A SUSTAINABLE PHARMACEUTICAL CARE APPROACH TO PREVENTION AND MANAGEMENT OF DIGOXIN TOXICITY

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Abstract

Digoxin, as a treatment option in cardiology, is limited by its narrow therapeutic index. The use of digoxin in Malta is not protocol-regulated and this may pose efficacy and safety risks to the patient. Clinical guidelines recommend targeting a serum digoxin concentration (SDC) between 0.5 and 0.9 ng/ml.[1,2,3] The Pathology Laboratory and Drug Information Unit (DIU) at Mater Dei Hospital (MDH) apply a SDC reference range of 0.9 to 2.0 ng/ml.

The objectives were to determine the number of digoxin-treated patients in Malta, analyse SDCs recorded at MDH, assess adherence to the clinically recommended SDC target and review queries concerning digoxin processed by the DIU.

Data for SDCs recorded at the Pathology Laboratory from January 2008 to December 2017 was collected. Patient variables selected for inclusion in the analyses were gender, age, origin of SDC request, referring physician, reason for SDC request, serum potassium (K^+) and estimated glomerular filtration rate (eGFR). Enquiries processed at the DIU between April 2002 and September 2014 were analysed. The JASP software package version 0.7.5.6 was used to generate descriptive statistics ($p<0.05$ was considered to be statistically significant).

The number of patients being treated with digoxin in Malta was 2,059 (January 2017)**.** A total of 19,065 valid SDCs from 6,107 patients (63% female, mean age 78±11, range 1-117 years) were analysed. The mean number of SDCs per patient was 3.12±3.35 (range 1-45). The mean SDC was 1.31±1.01 ng/ml (range <0.1-20.0 ng/ml). Variations from the clinically recommended target SDC (0.5-0.9 ng/ml) were 32% within, 11% below and 57% (17% >2.0 ng/ml) above. Eighty-four per cent of SDC requests originated from

MDH, 36% from the Accident and Emergency Department (mean SDC 1.17±1.01 range <0.1-11 ng/ml), and 16% from other health care facilities. Mean serum K^+ levels in patients with SDCs ≥2.0 ng/ml were significantly higher than patients within range (4.66±0.66 / 4.53±0.69 mEq/L, p=0.020). Patients recording SDCs above the recommended 0.9 ng/ml upper limit exhibited significantly lower eGFR compared to those below 0.9 ng/ml (66.76±36.43 / 73.84±35.21 mL/min/1.73m², p<0.001). Out of a total of 14,368 reviews processed by the DIU, 91 (0.6%) enquiries concerned digoxin. The top three enquiries were related to administration (26%), interactions (19%) and dosing (15%).

The mean SDC of 1.31±1.01 ng/ml is higher than the current clinically recommended target SDC. Periodic evaluation of serum K^+ and renal function with SDC monitoring is necessary to maintain SDCs within the recommended target range. The number of queries regarding digoxin is low (0.6%) compared to the number of out-of-range SDCs (68%), indicating the need for the DIU to disseminate its services. Consensus on a common target SDC range amongst health care providers in Malta, in line with international guidelines, is necessary to ensure a standardised approach to care. Further investigation to establish the clinical significance of these signals and their potential impact on patient health outcomes is warranted.

Keywords: digoxin, drug information unit, serum digoxin concentration

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List of Abbreviations

A&E	Accident and Emergency
ACC	American College of Cardiology
ACEi	Angiotensin Converting Enzyme Inhibitor
AF	Atrial Fibrillation
AHA	American Heart Association
AHSP	American Society of Health System Pharmacists
ARB	Angiotensin II Receptor Blocker
CCS	Canadian Cardiovascular Society
CPPU	Clinical Pharmacy Practice Unit
DIG	Digitalis Investigation Group
DIU	Drug Information Unit
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
HF	Heart Failure
HFrEF	Heart Failure Reduced Ejection Fraction
HFSA	Heart Failure Society of America
IP	Inpatient

JC	Joint Commission
LIS	Laboratory Information System
LVEF	Left Ventricular Ejection Fraction
MUR	Medicine Use Review
NICE	National Institute for Health and Care Excellence
OP	Outpatient
PCP	Primary Care Physician
PL	Pathology Laboratory
NACNS	National Association of Clinical Nurse Specialists
NTOCC	National Transitions of Care Coalition
RAAS	Renin Aldosterone Angiotensin System
RFR	Reason for Request
RCT	Randomised Controlled Trial
RIA	Radio Immunoassay
SD	Standard Deviation
SDC	Serum Digoxin Concentration
SIGN	Scottish Intercollegiate Guidelines Network
TDM	Therapeutic Drug Monitoring
TI	Therapeutic Index

UK	United Kingdom
US	United States
USD	United States Dollar
V_d	Volume of distribution

Chapter 1: Introduction

1.1 Origins of digoxin

Digoxin is one of the oldest drugs within the cardiovascular therapeutic formulary still in utilisation (Ambrosy *et al.*, 2014). Digoxin is a cardiac glycoside. Plants containing cardiac glycosides were first documented as a medical intervention in ancient Egypt and later on in Wales in the thirteenth century (Gheorghiade *et al.,* 2004; Norn and Kruse, 2004). A distinctive feature of glycosides is an aglycone or genin ring coupled to one or more sugars (Laursen *et al.*, 2015). Digoxin consists of the aglycone ring digoxigenin and three sugars, with a molecular formula of $C_{41}H_{64}O_{14}$ (Bond *et al*., 1989).

The active molecule for digoxin is extracted from *digitalis lanata*, the woolly foxglove plant, a member of the snapdragon family (Hollman, 1985). In the mid-sixteenth century the German botanist Fuchs introduced the term *digitalis purpurea* to formally classify the foxglove (Somberg *et al.*, 1985). The main location for cultivation of *digitalis lanata* is the Netherlands, where sub-species of the plant containing a greater innate concentration of digoxin and a lower content of digoxin-like compounds, are bred. Digoxin-like compounds complicate the extraction and purification process and increase production time and cost (Mastenbroek, 1985). The leaves of the plant, the part of the foxglove with the highest concentration of digoxin, are macerated and extraction via an aqueous-alcohol solvent is carried out (Moore and Taylor, 1997). Synthetic methods for the manufacture and supply of digoxin have not been proven to be commercially viable (Sauerwein *et al.*, 1991; Giri *et al.*, 2001; Li *et al.*, 2007).

There is evidence that digoxin or digoxin-like compounds are synthesised by the body, a finding that further reinforces the hypothesis that the pharmacological action of digoxin is due to a mechanism which is more complex than that initially assumed (Goto *et al.*, 1990; Manunta *et al.*, 2011; Buckalew, 2015).

Sir William Withering (1741-1799), an eminent English physician, botanist, geologist and chemist is credited with the elucidation of the pharmacological properties of digoxin. Sir William authored 'An account of the Foxglove and some of its medical uses with practical remarks on dropsy, and other diseases' in 1785. This publication is considered to be the original medical reference on the medicinal use of digoxin in 'dropsy', as oedema and heart failure were described at the time. The quote, "After all, in spite of opinion, prejudice or error, time will fix the real value upon this discovery," is drawn from this work. The sentiment expressed is still relevant, as despite having been accepted as a pharmaceutical option for over 200 years, practitioners still exhibit conflicting opinions over the manner of utilisation of digoxin and its role in cardiovascular therapeutics (Gheorghiade, *et al.*, 2006; Whitbeck *et al.*, 2013; Pastori *et al.*, 2015).

Sir William Withering was the first to carry out a series of limited clinical trials with digoxin, experiment with the optimal manner of compound preparation and document the occurrence of adverse reactions and their manifestation (Albert *et al.*, 2015). The initial subjects of his experiments were middle-aged country women in the vicinity of his residence in Birmingham, United Kingdom (UK). Withering did not enjoy access to the quality of clinical evidence that is commonly available and accepted nowadays, yet he was the first to suspect that digoxin exerted what is defined as a positive inotropic effect

on the heart: “that it has a power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends” (Krikler, 1985). Concurrently, Withering determined digoxin dosage by empirical methods, gradually increasing the strength of the elixir until it provoked the manifestation of adverse effects, mainly nausea and vomiting (Burchell, 1983; Krikler, 1985).

1.2 Pharmacology and pharmacokinetics of digoxin

Study of the detailed pharmacology of the digoxin molecule was made possible in 1969 following the refinement of radioimmunoassay (RIA) analytical processes. Application of this technique allowed researchers to gain insights into the behaviour of the plasma concentration of digoxin with respect to dosage and toxicity, and elucidate the manner of its interaction with other drug molecules (Greenwood *et al*., 1974; Dodek, 1977; Haber, 1985). Further advances in investigative laboratory techniques led to evolution of the RIA into a highly specific enzyme immunoassay, and have made the quantification of digoxin in blood more accurate and accessible (Rosenthal *et al.*, 1976; Higashi *et al.*, 2016).

In conformity with Sir William Withering’s discovery and initial use, digoxin was considered to be a positive inotrope, increasing the contractility of the myocardium, consequently improving cardiac function and output (Braunwald, 1985; Rajapreyar *et al*, 2014; Quashie *et al.*, 2017). In the last decades of the twentieth century, further pharmacological properties were attributed to digoxin, namely its autonomic and neuro-humoral effects (Griffiths *et al.*, 1982; McGarry and Williams, 1993). These actions are observed at lower serum digoxin concentrations (SDCs), accompanied by a weaker inotropic effect and a safer therapeutic profile (Francis, 2008; Francis *et al.*, 2014).

In its inotropic guise, digoxin inhibits the action of the Na^+/K^+/ATPase pump in myocardial tissue, where it accumulates in the post-distribution phase following administration (Dostanic-Larson *et al.*, 2005; Bagrov *et al.*, 2009; Francis *et al.*, 2014). This leads to elevated intracellular Na^+ levels, causing a reversal of the Na^+/Ca^{2+} exchanger. Under normal conditions this cellular membrane pump exports one Ca^{2+} ion and imports three Na^+ into myocardial cells. This reversal raises intracellular Ca^{2+} ion levels and enables increased myocardial contractility without a concomitant increase in energy expenditure. This *modus operandi* suggests the potential for an inverse correlation of toxicity and serum potassium (K^+) levels, by which hypokalemia induces digoxin toxicity and K^+ competes for the same binding site on the Na^+/K^+/ATPase pump. Consequently, low serum K^+ levels result in potentiation of the pharmacological effect of digoxin and the emergence of digoxin toxicity (Chamberlain *et al.*, 1970; Macdonald and Struthers, 2004).

The administration of digoxin elicits a beneficial reaction from the autonomic nervous system by means of its effect on haemodynamics and responsiveness of the body to circulating neurotransmitters. This action is brought about by an increase in the sensitivity of arterial baroreceptors and chemoreceptors, inducing a physiological response and stimulation of inhibitory sympathetic activity (Gheorghiade *et al.*, 1987; Pugh *et al.*, 1989). Digoxin increases end-organ response to vagal stimulation and acetylcholine (Watanabe, 1985).

Digoxin reduces heart rate in heart failure (HF) patients in sinus rhythm and decreases plasma renin activity (Young *et al.*, 1998). Inhibition of the renin angiotensin aldosterone

system (RAAS) and desensitisation of the baroreceptors that provoke the secretion of vasoconstrictor agents provide the basis for the beneficial effect of digoxin. These actions assist in the improvement of the physiological parameters of patients with reduced left ventricular ejection fraction (LVEF). The inotropic effect of digoxin on cardiac muscle is no longer considered to be beneficial since it is on the basis of this action that digoxin contributes to increased mortality and morbidity by progressively increasing myocardial contractility and heart rate and provoking tachyarrythmias (Bhatia, 1986). Withdrawal of digoxin therapy has been demonstrated to initiate a decline in clinical condition in HF patients (Pugh *et al.*, 1989; Uretsky *et al.*, 1993). In atrial fibrillation (AF) digoxin provides a clinical benefit by inhibiting atrioventricular conduction, enabling heart rate control in resting patients (Whitbeck *et al.*, 2013; Eisen *et al.*, 2017).

An understanding of the absorption, distribution, metabolism and elimination of digoxin in the body is essential to determine digoxin dosing and SDC levels (Jelliffe, 2014; Jelliffe *et al*., 2014). Absorption of digoxin takes place in the intestinal tract, primarily in the proximal part of the small intestine. Omeprazole, a commonly prescribed drug, has been demonstrated to increase the absorption of digoxin, and is a potential problem in cases of polypharmacy (Currie *et al*., 2011). Digoxin follows a two-compartment model of distribution in the body following ingestion. It is hydrophilic and initially distributes in the plasma and then concentrates in specific tissues, namely the myocardium, kidneys and skeletal muscle (Sica *et al*., 2005). A stable SDC is obtained six hours following oral dosing and this time-frame is recommended when drawing blood samples for the purpose of SDC determinations (Ali *et al*., 2013). Digoxin is metabolised in the stomach and the liver, with decreased perfusion to the visceral organs resulting in elevated SDCs. Seventy

to eighty-five percent of an oral dose of digoxin is excreted unchanged through the kidneys (Currie *et al.*, 2011). The efficacy of digoxin in HF is not impacted by declining renal function, as demonstrated by Shlipak *et al* (2004). P-glycoprotein (P-gp) is a transporting entity that binds to adenosine triphosphate (ATP). It is involved both in the absorption of digoxin in the intestinal cavity and in its elimination through the kidneys (Neuhoff *et al*., 2013; Jelliffe, 2014).

SDCs are impacted by a number of parameters, the most notable being serum K^+ levels, renal function, age and drug-drug interactions**.** Hypokalaemia may lead to digoxin toxicity with a potentiation of the effect of digoxin due to reduced competition at the common receptor binding site at the Na^+/K^+/ATPase pump at an intracellular membrane level. Conversely, hyperkalaemia can be an indication of digoxin toxicity, as a reflection of the displacement of K^+ ions from the same receptor by digoxin (Macdonald and Struthers, 2004; Orrico *et al.*, 2011; Refat Ragab, Khalid Al-Mazroua *et al.*, 2012**).** Diuretic-induced serum K^+ loss can be a factor leading to the potentiation of the effect of digoxin and evaluation of concomitant drug therapy, such as non-potassium sparing diuretics, may be necessary (Brenes-Salazar *et al.*, 2015). The addition of a weak, potassium conserving diuretic, such as spironolactone, may be considered. Antagonists of the RAAS are included in the European Society of Cardiology (ESC) treatment algorithm for their prognostic benefit in HF patients on optimal treatment. The importance of serum K^+ levels is such that SDC results considered in isolation, in the absence of corresponding K^+ levels, cannot be considered to provide sufficient information to construct a coherent clinical scenario (Allen and O'Connor, 2007; Pincus, 2016).

Renal function is a primary factor to consider in cases of suspected digoxin toxicity, as minor variations in digoxin elimination can result in SDCs exceeding the narrow recommended therapeutic range (0.5-0.9 ng/ml) (Williams and Erickson, 1998; Mcmahon *et al.*, 2014). A reduced estimated glomerular filtration rate (eGFR) leads to decreased elimination of digoxin, with a greater percentage of the initial digoxin dose circulating in the bloodstream, necessitating a downwards adjustment in dose. Impairment of renal function appears to be a result of a reduction in the cellularity of the proximal renal tubules and in the amount of a C4 anion transporting peptide; a direct correlation has been demonstrated between the abundance of C4 peptide and digoxin clearance (Scotcher *et al.*, 2017). Hence, renal impairment is one of the most important co-morbidities to be taken into consideration in the context of digoxin therapy. Monitoring of renal function is a vital parameter in establishing and adjusting digoxin dosing regimens (Bauman *et al.*, 2006; Brenes-Salazar *et al.*, 2015).

The effect on ageing on SDC levels is another primary concern as the majority of digoxin-treated patients are elderly due to the nature of the underlying indication for the usage of digoxin. Ageing brings about clinically significant variations in the basic pharmacokinetic parameters used in the evaluation of digoxin therapeutics and dosing. The absorption, distribution, metabolism and elimination of digoxin are all impacted (Currie *et al.*, 2011). Decreased perfusion of the gastrointestinal tract leads to slower uptake of an oral dose of digoxin, with an increased time to attain peak serum drug levels. A reduction in lean body mass in the elderly leads to a decreased volume of distribution (V_d) for digoxin and consequently to raised SDCs (Currie *et al.*, 2011). Lower SDCs are associated with symptomatic relief and reduced mortality. SDC levels have been directly correlated to

dose in older (>65 years) patients, as opposed to younger patients (<65 years) where diuretic posology is correlated to SDC (Goldberger and Goldberger, 2012). A number of formulae for the estimation of digoxin dosing take patient body weight into consideration. Nomograms developed by Bauman *et al*, and formulae by Choi *et al* and Komatsu *et al* include body weight, but do not make allowances for lean body mass (Bauman *et al.*, 2006; Choi *et al.*, 2014; Komatsu *et al.*, 2015). The formulae allow for variations in patient age, however no evidence is available to ascertain whether the introduction of the age variable considers the reduction in lean body mass. Care must be taken not to arbitrarily dose obese patients with proportionally higher doses of digoxin. Digoxin does not distribute to adipose tissue, hence high doses administered to obese patients with minimal proportions of muscular tissue may result in elevated SDCs (Ewy *et al*., 1971; Salazar and Corcoran, 1988). Independently of digoxin therapy and SDC levels, obese patients with HF with a reduced ejection fraction (HFrEF) exhibit better survival rates compared to patients with a body mass index within the range designated as ideal. (Haass *et al.*, 2011). This logically-inverse association of weight to survival is termed the obesity paradox (Curtis *et al.*, 2005; Amundson *et al*., 2010). Ageing brings about a 30-40% reduction in visceral perfusion and hepatic circulation, and impacts the metabolism of digoxin, although not to an appreciable extent (Currie *et al*., 2011). The importance of renal function in the elimination of digoxin from the body has been emphasised earlier and is relevant in the elderly as renal function declines with increasing age (Lubran, 1995; Vidal *et al.*, 2005; Pawlosky *et al.*, 2013).

Polypharmacy is prevalent in digoxin-treated patients and drug-drug interactions of digoxin with drugs such as amiodarone, rifampicin and verapamil may occur. Verapamil

and amiodarone inhibit the P-gp-mediated excretion of digoxin and may precipitate digoxin toxicity (Neto *et al.*, 2012; Kashyap *et al.*, 2013). Rifampicin accelerates the metabolism of digoxin resulting in sub-therapeutic SDCs (Chen and Raymond, 2006). Hence care should be exercised in the concomitant administration of digoxin and other drugs, since potential drug-drug interactions exert a direct effect on SDC levels and therapeutic outcomes (Neuhoff *et al*., 2013; Jelliffe, 2014).

These physiological and contextual factors often present themselves with deficits in compliance, consistency and concordance in the dosing, monitoring and administration of digoxin where in such cases the potential for adverse effects increases (Weedle *et al.*, 1988; Neto *et al.*, 2012; Kashyap *et al.*, 2013).

1.3 Clinical applications of digoxin

Both HF and AF are conditions which exhibit a non-linear increase in frequency with age. Ten per cent of individuals over the age of 80 present with heart failure, as opposed to 1 to 2% of the general population. Similar trends are observed with AF, with the condition "present in 0.12–0.16% of those younger than 49 years, in 3.7–4.2% of those aged 60–70 years, and in 10–17% of those aged 80 years or older" (Colilla *et al.*, 2013; Zoni-Berisso *et al.*, 2014). AF is associated with an increased mortality risk of 1.5-1.9 fold (Benjamin *et al.*, 1998) and HF survival rates are less than 50% over a five-year timeframe following initial diagnosis (Mosterd and Hoes, 2007; Pons *et al.*, 2010). As the global population ages, the relevance of HF and AF interventions has increased in importance in parallel to the incidence of these conditions (Bui *et al*., 2008; Roger, 2013).

A higher incidence of HF and AF is leading to an increase in health care needs and expenditure (Bui *et al.*, 2008; Bui *et al.*, 2011). In the latest National Health and Nutrition Examination Survey carried out in the US, 6.5 million patients were classified as suffering from HF (Benjamin *et al.*, 2017). This indicates a greater demand for the utilisation and monitoring of interventions for patients suffering from HF and AF, conditions for which the use of digoxin is indicated. As the incidence of toxicity and adverse effects is greater in elderly patients on digoxin, the burden on society is amplified, both from a financial and humanistic perspective (Lecointre *et al.*, 2001; See *et al.*, 2014).

Digoxin in HF can improve cardiac output through its inotropic effect and reduces the reflex reaction of the body to lower organ perfusion and circulatory pressure by modulating the autonomic and neurohormonal response (Gheorghiade *et al.*, 1987; Gheorghiade *et al.*, 2006; Stucky and Goldberger, 2015). In AF, digoxin is used in an effort to control situations of acute or chronic tachycardia (Ouyang *et al.*, 2015; Eisen *et al.*, 2017).

The literature is inconclusive on the subject of whether digoxin in HF and AF is beneficial, neutral or detrimental in its effect. Pro-digoxin advocates promote its continued utility on the basis of the historical evidence and empirical knowledge accumulated over years of use (Young *et al.*, 1998; Adams *et al.*, 2005; Gheorghiade *et al.*, 2006; Ambrosy *et al.*, 2014). Those in opposition to this stance argue in favour of putting digoxin away and concentrating on novel molecular entities, such as neprilysin, with clearly proven safety and efficacy (Rathore *et al.*, 2003; Freeman *et al.*, 2013; Whitbeck *et al.*, 2013; Washam *et al.*, 2015).

A high quality evidence base provides a degree of certainty in predicting clinical outcomes and patient benefit, and this evidence is not present in the case of digoxin (Ziff *et al.*, 2015; Ziff and Kotecha, 2016). The Digitalis Investigation Group (DIG) trial is the only large-scale, multi-centre, randomised controlled trial (RCT) carried out on digoxin. The primary findings from the DIG trial indicated a decrease in hospitalisation rates in patients with HFrEF on optimal therapy. No effect on all-cause mortality was detected; all patients were taking an angiotensin-converting enzyme inhibitor (ACEi) and diuretics and were on digoxin 0.25mg daily (The Digitalis Investigation Group, 1997). Other post-hoc analyses of the DIG trial data have demonstrated benefit in selected patient groups, such as in diabetics (Abdul-Rahim *et al.*, 2016), and elucidated the possibility of gender-specific effects on mortality (Rathore *et al.*, 2002). The effects of digoxin in patients with AF do not appear to be positive, with a number of studies demonstrating increased all-cause mortality, sudden death and increased rates of hospitalisation in digoxin-treated patients (Pastori *et al.*, 2015; Washam *et al.*, 2015).

The relevance of the 1997 DIG trial to current clinical practice is diminished. At the time, HF and AF therapies differed greatly, both in approach and in pharmacological content, compared to the present day. Beta-blockers were not routinely prescribed or recommended as one of the cornerstones of HF therapy (Hernandez *et al.*, 2009; Yancy *et al.*, 2013). It was previously thought that adding a beta-blocker in HF would further weaken the heart (Bristow *et al.*, 1994). It has since been demonstrated that attenuating the heart rate in HF improves cardiac output by mediating the reaction of the body to a decreased cardiac output. As a consequence of a lower heart rate, the left ventricle

employs more time per contraction and stroke volume is increased (Metra *et al.*, 2002; Brenes-Salazar *et al.*, 2015; Metra, 2016).

On the basis of the lack of evidence for the clinical safety and efficacy of digoxin, a number of researchers argue for the withdrawal of digoxin from common use. Manolis, in a 2015 paper titled 'The end of the digoxin era?', concludes by stating that digoxin should only be reserved for 'lost causes' when all therapies have failed. In Manolis's opinion, the disadvantages and intricacies of treatment with digoxin, coupled with the lack of more recent and reliable trial data, outweigh any possible benefits (Manolis, 2015). Ziff and Kotechka take the middle ground, and make a case for more RCTs involving digoxin (Ziff and Kotecha, 2016). The difficulties in planning and carrying out such studies are various, with the main obstacle being the ethical dilemma of placing subjects on digoxin when they could potentially be treated with more effective, life-saving or at the least, life-improving, therapies (Woodman, 2014; Ziff and Kotecha, 2016).

Literature supporting the use of digoxin in HF and AF is not conclusive, hence the non-optimal levels of recommendation. The lack of current, full-scale RCTs for digoxin is the primary reason for a measured and selective approach to the use of digoxin in clinical application (Joffe *et al.*, 2013; Konstantinou *et al.*, 2016).

1.4 Guidelines for digoxin in heart failure and atrial fibrillation

Guidelines for digoxin in HF and AF published by the European Society of Cardiology (ESC), the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA), the Heart Failure Society of America (HFSA), the National Institute for Health and Care Excellence (NICE)[1,2], and the Scottish Intercollegiate Guidelines Network (SIGN)[3,4] were consulted (Lindenfeld *et al.*, 2010; Yancy *et al.*, 2013; Kirchhof *et al.*, 2016). The ESC is the foremost institution in Europe regarding cardiovascular therapeutics, with the ACCF/AHA and the HFSA fulfilling this role in North America. Cardiologists in Malta utilise guidelines issued by the ESC as their primary point of reference. The NICE and SIGN are the competent bodies in the UK entrusted with issuing professional and patient guidelines for evidence-based practice. The pharmacy profession in Malta bases many of its practice recommendations on guidelines issued by the NICE.

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[1] National Institute for Health and Care Excellence (NICE). Chronic heart failure in adults: management CG108 [Online]. UK: NICE; 2010 [cited 2018 Jan 18] Available from: https://www.nice.org.uk/guidance/cg108/resources/chronic-heart-failure-in-adults-management-pdf35109335688901.

[2] National Institute for Health and Care Excellence (NICE). Atrial fibrillation: managementCG180 [Online].UK: NICE; 2014 [cited 2018 Jan 18] Available from: https://www.nice.org.uk/guidance/cg180/resources/atrial-fibrillation-management-pdf-35109805981381.

[3] Scottish Intercollegiate Guidelines Network (SIGN). Management of Chronic Heart Failure [Online]. UK: SIGN; 2016 [cited 2018 Jan 18]. Available from: http://www.sign.ac.uk/assets/sign147.pdf.

