

**EVALUATION OF POTENTIAL INAPPROPRIATE MEDICATION IN  
ELDERLY PATIENTS ADMITTED TO MUHIMBILI NATIONAL  
HOSPITAL USING THE STOPP/START CRITERIA**

**Bernard T. Makala, B.Pharm**

**MSc (Clinical Pharmacology) Dissertation  
Muhimbili University of Health and Allied Science  
October, 2014**

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**By,**

**Bernard T. Makala, B.Pharm**

**A dissertation Submitted in (Partial) fulfillment of the Requirements for  
The Degree of Masters of Science in Clinical Pharmacology of  
Muhimbili University of Health and Allied Science**

**Muhimbili University of Health and Allied Science  
October, 2014**

**CERTIFICATION**

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled *“Evaluation of Potential Inappropriate Medication in Elderly Patients Admitted to Muhimbili National Hospital Using the STOPP/START Criteria,”* in (Partial) fulfillment of the requirement for the degree of Master of Science in Clinical Pharmacology of Muhimbili University of Health and Allied Sciences.

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**Dr. Philip Sasi**  
**Main Supervisor**

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Date

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**Prof. J.G. Sayi**  
Co-Supervisor

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## **DEDICATIONS**

I dedicate the results of this study to my father, Mr. T. Makala, my mother Mrs. J. Makala, my son Jayce-Eli and to my lovely wife Lisa H. Makala. Thank you!

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**LIST OF ABBREVIATIONS**

<b>ADR</b>	Adverse drug reaction
<b>MNH</b>	Muhimbili national hospital
<b>MNH</b>	Muhimbili National Hospital
<b>MUHAS</b>	Muhimbili university of Health and allied sciences
<b>PIM</b>	Potential Inappropriate Medication
<b>PIP</b>	Potential inappropriate prescription
<b>POM</b>	Potential omission medication
<b>POP</b>	Potential omission prescription
<b>START</b>	Screening Tool to Alert doctors to the Right Treatment
<b>STOPP</b>	Screening Tool of Older Person's potentially inappropriate Prescriptions
<b>WHO</b>	World Health Organization

## DEFINATION OF KEY TERMS

**Adverse drug reactions:** any injury resulting from drug therapy – from appropriate care, or unsuitable or suboptimal care. ADEs include adverse reactions during normal use of a medicine, and any harm due to medication error whether of omission or commission.

**Cardiac index:** is a hemodynamics parameter that relates the cardiac output (CO) to body surface area (BSA), thus relating heart performance to the size of the individual.

**Co-morbidity:** is either the presence of one or more disorders (or diseases) in addition to a primary disease or disorder, or the effect of such additional disorders or diseases.

**Creatinine clearance:** is the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR and is expressed as mL/min.

**Definite:** The reaction (a) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (b) followed a recognized response to the suspected drug, and (c) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.

**Delphi method/process:** is a structured communication technique, originally developed as a systematic, interactive forecasting method which relies on a panel of experts. The Modified Delphi Technique uses mail or email to gather information, provide feedback, and report conclusions.

**Doubtful:** The reaction was likely related to factors other than a drug.

**Elderly:** Being past middle age and approaching old age, in this study it includes individuals aged 65 years old and above.

**Geriatric services:** Special care for the diagnosis, treatment, and management of diseases and conditions of older adults.

**Glomerular filtration:** the renal process whereby fluid in the blood is filtered across the capillaries of the glomerulus and into the urinary space of Bowman's capsule.

**Hydrophilic drug:** Drugs that associate with water molecules and are easily dissolved in water.

**Hydrophobic drug:** these are drugs which are nonpolar and do not dissolve in water.

**Maximum breathing capacity:** The volume of gas that can be breathed in 15 seconds when a person breathes as deeply and quickly as possible.

**Morbidity:** a diseased state or symptom, the incidence of disease.

**Mortality:** the state or condition of being subject to death; mortal character.

**Pharmacodynamics:** is the study of the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect.

**Pharmacokinetics:** A process by which a drug is absorbed, distributed, metabolized, and eliminated by the body.

**Pharmacotherapy:** is the treatment of disease through the administration of drugs

**Possible:** The reaction (a) followed a temporal sequence after a drug, (b) possibly followed a recognized pattern to the suspected drug, and (c) could be explained by characteristics of the patient's disease.

**Potential inappropriate medication (PIM):** The use of medicines that pose more risk than benefit, particularly where safer alternatives exist. It also includes the misuse of medicines (inappropriate dose or duration), the prescription of medicines with clinically significant drug-drug and drug-disease interactions, and importantly, the under-use of potentially beneficial medications.

**Probable:** The reaction (a) followed a reasonable temporal sequence after a drug, (b) followed a recognized response to the suspected drug, (c) was confirmed by withdrawal but not by exposure to the drug, and (d) could not be reasonably explained by the known characteristics of the patient's clinical state.

**The Naranjo algorithm or Naranjo Scale:** is a questionnaire designed by Naranjo *et al.* for determining the likelihood of whether an ADR (adverse drug reaction) is actually due to the drug rather than the result of other factors. Probability is assigned via a score termed definite, probable, possible, or doubtful.

**Therapeutic window of a drug:** is the range of drug concentrations which can treat disease effectively while staying within the safety range.

**Typical patient:** Is the one that has condition which are considered normal in individual having common characteristics. In this study typical patient includes all individual having eGFR more than  $85 \text{ ml min}^{-1} \text{ per } 1.73 \text{ m}^{-2}$ .

**Volume of Distribution:** is a pharmacological, theoretical volume that the total amount of administered drug would have to occupy (if it were uniformly distributed), to provide the same concentration as it currently is in blood plasma.



## ABSTRACTS

**Background:** Prescribing in elderly is a challenging and complex process due to age and physiological related changes which compromise drug handling and response. The process is further complicated by presence of co morbidity and co medication. Elderly population is increasing worldwide including Tanzania, Thus with an increase in this elderly population, quality and safety of medication becomes more important for improving health and drug use.

**Aim of the study:** We have conducted a study on potential inappropriate in medication elderly patients using the STOPP/START criteria and in addition the study assessed the magnitude of reduced renal function requiring dose adjustment.

**Methodology:** This was a descriptive study conducted using medical records from MNH, involving 297 elderly patients admitted at Muhimbili national hospital between September 2013 and February 2014. Data was analyzed by STATA software Version 12. (Stata Corp. College Station, Texas, USA) and summarized using appropriate standard statistics. Statistical tests i.e. chi square, T –test and fisher exact was used to measure associations. A P value of <0.05 was considered to be statistically significant.

**Results:** sixty one patient out of 297 (20.5%) had at least one potential inappropriate medication (PIM). Many patients with at least one inappropriate medication were admitted through emergency medicine department (22.5%). Majority of PIM were related to Glibenclamide use in patient with type two diabetics (21.3%). A total of 58 (19.5%) medications were omitted and majority (67.2 %) of the patient to whom medication were omitted came from emergency admission. A significant reduction in renal function was very common in our cohort; about 200 (68%) out of 297 had an eGFR of less than 60 ml min<sup>-1</sup>per 1.73 m<sup>-2</sup>. Of the 200 patients with significantly reduced renal functions, 117 (58.5%) were females; in the 297 elderly patients, 116 (39.3%) of them had a moderate reduction in eGFR and thirty-five patients out of 297 (11.8%) were in end stage renal diseases.

**Conclusion:** Potential inappropriate medication, medication omission, and reduced renal function are common among elderly patients admitted at MNH.

## **CHAPTER ONE**

### **1.0 INTRODUCTION AND LITERATURE REVIEW**

#### **1.1 AGING PROCESS**

The aging process is accompanied by progressive deterioration of organ systems and tissues; deterioration of the organ systems affects the cellular homeostatic ability of the body. Cellular homeostatic mechanism which involves extracellular fluid volumes, decreases in organ mass and loss of the functional reserve body's system are usually associated with aging (Dodds et al . 2006;Nigam et al. 2012).These losses ultimately affect the body's physiologic function for example renal function and pharmacologic process like pharmacokinetics and pharmacodynamics, eventually the pharmacological properties of a drug may be altered.

##### **1.1.1 Age related changes and their effect on PK**

Pharmacokinetics properties such as volume of distribution (Vd), drug clearance, and metabolism as well as pharmacodynamics mechanisms are affected in elderly patients. Total body water and lean body mass are reduced in elderly people with relative increase in total body fat (Nigam et al. 2012; Masoodi et al. 2008). These changes affect the volume of distribution of hydrophilic and hydrophobic drugs; for example hydrophilic drugs like Digoxin and Lithium will have an increased plasma concentration hence dose adjustment in such situation may be warranted (Masoodi et al. 2008). However, hydrophobic drugs like Thiopental and benzodiazepines will have an increased volume of distribution and their accumulation in the body over the course of time cannot be avoided if dose adjustment is not done (Masoodi et al. 2008; Klotowska et al. 2013; Guaraldo et al. 2011).

Drugs which require prior activation by the liver through first pass metabolism are also affected since the hepatic mass, hepatic blood flow and efficiency of Cytochrome P450 enzymes are reduced in elderly people. Blood flow is further complicated by the changes in the heart since its ability to pump blood throughout the body is reduced (Hunt at al. 1992).Drugs such as beta blockers, and Nitrates which are highly subjected to first-pass

metabolism will have a higher bioavailability and increased half-life due to the reduced clearance.

### **1.1.2 Age related change in renal function and its effect on pharmacokinetics**

Age related changes in Glomerular filtration rate (GFR) are often considered the most crucial pharmacokinetics changes in old age (Le Couteur et al. 1997; Turnheim et al. 1998; Muhlberg et al. 1999). Total renal blood flow decreases by approximately 10 percent per decade in the adult years and for this reason elderly patients are considered as renally insufficient (Turnheim et al. 1998). Studies have shown that adverse drug reactions correlates exponentially with renal function (Cantu et al. 1992); hence, there is a need to monitor and adjust the dose of renally cleared drugs particularly the ones with narrow therapeutic range. For the purpose of assessing the renal function of the elderly people the chronic kidney disease epidemiologic equation (CKD-EPI) has been used.

The CKD-EPI equation was developed in 2009 to estimate GFR from serum creatinine, age, sex, and race. The equation was developed from 8254 high risk individuals and externally validated from 3896 individuals (Levey et al. 2009; Stevens et al. 2010). The equation has been found to be superior in estimating renal function compared to other equations such as Modification of Diet and Renal Disease equation (MDRD) and Cockcroft-Gault (Zhu et al. 2014; Willems et al. 2013). The equation is recommended by the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) to be used on routine basis.

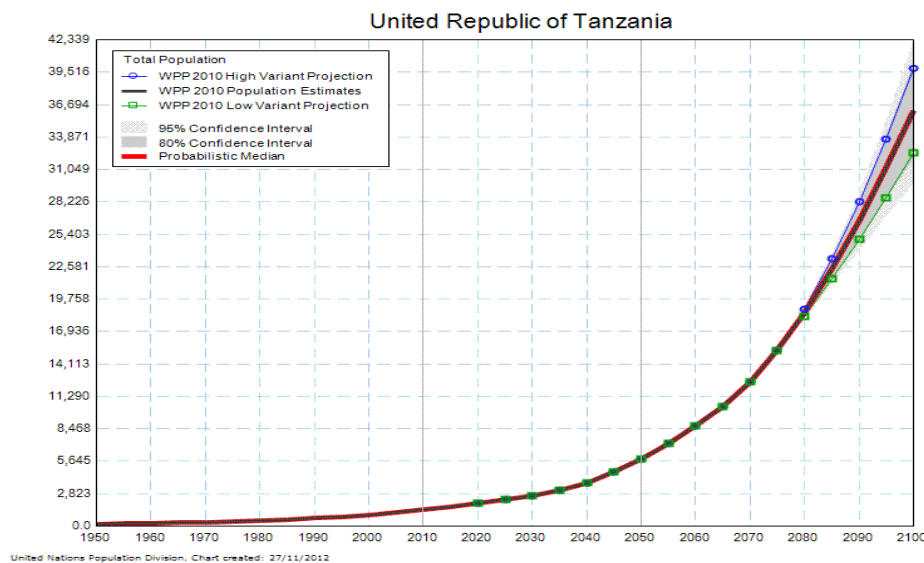
Patients with estimated GFR < 60 ml/min/1.73m<sup>2</sup> are considered having significantly reduced renal function and hence will require dose adjustments (McCormack et al. 2012). Reduced renal function will be categorized by the therapeutic classification; Kidney damage with mild decrease in GFR(60-89), Moderate decrease in GFR (30-59), Severe decrease in GFR (16-29), and Kidney Failure GFR (<15). Drugs with narrow therapeutic range and those which were predominantly excreted by kidney (>70%) were considered for dosage adjustment. Dose size, frequency of administration, and combination of both when appropriate were used to adjust the dose.

