Patient selection for ambulatory cardiac monitoring in the Indian healthcare environment

ABSTRACT

Cardiovascular disease (CVD) in India comprises the bulk of non-communicable diseases, resulting in 2 million deaths per year. The incidence of CVD in India is estimated to be up to four times higher than in other countries. Though the quantification of the prevalence of rhythm disorders in India is not available, it can be inferred to be proportionately high. Identification and treatment of arrhythmia is limited by several socioeconomic factors including low health insurance penetration, limited reimbursement and high out-of-pocket expenditures. Thus, there exists a need in India to (1) select an appropriate tool that is both high yielding and cost effective and (2) employ a suitable patient selection method. This paper focuses on these two aspects for cardiac arrhythmia diagnosis using ambulatory monitoring technology, while keeping in mind the dynamics of the Indian healthcare setting.

INTRODUCTION

Under normal circumstances, the heart functions as a pump to circulate oxygenated blood to various parts of the body by orchestrating a symphony of electrical and mechanical interactions. Perturbations in the electrical conduction of impulses in the heart which is called cardiac arrhythmia, can disturb this rhythm, sometimes with fatal consequences if not treated swiftly.[1] The magnitude of cardiovascular disease (CVD) in India has reached pandemic proportions, with CVD accounting for 24% of all non-communicable deaths in India,[2] resulting in 2 million deaths per year.[3] The incidence of CVD is estimated to be 50–400% higher in Indians as compared with other ethnicities.[4] Though research to quantify the prevalence of rhythm disorders in India is scarce, the figure can be extrapolated using the global prevalence for arrhythmia, 5.3%.[5] With a population of 1.2 billion, this amounts to approximately 6 million individuals in India with some form of cardiac arrhythmia.

Most importantly, cardiac arrhythmias are frequently harbingers of a significant structural heart disease (SHD) that may remain undetected until the occurrence of severe symptoms or even sudden cardiac death (SCD). Moreover, early detection of symptoms of cardiac disease or of hints to life-threatening cardiac arrhythmias could potentially save many lives either in patients with yet undiagnosed cardiac disease or with already known cardiac disease, as sudden death seems to occur sooner in patients in India with postmyocardial infarction (MI), compared with the western population.[6] Indeed, recent reports from both general population and rural areas in India highlight that SCD accounts for 10–17% of overall mortality, known CVD being the leading independent predisposing factor.[7 8] Thus, identification of rhythm disorders could prompt patients with only mild symptoms to seek medical attention and could lead to detection of relevant heart diseases that would be ultimately treated by tailored therapy. Furthermore, a high-yielding diagnostic test would increase medical efficiency in the workup of symptomatic patients at intermediate risk of heart disease at an affordable cost.

Proper identification and treatment of arrhythmia in India is mitigated by limited access to medical care, poor healthcare infrastructure and the lack of well-developed financial schemes to cover the cost of medical services.[9] Compounding the socioeconomic problem is the transient nature of some symptomatic arrhythmia, such as sinoatrial block or ventricular tachycardia (VT). The rudimentary nature of diagnosis often results in a missed diagnosis, causing the patient to remain in the diagnostic loop indefinitely. Some of the transient arrhythmias, such as non-sustained VT, can lead to SCD, while others, such as transient syncope due to sinus node or atrioventricular conduction disorder, can lead to occupational hazards resulting from loss of consciousness at precarious times. Living with an arrhythmia can also negatively affect quality of life.[10] A majority of physicians rely on resting ECG or Holter monitors for analysis, both of which may be inadequate tools for transient arrhythmia detection since the window of detection (30 s or up to 48 h, respectively) is insufficient for infrequent arrhythmia detection.

Aside from the clinical aspects of efficient arrhythmia management, patient economics also play a major role in India's healthcare system. In India, approximately 70% of all healthcare expenditure is out of pocket, government health-related spending is less than 5% of the gross domestic product (GDP) (as compared with 17.6% of GDP in the USA), and 35% of hospitalised Indians fall below the poverty line.[11 12] These facts often place pressure on the cost-conscious Indian consumer when opting for diagnostics for symptoms investigation or suspected arrhythmia detection when the certainty of finding a cause is dubious. Hence, in terms of arrhythmia diagnosis, there exists a need in India to (1) select an appropriate tool that is both high yielding and cost effective and (2) employ a suitable patient selection method. This paper focuses on these two aspects for cardiac arrhythmia diagnosis using ambulatory monitoring technology, while keeping in mind the dynamics of the Indian healthcare setting.

INITIAL ASSESSMENT OF ARRHYTHMIA

For non-emergency situations, proper initial management of a suspected arrhythmia can lead to successful and efficient identification and treatment if necessary. Initial assessment includes a complete medical history relevant to the present symptoms. This includes date of the index symptoms, duration, any associated trauma, any recurrence of the event, medications and allergies. Symptoms history notation and clinical examination may not lead to a definite diagnosis in the majority of patients and often trigger further diagnostic evaluations. Past history of heart disease, hypertension, diabetes mellitus, surgical history (with particular attention to previous heart surgery, coronary artery bypass graft, etc) or any other diseases are also important to document.

A physical exam focuses on vital signs, haemodynamic stability and possible SHD. Blood tests could include troponin level measurements (for suspected coronary artery disease), urea, creatinine, electrolytes and thyroid function tests.[13] Central to the diagnosis of a cardiac cause is the resting ECG. In India, the resting ECG is the first tool of choice for suspected arrhythmia disorders and syncope evaluation (Shrivastav, unpublished data). Neurological testing is helpful only when additional neurological symptoms are present, as diagnostic yield of electroencephalography, computer axial tomography, and Doppler ultrasound is 2–5% in such cases.[14] Initial patient examination in itself has a highly variable yield that is also dependent on the specific setting, ranging for instance, from 5.2% to 69% in patients with syncope.[15]

Management of arrhythmias in an emergency setting is important if immediate life-saving measures are required. In a study of 110 patients admitted for an acute condition, almost half manifested changes in the ECG, 20% of whom were positively affected by treatment.[16]

THE EXTERNAL LOOP RECORDER

External loop recorders (ELRs) are cardiac monitors that help diagnose suspected cardiac arrhythmias through the use of ambulatory monitoring technology. Several varieties of ELRs exist. A typical modern system includes a monitor that is applied on to the patient's chest like a self-adhesive bandage for an extended monitoring period such as 7 or 14 days. Small form factor chest patches are available, thereby minimising interference with the patient's daily activities. Some offerings are water resistant, allowing the patient to shower without removing the device. The patient must also carry a cell phone-sized transmitter.[17 18]

