TITLE

New Perspectives on Diagnosis and Misdiagnosis in Blackouts

A thesis submitted to the University of Manchester for the degree of

Doctor of Medicine (MD)

in the

Faculty of Medical and Human Sciences

2013

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CONTENTS

Word count: 29,210

Abstract

The University of Manchester

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Patients presenting with an abrupt loss of postural control are commonly said to have had 'collapse?cause'. This is a common presentation, accounting for up to 6% of emergency department cases, and 3% of hospital admissions. However, collapse?cause is a 'catch-all' term and there are many different causes which include falls, transient ischemic attacks, cerebrovascular accidents, road traffic accidents, metabolic abnormalities, intoxication, and transient loss of consciousness, (TLOC or 'blackout'). A majority of patients fall into the latter category. Where TLOC has occurred, the causes are syncope, epilepsy and psychogenic blackouts. The clinical features of these three conditions can often be similar, albeit with subtle differences. A wide variation exists in the way such patients are assessed, investigated and managed, who manages them and where. There is an absence of simple clinical tools for assessment, poor risk stratification, inappropriate and overuse of investigations. Hospitalisation is often unnecessary and misdiagnoses are common. In this thesis, the problem of TLOC has been addressed in four projects. Section 1 (Chapter II): reports a simple new risk stratification scheme for patients presenting with TLOC, assessed in a specialist nurse lead, cardiologist supervised (SP), Rapid Access Blackouts Triage Clinic - RABTC. Frequently, after triage, a patient may be deemed to be at low risk, but blackouts continue, the cause remains unclear, and conventional tests, have been unhelpful. In Chapter III, we describe the option of investigating such patients by long term (up to 3 years) ECG monitoring using an implantable loop recorder (ILR). In order to address the specific question of misdiagnosis of epilepsy where convulsive syncope might be the true diagnosis, the REVISE Study- **REV**eal in the **I**nvestigation of **S**yncope and **E**pilepsy was undertaken, which is described in Chapter IV. Lastly, convulsive syncope is the likely explanation for a misdiagnosis in patients diagnosed with epilepsy, but the incidence of cardiac disease in patients with brain injury and epilepsy is unknown. Therefore a cohort of patients in a residential epilepsy centre was studied. In this setting, residents typically had a history of brain injury and suffered from recurrent epileptic seizures. The findings of cardiology assessment are presented in Section 4 (Chapter V).

Summary

'New Perspectives on Diagnosis and Misdiagnosis in Patients with Blackouts'

Sections:

(a) Role and impact of systematic clinical and ECG triage in patients presenting with blackouts

(b) Outcomes from the use of Reveal implantable ECG in patients with blackouts

(c) REVISE Study – **REV**eal in the **I**nvestigation of **S**yncope and **E**pilepsy

(d) Cardiovascular screening in patients with epilepsy and special needs

Patients presenting with an abrupt loss of postural control are commonly said to have had 'collapse?cause'. This is a common presentation, accounting for up to 6% of emergency department cases, and 3% of hospital admissions. However, collapse?cause is a "catch-all" term and there are many different causes. These include; falls, transient ischemic attacks, cerebrovascular accidents, road traffic accidents, metabolic abnormalities, drug and alcohol intoxication, and transient loss of consciousness, (TLOC or 'blackout'). A majority of patients fall into the latter category. Where TLOC has occurred, the causes are syncope, epilepsy and psychogenic blackouts. The clinical features of these three conditions can often be similar, albeit with subtle differences. The task for clinicians is; to determine if TLOC took place, (which can be difficult, for example in the elderly, who may forget), to decide if the patient is at high risk, to attribute a cause, and to prevent recurrences. A wide variation exists in the way such patients are assessed, investigated and managed, who manages them and where. There is an absence of simple clinical tools for assessment, poor risk stratification, inappropriate and overuse of investigations. Hospitalisation is often

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unnecessary and misdiagnoses are common. Up to 30% of adults and 40% of children diagnosed and treated for epilepsy do not have it, amounting to at least 100,000 patients in the UK.

In this thesis, the problem of TLOC has been addressed in four projects. Section 1 (Chapter II): This section reports a simple new risk stratification scheme for patients presenting with TLOC, assessed in a specialist nurse lead, cardiologist supervised (SP), Rapid Access Blackouts Triage Clinic - RABTC. Many studies have shown that when the simple clinical assessment is done well, management is cost-effective. Whilst 50-90% of patients are reported to be diagnosed by simple clinical evaluation and a 12-lead ECG, only 10-15% of patients are diagnosed by costly tests in secondary care, such as brain MRI scanning and carotid imaging. Nevertheless, low-risk patients are frequently admitted for long periods for costly investigations with a low yield. In our own local setting in 2004, 300 patients were admitted to Manchester Royal Infirmary for an average of 9 days at an average cost of £7,500, and none went home with a diagnosis. The RABTC has run in the Manchester Heart Centre since 2007, and over 1600 patients have been assessed. The first section of this thesis reviews the early experience of nurse-lead triage using clinical features and the 12-lead ECG, and the medium term outcomes after diagnosis and treatment or lifestyle advice.

Frequently, after triage, a patient may be deemed to be at low risk, but blackouts continue, the cause remains unclear, and conventional tests, such as external ambulatory monitoring and tilt testing have been unhelpful. Where the simple approach fails to determine the cause or detail of a blackout, one option is implantation of an ECG loop recorder, (ILR), for long

term ECG monitoring up to 3 years. The Manchester Heart Centre embraced this technology in large numbers from its early availability in 1997.

Section 2 (Chapter III): In section 2, the results of ILR use in 357 patients assessed at the Manchester Royal Infirmary are given. Over many years it has become clear that convulsive syncope is easily mistaken for generalised epilepsy. Convulsive syncope commonly presents with abrupt TLOC without warning, abnormal limb movements, injuries, tongue-biting, incontinence and a period of post TLOC confusion. This is the likely explanation for the common misdiagnosis of epilepsy. If there is an apparent convulsive episode of blackout, and no evidence of structural heart disease, doctors might easily conclude that the diagnosis must be epilepsy. Frequently, brain imaging and an inter-ictal EEG are done, even though they are often normal in true epilepsy.

Section 3 (Chapter IV): In order to address the specific question of misdiagnosis of epilepsy where convulsive syncope might be the true diagnosis, the REVISE Study **- REV**eal in the **I**nvestigation of **S**yncope and **E**pilepsy was undertaken. This reports the use of ILRs in a population of patients with a diagnosis of epilepsy where neurological review deemed a likely misdiagnosis, and convulsive reflex syncope was thought be a likely explanation.

Section 4 (Chapter V): Convulsive syncope is the likely explanation for a misdiagnosis in patients diagnosed with epilepsy, but the incidence of cardiac disease in patients with brain injury and epilepsy is unknown. Therefore a cohort of patients in a residential epilepsy centre was studied. In this setting, residents typically had a history of brain injury and suffered

from recurrent epileptic seizures. The findings of cardiology assessment are presented in section 4.

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Dedication

This thesis is dedicated to Dr Adam Fitzpatrick, Consultant Cardiologist, Manchester Heart Centre, Manchester Royal Infirmary, Manchester.

I have had the privilege of working with this excellent clinician since 2003. He not only gave me the opportunity to do this research and is my supervisor for this thesis but in the field of cardiology and arrhythmias and syncope in particular, has been my mentor and guide, inspiring me to achieve greater heights and excellence. In addition, he is an exceptional human being.

Acknowledgement

I would like to acknowledge the patience and forbearance displayed by my wife, Anjali and son, Pravar, during the long hours I had to spend in the compilation of this thesis, thus taking away some valuable 'family time'.

The Author

The author, Dr Sanjiv Petkar, is currently working as a substantive Consultant Cardiologist/Electrophysiologist at the New Cross Hospital, Wolverhampton, UK since May 2010.

He undertook his initial medical training overseas, in India. After obtaining his undergraduate degree of MBBS, he went on to do a post graduate degree in general medicine (MD Medicine), and was awarded 3 gold medals in the process for standing first in the University. Subsequently, he was selected (through a stiff competitive examination) to be only one of 5 doctors all over India to undergo a post doctoral fellowship in cardiology. He undertook this training at the GB Pant Hospital, Delhi, India, obtaining the degree of DM (Cardiology) in the process.

He moved to the UK in 1996 and retrained in medicine and cardiology, obtaining the Diploma of the Royal College of Physicians (MRCP) in 1998. Between 2003 and 2009, he worked at the Manchester Heart Centre, Manchester Royal Infirmary. Under the supervision of Dr Fitzpatrick, Consultant Cardiologist, he learnt how to assess, investigate and manage patients with syncope. As a Guideline Development Group Member, he formulated the NICE Guidance on Transient Loss of Consciousness in Adults, which were published in August 2010. This was the first opportunity in his career to undertake a period of scientific research.

Chapter I

Introduction & Background

It is common to come across patients with 'collapse?cause' in emergency care in hospitals. The term 'collapse' is commonly used to describe patients who have suffered an abrupt loss of postural control. However, it is likely that some clinicians use 'collapse' when 'loss of consciousness' is meant.

There are many causes of 'collapse' (Blanc and Benditt, 2003) (Figure 1). These include; road traffic accidents, falls, syncope, epilepsy, cerebrovascular accidents, transient ischemic attacks, drug or alcohol intoxication, and hypoglycaemia. However, by far the commonest cause is syncope. 'Collapse' is not synonymous with transient loss of consciousness, though loss of consciousness frequently results in 'collapse'. Stedman's Medical Dictionary (Stedman's 2011) defines loss of consciousness as 'a mental state that involves near or complete lack of responsiveness to people and other environmental stimuli'. Collapse is 'an abrupt loss of postural control'. This may occur with a fall where consciousness is unchanged or with a blackout where consciousness is lost. In those patients in whom a 'collapse' is caused by loss of consciousness, the duration of unconsciousness is usually transient (Transient Loss of Consciousness - TLOC). TLOC is often referred to by patients, families, and neurologists, as a 'blackout', and similarly, the Oxford English Dictionary defines a 'blackout' as a 'temporary complete loss of consciousness.' Loss of consciousness is the major cause of collapse, and has several important mechanisms that are very different in pathophysiology.

Figure 1. Overview of the problem of Collapse?cause
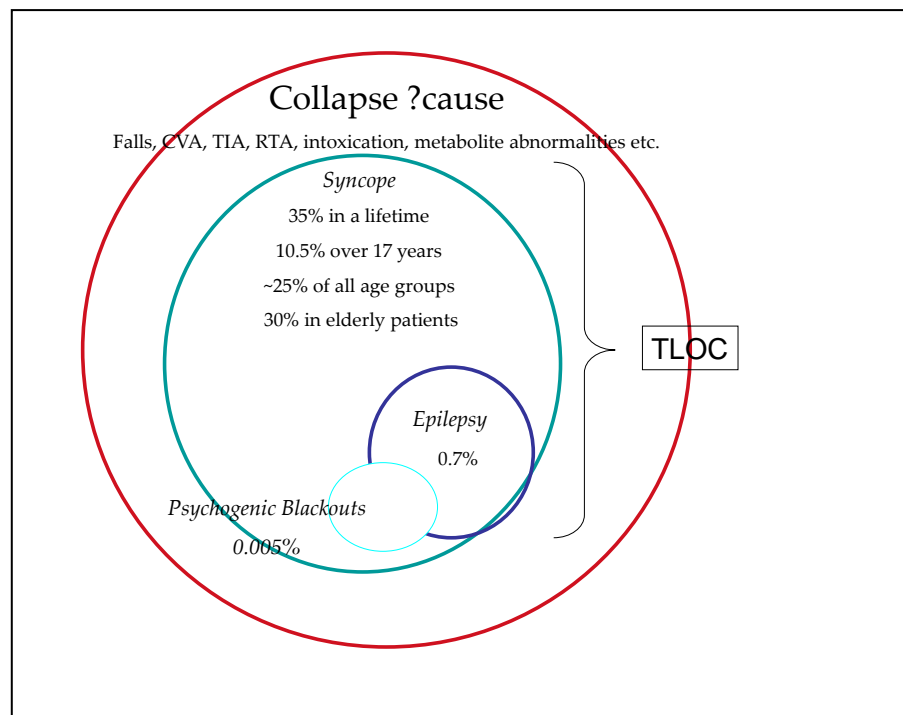
Abbreviations: CVA = cerebrovascular accident; RTA= road traffic accident;

TIA= transient ischemic attack; TLOC=transient loss of consciousness

Common causes of TLOC:

The three common causes of blackouts/TLOC are syncope, epilepsy and psychogenic blackouts (NICE 2009). While the pathophysiology of these conditions is very different, presenting clinical features can be very similar. For example, abnormal limb movements may be seen in Reflex Syncope, generalized epilepsy and psychogenic blackouts.

Syncope

The word syncope is derived from Greek: 'syn' meaning 'with' and 'kopto' meaning 'I cut' or 'I interrupt' (Blanc and Benditt, 2003).

The European Society of Cardiology (Moya et al, 2009) defined syncope as, 'TLOC due to transient global cerebral hypoperfusion characterised by rapid onset, short duration and spontaneous complete recovery'. The National Institute of Clinical Excellence issued guidelines on Transient Loss of Consciousness in Adults and Young Adults (NICE 2010), defining syncope more succinctly as 'a spontaneous, transient, complete loss of consciousness with complete recovery'. This is inexact, because most authorities require the definition of syncope to include the pathophysiology, namely lack of cerebral blood flow. If the pathophysiology is not included, then 'syncope' is merely synonymous with T-LOC, and takes the understanding of the cause no further.

Syncope, in turn, is a phenomenon with many causes (Table 1). The prognosis in patients depends on the underlying cause, and the presence or absence of any structural heart disease. In broad terms, if syncope is due cardiac disease, embolism or haemorrhage, the prognosis is poor, whereas the absence of structural or electrical heart disease confers a good prognosis. The relative frequency of causes of syncope and the impact on prognosis is discussed later in this chapter.

Table 1. Causes of syncope (adapted from Moya et al 2009)

Reflex (neutrally mediated) syncope

Vasovagal: Mediated by emotional distress: fear, pain, instrumentation, blood phobia, or by orthostatic stress

Situational: cough, sneeze, gastrointestinal stimulation (swallow, defaecation, visceral pain), micturition (post micturition), post exercise, post prandial, others (e.g., laughter, brass instrument playing, weightlifting)

Carotid sinus syncope

Atypical forms (without apparent triggers and/or atypical presentation)

Syncope due to orthostatic hypotension

Primary autonomic failure: pure autonomic failure, multi system atrophy, Parkinson's disease with autonomic failure, Lewy body dementia

Secondary autonomic failure: diabetes, amyloidosis, uraemia, spinal cord injuries

Drug induced orthostatic hypotension: alcohol, vasodilators, diuretics, phenothiazines, antidepressants

Volume depletion: haemorrhage, diarrhoea, vomiting, salt depletion

Cardiac Syncope (cardiovascular)

Arrhythmia as primary cause:

Bradycardia: sinus node dysfunction (including bradycardia/tachycardia syndrome), atrioventricular conduction system disease, implanted device malfunction

Tachycardia: supraventricular, ventricular (idiopathic, secondary to structural heart disease, or to channelopathies)

Drug induced bradycardias and tachycardias

Structural disease: *Cardiac:* cardiac valvular disease, acute myocardial infarction/ischaemia. Hypertrophic cardiomyopathy, cardiac masses (atrial myxoma, tumors etc.), pericardial disease/ tamponade, congenital anomalies of coronary arteries, prosthetic valve dysfunction

Others: pulmonary embolism, acute aortic dissection, pulmonary hypertension

Epilepsy

The International League Against Epilepsy (ILAE) (Fisher et al, 2005) and the International Bureau of Epilepsy (IBE) define epilepsy as a 'disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition'. In turn, an 'epileptic seizure' is defined as a 'transient occurrence of signs and/or symptoms due to abnormal excessive or asynchronous neuronal activity in the brain'. It is important to note that an 'epileptic seizure' suffered by an individual may never recur, and the diagnosis of epilepsy should be reserved for those patients with recurrent 'epileptic seizures'.

Psychogenic Seizures

Psychogenic blackouts have been defined as 'episodes of altered movement, sensation, or experience similar to epilepsy, but caused by a psychological process and not associated with abnormal electrical discharges in the brain'

(Rueber and Elger, 2003), to which should probably be added 'or changes in cerebral perfusion', so that the mechanism of syncope can be excluded. It is an abnormality of the psyche which results in an <u>apparent</u> loss of consciousness (Brignole et al, 2004). It is also referred to in the scientific literature as non-epileptic attack disorder or dissociative (conversion) disorder.

It is common for patients with epilepsy to present with abnormal limb movements and other motor manifestations of a seizure or convulsion during an attack. However, patients with syncope commonly present with abnormal limb movements, and this is widely underappreciated. The phenomenon of 'seizure' during syncope was elegantly demonstrated in the study by Lempert et al (1994). He induced syncope by evoking the 'mess trick' in 59 healthy German medical students. All events were monitored by two video cameras. TLOC with collapse, for a mean duration of 12.1±4.4 seconds, was seen in 42/56 (75%) of the subjects. Myoclonic jerks were observed in 38/42 (90.5%). This consisted of multifocal arrhythmic jerks in proximal and distal muscles, with some additional movements seen in 79% of the cohort. What was observed and recorded therefore, were the effects of anoxic irritation of the brain when the "mess trick" transiently cut cerebral perfusion below a level where consciousness and postural tone could be maintained and included myoclonic jerks caused by anoxic irritation of the motor cortex. In another study by Zaidi et al (2000), 63% of patients with a positive tilt test exhibited myoclonic jerks. While abnormal limb movements can be seen in patients during a syncopal attack, the manner of abnormal movements differs from those seen in epilepsy. Myoclonic jerks are distinguishable from tonic-clonic movements, particlularly by an expert, but not necessarily by a by-stander witness to a blackout. A lack of knowledge of this in an eye-witness can easily result in syncope being misinterpreted as

epilepsy. Where this occurs, it is 'convulsive syncope' that has been witnessed, not generalized epilepsy. A misdiagnosis of convulsive syncope as generalized epilepsy probably accounts for the high incidence of misdiagnosis of epilepsy.

Other clinical features (Blanc and Benditt, 2003) which help to distinguish epilepsy from syncope are as follows (Table 2):

Table 2: Differentiating clinical features between epilepsy and syncope

Clinical findings that suggest the diagnosis	*Epilepsy Likely*	*Syncope likely*
Symptoms before the event	-Blue face -Aura (such as olfactory illusions)	Nausea, vomiting, abdominal discomfort, feeling of cold, sweating (neutrally-mediated)
Findings during loss of consciousness (as observed by an eye-witness	- Tonic-clonic movements are usually prolonged and their onset coincides with loss of consciousness (<15 secs) - Hemilateral clonic movement - Clear automatisms such as chewing or lip smacking or frothing at the mouth - Tongue biting – side of the tongue	Jerky movements are always of short duration and they start after the loss of consciousness - Tongue biting - tip of the tongue

Symptoms after the event	- Prolonged confusion - Aching muscles	- Usually short duration - Nausea, vomiting, pallor (neurally mediated)

Symptoms of TLOC are episodic and infrequent and usually patients are well when they see a clinician. They are able to give a history of the events before and after an event. As highlighted in the above table, often clinicians are dependent on the accuracy of an eye witness account, if available, on the events during an episode of TLOC. In addition, opportunities for measuring physiological parameters during an episode of TLOC are limited, being hampered by the availability and cost of technology. Health care practitioners therefore fall back on clinical assessment to establish a diagnosis, prevent a misdiagnosis and deliver appropriate treatment. However, when all causes of TLOC can present with or without warning, abnormal limb movements such as myoclonic jerks or tonic-clonic activity, incontinence, tongue biting and injuries, and clinical assessment is very variable, misdiagnoses occur. This thesis has examined some aspects of these challenges and how to overcome them.

TLOC is very common, and a great burden on the NHS.

The cumulative lifetime incidence of syncope (i.e. the percentage of people who have experienced at least one episode in their life) ranges from 35 to 50% (Soteriades et al 2002; Serletis et al 2006; Ganzeboom et al, 2006). The original Framingham Heart Study and the Framingham Offspring Study (Soteriades et al 2002), assessed the incidence of TLOC among 7814

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participants (3563 men and 4251 women) over a 17 year period (1971 to 1998). In this primary care longitudinal study, 822 (10.5%) reported an episode of TLOC with an incidence of first reported TLOC of 6.2 per 1000 person years. Transient loss of consciousness was more common with increasing age, with a sharp rise at 70 years. Overall, just over half (56 percent) of participants with an episode of TLOC reported seeing a doctor or visiting a hospital for evaluation. A majority of patients 570 (78.4%) reported only one episode of TLOC with 17.6% experiencing TLOC on a second occasion. The risk of recurrence was especially high among those with a cardiac cause of TLOC i.e., syncope.

In another primary care study undertaken in the Netherlands (Colman et al 2004) the reasons for patients visiting their general practitioners was examined. It showed that 2 to 9 per 1000 encounters were for blackouts or fainting, with Reflex Syncope the most likely underlying condition.

Among the causes of TLOC, syncope is the most common. Globally, it accounts for 1.0-1.5% of emergency room visits and up to 6% of general hospital admissions (Silverstein et al 1982; Ammirati et al 1999; Blanc et al 2002; Quinn et al 2004). Syncope occurs twice more often in women than in men (Colman 2004 et al; Gazenboom 2006). Among the elderly in long term care, the annual incidence of syncope has been reported to be as high as 6% (Lipsitz et al 1985).

Among the other common causes of TLOC, epilepsy, though the commonest chronic neurological disorder in the United Kingdom, is much less common than syncope. The annual incidence of epilepsy in the UK is 50 per 100,000 population (30,000 new cases per year), with a lifetime prevalence of 0.5-1.0%

(Stokes et al, 2004). There are estimated to be between 260,000 and 416,000 patients with epilepsy in England and Wales (Stokes et al, 2004) at any time.

Reliable information on the incidence or prevalence of psychogenic blackouts in the general population is lacking but is estimated to be between 2 and 33 per 100,000 population (Benbadis and Allen Hauser, 2000). It coexists with epilepsy and can be found in up to 20% of patients referred for surgery for refractory epilepsy (Rueber and Elger, 2003). Psychogenic blackouts typically present in women between 20 and 30 years of age (Rueber and Elger, 2003) with up to 80% having previously presented with unexplained symptoms (Mellers, 2005).

Why is a diagnosis so important?

Diagnosis of the cause of an episode of TLOC is very important as appropriate assessment of the cause of TLOC and the correct treatment cannot proceed without a diagnosis. Review of the literature reveals that up to 30% of adults and 40% of children are misdiagnosed. Frequently, patients with convulsive syncope are misdiagnosed as suffering from epilepsy because of a number of reasons. Firstly, it is poorly appreciated that convulsive syncope can present with abnormal movements of the arms and legs, similar to generalised epilepsy. Usually when such patients are assessed, they are well and have no significant findings, having recovered from their episode of TLOC. A history of abnormal movements ('seizure') thus may prompt referral for neurological assessment. Secondly, it is known that ECGs are only done in about 4% of neurology clinics. Where epilepsy is suspected and a patient referred for a neurological assessment without a triage assessment, an ECG may not be done or may be misinterpreted,

missing a significant abnormality. There are small but significant numbers of patients with a diagnosis of epilepsy who die of sudden cardiac arrest each year. Registry data shows that the underlying diagnosis in some (~6%) of these patients is Long QT syndrome (Moss AJ et al 1991).   Lastly, a diagnosis of epilepsy has a major impact on patients and families, and epilepsy drug treatment has serious potential adverse effects, including foetal deformities. .

Why clinical triage for blackouts?

There is a tendency on the part of physicians looking after patients with TLOC to use tests and neglect clinical evaluation. Uncertainties lead to dependency on tests, and uncertainties are inevitable when no tests are done at the time of the blackout, and patients may appear completely normal during the hospital stay. House staff will tend to request a battery of tests at the onset of an admission after TLOC, hoping that this will provide a diagnosis in the shortest period of time. These tests will often be negative, and rather than shortening hospital stay, may result in a patient being detained in hospital because of pressures on investigations such as brain scanning. Local data demonstrated this phenomenon. Between April 2003 and March 2004, 305 patients (age: 65.6 ± 21.6 years) were admitted to the Central Manchester and Manchester Children's NHS Trust for Syncope and Collapse. Their mean length of stay was 7.61 ± 13.9 days at an average cost of £7500. A majority of the patients were admitted under the General Physicians and left the hospital without a diagnosis implying that they had not been risk stratified (personal communication, Caroline Davidson, Director of Planning, Manchester Primary Care Group, 2004). Linzer et al, 1997, undertook a meta- analysis of 6 published studies and showed that in

half of patients, it was possible to establish a diagnosis of the cause of TLOC using simple methods i.e. history, physical examination and an ECG. In addition, the results of the Fainting Assessment Study (van Dijk et al, 2008) showed that attending physicians could make a diagnosis, based on initial evaluation, in 63% of patients with TLOC, with an overall diagnostic accuracy of 88%. The authors therefore concluded that the use of additional testing, beyond history, physical examination, and ECG could be avoided in many patients presenting with TLOC.

On the other hand, the following three studies highlight the tendency of physicians looking after patients with TLOC to rely on tests, in the process over investigating patients and wasting scarce resources.

Calkins et al (1993) evaluated the cost of prior diagnostic evaluation in 30 consecutive patients referred for evaluation of syncope to the University of Michigan Medical Centre, USA where the history was typical for vasodepressor syncope. Calkins 30 patients represented 19% of the 158 patients referred to this center for evaluation of syncope. A mean of 4±2 major diagnostic tests [e.g., echocardiography, Holter monitoring, computerized tomographic (CT) scans of the head, electroencephalograms (EEGs), magnetic resonance imaging (MRI), glucose tolerance tests, and carotid Doppler studies] had been performed prior to referral at a mean cost (at 1991 cost levels) of $3,763±3,820 and a median cost of $2,678 (range: 0-$16,606). Hence, the results showed that failure to adequately assess and rely upon the clinical features of vasodepressor syncope resulted in up to $16,000 of unnecessary diagnostic testing.

Pires et al (2001) evaluated diagnostic patterns and trends, and use of specialty consultations in the evaluation of syncope in 649 patients. They found that costly low yield neurological tests were overused, higher yield

cardiovascular tests were underused and that untargeted random use of specialist evaluations did not contribute to an increase in diagnoses. In their opinion, the increased use of specific tests directed by history and results of physical examination could improve diagnostic yield and decrease the cost of evaluating TLOC.

