Spécificité de l'insuffisance cardiaque chez la femme

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CHU Bicêtre

Le Kremlin Bicêtre, APHP

Conflits d’intérets

Nom de la Société	Type d’affiliation	Période
NOVARTIS	Consulting	2020-22
VIFOR	Consulting	2020-22
ASTRAZENECA	Expert	2020-22

Cardiovascular disease in women

35%

of all deaths in women worldwide are caused by cardiovascular disease

275 million

women were diagnosed with cardiovascular disease in 2019

8·9 million

women died from cardiovascular disease in 2019

Cardiovascular disease among women is

understudied,
under-recognised,
underdiagnosed,
undertreated,
and women are
under-represented in
clinical trials.

Read more:

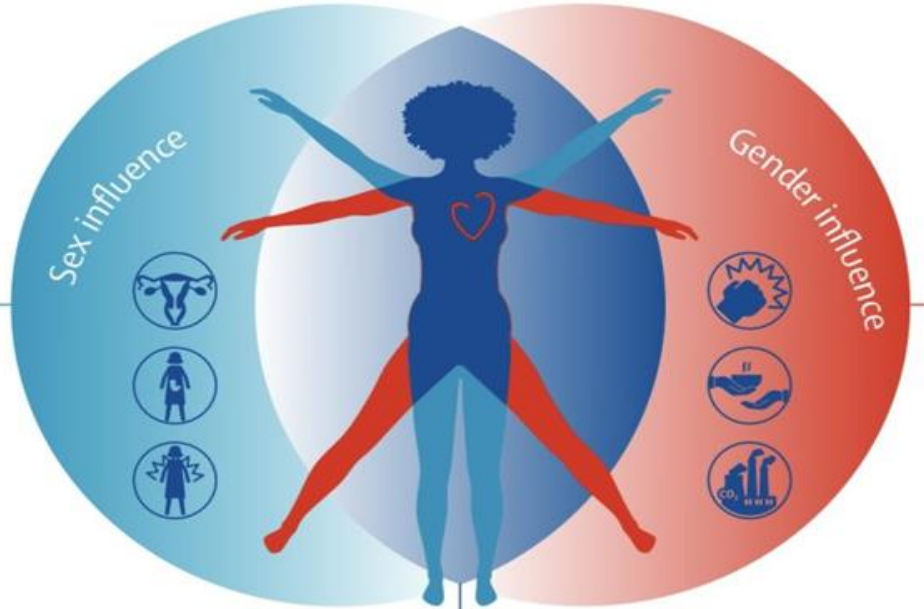
The *Lancet* women and cardiovascular disease Commission: reducing the global burden by 2030

Risk factors for cardiovascular disease in women

Well-established, sex-specific, and under-recognised risk factors

Sex-specific risk factors

- Premature menopause
- Gestational diabetes
- Hypertensive disorders of pregnancy
- Preterm delivery
- Polycystic ovary syndrome
- Systemic inflammatory and autoimmune disorders



Under-recognised risk factors

- Psychosocial risk factors
- Abuse and intimate partner violence
- Socioeconomic deprivation
- Poor health literacy
- Environmental risk factors

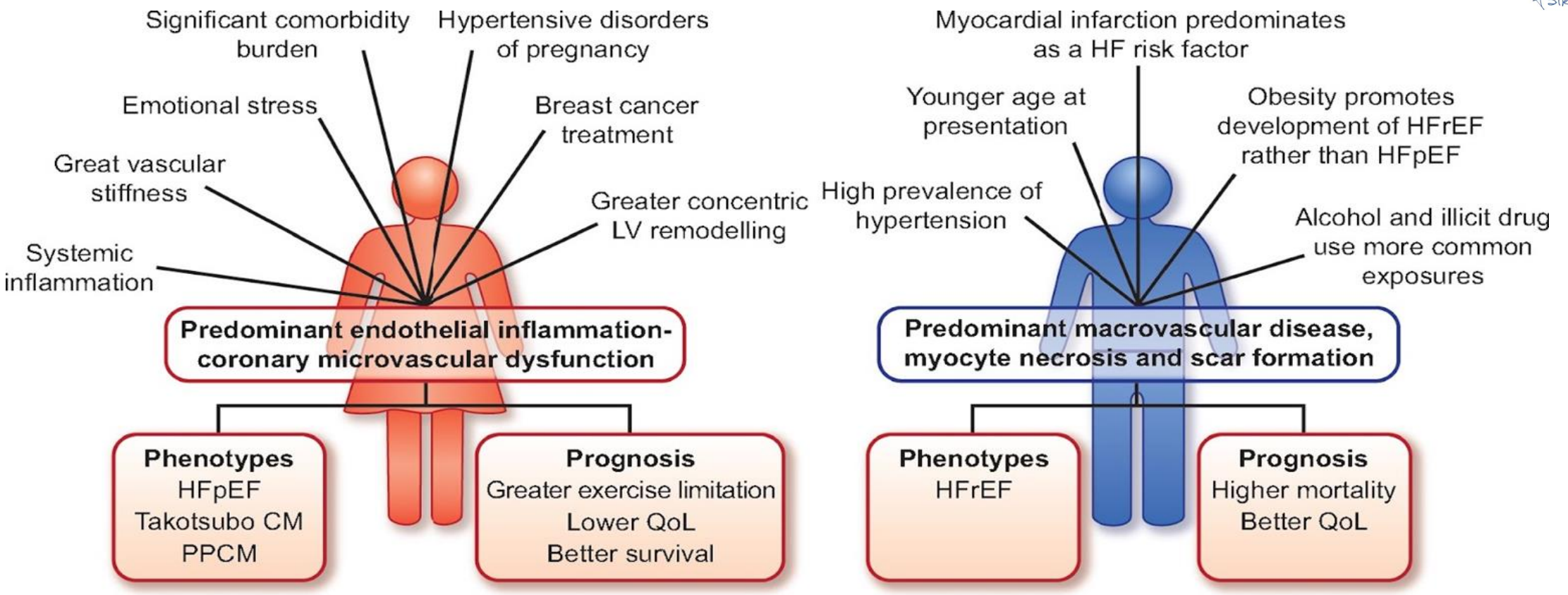
Well-established risk factors

- Hypertension
- Dyslipidaemia
- Diabetes
- Obesity
- Unhealthy diet
- Sedentary lifestyle
- Smoking or tobacco use

Acknowledging the effects of these risk factors is crucial to understanding cardiovascular disease in women.

Read more: The *Lancet* women and cardiovascular disease Commission: reducing the global burden by 2030

Sex impacts on almost every facet of heart failure, from risk factors to ...

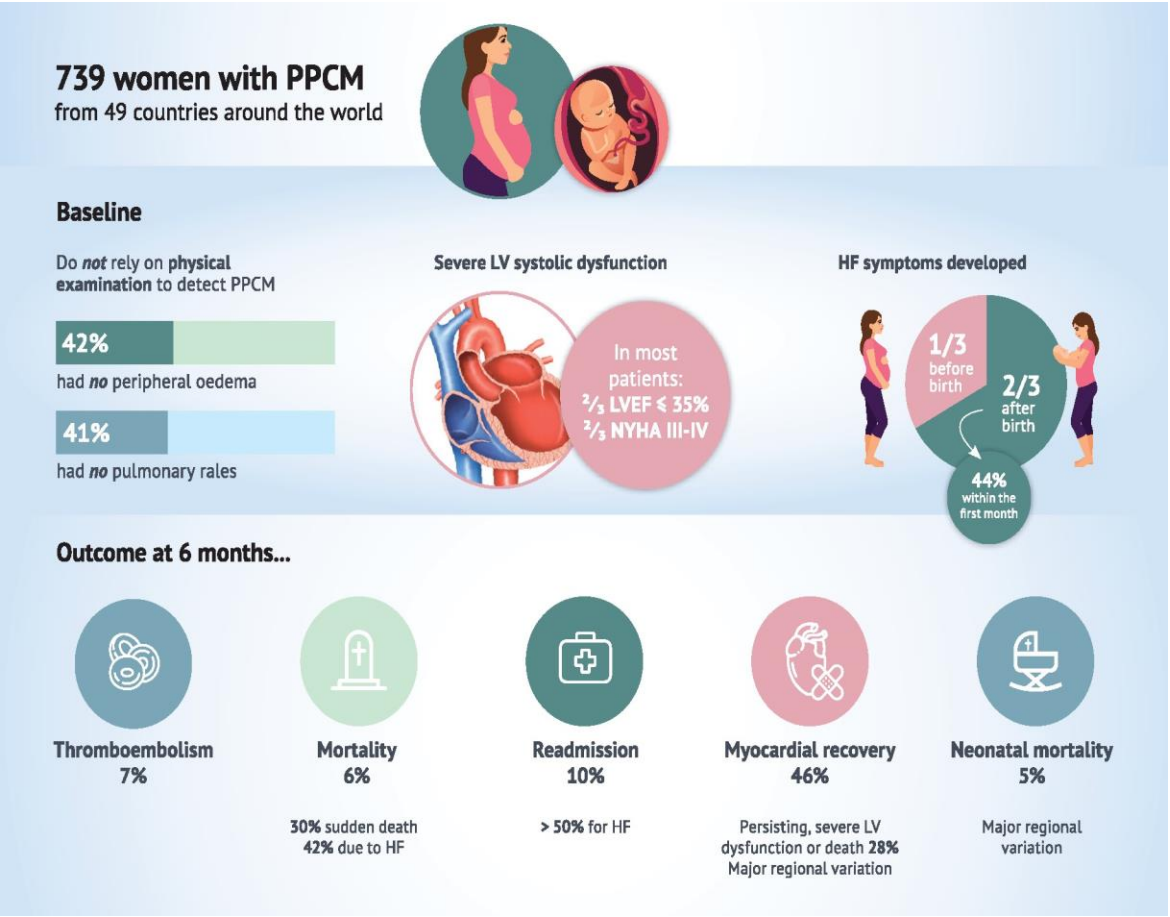


Eur Heart J, Volume 40, Issue 47, 14 December 2019, Pages 3859–3868c, https://doi.org/10.1093/eurheartj/ehz835

