Assessment of Drug Therapy Problems among Ambulatory Heart failure Patients at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

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This is to certify that the thesis prepared by Elham Seid entitled ***"Assessment of Drug Therapy Problems among Ambulatory Heart Failure Patients at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia"*** and submitted in partial fulfillment of the requirements for the degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

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Drug therapy problems (DTPs) are a major concern in health care and have been identified as contributing to negative clinical outcomes. The Care of heart failure patients is commonly complicated by the presence of comorbidity and poly-pharmacy, which inturn intensify the risk of occurrence of DTP. The occurrence of DTPs in heart failure patients is associated with worsening of disease, frequent hospitalization, adverse drug event, drug-drug interaction, and poor patient compliance. There is limited evidence regarding DTPs in heart failure patients. Thus, this study aimed at assessing DTPs and medication adherence among ambulatory heart failure patients at Tikur Anbessa Specialized Hospital (TASH).A hospital based cross sectional study was conducted on 423 heart failure patients who had follow up at TASH. Data collection was done through patient interview and chart review. Majority of the patients were in New York Heart Association class III (55.6%) and 66% of patients had preserved systolic function. About half of the etiology of heart failure was chronic rheumatic valvular heart disease (50.8%). Of the 423 participants, 277(65.4%) had DTPs with average number of 2 ± 0.86 per patient. The most common DTPs identified were Drug interaction (40.5%) followed by not the most effective drug (17.5%), ADR (14.7%), inappropriate dosage (9.7%) and the need for preventive drug therapy (9.6%). β blockers were the most frequent drug class involved in DTPs followed by ACEIs, mineralocorticoid receptor antagonist, and antiplatelets. Metoprolol tartrate and Nifedipine were drugs with the highest drug risk ratio. Age, gender, presence of comorbidity, average number of drugs per day and left ventricular ejection fraction were an important risk factor for DTPs. The rate of medication non-adherence was 45.2%. Duration of treatment, average number of medication per day and ADR were found to have significant association with medication non-adherence. Prevalence of DTPs among heart failure patients was high and about 45.2% of the patients were non-adherent to their medication. Detection and prevention of DTPs along with identifying patients at risk can save lives, help to adopt efficient strategies to closely monitor patients at risk, enhance patient's quality of life and optimize healthcare costs.

Key words: Drug therapy problem, adherence, Heart failure, Tikur Anbessa Specializes Hospital

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List of Abbreviations and Acronyms

ACEIS	Angiotensin converting enzyme inhibitors
ADR	Adverse drug reaction
AHA/ACC	American heart association American college of cardiology
ARBs	Angiotensin receptor blockers
CVD	Cardiovascular disease
CMP	Cardiomyopathy
CRVHD	Chronic rheumatic valvular heart disease
DDI	Drug-Drug interaction
DI	Drug interaction
DM	Diabetes mellitus
DNOs	Drug related negative outcomes
DRPs	Drug related problems
DTPs	Drug therapy problems
HF	Heart failure
HHD	Hypertensive heart disease
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HTN	Hypertension
LVEF	Left ventricular ejection fraction
MMAS	Morisky medication adherence scale
MRA	Mineralocorticoid receptor antagonist
NYHA	New York heart association
RCT	Randomized control trials
RHD	Rheumatic heart disease
SSA	Sub-Sahran Africa
TASH	Tikur Anbessa specialized hospital
UGIB	Upper gastro intestinal bleeding
WHO	World health organization

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1 Introduction

1.1 Background

Heart Disease remains the major public health concern and leading cause of death worldwide. Cardiovascular disease (CVD) accounted for nearly 836,546 deaths in the US, among these 9% of the death is due to Heart Failure (HF) (Benjamin et al., 2018). Most of the CVD deaths take place in low- and middle-income countries and sub-Saharan Africa (SSA) contributed for 5.5% of the global CVD deaths (Mensah et al., 2015).Similarly, data from different parts of Ethiopia showed that the leading cause of death from non-communicable diseases was CVD (Tefera et al., 2017, Misganaw et al., 2012). According to the American Heart Association (AHA) projection, future direct medical costs of HF will increase from $31 billion in 2012 to $70 billion in 2030 (Al-Khatib et al.). HF is also a major health and socio-economic burden in SSA, owing to its high prevalence, mortality and impact on young, economically active individuals (Glezeva et al., 2015, Kraus et al., 2016, Ntusi and Mayosi, 2009, Hewitson et al., 2017). The situation is worsened by the fact that this high level of premature mortality places a particular strain to African countries whose health systems are already struggling to deal with the double burden of both communicable and non-communicable disease (Tefera et al., 2017, Hewitson et al., 2017, Kengne et al., 2012, Mocumbi, 2012).

HF is a complex clinical syndrome characterized by typical symptoms like breathlessness, ankle swelling and fatigue, which may limit exercise tolerance and fluid retention leading to pulmonary congestion and peripheral edema. HF is caused by any structural or functional cardiac abnormality, resulting in impairment of ventricular filling or ejection of blood. There is no single diagnostic test for HF because it is largely a clinical diagnosis based on a careful history and physical examination (Al-Khatib et al., Ponikowski et al., 2016). Both the, American College of Cardiology and American heart association ACC/AHA stages of HF and the New York Heart Association (NYHA) functional classification provide useful information about the development and severity of HF, respectively(Ponikowski et al., 2016).

HF is caused by various groups of etiologies, each requiring unique management. The etiology of HF differs between high income countries and middle to low income countries (Kraus et al., 2016). The vast majority of HF causes in SSA are due to the major non-ischemic causes

(Watkins and Daskalakis, 2015, Abdissa et al., 2014, Damasceno et al., 2012). Rheumatic heart disease (RHD), cardiomyopathy (CMP) and hypertension (HTN) account for over 90 % of cases (Ntusi and Mayosi, 2009). Ischemic heart disease (IHD) was a rare cause of HF in SSA. However, IHD become more common in SSA due to change in lifestyle, diet and risk prone behavior and other consequence of progressive urbanization and westernization life style adapted in urban areas (Ntusi and Mayosi, 2009, Tesfaye, 2008, Keates et al., 2017, Dalal et al., 2011).
HF can be described as reduced ejection fraction (EF<40), mid-range (EF40-49) or preserved (EF ≥50) based on measurement of left ventricular ejection fraction (LVEF). The etiology, epidemiology and response to treatment are different between heart failure patients with preserved ejection fraction (HFpEF) and heart failure patients with reduced ejection fraction (HFrEF). Patients with HFpEF tend to be older, more often women and have hypertension or atrial fibrillation (Al-Khatib et al., Ponikowski et al., 2016).

The goal of treatment for asymptomatic HF patients (class I) is to slowdown disease progression by blocking neuro-hormonal system. For those who develop symptom (classII-IV), the goal is to reduce symptom, reduce disease progression, prolong survival and improve quality of life (Mann and Felker, 2014). Neuro-hormonal antagonists (angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonist(MRA) and evidence based beta-blockers have been shown to improve survival in patients with HFrEF and are recommended for the treatment, unless contraindicated or not tolerated. The dose of these medication should be up-titrated to the maximum tolerated dose in order to achieve adequate inhibition of the renin–angiotensin–aldosterone system (RAAS) (Ponikowski et al., 2016). Other treatment recommended in selected symptomatic patients includes diuretics and digoxin (Ponikowski et al., 2016, Mann and Felker, 2014). No treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF or HFmrEF. The management of HFpEFis focused on management of congestion and comorbid conditions (Mann and Felker, 2014).

The care of HF patients is commonly complicated by the presence of comorbidity and poly-pharmacy, which in turn intensify risk of occurrence of drug therapy problem(DTP) (Wong et al., 2011, Viktil et al., 2007). A DTP is any undesirable event or circumstance experienced by a patient that involves, or is suspected to involve, drug therapy, and that interferes with achieving

the desired goals of therapy. DTPs have been categorized by different research groups into different classification systems. According to Cipolle text book of pharmaceutical care practice, there are 7 categories of DTP that involve indication, effectiveness, safety and compliance (Cipolle et al., 2014). In patients with HF, the frequency of DTPs has been reported to be as high as 78%. In addition, the presence of a DTP has been related to negative clinical outcomes (Gastelurrutia et al., 2011). HF patients have multiple comorbidities and they have a complex regimen of drug treatment. Thus, patients often have difficulty adhering to current guideline recommended medications(Conn et al., 1994, Lee et al., 2015). Adherence is defined by the World Health Organization (WHO) as "the extent to which a person's behavior taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"(Sabaté, 2003).

Non-adherence is a powerful confounder of evidence-based practice and can adversely affect clinical outcome and quality of life resulting in HF exacerbation, frequent emergency visit and increased risk of mortality (Ruppar et al., 2016, MUJTABA et al., 2012).

Drivers for non-adherence are multifactorial and patient specific including treatment, patient and health care related factors. Therefore collaborative intervention is needed to overcome non-adherence in HF patients (Sabaté, 2003).

1.2 Statement of the problem

HF is the only major CVD increasing in prevalence (Bungard et al., 2001). Despite the availability of effective treatment, HF is still associated with substantial morbidity and mortality(Gastelurrutia et al., 2011). It is also associated with recurrent hospitalization owing to its high prevalence and poor clinical outcomes (Al-Khatib et al.). Personal, economic, and healthcare burden of HF is expected to increase in the future as longevity improves, placing further pressure on finite health care resources (Hsu et al., 2016). DTPs may arise at all stages of the medication process from prescription to follow-up of treatment (Shareef et al., 2015). Various studies showed that DTPs are the dominant reason for hospital admission and emergency department visits (Howard et al., 2003, Baena et al., 2006, Patel and Zed, 2002). A literature review concerning medication related problem indicated that 28% of all emergency department visits were medication-related, and 24% of the DRP (drug related problem) result in hospital admission, out of which 70% were preventable (Patel and Zed, 2002).

The occurrence of DTP may compromise the effectiveness of treatment and prevent patients from achieving therapeutic goal, which lead to worsening of disease, reduced quality of life, and augment the risk of morbidity and mortality (Bhagavathula et al., 2017, Hussein et al., 2014). HF patients are at high risk of having DTPs (Hsu et al., 2016). As it forms an end stage of different CVD, it involves management of multiple medical conditions so patients need medication not only for HF but also for the management of comorbidities. The increased number of drugs prescribed has an important impact on HF, as it is associated with negative health outcomes including frequent hospitalization, waste of resources, adverse drug event, potential drug-drug interaction, and poor patient compliance (Abdela et al., 2016, Viktil et al., 2007, Flesch and Erdmann, 2006, Rushton and Kadam, 2011). Patients with HF are particularly vulnerable to drug-drug interaction (DDI) due to their older age, complexity of drug regimen, poly-pharmacy and influence of heart disease on drug metabolism (UV et al., 2011). DDI is said to account for a number of severe ADR (adverse drug reaction) resulting in hospitalizations and emergency department visits (Sharma et al., 2014). The majority of significant ADR and DDI are preventable. To optimize patient safety, healthcare providers must have a clear understanding of the magnitude and clinical significance of these problems, which assist clinicians to provide evidence-based and cost-effective health care (Barbara S. Wiggins et al., 2016).

Adherence to evidence based medication is crucial. Non-adherence to HF medication is associated with increased hospitalization (Aggarwal et al., 2015, Knafl and Riegel, 2014), emergency visit (Davis et al., 2014), worsening symptom and disease progression, and overall increase in healthcare cost (Aggarwal et al., 2015). Rate of non-adherence in HF patients is estimated to be between 40-60% (Wu et al., 2008). In persons with HF, event-free survival was significantly better when HF medication taken was ≥ 88% (Wu et al., 2009). Factors that contribute to medication non-adherence can be divided in to patient and family related factors, treatment related factors and economic related factors (Hekmatpou et al., 2009). Identifying barriers to medication adherence, and interventions to address, and reduce non-adherence have the potential to improve clinical outcomes in HF patients (Davis et al., 2014).

Generally optimization of drug therapy and preventing DTPs are major factors to improve health care, reduce expenditure, and potentially save lives (Al-Azzam et al., 2016). In practice, most HF patients are treated as outpatients, and their care in this setting is challenging; less time is available for outpatient evaluation, and much more reliance is placed on appointment visits. Therefore early identification of DTPs along with awareness of drugs with highest drug risk ratio are an important component of drug therapy and also enhance the prevention and management of DTPs by enabling practitioners to develop a better care plan. However, studies regarding DTPs in ambulatory HF patients are limited in Ethiopia. Thus, the present study aimed to assess DTPs and medication adherence among ambulatory HF patients. Therefore, based on the study findings medication therapy management (MTM) service will be provided for the patients, where pharmacists will work collaboratively with physician and other health care professionals to optimize medication use. Moreover the result of the study will provide valuable insights for the healthcare professionals on drug related needs of HF patients and can also be used as baseline information to establish guidelines and influence decision makers regarding DTPs. The finding may be useful as a baseline for future studies.

