Insuffisance cardiaque et Diabète : 2019

Mark Liszkowski MD
Cardiologue en Insuffisance cardiaque
Transplantation et assistance mécanique
Intensiviste
Institut de Cardiologie de Montréal

INSTITUT DE CARDIOLOGIE DE MONTRÉAL

Université de Montréal

Objectifs

- Insuffisance cardiaque et le diabète
- Traitement de l'insuffisance cardiaque chez les diabétiques
- Traitement du diabète chez les patients avec insuffisance cardiaque
- Conclusions

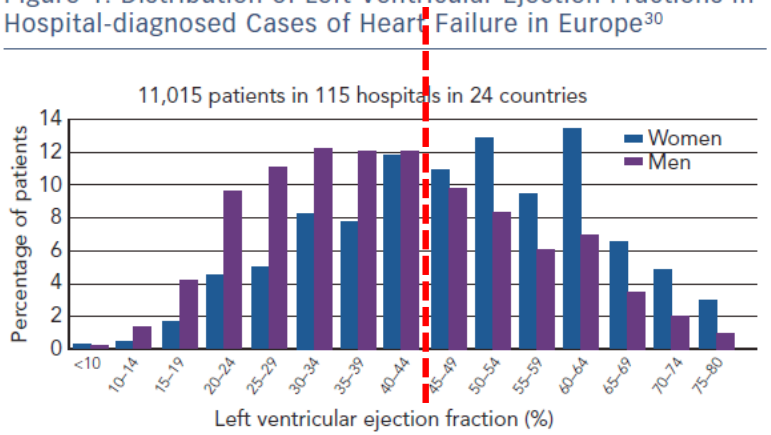
1- Insuffisance cardiaque

- Insuffisance cardiaque
  - Dyspnée 2ere congestion vasculaire
  - Indépendant de la fraction d'ejection du VG

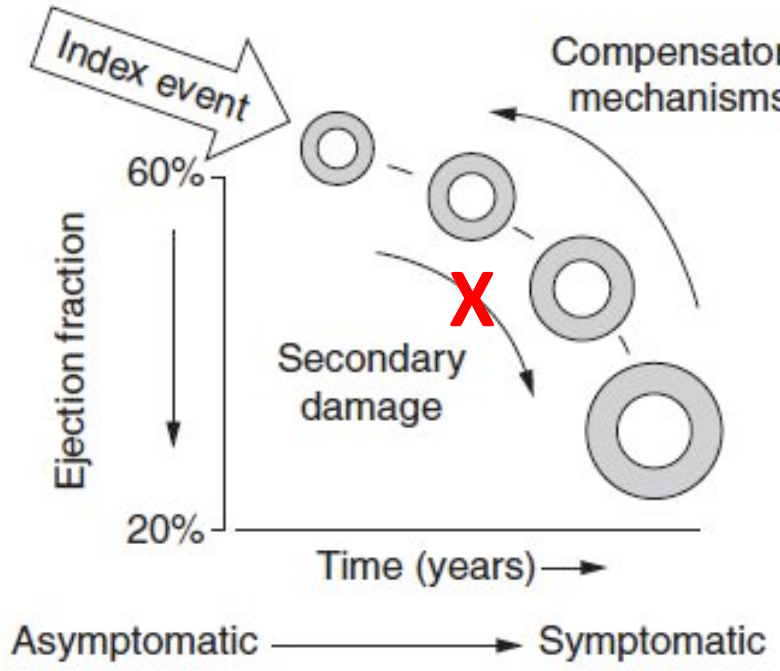
- Souvent non-diagnostiquée
  - ntBNP, échographie et MIBI/coronarographie

- Traitement et suivi souvent inadéquats
  - 20% des patients suivis par un cardiologue
  - 50-80% sous-traités médicalement

Figure 1: Distribution of Left Ventricular Ejection Fractions in Hospital-diagnosed Cases of Heart Failure in Europe[30]

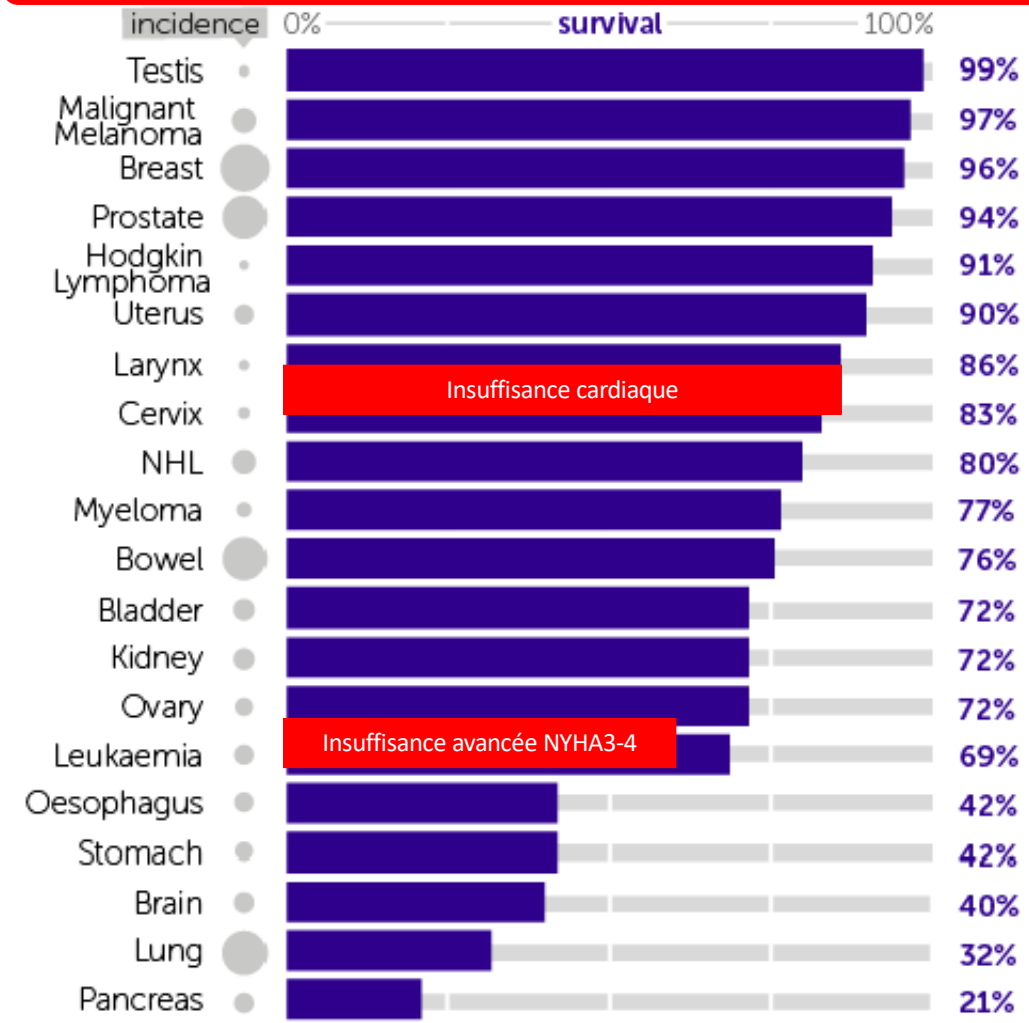


Pathophysiologie



RAAS
Catécholamines
Fibrose
Remodelage
Rétention Na/H2O

Survie à 1 an


incidence
0%
survival
100%
Testis
99%
Malignant Melanoma
97%
Breast
96%
Prostate
94%
Hodgkin Lymphoma
91%
Uterus
90%
Larynx
86%
Cervix
83%
NHL
80%
Myeloma
77%
Bowel
76%
Bladder
72%
Kidney
72%
Ovary
72%
Leukaemia
69%
Oesophagus
42%
Stomach
42%
Brain
40%
Lung
32%
Pancreas
21%
Insuffisance cardiaque
Insuffisance avancée NYHA3-4

Canadian Journal of Cardiology 33 (2017) 1342–1433

Society Guidelines

2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure

Primary Panel: Justin A. Ezekowitz, MBBCh (Chair),[a] Eileen O'Meara, MD (Co-chair),[b]

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Recommandations CCS 2017

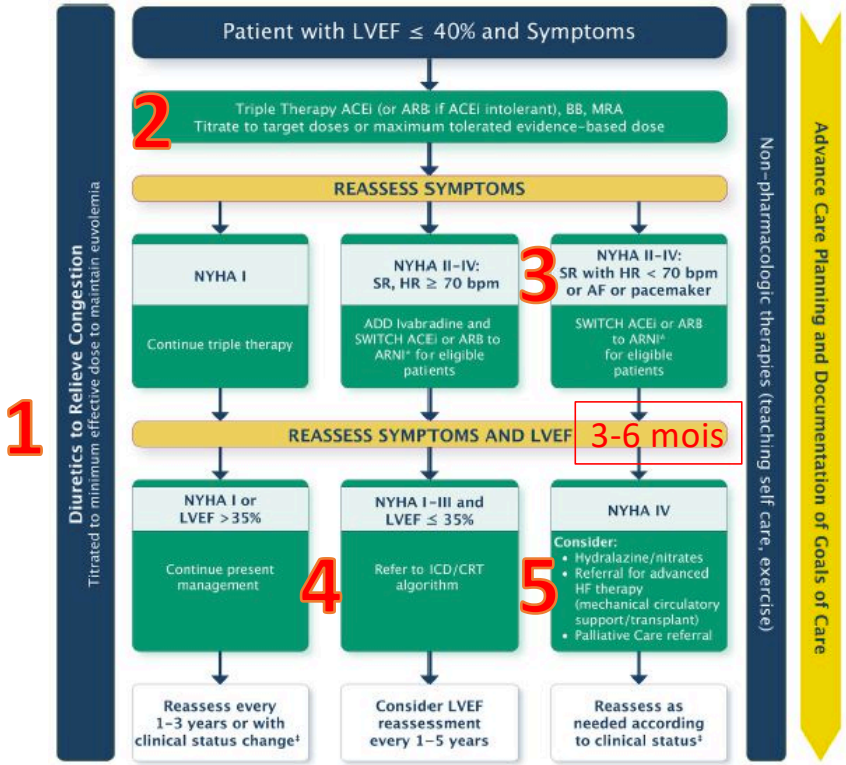


Table 11. Evidence-based drugs and oral doses as shown in large clinical trials

Drug	Start dose	Target dose
ACEi		
Enalapril	1.25-2.5 mg BID	10 mg BID/20 BID in NYHA class IV
Lisinopril	2.5-5 mg daily	20-35 mg daily
Perindopril	2-4 mg daily	4-8 mg
Ramipril	1.25-2.5 mg BID	5 mg BID
Trandolapril	1-2 mg daily	4 mg daily
ARB		
Candesartan	4-8 mg daily	32 mg daily
Valsartan	40 mg BID	160 mg BID
β-Blockers		
Carvedilol	3.125 mg BID	25 mg BID/50 mg BID (> 85 kg)
Bisoprolol	1.25 mg daily	10 mg daily
Metoprolol CR/XL*	12.5-25 mg daily	200 mg daily
MRA		
Spironolactone	12.5 mg daily	50 mg daily
Eplerenone	25 mg daily	50 mg daily
ARNI		
Sacubitril/valsartan	50-100 mg BID	200 mg BID
I_f inhibitor		
Ivabradine	2.5-5 mg BID	7.5 mg BID
Vasodilators		
Isosorbide dinitrate	20 mg TID	40 mg TID
Hydralazine	37.5 mg TID	75-100 mg TID or QID

European Heart Journal (2016) **37**, 2129–2200

Bénéfice additif des thérapies

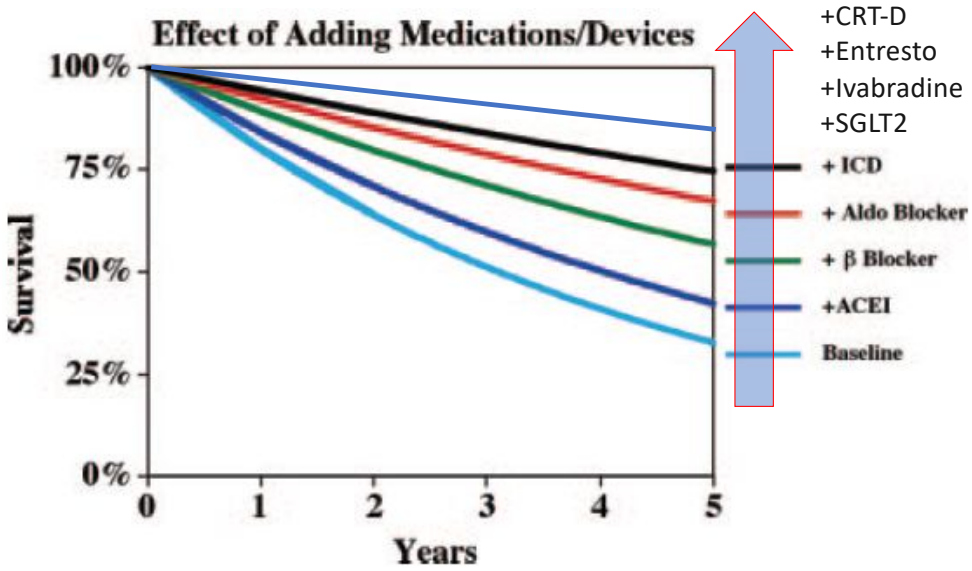
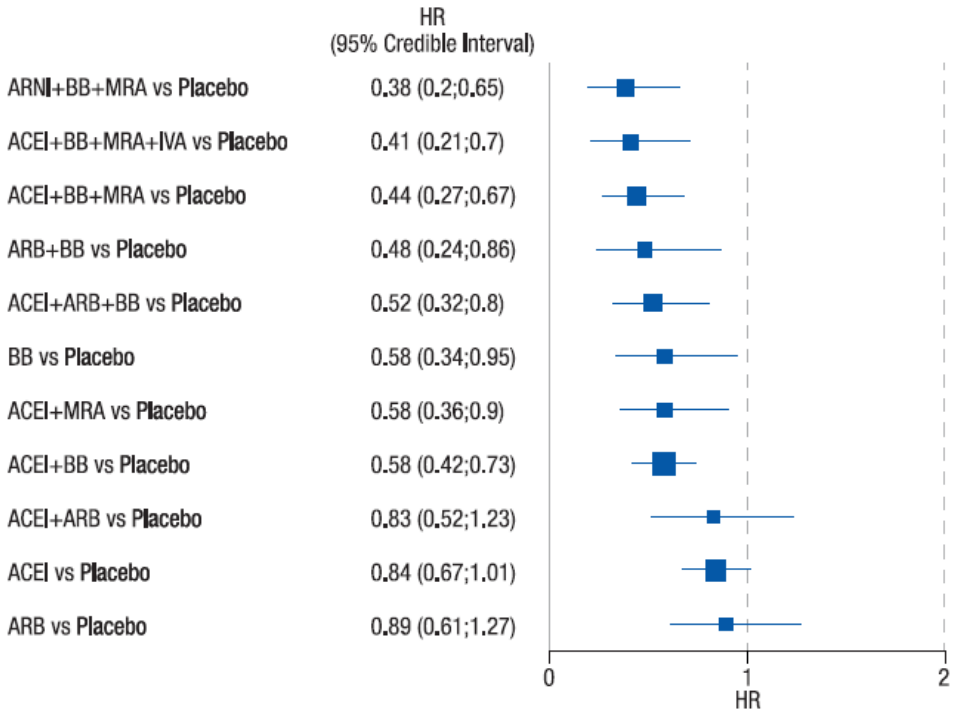


Figure 5. The predicted effects on survival of sequentially adding medications and an ICD for a heart failure patient with an annual mortality of 20% and a mean survival of 4.1 years at baseline. Adding an ACE inhibitor (ACEI), a β-blocker, an aldosterone (Aldo) blocker, and an ICD decreases the annual mortality by 70% (20% to 6%) and increases the mean survival by 5.6 years (mean survival 4.1, 5.0, 6.6, 8.2, and 9.7 years, respectively).

