS HF Guidelines 2019: Some Practical Tips

- Patients with ***severe LV dilatation*** (> 70mm) and less than severe MR might be poor candidates

- Patients with FMR ***should first receive maximally tolerated medical therapy*** for a minimum period of time (3 months), before intervention considered

- Patients considered for PMVR ***should be referred to centres*** with:
  - experience in the evaluation of patients with advanced HF
  - high volumes of patients with valve disease managed medically and surgically
  - high likelihood of achieving the volume of PMVR (e.g. 2-4 per month) required for developing and maintaining competence in well-selected patients

2019 Update of SGLT2 Inhibitors for Prevention and Management of HF:

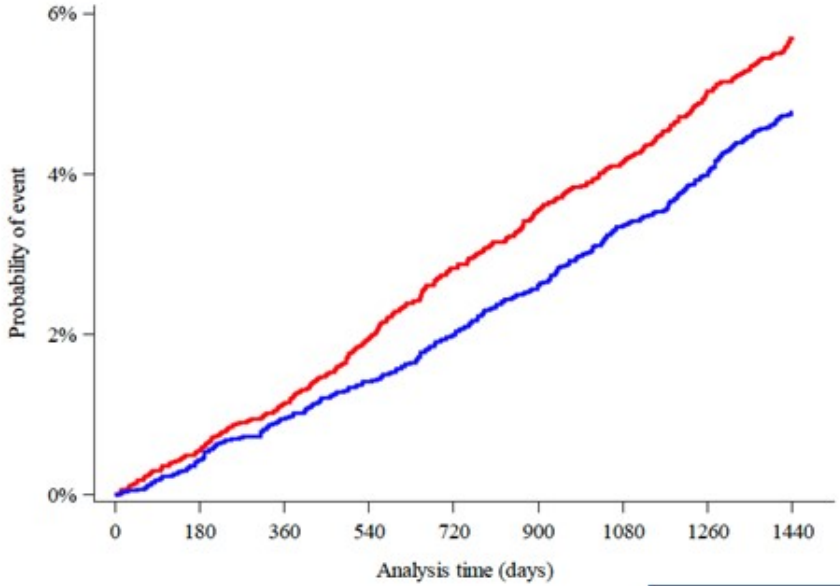
New Information Since the 2017 HF Guidelines Update

Sean A. Virani MD, MSc, MPH, FRCPC, FCCS
Associate Professor of Medicine, UBC
Past-President and Chair, Canadian Heart Failure Society

