

# The detection and treatment of subclinical atrial fibrillation: evaluating the IMPACT of a comprehensive strategy based on remote arrhythmia monitoring

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**This editorial refers to ‘Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices’<sup>†</sup>, by D.T. Martin et al., on page 1660.**

Atrial fibrillation (AF) is the most common clinical arrhythmia, which is responsible for at least 15% of all strokes, and is the leading cause of stroke among patients >75 years old.<sup>1</sup> Moreover, strokes due to AF are largely avoidable, as the use of oral anticoagulants (OACs),<sup>2,3</sup> along with the diagnosis and treatment of hypertension,<sup>4</sup> can prevent >65% of all strokes. The results of large cohort studies in pacemaker patients demonstrate that AF is frequently ‘subclinical’ (either asymptomatic or which evades clinical detection),<sup>5,6</sup> suggesting that the true burden of AF in patients over the age of 65 years is much greater than previously appreciated. These studies also show that subclinical AF (Figure 1) is associated with up to a 2.5-fold increase in the risk of stroke,<sup>5,7</sup> highlighting the importance of recognizing this condition in patients with pacemakers and implantable cardioverter defibrillators (ICDs).

Martin and colleagues now present the results of the IMPACT trial,<sup>8</sup> a 2718 patient, prospective randomized trial that evaluated a strategy to diagnose and manage patients with ICD-detected AF, in patients without contraindications to OACs. Although the patient population was broad and simply defined, the intervention studied by the investigators was quite complex. Patients in the intervention arm of IMPACT had continuous home monitoring of their Biotronik defibrillators for the detection of AF lasting >36 out of 48 consecutive beats, and at an atrial rate of at least 200/min. The initiation and subsequent withdrawal of OACs was then guided by the patients’ CHADS<sub>2</sub> score, the burden of AF, and the time since the last AF

episode. In patients with a CHADS<sub>2</sub> score of 1 or 2, an OAC was started if the burden of AF was ≥48 h over two consecutive days, while the burden needed to be only 24 h over 2 days in patients with a CHADS<sub>2</sub> score of 3 or 4. In patients with a prior stroke or embolism, any duration of AF triggered the initiation of an oral OAC. This latter group of patients continued OACs indefinitely, while OACs were to be withdrawn if no AF recurred for 30 days in patients with a CHADS<sub>2</sub> score of 1 or 2, and 90 days for those with a CHADS<sub>2</sub> score of 3 or 4. Investigators were free to use any OAC approved for use in patients with AF; ~80% of OAC-treated patients received vitamin K antagonists and 20% received direct OACs. Patients were followed for a median of 2 years, for the composite primary outcome of stroke, systemic embolism, and major bleeding.

The IMPACT trial was prematurely terminated for futility, after 63 primary events among 1357 patients in the intervention arm and 61 events among 1361 patients in the control arm; hazard ratio (HR) 1.06,  $P = 0.73$ .<sup>8</sup> Although this is a neutral result, there were non-significant trends for fewer ischaemic strokes [HR 0.79; 95% confidence interval (CI) 0.45–1.39] and more major bleeds (HR 1.39; 95% CI 0.89–2.17) in the intervention arm.<sup>8</sup> Overall, IMPACT failed to demonstrate a reduction in stroke and bleeding complications in ICD patients managed with a strategy of remote monitoring for subclinical AF, coupled with a risk-based algorithm for OAC initiation and maintenance. However, IMPACT has several design features which preclude any definitive statements regarding the viability of an AF monitoring and treatment strategy in this population.

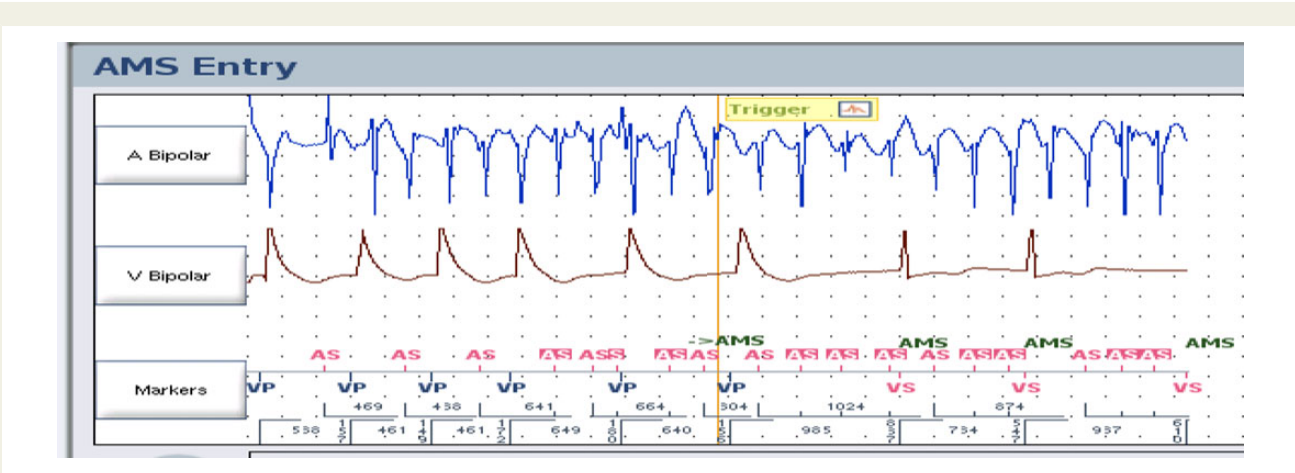
One important issue with the IMPACT trial was the use of a composite primary outcome which included both stroke and major bleeding. The goal of remote monitoring was to increase the use of OACs for ICD-detected AF, a therapy which has been shown to

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**Figure 1** Atrial fibrillation detected by a dual-chamber pacemaker.