Circulation. 2006;113:1424-1433

Bénéfice additif des thérapies

Mortalité cardiovasculaire

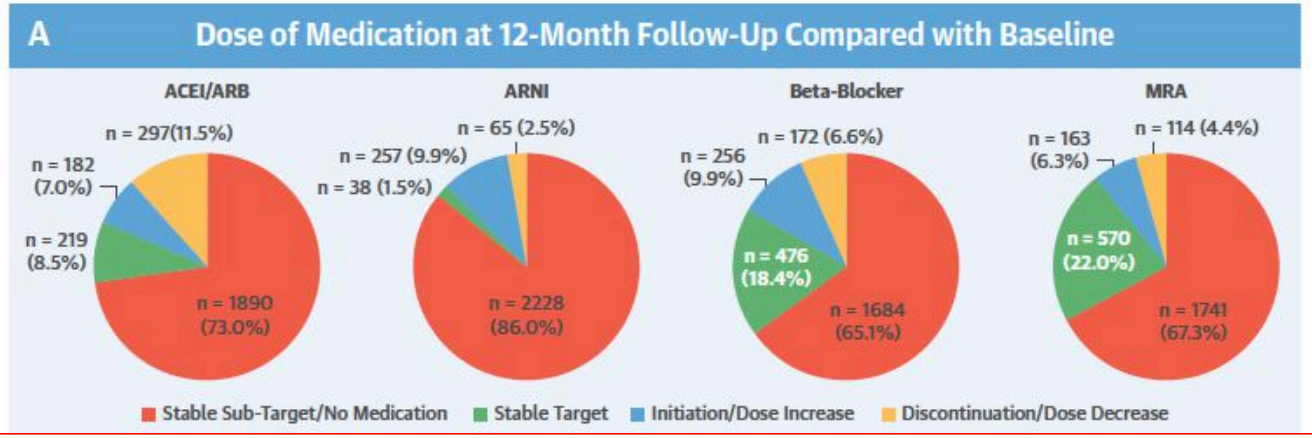


Komajda M, et al. Eur J Heart Fail 2018 .

Traitement de l'insuffisance cardiaque:
Nettement insuffisant!

Titration of Medical Therapy for Heart Failure With Reduced Ejection Fraction

CENTRAL ILLUSTRATION Changes in Use and Dose of GDMT Over 12 Months Among Patients With Chronic Heart Failure With Reduced Ejection Fraction in Contemporary U.S. Outpatient Practice



JACC VOL. 73, NO. 19, 2019
MAY 21, 2019:2365–83

Registre CHAMP-HF: utilization des thérapies

	ACEI/ARB	ARNI	ACEI/ARB/ ARNI	Beta-Blocker	MRA
Without Contraindication and Not Treated	1374	3029	920	1159	2317
Treated	2107	452	2536	2351	1163
With Contraindication	37	37	62	8	38

Greene, S.J. et al. J Am Coll Cardiol. 2018;72(4):351-66.

1- Insuffisance cardiaque (IC) et diabète (Db)

European Journal of Heart Failure (2018) 20, 853–872
doi:10.1002/ejhf.1170

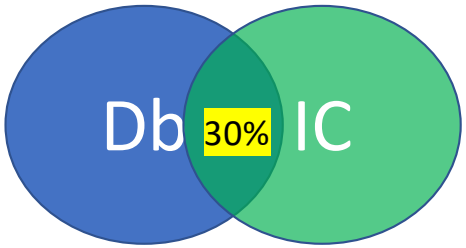
HFA POSITION STATEMENT

Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

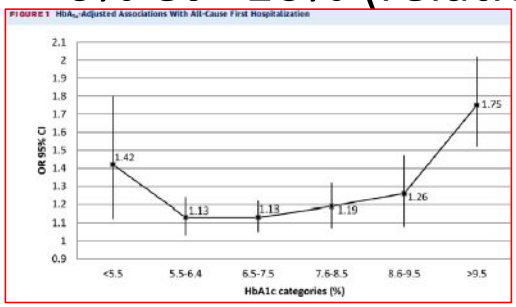
AHA SCIENTIFIC STATEMENT

Type 2 Diabetes Mellitus and Heart Failure

A Scientific Statement From the American Heart Association and the Heart Failure Society of America



- Incidence d'IC = 12%-20%
- Db augmente le risque d'IC 2-4x
- Le Db en IC augmente le risque de ***mortalité de 1.5-2x*** et la ***ré-hospitalization de 2.5x***
- Mortalité en IC accrue avec HbA1c <6% et >10% (relation en U)



Association Between Type 2 Diabetes and All-Cause Hospitalization and Mortality in the UK General Heart Failure Population

Stratification by Diabetic Glycemic Control and Medication Intensification

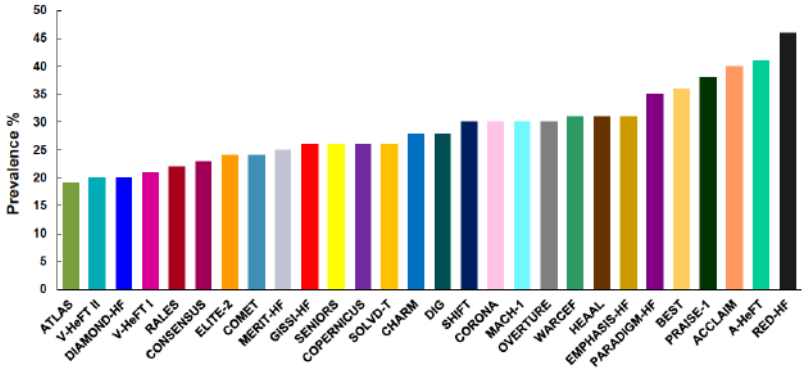
1- Prevalence de Db en IC

Table 3 Prevalence of type 2 diabetes mellitus in selected trials of heart failure

Trial	Prevalence of T2DM
Trials of HFrEF	
PARADIGM-HF[31]	35%
SHIFT[32]	30%
EchoCRT[33]	41%
HF-ACTION[34]	32%
SENIORS[35]	26%
SOLVD[36]	15%
MERIT-HF[37]	25%
CHARM-Added[38]	29%
DIG-REF[39]	28%
Trials of HFpEF	
I-Preserve[40]	27%
PEP-CHF[41]	21%
DIG-PEF[42]	29%
CHARM-Preserved[43]	28%
TOPCAT[44]	33%
Trials of acute HF	
EVEREST[45]	39%
TRUE-AHF[46]	39%
ASCEND-HF[47]	42.6%
RELAX-AHF-2[48]	47%

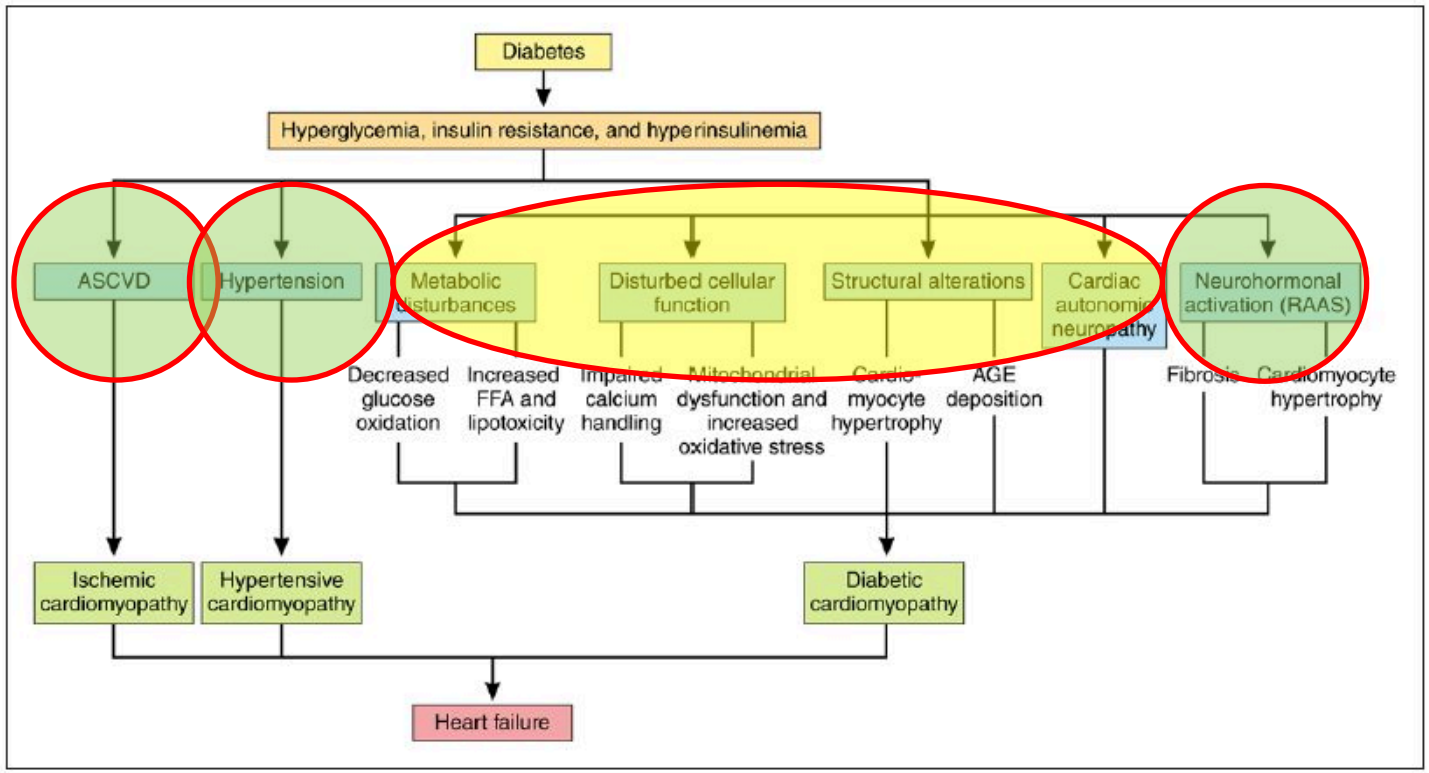
HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2DM, type 2 diabetes mellitus.

- Co-existance du Db et IC (25-40%)
- Associations avec le Db
  - Hypertension
  - Maladie coronarienne
  - Insuffisance rénale
  - Effets du Db sur le myocarde

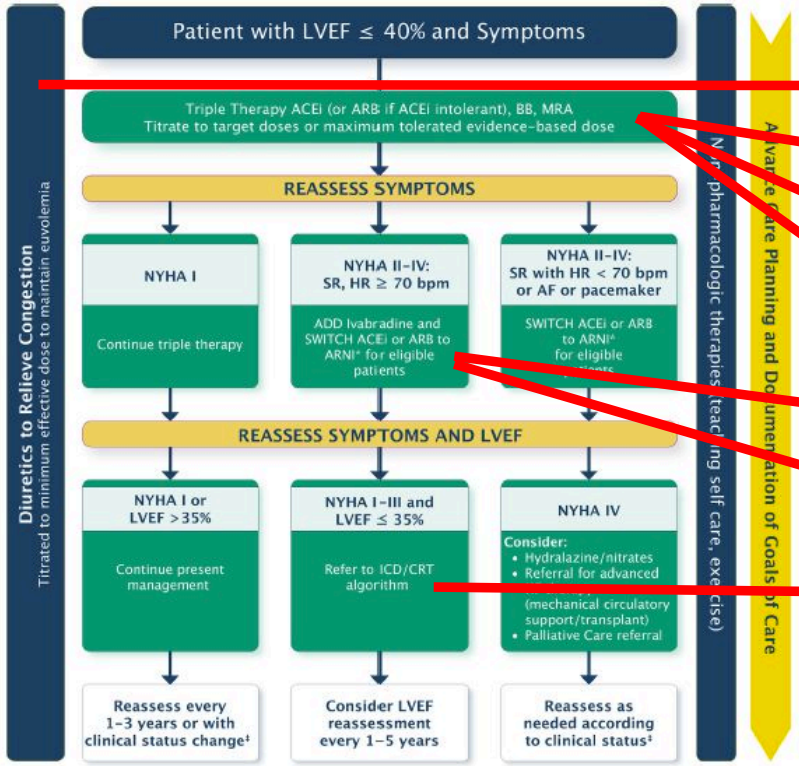


1- Insuffisance cardiaque et diabète

Low Wang et al Cardiovascular Disease in Diabetes Mellitus



1- Insuffisance cardiaque et diabète



- Diurétiques
- IECA/ARA
- Aldactone
- Beta-bloquant
- Sacubitril-Valsartan (Entresto)
- Ivabradine
- Défibrillateurs/CRT
- Revascularisation

Canadian Journal of Cardiology 33 (2017) 366–377

Review

Diabetes for Cardiologists: Practical Issues in Diagnosis and Management

Circulation

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Contents lists available at ScienceDirect
Canadian Journal of Diabetes
journal homepage: www.canadianjournalofdiabetes.com

2018 Clinical Practice Guidelines

Treatment of Diabetes in People With Heart Failure

Diabetes Canada Clinical Practice Guidelines Expert Committee
Kim A. Connelly MBBS, PhD, FCCS, Richard E. Gilbert MBBS, PhD, Peter Liu MD, FRCPC, FACC

Can J Diabetes 42 (2018) S196–S200

Diabetes Mellitus and Heart Failure

Michael Lehrke, MD, Nikolaus Marx, MD
Department of Internal Medicine I, University Hospital Aachen, Germany.

