CENTRE HOSPITALIER CAYENNE
Andrée Rosemon

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload.

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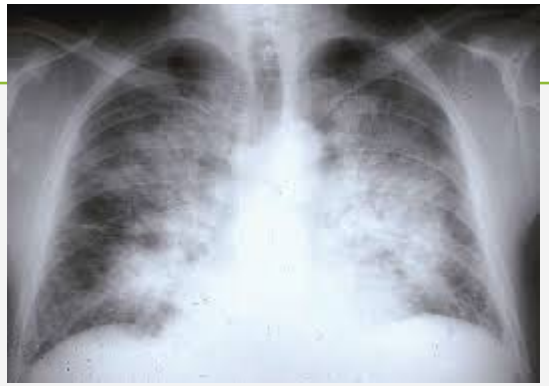
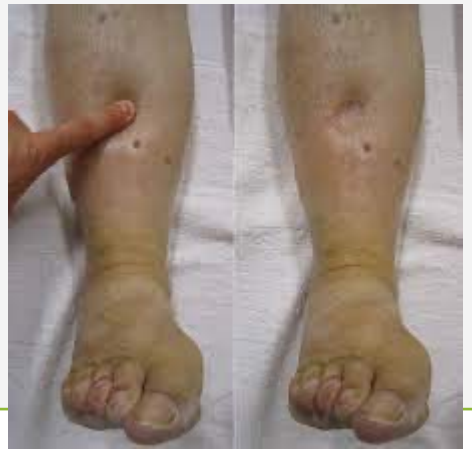
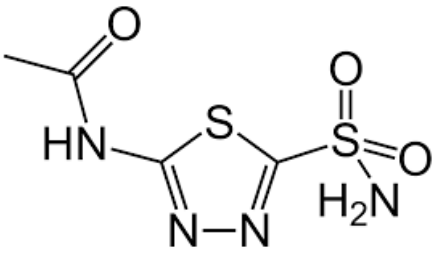
Contexte de l'article

- Décompensation aigue d'ICC = Dyspnée, OMI, Asthénie.
- 1er motif d'hospitalisation chez > 65 ans.
- Mortalité élevée.
- Beaucoup de retour à domicile avec signes de surcharge.
- Décompensation d'insuffisance cardiaque : diurétiques de l'anse à forte dose.





