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DOCTORAL THESIS

THE ROLE OF INFLAMMATION IN PERICORONARY EPICARDIAL ADIPOSE TISSUE IN THE PROGRESSION AND VULNERABILIZATION OF ATHEROSCLEROTIC PLAQUES

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- SUMMARY -

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1. BACKGROUND/INTRODUCTION

Cardiovascular diseases (CVDs) are the leading global cause of death, with ischemic heart disease and stroke accounting for the majority of cases. In Romania, CVDs contribute to over half of all mortalities, significantly exceeding the European average. Early detection and prevention are essential, yet current risk assessment tools based on traditional metrics often fail to identify high-risk individuals, particularly those with non-obstructive or subclinical coronary artery disease (CAD).

Cardiac computed tomography (CCT) has emerged as a gold-standard, non-invasive imaging tool, providing detailed insight into coronary anatomy, plaque composition, and the presence of high-risk features. However, conventional plaque evaluation based on luminal stenosis or calcium scoring has limitations, especially in detecting biologically active, inflammation-prone plaques.

Recent advances have enabled CCT to assess pericoronary adipose tissue (PCAT) inflammation via the Fat Attenuation Index (FAI)—a novel radiomic biomarker that reflects localized coronary inflammation. Elevated FAI is associated with vulnerable plaque characteristics and predicts adverse cardiovascular outcomes, even in patients with zero calcium scores. Moreover, FAI dynamically responds to interventions such as statin or anti-inflammatory therapy, making it a valuable tool for monitoring disease activity and treatment efficacy.

The relevance of inflammation-focused imaging has been further highlighted in the context of COVID-19, which is linked to persistent coronary inflammation and increased plaque vulnerability. Artificial intelligence (AI)-driven platforms like CaRi-Heart® have facilitated the integration of anatomical and inflammatory data into personalized risk prediction models.

2. STUDY OBJECTIVES

The aim of the thesis is to investigate the role of **PCAT inflammation** in the **progression and destabilization of atherosclerotic plaques**, **using CCT** and **radiomic analysis**—specifically the **FAI**—as non-invasive imaging biomarkers.

The thesis seeks to:

- Establish how local coronary inflammation, as assessed by FAI, correlates with **plaque vulnerability**, especially in **non-obstructive CAD**.
- Evaluate the **impact of systemic inflammatory conditions** (such as **COVID-19**) on coronary inflammation and plaque destabilization.
- Examine the **relationship between coronary artery calcium scores (CACs)**, plaque morphology, and inflammation.
- Assess the **effectiveness of high-dose statin therapy** in reducing pericoronary inflammation and stabilizing atherosclerotic plaques over time.
- Highlight the clinical **utility of AI-powered CCT platforms like CaRi-Heart®** for improving individualized risk prediction and preventive cardiology.

Overall, the thesis aims to support a paradigm shift from purely anatomical to inflammation-focused cardiovascular imaging, enabling early identification of high-risk individuals and more personalized therapeutic strategies.

3. MATERIAL AND METHODS

The research comprises a prospective, single-center observational study conducted at the Center for Advanced Research in Multimodality Cardiac Imaging, Cardiomed Medical Center in Târgu Mureș, Romania. **A total of 668 patients and approximately 2,000 coronary segments were included**, analyzed across three distinct substudies (summarized in Figure 1). All imaging was performed using 128-slice CCT.

