Zio® System Publications

Peer-reviewed publications demonstrating the clinical validity and utility of the Zio system

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Steinhubl, S., et al. **Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation: The mSToPS Randomized Clinical Trial.** *JAMA, 2018.*

Keywords: Atrial Fibrillation, Silent AF, Screening, Targeted Detection, Suspect AF, Asymptomatic

Using the Zio system, researchers at the Scripps Translational Science Institute (STSI) launched a pragmatic, prospective, randomized clinical trial aimed at determining whether a wearable ECG patch can improve the diagnosis of atrial fibrillation relative to routine care. A partnership between STSI, Aetna (payer), Janssen Pharmaceuticals and iRhythm Technologies, Inc.

- 2659 individuals at increased risk for AF were identified using Aetna claims data. This group was randomized to immediate monitoring using the Zio monitor or delayed monitoring by 4 months. These individuals showed no symptoms (asymptomatic) and were not diagnosed with AF.
- At 4 months, Zio monitoring led to a significantly higher rate of AF diagnosis (3.9%) vs. those who received routine care (0.9%).
- At 1 year, Zio monitoring led to a significantly higher rate of AF diagnosis (6.7%) vs. those who received routine care (2.6%).
- Zio monitoring also detected other actionable arrhythmias, including ventricular tachycardia (VT), pause, AV block and symptomatic supraventricular tachycardia (SVT).
- Active monitoring was associated with the increased initiation of anticoagulants (5.7%), antiarrhythmic medication (0.8%) and new pacemakers (0.8%).

Among individuals at increased risk for AF, use of a wearable ECG patch facilitated AF diagnosis.

Reed, MJ., et al. **Diagnostic yield of an ambulatory patch monitor in patients with unexplained syncope after initial evaluation in the emergency department: the PATCH-ED study.** *Emergency Medicine Journal, 2018.*

Keywords: Atrial Fibrillation, Syncope, ED, Emergency, Diagnostic Yield

Diagnosing underlying arrhythmias in emergency department (ED) syncope patients is problematic and difficult. Many patients wait for months for tests that commonly fail to detect the underlying cause for the syncopal episode. This study investigated the diagnostic yield, prevalence, patient satisfaction and compliance of an ambulatory patch monitor in ED patients with unexplained syncope.

- A prospective study conducted over two years, recruited 86 patients.
- Patients were >16 years old, presented with unexplained syncope and within 6 hours were given Zio XT and monitored for 14 days.
- Primary endpoint was symptomatic significant arrhythmia at 90-day follow-up.
- At 90 days, Zio XT detected 10.5% arrhythmias vs. 2.0% in control group.
- Of the detected, 27.9% (24 patients) had significant arrhythmias, of which 5 were serious. *(cont'd on the next page)*

- Of the detected, 30.2% (26 patients) had serious outcomes (major adverse events and/or death).
- Diagnostic finding was 73.7% within ± 45s of a triggered event and 61% for sinus rhythm or ectopic beats only.

This study showed that early ambulatory monitoring in ED patients with unexplained syncope is likely warranted and has the potential to change current management of syncope patients. The Zio XT monitor has the potential to reduce hospital admissions and change first-line monitoring devices from low diagnostic yield to higher yield. Early diagnosis can lead to early treatment thereby reducing morbidity and increasing quality of life.

Go, AS., et al. **Association of Burden of Atrial Fibrillation With Risk of Ischemic Stroke in Adults With Paroxysmal Atrial Fibrillation: The KP-RHYTHM Study.** *JAMA Cardiology, 2018.*

Keywords: Atrial Fibrillation, AF Burden, Stroke Risk, Paroxysmal AF, PAF

Atrial fibrillation is a potent risk factor for stroke, but whether the burden of AF in patients with paroxysmal AF independently influences the risk of thromboembolism (TE) remains unclear. Researchers at Kaiser-Permanente conducted a retrospective study of patients who were monitored with Zio to determine if an association exists between AF burden and the risk of ischemic stroke and other TE in PAF individuals.

- AF burden was defined as the percentage of analyzable wear time in atrial fibrillation or flutter during the up-to-14-day monitoring period.
- In a cohort of 1,965 adults with PAF, AF burden greater than 11.4% led to a more than three-fold increase of stroke or TE events. This is while the PAF individuals were not on anticoagulants.
- Data showed no association between the duration of the longest AF episode and the risk of stroke.
- Other standard risk scores (CHA_2DS_2-VASc, ATRIA) were also not associated with the risk of stroke.
- The median wear time of the Zio monitor was 14 days.