Acétazolamide



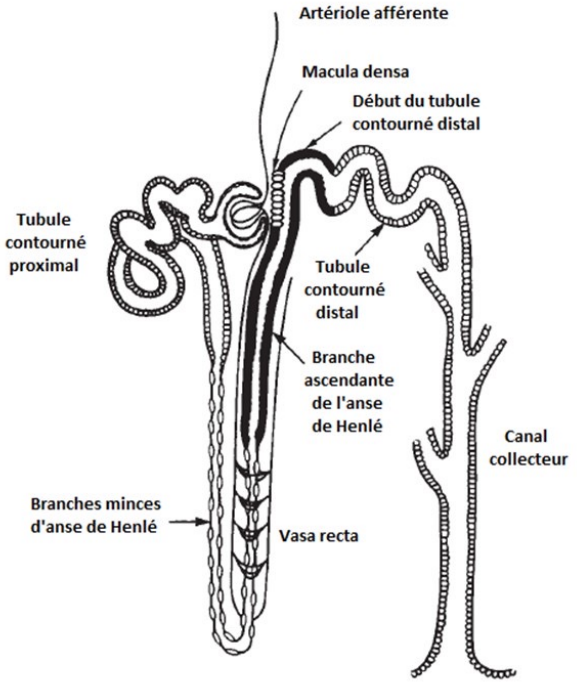
Inhibiteur de l'anhydrase carbonique

Effet sur tubule contourné proximal

Diminution de la réabsorption du Na

Augmentation de l'efficacité des diurétiques de l'anse

Glaucome, HTIC, intoxications…



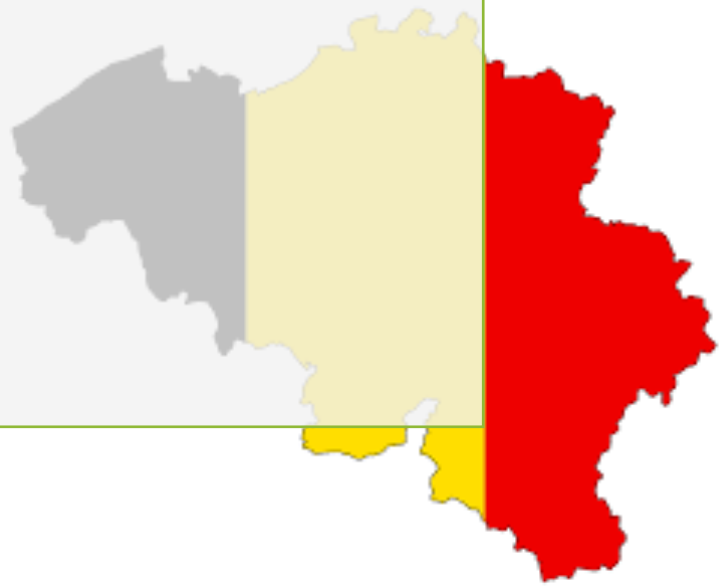
Design de l'étude

Essai **thérapeutique** contre **placebo**, multicentrique, **randomisé**, en **double aveugle**.

Acétazolamide vs Placebo

Novembre 2018 à janvier 2022

519 inclus.



Design de l'étude

Critères d'inclusion :

- Adultes
- Décompensation cardiaque : 1 signe au moins de surcharge volémique (OMI, épanchement pleural, ascite).
- NT-proBNP > 1000 pg/mm
- Traitement par DU (40 mg).

Critères d'exclusion :

- Traitement par acétazolamide en cours
- Traitement par inhibiteur SGLT-2
- PA < 90 mmHg
- DFG < 20 ml/min
- > 80 mg de furosémide après l'admission

Randomisation 1:1

500 mg ATZ ou Placebo

Jusqu'à diminution complète des symptômes

+ furosémide, dose quotidienne *2

Surveillance diurèse

Surveillance score de congestion

Congestion Score

Score clinique : 0 à 10.

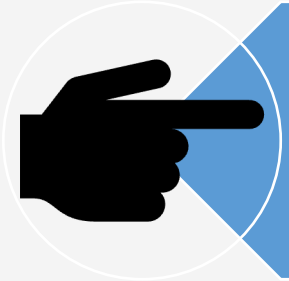
Œdème	Absence = 0	Trace = 1	Godet = 2	Supérieur à la cheville =3	Supérieur au genou = 4
Épanchement pleural	Absence = 0	Mineur (non ponctionnable) = 2		Majeur = 3	
Ascite	Absence = 0	Mineure (non ponctionable) = 2		Majeure = 3	

Evaluation avant prise de furosémide.

Critères de jugements

CJP

Congestion Score à J 3 = 0



CJS :

Mortalité toute cause OU ré-hospitalisation à M3 + nombres de jours d'hospitalisation

+ surveillance des effets indésirables et critères d'arrêt du traitement.

