Sodium-glucose cotransporter inhibitors effects on endothelial function and atherosclerosis biomarkers in acute coronary syndrome patients: A pilot study

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Introduction

Sodium-Glucose Cotransporter Inhibitors (SGLT2i) have shown cardiovascular benefits beyond their antidiabetic effect.

They exhibit potential anti-inflammatory and anti-atherosclerotic pathways, improving lipid profiles and endothelial function.

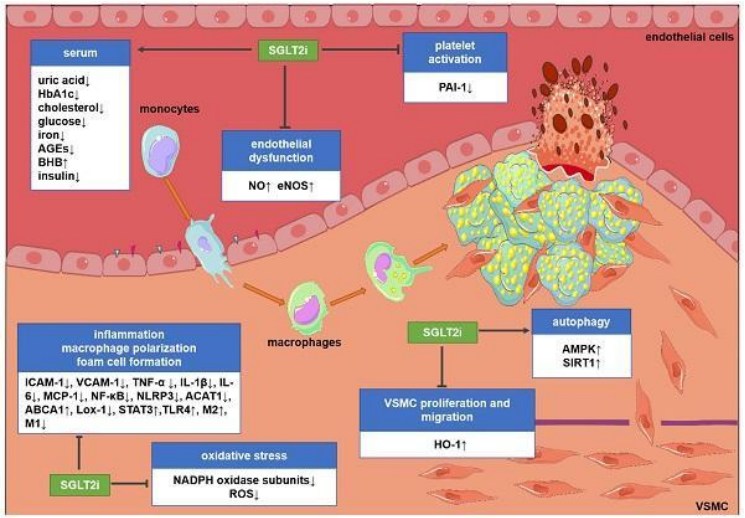


Figure 1: Potential molecular targets of SGLT2i in atherosclerosis [1]

- Our study aimed to assess the **effects** of **early SGLT2i initiation** during **acute coronary syndrome** (ACS) on endothelial function (EF) and atherosclerosis biomarkers.

1 .Zhenghong Liu et al., « Impact of Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors on Atherosclerosis: From Pharmacology to Pre-Clinical and Clinical Therapeutics », Theranostics 11, no 9 (2021): 4502-15

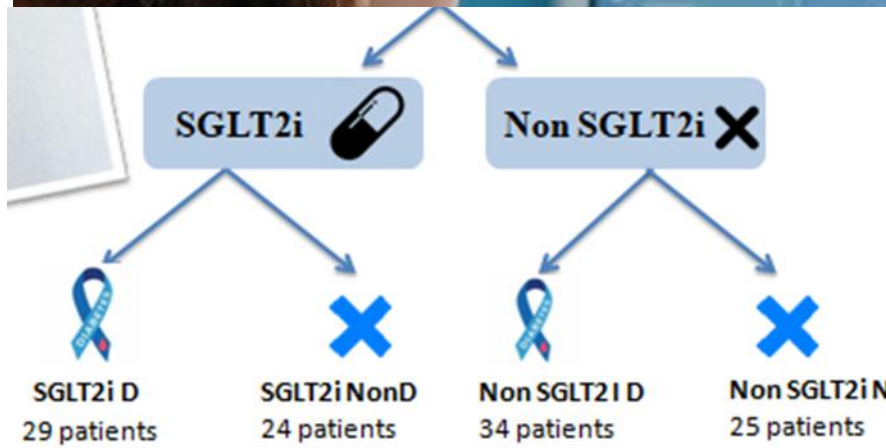
Methods

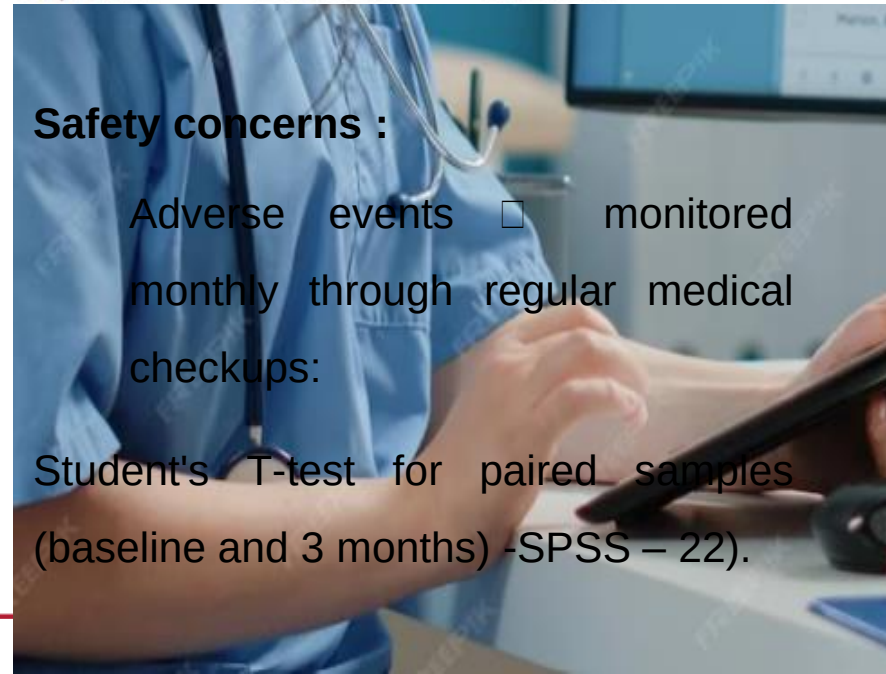
ATH-SGLT2i is **prospective observational study** from **September 2022 to June 2023** enrolling **SGLT2i naive patients** admitted for **acute coronary syndrome** that were prescribed **Dapagliflozin** driven by a **clinical indication (class I : HF / Secondary prevention in DT).**