### 1.1.3 Age related changes and their effect on PD

In elderly patients, it has been shown that some receptors e.g. beta receptors, their sensitivity is reduced, while others e.g. opioid and warfarin sensitivity is increased (Gage et al. 2000; Beers et al. 2000).

## 1.2 THE ELDERLY POPULATION

Worldwide, the elderly population is expected almost to triple that is increasing from 672 million in 2005 to almost 1.9 billion by 2050. Twenty percent (20%) of the population in the developed countries is over 60 years old and is expected to be 32% by the year 2050. Meanwhile the elderly population in developing countries is expected to rise from 8% in 2005 to almost 20% by 2050 (World Population Prospects, 2005). In Tanzania data from HelpAge International, an organization dedicated to improve elderly wellbeing indicates that about 5.7% of 38 million individuals is over 65 years old, and anticipated to double by year 2050. Similar growth trend has been demonstrated by World Population Prospects (Figure 1.1). Thus with an increase in elderly population, quality and appropriateness use of medication in elderly becomes more important to ensure safe, appropriate and economic drug use.



**Figure 1.1: The estimates and probabilistic projections of the population age 65 and above of Tanzania per 1000 of population (1950-2100). Source: World population prospects, 2010.**

### 1.3 GERIATRIC PHARMACOTHERATY

Pharmacotherapy is the area of pharmacy practice that is responsible for ensuring the safety, appropriateness, and economical use of medicine in patient care. In general, appropriate prescribing is a wide term, but some elements have been set to ensure appropriateness of the prescribing process, these elements involve the interaction between the patient, doctor and the pharmacist and may include the following; a thorough evaluation of the patients need and problems, a targeted intervention and selection of appropriate interventions thereafter, evaluation of non-pharmacologic approach possibilities before medications, and appropriate information to the patient; dose, how to take and when to take, and last is to monitor the patient on regular basis.

The word inappropriate prescribing (IP) comprises many aspect but in a simple way it can be described as underuse/overuse of medications or the use of medications where the risks outweigh the benefits especially when a safe and effective alternative is available (Beers et al. 1997; Spinewine et al. 2007).

The aspect of IP includes:

**Polypharmacy:** The use of multiple medications and or administration of more medications that are not clinically required.

**Over prescribing:** The use of medications at higher doses or frequencies longer than clinically indicated or use of medications for longer course of therapy.

**Adverse drug reactions and Drug disease interactions:** The use of medications with known risk of adverse drug-drug or adverse drug-disease interactions and those who are likely to worsen the clinical problem for example the use of benzodiazepines in older patients with a past history of falls.

**Underuse of medications:** Failure to prescribe a clinically beneficial medication with no strong reason and where there is no contraindication to a patient (Barry et al. 2007; Gallagher et al. 2007; Spinewine et al. 2007; Steinman et al. 2006).

### **1.3.1 Inappropriate medication in elderly patient**

Drug prescribing for elderly patients has always been a complex and challenging process because of the age and physiologic related changes. Moreover, elderly people have multiple diseases and thus medications for such diseases increase the complexity of prescribing in the elderly (Hamilton et al. 2009). With increasing elderly population worldwide, the potential inappropriate medication for the elderly people becomes a worldwide concern (Spinewine et al. 2007). It has been found that the prevalence of inappropriate medication in elderly patients in the developed countries to be as high as 21%-37% among elderly patients seen at outpatient department (OPD) and up to 40% in nursing home residents (Steinman et al. 2006; Dhall et al. 2002; Willcox et al. 1994). These values are higher despite well developed and functional geriatric services and geriatric specialists available. Our country having no geriatric services and specialized personnel, the prevalence of inappropriate medication may be even higher leading to an increased risk of morbidity including development of adverse drug reactions and mortality. Morbidity and mortality in the elderly correlates significantly with age (Olyaei et al. 2009) and some of this burden may be attributed to inappropriate use of medications.

In order to assess the current level of medications in elderly patients with the ultimate goal of reducing the prevalence of potentially inappropriate medications, many explicit and implicit tools have been developed.

## **1.4 SCREENING TOOLS TO ASSESS INAPPROPRIATE MEDICATIONS**

Screening tools to assess the appropriateness of prescribing may contain either explicit or implicit criteria or a combination of both. Explicit criteria are specific statements of inappropriateness, originating from evidence based guidelines, reviews, expert opinions and consensus techniques. Whereas in implicit criteria clinicians use patient-specific data and published work to make judgments about the appropriateness of medication usage in patients (Spinewine et al. 2007).

### **1.4.1 Explicit Criteria**

Many explicit criteria have been developed, most of them named after their founder or by the group that developed them. The following are some examples:

**McLeod Criteria**

Founded by McLeod et al 1997, and validated by 32 geriatric pharmacologists in Canada. Final list contained 38 cases of potential inappropriate prescribed medications. McLeod included 18 medications that are contraindicated in elderly patients, 16 potentially drug-disease interactions, and 4 drug-drug interactions. Each criteria had a description for anticipated risk to the patient and an alternative therapy was suggested. For example the long term use of barbiturates for insomnia was considered inappropriate because it may cause falls or fractures, instead non therapy or short acting benzodiazepines was recommended (McLeod et al. 1997).

**Improving Prescribing In the Elderly Tool (IPET)**

Founded by Naugler et al in 2000, a Canadian based guideline derived from McLeod. This has 14 different drug/disease interactions which must be avoided in elderly, it consist of short sentence which contains drug and a warning, for example beta blockers and chronic obstructive airways diseases, beta blockers and congestive heart diseases. However, the IPET criteria does not address under prescribing issues.

**Beers Criteria**

The Beers criteria were originally formulated in 1991 (Beers et al. 1991), and it was specifically designed for old nursing home residents, the criteria was later updated to include general older people (Fick et al. 2003). Beers criteria consists of two lists of medications to be avoided in old people, the first list is independent of diagnosis, and second list is diagnosis dependent. Beers criteria did not address under-prescribing, drug-drug and drug-disease interactions or drug class duplication (Hamilton et al. 2009) and these are considered as the biggest limitations of Beers criteria and in order to address these shortcomings the STOPP and START criteria were developed.

## **Screening Tool of Old People's Potentially Inappropriate Prescriptions (STOPP) and Screening Tool To Alert Doctors To The Right Treatment (START)**

The STOPP /START criteria are evidence-based sets of criteria, which were developed in Ireland using a modified Delphi process that involved 18 experts in geriatric pharmacotherapy from across the United Kingdom and Ireland.

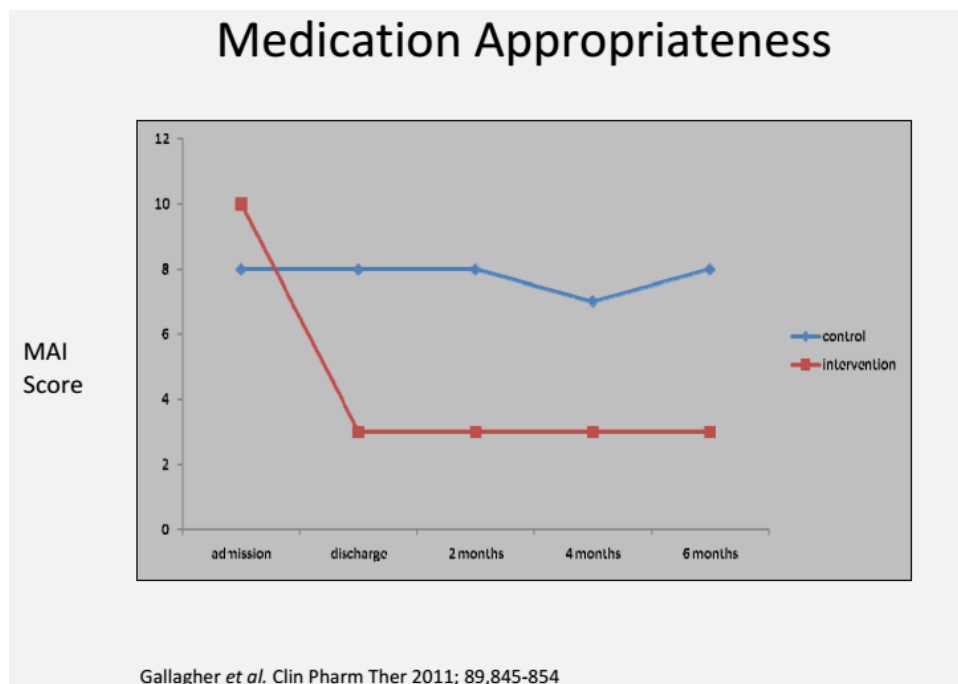
STOPP (Appendix 2) consists of 65 criteria that help researchers and healthcare personnel systematically identify potentially inappropriate medications (PIMs). START (Appendix 3) consisting of 22 criteria, which identifies potential prescribing omissions (PPOs). These tools have been shown to be superior in identifying PIMs compared to previous tools such as the Beers criteria (Yayla et al. 2013; Hamilton et al. 2009; Gallagher et al. 2008; Lang et al. 2009; Karandikar et al. 2013). STOPP/START criteria have been arranged according to the physiologic function making them easy to use. They also include references to drug class duplication, drug-drug and drug-disease interactions (Baeyens et al. 2009; Hamilton et al. 2009). The tools have been used in different countries and yielded comparable results (Baeyens et al. 2009; Yayla et al. 2013). The aim of the STOPP and START criteria was to provide explicit and evidence based medications in order to avoid common potentially inappropriate medications and potential prescribing omissions, this will help to; improving medication appropriateness, prevent adverse drug events and reduce drug costs.

### **Improving Medication Appropriateness**

Medication appropriateness can be evaluated by using medication appropriate index (MAI) developed by Hanlon et al. MAI was developed to assist physician and pharmacist in assessing the medication appropriateness in a given patient. MAI requires a physician or pharmacist to rate ten explicit criteria to determine if the given drug was appropriate, the criteria includes; indication, effectiveness, dosage, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration and expense. Each criteria is assigned weight in order to obtain the total summation score. A weight of three is given for indication and effectiveness. A weight of two is assigned to dosage, correct directions, drug-drug interactions, and drug-disease interactions and a weight of one is assigned to practical



directions, expense, duplication, and duration. These ratings generate a weighted score that interprets prescribing appropriateness ranging from 0 to 18 that is 0 no inappropriate medications and 18, all medications are inappropriate (Samsa et al. 1994). Studies have shown that by comparing normal practice in geriatrics and intervention practice using STOPP and START criteria; the medication appropriateness measured by MAI scored significant low value (Figure 1.2), similarly, underuse of potential beneficial medication was highly reduced in the intervention group (Gallagher et al. 2011).



**Figure 1.2: Medication appropriateness index (source: Gallagher et al. Clin Pharm Ther 2011; 89, 845-859).**

### **Prevent Adverse Drug Events and Reducing Drug Costs**

STOPP criteria has been found to be helpful in identifying adverse drug reactions for example, in the study conducted by Hamilton and others, found that ADRs as high as 62.2 % were detected by the STOPP criteria (Hamilton et al. 2011) .Identifying potential inappropriate medication can help to reduce the cost to the patient, institutional as well as the government

(Hamilton et al. 2011; Gallagher et al. 2011). A study conducted in Ireland on 338,801 people using 30 STOPP criteria, identified the prevalence of PIM as 30% and the cost of those medications which were inappropriately prescribed was 45,631,319 Euros, which corresponds to 9% in overall expenditure on pharmaceuticals in elderly patients above 70 years old (Cahir et al. 2010).

### **The Naranjo Criteria**

Potential inappropriate medication has a negative outcome including ADRs (Hamilton et al. 2009); identifying the agent responsible for ADRs patient management may be improved. For this reason, the Naranjo algorithm scale(Appendix 4) was developed, the Naranjo algorithm scale is used to identify and classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose – response relationships and previous patient experience with the medication (Hamilton et al. 2009).The ADR is assigned to a probability category from the total score as follows: definite if the overall score is 9 or greater, probable for a score of 5–8, possible for 1–4 and doubtful if the score is 0.The method is simple, reliable and has been validated (Michel et al. 1986),besides the tool is widely used in various adverse drug reaction studies and has inter-rater agreement scores superior to subjective clinical judgment .

Therefore, using the above criteria the current study assessed magnitude of potential inappropriate medication and relationship to ADR in elderly patients admitted to Muhimbili National Hospital. In addition the study assessed the magnitude of reduced renal function which requires dose adjustment.