Population

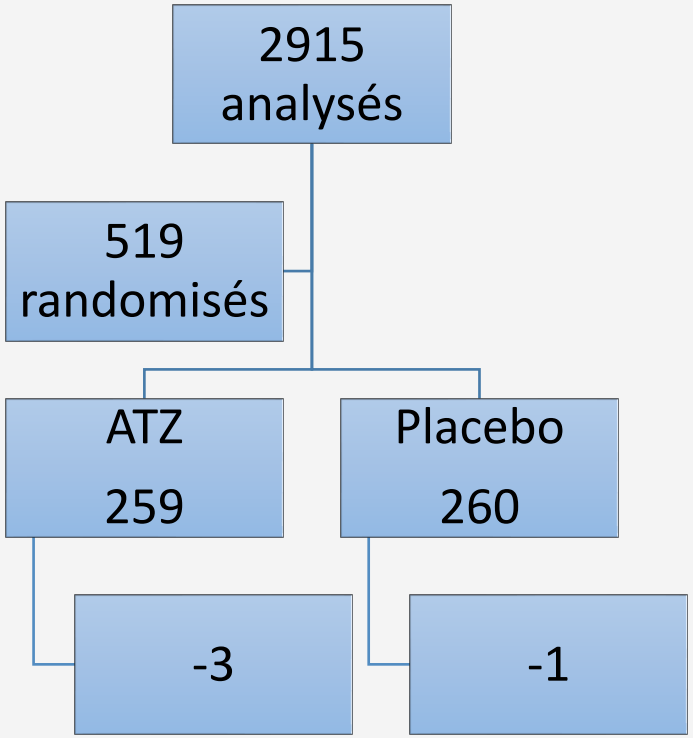


Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=260)	Acetazolamide (N=259)	Total (N=519)
Age — yr	78.5±8.8	77.9 ±9.0	78.2±8.9
Male sex — no. (%)	155 (59.6)	170 (65.6)	325 (62.6)
White race — no. (%)†	256 (98.5)	258 (99.6)	514 (99.0)
Heart rate — beats/min	77±18	79±19	78±18
Blood pressure — mm Hg			
Systolic	127±22	126±20	127±21
Diastolic	73±13	72±13	72±13
Weight — kg	84.4±19.7	85.3±23.0	84.8±21.4
Median congestion score at baseline (IQR)‡	4 (3–6)	4 (3–5)	4 (3–6)
Components of congestion score — no. (%)			
Edema§	241 (92.7)	237 (91.5)	478 (92.1)
Pleural effusion	143 (55.0)	130 (50.2)	273 (52.6)
Ascites	25 (9.6)	21 (8.1)	46 (8.9)
Median home maintenance dose of furosemide equivalent (IQR) — mg	60 (40–100)	80 (40–120)	60 (40–100)
Left ventricular ejection fraction			
Mean — %	43±15	43±15	43±15
≤40% — no. (%)	111 (42.7)	113 (43.6)	224 (43.2)
Median NT-proBNP (IQR) — pg/ml	6483 (3262–11,839)	5600 (3034–10,100)	6173 (3068–10,896)
NYHA functional class — no. (%)			
II	35 (13.5)	31 (12.0)	66 (12.7)
III	148 (56.9)	148 (57.1)	296 (57.0)
IV	77 (29.6)	80 (30.9)	157 (30.3)
Ischemic cause — no. (%)	113 (43.5)	119 (45.9)	232 (44.7)
Serum hemoglobin — g/dl	11.9±2.0	11.9±2.0	11.9±2.0
Sodium — mmol/liter	140±4	139±4	139±4
Median serum creatinine (IQR) — mg/dl	1.5 (1.2–1.9)	1.5 (1.2–2.0)	1.5 (1.2–1.9)
Estimated GFR			
Median (IQR) — ml/min/1.73 m²	38 (29–51)	40 (30–52)	39 (29–52)
<60 ml/min/1.73 m² — no. (%)	215 (82.7)	209 (80.7)	424 (81.7)
Coexisting conditions — no. (%)			
History of atrial fibrillation	189 (72.7)	187 (72.2)	376 (72.4)
Diabetes	133 (51.2)	112 (43.2)	245 (47.2)
Hypertension	207 (79.6)	182 (70.3)	389 (75.0)
Treatment — no. (%)			
ACE inhibitor, ARB, or ARNI	140 (53.8)	130 (50.2)	270 (52.0)
Beta-blocker	212 (81.5)	207 (79.9)	419 (80.7)
Mineralocorticoid receptor antagonist	103 (39.6)	113 (43.6)	216 (41.6)
Loop diuretic	260 (100.0)	259 (100.0)	519 (100.0)
Implantable cardioverter–defibrillator	41 (15.8)	38 (14.7)	79 (15.2)
Cardiac-resynchronization therapy	25 (9.6)	36 (13.9)	61 (11.8)

Résultats

CJP : diminution complète des symptômes à J3 : 42,2% groupe AZT vs 30,5% groupe Placebo Risque relatif 1,46; 95% CI [1,17 ; 1,82] p < 0,001

Congestion score = 0 à la sortie d'hospitalisation : RR = 1,27 pour AZT.