Quelques étiologies particulières

Cardiopathie de péripartum: ESC EORP registry

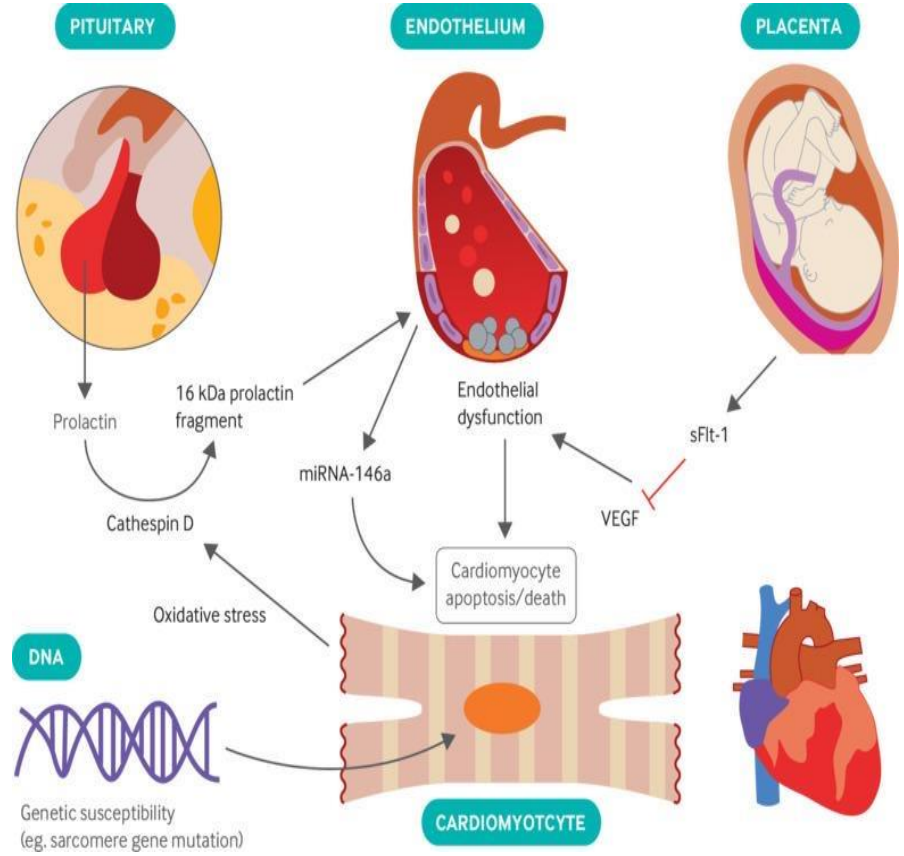
- Qu'est-ce que c'est? Dysfonction VG aigué ou progressive
- Quand? Dernier trimètre de grossesse, pendant l'accouchement ou premiers moins après l'accouchement
- Qui? Les femmes sans pathologie cardiaque connue



Eur Heart J, Volume 41, Issue 39, 14 October 2020, Pages 3787–3797, https://doi.org/10.1093/eurheartj/ehaa455.

Cardiopathie de péripartum: hypothèse vasculo-hormonal

- Inflammation et stress oxydative
- Elévation des anticorps anti troponine I et myosine (chaine lourd 7)
- Le clivage conduisant à la production de la prolactine N-terminal 16kDA qui provoque la dysfonction endothéliale

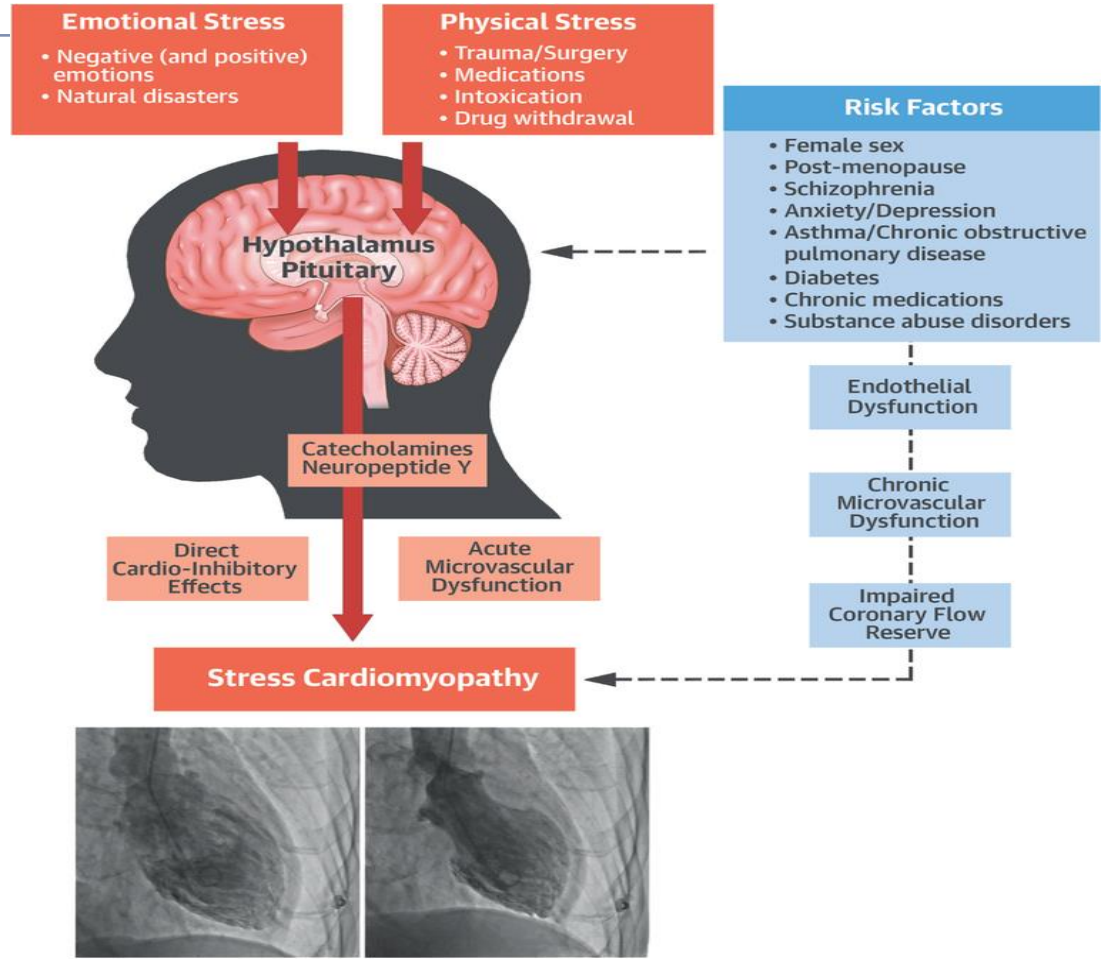


European Heart Journal (2021) 42, 3094-3102

J Am Coll Cardiol. 2020; 75 (2): 207-21

Cardiomyopathie de stress: TAKOTSUBO

- ICA avec dysfonction cardiaque réversible
- Elévation de catécholamines
- Ratio F/H 9:1



J Am Coll Cardiol 2018; 72: 1955-1971

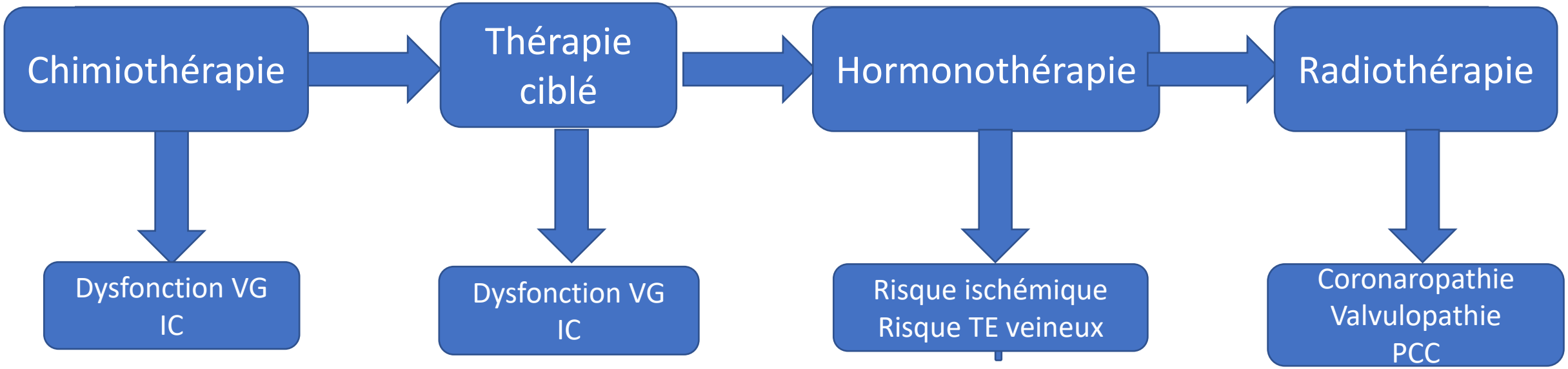
Cardiopathie toxique:
Cancer du sein

Avec **58 968** nouveaux cas en 2017, le cancer du sein est le plus fréquent chez la femme avant le cancer colorectal (20 837cas) et le cancer du poumon (16 849 cas).