### **1.5 STATEMENT OF THE PROBLEM**

The goal of any pharmacotherapy is to ensure safety, appropriateness, and economical use of medications. It is a challenge to achieve these goals in elderly patients who already have a compromised PK and PD, multiple diseases and medications. Furthermore, elderly people represent a vulnerable population which is usually not involved in drug development and testing. With those alarming safety issues yet drug utilization in elderly patients is higher compared to the young population (Kaufman et al. 2002). For example the elderly constitute 12% of the population in the US but consume 31% of all prescribed drugs (Monane et al. 1998). These multiple risk factors explain our concern over the potential drug safety in our settings. In order to confirm this safety concern, we have conducted a study to identify potential inappropriate medication and adverse drug reactions in elderly patients admitted to Muhimbili National Hospital using STOPP/START criteria.

## **1.6 RATIONALE**

Elderly people represent a vulnerable population which requires specialist attention, however geriatric health services in our country are poorly developed (Minja. 2011), possibly because elderly people are regarded by the society and government as a small non-productive population (Minja. 2011). However, due to their expertise some elderly people are still being employed in various Governmental and Nongovernmental organizations, and as human beings, they have a right to quality services. Data from help age Tanzania indicates that approximately 5.7% of Tanzania's population of 38 million is over the age of 60 years and it is expected to rise up to 11% by the year 2050. This means that drug utilization and possibly inappropriate prescribing in elderly will increase. It is known that inappropriate medication in elderly is a common cause of morbidity, mortality and overutilization of health resources (Fadare et al. 2013; Zuckerman et al. 2006; Klarin et al. 2005; lau et al. 2005). Thus with an increase in this elderly population, quality and safety of medication becomes more important for improving health and drug use. Therefore it is important to evaluate health care services for the elderly including prescribing of medications to ensure drugs are used safely, appropriately and economically. To our knowledge, there are no studies to assess potential inappropriate medication in elderly and associated adverse drug reactions have been done in Tanzania. Knowing the drug prescribing pattern and its influence on development of adverse drug reactions will generate valuable information which will help to inform Muhimbili National Hospital (MNH) and other health stakeholders including Ministry of Health and Social Welfare.

## **1.7 OBJECTIVES**

### **1.7.1 Broad objective**

To study medications prescribed to elderly patients and their association with adverse drug reactions.

### **1.7.2 Specific objectives**

- i. To determine the prevalence of potentially inappropriate medication in elderly patients using the Screening Tool of Older Person's Potentially Inappropriate Prescription (STOPP criteria).
- ii. To determine the prevalence of potential medication omission using Screen Tool to Alert Doctors to the Right Treatment (START criteria).
- iii. To determine the proportion of the elderly patient that required dose adjustment based on their renal function.
- iv. To investigate the relationship between lack of dose adjustment (where indicated) and development of adverse drug reactions.
- v. To investigate causality between potentially inappropriate medication and occurrence of ADRs using the Naranjo algorithm scale.

## **1.8 HYPOTHESIS**

Potential inappropriate medication are common in elderly patient admitted to Muhimbili National Hospital.

## CHAPTER TWO

### 2.1 MATERIAL AND METHODOLOGY

#### 2.1.1 Study design and site

This was a descriptive study conducted using medical records from MNH, which is the largest tertiary facility situated in Dar es Salam city, Tanzania. The hospital gives service to a population of about 4.36 million (Census.2012) people living in Dar es Salam as well as referred patients from hospitals all over the country. The general medical wards contain 1400 beds with an admission rate of 500 people per week (Bolt et al. 2003). Data for the study was extracted from the hospital database (Jeeva ver 2.0 Napier healthcare solutions) which contains information of all inpatients and outpatients. Extracted data was cross checked with patient's medical record file (hard copy) to obtain missing information. Required information was captured by Data extraction form (appendix 1); the data collection started after obtaining ethical clearance from university ethical committee (appendix 5). Permission to collect data from hospital database was obtained from the MNH Director (appendix 6).

#### 2.1.2 Study population

Medical records of patients from the hospital database admitted between September 2013 and February 2014 was included in this study. Patients who do not have information like, serum creatinine, and age were excluded. For the purpose of sample size calculation inappropriate medication prevalence of 25.5% was used. This was based on the study by Fadare et al. 2013 in Nigeria since no similar studies had been conducted in Tanzania using same tools. Because the proposed study was a cross sectional study with primary aim of determining prevalence of potential inappropriate medication the sample size was calculated by the formula below (Fox et al. 2009).

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

n = sample size of elderly patients

$p$  = estimated proportion of potential inappropriate prescribing in elderly patients.

$z$  = standard normal variation at 95% confidence interval =1.96

$\epsilon$  = margin of error= 5%

$$n = \frac{[(1.96)^2 \times 0.255 (1-0.255)]}{(0.05)^2} = 291$$

The study therefore included medical records of 300 eligible patients

## **2.2 DATA COLLECTION**

The principal investigator assisted by three research assistant who were well trained on the objectives of the study and importance of different variables, were involved in the data collection process. These research assistant were Medical students (MD5) from MUHAS and their work was only to extract data from the files. Data were cross checked by the principal investigator for its accuracy and with the help of the tools the principal investigator evaluated the inappropriate medication and associated adverse drug reactions.

## **2.3 ETHICAL CONSIDERATION**

This was a non-invasive study; since there was no procedure involving direct contact with patients. Study numbers were used to make it anonymous as no personal identifiers were entered into the data-capturing sheet. The documents with the patient's details were treated as confidential material. Ethical clearance was obtained from Muhimbili University of health and allied sciences (MUHAS) ethical committee (Appendix 5); Permission to conduct the study and to use patient records in Muhimbili national hospital was sought from the MNH authority (Appendix 6).

### **Inclusion and exclusion Criteria**

Those patients who were 65 years old and above, who had been admitted in Mwaissela ward at MNH, and who had serum creatinine value were included in this study. ICU Patients were excluded.

## **2.4 STUDY PROCEDURES**

### **2.4.1 Database Description**

The hospital database used was JEEVA (Napier HealthCare solution Ver 2.0). It has a total of twenty six modules (26), covering different department i.e. Pharmacy, Laboratory, Medical records, Store, Finance etc. All these modules are interlinked together with medical record number (MRN). This MRN is generated automatically by the system upon first admission, and it is unique for each patient.

The modules that deal with clinical information includes:

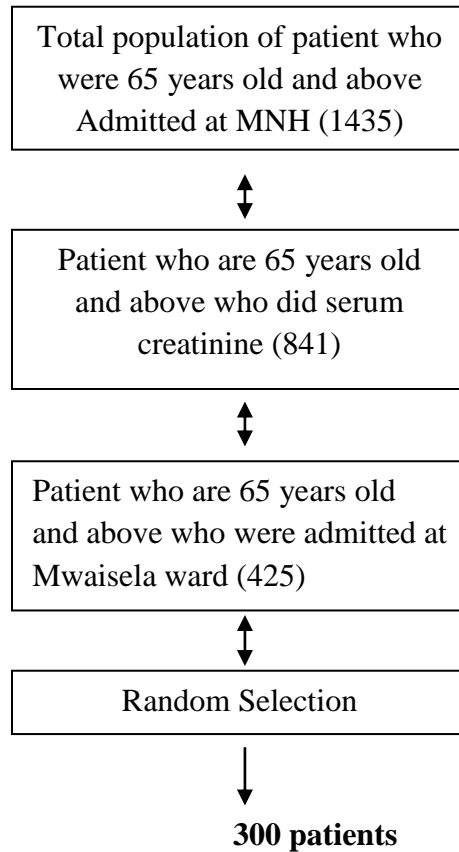
- Outpatient and inpatient modules; deals with all information relating to outpatients and inpatient respectively.
- Doctors consultations module; contains all the information the doctor has obtained from the patient e.g. signs and symptoms, diagnosis, medicine request from the pharmacy, requested test etc.
- Nursing station module; involve patient who are in specific wards, information like discharge summary, drug orders, and lab results can be viewed by the nurse, at the nursing stations.
- Other modules are Pharmacy, Medical records, Laboratory, Operation theatre, and Radiology.

### **2.4.2 Patient selection**

The list of all patients who were 65 years old and above admitted at Mwaisela ward between September 2013 and February 2014 were obtained from the Hospital database (Jeeva Ver 2.0 Napier healthcare solution) and exported to Microsoft excel 2007 (Figure 2.1). The data was inspected for eligibility by using inclusion and exclusion criteria, ineligible data was deleted. Then medical records of 300 patients were randomly selected using Microsoft excel 2007, the study aimed to use hospital database for data collection, however due to some incomplete information in the database, the physical files were used to obtain the missing information. The information obtained from the data base provided valuable information regarding



exclusion and inclusion criteria in sample size selection. Laboratory and demographic data was captured by a special designed form (Appendix 1).



**Figure 2.1: Selection flow chart**

### 2.4.3 Sample size selection

Three hundred (300) patients were randomly selected using Microsoft Office Excel 2007 by the following method:

- I. In the excel sheet containing data two empty columns were inserted column (A and B)
- II. Into first of the inserted column (A) random number ranges from zero to one were generated using command RAND ().Then the random number generated were copied to the entire first column (A)

- III. The random number generated were copied (special) to the column B
- IV. Then column B were sorted by ascending order, this gave the random sample of 425 of which three hundred patient were serial selected from 1 to 300.

#### **2.4.4 Evaluation of inappropriate prescribing**

The obtained data were assessed using validated tools; STOPP/START (Appendix 2 and 3). Once inappropriate medication were identified the Naranjo algorithm scale was used (Appendix 4) to assess the relationship between ADR and PIM. The symptoms recorded in the data extraction sheet were scored using Naranjo algorithm scale to see if they were related to inappropriate medication. The completed assessed information was transcribed into Microsoft access database and converted to STATA format ready to be imported for analysis.

#### **2.4.5 Estimation of patient renal functions and need for dose adjustment**

The dose adjustment for renally cleared drugs was derived from each patient's estimated Glomerular filtration rate (eGFR). Patient with eGFR of less than  $60 \text{ ml min}^{-1} \text{ per } 1.73 \text{ m}^{-2}$  was considered as renal insufficient and hence needed dose adjustment (McCormack et al 2012). eGFR was estimated by chronic kidney disease epidemiology collaboration (CKD-EPI) equation (2009).

### The CKD-EPI equation

a) CKD-EPI equation expressed as a single equation:

I. For Female

$$\text{GFR} = 141 \times \min(\text{Scr} / \kappa, 1)^\alpha \times \max(\text{Scr} / \kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \times 1.159$$

II. For Male

$$\text{GFR} = 141 \times \min(\text{Scr} / \kappa, 1)^\alpha \times \max(\text{Scr} / \kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.159$$

Where:

Scr is serum creatinine in micromole/L,

$\kappa$  is equation constant factor for females (0.7) and for males (0.9) respectively,

$\alpha$  is equation constant factor for females (-0.329) and for males (-0.411) respectively.

Min indicates the minimum of Scr /  $\kappa$  or 1, and

Max indicates the maximum of Scr /  $\kappa$  or 1.

b) Renal function (RF) =  $\frac{\text{eGFR of the patient}}{\text{eGFR of the typical patient (85)}}$

(Malcom. 1995)

c) The required dose for patient with renal impairment will be calculated as follows

$$\text{Adjusted dose} = \text{Normal dose} \times \text{RF}$$

d) The dose frequency for patient with renal impairment will be calculated as follows

$$\text{Adjusted dose interval} = \frac{\text{Normal dose interval (Hours)}}{\text{RF}}$$

RF

#### **2.4.6 Data Analysis**

Patient's study number was used as a unique identifier in a special designed data capturing form (Appendix 1). Data were transcribed into Microsoft access database cleaned and converted to STATA reading format. Data was analyzed by using STATA software Version 12.1(Stata Corp. College Station, Texas, USA). Patient characteristics were described using cross-tabulations, frequencies, and percentages for categorical variables and using means and medians for continuous variables. To test for associations in bivariate analysis of these categorical variables, chi square test and student t test were used when appropriate. Duration of hospital stay between those with potential inappropriate medication and those with none was compared. A p value of  $<0.05$  was considered as statistically significant.

## CHAPTER THREE

### 3.1 RESULTS

This was a descriptive study conducted using medical records from MNH. The study involved patients records for 297 elderly patients admitted at Muhimbili national hospital between September 2013 and February 2014. Three hundred patients were included in this study after random selection. Three patients who did not have serum creatinine measurement were excluded from the study.

#### 3.1.1 Baseline characteristics.

Two hundred ninety seven (297) elderly patients were included in the study with a mean age of 74 years ( $\pm$ SD 7.3). Females represented the majority and accounted for 55 % of the total population (Table 3.1).