Most advanced ELRs offer an end-to-end patient solution, complete with near-real-time event monitoring. Event monitors record segments of ECGs (preindex and postindex event), with recording initiation triggered by patient activation and/or by an internal, automatic preprogrammed detection algorithm (auto triggering). Auto-triggered recorders have significant advantages over those with only patient-triggered options. Auto-triggered event recorders record more arrhythmic events (72–80%) than patient-triggered recorders (17–75%).[19] Traced data is transmitted to the doctor's office, clinic, or hospital. Some event recorders send the data to a monitoring centre which is staffed by qualified ECG technicians. The trained cardiac technicians at the monitoring centre analyse the ECGs and send a comprehensive report at the end of the monitoring period. In general, the ELR is intended for outpatient use, and doctors would place the ELR on patients in their clinic during outpatient hours. A pilot trial in India using the ELR was recently completed.[20]

The device selection for ambulatory monitoring should be governed by the frequency of symptoms. The ELR has a very useful role when the frequency of recurrent symptoms is 4–6 weeks.[21] Symptoms that are constant can be recorded by resting ECG, and symptoms that manifest daily can be evaluated by a 24 or 48 h Holter monitor. Example ECGs from an ELR are shown in figure 1. For very infrequent symptoms, like once or twice annually, a longer-term monitoring solution, such as the implantable loop recorder (ILR) (usable for up to 18 months), as shown in table 1, should be considered.

Recent advances in smartphone technologies have also introduced new possibilities in the realm of cardiac arrhythmia diagnosis. Combining the power of the ubiquitous smartphone for diagnostics and telemedicine has potential to increase access to healthcare while reducing cost. However, more rigorous research is required to validate the technology and create a comprehensive evidence base.[22 23]

THE NEED FOR EFFICIENT PATIENT SELECTION

According to the Indian Ministry of Health and Family Welfare, only 3–5% of Indians are covered by any form of health insurance.[24] For those who are covered, 86% saw an average premium cost increase of over 10% in just 3 years due to the rising cost of healthcare in India.[25] The result is that a majority of Indian patients are paying for their own medical care.[11] Even for those with coverage, rising healthcare costs are placing some therapies out of the policy's sum assured range. Compounding the problem is the dearth of financial options, which further promotes a consumerism type of behaviour among middle-class Indian patients who often shy away from necessary diagnostics and therapy in lieu of other necessary non-medical expenditures. Delay in treatment may exacerbate the situation, mitigate early intervention possibilities, and lead to more extensive treatment in the future. Thus, in addition to good clinical practice, a strong economic case exists for quick and efficient diagnosis of cardiac arrhythmia and symptoms.

The ultimate diagnostic goal, regardless of presenting aetiology, is to correlate symptoms to disturbances in heart rhythm, or to show a lack of association of the symptom to a rhythm as evidence of non-cardiac cause. Efficient diagnosis relies on the judicious use of tools. A patient may quickly lose confidence and motivation if a battery of diagnostic tests results in no diagnosis. Studies have shown that when standardised diagnostic algorithms are used, the number of tests required for diagnosis decreases, and the diagnostic yield of such tests increases substantially.[26] In terms of syncope diagnosis, for example, Croci and colleagues reported that two or less tests were necessary for diagnosis of syncope in 66% of patients.[27] An initial patient evaluation before expensive cardiac tests were performed reduced the number of tests required, and also increased the diagnostic yield of the subsequent tests. This was most likely due to the screening of higher-risk cardiac patients.

ELRs are a useful tool for diagnosis of arrhythmia. The European Heart Rhythm Association's Task Force on indications for use of diagnostic implantable and external ECG loop recorders has recommended the use of ELRs as a class IIA indication in patients with recurrent syncope or presyncope who have[28]:

- intersymptom interval of ≤4 weeks
- suspicion of arrhythmic origin
- no high-risk criteria that require immediate hospitalisation or attention.

The Task Force also delineated classes of interpretation for ILRs and ELRs. Class I: findings are diagnostic when the following are met:

- correlation is made between an arrhythmia and syncope
- without correlation, periods of Mobitz II or 3rd-degree atrio ventricular (AV) block, or pause greater than 3 s (with some exceptions during sleep or medication), prolonged atrial or VT
- with no correlation, an arrhythmic cause is ruled out when syncope occurs and no arrhythmia is detected.

Class III: findings are not diagnostic when the following are met:

- presyncope without any relevant arrhythmias
- asymptomatic arrhythmias
- sinus bradycardia without syncope.

The diagnostic yield and usefulness of loop recorders increases with proper patient selection. Additionally, ambulatory monitoring with ELRs can be useful for patients with a non-diagnostic Holter exam, in postacute MI with ejection fraction (EF) <40%, in patients with history of rheumatic heart disease (RHD), palpitations, or patients above age 60 years with depressed EF and structural heart disease. ELRs are also useful for AF monitoring post ablation and AF monitoring for antiarrhythmic drug titration. Regardless of the usefulness of the tool, diagnostic yield is a function of patient selection. A patient selection tip card can be used ubiquitously for consistent patient selection, regardless of the level of training of the physician. Each of these recommendations for selection of patients for long-term ambulatory ECG monitoring is considered further.

PATIENT SELECTION, DIAGNOSTIC YIELD AND SYMPTOM FREQUENCY

Syncope

Syncope is defined as a sudden, transient loss of consciousness, typically occurring when a fall in blood pressure disrupts the