Farwell and Sulke (2004) assessed the efficacy of a protocol for diagnosis and management of syncope in a district general hospital in the United Kingdom. They prospectively compared 421 patients with syncope from January 2000 with 660 retrospective patients from the calendar year 1998. They found that by 2001, the behavior of clinicians had undergone a change and that they were using tests with the highest diagnostic yield more often. However, disappointingly, non-diagnostic tests, resulting in wasted resources, were still being used (e.g. chest radiography, electroencephalography and carotid Doppler studies).

At the initial presentation, it is very important to assess the prognosis of the patient with TLOC and it is dependent on the cause of TLOC. This is because the Framingham Heart Study and the Framingham Offspring Study (Soteriades et al 2002), showed that the risk of death was increased by 31 percent among all participants with syncope and was doubled among participants with cardiac syncope, when compared with those without syncope. Syncope of unknown cause was associated with an intermediate increased risk of death while vasovagal syncope (including orthostatic syncope, medication-related syncope, and syncope due to other, infrequent causes) was associated with a benign prognosis. Olshansky et al (2008) compared the outcome in patients with and without syncope enrolled in the Sudden Cardiac Death in Heart Failure Study (SCD-HeFT). Patients in this study had left ventricular systolic dysfunction with an ejection fraction of

≤35% of ischemic as well as non ischemic aetiology. Like the Framingham Heart Study (Soteriades et al 2002) syncope in the presence of underlying cardiac disease was associated with an increased mortality, regardless of the treatment arm (placebo, amiodarone or implantable cardioverter defibrillator). Other studies (Middlekauff et al 1993; Brignole et al 2004; Colman et al 2004) have also shown similar results.

Because clinical assessment can be neglected in favour of tests, a 12-lead ECG is the highest yield test, identifiable clinical risk factors determine prognosis and because misdiagnosis is both common and damaging, we decided to design and establish a clinical triage setting for blackouts. The aim was to provide a standardized clinical assessment using a computerized assessment tool incorporating a detailed questioning of the clinical background, build-up to, features of, and recovery from TLOC, from the patient and eye-witnesses. In another novel approach, we recruited specialist nurses in cardiology/arrhythmias, epilepsy and falls to undertake the computerized assessments. A Specialist-Nurse-Lead Rapid Access Blackouts Triage Clinic was therefore established at the Manchester Heart Centre, Manchester Royal Infirmary in 2007. A clinical assessment was aimed at diagnosing the cause of TLOC, triaging patients into the right care pathway and risk stratifying them into 'high' and 'low' risk groups, utilizing a new risk stratification scheme, and ensuring rapid onward specialist assessment in non-cardiac and high risk patients.

By using this approach, we aimed to:

- diagnose the cause of TLOC, at the initial assessment where possible
- decrease hospitalization for low risk patients with blackouts/TLOC
- decrease the use of unnecessary investigations

- direct patients to the most appropriate specialist care promptly, and prevent patients becoming 'stuck' in the wrong care-pathway
- prevent patients with TLOC being managed in different settings [viz.; Falls Clinics required by the National Service Framework for the Older People (2001), Epilepsy Clinics, required by National Institute of Clinical Excellence Guidelines for Epilepsy (2004) and Syncope Clinics, required by the National Service Framework for Heart Diseases- Chapter 8 (2005)]
- develop cross-specialty specialist nursing experience and skills in blackouts/TLoC

Why nurse-led assessments?

In order to provide capacity for rapid access, which would be very difficult to ensure in conventional consultant-led clinics, specialist nurses from a number of disciplines were deployed, working with a structured interview and recording all data electronically. A cardiologist, (SP), supported the nurses, reviewed the ECG, made a secure diagnosis and advised treatment where appropriate, and organised further tests or onward referral. Specialist nurses from cardiac arrhythmias, epilepsy and falls services were used in this clinic. A consultant cardiologist supported all clinical activity, interpreted findings and results, agreed diagnosis and treatment and the direction of referral where required. Where further tests such as echocardiography and ambulatory ECG monitoring were undiagnostic, a number of patients would be considered for an implantable ECG loop recorder, (ILR). These small devices provide automatic and patient activated recordings of up to 15 minutes of single channel ECG. They can be implanted in 15-20 minutes under local anaesthetic as a day case. Battery life

is up to 3 years, and they can have episodes downloaded at home using a telephone connection linked to an internet site. Episodes are notable for the bradycardia/asystole associated with Reflex Syncope, and also negative findings during TLOC, which have some negative significance for diagnosis.

Since the early 1990's the role of nurses in the United Kingdom has been evolving (Daly and Carnwell, 2003). It is common to see experienced nurses running clinics on their own, with support from medical colleagues when needed. A unique feature of the Manchester Rapid Access Blackouts Triage clinic was that it was led by three nurses from different specialities relevant to TLOC – a Specialist Arrhythmia Nurse, a Specialist Falls Nurse and a Specialist Epilepsy Nurse. As noted above (Soteriades et al, 2002, Colman et al 2004), studies confirm that patients with syncope form the bulk of those presenting with TLOC. Syncope is a cardiovascular problem (a decrease in blood pressure with or without a change in heart rate) caused either by a disorder of the autonomic nervous system (i.e. Reflex Syncope), a structural cardiac abnormality (e.g. aortic stenosis, severe left ventricular dysfunction) or an arrhythmia (i.e. bradyarrhythmias/tachyarrhythmias), so having a nurse with cardiac training is very desirable. Specialist Arrhythmia Nurses provide 'a seamless pathway of care for patients with arrhythmias' (British Heart Foundation, 2008) and it was therefore most appropriate that a person with such skills was included in the team which evaluated patients with blackouts/TLOC. However, a nurse with falls experience is also invaluable. In the United Kingdom, 28-33% of the population over 65 years and 32-42% of the population over 75 years fall each year (Masud and Morris, 2002). It is well recognised that among the elderly (≥65 years of age) who present with falls, 1 in 3 of them have had a syncopal event. These patients frequently do not recall losing consciousness because of retrograde amnesia for the event

(Shaw FE, Kenny RA 1997). A Specialist Falls Nurse was therefore at the forefront in assessing patients in the Rapid Access Blackouts Triage Clinic. About one quarter of patients with epilepsy are misdiagnosed, and many more have undiagnosed psychogenic blackouts, factors well known to nurses with a broad range of competencies in assessing, educating and treating patients with epilepsy. Specialist Epilepsy Nurses already have a track record of improving the quality of care in patients with epilepsy (Bradley and Lindsay 2008) and therefore the Specialist Epilepsy Nurse from the Manchester Primary Care Trust was incorporated into the team.

Collection and Storage of Clinical Assessment Data

In the RABTC we evaluated all patients by means of a thorough history, eye-witness history if possible, examination and an ECG, since these are known to be the activities with the highest diagnostic yield in patients with TLOC (Linzer et al, 1997, van Dijk et al 2008). To aid detailed history taking, a customised, web-based computerized questionnaire featuring 60 standard questions/data fields, featuring embedded video-clips to aid eye-witness recognition, was specified, designed and created by SP with local IT staff in the Manchester Heart Centre. This method had the advantage of all patients being asked the same set of questions, without any omissions, and of short training cycles for other nurses joining the clinic or setting up a clinic in a different NHS hospital. Previous resource-consumption was also assessed with; source of referral, number of admissions for blackouts, dates, and hospitals admitted recorded. Hospitalisation was confirmed by review of the paper medical records and hospital IT systems. Based on the information obtained, patients were triaged into High or Low Risk groups. The web-based data from the TLOC assessments are saved on secure computer

servers in the Manchester Heart Centre. Since inception of the RABTC in 2007, 29 users from 12 other NHS hospitals in England have registered to use the assessment tool in their own RABTC, and 4 centers have clinics running.

What tests must be done in all patients?

All patients underwent a 12 lead ECG and patients more than 40 years of age also underwent a supine carotid sinus massage. Though desirable, due to lack of adequate manpower, it was not possible to undertake upright carotid sinus massage for deserving patients in the same visit. Those needing an upright carotid sinus massage were brought back to the Manchester Heart Centre on another day for this test. Other tests such as echocardiography and ambulatory ECG were undertaken as indicated. Tests with the highest diagnostic yield, depending on the apparent cause of TLOC were chosen, thus avoiding waste of resources (Calkins et al 1993, Pires et al 2001, Farwell and Sulke 2004).

We examined these challenges to doctors and patients and the costs to the healthcare system through 4 projects:-

Project 1. The Rapid Access Blackouts Triage Clinic:

This project, described in Chapter II, consisted of prospectively evaluating a new algorithm for clinical assessment and risk stratification for patients with TLOC. This was achieved through the establishment of a Rapid Access Blackouts Triage Clinic, RABTC, at the Manchester Heart Centre in May 2007. The RABTC was established with the aim of ensuring that all TLOC patients had a thorough history, eye-witness history if possible, examination and an ECG, since these are known to be the activities with the highest diagnostic yield in patients with TLOC (Linzer et al, 1997, van Dijk et al 2008). Medical staffing was by junior and senior cardiologists. However,

where a patient required onward referral for evaluation by another specialist, e.g., by a neurologist, this was facilitated. The goals of evaluation in a patient with TLOC are dealt with in the initial part of this chapter. Subsequently, the evaluation of 327 patients attending the Rapid Access Blackouts Triage Clinic, between May 2007 and 2009, is described. The data presented emphasise the following aspects:

(i) the initial experience

(ii) the outcome of the risk stratification scheme on follow-up over 4 years

(iii) the accuracy of the original diagnosis when compared to that on follow-up

(iv) the yield of implantable loop recorders in this cohort of patients

(v) the outcome of referrals to other specialties and

(vi) the outcome of device implantation (permanent pacemakers, implantable cardioverter defibrillators, cardiac resynchronisation therapy) in this group of patients.

Project 2.

This project deals with the use of ILRs in the patient who cannot be diagnosed by clinical evaluation and 12 lead ECG.

Experience with the ILR since 1997 at Manchester Royal Infirmary led to the conclusion that a misinterpretation of the appearance of convulsive syncope as generalised epilepsy underlies the known incidence of 20-30% of misdiagnosis of epilepsy. Where no obvious structural or cardiac cause for syncope exists, doctors might conclude that the diagnosis must be one of epilepsy, especially in the absence of a recording of any physiological

evidence from a blackout. Also, in an attempt to extrapolate from the findings of laboratory tests to the true cause of TLOC, a number of tests are done at a distance from the clinical event. These tests include ambulatory ECG monitoring, tilt-table testing, electroencephalography and brain imaging, but it is known that these tests have a low diagnostic yield with a relatively high cost, (Calkins et al 1993, Pires et al 2001, Farwell and Sulke 2004). At Manchester Royal Infirmary, however, we had prioritised the use of the implantable ECG loop recorder, (ILR) since the mid 1990's. This instrument allows the clinician to determine the heart rate and rhythm at the time of TLOC. This project evaluated the value of this investigative tool in the management of patients with TLOC. As already mentioned, data from 62 patients from this project was compared to the 42 patients from Project 3, the REVISE study.

Project 3.

The REVISE study- **REV**eal in the **I**nvestigation of **S**yncope and **E**pilepsy focussed on evaluating the extent of misinterpretation of convulsive syncope as epilepsy.

As already mentioned, syncope, epilepsy and psychogenic blackouts can all present with similar clinical features making the task of establishing a diagnosis challenging. Published studies, based on clinical review, and supplemented by tilt testing in some cases, estimate that between 13 and 42% (Smith et al, 1999; Zaidi et al 2000; Chadwick D, Smith D 2002) of patients with epilepsy are incorrectly diagnosed or misdiagnosed. The likely alternative diagnosis is syncope, the most prevalent cause of TLOC, but with convulsive featues whose significance is misunderstood.

Building on the experience of the ILR in TLOC, the REVISE Study, the third of the projects, was a separate prospective study which recruited patients with TLOC, who in the opinion of a neurologist with a special interest in epilepsy, were either misdiagnosed as epilepsy or in those in whom the diagnosis of epilepsy was in doubt. All patients (n=41) included in this study were systematically subjected to a number of cardiological as well as neurological tests frequently used in TLOC cases, but including the implantation of a loop recorder. This strategy enabled us to record a physiological parameter i.e. heart rate and rhythm, at the time of symptoms. The aim of this study was to determine the incidence of misdiagnosis of epilepsy when prolonged ECG monitoring using an implantable loop recorder captured profound bradycardia or asystole. To compare the added value of other tests, tilt testing, ECG monitoring, echocardiography, EEG and brain imaging were done in this group of patients. The results of this prospective study have also been compared with a group of 62 patients, presenting with similar symptomatology, who were indentified retrospectively, described in Project 2.

Project 4.

We have previously reported that many patients diagnosed with epilepsy could have a cardiovascular cause giving rise to convulsive syncope, (Zaidi et al 2004). However, in approaching patients with possible convulsive syncope, the extent to which abnormal cardiovascular findings might be present must be known. In patients with a history of brain injury, epilepsy is probably a much more likely cause of collapse than convulsive syncope. Therefore, thorough cardiovascular examination of patients with a history of brain injury and epilepsy, could give a background understanding of

cardiovascular findings that could affect the balance of evidence in reaching a clinical diagnosis.

The fourth and the last project, described in Chapter V, was undertaken at the David Lewis Centre for Epilepsy, Nr Alderley Edge. In order to assess the incidence of cardiac and electrocardiographic abnormalities in patients with definite epilepsy, a cohort of patients in an epilepsy centre underwent cardiological assessment, and the findings are presented in Chapter V. Little is known about underlying cardiovascular disease in such patients who have not been systematically studied. Also the incidence of misdiagnosis in this population is not known, and cardiovascular screening could help understand this. Therefore, two hundred and fourteen patients with long standing epilepsy underwent systematic cardiovascular screening using ECG, echo and 24 hour ambulatory monitoring, after setting up a satellite outreach clinic. The findings of this evaluation form the basis of this chapter.

Chapter II

Role and Impact of Clinical and ECG triage in patients presenting with blackouts

Introduction:

As stated in the Chapter 1, TLOC usually presents as Collapse?cause. The three most common causes of TLOC are syncope, epilepsy and psychogenic blackouts, amongst which syncope is the most prevalent. Syncope, in turn, is a symptom with many causes, the prognosis being dependent on its cause (Middlekauff et al 1993; Soteriades et al 2002; Brignole et al 2004; Colman et al 2004). The underlying condition may range from very serious e.g. hypertrophic cardiomyopathy or severe aortic stenosis to the benign such as a simple faint.

Review of the published literature reveals a significant amount of heterogeneity in the way patients presenting with TLOC are managed (evaluation, investigations, treatment). Though patients with TLOC can present to primary as well as secondary care, a vast majority of these reports have originated from secondary care and that too in the emergency care setting. McClaren et al (1994) even suggested that the heterogeneity of the underlying conditions causing TLOC precluded the use of standardised guidelines for assessment of these patients in the Emergency Department. This view is not supported by others, as evidenced by the number of publications over the years by workers who have attempted to find clinical and cost effective ways of dealing with such patients.

The first part of this chapter will look at the goals of evaluation of a patient presenting with TLOC, and the second part will elaborate on the experience of the Manchester Rapid Access Blackouts Triage Clinic.

Goals of evaluation of a patient who presents with TLOC?

The ultimate goal of any clinician when presented with a case of TLOC should be to diagnose the cause of TLOC and deliver the most effective treatment as quickly as possible. As highlighted in the subsequent sections, this is not always the case for a variety of reasons.

Four steps (Figure 1) which are useful in the evaluation of any patient presenting with TLOC are as follows:

Step 1: Is the collapse due to TLOC?

In the first instance, the clinician has to establish that the patient with Collapse?cause indeed has suffered an episode of TLOC and not another condition like TLOC e.g., fall, prolonged loss of consciousness etc. If TLOC is suspected or confirmed, it would be appropriate to proceed to Step 2, otherwise, treatment for the presenting condition should be promptly instituted.

Step 2: If there has been TLOC, try and establish the cause?

If Step 1 confirms the presence of TLOC or there is reasonable clinical suspicion of TLOC, the next step would be to try and differentiate between

the different causes of TLOC, viz., syncope, epilepsy and psychogenic blackouts.

This is usually done by taking a good history, undertaking a clinical examination and performing a 12 lead ECG. Such an approach allows a diagnosis of the cause of TLOC to be established in at least half to two thirds of cases (Linzer et al 1997, van Dijk et al 2008). The Fainting Assessment Study (van Dijk et al 2008) showed that attending physicians could make a diagnosis, based on initial evaluation, in 63% of patients with TLOC, with an overall diagnostic accuracy of 88%. The authors of this study concluded that the use of additional testing, beyond history, physical examination, and ECG could be avoided in many patients presenting with TLOC.

While the above studies lend credence to the fact that clinical features are important in TLOC, it is important to appreciate that considerable overlap exists in the presenting features of these three common causes of TLOC viz., syncope, epilepsy and psychogenic blackouts, which may make the task of arriving at a diagnosis difficult. In this context, it is important not to overlook the fact that syncope, can be misinterpreted as epilepsy.

Step 3: The third goal would be to identify and immediately treat those patients with TLOC who present with life threatening causes e.g., those with ventricular tachycardia, high grade atrioventricular block, status epilepticus etc.

Step 4: In those patients with TLOC who do not have an immediately life threatening condition, the fourth step would be to determine their further management. A diagnosis may have been reached in Step 2, and a

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management plan determined. The clinician would have to decide whether it would be safe for patients to be discharged and treated as an outpatient. In those in whom the cause of TLOC is unclear, the clinician needs to decide about the need for further investigations, the type of these investigations and whether there is any need for immediate hospitalization in order to carry out these investigations (Gallagher 1997). Recommendations for hospital admission would need to be based on the potential for adverse outcomes if further evaluation and workup is delayed (Brignole et al 2004; Huff et al 2007; Grossman et al 2002; Quinn et al 2005). Such an approach would conserve resources by decreasing the number of unnecessary investigations performed and/or hospitalization.

Literature review shows that there is a tendency on the part of clinicians to neglect the initial evaluation, order investigations and hospitalise patients unnecessarily, even when the diagnosis is secure and benign. Such an approach wastes resources, as evidenced by the following studies.

Calkins et al (1993) evaluated the cost of prior diagnostic evaluation in 30 consecutive patients with a typical history of vasodepressor syncope, out of a total of 158 patients (30/158, 19%) referred to the University of Michigan Medical centre for evaluation of syncope. A mean of 4±2 major diagnostic tests had been performed prior to referral at a mean cost (at 1991 cost levels) of $3,763±3,820 and a median cost of $2,678 (range: 0-$16,606). These tests included echocardiography, Holter monitoring, computerized tomographic (CT) scans of the head, electroencephalograms (EEGs), magnetic resonance imaging (MRI), glucose tolerance tests, and carotid Doppler studies. Failure to adequately assess and rely upon the clinical features of vasodepressor syncope resulted in up to $16,000 of unnecessary diagnostic testing.

Pires et al (2001) evaluated diagnostic patterns and trends, and use of specialty consultations in the evaluation of 649 patients with syncope. They found that costly low yield neurological tests were overused and higher yield cardiovascular tests were underused. Untargeted random use of specialist evaluations did not contribute to an increase in diagnoses. The authors concluded that the increased use of specific tests directed by history and results of physical examination may improve diagnostic yield and decrease the cost of evaluating TLOC.

Farwell and Sulke (2004) assessed the efficacy of a protocol for diagnosis and management of syncope in a district general hospital in the United Kingdom. They prospectively compared 421 patients with syncope from January 2000 onwards with 660 retrospective patients from the calendar year 1998. They found that tests with the highest diagnostic yield had increased by 2001, but that non-diagnostic tests were still being used (e.g. chest radiography, electroencephalography and carotid Doppler studies). The costs of investigation and hospital stay also rose from £611 to £1384 per patient (p<0.001) and costs per diagnosis increased from £870 to £1949 (p<0.001).

Figure 1. Schema detailing the optimal step wise assessment and management of patients presenting with Collapse?cause

Abbreviations: AV block=atrioventricular block; TLOC= transient loss of consciousness
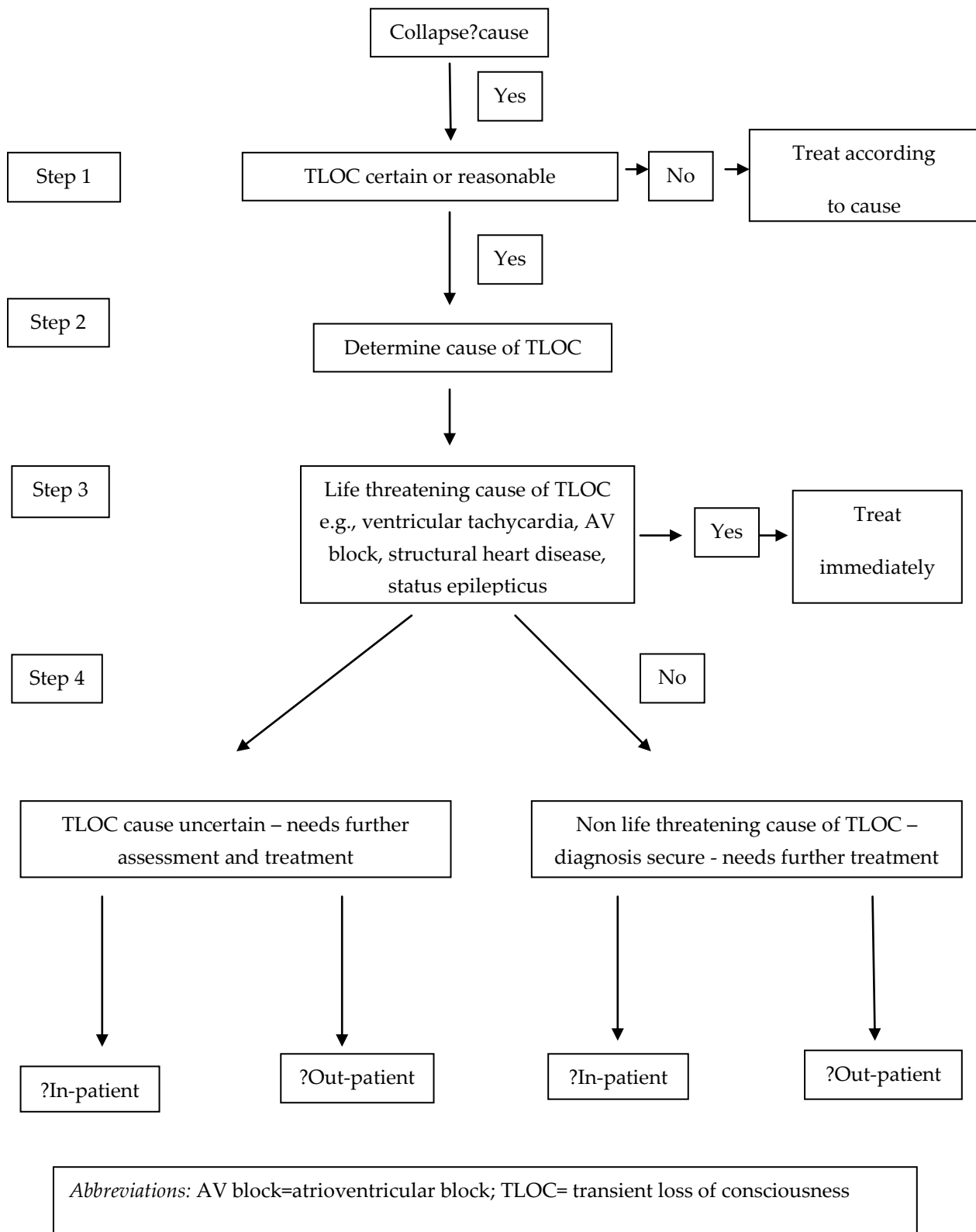
With these goals in mind and to improve the care of patients with blackouts the world's first Rapid Access Blackouts Triage Clinic (RABTC) was started at the Manchester Heart Centre, Manchester Royal Infirmary in May 2007.

This weekly outpatient clinic, had the following goals:

- To provide a rapid assessment i.e., within 2 weeks of referral
- To assess and diagnose the cause of blackouts/TLOC
- To triage patients into the right care pathway and also into 'high' and 'low' risk groups, ensuring rapid specialist assessment in high risk patients

Aims:

The clinic aimed to:

- decrease hospitalization for low risk patients with blackouts/TLOC
- decrease the use of unnecessary investigations
- direct patients to the most appropriate specialist care promptly
- prevent patients with TLOC being managed in 3 separate settings [viz.; Falls Clinics required by the National Service Framework for the Older People (2001), Epilepsy Clinics, required by National Institute of Clinical Excellence Guidelines for Epilepsy (2004) and Syncope Clinics, required by the National Service Framework for Heart Diseases- Chapter 8 (2005)]
- prevent patients becoming 'stuck' in a care- pathway
- develop cross-specialty nursing experience and skills in blackouts/TLOC

Though not directly assessed in this project, we also mulled the feasibility of setting up satellite computerized web based clinics in other hospitals in the UK in future depending on the results of this project

Methods (Figures 2-5):

The RABTC was set up in consultation with the Emergency Department, General Physicians, Care of the Elderly Physicians, Falls Clinic, Transient Ischemic Attack Clinic and the Neurologists, as patients with blackouts/T-LOC are managed in diverse settings. Referrals were encouraged with Collapse?cause, suspected of having a blackout/TLOC, and who were suitable for assessment in an outpatient setting. Suitable referrals from General Practitioners were also directed to this clinic. The clinic was led by Specialist Nurses from the Arrhythmia, Falls and Epilepsy Teams, with medical cover provided by an Associate Specialist in Cardiology and/or Consultant Cardiologist.

Patients received an Information Sheet, giving them information about the clinic and what to expect on the day of their appointment. Patients were asked to attend with an eyewitness so that detailed information about the events during the blackout/TLOC could be obtained.