[4] Scottish Intercollegiate Guidelines Network (SIGN). Cardiac arrhythmias in coronary heart disease: A national clinical guideline [Online]. UK: SIGN; 2007 [cited 2018 Jan 18]. Available from: http://www.sign.ac.uk/assets/sign94.pdf.

The immediate introduction of both a beta-blocker and an ACEi in HFrEF is advocated by all the afore-mentioned guidelines. The common approach to digoxin is to restrict its use to those cases of HFrEF, and in AF with HF, where the main goal of therapy is to reduce patient hospitalisation and improve quality of care, after use of first and second-line options (Yancy *et al.*, 2013; Chen *et al.*, 2015). In cases of AF without HF, studies indicate an increase in all-cause mortality; here the positive inotropic effect and beneficial neurohormonal modulation of digoxin are not required, with the unwanted negative addition of pro-arrhythmia and bradycardia as adverse effects of therapy (Whitbeck *et al.*, 2013; Ouyang *et al.*, 2015; Pastori *et al.*, 2015).

1.4.1 Heart failure

The latest ESC guidelines for HF were published in 2016 (Ponikowski *et al.*, 2016). Digoxin in acute and chronic HF is given a Class IIb, level of evidence B recommendation and is classified under other treatments with less certain benefits. Digoxin is reserved for patients in whom first and second-line therapies do not elicit the desired health outcomes and sufficient improvement in patient quality of life and who are still symptomatic (Figure 1.1).

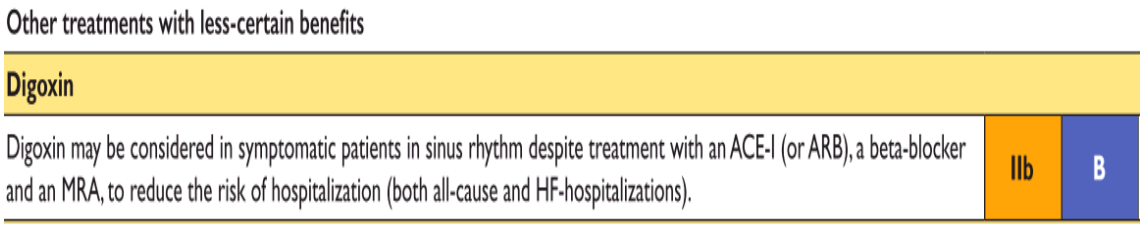

Figure 1-1 - Recommendation for digoxin in heart failure

Reproduced from: Ponikowski P, Voors A, Anker SD, Bueno H, Cleland J, Coats AJ, et al. 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2016;37:2129–200.

The ESC guidelines include digoxin therapy in chronic HF as the last line of pharmacological therapy prior to the consideration of mechanical aids or heart transplantation (Table 1.1).

Table 1-1 – European Society of Cardiology pharmacological treatment algorithm for heart failure

Rationale	Pharmacological therapy
Initiate therapy	Beta-blocker + angiotensin converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)
Inhibit renin angiotensin aldosterone system	Add aldosterone antagonist
Replace ACEi	Add neprilysin inhibitor
Rate control (patients in sinus rhythm and pulse >75bpm)	Add ivabradine
Symptomatic sedentary patients	Add digoxin

Adapted from: Ponikowski P, Voors A, Anker SD, Bueno H, Cleland J, Coats AJ, et al. 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2016;37:2129–200.

In the 2013 ACCF/AHA guidelines (Yancy *et al*., 2013), digoxin is given a Class IIa, level of evidence B recommendation for HF. The text of the ACCF/AHA recommendation is non-committal and indicates the potential benefits of digoxin therapy in HFrEF, unless contraindicated, to decrease hospitalisation. The guidelines further recommend the use of digoxin be restricted to patients who remain symptomatic despite the application of first and second line therapeutic options. A target SDC between 0.5 and 0.9 ng/ml is recommended, with reference to the neutral effect of higher and possibly toxic SDC levels on the beneficial action of digoxin. The lack of concrete evidence connecting SDC monitoring and improved therapeutic efficacy is noted. A 'Heart Failure update focused on Pharmacological Therapy' was issued in March 2016 in which novel therapies such angiotensin receptor–neprilysin inhibitor combinations and ivabradine are included. No reference to digoxin is made in the update (Yancy *et al.*, 2016). The HFSA issued a full HF practice guideline in 2010, and recommends use of digoxin in patients with an LVEF ≤40% who are symptomatic whilst on optimal therapy (Lindenfeld *et al.*, 2010).

The NICE issued guidelines for digoxin use in chronic HF in 2010, as Clinical Guideline 108.[1] The NICE guidelines emphasise non-reliance on SDCs to determine achievement of therapeutic goals and highlight the monitoring of serum K^+ in patients on digoxin therapy. Digoxin is indicated in "worsening or severe heart failure due to left ventricular

[1] National Institute for Health and Care Excellence (NICE). Chronic heart failure in adults: management CG108 [Online]. UK: NICE; 2010 [cited 2018 Jan 18] Available from: https://www.nice.org.uk/guidance/cg108/resources/chronic-heart-failure-in-adults-management-pdf35109335688901.

systolic dysfunction despite first- and second-line treatment for heart failure". The SIGN[3] follows a therapeutic rationale similar to that of the NICE guidelines with digoxin recommended as an add-on treatment in cases of primary treatment modality failure.

1.4.2 Atrial fibrillation

ESC guidelines for AF issued in 2016 provide a recommendation for both a chronic and an acute setting. For long-term rate control in AF with HF (LVEF ≤40%), digoxin is given a Class I, level of evidence B recommendation (Figure 1.2). Digoxin is suggested for the management of rapid, new-onset AF, both in HF patients and in patients with an LVEF ≥40%, administered via the intravenous route as a bolus dose (Kirchhof *et al.*, 2016).

[3] Scottish Intercollegiate Guidelines Network (SIGN). Management of Chronic Heart Failure [Online]. UK: SIGN; 2016 [cited 2018 Jan 18]. Available from: http://www.sign.ac.uk/assets/sign147.pdf.

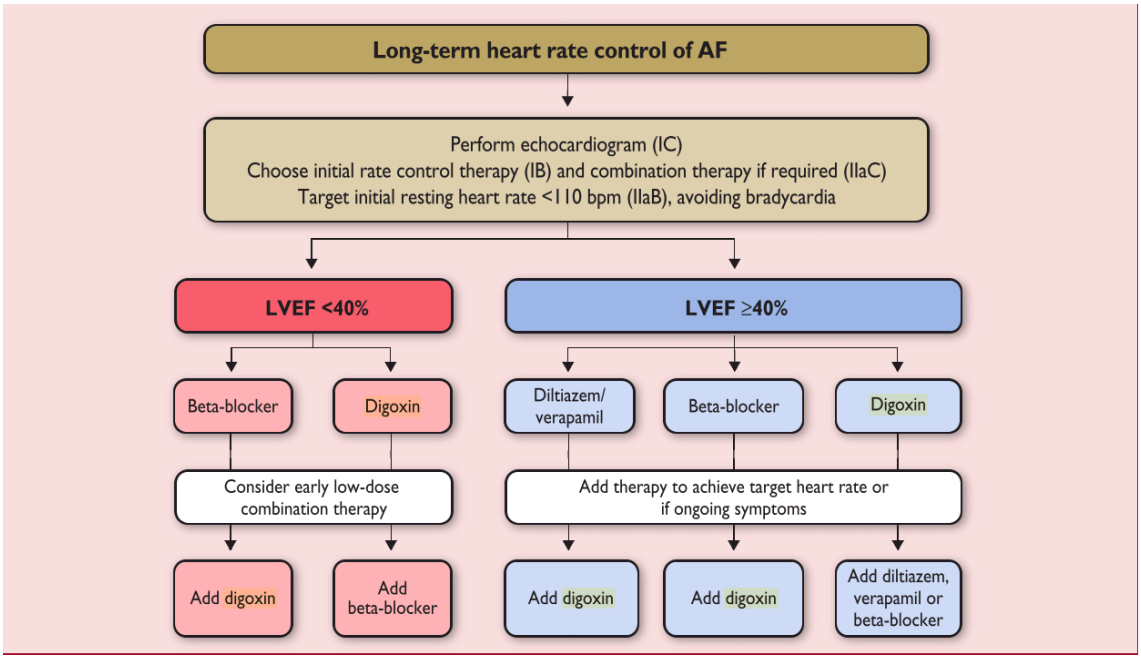

Figure 1-2 – European Society of Cardiology algorithm for long term rate control in atrial fibrillation

Reproduced from: Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016; 18: 1609–78.

In AF, the 2014 ACCF/ACA guidelines recommend that digoxin is given as an adjunct to beta-blocker therapy for heart rate control in an acute setting, with a Class IIa, level of evidence B recommendation. In a resting patient with HFrEF digoxin has a Class I , level of evidence C recommendation (January *et al.*, 2014). The HFSA guidelines recommend digoxin for heart rate control in AF with HF, strength of evidence B (Lindenfeld *et al.*, 2010).

The NICE guidelines for AF are Clinical Guideline 180[2], published in June 2014. The recommendation is for ”digoxin monotherapy for people with non-paroxysmal atrial fibrillation only if they are sedentary” for heart rate control, or in combination with either a beta-blocker or diltiazem in the case of failure of a single drug approach. Digoxin is not indicated for post-operative atrial fibrillation. The SIGN guidelines[4] for AF were last updated in 2007. These guidelines recommend digoxin in combination with a beta-blocker for heart rate control in AF.

1.5 Digoxin toxicity

Digoxin subscribes to the often-quoted maxim by Paracelsus (1493-1541), German-Swiss physician and alchemist who established the role of chemistry in medicine, who suggested that “Only the dose makes a thing not a poison”. The possibility of digoxin intoxication and the more significant manifestations associated with the adverse effects of over-dosage were first documented by Sir William Withering in the late eighteenth century (Braunwald, 1985; Krikler, 1985). Digoxin has a narrow therapeutic index (TI), with minimal variance between an optimal therapeutic dose and a toxic dose. Most patients suffer no overt toxic effects if SDCs are maintained between 0.8 and 2.0 ng/ml (Terra *et al*., 1999; Goldberger and Goldberger, 2012). Digoxin toxicity can occur at levels below

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[2] National Institute for Health and Care Excellence (NICE). Atrial fibrillation: managementCG180 [Online]. UK: NICE; 2014 [cited 2018 Jan 18] Available from: https://www.nice.org.uk/guidance/cg180/resources/atrial-fibrillation-management-pdf-35109805981381.

[4] Scottish Intercollegiate Guidelines Network (SIGN). Cardiac arrhythmias in coronary heart disease: A national clinical guideline [Online]. UK: SIGN; 2007 [cited 2018 Jan 18]. Available from: http://www.sign.ac.uk/assets/sign94.pdf.

the traditional 2.0 ng/ml threshold, in the presence of electrolyte imbalances, especially in cases of hypokalaemia and hypomagnesaemia (Yancy *et al*., 2013).

Digoxin toxicity or overdosage may cause a yellowish aura presenting around the visual field, a condition known as xanthopsia (Gruener, 2013). This phenomenon implicates digoxin in some of the most original and valuable works of art, as it is suspected that digitalis treatment, and possibly toxicity, may have induced Vincent Van Gogh to colour his later works with his characteristic orange and yellow hues (Wolf, 2001). On a more sinister note, digoxin gained notoriety in the 1970s as one of the chemical compounds employed by nurse Charles Cullen to fatally intoxicate an unquantified number of patients in the US (Franklin, 2004; Yorker *et al.*, 2006).The foxglove plant is indigenous to various European countries, and accidental toxicity, although rare, is still recorded. Bonfanti *et al* document a recent case of an Italian couple who consumed excessive doses of digoxin through a case of mistaken identification of a plant species (Bonfanti *et al.*, 2017).

The signs of digoxin toxicity have been traditionally divided into cardiac and extra-cardiac symptoms. An excess of serum digoxin leads to an increase in intracellular Na^+, which in turn leads to an overload of Ca^{2+} and the potential for a wide range of cardiac irregularities. Tachycardias, bradycardias, heart block and combinations of these disturbances in cardiac function are all associated with digoxin but are not specific to the drug. Hence, cardiac symptoms considered in isolation are not a useful indicator in the clinical diagnosis of digoxin-induced cardiac abnormalities. The exceptions to this statement are new-onset Mobitz type I AV block, an accelerated junctional rhythm with

or without high-degree AV block, non-paroxysmal atrial tachycardia with AV block, and bidirectional ventricular tachycardia (Williamson, 1998; Murrin, 2003; Bauman *et al., 2006).*

The extra-cardiac manifestations of digoxin can be classified as those impacting the gastro-intestinal system (nausea, vomiting and diarrhoea), the central nervous system (fatigue, dizziness and lethargy) and ocular function (xanthopsia, blurred vision and spots). Similarly, to the cardiac symptoms of digoxin overdose, none of these signs are specific to digoxin and must be evaluated in the context of the clinical condition of the patient. A confirmed diagnosis can be established once an SDC has been drawn and clinical symptoms have been correlated to the current physiological parameters available (Bauman *et al.*, 2006; Limon *et al.*, 2016).

The symptoms of digoxin toxicity can often be mistakenly interpreted as signs of ageing or physical incompetence which is of great concern, since the majority of digoxin patients are elderly (Bui *et al.*, 2011; Colilla *et al.*, 2013). In a study of admissions to Accident and Emergency Units (A&E) in the US, See *et al* in 2014, demonstrated that digoxin toxicity was responsible for 3.3% of A&E visits and 5.9% of hospital admissions related to adverse drug reactions in patients aged over 85 years. This is in contrast to the 1% of A&E visits attributed to digoxin in patients over 40 years and under 85 years of age (See *et al.*, 2014).

A raised level of awareness must be adopted from a prescribing, dispensing and practice perspective to monitor for adverse effects and educate patients on potential therapeutic consequences (Whiting *et al.*, 1978; Currie *et al.*, 2011; Jelinek and Warner, 2011; Brenes-Salazar *et al.*, 2015; Martin-Suarez *et al.*, 2016).

1.6 Therapeutic drug monitoring for digoxin

Therapeutic drug monitoring (TDM) is not mandatory for all drugs. Digoxin satisfies a number of basic assumptions that establish the requirement for SDC determinations as part of a therapeutic regimen (Kang and Lee, 2009). The basic properties of digoxin in this context, as adapted from Ali *et al* (2013) are: (i) a narrow TI, (ii) an established relationship between its SDC and therapeutic response and/or toxicity, (iii) a large individual variability at steady state SDCs at any given dose, (iv) a poor relationship between SDC and dosage, (v) a poorly defined end point or difficulty in clinically predicting the response, (vi) toxicity is difficult to distinguish from a patient's underlying disease, and (vii) efficacy is difficult to establish clinically (Ali *et al.*, 2013).

Attempts at utilising technology and electronic means to improve monitoring, to detect the emergence of toxicity and to modify digoxin therapy accordingly, are documented in the British Heart Journal as early as 1978. Whiting *et al* (1978) reviewed the application of a first-generation computer algorithm to the evaluation of digitalis therapy in a group of 42 patients and dosage adjustment was recommended for 26 patients. Despite the small sample size, this study provided an immediate indication of the complexities of using digitalis in the elderly (Whiting *et al.*, 1978).

The accepted safe upper limit for SDCs has traditionally been established at 2.0 ng/ml (Bauman *et al.*, 2006; Goldberger and Goldberger, 2012). This arbitrary figure was based on a landmark study by Smith *et al* (1969), which established therapeutic and toxic SDC ranges for digoxin based on a sample of 39 patients (Smith *et al.*, 1969). Most laboratories worldwide continue to utilise a SDC reference range of 0.5 to 2.0 ng/ml (Van Veldhuisen, 2002; Goldberger and Goldberger, 2012; Stucky and Goldberger, 2015). The Pathology Laboratory at Mater Dei Hospital (MDH), the largest general hospital in Malta, indicates a reference range of 0.9 to 2.0 ng/ml on patient result sheets. The Drug Information Unit (DIU) at MDH presently issues a sheet for reference purposes to government pharmacists and clinicians, recommending the same SDC reference range (0.9-2.0 ng/ml). The relevance of an upper limit of 2.0 ng/ml is arguable in the current clinical context, given that a considerable number of studies have strongly indicated that a lower therapeutic limit is associated with decreased adverse effects and reduced mortality. Digoxin has been shown to exert the full extent of its beneficial neurohormonal effect at levels below 1.0 ng/ml (Bauman *et al.*, 2006; Freeman *et al.*, 2013; Pastori *et al.*, 2015).

Post-hoc analyses of the DIG trial have suggested that SDCs between 0.5 and 0.9 ng/ml are safe, and provide the benefits of reduced hospitalisation and mortality (Adams *et al.*, 2014; Stucky and Goldberger, 2015). The positive correlation between lower SDCs and mortality has been supported by other researchers, notably analysis of the PROVED and RADIANCE trials, which demonstrated that SDCs within the 0.5-0.9 ng/ml range provided the same benefit to HF patients as SDCs >1.2 ng/ml (Packer *et al.*, 1993; Young *et al.*, 1998). Elevated SDCs are associated with increased adverse effects and patient

mortality. Chan *et al* demonstrated an 11% increase in mortality for every 1 ng/ml increase in SDC levels (Chan *et al.*, 2010).

Guidelines by the ESC, ACCF/AHA and the HFSA recommend maintaining SDCs below 1.0 ng/ml (Table 1.2). SDC testing as a part of a digoxin treatment regimen is not recommended in current guidelines, except for the 2016 HFSA guidelines (Table 1.3).

Table 1-2 - SDC ranges recommended by competent entities

Entity	Year	Indication	SDC range (ng/ml)
DIU	2013[a]	Not specified	0.5-2.0
PL	2017[b]	Not specified	0.9-2.0
ESC	2016[c]	HF	Not specified
	2016[d]	AF	0.5-0.9
ACCF/AHA	2013[e]	HF	<1.0
	2014[f]	AF	Not specified
HFSA	2010[g]	HF	0.5-0.9
	2010[g]	AF	0.5-0.9
NICE	2010[h]	HF	Not specified
	2014[i]	AF	Not specified
SIGN	2016[j]	HF	Not specified
	2007[k]	AF	Not specified

Key: ACCF/AHA – American College of Cardiology Foundation/American Heart Association, DIU – Drug Information Unit (Mater De Hospital), ESC – European Society of Cardiology, HFSA – Heart Failure Society of America, NICE – National Institute for Healthcare and Excellence, PL – Pathology Laboratory (Mater Dei Hospital), SIGN – Scottish Intercollegiate Guidelines Network

Table 1-3 - SDC monitoring recommended by competent entities

Entity	Year	Indication	Reason for SDC testing
DIU	2013[a]	Not specified	Specific cases
PL	2017[b]	Not specified	Not specified
ESC	2016[c]	HF	Not specified
	2016[d]	AF	Dosing
ACCF/AHA	2013[e]	HF	Not specified
	2014[f]	AF	Routine
HFSA	2010[g]	HF	Specific cases
	2010[g]	AF	Not specified
NICE	2010[h]	HF	Toxicity
	2014[i]	AF	Not specified
SIGN	2016[j]	HF	Not specified
	2007[k]	AF	Not specified

Key: ACCF/AHA – American College of Cardiology Foundation/American Heart Association, DIU – Drug Information Unit (Mater Dei Hospital), ESC – European Society of Cardiology, HFSA – Heart Failure Society of America, NICE – National Institute for Healthcare and Excellence, PL – Pathology Laboratory (Mater Dei Hospital), SIGN – Scottish Intercollegiate Guidelines Network

[a]Drug Information Unit, Mater Dei Hospital, Malta.

[b]Pathology laboratory, Mater Dei Hospital, Malta.

[c]Ponikowski P, Voors A, Anker SD, Bueno H, Cleland J, Coats AJ, et al. 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2016;37:2129–200.

[d]Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016;18 (11):1609–78.

[e]Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2013;62(16):e147–239.

[f]January C, Wann L, Alpert J, Calkins H, Cleveland J, Cigarroa J, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014;130(23):2071-104.

[g]Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. Executive Summary: Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail. 2010;16(6):475–539.

[h]National Institute for Health and Care Excellence (NICE). Chronic heart failure in adults: management CG108 [Online]. UK: NICE; 2010 [cited 2018 Jan 18] Available from: https://www.nice.org.uk/guidance/cg108/resources/chronic-heart-failure-in-adults management-pdf-35109335688901.

[i]National Institute for Health and Care Excellence (NICE). Atrial fibrillation: managementCG180 [Online]. UK: NICE; 2014 [cited 2018 Jan 18] Available from: https://www.nice.org.uk/guidance/cg180/resources/atrial-fibrillation-management-pdf-35109805981381.

[j]Scottish Intercollegiate Guidelines Network (SIGN). Management of Chronic Heart Failure [Online]. UK: SIGN; 2016 [cited 2018 Jan 18]. Available from: http://www.sign.ac.uk/assets/sign147.pdf.

[k]Scottish Intercollegiate Guidelines Network (SIGN). Cardiac arrhythmias in coronary heart disease: A national clinical guideline [Online]. UK: SIGN; 2007 [cited 2018 Jan 18]. Available from: http://www.sign.ac.uk/assets/sign94.pdf.

1.7 Treatment of digoxin toxicity

Hypokalaemia may precipitate acute digoxin toxicity and normalisation of serum K^+ concentrations via K^+ supplementation is an immediate intervention. In cases of chronic digoxin toxicity, hyperkalaemia will be present. When withholding or withdrawal of digoxin therapy is not sufficiently timely or expedient to reverse the consequences of digoxin toxicity, rectification of the condition by infusion of digoxin specific antibodies or fragment antigen binding (Fab) fragments is necessary (Eyer *et al.*, 2010; Lloyd, 2015; Hauptman *et al.*, 2016)**.** Fab fragments are regions on antibodies specific to the molecule to be targeted, in this case the digoxin molecule. Selective binding ensures rapid neutralisation of the toxic effect of elevated serum digoxin levels (Janeway *et al.*, 2001).

Digibind® is stocked at Mater Dei Hospital, the main acute hospital in Malta, for utilisation in cases of digoxin toxicity. Apart from a lack of consensus among clinicians on approaches to the timing of digoxin Fab treatment, cost considerations are relevant from a societal and organisational perspective (DiDomenico *et al*., 2000; Claus *et al*., 2012). One vial of Digibind® 38mg costs $728 (USD) and one vial of Digifab® 40mg $617 (USD). Since treatment with either of the antidotes can involve the administration of one to ten vials, the cost factor can be appreciated. The adoption of a holistic approach to an event of digoxin toxicity is recommended, as Di Domenico *et al* have demonstrated that treatment with Fab, although costly on a per unit basis, is cost-effective across the whole intervention. Length of hospital stay was decreased by 1.5 days and total cost of the care event to the state was reduced when Fab is infused in patients with an SDC>3.5 ng/ml (DiDomenico *et al*., 2000).

There is no widely accepted standard guideline or protocol to aid in the process of deciding whether or not to infuse Fab fragments (Van Veldhuisen, 2002; Goldberger and Goldberger, 2012). Key points to be considered as indicators of the necessity to utilise antibodies for digoxin toxicity are: (i) a serum K^+ level >5.0 mml/L; K^+ levels above this concentration are associated with a very poor prognosis, (ii) serious cardiac events including arrhythmias and cardiac arrest, (iii) end-organ dysfunction, (iv) serious clinical features despite a low SDC (< 2.0 ng/ml) or a SDC > 12.0 ng/ml (Pincus, 2016).

Cases where serum digoxin levels have been drawn in close proximity to the administration of the antidote have been noted, evidencing a lack of basic knowledge by the clinicians involved. In such instances, SDCs reported are abnormally elevated as the antidote takes approximately seven days to clear from the circulatory system and the SDC analytical procedure registers both free and bound digoxin (Eyer *et al.*, 2010; Pincus, 2016). In large catchment areas with a number of laboratories issuing SDC results for the same patients, the use of analytical machines calibrated to different standards and utilising varying methods of SDC determination can lead to a non-standardised output of results and an incorrect interpretation of the presenting clinical picture (Rogers *et al.*, 2010).

The two concepts of digoxin toxicity and care transitions are interlinked. The complexities of digoxin therapy are inherently linked to the characteristics of patients to whom digoxin is administered. A holistic evaluation of the approach to care for patients on digoxin therapy not only involves the strictly defined pharmaceutical aspect of treatment but encompasses the social and multi-disciplinary facets of humanistic function.

In certain instances, care failure in digoxin-treated patients is not due to inappropriate pharmacological choices but to a lack of communication within the care chain (McDonagh *et al.*, 2011; Krumholz, 2013). This lack of communication is highest at the point of transition from one care setting to another. Within the greater context of therapeutics and patient health outcomes, transitions of care have a vital role in the care process (Gleason *et al.*, 2010; Johnson *et al*., 2015; Erickson, 2016).

1.8 Transitions of care and digoxin

Digoxin-treated patients provide a prime example of a clinical scenario in which the application of co-ordinated care transitions and patient medication record accessibility is important. Digoxin therapy requires extreme caution with respect to posology, patient selection and the consistent maintenance of a therapeutic regimen at optimal and non-toxic levels, which necessitates consistent medication review and TDM to ensure optimal patient safety and efficacy outcomes (Abraham *et al*. 2012; Johnson *et al.* 2015).

Digoxin treatment cannot be considered as isolated monotherapy, but as part of a holistic HF or AF care process. Patients are generally not well-educated about their condition and do not adhere to the basic lifestyle modifications that have a disproportionately positive effect on their condition. Dietary factors, fluid intake monitoring and daily weights are key to preventing deterioration in clinical condition and rehospitalisation (Arnold *et al.*, 2008; Albert *et al.*, 2015). With respect to digoxin, patients must be made aware of the possible adverse effects and be informed to recognise and report to their immediate caregivers. Patients on digoxin are being treated for HF, AF or both, and a typical patient

will be elderly, suffering from multiple co-morbidities and possible cognitive impairment. Digoxin-treated patients inherently present a complex therapeutic scenario, since digoxin is indicated as a last resort for those patients in whom preferred pharmacological therapies have not had an optimal result (Naylor *et al.*, 2004; Gleason *et al.*, 2010).