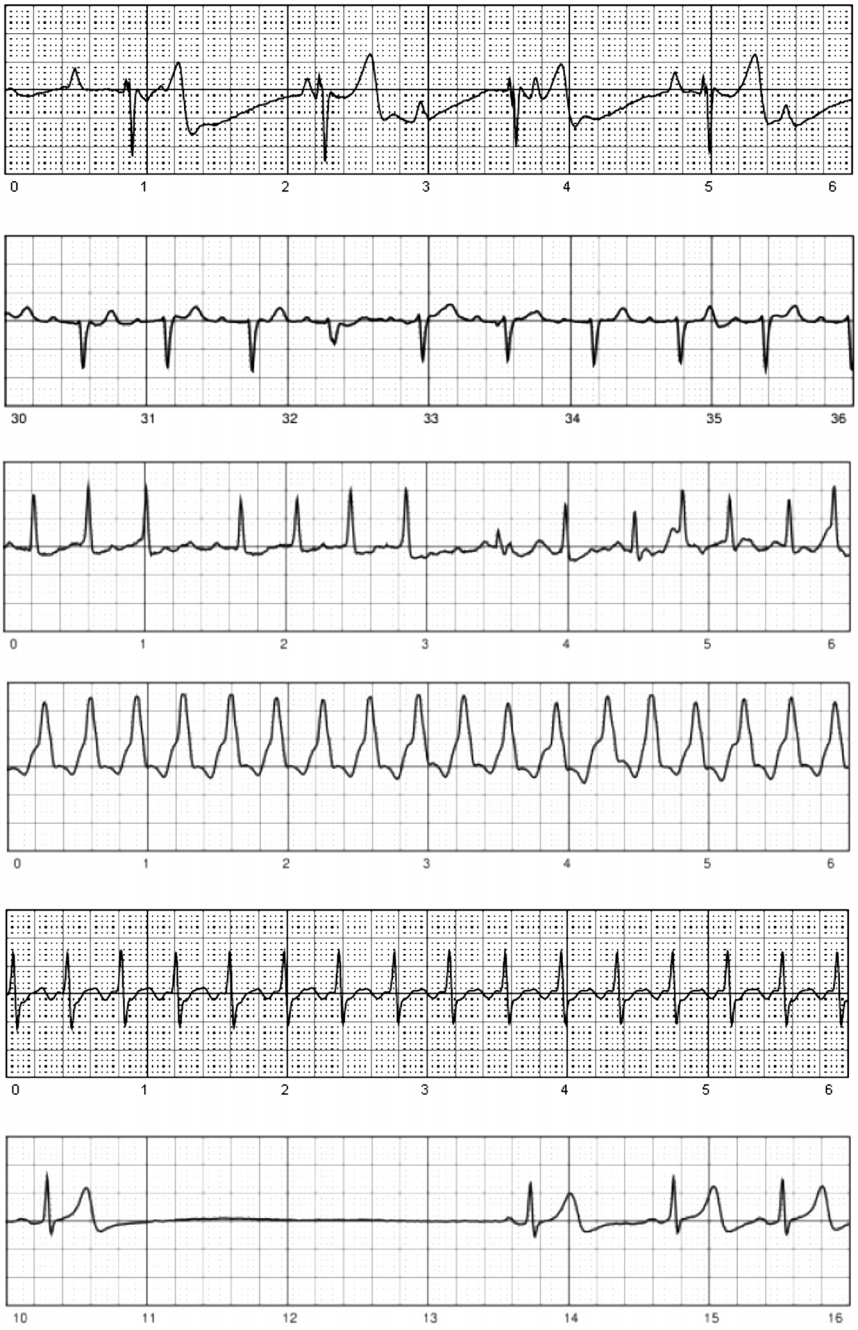

Figure 1 1st panel: 2nd-degree atrio ventricular (AV) block. 2nd panel: 1st-degree AV block. 3rd panel: Paroxysmal atrial fibrillation with and intermittent ventricular pacing. 4th panel: Ventricular tachycardia. 5th panel: Atrial flutter. 6th panel: Sinus pause.

supply of oxygenated blood to the brain. A patient may faint or pass out for several seconds during this episode.[28–30] The cause of syncope could be cardiac related (18%), neurogenic (10%), orthostatic (8%), medication related (3%), psychiatric (2%), or unknown (34%).[31] Syncope-related issues account for a substantial number of emergency department visits in India and around the world,[32] resulting in 3–6% of emergency room visits, and 0.5–2% of hospitalisations annually.[33]

Table 1 Frequency of symptoms and suggested monitoring modality

Frequency of symptoms	Suggested device
Continuous	12-lead ECG
Daily	24/48 h Holter
Weekly or monthly	7-day external loop recorder
Annual	Implantable loop recorder

The diagnosis of syncope is often difficult because of the transient nature and diverse causes of the event. The full workup for syncope is well described elsewhere.[31] Holter monitors are commonly used with syncopal patients, with a yield of 6–20%.[34] However, the Holter diagnostic yield is largely overestimated. Among 826 elderly syncopal patients, the overall diagnostic yield was 8.6%.[30] Additionally, 4.4% of patients whose symptoms were not explained by Holter recordings received a pacemaker, compared with 5.4% of those whose symptoms

were diagnosed by Holter[30]; thus, a Holter-guided approach to syncopal patients holds a very low yield. The Holter diagnostic yield is extremely disappointing in syncopal paediatric patients, 0.4% over 234 patients, where abnormal findings were more common in children with known SHD.[35] In a prospective randomised trial of 100 patients that compared Holter monitors to loop recorders for obtaining a symptom to rhythm correlation, loop recorders were more effective than Holter monitors as an initial diagnostic modality for detecting syncope and presyncope. The overall diagnostic yield for loop recorders for syncope has been reported to be 56%.[36] ILRs have been reported to have a yield of 50–85% in syncopal patients.[37–39]

The diagnostic yield of any ambulatory monitoring system is indeed related to the length of the monitoring period. Studies have shown that symptom to rhythm correlation was obtained in 13% of patients within 2 days, whereas 39% correlation was obtained within 2 weeks.[36] A large 17-centre study focused on the diagnosis of cardiac arrhythmia showed that the mean time to diagnosis for mobile cardiac outpatient telemetry was 7 days, and the mean time to diagnosis using ELRs (mainly patient-activated versions only) was 9 days. The time to diagnosis could have been shorter if the recorder was equipped with auto triggering algorithms, as yield with auto-triggering features has been shown to be higher.[40] ELRs have the greatest role in patients whose symptoms present with frequency of recurrence between 4 and 6 weeks.[21 41]

Furthermore, previous studies with 24 h Holters have shown that when patient selection criteria are used with syncopal patients, diagnostic yield doubled. Sarasin *et al* demonstrated in a study of 140 patients that when restricting Holter monitoring to high-risk patients, yield increased from 6% in unselected patients to 12% in the high-risk group. The authors further suggest that using such selection criteria for syncopal patients as an initial step could avoid a series of other expensive diagnostic procedures.[28]

Non-diagnostic Holter test

Holter monitoring is non-diagnostic in up to 90% of cases for recurrent unexplained syncope.[42] For symptomatic patients, inconclusive diagnostic tests can be frustrating and depressing. In some cases, distress, depression and anxiety can lead to illness behaviours, ultimately resulting in a lower quality of life.[43] The effect of depression can also lead to low compliance for medication and less than optimal risk factor control.[44] In the Indian scenario with most patients paying out of pocket, a series of non-diagnostic tests can affect decisions for further testing.[45] On the contrary, reassuring a patient about benign vasovagal fainting owing to extended monitoring by an ELR would significantly impact the quality of life. Clinically, the results of delaying a diagnosis due to a non-diagnostic Holter exam can also place patients at risk for a harmful cardiac event, subject them to unnecessary medical treatment, and promote the inappropriate use of medical resources.[46]