Characterizing AF burden in PAF patients could assist patients and physicians in having a more informed, shared decision-making discussion about stroke prevention strategies, including the initiation of anticoagulants.

Muse, ED., et al. **Validation of a genetic risk score for atrial fibrillation: A prospective multicenter cohort study.** *PLOS Medicine, 2018.*

Keywords: Atrial Fibrillation, Stroke Risk, Genetics, Risk Score

Atrial fibrillation is a common heart rhythm disorder that can lead to devastating strokes. Clinical factors such as age, blood pressure and obesity can increase likelihood of developing AF, and several genetic determinants of AF also play a role. Researchers assessed whether a genetic risk score (GRS) can be used to better identify patients at the highest risk for developing AF.

- Individuals >40 years old with at least 1 clinical risk factor for AF presenting with either symptoms of AF or with the first diagnosis of AF on ECG were included in the study.
- Individuals were monitored by patch-based or long-term Holter monitors for up to 2 weeks.
- Blood samples were taken and DNA isolated. An AF genetic risk score (GRS) was calculated for each participant.
- Found that individuals with the highest AF GRSs were 3x more likely to be diagnosed with AF than those with the lowest AF GRSs.

This study showed that genetic risk factors could be incorporated into the overall risk assessment strategy to better identify AF in individuals with the highest risk of developing AF. This may also be helpful for patients with stroke from an unknown origin. In the future, genomic risk information may be useful in helping to prevent arrhythmia from occurring.

Verba, S.D., Jensen, B.T. and Lynn, J.S. **Electrocardiographic Responses to Deer Hunting in Men and Women.** *Wilderness & Environmental Medicine, 2016*

Keywords: Arrhythmia detection during exercise

Deer hunting includes various stimuli resulting in augmented sympathetic activity, increased heart rate (HR) response and rhythm changes. Collectively, these superimposed stresses may increase an individual's risk for cardiovascular events. Utilizing the Zio system, this study evaluates HR and rhythm responses in multiple phases of deer hunting in men and women with and without cardiovascular disease (CVD).

- Nineteen participants, 6 female, age 38.3 ± 13.8 years (mean ± SD) with body mass index 29.2 ± 6.9 kg/m^2 followed their normal hunting routine.
- Three hunters recorded HR ≥85% of their age-predicted heart rate maximum (HRmax) for 1 to 2 minutes.
- Arrhythmias were detected in both participants with CVD and in 8 without CVD: premature atrial, junctional and ventricular complexes.
- Fifteen of 19 hunters experienced "buck fever" (acute extreme excitation), with 7 reaching ≥85% HRmax for up to 1 minute.
- The unobtrusive profile of the device resulted in high subject compliance and device adherence during all phases of the hunt. The HRs and ECG recordings had good signal quality for analysis.

Men and women with and without CVD recorded substantial increases in HR and clinically relevant arrhythmias while deer hunting.

Steinhubl, S., et al. **Rationale and design of a home-based trial using wearable sensors to detect asymptomatic atrial fibrillation in a targeted population: The mHealth Screening To Prevent Strokes (mSToPS) trial.** *American Heart Journal, 2016*

Keywords: Atrial Fibrillation, Silent AFib Screening

Researchers at the Scripps Translational Science Institute (STSI) have launched a home-based clinical trial using the Zio system to identify patients with asymptomatic atrial fibrillation (AFib).

- The mSToPS clinical trial aims to determine whether screening select individuals in their homes using wearable sensor technology can detect asymptomatic AFib more efficiently than routine care, such as primary care visits.
- To conduct the study, STSI has teamed with iRhythm, Aetna's Innovation Labs and Healthagen Outcomes units, Janssen Pharmaceuticals and Amiigo consumer heart rate tracker.
- 2,100 active monitoring participants will be compared to 4,000 usual care beneficiaries.
- Participants will undergo continuous single-lead ECG monitoring using the Zio XT monitor for the first two weeks and last two weeks of the four-month monitoring period.

Olivotto, I., et al. **A Novel Approach Targeting the Complex Pathophysiology of Hypertrophic Cardiomyopathy: Designing the Late Sodium Current Inhibition with Eleclazine on Exercise Capacity in Subjects with Symptomatic HCM (LIBERTY-HCM) Trial.** *Circulation: Heart Failure, 2016*

Keywords: Drug Trials, Heart Failure and Arrhythmia Detection

This publication is a methods paper describing how the clinical trial for Gilead's investigational drug Eleclazine will progress.