Studies have demonstrated that involvement of a multidisciplinary care team in the treatment of HF patients at an inpatient level and the continuation of a harmonised care process across various settings of care leads to decreased mortality rates and episodes of decompensation and hospitalisation (Cykert, 2012; Gheorghiade *et al.*, 2013). Bundy *et al* stated that the use of patient records in combination with medication monitoring or Medicine Use Reviews (MUR) can improve therapeutic outcomes (Bundy *et al.*, 2012). The pharmacist has a pivotal and unique role in the digoxin pharmaceutical care process. As the patients' primary point of contact within a community setting, the pharmacist has the potential to act as a conduit for two-way information exchange between patients and tertiary care providers (Hume *et al.*, 2012; Kristeller, 2014; Erickson, 2016).

The relevance of care transitions to digoxin-treated patients is evidenced by an examination of the concept by the National Transitions of Care Coalition (NTOCC), which identifies the major points within a care process where treatment error or failure may occur due to a modification in care-giver or care-setting, amongst other factors. [5]

[5] National Transitions of Care Coalition (NTOCC). Transitions of Care: measures [Online]. NTOCC; 2008 [cited 2018 Jan 18]. Available from: http://www.ntocc.org/Portals/0/PDF/Resources/TransitionsOfCare_Measures.pdf.

The NTOCC paper has revealed the contradictory practice of having patients treated at optimal care levels in a particular setting and then not implementing a process that enables a seamless transition to the next environment (Farris *et al.*, 2014). Apart from being detrimental to a patient's quality of life, such deficits constitute inefficiency in the utilisation of limited resources, as duplication of services, and fluctuations in a patient's general health condition may occur. Analysis of the main causes of failure in care transitions and the implementation of basic measures to reduce deficiencies is the first step to improved care and patient well-being (Abraham *et al.*, 2012).

These main points of failure, in the context of the digoxin care process, can be identified as: (i) poor communication between the prescriber and the patient, (ii) inadequate preparation for discharge for the patient and caregiver, (iii) inadequate follow-up on an outpatient level, (iv) poor understanding of dosing, (v) poor understanding of adverse effects, (vi) inadequate initial treatment and (vii) inadequate monitoring of serum K^+ and renal function.[6]

[6] The Joint Commission Enterprise. Hot Topics in Healthcare: Transitions of Care [Online]. New York: The Joint Commission; 2016 [cited 2018 Jan 18]. Available from: https://www.jointcommission.org/assets/1/18/Hot_Topics_Transitions_of_Care.pdf.

The inconsistent level of treatment and patient care failure arising during these transitional phases is evidenced by the emphasis placed upon developing models for improved transitional processes by various healthcare providers and regulators.[7]

The US is a major proponent of care transition initiatives and legislation on thirty-day readmission rates to hospitals has tied financial remuneration to improved rates (Kristensen *et al*., 2015). This in turn has re-energised focus on developing systems to standardise the provision of care along the patient's various care settings, and reduce the potential sources of failure (Salerno *et al.*, 2017). The American Society of Health System Pharmacists (ASHP) developed "Guidelines for a Standardized Method for Pharmaceutical Care". This document makes the case for a replicable and consistent method of pharmaceutical care delivery across all healthcare areas, both within the same setting, and following transfer from one setting (tertiary care) to another (community care).[8]

A 2015 statement released by the AHA highlights the complexity of transitional care, in the context of chronic HF patients. The position paper reviewed transitions of care in HF and evaluated the different approaches being adopted by healthcare organisations and

[7] National Transitions of Care Coalition (NTOCC). Transitions of Care: measures [Online]. NTOCC; 2008 [cited 2018 Jan 18]. Available from: http://www.ntocc.org/Portals/0/PDF/Resources/TransitionsOfCare_Measures.pdf

[8] American Society of Health System Pharmacists (ASHP). Guidelines for a Standardized Method for Pharmaceutical Care [Online]. New York. ASHP; 2016 [cited 2018 Jan 18]. Available from: https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/standardized-method-pharmaceutical-care.ashx?la=en&hash=55D9C732A17801E11D9491249DA16D9FFC5F4543.

concluded that a major point of failure is a lack of uniformity in the methodology being implemented. The attainment of a consensus by the main stakeholders is suggested to enable the development and implementation of a seamless care process, with the ultimate goal of improved clinical outcomes and patient well-being. The eight common features identified amongst the programmes reviewed were: (i) telephone follow-up, (ii) education, (iii) self-management, (iv) weight management, (v) sodium restriction/dietary advice, (vi) exercise recommendations, (vii) medication review and (viii) social/psychological support (Albert, et al., 2015).

These features form the foundation of HF treatment and palliative care, in the context of a chronic setting and are relevant to digoxin therapy. A point of interest is that a nurse or advanced practice nurse practitioner was defined as the main care provider for the programmes. Medication errors, both in administration and transcription of regimen are common sources of treatment failure, yet the pharmacist is not presently identified as having an active role to play in transitional care (Abraham *et al.*, 2012; Kwan *et al.*, 2013).

The Canadian Cardiovascular Society (CCS) published guidelines for transitional care in HF following a conference in 2008. The guideline is based on the fundamentals of access within a reasonable time frame to medical services according to the severity of cardiovascular disease and the establishment of a framework for patient handover from specialist to primary care physician (Arnold *et al.*, 2008). The pharmacist is not referred to in any of the three publications reviewed on the provision of seamless care.

The NICE guidelines for HF refer to the scope of adopting a holistic approach to patient management, and a definite time-scale for initial and long-term follow-up with the key healthcare providers included in the care plan, is emphasised. Monitoring of SDCs is only recommended in cases of compromised renal function and suspected digoxin toxicity, and not as a routine measure. This may be in conflict with developments in the approach to digoxin therapy as espoused by Bauman *et al*, whereby lower mean serum digoxin levels are associated with improved patient outcomes and lower mortality (Bauman *et al.*, 2006).

In the context of seamless care, the SIGN emphasises the importance of co-ordination of the multi-disciplinary team and continuation of patient management into the community setting. The role of the pharmacist in this area is clearly defined particularly with respect to assessment of compliance and follow up with clinicians to optimise pharmacological intervention. Reference is made to the need for monitoring for drug interactions and symptoms of bradycardia. Naidoo *et al* have demonstrated improved clinical outcomes in situations of consistent patient follow-up and review post-discharge from a tertiary setting with patients on digoxin (Naidoo *et al.*, 2015).

1.9 Rationale for the study

Four aspects of digoxin therapy in Malta were the stimuli for the research carried out. The first aspect was the absence of collated data for digoxin-treated patients. Epidemiological data specific to the population being treated forms an integral part of the clinical practice evidence base (Felker *et al.*, 2014; Thorvaldsen *et al.*, 2016). Pharmaceutical care and evidence-based medicine is not confined to a strict interpretation of guidelines issued by competent bodies, but includes the utilisation of all available information to aid decision-

making (Fonarow *et al.*, 2010; Wenger *et al.*, 2016). Clinicians are not in a position to evaluate digoxin therapy from a societal perspective in order to tailor their therapeutic decisions to an individualised patient approach without access to population-specific information. Pre-empting unwanted and harmful effects of pharmaceutical therapy by evaluating data specific to the patient and the environment in question is an approach that promotes improved health outcomes and patient quality of life (QOL) (Hepler and Strand, 1990; Millonig *et al*., Jackson and Ellis, 2002; Jisha and Minaz, 2011).

The second aspect was the lack of consensus on the adoption of a commonly accepted target SDC range. Current guidelines by the ESC, HFSA and ACCF/ACA recommend an upper SDC limit of 0.9 ng/ml. Both the Pathology Laboratory and the DIU at MDH suggest a range of 0.9 to 2.0 ng/ml (Table 1.2). A review of the literature reveals that maintaining SDCs below an upper limit of 0.9 ng/ml minimises adverse effects and reduces patient hospitalisation and mortality (Adams *et al.*, 2005; Ahmed *et al.*, 2007, 2008; Goldberger and Goldberger, 2012; Ambrosy *et al.*, 2014; Khan and Gheorghiade, 2015; Ziff *et al.*, 2015). These conflicting recommendations may be a potential source of treatment failure and patient harm and warranted study of patients' mean SDC levels in this context.

The third aspect was that prior to this research no formal analysis or published work appeared to have been carried out on the content of the requests processed by the DIU. Digoxin therapy is inherently complex and it may be construed that health care professionals would require a point of reference in certain instances. The Drug

Information Unit (DIU) at MDH is the only source of specialised drug information in Malta.

The fourth aspect considered was that no protocols or guidelines are in place in Malta as an aid for the pharmacist within the pharmaceutical care process for a patient on digoxin. Improvement in the quality of pharmaceutical care provided has been demonstrated to result in a lower incidence of the adverse effects of drug therapy and in increased levels of patient satisfaction and QOL (Hepler and Strand, 1990; Olsson *et al*., 2011). Apart from the intangible benefit of ameliorated patient well-being, an improved pharmaceutical care process leads to a potential reduction in hospitalisation and mortality (Hepler and Strand, 1990; Jisha and Minaz, 2011). The development and implementation of practice points for digoxin within the pharmaceutical care process would result in added value to the pivotal role which pharmacists perform in Malta, where they enjoy a position of trust within the community.

1.10 Aim and objectives

The aim of the research was to evaluate digoxin therapy in Malta in the context of serum digoxin concentrations.

The objectives were to:

(i) Determine the number of digoxin-treated patients in Malta

(ii) Collect data for SDCs processed at the Pathology Laboratory at MDH, relate the SDC levels to age, gender, origin of request, reason for request, referring speciality, serum potassium levels and renal function and assess adherence to the clinically recommended target SDC range

(iii) Assess queries concerning digoxin processed by the Drug Information Unit at MDH

(iv) Develop practice points for community pharmacists in Malta for digoxin-treated patients

Chapter 2: Methodology

The methodology adopted was divided into five parts: (i) establishment of the number of patients on digoxin in Malta, (ii) collection and analysis of retrospective SDC data from MDH (2008-2017), (iii) classification of SDCs according to the clinically recommended target SDC, (iv) analysis of requests for digoxin handled by the Drug Information Unit at MDH (2002-2014) and (v) development of digoxin practice points for community pharmacists.

2.1 Study setting

The setting for the study was MDH where all SDC testing requested by the state health system and individuals entitled to free health care in Malta is processed at the Pathology Laboratory. The Pathology Laboratory implemented a new database for processing and storing SDC requests and results in January 2008 and there are no records for biochemistry tests carried out at MDH or Saint Luke's Hospital prior to 2008. The Pathology Laboratory utilises a Cobas Hitachi Elecyc 2010 clinical analyser which operates on the basis of electrochemiluminescence immunoassay technology (ELICIA). The clinical analyser information system collects output from the laboratory floor; this system is overlaid by the Laboratory Information System (LIS), which is the interface for supervisory personnel and senior pathologists in charge of releasing final results.

The Drug Information Unit (DIU) at MDH forms part of the Clinical Pharmacy Practice Unit (CPPU) and is staffed by eight pharmacists. In March 2017, the DIU was operated Monday to Fridays from 7.30am to 3.30pm, with a roster pharmacist on duty from 7.30am to 1.30pm on Saturdays. In the remaining hours, any urgent queries were directed to the

inpatient pharmacy department where the pharmacist on shift is tasked with responding to information requests. Record keeping at the DIU commenced in 2002.

The Pharmacy of Your Choice (POYC) is the state system whereby patients in Malta collect their chronic medicine entitlements from a community pharmacy of their choice in eight-weekly cycles in Malta.

Digoxin is available in Malta as tablets (0.0626 and 0.25 mg) or 0.05mg/5ml suspension. Digoxin has the advantage of being inexpensive (local retail price for a box of Lanoxin® 0.0625mg x 500 tablets is € 31.68, January 2018) and readily available. No data is collected for private retail sales of digoxin; anecdotal evidence indicates an insignificant private retail market for digoxin for human consumption in Malta despite its availability in community pharmacies.

2.2 Study approvals

Approval from the Chief Executive Officer, Data Protection Officer, and the Chairman of the Department of Pathology, and Head of the Pharmacy Department, at MDH and the Head of the POYC unit was obtained. The University Research Ethics Committee granted approval for the study (Ref: 53/2016, Appendix I).

2.3 Establishing the number of digoxin-treated patients in Malta

Three options, using data from POYC records, for determining the number of digoxin-treated patients were identified: (i) the number of patients entitled via the Schedule V (chronic conditions) provision only, which would exclude patients receiving digoxin through the means-tested Schedule II provision, (ii) the number of patients registered on the POYC web-based pharmaceutical dispensing IT system. This system enables patient entitlements and dispensing records to be accessed by pharmacists and POYC staff and includes all entitled patients, even patients not currently being dispensed digoxin and (iii) the quantity of digoxin dispensed to each patient over the previous four months, where the dose could also be identified.

The third option was selected. The advantages of this option were two-fold. Firstly, the data was current and would reflect the number of patients on digoxin over the last four months. Secondly, implementation of the POYC system commenced in 2008, following a staggered nationwide roll-out. Information collected from the early stages would not be relevant since not all the community pharmacies would have been integrated and some patients may still have been collecting their state entitlements from the health centre pharmacies or from MDH, for which no records were accessible. The POYC system was assumed to have attained a state of full penetration after 9 years on a national level, at the time of the study, and data collected construed to represent the whole population receiving chronic medicine through the state system. Another assumption with the method selected was that all patients being treated with digoxin were obtaining their treatment through the state system and not through the private retail market. The basis for this assumption was that digoxin-treated patients are receiving multiple pharmacotherapies hence are utilising

the POYC scheme to collect their other medicines; despite the low cost of digoxin, patients would still avail themselves of the POYC system and obtain all their medicines in one instance.

It was established with the POYC unit that any reference to patient identity would be omitted from the data prior to transfer to maintain confidentiality. Dispensing records for a four- month period (October 2016 to January 2017) were extracted; two eight-week cycles were analysed to include any patients who may have missed a prescription cycle. Duplicate patient dispensing transactions were deleted from the data set and the figures adjusted to reflect supplies for 28-day periods. This resulted in a cross-sectional snapshot of all patients obtaining digoxin through the POYC system in Malta for the study period. Microsoft Excel© 2016 was used to generate the number of patients being supplied digoxin monthly, the dosage forms being supplied, and the mean daily dose.

2.4 Retrospective analysis of SDCs

2.4.1 Study period and selection of variables for analysis

The period for the retrospective analysis was set from the commencement of the collection of data at the Pathology Laboratory (January 2008) to the 31st December 2017, a ten-year period. The relationship between SDCs and serum K^+ and SDCs and renal function was assessed for 2017.

Patient variables to be included in the analysis were identified, namely: (i) test date, (ii) SDC result (iii) gender (iv) age (v) origin of SDC request (vi) requesting physician (vii) reason for SDC request, (viii) timing of SDC test compared to the last digoxin dose administration, (ix) serum K^+ level results and (x) eGFR results.

2.4.2 Data analysis

A pilot data set for a thirteen-month period (January 2015 to February 2016) was generated to test the viability of the export format and to determine whether the patient variables identified were applicable. The pilot study revealed that SDC dose timing was not available through the Pathology Laboratory system and hence was omitted from the final analysis.

The data for the retrospective analysis was exported by the Pathology Laboratory IT manager and copied onto a data storage device. No information was exchanged via electronic mail to maintain confidentiality of patient data. Records provided by the Pathology Laboratory were assessed for completeness and validity for the following fields: (i) SDC result (ii) gender (iii) age (iv) origin of request, (vi) requesting physician and (vii) reason for request, using the filter function in Microsoft Excel©. Records without an SDC result, with a value other than an alpha-numeric value in the SDC result field, missing entries for date, age, gender, origin of request and requesting physician were excluded. Non-numeric SDC result values (numerals preceded by > or <) were omitted.

When analysing the origin of request, 565 entries were identified, of which a number were referring to the same location, denoted by means of varying abbreviations. For the purpose of the study the origin of SDC requests were filtered into six locations, namely MDH, Public Health Centres (HC), Gozo General Hospital (GGH), Rehabilitation Hospital Karin Grech (RHKG), Residential Care Homes (RCH) and other requesting locations (Other). A level of secondary origin was devised, enabling differentiation between various areas at MDH. MDH SDC requests were classified into five areas (Table 2.1).

Table 2-1 - Origin of SDC request at Mater Dei Hospital

MDH origin of request
Accident and Emergency
Cardiac inpatients
Non-cardiac inpatients
Cardiac outpatients
Non-cardiac outpatients

The number of SDC requests emanating from the A&E department was tabled together with the total number of admissions to the department for the years 2008 to 2015; 2015 was the latest year for which admission figures for the A&E department were available.

The list of requesting physicians was exported to .csv format and analysed using the JASP software package. After the removal of duplicate entries, 626 individual physicians were identified. Out of this total, 75 physicians accounted for 78% of all the SDCs (14,855 results). These 75 physicians were classified according to medical speciality using the online register available from the website of the Maltese Medical Council, with 18 medical specialities identified.[9]

Analysis of the reason for request field (RFR) necessitated reclassification of the entries to a structured format since no drop-down menu of set reasons is provided to the healthcare professional requesting the SDC. Classification was based on the physiological basis for the diagnosis listed (Table 2.2). The reason for request field was filtered for the following characteristics where listed by the referring party: (i) digoxin toxicity (ii) electrolyte abnormalities (iii) timing of sample (iv) patient falls (v) co-morbidities – AF only, HF only, both HF and AF, Ischaemic Heart Disease, Kidney Disease, Diabetes Mellitus and (vi) concomitant administration of other drugs.

[9] Malta Medical Council. Medical and Dental Specialists Register [Online]. Malta: Malta Medical Council; 2017 [cited 2018 Jan 18] Available from: https://health.gov.mt/en/regcounc/medicalcouncil/Documents/registers/mcsac.pdf

Table 2-2 - Classification of SDCs by reason for request

Reason for request
Cardiac symptoms
Central Nervous System disturbances
Circulatory symptoms
Digoxin toxicity
Electrolyte imbalance
Endocrine symptoms
Gastro-intestinal symptoms
Haematological symptoms
Hepatic abnormalities
Ophthalmic symptoms
Renal abnormalities
Respiratory symptoms
Routine testing
Systemic disturbances
Miscellaneous symptoms
Not recorded

The relationship between SDC levels and serum K^+ and SDCs and renal function was investigated, with eGFR used as a metric for renal function. The number of tests conducted at MDH in 2017 were 508,558 for serum K^+ and 533,308 for eGFR. SDC, serum K^+ and eGFR results for 2017 were extracted from the Pathology Laboratory information system and imported into a Microsoft Access© 2016 database as separate tables. The K^+ and eGFR tables were individually linked to the SDC results table and database queries run to extract the following: (i) all serum K^+ results with an identical laboratory specimen number present in the SDC table and (ii) all eGFR results with an identical laboratory specimen number present in the SDC table. In this manner the comparison of SDC and serum K^+ results, and SDC and eGFR results for samples drawn at the same time was possible. Out of 1,994 initial matches for SDC and serum K^+ results a final 1,406 results were included. Means for K^+ were generated for the whole set, and subsets for K^+ relating to SDCs in the ranges <0.1-0.9 ng/ml, >0.9-1.99 ng/ml and ≥2.0 ng/ml. Out of 1,464 initial matches for SDC and eGFR results a final 1,439 results were included. Means for eGFR were generated for the whole set, and subsets for eGFRs relating to SDCs in the ranges <0.1-0.9 ng/ml, >0.9-1.99 ng/ml and ≥2.0 ng/ml.

2.4.3 Statistical analysis

Statistical analysis was carried out using the JASP statistical software package. Descriptive statistics were generated for the SDC results and patient variables for age and gender, with the mean, median, mode and range reported. Frequency tables for the origin of request and referring physician were generated. Comparison of means was carried out using the Independent Samples T-test. The Analysis of Variance (ANOVA) test was used in cases when more than two means were compared for variance. A level of significance of $p<0.05$ was adopted throughout.

2.5 Assessment of adherence to the clinically recommended target SDC range

The target SDC range was established at 0.5 to 0.9 ng/ml, as suggested in HFSA and ESC guidelines (Lindenfeld *et al.*, 2010; Kirchhof *et al.*, 2016). SDC values from <0.1-0.49 were classified as sub-therapeutic, 0.5-0.9 ng/ml as within the target range and those > 0.90 ng/ml as above the designated upper limit. SDCs ≥ 2.0 were further classified as potentially toxic. The following hypothesis was developed and tested:

$$H_0 : \text{The mean SDC for the patient cohort is} \leq 0.9 \text{ ng/ml}$$

$$H_1 : \text{The mean SDC for the patient cohort is} > 0.9 \text{ ng/ml}$$

2.6 Analysis of requests for digoxin at the Drug Information Unit

Data for a thirteen-year period (2002-2014) was analysed. The recording of information at the DIU commenced in 2002. The records for the first three years consisted of short notes with the date, drug involved and the issue resolved. As of 2005 the individual requesting the information was noted on the basis of professional competence (physician, pharmacist, nurse) as was the request location (MDH, health centre, private pharmacy). The time taken to resolve a query was added to the Microsoft Excel© sheet at this time. The data was supplied in the form of 14 separate Microsoft Excel© sheets; these were merged into a single worksheet. Each record contained nine fields: record identifier, date, query category, query, requesting id, request location, request category, processed by and time. The requesting id, request location, processed by, and time fields were removed. A unique index for each record in the format DIUYYYY0001 - the first entry in 2002 designated as DIU2002001 – was generated to facilitate the application of the Microsoft Excel© filter function. 'Digoxin' was used as the filtering parameter to extract records pertaining to the information requests for digoxin.

The DIU staff applied 19 sub-categories to the drug information requested in order to classify the pharmaceutical nature of the request. These were adopted by the researcher, except in the cases of synonyms (merged) and uncommon or non-specific categorisations (grouped under general information) (Table 2.3). The same methodology was applied to the field describing the professional status of the enquiring entity. Fields for physician, general practitioner, health centre physician and consultant physician were merged, as were those for pharmacist and clinical pharmacist.

Table 2-3 - Categories of requests for digoxin at the Drug Information Unit

Category of request
Administration
Adverse effects
Advice
Availability
Compatibility
Dosage
General information
Identification of tablet
Interactions
Pharmacotherapeutic intervention
Monitoring
Pharmacology/pharmacokinetics
Renal/hepatic reactions
Stability/storage
Toxicity

2.7 Development of digoxin practice points for community pharmacists

Care transition guidelines with reference to HF and digoxin therapy and the continuation of care were accessed through PubMed, the Cochrane Library, Google, Directory of Open Access Journals and the University of Malta Library search engine (HyDi). Guidelines issued by the American Society of Hospital Pharmacists (ASHP), and position papers by the American Heart Association (AHA) and the Canadian Cardiovascular Society (CCS) were reviewed in the development of practice points for community pharmacists for digoxin-treated patients in Malta. The ASHP guideline put forward nine features of a common approach to pharmaceutical care processes. The position paper by the AHA also suggested nine main recommendations for an improved transitional care process. The CCS developed guidelines for the clinical aspect of a care transition. These three sets of recommendations were tabulated and evaluated with specific application to the pharmaceutical care process for digoxin (Tables 2.4, 2.5, 2.6). Analysis of the process flow for the prominent factors impeding the transition of care in HF patients, was carried out utilising methodology followed by the AHA position paper (Figure 2.1). Four central themes were defined as being central to the three publications reviewed: patient medication records, the pharmaceutical treatment process, pharmaceutical care information exchange and the patient's humanistic perspective. These four areas were addressed in the context of digoxin therapy and the suggestions made by the three bodies. A list of practice points and reference tables, intended for use in a community pharmacy setting and specific to the pharmaceutical care process for digoxin, were drafted. A panel consisting of two cardiologists, a pharmacist working in academia, a senior clinical pharmacist and five community pharmacists validated the draft practice points. The initial

draft was amended on the basis of the panel's recommendations to develop the final version.

Table 2-4 - American Society of Hospital Pharmacists suggestions for care transitions

Collect and organise patient specific information
Determine the presence of medication related issues
Draw up a list of patient health needs
Determine pharmaceutical care goals
Design a pharmacotherapeutic regimen
Design a monitoring plan
Consult with a multi-disciplinary team on the last three items
Evaluate the above in action
Effect the necessary adjustments to the plans

Adapted from: American Society of Health System Pharmacists (ASHP). Guidelines for a Standardized Method for Pharmaceutical Care [Online]. USA: ASHP; 2016 [cited 2018 Jan 18]. Available from: http://www.ashp.org/DocLibrary/BestPractices/OrgGdlStndMethod.aspx.

Table 2-5 - American Heart Association suggestions for care transitions in a heart failure setting

Systematically implement principles of transition of care programs in high-risk patients with chronic HF.
Routinely assess patients for high-risk characteristics that may be associated with poor post-discharge clinical outcomes.
Ensure that qualified and trained HF nurse or other healthcare providers of clinical HF provide care services.
Allot adequate time in the hospital and post-acute setting to deliver complex chronic HF interventions and to assess patient and caregiver responsiveness.
Implement handoff procedures at hospital or post–acute care discharge.
Develop, monitor, and ensure transparency of results of quality measures using a structure, process, and outcome framework.
Consider patients' perceptions of Quality of Life (QoL) as a surrogate for physical, psychological, and social concerns that require support during the transition of care process.
Ensure availability of transition of care component details in writing
Use health informatics technology to assist with program sustainability. Informatics should be patient and healthcare provider centric.

Adapted from: Albert NM, Barnason S, Deswal A, Hernandez A, Kociol R, Lee E, et al. Transitions of care in heart failure: A scientific statement from the American Heart Association. Circ Hear Fail. 2015;8(2):384–409.