1.3 Literature review

1.3.1Prevalence and type of Drug therapy problems

Data regarding DTPs among HF patients are scanty, as many of DTPs focused on cardiovascular inpatients. However, the prevalence of DTPs among HF patients has been reported to be as high as 78% in a study done in Barcelona that assessed prevalence and characteristics of drug related negative outcomes (DNOs) among HF patient (Gastelurrutia et al., 2011). According to the report, a total of 147 DNOs were detected with a mean of 1.5 DNOs per patient. The most frequent DNOs identified were insufficiently treated health problem (31%), inappropriate dose, drug regimen, and/or duration (22%), adverse effects probability (16%), and non-adherence (14%)

A study at Boston in 2017 included a total of 60 HF patients. The aim was to assess drug related issues in an outpatient HF heart failure population. The majority of identified drug related issues are related to ADR (77%), drug interaction (DI) (58%), suboptimal therapeutic choice (55%) and untreated medical condition (43%). The most common ADR was dry cough followed by peripheral edema, gynecomastia and angioedema (Dempsey et al., 2017).

Likewise, a study done at 3 hospitals in Taiwan over a two year period (from October 2008-December 2010) described the frequency, types, and temporal occurrence of DRPs in Taiwanese HF patients. A total of 796 DRPs were identified from 78 of 141 patients. The DRPs most frequently recorded were the need for laboratory tests (32.7%) followed by potential interaction (29.6%), non-allergic side effects (13.3%), and insufficient awareness of health and disease (9.5%) (Hsu et al., 2016).

DTPs are highly associated with clinical outcomes, healthcare costs and quality of life. According to a cross-sectional study among 85 cardiovascular out patients in Switzerland, 69% of patients had at least one DTP. The most common DTP were indication related problem, including need additional drug therapy (need of ASA or statin) and unnecessary drug therapy (e.g., use of digoxin or allopurinol without any indication) (Niquille and Bugnon, 2010).

An observational study at five hospitals in Jordan included 2,898 out patients who visited cardiology, endocrine and respiratory outpatient clinics. Total number of DRP was 32,348 with a mean of 11.2 DRP/patient. HTN, diabetes mellitus (DM), dyslipidemia, IHD, and HF were associated with significantly higher numbers of DRP. The most common DRPs were a need for

additional or more frequent monitoring(41.73%), non- adherence to non-pharmacological therapy (13.45%) and the patient was not given instruction or self-care advice(12.37%)(Al-Azzam et al., 2016).

The rise in number of medication use has important impact on HF as it carries a high risk of DI. Different studies showed that DI was the primarily encountered DTP. According to a study in India, 53 DTPs were identified from 44 cardiovascular patients. The most common DTP encountered was DI (49%) and the drugs most frequently involved in were antiplatelet agents, antihypertensive and gastrointestinal drugs (Shareef et al., 2015).

Similarly in another study done by Abraham et al.(Abraham, 2014), DI was the most frequent DTPs in congestive cardiac failure patients (46.19%) followed by drug over dosage (17.26%), drug duplication (11.17%) and drug under dosage (10.41%).

A cross-sectional study at Jimma Ethiopia included 332 cardiovascular patients. A total of 1249 drugs with average of 3.76 drugs per prescription were prescribed. The frequency of potential DIs was found to be 241 (72.6%). Among these 29.6% of the potential DIs were major DI (Chelkeba et al., 2017).

Randomized control trials have shown pharmacologic inhibition of the renin-angiotensin system, beta blockers and MRAs were associated with reduced mortality and improved outcomes. However, these medications are still under-prescribed and under-utilized (Meid et al., 2015). In a retrospective observational study of 125 patients with chronic HF, of all patients studied, 25% were receiving either no ACE inhibitor or only a low dose. Majority of theme (64%) had no identifiable contraindication to receiving a high dose (McMullan and Silke, 2001).

Another study in Australia showed beta blockers were prescribed to 80% of patients (more than 85% were on sub-optimal doses) and 70% were prescribed ACE inhibitors (approximately 50% were on sub-optimal dose). An increase in dosage of these medications and utilization of combination therapy of these medications was poor (Driscoll et al., 2007).

1.3.2 Drug and drug class associated with DTP

HF medications are the most implicated drug class in DTP in a number of literatures. A hospital based interventional study conducted in Barcelona showed that twenty-two percent of the DNOs were due to HF medications like ACEIs/ARBs, beta-blockers, MRAs, diuretics, potassium

supplements, and digoxin(Gastelurrutia et al., 2011). Another study in Taiwanese HF patients identified the principal drugs and drug class associated with DRPs. ACEI/ARB (21%) and diuretics (21%) ranked first among all drug class followed by warfarin (12.5%), spironolactone (10.1%), and b-blockers (7.9%). Drug risk ratio was calculated and warfarin had high risk ratios for DRPs (Hsu et al., 2016). Another study also showed that DRPs and drug risk ratio were found to be high in drug categories like anti-hypertensives, antiplatelet drugs and anticoagulants (Abraham, 2014).

1.3.3 Factors associated with DTP

There are different risk factors that predispose HF patients to develop DTP. Factors that influence drug therapy in different studies include sex (Bhagavathula et al., 2017, Tigabu et al., 2014, Urbina et al., 2015),age (Shareef et al., 2015, Tigabu et al., 2014),presence of comorbidity(Hussein et al., 2014, Abraham, 2014, Tegegne et al., 2015), and average number of medication per day(Gastelurrutia et al., 2011, Shareef et al., 2015, Abraham, 2014, Urbina et al., 2015). A similar study in Jordan indicated that the numbers of DTPs were associated with older age, being unmarried, having an education level of high school or less, not having health insurance, and the presence of certain clinical conditions, including hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, and HF (Al-Azzam et al., 2016).

A cross sectional study conducted among 227 cardiovascular patients at Gondar University assessed risk factors for developing DRPs in patients with CVD. The study included 227 patients. Majority of patients were diagnosed with HF. Some of the variables such as outpatients, patients with cardiomyopathy and angina, prescribing large number of drugs, the presence of Poly-pharmacy and using other non-cardiac related drugs influenced a greater extent to develop at least one DRP (Abdela et al., 2016).

1.3.4 Prevalence and Predictors of non-adherence among heart failure patients

Non-adherence to HF medications is common due to presence of poly-pharmacy and complexity of regimen. Non-adherence to guideline recommended medication in HF patients is associated with recurrent hospitalization, increased health care cost, treatment failures and poor outcomes (Conn et al., 1994). Rate of adherence is different among studies due to a difference in setting and measurement scale used to assess adherence. Across sectional study at two specialized HF clinics in Brazil assessed treatment adherence using a 10-item questionnaire that consists of

adherence related to pharmacologic and non-pharmacologic treatment. Adherence was considered adequate if the patient showed a score of ≥ 18 points. A total of 236 (63.5%) patients showed an adherence rate lower than the cutoff point (<18 points) (Silva et al., 2015).

According to a pilot study conducted in Columbia University, medication adherence was assessed by Morisky Medication scale (MMAS- 4). At baseline sixty percent of patients reported sometimes forgetting to take their medications. At 30-day follow-up, 1 out of 10 patients reported being readmitted to the hospital within the past month, and 50% of patients reported non-adherence to their medications (60). Similarly in an observational study conducted among cardiac failure patients in Pakistan,72.7% were non-compliant to their medication (Mujtaba et al., 2011).

A relatively lower rate of non-adherence was found in prospective observational study at the HF ambulatory clinic of a university hospital in Barcelona (Spain) in which only 14% of patients were non-adherent to their medication (Gastelurrutia et al., 2011). Another study conducted among HF patients at three hospitals in USA showed that a total of 63 (28.9%) patients had poor adherence from 218 HF patients(Knafl and Riegel, 2014). Similarly, lower rates of medication non-adherence were found in studies done in Cuba (36.4%)(Despaigne et al., 2012, Van Der Wal et al., 2005)and the Netherlands (27.9%) (Despaigne et al., 2012, Van Der Wal et al., 2005).

There are a number of factors that contribute to medication non-adherence including patient related factors, treatment related factors and economic related factors. Identifying barriers of non-adherence reduce hospitalization and unnecessary health expenditure(Hekmatpou et al., 2009).

The study conducted in Columbia University identified factors associated with medication adherence among heart failure patients. The most common factors for non-adherence were forgetting to take their medications due to distractions in daily life (30%), being away from home(20%), having more than one medication to take(20%), and feeling well enough not to take it(20%) (Aggarwal et al., 2015). Likewise, according to a prospective cohort study conducted among HF patients in USA three risk factors for poor adherence was identified. These were a higher number of comorbid conditions with a higher total number of daily medicines, older age with poorer global sleep quality, and fewer months since diagnosis of HF (Knafl and Riegel, 2014).

Presence of comorbidity and number of medication were the most frequent reasons for non-adherence in studies done in Cuba (Despaigne et al., 2012) and Brazil (Silva et al., 2015).

In Hospital based cross-sectional study at Jimma adherence to self-care behaviors and knowledge about the disease were assessed among adult patients with HF. Multivariate analysis showed that age, co-morbidity, NYHA functional class and HF knowledge score were independent predictors of poor adherence to self-care behaviors (Sewagegn et al., 2015).

2 Objectives

2.1 General objective

- ✓ To assess drug therapy problem and medication adherence among heart failure out patients at adult cardiac clinic of Tikur Anbessa Specialized Hospital

2.2 Specific objectives

- ✓ To determine the prevalence of DTP among ambulatory HF patients
- ✓ To determine the most common drugs and drug classes involved in DTPs
- ✓ To identify contributing factors for DTPs among HF patients
- ✓ To determine the rate of adherence
- ✓ To identify factors contributing to non-adherence to HF treatment

3 Methods

3.1 Study setting

The study was conducted at TASH.TASH was inaugurated in 1972. It is a 700 bed tertiary care teaching hospital of Addis Ababa University. This hospital offers diagnosis and treatment for approximately 370,000 - 400,000 patients a year. On the other hand, as the largest teaching hospital of the country, it trains large number of undergraduate and graduate students. It is also an institution where specialized clinical services that are not available in other public or private institutions are rendered to the whole nation. Adult cardiac clinic is one of the outpatient services where cardiac patients are followed up. The clinic is staffed with cardiologists, cardiology fellows, residents and nurses. The clinic provides services four days per week on average for 180 HF patients.

3.2 Study design and Study period

A hospital based cross sectional study design was employed from 20 June to 20 August2017 at adult cardiac clinic of TASH

3.3 Population

3.3.1 Source population

- All HF patients who attended adult cardiac clinic of TASH

3.3.2 Study population

- All HF patients who had follow up within the study period and who fulfilled the inclusion criteria

3.4 Inclusion and exclusion criteria

3.4.1 Inclusion criteria

- Patients age ≥14 and diagnosed with HF, who were on active follow up and receiving treatment for at least 6 months
- Patients who had complete medical records including Echocardiography findings

3.4.2 Exclusion criteria

- Patients who could not respond for e.g., too sick to be interviewed

- Patients who were not willing to participate
- Patients who didn't have caregiver to facilitate communication (for those who couldn't speak Amharic)

3.5 Sample size determination and sampling technique

3.5.1 Sample size determination

Sample size was computed based on single population proportion formula. Since there was no previous study done on DTP among HF in Ethiopia, the proportion (P) of DTP in HF patients was taken as 50 %.

$$n = \frac{z^2 \times p(1-p)}{D^2} z$$

Where n - required sample size

Z - Confidence level at 95% (standard value =1.960) at $\alpha / 2$

p – Prevalence =50 % (0.5)

D – Margin of error at 5% (0.05)

$$n = \frac{(1.960)^2 * 0.5(1-0.5)}{(0.05)^2}$$

n=384.16≈ 384 Taking 10% contingency, the total sample size would be 423, based on this 423 patients were included in the study

3.5.2 Sampling technique

Systematic random Sampling technique was used to select HF. Sampling interval (k^{th}) was determined by dividing the total number of HF patients that came within the study period (two month) by the allocated sample size.

Total no of patients within 2 month= 1440 Sample size=423

$$K = \frac{1440}{423} = 3$$

The first patient was selected randomly then every 3^{rd} patient was selected from the patient registration list until the required sample was reached.