All patients underwent a 12 lead electrocardiogram. Those ≥40 years of age also underwent supine carotid sinus massage. Due to lack of adequate manpower, it was not possible to undertake an upright carotid sinus massage on the same day. Verbal consent was taken before performing this procedure. Sequentially, each carotid artery was massaged for 15 seconds, in line with the cricothyroid cartilage, while recording an ECG. In those who

had an abnormal massage (defined as a pause of ≥ 3 seconds in duration), patients were asked if they had any symptoms during the massage. Absence of symptoms of dizziness, presyncope, syncope, was defined as carotid sinus hypersensitivity. Only if symptoms were reproduced, were patients diagnosed as suffering from carotid sinus syndrome. Patients then underwent a detailed assessment by one of the Specialist Nurses, using a customised, web-based computerised questionnaire featuring 60 standard questions/data fields, featuring embedded video-clips to aid eye-witness recognition, and generating an automated report (http://mhcweb.cmft.nwest.nhs.uk). Previous resource-consumption was assessed with; source of referral, number of admissions for blackouts, dates, and hospitals admitted. Wherever possible, hospitalisation was confirmed by review of the medical records and hospital IT systems. Attendance in the emergency department was not considered hospitalisation. Lying and standing blood pressures were undertaken.

Based on the information obtained, the following algorithm (Figure 2) was followed:
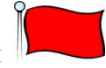
Figure 2. **Care Pathway for patients with blackouts/TLOC used in RABTC**
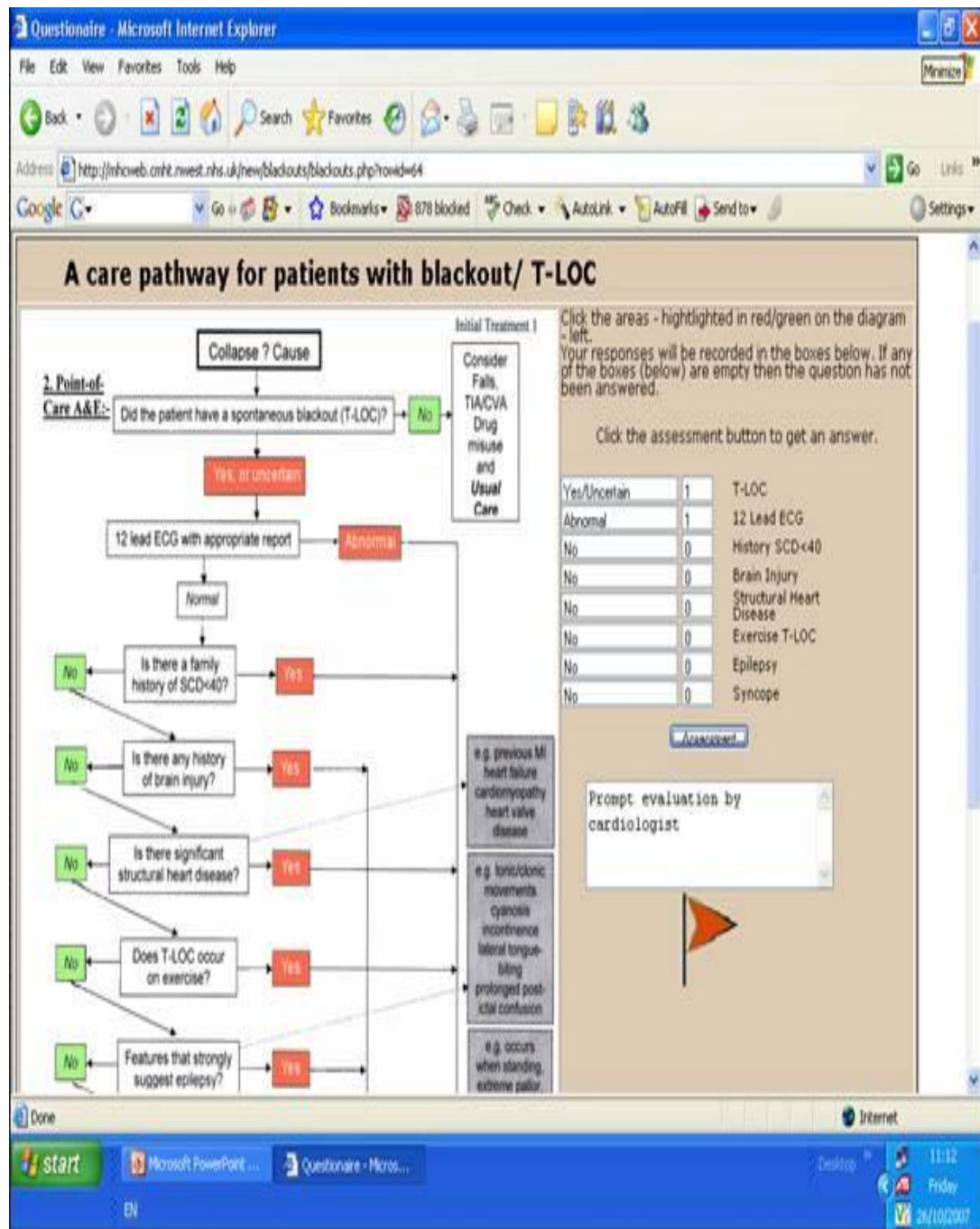
 Abbreviations: ECG=electrocardiogram; SCD=sudden cardiac death; TLOC=transient loss of consciousness

Following this, patients were triaged into High or Low Risk groups.

High Risk ('Red Flags') features were considered to be the following:

Cardiac:

(a) an abnormal 12 lead ECG

(b) presence of structural heart disease

(c) family history of sudden cardiac death ≤ 40 years or

(d) TLOC occurring during exercise

Neurology:

(a) history of brain injury

(b) history suggestive of epilepsy

(c) new neurological deficit

Patients were considered to be at *Low Risk ('Green Flags')* in the absence of any High Risk features.

Once assessment and triage were completed, patients were either reassured and discharged to primary care, or had further investigations (some available on the same day e.g., echocardiograms, 24 hour tapes), treatment (e.g., permanent pacemakers, implantable ECG loop recorders etc.), or referred onward to other specialities. Patients who needed cardiology follow-up were reviewed in the Cardiology Out Patient clinic.

Follow-up data: Readmissions after RABTC triage for TLOC were evaluated by review of medical records and by postal questionnaire. The latter asked whether patients had been admitted to hospital for a further blackout since

their RABTC evaluation.   If a 'fall' or 'collapse' was reported, this was assumed to have been a recurrent blackout.

Figure 3. Specialist Nurse Sr Nicola Rice using the Customised Web based questionnaire in the clinic

3 Specialist nurses: Falls, EP, epilepsy
– Sr Win Bell, Arrhythmia/Electrophysiology Nurse
– Sr Nicola Rice, Falls Nurse
– Sr Pamela Iddon, Epilepsy Nurse

Abbreviation: EP= electrophysiology; Sr=Sister

Figure 4. The Manchester Heart Centre website
(http://mhcweb.cmft.nwest.nhs.uk) **on which the customised questionnaire**

Figure 5. Screen shot of the customised web based questionnaire: showing the tabs for different sections at the top of the screen
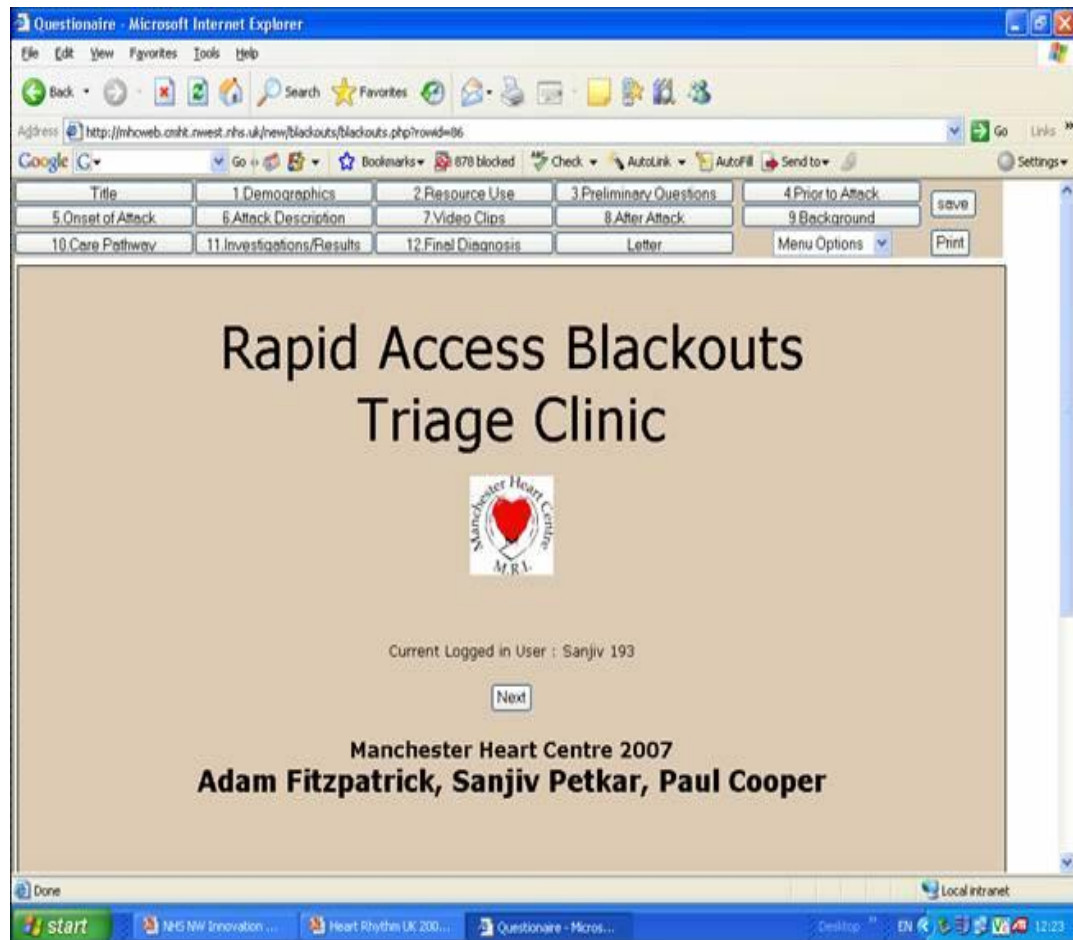
Statistical Analysis:

Continuous variables are mean±SD, median and range are given where appropriate. Percentages have been used for categorical variables. Comparisons were made using two tailed Students *t*-test. P <0.05 was significant. For statistical analysis, comparisons were made between blackouts patients at high risk and low risk. Graph Pad Prism Statistical Package was used for analysis.

Results:

The RABTC started in May 2007. By May 2009 327 patients had been seen. A vast majority of these referrals were appropriate (307/327, 93.9%) having had an episode of TLOC. Those patients who had suffered an episode of TLOC were divided into High and Low Risk groups as defined above. A majority of patients were found to be in the High Risk group, 183/307 (59.6%) (Figure 6*).*
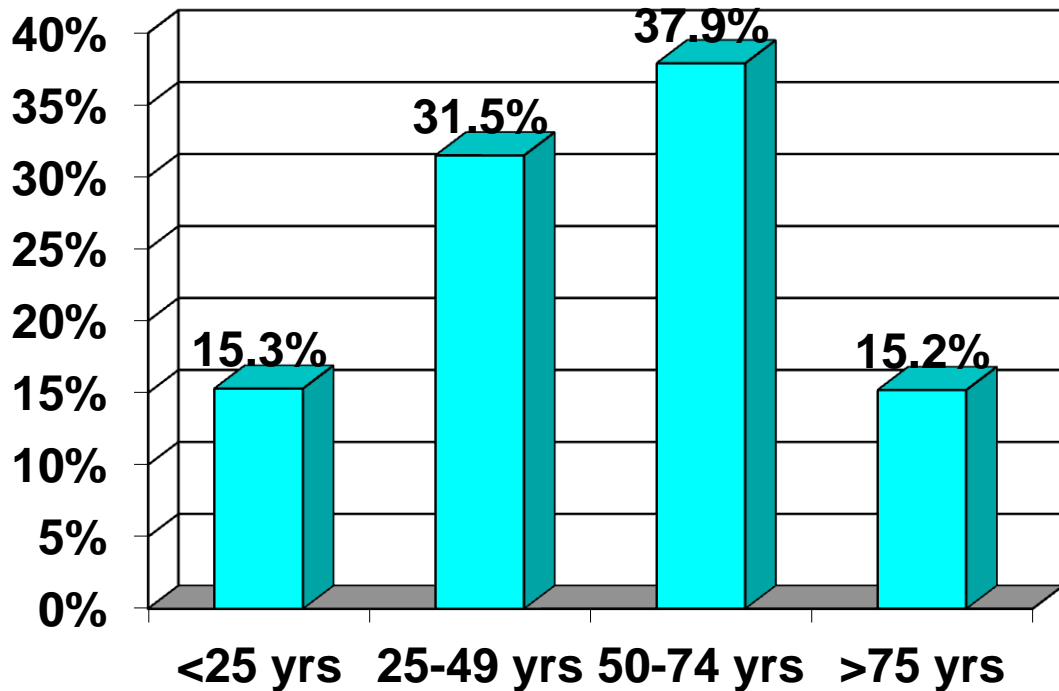
Figure 6. Distribution of patients into 'High' and 'Low' risk groups
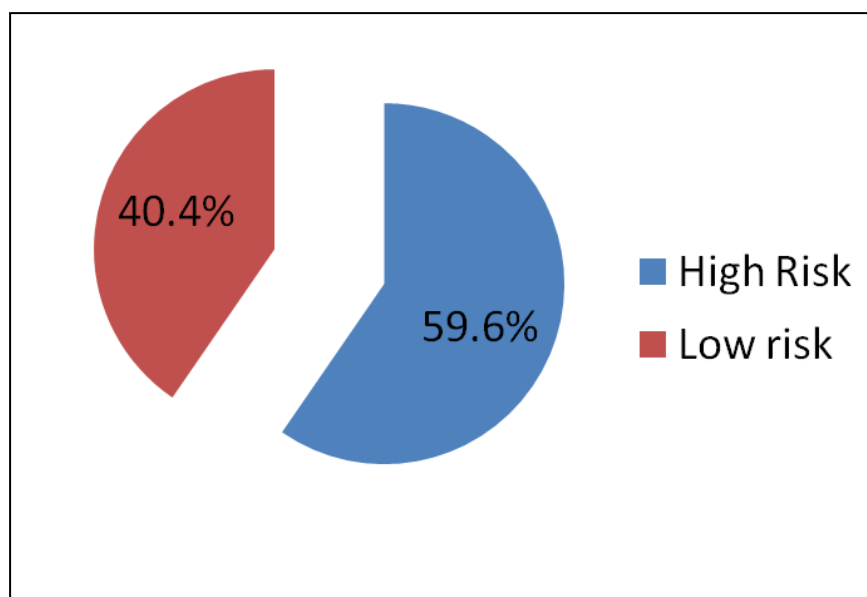
Demographics (Figure 7):

The mean age of referrals was 50.8±21.4 years (median: 52, range: 16-96 years), of which 143, (43.7%), were males. A majority of patients were between 50-75 years of age.

Figure 7. Age distribution of patients attending the RABTC

Abbreviations: RABTC=Rapid Access Blackouts Triage Clinic; yrs=years

Time from referral:

The overall time from referral to assessment was 35±19 days, (median: 31, range: 1-136 days). Delays to evaluation fell significantly from the first hundred patients (39±22 days) to the most recent referrals, (30±14 days, p <0.05). The number of patients that the nurses were able and willing to assess in each clinic rose to 9, but there were insufficient resources to hold more than one clinic each week, since none of the nurses had the RABTC specified in their work-schedule in advance, and their time was donated. Only 9% of patients could therefore be seen within 14 days of referral.

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Referral Source:

The referral source for all 327 patients is given in Figure 9. The largest number of referrals came from GP's, followed by general physicians. Inspite of adequate engagement with clinicians before setting up the RABTC, disappointingly, only 6.1% of referrals were from Accident and Emergency Department.

Figure 8. Source of referrals for patients attending RABTC
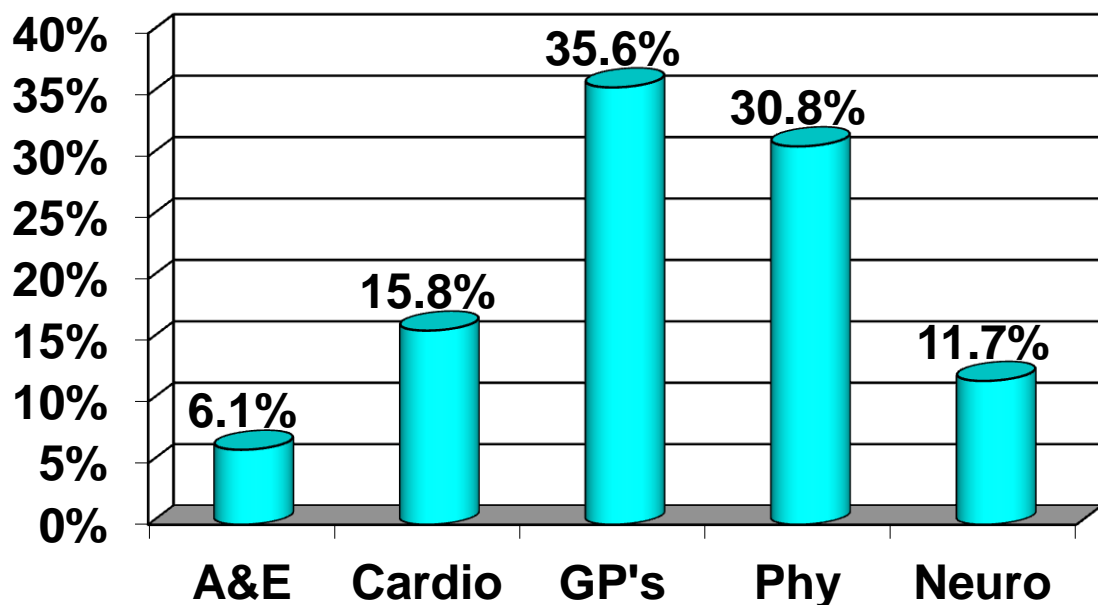
Abbreviations: A&E=Accident and Emergency; Cardio=cardiologists; GP's=General Practitioners; Neuro=Neurologists; Phy=Physicians; RABTC=Rapid Access Blackouts Triage Clinic

Duration of Symptoms:

The duration of symptoms from the time of first presentation for the whole cohort (n=327) was 38.2±75, median: 12 months range: 1-696 months. Patients in the TLOC (n=307) group had been symptomatic for 40±77 months (median: 12, range: 1-696 months).

Hospitalisation:

Forty four percent [145/327(44.3%)] of entire cohort had been hospitalised before evaluation in the RABTC. The mean number of hospitalisations was 1.6±1.4 (median: 1, range: 1-11). Nearly half of the TLOC patients, (145/307, 46.2%), had been hospitalised before evaluation in the RABTC. Within this cohort, high risk cases had been hospitalised significantly more often than those in the low risk group (51.9% versus 37.9%, p<0.002).

Admitting Hospitals:

The largest subgroup of previous admissions was to our own institution, (49%), with 32.4% admitted elsewhere in Greater Manchester, and the remainder beyond. (Figure 9)

Figure 9. Admitting Hospitals
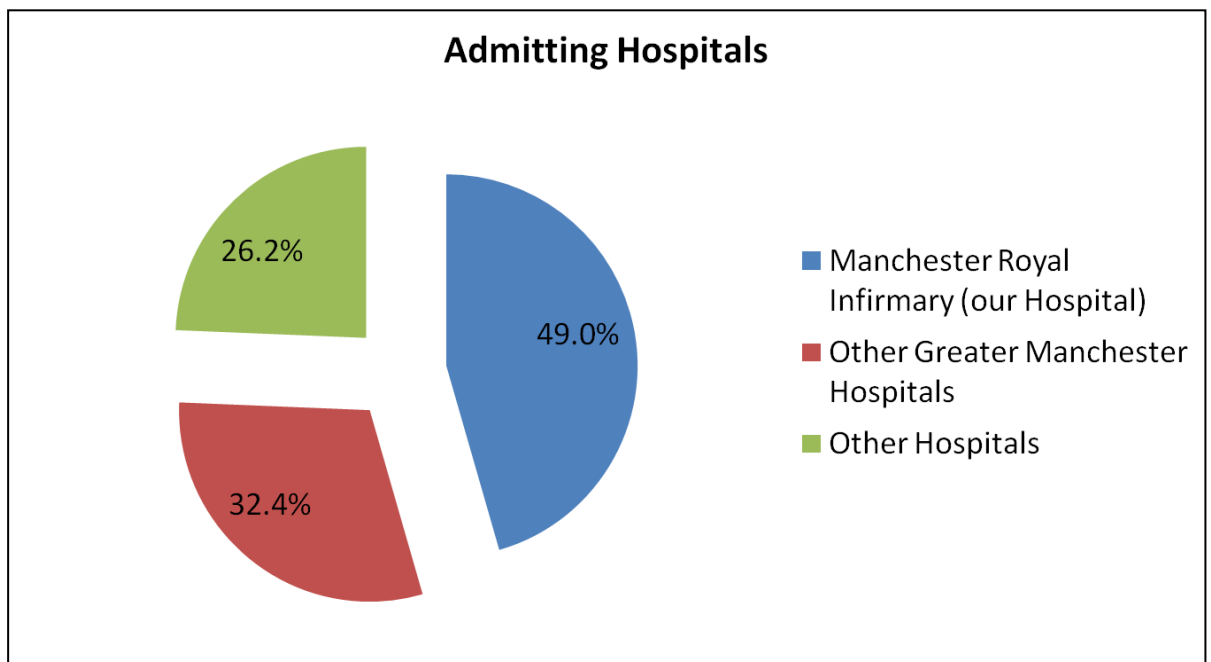
Diagnosis after initial assessment (Table 6):

A majority of blackout patients had syncope (78.5%), of which Reflex Syncope was the most common cause (38.1%). Whilst syncope was diagnosed in a further 69 patients (22.5%) the exact cause of syncope was uncertain. A further 61 (19.9%) patients, had suffered blackout(s), but the cause was not clear from the triage in the RABTC. Psychogenic blackouts i.e. patients with signs or symptoms similar to TLOC but with *apparent*, loss of consciousness was diagnosed in 4.2% of patients.

Table 6. Diagnosis after Initial Assessment

Diagnosis after initial assessment	N=307 (%)	High Risk N=183 (%)	Low Risk N=124 (%)	P value High vs Low Risk
Syncope	241 (78.5)	143(78.1)	98(79.0)	ns
Cause of Syncope:				
Reflex Syncope	117 (38.1)	48(26.2)	69(55.7)	<0.001*
Cardiac Syncope	35(11.4)	34(18.6)	1(8.1)	<0.0010*
OH	20(6.5)	14(7.7)	6(4.8)	ns
?cause	69 (22.5)	47(25.7)	22(17.7)	ns
Epilepsy	9 (2.9)	9(4.9)	0(0)	<0.012*
Psychogenic blackouts	13(4.2)	3(1.6)	10(8.1)	<0.010*
Undiagnosed (TLOC +ve, but cause uncertain)	61(19.9)	38(20.8)	23(18.6)	ns

Abbreviations: OH= orthostatic hypotension; TLOC= transient loss of consciousness

*Risk stratificatio*n *(Figure 10):*

The majority of TLOC patients fell into the high risk category because of an abnormal ECG with or without additional structural heart disease. Overall, 50 patients, (27.3%), had an abnormal ECG and structural heart disease.

Figure 10. Distribution of risk factors among patients attending RABTC
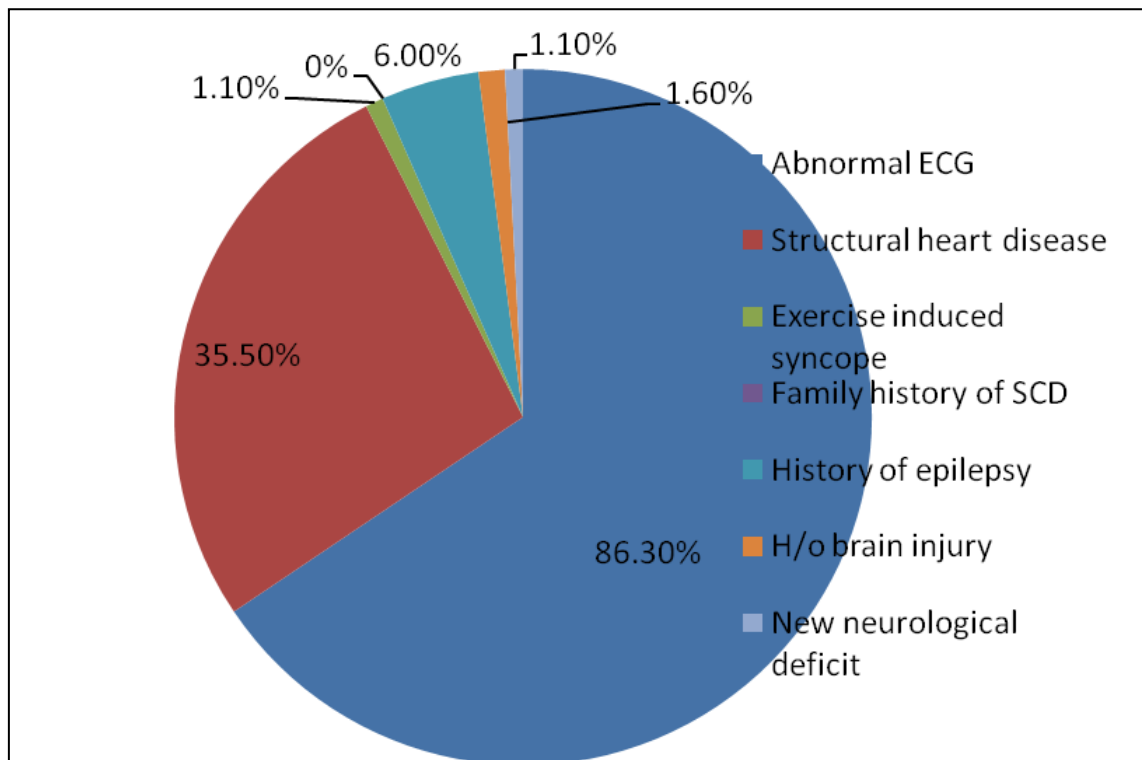
Abbreviations: ECG= electrocardiogram; H/o= history off; RABTC= Rapid Access Blackouts Triage Clinic; SCD= sudden cardiac death.