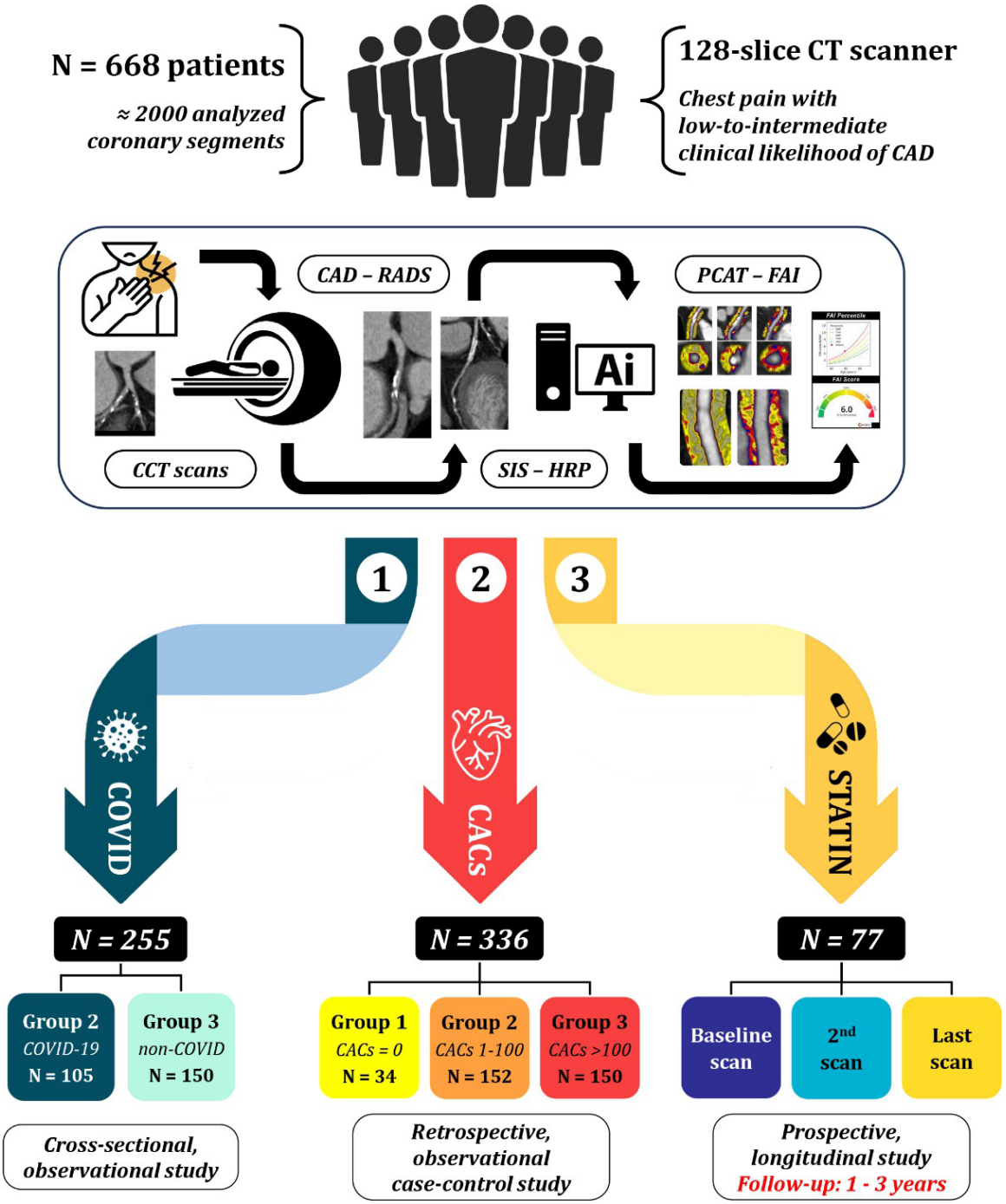

Figure 1. Schematic summary of the three substudies, illustrating patient selection, cohort distribution, imaging methods, and follow-up. All patients (N = 668) underwent 128-slice CCT for CAD assessment using CAD-RADS and AI-based pericoronary FAI analysis. **Substudy 1** (COVID study, N = 255) was cross-sectional; **Substudy 2** (CACs study, N = 336) was retrospective and stratified by CACs; **Substudy 3** (STATIN study, N = 77) was prospective with serial imaging over 1–3 years.

Substudy 1 – Post-COVID-19 Coronary Inflammation: (1) Design: Cross-sectional observational study; (2) Patients: 255 individuals with angina-like symptoms and low-to-intermediate pretest probability of CAD; (3) Stratification: COVID-19 recovered vs. non-infected control group; (4) Objective: Assess pericoronary inflammation via FAI using CaRi-Heart® AI platform; (5) Exclusion criteria: Extensive CACs (>1000), arrhythmias, obesity, non-cardiac chest pain, prior MI, ACS requiring intervention.

Substudy 2 – CACs and Plaque Vulnerability: (1) Design: Retrospective, case-control study (part of the INTEL-FAT project); (2) Patients: 336 adults with no prior cardiovascular disease; (3) Groups: Stratified into CACs = 0, 1–100, and >100; (4) Objective: Analyze the link between calcium scores, high-risk plaque (HRP) features, and FAI; (5) Exclusion criteria: Known CAD, diabetes, prior PCI/CABG, ACS, poor imaging quality.