3.6 Study variables

3.6.1 Dependent variable

- Drug therapy problem
- Adherence

3.6.2 Independent variable

- Socio demographic characteristics (age, sex, marital status, educational status , source of medication)
- Clinical characteristics (Comorbidity, LVEF, NYHA class, frequency of appointment, type and number of drug, duration of heart failure treatment)

3.7 Data collection and management

3.7.1 Data collection instruments

Relevant information regarding patient demographics and clinical data was collected by patient interview (Annex I). Data on patients clinical characteristics (e.g., etiology of HF, echocardiographic parameters, NYHA functional class, comorbidities, history of allergies, vital signs, pertinent laboratory values, relevant past medical and medication history, current medication, duration of heart failure treatment) were obtained by using data abstraction format from patient charts (Annex 2). Key informant interview was administered for 6 physicians (Annex 4).

Identification of drug therapy problems

The DTP evaluation tool was prepared based on Cipolle DTP categories with a slight modification(Cipolle et al., 2014).DTPs were identified by using most updated guidelines like European Society of cardiology and AHA. Drug-drug interaction was evaluated using Micromedex® health care series software.

Assessment of Adherence

Medication non adherence is a major issue in heart failure patients due to this in the current study adherence was considered as a major objective and done separately by using MMAS-8. Morisky medication adherence Scale (MMAS-8): an 8-item self-reported Adherence measure was used to assess patient Adherence to HF medications. It consists of eight questions with closed dichotomous (yes / no) answers. From the eight items, only one question is answered positively.

The last question has a five point Likert scale: “never”, “once in a while”, “sometimes”, “usually”, and “always.” The degree of adherence was determined according to the score resulting from the sum of all the correct answers: high adherence (eight points), average adherence (6 to < 8 points) and poor adherence (< 6 points)

3.7.2 Data collection procedure

Patients were approached at the appointment office right after they visited their physician. Data regarding to patient demographics and medication adherence were obtained by interviewing patients. For the secondary data, the HMIS registration book was used to get the card numbers of HF patients. After getting card number an in-depth review of each patient’s medical record and medication profile was performed using data abstraction format. DTPs were identified by evaluating the appropriateness of prescriptions in terms of indication, dosage effectiveness and safety. Effectiveness and dosage related issues were identified through comparing patient’s treatment with the evidence-based guideline recommendations. Patients’ clinical characteristics were taken into account when deciding about the appropriateness of dosage regimen. Adverse drug reactions were identified from patient chart (by investigating patient’s data for any possible adverse reaction related to patients’ medications).At least 3 consecutive patient appointments were reviewed from the chart to identify whether or not the patient is on goal of treatment (NYHA class goal Pulse blood pressure or fasting blood sugar). Two Nurses were involved in patient interview. The principal investigator and one clinical pharmacist reviewed and filled patient chart using data abstraction format at the same day with each patient follow up. The principal investigator identified all DTPs.

3.8 Data quality assurance

The data collection format was pretested on 22 patients (5% of the sample size) to check for uniformity and understandability of the checklist. The tool was modified after the result obtained from the pretest. One day training was given to data collectors by the principal investigator on how to collect data from patient chart and how to conduct patient interview. The principal investigator had supervised the data collection process and was giving feedback and correction on daily basis.

3.9 Data analysis

The data was entered into EPI-info V.7.2.1 and analyzed using Statistical package for social sciences (SPSS) version 21. Descriptive statistics was used for analyses of socio-demographic variables and to characterize DTPs. Categorical variables were described by frequencies and percentages, and continuous variables were described by means and standard deviations. A bivariate analysis was performed with binary logistic regression to assess association between the dependent and independent variables and to identify candidate for multivariate analysis. Those variables with a p value<0.25 in bivariate analysis were introduced to multivariate analysis and those variables with a p value<0.05 were considered as significant in multivariate analysis. Odds ratio (OR) with 95% confidence interval was also computed for each variable for the corresponding *P* value to see the strength of association. Drug risk ratio (frequency of involvement in DRP divided by frequency of prescription) was used to identify drugs at high risk of creating DRP. Finally, the result was summarized and described using tables and figures.

3.10 Ethical consideration

Ethical clearance was obtained from the ethical review committee of School of Pharmacy, Addis Ababa University. Written and verbal consent was obtained from participants. All study participants were informed about the purpose of the study and their participation was voluntary. The Participant was assured that lack of willingness to involve in the study wouldn't affect the service they get. Privacy of participants was ensured since patients were interviewed in a different room. All information obtained from the participants were kept confidential and the data was used for the research purpose only.

3.11 Operational definition

- Drug therapy problem – is any undesirable event experienced by a patient which involves, or is suspected to involve, drug therapy, and that interferes with achieving the desired goals of therapy, which can be identified using European society of cardiology and the American heart association (AHA) heart failure management guidelines
- Unnecessary drug therapy: The patient is taking a medication for no medically valid indication
- Non-drug therapy more appropriate: The medical condition is most appropriately treated with non-drug therapy
- More effective drug available (not the most effective drug): Patient is not on first-line treatment agent in accordance with published guidelines for a particular condition (with no documented contraindication to its use)
- Prophylactic/preventive: A drug therapy required to prevent development of new condition or to prevent disease progression
- Synergistic /additive effect: The patient requires additional or combination therapy to achieve treatment goal
- Suboptimal dosing: Medications are not titrated towards established target doses or towards highest tolerated dose
- Dosage high: The dose is high enough to cause ADR
- Drug interaction: presence of major drug-drug interaction
- ADR: Any noxious, unintended, and undesired effect associated with the drug experienced by the patient that is documented in the patient chart
- Comorbidity : Presence of cardiac risk factors and complications like HTN, Dyslipidemia , DM, Atrial fibrillation and other non-cardiac disease
- Adherence: Is drug taking behavior of a patient measured with Morisky scale in which the patient is considered adherence if he/she score 7-8 and non- adherent if the patient score ≤ 6
- Poly-pharmacy: The daily consumption of 5or more medications. Different strengths of the same drug were counted as one item. However, formulations of one drug requiring different routes of administration were regarded as separate items.

4 Results

4.1 Demographic characteristics of patients

In this study, 423 HF patients were included and the mean age was 46.52± 17. About half of the patients were in the age group of 36-60 years (50.6%). More than half of the patients were females (52.7%), while 63.8% and 31.4% of the patients were married and illiterate, respectively. Regarding social drug use behavior, most of the patients didn't use any of the social drugs. Regarding coverage of drug cost as many as 53.7% of patients paid for their medication (Table1).

Table 1: Socio demographic characteristics of heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, June - August, 2017 Tikur Anbessa

Socio demographic	Category	Number (%)	Mean ± SD
Gender	Male	200 (47.3)	
	Female	223 (52.7)	
Age	14-35	111 (26.2)	
	36-60	2 14(50.6)	46.52± 17
	>60	98 (23.2)	
Marital status	Single	105 (24.8)	
	Married	270 (63.8)	
	Divorced	17 (4)	
	Widowed	31 (7.3)	
Educational status	No formal education	133(31.4)	
	Primary	126(29.8)	
	Secondary	120 (28.4)	
	Diploma and above	44 (10.4)	
Social drug use	Cigarette Smoking	3 (0.7)	
	Alcohol use	21(5)	
	Khat chewing	14 (3.3)	
Source of medication	Free	196 (46.3)	
	Paid	227 (53.7)	

4.2 Clinical characteristics of patients and medications used

More than half of the patients were on treatment for less than five years (55.5%) and were in NYHA functional classIII (55.6%).Sixty-six percent of patients had preserved systolic function. Most of the patients reported that they didn't experience drug allergy, only five patients (1.2%) experienced penicillin allergy (Table 2).

Table 2: Clinical characteristics of heart failure patient attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August, 2017

Clinical CXS	Category	Number (%)	Mean ± SD	Range
Duration of HF	≤5years	235(55.5)		
treatment	6-10yrs	135(32)	6 ±4.6	6month-35yrs
	>10yrs	53(12.4)		
Frequency of follow up	≤3 month	316(74.7)		
	≥4 month	107 (25.3)		
NYHA class	Class I	63 (14.9)		
	Class II	125 (29.6)		
	Class III	235 (55.6)		
LVEF	HFrEF	104 (24.9%)	55.43±14.4	15-81
	HFmrEF	39 (9.2%)		
	HFpEF	280 (66.2%)		
Known drug allergy	No	418 (98.8)		
	Yes	5 (1.2)		

The common etiology of HF was chronic rheumatic valvular heart disease (CRVHD) (50.8%), followed by IHD (21.5%), Hypertensive heart disease (HHD) (14.7%) and cardiomyopathy (CMP) (10.6%)(Figure 1).

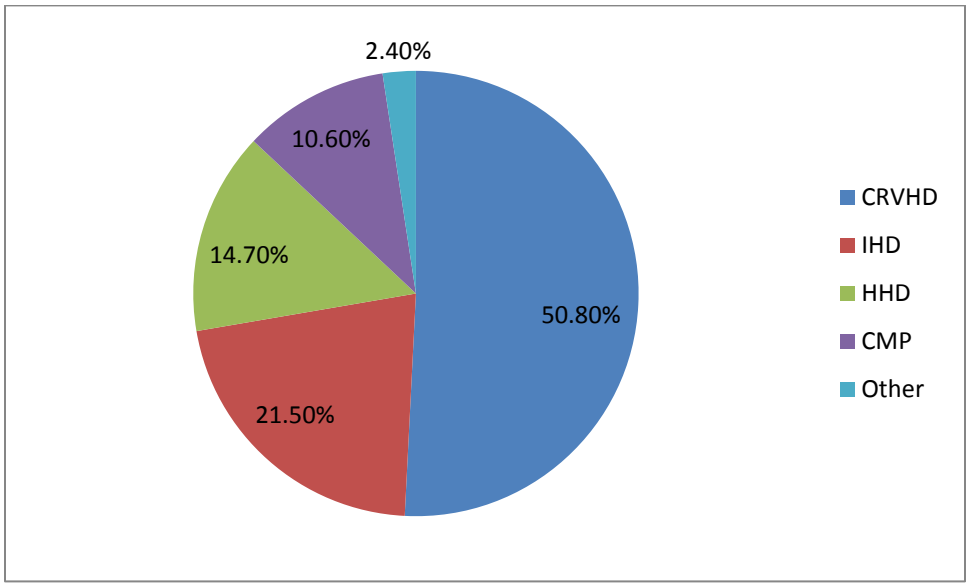

Figure 1: Etiology of heart failure among heart failure patients at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August , 2017:*Other: Degenerative valvular heart disease, corpulomonale, congenital heart disease; CMP: cardiomyopathy, IHD: ischemic heart disease, HHD: hypertensive heart disease, VHD: valvular heart disease

Three-fourth of patients had one or more comorbidities. A single comorbidity was found in 40.9% of patients, while 21.5% and 8.3% of patients had 2 and 3 comorbidities, respectively. A maximum of five comorbidities were encountered in 6 patients. The average number of comorbidity was 1.7±0.9.

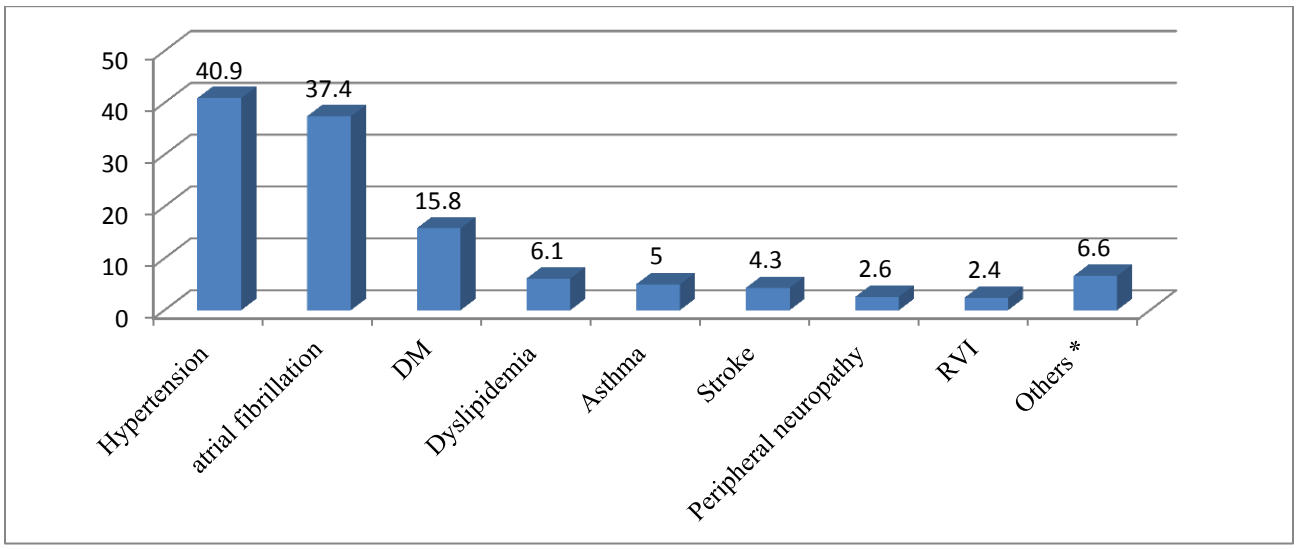

Figure 2: Common comorbidities of heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August , 2017 *Others; Hypothyroidism, hyperthyroidism, cancer, anemia, TB, Pericarditis, BPH and gout
DM: diabetes mellitus, RVI: retroviral infection

The most common documented cardiac-related comorbidities were hypertension (40.9%), atrial fibrillation (37.4%) and dyslipidemia (6.1%). The top five non-cardiac comorbidities included diabetes (15.8%), asthma (5%), chronic kidney disease (4.3%), stroke (4.3%) and peripheral neuropathy (2.6%) (Figure 2).