- 2 groups according to their real intake of the treatment
- then to 4 subgroups taking into account also their diabetic status.

Endpoints included :

- **Flow Mediated Dilation (FMD) :** by the same operator according to the expert consensus recommendations for the assessment of FMD in humans [1], under fasting and non-smoking conditions in a temperature-controlled room after a 15 min rest
- **Carotid Intima Media Thickness (CIMT) :** Baseline and 3 months by the same operator using GE-E9L-D 10 MHz phased-array probe,
- **Lipid profile**





Safety concerns :

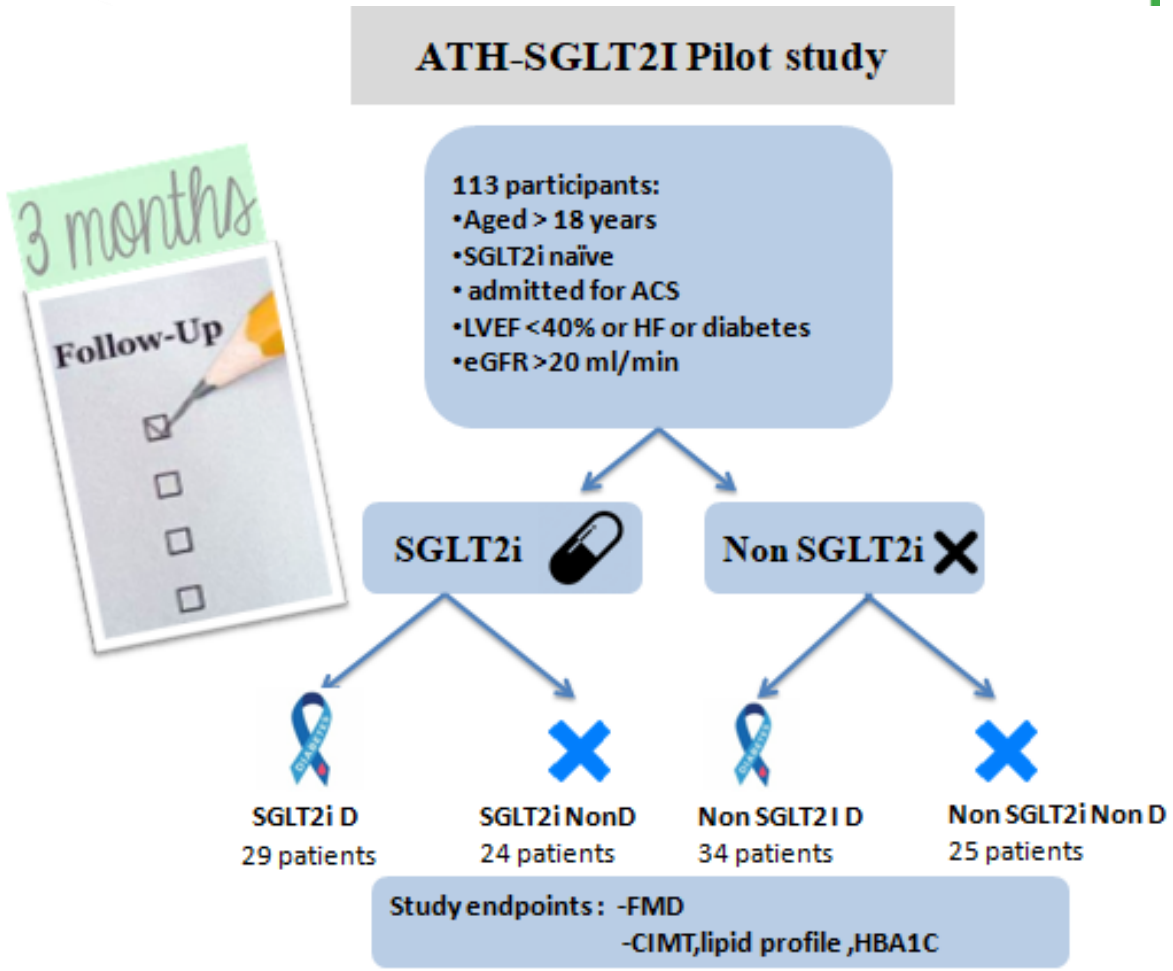
Adverse events monitored monthly through regular medical checkups:

