Novel Arrhythmia Monitoring Technologies

Long Term ECG Monitoring: Its Role in Clinical Drug Development and Population Screening
(Cardiac Safety Research Consortium)

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In affiliation with

Valley Health System

Cleveland Clinic
Heart and Vascular Institute
The Need for ECG Monitoring to Assess Cardiovascular Drug Safety

Parameters for consideration

- Heart rate
- Ectopic beats
- Repolarization morphology
  - TWA
- Beat-to-beat variability
  - HRV
- Heart rate dependent repolarization abnormalities
  - Corrected QT interval
- Autonomic nervous system
  - HRT

Farkas AS, Nattel S. *Drugs* 2010: 70 (5): 573-603
ECG Monitoring Tools for Diagnosis and Evaluation

• What are we trying to diagnose?
  – Change in ECG parameter – heart rate, PR interval, QRS duration, QT interval
  – Development of a new arrhythmia – atrial or ventricular ectopy, atrial fibrillation, non-sustained ventricular tachycardia, torsade de pointes
  – Suppression of an existing arrhythmia

• What are the available tools for diagnosis?
  – Is there a gold standard?
  – How long do we need to monitor?
  – Is “real time” feedback necessary?
**ECG Monitoring Tools for Diagnosis and Evaluation**

**Suboptimal**

- Rhythm strip
- 12-lead ECG
- 24-hr Holter
- 7-30 day ECG monitor
- ILR
- Permanent ECG Recorder With Wireless Transmission

**Ideal**

**ECGs** No asymptomatic arrhythmias; limited duration (QT)

**24-48 hour Holter monitoring** Short duration

**Event recorders**
- Non-looping require frequent manual activations and/or symptoms
- Limited sensitivity/specificity of auto trigger algorithms

**Outpatient cardiovascular telemetry monitoring**
- Requires continuous wearing (patient compliance)
- Limited monitoring time

**Implantable loop recorders** (Time to AF recurrence; AF burden)

Mittal S et al. JACC 2011; 58: 1741-1749
ECG Monitoring Tools for Diagnosis and Evaluation

External Ambulatory ECG Monitoring

A. Holter monitoring
- Patient wears monitor (typically 24-48 hours)
- Patient keeps diary of symptoms and times when they occur
- Patient returns monitor to technician to be scanned after recording period
- Technician gives physician final report

B. Event monitoring
- Patient carries monitor (typically 30 days)
- Patient places monitor on chest to record during symptom
- Patient transmits data over telephone to monitoring station
- Monitoring station sends data to physician

C. Loop monitoring
- Patient wears monitor (typically 30 days)
- Patient activates monitor during symptom (some devices auto-trigger if arrhythmia is detected and alert patient)
- Patient transmits data over telephone to monitoring station
- Monitoring station sends data to physician

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ECG Monitoring Tools for Diagnosis and Evaluation

Suboptimal

Rhythm strip
12-lead ECG
24-hr Holter
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ILR

Smartphone applications

Ideal

Permanent ECG Recorder With Wireless Transmission

Mittal S et al. JACC 2011; 58: 1741-1749
Smartphone Based Diagnosis

- Evaluate symptoms
- Assess heart rate, PR interval, QRS duration
- Assess rhythm, AV conduction
  - Exclude second or third degree heart block
  - Exclude persistent atrial fibrillation
ECG Monitoring Tools for Diagnosis and Evaluation

Suboptimal

Rhythm strip

12-lead ECG

24-hr Holter

7-30 day ECG monitor

ILR

Permanent ECG Recorder With Wireless Transmission

Ideal

Smartphone applications
Generation 1: 30-sec rhythm strip

Smartphone applications
Generation 2: 6-lead ECG

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Smartphone Based Diagnosis

Assess QT interval
ECG Monitoring Tools for Diagnosis and Evaluation

Second Generation External Ambulatory ECG Monitoring

A. Holter monitoring (up to 7-14 days)
- Patient wears monitor patch
- Patch monitor records all ECG data during period
- Patient mails back monitor after recording period to central receiving station
- Technician reviews data and sends report to physician

B. Ambulatory Telemetry monitoring - (Non-Real Time)
- Patient wears monitor (up to 30 days)
- Monitor sends all ECG data to a handheld device
- The handheld device transmits ECG data to a central monitoring station
- Physicians are notified by technician if significant arrhythmia is detected

C. Ambulatory Telemetry monitoring - (Real Time)
- Patient wears monitor (up to 30 days)
- Monitor sends all ECG data continuously to central monitoring station
- Physicians are notified by technician if significant arrhythmia is detected
- Physicians can also log onto secure web server at any time to view real time ECG data