**Table 1** Components of the atrial fibrillation detection and treatment strategy in the intervention arm of IMPACT

Component	Issues with component
Reliable detection of AF by the ICD	This component appears well validated in numerous studies <sup>5,6</sup>
Identification of AF via ICD remote monitoring leads to appropriate physician prescription of an OAC	In IMPACT, the identification of AF using remote monitoring led to a modest increase in OAC use among patients in the study's intervention arm (72% vs. 60% of protocol-indicated patients) <sup>8</sup>
Remote monitoring reduces the time to physician intervention	Although time to OAC initiation was reduced in the intervention arm (3 vs. 54 days), data from ASSERT suggest that stroke risk is not increased for several months after the initial detection of subclinical AF, <sup>5</sup> calling into question the benefits of reducing the time to treatment initiation
Treatment of ICD-detected, subclinical AF prevents stroke, and does so to a similar extent as in clinical AF	Virtually all randomized trials which established the value of OAC in AF patients excluded patients with subclinical AF detected via long-term continuous monitoring. <sup>2,3</sup> The treatment effect of an OAC for subclinical AF is assumed
Withdrawal of an OAC after an AF-free interval is safe; associated with fewer major bleeds and no excess of stroke	Data from TRENDS, ASSERT, and IMPACT suggest that in most cases, AF is not temporally associated with stroke, <sup>7,9</sup> suggesting a strategy of OAC withdrawal may not be prudent

AF, atrial fibrillation; ICD, implantable cardioverter defibrillator; OAC, oral anticoagulant.

reduce stroke in patients with clinical AF, but at a cost of increasing bleeding.<sup>2</sup> Although the use of a composite primary outcome was desirable given the low stroke rates seen in early pacemaker and ICD studies of subclinical AF,<sup>5,6</sup> the use of an OAC would be expected (and was observed) to reduce one component of this composite (stroke) while increasing another (major bleed). Thus, the components of the composite outcome offset each other, contributing to the neutral overall result.

The intervention evaluated in IMPACT was not simply the use of OACs to treat subclinical AF, but rather a comprehensive and complex strategy of AF monitoring and treatment. In retrospect, it was ambitious to evaluate this strategy in its entirety, as its success was dependent on the success of several individual components (Table 1), some of which were based on unproven assumptions. Over 25% of patients in IMPACT developed AF meeting protocol criteria for an OAC; however, in the intervention arm there was only a modest increase in the use of an OAC, in large part due to the very high use of OACs (60%) in control group patients with AF.<sup>8</sup> Although

the use of remote monitoring reduced the time to OAC initiation by >50 days,<sup>8</sup> this produced a rather modest increase in the number of patient-years of OAC treatment in the intervention arm. Furthermore, data from ASSERT suggest that the risk of stroke may not go up for several months after subclinical AF is first detected,<sup>5</sup> calling into question the value of such rapid initiation of an OAC. Finally, data from both TRENDS and ASSERT suggest that in the majority of cases of subclinical AF-associated stroke, no AF occurs within 1–3 months of the stroke.<sup>7,9</sup> These data challenge IMPACT's strategy of OAC withdrawal after an AF-free interval. In fact, data from IMPACT reveal that for 3 of the 29 patients with AF-associated stroke, previously initiated OAC was withdrawn in the 6 months prior to their stroke.<sup>8</sup>

Finally, it is an assumption that OACs prevent stroke in patients with subclinical AF detected by long-term continuous monitoring to a similar extent as in clinically diagnosed AF. The pacemaker cohort studies suggest that after adjustment for clinical stroke risk factors, subclinical AF is associated with a lower absolute stroke

risk than is observed with clinical AF.<sup>2,3,5,6</sup> Furthermore, it appears that in some cases, subclinical AF may act as a stroke risk marker, given the lack of a temporal relationship between subclinical AF and stroke,<sup>7,9</sup> and the observation that subclinical atrial arrhythmias lasting as briefly as 20 beats are associated with an increase in stroke risk.<sup>10</sup> As OACs carry an important risk of major bleeding, it is critical that we directly evaluate the value of this therapy among patients with subclinical AF. The ARTESiA trial (NCT 01938248) has just begun, and is randomizing patients with cardiac device-detected subclinical AF to receive apixaban vs. aspirin, and will continue for ~4 years to evaluate the primary outcome of ischaemic stroke and systemic embolism.

The IMPACT study highlights the challenges of conducting long-term trials in rapidly evolving fields. In the years following the design and initiation of IMPACT,<sup>11</sup> we not only witnessed the introduction of the direct-acting OACs, but also observed an evolution in our understanding of the relationship between subclinical AF and stroke.<sup>5–7,9,10</sup> The investigators should be commended for their tenacity in completing the trial, and, although it ultimately had a neutral result, it provides important insights and corroborates some of our new thinking on this topic. With the recent explosion in the number of technologies available for the detection of AF in the general population,<sup>12,13</sup> we need more studies in this area, so that we can learn how to best use AF detection technologies to prevent stroke.

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