The American Journal of Medicine (2017)

ESC European Society of Cardiology
European Heart Journal (2018) 39, 4243–4254
doi:10.1093/eurheartj/ehy596

CURRENT OPINION
Heart failure/cardiomyopathy

Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association–European Society of Cardiology

THE PRESENT AND FUTURE: *JACC* STATE-OF-THE-ART REVIEW

Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes

JACC State-of-the-Art Review

Thomas A. Zelniker, MD, MSc,[a,b] Eugene Braunwald, MD[a,b]

1- Insuffisance cardiaque et diabète

- Les recommandations récentes (CCS, AHA, ESC) nous informant:
  - 1) associations et co-existance du Db et de l'IC
  - 2) morbidité et mortalité accrue avec la combinaison des maladies
  - 3) revision des thérapies en IC chez les patients diabétiques
  - 4) revision des thérapies en Db chez les patients avec IC

2- Traitement de l'IC chez les Db

Table 5. DM Subgroup Data From Pivotal HF Trials

Trial and Year	Drug/Device Studied	Patient Population	N	% With DM	
ACE inhibitor					
CONSENSUS[175] 1987	Enalapril	NYHA IV	253	22	From meta- in non-DM
SAVE[176] 1992	Captopril				
SOLVD-Treatment[177] 1991	Enalapril				
TRACE[178] 1995	Trandolapril				
ARB					
Val-HeFT[180] 2001	Valsartan				
HEAAL[181] 2009	Losartan 150 mg vs 50 mg daily (target doses)				
VALIANT[182] 2003	Valsartan vs valsartan plus captopril vs captopril				
CHARM-Program 2008	Candesartan				
ARNI					
PARADIGM-HF[183] 2014	Sacubitril-valsartan vs enalapril	NYHA II–IV EF ≤40%			
β-Blocker					
CIBIS-II[185] 1999	Bisoprolol	NYHA III–IV EF ≤35%			
COPERNICUS[187] 2001	Carvedilol	HF with EF ≤25			
MERIT-HF[188] 1999	Metoprolol succinate	NYHA IIIB–IV EF ≤25%			
MRA					
RALES[190] 1999	Spironolactone	NYHA III–IV EF ≤35%			
EMPHASIS-HF[191] 2011	Eplerenone	NYHA II EF ≤35%			

Trial and Year	Drug/Device Studied	Patient Population	N	% With DM	Treatment Effects by DM Status
EPHESUS[193] 2003	Eplerenone	Acute MI complicated by LVSD (EF ≤40%) and HF	6632	32	No interaction of DM status with mortality (P=0.35) Secondary paper: RRR for cardiovascular death or cardiovascular hospitalization of 17% in DM (P=0.031); greater ARR hospitalization in DM cohort (5.1%) than non-DM (3%)[194]
Ivabradine					
SHIFT[195] 2010	Ivabradine	HF with LVEF ≤35% in normal sinus rhythm with HR ≥70 bpm	6558	30	Secondary paper: ivabradine significantly reduced cardiovascular death or HF hospitalization in patients with and without DM (interaction P=0.57); HR, 0.84 (95% CI, 0.75–0.95) in non-DM vs 0.80 (95% CI, 0.68–0.94) in DM[196] For HF hospitalization, HR 0.77 (95% CI, 0.67–0.89) in non-DM vs 0.71 (95% CI, 0.59–0.86) in DM. Interaction P=0.53
ICD/CRT					
MADIT-II[197] 2002	ICD	Prior MI EF ≤30%	1232	35	Primary paper indicated no differential effect of defibrillator therapy on survival according to DM status Secondary paper: reduction in death with ICD was similar in non-DM (HR, 0.71 [95% CI, 0.49–1.05]) and DM (HR, 0.61 [95% CI, 0.38–0.98])[198]
SCD-HeFT[199] 2005	ICD vs amiodarone vs placebo	NYHA II–III EF ≤35%	2521	30	DM was not a prespecified subgroup of interest Reduction in death with ICD in non-DM was 0.67 (97.5% CI, 0.50–0.90) vs 0.95 (97.5% CI, 0.68–1.33) in DM
COMPANION[200] 2004	CRT-P, CRT-D, or medical therapy	NYHA III–IV QRS ≥120 ms	1520	41	Secondary paper: CRT (pooled) had a consistent benefit in DM patients across the trial end points.[201] With CRT, patients with DM had reduced all-cause mortality or all-cause hospitalization (HR, 0.77 [95% CI, 0.62–0.97]), all-cause mortality or HF hospitalization (HR, 0.52 [95% CI, 0.40–0.69]), and all-cause mortality (HR, 0.67 [95% CI, 0.45–0.99]) compared with medical therapy
CARE-HF[202] 2005	CRT	NYHA III–IV EF ≤35% QRS ≥120 ms LVEDD ≥30 mm	813	29	Secondary paper: DM did not influence the beneficial effect of CRT on any end point.[203] CRT reduced all-cause mortality and HF hospitalization with similar echocardiographic benefits in those with and without DM
MADIT-CRT[204] 2009	CRT-D vs ICD alone	NYHA I–II EF ≤30% QRS ≥130 ms	1820	30	Secondary paper: CRT-D was associated with a significant reduction in risk of death or HF hospitalization[205] in both DM (HR, 0.56; P=0.001) and non-DM (HR, 0.67; P=0.003) patients (interaction P=0.44)
RAFT[206] 2010	CRT-D vs ICD alone	NYHA II–III EF ≤30% Intrinsic QRS ≥120 ms or paced ≥200 ms	1798	34	A prespecified DM interaction analysis was not significant (P=0.22).

2- Traitement de l'IC chez les Db

- **IECA**
- **ARA**

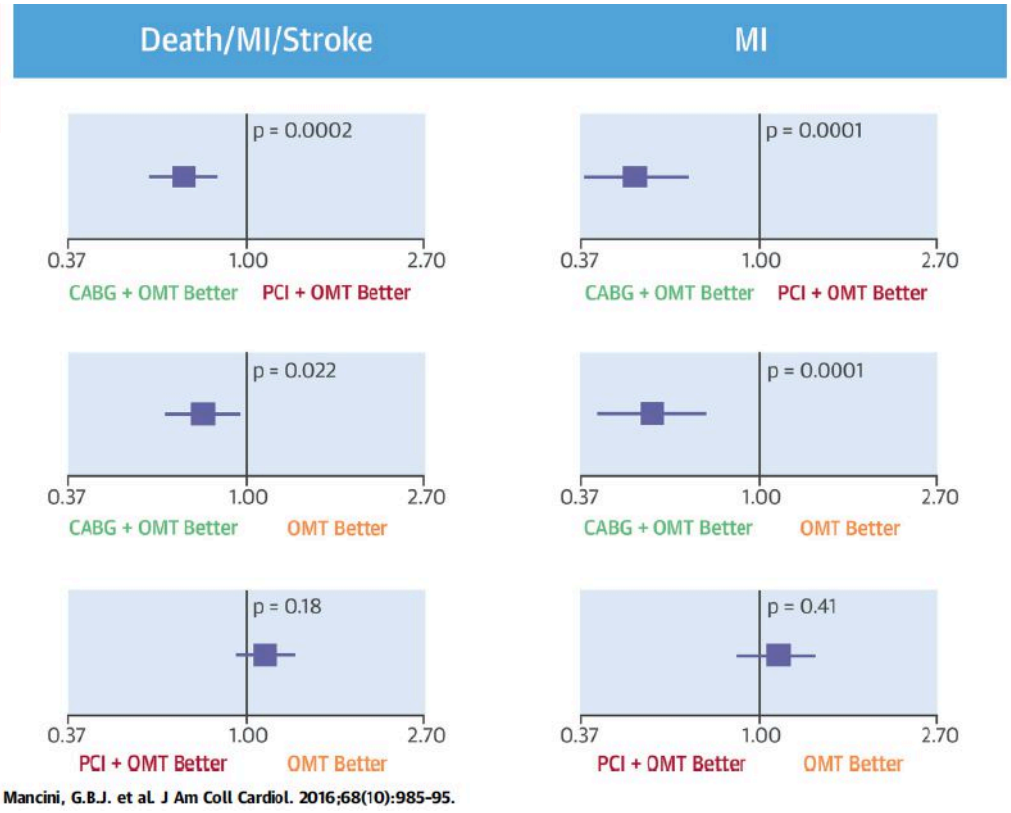
} *Efficaces, risque d'hyper K+*

- **Béta bloquants** *(hypoglycémie rare <0.6%)*
- **Inhibitors des récepteurs de minéralocorticoides** *(risque Hyper K+)*
- **Sacubitril-Valsartan** *(plus efficace qu'enalapril, reduction HbA1c, moins d'insuline et moins d'hyperK+)*
- **Nitrates et hydralazine** *(efficace)*
- **Ivabradine** *(efficace)*
- **Défibrillateurs** *(efficace + car risque de mort subite augmenté 2x avec Db)*
- **CRT (resynchromisation)** *(efficace)*

Stratégies de revascularization

Pontages >PTCA ou Rx medical pour MCAS stable

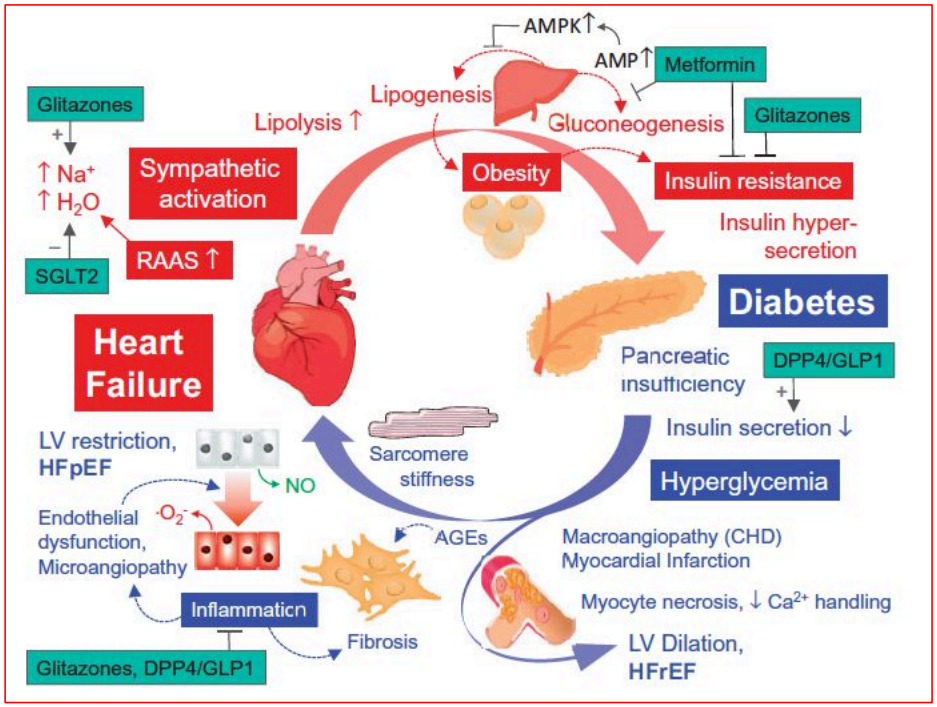
Medical Treatment and Revascularization Options in Patients With Type 2 Diabetes and Coronary Disease

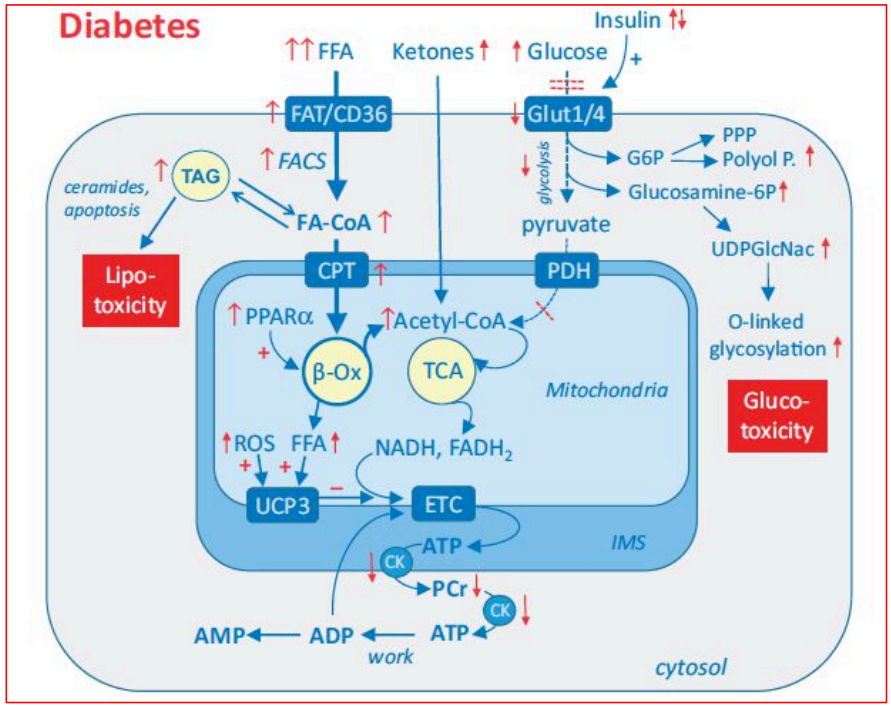


Mancini, G.B.J. et al. J Am Coll Cardiol. 2016;68(10):985-95.