Table 2-6 - Canadian Cardiovascular Society suggestions for care transitions in a heart failure setting

Record diagnoses
Identify current problems and condition at discharge
List recommendations from subspecialty consultants, if applicable
List medications
Current drugs and doses
Drugs requiring dose titration (advise when to titrate, what to watch for, target dose)
Provide current laboratory results (when to repeat, what to monitor, how to respond)
Identify follow-up plan/tests (give timeframe to return, to see PCP, other providers)
Identify resuscitation and other end-of-life issues discussed in hospital

Adapted from: Arnold JMO, Howlett JG, Ducharme A, Ezekowitz JA, Gardner MJ, Giannetti N, et al. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure – 2008 update: Best practices for the transition of care of heart failure patients, and the recognition, investigation and treatment of cardiomyopathies. Can J Cardiol. 2008;24(1):21–40.

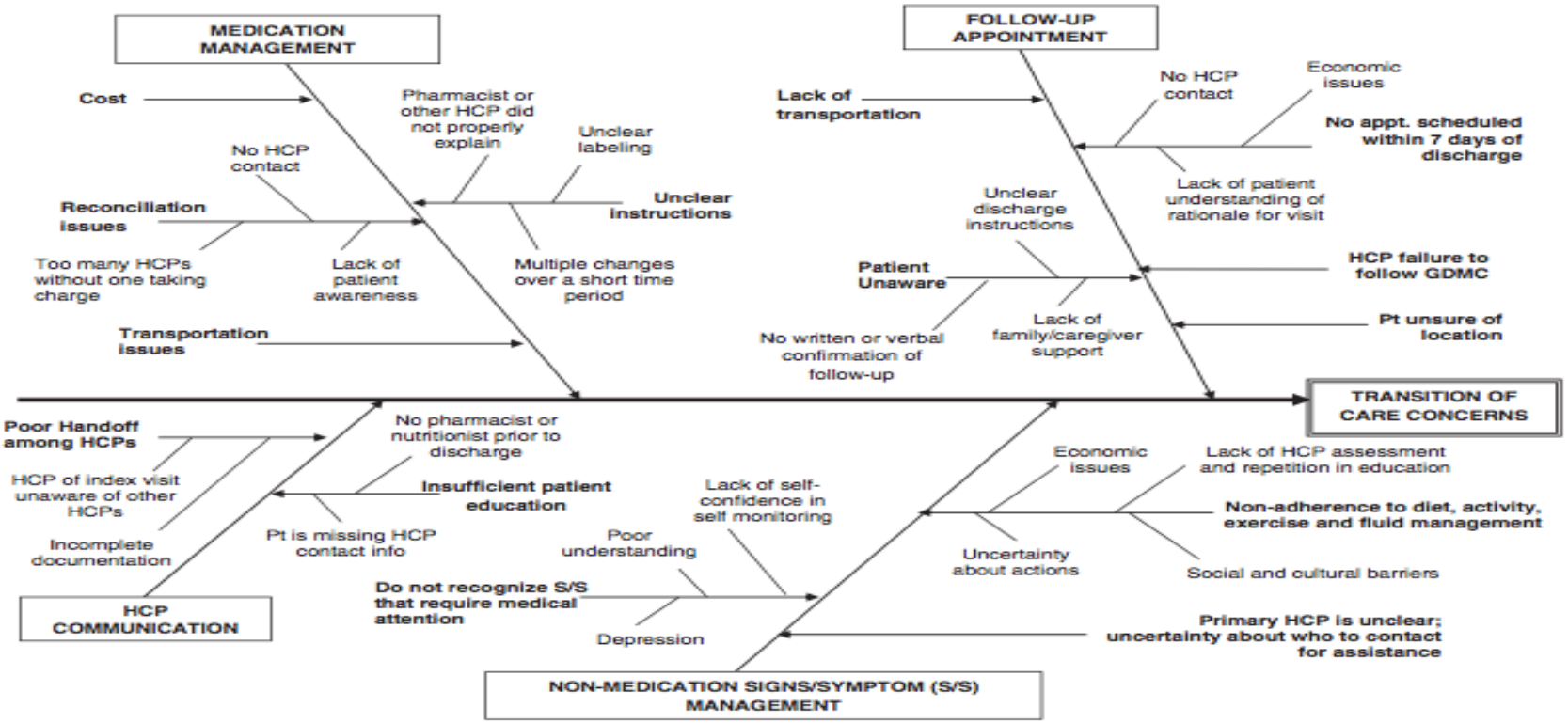

Figure. Prominent factors impeding transition of care in chronic heart failure care. GDMC indicates guideline-directed medical care; HCP, healthcare provider; and Pt, patient.

Figure 2.1 - Factors impeding transition of care in chronic heart failure

Reproduced from: Albert NM, Barnason S, Deswal A, Hernandez A, Kociol R, Lee E, et al. Transitions of care in heart failure: A scientific statement from the American Heart Association. Circ Hear Fail. 2015;8(2):384–409.

Chapter 3: Results

3.1 Digoxin-treated patients in Malta

In January 2017, a total of 2,059 patients enrolled in the POYC system were identified as being on regular digoxin treatment. A total of 148,090 individual doses of digoxin were dispensed in the same month.

The patients were subdivided according to the dosage form and dose of digoxin supplied, with 78.2% (n=1,609) of patients receiving the 0.0625mg dose in tablet form (Table 3.1).

Table 3-1 - Patients dispensed digoxin by dosage form and dose (N=2,059)

Dosage form	Dose	Number of patients	Percentage (%)
Tablets	0.0625mg	**1,609**	**78.2**
Tablets	0.25mg	447	21.6
Suspension	0.05mg/ml	3	0.1

The mean daily dose of digoxin per patient was 0.13±0.08 mg (range 0.03125 - 0.50mg). Forty-five per cent (n=918) of patients were taking 0.0625mg of digoxin daily (Figure 3.1).

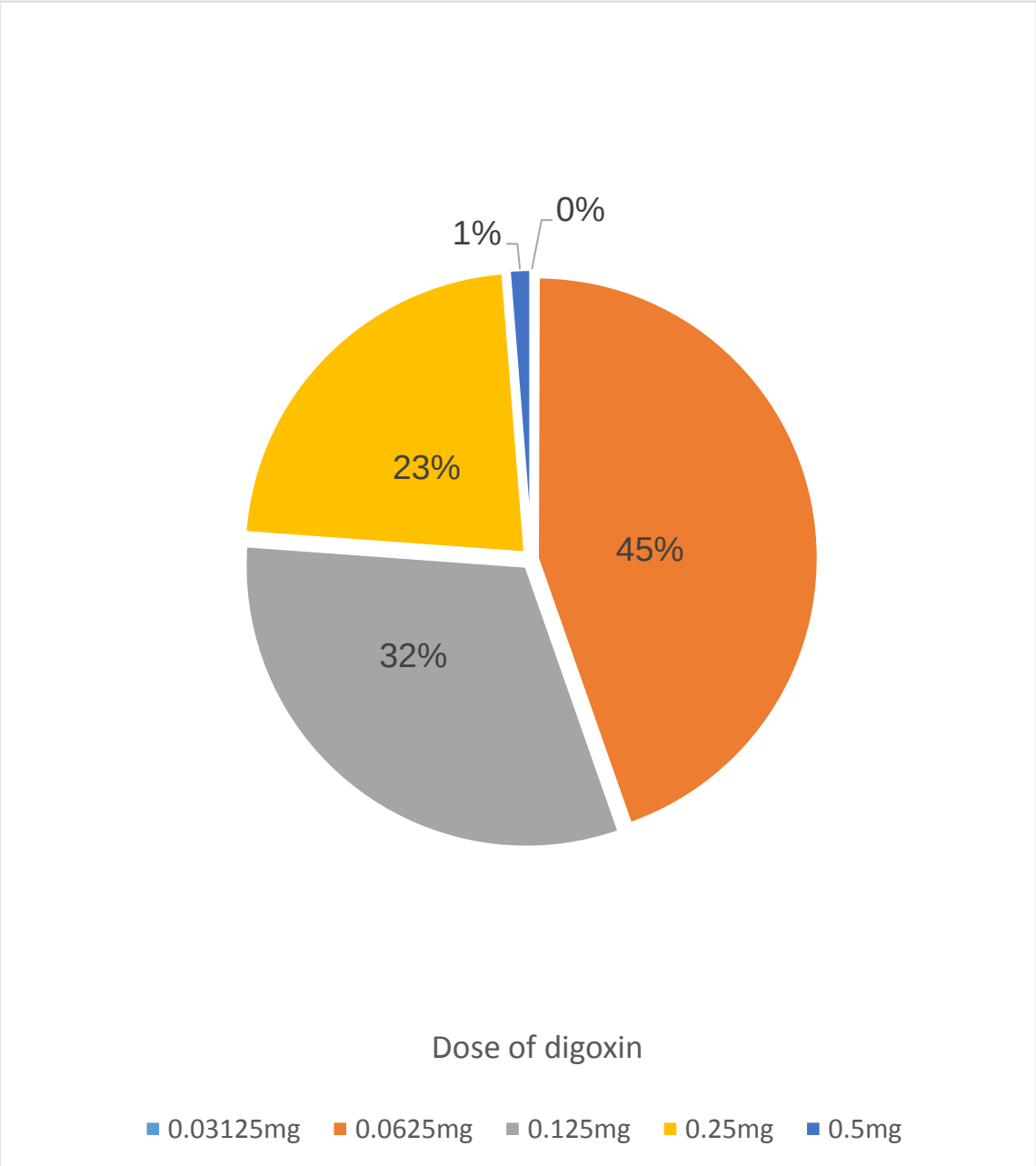

Figure 3-1 - Percentage of patients by daily digoxin dose (N=2,059)

3.2 Retrospective analysis of SDCs

Out of an initial 20,146 SDCs retrieved, 1,081 SDCs were invalid or incomplete. A total of 19,065 valid SDC results from 6,107 individual patients were included in the final analysis (Figure 3.2). The mean SDC was 1.31±1.01 ng/ml (range <0.1-2.0 ng/ml, median 1.1 ng/ml, mode 0.8 ng/ml).

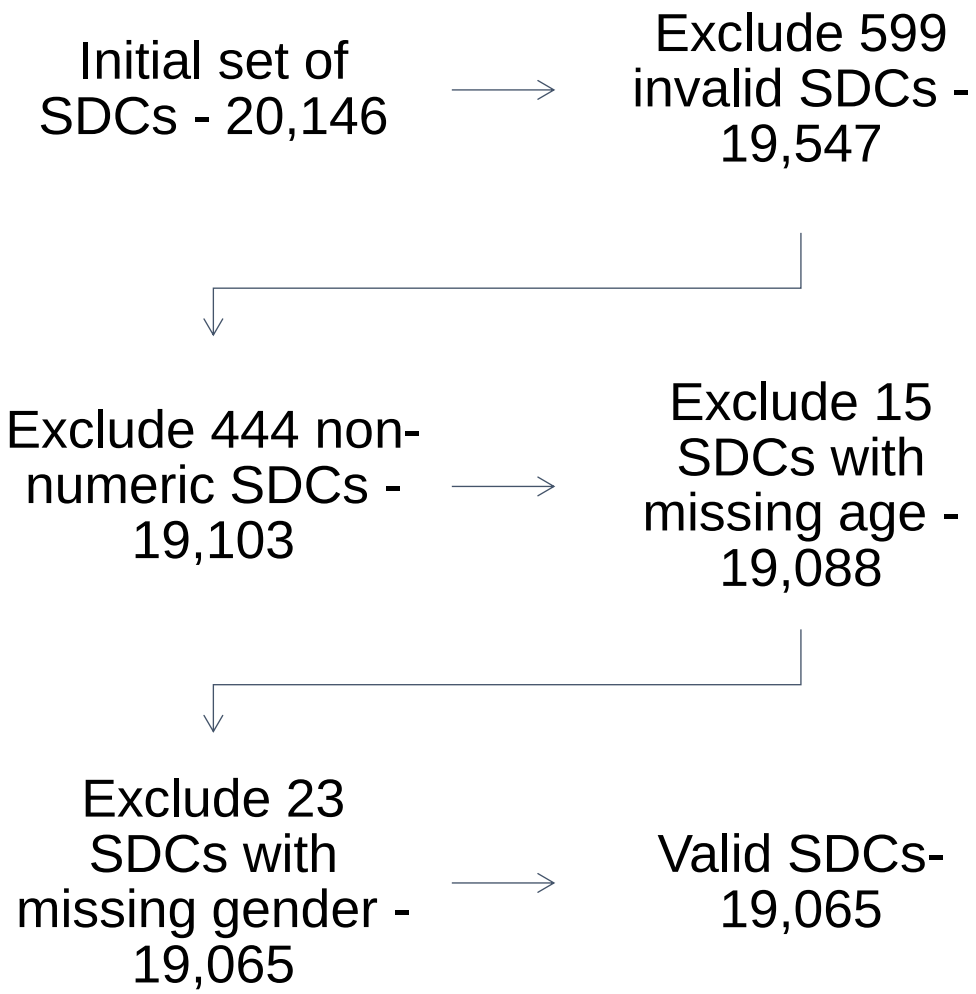

Figure 3-2 - Process for SDC analysis

The main reasons noted for the 599 SDCs excluded on the basis of an invalid or null laboratory output were a haemolysed or contaminated specimen, an insufficient sample volume, unavailability of the SDC test at the Pathology Laboratory or an incorrect patient identification field.

3.2.1 Distribution of SDCs by year

The largest number of SDCs were processed in 2012 (n=2,256). The mean number of SDC requests per year was 1,907±182 (Table 3.2). A mean of 980±80 individual patients were tested annually.

Table 3-2 - Distribution of SDCs by year (N=19,065)

Year	Number of SDCs processed
2008	1,936
2009	1,793
2010	1,986
2011	2,149
2012	**2,256**
2013	1,892
2014	1,740
2015	1,836
2016	1,800
2017	1,677

The highest mean SDC was registered in 2011 (1.48±1.25 ng/ml), and the lowest in 2009 (1.18±0.90 ng/ml). In each year the mean SDC significantly exceeded the upper limit for the target SDC range (0.9 ng/ml) ($p<0.001$) (Table 3.3).

Table 3-3 - Descriptive statistics for SDC results by year (N=19,065)

Year	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
Number of SDCs	1,936	1,793	1,986	2,149	2,256	1,892	1,740	1,836	1,800	1,677
Mean (ng/ml)	1.23	**1.18**	1.28	**1.48**	1.40	1.24	1.30	1.29	1.29	1.39
Standard deviation (ng/ml)	0.97	0.90	0.97	1.25	1.1	0.91	0.85	0.85	0.93	1.19
Median (ng/ml)	1	1	1.1	1.2	1.1	1	1.1	1.1	1	1.1
Mode (ng/ml)	0.9	0.5	0.8	0.8	0.8	0.8	0.8	0.9	0.7	0.7
Minimum (ng/ml)	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Maximum (ng/ml)	11	8.7	8.8	20.0	12.7	15.1	8.4	10.2	10.5	15.9

3.2.2 Gender

Female patients comprised 65% (n=3,699) of the sample population (Figure 3.3).

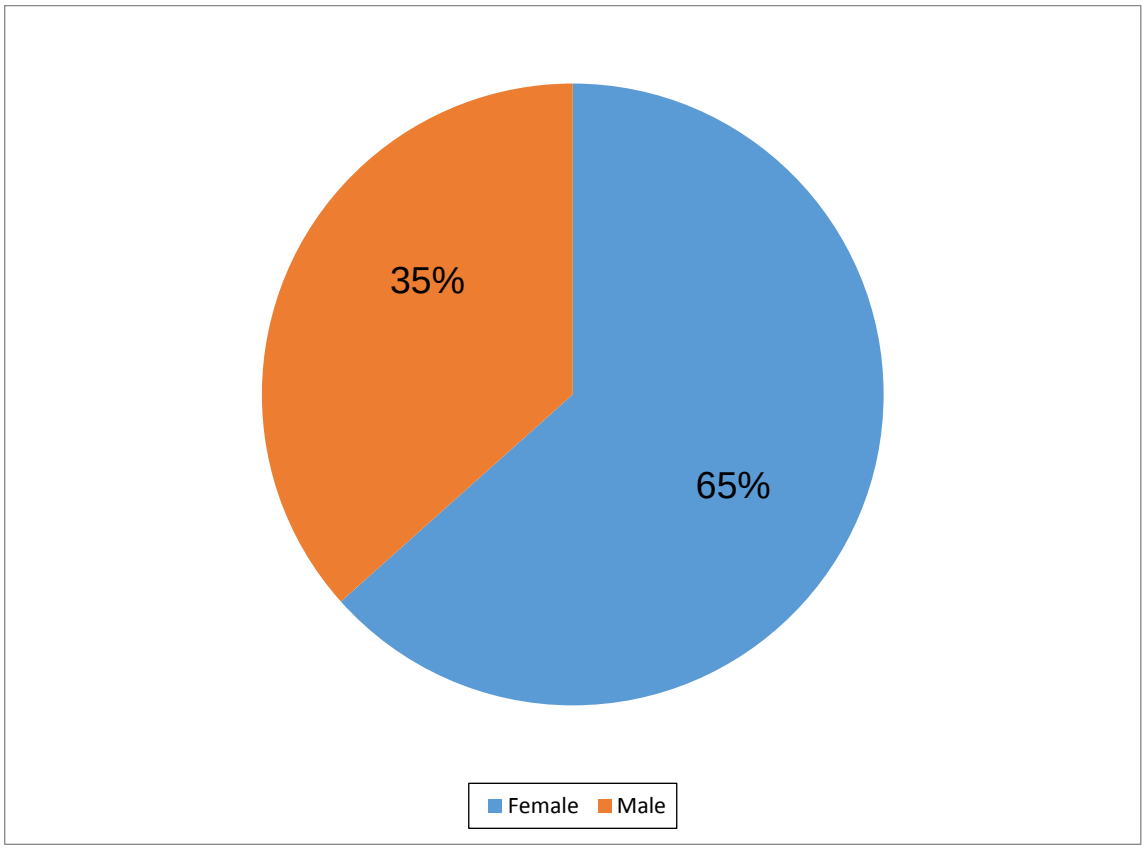

Figure 3-3 - Percentage gender distribution of patients (N=6,107)

SDCs collected from female patients (mean 1.36±1.02 ng/ml) exhibited a significantly higher mean than SDCs from male patients (1.22±0.98 ng/ml, $p<0.001$).

3.2.3 Age

Forty-eight per cent of patients were over 80 years of age and 33% were between 71 and 80 years. The mean age for the cohort of 6,107 patients was 78±11 years (median 80 years, mode 81 years). The ages recorded ranged from a neonate up to a 117 year- old patient (Figure 3.4).

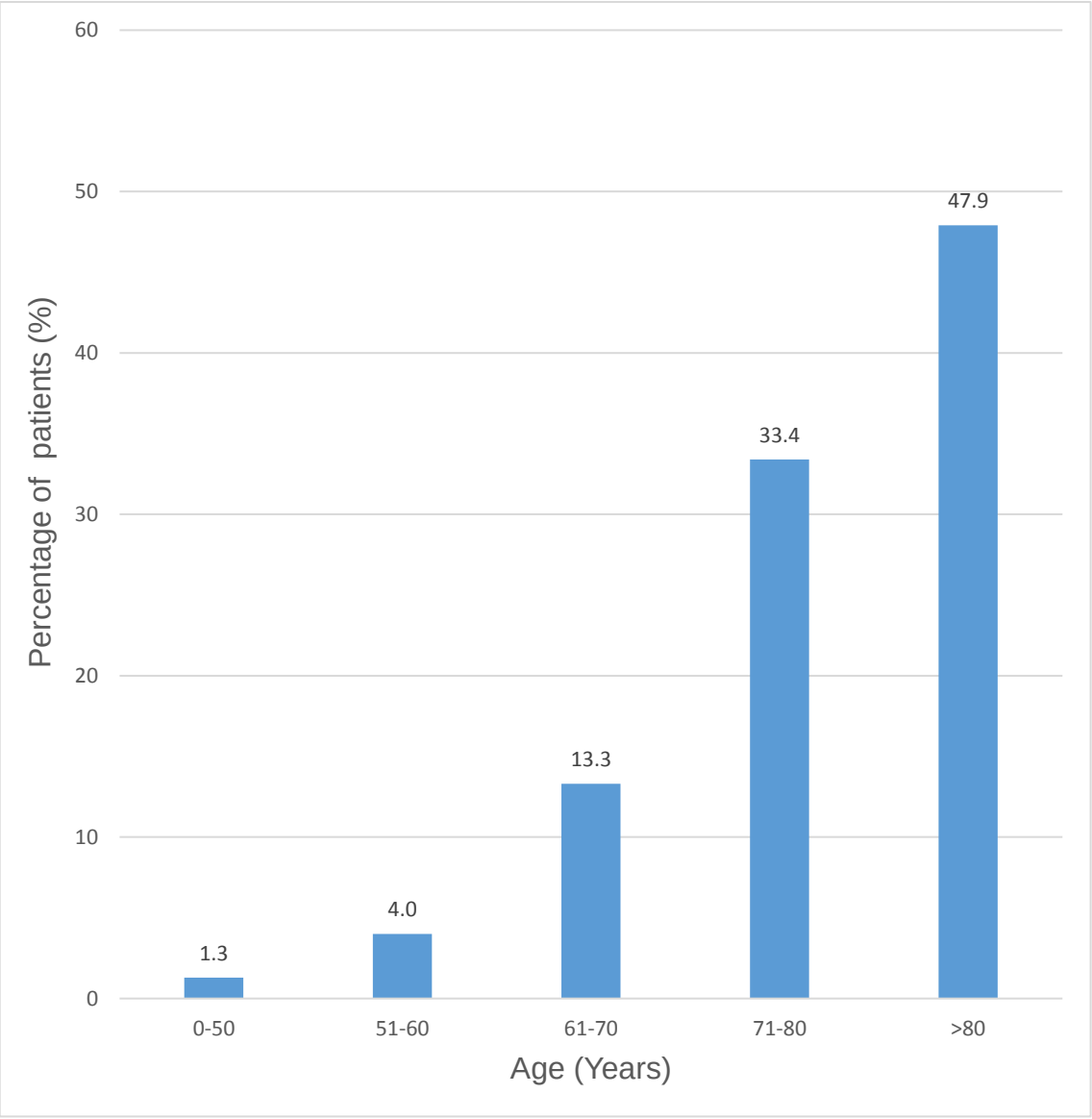

Figure 3-4 - Patient distribution by age (2008-2017, N=6,107)

Female patients (79.85±10.04 years) were significantly older than their male counterparts (75.2±11.75 years, $p < 0.001$). Patients from the sub-group >80 years recorded the largest number of SDCs (n=9,133) and the highest mean SDC (1.33±1.07 ng/ml). The sub-group of patients <50 years had the least number of SDCs (257) and lowest mean SDC (1.06±1.22 ng/ml) (Table 3.4). All sub-groups of SDCs by patient age were significantly above the recommended upper limit of 0.90 ng/ml for SDCs ($p<0.05$).

Table 3-4 - Mean SDC by age group (N=19,065)

Age group (years)	**Number of SDCs**	**Mean SDC (±SD)** (ng/ml)
0-50	**257**	**1.06 (±1.22)**
51-60	770	1.26 (±0.96)
61-70	2,533	1.29 (±1.00)
71-80	6,372	1.31 (±1.04)
>80	**9,133**	**1.33 (±1.07)**

3.2.4 Origin of SDC request

The largest number of SDC requests originated from MDH (84%, n=16,038) (Figure 3.5).

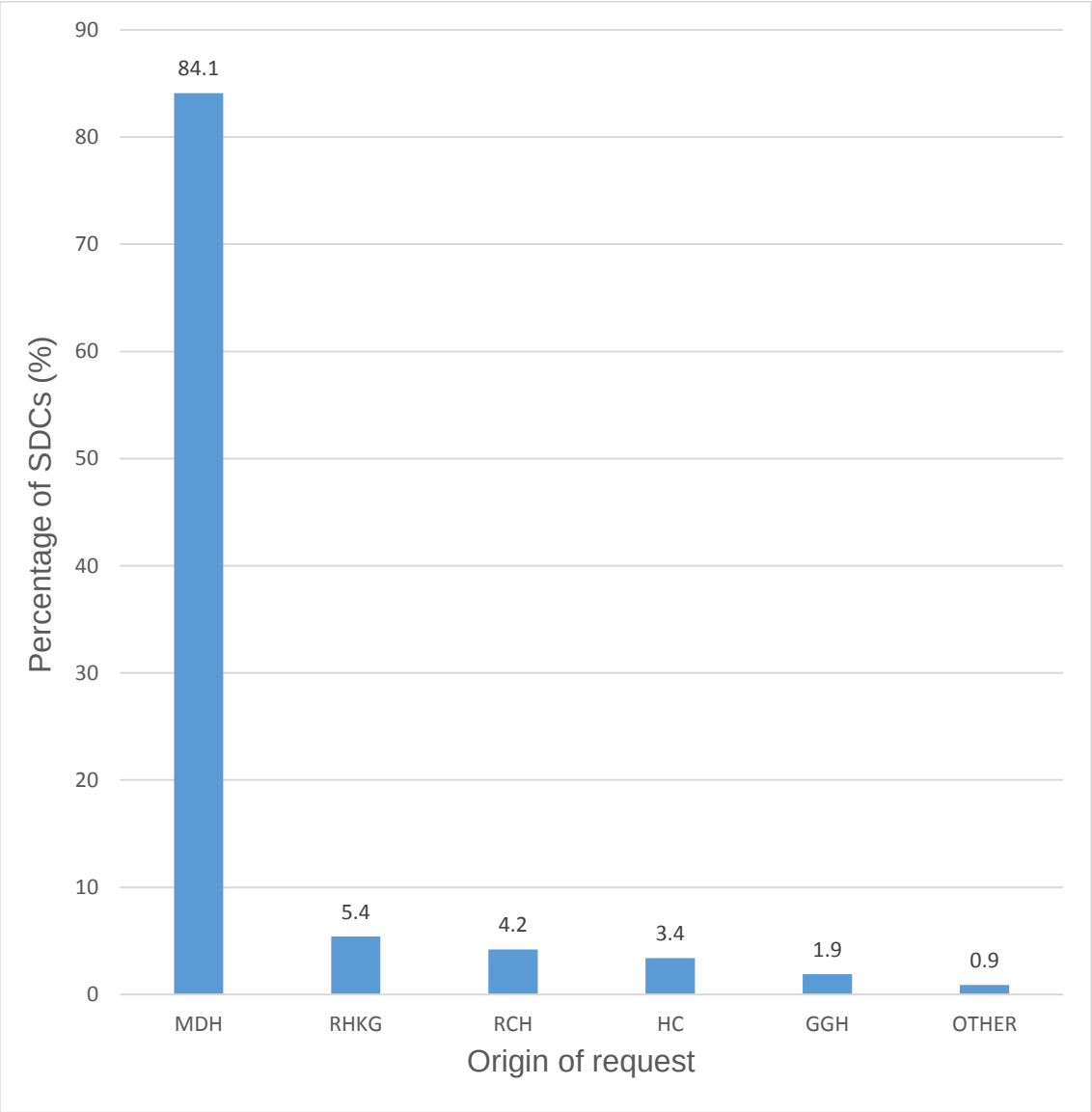

Figure 3-5 - SDC distribution by origin of SDC request (N=19,065)

Key: MDH – Mater Dei Hospital, RHKG – Rehabilitation Hospital Karin Grech, RCH – Residential Care Home, HC – Health Centre, GGH – Gozo General Hospital, Other – Mount Carmel Hospital, St. James Hospital, Sir Anthony Mamo Oncology Centre

Patients from Gozo General Hospital registered the highest mean SDC (1.41±1.26 ng/ml) compared to the lowest mean SDC at public health centres (1.05±0.64 ng/ml). The difference was statistically significant ($p<0.001$), (Table 3.5).