Postmyocardial infarction with low EF

Clinically significant arrhythmias may be observed in patients after acute MI and with low left ventricular EF (≤40%). Such results were observed in the Cardiac Arrhythmias and RIsk Stratification after Myocardial infarction (CARISMA) trial, a multicentre observational centre with 300 patients with low left EF 2 months after acute MI. Patients were implanted with an ILR. The arrhythmias detected by the ILR included paroxysmal AF (21%), permanent AF (4%), atrial tachycardia (7%), 3rd-degree AV block (11%), idioventricular rhythm (7%), and non-sustained VT (NSVT, 7%).[47] The study demonstrated that NSVT associated with inducible VT or high-degree AV block were frequent in low EF patients within 2 months post-MI. An indication for pacemaker or implantable cardioverter defibrillator was found in nine out of 29 subselected patients.[47] An important finding of this study was the high incidence of 2nd-degree and 3rd-degree AV block associated with an increase in all-cause mortality and cardiac death.[48] Table 2 lists the incidence of cardiac arrhythmias as recorded in the study. Middle-aged Indian post-MI patients have a worse prognosis compared with the Western population, total and sudden mortality being 10% and 6.5%, respectively, 1 month after discharge from the target MI. Notably, 54% of all SCD occurred within the first month after the MI.[6] This observation calls for prioritisation of therapeutic interventions in such a young high-risk population where early detection by ELR monitoring could potentially impact overall survival. Indeed, the detection of depolarisation abnormalities and rhythm disorders would trigger revascularisation interventions and SCD prevention strategies to decrease total mortality.

History of rheumatologic diseases

RHD is a complication of rheumatic fever that manifests as valvular damage and carditis. An estimated 15.6 million people worldwide have RHD, with over 200 000 deaths per year related to this disease.[49] Globally, 97% of such cases occur in developing countries.[50] The incidence of RHD in India is on the rise. A study by the All India Institute of Medical Sciences (AIIMS) found that the prevalence of RHD among children in India to be approximately 20.4 cases per 1000.[51] RHD also appears to be more prevalent in adolescents or school-aged children.[52] Some studies have shown that 90% of cases of RHD are clinically silent, making the disease very difficult to detect.[53]

Arrhythmia and conduction defects are common manifestations for patients with a history of rheumatic diseases. Some of these problems may arise from the use of certain pharmacologics to treat the primary rheumatologic condition.[53] A list of the common arrhythmias and conduction deficits associated with rheumatologic diseases is shown in table 3. Very little research exists to determine an arrhythmia prevalence rate with RHD. However, in a recent survey in India, RHD was found to be the aetiology of AF in 50–60% of patients.[54] Other abnormalities associated with RHD may include bundle branch blocks, nonspecific sinus tachycardia-T wave changes, and atrial and ventricular premature complexes.[52] Significant RHD is usually detected by echocardiography in symptomatic patients: this may reveal significant atrial muscle and mitral valve disruption.[52 55–57]

Long-term monitoring for arrhythmia in RHD patients can proactively discover threatening arrhythmias. In particular, for

Table 2 Incidence of cardiac arrhythmias recorded by a implantable cardiac monitor[48]

Arrhythmia	Patient (n) (%)	Events
Sinus bradycardia (≤30 bpm, ≥8 bpm)	20 (6.7)	111
Sinus arrest (≥5 s)	16 (5.4)	23
AF (≥125 bpm, ≥16 beats)	82 (27.6)	538
NSVT (≥125 bpm, ≥16 beats, <30 s)	39 (13.1)	64
VT (≥125 bpm, ≥30 s)	9 (3)	20
VF (≥125 bpm, ≥16 beats)	8 (2.7)	19
Any arrhythmia	137 (46.1)	885

AF, atrial fibrillation; NSVT, non-sustained ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia

Table 3 Common conduction deficits associated with rheumatological diseases

Disease	Prevalence	Associated arrhythmias	Conduction defects
Rheumatoid arthritis	7M in India[80]	–	AV block, BBB
Systemic lupus erythematosus	14–60 per 100 k[81]	ST, PAC, AFr	AV and IV blocks, SSS
Systemic sclerosis	~250 per 1M[82 83]	V arrhythmias, PVC, VT	BBB, 1AV
Polymyositis and dermatomyositis	2–10 per 1M[82]	VT (rare)	LAH, BBB
Mixed connective tissue disease	2.1 per 1M (Norway), rare in India[84 85]	ST	IV block, complete AV block
Sjogren's syndrome	3% for those over 50 years[82]	V arrhythmias (unclear)	1AV, complete AV block
Takayasu arteritis	2.6 per 1M[86]	V arrhythmias (rare)	CHB
Kawasaki disease	As high as 60–150 per 100 k in kids <5 years[87]	VT (rare)	
Behcet's disease	<1 case per 100 k in USA[88]	V arrhythmias (rare)	
Wegener's granulomatosis	3 per 100 k in USA[89]	SV, AT, AF, AFl	
Sarcoidosis	16.5–19 per 100 k[90]	VT	IV blocks
Antiphospholipid syndrome	1–5% of healthy population[91 92]	V arrhythmias	CHB

Modified from Eisen *et al*.[53]
1AV, 1st-degree AV block; AFl, atrial flutter; AFr, atrial fibrillation; AT, atrial tachycardia; BBB, bundle branch block; CHB, complete heart block; IV, intraventricular; k, thousand; LAH, left anterior hemiblock; M, million; PAC, premature atrial contraction; PVC, premature ventricular contraction; SSS, sick sinus syndrome; ST, sinus tachycardia; SV, supraventricular arrhythmia; V, ventricular; VT, ventricular tachycardia.

patients with AF, the chances of embolic stroke are increased substantially.[58 59] As AF begets AF, the sooner the discovery of AF, the sooner treatment can be administered, thereby improving patient survival rates and quality of life.

Structural heart disease patients

The diagnostic yield for syncope has been shown to be higher for elderly male patients with SHD and low EF. In terms of syncope detection, the presence of SHD is a major predictive factor with a sensitivity and specificity of 95% and 45%, respectively. In an observational perspective study of 2052 patients with unexplained syncope who underwent ILR implantation, 58% of the patients with SHD had an ECG recording, and all but two of the patients had an arrhythmia during the time of syncope, including paroxysmal or persistent AV block, atrial tachycardia, sinus bradycardia or arrest and VT or fibrillation.[60]

Furthermore, a subgroup analysis of 4877 Holter studies demonstrated a higher diagnostic yield for syncope for male patients over age 60 years with SHD and left ventricular ejection fraction <50%.[30] Age seemed to be an important characteristic for this subgroup, as a diagnosis was found via Holter in 12% of the patients over age 60 years versus only 2% for those below 60 years.[28] In most situations, Holter monitoring was performed for 24 h or 48 h. The diagnostic yield for this high-risk group perhaps could have been increased if the duration of monitoring were longer.

