Heart failure with reduced left ventricular ejection fraction in patients aged 70 years or older in Malta – Epidemiology and treatment outcome of ACE inhibitors and Angiotensin Receptor Blockers

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Thesis Abstract

Heart failure with reduced left ventricular ejection fraction in patients aged 70 years or older in Malta – Epidemiology and treatment outcome of ACE inhibitors and Angiotensin Receptor Blockers

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Approximately 80% of patients suffering from heart failure (HF) with reduced ejection fraction are elderly aged ≥70 years. Yet, patients aged over 70 years are under-represented in clinical trials that shaped current treatment. Results from large observational studies that followed are now used to extrapolate the same expected benefit on the present patient population. However, suitable representation of the real world remains problematic with longer survival and wider, multimodal treatment. This single-centre, retrospective research evaluated current and predicted burden of disease in the Maltese population and re-examined two key effectiveness aspects of renin angiotensin system (RAS) blockade with a focus on patients aged ≥70 years at incident diagnosis. First, are angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) effective at reducing all-cause mortality and HF hospitalisation? Second, are ARB effective as ACEI in this population? Incidence rates from 2007 to 2017 demonstrated fast rising trends of incident diagnosis accompanied by similar trends for related mortality with a sex gap where males fared worse. ACEI were prevalent in males while ARB were preferred in females. Treatment decreased with age and females experienced earlier treatment denial. Survival analysis revealed significant mortality reduction with ACEI and ARB that compared with younger patients, persisted for at least 3 years post incident diagnosis, and remained incremental with background treatment despite additional comorbidity. The sex disparity in preferential treatment was irrelevant because ARB were comparable to ACEI at reducing mortality. These findings were demonstrated by cohorts of patients aged ≥70 years at incident diagnosis. The influence of treatment on HF hospitalisation was heavily confounded by selection bias that precluded any conclusions. Nonetheless, if treatment is maintained the positive benefit of both RAS inhibitors of reduced mortality in elderly patients has a beneficial impact on the predicted disease burden that shall keep rising until 2040.

Key words or phrases: heart failure, elderly patients, ejection fraction, ACEI, ARB, hospitalisation, mortality, effectiveness.

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"In examining disease, we gain wisdom about anatomy and physiology and biology. In examining the person with disease, we gain wisdom about life."
Oliver W. Sacks, The Man Who Mistook His Wife for a Hat

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List of Abbreviations

ACC/AHA	American college of cardiology / American heart association
ACEI	Angiotensin converting enzyme inhibitors
AMI	Acute Myocardial Infarction
ARB	Angiotensin receptor blockers
ARNI	Angiotensin Receptor-Neprilysin Inhibitor
CABG	Coronary artery bypass graft
CHF	Chronic heart failure
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EU	European Union
GDMT	Guideline directed medical therapy
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ICD 10	International Classification of Diseases 10th revision
ICDs	Implantable cardioverter defibrillators
IRR	Incident rate ratio
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MI	Myocardial infarction
NYHA	New York Heart Association
OR	Odds ratio
PASS	Power analysis and sample size (NCSS LLC statistical software)
PCI	Percutaneous coronary intervention
PTCA	Percutaneous transluminal coronary angioplasty
RAS	Renin angiotensin system
RR	Risk ratio
SGLT2	Sodium-glucose cotransporter-2
SPSS	Statistical Package for the Social Sciences
UK	United Kingdom
USA	United States of America

Glossary of Terms

All-cause mortality

Mortality from all causes including cardiovascular and non-cardiovascular reasons. Often stated as a measure of number of deaths over a specified time and interpreted as a mortality rate. This can also be adjusted for age to give the mortality rate for a specific age group. The International Classification of Diseases provides codes for standardized classification of causes and ICD-10 was the current version for this research.

Annual / mean incidence

Incidence is the rate of new cases or events over a specified period for the population at risk for the event. Hence annual incidence is the rate over one year. Mean incidence is the 11-year average of multiple annual incidence rates from 2007 to 2017 and is a measure used for statistical comparison. In this case the population at risk is also prespecified by age ≥ 50 years or ≥ 70 years.