- Hypertrophic Cardiomyopathy (HCM) is complex and not well understood. As HCM progresses, there are a number of potentially serious health consequences that occur, including diastolic heart failure, microvascular dysfunction, atrial fibrillation (AFib) and sudden cardiac death.
- Extended cardiac monitoring with the Zio system allows researchers to capture additional relevant information. This may help better determine the pathophysiology of HCM and advance the development of investigational treatment options to address a significant unmet medical need.

Chen, L., et al. **Persistent but not Paroxysmal Atrial Fibrillation Is Independently Associated With Lower Cognitive Function: ARIC Study.** *Journal of the American College of Cardiology, 2016*

Keywords: AFib Burden and Cognition, Atrial Fibrillation

Study results showed an association between a high burden of atrial fibrillation (AFib) and lower cognitive function. Previous studies have shown a relationship between AFib, cognitive decline and increased risk of dementia. However, this study demonstrates a correlation between high AFib burden — the percent of time a person has AFib — and cognition.

- The study was based on 325 participants from the Atherosclerosis Risk in Communities (ARIC) Study who wore the Zio monitor.
- Compared with participants who did not have AFib, participants with AFib burden of 100% (persistent AFib) had lower Animal Naming (AN), Trail Making Test part B and Digit Span Backwards (DSB) scores. These are standard cognitive assessment tests.
- By contrast, participants with an AFib burden of 1% to 6% did not have lower cognitive test scores than those without AFib.

Solomon, M., et al. **Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring.** *BMC Cardiovascular Disorders, 2016*

Keywords: Zio System, Arrhythmia Detection, High Risk Arrhythmias

Kaiser researchers examined 128,401 episodes of monitoring between October 2011 and 2013 using iRhythm's Zio system, for which the average monitor wear time was nearly 10 days and more than one quarter were worn for 14 days.

- 18.3% of recordings had at least one episode of non-sustained ventricular tachycardia (NSVT), 0.2% with sustained VT, 1.4% with a sinus pause >3 seconds (SP), 0.4% with a pause during atrial fibrillation >5 seconds (AFP) and 1.2% with high-grade heart block (HGHB).
- Median time to first arrhythmia: 74 hours for NSVT, 22 hours for sustained VT, 22 hours for SP, 31 hours for AFP and 40 hours for HGHB.
- A significant percentage of potentially high-risk arrhythmias were not identified within 48 hours of ambulatory ECG monitoring. Longer-term continuous ambulatory ECG monitoring provides incremental detection of these potentially clinically relevant events.

Fung, E., et al. **Electrocardiographic Patch Devices and Contemporary Wireless Cardiac Monitoring.** *Frontiers in Physiology, 2015*

Keywords: Atrial Fibrillation, Long Term Continuous ECG Monitoring

Adhesive ECG patch devices are becoming the standard for detecting arrhythmias in the outpatient setting when short- to medium-term monitoring is indicated. These cardiac devices and related digital mobile health technologies are reshaping the clinician-patient interface with important implications for future healthcare delivery.

- Studies highlight the challenges in diagnosing atrial fibrillation (AFib) with conventional monitoring even in relatively high arrhythmia burden patients with paroxysms. Studies support the use of prolonged ECG monitoring in most patients suspected to have atrial arrhythmia(s) and/or neurologic symptoms suggestive of impending or ongoing TIA or stroke.
- Prolonged ECG monitoring studies have revealed that AFib remains vastly under-diagnosed and that duration of cardiac monitoring following acute ischemic stroke should be extended beyond 24–48 hours (Schuchert et al., 1999; Tayal et al., 2008; Elijovich et al., 2009).
- In another study of 56 patients with cryptogenic TIA or stroke, AFib was diagnosed after a median of 7 days (Tayal et al., 2008).

Turakhia, M., et al. **Feasibility of Extended Ambulatory Electrocardiogram Monitoring to Identify Silent Atrial Fibrillation in High-Risk Patients: The Screening Study for Undiagnosed Atrial Fibrillation (STUDY-AF).** *Clinical Cardiology Journal, 2015*

Keywords: Sub-clinical Atrial Fibrillation Detection in High Risk Populations, Silent AFib

Prospective study of 75 male patients screened using Zio by iRhythm detected atrial fibrillation (AFib) and atrial tachycardia (AT) in 11% of asymptomatic (silent AFib) patients with known risk factors.