Table 3-5 - Mean SDC by origin of request (N=19,065)

Origin of request	**Number of SDCs**	**Mean SDC (±SD)** (ng/ml**)**
MDH	**16,038**	1.33 (±1.03)
RHKG	1,030	1.26(±0.87)
RCH	800	1.28(±0.86)
HC	653	**1.05(±0.64)**
GGH	370	**1.41(±1.26)**
Other	174	1.19(±0.79)

Key: MDH – Mater Dei Hospital, RHKG – Rehabilitation Hospital Karin Grech, RCH – Residential Care Home, HC – Health Centre, GGH – Gozo General Hospital, Other – Mount Carmel Hospital, St. James Hospital, Sir Anthony Mamo Oncology Centre

As regards MDH requests (n=16,038), the A&E Department contributed the largest percentage of SDC requests (35.5%), followed by non-cardiac inpatients (28.1%) (Table 3.6).

Table 3-6 - Percentage of SDCs by MDH origin of request (N=16,038)

MDH origin of request	Percentage of SDCs
A&E	**35.5**
Non-cardiac inpatients	28.1
Cardiac inpatients	13.4
Non-cardiac outpatients	7.2
Cardiac outpatients	0.1

The greatest percentage of A&E admissions resulting in an SDC request was in 2012, with 0.94% of admissions (Table 3.7).

Table 3-7 - SDC requests from A&E and total A&E admissions (n=5,785; 2008-2015)

Year	Total attendance (A&E)	Number of SDCs (A&E)	Percentage SDCs (A&E)/total attendance (A&E)
2008	106,907	623	0.58
2009	101,439	652	0.64
2010	107,102	708	0.66
2011	110,279	909	0.82
2012	111,533	**1,052**	**0.94**
2013	115,706	757	0.65
2014	119,941	485	0.40
2015	128,747	599	0.47

A total of 6,754 SDCs originated from the A&E department (mean 1.17±1.01 ng/ml, range <0.1-10.8 ng/ml, median 0.9 ng/ml, mode 0.7 ng/ml). The mean age of patients at the A&E for which an SDC was requested was 79±11 years (range 0-111 years). The percentage of SDCs from the A&E as a fraction of the total number of SDCs ranged from 28% in 2017 to 47% in 2012 (Table 3.8).

Table 3-8 - SDCs from the A&E (n=6,754)

Year	Number of SDCs (Total)	Number of SDCs (A&E)	% SDCs (A&E)/total SDCs
2008	1,936	623	32.2
2009	1,793	652	36.4
2010	1,986	708	35.7
2011	2,149	909	42.3
2012	2,256	**1,052**	**46.6**
2013	1,892	757	40.0
2014	1,740	485	27.9
2015	1,836	599	32.6
2016	1,800	505	28.1
2017	1,677	**464**	**27.7**

3.2.5 Requesting physician

The top three medical specialities requesting SDC testing were general medicine (22%), nephrology (11%) and cardiology (9%).Twenty-one percent of the SDCs analysed did not have the identity of the referring physician recorded in the request form (Figure 3.6).

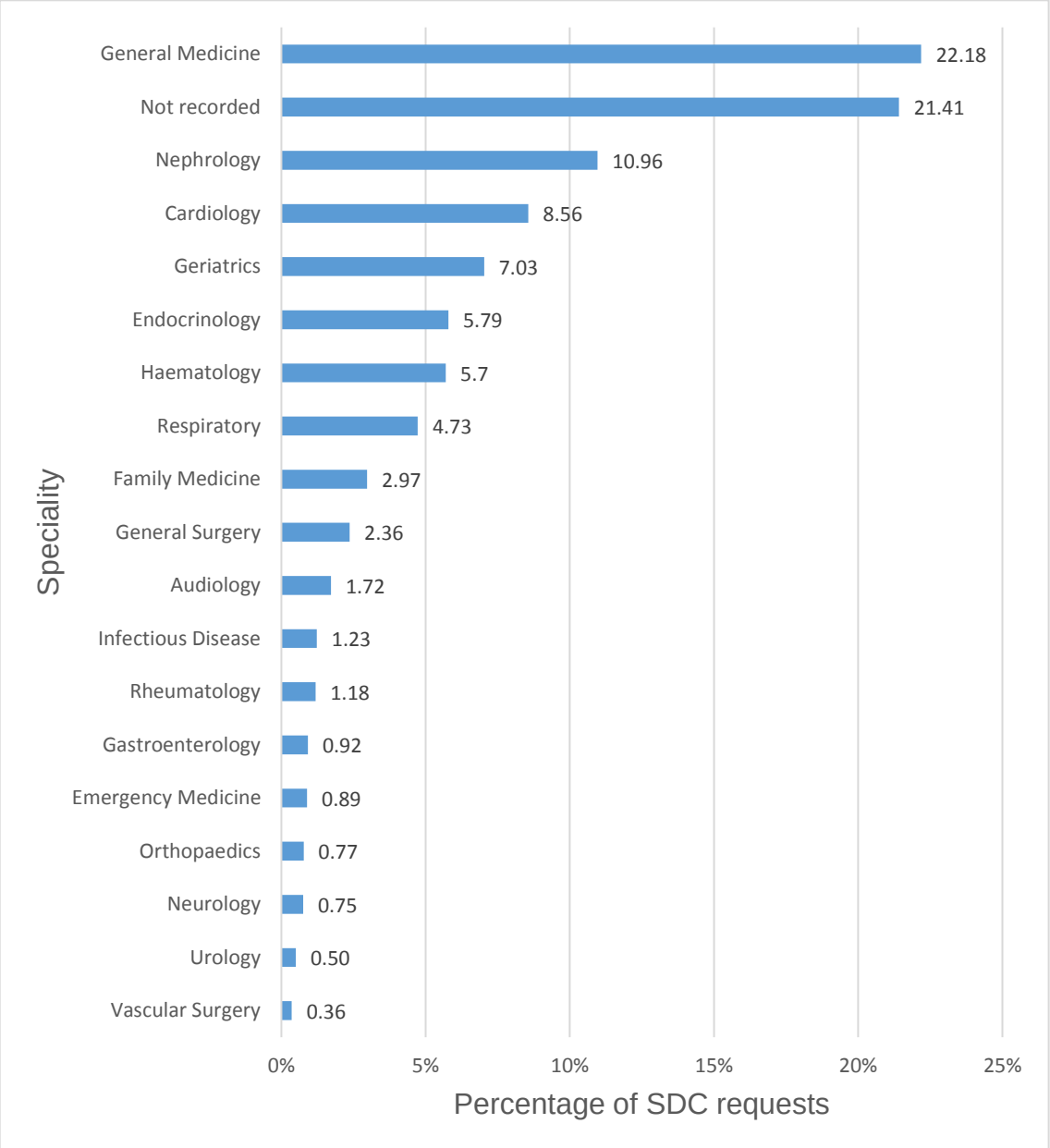

Figure 3-6 - SDCs by speciality of requesting physician (2008-2016; n=14,855)

3.2.6 Reason for SDC request

The majority of SDCs were requested as a routine procedure, 34.6% (n=6,017) followed by 21.96% (n=3,819) due to cardiac symptoms. The reason for request was not recorded in 10.71% (n=1,862) of the SDCs analysed. The highest mean SDC was recorded in those tests requested for digoxin toxicity (2.16±1.57 ng/ml), with patients diagnosed with renal function abnormalities (1.59±1.07 ng/ml) and electrolyte imbalances (1.50±1.09 ng/ml) registering the second and third highest mean SDC. All sub-groups for the reason for request field were significantly ($p<0.05$) above the upper limit of the recommended target SDC range (0.9 ng/ml) (Table 3.9).

Table 3-9 – Mean SDC by reason for request (2008-2016; n=17,388)

Reason for request	Number of SDCs	Percent (%)	Mean SDC±SD (ng/ml)
Cardiac symptoms	**3,819**	**21.96**	**1.25±0.93**
Routine testing	**6,017**	**34.6**	**1.34±0.90**
Not recorded	**1,862**	**10.71**	**1.31±1.16**
Respiratory symptoms	1,439	8.28	1.15±0.85
Systemic disturbances	1,302	7.49	1.23±0.98
CNS disturbances	759	4.37	1.09±0.86
Digoxin toxicity	521	3	2.16±1.57
Gastro-intestinal symptoms	471	2.71	1.35±1.24
Circulatory symptoms	286	1.64	1.05±0.75
Renal abnormalities	283	1.63	1.59±1.07
Electrolyte imbalance	249	1.43	1.50±1.09
Haematological symptoms	163	0.94	1.36±0.91
Endocrine symptoms	122	0.7	1.05±0.67
Hepatic abnormalities	91	0.52	1.24±0.92
Ophthalmic symptoms	4	0.02	1.20±0.93

Hyperkalaemic patients registered the highest mean SDC (1.52±1.22 ng/ml) which although elevated as compared to the whole cohort of SDCs (1.31±1.01 ng/ml) in the retrospective study, was not statistically significant (p=0.076). There was no significant difference between SDCs from patients recorded as suffering from HF (1.32±0.88) or AF (1.27±0.8), both between the two sub-sets (p=0.219) and compared to the whole patient cohort (HF, p=0.749 and AF, p=0.113). Those patients recorded as having suffered a fall had a significantly lower SDC than the cohort mean (1.01±0.91 ng/ml, p<0.001). (Table 3.10).

Table 3-10 – Mean SDC and selected parameters (2008-2016; N=17,388; n=2,693)

Parameter	**Number of SDCs**	**Mean SDC±SD** (ng/ml)
Hyperkalaemia	**114**	**1.52±1.22**
Warfarin	256	1.38±0.95
Timing	117	1.37±0.90
Both HF and AF	43	1.33±1.12
HF only	**699**	**1.32±0.88**
AF only	**1,148**	**1.27±0.80**
Ischaemic Heart Disease	80	1.14±0.51
Diabetes Mellitus	88	1.06±0.67
Hypokalaemia	31	1.02±0.80
Falls	117	1.01±0.91

3.2.7 Serum potassium levels and SDCs

The number of correlated SDC and serum K^+ results extracted was 1,406, out of a total 1,677 SDC requests in 2017. The mean serum K^+ level recorded was 4.53 ±0.69 mEq/L (range 2.75 – 9.32, median 4.52, mode 4.17 mEq/L), within the reference range for serum K^+ of 3.6-5.2 mEq/L.[10] The mean SDC was 1.41±1.19 ng/ml (range <0.01 – 15.9, median 1.1, mode 0.9 ng/ml). No significant difference between serum K^+ levels for the SDC subset below the upper limit for the recommended target SDC range (0.9 ng/ml) and that above the target range was registered (p=0.103). Serum K^+ levels for those SDCs classified as potentially toxic (≥ 2.0 ng/ml) were significantly higher than those below the recommended target range upper limit (p=0.020) (Table 3.11).

Table 3-11 - Serum potassium and SDC ranges (2017; n=1,406)

	SDC ≤0.9 ng/ml	**SDC >0.9 ng/ml**	**SDC ≥2.0 ng/ml**
Number	563	843	270
Percentage (%)	40.04	59.96	19.20
Mean serum K^+±SD (mEq/L)	4.54±0.73	4.53±0.67	4.66±0.66

[10] Mayomedicallaboratories.com. Test ID: KCCL [Online]. Mayomedicallaboratories.com; 2018 [cited 2018 Jan 18]. Available from: https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/81390.

3.2.8 Estimated glomelular filtration rate and SDCs

The number of correlated SDC and eGFR results extracted was 1,439, out of a total 1,677 SDC requests in 2017. The mean eGFR recorded was 69.6 ±36.1 mL/min/1.73 m² (range 5 – 358, median 67, mode 60 mL/min/1.73 m²) classifying it as representative of stage 2 kidney disease with a mildly decreased eGFR.[11] The mean SDCs was 1.41±1.20 ng/ml (range <0.01 – 15.9, median 1.1, mode 0.9 ng/ml). A significant difference between eGFR results for the SDC subset below the upper limit for the recommended target SDC range (0.9 ng/ml) and that above the target range was observed ($p<0.001$). eGFR results for those SDCs classified as potentially toxic (≥2.0 ng/ml) were significantly lower than SDCs below the recommended target range upper limit ($p<0.001$) (Table 3.12).

Table 3-12 – Estimated glomerular filtration rate and SDC ranges (2017; n=1,439)

	SDC ≤0.9 ng/ml	**SDC >0.9 ng/ml**	**SDC ≥2.0 ng/ml**
Number	577	862	270
Percent (%)	40.10	59.9	18.80
Mean eGFR±SD (mL/min/1.73 m²)	73.84±35.21	66.76±36.43	64.39±34.23

[11] National Kidney Foundation (NKF). Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification [Online]. UK: NKF; 2016 [cited 2018 Jan 18]. Available from: http://www2.kidney.org/professionals/kdoqi/guidelines_ckd/p4_class_g1.htm.

3.3 Adherence to the clinically recommended target SDC

Out of the total 19,065 SDCs included in the retrospective analysis, 32% (n=6,103) were found to be within the target SDC range recommended by the guidelines (0.5-0.9 ng/ml) (Figure 3.7).

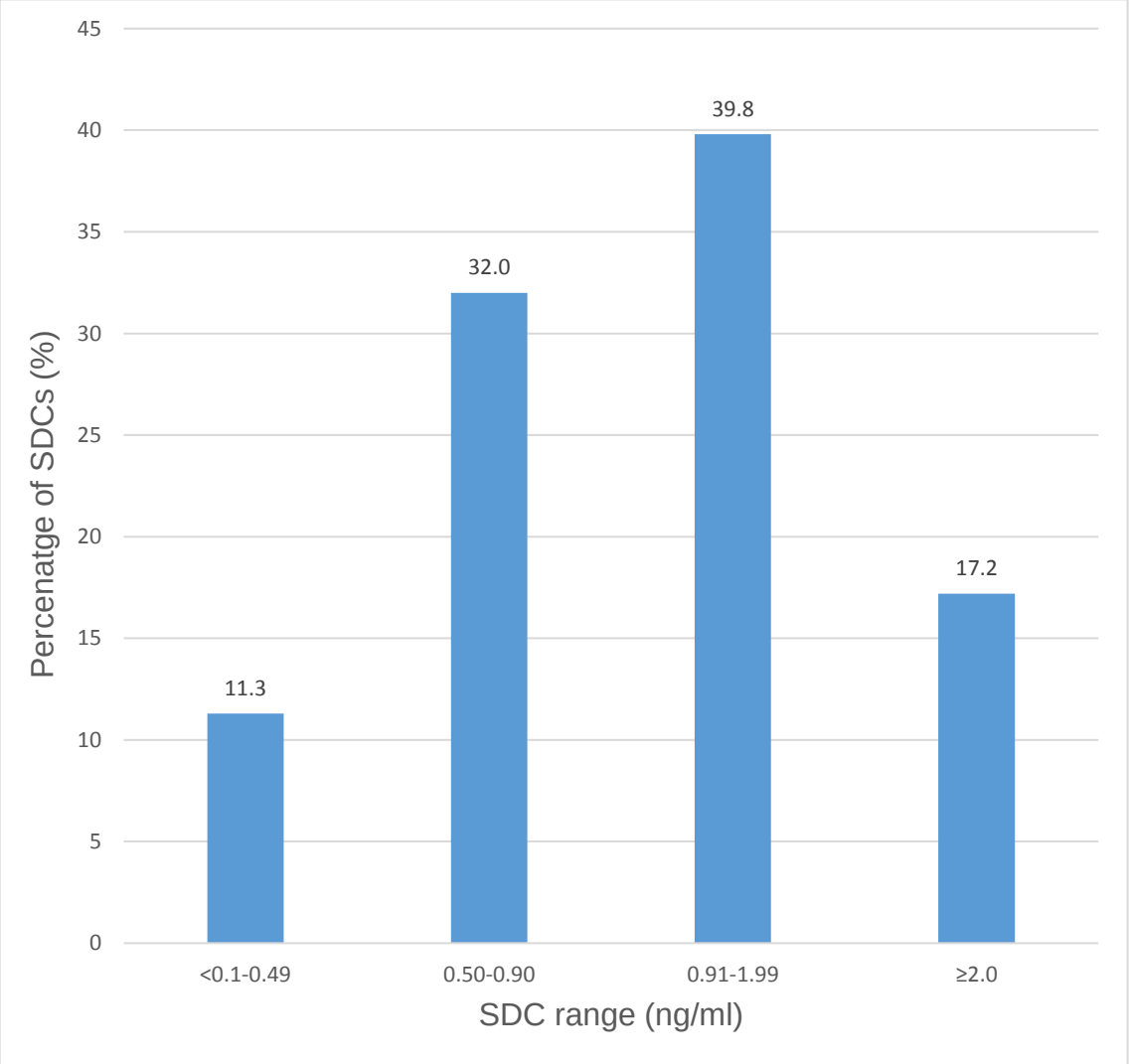

Figure 3-7 - Classification of SDCs by target therapeutic range (2008-2017; N=19,065)

Sixty-eight percent of the SDCs were out of range; 57% were >0.90 ng/ml. Out of these 57%, 17.2% were ≥2.0 ng/ml, the designated limit for potential serum digoxin toxicity (Figure 3.8).

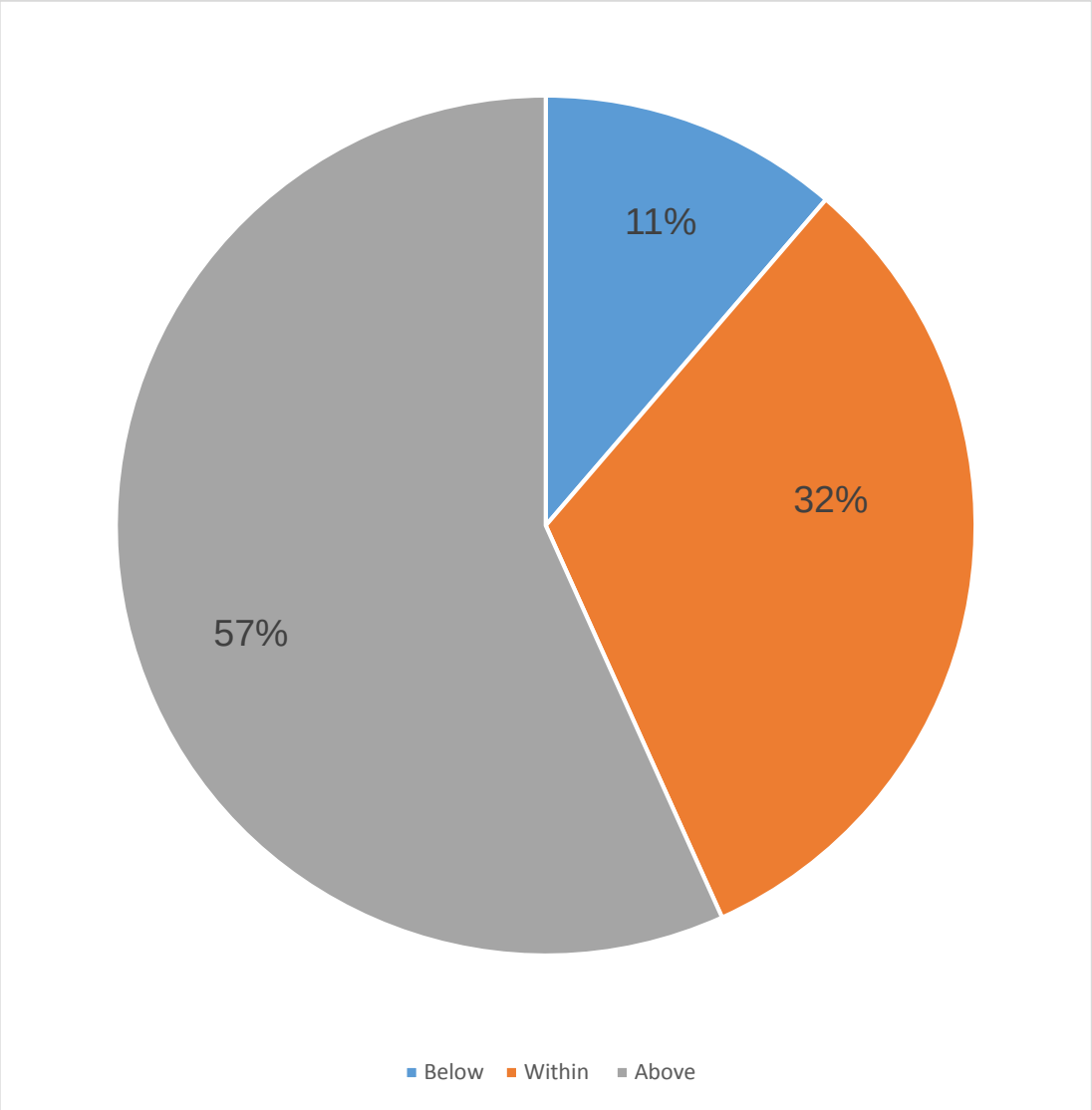

Figure 3-8 – Adherence to recommended target SDC range (2008-2017; N=19,065)

The mean sample SDC was 1.31±1.01 ng/ml (2008-2017; n=19,065) and was significantly higher than the target upper limit of 0.9 ng/ml (p<0.001). The hypothesis was tested for sub-groups of the sample, divided by gender, age and origin of request. All sub-groups recorded a mean SDC that was not compliant to the recommended SDC upper limit (Table 3.13).

Table 3-13 - Adherence of sub-groups to target SDC (2008-2017; N=19,605)

	Number of SDCs	Mean (ng/ml)	Mean SDC above upper limit of SDC target range	p value
Total	19,065	1.31	Yes	<0.001
Male	6,970	1.22		
Female	12,095	1.36		
Age (0-50)	257	1.06		0.019
Age (51-60)	770	1.26		<0.001
Age (61-70)	2,533	1.29		
Age (71-80)	6,372	1.31		
Age (>80)	9,133	1.33		
MDH	14,783	1.32		
RHKG	910	1.26		
HC	603	1.03		
RCH	629	1.28		
GGH	311	1.43		
Other	152	1.19		

Key: MDH – Mater Dei Hospital, RHKG – Rehabilitation Hospital Karin Grech, HC – Health Centre, RCH – Residential Care Home, GGH – Gozo General Hospital, Other – Mount Carmel Hospital, St. James Hospital, Sir Anthony Mamo Oncology Centre

A total of 3,282 SDCs were ≥2.0 ng/ml, the threshold for digoxin toxicity. In concordance with the trend exhibited by the whole cohort, the majority (88%) were recorded at MDH. The largest percentage of SDCs ≥2.0 ng/ml was recorded in 2011 (18.6%)(Table 3.14).

Table 3-14 - SDCs ≥ 2.0 ng/ml by year (n=3,282)

Year	Number of SDCs ≥ 2.0 ng/ml	% of SDCs ≥ 2.0 ng/ml (%)
2008	327	16.9
2009	264	14.7
2010	359	18.1
2011	**481**	**22.4**
2012	434	19.2
2013	269	14.2
2014	285	16.4
2015	278	15.1
2016	287	15.9
2017	298	17.8

The percentage of digoxin-treated female patients (73%, n=658), admitted to the A&E department at MDH with potentially toxic SDCs (≥2.0 ng/ml) was significantly higher compared to males ($p<0.001$). There was no significant difference in the mean SDCs collected from female (3.18±1.37 ng/ml) and male patients (3.04±1.38 ng/ml) for this sub-group of SDCs from the A&E department ($p=0.182$). Female patients in this sub-group of SDCs had a mean age of 81.0±8.3 years with male patients five years younger (76.4±11.0 years).

3.4 Requests for information at the Drug Information Unit

A total of 14,368 requests for information were processed at the DIU from 2002 to 2014, with 0.6% (n=91) queries concerning digoxin. The highest number of queries for digoxin was registered in 2012 (n=23), and the lowest in 2002 (n=2) (Table 3.15).

Table 3-15 - Queries for digoxin at the Drug Information Unit (2002-2014; N=14,368)

Year	Total number of queries	Number of queries for digoxin
2002	**226**	**2**
2003	480	5
2004	760	5
2005	836	3
2006	772	3
2007	758	3
2008	1,033	5
2009	1,563	5
2010	1,718	10
2011	1,873	12
2012	**2,001**	**23**
2013	1,471	6
2014	877	9
Total	**14,368**	**91**

3.4.1 Digoxin queries

The top three queries for digoxin, classified according to the reason for the request were administration 26% (n=24), interactions 19% (n=15) and dosage 15% (n=14) (Figure 3.9).