CJS : Pas de différence significative entre les groupes.

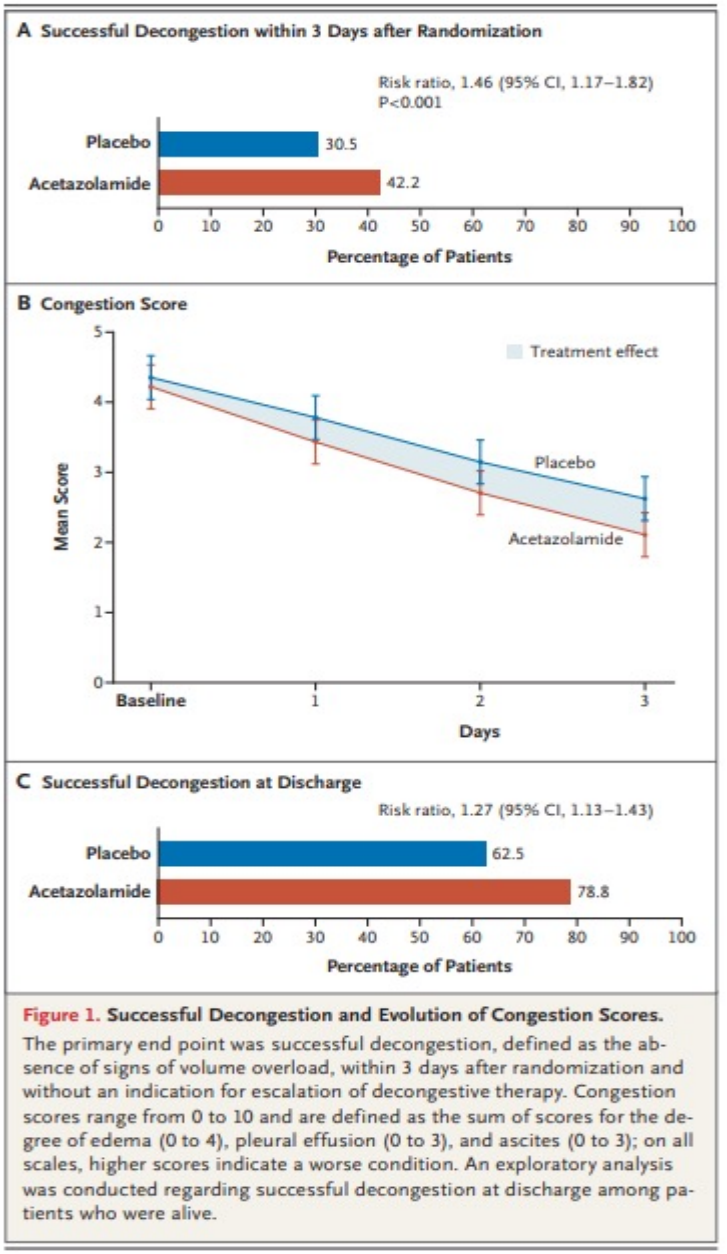


Figure 1. Successful Decongestion and Evolution of Congestion Scores.
The primary end point was successful decongestion, defined as the absence of signs of volume overload, within 3 days after randomization and without an indication for escalation of decongestive therapy. Congestion scores range from 0 to 10 and are defined as the sum of scores for the degree of edema (0 to 4), pleural effusion (0 to 3), and ascites (0 to 3); on all scales, higher scores indicate a worse condition. An exploratory analysis was conducted regarding successful decongestion at discharge among patients who were alive.