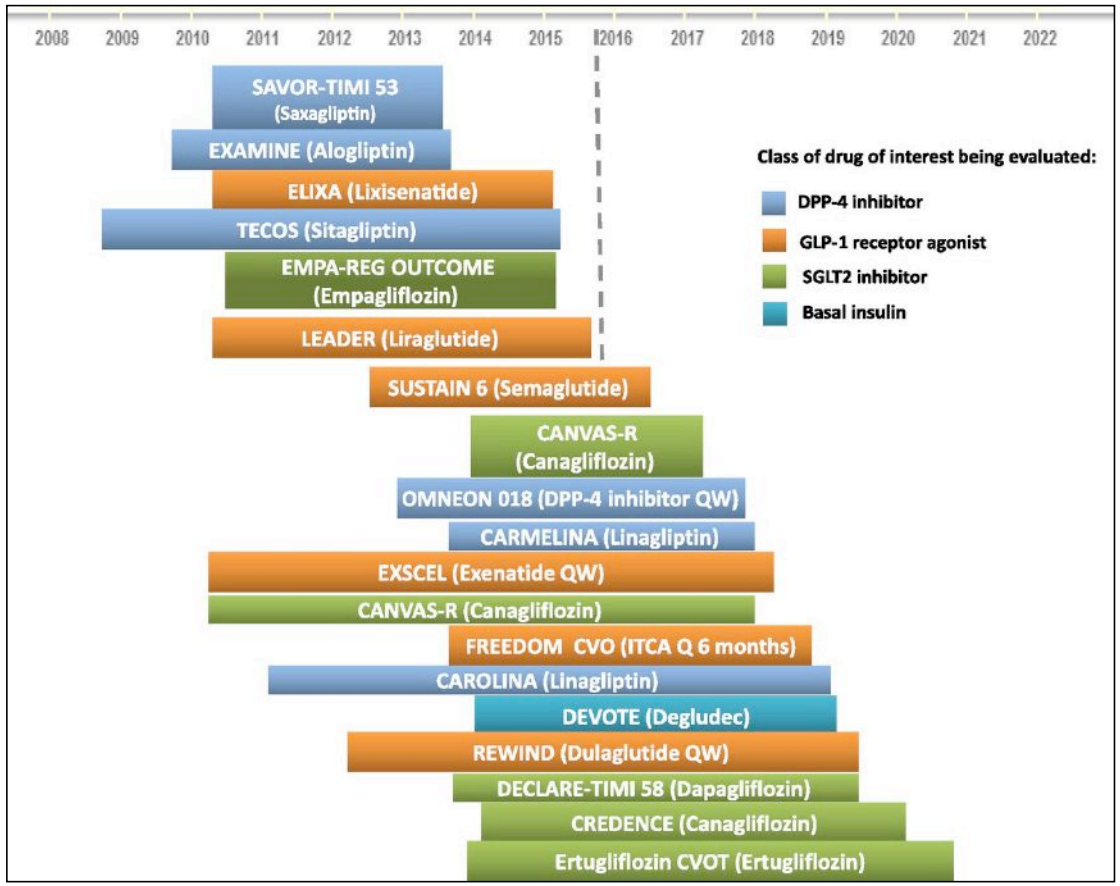
J Am Coll Cardiol 2016;68:985-95

3- Le diabète en IC





3- Le diabète en IC



3- Le diabète en IC

Biguanides: Metformin

Sulphonylurés: glyburide

Thiazolidinediones: -glitazones

Insuline

Agonistes GLP-1: - glutides (injectés)

Inhibiteurs DPP-4: -gliptines

SGLT-2: -gliflozines

3- Diabète en IC

Canadian Journal of Cardiology 33 (2017) 366–377

Review

Diabetes for Cardiologists: Practical Issues in Diagnosis and Management

CV Considerations	Risk of Hypoglycemia*	Class	Agents	Key CV Outcome Trial	Maximum Dosage	Heart Failure	Relative A1C Lowering	Renal Dosage Adjustment	BP Lowering	Weight Change	Issues in the Frail	Cost
CV superiority demonstrated as primary end point‡ in RCT by at least 1 agent in each class	Rare	Incretin Agents: GLP-1 Receptor Agonists	Liraglutide	LEADER[69]	1.8 mg daily		↓↓/ ↓↓↓	Yes	Yes	↓↓	Injections; GI side effects may lead to dehydration	$$$$
			Dulaglutide		1.5 mg weekly							
			Exenatide		10 mcg BID or 2 mg weekly							
	Rare	SGLT2 Inhibitors	Empagliflozin	EMPA-REG OUTCOME[95]	25 mg daily	Decreased	↓↓/ ↓↓↓	Yes	Yes	↓↓	Dehydration, hypotension	$$$
			Canagliflozin		300 mg daily							
			Dapagliflozin†		10 mg daily							
CV safety demonstrated as primary end point‡ in RCT by 1 or more agents in each class	Rare	Incretin Agents: DPP-4 Inhibitors§	Alogliptin†	EXAMINE[87]	25 mg daily		↓↓	Yes		0/↓		$$$
			Sitagliptin†	TECOS[88]	100 mg daily							
			Saxagliptin†	SAVOR[83]	5 mg daily	Increased						
			Linagliptin†		5 mg daily			No				
	Rare	Thiazolidinediones	Pioglitazone	PROACTIVE[90]	45 mg daily	Increased	↓↓	Yes	Yes	↑↑	Fractures; fluid retention	$$
			Rosiglitazone†	RECORD[91]	8 mg daily							
	Yes	Insulins	Glargine basal insulin	ORIGIN[92]	No maximum		↓↓↓	No		↑↑	Injections, hypoglycemia	$$$$
			Other basal/bolus insulins									$/ $$$$
CV Safety Unknown or RCT results not yet available	None	Weight Loss Agent	Orlistat		120 mg TID		↓	No		↓	Dehydration	$$$
	Rare	Alpha-glucosidase Inhibitors	Acarbose		100 mg TID		↓	Yes	Yes	↓		$$
	Yes	Insulin Secretagogues: Meglitinides	Nateglinide		120 mg TID		↓↓	No		↑	Hypoglycemia	$$
			Repaglinide		4 mg QID with food							
	Yes	Insulin Secretagogues: Sulfonylureas	Gliclazide	ADVANCE[57,9]	160 mg BID (MR: 120 mg daily)		↓↓	Yes		↑	Hypoglycemia	$
			Glimepiride‖		8 mg daily							
			Glyburide		10 mg BID							

3- Diabète en IC

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	CKD Stage	5	4		3			2/1
	eGFR (mL/min/1.73 m^2)	< 15	15 - 24	25 - 29	30 - 44	45 - 49	50 - 59	≥ 60
Class	**Drug**							
Biguanide	Metformin				500 mg BID/TID			850mg TID/1000 mg BID
Incretin Agents: GLP-1 Receptor Agonists	Liraglutide				1.8 mg sc daily		1.8 mg sc daily	
	Dulaglutide	0.75 – 1.5 mg sc per week					1.5 mg sc per week	
	Exenatide				5 mcg sc BID		10 mcg sc BID/2 mg per week	
SGLT2 Inhibitors	Empagliflozin					25 mg daily		25 mg daily
	Canagliflozin					100 mg daily		300 mg daily
	Dapagliflozin							10 mg daily
Incretin Agents: DPP-4 Inhibitors	Alogliptin	6.25 mg daily			12.5 mg daily		25 mg daily	
	Sitagliptin	25 mg daily			50 mg daily		100 mg daily	
	Saxagliptin		2.5 mg daily				5 mg	
	Linagliptin	5 mg/d	5 mg daily					
Thiazolidinediones	Pioglitazone	Risk of heart failure			45 mg daily			
	Rosiglitazone				8 mg daily			
Insulins	Glargine basal insulin	sc dosing						
	Other basal/bolus insulins	sc dosing						
Thiazolidinediones	Pioglitazone	Risk of heart failure			45 mg daily			
	Rosiglitazone				8 mg daily			
Weight Loss Agent	Orlistat	120 mg TID						
Alpha-glucosidase Inhibitor	Acarbose		100 mg TID					
Insulin Secretagogues: Meglitinides	Nateglinide	120 mg TID						
	Repaglinide	4 mg QID (with food)						
Insulin Secretagogues: Sulfonylureas	Gliclazide		hypoglycemia		160 mg BID or 120 mg daily (MR formulation)			
	Glimepiride				4 mg BID			
	Glyburide				hypoglycemia		10 mg BID	

3- Diabète en IC

Table 8 Heart failure outcomes in published large cardiovascular outcome trials in patients with type 2 diabetes mellitus

Study	Antidiabetic drug	Comparator	Results
DPP4 inhibitors			
SAVOR-TIMI 53[16,17]	Saxagliptin	Placebo	Increase in HF hospitalization
EXAMINE[19,184]	Alogliptin	Placebo	No statistically significant increase in HF hospitalization
TECOS[18,185]	Sitagliptin	Placebo	No effect on HF hospitalization
GLP-1 receptor agonists			
ELIXA[23]	Lixisenatide	Placebo	No effect on HF hospitalization
LEADER[22]	Liraglutide	Placebo	No effect on HF hospitalization
SUSTAIN-6[186]	Semaglutide	Placebo	No effect on HF hospitalization
EXSCEL[24]	Exenatide	Placebo	No effect on HF hospitalization
SGLT2 inhibitors			
EMPA-REG OUTCOME[20]	Empagliflozin	Placebo	Reduced HF hospitalization
CANVAS[21]	Canagliflozin	Placebo	Reduced HF hospitalization
Declare TIMI 58	Dapagliflozin	Placebo	Reduced HF Hospitalization

Thiazolidinediones (glitazones) – contre-indiquées en IC

3- Le diabète en IC

Biguanides: Metformin

Sulphonylurés: glyburide

Thiazolidinediones: -glitazones

Insuline

Agonistes GLP-1: - glutides (injectés)(t)

Inhibiteurs DPP-4: -gliptines

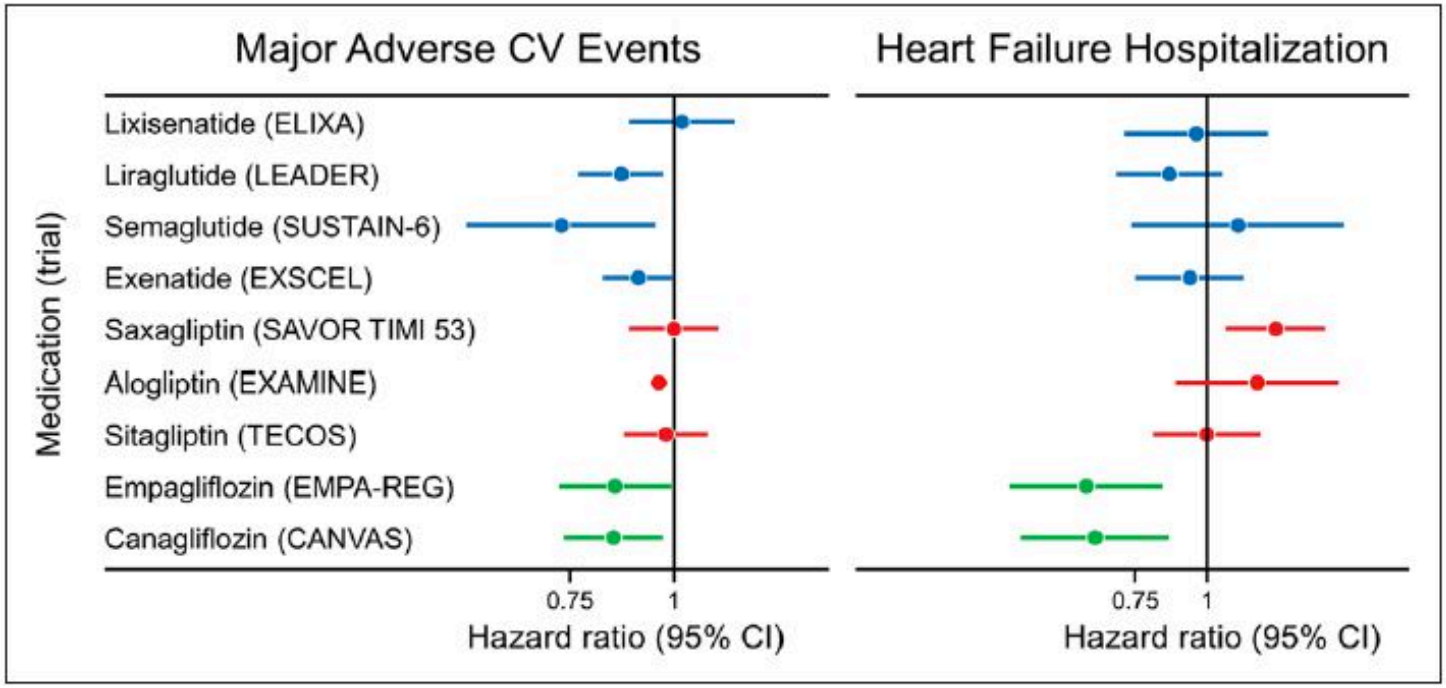
SGLT-2: -gliflozines

Table 7 Summary of evidence for type 2 antidiabetic drugs in patients with prevalent heart failure

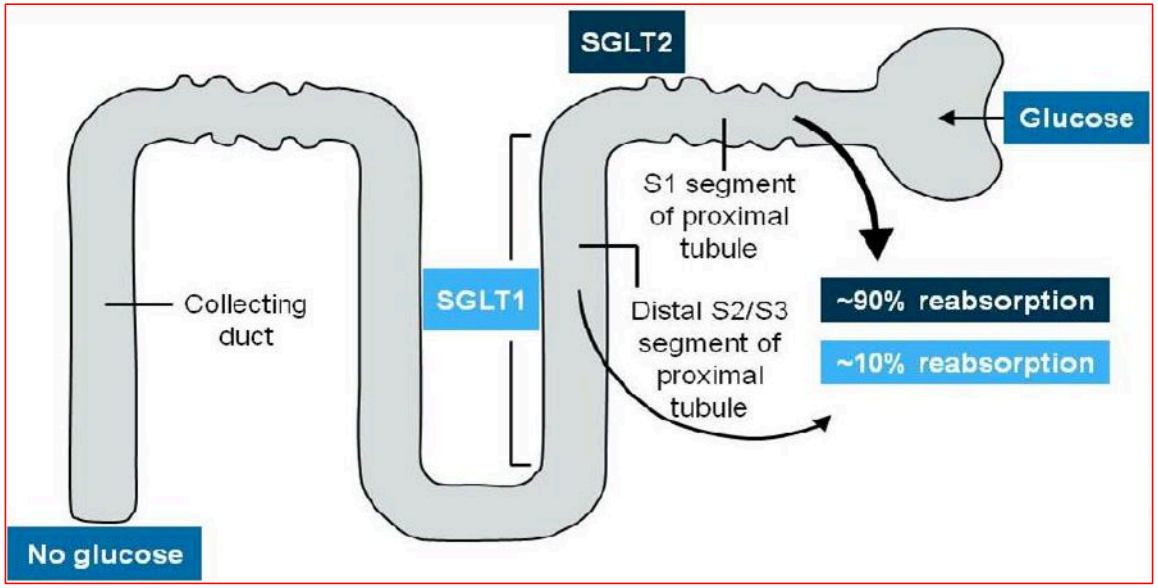
Class of drug	Evidence
SGLT2 inhibitors (e.g. empagliflozin, canagliflozin)	No RCTs in HF. Large RCTs in patients with HF with an without T2DM are underway.
Metformin	No RCTs in HF. In observational studies in HF, metformin is associated with lower mortality rates than sulphonylureas or insulin.[179] Benefit/risk ratio unknown.
GLP-1 receptor antagonists (e.g. liraglutide, albiglutide)	No large RCTs. Liraglutide - two small RCTs reported no effect on (i) LV function,[180] (ii) hierarchical composite of death/HF hospitalization/BNP change.[181] Benefit/risk ratio unknown.
Sulphonylureas	No RCTs in HF. Data equivocal. Some observational data suggest an increased mortality risk with sulphonylureas compared with metformin.[179,182]
Insulin	No RCTs in HF. In observational studies in HF, insulin was associated with higher mortality rates than metformin.[179] Benefit/risk ratio unknown.
DPP4 inhibitors	No RCTs in HF (saxagliptin contraindicated in HF[16,17]). Benefit/risk ratio unknown.