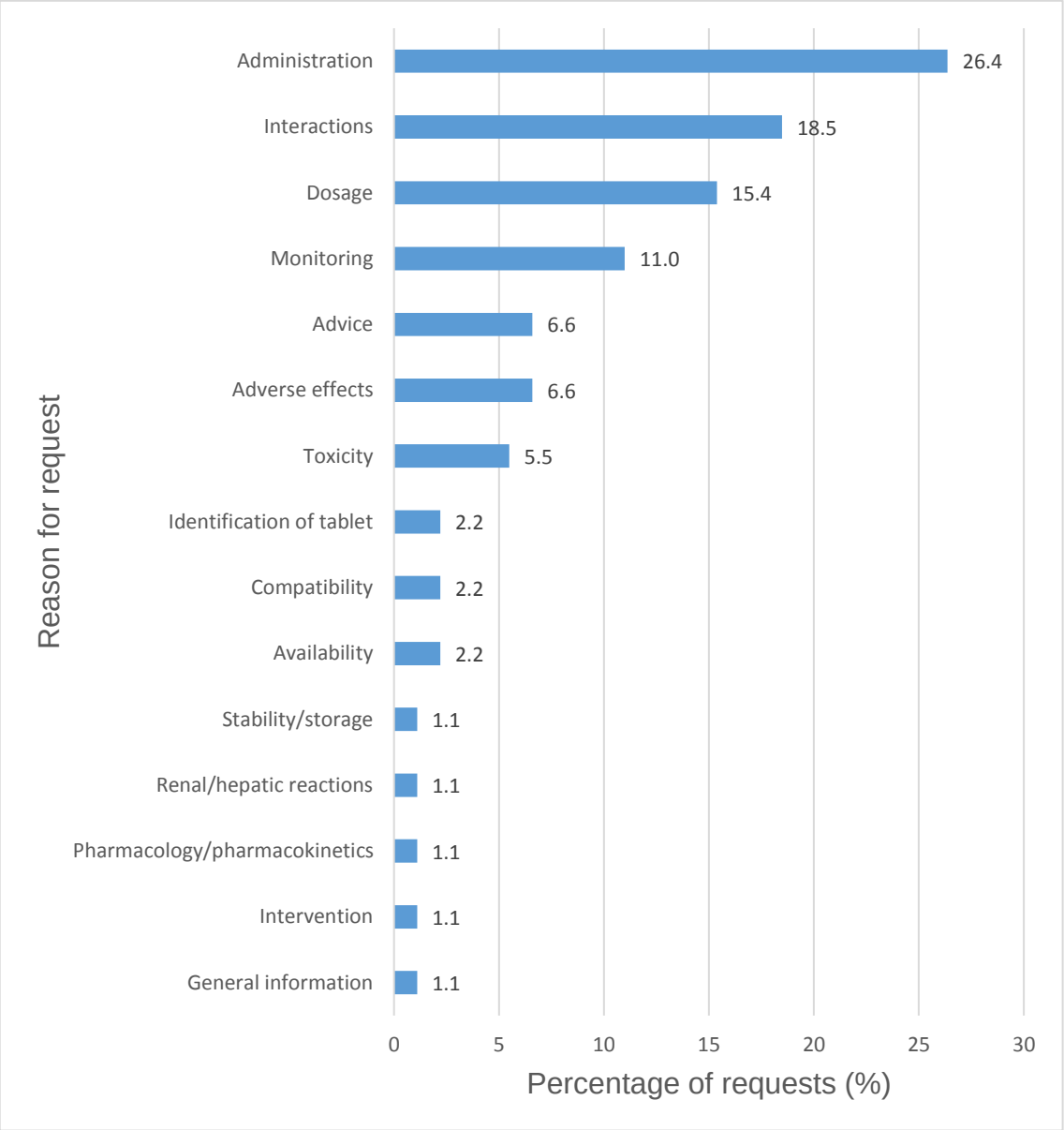

Figure 3-9 – Reason for requests for digoxin at the Drug Information Unit (2002-2014; N=91)

3.4.2 Status of enquiring party

The top three enquiring parties for requests to the DIU regarding digoxin were pharmacists 32% (n=29), nurses 22% (n=20) and physicians 22% (n=20). Twenty-two percent (n=20) of requests had no enquirer recorded (Figure 3.10).

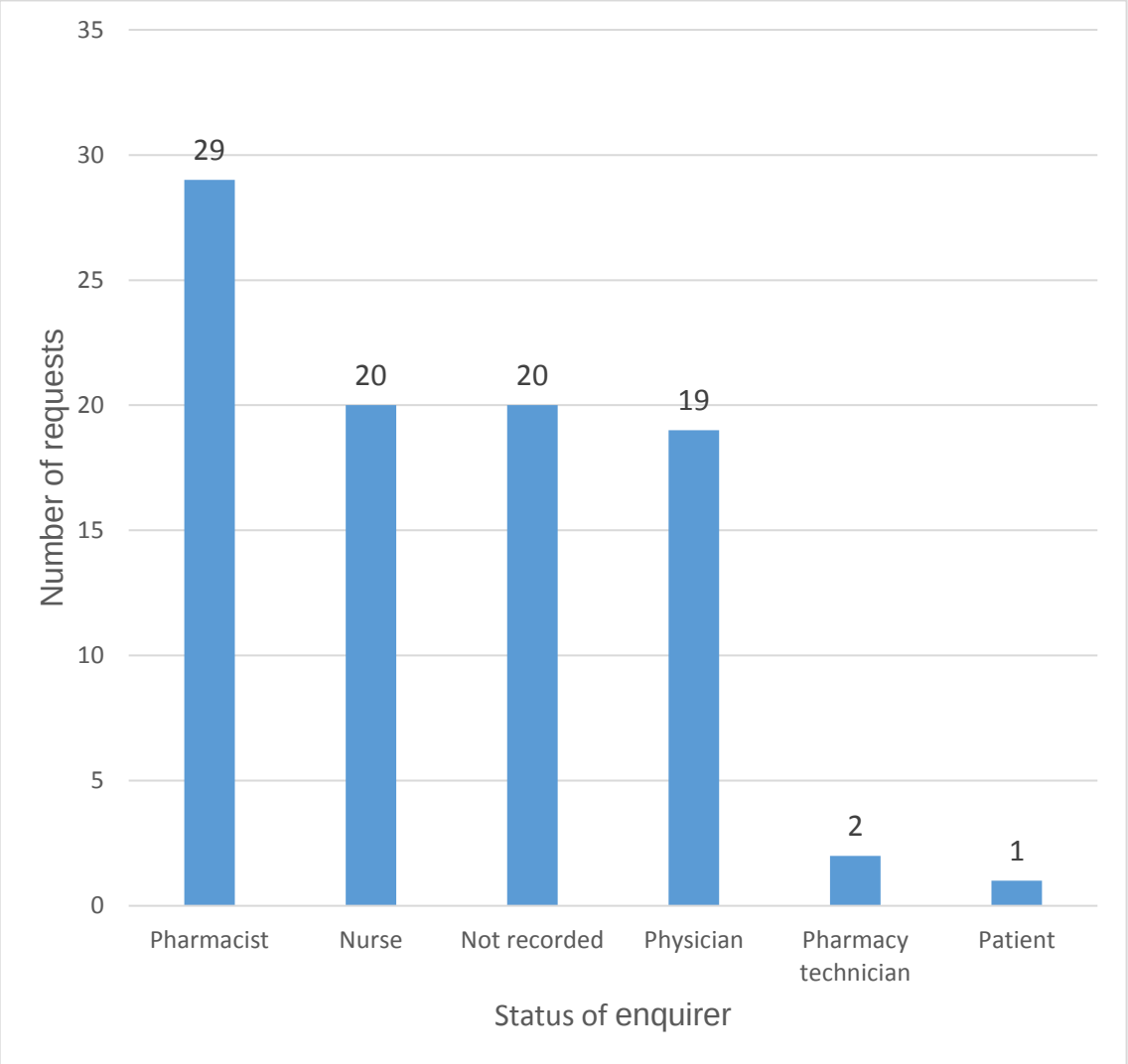

Figure 3-10 - Queries for digoxin at the Drug Information Unit by status of enquirer (2002-2014; N=91)

3.5 Practice points for digoxin for community pharmacists

Following review of the publications in Section 2.7, a table based on the four areas of major importance to digoxin therapy identified was compiled (Table 3.16). The areas of patient medication records, digoxin therapy, pharmaceutical care process and humanistic aspects were reviewed for aspects relevant to the context of a community pharmacy dispensing scenario for digoxin and further expanded into sub-divisions. Each sub-division was allocated an abridged check-list reference, a description of the process suggested and a rationale for inclusion of the process.

The practice areas and check-list points developed in Table 3.16 were formatted into a practice point sheet for use by for community pharmacists whilst dispensing digoxin (Figure 3.11). A booklet was produced for dissemination to community pharmacists (Appendix II).

Table 3-16 - Expansion of areas identified for practice points

Patient medication records	Check-list	Process	Rationale
Medical history	Indication for digoxin, comorbidities and medication	Examine patient records and establish current medical situation to enable a complete clinical picture. Ideally, collate medical information into one easily accessible electronic source.	Patients possess multiple paper-based records and treatment schedules from various state entities that are complex to assimilate in their original form; digoxin-treated patients generally have a number of medications and a lengthy medical history.
Documentation status	Level of completeness and updating	Establish whether all vital records regarding medical history are present and all necessary pharmaceutical care permits and documentation are in order and valid. All processes carried out by the pharmacy team should be added to a patient's profile.	Complete and updated medical records are essential for a holistic clinical evaluation. Validity of all pharmaceutical permits is vital to ensure continuity of care and patient wellbeing.

Digoxin therapy	Check-list	Process	Rationale
Digoxin dose	Dose and adverse effects	Carry out a brief review of digoxin dosage and adverse effects at each prescription cycle. Query the patient on the correctness of the daily dose being taken (confusion in the elderly may lead to a higher dose being mistakenly ingested). Sensations of weakness, dizziness and unexplained fainting and falls are to queried further.	Dosage issues can be resolved using the Digoxin Calc© application, or a dosing nomogram, rather than relying on empirical methods. The manifestation of adverse effects might be subtle and due to a recent course of antibiotics (erythromycin) or the addition of proton-pump inhibitor (omeprazole) to the therapeutic regimen.
Monitoring	SDC, K+, eGFR, BP and HR[1]	Examine records for SDC level and K+ testing, together with an evaluation of renal function in those >70 years. Testing should be carried out biannually.	Weight evaluation is a concern in the elderly due to a reduced lean body mass. Monitor weight, BP, HGT and in HF patients, lower limb oedema and pulmonary congestion.
Medicines use review (MUR)	Date of last therapeutic overview	Conduct a biannual MUR to establish and eliminate drug-drug interactions, dosing issues and clinical concerns.	SDCs are impacted by drugs in common use in HF and AF, with particular reference to amiodarone and verapamil. The clinical condition of the patient is an essential component of the MUR and must be considered when evaluating digoxin therapy.

[1]BP-Blood Pressure; eGFR-estimated Glomerular Filtration Rate; HR-Heart Rate; QOL-Quality of Life; SDC-Serum Digoxin Concentration

Pharmaceutical care process	Check-list	Process	Rationale
Health care providers	Identity of GP and consultant physician	Establish a contact points for the patient's primary care supervisor and tertiary care consultant.	Modifications in therapy and/or issues relating to pharmaceutical care plans may need to be discussed and clinicians informed of a change in the patient's condition. It might not be possible to wait until the next scheduled appointment.
Information exchange	Need to update the above	Establish whether the patient has any issues or changes in clinical status that require the other members of the health care team to be informed.	Information shared across the whole team improves outcomes. Consultant physician at Mater Dei could be updated bi-monthly via email regarding BP, HGT, weight and general condition. Updates following outpatient visits could be emailed to the patient's POYC pharmacy.
Care transitions	Need for medicines reconciliation	Conduct a thorough reconciliation of pharmaceutical therapies following any transition from one care setting to another. This should be done in the presence of the patient or carer to ensure complete awareness of dosing schedules.	Medicines reconciliation is vital as polypharmacy is prevalent in patients on digoxin. Confusion is common amongst patients who have just been discharged or admitted to a new setting (long term care facility). Amendments to therapy are sometimes not recorded across multiple care settings leading to patient confusion and inadequate and potentially dangerous therapeutic scenarios. Digoxin is particularly susceptible in view of its narrow therapeutic index and the emergence of toxicity.

Humanistic aspect	Check-list	Process	Rationale
Awareness of therapy	Knowledge of adverse effects and aim of therapy	Evaluate patient education regarding the reason for taking digoxin and the knowledge of the common side-effects of the drug.	Critical, self-reporting of clinical condition is the primary method of detection for digoxin toxicity; falls, gastro-intestinal disturbances, and fatigue should be reported for review.
Social status and condition	Quality of life (QOL) and general level of satisfaction	Is the patient not only experiencing optimal pharmacotherapy, but also functioning on a satisfactory social and humanistic level? Communication on a personal level with the patients and empathy is an important tool in the pharmaceutical care process.	Quality of life is a major factor in digoxin therapy; adverse effects may be reducing a patient's Quality of Life (QOL); conversely digoxin may improve QOL without a significant change in physiological parameters.
Domiciliary care-giver	Awareness of adverse effects and compliance	Companions or family members should be instructed on the common manifestations of digoxin toxicity, compliance and monitoring.	Patients may be weak or senile and may not be in a position to comply with their therapy and self-monitor for adverse effects and changes in clinical status.

Digoxin practice points

Community pharmacist dispensing check list

Patient records	Query
Medical history	☐ Indication for digoxin, comorbidities and medication
Documentation status	☐ Level of completeness and updating

Digoxin therapy	Query
Dose and adverse effects	☐ Manifestation of adverse effects
Monitoring of parameters	☐ SDC[1], serum K^+, eGFR[1], BP[1] and HR[1]
Medicines use review (MUR)	☐ Date of last therapeutic overview

Pharmaceutical care process	Query
Health care providers	☐ Identity of primary care GP and consultant physician
Information exchange	☐ Need to update the above on current condition
Care transitions	☐ Need for medicines reconciliation

Humanistic aspect	Query
Awareness of therapy	☐ Knowledge of adverse effects and aim of therapy
Social status and condition	☐ QOL[1] and general level of satisfaction
Domiciliary care-giver	☐ Awareness of adverse effects and compliance

[1] BP-Blood Pressure; eGFR-estimated Glomerular Filtration Rate; HR-Heart Rate; QOL-Quality of Life; SDC-Serum Digoxin Concentration

Figure 3-11 - Digoxin practice points

3.6 Dissemination of results

A poster titled 'Retrospective analysis of serum digoxin concentrations at Mater Dei Hospital' was presented at the Maltese Cardiac Society Conference held at MDH in 20-23rd October 2016 (Appendix III).

A poster titled 'Serum Digoxin Concentrations: Clinical Signals' was presented at the 77th FIP World Congress of Pharmacy and Pharmaceutical Sciences held in Seoul, South Korea, 10–14th September 2017 (Appendix III).

Chapter 4: Discussion

The research established the number of digoxin-treated patients in Malta, conducted a retrospective analysis of SDC tests performed at MDH over a ten-year period (2008-2017), determined a mean SDC value for the period studied and analysed requests processed at the Drug Information Unit at MDH over a fourteen-year period (2002-2014). A set of practice points intended as an aid to community pharmacists when dispensing digoxin was developed and validated.

The main findings of the research were:

(i) In January 2017, 2,059 patients were being treated with digoxin in Malta, with 80% of these patients over the age of 70 years.

(ii) The mean SDC for the ten-year period assessed was 1.31±1.01 ng/ml. A mean of 980±80 patients were tested annually.

(iii) The mean SDC recorded was significantly higher than the upper limit (0.9 ng/ml) recommended by current guidelines ($p<0.001$). The sub-group of patients recording SDCs ≥2.0 ng/ml exhibited significantly elevated serum K^+ (4.66±0.66 mEq/L)($p=0.020$) and significantly reduced renal function (eGFR 64.39±34.23 mL/min/1.73 m²)($p<0.001$).

(iv) The DIU did not process a large number of requests regarding digoxin in the period, 91 (0.6%) out of a total of 14,368.

4.1 Retrospective analysis of SDCs at Mater Dei Hospital

Evaluation of the results of the retrospective analysis of SDCs at MDH was undertaken from two main perspectives. The first was the analysis of SDC results in the context of frequency of SDC testing, demographic characteristics of patients and parameters impacting SDC levels, namely gender, age, origin of SDC request, serum K^+ and renal function. The importance of periodic SDC and renal function monitoring is discussed in view of the findings of the study indicating an elevated mean SDC and a direct correlation between reduced renal function and elevated SDCs. The second perspective adopted for analysis was that of assessing the SDC results in the light of recommended target SDC ranges by competent entities (Table 1.2), with particular emphasis on the necessity of maintaining SDCs below the upper limit of 0.9 ng/ml recommended by guidelines and referenced in the literature.

The study reported a mean of 980±80 patients having a SDC requested each year, which when aligned with the number of patients on digoxin in January 2017 (2,059), represents 48% of the digoxin-treated patient population in Malta being tested annually. The proportion of patients being tested appears to be elevated in the absence of a protocol mandating regular SDC monitoring. Two reasons may be proposed for this observation. Firstly, SDCs do not form part of a standard protocol or practice guideline for digoxin-treated patients, hence SDC levels are drawn whenever a digoxin-treated patient is hospitalised; 84% of SDCs analysed in the research originated from MDH. This may result in SDCs being requested in the absence of signs of overt toxicity or classic manifestations of digoxin-induced adverse effects. The care professionals entrusted with making the request might not be referring to the DIU or alternative sources of specialised

pharmacotherapeutic information on digoxin therapy and taking the SDC request option as a first choice. Secondly, patients on digoxin in Malta may be over-digitalised (mean cohort SDC 1.31±1.01 ng/ml). Chronically high digoxin dosing may lead to long-term poisoning without ever recording SDCs >2.0 ng/ml (Pincus, 2016). The mean dose of digoxin for patients in Malta (estimated at 0.13mg daily) appears to be elevated in comparison to their mean age (78±11 years).

Current guidelines do not all consider SDCs as an essential metric for the efficacy of digoxin, or of therapeutic follow-up or pharmaceutical care, with the ESC the only entity to recommend routine monitoring. The HFSA and the DIU suggest that SDCs be collected in specific instances (Table 1.3) (Lindenfeld *et al.*, 2010; Yancy *et al.*, 2013; Dickstein *et al.*, 2016). This appears to be contrary to the literature that demonstrates that consistent SDC review enables tighter serum level control and optimises treatment, whilst minimising the negative effects of digoxin (Shakib, 2005; Refat Ragab *et al*., 2012; Benlmouden and Billaud, 2016).

Gender distribution for the patients included in the study exhibited a significant bias towards females (65%). Compared to their male counterparts (1.22±0.98 ng/ml), female subjects (1.36±1.02 ng/ml), exhibited a significantly higher mean SDC ($p<0.001$). This variation could present via two mechanisms. It may be representative of the gender distribution for the Maltese population. Support for this hypothesis is provided by the longer life expectancy for women compared to men, which could result in a greater proportion of women being diagnosed with HF and AF. Alternatively, it may indicate that females are more susceptible to the adverse effects of treatment with cardiac glycosides

and consequently more SDCs are requested for the female cohort. The physiological rationale for a potential gender bias in digoxin kinetics and pharmacological action has its basis in the lipophilic properties of digoxin and its dependency for elimination from the body on the kidneys (Meibohm *et al.*, 2002; Sica *et al.*, 2005). Women possess a higher percentage of body fat and conversely a lower muscle mass and lean body weight. Female heart failure patients demonstrate a tendency to be overweight, diabetic and suffer from multiple co-morbidities (Kalon *et al.*, 1993; Adams *et al.*, 2005).

The gender bias reported in the retrospective analysis of SDCs at MDH is in concordance with an initial post-hoc analysis of the DIG trial data. In two consecutive studies, Rathore *et al* (2002, 2003) demonstrated that women treated with digoxin exhibited greater all-cause mortality than men, in patient cohorts with HF and reduced left ventricular function (Rathore *et al.*, 2002; Rathore *et al.*, 2003). In contrast, Freeman *et al* (2013) refuted this hypothesis in a retrospective analysis of a Kaiser Permanente health care database in the US (Freeman *et al.*, 2013). This paper did not confirm the association between gender and an increased risk of death and posited that digoxin-treated patients were exposed to a higher risk of death compared to the control group (not on digoxin). The same conclusion was reported by Adams *et al* (2005). In their work, another re-evaluation of the DIG trial data, no difference in mortality between sexes was observed, with digoxin exerting a beneficial effect on morbidity at therapeutic levels between 0.5 and 0.9 ng/ml (Adams *et al.*, 2005). Domanski *et al* (2005) in a post-hoc study of SOLVD trial data, again conclude that digoxin use in HF exhibits no gender bias in its effect on patient mortality (The SOLVD Investigators, 1992; Domanski *et al.*, 2005). This is further upheld by Ahmed *et al* (2006, 2008) in two separate papers, in which the researchers demonstrate the positive

effect of digoxin on mortality in HF patients, without there being any significant differences between sub-groups divided by gender (Ahmed *et al.*, 2006, 2008). Flory *et al* (2012) disagree with Rathore, with a relatively large cohort of just over 20,000 digoxin-treated patients analysed. No association was observed between female sex and an increase in mortality due to digoxin treatment, and this work further appears to support the assumption that gender has no relationship to the effect of digoxin (Flory *et al.*, 2012).

The mean age of the patient cohort in the study was 78±11 years. This was within expected parameters given that HF and AF predominate in patients from 75 years upwards (Bui *et al.*, 2008; Mozaffarian *et al.*, 2015). The age range distribution curve was skewed to the right, with 80% of the cohort over the age of 70, confirming the high concentration of patients above the mean. Mean SDCs increased in proportion to age with patients >50 years recording significantly higher SDC means than those <50 years. Renal function in patients >50 years (69.20±35.50 mL/min/173m^2) was significantly reduced compared to those <50 years (164.67±54.13 mL/min/173m^2, $p<0.001$), confirming that renal function declines with increasing age leading to reduced elimination of digoxin and elevated SDCs (Lubran, 1995; Vidal *et al.*, 2005; Pawlosky *et al.*, 2013). The age distribution exhibited by the patients included in the retrospective analysis of SDCs, indicates that 6% of Maltese over the age of 80 are potentially being treated with digoxin. This appears to be a disproportionally large number in the context of the incidence of HF and AF (8-10% >80 years) (Bui *et al.*, 2011; Roger, 2013). A re-assessment of digoxin prescription volumes and indication for prescribing, is warranted to verify the trends exhibited in prescribing. These trends, if in concordance to issued guidelines and practice in other countries, should indicate a consistent decline in the number of prescriptions

issued. As an example, the number of prescriptions for digoxin in the USA declined from 17,830,764 to 5,860,768, in the period 2004-2014.[12]

The majority of the SDC requests emanated from Mater Dei Hospital, comprising 84% of the total, with those from the A&E department constituting 43% of the SDCs from MDH. See *et al* (2014) reviewed the subject of emergency department admissions for elevated serum digoxin levels in the US and concluded that the incidence of digoxin toxicity was not on the decline and had remained constant over the period studied, (2005-2010) (See *et al.*, 2014). The researchers suggested that SDC monitoring should be further refined to enable improved therapeutic control and not be restricted to suspected incidents of digoxin toxicity. The following observations can be made upon comparison of the results from the retrospective study of SDCs at MDH to the paper by See *et al* (2014): (i) in a local context, one cannot draw comparisons to data prior to 2008, as none is available. This highlights the need for the ongoing collection and collation of clinical and physiological markers to enable the maintenance of an updated epidemiological evidence base, (ii) the rate of admission for female patients to the A&E in the US was twice that of males. The retrospective study reported a ratio of almost 3:1 with 74% of patients with an SDC $\geq$ 2.0 ng/ml being female, (iii) 95% of visits for digoxin toxicity reported a level $\geq$ 2.0 ng/ml in the paper by *See et al* (2014). Levels higher than 2.0 ng/ml constituted 13% of all SDC requests emanating from the A&E department in Malta. This could be due to two possible factors. Firstly, local digoxin-treated patients may exhibit a lower incidence

[12] Agency for Health Care Research and Quality (AHCRQ). Medical Expenditure Panel Survey [Online]. USA: AHCRQ; 2017 [cited 2018 Jan 18] Available from: https://meps.ahrq.gov/mepsweb/.

of toxicity. This rationale could be refuted by the main finding of the retrospective analysis - the mean SDC for the digoxin-treated population was reported as 1.31±1.01 ng/ml. A second hypothesis may imply that a percentage of the requests referred from the A&E department are routine or for the purpose of differential diagnosis and not stimulated by overt symptoms of digoxin toxicity. Support for this second hypothesis is provided by the mean SDC for serum digoxin level tests requested from the A&E department (1.17±1.01 ng/ml), which was significantly lower than the cohort mean (1.31±1.01 ng/ml, $p<0.001$). Based on the rationale that those patients admitted to the A&E department would be manifesting symptoms of overt digoxin toxicity to necessitate SDC testing, the converse would have been an expected finding. This may be explained if one reasons that the trigger for an SDC request at the A&E is the presence of digoxin on a patient's treatment sheet, and not a clinical symptom. The manifestations of digoxin toxicity are generic and non-specific and can be associated with multiple conditions, which could lead to the utilisation of the SDC as a tool in the differential diagnosis of a patient's condition. In this context, caution must be exercised as SDC levels considered to be toxic do not necessarily lead to manifest toxicity. The opposite situation may present, in which certain patients may exhibit symptoms of overt toxicity, such as nausea, blurred vision and dizziness, at levels commonly assumed to be safe. (Williamson, 1998; Goldberger and Goldberger, 2012; Benlmouden and Billaud, 2016).