- Le cancer du sein se situe en tête de la mortalité, avec 11 883 décès en 2017, mais le taux de mortalité diminue de - 1,5% par an en France depuis 2005.
- Taux d'incidence a doublé en 25 ans
- **Une Française sur 9**

Les traitements médicaux: TOUTES les thérapeutiques sont potentiellement cardio-toxiques

Qui vont s'administrer successivement et donc se potentialiser



Toxicité en théorie type I, effet dose, toxicité cumulative

Toxicité en théorie réversible, type II, pas de lien avec la dose, effet suspensif

Quand les anthracyclines abiment… Trastuzumab empêche la réparation: délai 3 mois entre les deux

IC, femme et épidémiologie

IC : Prévalence et mortalité de l'IC selon le sexe

Aux USA

Table 20-2. Heart Failure

Population Group	Prevalence, 2013–2016, Age ≥20 y	Incidence, 2014, Age ≥55 y	Mortality, 2016, All Ages*	Hospital Discharge, 2014, All Ages	Cost, 2012†
Both sexes	6 200 000 (2.2%)	1 000 000	78 356	900 000	$30.7 billion
Males	3 000 000 (2.4%)	495 000	35 424 (45.2%)‡	462 000	…
Females	3 200 000 (2.1%)	505 000	42 932 (54.8%)‡	438 000	…
NH white males	2.2%	430 000§	29 155	…	…
NH white females	1.9%	425 000§	35 526	…	…
NH black males	3.5%	65 000§	3777	…	…
NH black females	3.9%	80 000§	4584	…	…
Hispanic males	2.5%	…	1721	…	…
Hispanic females	2.1%	…	1905	…	…
NH Asian males	1.7%	…	561‖	…	…
NH Asian females	0.7%	…	715‖	…	…
NH American Indian or Alaska Native	…	…	262	…	…

Heart failure includes people who answered "yes" to the question of ever having congestive heart failure. Ellipses (…) indicate data not available; and NH, non-Hispanic.

* Mortality data for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

† Cost data are from Heidenreich et al.[15]

‡ These percentages represent the portion of total mortality attributable to heart failure that is for males vs females.

§ Estimates for whites include other nonblack races.

‖ Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

Sources: Prevalence: National Health and Nutrition Examination Survey 2013 to 2016 (National Center for Health Statistics [NCHS]) and National Heart, Lung, and Blood Institute (NHLBI). Percentages are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2016 US population estimates. These data are based on self-reports. Incidence: Atherosclerosis Risk in Communities Study Community Surveillance, 2005 to 2014 from the NHLBI. Mortality: Centers for Disease Control and Prevention/NCHS, 2016 Mortality Multiple Cause-of-Death–United States. Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Healthcare Cost and Utilization Project, Hospital Discharges, 2014 (data include those inpatients discharged alive, dead, or status unknown).

Benjamin EJ, et al. *Circulation* 2019; **139:** e56–528.

PURE : a prospective cohort study Incidence of CV diseases

202 072 individuals

age of women 50·8 (SD 9·9)

men 51·7 (10)

followed up

for a median of 9·5 (IQR 8·5–10·9) years

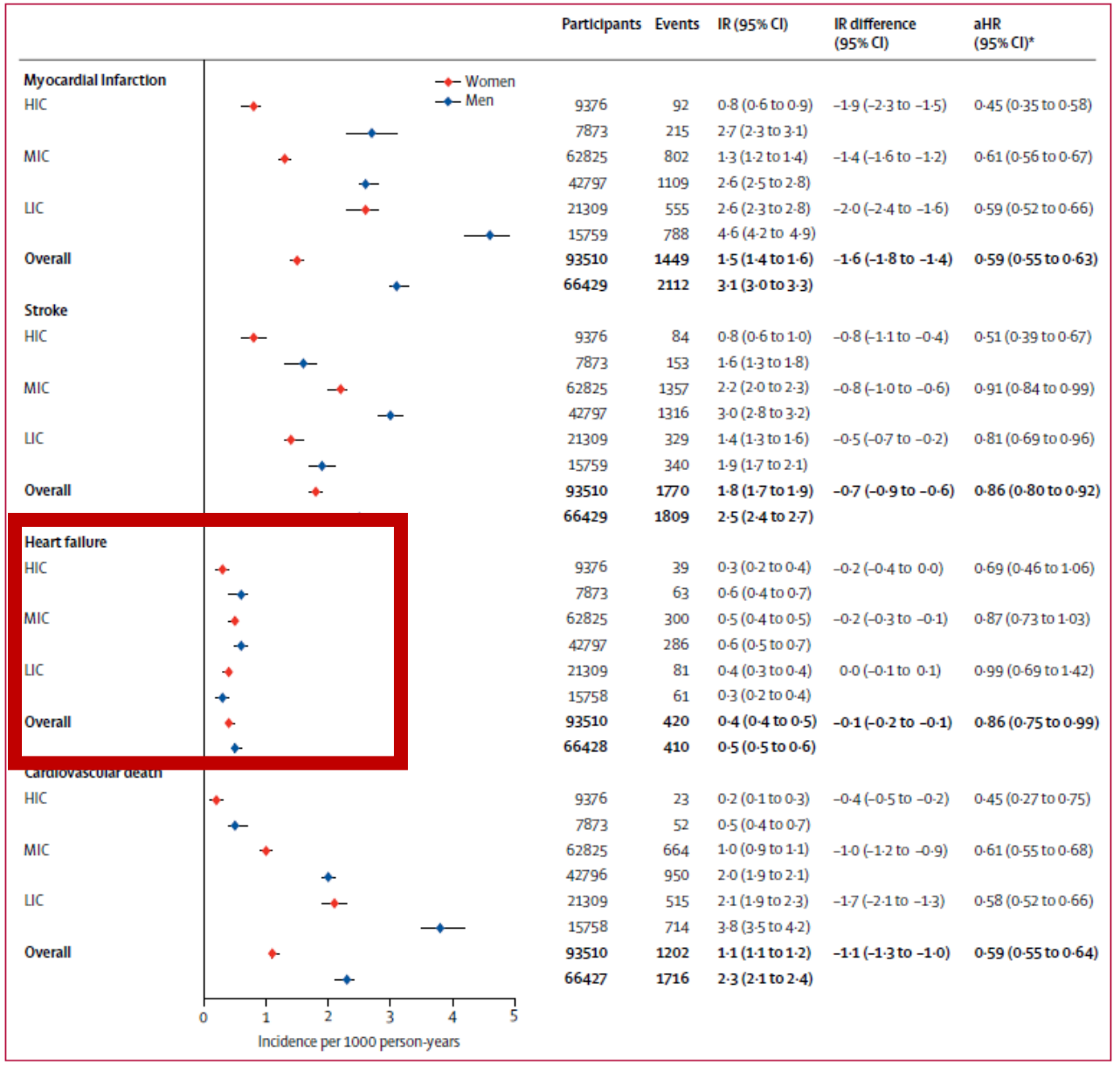


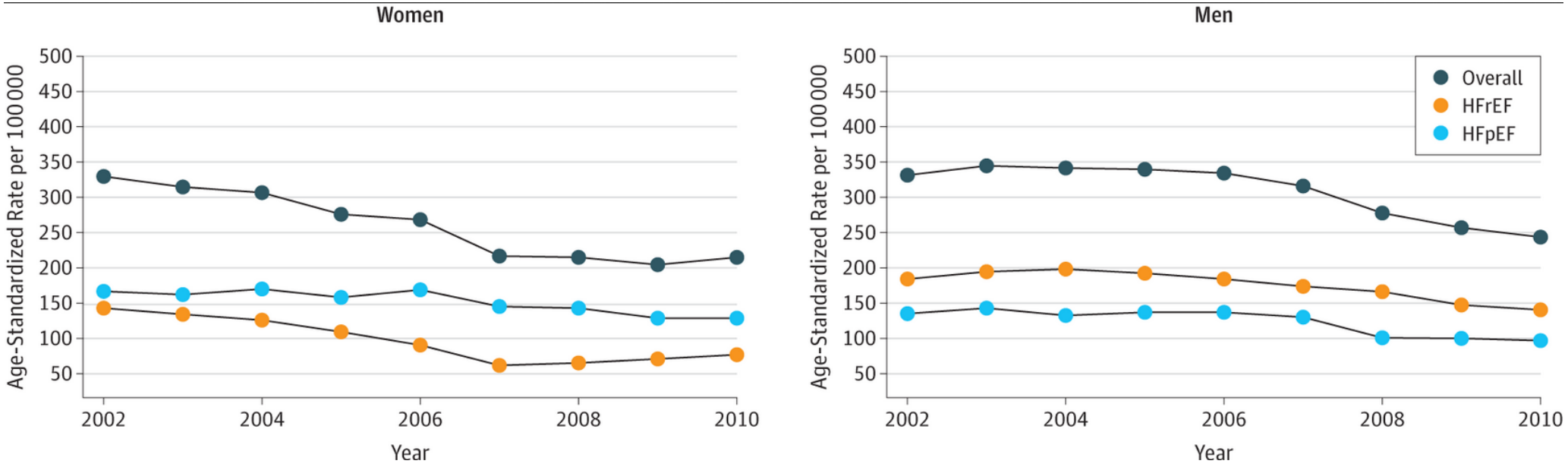
Figure 2: **Age-standardised incidence rates per 1000 person-years of myocardial infarction, stroke, heart failure, and cardiovascular death in those without previous cardiovascular disease**

Errors bars represent 95% CIs. Of note, 385 other major cardiovascular events (261 in women and 124 in men) included in major cardiovascular are not presented above. Data are not presented by geographical region because the numbers of events of myocardial infarction, stroke, and heart failure are substantially reduced resulting in unstable estimates. Interaction between country economic status and sex p=0·0001 for myocardial infarction events; p=0·0001 for stroke events;

***Lancet* 2020; 396: 97–109**

HFrEF or HFpEF

In the population-based Olmsted County study of incident HF from 2000 to 2010



Gerber Y, et al. JAMA Intern Med 2015;175: 996–1004.

