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Lessons from the trials

# Diabetes and silent atrial fibrillation: A dangerous liaison?

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## ABSTRACT

Diabetic patients have higher risk of stroke when compared to non-diabetics and in 25% of patients the cause of stroke is unknown. Marfella et al hypothesized that subclinical episodes of atrial fibrillation may be a common etiologic factor. 464 type-2 diabetic patients were compared to 240 health controls and were followed-up for 37 months. Silent cerebral infarcts at baseline were more common among diabetic patients with silent AF (176 patients) when compared to non-silent AF group (288 patients) (61% vs. 29%;  $p < 0.001$ ) and was associated with higher number of stroke at follow-up.

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## INTRODUCTION

Patients with diabetes mellitus (DM) have increased risk of stroke compared with those without DM and in one quarter of these patients the cause of stroke is unknown.<sup>1</sup> DM is also an independent determinant of AF, and diabetic patients frequently have asymptomatic (e.g., silent) AF.<sup>2-3</sup> Marfella et al<sup>4</sup> hypothesized that subclinical episodes of AF may be common etiologic factor in these patients.

## THE STUDY

The study was conducted in 4 institutions (1 clinic, 2 hospitals, and 1 outpatient clinic) in Italy and the recruitment period was 4 years (from January 1, 2005, to January 1, 2009). Patients were subsequently followed-up for 3 years. The inclusion criteria were; age < 60 years, successful quarterly 48-h electrocardiographic (ECG) Holter monitoring (48HM), and assessment of the presence/absence of SCI by magnetic resonance imaging (MRI) of the brain. The exclusion criteria at initial diagnosis were; arrhythmia, documented persistent and/or permanent AF, documented stroke or transient ischemic attack, anti-coagulation therapy, coronary artery or valvular heart disease, cardiomyopathy, history of congestive heart failure, hypertension, carotid and peripheral vascular disease, hyperthyroidism, chronic obstructive pulmonary disease, obstructive sleep apnea, and hepatic damage.

Of the 1992 diabetic patients initially screened for the study only 464 met the inclusion criteria and were compared to 240 healthy subjects without diabetes (control group). All selected patients underwent 48-h ambulatory ECG recording at 3, 6, 9, and 12 months during the screening for AF and then annually for another 3 years. Baseline AF was classified as episode, paroxysmal, persistent, or permanent. Silent (i.e., asymptomatic) AF may present as any of the temporal forms of AF. Patients were sub-classified according to the presence of silent episodes of AF (SAFE group) and the absence of silent episodes of AF (non-SAFE group).

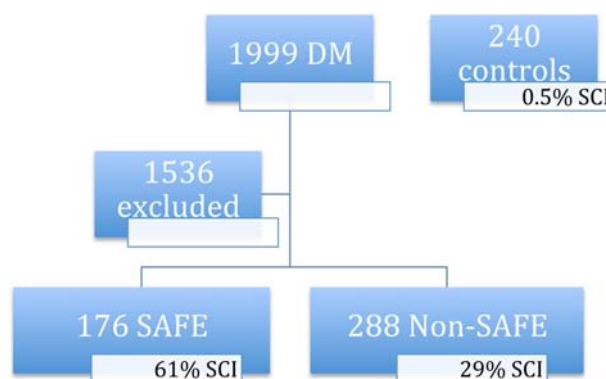
In all patients, MRI of the brain was performed within 30 days of the baseline 48HM. Silent cerebral infarct (SCI) was defined as a low signal intensity area on T<sub>1</sub>-weighted images that was also visible as a hyperintense lesion on T<sub>2</sub>-weighted images. All SCIs detected were lacunar infarcts with a size of < 15 mm. During the follow-up visits, 48HM rhythm documentation and documentation of clinical data as well as complications were performed. All patients were treated with aspirin 75 to 325 mg/day; if the CHADS<sub>2</sub> (congestive heart failure, hypertension, Age  $\geq$  75 years, diabetes mellitus, previous stroke/transient ischemic attack) score was  $\geq$  2, antiplatelet therapy was switched to oral anticoagulation therapy. Stroke events were diagnosed by the physician who was caring for the patient at the time of the event, on the basis of sudden onset of a neurological deficit that persisted for > 24 h in the absence of any other disease process that could explain the symptom. By design, therapeutic options were not evaluated.

## RESULTS

Cumulative quarterly 48HM (192 h for each patient) showed a greater prevalence of subclinical episodes of AF among patients with diabetes (n = 1,992) compared with matched healthy subjects (n = 240) (11% vs. 1.6%; p < 0.001). Of the 1,992 patients patients with type 2 diabetes screened, 176 (9%) met the inclusion criteria for silent episodes of AF (SAFE group), whereas 288 (15%) met the inclusion criteria for only clinical characteristics (non-SAFE group).