Mittal S et al. JACC 2011; 58: 1741-1749
ECG Monitoring Tools for Diagnosis and Evaluation

- **Suboptimal**
  - Rhythm strip
  - 12-lead ECG
  - 24-hr Holter

- **Ideal**
  - 7-30 day ECG monitor
  - ILR
  - Permanent ECG Recorder With Wireless Transmission

Smartphone applications
- Generation 1: 30-sec rhythm strip
- Generation 2: 6-lead ECG

Patch Based Monitor
- Real-Time Review
ECG Monitoring Tools for Diagnosis and Evaluation

SEEQ™ MCT Wearable Sensor

- Each sensor can be worn for 7.5 days
- Adhesive-backed sensor is applied to chest
- Communicates with the wireless transmitter
- Auto / patient triggered arrhythmia detection / storage

SEEQ™ MCT Transmitter

- Relays sensor data continuously via cellular signals to monitoring center
- Battery life is 12 hours
- Must be within 30 feet of the transmitter for successful data transmission
ECG Monitoring Tools for Diagnosis and Evaluation

**Automatic:**
- Rate ≥ 130 bpm
- Rate ≤ 40 bpm
- Pause ≥ 3 sec
- AV block
- Atrial fibrillation
- PVCs; VT/VF
- Every 24 hours

**Patient-Triggered:**
Driven by use of the Patient Trigger Button on Transmitter
The More You Look…
The More You Shall Find

ECG Monitoring Tools for Diagnosis and Evaluation

Mittal S et al. JACC 2011; 58: 1741-1749
ILR Based Daily ECG Monitoring

Wireless
Reveal LINQ™ ICM

Cellular
MyCareLink™ Patient Monitor

Simplified Insertion Procedure
Patient Assistant

No Real-Time Data Transmission

Streamlined Reports

Valley Health System
In affiliation with Cleveland Clinic
Heart and Vascular Institute
ECG Monitoring Tools for Diagnosis and Evaluation

Charitos EI et al. *J Am Coll Cardiol* 2014; 63: 2840-2848
ECG Monitoring Tools for Diagnosis and Evaluation

**Strength**

- Each sensor can be worn for 7.5 days - waterproof
- Compliance can be monitored real time
- Each patient can serve as his/her own control – assess baseline burden of arrhythmia
- Notification criteria can be tailored
- Human review

**Weakness**

- Impractical to monitor for more than 4 weeks
- Single lead – not well suited for QT analysis
- Atrial fibrillation (AF) burden not entirely reflective of true burden – ignores AF density
The most commonly observed clinically actionable event was the presence of non-sustained ventricular tachycardia (≥ 5 beats)
Ongoing Clinical Trials

• Genetically targeted therapy for the prevention of symptomatic atrial fibrillation in patients with heart failure (GENETIC-AF) [NCT01970501]
  – Time to first event of symptomatic atrial fibrillation/atrial flutter

• Efficacy of perindopril to prevent recurrence of atrial fibrillation in patients with essential hypertension (CTAF-2) [NCT00461903]
  – Primary endpoint: time to first sustained recurrence of AF

• A blinded study to evaluate effect on atrial fibrillation burden in patients with paroxysmal atrial fibrillation [NCT02156076]
  – Primary endpoint: Percent change from baseline in AF burden [Time Frame: day 8 to 29]
ECG Monitoring Tools for Diagnosis and Evaluation

Charitos EI et al. Circulation 2012; 126: 806-814
Using ECG Monitoring Technologies Synergistically

- **Safety**
  - Assess baseline for each patient
  - Assess heart rate, AV conduction, QRS duration, QT interval
- **Efficacy**
  - Assess time to symptomatic recurrences
  - Ascertain density of atrial fibrillation
  - Exclude persistent atrial fibrillation
  - Better “non-invasive” assessment of atrial fibrillation burden
  - Real-time notification of “concerning” arrhythmias
The Future is Almost Here
Conclusions

- ECG monitoring is critical for assessing drugs for safety and many cardiovascular drugs for efficacy.
- Increased recognition that patients have arrhythmias at baseline.
- In the past 5 years, there has been a major evolution in available ECG monitoring technologies:
  - Smartphones, patch based real-time data acquisition and transmission, implantable cardiac monitors.
  - Each has its strengths and weaknesses; no gold standard currently exists.
- Possible role of using technologies synergistically.
- Development of “wearables” that facilitate long-term ECG monitoring holds great promise.