European Journal of Heart Failure (2018) 20, 853–872

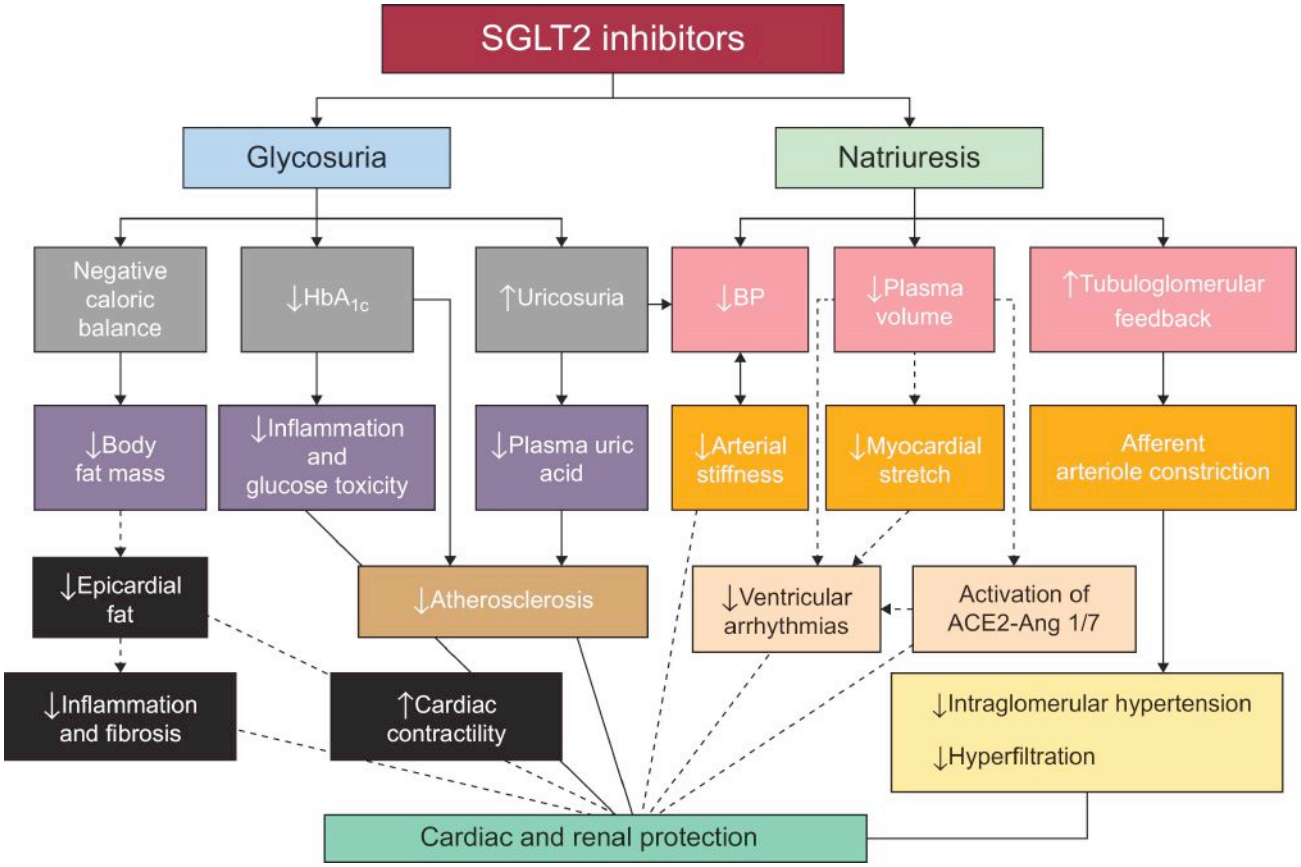
3- Diabète en IC



3- Inhibiteurs SGLT-2



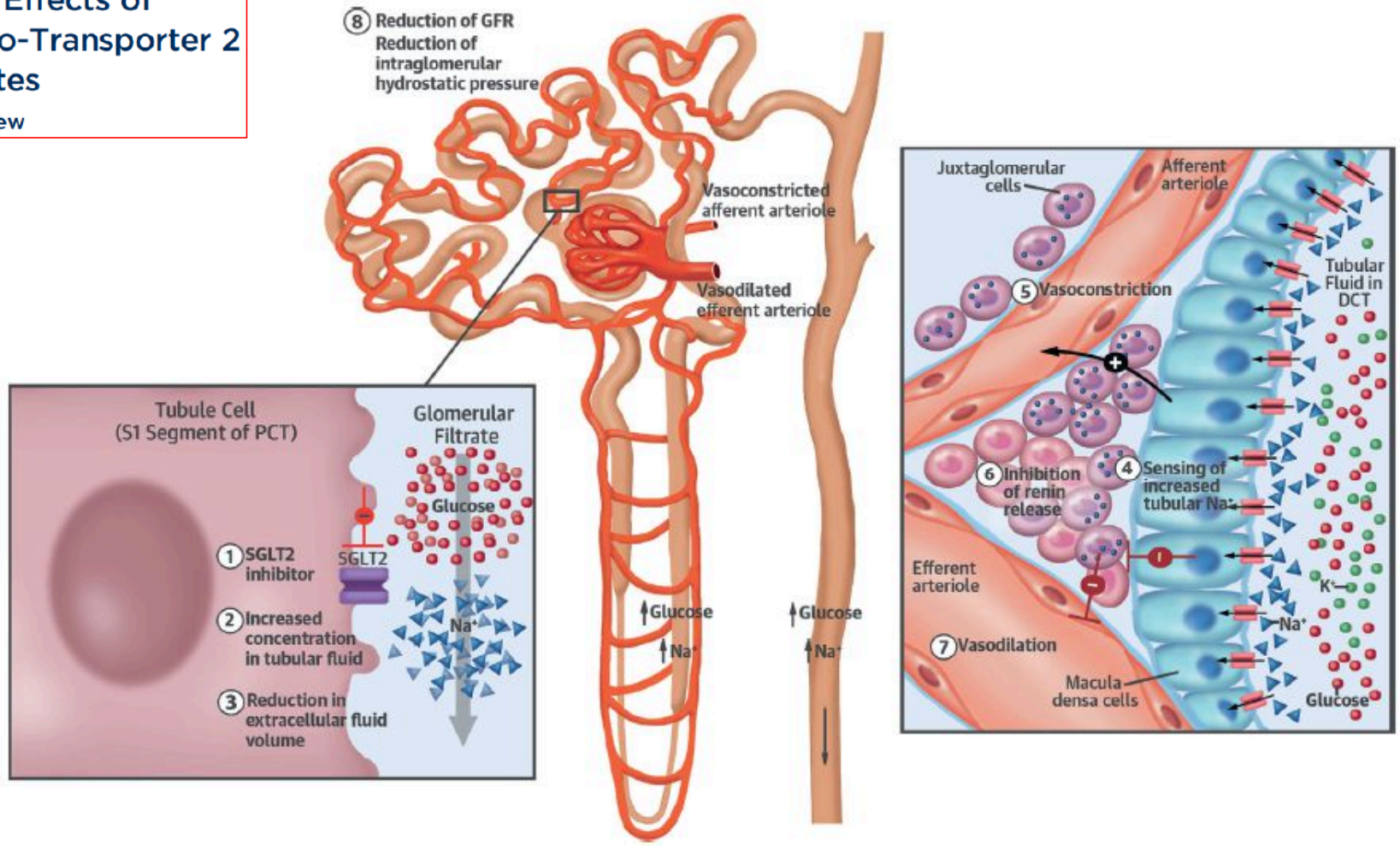
Protection cardio-rénale des inhibiteurs SGLT2



THE PRESENT AND FUTURE: *JACC* STATE-OF-THE-ART REVIEW

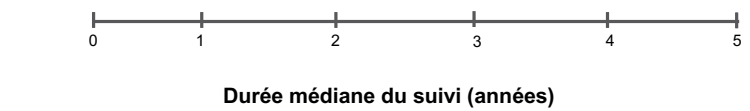
Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes

JACC State-of-the-Art Review



Études sur les effets CV des inhibiteurs du SGLT2

	Principaux critères d'inclusion	TFGe[a]	Taux d'HbA_{1c},%	Durée médiane du suivi (années)	Taux d'ECVM dans le groupe placebo
Étude DECLARE-TIMI 58[1] (N = 17 160)	≥ 55 ans (hommes) ou ≥ 60 ans (femmes) et ≥ 1 facteur de risque CV OU ≥ 40 ans et MCVA	≥ 60	De 6,5 à < 12,0	Dapagliflozine à 10 mg / Placebo — 4,2	24,2 par 1000 A-P
Programme CANVAS[2] (N = 10 142)	≥ 30 ans et MCVA OU ≥ 50 ans et multiples facteurs de risque CV	> 30	De ≥ 7,0 à < 10,5	Canagliflozine à 100 mg ou à 300 mg / Placebo — 2,4	31,5 par 1000 A-P
Étude EMPA-REG OUTCOME[3] (N = 7020)	≥ 18 ans et MCVA	≥ 30	De ≥ 7,0 à < 10,0	Empagliflozine à 10 mg ou à 25 mg / Placebo — 3,1	43,9 par 1000 A-P



[a]En mL/min/1,73 m^2.

MCVA, maladie cardiovasculaire athéroscléreuse; CV, cardiovasculaire; TFGe, taux de filtration glomérulaire estimé; HbA_{1c}, hémoglobine glyquée; ECVM, événement cardiovasculaire majeur; A-P, année-patient; R, répartition aléatoire; SGLT2, cotransporteur sodium-glucose de type 2.

1 Wiviott SD *et al. N Engl J Med* 2019;380:347-357; 2. Neal B *et al. N Engl J Med* 2017;377:644-657; 3. Zinman B *et al. N Engl J Med* 2015;373:2117-2128.

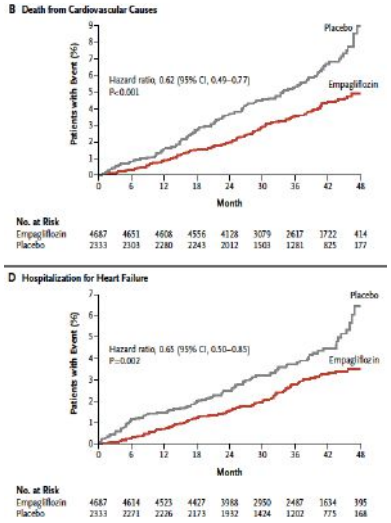
Inhibiteurs SGLT2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D.,