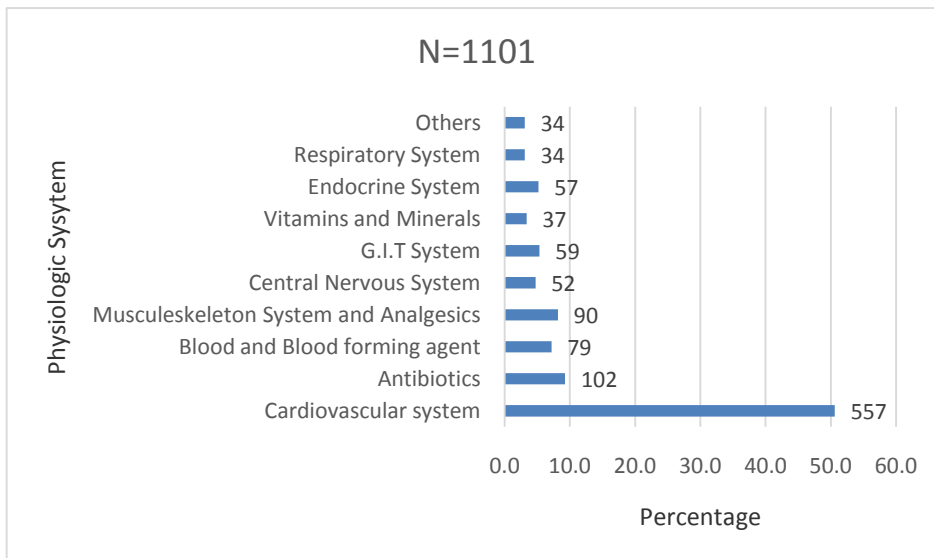
A significant reduction in renal function was very common in our cohort, 200 (68%) in 297 had an eGFR less than 60 ml /min<sup>-1</sup>per 1.73 m<sup>-2</sup>. Of the 200 patients with significantly reduced renal functions, 117 (58.5%) were females. Out of the two hundred and ninety seven elderly patient, 116 (39.3%) of them had a moderate reduction in eGFR and 35 out of 297 (11.8%) had end stage renal diseases (Table 3.1). Inappropriate drug dosing in compromised renal function may cause toxicity or ineffective therapy in particular for renally cleared drugs.

**Table 3.1: Base line characteristics (N=297)**

S.N	Characteristics	N (%)
1.	<b>Age in years</b> 65-74 75-84 85 > <b>Mean age (73.8),SD (7.3)</b>	185(62%) 75(25%) 37(13%)
2.	<b>Sex</b> Male Female	133(45%) 164(55%)
3.	<b>Serum creatinine(micromole/L)</b> Maximum Minimum <b>Mean serum creatinine (114),SD(28)</b>	<b>N=295</b> 3270.5 50.6
4.	<b>*Reduction in renal function eGFR (min-1per 1.73 m-2)</b>	<b>Age (Years)</b>
		<b>65-74</b> <b>75-84</b> <b>Above 85</b>
	60-89	38    10    2
	30-59	70    30    16
	16-29	29    11    9
	Below 15	18    10    7
		50 (17%) 116(39%) 49 (17%) 35 (12%)
5.	<b>Admission Type</b> Normal Admission Emergency	128(43%) 169(57%)
6	<b>Discharge Outcome</b> Dead Alive	122(41%) 177(59.5%)
7.	<b>Duration of Hospitalization(Days)</b> < 8 8-14 >15 Mean 8 Days(sd 7.1)	189(64%) 71(24%) 37(13%)
8.	<b>Blood pressure on admission</b> Normal Prehypertension Stage one Hypertension Stage two Hypertension	<b>N=257</b> 61(24%) 52(20%) 58(23%) 86(33%)

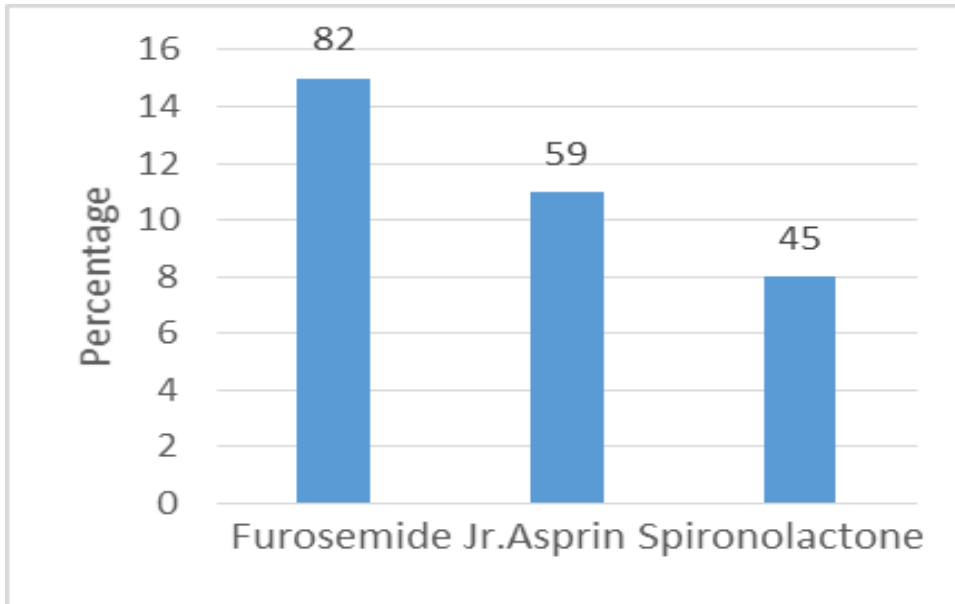
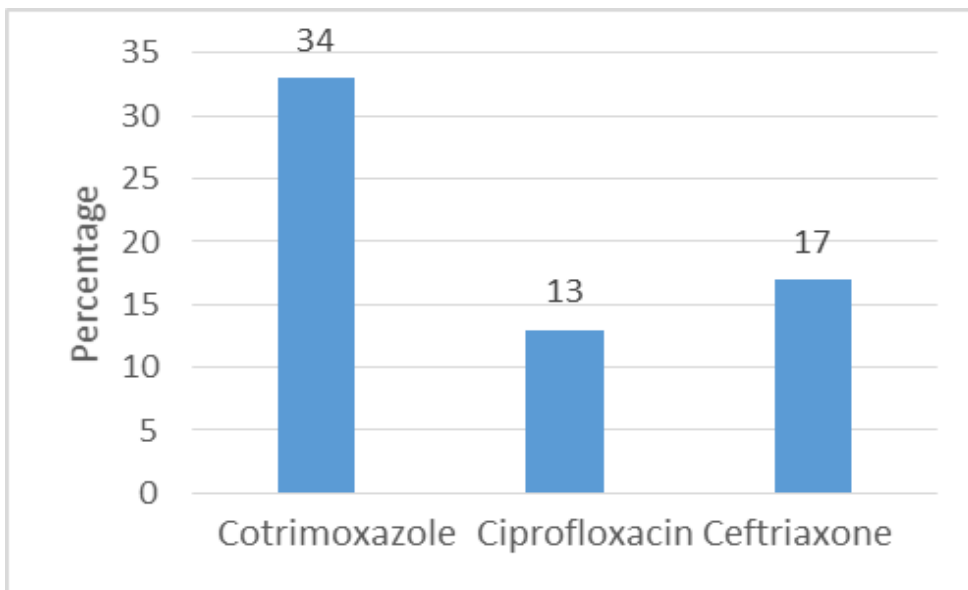
\* Kidney damage with mild decrease in GFR (60-89), Moderate decrease in GFR (30-59), Severe decrease in GFR (16-29), Kidney Failure (<15).

A total of one thousand, one hundred and one (1101) medications were prescribed, and those acting on the cardiovascular system constituted majority of the medications (50.6%), followed by antibacterial (9.3%) and drugs that act on musculoskeletal system and analgesics (8.1%) (Figure 3.1). The most frequently prescribed antibacterial (Figure 3.2b) were co-trimoxazole (33%), followed by ciprofloxacin (17%) and ceftriaxone (13%). Unlike what is expected in young population, the use of antibacterial was less compared to drugs acting on the cardiovascular system, suggesting that infectious diseases were not very common in the elderly.



**Figure 3.1 Medication prescribed based on Physiologic system**

Among drugs that act on the cardiovascular system, Furosemide (15%), Aspirin (11%), and Spironolactone (8%) were frequently prescribed (Figure 3.2a).

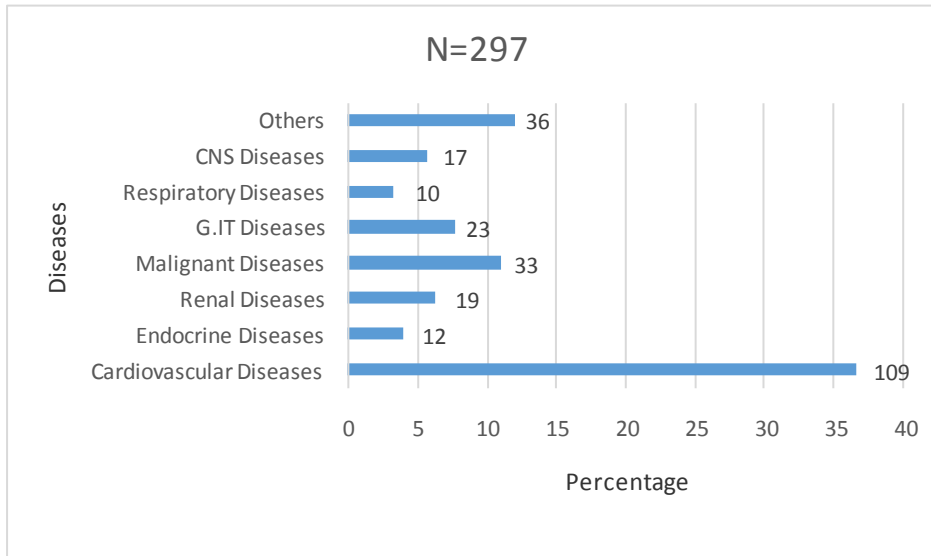
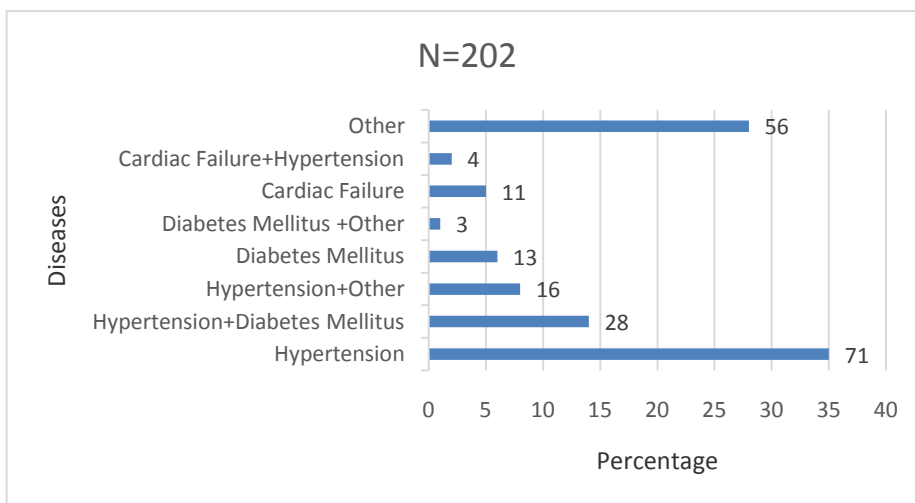
**A****B**

**Figure 3.2 (A) Most frequently prescribed cardiovascular medications, (B) Most frequently prescribed antibacterial**



Medications like captopril, and atenolol that act on the cardiovascular system requires dosage adjustment according to renal function. Assessment of the dosage requirement of all renally cleared drugs was not investigated in this study. This study focused only on medications with narrow therapeutic range and those which are almost excreted unchanged by the kidney. Twenty-four patients were prescribed one of the following medications which have narrow therapeutic range ; Gentamycin, Digoxin, Aminophylline and Gabapentin, which is predominantly excreted by kidney, dose adjustment based on renal function was required for these drugs, however the dose adjustment was not done, and fourteen out of twenty-four patients developed adverse drug reactions.

Cardiovascular diseases were the main cause of morbidity; accounting to about 36.7% of all admissions (Figure 3.3a). About 50 % (N=119) of admitted patients had a history of either hypertension alone or hypertension with other diseases (Figure 3.3b), and on admission many of our patients were in hypertension stage 2 (Table 3.1). Moreover, mortality was very high, where a total of 122 patients of two ninety-seven (297) patients, died (41.1%). Patients with a diagnosis related to the cardiovascular system were many among those who died (57.8%). Cancer was the second most common disease in our cohort. In general, majority (56.9%) of the elderly patients were admitted through emergency medicine department in this study.