IC : Différence liées au sexe selon l'âge

26 725 women and 29 234 men over age 45 years with a new diagnosis of heart failure between 2000-2017 England

Table 2 Age specific all-cause mortality rates[a] at 1, 5, 10, and 15 years after a diagnosis of heart failure by gender and age category (expressed as a percentage of those who died)

Age category	1-year MR	5-year MR	10-year MR	15-year MR
45–64 years				
Men	11.5 (10.7–12.4)	22.6 (21.5–23.7)	29.2 (28.0–30.5)	30.9 (29.7–32.2)
Women	10.3 (9.04–11.6)	23.1 (21.3–24.8)	29.8 (27.9–31.8)	32.1 (30.2–34.1)
65–74 years				
Men	16.2 (15.3–17.0)	35.2 (34.1–36.3)	45.9 (44.8–47.0)	48.7 (47.6–49.8)
Women	16.1 (15.0–17.1)	33.6 (32.3–34.9)	43.5 (42.1–44.9)	46.2 (44.8–47.6)
75–84 years				
Men	24.2 (23.4–25.0)	50.4 (49.4–51.3)	59.9 (58.9–60.8)	61.3 (60.4–62.2)
Women	21.2 (20.4–22.0)	44.0 (43.0–44.9)	54.2 (53.3–55.2)	56.0 (55.1–57.0)
≥85 years				
Men	36.4 (35.2–37.7)	64.8 (63.5–66.0)	–	–
Women	36.3 (35.4–37.3)	61.9 (61.0–62.9)	–	–

MR, mortality rate. [a]MR refers to the percentage of the baseline population who have died at each time point.

Characteristic	Men	Women	*P*-value
Overall, *n* (%)	29 234 (100)	26 725 (100)	
Place of diagnosis, *n* (%)			0.005
Primary care	16 796 (57.5)	15 038 (56.3)	
Hospital	12 438 (42.5)	11 687 (43.7)	
Age, years, mean ± SD	74.8 ± 10.6	79.6 ± 9.87	<0.001

Taylor CJ, et al. European journal of heart failure. 2021;23(1):3-12.

IC FE basse Impact chez la femme

12 058 hommes and 3 357 femmes

ICFER

Femmes

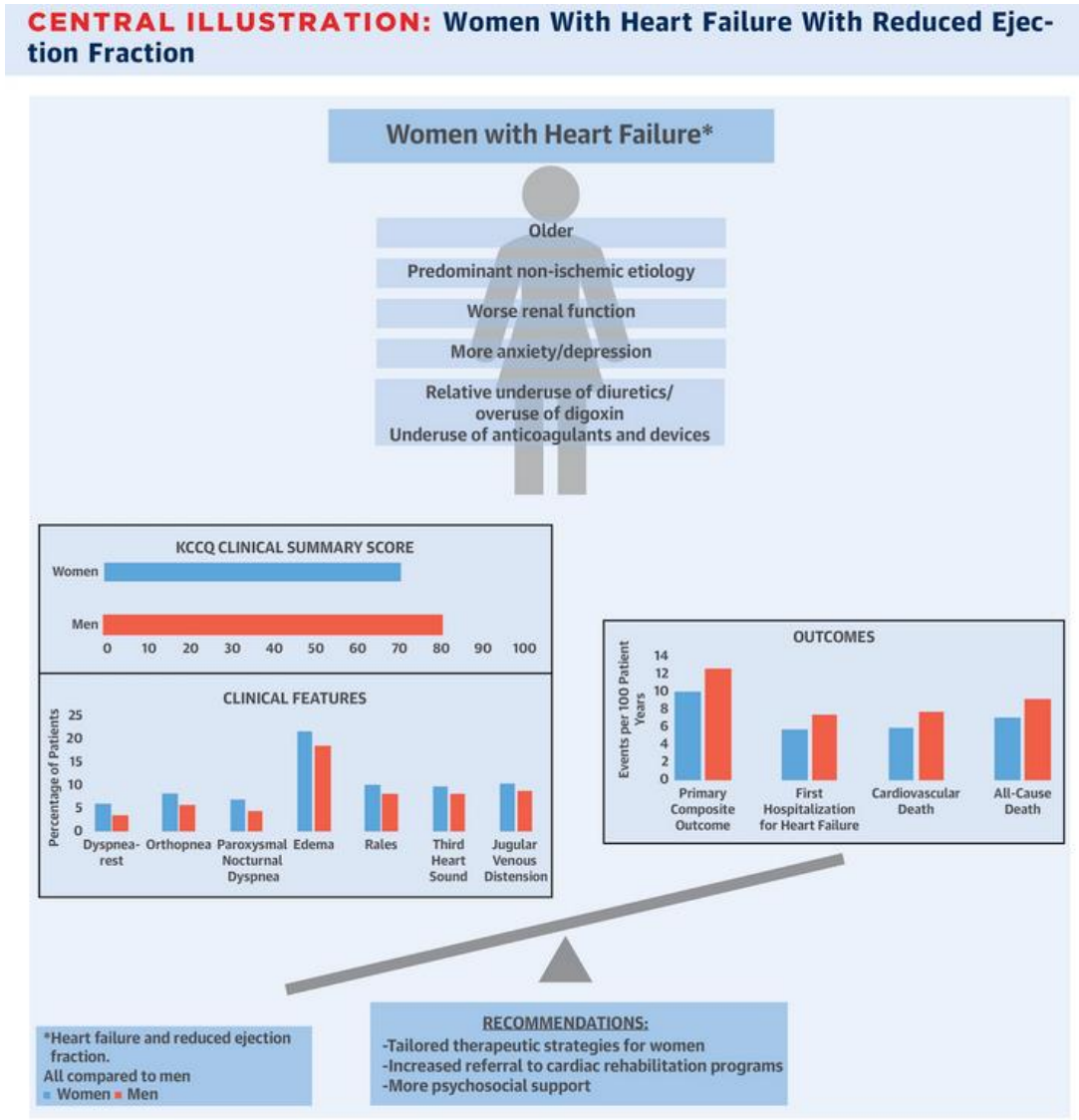
Plus agées

Plus obese

Plus HTP et FC plus élevée

Moins de comorbidités sauf HTA

Plus de symptomes et signes



Dewan P, et al. J Am Coll Cardiol 2019;73:29–40.

Qualité de vie

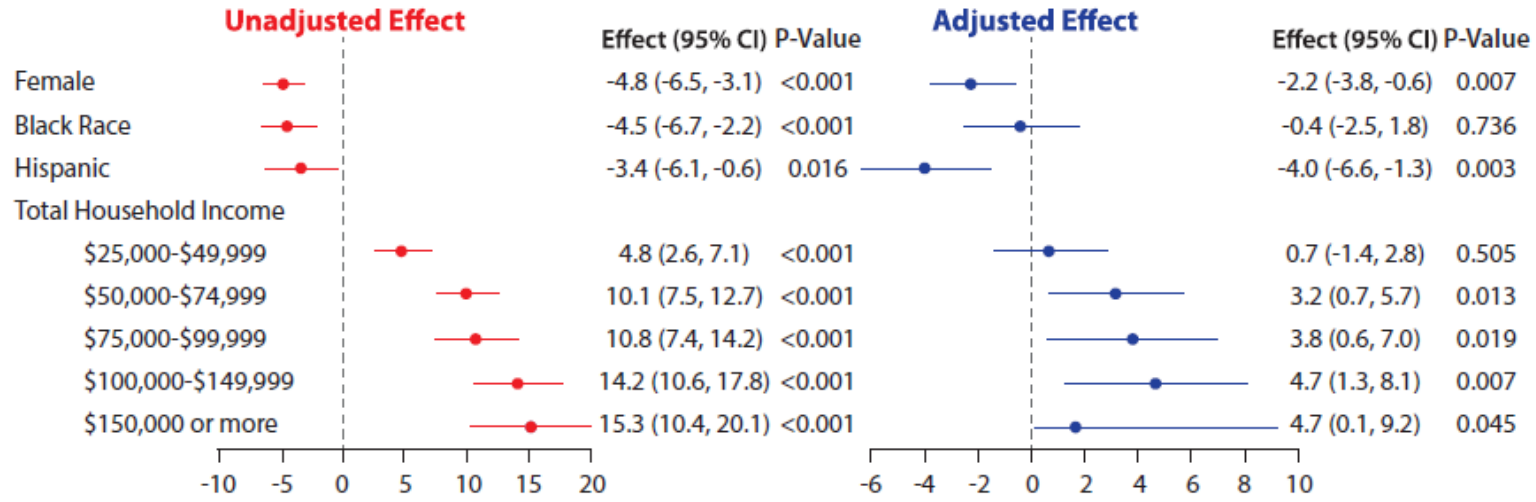
CHAMP-HF

3494 patients

140 U.S. clinics

IC FER

FIGURE 2 Unadjusted and Adjusted Mean KCCQ-os Score Disparities by Sex, Race/Ethnicity, and Socioeconomic Status



Candidate variables considered for multivariate analyses were age, sex, race, BMI, insurance status, highest level of education, house income, employment status, diabetes mellitus, CKD, COPD, depression, tobacco use/smoking, atrial fibrillation, CAD, hypertension, hyperlipidemia, ventricular tachycardia/fibrillation, CRT, number of prior HF hospitalizations, systolic blood pressure, heart rate, LVEF, ACEi/ARB, beta-blocker, MRA, ARNI, loop diuretic agent, hydralazine, digoxin, ivabradine, inotrope, and number of HF medications. Variables included in multivariate analysis after backward selection were age, sex, race, BMI, house income, employment status, CKD, COPD, depression, atrial fibrillation, number of prior HF hospitalizations, systolic blood pressure, heart rate, LVEF, ARNI, loop diuretic therapy, ivabradine, and inotrope. Reference category for sex was male. Reference category for race/ethnicity was white. Reference category for total household income was <$25,000 (annually). ACEi/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid antagonist; other abbreviations as in Tables 1 and 2.