A total of 2097 medications were used. The mean number of drugs per day was 4.96±1.62 per patient. Approximately, two-third of the patients received 5-10 drugs per day. Commonly prescribed drug classes were diuretics (578), beta blockers (305), ACEIs (188), antiplatelet (171), statins (147), anticoagulant (140) and cardiac glycosides (109) (Figure 3). The most frequently prescribed specific drugs were furosemide (294), spironolactone (236), Enalapril (188), benzathine penicillin (181), aspirin (171) and atenolol (170) (Figure 3).

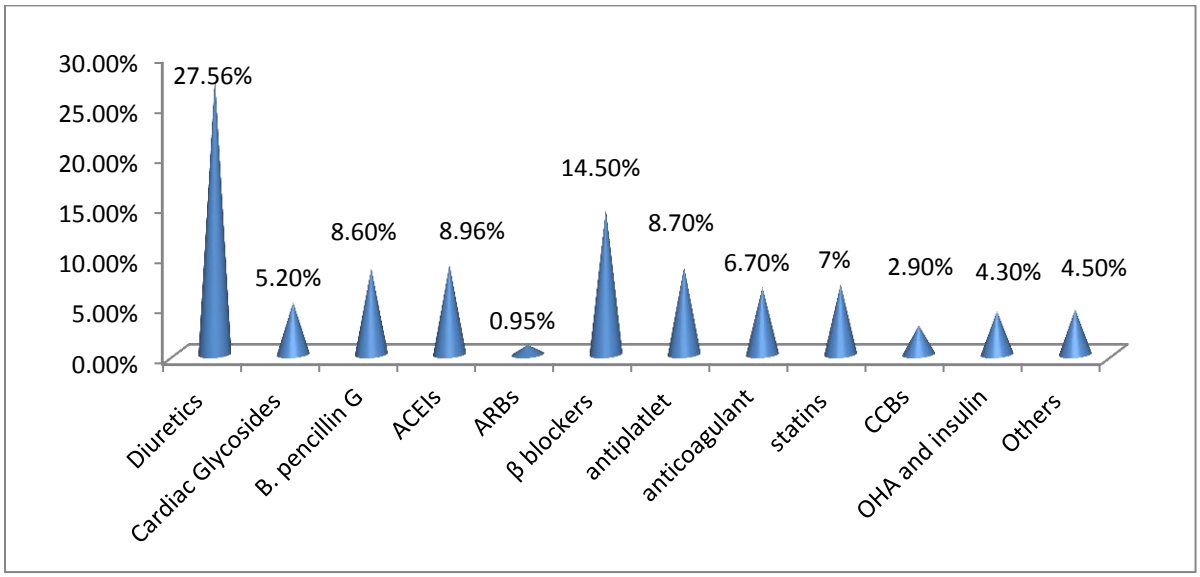

Figure 3: Frequently prescribed drug class in heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August , 2017 Others: anti arrhythmic, Antianginal agent, antithyroid, antiTB, HAART, Iron salt NSAIDs, Xanthine Oxidase Inhibitor, tricyclic antidepressant; ACIEs: angiotensin converting enzyme inhibitors, ARBs: angiotensin receptor blockers, CCBs: calcium channel blockers, OHA: oral hypoglycemic agents

4.3 Prevalence of DTP

A total of 572DTPs were identified from 277(65.5%) of study participants. One DTP was identified in 80 (28.9%) patients, 2 DTPs in 112 (40.4%) patients and≥3 DTPs in 85 (30.7%) patients. The average number of DTP per patient was 2.1 ±0.9(Figure 4).

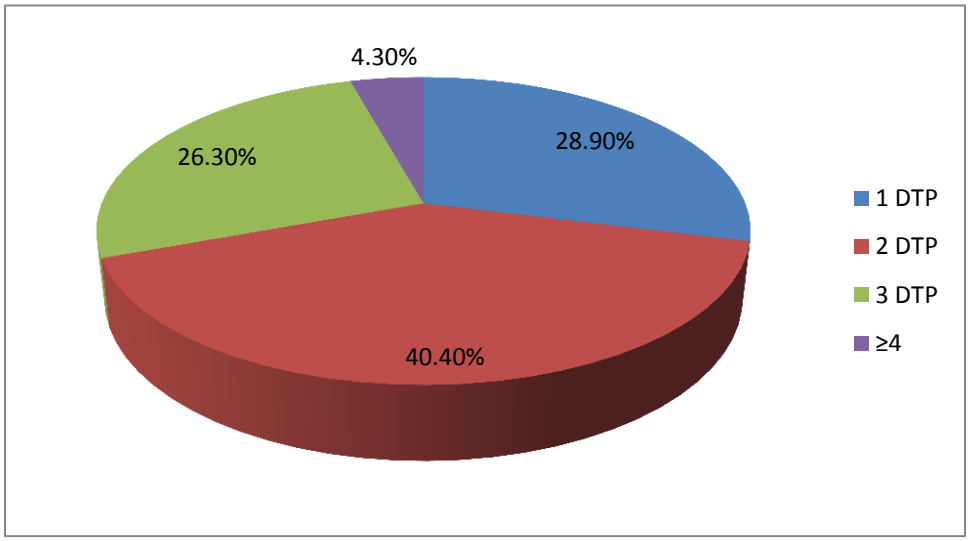

Figure 4: Number of drug therapy problems per patient among heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August , 2017

4.3.1 Type of and drugs involved in DTPs

The most common DTPs identified were DI (40.5%) followed by not the most effective drug (17.5%), ADR (14.7%), the need for preventive/prophylactic drug therapy (9.6%), and inappropriate dosage (9%) (Table 3)

Table 3: Type of DTP identified from heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August, 2017

Type of DRP	Specific DTP	No	Percent
Drug interaction		232	40.5
Adverse drug reaction	Undesired effect	74	14.7
	Unsafe drug for the patient	5	
	Allergic reaction	5	
Effectiveness	Not the most effective drug	100	17.5
Inappropriate dose	Suboptimal dose	52	9
	Dose high	4	0.7
Need additional drug therapy	Prophylactic	55	9.6
	Synergy	14	2.45
Unnecessary drug therapy	No medical indication	17	2.97
	Non drug therapy	14	2.45

The most frequent drug class involved in DTPs was beta blockers followed by ACEIs, MRA, and antiplatelet, anticoagulants, loop diuretics, cardiac glycosides and CCBs (Figure 6)

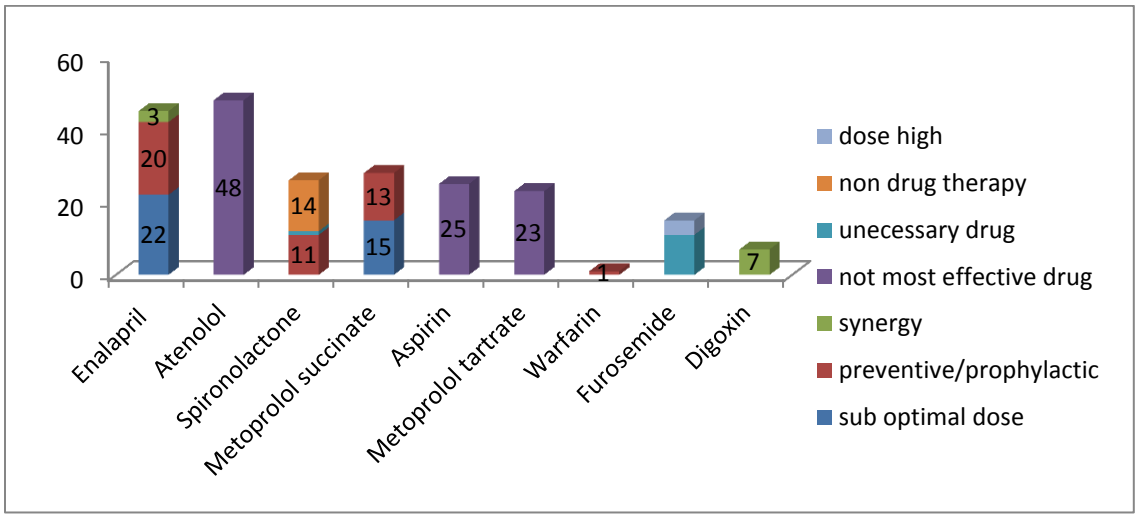

Figure 5: Drug classes involved in specific type of drug therapy problems among heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August , 2017

A total of 120 (43.3%) patients with CRVHD had DTP, while 77(27.8%),32(11.5%),41(14.8%) and 7 (2.5%) number of patients with IHD, HHD, CMP and other cause of heart failure had DTPs, respectively. The type of DTPs with cause of heart failure are listed in (Table 4).

Table 4: Disaggregation of type of drug therapy problems by cause among heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August , 2017

DTP	CRVHD	IHD	HHD	CMP	Others
No medical indication	-	14	2	1	-
Non drug therapy more appropriate	13	-	-	-	1
Prophylactic/preventive drug therapy	15	25	3	12	-
Synergistic	7	-	7	-	-
More effective drug available	23	50	5	18	4
Dose low	3	29	-	20	-
Dose high	4	-	-	-	-
ADR	36	22	21	4	1
DI	101	67	23	35	6

A total of 232 significant DDIs were identified. At least one DI was found in 120 patients, 2 in 45 patients, three in 37 patients and more than three in 30 patients. The top 5 DI in descending order of prevalence were: use of loop diuretic with aspirin, spironolactone with digoxin, ACEIs with spironolactone, Aspirin with spironolactone and use of Aspirin with metformin. Other most Frequent DIs is outlined in Table 6.

Table 5: Frequency of major drug interaction in heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August , 2017

Drugs involved in DI	Frequency	Severity	Possible effect
Aspirin +Furosemide	89	Major	Risk of nephrotoxicity
Spironolactone +Digoxin	85	Major	Digoxin toxicity
Spironolactone +Enalapril	83	Major	Risk of hyperkalemia
Spironolactone +Aspirin	68	Major	Risk of nephrotoxicity
Aspirin +Metformin	28	Major	Risk of hypoglycemia
Aspirin +HCT	23	Major	Risk of nephrotoxicity
Aspirin +digoxin	23	Major	Increase serum dioxin level
Aspirin +Glibenclamide	20	Major	Risk of hypoglycemia
Aspirin +Warfarin	16	Major	Increased risk of bleeding
Aspirin +Clopidogrel	12	Major	Increased risk of bleeding
Aspirin +Amitriptyline	7	Major	Increased risk of bleeding
Clopidogrel +Omeprazole	2	Major	Decrease concentration of Clopidogrel
Digoxin +HCT	1	Major	Digoxin toxicity
Warfarin +Allopurinol	1	Major	Increase INR
Warfarin + Clopidogrel	1	Major	Bleeding
Amlodipine +Simvastatin	1	Major	Myopathy

A total of 84 patients experienced medication adverse effects. Some of the most common ADR encountered included bleeding, dry cough, and peripheral edema (Table 5).

Table 6: Types and prevalence of ADRs identified from heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August , 2017

Drug	ADR	Frequency	Percentage
Warfarin	Bleeding	22	27.3
	GI irritation	1	
Enalapril	Dry cough	20	25
	Angioedema	1	
Nifedipine	Peripheral edema	11	13
Benzathine G. penicillin	Allergy	5	5.9
Aspirin	Unsafe drug	4	4.8
Aspirin+clopidogrel	UGIB	4	4.8
Atenolol	Bradycardia	2	4.8
	Bronchospasm	2	
Furosemide	Hypotension	4	4.8
Atorvastatin	Myopathy	2	3.5
	Unsafe drug	1	
Enalapril+ spironolactone	Hyperkalemia	3	3.5
Spironolactone	Gynecomastia	2	2.4
Total		84	100

UGIB upper gastro intestinal bleeding GI gastro intestinal

Drug risk ratio was calculated for each drug. A higher drug risk ratio was found for Nifedipine (0.7) followed by Metoprolol tartrate (0.6), atenolol (0.33) and enalapril (0.25). In the contrary furosemide was the most frequently used drug with the lowest drug risk ratio (0.07) Figure 7.