**A****B**

**Figure 3.3 (A) Final Diagnosis, (B) Past Medical History**

### **3.1.2 Prevalence of potential inappropriate medication using STOPP criteria.**

A total of sixty-one patients out of 297 (20.5%) had at least one potentially inappropriate medication (PIM) as per STOPP criteria. The most common PIM involved the use of Glibenclamide in type 2 Diabetes Mellitus and NSAIDs use in contraindicated medical conditions followed by the use of loop diuretics (Table 3.2). The use of Loop diuretics in independent ankle edema only (no clinical sign of heart failure) is inappropriate in elderly because there is no evidence of efficacy, instead compression hosiery (garment worn directly on feet and legs) is usually more appropriate. Our study identified 9 (14.8%) patient out of 61 who used loop diuretics inappropriately. WHO recommends the use of pain medication in a prescribed order from nonopioids (e.g. NSAIDs); mild opioids (e.g. Codeine) to strong opioids (e.g. Morphine). In this study nine (14.8%) patient out of 61 used opioids as the first line therapy for mild-moderate pain (Table 3.2). The risk of inappropriate medication varies from drug to drug e.g., Glibenclamide is associated with prolonged hypoglycemia in elderly patients (Table 3.2) and drugs belonging to NSAIDs group have been implicated to increase the risk of renal dysfunction, hypertension and heart Failure (Table 3.2).

**Table 3.2: Observed potential inappropriate medication using STOPP criteria**

<b>Potential inappropriate medication</b>	<b>Contraindicated Risk</b>	<b>Observed PIM N (%)</b>
NSAIDS with chronic renal failure	Risk of deterioration in renal failure	6(9.8%)
NSAID with Heart Failure	Risk of exacerbation of heart failure	3(4.9%)
NSAIDS with moderate-severe blood pressure(160/100mmhg 179/109mmhg; Severe above 179/109mmhg)	Risk of exacerbation of hypertension	3(4.9%)
Alpha blockers in males with frequent incontinence	Risk of urinary frequency and worsening of incontinence	1(1%)
Aspirin at dose of >150 per day	Increased bleeding risk, no evidence for increased efficacy	2(3.3%)
Aspirin with past history of peptic ulcers diseases without histamine H2 receptor antagonist or proton pump inhibitors	Risk of bleeding	2(3.3%)
Drug that adversely affect those prone to falls; Benzodiazepines.	Sedative, May cause reduced sensorium, impair balance	1(1.6%)
Calcium channel blockers with chronic constipation	May exacerbate constipation	2(3.3%)
Digoxin at long-term dose>125micromg/d with impaired renal function	Increased risk of toxicity	4(6.6%)
Loop Diuretics for independent ankle edema only i.e. no clinical sign of heart failure	No evidence of efficacy, compression hosiery usually more appropriate	9(14.8%)
Glibenclamide with type two diabetes mellitus	Risk of prolonged hypoglycemia	13(21.31%)
Loperamide for treatment of diarrhea of unknown cause	Risk of delay diagnosis, may exacerbate constipation with over flow diarrhea, may precipitate toxic mega colon in inflammatory bowel disease, may delay recovery in unrecognized gastroenteritis	1(1.6%)
Regular opiates for more than two weeks in those with chronic constipation without concurrent use of laxatives	Risk of severe constipation	1(1.6%)
Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	Unnecessary exposure to long-term side-effects of systemic steroids	4(6.6%)
Use of powerful opiates as first line therapy for mild-moderate pain	WHO analgesic ladder not observed	9(14.8%)
<b>Total</b>		<b>61</b>

Many patient with at least one inappropriate medication came from emergency admission (22.5%); however, the association between emergency admission and PIM was not statistically significant (Table 3.3).

**Table 3.3: The association between admission and inappropriate medication**

PIM	Type of Admission		
	Normal	Emergency	Total
Yes	23(17.9%)	38(22.5%)	61(20.54%)
No	105(82%)	131(77.5%)	236(79.5%)
Total	128(100%)	169(100%)	297(100%)
	<b>P=0.9103</b>		

Inappropriate medication may lead to an increase hospitalization, adverse drug reactions and increased cost to the patient. Our study showed no significant difference between hospitalization duration and potential inappropriate medication (Table 3.4), majority of elderly patient with inappropriate medication (62.3%) stayed for less than eight days.

**Table 3.4: Patients who had PIM and hospitalization duration**

PIM	Hospitalization duration(days)			
	Below 8	8-14	15 and above	Total
Yes	38(20.1%)	15(21.1%)	8(21.6%)	61(20.5%)
No	151(79.8%)	56(78.9%)	29(78.4%)	236(79.5%)
Total	189(100%)	71(100%)	37(100%)	297 (100%)
	<b>P= 1.77</b>			

Twenty-five (40.1%) patient out of sixty-one (61) with potential inappropriate medication died (Table 3.5).The association between death and inappropriate medication was not statistical significant ( $p=0.82$ ).Nine patients (14.75%) developed adverse drug reaction and were identified by the Naranjo criteria of which six of them were probable (66%) and three (33.3%) as possible.

**Table 3.5: PIM and admission outcome**

PIM	Admission outcome		
	Alive	Dead	Total
Yes	36(20.4%)	25(20.7%)	61(20.5%)
No	140(79.6%)	96(79.34%)	236(79.5%)
Total	176(100%)	121(100%)	297(100)
	<b>P=0.82</b>		

### **3.1.3 Omitted Medication (OM)**

A total of 58 (19.5%) medications were omitted and majority (67.2 %) of the patient to whom medications omitted came from emergency admission. Fifty eight medications were omitted, of which 29 (50%) were related to aspirin therapy (Table 3.6). Between the two sexes in term of medication omission, women had higher omissions compared to the men (67% versus 33%). More than forty percent (40%) of the patient had more than one omitted drug and thirty-nine (67.24%) elderly patients who had at least one omitted medication were hospitalized less than eight days but the association between hospitalization duration and OM was not statistically significant ( $p=0.66$ ).

**Table 3.6: Omitted medication using START**

<b>Drugs</b>	<b>Omitted Medication N (%)</b>
Aspirin or clopidogrel with coronary or peripheral vascular diseases	15 (25.8)
Aspirin therapy in diabetics with well controlled blood pressure	13(22.4)
Aspirin or warfarin for atrial fibrillation	1(1.7)
B2 agonist or anticholinergic for mild to moderate asthma or COPD	4(6.8)
Calcium and Vitamin D with known osteoporosis	4(6.8)
Statins for those with coronary, cerebral or PVD (where patient is independent of ADL's and life expectancy is > 5yrs)	5(8.6)
Statin in diabetics with cholesterol > 5 or additional CV risks	6(10.3)
DMARD (disease modifying anti-rheumatic drug) for moderate to severe rheumatoid arthritis > 12 weeks	1(1.7)
Metformin with type 2 DM +/- metabolic syndrome (unless BUN >12 mmol/L or creatinine > 200 mmol/L)	2(3.4)
Inhaled steroid for moderate to severe asthma or COPD	3(5.2)
Fibre supplement for chronic diverticular disease with constipation	1(1.7)
ACEi or ARB in diabetes with nephropathy (proteinuria or microalbuminuria) +/- renal impairment (BUN >8 mmol/L or creatinine >130 mmol/L)	1(1.7)
Antihypertensive therapy with systolic BP > 160mmHg	1(1.7)
ACEi with CHF or after acute MI	1(1.7)



### **3.1.4 Renal Function in Elderly**

Reduced renal function was very common in elderly patients, with females being about 58.5% of the patients with reduced renal function. Although many patients with reduced renal function were females, there was no correlation between sex and reduced renal function ( $p=0.103$ ). Majority of the patients with reduced renal function stayed less than eight days, but we did not find any statistical association between hospitalization duration and reduced renal function ( $p=0.17$ ). About eighty six patients out of two hundred with reduced renal function (43%) died, however the study did not find any correlation between death and reduced renal function ( $p=0.17$ ).

### **3.1.5 Dose Adjustment**

Renal Function decreases with age, patients with moderate decrease in eGFR and above usually need attention regarding medications, particularly those with narrow therapeutic range and those which are renally cleared. (Table 3.1), since renal function plays an important role in drug clearance, dose adjustment is recommended in patients with eGFR less than 60 ml/min-1 per 1.73 m<sup>2</sup>. Two hundred patients out of 297 (67.3%) required dosage adjustment, our study focused only on the patients who were treated with drugs having narrow therapeutic range and those which were predominantly excreted by kidney, therefore dose adjustment was necessary. Twenty-four patient out of 200 (12%) with moderate decrease in eGFR and beyond, were prescribed these medications (Table 3.7), but the dose was not adjusted, and fourteen patients out twenty-four developed adverse drug reactions (ADRs). ADRs are undesired harmful effects which results from a medication, our study focused on ADRs that developed during hospitalization only. The fourteen ADRs identified 1 (7.1%) was related to the use of Gentamycin and included the following reactions; itching, rash, allergic reaction, dizziness, loss of appetite and stomach upset. ADRs related to digoxin toxicity were more, 13 out of the 14 (92.8%) had at least three of the following ADRs; irregular heartbeats, bloody or black stools, blurred vision and hallucinations (Table 3.7). Digoxin has been used for many years in treating cardiovascular diseases but the use of digoxin in patients with reduced renal function is associated with an increase in morbidity and mortality; hence, thirteen patients were exposed to that risk.

**Table 3.7: Dosage adjustment based on renal function**

<b>Drug</b>	<b>Prescribed daily Dose (Mg)</b>	<b>Adjusted Daily Dose (Mg)</b>	<b>ADR Developed</b>	<b>Observed ADRs</b>
Digoxin	0.125	0.06	Yes	Irregular heartbeat, black stools
Digoxin	0.125	0.018	Yes	Irregular heartbeat, confusions
Digoxin	0.75	0.42	Yes	blurred vision, confusions, hallucination
Digoxin	0.125	0.028	Yes	Irregular heartbeat, blurred vision
Digoxin	0.125	0.029	Yes	Irregular heartbeat
Digoxin	0.125	0.085	Yes	Bloody stools; Impaired vision.
Digoxin	0.125	0.132	Yes	Irregular heartbeat
Digoxin	0.125	0.044	Yes	Blurred vision, Confusions.
Digoxin	0.125	0.073	Yes	Blurred vision, Irregular heartbeat
Digoxin	0.75	0.092	Yes	Bloody stool
Digoxin	0.25	0.164	Yes	Hallucinations, confusions, Irregular heartbeat
Digoxin	0.25	0.176	Yes	Irregular heartbeat
Digoxin	0.125	0.07	Yes	blurred vision, bloody stool, Irregular heartbeat
Gabapentin	300	174.9	No	
Gabapentin	300	107.7	No	
Gabapentin	300	186.3	No	
Gabapentin	300	211.8	No	
Gabapentin	300	204.7	No	
Gabapentin	300	158.8	No	
Gabapentin	300	204.7	No	
Gabapentin	300	194.1	No	
Gabapentin	300	201.2	No	
Gentamycin	160	103.6	Yes	Itching, rash, dizziness, loss of appetite, stomach upset and pain
Aminophylline	400	277.6	No	

## CHAPTER FOUR

### 4.0 DISCUSSION

The study investigated the medication prescribed to elderly patients and its association with adverse drug reactions. We have found that inappropriate medication, underuse of potential beneficial medications and patients with reduced renal function are very common among elderly admitted to MNH.

To the best of our knowledge, this is the first study conducted in Tanzania using STOPP/START criteria though such studies were conducted in Europe and other developing countries like India and Nigeria. In our study, 20.5% of the patients had at least one inappropriate medication. The inappropriate medication was detected by using fifteen (15) criteria in the STOPP tool. Our results were comparable to those conducted in Nigeria (25.5%), and Ireland (25%)(Fadare et al. 2013). However our estimation of PIM was higher than other countries like Turkey (9.8%) and Croatia (2.2%),the low PIM observed in Croatia was due to the introduction of computerized system in the pharmacy to detect PIM and intensive training of their health care providers, Similar effort was adopted in Turkey as well(Fadare et al. 2013). The risk of inappropriate medication varies from drug to drug, our study did not find any statistical significant association between PIM and Sex ( $p=0.34$ ), which was similar to other studies conducted elsewhere (Cahir et al. 2010). Despite the known risk of hypoglycemic action of Glibenclamide in elderly with type two diabetes mellitus, it was the most frequent inappropriate medication identified. A meta-analysis of 21 studies showed that Glibenclamide was associated with an 83 % greater risk of producing at least one hypoglycemic episode compared to other sulfonylureas (Gangji et al.2007). Another retrospective cohort study (n=13,963) by Shorr et al. 1996, Glibenclamide had the highest level of hypoglycemia at 16.6 per 1000 per person-years compared with Gliplizide. A retrospective cohort study of more than 33,000 patients in the UK by Van Staa et al. 1997, showed that the risk of hypoglycemia was higher with Glibenclamide when compared to other sulfonylureas. We have observed hypoglycemic reactions in four out of thirteen patients

(31%). These episodes of hypoglycemia were identified by The Naranjo criteria as related to Glibenclamide use. Our results suggest that the reaction was common like those reported in other studies (Ganji et al. 2007; Shorr et al. 1996; Staa et al. 1997). The high prevalence of Glibenclamide hypoglycemic episodes among elderly has been linked to polypharmacy, intercurrent illness, and deterioration of physiologic function such as declining renal and hepatic functions (Shorr et al. 1996).