A review of TDM procedures at Christchurch Hospital, New Zealand, revealed that in around half of the SDC requests, the test was performed with no clear indication.[13] Tatlistu *et al* in Turkey, demonstrated that 66 patients out of a total of 99 studied were being prescribed digoxin inappropriately (Tatlisu *et al.*, 2015). A similar observation was recorded by Turkish researchers Biteker *et al* (2016), in a sub-analysis of the ReAl-life Multicentre Survey Evaluating Stroke Prevention Strategies study (RAMSES), with almost 60% of patients on digoxin receiving the drug for an inappropriate clinical indication (Başaran *et al.*, 2016; Biteker *et al.*, 2016). In the event that patients who have been prescribed digoxin inappropriately are identified, caution should be exercised. The advantages and disadvantages of discontinuing therapy should be evaluated prior to suggesting modifications to a specific therapeutic approach. Withdrawal of digoxin therapy has been proven to result in a deterioration of patients' condition; in certain situations maintenance of clinical stability is preferable over withdrawal of the drug from a patient's treatment regimen (Packer *et al.*, 1993; Ahmed *et al.*, 2007).

The preceding observations regarding the appropriateness of SDC requests and the indication for digoxin therapy are not generalisable to the Maltese population of digoxin-treated patients, however they do stimulate the necessity for an exhaustive evaluation of the Maltese patient cohort. A great proportion (81% >70 years) of this patient cohort are elderly, and potentially have been on digoxin for an extended period of time without periodic review. In addition, local patient clinical histories are not collated electronically

[13] Canterbury District Health Board. Bulletin [Online]. New Zealand: Canterbury District Health Board; 2002 [cited 2018 Jan 18] Available from: http://www.druginformation.co.nz/Bulletins/Digoxin.pdf.

and are not recorded in a consistent manner across care settings. The lack of an indication for digoxin within the data reviewed for the retrospective study of SDCs did not allow an analysis from this aspect and this point should be included in a patient data collection form for a potential prospective study.

In the context of clinical practice, SDCs cannot be considered to provide a clear picture in the absence of accompanying serum potassium and renal function values, hence random testing does not lead to appropriate treatment modifications (Orrico *et al*, 2011). Presently, patients in Malta do not undergo a systematic periodic review of digoxin therapy and SDCs, serum K^+ and renal function tests are not consistently recorded. Routine SDC, serum K^+ and renal function monitoring is a necessary aspect of a holistic digoxin treatment algorithm for patients in Malta. The importance of this last statement is reinforced by the results of the retrospective study. Serum K^+ levels in patients recording levels ≥2.0 ng/ml (4.66±0.66 mEq/L) were significantly higher than those within range (4.53±0.69 mEq/L, p=0.020). No significant difference was demonstrated between serum K^+ levels for SDCs >0.9 ng/ml (4.54±0.73 mEq/L) and those >0.9 ng/ml (4.53±0.67 mEq/L, p=0.829). The relevance of these results must be evaluated in the context of the following: (i) serum K^+ may be below or above a patient's baseline level in cases of digoxin toxicity, depending whether the toxicity is acute or chronic in aetiology, (ii) serum K^+ levels within the recommended reference range of 3.6-5.2 mEq/L may still precipitate variations in SDC levels (SDCs >2.0 ng/ml had a mean serum K^+ of 4.66±0.66 mEq/L) and (iii) serum K^+ test results at the Pathology Laboratory may vary in accuracy depending on the location of sample extraction. Serum K^+ samples are thermosensitive and haemolyse if not transported under the required conditions.

Patients recording SDCs above the recommended 0.9 ng/ml upper limit for the therapeutic range for digoxin exhibited a significantly decreased level of renal function (66.76±36.42 mL/min/173m^2) compared to those patients with SDCs <0.9 ng/ml (73.84±35.21 mL/min/173m^2, p<0.001). This can be construed as an expected finding as renal function follows a linear deterioration with age and 81% of patient cohort were over the age of 70 (Lubran, 1995; Delanaye *et al.*, 2012). The whole cohort of SDCs cross-matched with simultaneous eGFR tests registered a mean eGFR of 69.6±36.1 mL/min/173m^2. Referring to a nomogram developed by Bauman *et al* and Di Domenico *et al* (Bauman *et al.*, 2006; DiDomenico *et al.*, 2014), patients would need to record a creatine clearance over 40mL/min to justify a dose of 0.125mg digoxin daily. Hence the mean eGFR reported for the patient cohort hypothetically justifies the use of a digoxin dose of 0.125mg daily (the present study reports a mean daily digoxin dose of 0.13mg daily). A caveat to this previous observation is that data obtained for the dose distribution for digoxin was not linked to patient age and there was no possibility of determining the dose distribution according to age group. Patients recording a potentially toxic SDC ≥2.0 ng/ml exhibited a significantly lower eGFR (64.38±34.23 mL/min/173m^2) than those below the recommended upper SDC limit of 0.9 ng/ml (73.84±35.21 mL/min/173m^2, p<0.001). The use of digoxin in AF may require higher doses than considered ordinarily safe, and this may have contributed to the elevated mean SDC (Pastori *et al.*, 2015; Virgadamo *et al.*, 2015).

The conclusions drawn from the interlinked SDC and serum K^+ and eGFR data reinforce the principle that the execution of an optimal pharmacotherapeutic strategy necessitates the systematic collation of physiological parameters and clinical condition. The lack of

an accessible centralised electronic data repository for patient medical records in Malta prevents the transfer of information across the whole spectrum of treatment settings which a patient experiences in the course of access to health care services. This may be the cause of diminished intervention efficiency or care failure for the digoxin-treated patient in Malta, as transitions between care settings increase in frequency in the age groups in which digoxin use is predominant (Gleason *et al.*, 2010; Kwan *et al.*, 2013). Routine SDC, serum K^+ and eGFR monitoring on a biannual basis has been recommended in practice points drafted as part of the research (Figure 3.12).

Marshall (1992) carried out a small-scale local study in 1992, with an early-generation computer algorithm utilised to predict serum digoxin levels and dosing regimens. The setting was a residential home for the elderly with a sample size of 49 patients. The mean SDC for the sample in this study was established as 1.07 ng/ml, which indicates close control of serum digoxin levels in an elderly population cohort. This appears to be the only work done locally with respect to TDM and digoxin (Marshall, 1992).

Studies have been carried out in Malta to assess the adherence of HF patients to therapeutic recommendations based on adopted guidelines (Schembri *et al*, 2004; Anastasi, 2017). In the earlier study, out of a sample of 97 patients, 95 were taking a diuretic, 72 were on an ACEi or an ARB, 12 were taking spironolactone, 9 were on a beta-blocker, and 24 were taking digoxin (Schembri *et al.*, 2004). Two significant observations may be made: (i) a low percentage of patients were prescribed beta-blockers despite the guidelines recommending beta-blockers as first-line therapy in HF and (ii) a quarter of the HF patients were on digoxin despite not having an optimal level of first and

second line therapies. Anastasi (2017) reports 10 patients on digoxin out of a study cohort of 50; the study confirms the low level of adherence to beta-blocker usage reported by Schembri *et al* (2004) 13 years earlier and in addition a low adherence to digoxin therapy (Anastasi, 2017).

4.2 Classification of SDCs within recommended target range

The significance of the mean SDC of 1.31±1.01 ng/ml reported for the patient cohort assessed in the retrospective analysis is a clinical signal that should not be ignored. The importance of this mean SDC is amplified when one considers that 68% of the 19,065 SDCs included in the analysis were not within the clinically recommended SDC range of 0.5-0.9 ng/ml. Out of this number, 57 % were found to have levels ≥0.9 ng/ml, with 17% ≥2.0 ng/ml, whilst 11% of SDCs were reported below the minimum level recommended to achieve therapeutic efficacy. These findings provide an initial basis for the epidemiological analysis of SDC levels for digoxin-treated patients in Malta.

The implications of the large number of SDCs which were not within the recommended therapeutic range can be divided into two categories. The first are the consequences of over-dosing, which can lead to chronic or acute digoxin toxicity. A SDC ≥2.0 ng/ml does not necessarily indicate overt toxicity, but exposes patients to a greater predisposition to the emergence of adverse effects (Rogers *et al.*, 2010; Jelliffe *et al.*, 2014a). The second group are the implications concerning those patients who are sub-therapeutic with respect to serum digoxin level; in these situations the consequences of inadequately treating the underlying condition are no doubt just as serious in nature and effect (Lim *et al.*, 2015).

The deviations observed from the recommended SDC target range may be an indication of inadequate follow-up, on the part of the patient or the care-provider; an evaluation of clinical condition is necessary, as certain individuals may experience a therapeutic effect with digoxin at levels not normally associated with clinical efficacy, especially with respect to the neurohormonal effects of the drug (Terra *et al.*, 1999; Li *et al.*, 2014; Perri *et al.*, 2015).

The controversy over the use of digoxin revolves around its clinical utility and a lack of consensus on a specific SDC range to target in clinical practice. Baumann *et al*, Goldberger and Goldberger, and Gheorghiade have highlighted the beneficial properties of digoxin (Gheorghiade *et al.*, 2004; Bauman *et al.*, 2006; Gheorghiade *et al*., 2006; Goldberger and Goldberger, 2012). The common rationale drawn from these works is that SDCs are maintained within a narrow and low therapeutic range (0.5-0.9 ng/ml) in an effort to emphasise the beneficial effects of the drug, whilst mitigating the possibility of adverse reactions.

In this context of SDCs and patient mortality, reference is once again made to the two studies published by Rathore *et al* in 2002 and 2003. The first, apart from raising a controversial issue by postulating that digoxin was gender-specific in its propensity for adverse effects and mortality, reported median SDC figures for both genders within the recommended therapeutic range (0.6-0.9 ng/ml) (Rathore *et al*., 2002). The second study by Rathore *et al* provided a solid argument for the strict reduction of serum digoxin levels. It demonstrated a 6.3% reduction in mortality in digoxin-treated patients with SDCs below 0.8 ng/ml, whilst subjects with serum digoxin levels above 1.2 ng/ml were

observed to be at a higher risk of death. Patients with SDCs between 0.8 and 1.2 ng/ml derived no benefit from the drug, with no decrease in all-cause mortality (Rathore *et al.*, 2003). A prospective study of digoxin use in AF in Sweden in 2007 demonstrated that patients on long-term digoxin therapy were at a higher risk of death, compared to the control group (Hallberg *et al.*, 2007).

Studies published in recent years have further demonstrated the need for a re-evaluation of the role of digoxin in contemporary medicine and a readjustment to protocols with respect to SDC target ranges and monitoring procedures. Freeman *et al* (2013) examined the records of a large cohort of patients with incident HF within a county in the US and established that patients on digoxin exhibited an increased risk of mortality. SDC levels did not vary significantly between the patients who died, and those who survived. Mean SDCs recorded were 1.02 ng/ml, at the borderline of the threshold currently defined as the upper limit (1.0 ng/ml). Out of the 2,891 patients with incident HF included in the study, 18% were on digoxin (Freeman *et al.*, 2013).

Whitbeck *et al* (2013) carried out a sub-analysis of the AF Follow-Up Investigation of Rhythm Management (AFFIRM) study; the study compared patients on rate or rhythm control strategies for AF. AF patients on digoxin, 69.4% or 2,816 subjects, were found to have an increased risk of all-cause mortality. The AFFIRM study protocol dictated the maintenance of high serum digoxin levels (>1.0 ng/ml); this approach increased the potential for toxicity and adverse effects associated with digoxin. Monitoring and dosing data are not available for this study, hence no mean SDC for the patient cohort was reported (Whitbeck *et al.*, 2013). The higher mortality statistics for patients on digoxin

must be viewed in the context that study protocols necessitating SDCs above 1.0 ng.ml will have an inherent bias towards an increased patient mortality with digoxin. The negative effect of digoxin use on patient survival is refuted by Mulder *et al* (2014) and Rodriguez-Mañero *et al* (2014); both these studies did not find an association between digoxin use and an increase in patient mortality (Mulder *et al.*, 2014; Rodríguez-Mañero *et al.*, 2014).

The two largest meta-analyses for digoxin were published in 2015 and both concluded that digoxin must be utilised with caution. Ziff *et al* (2015), considered 621,000 subjects in the studies reviewed and confirmed the main finding of the DIG trial in 1997, that is, the neutral effect of digoxin on mortality with a concomitant reduction in patient hospitalisation (The Digitalis Investigation Group, 1997; Ziff *et al.*, 2015). Vamos *et al* (2015), examined studies covering over 300,000 patients and concluded that "digoxin use was associated with an increased relative risk of all-cause mortality". The risk was greater for AF patients (29%) compared to HF patients (14%). A hypothetical explanation for this variation could be that, as referred to earlier, digoxin use for rate control in AF requires higher dosing regimens than in HF. In addition, the effect of digoxin on haemodynamics and the sympathetic nervous system, whilst beneficial in HF, could contribute to the increased risk of pro-arrhythmias and tachycardia observed in AF patients. The paper concludes by stressing the importance of strict SDC control, in both HF and AF patients (Vamos *et al.*, 2015).

Proceedings of the American College of Cardiology conference in Washington, US in March 2017, have further strengthened the body of evidence for consistent monitoring of

SDC levels and maintaining them below a defined serum concentration.[14] Results from a sub-analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) were presented (Granger *et al.*, 2011). A total of 17,897 patients were enrolled in the ARISTOTLE trial, of whom 5,824 (32.5%) were taking digoxin at the commencement of the study. The sub-analysis established a direct relationship between serum digoxin levels and mortality, with the risk of death increasing proportionally to SDC. Patient mortality risk increased by 19% for every 0.5 ng/ml increment in SDC levels; in those patients whose SDCs exceeded 1.2 ng/ml the risk of death increased by 56%. Patients who were digoxin-naïve and were started on the drug exhibited a 78% increase in all-cause mortality. The results of the sub-analysis of the ARISTOTLE study are qualified by a lack of patient randomisation, no knowledge of the commencement date of treatment for those patients already on digoxin and by the potential effect of confounding factors which were not considered. The association of digoxin therapy in AF with increased mortality has been confirmed through recent work by Adedinsewo *et al* (2017), and Eisen *et al* (2017); in contrast Wu *et al* (2017) report no association between digoxin use and an increase in mortality in digoxin-naïve AF A&E patients, after adjusting for confounding factors (Adedinsewo *et al.*, 2017; Eisen *et al.*, 2017; Wu *et al.*, 2017).

[14] American College of Cardiology. American Conference of Cardiology 2017 [Online]. Washington. American College of Cardiology; 2017 [cited 2018 Jan 18]. Available from: http://www.acc.org/latest-in-cardiology/articles/2017/03/13/17/58/sun-1045-am-aristotle-digoxin-and-mortality-in-afib-patients-with-and-without-hf-acc-2017?w_nav=LC#sthash.jTwQn22V.dpuf.

Research carried out following the DIG trial (The Digitalis Investigation Group, 1997) has provided evidence that serum digoxin levels above 0.9-1.0 ng/ml are deleterious to the digoxin-treated patient and that consistently elevated SDC levels over 1.0 ng/ml (Rathore *et al*., 2002; Goldberger and Goldberger, 2012) lead to increased all-cause mortality in both HF and AF patients (Pastori *et al.*, 2015; Vamos *et al*., 2015). Van Veldhuisen (2002) made a strong case for tight SDC control and a second RCT for digoxin, with emphasis on keeping the target SDC below 1.0 ng/ml (Van Veldhuisen, 2002). Notwithstanding that this was back in 2002, no concrete widespread acceptance of this necessity has been adopted by the medical and pharmaceutical community (Goldberger and Goldberger, 2012). An identical argument is presented by Stucky *et al* (2015) and this applies to the situation in Malta, where clinicians are presently confronted with conflicting recommendations for an optimum SDC target range (Stucky and Goldberger, 2015). Bavendiek *et al* (2017) recommend adhering to the target SDC range recommended by the guidelines (0.5-0.9 ng/ml) and utilising digoxin with caution and in accordance to the most recent high quality evidence (Bavendiek *et al.*, 2017). The Elecyc 2010© analyser documentation at the MDH Pathology Laboratory provides a brief explanation of the rationale for a reduction in the recommended safe therapeutic range, and suggests that a range between 0.6 and 1.2 ng/ml might be best practice, with the upper limit being reduced further to 1.0 ng/ml. Results output from the MDH Pathology Laboratory adopt the suggested SDC reference range of 0.9-2.0 ng/ml. Where referred to by current guidelines, an upper limit of <1.0 ng/ml is recommended (Table 1.4). The lack of a standard reference range for SDCs disseminated amongst health care providers in may mislead practitioners into sustaining a clinical situation with higher SDCs than necessary, by not flagging values above the upper limit recommended in the guidelines

and literature. These observations add further import to the retrospective study at Mater Dei, which has reported 57% of SDCs as being ≥0.9 ng/ml.

A therapeutic regimen for digoxin that dictates strict SDC control as recommended by the guidelines and backed by the literature is based on: (i) patient-specific dosing and (ii) periodic SDC monitoring evaluated in conjunction with the current clinical status of the patient. Whilst elevated SDCs are associated with increased all-cause mortality, sub-therapeutic levels are just as strong an indication of deficiencies in the pharmaceutical care process (Ab Rahman and Hamzah, 2008; Benlmouden and Billaud, 2016; Pincus, 2016).

Access to a tool that aids the process of digoxin dose selection and incorporates patient specific variables is essential in accurately maintaining serum drug levels within a narrow target SDC range (Jelliffe, 2014; Jelliffe *et al.*, 2014b). Jeliffe and Brooker developed the first dosing nomogram for digoxin (Jelliffe and Brooker, 1974). Konishi *et al* devised a predictive equation based on renal function (Konishi *et al.*, 2002) and Bauman and Di Domenico improved this method of determining digoxin posology by integrating a patient's ideal body weight and creatine clearance into the computation, providing a scientific basis for the procedure (Bauman *et al.*, 2006). In 2014, researchers led by Di Domenico at the University of Illinois, studied the effect of using this nomogram on the efficiency of achieving a steady-state SDC of between 0.5-0.9 ng/ml. Patients dosed using the nomogram had lower daily doses of digoxin (149±67 / 177±74 mcg, p=0.020) and lower mean SDCs (0.52±0.30 / 1.12±0.58 ng/ml, p<0.001) and exhibited a greater percentage of SDCs below 1.0 ng/ml than the control group (85%/44.9%) (DiDomenico

et al., 2014). Komatsu *et al* demonstrated the utility of using population parameters in determining optimal dosing and achieving the desired SDC (Komatsu *et al.*, 2015). These approaches are in contrast to the general method of empirical dosing, with no consideration of any of the parameters that impact the end result and provide an improvement in the quality of pharmaceutical care provided (Jelliffe and Brooker, 1974; Bauman *et al.*, 2006; DiDomenico *et al.*, 2014). Increased accessibility to the dosing nomogram was provided by University of Illinois researchers by placing it online and developing a mobile application.[15] Dissemination of this application in local practice could improve dosing regimens in one simple step; a caveat to this is the necessity for a recent renal function test to enable the entry of the value for creatine clearance.

The results of the analysis of the reason for request and the interlinked SDC and eGFR results provide evidence for the introduction of protocols that dictate the utilisation of one or more of the aforementioned tools. Patients recorded as exhibiting reduced renal function at the time of SDC request reported a significantly higher mean SDC than the rest of the cohort. The mean eGFR for patients above the recommended SDC upper limit of 0.9 ng/ml was significantly higher than those patients with SDCs below the limit. These results reinforce the necessity of combining the various aspects of pharmaceutical care to optimise outcomes. The introduction of periodic (bi-annual) screening of eGFR values would aid tailoring of the digoxin dose administered in accordance to their renal function and potentially reduce the number of SDCs above the recommended upper limit.

[15] Clinicalc.com. Digoxin Dosage Calculator [Online]. Clincalc.com; 2017 [cited 2018 Jan 18]. Available from: http://clincalc.com/digoxin/.

4.3 Review of requests at the Drug Information Unit

In the period 2002 to 2014, 91 requests concerning digoxin were made to the DIU, in contrast to the 19,065 SDCs processed at the Pathology Laboratory from 2008 to 2017. These figures provide evidence for the extent of utilisation of the DIU by the public and health care professionals. A lack of patient and health care provider knowledge of the unit and its function within the holistic sphere of the provision of care may be indicated by the results. The prevalent source of referral to the DIU was a hospital or a clinical pharmacist, indicating a level of awareness within the pharmacy profession of the necessity to verify and expand drug information prior to recommending a therapeutic decision (Vukmirović *et al.*, 2012). It is pertinent to note that drug information quality is essential, and should be evidence-based to avoid the simple transposition of theoretical algorithms to clinical practice (Vidal *et al.*, 2005).

The number of requests for digoxin (91 requests in 14 years or a mean of 6.5 requests annually) compared to the number of patients being treated with the drug (2,059) is negligible. This is in contrast to the mean number of SDCs requested annually (1,907); potentially 48% of all patients are tested on a yearly basis, yet clinicians do not appear to query the DIU regarding potential issues that could have been encountered.

Requests for information regarding toxicity are not in the top categories of digoxin queries, with 5.5% of the total. This does not appear to parallel the finding from the retrospective study, which indicated an elevated mean SDC level, with a significant proportion (17%) of patients with a SDC over 2.0 ng/ml. Over one-fourth of the requests

(26%) concerned the subject of digoxin administration; monitoring, another category directly related to toxicity, comprised 11% of the total.

An unfortunate lacuna in the service provided by the DIU and an issue which can be of great detriment to the level of care at MDH and to patient outcomes is the service provided outside of ordinary working hours. A study by Cassar (2015) evidenced the necessity of an improvement in the service during the hours not directly covered by DIU staff. The researcher concluded that an improved staffing algorithm be developed to maintain minimum standards of service provision at all hours. Suggestions for an IT update to the reporting system, implemented in December 2014, and more frequent monitoring of reference resources in printed form were proposed (Cassar, 2015).

Therapeutic approaches to the pharmaceutical care process for digoxin-treated patients in Malta need to be refined in order to ameliorate the quality of care provided. The DIU has an important role to play in this process, and an increased level of utilisation by professionals and patients could lead to an increased awareness of and a reduction in digoxin-induced side-effects, reduced utilisation of Accident and Emergency services, and a reduction in unwarranted SDC requests (Vidal *et al.*, 2005; Fischer *et al*., 2012; Vukmirović *et al.*, 2012). The analysis of requests made to the DIU indicates a general lack of knowledge amongst health care professionals and the public, regarding its ability to aid informed decisions at a clinical level. The DIU appears to be underutilised to the potential detriment of the quality of pharmaceutical care provided and patient well-being.

4.4 Limitations of the study

The following study limitations were identified:

(i) The retrospective nature of the analysis of SDCs. A prospective study, as recommended in Section 4.5, would have clearly defined patient variables established prior to data collection, and would allow review of patients at set time-intervals, enabling a holistic evaluation of SDC levels, related parameters such as serum K^+ and renal function. The variation of SDC levels together with the aforementioned parameters would be evaluated in the context of the patient's clinical condition and possible modifications to treatment.

(ii) The lack of complete information on the timing of serum blood sample collection with respect to the last dosing interval for digoxin, which may have influenced the final SDC level. The timing of blood sample extraction with regards to SDCs is vital. An accurate determination of steady state levels and comparison of various tests should only be carried out with samples drawn at trough states. A trough level of digoxin occurs at least six hours after the last dosing interval (Kang and Lee, 2009; Benlmouden and Billaud, 2016). The effect of the timing of sample collection was not a factor that could be quantified and should be considered when evaluating the mean SDC level obtained.

In this context, the small number of SDCs (117) recorded for sample withdrawal six hours post-dose exhibited a mean of 1.37±0.90 ng/ml (Table 3.11), which was not significantly different from the mean SDC for the patient

cohort (1.31±1.01)(p=0.509). The need for an interface between the clinical analyser and the Laboratory Information System (LIS) at the Pathology Laboratory has been the source of a particular issue with respect to SDCs. Hospital staff are provided with an electronic request form with various mandatory fields that must be completed to enable the form to be accepted. The timing of the last digoxin dose is not currently one of these mandatory fields. In the event that a policy to always complete this particular field, were to be adopted, the data collected would still not be available to health care professionals and epidemiologists as the LIS is not capable of extracting all fields as required from the clinical analysis system database. These fields are fixed and can only be amended through custom alteration to the computer program by the system vendor. Since the ideal time for sample extraction would be at serum trough levels to enable direct comparisons between tests, this limitation would not apply to those samples drawn at the A&E department, as it can be assumed that these are requested and processed as soon as possible.

(iii) The analysis of the reason for request field was complicated due to the complete lack of uniformity in the recording of this variable. The recording of the classification of presenting complaints and symptoms exhibited by the patient varied greatly from one physician to another, in the absence of a fixed set of options. Implementing a fixed list of presenting symptoms within the request form, as a drop-down function, would enable improved and more accurate data analysis and expedient epidemiological analyses.

(iv) Patient co-morbidities and/or diagnosis. These fields are available in the test request form but are not tagged as mandatory fields. No accurate patient data regarding co-morbidities and disease progression was recorded. The primary diagnosis stimulating the prescription of digoxin is relevant in determining and establishing the link between the digoxin and co-morbidities. Introducing a policy for mandatory completion of this field in standard format could resolve this issue and provide improved data for epidemiological analysis.

(v) The lack of collated and accessible mortality statistics to evaluate the association between digoxin and patient mortality. Establishing death as a primary end-point would allow patients to be followed through the whole treatment process and monitoring mortality rates in combination with SDC levels could provide evidence for any possible relationship between the adverse effects of digoxin therapy and all-cause mortality within the Maltese digoxin-treated population. (Freeman *et al.*, 2013; Whitbeck *et al.*, 2013; Adams *et al.*, 2014). Presently, the only route to establishing mortality and cause would be to request every patient's medical records in hard copy from MDH archives and research individual files.