Primary Endpoints

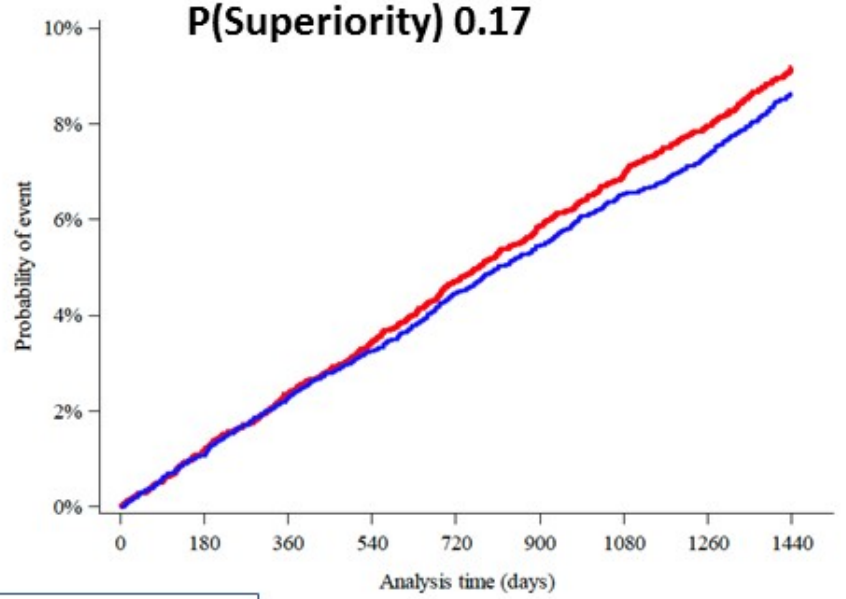
CVD/HHF

4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005



MACE

8.8% vs 9.4%
HR 0.93 (0.84-1.03)
P(Noninferiority) <0.001
P(Superiority) 0.17



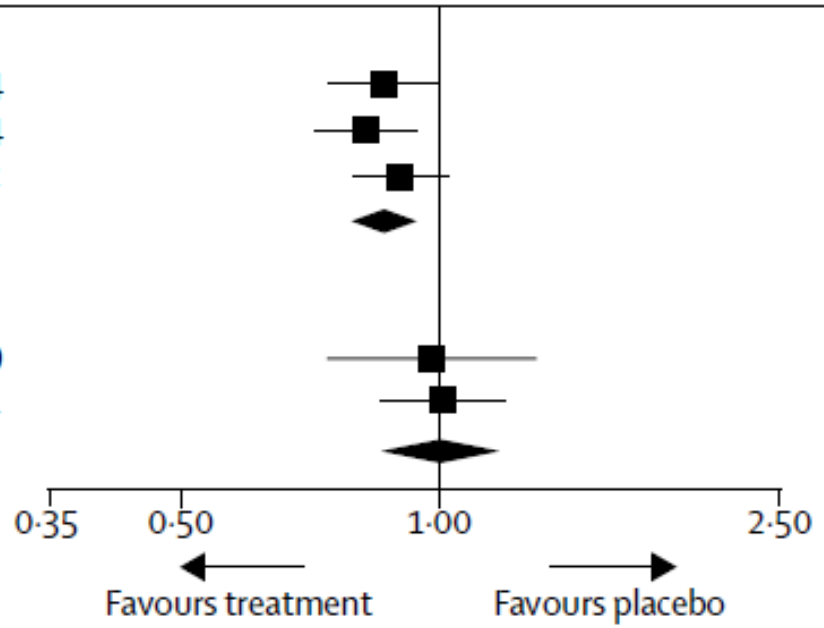
Dapagliflozin
Placebo

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

CANADIAN CARDIOVASCULAR CONGRESS
CONGRÈS CANADIEN SUR LA SANTÉ CARDIOVASCULAIRE

Primary MACE endpoint by CV status

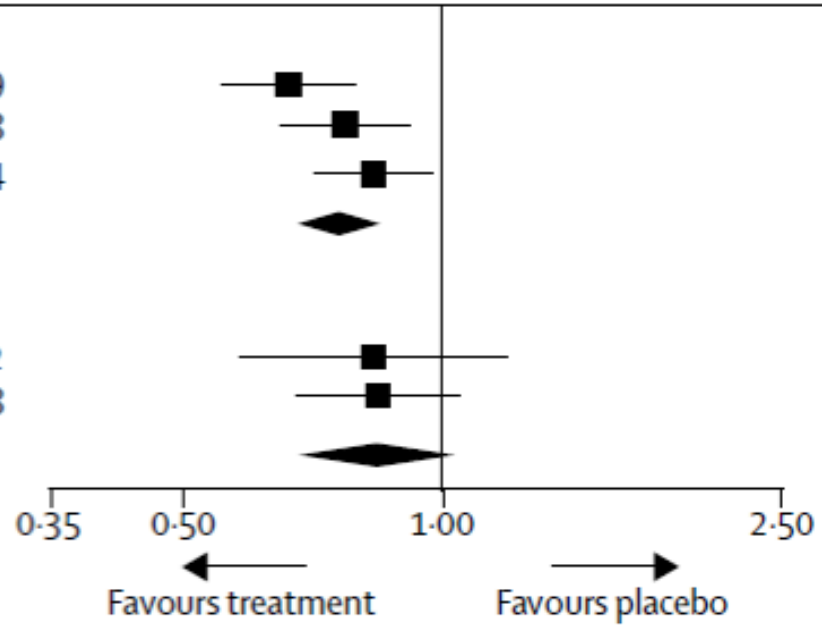
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474/6974	3500/6974	1020	36·8	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)								**0·86 (0·80–0·93)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108/10 186	5078/10 186	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								**1·00 (0·87–1·16)**



www.thelancet.com Published online November 10, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32590-X

Hospitalization for HF endpoint by CV status

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9	0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8	0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	23·9	36·4	0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)							**0·76 (0·69–0·84)**
Patients with multiple risk factors							
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2	0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·4	69·8	0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)							**0·84 (0·69–1·01)**



www.thelancet.com Published online November 10, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32590-X

2019 CCS HF Recommendation

1. **UPDATED** We recommend SGLT2 inhibitors, such as empagliflozin, canagliflozin or dapagliflozin, be used for treatment of patients with type 2 diabetes and atherosclerotic cardiovascular disease to reduce the risk of HF hospitalization and death (**Strong Recommendation; High-Quality Evidence**).