J Am Coll Cardiol HF 2018;6:465–73

ICA

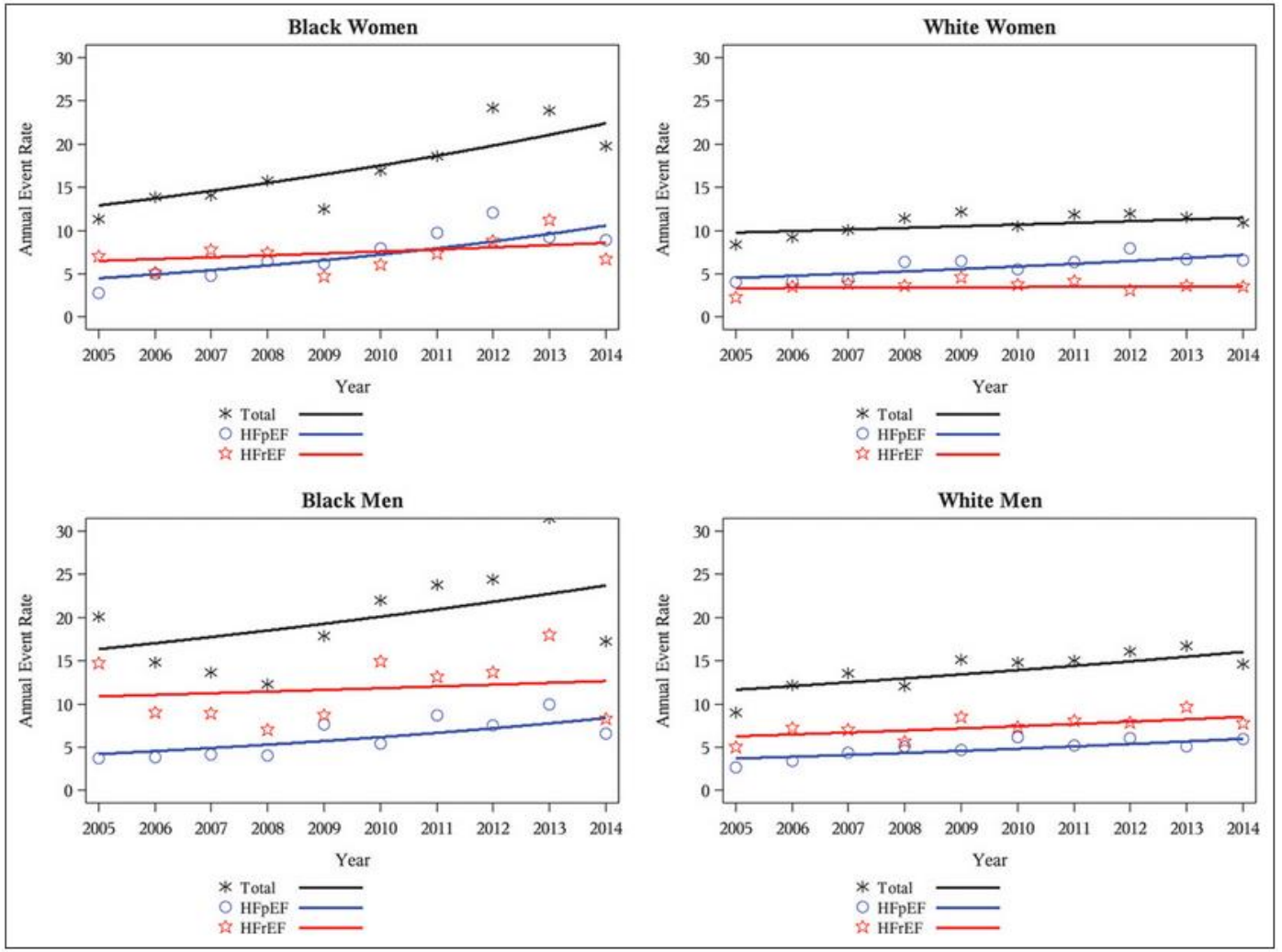


Figure 2. Age-adjusted annual event rates per 1000 for first hospitalized acute decompensated heart failure events, by heart failure type, race, and sex: ARIC study (Atherosclerosis Risk in Communities) Heart Failure Community Surveillance, 2005 to 2014.

Chang PP, ARIC Study Community Surveillance. Circulation 2018;138:12–24.

I PRESERVED et femme

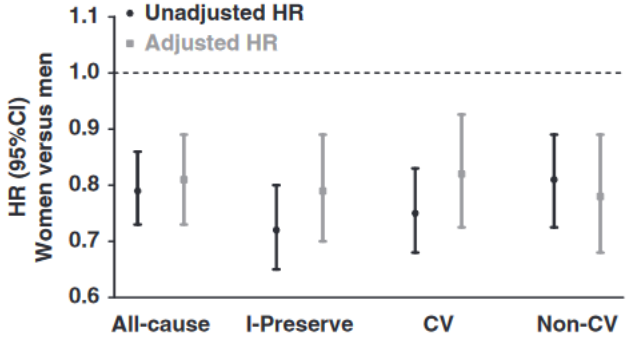


Figure 1. Association between sex and time to first event. Hazard ratios (HRs) for women versus men for first events, where HR

Table 2. Association Between Sex and Time to First Outcomes

	No. of Events			Event Rate Per 100 Patient-Years		Univariable Analysis		Multivariable Analysis*	
Outcome	All Patients	Women	Men	Women	Men	HR (95% CI), Women vs Men	*P* Value	HR (95% CI), Women vs Men	*P* Value
All-cause death	881	447	434	4.32	6.72	0.64 (0.56–0.73)	<0.001	0.70 (0.59–0.83)	<0.001
All-cause hospitalization or death	2430	1382	1049	19.42	25.05	0.79 (0.73–0.86)	<0.001	0.80 (0.72–0.89)	<0.001
Cardiovascular hospitalization or death	1754	970	784	11.76	15.97	0.75 (0.68–0.83)	<0.001	0.81 (0.72–0.92)	0.001
Noncardiovascular hospitalization or death	1483	846	638	9.89	12.40	0.81 (0.72–0.89)	<0.001	0.78 (0.69–0.90)	<0.001
Heart failure hospitalization or death	716	420	296	4.43	5.02	0.89 (0.77–1.04)	0.140	0.94 (0.77–1.14)	0.51
First all-cause hospitalization	2278	1314	964	18.43	23.14	0.82 (0.75–0.88)	<0.001	0.77 (0.66–0.89)	<0.001

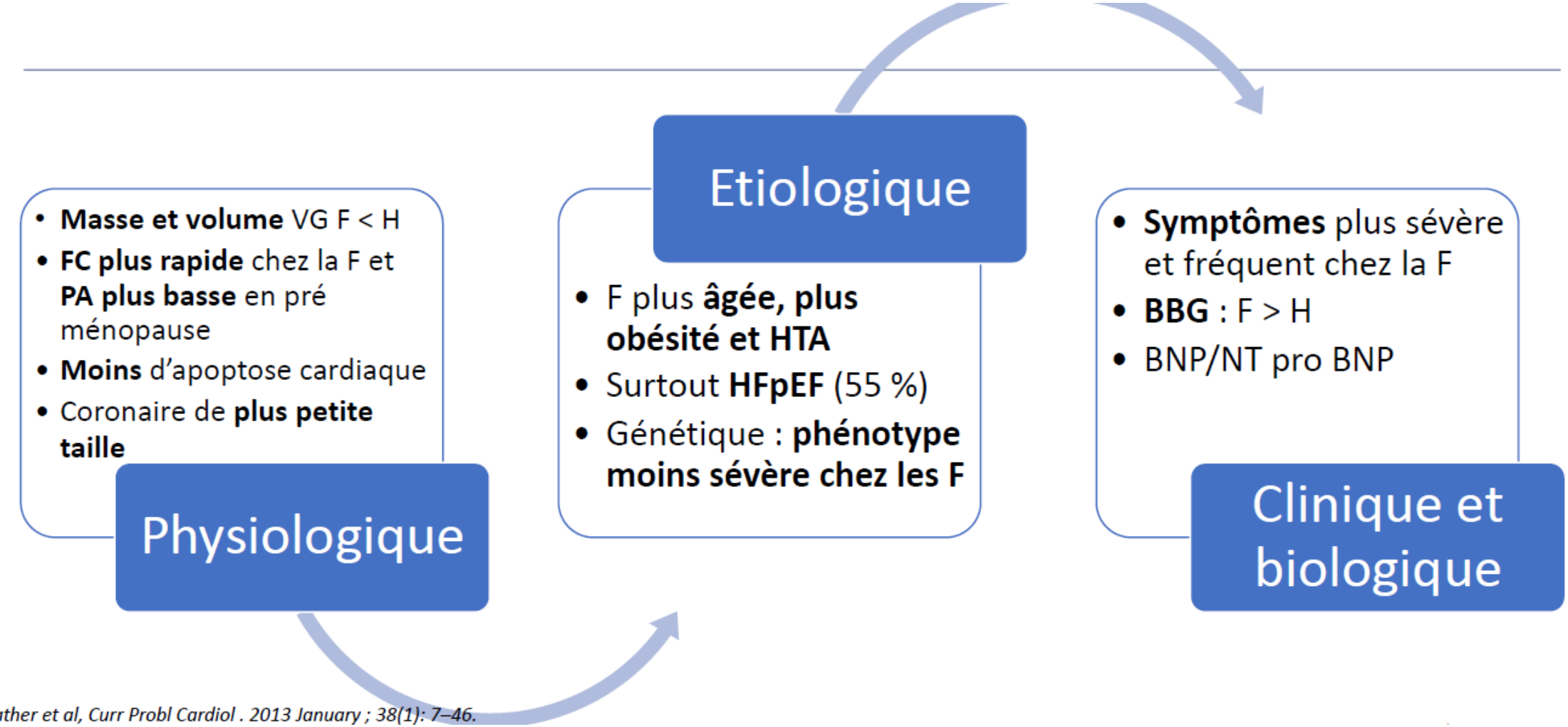
HR indicates hazards ratio; HF, heart failure; PCI/CABG, percutaneous coronary intervention/coronary artery bypass surgery; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