Palpitations

Palpitations can be described as the feeling of one's heart skipping a beat. Establishing the cause of palpitations is difficult and may not always be possible. Palpitations are a very common symptom to a number of potential cardiac and non-cardiac issues. Palpitations can be caused by premature atrial or ventricular contractions and can be generally benign. The general categories of causes of palpitations can include arrhythmia, psychiatric causes (stress, anxiety), drugs and medications, non-arrhythmic cardiac causes (pericarditis, valvular disease, etc), or extracardiac causes (fever, anaemia, etc).[61]

Suspicion of cardiac cause of palpitations can be narrowed by associating other symptoms along with palpitations, such as shortness of breath, chest pain, arm pain and so on. To deduce a cardiac cause of palpitations with more definition, Holter monitors are often used. However, a controlled clinical trial concluded that cardiac auto-activated loop recorders yield more diagnoses and are more cost effective than 48 h Holter monitoring for patients with palpitations.[62] The yield for Holter monitoring for palpitations is 35–39%.[63] Because of the ambiguous cause of palpitations, it is particularly important to correlate the symptom with a rhythm. Seven-day loop recorders with patient activation (so the patient may trigger when symptomatic) would be appropriate when symptom frequency is less than 4 weeks.

Monitoring for AF

Atrial fibrillation (AF) is a complex disease that is best managed with early detection and treatment. The risk for embolic stroke for patients with AF lasting more than 24 h is elevated 3-fold.[17 58] In patients implanted with pacemakers capable of monitoring AF occurrence, asymptomatic AF was detected in 59% of patients along follow-up, and 38% of patients had asymptomatic AF lasting more than 48 h.[64] Since AF episodes lasting >24 h are independently associated with a 3-fold increased risk of arterial embolism compared with short-lasting AF episodes,[65] the importance of an ELR that can measure the AF burden cannot be overlooked in clinical practice. Indeed, the combination of symptoms and serial ECG recordings yield only 68% sensitivity and 58% specificity for symptomatic AF detection in recurrent AF patients.[64]

Together, AF and atrial flutter account for 10% of all strokes, and half of all cardioembolic strokes.[66] The prevalence of AF is >7% among those age 80 years and older.[67] In the USA, over 2 million people are living with AF, and 75 000 strokes occur in such patients annually.[68] AF is detected in about 20–25% of patients with stroke of yet undefined aetiology, but is increasingly detected in the first week after the target event also in those patients presenting in sinus rhythm. When Holter monitoring is extended from 1 day to 7 days after a stroke, AF detection increases from 4% to 13% of patients.[69]

A recent study reported that rhythm monitoring after a stroke event is highly cost effective to prevent recurrences and to decrease the costs linked to further morbidity.[70] However, AF detection requires maintaining the patient in an expensive environment with monitoring capability (stroke unit, intensive care unit) longer than needed, whereas the same task can be accomplished by ELRs in a rehabilitation facility.

Studies have shown that increasing the duration of monitoring for AF increases the probability of AF detection.[63–66 71] The

optimal duration of rhythm monitoring is yet undefined, with a hint that the longer the better; this makes automatically triggered ELR the ideal tool for AF detection in stroke patients,[70 72] with a potential to the implementation of interventions to decrease stroke recurrence, thereby impacting patients' quality of life. Moreover, Sobocinski *et al*[72] reported the current experience in 249 consecutive patients in Stockholm, with ischaemic stroke and no prior AF history: when an intermittent 10 s single-lead ECG recording was obtained twice daily over a 30-day period after the target event, it detected significantly more patients with AF than a 24 h Holter monitoring recorded in the first week: 12 of 17 patients with AF were identified by serial ECG recording only, compared with 2 of 17 by Holter monitoring only.[72]

Management of AF is a challenging clinical problem in itself. In the Indian environment, this challenge is often compounded by the dearth of antiarrhythmic drugs, low penetration of radio frequency ablation, and the exacerbation of the issue by the prevalence of rheumatic valvular heart disease.[73]

There are currently no clinical guidelines that guide practitioners for the use of ambulatory monitoring specifically for AF patients.[74] However, ambulatory arrhythmia monitoring technology can be beneficial for burden monitoring of paroxysmal AF, diagnosis of AF as a cause of cryptogenic stroke, and for the titration of antiarrhythmic therapy.

The rate of AF diagnosis remains low, primarily because of its often asymptomatic nature. One-third of patients with AF are unaware of their diagnosis, and a quarter of those with AF-related stroke had no prior AF diagnosis.[63 64] Unfortunately, Holter monitors have an average yield of only 1–5% for AF detection.[71] Detection of AF often leads to a change in the medical management of the patient, such as starting oral anticoagulation therapy,[71] or improving rhythm/rate control to prevent heart failure-related hospitalisations that are proven to represent 75% of the global expenditures for heart failure management.[75] Early detection and treatment is preferred, and a comprehensive monitoring strategy can help achieve this goal.

Ambulatory monitoring has also been proposed to assess the effects of antiarrhythmic therapy. It provides a quantitative assessment of drug efficacy. The main theory for this technique is that serial monitoring of the ECG from a baseline while adjusting level of therapy will aid in mitigating the frequency or type of arrhythmia.

The American College of Cardiology, and the American Heart Association have delineated the following guidelines for ambulatory ECG assessment for antiarrhythmic therapy.[76]

Class I: assessment of antiarrhythmic drug response for well-characterised baselines (reproducible and sufficient frequency). Class IIa: detection of proarrhythmic responses in high-risk patients. Class IIb: (1) rate control assessment during AF and (2) documentation of arrhythmia during antiarrhythmic therapy.

Recent studies also suggest that reliance on symptom mitigation, or resting ECGs for the abolition of AF, can overestimate the success rate of ablation procedures and misconstrue patients with paroxysmal AF as being in sinus rhythm. Forty-eight-hour Holter monitoring can also lead to success overestimation. A study of 647 patients involving AF detection demonstrated that longer-duration monitoring was superior to intermittent rhythm monitoring for detection of AF.[77]

CONTRAINDICATIONS FOR AMBULATORY MONITORING

Though long-term ECG monitoring has many diagnostic benefits, it should be avoided for patients with acute medical issues or high-risk criteria that require immediate medical attention. The list for such criteria is nondescript, but could include acute angina, severe anaemia, acute kidney failure, or a plethora of other pressing issues. Furthermore, some patients may exhibit contact dermatitis to the self-adhesive ECG electrodes. In such cases, the skin irritation may interfere with patient compliance. In India, where much of the subcontinent is subject to a humid subtropical climate, excessive perspiration may exacerbate this situation. Though instances of severe rash may be rare, continuation of monitoring should be under the medical management of the physician and individual patient.