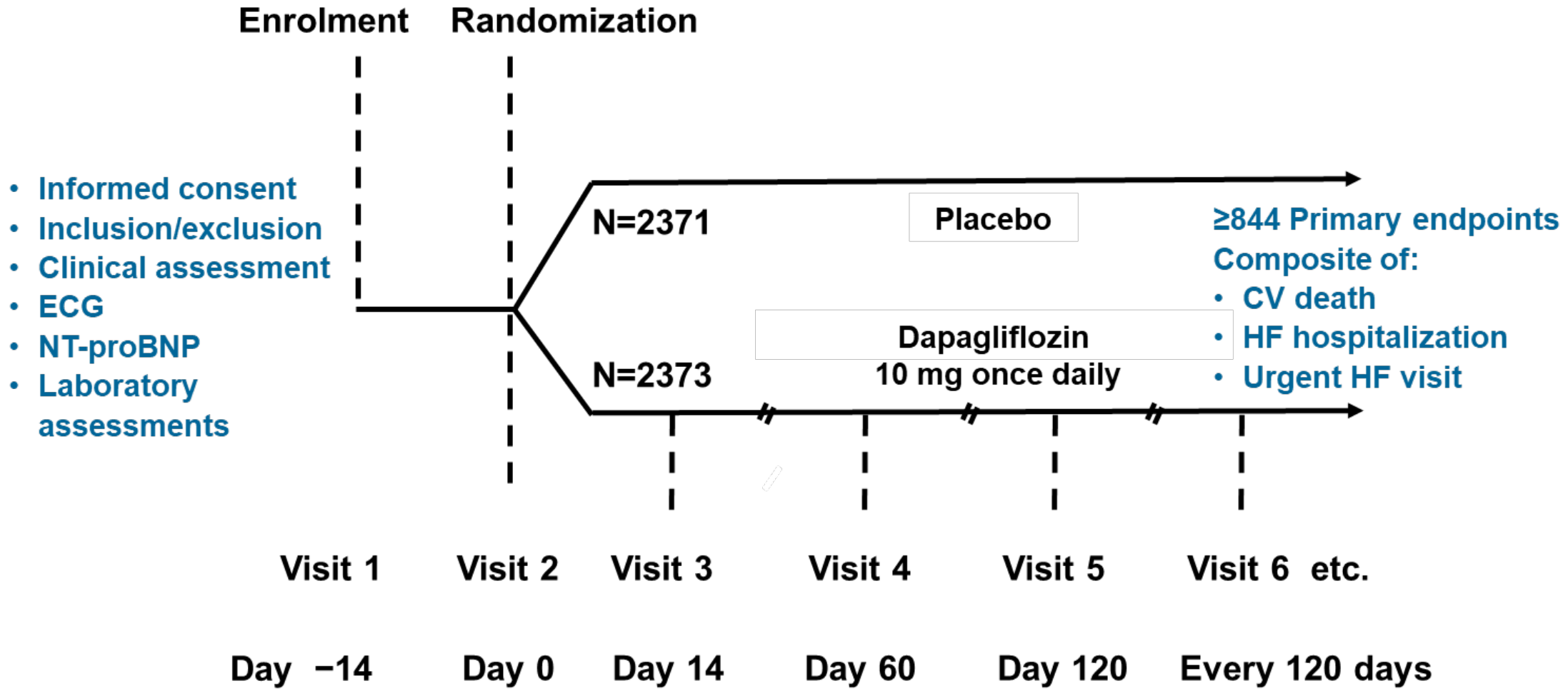
2. **NEW** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with type 2 diabetes aged >50 years with additional risk factors for atherosclerotic cardiovascular disease to reduce the risk of hospitalization for HF (**Strong Recommendation; High-Quality Evidence**).