*Adjusted for age, obesity, New York Heart Association status, HF cause, HF hospitalization within 6 mo, comorbidities/risk factors (history of hypertension, stable angina, myocardial infarction, PCI/CABG, atrial fibrillation, diabetes, stroke/TIA, COPD/asthma, valve disease, smoking), ejection fraction capped at 60%, heart rate, systolic blood pressure, hemoglobin, ln-NT-pro-BNP, natural log-neutrophil count, glomerular filtration rate capped at 90 mL/min per 1.73 m^2, and all medications.

†Death from any cause or hospitalization for protocol-specified cardiovascular cause (HF, myocardial infarction, arrhythmia, or stroke).

Lam CS, et al. I PRESERVE trial. Circ Heart Fail 2012;5:571–578.

Et le traitement ?

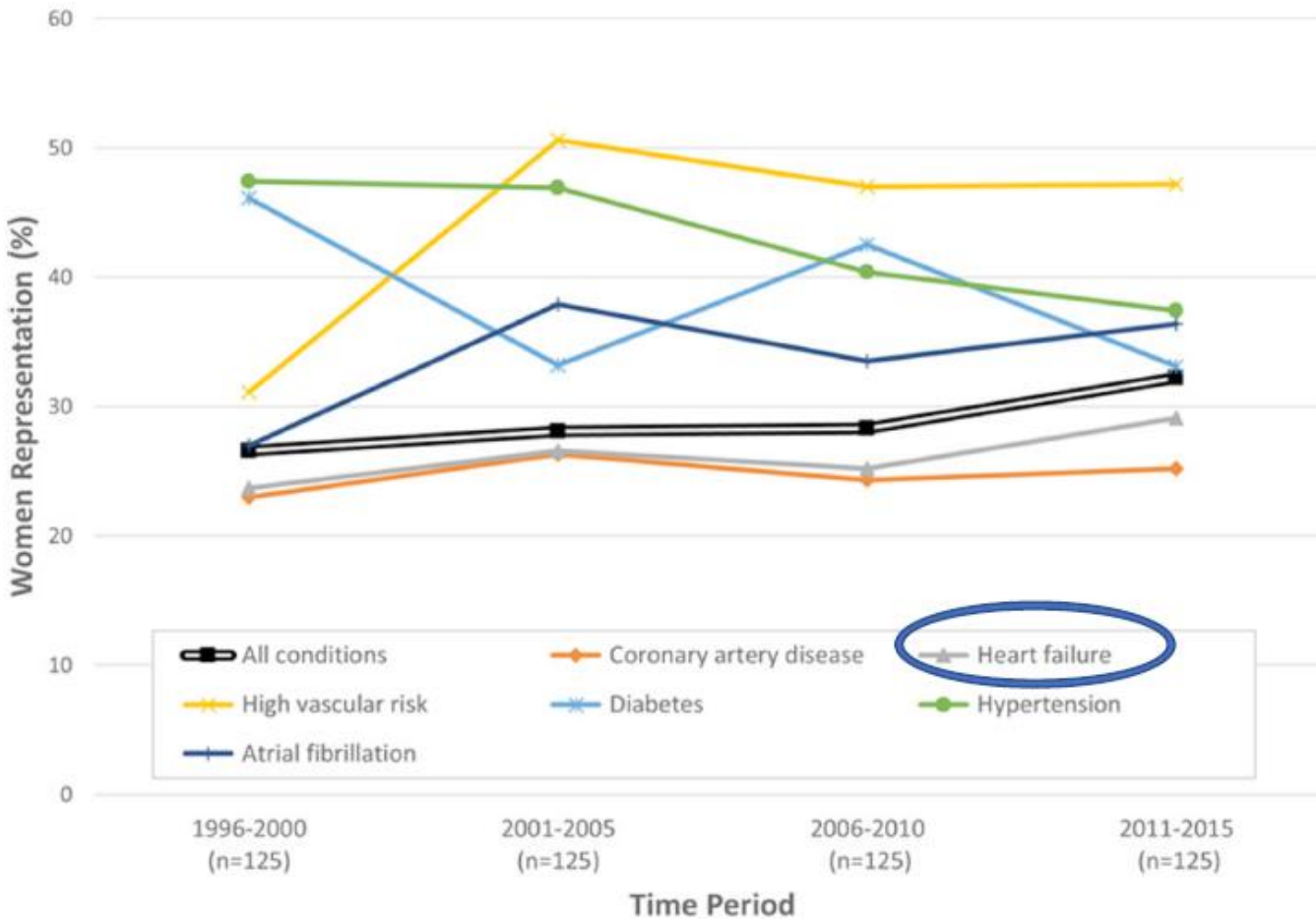


ɹirweather et al, Curr Probl Cardiol . 2013 January ; 38(1): 7–46.

Problématique scientifique

- **Sous représentation des femmes et des sujets âgés** dans les études CV
- Entre 1996 et 2015 :
  - 60 ans en moyenne
  - 25 % de femmes (mais F = 60 % HF ..)
- En amélioration …
- Ancienneté des méta-analyses sur le genre

=> Manque de données



Nguyen et al. Circ Cardiovasc Qual Outcomes. 2018;11:e004713

Problématique socio-médicale

➢ Problématique de **la vision médicale :**

- F moins optimisée et traitée
- PEC différente si le médecin est un H ou une F (liés aux symptômes et à l'âge)

Tamargo, EHJ Cardiovascular Pharmacotherapy (2017) 3, 163–182

➢ **Thérapeutique** :

- F surtout HFpEF
- Observance F > H ? discordance

Hoang-Kim et al. BMC Cardiovascular Disorders (2020) 20:223

➢ **Sociale** :

- **Moins bonne qualité vie** chez la F mais **sans retentissement** sur la mortalité
- Foetotoxicité / grossesse

Ravera et al, European Journal of Heart Failure (2021) 23, 567–577

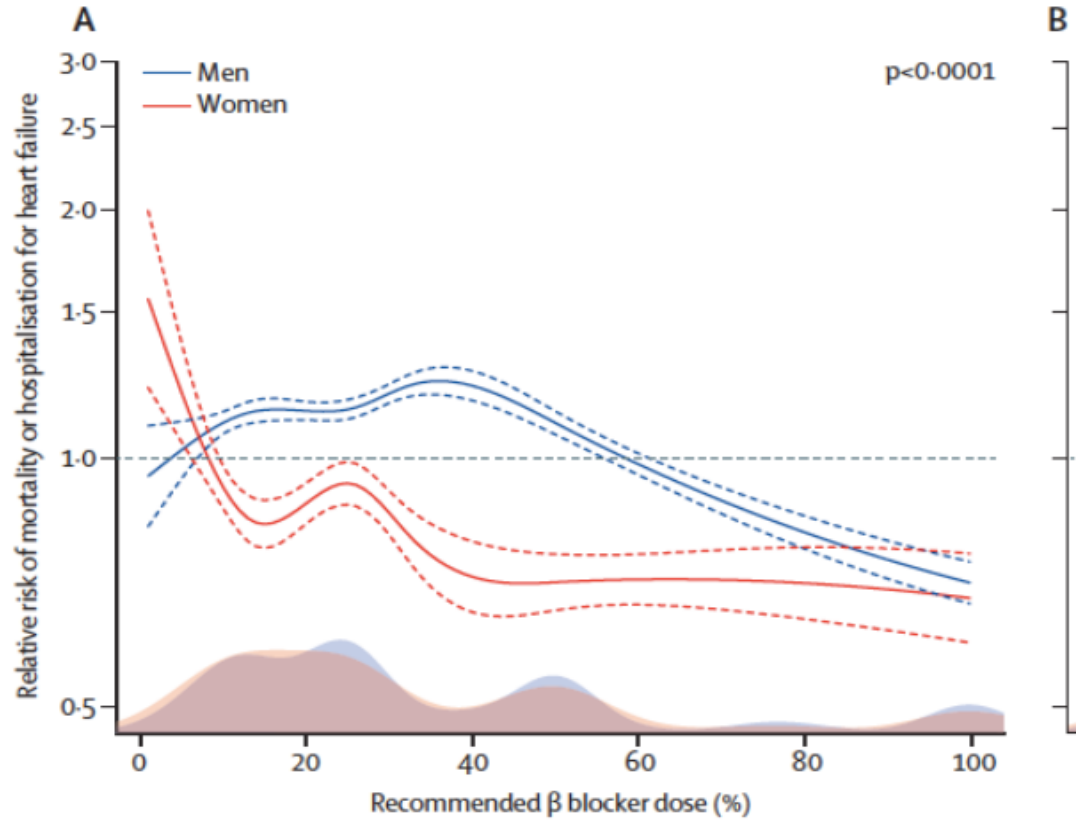
Réponse clinique et particularités pharmacologiques