- Inclusion criteria were age ≥55 years and ≥2 of the following risk factors: coronary disease, heart failure, hypertension, diabetes, sleep apnea. Patients were excluded with prior AFib, stroke, transient ischemic attack, implantable pacemaker or defibrillator, or palpitations or syncope in the prior year.
- AFib was detected in 4 subjects (5.3%; mean AFib burden 28%).
- AT ≥60 seconds was present in 5 subjects (6.7%).
- The combined diagnostic yield of sustained AT/AFib was 11%.
- Found a high prevalence of asymptomatic AT and frequent supraventricular ectopic complexes, which may be relevant to development of AFib or stroke.

Arnold R. and Layton A. **Cost Analysis and Clinical Outcomes of Ambulatory Care Monitoring in Medicare Patients: Describing the Diagnostic Odyssey.** *Journal of Health Economics and Outcomes Research, 2015*

Keywords: Diagnostic Odyssey, Failure of Holter to Diagnose Arrhythmias

This is a non-Zio study. Claims analysis performed using a 5% random sample of Medicare beneficiaries' claims from Fee-for-Service Standard Analytic Files (SAF). The analysis was limited to patients with full benefits for 1 year prior and 2 years post the index Holter event, with no prior arrhythmia or Holter.

- Clinicians were unable to rule-in or rule-out arrhythmias in 11.1% of the claims evaluated, even after repeated Holter monitoring.
- In spite of this failure, there was a total allowed charge of more than $45 million, which calculates to more than $23,000 per involved patient.
- When extrapolated over the entire Medicare Fee-for-Service population, this category was estimated to have cost more than $900 million over the 2-year study period.

Tung, C., Turakhia, M. and Lansberg, M. **Diagnostic Yield of Extended Cardiac Patch Monitoring in Patients with Stroke or TIA.** *Frontiers in Neurology, 2014*

Keywords: Zio System, Stroke/TIA Patients

Retrospective study of 1,171 patients monitored using the Zio system between January 2012 and June 2013 with an indication of TIA or stroke.

- Zio monitoring had high patient compliance (median wear time 13.0 days) and analyzable time (98.7%).
    - » Demonstrates that the cardiac patch, a novel device for detection of atrial fibrillation (AFib) and other cardiac arrhythmias, is well tolerated by stroke and TIA patients.
- AFib was present in 5.0% of reports.
    - » The mean AFib burden was 12.7%, demonstrating the transient nature of the arrhythmia which can complicate detection.
- The high rate of SVT detection (70%) in this patient population with a history of stroke or TIA is noteworthy as it may be a precursor to AFib.

Eisenberg, E., et al. **Chronic Ambulatory Monitoring: Results of a Large Single-Center Experience.** *The Journal of Innovations in Cardiac Rhythm Management, 2014*

Keywords: Arrhythmia Detection, Long-Term Continuous ECG Monitoring

Researchers reviewed data from 524 consecutive patients referred to an academic electrophysiology practice and prescribed a Zio monitor. Patients were instructed to wear the device for up to 14 days and to activate a trigger button on the device when they experienced symptoms.

- Overall, 99% of patients had some recorded arrhythmia, which included ectopy.
- The most clinically significant arrhythmias were atrial fibrillation/flutter (AFib) in 105 patients (20%) and non-sustained ventricular tachycardia in 79 patients (15%).
- Over one-third of initial arrhythmias were recorded after 48 hours.
- The most common rhythm associated with patient-triggered symptoms was normal sinus (50%).
- The majority of AFib episodes (62%) were asymptomatic.
- Long-term ECG monitoring detected arrhythmias in all subjects, and a large percentage were detected after 48 hours. Patient-reported symptoms did not correlate with arrhythmias, including AF, in half of all symptom recordings.

Schreiber, D., et al. **Ambulatory Cardiac Monitoring for Discharged Emergency Department Patients with Possible Cardiac Arrhythmias.** *Western Journal of Emergency Medicine, 2014*

Keywords: Zio by iRhythm in ED Patients

Retrospective study of 174 adult ED patients with symptoms of possible cardiac arrhythmia who were discharged with a Zio monitor from one of 3 academic EDs in the US. Study aimed to determine the diagnostic yield of the Zio system and the value of prolonged monitoring of these patients.

- The Zio system had a higher diagnostic yield of 63% in low-risk patients discharged from the ED, compared to 15% found with 24- to 48-hour Holter monitoring in previous studies.
- 53% of patients with symptoms, as noted by depressing the event button on the Zio monitor, did not have an arrhythmia present at the time. This symptom-rhythm correlation is helpful when ruling out the presence of arrhythmia when symptoms are noted.
- The median time to the first triggered arrhythmia for potentially serious arrhythmias (ventricular tachycardia and pauses >3 seconds) was 3.1 and 4.2 days, outside of the detection window of traditional Holter monitoring.
- The Zio system is clinically useful in an ED setting as it provides relatively prompt diagnoses of both normal sinus rhythm in symptomatic patients as well as serious asymptomatic arrhythmias in others.