NSAIDs are widely used for the treatment of rheumatoid arthritis, osteoarthritis, pain, and inflammation resulting from various musculoskeletal disorders (Cahir et al. 2010). Our data show that NSAIDs were the third most prescribed medication (8.1%) and the second most inappropriately used medication (19.6%). The use of NSAIDs in the elderly is associated with risk of exacerbation of renal failure, heart failure, and hypertension (Gooch et al. 2007). Furthermore, the risk of developing acute renal failure is three times more among NSAIDs users than non-NSAIDs users (Huerta et al. 2005). Most of our patients had renal impairment and cardiovascular diseases, and hence NSAIDs use really posed a high risk. Dunn and others (1984) linked the blocking effect of NSAIDs on cyclooxygenase activity and a reduction of prostaglandins synthesis. In our study, NSAIDs were prescribed in twelve patients (19.6%) out of 61. These patients were at a risk of exacerbation their cardiovascular and renal functions. But since musculoskeletal complains are very common in older people, studies suggest that Physiotherapy and exercise may be used in some of the patients instead of prolonged dose of NSAIDs to avoid unnecessary NSAIDs associated risk (Cahir et al. 2010).

#### **4.1 Implication of PIM prevalence and Its Outcome**

In our study we have found that in every hundred elderly patients twenty of them are more likely to have inappropriate prescribed medications. According to the 2012, census, the total population of Tanzania was about Forty four million (44,928, 932) out of whom 3.8% (1,707,299 people) were above 64 years old. Therefore, in that population, 20.5% are at risk of inappropriate medication i.e. 349996 individuals, and as the population of elderly increases due to the availability of health care services, increased access and utilization of health care

services, the increasing in elderly population will most likely cause an overt in PIM prevalence as well.

PIM has always been linked with development of adverse drug reactions, increased morbidity and mortality, and hospital utilization thereby imposing higher cost to the elderly (Hamilton et al. 2009; Cahir et al. 2010). Our data suggest that PIM in elderly patients admitted at MNH was high, however the study did not find any statistical significant association between PIM and negative outcome; death, increased hospitalization duration and ADRs. These discrepancies may be attributed to the study design and sample size.

Early aspirin or clopidogrel use has benefits in many patients particular elderly. Our data demonstrated that twenty nine (50%) of elderly patients with medication omissions were related to aspirin or clopidogrel therapy, followed by statins. A study conducted by Ryan et al. 2009, demonstrated similar results. Aspirin and statins therapy play an important role in cardiovascular diseases; they reduces the incidence of cardiovascular accidents and mortality in elderly patients. As the risk of cardiovascular accidents increases with older age these drugs have a crucial role in the wellbeing of the elderly. Several studies have indicated the risk of under prescribing aspirin and statins in this age cohort. Portnay et al. 2005, indicated the role of aspirin therapy in elderly patient with acute myocardial infarction. In this cohort study (n=118,992), it was found that the rate of mortality was significantly lower in the elderly patient on aspirin therapy(16.1% ) versus (19%) in control during one month of the study and at six month 24.7% versus 27.5%. Another combined meta-analysis of two trials, Chinese acute stroke trial, and intervention stroke trial conducted by Chen et al. 2000, the rate of recurrence of stroke and death was significant lower in aspirin therapy than in the control group. In review of 9 randomized trial with a total of 41399 patients by Sandercock et al. 2003, who compared antiplatelet treatment (started within 14 days of stroke) with a control in patients with definite or presumed ischemic stroke, poor outcome was significantly reduced in patient receiving aspirin than in the control group.

The benefits of aspirin are complimented with clopidogrel, whereby the efficacy is increased when they are used together. An intervention study (n=45,852) conducted by Bhatt et al. 2004 found that the group receiving aspirin and clopidogrel (n=22,961, %=9.2) had significantly fewer reinfarctions, stroke and deaths compared to the group given aspirin or clopidogrel alone (n=2310, %= 10.1). In our study statins were the second most omitted medications. Several observational studies have demonstrated that there is a clear correlation between plasma cholesterol level and the incidence of coronary heart disease (Remnell et al. 1980). Hence by reducing the plasma cholesterol level the incidence of CHD might also be reduced, as demonstrated by Taylor et al. 2014. The CARE trial (1996) investigated the role of aspirin in preventing primary and secondary stroke, the study included about 4159 patients who were on statin based therapy (pravastatin); the intervention group had significant reductions in stroke compared to control group. Similarly, the MIRACL trial in 2001 (n=3086) demonstrated that atorvastatin, can reduce the incidence of fatal or nonfatal stroke by 50%.

It is always important to get all the appropriate medicines and therefore medication omission could cause more harm. Based on the above discussion the role of aspirin/clopidogrel and statins is inevitable, hence, proper guideline and education on the importance of the above medicine should be addressed.

#### **4.2 Renal Function among elderly patients at MNH**

Renal function decreases with aging, our study had found that about two hundred (67.3%) had eGFR less than  $60 \text{ ml min}^{-1} \text{ per } 1.73 \text{ m}^{-2}$ , with the majority of the patients having a moderate decrease in eGFR (stage 3). The prevalence of renal dysfunction among females was higher than males. Several studies have found similar results; a study by Brown et al. 2003, reported remarkably high prevalence in both men and women, but women had a tendency to have a higher prevalence of CKD than men (14.4% in men and 16.2% in women). A study by Chadban et al. 2003, demonstrated that females have a high prevalence of renal dysfunction than males, and the difference was highly significant (9.3% in men and 13.0% in women), these results were comparable with our results. The high prevalence of renal impairment among females may be due to several factors such as; the eGFR is estimated based on serum

creatinine which is dependent on muscle mass, it is known that females have less muscle compare to males. Most of older females have multiple diseases and disability (Redondo-sendino et al. 2006), and this might have contributed to this higher prevalence.

In our study death among patients with renal impairment was high (43%), similar trends have been reported in several studies; Santacruz et al. 1996 in a study “Mortality rate in elderly patient with acute renal failure” reported the mortality rate of 53%. Similarly Xue and others (2006) have found that deaths in hospitalized patient were 34.5% in patients discharged with renal failure as the principal diagnosis, and 48.6% with renal failure as a secondary diagnosis these results show similar trend to our results.

Renal function plays an important role in drug clearance where, increased renal function results in sub therapeutic concentrations while decreased renal functions results in toxic accumulations. On top of that, drug dosage adjustment is an uncommon practice in most of the African hospitals (Alahdal et al. 2012). This means as per present study, two hundred patients were at a risk of having toxicity because of their diminished renal function. The present study focused only on drugs with narrow therapeutic range and those who are predominantly excreted by kidney which needed dosage adjustment. Out of the twenty four patients who used drugs with narrow therapeutic ranges, fourteen (58.3%) had developed ADRs, most of which were due to digoxin toxicity. In a study by Howard and colleagues (2007), 1 out of 10 of hospitalized elderly patients was due to digoxin toxicity. Patients with renal insufficiency who were treated with digoxin had higher mortality rates. A study by Chan et al. 2000 indicated that digoxin was associated with mortality in end stage renal disease. Another study by Shlipak et al. 2004, showed that the risk of mortality was high in patient on digoxin therapy with eGFR less than 50.

Renal failure is associated with high morbidity and mortality in elderly patients. We recommend that the assessment of kidney function be included in clinical examinations of elderly patients. This will help in the evaluation of the best therapeutic agent in elderly, as well as providing valuable information regarding drug dose adjustment.

In our study the main cause of morbidity was cardiovascular diseases, which accounted for 36.7% of total final diagnoses made and 50.6 % of the medications prescribed were for the cardiovascular disorders. While infectious diseases affect most of the younger people this appears not to be the case in the elderly patients where non-communicable diseases were predominant. Several studies in the world have shown a similar trend in morbidity (Fadare et al. 2013; Shenoy et al. 2006; Wahab et al. 2007; Murray et al. 1997). The high prevalence of cardiovascular diseases may be attributed to life style and dietary habits in developing countries (Murray et al. 1997). The reported deaths in our study were very high about 122 (41%) out of 297 patients. In the study by Sanya et al. 2011, deaths reported in elderly on admissions were 27.2%, and a large proportion of the patients who died had cardiovascular diseases. Similarly Silva et al. 2010 reported deaths in elderly patients as high as 16.4% .These differences in deaths reported can be due to various reasons which may include; patient's state on admission, severity of illness on admission availability of proper medications and specialized personnel for geriatric patients. Majority of our patient were admitted through the emergency medicine suggesting that they were critically ill.



## **CHAPTER FIVE**

### **5.0. RECOMMENDATION AND CONCLUSION**

#### **5.1 Limitations**

Being a retrospective study, our study has some limitations; the lack of detailed diagnosis both in the database and physical files affected the study, since some of the STOPP and START criteria required a diagnosis in the evaluation process. The evaluation was based on prescribed medicine which may include medicine in misdiagnosis. The study did not confirm if the patient had indeed taken the prescribed medications. The STOPP and START tools contains about 65 and 22 criteria respectively. In our study we had managed to use only 15 STOPP and 14 START criteria, suggesting that unavailability of variety of medications may have influence on the study. However, we cannot fail to appreciate the information obtained from this study regarding PIM, POM and CKD-EPI in our country that were not available.

#### **5.2 Policy Implication and Recommendations**

Our study has shown that PIM increases unnecessary cost to the patient as well as morbidity and mortality, although we did not find any statistical significant association between PIM and negative outcomes (morbidity, mortality and hospitalization duration), reports of negative outcome in elderly patients are several; some studies have linked these outcomes with inappropriate medication, medication omission, and reduced renal function.

The prevalence of 20.5% of PIM and 68% of the individual who requires dosage adjustment, and 19.5% who were denied potential beneficial medication are quite high. As elderly population is increasing measures must be set to tackle the situation. To increase awareness of elderly special needs, it is important that the clinicians are made aware of the benefits of proper medication particular to the elderly. Therefore were recommending a big study to incorporate many patients to give a convincing picture for developing an interventions to assess the feasibility and the cost effectiveness of using STOPP and START criteria so that they can be adopted and incorporated in everyday practice. The study also encourage

clinicians to perform comprehensive geriatric assessment including renal function in order to assess the need of dosage adjustment.

### **5.3 Conclusion**

Our study concludes that, the prevalence of PIM, POM and reduced renal function to be high. Of all 279 patients, 20.5%, 19.5% and 67.3% had at least one inappropriate medication, at least one omitted medication and renal insufficiency stage three or higher respectively. In order to improve patient health, the prescribing habit among the elderly needs to be reviewed. We are also encouraging further studies to focus on measuring the economic outcome of PIM and linking PIM and POM with negative outcomes.

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**APPENDICES**

**Appendix 1: Data Extraction Form**

Hospital Admission number: .....

Study Number: .....

Date of Data extraction: ...../...../.....

Date of Admission: ...../...../.....

Date of Birth: ...../...../.....

Date of Discharge: ...../...../.....

Gender: M  F

Hospitalization duration: .....

Age: .....

Final Diagnosis: .....

**LAB:**

Serum creatinine: .....

1) Medication prescribed

.....  
.....  
.....  
.....  
.....  
.....  
.....  
.....  
.....



6) Was any ADR developed? Yes  No

7) Was developed ADR due to inappropriate prescribing? as per Naranjo criteria Yes    
No

ADR and Naranjo algorithm scale

S.N	ADR	Naranjo Score			
	ADR <sub>1</sub>	Definite <input type="checkbox"/>	Probable <input type="checkbox"/>	Possible <input type="checkbox"/>	Doubtful <input type="checkbox"/>
	ADR <sub>2</sub>	Definite <input type="checkbox"/>	Probable <input type="checkbox"/>	Possible <input type="checkbox"/>	Doubtful <input type="checkbox"/>
	ADR <sub>3</sub>	Definite <input type="checkbox"/>	Probable <input type="checkbox"/>	Possible <input type="checkbox"/>	Doubtful <input type="checkbox"/>
	ADR <sub>4</sub>	Definite <input type="checkbox"/>	Probable <input type="checkbox"/>	Possible <input type="checkbox"/>	Doubtful <input type="checkbox"/>

8) Was there any renally cleared drug? Yes  No

Table of renally cleared drugs

S.N	Drugs	Prescribed dose(mg)	Dose interval (Hrs)	Start date	Stop date	Adjusted dose=Normal dose $\times$ RF	Adjusted dose interval=Normal dose interval(Hrs)/RF	Comment

9) Was the dose adjusted? Yes  No

10) Was there any potential omission medication (POM) as per START? Yes  No

(d) Which drugs were omitted as per START?