Résultats

Analyse de sensibilité si pas d'escalade thérapeutique

Pas de différence en terme d'effets indésirables

Table 2. Primary and Secondary End Points, Sensitivity and Exploratory Analyses, and Adverse Events.*

Variable	Placebo (N=259)	Acetazolamide (N=256)	Treatment Effect (95% CI)	P Value
Primary end point				
Successful decongestion within 3 days after randomization — no. (%)†	79 (30.5)	108 (42.2)	Risk ratio, 1.46 (1.17–1.82)	<0.001
Secondary end points				
Duration of hospital stay (95% CI) — days‡	9.9 (9.1–10.8)	8.8 (8.0–9.5)	0.89 (0.81–0.98)	
Death from any cause or rehospitalization for heart failure during 3 mo of follow-up — no. (%)	72 (27.8)	76 (29.7)	Hazard ratio, 1.07 (0.78–1.48)	
Sensitivity analysis of primary end point				
Successful decongestion within 3 days after randomization, regardless of escalation of therapy — no. (%)§	86 (33.2)	115 (44.9)	Risk ratio, 1.42 (1.15–1.76)	
Exploratory analysis				
Successful decongestion at discharge among patients who were alive — no./total no. (%)	145/232 (62.5)	190/241 (78.8)	Risk ratio, 1.27 (1.13–1.43)	
Death from any cause at 3 mo — no. (%)	31 (12.0)	39 (15.2)	Hazard ratio, 1.28 (0.78–2.05)	
Rehospitalization for heart failure at 3 mo — no. (%)	45 (17.4)	47 (18.4)	Hazard ratio, 1.07 (0.71–1.59)	
Adverse events				
During treatment phase — no. (%)				
Combined renal safety end point	2 (0.8)	7 (2.7)	—	0.10
Doubling of serum creatinine level from baseline	0	2 (0.8)	—	0.24
≥50% sustained decrease in estimated GFR	1 (0.4)	4 (1.6)	—	0.21
Renal-replacement therapy during index hospitalization	1 (0.4)	4 (1.6)	—	0.21
Severe metabolic acidosis¶	0	0	—	—
Hypokalemia‖	10 (3.9)	14 (5.5)	—	0.39
Hypotension**	9 (3.5)	17 (6.6)	—	0.11
During 3 mo of follow-up — no. (%)				
Serious adverse event	124 (47.9)	123 (48.0)	—	1.00
Adverse event related to placebo or acetazolamide	3 (1.2)	8 (3.1)	—	0.14
Cardiovascular adverse event	122 (47.1)	113 (44.1)	—	0.53

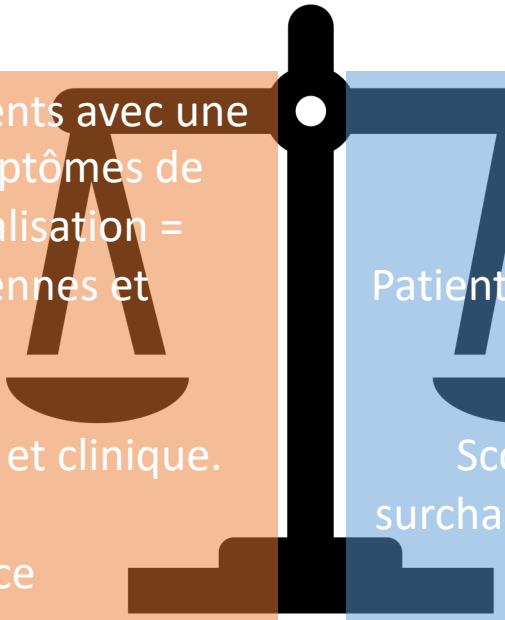
Discussion

Plus grand pourcentage de patients avec une diminution complète des symptômes de surcharge en sortie d'hospitalisation = recommandations européennes et américaines.

Protocole simple, score simple et clinique.

Bon profil de tolérance

Patients représentatifs : IRC stade III, CS = 4 …



Limites :
Population étudiée = Belges

Patients chroniques : stratégie non testée pour épisodes inauguraux

Score de congestion : reflet de la surcharge extracellulaire (pas de patients Dry).

Patients exclus si traitement par SGLT2 : site d'action semblable, mais efficacité différente.