Variation : absorption / distribution / métabolisation

- Chez la F [1,2,4] : IEC, ARAII, BB = **concentration plasmatique 2,5 x plus élevée :**
- Répartition masse graisseuse et V de distribution
- Variation CYP 450, DFG et méta hépatique

- **Bénéfice moindre des traitements à dose max** IEC, BB et ARA II pour HFrEF [2,4]
- Plus d'EI (toux et IEC…) [3]

1. *Soldin et al, Clin Pharmacokinet 2009;48:143–157*
2. *Lam et al, European Heart Journal (2019) 40, 3859–3868*
3. *Jochmann et al, Eur Heart J 2005;26: 1585–1595*



4. Santema et al, Lancet 2019; 394: 1254–63

Insuffisance cardiaque aiguë

Contexte :

- Prise en charge et symptômes différents
- Nombre de réhospitalisation idem mais **plus de réhospitalisation précoce** (environnement) versus tardive pour les H (observance)

Hoang-Kim et al. BMC Cardiovascular Disorders (2020) 20:223

Prise en charge et diurétique :

- Natriurèse pic H > F PO ou IV ?
- Plus d'EI des diurétiques chez les F (hypoK …)

Franson et al, Int J Clin Pharmacol Ther. 1996 Mar;34(3):101-5
Seeland U et al.Handb Exp Pharmacol. 2012;(214):211-36

Bétabloquants

HFrEF :

Drug class	Study	Drug	Published (year)	LVEF	% women	No. of women	Primary endpoint	Sex-specific outcome
B-blocker	CIBIS II	Bisoprolol	1999	≤35%	19	515	Mortality	Significant benefit in men and women
	COPERNICUS	Carvedilol	2001	<25%	20	465	Mortality	Significant benefit in men, trend towards benefit in women
	MERIT-HF	Metoprolol	1999	≤40%	23	898	Mortality or all-cause hospitalization	Significant benefit in men, not in women
	SENIORS	Nebivolol	2005	≤35%	37	785	Mortality or cardiovascular hospital admission	HR 0.93 (0.78-1.11) in men HR 0.72 (0.55-0.93) in women p for interaction 0.11

Supplement HFrEF drug therapy trials Lam et al, European Heart Journal (2019) 40, 3859–3868

- Diminution de la mortalité similaire H/F (sur études poolées)
- Dose ? Diminution du risque de 30% dès dose 40-60 % de la dose cible [2],
- EI sont supérieurs chez la F > H [1,2,3] (ex du métoprolol)

HFpEF : pas d'effets H et F [3]

Seeland U et al.Handb Exp Pharmacol. 2012;(214):211-36; 2. Shekelle et al, J Am Coll Cardiol 2003;41:1529 –38; 3.Lam et al, European Heart Journal (2019) 40, 3859

IEC et ARA II

IEC

- **HFrEF** : survie uniquement sur les H

  Plutôt si HF symptomatique
- Pas d'effet sur **HFpEF**

ARA II

- Pas de résultat significatif sur la mortalité pour le valsartan H et F
- Pas de différence sur le sexe

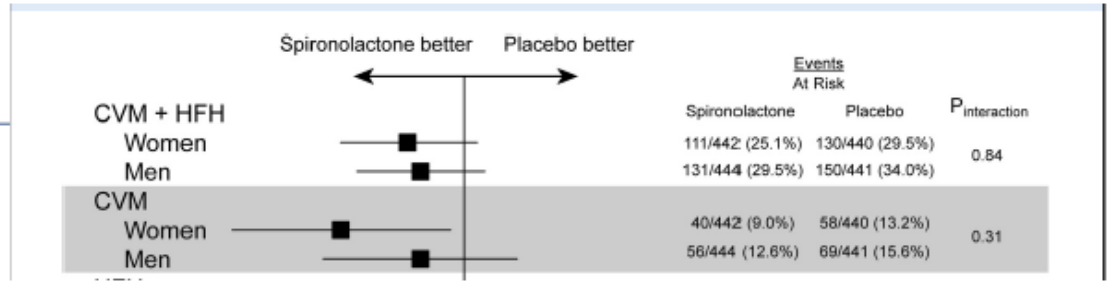
Drug class	Study	Drug	Published (year)	LVEF	% women	No. of women	Primary endpoint	Sex-specific outcome
ACE-I	SOLVD-Treatment	Enalapril	1991	≤35%	20	505	Mortality	Significant benefit in men, trend towards benefit in women
	CONSENSUS	Enalapril	1987	≤35%	30	74	Mortality	Significant benefit in men, not in women
ARB	CHARM	Candesartan	2004	≤40%	26	1188	Cardiovascular death or HF hospitalization	No sex difference in primary endpoint, p for interaction 0.95
	Val-HeFT	Valsartan	2001	<40%	20	1003	Mortality or HF hospitalization/ED presentation	Significant benefit in men, trend towards benefit in women

Supplement HFrEF drug therapy trials Lam et al, European Heart Journal (2019) 40, 3859–3868

Anti-aldostérone : spironolactone et éplérénone

HFrEF : effets similaires H/F (eplerenone ?)

RALES, EPHESUS et EMPHASIS-HF

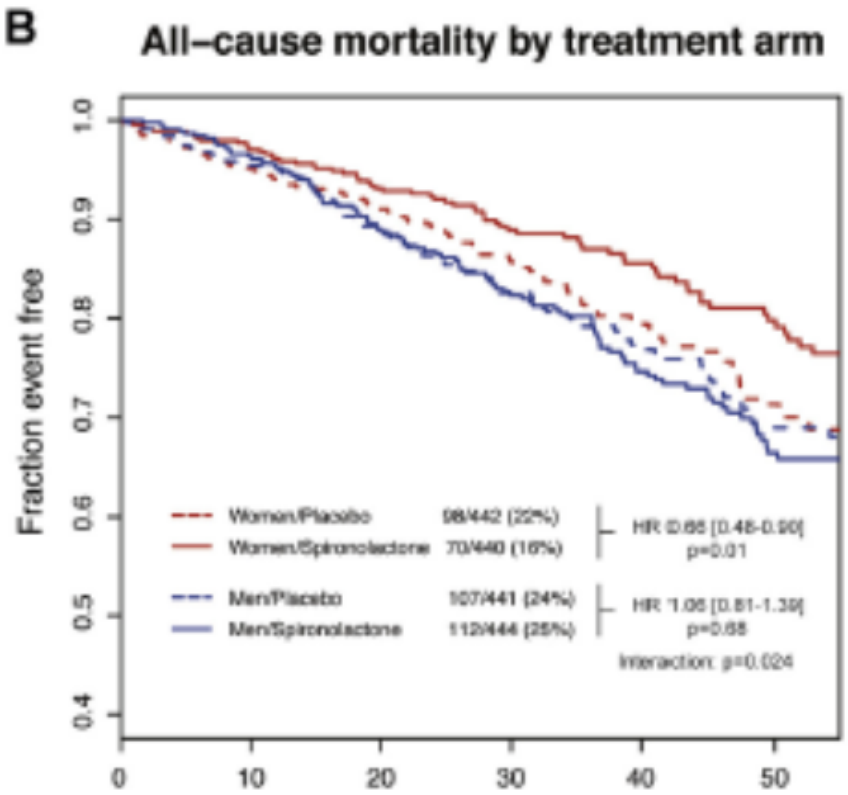


HFpEF :

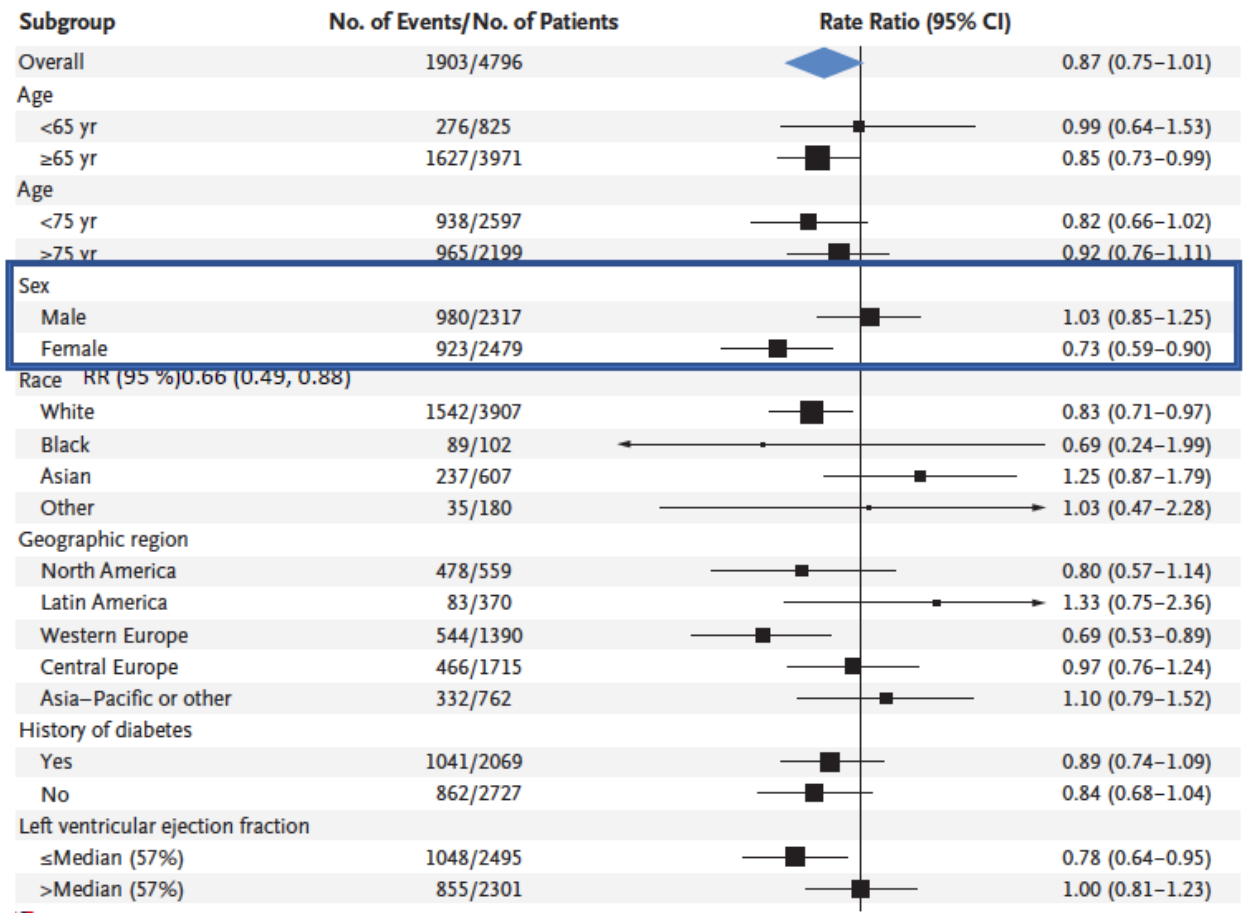
- Etude post-hoc TOPCAT spironolactone vs placebo
- Effets bénéfique dans la mortalité toute cause F > H