S.N	POM	Indication



## **Appendix 2: STOPP CRITERIA**

The following prescriptions are potentially inappropriate in persons aged  $\geq 65$  years of age

### **A. Cardiovascular System**

1. Digoxin at a long-term dose  $> 125\mu\text{g}/\text{day}$  with impaired renal function \* (increased risk of toxicity).
2. Loop diuretic for dependent ankle oedema only i.e. no clinical signs of heart failure (no evidence of efficacy, compression hosiery usually more appropriate).
3. Loop diuretic as first-line monotherapy for hypertension (safer, more effective alternatives available).
4. Thiazide diuretic with a history of gout (may exacerbate gout).
5. Non-cardio selective beta-blocker with Chronic Obstructive Pulmonary Disease (COPD) (risk of bronchospasm).
6. Beta-blocker in combination with verapamil (risk of symptomatic heart block).
7. Use of diltiazem or verapamil with NYHA Class III or IV heart failure (may worsen heart failure).
8. Calcium channel blockers with chronic constipation (may exacerbate constipation).
9. Use of aspirin and warfarin in combination without histamine H<sub>2</sub> receptor antagonist (except cimetidine because of interaction with warfarin) or proton pump inhibitor (high risk of gastrointestinal bleeding).
10. Dipyridamole as monotherapy for cardiovascular secondary prevention (no evidence for efficacy).

11. Aspirin with a past history of peptic ulcer disease without histamine H2 receptor antagonist or Proton Pump Inhibitor (risk of bleeding).
12. Aspirin at dose > 150mg day (increased bleeding risk, no evidence for increased efficacy).
13. Aspirin with no history of coronary, cerebral or peripheral arterial symptoms or occlusive arterial event (not indicated).
14. Aspirin to treat dizziness not clearly attributable to cerebrovascular disease (not indicated).
15. Warfarin for first, uncomplicated deep venous thrombosis for longer than 6 months duration (no proven added benefit).
16. Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration (no proven benefit).
17. Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder (high risk of bleeding).

\* Estimated GFR <50ml/min.

## **B. Central Nervous System and Psychotropic Drugs**

1. Tricyclic antidepressants (TCA's) with dementia (risk of worsening cognitive impairment).
2. TCA's with glaucoma (likely to exacerbate glaucoma).
3. TCA's with cardiac conductive abnormalities (pro-arrhythmic effects).
4. TCA's with constipation (likely to worsen constipation).
5. TCA's with an opiate or calcium channel blocker (risk of severe constipation).

6. TCA's with prostatism or prior history of urinary retention (risk of urinary retention).
7. Long-term (i.e. > 1 month), long-acting benzodiazepines e.g. chlordiazepoxide, fluzepam, nitrazepam, chlorazepate and benzodiazepines with long-acting metabolites e.g. diazepam (risk of prolonged sedation, confusion, impaired balance, falls).
8. Long-term (i.e. > 1 month) neuroleptics as long-term hypnotics (risk of confusion, hypotension, extra-pyramidal side effects, falls).
9. Long-term neuroleptics (> 1 month) in those with parkinsonism (likely to worsen extra-pyramidal symptoms)
10. Phenothiazines in patients with epilepsy (may lower seizure threshold).
11. Anticholinergics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity).
12. Selective serotonin re-uptake inhibitors (SSRI's) with a history of clinically significant hyponatraemia (non-iatrogenic hyponatraemia <130mmol/l within the previous 2 months).
13. Prolonged use (> 1 week) of first generation antihistamines i.e. diphenhydramine, chlorpheniramine, cyclizine, promethazine (risk of sedation and anti-cholinergic side effects).

### **C. Gastrointestinal System**

1. Diphenoxylate, loperamide or codeine phosphate for treatment of diarrhoea of unknown cause (risk of delayed diagnosis, may exacerbate constipation with overflow diarrhoea, may precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognised gastroenteritis).

2. Diphenoxylate, loperamide or codeine phosphate for treatment of severe infective gastroenteritis i.e. bloody diarrhoea, high fever or severe systemic toxicity (risk of exacerbation or protraction of infection)
3. Prochlorperazine (Stemetil) or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonism).
4. PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks (earlier discontinuation or dose reduction for maintenance/prophylactic treatment of peptic ulcer disease, oesophagitis or GORD indicated).
5. Anticholinergic antispasmodic drugs with chronic constipation (risk of exacerbation of constipation).

#### **D. Respiratory System**

1. Theophylline as monotherapy for COPD. (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index)
2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic steroids).
3. Nebulised ipratropium with glaucoma (may exacerbate glaucoma).

#### **E. Musculoskeletal System**

1. Non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent histamine H<sub>2</sub> receptor antagonist, PPI or misoprostol (risk of peptic ulcer relapse).
2. NSAID with moderate-severe hypertension (moderate: 160/100mmHg – 179/109mmHg; severe:  $\geq$ 180/110mmHg) (risk of exacerbation of hypertension).
3. NSAID with heart failure (risk of exacerbation of heart failure).

4. Long-term use of NSAID (>3 months) for relief of mild joint pain in osteoarthritis (simple analgesics preferable and usually as effective for pain relief)
5. Warfarin and NSAID together (risk of gastrointestinal bleeding).
6. NSAID with chronic renal failure\* (risk of deterioration in renal function). \* Estimated GFR 20-50ml/min.
7. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis or osteoarthritis (risk of major systemic corticosteroid side-effects).
8. Long-term NSAID or colchicine for chronic treatment of gout where there is no contraindication to allopurinol (allopurinol first choice prophylactic drug in gout)

**F. Urogenital System**

1. Bladder antimuscarinic drugs with dementia (risk of increased confusion, agitation).
2. Bladder antimuscarinic drugs with chronic glaucoma (risk of acute exacerbation of glaucoma).
3. Bladder antimuscarinic drugs with chronic constipation (risk of exacerbation of constipation).
4. Bladder antimuscarinic drugs with chronic prostatism (risk of urinary retention).
5. Alpha-blockers in males with frequent incontinence i.e. one or more episodes of incontinence daily (risk of urinary frequency and worsening of incontinence).
6. Alpha-blockers with long-term urinary catheter in situ i.e. more than 2 months (drug not indicated).

**G. Endocrine System**

1. Glibenclamide or chlorpropamide with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).
2. Beta-blockers in those with diabetes mellitus and frequent hypoglycaemic episodes i.e.  $\geq 1$  episode per month (risk of masking hypoglycaemic symptoms).
3. Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence)
4. Oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).

**H. Drugs that adversely affect those prone to falls ( $\geq 1$  fall in past three months)**

1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance).
2. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).
3. First generation antihistamines (sedative, may impair sensorium).
4. Vasodilator drugs known to cause hypotension in those with persistent postural hypotension i.e. recurrent  $> 20\text{mmHg}$  drop in systolic blood pressure (risk of syncope, falls).
5. Long-term opiates in those with recurrent falls (risk of drowsiness, postural hypotension, vertigo).

**I. Analgesic Drugs**

1. Use of long-term powerful opiates e.g. morphine or fentanyl as first line therapy for mild-moderate pain (WHO analgesic ladder not observed).
2. Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives (risk of severe constipation).
3. Long-term opiates in those with dementia unless indicated for palliative care or management of moderate/severe chronic pain syndrome (risk of exacerbation of cognitive impairment).

**J. Duplicate Drug Classes**

Any regular duplicate drug class prescription e.g. two concurrent opiates, NSAID's, SSRI's, loop diuretics, ACE inhibitors (optimisation of monotherapy within a single drug class should be observed prior to considering a new class of drug). This excludes duplicate prescribing of drugs that may be required on a prn basis e.g. inhaled beta2 agonists (long and short acting) for asthma or COPD, and opiates for management of breakthrough pain.

### **Appendix 3: START CRITERIA**

**Cardiovascular** (following therapies are recommended assuming there are no contraindications)

- Warfarin for chronic A.fib
- Aspirin for chronic A. fib (warfarin contraindicated)
- Aspirin or Clopidogrel with coronary, cerebral or PVD (patient in sinus rhythm)
- Antihypertensive therapy with systolic BP > 160mmHg
- Statins for those with coronary, cerebral or PVD (where patient is independent of ADL's and life expectancy is > 5yrs)
- ACEi with CHF or after acute MI
- Beta blocker with chronic stable angina

### **Respiratory**

- B2 agonist or anticholinergic for mild to moderate asthma or COPD
- Inhaled steroid for moderate to severe asthma or COPD
- Continuous oxygen where chronic type 1 or 2 respiratory failure has been documented

### **Central Nervous System**

- Levodopa for idiopathic parkinson's with functional impairment and disability
- Antidepressant for clear cut depressive symptoms  $\geq$  3 months

### **Gastrointestinal System**

- PPI's for chronic, severe GERD, or peptic stricture requiring dilation
- Fibre supplement for chronic diverticular disease with constipation.



**Locomotor System**

- DMARD (disease modifying anti-rheumatic drug) for moderate to severe rheumatoid arthritis > 12 weeks
- Bisphosphonate for those on glucocorticoids > 1 month
- Calcium and Vitamin D with known osteoporosis.

**Endocrine System**

- Metformin with type 2 DM +/- metabolic syndrome (unless BUN >12 mmol/L or creatinine > 200 mmol/L)
- ACEi or ARB in diabetes with nephropathy (proteinuria or microalbuminuria) +/- renal impairment (BUN >8 mmol/L or creatinine >130 mmol/L)
- Aspirin therapy in diabetics with well controlled BP
- Statin in diabetics with cholesterol > 5 or additional CV risks

**Appendix 4: The Naranjo Algorithm (Adverse Drug Reaction Probability Scale)****Adverse Drug Reaction Probability Score**

<b>Question</b>	<b>Yes</b>	<b>No</b>	<b>Do Not Know</b>	<b>Score</b>
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less	+1	0	0	

severe when the dose was decreased?				
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
	<b>Total Score:</b>			

#### The Naranjo Algorithm - ADR Probability Scale

Score	Interpretation of Scores
<b>Total Score <math>\geq 9</math></b>	<b>Definite.</b> The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure.
<b>Total Score 5 to 8</b>	<b>Probable.</b> The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
<b>Total Score 1 to 4</b>	<b>Possible.</b> The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
<b>Total Score <math>\leq 0</math></b>	<b>Doubtful.</b> The reaction was likely related to factors other than a drug.

## **Instructions**

The response “Do not know” should be used sparingly and only when the quality of the data does not permit a “Yes” or “No” answer. “Do not know” can be applicable if the information is not available and also if the question is inapplicable to the case. When more than one drug is involved or suspected, the ADR Probability Scale is usually applied separately to each of the possible etiologic agents, and the drug with the highest score should be considered the causative agent. In addition, the potential of interaction should be evaluated.

**Question 1.** Are there previous conclusive reports on this reaction? The answer “Yes” (+1) applies if there have been two or more published reports in which the adverse reaction has been described in detail or if the adverse reaction is listed in a reliable source, such as a medical textbook, review article on the medication or on adverse drug reactions, or the product package insert. The response “No” applies when the adverse event has not been described previously or if only one report has been published, or if published reports were considered inconclusive or unconvincing. The answer “Do not know” is applicable only when there is no information, because the agent has not been available for an adequate period of time or has not been previously evaluated for this adverse reaction. The scores given for “No” and “Do not know” are the same (0), so it is not critical to decide between these two answers.

**Question 2.** Did the adverse event appear after the suspected drug was administered? This question evaluates the temporal relationship between the reaction and administration of the medication. The answer “Yes” (+2) applies if there is definitive evidence that the adverse event occurred after the medication was started. “No” (-1) applies when the adverse event developed before the first dose of the drug. “Do not know” (0) applies if the information is not available or is unclear.

Question 3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered? This question evaluates the response to dechallenge or stopping the medication. The answer “Yes” (+1) applies if the adverse event diminishes or disappears at

any time after stopping the medication, or if the reaction disappears upon administration of a specific pharmacologic antagonist (for example, an anticholinergic given for a cholinergic reaction to physostigmine). The answer “No” (0) applies if the adverse event does not improve or improves in response to a nonspecific therapy or an antidote to another medication or treatment of the underlying disease. The answer “Do not know” (0) applies if the medication was not stopped or the subsequent course was unknown, inconclusive, or unclear.

**Question 4.** Did the adverse event reappear when the drug was readministered? This question evaluates the response to rechallenge or reexposure. An answer of “Yes” (+2) indicates that the medication was stopped, the adverse event resolved or improved, and there was an unequivocal reappearance or worsening of the reaction when the medicine was restarted in a similar dose and by the same route. The Naranjo scale also allows for a “Yes” if the causal association is well known and rechallenge cannot be done for clinical or ethical reasons. An answer of “No” (-1) only applies if rechallenge was done, but the adverse event did not reappear or worsen. The answer “Do not know” (0) applies if rechallenge was not done or information on rechallenge is not available or the reaction was ambiguous.