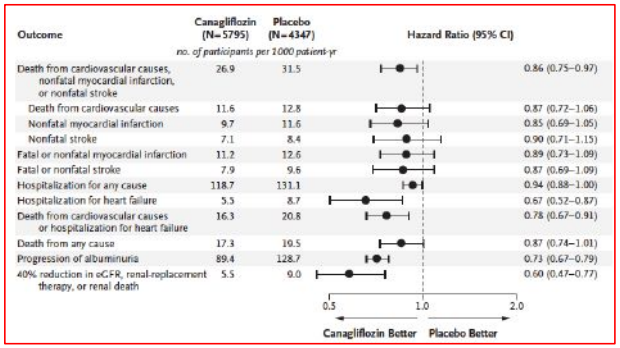


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D.,

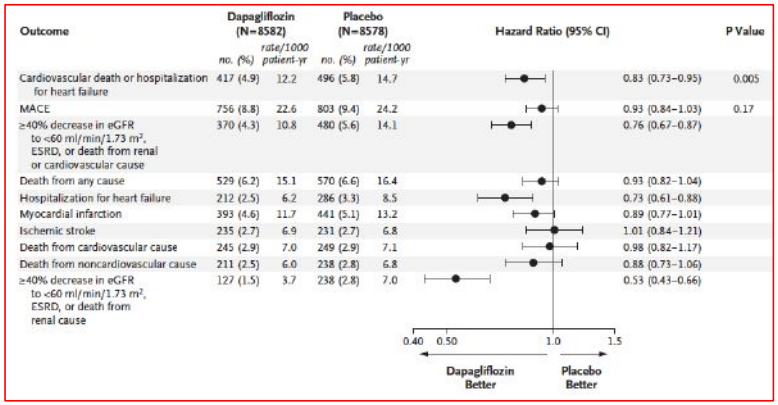


The NEW ENGLAND JOURNAL of MEDICINE

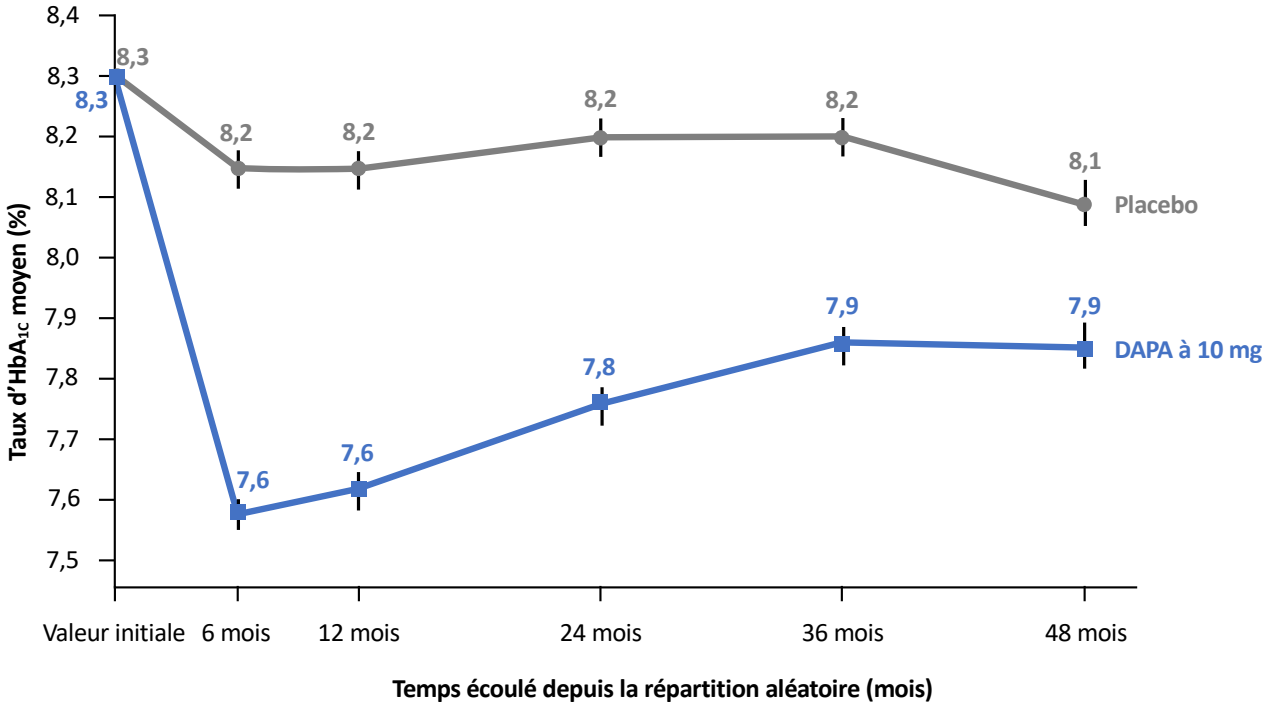
ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman,



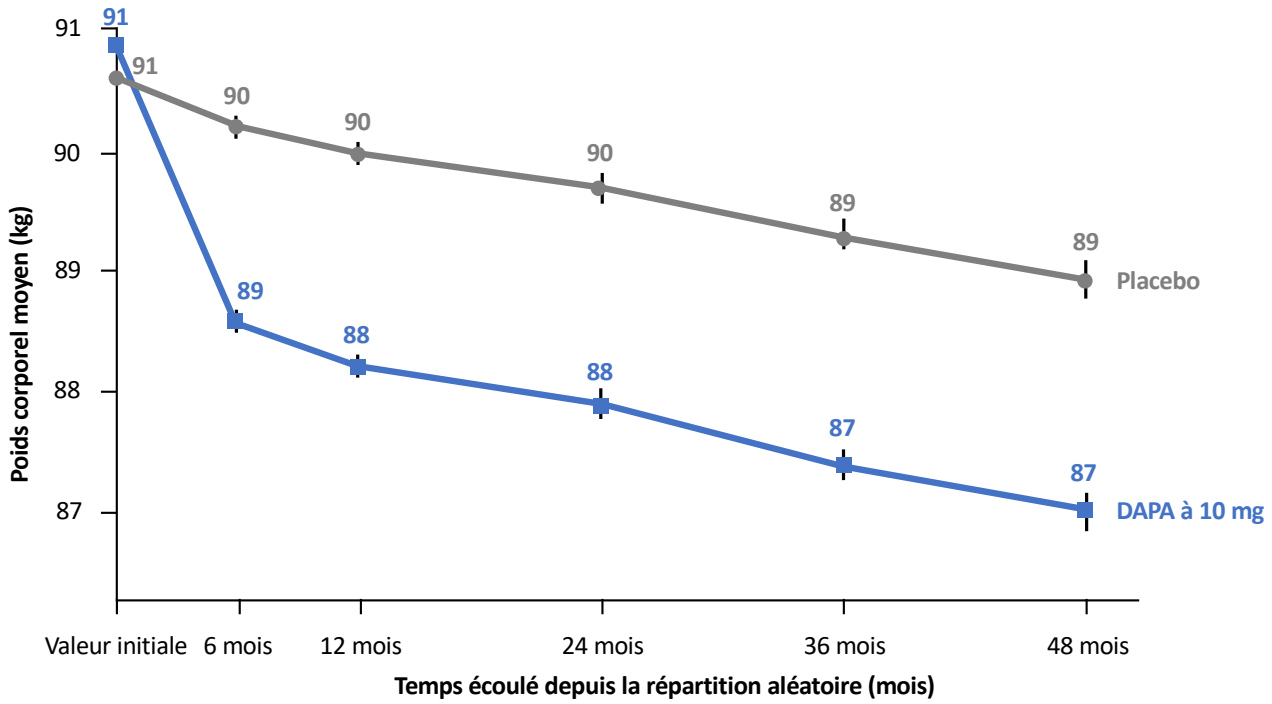
Évolution du taux d'HbA_{1c} moyen ajusté en fonction du temps



DAPA, dapagliflozine; HbA_{1c}, hémoglobine glyquée.

Wiviott SD *et al.* Article et matériel supplémentaire. *New Engl J Med* 2019;380:347-357.

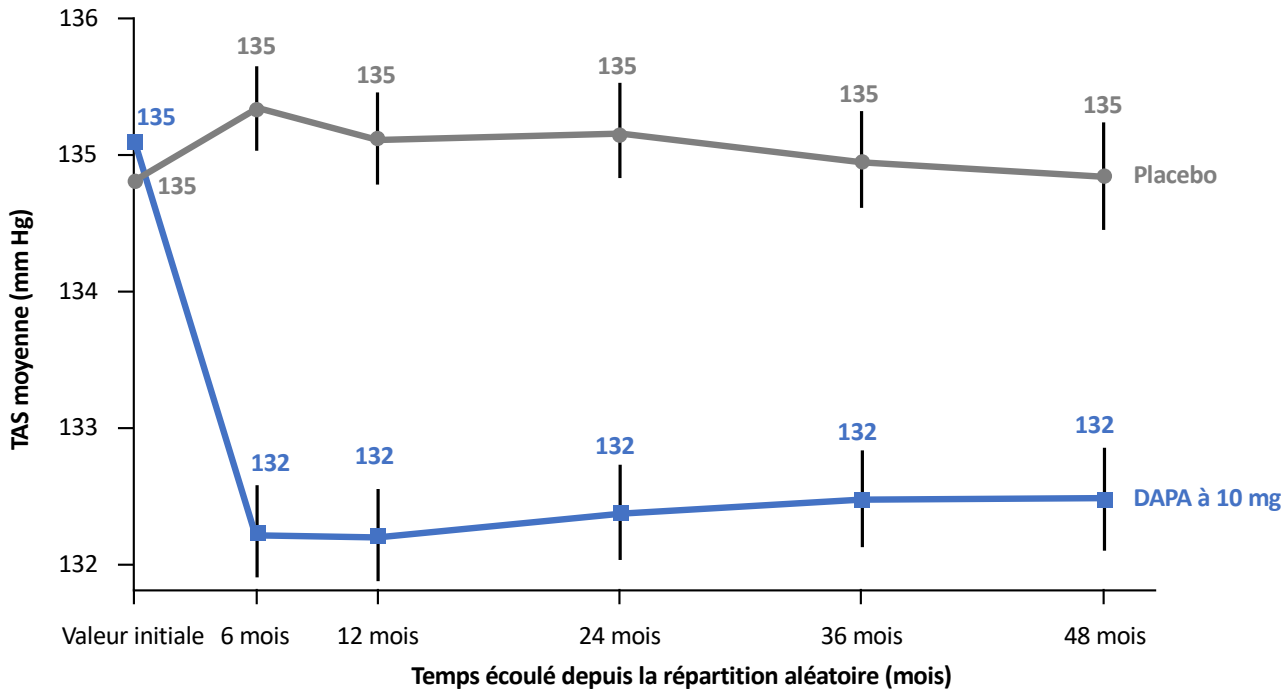
Évolution du poids corporel moyen ajusté en fonction du temps



DAPA, dapagliflozine.

Wiviott SD *et al.* Article et matériel supplémentaire. *New Engl J Med* 2019;380:347-357.

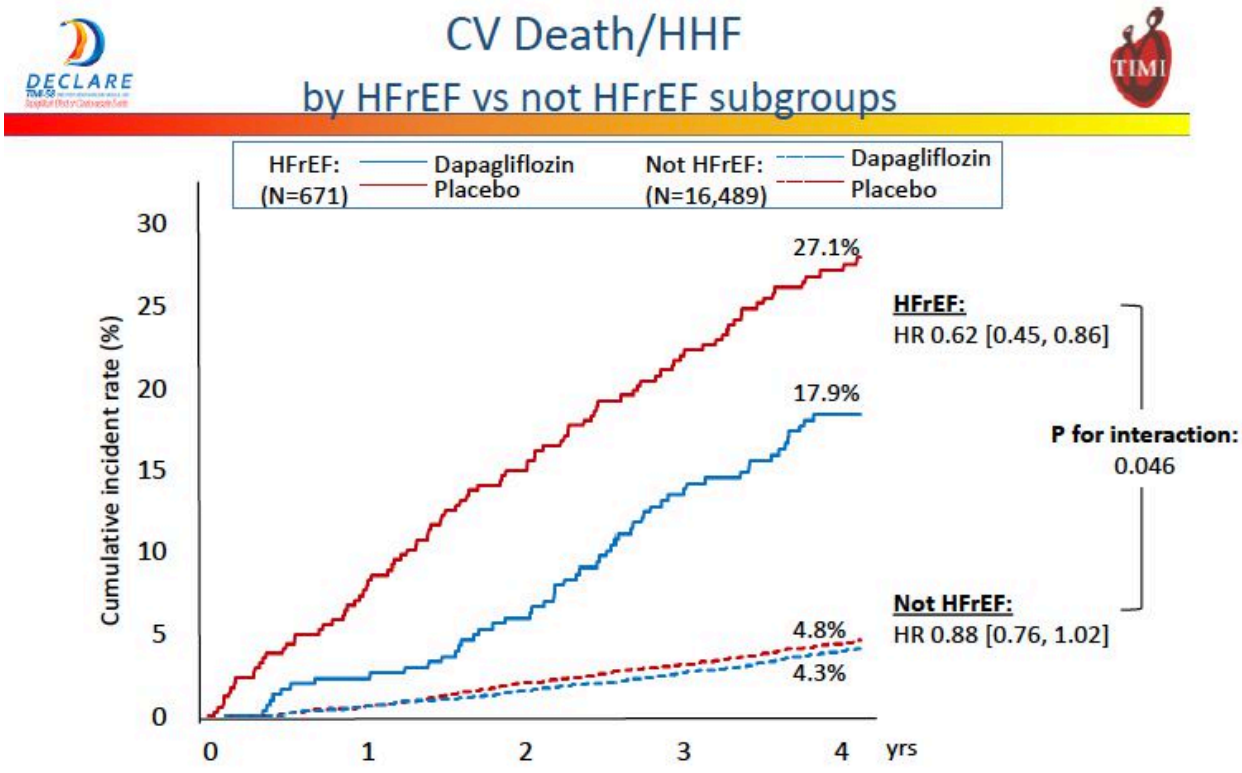
Évolution de la tension artérielle systolique moyenne ajustée en fonction du temps



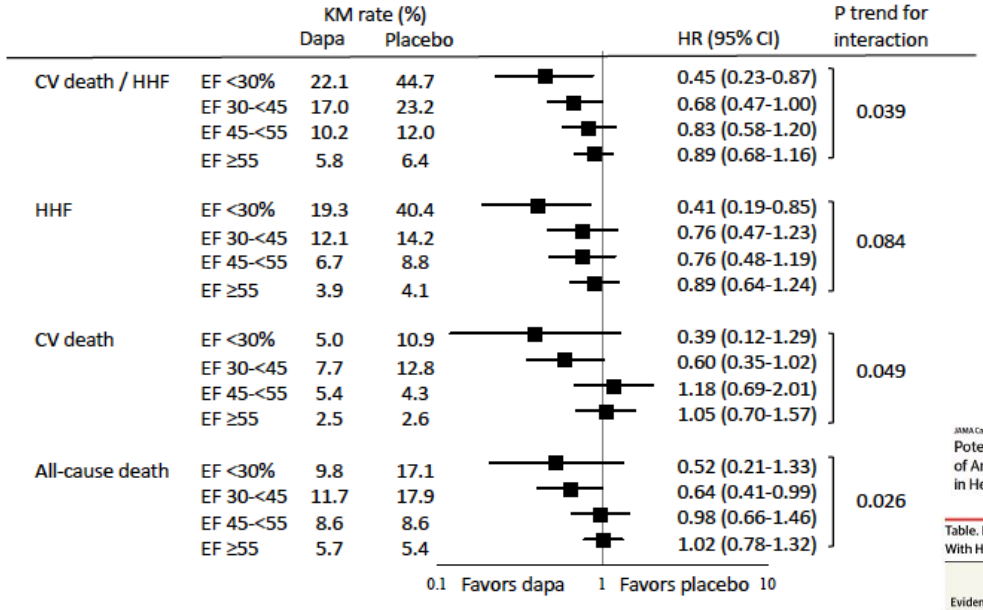
DAPA, dapagliflozine; TAS, tension artérielle systolique.

Wiviott SD *et al.* Article et matériel supplémentaire. *N Engl J Med* 2019;380:347-357.

Inhibiteurs SGLT-2



Outcomes by Different EF



- Dapagliflozin reduced CV death (NNT_{4y}=19) and all-cause mortality (NNT_{4y}=16) in patients with HFrEF, but not in those without HFrEF.