Effet supérieur des AA chez la femme en post IDM ? Chez l'animal

Merill et al, JACC HF 2019;7:228–38



Sacubitril/Valsartan



Subgroup	No. of Events/No. of Patients	Rate Ratio (95% CI)
Overall	1903/4796	0.87 (0.75–1.01)
Age		
<65 yr	276/825	0.99 (0.64–1.53)
≥65 yr	1627/3971	0.85 (0.73–0.99)
Age		
<75 yr	938/2597	0.82 (0.66–1.02)
≥75 yr	965/2199	0.92 (0.76–1.11)
Sex		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
Race RR (95 %)0.66 (0.49, 0.88)		
White	1542/3907	0.83 (0.71–0.97)
Black	89/102	0.69 (0.24–1.99)
Asian	237/607	1.25 (0.87–1.79)
Other	35/180	1.03 (0.47–2.28)
Geographic region		
North America	478/559	0.80 (0.57–1.14)
Latin America	83/370	1.33 (0.75–2.36)
Western Europe	544/1390	0.69 (0.53–0.89)
Central Europe	466/1715	0.97 (0.76–1.24)
Asia–Pacific or other	332/762	1.10 (0.79–1.52)
History of diabetes		
Yes	1041/2069	0.89 (0.74–1.09)
No	862/2727	0.84 (0.68–1.04)
Left ventricular ejection fraction		
≤Median (57%)	1048/2495	0.78 (0.64–0.95)
>Median (57%)	855/2301	1.00 (0.81–1.23)

PARADIGM HF (HFrEF): pas de différence sur le sexe

PARAGON-HF (HFpEF):

- Etude « négative »
- 50 % femmes sous ARNi et valsartan,
- Analyse en sous groupe : tendance + sur le critère principal

PARAGON-HF, N Engl J Med 2019;381:1609-20.

ISGLT 2

HFrEF : pas de différences ? (24 % F dans DAPA-HF et EMPEROR-reduced)

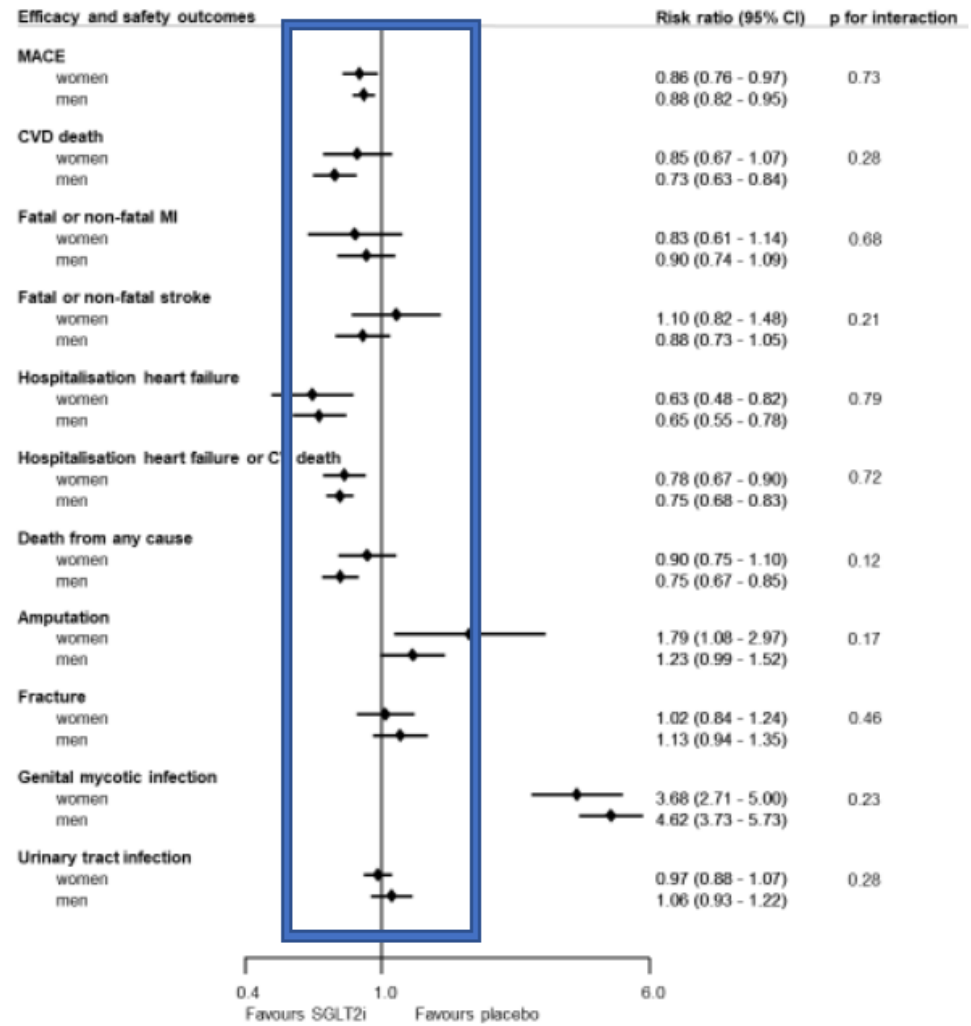
HFpEF : % 50 F dans études HFpEF

Effet sur le genre ?

- Etudes animales : uprégulation ISGLT2 F > H
- Etude comparative des ISGLT2 sur les complications CV du diabète
- Entre 20 et 40% de femmes,
- **Même safety et même résultats**

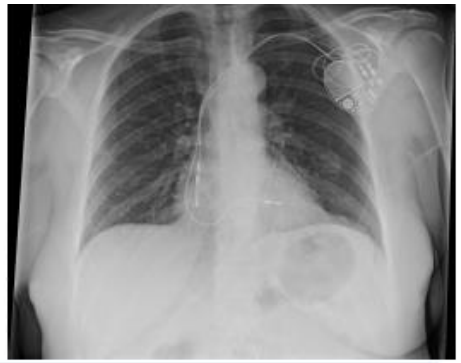
Rådholm K et al, Diabetes Obes Metab. 2020 Feb;22(2):263-266

Figure 1. Risk ratios and 95% confidence intervals for efficacy and safety outcomes by sex and overall, for participants with SGLT2 inhibitor (SGT2i) treatment versus placebo.



SGLT2i: sodium glucose cotransporter 2 inhibitors

DAI et CRT



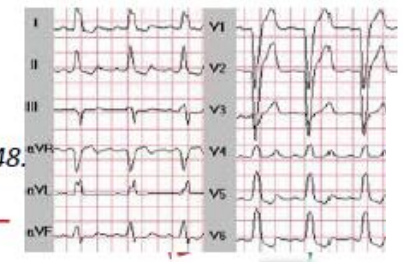
DAI :

- Moins d'implantation chez la F [1]
- Efficacité sur la survie ?
- Plus de complications chez les F post-implantation [2]

➢ Pronostic de la mortalité plutôt sur **défaillance cardiaque F** > H sur mort subite [1] (lié CMI)

Resynchronisation :

- Meilleure efficacité chez la F :
  - Meilleur réponse au remodelage [3]
  - CM non-ischémique
- > 1 an (15 versus 8% pour la mortalité toute cause à 2 ans)
- Rediscuter la valeur BBG H versus F ?



Lam et al, European Heart Journal (2019) 40, 3859–3868; 2. Russo et al, Am Heart J. 2015 August ; 170(2): 330–338. ; 3. Yin F-H, PLoS ONE, 2017 12(4): e0176248.

Réadaptation cardiaque

- Pic VO2 plus faible chez les F

Harvey RE et al, Womens Health (Lond). 2015 Mar;11(2):239-257

- Cycle souvent incomplet de réadaptation chez F
- Meilleur bénéfice F > H si terminée
- Effet sur FDRCV
- Pas de programme spécifique dans le cas de la CMPP

Lam et al, European Heart Journal (2019) 40, 3859–3868

Conclusion

- Problématique des **différences physiologique et métabolique**
- Problématique de la **sous représentation** dans les études en générales et de la prédominance HFpEF chez la femme
- <u>En pratique :</u>
  - HFrEF : **Même traitement** (diurétique, ARNi > IEC, BB, aldo, ISGLT 2) **Resynchronisation** ++
  - Question de la dose => moins de **dose « maximale » ?**
  - HFpEF : **ARNi ? Anti aldostérone**
- Intérêt études plus larges