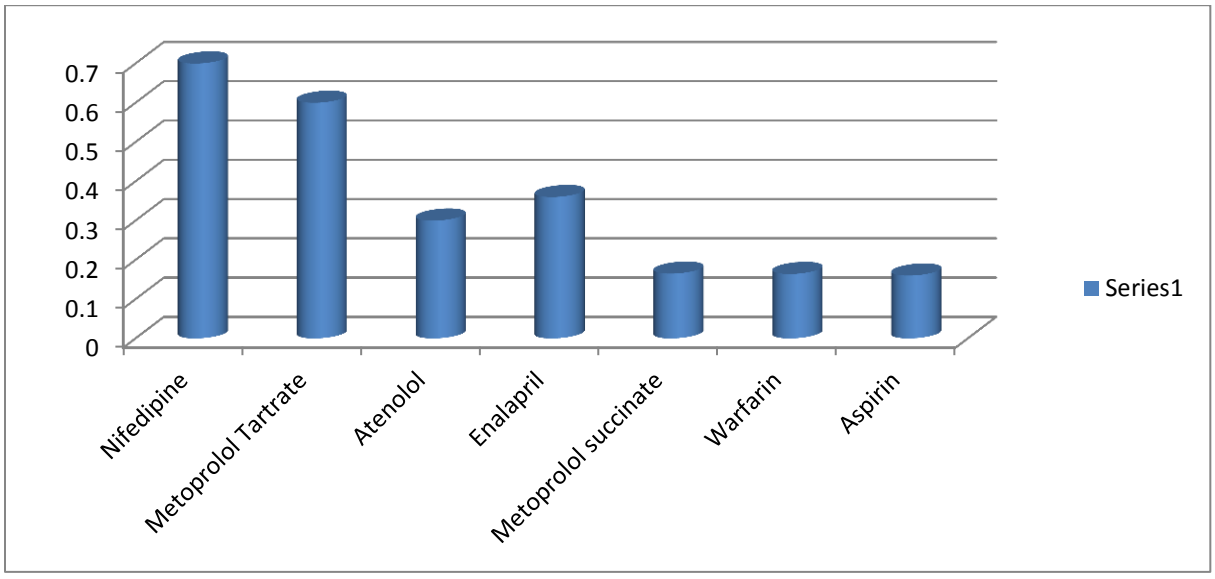

Figure 6: Drug risk ratio of commonly used drugs among heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August , 2017

4.4 Predictors of occurrence of DTP

Perceived demographic and clinical factors which satisfied the conditions for multi-variable logistic regression analysis were age, gender, duration of HF treatment, average number of drugs/day, presence of comorbidity and LVEF. Factors significantly associated with the occurrence of DTP in the logistic regression analysis were age, gender, presence of comorbidity, average number of drugs per day and LVEF. Females were 3 times more likely to develop DTPs compared to males (adjusted odds ratio [AOR] =3[95% CI: 1.524- 5.943]). Patients aged between 36-60 years were 4.3 times more likely to develop DTPs compared to patients whose age was <35 years. Patients with reduced ejection fraction were 6.6 times more likely to develop DTPs than patients with preserved ejection fraction (adjusted odds ratio [AOR] =6.69[95% CI: 2.706-16.581]). The odds of DTPs were 8.7 times higher among patients who took an average of 5 or more drugs per day as compared to patients who took less than five drugs per day (Table 7).

Table 7: Predictors of occurrence of drug therapy problems in heart failure patients attending cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August, 2017

Variables	Category	DTPs (%)		COR (95% CI)	AOR (95% CI)
		Yes	No		
Gender	Male	105(37.9)	95(65)	1.00	1.00
	Female	172(62)	51(35)	3.05(2.009-4.635)	3.0(1.524-5.94)*
Age	14-35	22(7.9)	89(60.9)	1.00	1.00
	36-60	171(62)	43(29.4)	16.08(9.061-28.56)	4.31(1.966-11.04)*
	>60	84(30.3)	14(9.6)	24.27(11.657-50.54)	4.65(1.576-11.82)*
Left ventricular	HFpEF	183(66)	136(93)	1.00	1.00
ejection fraction	HFrEF	94(34)	10(7)	6.98(3.509-13.909)	6.69(2.706-16.56)*
Comorbidity	No	12(4.3)	93(63.6)	1.00	1.00
	Yes	265(95.6)	53(36.4)	5.71(2.864-11.386)	5.23(1.903-14.39)*
Number of	<5	39(14)	116(79.5)	1.00	1.00
medications	≥5	238(86)	30(20.5)	23.56(13.95-39.89)	8.76(4.344-17.68)*

HFpEF: heart failure with preserved ejection fraction HFrEF: heart failure with reduced ejection fraction

4.5 Adherence status and possible reasons for non-adherence

According to Morisky scale, 208 (49.2%) participants had good adherence, while 24(5.7%) and 191 (45.2%) of participants had medium and poor adherence, respectively. However the final adherence was re-categorized into two in such a manner that participants who scored seven or eight were re-assigned as adherent (Figure 8).

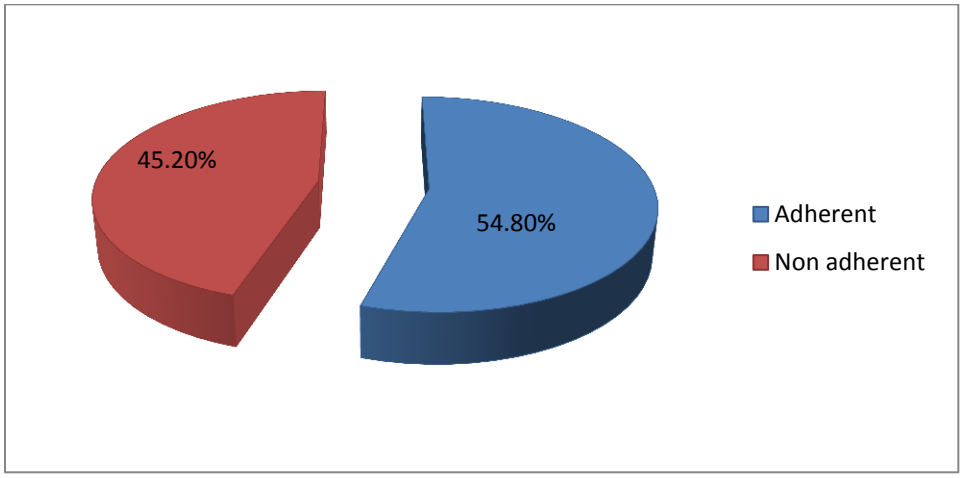

Figure 7: Adherence status of heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June –August , 2017

Patients' adherence was affected by different factors. The major factors stated by the patients included forgetfulness, regimen complexity, unavailability of medication, drug caused side effect, cost of medication and patient belief on drug efficacy (Table 8).

Table 8: Possible reasons for non-adherence reported by heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August , 2017

		Frequency	Percent
Possible reasons for non-adherence	Forgetfulness	184	43.5
	Drug caused side effect	82	19.3
	Complexity of regimen	170	40
	Cost of medication	63	14.9
	Unavailability of the medication	95	22.5
	Patient feel worse	83	19.6

4.6 Predictors of Non-adherence

Age, sex, educational status, source of medication, duration of heart failure treatment, number of medication and ADR fulfilled the criteria for multi-variable binary logistic regression. Association was observed between duration of treatment, average number of medication per day and ADR. Patients who took an average of 5-9 drugs per day were 4 times more likely to be non-adherent compared to patients who took less than 5 drugs per day (AOR=4.4 [2.49-7.9]). For each increase in duration of treatment, non-adherence to medication increased by 1.2 (AOR = 1.223 [95% CI: 1.148-1.308]).The odds of being non-adherent were 2.7 times higher among patients who developed ADR compared to those who did not develop ADR (AOR = 2.7 [95% CI: 1.495-6.686]) (Table 9).

Table 9: Multivariable logistic regression analysis of factors associated with medication adherence among heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August , 2017

Variables	Category	Adherent		COR (95% CI)	AOR (95% CI)
		No	Yes		
Gender	Male	73(38.2)	127(54.7)	1.00	1.00
	Female	118(61.8)	105(45.2)	1.955(1.324-2.887)	1.266(0.774-2.07)
Age	14-35	22(11.5)	8938.3)	1.00	1.00
	36-60	107(56)	107(46)	4.045(2.362-6.929)	1.24(0.630-2.446)
	>60	62(32.5)	36(15.5)	6.967(3.742-12.97)	1.50(0.677-3.343)
Educational status	Primary and less	130(68)	129(55.6)	1.00	1.00
	Secondary and above	61(32)	103(44.4)	0.58(0.394-0.876)	0.83(0.495-1.402)
Source of medication	Out of pocket	90(47)	137(59)	1.00	1.00
	Free	101(53)	95(41)	1.61(1.100-2.381)	1.48(0.914-2.418)
duration of	≤ 5yrs	120(51)	115(49)		
	6-10yrs	109(80.7)	26(19.3)	1.27(1.198-1.358)	1.2(1.148-1.308)*
	>10yrs	48(90.5)	5(9.5)		
Number of	<5	31(16.2)	124(53.4)	1.00	1.00
medications	≥5	160(84)	108(46.5)	5.92(3.729-9.416)	4.4(2.491-7.907)*
ADR	No	131(68.5)	208(89.6)	1.00	1.00
	Yes	60(31.4)	24(10.4)	3.97(2.357-6.686)	2.7(1.495-6.686)*

4.7 Examples of drug therapy problems identified in study subjects

Table 10: Examples of drug therapy problems identified from heart failure patients attending at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia June – August, 2017

No	Description of DTP	Type of DTP
1	A 30 year old female patient with CRVHD was on furosemide 40mg BID, spironolactone 25mg and digoxin 0.125mg. Her BP was 90/40 and she had experienced side effect like hypotension due to the high dose of furosemide	Dose high, ADR and DI (between spironolactone and digoxin)
2	A 65 year old male patient with CRVHD, AF and HTN was on furosemide 40mg , spironolactone 25mg, enalapril 10mg BID, Metoprolol succinate 25mg and warfarin 5mg. spironolactone and enalapril have major drug interaction that may lead to hyperkalemia (potassium level was 6)	ADR and DI
3	A 20 year old male patient with CRVHD and AF was on ASA 81mg, furosemide 40mg, spironolactone 25mg, atenolol 50mg and digoxin 0.125mg. However ASA is less effective in preventing stroke	Not the most effective drug
4	A 19 year old female patient with CRVHD and AF was taking furosemide 40mg, spironolactone 25mg, digoxin 0.125mg, warfarin 5mg. Her pulse rate was not controlled by digoxin alone	Need addition of β blocker
5	A 26 year old female with CRVHD furosemide 20mg, spironolactone 25mg enalapril 10mg. However in patient with low dose diuretics hypokalemia can be prevented by increasing dietary potassium intake. Besides the patient is also taking enalapril which might put her to risk of drug-drug interaction	Non drug therapy more appropriate,drug interaction
6	A 21 year old female patient with CRVHD on furosemide 60mg BID, spironolactone 50mg and enalapril 5mg. the patient experienced ADR like gynecomastia	ADR