COST EFFECTIVENESS

In India, resting ECG remains the first choice as diagnostic tool for symptomatic patients with suspected heart disease or arrhythmia. Over 150 million resting ECGs are performed globally on an annual basis.[78] The yield of the resting ECG, usually 30 s in duration, is only 12%.[26] The cost range of a 12-lead ECG recording in India is between Rs 150 and Rs 500 , inclusive of government hospitals and private centres, respectively (personal observation). Given the low cost and little time investment by the patient and hospital staff, the resting ECG seems a logical first step despite the low yield.

Further investigation is warranted when the primary measures are ineffective. The next step usually involves referral to a specialist or Holter monitoring.[24] The average cost to the patient for 48 h Holter monitoring ranges between Rs 1500 and Rs 3000, much of the variability due to private versus public institution cost structures. The initial cost for a 7-day ELR can be more than twice the cost of a 48 h Holter. Upon first evaluation, patients may opt for the diagnostic modality with the lower upfront cost. However, when the poor diagnostic yield and low patient compliance of the Holter are taken into account, the ELR is a much more cost-effective option. This notion was confirmed in a study of 43 patients who were selected either for event monitoring or Holter monitoring: event monitors resulted in a cost saving of US$213 for each additional diagnostic rhythm strip obtained during symptoms.[62]

The reduced upfront cost of lower-yielding diagnostics is often a red herring for more efficacious, longer-duration monitoring methods. Patients who select a less expensive diagnostic method that is for a shorter duration, may not have a useful result and often ultimately pay for more expensive, higher-yielding modalities in order to arrive at a diagnosis.

Another often overlooked metric for cost effectiveness is the amount of time required to analyse collected patient data. A cardiologist can interpret a Holter monitor recording in 16 min, provided that background noise, artefacts and QRS classification are worked out upstream by qualified technicians, whereas ELR data are interpreted in about 2 min.[62] Additionally, if a monitoring centre is used, the work load required by the clinic staff is reduced as the reporting and interpretation are done by the ECG-qualified technicians at the centre. Such arrhythmia-monitoring centres have been shown to reduce the number of low-risk patients who are unnecessarily referred to specialty centres,[79] thereby limiting resource deployment.

CONCLUSION

Because of limited reimbursement and insurance coverage in India, the judicious use of high-yield diagnostic tools is important. Particularly for developing countries, proper patient selection for diagnosis of arrhythmia can lead to improved patient outcomes, higher diagnostic yield, more efficient use of medical resources and less time and money spent by the patient. ELRs are the paradigm of a cost-effective new technology with a potential to replace Holter in the workup of patients with

symptom frequency less than thrice a week that is still largely underused by the medical community.

Maneesh Shrivastav,[1] Rajendra Shrivastav,[2] Jitendra Makkar,[3] Mauro Biffi[4]

[1]India Medtronic Private Limited, Mumbai, Maharashtra, India
[2]Private Surgical Practice, Pontiac, Illinois, USA
[3]Department of Cardiology, Fortis Escorts Hospital, Jaipur, India
[4]Institute of Cardiology, University of Bologna, Bologna, Italy

Correspondence to Dr Maneesh Shrivastav, India Medtronic Private Limited, 1241Solitaire Corporate Park, Andheri-Ghatkopar Link Road, Andheri East, Mumbai 400 093, India; maneesh@ieee.org

Contributors MS: main author for composition, figures, graphs, abstract, responsible for submission, corresponding author. RS: responsible for writing clinical and emergency medicine sections. JM: senior electrophysiologist responsible for reviewing clinical sections, use cases of diagnostics and discussing comparative measures for arrhythmia detection. MB: senior electrophysiologist responsible for writing clinical sections and discussing comparative measures for arrhythmia detection.