Onward Care (Table 7):

Table 7. Onward Care

Disposal	*Whole cohort N=307 (%)*	*High Risk N=183 (%)*	*Low Risk N=124 (%)*	*P value High vs Low*
Treatment given	135 (44.0)	65 (35.5)	70 (56.5)	*<0.001**
Discharged to primary care	33 (10.8)	13 (7.1)	20 (16.1)	*<0.012**
Devices	20(14.8)	20(30.8)	0(0)	*<0.001**
PPM	18 (13.3)	18(27.7)	0(0)	*<0.001**
BiVICD	2(1.5)	2(3.1)	0(0)	*ns*
EPS ± Ablation	1(0.7)	1(1.5)	0(0)	*ns*
Lifestyle changes	84(62.2)	32(49.2)	52(74.3)	*0.0027**
Drug Withdrawal	6(4.4)	3(4.6)	3(4.3)	*ns*
Drug Addition	21(15.6)	12(18.5)	9(12.8)	ns

Abbreviations: BiVICD= biventricular implantable cardioverter defibrillator; EPS= electrophysiology study; PPM= permanent pacemaker, RABTC=Rapid Access Blackouts Triage Clinic

The management of onward care after RABTC assessment is summarised in

Table 7. In 144 out of 307 (44%) patients a diagnosis and treatment was provided without further specialist evaluation. Thirty three patients (10.8%) were discharged back to primary care with reassurance. Twenty eight (9.1%) patients were referred on for detailed specialist evaluation, of which the majority of referrals (24/28, 85.7%) were to neurologists.

Follow-up:

Of the original cohort of 327 patients, 20 (6.1%) did not have TLOC and so were excluded from further analysis. The mean age of the remainder was 51 ± 21 (16–96) years. A majority of the patients were between 50 and 75 years of age, 43% were males and 60% (183/307) were considered to be High Risk. The duration of follow-up was 633 ± 342 days (range: 13 -1451, median 657).

(i) Accuracy of initial diagnosis when compared to that on follow-up:

On initial evaluation, 292 of 307 patients (95.1%) were found to have a single cause of TLOC. Two or more causes of TLOC were found in the remainder (4.9%, 15/30).

In a majority of cases, the initial diagnosis did not change on follow-up, remaining the same in 222/292, 76% patients with a single cause of TLOC and 10/15 (66.7%) with two or more causes of TLOC.

Subgroup analysis of the various causes of TLOC showed that there was an increase in the number of cases diagnosed with Cardiac Syncope ($p<0.05$) with a corresponding decrease in the number with Syncope?cause ($p<0.05$) and Undiagnosed ($p<0.05$) (Figure 11). A cause of TLOC could not be

determined in 33 (10.8%) patients on follow-up because an overwhelming majority (30/33, 99.5%) did not have a recurrence of their symptoms.

Figure 11. Change in diagnosis on follow-up among those with a single cause of TLOC.
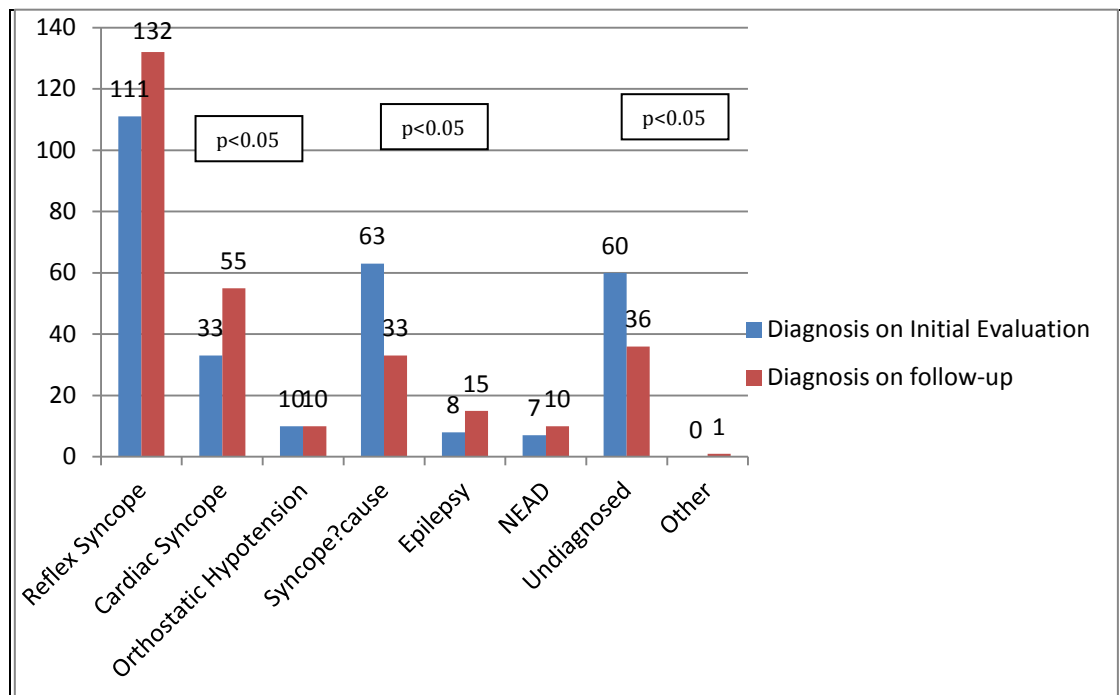
Abbreviations: psychogenic blackouts=non epileptic attack disorder; TLOC=transient loss of consciousness

The accuracy of diagnosis on initial evaluation was compared with that on follow-up (Table 8). A high degree of concordance was seen for the following diagnostic groups i.e., Reflex Syncope, cardiac syncope, orthostatic hypotension, epilepsy and non epileptic attack disorder.

Table 8. Accuracy of the initial diagnosis of TLOC on follow-up

Initial Diagnosis (n=292)	Diagnosis on Follow-up							Accuracy of In Diag (%)
	Reflex Syncope	Cardiac Syncope	OH	Syncope ?cause	Epilepsy	Psy BO	Undiag	
Reflex Syncope (111)	107	2	0	1	1	0	0	96.4
Cardiac Syncope (33)	0	32	0	1	0	0	0	97.0
OH(10)	1	1	8	0	0	0	0	80.0
Syncope ?cause (63)	13	17	2	29	0	0	2	46.0
Epilepsy (8)	1	0	0	0	6	0	1	75.0
Psy BO(7)	2	0	0	0	0	5	0	71.4
Undiagnosed (60)	8	3	0	2	8	5	34	56.7

Abbreviations: In Diag= initial diagnosis; Psy BO= psychogenic blackouts

(ii) Yield of ILR's:

After initial evaluation, 97 of the 307 (31.6%) patients were advised to undergo an ILR, of which 75 (24.4%) underwent it.

The diagnosis at implant and on follow-up in those who underwent an ILR is given below (Figure 12, Table 9):

Figure 12. Diagnosis at implant and follow-up in those undergoing an ILR

Abbreviations: OH= orthostatic hypotension; Undiag=undiagnosed
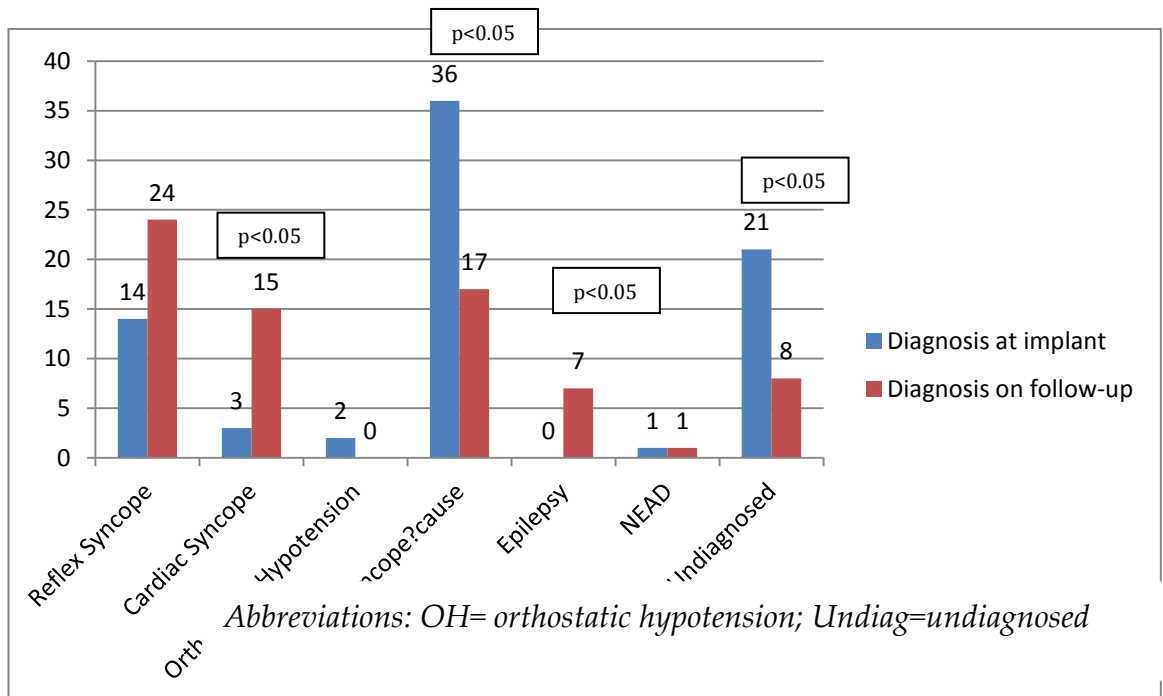
Abbreviations: ILR= implantable loop recorder; psychogenic blackouts=non epileptic attack disorder

Table 9. Diagnosis at implant and follow-up in those undergoing an implantable loop recorder

Initial Diagnosis (n=75)	Diagnosis on Follow-up						
	Reflex Syn	Cardiac Syncope	OH	Syncope?cause	Epilepsy	Psy BO	Undiagnosed
Reflex Syn (14)	13	1	0	0	0	0	0
Cardiac Syncope (3)	0	2	0	1	0	0	0
OH(2)	0	0	2	1	0	0	0
Syncope?cause (36)	8	10	4	15	0	0	0
Epilepsy(0)	0	0	0	0	0	0	0
Psy BO (1)	1	0	0	0	0	0	0
Undiagnosed (21)	2	2	0	1	7	1	8

Abbreviations: OH=orthostatic hypotension; Psy BO=psychogenic blackouts; Syn= syncope

ECG - symptom correlation was achieved in 63/75 (84%) patients. In 13 (17.3%) of patients a bradyarrhythmia was documented at the time of symptoms which was treated with a permanent pacemaker. Normal sinus rhythm was found in 41/63 patients (65.1%). These patients could be reassured that a cardiac arrhythmia was not the cause of their symptoms. However, due to the lack of ability of an ILR to record blood pressure, a distinction between syncope due to vasodepression or psychogenic as the cause of TLOC could not be made with any degree of certainity. The use of the ILR resulted in a significantly larger proportion of patients being diagnosed as Cardiac Syncope and epilepsy on follow-up, with a corresponding decrease in those with Syncope?cause and Undiagnosed (p<0.05).

Two thirds (50/75) of those patients who underwent an ILR had been triaged to the 'High Risk' Group on initial presentation. A vast majority of this group (40/50, 80%) had an ECG-symptom correlation with an abnormal heart rhythm documented in 57.5% (23/40), leading to a potential change in treatment. Among the remainder (25/75), who belonged to the 'Low Risk' Group, ECG-symptom correlation was higher (23/25, 92%, p<0.05) when compared to the 'High Risk' Group, but this was not statistically significant. A majority of the ILR downloads (18/23, 78.3%) showed normal sinus rhythm only.

(iii) Outcome of referral to other specialties (Table 10):

Twenty eight (9.1%) patients from the original cohort were referred on for detailed specialist evaluation, or an opinion was sought from other specialists, of which the majority of referrals (24/28, 85.7%) were to

neurologists.   Two patients (2/28, 7.1%) were each referred to two specialities, Neurology and Endocrine in one and Neurology and Vascular Surgery in the other. There were no statistically significant differences between the High and Low Risk groups.

Table 10. Outcome of referral to other specialties

Specialty	Whole Cohort N=28(%)	High Risk N=21(%)	Low Risk N=7(%)	P value (High vs Low Risk)
Neurology	24 (85.7)	18 (85.7)	6 (85.7)	1.00
ENT	1 (3.6)	0 (0)	1 (14.3)	0.072
Endocrine	2 (7.1)	2 (9.5)	0 (0)	0.37
Respiratory	1 (3.6)	1 (4.8)	0 (0)	0.55
Stroke Team	1 (3.6)	1 (4.8)	0 (0)	0.55
Vascular Surgery	1 (3.6)	1 (4.8)	0 (0)	0.55

Abbreviations: ENT = Ear, Nose and Throat

Further neurological evaluation helped to achieve a diagnosis in 13/24 (54.2%) of referred patients. The diagnostic outcomes in this group were as follows: Reflex Syncope: 4/24 (16.7%), Epilepsy: 3/24 (12.5%), not seizure: 3/24 (12.5%), Unexplained TLOC, epilepsy not excluded: 3/24 (12.5%), alcohol related seizure: 2/24 (8.3%) and Parkinson's disease: 1/24 (4.2%). No data was available for the remainder [8/24 (33.3%)]. Two (7.1%) patients referred to the Endocrinology Department and one (1/28, 3.6%) to the ENT surgeons had normal evaluations. One patient each did not attend the Respiratory, Stroke and Vascular Surgery Departments.

(iv) Outcome of device implantation (permanent pacemakers, implantable cardioverter defibrillators, cardiac resynchronisation therapy)

A total of 38/307 (12.4%) patients, mean age 65.7±20.7 years (range: 20-90, median: 73) who attended the RABTC received devices, a vast majority (94.7%) of which were pacemakers. Two patients received biventricular implantable cardioverter defibrillators and one patient an implantable cardioverter defibrillator. Twenty (20/38, 52.6%) of these patients were identified at initial evaluation and the rest on follow-up. The diagnosis, in a vast majority of cases (16/20, 80%), who were suitable for devices on this initial evaluation was Cardiac Syncope and in the remainder (4/20, 20%, Reflex Syncope). All patients identified at the initial evaluation and 13 of those identified on follow-up (total: 33/38, 86.8%) belonged to the High Risk Group. A majority of the patients (32/38, 84.2%) had an abnormal ECG on initial evaluation, details of which are given below (Table 11). Forty percent of patients had (13/32, 40.6%) had multiple abnormalities.

Table 11. ECG abnormalities on initial presentation in patients undergoing device implantation

ECG finding	N=32 (%)
Sinus bradycardia	5 (15.6)
First degree heart block	12 (37.5)
High grade AV block	1 (3.1)
RBBB	2 (6.3)
LBBB	10 (31.3)
Non specific intraventricular conduction defect	2 (6.3)
Left axis deviation	7 (21.9)
Old myocardial infarction	3 (9.4)
Left ventricular hypertrophy	1 (3.1)
Brugada Syndrome	1 (3.1)

Abbreviations: AV= atrioventricular; LBBB= left bundle branch block; RBBB=right bundle branch block.

An ILR identified the need for a device in 11/18 (61.1%) patients on follow-up. The initial diagnosis in this group of patients was as follows: Syncope?cause: 6/11 (54.5%), Reflex Syncope: 4/11 (36.4%) and Undiagnosed: 1/11(9.1%). The mean follow-up after device insertion was 569 days ±314 days (range: 40-1115, median: 568 days). Eighty percent of those receiving devices were asymptomatic on follow-up. In 20% of cases, TLOC was

recurrent inspite of device implantation, a figure which is similar (25%) to that seen in patients included in the ISSUE III study (Brignole et al 2012), which was a double blind randomized placebo controlled study. In this study, patients with Reflex Syncope and documented asystole underwent permanent pacemaker implantation. The group with pacemaker 'on' was compared to those in whom the pacemaker had been switched 'off'.

(v) *Mortality:*

Fourteen (14/307, 4.5%) patients died over the follow period. All of these patients belonged to the High Risk Group. The mean age of those who died was 82.1±9.4 years (66-93, median 93) with the mean time of death after evaluation in the RABTC being 411±243 days (122-1007, median 331). The cause of death was not related to the cause of TLOC.

Discussion:

In this project, we describe a cohort of 327 patients who were evaluated in the outpatient RABTC clinic between May 2007 and 2009 and who were subsequently followed up for 633±342 days, 13 -1451, median 657. The unique feature of this clinic was that it triaged patients with TLOC/blackouts rather than syncope alone.

Another important feature of this clinic was the role of specialist nurses for triage process, not undertaken anywhere in the world. Since the early 1990's the role of nurses in the United Kingdom has been evolving (Daly and Carnwell, 2003). It is common to see experienced nurses running clinics on their own, with support from medical colleagues when needed. A unique feature of the Manchester Rapid Access Blackouts Triage clinic was that it is

led by three Specialist Nurses– the Specialist Arrhythmia Nurse, the Specialist Falls Nurse and the Specialist Epilepsy Nurse. Epidemiological studies (Colman et al 2004; Soteriades et al, 2002) confirm that syncope is the most common cause of a blackout/ TLOC. Syncope is a cardiovascular problem (a decrease in blood pressure with or without a change in heart rate) caused either by a disorder of the autonomic nervous system (i.e. Reflex Syncope), a structural cardiac abnormality (e.g. aortic stenosis, severe left ventricular dysfunction, left atrial myxoma, left atrial thrombus, pulmonary hypertension, pulmonary embolus, myocardial infarction) or an arrhythmia (i.e. bradyarrhythmias/ tachyarrhythmias). Recently, Arrhythmia Nurses, funded by the British Heart Foundation (2008), aim to provide 'a seamless pathway of care for patients with arrhythmias' and it is therefore appropriate that a Specialist Arrhythmia Nurse evaluates patients with blackouts/TLOC. In the United Kingdom, 28-33% of the population over 65 years and 32-42% of the population over 75 years fall each year (Masud and Morris, 2002). It is well recognised that among the elderly (≥65 years of age) who present with falls, 1 in 3 of them would have had a syncopal event. These patients do not recall loss of consciousness because of retrograde amnesia to the event (Brignole et al, 2004). It is therefore apt that a person with significant experience in managing patients with falls, the Specialist Falls Nurse, is also at the forefront in assessing patients in the Rapid Access Blackouts Triage Clinic. Last but not the least, as a proportion of patients attending the Rapid Access Blackouts Triage Clinic are bound to have seizures or psychogenic blackouts, there was a need for a person with a broad range of competencies in assessing, educating and treating patients with epilepsy to be part of the team. Specialist Epilepsy Nurses already have a track record of improving the quality of care in patients with epilepsy

(Bradley and Lindsay 2008) and therefore the Specialist Epilepsy Nurse from the Manchester Primary Care Trust was incorporated into the team.

Patients seen in this clinic were of an intermediate risk, as those requiring immediate treatment would have been managed as in-patients and not suitable for referral to the RABTC.

The new and unique algorithm used in the RABTC to triage patients with TLOC was successfully in evaluating and managing patients in an outpatient setting over a period of 4 years. It allowed 'High Risk' patients to be identified and treated effectively. This is evidenced by the fact that all the patients who died belonged to the 'High Risk' group. All of them died after a considerable length of time after evaluation in the RABTC. In addition, the 'Low Risk' patients could be identified and treated (reassurance, life style measures, and medical treatment) and discharged to primary care. There was no evidence on follow-up that they not were re-referred to the service.

Re-hospitalisation for the same condition was significantly reduced on follow-up.

Prognosis of patients with TLOC is dependent on its cause (Moya et al, 2009,Colman et al 2004, Soteriades ES et al 2002, Middlekauff HR, Stevenson WG, Saxon LA, 1993). Patients with Reflex Syncope have the best prognosis, those with cardiac syncope the worst, and those with an unknown cause of syncope or neurological causes of TLOC an intermediate prognosis (Moya et al, 2009, Colman et al 2004, Soteriades ES et al 2002, Middlekauff HR, Stevenson WG, Saxon LA, 1993). Review of the published literature shows that over the years, numerous risk stratification schemes have been experimented with and applied in an acute care setting to assess and treat patients with TLOC in an attempt to prevent serious adverse outcomes and

hence, favourably modify their prognosis. The number of patients included in these studies have ranged from 45 to 929 patients (Rodriguez-Entem F et al 2008, Birnbaum A et al 2008, OESIL study II 2000, Ammirati F et al 1999, Quinn JV et al 2004, Shen WK et al 2004, Brignole M et al 2006, Constantino G et al, 2008, Reed MJ et al 2007, Birnbaum A et al 2008, Sun BC et al 2007, Morag RM et al 2004, Sarasin FP et al 2007, Quinn J et al 2006, Grossman SA et al 2007, Crane SD 2002, Colivicchi F et al 2003, , Del Greco M et al 2003, Martin TP et al 1997). Results from these studies reveal a range of sensitivity and specificities (Quinn JV et al 2004, Reed MJ et al 2007, Birnbaum A et al 2008, Sun BC et al 2007, Quinn J et al 2006, Grossman SA et al 2007) in achieving the primary endpoint. While some of these schemes have been simple (OESIL study II 2000, Quinn JV et al 2004, Grossman SA et al 2007, Crane SD 2002) and others very detailed (Shen WK et al 2004, Grossman SA et al 2007) and hence difficult to implement in a busy Emergency Department, overall, undertaking risk stratification at initial assessment has been demonstrated to increase the percentage of patients achieving a definite diagnosis of the cause of TLOC (OESIL study II 2000, Shen WK et al 2004, Sarasin FP et al 2007, Grossman SA et al 2007) and decrease in-hospital stay (Shen WK et al 2004, Brignole M et al 2006). A variable effect has been seen on hospital admissions, mostly a decrease (Quinn JV et al 2004, Shen WK et al 2004, Brignole M et al 2006, Quinn J et al 2006), no effect (Morag RM et al 2004, Grossman SA et al 2007) and an increase in one study (Reed MJ et al 2007). It is difficult to compare the incidence of serious adverse events using the different risk stratification tools as the definition of this endpoint varied among studies. Nevertheless, it ranged from 6.1%-36% (Quinn JV et al 2004, Constantino G et al, 2008, Grossman SA et al 2007, Crane SD 2002). Moreover, most of the results relate to the outcome of patients in the shorter term, there being a paucity of data on medium term outcomes. Follow-up of

patients with TLOC using the many risk stratifications schemes mentioned above have been short, mostly confined to the first 30 days after initial assessment. Only two studies have (Ungar A et al 2010, Constantino G et al 2008) have analysed longer term outcomes. In the EGSYS 2 study (Ungar A et al 2010), the average length of follow-up was 614 ±73 days (range 0–782 days) and in the STePS Study (Constantino G et al 2008) 1 year. The mean follow-up in our study was 633±342 days (13 -1451, median 657) which is higher than the previously published studies (Ungar A et al 2010, Constantino G et al 2008). Only a minority (17.9%) had less than 1 year of follow-up with one third having two or more years of follow-up. To our knowledge this is the longest described follow-up of any group of patients presenting with TLOC anywhere in the world.

Linzer et al (1997) showed that a simple approach of taking a good history, undertaking a clinical examination and performing a 12 lead ECG allows a diagnosis to be made of the cause of TLOC in up to two thirds of cases. In the Fainting Assessment Study, van Dijk et al (2008) showed that attending physicians could make a diagnosis, based on initial evaluation, in 63% of patients with TLOC, with an overall diagnostic accuracy of 88%. In the study by Constantino et al (2008) the accuracy of the original diagnosis on follow-up was 76%. Our study was similar to the above studies in that it also used simple tools for the initial assessment of patients with TLOC, i.e., a customised structured web based clinical assessment tool along with a 12 lead ECG. Using this approach, we achieved a high accuracy of the original diagnosis, ranging from 71% for psychogenic blackoutsto 98% for Cardiac Syncope, figures which are comparable or even higher than the previously quoted studies (Constantino et al 2008, van Dijk et al 2008, Linzer et al 1997). In our study, in 10.8% of cases, the cause of TLOC could not be diagnosed.

Most published series have reported a figure of 13-54% (Brignole M et al 2006). We could find only one other series in which the percentage of patients in whom the cause of TLOC remained undiagnosed was less than ours, i.e., of 5%. (Brignole M et al, 2006).

Since its introduction in 1997, the ILR has become an invaluable tool to investigate patients presenting with recurrent unexplained syncope, able to achieve ECG-symptom correlation in ~ 60% (range: 17-87%) of patients (Parry SW, Matthews IG, 2010), the higher rates (>80%) seen in only two observational studies. More recently, the use of the ILR has been extended to the investigation of patients with troublesome Reflex Syncope. In two large randomised studies which have used the ILR for this indication, the ECG-symptom correlation ranged from 17.4 to 25.4% (Brignole M et al 2012, Brignole M et al 2006). In our study, the ILR was predominantly used in those with recurrent unexplained syncope (Syncope?cause) with a very high resulting ECG-symptom correlation of 84%. Our study also showed that the outcome of the ILR changed the diagnosis of the cause of TLOC in a significant number of patients undergoing the procedure. Also, our strategy of offering the ILR to those who were 'High Risk' and in whom the chance of detecting an abnormal heart rhythm was high, thus potentially leading to a change in treatment, appeared to be the most cost effective use of this investigative tool.

Twenty eight (9.1%) patients from the original cohort in our study were referred on for detailed specialist evaluation, or an opinion was sought from other specialists, of which the majority of referrals (24/28, 85.7%) were to neurologists. Guidelines (1, 34) advocate the referral of patients to the neurologists and/or to the psychologists/psychiatrics when the cause of TLOC is suspected to be either due to epilepsy, autonomic failure or

psychogenic blackouts. While this has been advocated, we are not aware of any published data on the outcomes of such referrals. We believe that this is the first published experience of the systematic referral and the evaluation of the outcome of such referrals in patients with TLOC. The fact that more than half of the patients referred with an uncertain cause of TLOC achieved a definitive diagnosis subsequent to evaluation by neurologists emphasises and highlights the need for cooperation and collaboration among different specialities in order that patients with TLOC receive the optimum care that they deserve.