7	A 66 year old male patient with IHD (EF 37%) and CKD was taking ASA 81mg, atorvastatin 40mg, enalapril 5mg, Metoprolol succinate 12.5mg for the past 2 years, however the dose of enalapril and Metoprolol should be up-titrated	Sub-optimal dose, Drug interaction
8	A 67 year old male patient with IHD (EF 35%) , dyslipidemia and DM was on atenolol 25mg, enalapril 10mg, furosemide 20mg, ASA 81mg, atorvastatin 40mg, MTF 500mg BID and glibenclamide 5mg BID. However, atenolol is not effective in HFrEF. The use of furosemide is unnecessary, since the patient didn't have any sign of fluid collection	Not the most effective drug, unnecessary, drug interaction
9	A 69 year old male patient with IHD (EF 39), and DM was taking Metoprolol tartrate 50mg BID, ASA 81mg, atorvastatin 40mg, metformin 500mg BID and NPH. In patient with HFrEF Metoprolol tartrate is not effective	Not the ,most effective drug, drug interaction
10	A 48 year old male patient with IHD (EF 30%) and atrial thrombus (duration of 6 month) was taking ASA 81mg, Clopidogrel 75mg, warfarin 5mg, lovastatin 20mg, enalapril 5mg, atenolol 25mg, However patient with a history of CVD should be on moderate-high intensity statin. The patient also experienced UGIB due to drug interaction	Not the most effective drug, ADR, DI
11	A 16 year old female NYHA class III patient with DCMP (EF 29) and RVI was taking TDF/3TC/EFZ, enalapril 5mg BID, Carvedilol 3.125 mg BID for more than a year. The patient is still symptomatic despite on ACEIs and β blocker treatment. Spironolactone can be considered in symptomatic patients with HFrEF and LVEF ≤35%.	Need additional drug
12	a 79 year old male patient with HHD and DM was taking amlodipine 5mg, enalapril 10mg BID, ASA 81mg,	Unsafe drug for the patient

	simvastatin 40mg and MTF 500mg BID. However, the guideline didn't recommend ASA use in adult > 70 year old (risk of bleeding) and statin >75 year old	
13	A 70 year old male patient with HHD (un controlled HTN BP 150/90 mm Hg), dyslipidemia and CKD was taking atorvastatin 40mg and Nifedipine 20mg BID. Enalapril is first line in patients with compelling indication like HTN+ CKD	Need additional drug
14	A 70 year old male patient with HHD, DM and gouty arthritis was on allopurinol 100mg, atenolol 50mg, glibenclamide 5mg, simvastatin 40mg and ASA 81mg. His BP wasn't controlled with current regimen (170/90) since the patient has compelling indication (DM) enalapril can be considered as synergistic therapy	Not the most effective (atenolol), Unsafe drug (ASA), need enalapril
15	A 50 year old female patient with HHD and DM was taking Nifedipine 20mg BID, HCT 25mg, ASA 81mg, MTF 500mg glibenclamide 10mg BID. This patient needs statin therapy. She had also experienced ankle edema due to Nifedipine and treatment was changed to amlodipine	Need additional drug(statin), ADR, drug interaction
16	A 27 year old female with CRVHD was on furosemide 20mg and atenolol 12.5mg. The patient is penicillin allergy and was not on alternative therapy	ADR Need alternative drug (macrolide)
17	A 38 year old female patient with IHD and DM was on Metoprolol succinate 25mg, enalapril 10mg, spironolactone 25mg, rosuvastatin 10mg, ASA 81mg, MTF 500mg, glibenclamide 5mg. the patient experienced drug induced angioedema and enalapril changed to losartan	ADR
18	A 52 year old female with DCMP and AF was on	ADR, need additional drug

	furosemide 40mg BID, spironolactone 25mg, enalapril 5mg BID and Metoprolol succinate 25mg. The patient refuse to take warfarin due to GI irritation	(GI irritation)

5. Discussion

HF patients are at high risk of having DTPs and adherence issues owing to presence of comorbidity, polypharmacy and complexity of drug regimen. The presence of DTPs in patients with HF is associated with detrimental health outcomes. Identification of type of DTP and factors associated with them is critical for prevention of DTPs and improving health outcome. The present study was aimed to determine DTPs among HF patients at adult cardiac clinic of TASH.

More than half of the patients were females, which was consistent with studies conducted elsewhere (Abdela et al., 2016, Hussein et al., 2014, Al-Azzam et al., 2016). The mean age of the patients was 46.5, with majority of the patients being in the age group of 36-60 years (50.6%). This finding is similar with the studies done in Gondar (Bhagavathula et al., 2017) and Jimma, Ethiopia (Tigabu et al., 2014). But, is different with studies done in Boston (Dempsey et al., 2017) and India (Abraham, 2014) with a mean age of 69 and 68.7, respectively. This difference might be due to the cause of HF, which is majorly CRVHD in the present study that appears to be common in young patients. NYHA functional classification is a useful prognostic tool to help tailor management of HF patients. A higher NYHA classes were associated with lower quality of life and poor outcome including higher mortality rate and hospitalization among ambulatory chronic HF patient(Ali Ahmed et al., 2006). Majority of patients (58%) within the age group of 36-60 years were in NYHA class III. This finding is similar with a study done in Barcelona, where 52% of HF patients were in NYHA class III(Gastelurrutia et al., 2011). This might be due to as age increase comorbidity and number of medication also increase, which may limit patients physical activity.

In the present study, 75% of the patients had comorbidities. However, this finding was lower than what was found in a hospital based observational study in India(Shareef et al., 2015) as well as in Jimma and Feleghiwot referral hospital in Ethiopia (Tegegne et al., 2015), where comorbidity was found to be 91.1% and 82.7%, respectively. The possible reason could be that these studies were done among cardiovascular inpatients in general, where a higher number of comorbidities are expected. Hypertension and atrial fibrillation were the 2 most cardiac related comorbidities and this is in line with a study done in Boston, where hypertension, dyslipidemia and atrial fibrillation accounts for the majority of comorbidities (Dempsey et al., 2017).

A total of 2097 drugs were used with a mean of 4.9 drugs per patient, which was comparable with some studies(Urbina et al., 2015, Tegegne et al., 2015)but different from others (Gastelurrutia et al., 2011, Hsu et al., 2016), where a mean of 10.2 and 17.6 drugs/patient were prescribed, respectively. The discrepancy could be due to the fact that patients in these studies tend to be older and IHD is the main etiology. Besides, more than 80% of the patients had comorbidities like hypertension and DM that require multiple therapies. Commonly prescribed drug classes in this study were diuretics, beta blockers and ACEIs. This finding was in line with a study done in Barcelona (Gastelurrutia et al., 2011), India (Abraham, 2014), and Gondar, Ethiopia (Abdela et al., 2016).

About 65% of participants had at least one DTP. Although there is a few studies done in HF patients per se, the prevalence of DTP reported in the present study is in line with studies conducted among cardiovascular patients in India (66.3%) (Abraham, 2014),Switzerland (69%) (Niquille and Bugnon, 2010) and Gondar Ethiopia (63.4%) (Abdela et al., 2016). However, it was lower than other studies done in Barcelona (78%)(Gastelurrutia et al., 2011) Bonga, Ethiopia (72%) (Gizaw and Dubale, 2017). The difference could be attributed to: i) the study in Barcelona was a cohort study and followed patients for 6 months, providing sufficient time for detection of DTPs; ii) difference in the classification and operationalization of DTP (For example, the Barcelona study included dispensing and administration related problems); and iii) nature of patients included in the study (for example, the Ethiopian study included cardiovascular patients and most of them had comorbidities that predispose them to receive multiple medications due to complications).

The most common DTPs encountered in the present study were DI, not the most effective drug, ADR, sub therapeutic dosage and the need for prophylactic or preventive drug therapy.

DI was the number one frequently identified DTP. DI is a major factor that may affect patient's clinical outcome by contributing to increased risk of adverse drug events related hospitalization and a higher health care cost. Likewise, other studies also indicated drug-drug interaction as the most prevalent DTPs (Hussein et al., 2014, Gastelurrutia et al., 2011, Abraham, 2014).

The most common DIs were between aspirin and furosemide, resulting in an increased risk of nephrotoxicity; spironolactone and digoxin, increasing the risk of digoxin toxicity; ACEIs and spironolactone, increasing risk of hyperkalemia; and aspirin use in combination with

spironolactone, resulting in an increased risk of nephrotoxicity. In this study, some interactions had resulted in significant adverse events. For example, from 12 IHD patients who used Aspirin with Clopidogrel, four patients developed UGIB, and hyperkalemia was developed among 2 patients who were on concurrent enalapril and spironolactone therapy. However, as the benefit of concurrent therapy outweighs the risk the patient should be closely monitored for presence of toxicity.

The second most common DTPs were effectiveness related problems. According to Cipolle *et al.* (2012) DTP classification, this category includes selection of a drug which is not the most effective for the indication being treated. In the present study, it accounted for 17.5% of the total DTPs. A higher prevalence (55%) was found in a study conducted among HF patients in Boston (Dempsey et al., 2017). The possible explanation for this might be that in the Boston study effectiveness was evaluated for both HF and comorbid conditions, since laboratory values and documented patient compliant were available for each patient. However, in our study, laboratory values were not available for all patients which might underestimate effectiveness of treatment for comorbid conditions.

Appropriateness of HF medication selection was made based on established guideline like AHA or ESC guidelines. For example, Aspirin was used for prevention of stroke in patients with atrial fibrillation instead of warfarin. However, according to the guideline, aspirin is less effective in preventing stroke compared to warfarin. Warfarin reduces the risk of stroke by two-thirds and mortality by one-quarter compared with aspirin or no therapy(Members: et al., 2016). The physicians working in cardiac clinic said that they used aspirin instead of warfarin because warfarin wasn't available, patient couldn't afford INR monitoring, patients live where INR monitoring wasn't available. The other effectiveness problem was the use of Atenolol and Metoprolol tartrate in patients with HFrEF, though Carvedilol, Metoprolol succinate and bisoprolol have only been shown to improve morbidity and mortality. Moreover, the efficacy of Metoprolol tartrate in reducing mortality in HF has not been proven (Ponikowski et al., 2016, Al-Khatib et al.). Metoprolol succinate provides more consistent plasma concentrations over a 24-hour period and appears to provide more favorable effects on heart rate variability, autonomic balance, and Blood pressure compared to the immediate-release Metoprolol(Wells et al., 2014).The reason for use of atenolol or Metoprolol tartrate instead of Metoprolol succinate

included, unavailability and cost related issues. In addition, they mentioned that it was difficult to review patient chart due to high load of patients, so most of the time they refill medications that the patients were taking.

The third DTP identified was ADR (14.7%). This was in close agreement with the Taiwan (13.5%) (Hsu et al., 2016) and Barcelona (16%) (Gastelurrutia et al., 2011)studies. A relatively higher and very high rate was reported from India (19%)(Shareef et al., 2015),Jimma and Feleghiwot referral hospital, Ethiopia (26%) (Tegegne et al., 2015)and Boston (93%) (Dempsey et al., 2017) studies. The possible explanation could be that either the studies were performed on cardiovascular inpatients or, cardiovascular patients with DM that increase the risk of ADR

Inappropriate dosing (suboptimal dose and dose high) accounted for 9.7 of all DTPs. Suboptimal dosing was identified in 9% of HF patients with reduced ejection fraction. This is concordant with studies done in Spain (6.7%)(Urbina et al., 2015), India (10.4%)(Abraham, 2014), and Jimma and Feleghiwot referral hospital, Ethiopia (7.5%) (Tegegne et al., 2015).

Even though there is strong evidence on the efficacy of beta blockers and ACE inhibitors/ARBs in improving HF outcomes and reducing mortality, they are generally prescribed at much lower doses than the doses achieved in randomized controlled trials(Hickey et al., 2016).In the current study, ACEIs and evidence based β blockers were not being titrated towards established guideline recommended target doses. These drugs should be up-titrated to the maximum tolerated dose that have been reported to be effective in clinical trials in stable patients in order to achieve adequate inhibition of the renin–angiotensin–aldosterone system(Ponikowski et al., 2016, Mann and Felker, 2014).Among the various reasons stated by the residents working at cardiac clinic for failure to up-titrate doses were comorbidity, fear of adverse effect, reluctance to change the treatment when a patient is stable, burden of monitoring, lack of clinical experience, and influence of previous trends.

In contrast, dose high occurred in 4 patients. A higher percentage was found in other studies (Dempsey et al., 2017, Hsu et al., 2016, Tegegne et al., 2015). The most common drug encountered as high dose was furosemide, in which patient experience hypotension related with the dose.

Among indication related problems, the need for prophylactic/preventive drug therapy accounted for 9.6%. This was in close agreement with Taiwan (7%)(Hsu et al., 2016), Jordan(7.6%)(Al-

Azzam et al., 2016) and India (9.4%) (Shareef et al., 2015) studies. A higher number of indication related problems were found in studies done in Barcelona (28.6%)(Gastelurrutia et al., 2011) and Boston 43% (Dempsey et al., 2017)(43%). The difference could be that o in both studies patient information regarding active disease, laboratory values and used medication was complete for each patient, therefore they also determined necessary medication for disease other than HF.

ACEIs and β blockers were among the most common drug categories needed for the prevention of cardiac remodeling and disease progression and this is in line with the Jimma and Feleghiwot study (Tegegne et al., 2015).

In the present study, unnecessary drug therapy was found in 5.4% of patients. This was comparable with the studies done in Barcelona (4.8%)(Gastelurrutia et al., 2011), India(5.66%)(Shareef et al., 2015)and Adama, Ethiopia (5.2%) (Hussein et al., 2014). However, this finding was higher than studies done in Spain (0.45%)(Urbina et al., 2015) and Jordan (2.47%)(Al-Azzam et al., 2016). The Spain study, was done among cardiovascular inpatients, which provides an opportunity to check prescribed drugs on daily basis.