Substudy 3 – Long-term Statin Impact on Inflammation: (1) Design: Prospective, longitudinal study; (2) Patients: 77 individuals with non-obstructive CAD and low-to-intermediate risk, followed over 1–3 years; (3) Objective: Evaluate effects of high-dose statin therapy on PCAT inflammation and plaque stabilization; (4) Imaging: Serial CCT and FAI analysis using CaRi-Heart®; (5) Exclusion criteria: Prior statin therapy, poor image quality, revascularization, comorbidities.

4. RESULTS

In a cohort of 668 patients, CCT combined with AI-powered pericoronary FAI analysis revealed robust associations between coronary inflammation, plaque morphology, and risk phenotypes. The findings confirm that FAI serves as a dynamic imaging biomarker of local vascular inflammation, capable of identifying biologically active and vulnerable plaques even in non-obstructive or low-CAC settings. Using the CaRi-Heart® platform, radiomic-derived inflammatory metrics provided novel insight into the interplay between systemic conditions, plaque biology, and therapeutic modulation.

Substudy 1 – Post-COVID-19 Coronary Inflammation

Patients with prior SARS-CoV-2 infection exhibited persistently elevated coronary inflammation, with significantly higher FAI-Score centiles across all major coronary arteries. The LAD, LCX, and RCA all showed increases, with the RCA consistently demonstrating the highest inflammatory activity. This regional pattern was particularly pronounced in post-COVID patients, suggesting that the RCA may be more vulnerable to inflammation-driven atherosclerosis in this setting.

Substudy 2 – CACs and Plaque Vulnerability

Despite a low to intermediate pre-test probability of CAD, patients across all CAC categories exhibited evidence of subclinical atherosclerosis and high-risk plaque features. Notably, 10.9% of CAC = 0 patients already had vulnerable plaque characteristics, with prevalence increasing steeply alongside higher calcium burden. CaRi-Heart® risk stratification reclassified a subset of CAC = 0 patients as high risk, highlighting the presence of biologically active disease even in the absence of calcification and underscoring the added value of AI-driven imaging for refining cardiovascular risk.

Substudy 3 – Long-term Statin Impact on Inflammation

Longitudinal follow-up demonstrated that high-dose statin therapy exerted both anti-inflammatory and plaque-stabilizing effects. FAI-Score values declined significantly across all coronary territories, accompanied by compositional changes in plaques from lipid-rich toward more fibrotic and calcified phenotypes. Correlation analysis confirmed strong links between perivascular inflammation and vulnerable plaque components, reinforcing the role of FAI as a biomarker of disease activity and therapeutic response.

5. GENERAL DISCUSSION

This This thesis examined the interplay between coronary inflammation, plaque vulnerability, and the effects of statin therapy using high-resolution CCT with AI-based radiomic analysis. The FAI proved to be a non-invasive marker of pericoronary inflammation, linking imaging with the biological activity of atherosclerosis. The substudies showed that post-COVID-19 patients display persistent coronary inflammation even without significant stenosis, that vulnerable plaque features can be present despite zero CAC, and that high-dose statins reduce FAI values while promoting a shift toward more stable plaque morphology.

Together these findings highlight the diagnostic and prognostic value of inflammation-sensitive imaging and support moving beyond traditional metrics toward integrated anatomical and functional assessment. AI-driven tools such as CaRi-Heart® may allow earlier identification of high-risk patients and personalized therapeutic strategies. Limitations include the single-center observational design, modest sample sizes, lack of invasive validation, and a follow-up limited to three years, underscoring the need for larger prospective multicenter studies.

6. GENERAL CONCLUSIONS

This research confirms that coronary inflammation plays a central role in atherosclerotic plaque destabilization and that FAI is a consistent non-invasive marker of vascular risk. Persistent post-COVID-19 coronary inflammation, vulnerable plaques in patients with minimal or no CAC, and statin-induced reductions in FAI collectively demonstrate the importance of incorporating biological markers into cardiovascular risk stratification. These results advocate for an inflammation-centered approach to CCT interpretation, paving the way for precision cardiology supported by AI-enhanced platforms.

7. THE ORIGINALITY OF THE THESIS

The originality of this work lies in applying AI-driven CCT analysis to quantify coronary inflammation and demonstrate its relevance in post-COVID-19 patients, in individuals with zero CAC, and during longitudinal statin therapy. By showing that FAI detects biologically active plaques overlooked by traditional calcium scoring and that therapy can shift plaque biology toward stability, this thesis bridges pathophysiology with clinical application. It contributes novel evidence supporting inflammation-targeted imaging as a cornerstone of future precision cardiology.