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

DAPA-HF Design

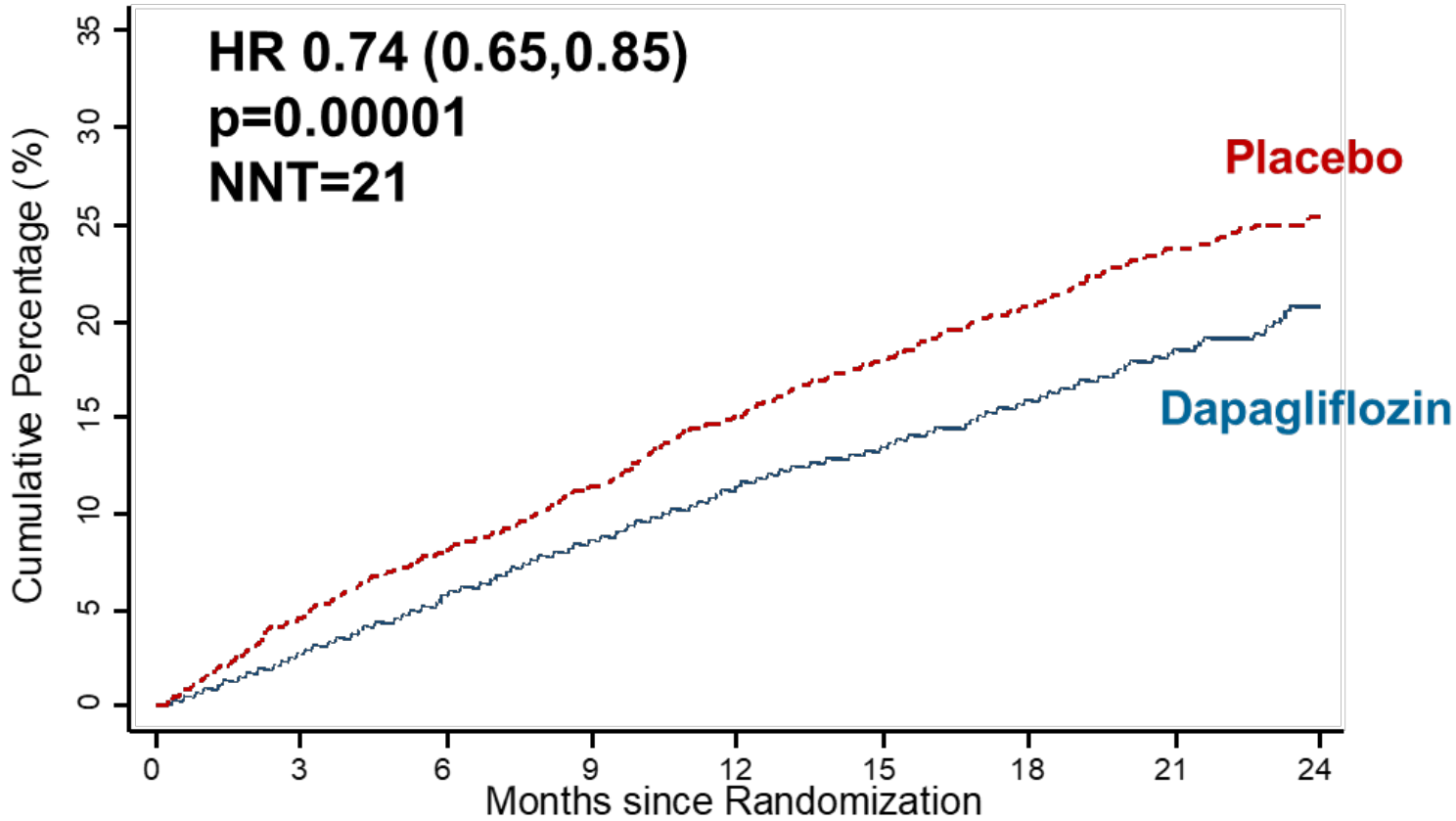


Dapa-HF vs Recent Trial Participants: Baseline medical therapy

	SHIFT (N=6505)	PARADIGM-HF (N=8442)	ATMOSPHERE (N=7063)	COMMANDER-HF (N=5022)	DAPA-HF (N=4744)
Diuretic	73	80	80	100	94
ACEi or ARB	-	100	100	93	94[a]
β-blocker	90	93	92	92	96
MRA	60	60	37	77	71
Ivabradine	N/A	1.5	1.0	-	5
Digitalis glycoside	22	30	32	9	19
CRT	1	7	6	-	8
ICD	4	15	15	-	26