A total of 38/307 (12.4%) patients who attended the RABTC received devices, a vast majority (94.7%) of which were pacemakers. Twenty (20/38, 52.6%) of these patients were identified at the initial evaluation, once again emphasising the use of simple tests needed for the effective and optimum diagnosis of patients presenting with TLOC (Constantino G 2008, van Dijk et al 2008, Linzer et al 1997). Also, 86.8% of those who ultimately received devices belonged to the 'High Risk' group, once again reinforcing the utility of risk stratification scheme implemented on initial evaluation. Cunnington et al (2008) analysed the patient journey from symptom onset to pacemaker implantation. They showed that 33 of their 95 patients (35%) had a Class I or IIa pacing indication which did not trigger a pacing referral. Forty-seven patients (49%) were referred electively with a median delay from symptoms to permanent pacemaker implantation of 380 days (range 33–7505 days). Twenty-three of the 47 elective patients (49%) had previous hospitalization with symptoms suggestive of bradycardia. We believe that a delay on the part of referring physicians/general practitioners for assessment of TLOC, similar to that found in the study by Cunnington et al (2008) was the reason for significant proportion of the 20 cases needing devices to be identified on initial evaluation. The indication for permanent pacemaker implantation in

our study was a mixture of AV block, Sick Sinus Syndrome and Reflex Syncope all of which are standard indications for pacing as advocated by the European Society of Cardiology guidelines (Brignole M et al 2013) and which are associated with improvement in symptoms, quality of life and in some cases, prognosis. In the present study, the mean follow-up after device insertion was almost two years (569 days ±314 days, range: 40-1115, median: 568 days) with 80% of those receiving devices being asymptomatic on follow-up, once again highlighting the fact that the most appropriate patients were identified for this type of treatment.

All patients who died on follow-up in our study had been identified on initial triage as belonging to the 'High Risk' group. The mortality in our study was 4.5%, which is lower than that quoted in the literature (Quinn JV et al 2004, Constantino G et al 2008, Sun BC et al 2007, Grossman SA et al 2007, Crane SD 2002.). In keeping with published results, where age > 65 years at presentation with TLOC was found to be a marker of increased mortality (Constantino G et al 2008,) Colivicchi F et al 2003, Martin TP et al 1997), in our study also, all those who died were more than 65 years of age. The cause of death was not related to the cause or mechanism of TLOC.

Limitations of the study:

In this study, all patients ≥40 years of age underwent a supine carotid sinus massage. An upright carotid sinus massage was only undertaken in a minority of patients. A second visit by the patient to the Manchester Heart Centre was necessary for the upright carotid sinus massage due to lack of personnel to undertake this test on their initial visit when attending the RABTC. It is possible that if facilities existed and all patients ≥40 years of age were subjected both to a supine and upright carotid sinus massage, the number of patients with a diagnosis of Reflex Syncope and multiple causes

of syncope on initial assessment would have increased.

In the cohort that we analysed, only 6% of referrals were from the Accident and Emergency Department. Greater cooperation between the Accident and Emergency Department and the RABTC and increasing the frequency of RABTC would not only increase the percentage of referrals to the clinic from the Accident and Emergency Department but also enable patients presenting with Collapse?cause to undergo a more structured assessment more quickly as proposed in Figure 1.

Conclusion:

'Collapse?cause' is a common problem in emergency care in the United Kingdom. In many patients collapse is a result of a blackout/TLOC. Literature review highlights deficiencies in the care of these patients. The algorithm used in the RABTC, run by Specialist Nurses, is highly effective in evaluating and managing patients presenting with TLOC/suspected TLOC. Using the algorithm, only a small percentage of patients were ultimately undiagnosed chiefly because of lack of symptoms on follow-up. The present study, with the longest follow-up to date anywhere in the world, shows the medium term effectiveness of patients with TLOC initially assessed in the RABTC using a simple customised structured web based clinical assessment tool. This method of assessment resulted in a high degree of accuracy of the original diagnosis of the cause of TLOC, a high ECG-symptom correlation by means of the ILR, the usefulness of collaboration with other specialities in patients with TLOC and the usefulness of device implantation (predominantly pacemakers) in improving the quality of life of deserving patients.

Chapter III

Outcomes from the use of long term Reveal implantable ECG devices in patients with blackouts

Introduction:

The previous chapter dealt with the clinical and ECG triage of patients presenting with an episode of TLOC. In a vast majority of patients (~50-75%), this approach is enough to arrive at a diagnosis of the cause of TLOC (Linzer et al, 1997, van Dijk et al, 2008). However, when the cause of TLOC is uncertain or needs confirmation in order that subsequent management is optimal, recourse has to be taken to investigations. When TLOC occurs during exercise, an exercise stress test is recommended while in cases where TLOC occurs in the setting of structural heart disease, it is reasonable to undertake imaging of the heart first and proceed to other investigations only if these do not yield the cause of TLOC (NICE 2010). Following 2 randomised controlled studies and a few observational ones, the value of the implantable loop recorder (ILR) in this group of patients has been known for some time (Parry SW, Matthews IG 2010). However, the PICTURE registry (Edvardsson N et al, 2011), which was published much later, showed that clinicians continued to use a plethora of non diagnostic tests to investigate such patients, even though the use of the implantable loop recorder was available to them.

This study examines the use of the ILR at the Manchester Heart Centre in patients with unexplained TLOC.

Methods:

An implantable loop recorder (ILR) is a small metallic instrument, the size of a small computer memory stick or a pack of chewing gum. It is inserted beneath the skin on the left side of the chest via a small surgical procedure undertaken using local anaesthesia. The ILR has a battery life of 3 years and is able to record digitally a single channel bipolar ECG stored as a loop. It can be set to record a bradycardia or a tachycardia automatically or frozen at the time of symptoms using a handheld activator. The biggest advantage of the ILR is that it allows the heart rhythm to be recorded at the time of TLOC in patients with infrequent and unpredictable symptoms with a high degree of accuracy.

At the Manchester Heart Centre, the ILR has been used in the following group of patients since 1996:

- to determine the degree of cardioinhibition during spontaneous episodes of TLOC in patients with Reflex Syncope and ongoing symptoms in whom other treatment modalities e.g., lifestyle measures of increased salt and fluid intake, drug treatment with midodrine etc. have failed.

- in patients in whom the cause of TLOC remains uncertain and the possibility of psychogenic blackouts cannot be ruled out

- in patients with a degree of structural heart disease, but not enough indication to implant a pacemaker or an implantable cardioverter defibrillator. The recording of a heart rhythm at the time of a spontaneous attack will help in decision making.

A retrospective analysis of the case records of all patients who underwent an ILR between 1996 and 2006 was undertaken and forms the basis of this report. Results of 62 of the patients from this study have been included in the

results of the REVISE study (retrospective group).

Results:

Between 1996 and 2006, 357 patients underwent a loop recorder implantation (Reveal/Reveal Plus, Medtronic Inc) at the Manchester Heart Centre for unexplained TLOC.

Demographics:

Mean age of the cohort was 54±18 years (range: 17-93 years, 40.9% males). Number of episodes of TLOC prior to insertion of an ILR was as follows (Table 1):

Table 1. Number of episodes of TLOC prior to insertion of ILR

Number of episodes of TLOC prior to insertion of ILR	N (%)
0-5	153 (42.9)
6-10	91 (25.5)
>11	62 (17.4)
Uncertain	51 (14.3)

Abbreviations: ILR=implantable loop recorder; TLOC=transient loss of consciousness

The mean duration of symptoms before ILR implantation was 78.7±113.6 months (range: 1-840 months).

Investigations:

All patients had undergone a 12 lead ECG prior to insertion of ILR. It was normal in 254/357 (71.1%).

Other tests undertaken in these patients were as follows:

(i) Echocardiogram: 220/357 (61.6%). A vast majority were normal: 172/220, 78.2%.

(ii) Ambulatory ECG recording: 202/357 (56.6%). The mean duration of recording was 52.3±42.7 hours (range: 14-330, median: 48 hours). Non diagnostic findings achieved only in 11/202 (5.5%)

(iii) Tilt testing: 194/357 (54.3%), positive in 37/194 (19.1%)

(iv) Carotid sinus massage: 115/357 (32.2%), positive in 6/115 (5.2%)

(v) Exercise stress test: 70/357 (19.6%)

(vi) Coronary angiography: 47/357 (13.2%)

(vii) Carotid Doppler: 29/357 (8.1%)

(viii) EEG: 82/357 (23.0%)

(ix) CT brain: 89/357 (24.9%)

(x) MR scan of the brain: 28/357 (7.8%)

Drug Therapy:

Of the 357 patients undergoing an ILR, 41 (11.5%) had been treated with fludrocortisone, 33 (9.2%) with midodrine, 61 (17.1%) with beta blockers, 9

(2.5%) with antidepressants and 82 (23.0%) with antiepileptics at some point of time.

ILR findings:

Overall, symptom-ECG correlation (SECGC) was achieved in 52.8% (189/357) of patients. Time to SECGC was 10.8±34.7 months (range: 1-410 months, median 5 months). Lack of ongoing symptoms after implantation of the ILR was the reason for not achieving SECGC in the majority: 89/168 (53.0%). In a minority 6% (10/168), improper activation of the ILR was the reason SECGC could not be obtained.

In those with SECGC, ILR findings were as follows (Table 2):

Table 2. Rhythm in those achieving ECG-symptom correlation by ILR

Rhythm on ILR (n=189)	*N(%)*
Sinus rhythm	128 (67.7)
Asystole – sinus arrest	28 (14.8)
Asystole – AV block	9 (4.8)
Paroxysmal atrial fibrillation	8 (4.2)
Supraventricular Tachycardia	11(5.8)
Ventricular Tachycardia	5 (2.6)

Abbreviations: ECG=electrocardiogram; ILR = implantable loop recorder

Based on the findings of the ILR, 62/189 (32.8%) patients underwent device implantation. A permanent pacemaker was implanted in 85.4% (53/62) patients, an implantable cardioverter defibrillator (ICD) in 6.5% (4/62), and a

biventricular ICD in 3.2% (2/62). Thirty six patients (19.0%) underwent electrophysiological studies.

Correlation between Tilt testing and ILR:

Overall, 194/357 (54.3%) patients underwent tilt table testing of which 37 (19.0%) were reported as 'positive'. Among those with a 'positive' test, 23 had SECGC on ILR. The findings on the ILR were as follows: sinus rhythm: 13/23 (56.5%), sinus arrest: 5/23 (21.7%), atrial fibrillation and sinus bradycardia (heart rate <40 beats per minute): 2/23 (8.7%) each and ventricular tachycardia: 1/23 (4.3%).

On the other hand, of the 189 patients who had SECGC by ILR, 106 underwent a tilt table test. The findings on the ILR among those with a 'positive' tilt test were as follows (Table 3):

Table 3. Correlation of ILR and Tilt Table results

ILR findings	Number	Number undergoing tilt table test	Tilt table test 'positive' n (%)
SECGC	189	106	23 (21.7)
Asystole	37	18	5 (27.8)
AF	8	2	1 (50.0)
SVT	11	4	0 (0)
VT	5	3	1 (33.3)

Abbreviations: ILR=implantable loop recorder; SECGC= symptom electrocardiogram correlation

Discussion:

This non randomised retrospective study showed that it was possible to achieve SECGC in 52.8% of patients who were implanted with an ILR. Moreover, the results of the ILR significantly changed the management in 62/357 (17.4%) of patients with unexplained TLOC. These patients had undergone a number of other tests previously which were inconclusive with regard to the cause of TLOC. Moreover, some of these patients had also been treated with a variety of medication, but continued to symptomatic inspite of the same.

The Randomised Assessment of Syncope Study (RAST) included 60 consecutive patients with unexplained syncope. An ILR was implanted in 30 patients while the remainder underwent prolonged external monitoring, tilt table testing and electrophysiological studies (conventional arm). Patients were allowed to cross over to the ILR arm if the results of the evaluations in the conventional arm were negative. Overall, a diagnosis of the cause of TLOC could be established in 55% with an ILR strategy as opposed to 19% with conventional testing (p=0.0014).

The Eastbourne Syncope Assessment Study (EaSyAs) randomised 201 unselected patients with unexplained syncope to an ILR versus conventional investigations and management. Thirty-three patients in the ILR group and only four in the conventional strategy group received an ECG diagnosis (33% vs 4%, p<0.0001).

Among the observational studies, the ISSUE (The International Study of Syncope of Uncertain Etiology - ISSUE Study, Moya et al, 2001) study is important as it one of the first studies to prove the benefit of ILR in this group of patients. It was a multicenter international prospective study aimed

at analyzing the diagnostic contribution of an ILR in 4 predefined groups of patients with syncope of uncertain origin. (i) Isolated syncope group: this group included patients without structural heart disease or with minor cardiac abnormalities that were considered to be without clinical relevance and not suggestive of a cardiac cause of syncope, absence of intraventricular conduction defects, and a negative complete work-up including tilt-testing (ii) Tilt-positive group: included patients with the same characteristics as those in the isolated syncope group but who had a positive response to tilt testing (iii) Suspected bradycardia group: included patients with bundle-branch block and a negative electrophysiological test and (iv) suspected tachycardia group: included patients with overt heart disease who were at risk of ventricular arrhythmia, because these were patients with previous myocardial infarction or cardiomyopathy with depressed ejection fraction or nonsustained ventricular tachycardia in whom an electrophysiological study did not induce sustained ventricular arrhythmias. The results of the ILR on follow-up of 3-15 months in 111 patients were similar in the isolated syncope group and the tilt-positive group: syncope recurred in 28 (34%) and 10 patients (34%), respectively, and electrocardiographic correlation was found in 24 (23%) and 8 (28%) patients, respectively. The most frequent finding, which was recorded in 46% and 62% of patients, respectively, was one or more prolonged asystolic pauses, mainly due to sinus arrest, preceded for a few minutes by progressive bradycardia or progressive tachycardia-bradycardia. Bradycardia without pauses was observed in 8% and 12% of cases, respectively. The remaining patients had normal sinus rhythm or sinus tachycardia, except for one, who had ectopic atrial tachycardia. In the tilt-positive group, an asystolic syncope was also recorded when the type of response to tilt-testing was vasodepressor or mixed. The authors showed that in both the groups, the findings were similar, that the cause of syncope

was very likely neurally mediated and the most frequent mechanism was a bradycardic reflex.

The use of tilt testing in this group of patients has significant limitations as detailed below:

(i) Most studies using tilt-testing have done so in patients who have already been labelled with 'syncope', not 'TLOC'. Few have studied unselected TLOC patients in order to evaluate tilt-testing as a discriminator of the underlying cause of TLOC. The evidence that tilt-testing can discriminate between causes of TLOC is limited. In one study (Fitzpatrick A 1996) of 145 unselected patients with T-LOC of uncertain cause presenting to the emergency department, the yield of tilt testing overall was only around 20%, it was not significantly enhanced by drug provocation, and was dependent on the clinical features of patients

(ii) The results of the tilt testing have a wide sensitivity and specificity. When patients with a positive tilt test are restudied by tilting, 50% of them will become negative, irrespective of whether they have received treatment (Petkar 2008)

(iii) Results of the tilt table test cannot be used to predict response to treatment. Sud S et al (2007) performed a meta-analysis to determine whether permanent pacemaker therapy prevents refractory vasovagal syncope in patients who were recruited based on the results of the tilt table tests. Nine randomised trials (2 double blind, 7 open label or single blind) were analysed. While permanent pacing reduced the risk of recurrent syncope in unblinded studies, and in studies comparing pacemaker algorithms, no effect was seen in double blind trials. The results did not change even when the analysis was restricted to patients with marked

cardioinhibitory response on the tilt table test. The meta-analysis concluded that the treatment effect of pacemakers in patients with Reflex Syncope guided by the results of the tilt table test had been overestimated and that the apparent response was due to a strong expectation response to pacing. Also, the results of the ISSUE III study and its registry (Brignole et al 2014, Brignole et al 2012) showed that patients with documented asystole on an ILR, who underwent pacemaker implantation, had a higher chance of recurrence of symptoms if they also had a tilt test which was positive as opposed to those who had a negative tilt test.

On the other hand, external recording of the heart rhythm is associated with a poor ECG symptom correlation because of infrequent and unpredictable nature of most syncopal episodes and is recommended only in select group of patients (NICE 2010)

When the results of our study are compared to those the above studies, some similarities as well as differences are evident.

Similarities:

(i) Similar group of patients, i.e., TLOC of uncertain cause (versus RAST, EaSyAS, ISSUE)

(ii) large proportion of patients had been subjected to non-diagnostic tests before being implanted with an ILR (versus PICTURE Registry).

(iii) In those with an abnormal heart rhythm on ILR, bradycardia was the most frequent abnormality (versus ISSUE)

(iv) poor diagnostic yield of ambulatory ECG recording (NICE 2010)

(v) lack of correlation between the ILR findings and the tilt table test results for this group of patients (versus RAST, EaSyAS, ISSUE)

Differences:

(i) Our study was retrospective and non randomised (versus RAST, EaSyAS)

(ii) Our study did not have pre defined subgroups (versus ISSUE)

(ii) SECGC correlation was much higher in our study (52.8% versus RAST, EaSyAS, ISSUE).

(iii) The ISSUE study had a higher incidence of bradycardic responses on the ILR than the present study (10.4%)

The ISSUE Investigators subsequently undertook a further study using ILR's in patients with Reflex Syncope. The International Study on Syncope of Uncertain Etiology 2 (ISSUE 2) (Brignole 2006) was a multi-center, prospective, observational study enrolling 442 patients with a diagnosis of suspected NMS from centers across Europe and the USA. The study assessed the effectiveness of a diagnostic and treatment strategy based on the initial evaluation by history, physical examination and ECG, early implantable loop recorder (ILR) implantation, and ILR-based specific therapy after syncope recurrence. Patients with three or more clinically severe syncopal episodes in the last 2 years without significant electrocardiographic and cardiac abnormalities were included. Patients with carotid sinus syncope and orthostatic hypotension were excluded. After loop recorder implantation, patients were followed up till the first documented episode of syncope and therapy was determined by the findings on the ILR. Among the 392 patients included in the study, 103 patients had a documented episode on the ILR. A long asystolic pause (median 11.5 sec duration) was present in 54% of cases, bradycardia < 40 bpm was present in 4% of cases, no or slight rhythm variation were present in 27% of cases, progressive sinus tachycardia was present in 7% of cases, primary tachyarrhythmia was present in 8% of cases.

53 patients received ILR-based specific therapy, mostly pacemaker therapy (n=47) and 50 patients received counselling (education and reassurance) and nonspecific therapy. Patient characteristics were well-matched for the two groups. The 1-year recurrence rate in patients assigned to a specific therapy was 10% compared with 41% without specific therapy (80% relative risk reduction for patients, p=0.002, and 92% for burden, p=0.002). The 1-year recurrence rate in patients with pacemakers was 5% (burden 0.05±0.15 episodes per patient/year). The authors therefore concluded that a strategy based on early application of the ILR with therapy delayed until documentation of syncope allowed a safe, specific and effective therapy for patients with recurrent suspected NMS. The authors also recommended that that early ILR use become standard practice for management (diagnosis andtreatment) of patients with severe recurrent suspected NMS.

We undertook a subgroup analysis in our study which met the ISSUE II study criteria. A total of 48 of 357 (13.4%) patients met this criteria i.e., normal ECG, no significant cardiac abnormality on the echocardiogram and a negative carotid sinus massage. SECGC was achieved in 24/48 (50%) patients, 4 of 24 (16.7%) of whom were found to have asystole (2 sinus arrest, 2 AV block). No cases of tachyarrhythmia's were seen. Tilt table test was negative in all 4 patients.

Conclusion:

Our study showed that the ILR could record a heart rhythm at the time of symptoms in a majority of patients in whom the diagnosis of the cause of

TLOC was unclear in spite of conventional testing and who continued to be symptomatic inspite of lifestyle measures and drug therapy. In 17.4% of patients, the results of the ILR led to a significant change in management strategy (implantation of devices). On the other hand, in those in whom an abnormality of the heart rhythm was absent at the time of symptoms of TLOC could be confidently reassured but they remain symptomatic with vasodepressor reflex syncope and still require management. Its lack is too often a fault of many syncope doctors.

Chapter IV

REVISE Study – *REVeal* in the *Investigation* of *Syncope* and *Epilepsy*

Introduction:

Syncope, epilepsy and psychogenic blackouts are the three most common causes of transient loss of consciousness (TLOC). All three disorders can present with abnormal limb movements (Lempert et al, 1994; Stokes et al, 2004; Mellers, 2005). In syncope, these abnormal movements are the result of hypotension or complete arrest of cerebral circulation causing cerebral irritation (Zaidi et al, 2000). Published retrospective and prospective studies (Zaidi et al, 2000; Smith et al, 1999; Scheepers et al, 1998, Josephson et al, 2007) estimate that between 12.9 and 41.9% of patients with epilepsy are misdiagnosed. According to The All Party Parliamentary Group on Epilepsy (2007), there are 74,000 patients in the United Kingdom who are taking epilepsy drugs that they do not need. The consequences of a misdiganosis of epilepsy can be devastating e.g., social stigmatisation, loss of productivity, loss of self esteem, ban on driving, young women of child bearing age being exposed to the harmful effects of antiepileptic drugs etc. (Petkar et al, 2006). It is estimated that the annual medical costs in England and Wales of treating patients misdiganosed with epilepsy is approximately £29 million with total costs in the region of £138 million (Juarez- Garcia et al, 2006). Nowack WJ (1997) reviewed 5 cases of non epileptic events misdiagnosed as epilepsy based on poorly characterised paroxysmal episodes and a few minor non specific EEG findings. He estimated the annual cost of non epileptic spells misdiagnosed as epilepsy can be estimated at between $ 650 million – $4000 million. Given its small sample size, the above figure may be an overestimate given that Sun BC, Emond JA, Camargo CA Jr. (2005) estimated the cost of syncope related hospitalisation to be in the range of $ 2.2 to 2.6 billion. A

common alternative diganosis in this group of patients is convulsive syncope (Zaidi et al, 2000; Smith et al, 1999; Scheepers et al, 1998; Josephson et al 2007).

Zaidi et al (2000) investigated 74 patients (33 men, mean age: 38.9±18 years, range: 16 to 77 years) with recurrent seizure like episodes and previously diagnosed as epilepsy, with tilt-testing and carotid sinus massage using continuous electrocardiogram (ECG), electroencephalography (EEG) and BP (blood pressure) monitoring. Thirty-six of 74 (48.6%) patients were continuing to have attacks despite appropriate antiepileptic drugs (AEDs) while in the rest, (n=38), there was continuing uncertainty about the diagnosis of epilepsy. Ten of the 74 patients had an implantable loop recorder (ILR). An alternative diagnosis was found in 31(41.9%) patients, including 13 (36.1%) of patients taking AEDs. Eleven of 13 patients (84.6%) on AEDs withdrew them and did well on treatment for syncope. In 2 patients, episodes of prolonged bradycardia correlated precisely with seizures on the ILR.

Smith et al (1999) undertook a retrospective analysis of the case records of 324 patients referred over 12 months with 'refractory epilepsy' to assess the frequency, causes and consequences of an erroneous diagnosis of epilepsy. These patients were referred to a single consultant and were seen in three different clinic settings (regional epilepsy clinic, centre based general neurology clinic and a district general hospital based general neurology clinic). One hundred eighty four of these patients had been exposed to antiepileptic drugs of whom 92 were said to have refractory seizures. Forty-six of 184 (26.1%) patients were found to be misdiagnosed and treated inappropriately or had been wrongly advised, chiefly due to prior inadequate clinical evaluation or misinterpretation of the findings of an EEG.

Syncope and psychogenic blackouts were the most common alternative diagnosis.

Scheepers et al (1998) undertook a population study, the CARE – Community Awareness and Resources for Epilepsy project, designed to assess the standards of epilepsy care within a geographical population in relation to diagnosis, seizure management and quality of life. The authors unexpectedly found a high frequency 49/214 (22.9%) of misdiagnosis of epilepsy upon neurological evaluation. All but two had AEDs withdrawn. Approximately 50% were subsequently found to have syncope. The diagnosis of epilepsy was disputed in a further 26 (12.2%) patients.

Josephson et al (2007) undertook a retrospective review of the outpatient adult epilepsy clinic charts of 1506 consecutive referrals to an epilepsy clinic. The mean age of the cohort was 38 ± 16 years. One hundred and ninety four (12.9%) of patients ultimately had Reflex Syncope and were found to be misdiagnosed. Some of these patients had an incorrect diagnosis for more than 10 years. Two thirds of the referrals were from primary care (including ED) and 18% from neurologists. Thirty five percent had been prescribed antiepileptic drugs prior to referral.

We hypothesised that many patients with a diagnosis of refractory epilepsy have syncope and that prolonged ECG monitoring with an implantable ECG monitor (ILR) will show that many such patients will have cardioinhibitory Reflex Syncope that responds to permanent pacing and allows antiepileptic drugs to be withdrawn.

Aims:

The aims of this study, were to (a) determine the incidence of misdiagnosis of epilepsy using an ILR and (b) to determine the value of tilt testing in this group of patients

Methods:

We evaluated 103 patients (Whole Cohort), consisting of two subgroups, one Retrospective (n=62) and the other Prospective (n=41). Both subgroups presented with similar symptomatology and were evaluated in similar ways.

Retrospective Group:

The Retrospective group was drawn from 335 patients who underwent an implantable ECG monitor (ILR) (Reveal®/Reveal Plus®, Medtronic Inc), for TLOC at the Manchester Heart Centre, Manchester Royal Infirmary, UK between 1996 and 2006. One hundred fifty seven (46.9%) of these patients had been referred by the neurologists, out of which 62/157 (39.5%) of the referrals were for 'epilepsy', with a 'possible' diagnosis of 'epilepsy' in 45/62 (72.6%) and a 'confirmed' diagnosis in the remainder [17/62 (27.4%)]. Apart from clinical assessment, all patients underwent a 12 lead electrocardiogram (ECG). Further cardiac investigations were undertaken as appropriate. In those patients who underwent a tilt test, a Finapres (Finapres Medical Systems BV, Paasheuvelweg 34a NL-1105 BJ Amsterdam ZO, The Netherlands) machine was used. Patients were tilted on a bed with foot board support for 45 minutes at a 60◦ angle, while monitoring their heart rate, blood pressure and symptoms. No drug provocation was used. The tilt test was considered positive if hypotension and/or bradycardia were accompanied by reproduction of the patient's symptoms. Decisions about treatment were dependant on the treating cardiologist. Follow-up was in the

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cardiology and neurology outpatient departments at the Manchester Heart Centre, Manchester Royal Infirmary and the Greater Manchester Centre for Neurosciences, Hope Hospital, Salford, respectively.

Prospective Group:

The prospective group consisted of patients who were recruited into the REVISE (*Rev*eal in the *I*nvestigation of *S*yncope and *E*pilepsy) study between 2007 and 2009. This was a prospective longitudinal study, using patients as their own controls. This study was also carried out at the Manchester Heart Centre, Manchester Royal Infirmary, UK. The protocol was passed by the local institutional ethics committee. All patients were initially reviewed by a neurologist with special interest in epilepsy in whose opinion either epilepsy had been misdiagnosed or that there was a doubt regarding the diagnosis of epilepsy.