Student's T-test for paired samples (baseline and 3 months) -SPSS – 22).

1.-Dick H J Thijssen et al., « Expert Consensus and Evidence-Based Recommendations for the Assessment of Flow-Mediated Dilation in Humans », *European Heart Journal* 40, nº 30 (7 août 2019): 2534-47, https://doi.org/10.1093/eurheartj/ehz350.

Results I

- A total of **133 patients** were enrolled, with a mean age of **60.9±10** years.
- Baseline characteristics showed :
  - a **predominantly male** population (84%) with varied **cardiovascular risk factors**.
  - **A significant difference** in **left ventricular ejection fraction** in SGLT2i compared to Non SGLT2i group.
  - **No significant differences** in **baseline atherosclerosis markers (FMD, CIMT)** in SGLT2i group compared to Non SGLT2i group.



Results II

- **In patients with no diabetes**, **Significant improvement in SGLT2i group while it deteriorated in non SGLT2i group** **in both subgroups of diabetes and non diabetes status patients** (Table 1).

Treatment with Dapagliflozin, FMD% was enhanced in both FMD and FMD%. This finding was observed in ... with a significant difference (p=0.008) (Table 3).

Table 3 : Comparison of change in FMD and FMD% between SGLT2iNonD and Non SGLT2iNonD, ATH-SGLT2i, Tunisia 2023

Table 1 : Comparison of change in FMD and FMD% between SGLT2i and Non SGLT2i , ATH-SGLT2i, Tunisia 2023

	SGLT2i Non D n=24	Non SGLT2i NonD n=25	P
ΔFMD	2.85±3.46	-0.25±4.33	**0.008**
ΔFMD% / ΔFMD	**1.72±1.04 / 1.08±1.63** (overlapping)	0.08±1.85 / -0.88±4 (overlapping)	**<0.001 / 0.001** (overlapping)

Table 2: Comparison of change in FMD and FMD% in SGLT2i patients : study of subgroups, Tunisia 2023

	SGLT2iD n=29	SGLT2i NonD n=24	P
ΔFMD%	0.31±1.26	0.9±1.19	0.09
ΔFMD	0.9±3.59	2.85±3.46	**0.04**

Δ: change from baseline,FMD: flow mediated dilation,FMD%:FMD rate,NonSGLT2i D : diabetic patients without Sodium Glucose cotransporter Inhibitors ,Non SGLT2i Non D : non diabetic patients without Sodium Glucose cotransporter2 Inhibitors .

- This **improvement** was significantly **higher in patients with no diabetes** in comparison with patients with diabetes within the SGLT2i group (Table 2).

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Results III

- CIMT wasn't significantly improved in SGLT2i group (Table 4).

Table 4: Comparison of CIMT change after 3 months between SLT2i intake and diabetic status subgroups, , ATH-SGLT2i, Tunisia 2023

CIMT	SGLT2i n=54		Non SGLT2i n=59		P- value
Δ CIMT (mm) mean±SD	-0.12 ± 1.03		-0.03 ± 1.31		0.7
	SGLT2i D *	**SGLT2i Non D ***	**Non SGLTi D****	**Non SGLT2i Non D ****	
	N=29	**N=24**	**N= 34**	**N=25**	
Δ CIMT (mm) mean±SD	-0.24 ± 0.8		-0.12 ± 0.73		0.38*
		0.02 ± 1.2		0.08 ±1.85	0.57**

Δ: change from baseline,CIMT: carotid intima-media thickness. SGLT2i: Sodium Glucose cotransporter inhibitors (group designation),D:diabetic (group designation).
p* probability value between SGLT2i subgroups
p** probability value between Non SGLT2i subgroups

- No statistical difference in **biological parameters**: TC, Triglycerides and HBA1C **between SGLT2i and Non SGLT2i groups**.