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit

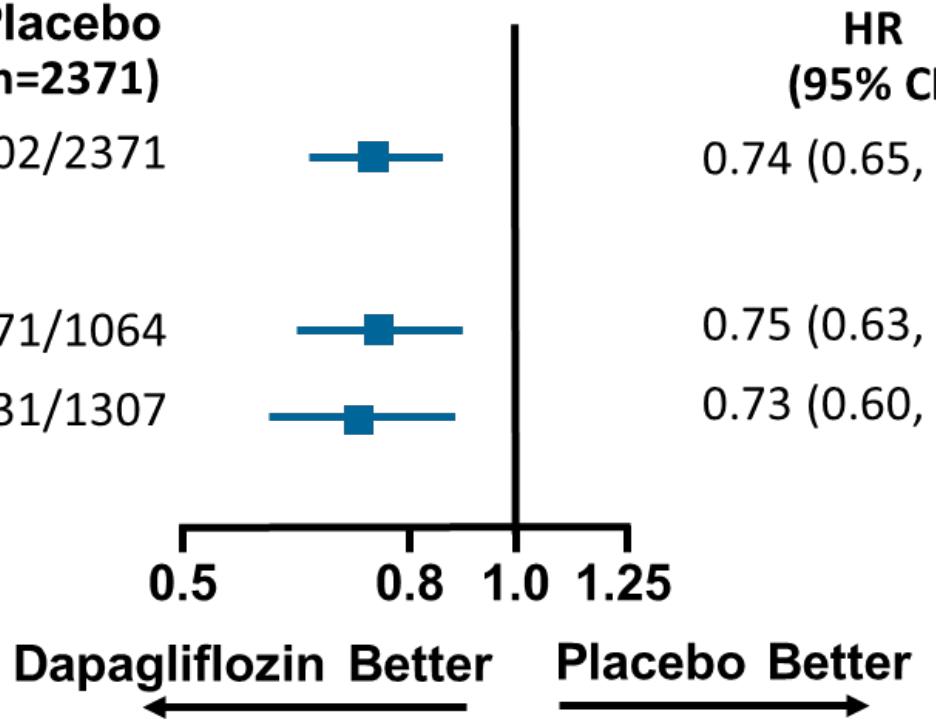


Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

No diabetes/diabetes subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

Safety/adverse events

Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Adverse events (AE) of interest (%)			
Volume depletion[+]	7.5	6.8	0.40
Renal AE[‡]	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycaemia	0.2	0.2	-
Diabetic ketoacidosis	0.1	0.0	-
AE leading to treatment discontinuation (%)	4.7	4.9	0.79
Any serious adverse event (incl. death) (%)	38	42	<0.01

[+] Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23

[‡] Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009

2019 HF Guidelines Update

4. **NEW** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate heart failure due to reduced left ventricular ejection fraction (LVEF ≤ 40%) and *concomitant type 2 Diabetes,* to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality (**Strong Recommendation; High-Quality Evidence**).
5. **NEW** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate heart failure due to reduced left ventricular ejection fraction (LVEF ≤ 40%) and *without concomitant Diabetes,* to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality (**Conditional Recommendation; High-Quality Evidence**).

Practical Tips

- The most common adverse effect of this class of medications are genital mycotic infections (GMI). Typically, GMI can be managed with antifungal and do not require discontinuation of therapy.

- SGLT2i may result in temporary reduction of eGFR up to 15% which generally resolves within 1-3 months. SGLT1i have also been associated with acute kidney injury and increase monitoring is warranted in those at risk.

- SGLT2 inhibitors do not cause hypoglycemia in the absence of concomitant insulin and / or secretagogues therapy. These background therapies may need to be adjusted to prevent hypoglycemia. These agents are contraindicated in Type 1 diabetes.

Practical Tips …

- SGLT2i should be held in the setting of concomitant dehydrating illness as part of 'Sick Day' management according to the Canadian Diabetes Association Recommendations for 'Sick Day' management *(ref: CDA, Canadian J Diabetes, 2018; 42: S316)*

- These agents have been associated with diabetic ketoacidosis (incidence 0.1%). Patient may present with normal or only modestly elevated blood glucose (< 14 mmol/L). On rare occasions, it may be associated with normal anion gap acidosis, which is best detected by measurement of serum ketones. Non-specific symptoms associated with DKA include: shortness of breath, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst and lethargy.

- Caution should be exercised when combining SGLT2 inhibitors, ARNI and diuretics given their concomitant effects on diuresis.

There are now 6 medications and 2 devices that reduce all cause mortality in patients with HF

Therapy	NNT Mortality 1 year	NNT Mortality 5 years
Medications		
ACEi/ARB	92	18
Beta blocker	40	8
MRA	75	15
SNI- Ivabradine	45	9
ARNi	80	14
SGLT2i	67	16
Devices		
ICD	70	14
CRT pacing	70	14

Fonarow, JAMA Cardiol, 2018; 3(12);1226-31.
Swedberg Lancet 2009

Summary

- Novel therapies for HFrEF improve HF related morbidity and mortality!
  - Percutanous mitral valve repair – patient selection and appropriate expertise is key
  - SGLT2 inhibitors for patients with AND without diabetes
  - SGLT2 inhibitors for prevention AND treatment of HF
  - Future studies will inform optimal timing, patient population and limitations of these therapies