Inclusion criteria for the prospective study were: (a) ≥3 episodes of TLOC in the last 12 months AND a normal, equivocal or non diagnostic 12 lead ECG, echocardiogram, 24 hour ECG, standard unprovoked electroencephalogram (EEG) and brain computed tomography(CT)/magnetic resonance (MR) scan. After recruitment, all patients underwent an ILR (Reveal Plus®/Reveal DX®, Medtronic Inc. Minneapolis, USA) and tilt table testing. Patients underwent follow-up every 3 months till at least 1 year after ILR implantation.

Tilt testing was undertaken using the Task Force® Monitor (APC Cardiovascular Ltd, Cheshire, UK). The protocol for tilt testing was the same as in the retrospective group.

The protocol allowed for treatment to be given, if necessary, during the course of the study. Decisions about treatment were left to the treating physician. Patients who had symptomatic pauses of ≥3 seconds on the ILR or a decrease in heart rate below 40 beats/min for 30 seconds, were offered permanent pacemaker implantation (PPM). If patients were on antiepileptic drugs (AED) at the start of the study, they were allowed to continue it. Also, antiepileptic drugs could be initiated during the study on the advice of the neurologist with a special interest in epilepsy.

At each follow-up visit, a record was kept of the symptomatic status of the patients, including the number of episodes of TLOC and the date of the episodes in the previous three months. All patients had their ILR downloaded and the findings correlated with their symptoms.

Statistical Methods:

Data are quoted as percentages and mean with standard deviations. Where indicated, medians and ranges have been stated. Results are presented for the Whole Cohort and separately for the Prospective and Retrospective Groups. The Students 't' test was used to compare percentages and means between the Prospective and Retrospective Groups using the GraphPad Prism statistical package.

Results:

Demographics (Table 1):

The mean age of the Whole Cohort was 46.4±17.4 years (median: 44, range: 18-80) with a slight female preponderance (58/103, 56.3%). Patients in the Prospective Group were younger than those in the Retrospective Group

(40.2±16.2 versus 50.5±17.0, p=0.0028). No differences in the age quartile distribution or sex between the two subgroups was found.

Duration of symptoms (Table 1):

The mean duration of symptoms for the Whole Cohort was 126.8±131.6 months (median: 96, range: 4-780) with no significant differences between the two sub groups, Prospective and Retrospective.

Diagnosis at enrolment (Table 1):

Approximately half (45/103, 43.7%) of the Whole Cohort was 'confirmed' to have epilepsy by the neurologists with numbers being significantly higher in the Prospective Group [28/41(68.3%) versus 17/62 (27.4%, p=<0.001). A 'doubt' regarding the diagnosis of epilepsy was expressed by the neurologists in 13/103 (12.6%) patients. All of these patients belonged to the Prospective Group. Neurologists diagnosed 'possible' epilepsy in the remainder of the cohort (45/103, 43.7%). All of these patients belonged to the Retrospective Group. Diagnosis of the type of epilepsy on referral was available only for the Retrospective subgroup. In a majority of cases, the treating neurologists were unable to classify the type of epilepsy (35/62, 56.5%). A diagnosis of partial epilepsy was made in 17/62 (27.4%) and generalised epilepsy in 10/62 (16.1%).

Table 1. Characteristics of patients included in the study

	Whole Cohort *N=103 (%)*	*Prospective Group* *N=41 (%)*	*Retrospective Group* *N=62 (%)*	*P value* *Prospective vs Retrospective*
Age (years)				
Mean ± standard deviation, median, range	46.4±17.4, 44,18-80	40.2±16.2, 39,18-80	50.5±17.0, 50.5, 19-80	0.0028*
Age Quartile (years)				
<25	11 (10.7)	7(17.1)	4 (6.5)	ns
25-49	48 (46.6)	22 (53.7)	26 (41.9)	ns
50-74	35 (34.0)	10 (24.4)	25 (40.3)	ns
>75	9 (8.7)	2 (4.9)	7 (11.3)	ns
Females	58 (56.3)	21 (63.4)	37 (59.7)	ns
Duration of symptoms (months)				
Mean ± SD, median, range	126.8±131.6, 96, 4-780	120±118, 96, 12-540	133.7 ±148.6, 96, 4-780	ns
Diagnosis at enrolment				
'Confirmed' epilepsy	45 (43.7)	28 (68.3)	17 (27.4)	<0.0001*
'Doubt' regarding the diagnosis of epilepsy	13 (12.6)	13 (31.7)	0 (0)	<0.0001*
'Possible' epilepsy	45 (43.7)	0 (0)	45 (72.6)	<0.0001*

*Abbreviations: ns= not significant, *= p value significant*

Initial diagnosis of epilepsy made by? (Table 2):

In a majority of cases (64/103, 62.1%), the initial diagnosis of epilepsy was made by a neurologist. In 17 patients (16.5%) it was not possible to determine the medical professional who made the initial diagnosis. This uncertainty about who made the initial diagnosis of epilepsy was higher in the Prospective Group as opposed to the Retrospective Group [15/41(36.6%) versus 2/62 (3.2%), p = <0.0001).

Table 2. Clinician making the initial diagnosis of epilepsy

Initial diagnosis of epilepsy made by	Whole cohort N=103 (%)	Prospective Group N=41(%)	Retrospective Group N=62 (%)	P value Prospective versus Retrospective
Neurologists	64 (62.1)	21 (51.2)	43 (69.4)	ns
Paediatrician	9 (8.7)	3 (7.3)	6 (9.7)	ns
General Physician	6 (5.8)	1 (2.4)	5 (8.1)	ns
General Practitioner	5 (4.9)	0 (0)	5 (8.1)	ns
Neuropsychiatrist	1 (1.0)	0 (0)	1 (1.6)	ns
Emergency Department Physician	1 (1.0)	1 (2.4)	0 (0)	ns
Uncertain	17 (16.5)	15 (36.6)	2 (3.2)	<0.0001*

*Abbreviations: ns= not significant, *= p value significant*

Antiepileptic drugs (Table 3):

More than three fourths (81/103, 78.6%) of the Whole Cohort had a history of using AED's. The mean number of drugs used per patient was 1.5±1.3 (median: 1.0, range: 0-10). History of use of AED's was significantly higher in the Retrospective Group than in the Prospective Group [57/62(91.9%) versus 24/41 (58.5%), p=<0.0001]. This maybe due to greater awareness of the clinical presentations of Reflex Syncope among the neurologists and hence the reluctance to prescribe antiepileptic drugs to the patients in the Prospective Group, till a firm diagnosis of the cause of TLOC was established.

In those with a history of AED use, a mixture of 'old' and 'new' AED's was found. The details of the AED drugs taken by patients in the Prospective as well as Retrospective Groups are given in Table 3. Significantly higher percentages of patients in the Prospective Group were prescribed Topiramate and Clobazam whereas the percentage of patients prescribed Phenytoin were higher in the Retrospective Group.

Table 3. Antiepileptic drugs

	Whole cohort *N=103 (%)*	*Prospective Group* *N=41(%)*	*Retrospective Group* *N=62(%)*	*P value Prospective versus Retrospective*
Number with h/o use of AED	81 (78.6)	24 (58.5)	57 (91.9)	<0.0001
Mean number of AED ± standard deviation, median, range	1.5±1.3, 1.0, 0-10	2.0±1.1, 2.0, 0-4	1.4±1.3, 1.0, 0-10	ns
Type of AED's				
Topiramate	8 (7.8)	8 (19.5)	0 (0)	0.0003*
Lamotrigine	17 (16.5)	8 (19.5)	9 (14.5)	ns
Carbamazepine	24 (23.3)	8 (19.5)	16 (25.8)	ns
Sodium valproate	25 (24.3)	8 (19.5)	17 (27.4)	ns
Levetiracetam	6 (5.8)	4 (9.8)	2 (3.2)	ns
Clobazam	4 (3.9)	4 (9.8)	0 (0)	0.0119*
Phenytoin	17 (16.5)	3 (7.3)	14 (22.6)	0.0407*
Phenobarbitone	7 (6.8)	2 (4.9)	5 (8.1)	ns
Oxycarbazepine	1 (1.0)	1 (2.4)	0 (0)	ns
Pregabalin	1 (1.0)	1 (2.4)	0 (0)	ns
Zonisamide	1 (1.0)	1 (2.4)	0 (0)	ns
Primidone	1 (1.0)	0 (0)	1 (1.6)	ns

*Abbreviations: AED= anti epileptic drugs; ns= not significant; *= p value significant*

Baseline 12 lead ECG (Table 4):

All patients in the study underwent a 12 lead ECG at baseline. A majority (83/103, 80.6%) of the ECG's were normal. Out of the 20/103 'abnormal' ECG's in the whole cohort, 9/20 (45.0%) had sinus bradycardia with a heart rate ranging from 45 to 60 beats/minute. There were more patients with an abnormal ECG in the Prospective Group [12/41 (29.3%) versus 8/62 (12.9%), p=0.0395), chiefly because of a larger number of patients with sinus bradycardia. No other significant differences between the Prospective and Retrospective Groups were identified.

Transthoracic echocardiogram (Table 4):

Results for the transthoracic echocardiogram were available for (76/103, 73.8%) of the Whole Cohort. All patients in the Prospective subgroup underwent an echocardiogram while more than half of the Retrospective group underwent this investigation. Overall, only a minority of patients were found to have structural heart disease. None of the patients had severe structural abnormalities of the heart.

External ECG monitoring(Table 4):

External ECG monitoring of the heart rhythm was available in 74/103 (71.9%) of the Whole Cohort. Significantly higher percentage of patients in the Prospective Group underwent this investigation [41/41, (100%) versus 33/62 (53.2%), p = <0.0001). No difference between the mean duration of monitoring was found among the two groups. No ECG-symptom correlation was seen either in the Prospective or Retrospective subgroups.

Table 4. Results of Investigations

	Whole cohort *N=103 (%)*	*Prospective Group* *N=41(%)*	*Retrospective Group* *N=62(%)*	*P value* *Prospective versus Retrospective*
Baseline ECG Findings				
Normal	83 (80.6)	29 (70.7)	54 (87.1)	0.0395*
Abnormal	20 (19.4)	12 (29.3)	8 (12.9)	0.0395*
Sinus bradycardia (heart rate between 45 and 60 beats per minute	9 (8.7)	8 (19.5)	1 (1.6)	0.0016*
Incomplete Right bundle branch block	2 (1.9)	1 (2.4)	1 (1.6)	ns
Complete right bundle branch block	2 (1.9)	1(2.4)	1 (1.6)	ns
Non progression of R across precordial leads	1 (1.0)	1 (2.4)	0 (0)	ns
Non specific T inversion	2 (1.9)	1 (2.4)	1 (1.6)	ns
Left ventricular hypertrophy	1 (1.0)	0 (0)	1 (1.6)	ns

Left bundle branch block	2 (1.9)	0 (0)	2 (3.2)	ns
Mildly prolonged QT interval (440 msecs)	1 (1.0)	0 (0)	1 (1.6)	ns
Transthoracic Echocardiogram				
Performed in	76 (73.8)	41 (100)	35 (56.5)	<0.001*
Normal	66 (64.1)	38 (92.7)	28 (45.2)	<0.001*
External ECG Monitoring				
Performed in	74 (71.9)	41(100)	33(53.2)	<0.001*
Duration (hours): mean ± standard deviation, median, range	41.2±33.7, 24.0, 14-168	38.0 ± 40.31, 24.0, 24-168	45.1±23.5, 42.0, 14-96	ns

*Abbreviations: ns= not significant, *= p value significant*

ILR data (Table 5):

Patients were followed up for a mean of 874±776 days after implantation of the ILR. The follow-up period was significantly longer in the Retrospective Group (1263±749 versus 239 ±171, p=0.0093). The mean number of downloads from the ILR for the Prospective subgroup were: 2.24±1.88 (median: 2.00, range: 0 – 9). This data was not available for the Retrospective subgroup.

ECG-symptom correlation by ILR (Table 5, Figures 1-3):

Sixty seven percent (69/103) of the whole cohort had ECG symptom correlation by ILR. An equal percentage of patients in both the Retrospective and Prospective Groups had ECG symptom correlation. Sinus arrest was the most common abnormal rhythm seen, occurring in 13/103 (12.6%) of the whole cohort. The mean length of asystole was 25.4±30.3 seconds (median: 11.2 seconds, range: 4-89 seconds) for patients in the Prospective Group. This value was not available for the Retrospective Group. Forty percent of the patients had normal sinus rhythm at the time of symptoms. Muscle artefacts suggestive of tonic-clonic seizures were seen in 4/103 (3.9%) patients (Figure 3). All of these patients belonged to the Prospective Group.

Table 5. ILR Findings

	Whole cohort N=103 (%)	Prosp N=41 (%)	Retro N=62 (%)	P value Pros vs Retro
Duration of follow-up after ILR (days): mean ± SD median, range	874±776, 630,6-3360	239 ±171, 213, 6-616	1263±749, 1050, 120-3360	0.0093*
ECG-symptom correlation achieved in	69 (67.0)	29 (70.7)	40 (64.5)	ns
Findings:				
Sinus arrest	13 (12.6)	4 (9.8)	9 (14.5)	ns
Sinus arrest with AV block	5 (4.9)	3 (7.3)	2 (3.2)	ns
Tachy-brady syndrome	2 (1.9)	0	2 (3.2)	ns
Severe symptomatic sinus bradycardia	2 (1.9)	0	2 (3.2)	ns
Normal sinus rhythm	43 (41.8)	18 (43.9)	25 (40.3)	ns
Muscle artefacts S/o TCS	4 (3.9)	4(9.8)	0 (0)	0.0119*

Abbreviations: ns= not significant, *= p value significant, s/o=suggestive of, TCS= tonic-clonic seizures; Pros=prospective, Retro= retrsopective

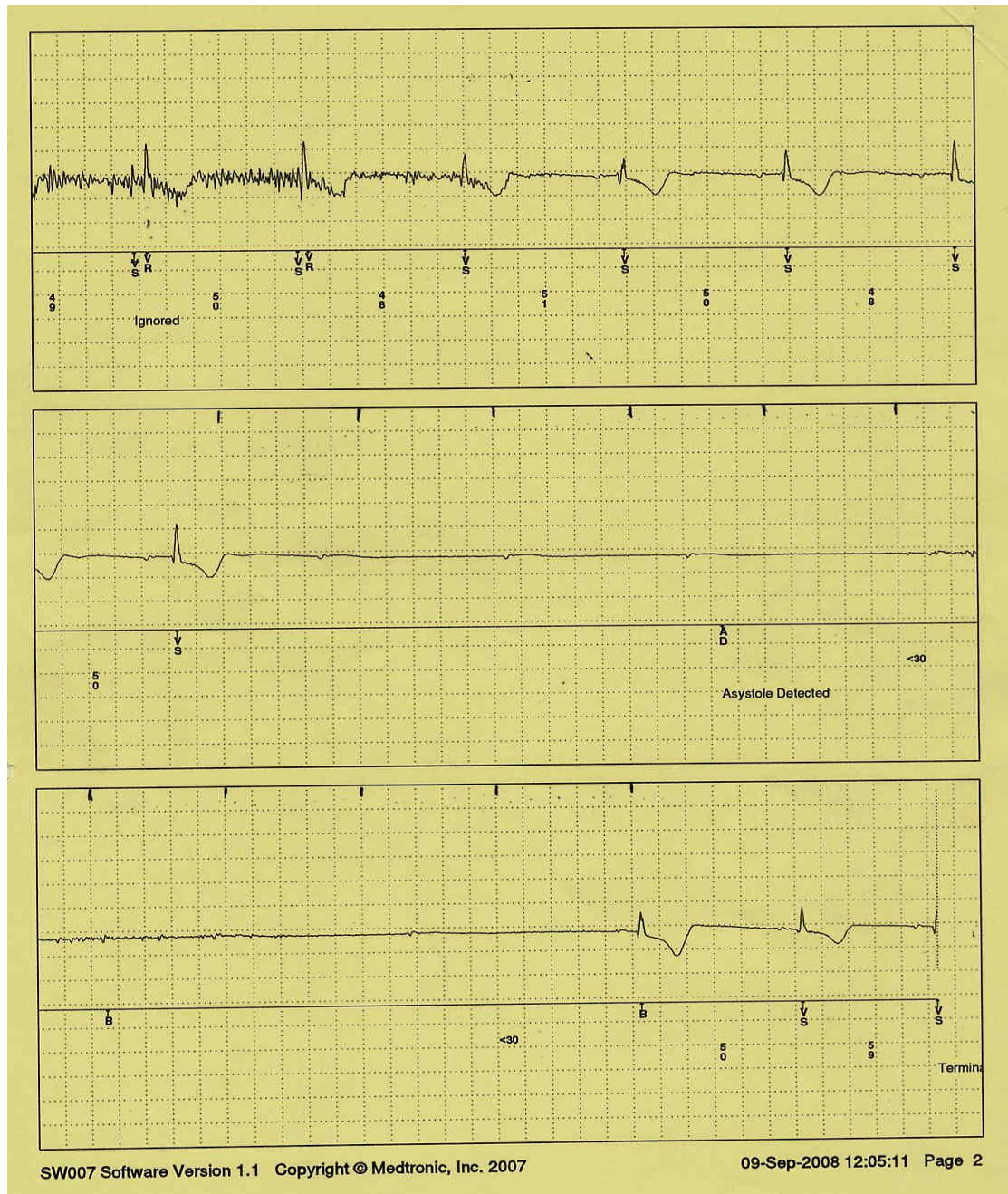**Figure 1: ILR download showing gradual slowing of sinus rate before occurrence of AV block**

Figure 2: ILR download. Panels (a), (b) and (c): Gradual slowing of heart rate before sinus arrest followed by escape rhythm
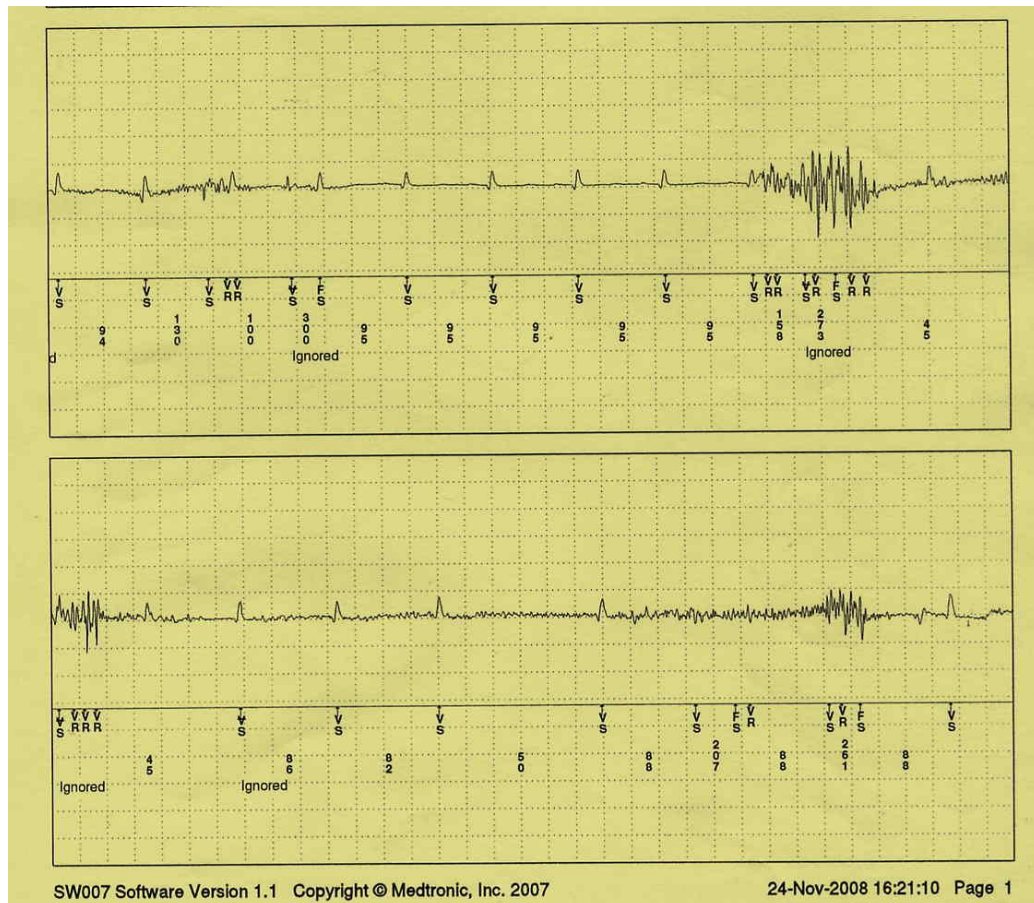
Figure 2. Panel (a):
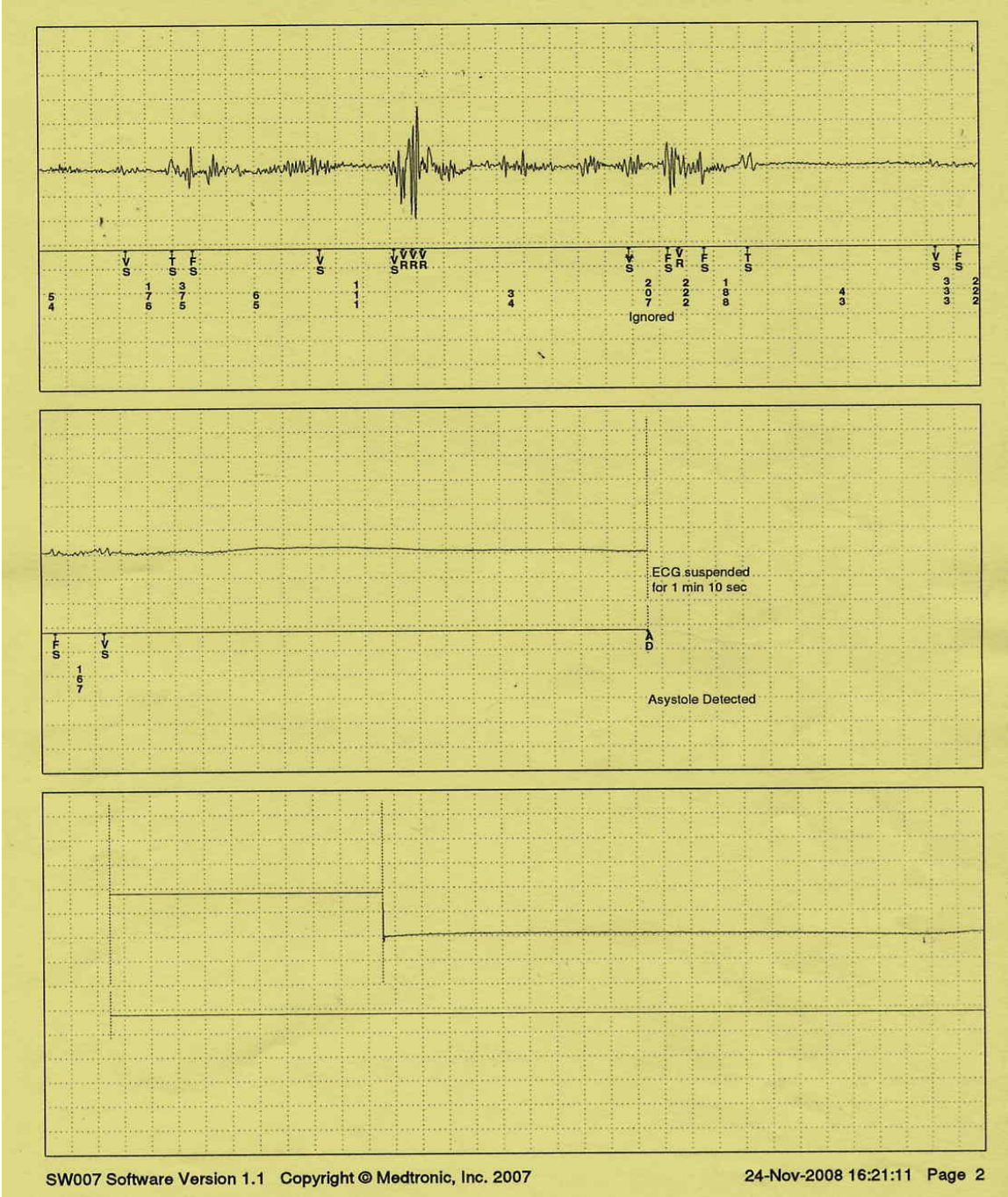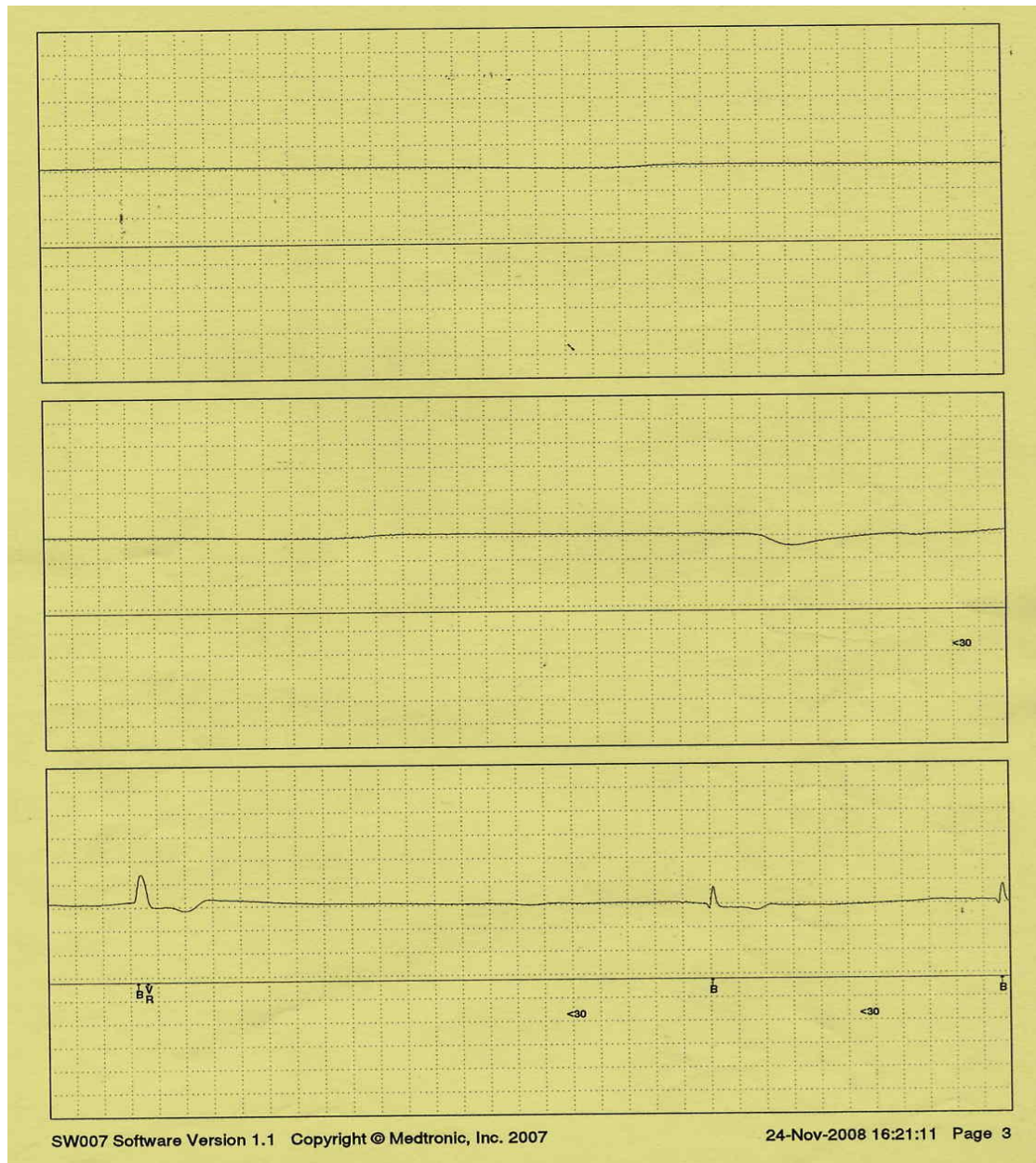
Figure 2: Panel (b) Sinus arrest and asystole