Discussion I

- **Atherosclerosis markers (FMD and FMD%) improved at 3 months in SGLT2i intake in comparison with patients who did not use SGLT2i :**
  - ✓ **EDIFIED study[1],** involving patients with an established ischemic disease who received 12 weeks of Dapagliflozin**. However : -** Patients were **not in the acute phase of CS**
    - All of them had **diabetes**
  - ✓ **DEFENCE study[2],** aiming to assess Dapagliflozin effect on endothelial function in early-stage diabetics FMD improvement in the subgroup with HBA1c >7%
    - Correlation between SGLT2i effect on FMD and glycemic control (HbA1c) (r=−0.4; p=0.017)

1. Fumika Shigiyama et al., « Effectiveness of Dapagliflozin on Vascular Endothelial Function and Glycemic Control in Patients with Early-Stage Type 2 Diabetes Mellitus: DEFENCE Study », Cardiovascular Diabetology 16, no 1 (décembre 2017): 84, https://doi.org/10.1186/s12933-017-0564-0.

1. Nur Aisyah Zainordin et al., « Effects of Dapagliflozin on Endothelial Dysfunction in Type 2 Diabetes With Established Ischemic Heart Disease (EDIFIED) », Journal of the Endocrine Society 4, no 1 (1 janvier 2020): bvz017, https://doi.org/10.1210/jendso/bvz017.

Discussion II

- **FMD% improvement was significantly higher in patients with no diabetes compared to patients with diabetes.**
- **In patients with no diabetes, FMD% was enhanced in SGLT2i group while it deteriorated in non SGLT2i group with a significant difference (p=0.008) :**

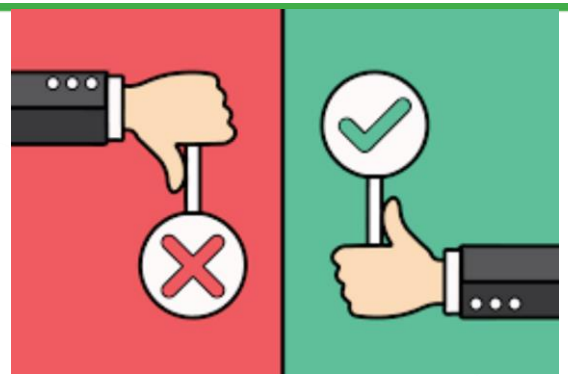
✓ Concerning **patients with no diabetes**, our study is to our knowledge, the first encompassing this specific population This finding did not corroborate previous studies on patients with diabetes [1].

However, it is supported by **preclinical studies :**

Alshnbari et al led, 2020 **Meta-analysis** [2] (including 24 studies using animals, vascular tissue, or vascular endothelial cells) in **both diabetic and non-diabetic models**.

 It suggested **direct underlying mechanisms of action of SGLT2i on endothelial function** independent of glucose-lowering effects.

1. Anna Solini et al., « Dapagliflozin Acutely Improves Endothelial Dysfunction, Reduces Aortic Stiffness and Renal Resistive Index in Type 2 Diabetic Patients: A Pilot Study », Cardiovascular Diabetology 16, no 1 (décembre 2017): 138, https://doi.org/10.1186/s12933-017-0621-8.
1. Alshnbari, A.S., Millar, S.A., O'Sullivan, S.E. et al. Effect of Sodium-Glucose Cotransporter-2 Inhibitors on Endothelial Function: A Systematic Review of Preclinical Studies. Diabetes Ther 11, 1947–1963 (2020). https://doi.org/10.1007/s13300-020-00885-zof



- **Observational design of the study**
- **A single-center study, small sample size**
- **Short duration of follow-up**

  The majority of experimental or clinical trials showed significant effects at 3 months

  The question remains whether **these effects** are **sustainable** in case of **SGLT2i continuation.**

✓ **Our study is to our knowledge, the first encompassing the specific population of patients with no diabetes, exploring effects of early initiation of SGLT2i** during **ACS**

✓ **New perspectives** Our insights suggest **promising new avenues for exploring the use of SGLT2 inhibitors** in patients with **acute coronary syndromes, independent of diabetic status,** to enhance **endothelial function and reduce atherosclerotic burden**

Nonetheless, before these preliminary findings can be translated into clinical practice, large-scale, randomized clinical trials are required.

Conclusions

Our study demonstrated that **early initiation of SGLT2i** during ACS leads to **significant improvements in EF**, as indicated by enhanced FMD and FMD%.

- Potential clinical **benefits of SGLT2i in addressing endothelial dysfunction among ACS patients**, irrespective of their diabetic status.

These insights suggest a promising avenue for enhancing public health strategies in **secondary prevention of cardiovascular diseases.**

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