The second unnecessary DTP was nondrug therapy more appropriate (2.4%). Spironolactone was used for prevention of hypokalemia in patients who are on low dose diuretic treatment with enalapril. This is in line with a study in Jimma and feleghiwot referral hospital in which, patients received potassium supplementation (Tegegne et al., 2015). The use of MRA is often associated with development of hyperkalemia, particularly when combined with ACEIS/ARB (Mann and Felker, 2014). In these patients hypokalemia can be prevented by increasing dietary intake of potassium.

In this study, beta blockers, ACEIs, MRA and antiplatelet were common drug classes involved in DTP, which was comparable with some studies (Gastelurrutia et al., 2011, Hsu et al., 2016, Abraham, 2014, Gizaw and Dubale, 2017). Although not specific to HF , studies done in Jimma(Tigabu et al., 2014) and Gondar, Ethiopia (Bhagavathula et al., 2017) showed cardiovascular medication as the second and third most common drug class involved in DTPs, respectively. It is essential to be aware and give attention to those drugs with the highest drug risk ratio since these drugs expose patients more often to DTPs. Metoprolol tartrate, Nifedipine, atenolol, enalapril, Metoprolol succinate, aspirin and warfarin were drugs found to be with the

highest drug risk ratio. This is concordant with the findings from Taiwan(Hsu et al., 2016) and India (Abraham, 2014) studies.

The identification of risk factors for DTPs is important, as it helps to identify the most susceptible patients, who require close monitoring of drug therapy. The result of this study showed age, female sex, LVEF, presence of comorbidity and Poly-pharmacy were found to be independent predictors, which increase the chance of having DTPs. Number of medication taken by a patient was significantly associated with DTPs in a number of studies, which showed that patients with multiple medications have a complex drug schedule which may contribute to the poor medication adherence, drug-drug interactions and side-effects of drugs (Gastelurrutia et al., 2011, Shareef et al., 2015, Abdela et al., 2016, Urbina et al., 2015).

Presence of comorbidity was another risk factor for the occurrence of DTPs. This was supported by similar studies done in Jordan (Al-Azzam et al., 2016), India (Abraham, 2014), and Ethiopia (Tegegne et al., 2015).Age and female sex were associated with an increased risk of developing DTPs. Age was also found to be a risk factor among cardiovascular patients in India(Abraham, 2014) and Jordan (Al-Azzam et al., 2016). As age increases, comorbidity and number of medication increase, which put patients to an increased risk for developing DTPs.

Female sex was as well a risk factor in studies done in Spain (Urbina et al., 2015) and Ethiopia(Bhagavathula et al., 2017). In another study, in Jimma, Ethiopia, females were 1.95 times more likely to have DTPs than male. Female patients in Ethiopia have poor economic power, which might make them to seek hospital care after multiple disorders had been developed, leading to multiple diagnosis and Poly-pharmacy(Tigabu et al., 2014).

Patients with reduced ejection fraction were at higher risk for developing DTPs. This might be due to patients with reduced ejection fraction mightn't be on cardio protective medication or may be on suboptimal dose.

Adherence to evidence based medication is crucial. Non-adherence to HF medication is associated with increase in hospitalization emergency visit, worsening symptom and disease progression and overall increase in health care cost(Aggarwal et al., 2015, Knafl and Riegel, 2014, Davis et al., 2014).

The prevalence of non-adherence to HF medication was 45.2%, which is in line with the findings in other local studies: Adama(44.8%)(Hussein et al., 2014), Jimma and feleghiwot

referral hospital (46.4%)(Tegegne et al., 2015). But, higher than the findings in USA (28.9%,) (Knafl and Riegel, 2014), Cuba (36.5%) (Despaigne et al., 2012), the Netherlands (28%)(Van Der Wal et al., 2005)and Barcelona (14%)(Gastelurrutia et al., 2011).This could be due to a difference in the setting (outpatient vs. inpatient), methods used to measure adherence, or severity of the disease. For example, the USA study measured adherence electronically by using medication event monitoring system. Since it records each time the container opened, the patients become more conscious towards their medication. Conversely, the result of non-adherence was lower than a study done in Brazil (63.5%)(Silva et al., 2015). The Brazil study included older HF patients therefore these patients tend to have an increased number of comorbidities and pill burden, which negatively affect adherence.

The major factors for poor adherence as stated by the patient were forgetfulness, regimen complexity, unavailability of medication, drug caused side effect, cost of medication and patient believe on drug efficacy. A study done in Pakistan (MUJTABA et al., 2012)and Adama(Hussein et al., 2014)also cited similar reasons for patient non adherence towards their medication.

In this study, duration of treatment, average number of medication per day and ADR were found to increase risk of medication non-adherence. Likewise number of medication was associated with poor adherence in studies done elsewhere (Knafl and Riegel, 2014, Silva et al., 2015, Despaigne et al., 2012).

6 Limitation of the study

- This was a cross-sectional study and addressed the current situation of DTPs. There were no interventions and follow up of patients.
- When identifying ADR no causal relationship were established
- Non-adherence was probably over estimated since self-reported adherence was used as a measure of adherence rate.
- The result of the study may not be generalized to all HF patients since it was a single centered study conducted in a hospital serving referred patients who have severe illnesses and more co-morbidities.

7 Conclusions

The most common etiology of HF was CRVHD. The most common prescribed drugs were diuretics, β blockers, ACEIs and antiplatelet. The study identified DRPs in 65% of HF patients. DI was the major DRP followed by not the most effective drug, ADR, inappropriate dose and the need for prophylactic/preventive therapy. The most common drugs involved in DTP were enalapril, atenolol, spironolactone, Metoprolol succinate and aspirin. Highest drug risk ratio were found for both Metoprolol tartrate and Nifedipine (0.7) followed by atenolol, enalapril, Metoprolol succinate and, aspirin. There was a stronger association between age, gender, LVEF, comorbidity and Poly-pharmacy and occurrence of DTP. The rate of medication non-adherence was 45.2% and the common reason for non-adherence was forgetfulness, complexity of drug regimen, medication unavailability and patient lack of confidence on drug efficacy. Duration of treatment ADR and Poly-pharmacy were found to have significant association with poor adherence.

8 Recommendations

- PFSA should ensure medication availability within the hospital
- Electrolyte tests should be considered for patients who took diuretics to check electrolyte abnormalities
- Physicians should monitor patients for signs of adverse drug effects, including doing laboratory tests as necessary
- There should be patient education program to improve medication adherence and patient attitude towards the disease and its treatment
- Potential drug-drug interactions should be checked especially for those drugs whose interaction lead to an adverse effect
- The number of physicians working at cardiac clinic and patient load should be proportionate so that physicians could have more time to spend with each patient
- Comprehensive guideline should be prepared for management of cardiovascular disease
- Further studies with a follow up of patients with intervention should be considered

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Annexes

Annex I: Data abstraction format from patient interviews

Part I. Patients socio-demographic characteristics (Use "X" in the Boxes)

Card no	Age	Gender ☐ Male ☐ Female	Pregnancy ☐ Yes ☐ No
Marital status	☐ Single	☐ Married	☐ Divorced ☐ widowed
Educational status	☐ No formal edu.	☐ Primary	☐ Second. ☐ Tertiary
Place of residence			
Social drug use	Cigarette smoking ☐ Yes ☐ No	Alcohol use ☐ Yes ☐ No	Khat chewing ☐ Yes ☐ No
Salt restriction	☐ Yes ☐ No		

Part II Clinical characteristics (supplementary to the information obtained from medical chart)

NO		
1	Duration of heart failure treatment	
2	Frequency of follow up	
3	Comorbidity	☐ Yes ☐ No
4	Total number of drug you are taking	
5	How do you get your medications	☐ Free ☐ Payment

Part-III: Assessment of adherence (MMAS-8)

No	Items	No	Yes
1	Do you sometimes forget to take your pills?	□1	□0
2	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?	□1	□0
3	Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?	□1	□0
4	When you travel or leave home, do you sometimes forget to bring along your medicine?	□1	□0
5	Did you take all your medicine yesterday?	□1	□0
6	When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	□1	□0
7	Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	□1	□0
8	How often do you have difficulty remembering to take all your medicine? **0.** Never **1**. Rarely **2.** Once in a while **3.** Sometimes **4.** Usually **5**. All the time		
	Total score		

If you have any problems that challenges your medication adherence please the select your reason (more than one answer is possible)

□ Patient forgets to take

□ Disbelief in drug effectiveness

□ Fear of adverse events

□ Drug product too expensive

□ Drug product not available

□ Patient felt worse

□ Regimen complexity

Annex II: Data abstraction format from patient medical chart

Card Number_____ Age (in year) ____Weight (kg) _____Height (cm) _____

Present compliant:

No	Clinical characteristics			
1	Duration of heart failure			
2	duration of heart failure medication			
3	Frequency of follow up			
4	NYHA class	Class 1 ☐		
		Class 2 ☐		
		Class 3 ☐		
		Class 4 ☐		
5	Known drug allergy	No ☐ yes ☐ (specify)		
6	Comorbidity	**Type of comorbidity**		**Etiology of heart failure**
		HTN ☐	MI ☐	CRVHD ☐
		DM ☐	Angina ☐	Hypertensive heart disease ☐
	Yes ☐ No ☐	Dyslipidemia	Arrhythmia	Ischemic heart disease ☐
		AF ☐		Cardiomyopathy ☐
		Stroke ☐		PMI ☐
		PAD ☐		
		DVT ☐		

7 Past medical conditions and medications

Medical condition/ Indication	Drug product (Generic Name)	Dosage regimen (dose, route, frequency, duration)	Date (dd/mm/yy)		Response Effectiveness/ safety profile
			Started	Stopped	

8 Physical Examination (PE)/vital signs: Consecutive record of visits

P/E	Date												
PR													
BP													

9. Physical Examination(PE)/**vital** signs: Consecutive record of visits

Parameters	Date(dd/mm/yy												
Lipid profiles	LDL: mg/dl												
	TG: mg/dl												
	HDL: mg/dl												
	Total cholesterol												
LFT	Date												
	SGPT (ALT												
	SGOT(AST)												
	ALP												
RFT	Date												
	BUN												
	SrCr												
	GFR												
Blood glucose	Date												
	FBS												
	RBS												
	HbA1C												
Electrolytes	Date												
	Na												
	K												
	Mg												
	Ca												
	Cl												
	Date												
CBC	WBC												
	RBC												
	Hgb												
	Hct												
	MCV												
	MCH												
	MCHC												
	PLT												
	PT												
	PTT												
	aPTT												
	INR												
Other	Echo ECG MRI												

10 Present medical condition and medication

Medical condition/ Indication	Drug product (Generic Name)	Dosage regimen (dose, route, frequency, duration)	Date (dd/mm/yy)		Response /safety
			Started	Stopped	

11 **Assessment of adverse drug reaction**

Was there any experienced adverse effect of the drugs? ☐ Yes ☐ No

If yes which of the following manifestation occur?

Bleeding	Dry cough	Ankle edema	UGIB
Penicillin allergy	Hyperkalemia	angioedema	Gynecomastia
Headache	Bradycardia	Bronchospasm	GI
Unsafe drug			

Please specify the drug product and time of event

Drug regimen	Adverse drug event	Date the event occurred

12 Is there any drug interaction ☐ Yes (specify) No ☐

Annex III: Modified DTPs Registration Format

DTPs Categories	Common Cause(s) of Drug therapy problem
1. Unnecessary drug therapy	□ No medical indication □ Non drug therapy more appropriate □ Others ,specify_____
2. Needs additional drug therapy	□ Untreated medical condition □ Preventive/ prophylactic □ Synergistic/ potentiating □ Others, specify_____
3. Ineffective drug product	□ More effective alternative is available □ Condition refractory to drug □ Dosage form inappropriate □ Not effective for condition □ Others, specify_____
4. Dose too low	□ Wrong dose □ Duration too short □ Others, specify_____
5. Adverse drug reaction	□ Undesired effect □ Unsafe drug for patient □ Drug interaction □ Dosage administered or changed too rapidly □ Allergic reactions □ Contraindications present □ Others, specify_____
6. Dose too high	□ Wrong dose □ Duration too long □ Others, specify_____

Annex IV Key informant interview for physicians

Title: Assessment of drug therapy problems among ambulatory heart failure patients attending at adult cardiac clinic of TASH

Aim of the study: to assess drug therapy problem and medication adherence and associated factors among heart failure patients at adult cardiac clinic of TASH.