JAMA Cardiology | Brief Report

Potential Mortality Reduction With Optimal Implementation of Angiotensin Receptor Neprilysin Inhibitor Therapy in Heart Failure

Table. Demonstrated Benefits of Evidence-Based Therapies for Patients With Heart Failure and Reduced Ejection Fraction

Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal Randomized Clinical Trial(s), %	NNT to Prevent All-Cause Mortality Over Time	NNT for All-Cause Mortality[a]
ACEI/ARB	17	22 over 42 mo	77
ARNI[b]	16	36 over 27 mo	80
β-Blocker	34	28 over 12 mo	28
Aldosterone antagonist	30	9 over 24 mo	18
Hydralazine/ nitrate	43	25 over 10 mo	21
CRT	36	12 over 24 mo	24
ICD	23	14 over 60 mo	70

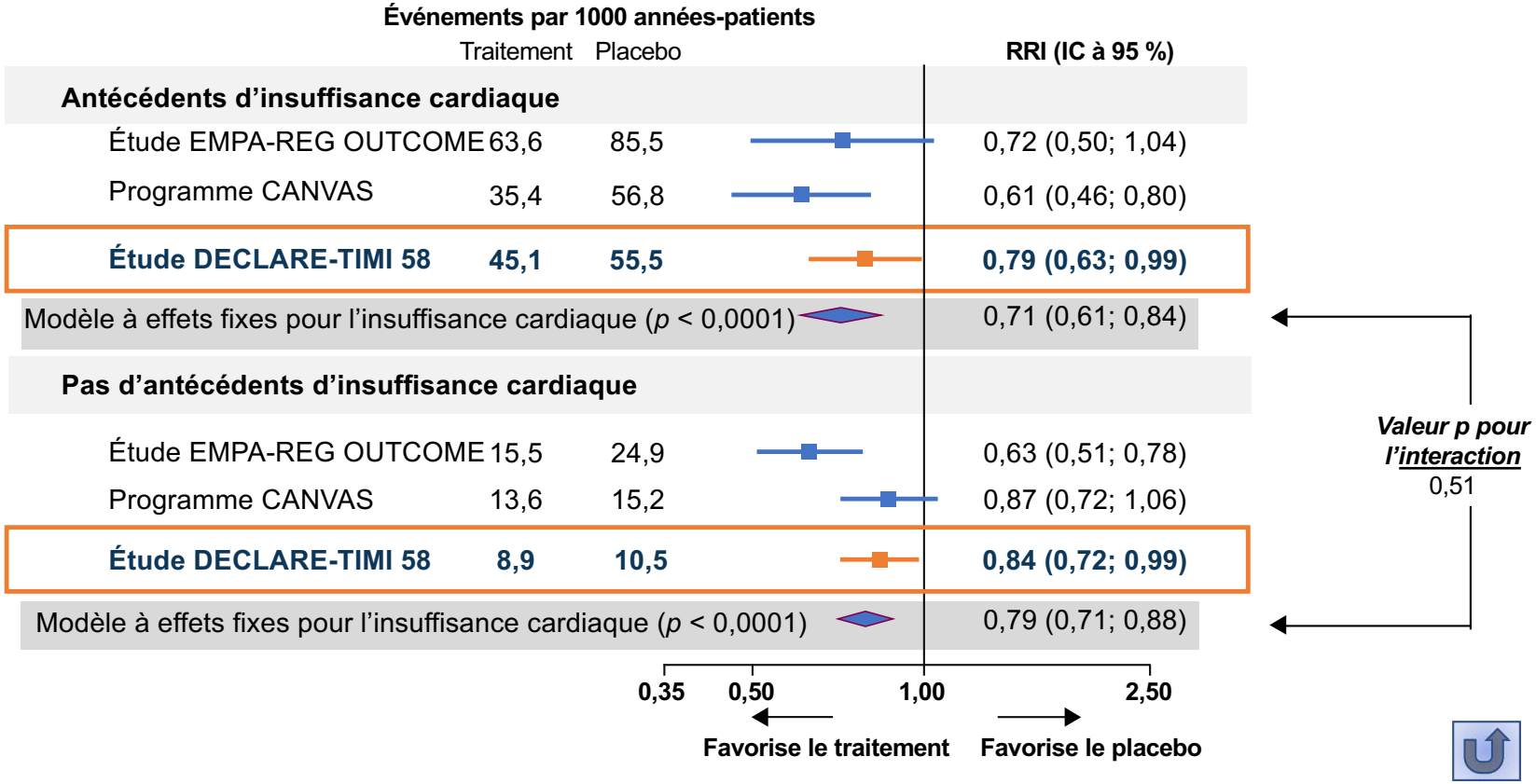
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRT cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator, NNT, number needed to treat.

[a] Standardized to 12 months.

[b] Benefit of ARNI therapy incremental to that achieved with ACEI therapy. For the other medications shown, the benefits are based on comparisons to placebo control.

JAMA Cardiol. 2016;1(6):714-717

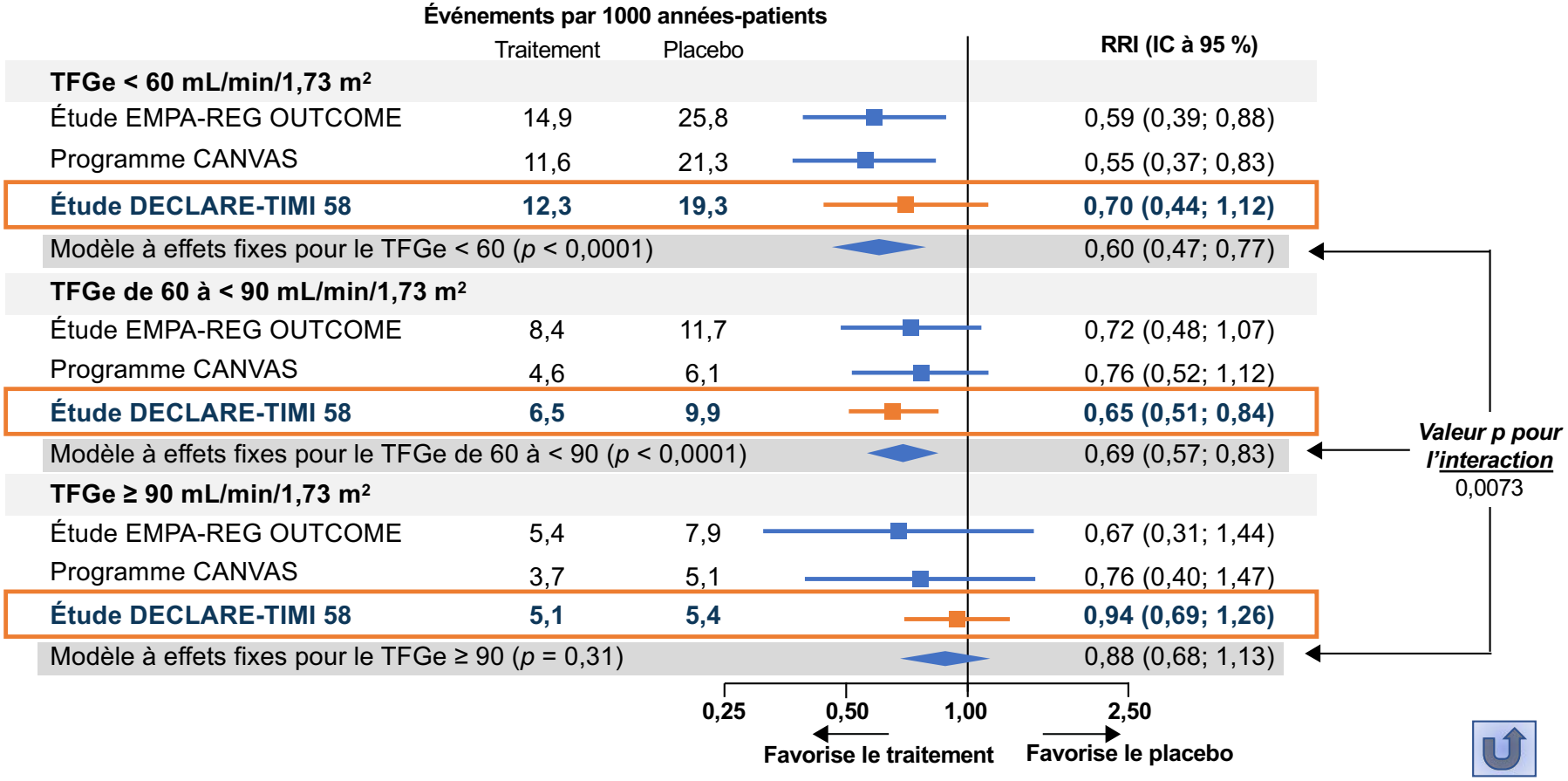
Critère composé de l'hIC ou du décès d'origine CV chez les patients ayant ou non des antécédents d'insuffisance cardiaque



Antécédents d'insuffisance cardiaque : statistique Q = 2,02, $p = 0,37$, $I^2 = 0,8$ %; pas d'antécédents d'insuffisance cardiaque : statistique Q = 5,89, $p = 0,0527$, $I^2 = 66$ %. Les tests utilisés pour établir les différences entre les sous-groupes étaient fondés sur des tests F dans une métarégression à effet aléatoire estimé selon une probabilité maximale restreinte et ajusté selon la méthode de Hartung-Knapp.
CV, cardiovasculaire; hHF, hospitalisation pour insuffisance cardiaque; RRI, rapport des risques instantanés.

Zelniker TA *et al. Lancet* 2019;393:31-39.

hIC selon la fonction rénale

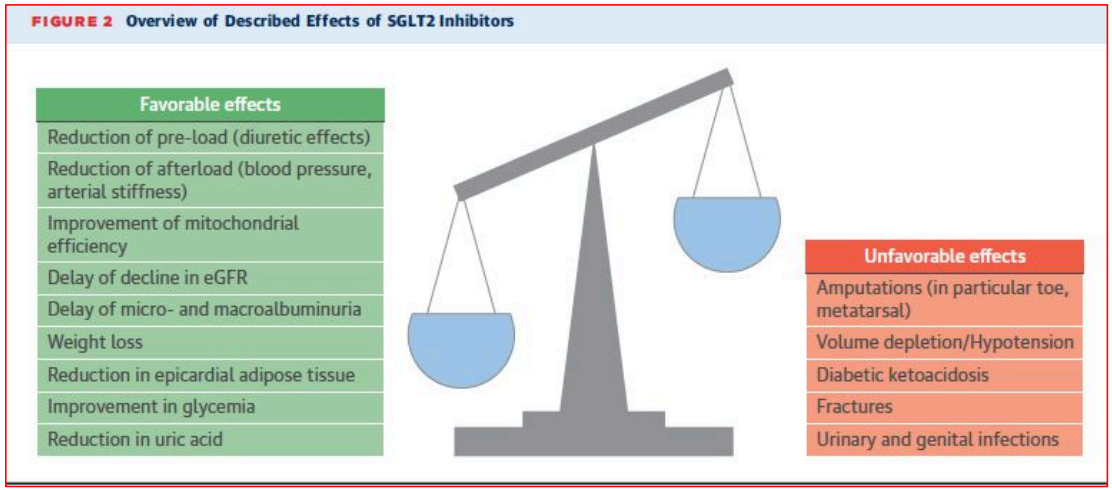


TFGe < 60 mL/min/1,73 m² : statistique Q = 0,60, p = 0,74, I^2 = 0 %; TFGe de 60 à < 90 mL/min/1,73 m² : statistique Q = 0,51, p = 0,78, I^2 = 0 %; MFR : statistique Q = 0,86, p = 0,65, I^2 = 0 %. Les tests utilisés pour établir les différences entre les sous-groupes étaient fondés sur des tests F dans une métarégression à effet aléatoire estimé selon une probabilité maximale restreinte et ajusté selon la méthode de Hartung-Knapp.
TFGe, taux de filtration glomérulaire estimé; hHF, hospitalisation pour insuffisance cardiaque; RRI, rapport des risques instantanés.

Zelniker TA *et al. Lancet* 2019;393:31-39.

Risques des inhibiteurs SGLT-2 (rares) ? Limités à certains medicaments

- Risques:
  - Amputations (orteilles)
  - Déshydratation
  - Acidocétose
  - Fractures
  - Infections génito-urinaires
  - Gangrène de Fournier



MI d'intérêt particulier et autres problèmes d'innocuité (Dapagliflozin)

Manifestation indésirable, n (%)	DAPA à 10 mg (N = 8574)	Placebo (N = 8569)	Rapport des risques instantanés (IC à 95 %)	Valeur *p*
Cancers[a]	481 (5,6)	486 (5,7)	0,99 (0,87 à 1,12)	0,83
Cancer de la vessie[a]	26 (0,3)	45 (0,5)	0,57 (0,35 à 0,93)	0,02
Manifestation hépatique[a]	82 (1,0)	87 (1,0)	0,92 (0,68 à 1,25)	0,60
Hypoglycémie, épisode majeur	58 (0,7)	83 (1,0)	0,68 (0,49 à 0,95)	0,02
Fracture	457 (5,3)	440 (5,1)	1,04 (0,91 à 1,18)	0,59
Lésion rénale aiguë	125 (1,5)	175 (2,0)	0,69 (0,55 à 0,87)	0,002
Symptômes de déplétion volémique	213 (2,5)	207 (2,4)	1,00 (0,83 à 1,21)	0,99
Réaction d'hypersensibilité[b]	32 (0,4)	36 (0,4)	0,87 (0,54 à 1,40)	0,57
Infection des voies urinaires[b]	127 (1,5)	133 (1,6)	0,93 (0,73 à 1,18)	0,54
Infection génitale[b,c]	76 (0,9)	9 (0,1)	8,36 (4,19 à 16,68)	< 0,001
Acidocétose diabétique[d]	27 (0,3)	12 (0,1)	2,18 (1,10 à 4,30)	0,02
Amputation	123 (1,4)	113 (1,3)	1,09 (0,84 à 1,40)	0,53
Gangrène de Fournier	1 (0,01)	5 (0,06)	s.o.	s.o.

[a] Confirmé par arbitrage; [b] Entraînant l'abandon du traitement à l'étude ou considéré comme une manifestation indésirable grave; [c] Les MI graves ont été rares; seulement 2 événements ont été signalés dans chaque groupe; [d] Jugé par arbitrage comme certain ou probable.