No significant differences in clinical and anthropometric characteristics were found between the study groups. Aspirin was used by 99% of the diabetic patients in both the SAFE and non-SAFE groups and 10% of the subjects in the control group, and none of the patients were being treated with a vitamin K antagonist at baseline. SCI was detected in 190 diabetic patients (41%) and only 1 healthy subject (0.5%). On MRI examination, SCI was more frequently detected in the SAFE group than in the non-SAFE group (61% vs. 29%; p < 0.01) (See [Figure 1](#)). Moreover, the absolute burden of AF was significantly correlated with both size (r = 0.574; p < 0.001) and number of SCIs (r = 0.591; p < 0.001).

After a mean follow-up period of 37.5  $\pm$  1.6 months, clinical AF developed in 20 patients (11%) with silent episodes of AF compared with only 13 patients (4%) without silent episodes of AF (p < 0.01). All patients with clinical AF were excluded from follow-up analysis. No AF was diagnosed in healthy subjects. Therefore, the stroke follow-up was performed in 156 patients in the SAFE group and 275 patients in the non-SAFE group. Over the course of the follow-up period, 26 patients in the SAFE group (15%) and 19 (7%) in the non-SAFE group were treated with a vitamin K antagonist, including 33



**Figure 1. A flow chart of patient selection and their risk of silent cerebral infarct (SCI).**

patients who had developed clinical AF. Despite the use of antiplatelet agents and a vitamin K antagonist, 43 stroke events occurred during follow-up. The cumulative percent of stroke-free survival was significantly lower in patients in the SAFE group. After  $37.5 \pm 1.6$  months, ischemic stroke developed in 27 patients in the SAFE group (17.3%) compared with 16 patients in the non-SAFE group (5.9%) ( $p < 0.01$ ).

Cox regression analysis revealed that the presence of silent episodes of AF (HR: 4.6; 95% CI: 2.7 to 9.1;  $p < 0.001$ ), systolic blood pressure (HR: 1.7; 95% CI: 1.02 to 2.92;  $p < 0.01$ ), and prevalence of SCI (HR: 3.1; 95% CI: 1.3 to 7.1;  $p < 0.005$ ) were associated with risk of stroke, whereas there were no significant other confounders (sex, body mass index, diastolic blood pressure, duration of diabetes, plasma glucose level, hemoglobin A<sub>1c</sub>, interventricular septum, and hyperlipidemia). Of the 43 stroke events, 42 were ischemic and 1 was hemorrhagic.

## DISCUSSION

The current study demonstrated that type 2 diabetic patients younger than 60 years and without clinical AF had high incidence of subclinical brief episodes of AF and the presence of these episodes was associated with an increased risk of SCI as well as the subsequent development of stroke independent of duration of diabetes and target organ damage. Moreover, the risk of SCI was higher when subclinical episodes of AF were of longer duration, as evidenced by a positive correlation between AF burden and SCI.

According to the investigators, the presence of SCI increased the risk of subsequent stroke by 2-4 times in the general population, independently of cardiovascular risk factors and suggested considering SCI as the most important diabetic target organ damage marker for stroke. In light of the data presented here, the investigators suggested that silent brain infarcts should not be considered just intermediates in the relationship between vascular risk factors and the risk of stroke but markers for other factors, such as brief episodes of AF, that lead to stroke. The investigators outlined some of the limitations of the study; first even if standardized recording technique were used, it is possible that many silent episodes of AF were missed. This could explain the relatively high risk of cerebrovascular events in those patients without documented AF.

In an accompanying editorial by Prystowsky and Padanilam<sup>5</sup> a number of issues were raised; first it was not clear from the study why a much lower percent of patients in the entire diabetic cohort (who had higher risk factors for the development of AF) had silent AF compared with those who met the study criteria (11% vs. 38%). Second; while the 11% incidence of subclinical AF is high, it is almost certainly an underestimation due to the intermittent nature of the monitoring for arrhythmia. Third, although the high prevalence of SCIs in the SAFE group may be readily attributed to AF, the non-SAFE group also had a relatively high prevalence of SCIs and they suggested that it is possible that SCIs could be unrelated to AF events in either population. They suggested that future studies of AF should evaluate SCI as end point.

This findings of this study if proven in larger studies will have major implications for the management of patients as diabetes mellitus is extremely common world wide and more so in the Middle east. In the Qatar Family Health Survey conducted in 1998, the overall incidence of DM was over 5% and it was

about 8% in those aged 15 years and older. This high incidence escalates with increasing age and was over 16% of those between the age of 40 and 49 years and over 28% in those 50 years and older.<sup>6</sup>

#### WHAT WE HAVE LEARNED?

Recently there has been increased interest in research in atrial fibrillation, specifically AF ablation and newer anticoagulants agents,<sup>7,8</sup> the current study highlights the importance of research in subclinical atrial fibrillation. Subclinical atrial fibrillation is common among patients with type-2 diabetes and may be a cause of subclinical and clinical cerebral infarctions. The findings of the current study if confirmed will result in significant changes in clinical practice, further research in a large sample of populations and perhaps the use of continuous monitoring rather intermittent monitoring for AF such as the use of implantable loop recorder are needed to overcome the limitations of the current study.

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