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REFERENCES

1 Shrivastav M, Shrivastav R, Iaizzo PA. Following the beat of cardiac potentials. *IEEE Potentials* 2007;26:19–25.
2 World Health Organization. Global health advisory. 2009.
3 Sullivan F. Analysis for the Indian healthcare industry. 2007.
4 DeMaria AN. Cardiology in India. *J Am Coll Cardiol* 2010;56:678–9.
5 Shu J, Zhou J, Patel C, *et al*. Pharmacotherapy of cardiac arrhythmias–basic science for clinicians. *Pacing Clin Electrophysiol* 2009;32:1454–65.
6 Rao BH, Sastry BKS, Korabathina R, *et al*. Sudden cardiac death after acute ST elevation myocardial infarction: insight from a developing country. *Heart Asia* 2012;4:83–9.
7 Madhavan SR, Reddy S, Panuganti PK, *et al*. Epidemiology of sudden cardiac death in rural South India—insights from the Andhra Pradesh rural health initiative. *Indian Pacing Electrophysiol Jo* 2011;11:93–102.
8 Rao BH, Sastry BK, Chugh SS, *et al*. Contribution of sudden cardiac death to total mortality in India—a population based study. *Int J Cardiol* 2012;154:163–7.
9 Pandian JD, Srikanth V, Read SJ, *et al*. Poverty and stroke in India: a time to act. *Stroke* 2007;38:3063–9.
10 Pulgaron ER, Wile D, Schneider K, *et al*. Quality of life and psychosocial functioning of children with cardiac arrhythmias. *Cardiol Young* 2012:1–7.
11 Compassion vs. cost: improving the prognosis for India's health care sector. *India Knowledge@Wharton*: Wharton, 2010.
12 Centers for Medicare & Medicaid Services. National Health Expenditure Data, 2012.
13 Cruickshank J. Initial management of cardiac arrhythmias. *Aust Fam Physician* 2008;37:516–20.
14 Linzer M, Yang EH, Estes NA III, *et al*. Diagnosing syncope. Part 1: Value of history, physical examination, and electrocardiography. Clinical Efficacy Assessment Project of the American College of Physicians. *Ann Intern Med* 1997;126:989–96.
15 van Dijk N, Boer KR, Colman N, *et al*. High diagnostic yield and accuracy of history, physical examination, and ECG in patients with transient loss of consciousness in FAST: the Fainting Assessment study. *J Cardiovasc Electrophysiol* 2008;19:48–55.
16 Boonyasirinant T, Suksamai J, Panintrarak P, *et al*. The incidence of clinically significant ECG abnormalities detected by routine everyday ECG: the first analysis from CCU/ICCU patients in Siriraj Hospital. *J Med Assoc Thai* 2012;95(Suppl 2): S173–8.
17 Engel JM, Chakravarthy N, Katra RP, *et al*. Estimation of patient compliance in application of adherent mobile cardiac telemetry device. *Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE*; 2011:1536–9.
18 Corventis Inc. St. Paul, Minnesota, USA.
19 Hoefman E, Bindels PJ, van Weert HC. Efficacy of diagnostic tools for detecting cardiac arrhythmias: systematic literature search. *Netherlands Heart J* 2010;18:543–51.
20 Shrivastav M, Padte S, Joshi C, *et al*. A 125 patient pilot study for ambulatory ECG monitoring using a wireless ELR in India. *Asia Pacific Heart Rhythm Society*. Taiwan, 2012.
21 Task Force members, Brignole M, Vardas P, *et al*. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace* 2009;11:671–87.
22 Bastawrous A, Armstrong MJ. Mobile health use in low- and high-income countries: an overview of the peer-reviewed literature. *J R Soc Med* 2013;106:130–42.
23 Lau JK, Lowres N, Neubeck L, *et al*. iPhone ECG application for community screening to detect silent atrial fibrillation: A novel technology to prevent stroke. *Int J Cardiol* 2013;165:193–4.
24 Rao K. Health insurance in India. *Financing and delivery of health care services in India*, 2005.
25 Mukherjee W. India Inc cuts down on employees' medical reimbursements as healthcare costs rise. *Economic Times* 2012.
26 Mitro P, Kirsch P, Valocik G, *et al*. A prospective study of the standardized diagnostic evaluation of syncope. *Europace* 2011;13:566–71.
27 Croci F, Brignole M, Alboni P, *et al*. The application of a standardized strategy of evaluation in patients with syncope referred to three syncope units. *Europace* 2002;4:351–5.
28 Sarasin FP, Carballo D, Slama S, *et al*. Usefulness of 24-h Holter monitoring in patients with unexplained syncope and a high likelihood of arrhythmias. *Int J Cardiol* 2005;101:203–7.
29 Soteriades ES, Evans JC, Larson MG, *et al*. Incidence and prognosis of syncope. *N Engl J Med* 2002;347:878–85.
30 Kuhne M, Schaer B, Moulay N, *et al*. Holter monitoring for syncope: diagnostic yield in different patient groups and impact on device implantation. *QJM* 2007;100:771–7.
31 Yadav P, Sethi A, Agarwal AK, *et al*. Syncope. *J Indian Acad Clin Med* 2003;4:286–91.
32 Shukla GJ, Zimetbaum PJ. Cardiology patient page. Syncope. *Circulation* 2006;113: e715–17.
33 Kapoor WN. Evaluation and management of the patient with syncope. *JAMA* 1992;268:2553–60.
34 Arya A, Haghjoo M, Khosrawi A, *et al*. Predictors of arrhythmic events during second day monitoring in patients with normal first day Holter recordings. *Indian Heart J* 2005;57:241–4.
35 Hegazy RA, Lotfy WN. The value of Holter monitoring in the assessment of Pediatric patients. *Indian pacing Electrophysiol J* 2007;7:204–14.
36 Sivakumaran S, Krahn AD, Klein GJ, *et al*. A prospective randomized comparison of loop recorders versus Holter monitors in patients with syncope or presyncope. *Am J Med* 2003;115:1–5.
37 Krahn AD, Klein GJ, Yee R, *et al*. Final results from a pilot study with an implantable loop recorder to determine the etiology of syncope in patients with negative noninvasive and invasive testing. *Am J Cardiol* 1998;82:117–19.
38 Krahn AD, Klein GJ, Yee R, *et al*. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. *Circulation* 2001;104:46–51.
39 Krahn AD, Klein GJ, Yee R, *et al*. Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators. *Circulation* 1999;99:406–10.
40 Rothman SA, Laughlin JC, Seltzer J, *et al*. The diagnosis of cardiac arrhythmias: a prospective multi-center randomized study comparing mobile cardiac outpatient telemetry versus standard loop event monitoring. *J Cardiovasc Electrophysiol* 2007;18:241–7.
41 Subbiah R, Gula LJ, Klein GJ, *et al*. Syncope: review of monitoring modalities. *Curr Cardiol Rev* 2008;4:41–8.
42 Seidl K, Rameken M, Breunung S, *et al*. Diagnostic assessment of recurrent unexplained syncope with a new subcutaneously implantable loop recorder. Reveal-Investigators. *Europace* 2000;2:256–62.
43 Herrmann-Lingen C. [Psychosomatic aspects of chronic heart failure. Nothing but depression?]. *Herz* 2011;36:135–40.
44 Herrmann-Lingen C. [Anxiety and depression in cardiology patients: how to diagnose, how to treat?]. *Herz* 2001;26:326–34.
45 Shanbhag S, Sumitha PV. Indian rural markets: issues and challenges for corporates. *Asia Pacific Journal of Research in Business Management* 2011;2:274–80.
46 Bogun F, Anh D, Kalahasty G, *et al*. Misdiagnosis of atrial fibrillation and its clinical consequences. *Am J Med* 2004;117:636–42.
47 Huikuri HV, Mahaux V, Bloch-Thomsen PE. Cardiac arrhythmias and risk stratification after myocardial infarction: results of the CARISMA pilot study. *Pacing Clin Electrophysiol* 2003;26:416–19.
48 Bloch Thomsen PE, Jons C, Raatikainen MJ, *et al*. Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study. *Circulation* 2010;122:1258–64.