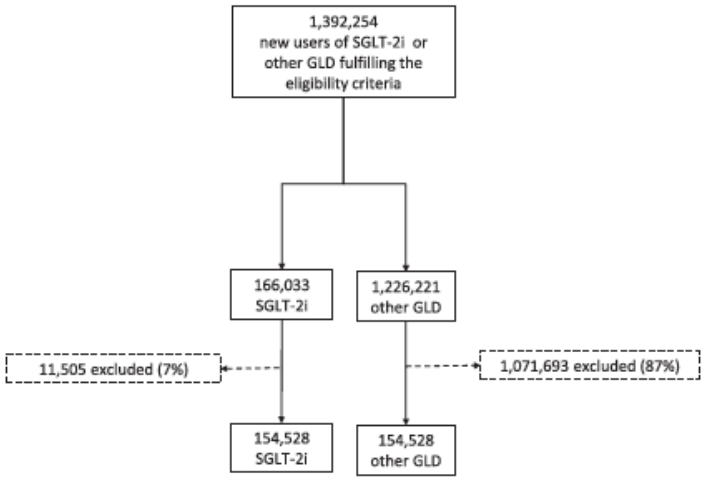
MI, manifestation indésirable; DAPA, dapagliflozine; s.o., sans objet.

Wiviott SD *et al.* Article et matériel supplémentaire. *New Engl J Med* 2019;380:347-357.

Inhibiteurs SGLT-2

Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs

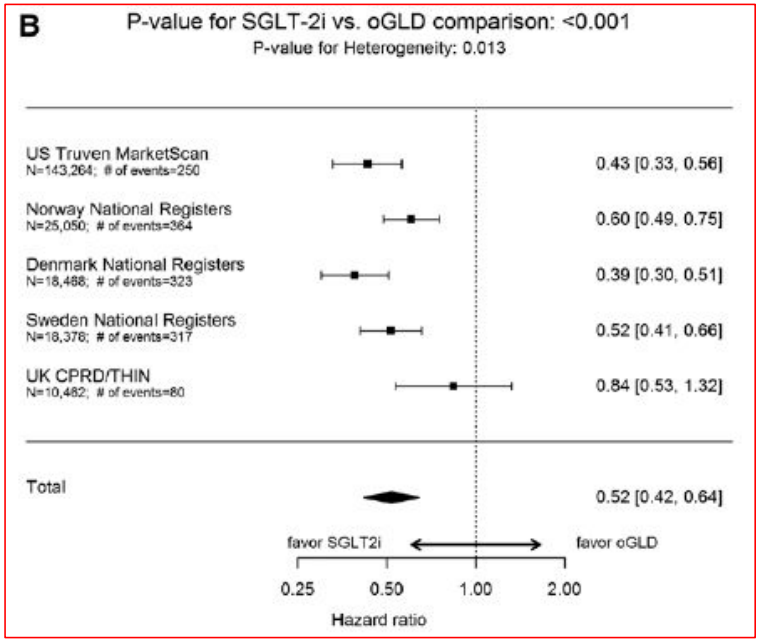
The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)



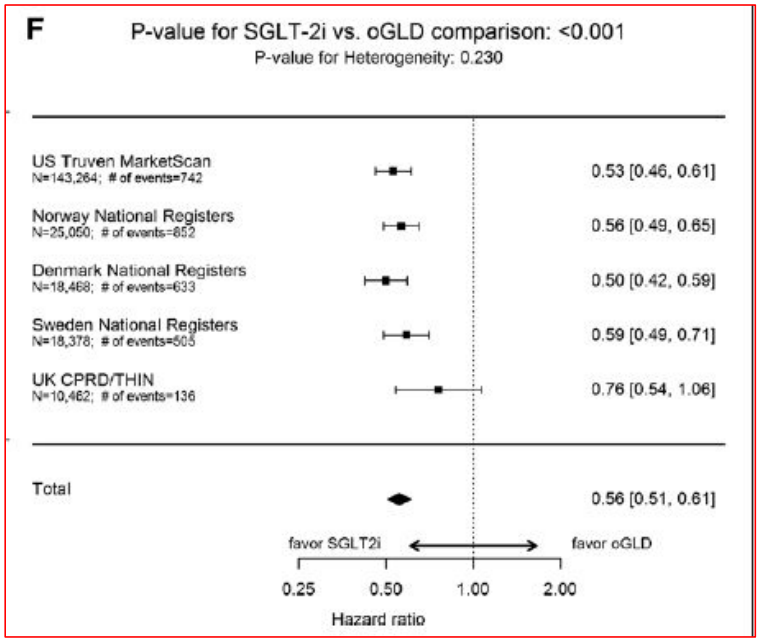
Circulation. 2017;136:249–259

Inhibiteurs SGLT-2

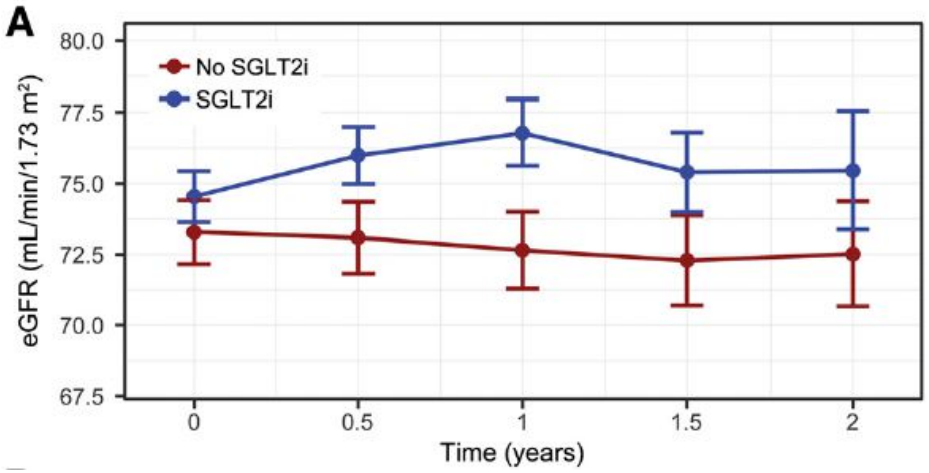
Mortalité CV



Hospit pour IC



Inhibiteurs SGLT-2 nephro-protection



1- preserve la filtration
2- diminue l'incidence de micro-alb

	CREDENCE NCT02065791	Dapa-CKD NCT03036150	SCORED NCT03315143	EMPA-Kidney NCT03594110
SGLT2-i	canagliflozin	dapagliflozin	sotagliflozin*	empagliflozin
Comparator	placebo	placebo	placebo	placebo
Patients	Type 2 DM GFR ≥30 <90 & UACR >300 ≤5000mg/g	Type 2 DM *and no DM* GFR ≥25 ≤75 & UACR ≥200 ≤5000mg/g	Type 2 DM CV risk factors GFR ≥25 ≤60	Type 2 DM *and no DM* GFR ≥20 <45 GFR ≥45 <90 & UACR ≥200 mg/g
No. of patients	4,461	~4000	10,500	~5000
Results	2019	2020	2022	2022

Diabetes Care Volume 42, February 2019

Conclusions

- Énorme interaction pathologique entre le Db et l'IC
- Les thérapies actuelles pour l'IC (triple Tx + Entresto + Ivabradine + ICD) – sont aussi efficacies chez les patients Db que non-Db
- Il faut se sensibiliser de chercher l'IC chez les patients avec le Db
- Maximiser les thérapies cardiaques éprouvées en IC
- Traitement du Db est rendu complexe
- SGLT2i semblent avoir un effet de classe pour diminuer la mortalité CV et progression de l'IC
- Certaines classes de Rx Db no sont pas recommandées

Circulation

AHA SCIENTIFIC STATEMENT

Type 2 Diabetes Mellitus and Heart Failure

A Scientific Statement From the American Heart Association and the Heart Failure Society of America

European Journal of Heart Failure (2018) 20, 853–872
doi:10.1002/ejhf.1170

HFA POSITION STATEMENT

Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

Canadian Journal of Cardiology 33 (2017) 366–377

Review

Diabetes for Cardiologists: Practical Issues in Diagnosis and Management

Table 1 Properties and Cardiovascular Effects of Noninsulin Glucose-Lowering Drugs for the Treatment of Type 2 Diabetes

Drug Class	CV Effects	Clinical Use in Patients with CVD
Biguanides	• Few randomized, but many observational studies available • Reduces risk of MI by 39%, diabetes-related endpoint by 32%, diabetes-related death by 42%, mortality by 36% (UKPDS) • Safety concerns on the association with sulfonylureas	• First choice in T2DM patients with and without atherosclerotic vascular disease • Precautions should be taken in patients with ACS, HF, CKD (stages IV and V) • Not indicated in the presence of acidosis or dehydration
Sulfonylureas	• Several observational studies available • Reduction of microvascular complications (UKPDS) • Increased CV mortality (UGDP trial) • Impairment of ischemic preconditioning (?)	• Combination therapy in T2DM patients with and without CVD (if HbA_{1c} target not achieved after ~3 mo of monotherapy with metformin) • Precautions should be taken in patients with multiple comorbidities, ACS, HF, and advanced CKD (stages IV and V)
Thiazolidinediones	• Reduce risk of MI and stroke (PROActive and IRIS trials with pioglitazone) • Improve diabetic dyslipidemia • Increase HF hospitalization	• Combination therapy in T2DM patients with and without CVD and/or CKD (up to stage V, eGFR <15 mL/min/1.73 m^2) • Precautions should be taken in patients with ACS • Contraindicated in patients with or at risk of HF
Glucagon-like peptide-1 receptor agonists	• Significant reduction of composite CV endpoints in LEADER and SUSTAIN-6 trials • No significant effects on CV mortality, nonfatal MI, and hospitalization for HF with liraglutide and semaglutide • Reduced risk of nonfatal stroke with semaglutide	• Combination therapy in T2DM patients with and without CVD (including HF and ACS) • Limited data in patients with advanced CKD (stages IV and V) • Exenatide is eliminated by renal mechanisms and should not be given in patients with severe ESRD • Liraglutide is not eliminated by renal or hepatic mechanisms, but it should be used with caution since there are only limited data in patients with renal or hepatic impairment
Dipeptidyl peptidase-4 inhibitors	• Well tolerated • No reduction of CV endpoints (SAVOR-TIMI 53, EXAMINE, TECOS) • Increased risk of HF with saxagliptin and alogliptin (?)	• Combination therapy in T2DM patients with and without CVD • Although sitagliptin seems to be safe, the use of alogliptin and saxagliptin in patients with pre-existing HF is still debated • Indicated in patients with CKD (any stage)
Sodium glucose cotransporter 2 inhibitors	• In the EMPA-REG OUTCOME trial, empagliflozin reduced CV death, HF hospitalization, and total mortality by 38%, 35%, and 32%, respectively • No direct effect on the rates of MI or stroke with empagliflozin • Reduction of systolic and diastolic BP	• Combination therapy in T2DM patients with and without CVD (paucity of data on SGLT2 in primary prevention) • Evidence of benefit in patients with HF • No evidence of benefit in ACS

Table 1 Cardiovascular Outcomes Results of SGLT2 inhibitors

Study	Drug	Proportion with Known CVD	Median study observation time	Primary outcome	Treatment reduced risk of primary outcome?	Treatment reduced risk of secondary outcome?
EMPA-REG OUTCOME	Empagliflozin	76%	3.1 years	CV death, nonfatal MI, or nonfatal stroke	Yes; 14% a]	Yes; 38% ↓ *in CV death; 32% ↓ in any cause death; 35% ↓ in hospitalization for heart failure*
CANVAS	Canagliflozin	82%	3.6 years	CV death, non-fatal MI, or non-fatal stroke	Yes; 14% ↓	Yes; 33% ↓ *in hospitalization for heart failure*
DECLARE-TIMI 58	Dapagliflozin	41%	4.2 years	CV death, MI, or stroke	No; non-inferior to placebo	Yes; 27% ↓ *in hospitalization for heart failure*

CV = cardiovascular; CVD = cardiovascular death; MI = myocardial infarction.

Table 2 Cardiovascular Outcomes Results of GLP-1 Receptor Agonists

Study	Drug	Proportion with Known CVD	Median study observation time	Primary outcome	Treatment reduced risk of primary outcome?	Treatment reduced risk of secondary outcome?
LEADER	Liraglutide	81%	3.8 years	CV death, nonfatal MI, or nonfatal stroke	Yes; 13% ↓	Yes; 22% ↓ *in CV death*
SUSTAIN-6	Semaglutide	83%	2.8 years	CV death, nonfatal MI, or nonfatal stroke	Yes; 26% ↓	Yes; 39% ↓ *in nonfatal stroke*
HARMONY	Albiglutide	71%	1.6 years	CV death, MI, or stroke	Yes; 22% ↓	Yes; 25% ↓ *in MI*
ELIXA	Lixisenatide	100%	2.1 years	CV death, MI, stroke, hospitalization for unstable angina	No; non-inferior to placebo	None
EXSCEL	Exenatide	73.1%	3.2 years	CV death, nonfatal MI, or nonfatal stroke	No; non-inferior to placebo	None

CV = cardiovascular; CVD = cardiovascular death; GLP-1 = glucagon-like peptide-1; MI = myocardial infarction.

RECOMMENDATIONS

1. Individuals with diabetes and heart failure should receive the same heart failure therapies as those identified in the evidence-based Canadian Cardiovascular Society Heart Failure recommendations (http://www.onlinecjc.ca/article/S0828-282X(17)30973-X/pdf) [Grade D, Consensus (23)].

2. Unless contraindicated, metformin may be used in people with type 2 diabetes and heart failure [Grade C, Level 3 (18,38)]. Metformin should be temporarily withheld if renal function acutely worsens, and should be discontinued if renal function significantly and chronically worsens [Grade D, Consensus].

3. For people with NYHA class I-IV, exposure to TZDs should be avoided [Grade A, Level 1 (41)].

4. Beta blockers should be prescribed when indicated for heart failure with reduced ejection fraction, as they provide similar benefits in people with or without diabetes [Grade B, Level 2 (19,33)].

5. In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR >30 mL/min/1.73 m^2, an SGLT2 inhibitor with demonstrated heart failure hospitalization reduction may be added to reduce the risk of heart failure hospitalization [Grade B, Level 2 (53) for empagliflozin; Grade C, Level 2 (54) for canagliflozin].

6. In adults with diabetes and heart failure with an eGFR <60 mL/min/1.73m^2 and/or if combined RAAS blockade is employed:
   a. Starting doses of ACE inhibitors or ARBs should be halved [Grade D, Consensus]
   b. Serum electrolytes and creatinine, BP and body weight, as well as heart failure symptoms and signs, should be monitored within 7–10 days of any initiation or titration of therapy [Grade D, Consensus]
   c. Dose-up titration should be more gradual (with monitoring of BP, serum potassium and creatinine) [Grade D, Consensus].