Barrett, P., et al. **Comparison of 24-Hour Holter Monitoring Versus 14-Day Novel Adhesive Patch Electrocardiographic Monitoring.** *American Journal of Medicine, 2014*

Keywords: Arrhythmia Detection with Zio Monitor Compared to Holter

Prospective study of 146 consecutive patients referred for evaluation of cardiac arrhythmia who underwent simultaneous ambulatory ECG recording with Zio by iRhythm and 24-hour Holter monitor.

- The Zio system detected 57% more arrhythmias: 96 arrhythmia events by the Zio monitor as compared to 61 arrhythmia events by the Holter monitor ($p<0.001$).
- 90% of the time, referring physicians reported the Zio system aided in a definitive diagnosis compared to 64% for Holter monitoring.
- 81% of patients preferred Zio monitor over Holter monitoring, which contributes to a longer wear time and improved arrhythmia detection.

Camm, C., et al. **Premature Ventricular Contraction Variability in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy.** *Journal of Cardiovascular Electrophysiology, 2014*

Keywords: Premature Ventricular Contraction, ARVD/C Diagnosis

First study to examine the 7-day variability in PVC frequency in patients with Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C). 40 patients received Zio monitors from the Johns Hopkins ARVD/C registry.

- Zio monitors were prescribed for 7 days and worn an average of 6.6 days.
- Substantial statistical variability in PVC counts was found between 24-hour periods. PVC burden was shown to be present in 76% of patients in this study. If only a single 24-hour Holter is applied, the 24-hour PVC count may be above or below the 500 PVC/24-hour threshold used for ARVD/C diagnosis.
- However, in patients already diagnosed with ARVD/C, the degree to which PVC variability is likely to impact clinical practice is not as well known and requires more research.

Ray, J., et al. **Syncope.** *Journal of Intensive Care Medicine, 2014*

Keywords: Syncope, Diagnostic ECG Monitoring

Syncope has a broad range of causes and pursuit of a correct diagnosis can be tedious and expensive. Cardiogenic syncope is the most common etiology in the critical care setting; prognosis and risk of cardiovascular mortality is significantly higher compared to other forms of syncope.

- The gold standard in the evaluation for syncope after the initial workup is the documentation of reproducible symptoms.
- Holter monitors are the least sensitive ECG monitoring technique. The Zio monitor has been shown to detect more arrhythmias and is less cumbersome to wear than traditional Holter monitors. It should be noted that the yield of Holter monitoring is around 1% to 2% while the Zio system is 66%.
- Zio by iRhythm is best used in individuals with a history of frequently undiagnosed syncope when episodes are likely to occur during the 14-day monitoring period.
- Implantable loop recorders are suggested as a first-line diagnostic tool for patients lacking classical etiological features.

Turakhia, M., et al. **Diagnostic Utility of a Novel Leadless Arrhythmia Monitoring Device.**
The American Journal of Cardiology, 2013

Keywords: Arrhythmia Detection with Long-Term Continuous ECG Monitoring

Retrospective data from 26,751 consecutive patients undergoing first-time Zio system studies during 2011 were analyzed for wear time, analyzable signal time, diagnostic yield and timing of arrhythmia detection.

- The mean wear time was 8 days and the median analyzable time was 99% of the total wear time.
- After 48 hours, the Zio system detected that:
    - 51% of patients had their first symptom-triggered arrhythmia
    - 47% of patients experienced their first symptomatic episode of atrial fibrillation
    - 37% of patients had their first symptomatic episode with AV block
    - 30% of patients had their first arrhythmia of any type

Rosenberg, M., et al. **Use of a Noninvasive Continuous Monitoring Device in the Management of Atrial Fibrillation: A Pilot Study.** *Pacing and Clinical Electrophysiology, 2013*

Keywords: Zio Monitor Compared to Holter, Change in Clinical Management for AFib

Prospective 74-patient study in which each patient simultaneously wore a Holter monitor for 24 hours and the Zio monitor for an average of 10.8 days.

- Over a 24-hour period, the Zio system and Holter monitor equally identified AFib events and estimated AFib burden.
- However, following Zio monitoring, AFib events were identified in 18 additional individuals and the documented pattern of AFib changed in 21 patients. Additionally, potentially malignant arrhythmias were first recorded on the Zio monitor after 24 hours of monitoring.
- Longer continuous monitoring with Zio resulted in a meaningful change in clinical management for 28.4% of patients.

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