Figure 2. Panel (c) Spontaneous termination of asystole by a ventricular ectopic beat and junctional rhythm

Figure 3. ILR download. Panel (a) Muscle artefacts suggestive of tonic phase (arrow) of tonic-clonic seizures
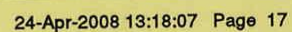
Figure 3. Panel (b) Clonic phase of tonic-clonic seizures – underlying normal QRS complexes are marked with arrows
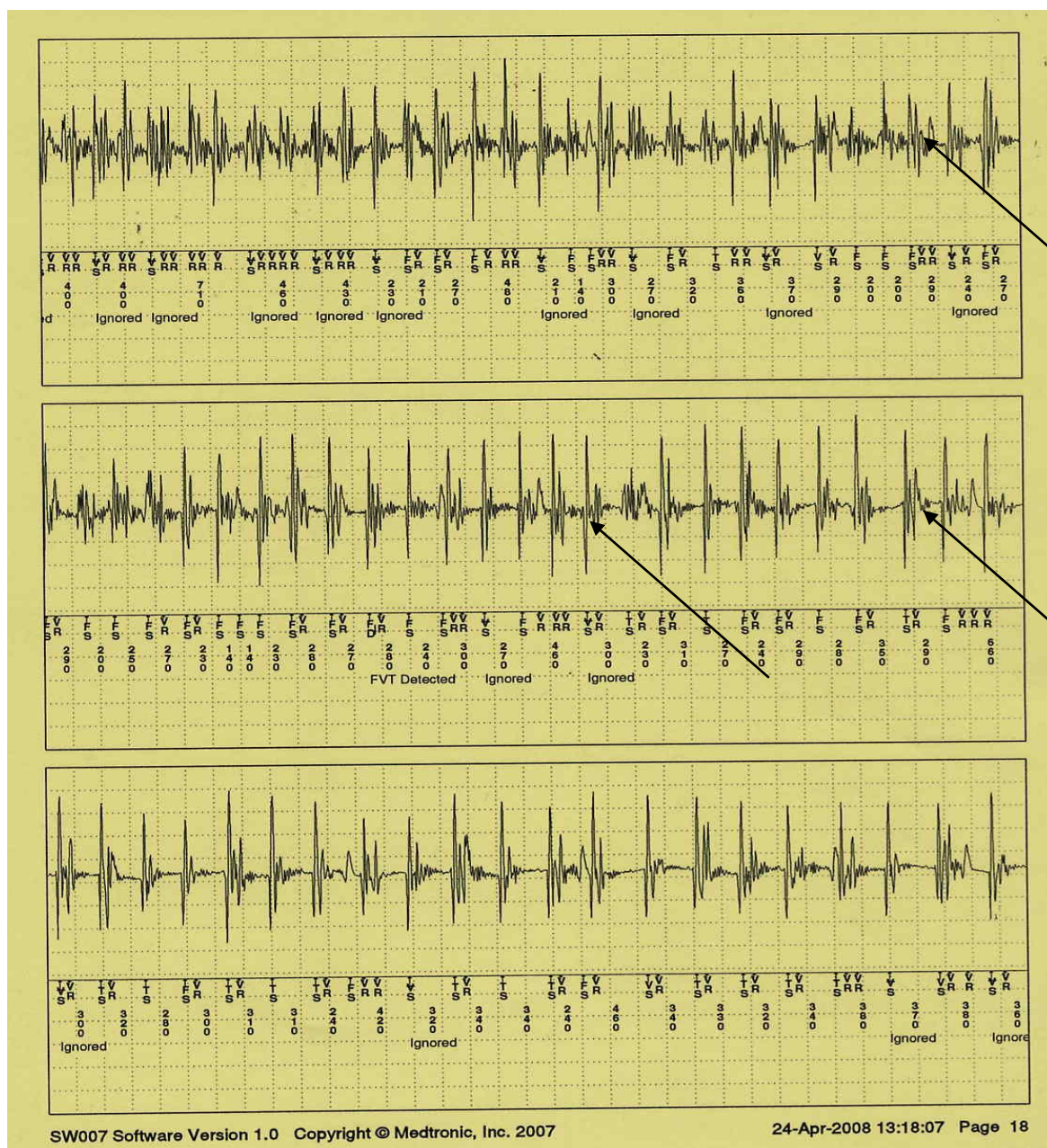
Figure 3. Panel (c) Less marked muscle artefacts – towards end of tonic-clonic phase

Further Treatment:

Based on the results of the ECG symptom correlation achieved by ILR, PPM was offered to 22/103 (21.4%) patients of the whole cohort, of which, 21 (20.4%) underwent it. Six patients from the Prospective Group and 15 patients from the Retrospective Group patients underwent dual chamber PPM. One patient from the Prospective Group refused to undergo the procedure. Five of the 6 (83.3%) patients from the Prospective Group and 12/15 (80.0%) patients from the Retrospective Group who were implanted with PPM's were asymptomatic on follow-up. Thus 17/21 (81.0%) of the whole cohort were free from symptoms after implantation of a pacemaker. Only 4/17 (23.5%) of these patients were still taking AED's. Thus, it can be safely concluded that in 13/103 (12.6%) patients, PPM on its own was responsible for amelioration of symptoms. The duration of follow-up for the Retrospective Group after PPM was: 42±25.6 months, (range: 15-91).

Antiepileptic drugs on follow-up:

Prospective Group: The number of patients on AED's on follow-up were 18/41 (43.9%) which was not significantly different (p=ns) when compared to the number of patients on AED at enrolment. AED's were withdrawn in 8/41 (19.5%) patients, 6/8 (75.0%) of whom were subsequently asymptomatic. Two of the 41 (4.9%) from the Prospective Group were started on antiepileptic treatment during the course of the study. Both of these patients had muscle artefacts suggestive of tonic-clonic seizures recorded on the ILR at the time of symptoms. One of them is asymptomatic 18 months after start of AED.

In the Retrospective Group, antiepileptic drugs were withdrawn in the majority after PPM [pre: 15/15 (100.0%) pre vs 6/15 (40.0%) post, p=0.001].

Tilt testing (Table 6):

Tilt Table Testing was undertaken in 81/103 (78.6%) of the Whole Cohort. It was positive in a minority – 14/103(13.6%), being vasodepressor in 10/103 (9.7%) and cardioinhibitory in 4/103 (3.9%). Significantly more number of patients from the Prospective Group underwent a tilt table test, but the percentage of patients who had a positive test and the type of response did not differ between the two subgroups.

Table 6. Results of tilt testing

Tilt testing	*Whole cohort* *N=103(%)*	*Prospective* *N=41 (%)*	*Retrospective* *N=62 (%)*	*P value* *Prospective versus Retrospective*
Undertaken in	81(78.6)	41 (100)	40 (64.5)	<0.001*
Positive Result	14(13.6)	6 (14.6)	8 (12.9)	ns
Vasodepressor Response	10 (9.7)	6 (14.6)	4(6.5)	ns
Cardioinhibitory Response	4 (3.9)	0 (0)	4(6.5)	ns

*Abbreviations: ns= not significant, *= p value significant, s/o=suggestive of, TCS= tonic-clonic seizures*

Correlation between patients with a positive Tilt test and ILR (Table 7):

In those with a positive tilt test, 12/14 (85.7%) of the Whole cohort had a positive ECG symptom correlation by means of the ILR. In the Prospective Group, all 6 patients with a positive tilt table test had ECG symptom correlation. ILR showed normal sinus rhythm. Among the Retrospective Group, in the 4 patients with vasodepressor positive tilt, ECG-symptom correlation by ILR was achieved in all in 4 (100%). Findings on ILR were: sinus arrest: 2/4 (50%), sinus tachycardia: 1/4(25%), and slow atrial fibrillation: 1/4 (25%). In the 4 patients with a with cardioinhibitory positive tilt test, ECG-symptom correlation was achieved by ILR in: 2/4 (50%). One of these patients had sinus arrest and the other was in sinus rhythm.

Table 7. Correlation between patients with a positive Tilt test and ILR

Positive Tilt test result	*ECG-Sx correlation Whole cohort N=14 (%)*	*ECG-Sx correlation Prospective group(findings) n=6*	*ECG-Sx correlation Retrospective Group (findings), n=8*
Vasodepressor Response	10 (71.4)	6 (sinus rhythm:6)	4/4 (sinus arrest:2, sinus rhythm: 1, Slow atrial fibrillation:1)
Cardioinhibitory Response	2 (14.3)	0	2/4 (sinus arrest:1, sinus rhythm:1)

Abbreviation: Sx=symptom

EEG (Table 8):

Seventy three of the 103 patients underwent an EEG, being abnormal in 18 (17.5%). However, in all but one patient, non specific, non diagnostic abnormalities were found. This patient belonged to the Prospective Group. A minority of 6/41 (14.6%) from the Prospective Group underwent sleep deprived EEG and 3/41 (7.3%) underwent a video-EEG telemetry.

Brain Imaging (Table 8):

Brain imaging, either computed tomography (CT) scan or magnetic resonance (MR) imaging was undertaken 82/103 (79.6%) of the Whole Cohort. This percentage was significantly more in the Prospective Group rather than the Retrospective Group [41/41 (100%) vs 41/62 (66.1%), p<0.001]. Only a minority of scans (10/103, 9.7%) among the Whole cohort were found to be abnormal, which in the opinion of the neurologist, could not explain the patients presenting symptoms.

Table 8. Neurological tests:

	Whole cohort N=103(%)	*Prospective N=41 (%)*	*Retrospective N=62 (%)*	*P value Prospective vs Retrospective*
EEG				
Undertaken in	73 (70.9)	41 (100)	32 (51.6)	<0.0001*
Abnormal	18 (17.5)	11 (26.8)	7 (11.3)	0.0426*
Brain Imaging				
Undertaken in	82 (79.6)	41 (100)	41 (66.1)	<0.0001*
Abnormal	10 (9.7)	4 (9.8)	5 (8.1)	ns

*Abbreviations: ns=not significant, *=p value significant,*

EEG=electroencephalograph

Discussion:

A diagnosis of the cause of TLOC is usually made clinically by analysing the presenting symptomatology. Investigations are usually done when the patient is well and interpreted in the light of the clinical presentation. While it is relatively easy, with current technology, to record heart rate and rhythm during TLOC, it is more difficult to measure other physiological information (blood pressure, neuronal activity) because of limitations in technology, frequency of symptoms and ready availibility of centres performing specialised tests. It is therefore not suprising that there is a delay in achieving a correct diagnosis or there is misdiagnosis. According to The All Party Parliamentary Group on Epilepsy (2007), there are 74,000 patients in the United Kingdom who are taking epilepsy drugs that they do not need. The consequences of a misdiganosis of epilepsy can be devastating e.g., social stigmatisation, loss of productivity, loss of self esteem, ban on driving, young women of child bearing age being exposed to the harmful effects of antiepileptic drugs etc. (Petkar et al, 2006). It is estimated that the annual medical costs in England and Wales of treating patients misdiganosed with epilepsy is approximately £29 million with total costs in the region of £138 million (Juarez-Garcia A et al, 2006).

This is the first study to systematically use the implantable ECG loop recorder (Reveal Plus®/Reveal DX®) in the evaluation of patients suspected to be misdiagnosed with epilepsy or in those in whom the diagnosis of epilepsy was in doubt. This study showed that 1 in 8 (13/103, 12.6%) patients with syncope were misdiagnosed as epilepsy. It is likely that the true diagnosis in these patients was Reflex Syncope and that convulsive movements noted during spontaneous episodes of TLOC were manifestations of 'convulsive syncope'. These patients were asymptomatic after implantation of a permanent pacemaker and withdrawal of

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antiepileptic drugs. It was also possible to diagnose generalised epilepsy (Stokes et al, 2004), manifesting as tonic-clonic seizures, by the pattern of muscle artefacts found on the loop recorder during an episode of TLOC in 4/103 (3.9%) patients.

The incidence of misdiagnosis of epilepsy reported in the literature varies between 12.9% and 41.9% (Zaidi et al, 2000; Smith et al, 1999; Scheepers et al, 1998, Josephson et al, 2007). Common alternative diagnoses are syncope and psychogenic blackouts (Benbadis SR, Allen Hauser W 2003, Reuber M, Elger CE 2003, Zaidi et al, 2000; Smith et al, 1999; Scheepers et al, 1998, Josephson et al, 2007,13-14). This study differs significantly from previous published literature (Zaidi et al, 2000; Smith et al, 1999; Scheepers   et al, 1998, Josephson et al, 2007) with respect to the methods used to arrive at a misdiagnosis.

The unique feature of the present study was that all patients underwent a highly specific test, that is, an ILR, thus enabling their heart rhythm to be recorded at the time of a spontaneous episode of TLOC. The use of the ILR allows a higher percentage of patients to have ECG-symptom correlation due to the longer duration of monitoring (Furukawa T, et al 2012). An ECG-symptom correlation was achieved by this test in 69/103 (67.0%) of patients in this studyThis is higher than the figure of 35% quoted in the literature for patients presenting with unexplained syncope and 27% for patients presenting with possible neurally mediated syncope (Brignole M et al, 2009) but comparable to the figure of 88% when used in highly selected patients (Brignole et al, 2009) . In only one other study (Zaidi et al, 2000) has the ILR been used to investigate patients with a suspected misdiagnosis of epilepsy. However, in that study, only a minority i.e. 10 of 74 (13.5%) patients underwent this test.

The second important difference between the present study and previous published literature is in the results of tilt testing in this group of patients. The study by Zaidi et al (2000) used tilt testing to arrive at a diagnosis of syncope, being positive in 25.7% of patients. Tilt testing was abnormal in a lower percentage of patients in our study, being positive in only 14/103 (13.6%) patients. Moreover, we did not find a good correlation between the results of the tilt test and the ILR. Such a disparity in the results of the tilt test and the ECG at the time of a spontaneous episode of TLOC is well recognised (Brignole M et al 2009). No such correlation between the results of the tilt test and the ILR was attempted in the study by Zaidi et al (2000). None of the patients in the study by Smith, Defalla and Chadwick (1999) and Josephson (2007) and an uncertain number of patients in the study by Scheepers (1998) underwent a tilt test. Unlike an ILR, the tilt test is a provoked test rather than a test which records a spontaneous episode of TLOC. There is a wide variation in the sensitivity and specificity of the tilt test (Moya et al 2009) and is probably responsible for the difference between the results of the present study and that by Zaidi (2000). Tilt testing is currently a Class IIb indication for differentiating syncope from epilepsy in the latest ESC guidelines on syncope (Moya et al 2009).

The third important difference between the present study and previous published literature is in the use of the ILR to establish a diagnosis of generalised epilepsy by the pattern of muscle artefacts noted during a spontaneous episode of TLOC. Such a pattern was found in 4/103 (3.9%) patients in the study (Figure 3). It has shown to correlate with EEG findings (Rugg-Gunn FJ et al 2004) in a small study of 12 patients. Two of the 4 patients (50%) were started on antiepileptic drugs after the recording of this pattern on the ILR. One of the two patients is asymptomatic after 18 months.

There are other differences between the present study and previous published literature on this topic. Seventy three (70.9%) of patients in the present study were subjected to an EEG. From the Prospective Group, 6/41(14.6%) underwent a sleep deprived EEG and 3/41 (7.3%) a 5 day video-EEG telemetry monitoring. The EEG was abnormal in 18/103 (17.5%) with a vast majority of patients showing non- specific and non diagnostic abnormalities. An interictal EEG or an ambulatory EEG, with or without brain imaging was used in a minority 23/186 (12.4%) of patients in the study by Smith, Defalla and Chadwick (1999). Scheepers, Clough and Pickles (1998) also used the same tests in their study, though the precise number of patients undergoing these tests is unclear from their publication. All patients in the study by Zaidi (2000) and 90% of patients in the study by Josephson (2007) were subjected to an EEG. Like tilt table testing, the standard EEG has a variable sensitivity and specificity in an individual with epilepsy (Stokes et al 2004). It is well recognised that an EEG should not be used in isolation to make a diagnosis of epilepsy but should be performed only to support a diagnosis and to define the epilepsy syndrome in those in whom the clinical history suggests that epilepsy is very likely (Stokes et al, 2004). Moreover, an EEG should not be performed in a patient suspected to have syncope because of the possibility of false positive results (Stokes et al, 2004). Patients in the present study were considered to have a misdiagnosis based on a clinical review by a neurologist with special interest in epilepsy and the results of the EEG were not acted upon. We feel that this was the right approach to adopt as misinterpretation of the EEG findings is one of the causes for a substantial proportion of patients to be misdiagnosed as epilepsy (Smith et al, 1999).

Any form of imaging was undertaken in only 28/186 (15.1%) in the study by Smith, Defalla and Chadwick (1999) and the type of imaging undertaken is unclear from their publication. MR scanning was undertaken in a uncertain number of patients in the study by Scheepers (1998). Josephson (2007) used CT in 51% and MR brain in only 15% of patients in their study. No imaging was undertaken by Zaidi (6). In the present study 82/103 (79.6%) patients underwent brain imaging, either in the form of CT or MR scanning. MR scanning is the investigation of choice in patients with epilepsy (Stokes et al, 2004).

Three fourths of the Whole Cohort also underwent external ambulatory ECG monitoring and an echocardiogram. These tests have not been used in any other studies (Zaidi et al, 2000; Smith et al, 1999; Scheepers et al, 1998, Josephson et al, 2007).

Limitations of the study:

The Whole Cohort comprises a mixture of patients recruited Prospective and those assessed retrospectively. This may have a bearing on the results.

This study used the ILR to record the heart rhythm during a spontaneous episode of TLOC. The limitation of this approach is that there are reports in the literature of patients with a true diagnosis of epilepsy also having asystolic pauses during an episode of spontaneous TLOC (Rugg Gunn FJ et al 2004, Rocamora et al 2003). It is possible that one patient in our study, who did not respond to permanent pacing fell in this category. However, she continues to be symptomatic in spite of restarting AED's and is now being

considered for a vagal nerve stimulator as treatment for resistant epilepsy (19).

The number of patients with a psychogenic cause of TLOC has not been investigated in this study. It is possible that some patients with normal sinus rhythm on their ILR during an episode of TLOC actually suffered from psychogenic blackouts. It would have only increased the number of patients misdiagnosed.

Conclusion:

This is the first prospective study to show, by means of ILR, a high incidence of bradyarrhthmias and asystole (21.4%) in patients misdiagnosed with epilepsy or where the diagnosis of epilepsy was in doubt. The likely diagnosis in these patients was convulsive syncope. Poor correlation between results of tilt testing and ILR were found. This study also showed the usefulness of the ILR in diagnosis of typical tonic clonic seizures by the pattern of muscle artefacts. The ILR should therefore be considered as the investigation of choice in this group of patients.

Chapter V

Cardiovascular screening in patients with epilepsy and special needs

Introduction:

Sudden Unexpected Death in Epilepsy (SUDEP) occurs with an incidence of 0.35-9.3/1000 patient years (Stollberger C, Finsterer J, 2004) and accounts for between 2 and 18% of all deaths in patients with epilepsy. While the precise pathophysiology of SUDEP is yet to be determined, cardiac arrhythmia is postulated to be among one of many possible mechanisms. The incidence of convulsive syncope misdiagnosed as epilepsy varies from 13-42% (Petkar et al 2012) depending on the type of investigative tools used. Moreover, examination of the data from the Long QT Registry (Moss AJ et al, 1991) reveals that up to 6% of patients with the congenital Long QT syndrome present with seizures. Apart from one retrospective study which analysed inter-ictal 12 lead ECG in patients with epilepsy and psychogenic blackouts(Krishnan V, Krishnamurthy KB 2013), thus far, cardiovascular evaluations in patients with epilepsy have largely concentrated on heart rate (Zijlmans M, Flanagan D, Gotman J 2002, van Elmpt WJC et al 2006), rhythm (Keilson MJ 1987, Nei M, Ho RT, Sperling MR, 2000, Nei M et al 2005), and occurrence of myocardial ischaemia during seizures (Tigaran S et al, 2007) in an attempt to ascertain any association between the two conditions. A number of case reports are available of 'ictal bradycardia', where an abnormality of the cardiac rhythm has been documented, usually during video-EEG monitoring during a seizure, and have subsequently been treated with a permanent pacemaker implantation (Tigaran S, Molgaard H and Dam M 2002, Almansori M, Ijaz M, Nizam Ahmed S 2006, Britton JW et al 2006, Schuele SU, Bermeo AC, Alexopoulos AV 2007, Schuele SU et al 2008, Rubboli G et al 2008, Rugg-Gunn FJ et al 2004).

Only 4 studies (Krishnan V, Krishnamurthy KB 2013, Tigaran S et al 2003, Keilson MJ et al 1987, Drake ME, Reider CR, Kay A 1993) have subjected patients with epilepsy to systematic cardiovascular evaluation in an attempt to establish a link between SUDEP and cardiac arrhythmias. Due to a lack of scientific studies, little is known about the value of an inter-ictal ECG, extent of underlying cardiovascular disease or the incidence of misdiagnosis in patients with epilepsy. In this study, we have prospectively evaluated the value of inter-ictal systematic cardiovascular evaluation in patients with prior brain injury and epilepsy.

Methods:

We examined two hundred and fourteen patients in a residential epilepsy centre (David Lewis Centre for Epilepsy, Nr Alderley Edge) where residents typically had a history of brain injury and suffered from recurrent epileptic seizures, undertaking systematic cardiological assessment using 12 lead ECG, echo and 24 hour ambulatory monitoring, after setting up a satellite outreach clinic. All patients prospectively underwent an inter-ictal 12 lead ECG. In addition to the automatic interpretation, all of them were also manually interpreted by cardiologists from the Manchester Heart Centre and the findings compared. Depending on the ECG findings, further investigations i.e., echocardiograms and ambulatory ECG monitoring were advised and undertaken.

Statistics:

Descriptive statistics have been reported as mean±SD, median and range. The 't test' was used to compare means. Spearman's correlation was used to correlate measured values and the Bland-Altman Test was used for calculating the Limits of Agreement. GraphPad Prism was the statistical package used for analysis.

Results:

Demographics:

Of the 214 patients who underwent a 12 lead ECG, 63.6% (136/214) were males. Mean age of the cohort was 38.1±17.6 years (median: 33.5, range: 17-83). A majority of the patients suffered from tonic-clonic seizures (Table 1).

Table 1. Distribution of the type of epilepsy

| Type of Epilepsy	Number of patients (%)
Atonic	3 (1.4)
Partial	4 (1.9)
Partial + generalised	4 (1.9)
Seizure free in the last 3 years	10 (4.7)
Unclassified	21 (9.8)
Partial + secondary generalised	25 (11.7)
Mixed generalised	30 (14.0)
Complex Partial	34 (15.9)
Tonic-Clonic	83 (38.8)

The mean duration of epilepsy was: 33.5±17.7 years (median 33, range: 2-73). On an average, patients were on 5±2.8 (median: 4, range: 0-15) antiepileptic drugs. A mean of: 3.6±3.7 (median: 3, range: 0-40) co-morbid conditions were identified in the study patients.

ECG Findings:

Satisfactory inter-ictal ECG's were obtainable in a majority (211/214, 98.6%) of patients. All patients were in sinus rhythm. One hundred and twenty nine ECG's were found to have some abnormality (129/214, 60.3%), the remainder being normal.

The five most common abnormalities were (Figure 1): incomplete RBBB: 17/214 (7.9%), non progression of R waves across precordial leads: 17/214(7.9%), ST-T wave changes: 15/214 (7.0%), right ventricular hypertrophy: 13/214 (6.1%) and RBBB with first degree heart block: 10/214(4.7%). A prolonged QT/QTc was found only in 4/214 (1.9%) of patients.