* The following questions are based on the results obtained from drug therapy problem among heart failure patients at adult cardiac clinic of TASH. Please respond by briefly stating your opinion. Your response on these questions will make possible for the identification of the reasons behind some of the drug therapy problem encountered in heart failure patients.

Please put your signature based on your Qualification

R1 _____

R2 _____

R3 _____

Thank you

1. In this study it was found that spironolactone was prescribed for almost all CRVHD patient who took furosemide, in your opinion what are the reasons to use spironolactone?
   A. To prevent hypokalemia when the dose of furosemide is ≥ 40mg
   B. To prevent hypokalemia when the dose of furosemide is ≥ 20mg
   C. For its remodeling effect
   D. Other(specify)
2. In this study patients who are allergic to penicillin didn't receive alternative prophylaxis what do you think the reason could be?

3. In this study it was found that dose of ACEIs and B blockers are not being titrated in patients with left ventricular systolic dysfunction. What do you think the reason and at what interval do you consider dose titration?

4. In patients with HHD when do you think ASA and statins should be initiated

5. What do you think the reason behind use of ASA instead of warfarin in patients with AF

6. In heart failure patients with reduced ejection fraction Metoprolol tartrate and atenolol was indicated what could be the possible reasons

7. Which one of the guideline for treatment of heart failure are you using
   A. AHA/ACC B ESC C Ethiopian national guideline for NCDs

Annex V English version of information sheet

Dear participant, Good Morning/Afternoon

Introduction

My name is_____ I am a member of the study that is carried out at Tikur Anbessa specialized hospital Addis Ababa, Ethiopia entitled "drug therapy problem among ambulatory Heart Failure patients at adult cardiac clinic of TASH'' The study is being conducted by Ms. Elham Seid from Addis Ababa University, school of Pharmacy, department of clinical Pharmacy and Pharmacology, post graduate program.

Objective

The main purpose of this study is to assess drug therapy problem among heart failure patients at adult cardiac clinic of TASH, Addis Ababa, Ethiopia. Your input will be extremely valuable as the information will be used to identify medication related problem and evaluate adherence

Significance

The result of the study will provide valuable insights for the healthcare professionals and policy makers about the incidence of Drug therapy problems and patient adherence and can also be used as base line information for further similar studies.

Expected Outcomes and/or Benefits

At the end of the study, drug therapy problems and patient adherence will be evaluated. Therefore, the study will identify and investigate the main gaps and challenges associated with drug use adherence and will propose possible recommendations that may benefit you directly or indirectly by improving heart failure treatment

If you have any questions concerning the study, please call Elham Seid(+251) 942-793833.

Thank you for your time

Annex VI: English version of informed consent form

The study is being conducted by Ms Elham Seid from Addis Ababa University, College of Health Sciences, School of Pharmacy, department of clinical Pharmacy and Pharmacology, post graduate program. The study will be conducted by interviewing and reviewing your medical chart. Therefore I am kindly requesting you to take part in this study by allowing your medical datat to be included in the study. The interview will take 10-15 minutes.Your name will not be written in the data collection form and will never be used in connection with any information you tell us. There is no risk associated with participating in this study. All information regarding your medical condition will be kept strictly confidential. Your participation is voluntary and you are not obligated to participate in the study. If you feel discomfort with study, it is your right to drop it anytime you want. If you have questions regarding this study, please feel free to contact the principal investigator via her address.

Elham Seid, Tell: +251- 942793933, e-mail: elaaseid@gmail.com

Signature of respondent Signature of interviewer

Thanks for your time

Annex VII: Questionnaire, Amharic version (የአማርኛ መጠይቅ ቅፅ)

አዲስ አበባ ዩኒቨርሲቲ፣ ጤና ሳይንስ ኮሌጅ፤ ፋርማሲት/ቤት፤ ፋርማኮሎጅና ክሊኒካል ፋርማሲ ትምህርት ክፍል

ቅጽ1: የጥናቱ መረጃ ቅጽ ፡፡

ውድ የቃለመጠይቅ ተሳታፊ፤ እንደምን አደሩ/ ዋሉ?

ስሜ_____ይባላል። “በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል በልብ በሽታ ታካሚዎች ላይ በመድሀኒት ህክምና ተያያዥ ችግሮች እና መድሀኒትን ባግባቡ በመዉሰድ ዙሪያ” በተሰኘ የድህረ ምረቃ ጥናት አባልነኝ። ጥናቱ የሚካሄውም በ ጥናቱ ተመራማሪ ኢልሃም ሰኢድ እና <u>በጥናቱ ዋና አማካሪ ፕ/ር ኤፍሬም እንግዳወርቅ</u> ከአዲስ አበባ ዩኒቨርሲቲ፣ ጤና ሳይንስ ኮሌጅ፤ ፋርማሲ ት/ቤት የድህረ ምረቃ ፕሮግራም ነው።

የጥናቱአላማ

የዚህ ጥናት ዋና አላማው በመድሀኒት ህክምና ተያያዥ ያላቸው ችግሮች መለየት፣ በታዘዘው መሰረት በአግባቡ እንዴት መድኃኒትዎን እንደሚወሰዱት፣ መድኃኒትዎን ሁል ጊዜ እንዳይወሰዱ የሚያደርጉ ዋና ዋና ክፍተቶችን እና የእርስዎ በህክምናዎ ላይ ያሎትን እርካታን በመለየትና የመፍትሄ ሀሳቦችን ማቅረብ ነው።

ከጥናቱ የሚጠበቁ ውጤቶች/ ጥቅሞች

በዚህ ጥናት ላይ በመድኃኒት ህክምናዎ ላይ የሚከሰቱ ችግሮች፤ በታዘዘው መሰረት በአግባቡ የአወሳሰድና የአጠቃቀም ክህሎትና የእርስዎን እርካታን ይጠናሉ። በተጨማሪም ከጥናቱ በሚገኙ ግኝቶች የልብ ህክምና ዉጤትን በተወሰነ መልኩ ለማሻሻል እንደሚቻል በመገመት፤ እርስዎ የጥቅሙ ተቋዳሽ ይሆናሉ ብለን እናምናለን። ጥናቱ የሚካሄደው የህክምና ካርድዎንና በመከለስና በቃለ መጠይቅ ነው፡፡ ስለዚህ የእርስዎ ቅንና ሐቀኛ መረጃ ለጥናቱ እጅግ በጣም ወሳኝ ነው።

የተከበረ ጊዜዎን ስለሰጡን እጅግ በጣም እናመሰግንዎታለን።

ቅጽ2፡ በቃለ መጠይቅ ለመሳተፍ የፈቃደኝነት ቃል መቀቢያ ቅጽ

በዚህ ጥናት የእርስዎ መረጃ ሙሉ በሙሉ በምስጥር የተጠበቀና ለምርምሩ አላማ ብቻ የሚዉል ነው። በተጨማሪም የእርስዎ ተሳታፊነት በፈቃደኝነት የተመሠረተ ነው። የጥናቱ አላምውን ተረድተውና ጊዜዎን ሰውተው፤ ከ 10-15 ደቂቃ ለሚፈጅ ቃለ-መጠይቅ መረጃ ለመስጠት ፍቃደኛ በመሆንዎ በቅድሚያ አመሰግናለሁ።

በየትኛውም ጊዜ ጥያቄ ካለዎት ኢልሃም ሰኢድ በ ስ.ቁ **+251942793833** ወይም

በ ኢ-ሜይል፡ elaaseid@gmail.com ይጠይቁን።

ሀ. የታካሚ ማህበረሰባዊ ባህርያቶች መረጃ በተመለከተ (መመርያ፡ ለመረጡት ምላሽ የx ምልክትን ያድርጉ)

ክፍል ነ. ማህበረሰባዊ ባህርያቶች:			
ነ.እድሜ፤		ክብደት	ቁመት
2.ፆታ፤	ወንድ ☐	ሴት ☐	**እርጉዝ:** አዎ ☐ አይደለም ☐
3 ሀይማኖት	እስላም ☐	ክርስትያን ☐	ፕሮቴስታንት ☐ ሌላ
4.የጋብቻ ሁኔታ፤	ያላገባ/ች ☐	ያገባ/ች ☐	አግብቶ/ታ የፈታ/ች ☐ ☐ ሚስቱ/በሷ የሞተችበት/ባት
5.የትምህርት ሁኔታ፤	ያልተማረ/ች ☐ ከ1ኛ-8ኛ ክፍል ☐	ከ9ኛ-12ኛ ክፍል ☐ ኮሌጅ ዲፕሎማ ☐	ዩኒቨርስቲ ዲግሪ እና ከዚ ያበላይ ☐
6.አሁን የሚኖሩበት	ከተማ ☐	ገጠር ☐	
7 የወርገቢ			

9 የማህበራዊ ሂወትዎ ሁኔታ	ሲጋራ ያጨሳሉ	አዎ ☐	አላጨስም ☐
	ጫት ይቅማሉ	አዎ ☐	አልቅምም ☐
	መጠጥ (የአልኮል) ይጠጣሉ	አዎ ☐	አልጠጣም ☐

ክፍል 2. የታካሚዎች በሽታ ባህርያት በተመለከተ ተጨማሪ መረጃ			
ነ. .የልብ በሽታ እንዳለብዎት ተመርምሮ ካወቁ ስንት ዓመት ሆኖቷል			
2.የልብ መድኃኒት መውሰድ ከጀመሩ ስንት ዓመት ሆኖቷል			
3 በልብ በሽታዎ ምክንያት ሆስፒታል ተኝተዉ ያዉቃሉ	አላውቅም ☐ አዎ (ምክንቱንይግለጹ)		
4 ተጨማሪ በሽታ አለብዎት	የለብኝም ☐ አዎ (ይግለጹ)		
5.በአሁኑ ጊዜ የሚወስዱት የልብ መድሀኒት ብዛት			
5 መድሃኒት የሚያገኙት በምን መልኩ ነዉ;	በግዢ ☐ በነጻ ☐		
6 በየስንት ጊዜ ክትትል ያደርጋሉ			

ክፍል4: ሞሪስኪ" መድኃኒትንበታዘዘውመሰረትበአግባቡስለመውሰድ" መለኪያ- 8		

;.l	**ጥያቄዎች**	አዎ	አይደለም
1	አንዳንድ ጊዜ መድኃኒትዎን ረስተው ሳይወስዱ ቀርተዉ ያዉቃሉ?	□	□
2	ሰዎች አንዳንድ ጊዜ ከመርሳት በተጨማሪ ባሉት የተለያዩ ምክንያቶች መድኃኒታቸውን ሳይወስዱ ይቀራሉ፡፡ ባለፉት ሁለት ሳምንታት፣መድኃኒትዎን ሳይወስዱ የቀሩበት ቀናቶች ነበሩ	□	□
3	መድኃኒትዎን እየወሰዱ ህመምዎ ሲባባስ ሐኪምዎን ሳያማክሩ መድኃኒትዎን አቋርጠው ያዉቃሉ	□	□
4	በጉዞ ወይም በሌላ ምክንያት ከቤትዎ አርቀው ሲጓዙ አንዳንድ ጊዜ መድኃኒትዎን ረስተውት ሳይወስዱት ያውቃሉ	□	□
5	በትላንትናው ዕለት ሁሉንም መድኃኒትዎን ወስደዋል	□	□
6	ህመምዎ ሲሻልዎት(የህመምስሜቶችሲጠፉ) አንዳንድ ጊዜ መድኃኒትዎን አቋርጠው ያውቃሉ	□	□
7	መድሀኒቶችን በየቀኑ መውሰድ ለአንዳንድ ሰዎች ምቾት ይነሳቸዋል። እርስዎ በህክምና ክትትልዎ ወቅት በየቀኑ ወይም አንድም ጊዜ ሳያዛንፉ መድሐኒ ትበትክክል ለመዉሰድ ተሰላችተዉ ያዉቃሉ	□	□
8	ሁሉንም መድሐኒቶች መውሰድ አለመዉሰድዎን ማስታወስ የከበድዎት ጊዜ አለ በፍፁም□አልፎአልፎ□አንዳንድጊዜ□አብዛኛውጊዜ□ሁልጊዜ□	□	□
	አጠቃላይድምር		

መድሃኒቱን በአግበቡ ካልወሰዱ እባክዎ ምክንያቱን ይግለጹ (ከ አንዴበላይመልስመምረጥይቻላል)

ምድሃኒቱን ስወስድ ህመሜ ስለሚባባስበኝ
መድሃኒቱን ማግኘት ስላልቻልኩ
ስለምረሳው
የምወስዳቸው መድሃኒቶች ብዙና ግራ የሚያጋቡ ስለሆኑ
መድሃኒቱ ውድ ስለሆነ
ሌላ ምክንያት.....