49 Bhardwaj R, Kandoria A, Marwah R, *et al*. Prevalence of rheumatic fever and rheumatic heart disease in rural population of Himachal- a population based study. *J of Assn of Physicians of India* 2012;60:13–4.
50 White H, Walsh W, Brown A, *et al*. Rheumatic heart disease in indigenous populations. *Heart Lung Circ* 2010;19:273–81.
51 Sinha K. Rheumatic heart disease on the rise in India. *Times of India*. Mumbai, 2012.
52 Saxena A, Ramakrishnan S, Roy A, *et al*. Prevalence and outcome of subclinical rheumatic heart disease in India: the RHEUMATIC (Rheumatic Heart Echo Utilisation and Monitoring Actuarial Trends in Indian Children) study. *Heart* 2011;97:2018–22.
53 Eisen A, Arnson Y, Dovrish Z, *et al*. Arrhythmias and conduction defects in rheumatological diseases–a comprehensive review. *Semin Arthritis Rheum* 2009;39:145–56.
54 Vora A. Management of atrial fibrillation in rheumatic valvular heart disease. *Curr Opin Cardiol* 2006;21:47–50.
55 Marijon E, Ou P, Celermajer DS, *et al*. Prevalence of rheumatic heart disease detected by echocardiographic screening. *N Engl J Med* 2007;357:470–6.
56 Nair M, Shah P, Batra R, *et al*. Chronic atrial fibrillation in patients with rheumatic heart disease: mapping and radiofrequency ablation of flutter circuits seen at initiation after cardioversion. *Circulation* 2001;104:802–9.
57 Walsh WF. Medical management of chronic rheumatic heart disease. *Heart Lung Circ* 2010;19:289–94.
58 Jung W, Zvereva V, Rillig A, *et al*. How to use implantable loop recorders in clinical trials and hybrid therapy. *J Interv Card Electrophysiol* 2011;32:227–32.
59 Engel G, Mead RH. Remote monitoring for atrial fibrillation. *Congest Heart Fail* 2008;14:14–18.
60 Solano A, Menozzi C, Maggi R, *et al*. Incidence, diagnostic yield and safety of the implantable loop-recorder to detect the mechanism of syncope in patients with and without structural heart disease. *Eur Heart J* 2004;25:1116–19.
61 Abbott AV. Diagnostic approach to palpitations. *Am Fam Physician* 2005;71:743–50.
62 Kinlay S, Leitch JW, Neil A, *et al*. Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with palpitations. A controlled clinical trial. *Ann Internal Medicine* 1996;124:16–20.
63 Scherr D, Dalal D, Henrikson CA, *et al*. Prospective comparison of the diagnostic utility of a standard event monitor versus a "leadless" portable ECG monitor in the evaluation of patients with palpitations. *J Interv Card Electrophysiol* 2008;22:39–44.
64 Israel CW, Gronefeld G, Ehrlich JR, *et al*. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. *J Am Coll Cardiol* 2004;43:47–52.
65 Capucci A, Santini M, Padeletti L, *et al*. Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. *J Am Coll Cardiol* 2005;46:1913–20.
66 Jabaudon D, Sztajzel J, Sievert K, *et al*. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. *Stroke J Cereb Circ* 2004;35:1647–51.
67 Conen D, Osswald S, Albert CM. Epidemiology of atrial fibrillation. *Swiss Med Wkly* 2009;139:346–52.
68 Patwardhan AM. Ablation surgery for atrial fibrillation: "freeze it or buzz it; just do it and cure it". *Indian pacing Electrophysiol J* 2005;5:251–3.
69 Stahrenberg R, Weber-Kruger M, Seegers J, *et al*. Enhanced detection of paroxysmal atrial fibrillation by early and prolonged continuous Holter monitoring in patients with cerebral ischemia presenting in sinus rhythm. *Stroke* 2010;41:2884–8.
70 Kamel H, Hegde M, Johnson DR, *et al*. Cost-effectiveness of outpatient cardiac monitoring to detect atrial fibrillation after ischemic stroke. *Stroke* 2010;41:1514–20.
71 Liao J, Khalid Z, Scallan C, *et al*. Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review. *Stroke* 2007;38:2935–40.
72 Doliwa Sobocinski P, Rooth E Anggardh, Kull V Frykman, *et al*. Improved screening for silent atrial fibrillation after ischaemic stroke. *Europace* 2012;14:1112–16.
73 Vora A. Approach to management of atrial fibrillation in the Indian scenario. *J Assoc Physicians India* 2007;55(Suppl):30–2.
74 Mittal S, Movsowitz C, Steinberg JS. Ambulatory external electrocardiographic monitoring: focus on atrial fibrillation. *J Am Coll Cardiol* 2011;58:1741–9.
75 American Heart Association. Heart and stroke statistical update, 2003.
76 Crawford MH, Bernstein SJ, Deedwania PC, *et al*. ACC/AHA Guidelines for Ambulatory Electrocardiography. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). Developed in collaboration with the North American Society for Pacing and Electrophysiology. *J Am Coll Cardiol* 1999;34:912–48.
77 Charitos EI, Stierle U, Ziegler PD, *et al*. A comprehensive evaluation of rhythm monitoring strategies for the detection of atrial fibrillation recurrence: insights from 647 continuously monitored patients and implications for monitoring after therapeutic interventions. *Circulation* 2012;126:806–14.
78 Ashley EA, Raxwal V, Froelicher V. An evidence-based review of the resting electrocardiogram as a screening technique for heart disease. *Prog Cardiovasc Dis* 2001;44:55–67.
79 Skipsey DA, Dawson FM, Breen C, *et al*. Evaluation of a direct access cardiac arrhythmia monitoring service. *Cardiol J* 2012;19:70–5.
80 Malaviya AN, Kapoor SK, Singh RR, *et al*. Prevalence of rheumatoid arthritis in the adult Indian population. *Rheumatol Int* 1993;13:131–4.
81 Malaviya AN, Singh RR, Singh YN, *et al*. Prevalence of systemic lupus erythematosus in India. *Lupus* 1993;2:115–18.
82 Gaubitz M. Epidemiology of connective tissue disorders. *Rheumatology* 2006;45 (Suppl 3):iii3–4.
83 Chifflot H, Fautrel B, Sordet C, *et al*. Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin Arthritis Rheum* 2008;37:223–35.
84 Gunnarsson R, Molberg O, Gilboe IM, *et al*. The prevalence and incidence of mixed connective tissue disease: a national multicentre survey of Norwegian patients. *Ann Rheum Dis* 2011;70:1047–51.
85 Sood A, Kumar A, Pande I, *et al*. Does mixed connective tissue disease exist in India? *Br J Rheumatol* 1995;34:539–41.
86 Hall S, Barr W, Lie JT, *et al*. Takayasu arteritis. A study of 32 North American patients. *Medicine* 1985;64:89–99.
87 India KDF. Kawasaki disease—Indian perspective, 2012.
88 Rabinovich CE, Wagner-Weiner L. Behcet syndrome, 2012.
89 Cotch MF, Hoffman GS, Yerg DE, *et al*. The epidemiology of Wegener's granulomatosis. Estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. *Arthritis Rheum* 1996;39:87–92.
90 Nunes H, Bouvry D, Soler P, *et al*. Sarcoidosis. *Orphanet J Rare Dis* 2007;2:46.
91 Mehndiratta MM, Bhattacharya A, Gupta M, *et al*. Antiphospholipid antibodies syndrome in 'Stroke in young'. *Neurology India* 1999;47:122–6.
92 Gezer S. Antiphospholipid syndrome. *Disease-a-month: DM* 2003;49:696–741.