Figure 1. Most common ECG abnormalities
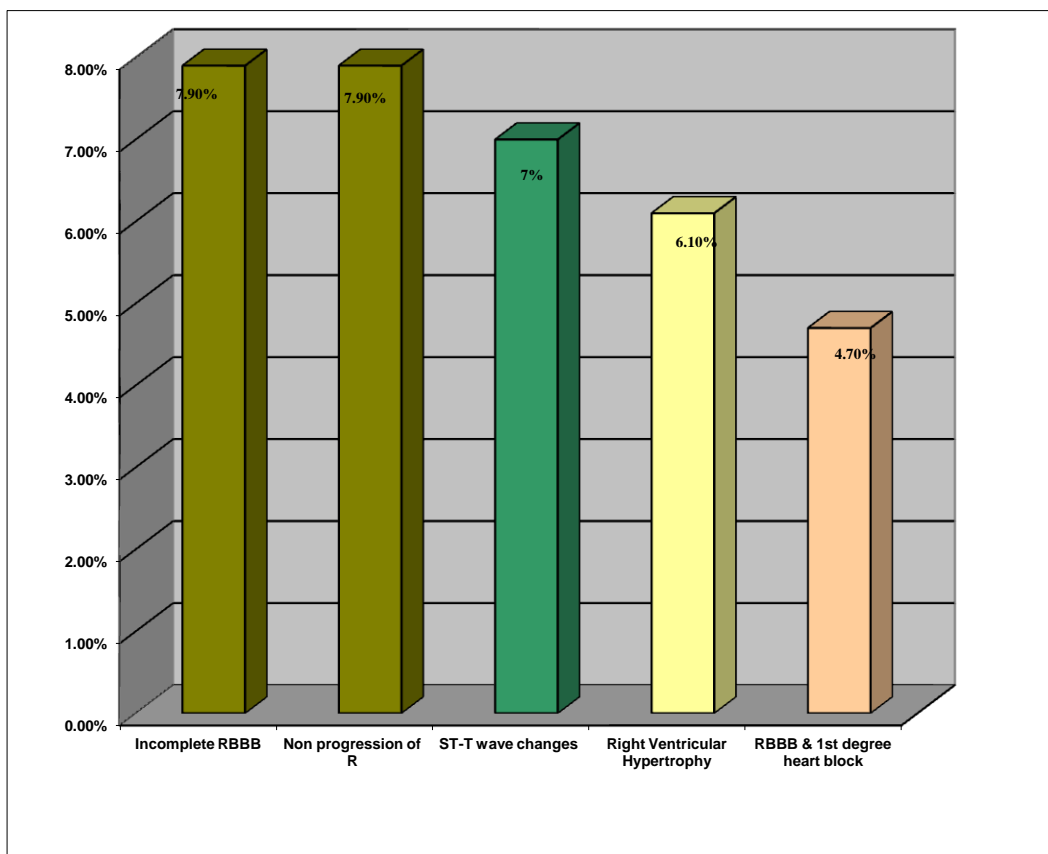
Abbreviations: RBBB= right bundle branch block

Comparison of Automatic versus Manual Interpretation of ECGs:

Heart Rate (Figure 2):

The mean heart rate as calculated automatically was 79.8±13.2 beats/minute which did not differ significantly from that obtained manually i.e. 79.1±13.5 beats/minute , p=ns. There was good correlation between the results by the two methods (r=0.962). The two tests varied in their results by -6.4 to +7.5 beats/minute by the Bland-Altman test.

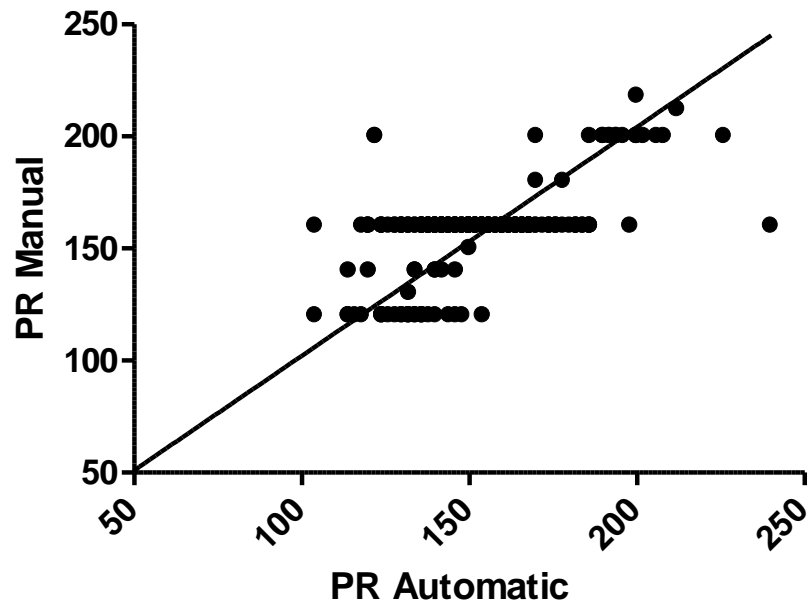**Figure 2.**

Correlation of HR Automatic vs Manual
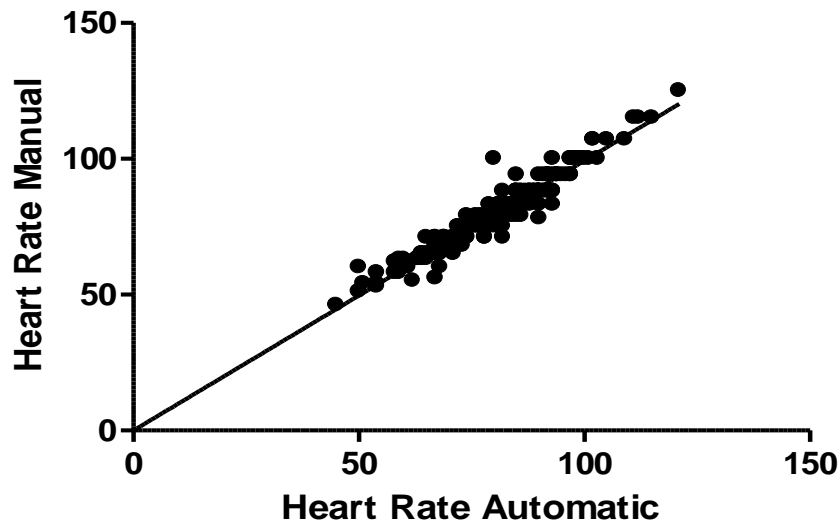
Abbreviation: HR= heart rate

PR Interval (Figure 3)

The mean PR interval calculated automatically was 153±23.3 msecs which was statistically significantly different from that obtained manually i.e. 158±21.4 msecs, p=0.014. Still there was good correlation between the results by the two methods (r=0.59), with a variation in the observed results of -42.0 to +32.2 msecs (Bland-Altman Test).

Figure 3. **Correlation of PR Automatic vs Manual**

QT Interval (Figure 4):

The mean QT interval measured automatically by the ECG machine was 354± 29.8 msecs, which did not differ statistically from that calculated manually i.e. 356±30.9 msecs, p=ns. There was good correlation between the two methods (r=0.74), the values between the two methods varying by -43.6 to +39.1 msecs (Bland-Altman Test).

Figure 4. **Correlation of QT Automatic vs Manual**
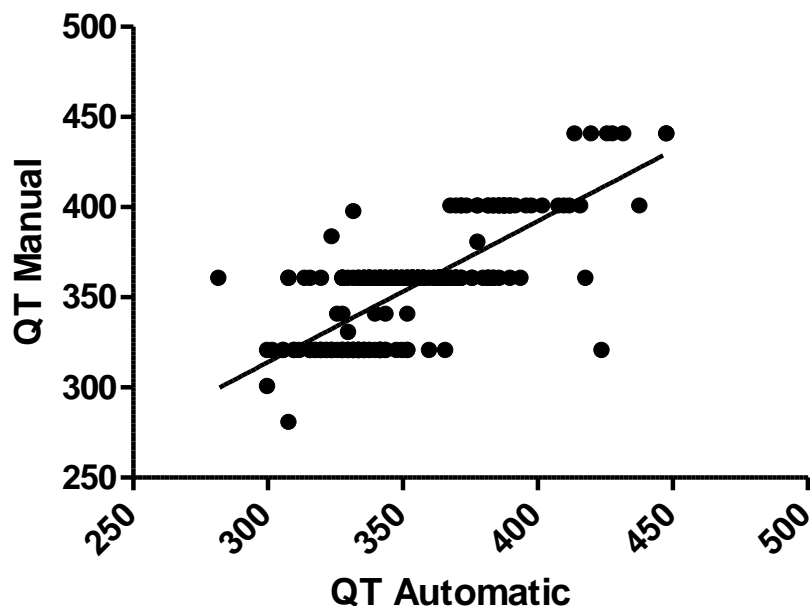
QTc Interval (Figure 5):

There was no statistically significant difference between the two methods in the calculation of the mean QTc (Automatic: 404±26.2 msecs vs 406±28.6 msecs, p=ns). The correlation between the two methods was weaker than with the QT interval but nevertheless statistically significant (r=0.57). The variation in the calculation of the QTc between the two methods was -52.1 to +48.2 mecs (Bland-Altman Method).

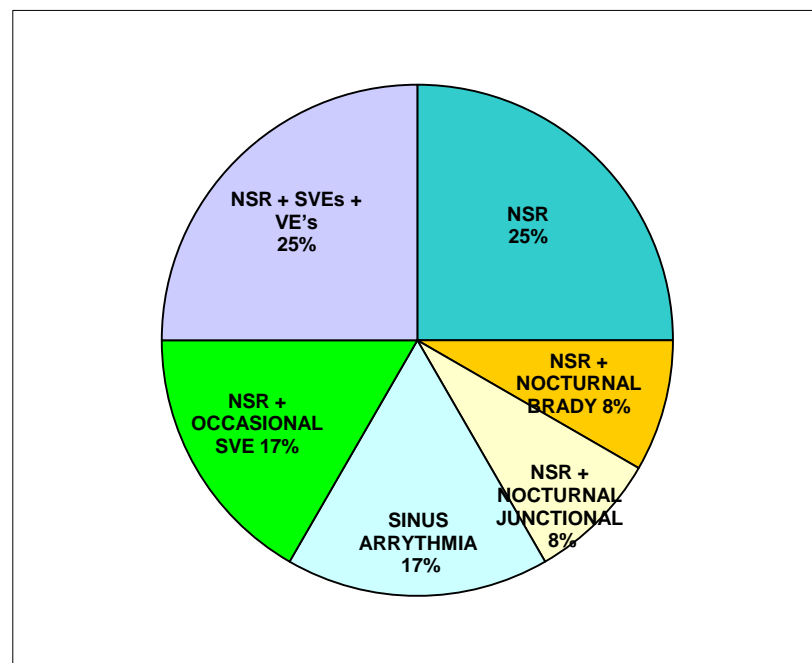**Figure 5.**

Correlation of QTc Automatic vs Manual
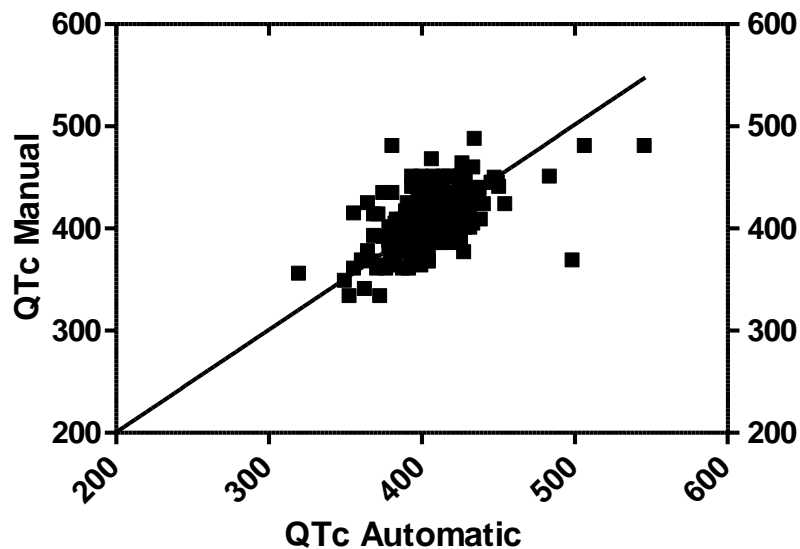
Echocardiograms:

Based on the results of the 12 lead ECG, transthoracic echocardiograms were advised in: 68/214 (31.8%) and were possible in: 25/68 (36.8%). A majority of the echocardiograms were: normal: 15/25 (60%). Abnormalities noted were: old myocardial infarction: 3/25 (12.0%), left ventricular hypetrophy: 2/25 (8%), and hypertrophic cardiomyopathy, atrial septal defect, mitral regurgitation and constrictive pericarditis: 1/25 (4%) each.

External ECG monitoring (Figure 6):

External ECG monitoring was advised in: 23/214 (10.8%) and was possible in half of them: 12/23 (52.2%). No significant abnormality of the heart rhythm was seen in those patients who underwent this test.

Figure 6. Results of external ECG monitoring

Abbreviations: NSR= normal sinus rhythm; SVE= supraventricular ectopics; VE= ventricular ectopics

Figure 7: Cause of death
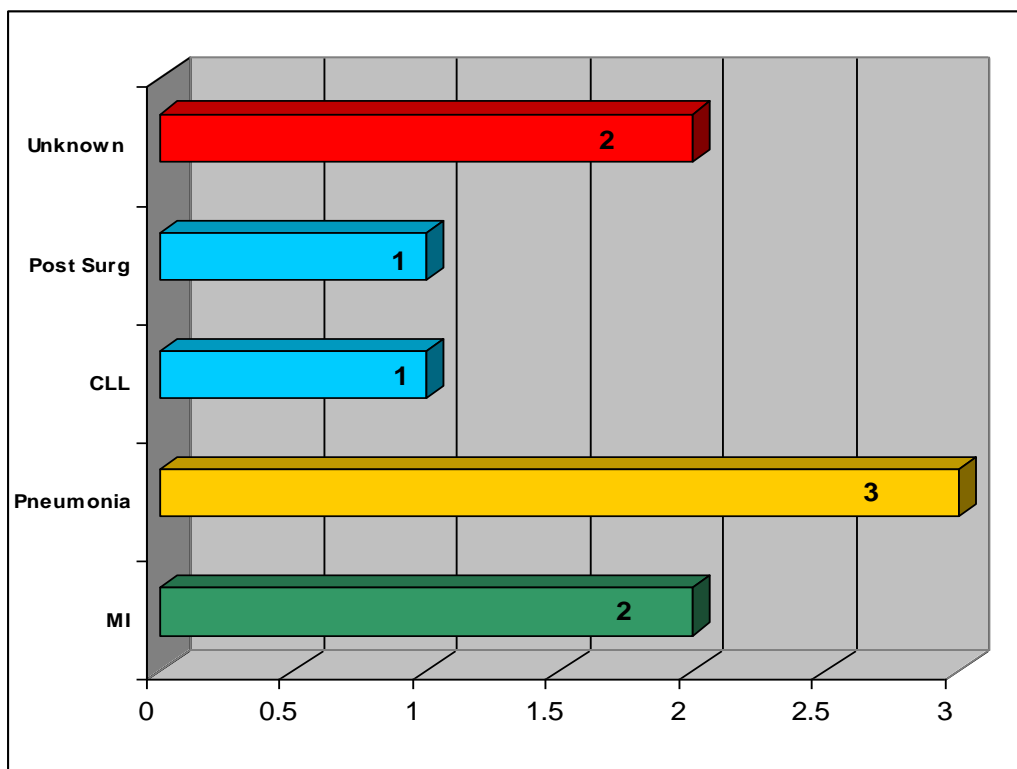
Abbreviations: CLL = chronic lymphoid leukemia; MI= myocardial infarction

There were 9 deaths during the study period. Seven of the nine deaths were witnessed as they occurred in hospitalised patients (not the David Lewis Centre). Causes of death were as follows: myocardial infarction: 2/9 (22.2%), pneumonia: 3/9 (33.3%), chronic lymphatic leukemia: 1/9 (11.1%), one as a result of complications post surgery: 1/9 (11.1%) and uncertain: 2/9 (22.2%). One of the unknown deaths was a 46 year old lady whose ECG had shown old extensive anterior and inferior wall myocardial infarction. It is presumed that she died due to cardiac causes. The second death, where the cause of death was uncertain, was a 79 year old lady with left ventricular

hypertrophy and ST-T changes on the 12 lead ECG. Both of these patients had suffered from tonic-clonic seizures and neither of them had undergone an echocardiogram, though it had been advised.

Discussion:

We have described our experience of systematic inter-ictal cardiovascular evaluation in a large cohort (n=214) of patients with epilepsy and special needs. We believe that this is the largest series of patients with epilepsy who have undergone such an evaluation. We could find only 4 published studies in which patients with epilepsy have been subjected to inter-ictal cardiovascular evaluation in an attempt to establish a link between SUDEP and cardiac arrhythmias.

Keilson MJ et al (1987) reviewed simultaneous EEG/ECG recordings of 338 patients with epilepsy for cardiac arrhythmias. High-risk cardiac arrhythmias were detected in a minority (18/338 - 5.3%) patients while low-risk arrhythmias or negative studies were found in the others. In 17 patients, the ECG was available during 56 seizure episodes, but no associated ventricular arrhythmias or conduction defects were identified. Their conclusion was that the incidence of serious cardiac arrhythmias predisposing to sudden death is not increased in patients with epilepsy.

Drake et al (1993) compared inter-ictal resting ECGs in 75 patients with epilepsy, comparing them with normal ECG's recorded in age-matched patients without cardiac or neurological disorders. Ventricular rate, PR interval, QRS duration, and QT interval (corrected for heart rate) were compared. Those with epilepsy were found to have higher heart rates and

longer QT durations than the age-matched controls but they were not outside the normal range.

Twenty-three subjects with drug refractory epilepsy were subjected by Tigaran et al (2002) to comprehensive cardiovascular evaluations, i.e., ECG, Holter-monitoring, echocardiography, ergometric exercise test and myocardial scintigraphy before and during video-EEG monitoring. If abnormalities were found, coronary angiography was also performed. ST-segment depression was found in 40% of patients long with a higher maximum heart rate during seizures, suggesting that cardiac ischaemia may occur in these patients.

Krishnan V and Krishnamurty B (2013) retrospectively analysed the inter-ictal ECG's of 195 adult patients below the age of 65 years with definite or probable epilepsy and compared it with those with non epileptic seizures. Patients with antipsychotic and/or antidepressant medications were included but patients with medical conditions or taking other medications that would otherwise confound ECG measurements were excluded. They found that patients with definite localization-related epilepsy displayed a significantly longer average PR interval (162.1 ms) than patients with non-epileptic seizures (148.8 ms). This effect was pronounced in female patients and did not vary with the number of antiepileptic drugs (AEDs) prescribed. Mean QTc intervals were not significantly different between patients with definite epilepsy (428 ms) and controls (422.6 ms). However, within females, this difference reached statistical significance (DE: 434.6 ms, NESs: 424.6 ms). Antiepileptic drug polytherapy was associated with a significantly lower QTc interval (416 ms in patients on 4–6 drugs and 436.4 ms in patients on 0–1 drugs). Levetiracetam was the most commonly used AED and was associated with the longest average PR (163 ms) and QTc (432 ms) intervals.

The mean QRS axis displayed a significant leftward shift in patients with localization-related epilepsy (35.6° versus 54.3° in patients with NESs) and also in female patients with DE (42.1° versus 55.4° in female patients with NESs). No differences were observed between patients with left versus right hemisphere seizure foci. The authors concluded that their findings may reflect cardiac structural changes and/or alterations in autonomic tone, the association of which with SUDEP needs further study.

This is the first study to prospectively and systematically evaluate patients with prior brain injury and epilepsy for cardiac abnormalities. We believe that the population included in our study was challenging as patients had epilepsy with special needs. There were a range of different types of epilepsy which was longstanding. Patients also had a wide range of co-morbid conditions. Inspite of the difficulties in evaluating such patients, good quality ECG's recordings could be obtained in a majority. A majority (60.3%) of the interictal ECG's obtained were abnormal. However, on further evaluation, only a minority had cardiac morbidity/structural heart disease. Moreover, a good correlation between automatic and manually read ECG's was seen. This can only be reassuring for neurologists whose ECG reading skills maybe somewhat dated. The overall cardiac mortality in this population was low, patients dying predominantly due to unrelated problems. No cases of SUDEP were noted. No cardiac cases misdiagnosed as epilepsy were encountered.

Conclusion:

Systematic inter-ictal evaluation of patients with epilepsy and special needs yielded a low rate of cardiac abnormalities and no case of misdiagnosis.

Future Directions

The RABTC showed that a simple structured assessment of patients presenting with TLOC helped to improve outcomes of patients. The accuracy of the initial diagnosis was high, a high proportion of patients benefited from appropriate investigations and treatment, especially pacemakers and a minisclue proportion of patients remained undiagnosed after 2 years of follow-up. It also demonstrated that cooperation between different healthcare professionals dealing with patients with TLOC was indeed possible. Since its introduction, it has now been expanded to other hospitals in the UK and the cumulative experience is in excess of 500 patients. However, the major limitation of the RABTC was that it mostly evaluated patients with an intermediate risk of an adverse event in future and not those with the highest or the most adverse prognosis. Developing pathways of care, including patients with the highest risk, like that implemented at the New Cross Hospital in Wolverhampton, and raising the awareness of medical professionals in primary and secondary care about the optimum management of patients with TLOC is likely to further improve the outcome of these patients in future. Similarly, raising the awareness of misdiagnosis of epilepsy, first described by Smith et al in 1999 and later on by Zaidi et al, the use of the ILR earlier in the diagnostic pathway and greater openness and cooperation between different healthcare professionals is also likely to improve the outcome of patients with TLOC in future. However, the above changes are unlikely to happen overnight as changing the habits of healthcare professionals is difficult. Only persistence will see the scenario change for the better in future.

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Glossary

Arrhythmia: An abnormal heart rhythm.

Asystole: Sustained absence of the heart's electrical activity.

Bradycardia: Slow heart rate (irrespective of rhythm), conventionally defined as less than 60 beats per minute.

Carotid sinus syncope: A form of neurally mediated syncope in which pressure on one or other carotid artery causes syncope.

Convulsive syncope: 'syncope accompanied by myoclonic jerks and other involuntary movements caused by transient insufficiency of blood supply to the brain

Déjà vu: An intense sensation that what is happening for the first time has already occurred previously. This is common particularly in adolescence, but may be a manifestation of a partial seizure (rather than occurring immediately before an epileptic seizure).

ECG (12-lead): Recording of the heart's electrical signals obtained by attaching electrodes in ten standard positions on the limbs and the surface of the chest. This provides a display of the electrical activity of the heart viewed from 12 different directions.

Epilepsy:

> Fits
>
> Seizures
>
> Seizure disorder

convulsions

External event recorder: A small portable recorder that is capable of monitoring and storing ECG recordings from electrodes on the skin. The device records the heart's rhythm during symptoms (including syncope) that occur intermittently. Excludes event recorders that do not perform continuous ECG monitoring (and therefore are not capable of documenting cardiac rhythm at the moment of TLoC).

Holter monitor/recorder: A small portable recorder that is capable of continuous ECG recording from electrodes on the skin.

Ictal arrhythmia: A disturbance of normal heart rhythm occurring during a seizure.

Implantable event recorder: Small implantable device capable of monitoring and storing ECG recordings of the heart's rhythm. It is also known as an implantable/insertable loop recorder.

Jamais vu: A feeling of lack of familiarity, that what should be familiar is happening for the first time; it is usually abnormal, it doesn't commonly occur in healthy people

Micturition syncope: A form of neurally mediated syncope provoked by straining while passing urine while standing.

Orthostatic hypotension: Condition in which a marked fall in blood pressure is provoked by a change in posture from lying to sitting, or from lying or sitting to standing. This may cause light-headedness (dizziness), a fall, or TLoC.

Post-ictal confusion: An abnormal state that follows an attack, usually referring to a disturbed condition after an epileptic seizure.

Prodromal symptoms: which precede the episode.

Psychogenic blackouts:

Non epileptic seizures

Non epileptic events

psuedoseizures

psychogenic pseudosyncope

psychogenic seizures

psychogenic non-epileptic seizures

Reflex Syncope is also known in the literature by the following names (in alphabetical order):

Blood illness injury phobia

Bradycardia syndrome

Emotional fainting

Malignant vasovagal syncope

Neurogenic syncope

Neurally mediated hypotension

Neurally mediated reflex syncope

Neurally mediated syncope

Neurocardiogenic syncope

Pallid breath holding spells

Pallid infantile syncope

Pallid syncope

Reflex anoxic seizures

Reflex asystolic syncope

Valsalva syncope

Vasodepressor syncope

Vasovagal syncope (VVS)

White breath-holding

In the English language, it is also called as fainting, blacking out, passing out or swooning

Situational syncope: A form of neurally mediated syncope occurring in certain specific situations (for example,cough syncope, micturition syncope, or swallowing syncope).

Structural heart disease: Any disease of the heart in which the structural components of the heart areabnormal. This encompasses heart muscle disease, valve disease and congenital heart disease.

Tilt test: Test in which a patient is exposed to passive head-up tilt, during which they have beat-to-beat measurement of heart rate and blood pressure, to try to demonstrate whether or not they have a provocable tendency to vasovagal syncope.

Appendix

Attached are the reprints of two first author articles published in peer reviewed scientific journals based on the work (Chapters II and IV) done as part of this dissertation.

(i) S Petkar, W Bell, N Rice, P Iddon, P Cooper, D McKee, N Curtis, M Hanley, J Stuart, K Mackway Jones and AP Fitzpatrick. Initial experience with a rapid access blackouts triage clinic. *Clinical Medicine* 2011; 11: 11–16 This article, as the name suggests, summarises the experience of the first 327 patients assessed in the Rapid Access Blackouts Triage Clinic, Manchester, since its inception in 2007 using simple tools for triage, namely, history and ECG.

(ii) Sanjiv Petkar, Tahir Hamid, Pamela Iddon, Anne Clifford , Nicola Rice, Richard Claire, David McKee, Nick Curtis, Paul N. Cooper, and Adam Paul Fitzpatrick. Prolonged implantable electrocardiographic monitoring indicates a high rate of misdiagnosis of epilepsy—REVISE study *Europace* 2012; 14: 1653–1660. This article describes the REVISE Study – **REV**eal in the **I**nvestigation of **S**yncope and **E**pilepsy (Chapter IV) in which a high proportion of patients with Reflex Syncope were misdiagnosed as epilepsy.

(iii) Wayne O. Adkisson and David G. Benditt. Treatment of 'refractory' epilepsy: syncope incogniti unmasked by implantable ambulatory electrocardiographic recordings. Europace 2012: 14: 1540–1542 is an editorial prompted on the findings of the REVISE study, published in the same issue of Europace.

(iv) Customised web based questionnaire: Headings under which the customized web based questionnaire was structured and which was used for assessment of patients with TLOC in the RABTC were as follows:

Title

1. Demographics

2. Resource Use

3. Preliminary Questions

4. Previous to Attack

5. Onset of Attack

6. Attack Description

7. Video Clips

8. After Attack

9. Background

10. Care Pathway

11. Investigations/Results

12. Final Diagnosis

Letter