(vi) The absence of information regarding the commencement date of digoxin therapy and any subsequent dose modifications. This is important in determining the incidence and timing of adverse effects, and the alterations to dosing over the treatment period. The date of initial prescribing for digoxin

would be relevant in determining temporal trends in the use of the drug and the indications which are being considered for its introduction into a patient's treatment regimen. Evaluation of the distribution of patients on digoxin, according to the date of commencement of digoxin therapy, is necessary in view of current guidelines. The proportions of "legacy" and newly prescribed patients must be established to distinguish between the two patient cohorts. Patients' co-morbidities and initial rationale for digoxin use are parameters required to carry out a comprehensive assessment of the clinical scenario and individualise therapy accordingly.

(vii) Biochemistry records at MDH are not available for the years prior to 2008. Discussion with staff at the Pathology Laboratory revealed that prior to this date, which coincided with the transfer of acute hospital services in Malta from Saint Luke's Hospital to MDH, no collated records were kept as proprietary storage programs exclusive to each analytical apparatus were not set to interface with one another. Hard copies were stored in individual patient files; other possible data was not deemed relevant for upload to the new chemistry system and discarded. Conducting a further reaching retrospective epidemiological evidence base was thus not possible. This limitation further strengthens the importance of the data collated and analysed, as it sets a baseline to which future work can be aligned.

4.5 Recommendations for future work

Four principal recommendations for future work were identified. The first is a prospective study of a sample of digoxin-treated patients in Malta. The results indicate that mean SDCs for digoxin-treated patients in Malta appear to be at potentially harmful levels and further investigation is warranted. The number of SDCs analysed (1907±180 per year) as compared to the total number of patients on digoxin (2,059, January 2017) adds significance to the necessity of considering and qualifying the importance and generalisability of the finding. A prospective evaluation of a cohort of patients selected from the 2,059 currently being treated with digoxin would provide a clearer picture of the level of pharmaceutical care being provided.

The clinical progression of the patient cohort could then be correlated to physiological parameters which would be recorded at each review. Pivotal to achieving a comprehensive evaluation is the inclusion of other factors that are known to interact or affect digoxin levels, with electrolyte levels and renal function the major parameters to be recorded. A complete medical history would be taken at an initial patient encounter with a comprehensive transcription of all pharmacotherapeutic treatment, in view of the numerous drug-drug interactions for digoxin. This primary meeting would also establish the baseline physiological parameters for comparison throughout the study. Since it has already been established that HF, and to a lesser extent AF, are palliative conditions, it would be pertinent to consider QOL. Digoxin, as evidenced by the DIG trial and other studies, reduces the rate of hospitalisation, whilst having a neutral effect on mortality. Hence digoxin still could have a niche role in palliative care, in the context of which QOL is just as relevant as the extension of life and an improvement in physiological markers.

A prospective study should include a QOL instrument in the periodic reviews forming the basis of the study. This would enable researchers to evaluate patients' humanistic dimension, as well as the progression of their medical condition.

The second recommendation is the implementation of a concerted campaign, with the active participation of all major stakeholders, to promote and disseminate the services provided by the DIU. This recommendation is based on the results of the analysis of requests made to the DIU, which indicated under-utilisation of the DIU, at least where digoxin is concerned. The availability of the services provided by the DIU need to be promoted, both within the sphere of health care professionals, and also to patients and the public. The concept of well-informed carers and patients is critical to all pharmaceutical care processes, but even more so in the case of drugs with narrow TIs. Educational campaigns must be implemented, together with access to drug information via electronic means. The Medicines Information Unit in the UK launched an updated version of their web portal for pharmacy-related requests in August 2016. Nine months after its launch, the website recorded around 5,000 individual page views per day and 40,000 unique user sessions per month.[16]A social media presence is necessary; social interaction now revolves around mobile communication devices, and any effort targeted at increasing utilisation and user penetration must follow this route. All requests at the DIU appeared to have been handled by telephone and to the researcher's best knowledge no dedicated website or information portal is in place (January 2018).

[16] Medicines Information Unit. Information Update [Online]. Medicines Information Unit; 2017 [Cited 2018 Jan 18]. Available from: https://www.sps.nhs.uk/wp-content/uploads/2017/06/MI-update-Jun-2017-national.pdf.

The third recommendation is to distribute the developed digoxin practice points to community pharmacists and develop them into a formal set of guidelines for digoxin (Section 3.5). The following would need to be carried out prior to the expansion of the practice points into guidelines:

(i) Conducting a pilot study with community pharmacists to test applicability, practicality and feasibility.

(ii) Consultation with stakeholders such as the licencing authority, the Cardiology Department at MDH and professional bodies. Endorsement by all involved would enhance the adoption of the guidelines.

(iii) Conversion to electronic formats. The guidelines would be made available in electronic format to enable ease of dissemination and access.

(iv) Developing a patient leaflet. An abridged and non-technical version could be developed for patient use, with emphasis on treatment review and awareness regarding commonly expected adverse effects of digoxin.

The fourth recommendation is the setting up of a working group of cardiologists, pharmacists and representatives from the Pathology Department at MDH. The remit of this group would be the establishment, adoption and dissemination of a common reference for target SDC range in Malta.

4.6 Clinical signals, study contributions and conclusions

The research flagged three principal clinical signals. The first was an indication of potentially elevated SDC levels in digoxin-treated patients in Malta. Fifty-seven per cent of the SDCs were above 0.9 ng/ml (the recommended upper limit for SDCs by the ESC, ACCF/AHA and HFSA guidelines), hence a significant number of patients may be in danger of harm from digoxin treatment. This statement is tempered by the limitations referring to the timing of sample collection and a lack of accompanying data regarding symptoms and clinical condition. Serum K^+ levels in patients with potentially toxic SDCs ($\geq$2.0 ng/ml) were significantly higher than those for patients within the recommended SDC range, demonstrating that hyperkalaemia may have precipitated acute digoxin toxicity and reinforcing the importance of serum K^+ level monitoring in the context of maintaining safe SDC levels. A significantly lower eGFR was recorded for those patients exhibiting elevated SDCs, indicating that periodic evaluation of renal function in combination with therapeutic review of digoxin-treated patients is warranted to reduce mean SDC levels, decrease the incidence of adverse effects and improve patient outcomes. The research was the first detailed retrospective analysis of SDCs in Malta and established a figure for the number of patients treated with digoxin; the mean daily dose administered to these patients is reported. This data has laid the basis for a clinical evidence-base in this niche area of cardiovascular therapeutics.

The second signal was the low level of referral to the DIU by health care professionals regarding digoxin therapy. The inherent complex nature of treatment with digoxin requires a multi-faceted approach to pharmacotherapy, with a consequent need to refer to specialised sources of drug information. Pro-active and expedient dissemination of DIU

services is a societal need that must be executed to improve the quality of pharmaceutical care, both for digoxin-treated patients, and across the whole spectrum of pharmaceutical interventions in Malta. The DIU must be promoted extensively amongst all sectors of Maltese society; improved patient and health care professional access to drug information can only result in a healthier and more productive society. The study appears to be the first collated research on the requests processed by the DIU for digoxin. This has stimulated awareness of the need to develop guidelines for patient care transitions for use in community pharmacy practice, with referral to the DIU forming an integral part of the recommendations.

The third signal is the lack of consensus among health care professionals in Malta regarding the definition and implementation of a commonly accepted SDC target range for digoxin. With conflicting reference ranges suggested by competent bodies namely the ESC, the ACCF/AHA, and the HFSA, the Pathology Laboratory at MDH and the DIU (Table 1.2), the clinical picture appears to be unclear. The agreement of all stakeholders on the adoption of a universally accepted and implemented reference range for SDCs across all health care settings is essential to maintain and improve the standard of care for digoxin-treated patients in Malta.

The potential for harm flagged by the clinical signals detected should not be ignored. The signals should be investigated through further research and provide the stimulus for modification to treatment protocols for digoxin in Malta. Despite diminishing proportions of HF and AF patients being started on digoxin, the number of patients currently on digoxin is significant (2,059). Digoxin has a Class I, level of evidence B recommendation

in ESC guidelines for AF, hence retaining its relevance in the cardio-therapeutic armamentarium. The application of the findings of this research to clinical practice should result in an improvement to the pharmaceutical care provided to digoxin-treated patients in Malta.

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Appendix I

Ethics approval

L-Università ta' Malta

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Ref No: **53/2016**

Thursday 14th December 2017

Flat 4, Outrigger Court
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Dear Mr John Vella,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

A sustainable pharmaceutical care approach to prevention and management of digoxin toxicity

The University Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

Appendix II

Digoxin practice points

Table of Contents

Digoxin practice points

Community pharmacist dispensing check list

Patient records	Query
Medical history	Indication for digoxin, comorbidities and medication
Documentation status	Level of completeness and updating

Digoxin therapy	Query
Dose and adverse effects	Manifestation of adverse effects
Monitoring of parameters	SDC[1], serum K^+, eGFR[1], BP[1] and HR[1]
Medicines use review (MUR)	Date of last therapeutic overview

Pharmaceutical care process	Query
Health care providers	Identity of primary care GP and consultant physician
Information exchange	Need to update the above on current condition
Care transitions	Need for medicines reconciliation

Humanistic aspect	Query
Awareness of therapy	Knowledge of adverse effects and aim of therapy
Social status and condition	QOL[1] and general level of satisfaction
Domiciliary care-giver	Awareness of adverse effects and compliance

[1] BP-Blood Pressure; eGFR-estimated Glomerular Filtration Rate; HR-Heart Rate; QOL-Quality of Life; SDC-Serum Digoxin Concentration

Patient medication records

Intervention aspect	Check-list	Process	Rationale
Medical history	Indication for digoxin, comorbidities and medication	Examine patient records and establish current medical situation to enable a complete clinical picture. Ideally, collate medical information into one easily accessible electronic source.	Patients possess multiple paper-based records and treatment schedules from various state entities that are complex to assimilate in their original form; digoxin-treated patients generally have a number of medications and a lengthy medical history.
Documentation status	Level of completeness and updating	Establish whether all vital records regarding medical history are present and whether all the necessary pharmaceutical care permits and documentation are in order and valid. All steps and processes carried out by the pharmacy team should be added to a patient's profile to enable optimal decision making in all settings.	Complete and updated medical records are essential for a holistic clinical evaluation. Validity of all pharmaceutical permits is vital to ensure continuity of care and patient wellbeing.

Digoxin therapy

Intervention aspect	Check-list	Process	Rationale
Digoxin dose	Dose and adverse effects	Carry out a brief review of digoxin dosage and adverse effects at each prescription cycle. Query the patient on the correctness of the daily dose being taken (confusion in the elderly may lead to a higher dose being mistakenly ingested). Sensations of weakness, dizziness and unexplained fainting and falls are to queried further.	Dosage issues can be resolved using the Digoxin Calc© application, or a dosing nomogram, rather than relying on empirical methods. The manifestation of adverse effects might be subtle and due to a recent course of antibiotics (clarithromycin) or the addition of proton-pump inhibitor (omeprazole) to the therapeutic regimen.
Monitoring	SDC, K+, eGFR, BP and HR[1]	Examine records for SDC level and K+ testing, together with an evaluation of renal function in those >70 years. Testing should be carried out biannually.	Weight evaluation is a concern in the elderly due to a reduced lean body mass. Monitor weight, BP, HGT and in HF patients, lower limb oedema and pulmonary congestion.
Medicines use review (MUR)	Date of last therapeutic overview	Conduct a biannual MUR to establish and eliminate drug-drug interactions, dosing issues and clinical concerns.	SDCs are impacted by drugs in common use in HF and AF, with particular reference to amiodarone and verapamil. The clinical condition of the patient is an essential component of the MUR and must be considered when evaluating digoxin therapy.

[1] BP-Blood Pressure; eGFR-estimated Glomerular Filtration Rate; HR-Heart Rate; QOL-Quality of Life; SDC-Serum Digoxin Concentration

Pharmaceutical care process

Intervention aspect	Check-list	Process	Rationale
Health care providers	Identity of GP and consultant physician	Establish a contact points for the patient's primary care supervisor and tertiary care consultant.	Modifications in therapy and/or issues relating to pharmaceutical care plans may need to be discussed and clinicians informed of a change in the patient's condition. It might not be possible to wait until the next scheduled appointment.
Information exchange	Need to update the above	Establish whether the patient has any issues or changes in clinical status that require the other members of the health care team to be informed.	Information shared across the whole team improves outcomes. Consultant physician at Mater Dei could be updated bi-monthly via email regarding BP, HGT, weight and general condition. Updates following outpatient visits could be emailed to the patient's POYC pharmacy.
Care transitions	Need for medicines reconciliation	Conduct a thorough reconciliation of pharmaceutical therapies following any transition from one care setting to another. This should be done in the presence of the patient or carer to ensure complete awareness of dosing schedules.	Medicines reconciliation is vital as polypharmacy is prevalent in patients on digoxin. Confusion is common amongst patients who have just been discharged or admitted to a new setting (long term care facility). Amendments to therapy are sometimes not recorded across multiple care settings leading to patient confusion and inadequate and potentially dangerous therapeutic scenarios. Digoxin is particularly susceptible in view of its narrow therapeutic index and the emergence of toxicity.

Humanistic aspect

Intervention aspect	Check-list	Process	Rationale
Awareness of therapy	Knowledge of adverse effects and aim of therapy	Evaluate patient education regarding the reason for taking digoxin and the knowledge of the common side-effects of the drug.	Critical, self-reporting of clinical condition is the primary method of detection for digoxin toxicity; falls, gastro-intestinal disturbances, and fatigue should be reported for review.
Social status and condition	QOL and general level of satisfaction	Is the patient not only experiencing optimal pharmacotherapy, but also functioning on a satisfactory social and humanistic level? Communication on a personal level with the patients and empathy is an important tool in the pharmaceutical care process.	Quality of life is a major factor in digoxin therapy; adverse effects may be reducing a patient's Quality of Life (QOL); conversely digoxin may improve QOL without a significant change in physiological parameters.
Domiciliary care-giver	Awareness of adverse effects and compliance	Companions or family members should be instructed on the common manifestations of digoxin toxicity, compliance and monitoring.	Patients may be weak or senile and may not be in a position to comply with their therapy and self-monitor for adverse effects and changes in clinical status.

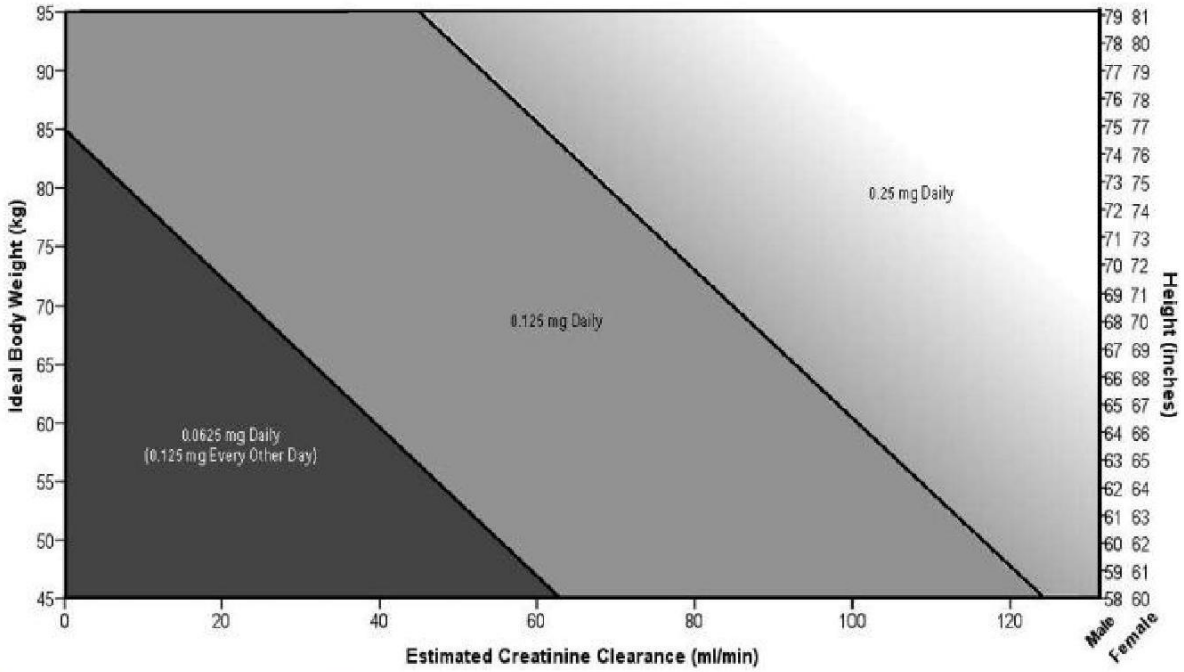

Figure 1- Nomogram devised by Di Domenico *et al*

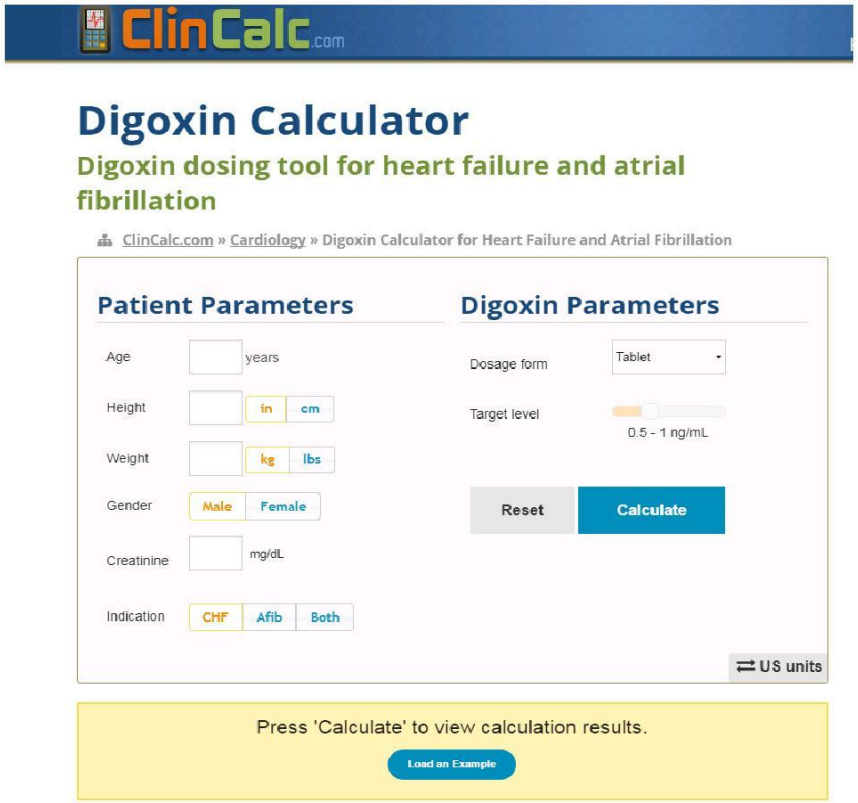

Figure 2 - Digoxin dose calculator(www.clinicalc.com/digoxin)

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Appendix III

Maltese Cardiac Society Conference 2016 – Poster presentation

Retrospective analysis of serum digoxin concentrations at Mater Dei Hospital

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INTRODUCTION

Digoxin as a therapeutic option in cardiology is limited by its narrow therapeutic index.[1]

Current evidence indicates that digoxin can exert its beneficial neurohormonal effects at significantly lower serum levels (<1.0ng/ml) than those previously considered optimal. [1,2]

AIMS

- To analyse serum digoxin concentrations (SDCs) at Mater Dei Hospital (MDH).
- To assess compliance to the clinically recommended SDC target (0.5-1.0ng/ml).
- To assess queries concerning digoxin processed by the Drug Information Unit (DIU) at MDH.

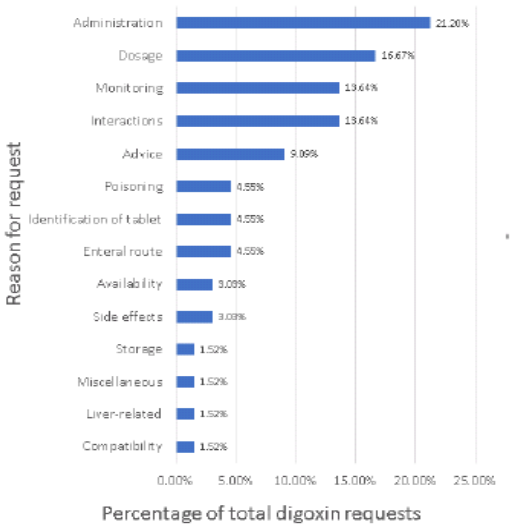
METHOD

- All SDCs recorded at the Pathology Laboratory at MDH from January 2008 to February 2016 were collected.
- Variables selected for inclusion in the analysis were gender, age, reason for testing, origin of request, referring physician and number of tests requested.
- The data were analysed using the JASP (Version 0.7.5.6) statistical package. Descriptive statistics and a comparison of means via the Student's t-test were carried out.
- The DIU at MDH was requested to provide information on all queries handled on record; data for the years 2009 to 2014 was forwarded. All incidences concerning digoxin were extracted and classified.

RESULTS

- 16,908 SDCs were processed between January 2008 and February 2016; 575 tests were considered to be invalid and excluded from the study.
- The 16,333 valid SDCs originated from 5,549 individual patients (60% female, 40% male; mean age 78 years, range 1-111 years). The mean number of SDCs per patient was 3 (mode 1, range 1-47).
- Mean SDC was 1.28ng/ml (range <0.1-20ng/ml), with 31% of SDCs categorised within, 19% below and 50% above the clinically recommended target (0.5-1.0ng/ml); 15% of SDCs >2.0ng/ml.
- 38% of requests originated from the A&E Department (mean 1.14ng/ml; range <0.1-11ng/ml).
- The DIU processed 66 requests concerning digoxin from 2009 to 2014, with administration (21.21%) and dosing (16.67%) queries being the most frequent

Figure 1 - DIU Queries for digoxin
(MDH 2009-2014)(N=66)



CONCLUSION

The mean SDC of 1.28 ng/ml is higher than the current clinically recommended target SDC[3]; SDCs above 1.0ng/ml are not beneficial and associated with an increase in adverse effects and all-cause mortality.[4,5]

Acknowledgement
Victor Bartolo, Pathology Laboratory IT Manager, Pathology Department, Mater Dei Hospital.

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SERUM DIGOXIN CONCENTRATIONS: CLINICAL SIGNALS

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INTRODUCTION

- Digoxin, as a treatment option in cardiology, is limited by its narrow therapeutic index.
- Current European Society of Cardiology (ESC) guidelines provide a Class 1 level of evidence B for digoxin in atrial fibrillation, and classify it as a treatment of uncertain benefit in heart failure.[1]
- Clinical guidelines recommend targeting a serum digoxin concentration (SDC) between 0.5 and 0.9 ng/ml, or <1.0 ng/ml.[1,2,3]

AIMS

- To determine the number of patients on digoxin in Malta
- To analyse SDCs recorded at Mater Dei Hospital (MDH)
- To determine adherence to the clinically recommended target SDC
- To assess queries concerning digoxin processed by the Drug Information Unit (DIU) at MDH

METHOD

Number of digoxin-treated patients

- Government pharmaceutical dispensing data for November 2016 to February 2017 was analysed and the number of patients receiving digoxin and the mean daily dose were determined.

Retrospective analysis of SDCs

- Data for SDCs recorded at the MDH Pathology Laboratory from January 2008 to December 2016 was collected.
- Patient variables selected for inclusion in the analyses were: SDC value, gender, age, origin of SDC request, referring physician and number of SDCs requested.
- The SDC values collected were compared to the SDC target range recommended by the ESC guidelines (0.5 to 0.9 ng/ml) and classified as below, within and above the target range.[1]

Requests for information at the DIU

- All enquiries processed by the DIU between April 2002 and December 2014 were collected and requests concerning digoxin were classified according to the reason for the query.
- The data was analysed using the JASP (Version 0.7.5.6) statistical package. Descriptive statistics and a comparison of means via the Student's t-test were carried out.

RESULTS

- In March 2017, 2,059 patients were receiving digoxin treatment via the government pharmaceutical system in Malta. Mean daily dose was 0.13 mg (range 0.03 –0.25 mg).
- A total of 17,388 valid SDCs from 5,653 patients (61% female, 39% male, mean age 78±11 years, range 1-111 years) were analysed.
- Mean number of SDCs per patient was 3 (range 1-47). Mean SDC was 1.30 ±0.99 ng/ml (range <0.1-2.0 ng/ml), with 32% of SDCs within the recommended range (Fig. 1).
- Eight-five percent of SDC requests originated from MDH, with 43% of these from the A&E (mean 1.17±1.01 ng/ml).
- Of the 14,369 queries processed by the DIU, 91 (0.6%) concerned digoxin. The top three enquiries were related to administration (26%), interactions (15%) and dosing (15%).

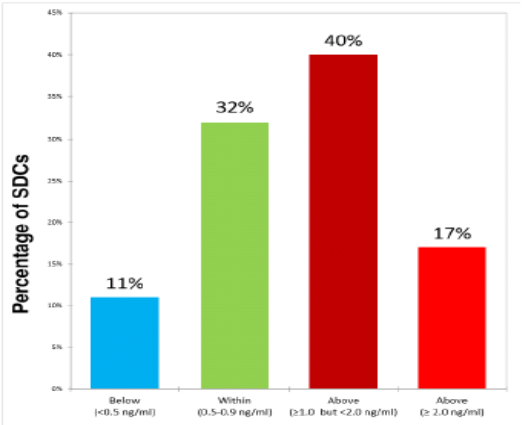

Figure1 - Variation from target SDC (0.5-0.9 ng/ml) N=17,388, MDH 2008-2016

CONCLUSION

The mean SDC of 1.30 ng/ml is above the upper limit for the clinically recommended target. The number of queries regarding digoxin is low (0.6%) compared to the number of out-of-range SDCs (68%), indicating the need for the DIU to disseminate its services. Further research is warranted to investigate the clinical implications of these signals.

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