**Question 5.** Are there alternative causes that could on their own have caused the reaction? This question assesses alternative explanations for the adverse event. Because adverse events are often nonspecific and can be manifestations of the disease being treated or an unrelated, concurrent disease or condition, other diagnoses need to be considered and excluded. The answer “No” (+2) applies if alternative causes have been excluded, based upon a systematic and complete evaluation, thus implicating the drug more strongly. A risk or susceptibility factor is not an alternative cause. The answer “Yes” (-1) applies when there is an alternative cause or explanation. “Do not know” (0) applies if the investigation of other causes is incomplete, inconclusive or was not done.

**Question 6.** Did the reaction reappear when a placebo was given? This question applies to clinical research studies in which a placebo was administered. The answer “Yes” (-1) applies

if the medication was stopped and the adverse reaction resolved or improved conclusively, and there was an unequivocal reappearance of the adverse event after administration of placebo (single or double blind). The answer “No” (+1) applies if the reaction did not reappear or worsen after administration of placebo. “Do not know” (0) applies if placebo challenge was not done or the results were inconclusive.

**Question 7.** Was the drug detected in blood or other fluids in concentrations known to be toxic? This question applies specifically to dose dependent adverse reactions when blood, urine, tissue or other specimen concentrations of the medicine are available. The answer “Yes” (+1) applies if the concentration is in the accepted toxic or supratherapeutic range. “No” (0) applies if the concentration is below the toxic range. The answer “Do not know” (0) applies if drug levels are not available or are inconclusive.

**Question 8.** Was the reaction more severe when the dose was increased or less severe when the dose was decreased? This question evaluates the dose response relationship of medication and the adverse reaction. “Yes” (+1) applies if the adverse event was more severe or worsened when the dose of the medication was increased, or was less severe and improved when the dose was decreased. “No” (0) applies if there was no appreciable change in the severity of the adverse event with dose modification. “Do not know” (0) applies if the dose or regimen was not altered or the information was not available or inconclusive.

**Question 9.** Did the patient have a similar reaction to the same or similar drugs in any previous exposure? This question is directed at past medical history of adverse reactions to the same or a structurally related drug. “Yes” (+1) applies when there is documentation of a previous similar reaction to the specific drug or a related medication. “No” (0) applies when the patient does not have a previous exposure to the same medicine or when the patient did not develop the adverse reaction in a previous exposure to the same or related drugs. “Do not know” (0) applies when there is no information on previous reactions or the information is inconclusive.

**Question 10.** Was the adverse event confirmed by any objective evidence? The final question assesses the quality of the data on which the adverse event is assessed. “Yes” (+1) indicates that there is laboratory test documentation of the adverse event or that the event was directly observed by a qualified person (for example, a skin rash described in nursing or physician notes). The answer “No” (0) applies when neither laboratory tests nor direct clinical documentation can verify the reaction. “Do not know” (0) applies if there is no specific information available (no laboratory testing and no clinical description) or the information is inconclusive. The scores given for “No” and “Do not know” are the same (0), so it is not critical to decide between these two answers.

Appendix 5: Ethical clearance

**MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED  
SCIENCES**

*Directorate of Postgraduate Studies*

P.O. BOX 65001  
DAR ES SALAAM  
TANZANIA.



Tel: +255-(0)22-2150302 Ext 207.  
Tel (Direct): +255-(0)22-2151378  
Telefax: 255-(0)22-2150465  
E-mail: [dpgs@muhas.ac.tz](mailto:dpgs@muhas.ac.tz)

Website: <http://www.muhas.ac.tz>

Ref. No. MU/PGS/SAEC/Vol.IX/

14<sup>th</sup> March, 2013

Mr. Bernard T. Makala,  
MSc. Clinical Pharmacology,  
**MUHAS.**

**Re: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED "EVALUATION OF POTENTIAL INAPPROPRIATE MEDICATION IN ELDERLY PATIENTS ADMITTED IN MUHIMBILI NATIONAL HOSPITAL USING THE STOPP/START CRITERIA"**

Reference is made to the above heading.

I am pleased to inform you that, the Chairman has on behalf of the Senate approved ethical clearance for the above-mentioned study.

Thus ethical clearance is granted and you may proceed with the planned study.

Please liaise with bursar's office to get your research fund.

Dr. J.R. Masalu  
**ACTING: DIRECTOR, POSTGRADUATE STUDIES**

c.c. Dean, School of Medicine,



## Appendix 6: Research Clearance

**MUHIMBILI NATIONAL HOSPITAL**

**Cables:** "MUHIMBILI"  
**Telephones:** 255-22-2151367-9  
**FAX:** 255-22-2150234  
**Web:** [www.mnh.or.tz](http://www.mnh.or.tz)



**Postal Address:**  
 P.O. Box 65000  
**DAR ES SALAAM**  
 Tanzania

**In reply please quote:**  
**Ref:**

19<sup>TH</sup> JAN 2014

**TO WHOM IT MAY CONCERN**  
**MUHIMBILI NATIONAL HOSPITAL**

**RE: RESEARCH CLEARANCE NO 501 2013/2014**

<b>Name of Researcher</b>	<b>BERNARD T MAKALA</b>
<b>Research Title</b>	<b>EVALUATION OF POTENTIAL INAPRO PRIATE MEDICATION IN ELDERLY PATIENTS ADMITTED IN MUHIMBILI NATIONAL HOSPITAL USING THE STOPP/START CRITERIA</b>
<b>Type of Research</b>	<b>DESCRIPTIVE RETROSPECTIVE STUDY</b>
<b>Valid Between</b>	<b>JAN 2014 TO APRIL 2014</b>

The above named has been allowed to conduct the stated research.

Please accord him/her and his/her assistants the necessary assistance/cooperation.

Sincerely,

  
**Dr. H.F. SWAI**  
**DIRECTOR OF MEDICAL SERVICES**

**DIRECTOR OF MEDICAL SERVICES**  
**MUHIMBILI NATIONAL HOSPITAL**  
 P. O. Box 65000  
 DAR-ES-SALAAM

## Appendix 7: Summary of the Studies conducted using different Tools

Table 1 Summary table of studies which have used the Beers' Criteria in a European setting

Study	Country	Care setting /age category	No of patients	Criteria	Outcomes
De Oliveira <i>et al.</i> '06	Portugal	Community-dwelling elders ≥65 yrs	213	1997 Beers ID Criteria & 2003 Beers ID Criteria	37.7% of the dataset were prescribed at least one inappropriate drug as defined by the 1997 Beers' criteria and 38.5% as defined by the 2003 Beers criteria
Rajska-Neumann <i>et al.</i> '07	Poland	Community-dwelling elders ≥75 Yrs	680	1997 Beers ID Criteria	28.2% of the subjects were prescribed at least one inappropriate drug.
De Wilde <i>et al.</i> '03	United Kingdom	Community-dwelling elders ≥65 yrs	162,000	2003 Beers ID&CD Criteria	32.3% of the subjects were prescribed at least one inappropriate drug.
Van Der Hoof <i>et al.</i> '97-'01	Holland	Community dwelling elderly ≥ 65	18,030-29,605.	1997 Beers ID &CD Criteria & 2003 Beers ID & CD Criteria	A PIP prevalence rate of 16.8-18.5% was reported when the 1997 Beers' criteria were used to assess PIP and a PIP prevalence of 19.1-20.0% was reported when the 2003 Beers criteria were used to define PIP.
Ay <i>et al.</i> '05	Turkey	Community dwelling elderly ≥ 70	1,019	1997 Beers ID & CD Criteria	In this study it was reported that 9.8% of the dataset were prescribed at least one inappropriate drug.
Pitkela <i>et al.</i> '02	Finland	Community dwelling elderly ≥65 yrs	2,511	1997 Beers ID & CD Criteria	It was reported that 12.5% of the patients studied were on at least one PIM.
Fialova <i>et al.</i> '05	Europe	Community dwelling elderly ≥65 yrs	2707	Modified 1997 Beers ID &CD Criteria & Modified 2003 Beers ID & CD Criteria	9.8% of the dataset were prescribed at least one inappropriate drug as defined by the 1997 Beers criteria and 16.9% as defined by the 2003 Beers criteria
Barry <i>et al.</i> '06	Ireland	Community-dwelling elders ≥65 yrs	350	2003 Beers ID Criteria & IPET	34% of the dataset received at least one PIM according to the Beers criteria, whereas a PIP prevalence of 22% was reported for IPET
Gallagher <i>et al.</i> '08	Ireland	Community-dwelling elders ≥65 yrs	597	2003 Beers ID & CD Criteria	32% of the patients in the dataset received at least one PIM according to Beers' criteria
Gallagher <i>et al.</i> '08	Ireland	Community-dwelling elders ≥65 yrs	715	STOPP Criteria & 2003 Beers ID & CD Criteria	In this dataset 34% of the patients were prescribed at least one PIM according to STOPP and 25% of the patients were prescribed a PIM according to the Beers' criteria
Ryan <i>et al.</i> '09	Ireland	Community dwelling elderly ≥ 65 yrs	500	2003 Beers ID & CD Criteria & IPET	In this study a PIP prevalence rate of 13% was reported for the Beers Criteria and 10.4% for IPET
Ryan <i>et al.</i> '09	Ireland	Community dwelling elderly ≥ 65	1,329	STOPP Criteria & 2003 Beers ID & CD Criteria	Beers' identified one or more PIMs in 18.4% of patients, whereas the STOPP criteria reported a PIP prevalence rate of 21.4%

Table 2 Summary table of Irish studies which have used the explicit criteria to investigate PIP prevalence

Study	Country	Care setting /age category	No of patients	Criteria	Main Outcomes
Barry <i>et al.</i> '06	Ireland	Community-dwelling elders $\geq 65$ yrs	350	2003 Beers ID Criteria & IPET	34% of the dataset received at least one PIM according to the Beers' criteria, whereas a PIP prevalence of 22% was reported for IPET
Gallagher <i>et al.</i> '08	Ireland	Community-dwelling elders $\geq 65$ yrs	597	2003 Beers ID & CD Criteria	32% of the patients in the dataset received at least one PIM according to Beers' criteria
Gallagher <i>et al.</i> '08	Ireland	Community-dwelling elders $\geq 65$ yrs	715	STOPP Criteria & 2003 Beers ID & CD Criteria	In this dataset 34% of the patients were prescribed at least one PIM according to STOPP and 25% of the patients were prescribed a PIM according to the Beers' criteria
Ryan <i>et al.</i> '09	Ireland	Community dwelling elderly $\geq 65$ yrs	500	2003 Beers ID & CD Criteria & IPET	In this study a PIP prevalence rate of 13% was reported for the Beers Criteria and 10.4% for IPET
Ryan <i>et al.</i> '09	Ireland	Community dwelling elderly $\geq 65$	1,329	STOPP Criteria & 2003 Beers ID & CD Criteria	Beers' identified one or more PIMs in 18.4% of patients, whereas the STOPP criteria reported a PIP prevalence rate of 21.4%
Cahir <i>et al.</i> '10	Ireland	Community dwelling elderly $\geq 70$ yrs	338802	STOPP Criteria	It was reported that 36% of the patients studied were on at least one PIM.
Hamilton <i>et al.</i> '10	Ireland	Community dwelling elderly $\geq 65$ yrs	500	STOPP Criteria & 2003 Beers ID & CD Criteria	This study found that 52% of the dataset was on at least one PIM as defined by the STOPP criteria and 27% of them were on at least one PIM as defined by the Beers' criteria.

Table 3 Summary table of studies which have used the STOPP Criteria

Study	Country	Care Setting /Age Category	No of patients	Criteria	Main Outcomes
Ryan <i>et al.</i> '09	Ireland	≥65 yrs Community dwelling elderly	1,329	2003 Beers ID & CD Criteria & STOPP Criteria	a PIM according to the Beers' criteria Beers' identified One or more PIMs was identified in 18.4% of patient, whereas the STOPP criteria reported a PIP prevalence rate of 21.4%. It was reported that 36% of the patients studied were on at least one PIM.
Cahir <i>et al.</i> '10	Ireland	Community dwelling elderly ≥70 yrs	338802	2003 Beers ID & CD Criteria & STOPP Criteria	
Lang <i>et al.</i> '10	Switzerland	Hospitalised elders	150	STOPP Criteria	A PIP prevalence of 77% was reported in this dataset of hospitalised elders.
Hamilton <i>et al.</i> '10	Ireland	Community dwelling elderly ≥65 yrs	500	STOPP Criteria & 2003 Beers ID & CD Criteria	This study found that 52% of the dataset was on at least one PIM as defined by the STOPP criteria and 27% of them were on at least one PIM as defined by the Beers' criteria.