As treated (AT)

A method of data analysis that classifies participants according to the actual treatment that they took rather than according to the treatment that they were assigned to. Apart from censoring based on a time-to-event analysis per protocol, patients are also censored for terminating ACEI or ARB and for switching groups during the 3-year follow-up. Therefore treatment switching is allowed and included with censoring. Analysis compares the outcome among those who took treatment with those who did not take treatment (or with new treatment), regardless of their initial treatment assignment at the start of randomisation. As a result, an ‘as treated’ comparison will be confounded if the reasons that moved participants to take or change treatment were associated with prognostic factors. Confounding arises in an ‘as treated’ analysis when not all prognostic factors are appropriately measured and adjusted for. Due to this disadvantage and also because it does not preserve randomisation, as-treated analysis is not favoured for use in a primary survival analysis model. However, this approach was preferred in this research as it gives a real-world scenario of treatment use. Furthermore, the studies were all inclusive with group allocation dependent on treatment and not based on randomization. The confounding effect size in the as treated method can be checked by intention-to-treat and per-protocol approaches.

Background heart failure therapy

Includes all drug treatment used for heart failure and excludes ACEI and ARB as the index drug classes under research. In this research this term refers to other treatment with life-saving benefit taken by heart failure patients in this study, that is two beta receptor blockers carvedilol and bisoprolol, aldosterone receptor antagonists (spironolactone and eplerenone), and hydralazine combined with nitrates. Also included is digoxin.

Baseline

Refers to the time origin of study commencement from which time-to-event or censoring is measured. In this research the time origin is taken as the point for incident diagnosis of HFrEF.

Cardiovascular risk factor

Biological characteristic, conduct, or social variable that increases the likelihood of suffering or dying from cardiovascular disease. These factors play an independent, causal part in promoting atherosclerosis or cardiovascular disease. Examples include hypertension, smoking, hypercholesterolaemia, and diabetes mellitus.

Charlson comorbidity score

A method using an index of predicting mortality by classifying and weighting comorbid conditions. To measure disease burden, a weighted score is assigned to each comorbid condition based on the relative risk of 1-year mortality. The index demonstrates strong ability to predict mortality. The version used in this research is the revised, validated index that includes ICD-10 coding algorithms to define Charlson scores and updated comorbidities. It also contains score weights that reflect advances in chronic disease management and improvements in treatments and technology, considering that patients now survive longer than they did in 1984 when the original Charlson weights were developed.

Cohort

A group of patients who share a common characteristic, such as a particular disease, biomarker, or demographic similarity. In cohort studies, the analysis of data usually involves estimation of rates of disease in the cohort during a defined period of observation. During this period, some of the cohort are exposed to a specific risk factor, treatment, or other characteristic. By measuring outcomes over a period of time, it is then possible to explore the impact of this variable. For this reason, the term *cohort* describes any designated group

of persons that are followed or traced over a period of time. Thus, *cohort study* is synonymous with *follow-up* , *longitudinal* , or *prospective study*.

Cumulative survival probability

A Kaplan-Meier plot displays the cumulative probability of an individual remaining alive or disease-free at any time after baseline. The survival duration of a subject is represented by the length of the horizontal intervals along the X-axis of serial times. The vertical line terminating an interval signifies the occurrence of an event of interest. The vertical distances between horizontal intervals illustrate the change in the cumulative probability of surviving a given time as seen in the Y-axis. The cumulative probability of surviving throughout the full period under study is determined by the last horizontal. This is because cumulative survival probability is the product of the survival probabilities up to that point in time and defines the probability at the beginning and throughout the interval. The log-rank test in a Kaplan-Meier plot tests for significant differences in cumulative survival probability between groups.

Hazard ratio

This is the most commonly used statistic for time to event variable. It is the ratio of hazards and equals to the hazard rate in the treatment (experimental) group divided by the hazard rate in the control (or comparator) group. Hazard rate represents the instantaneous event rate, which means the probability that an individual would experience an event at a particular given point in time after the intervention (or baseline). While the hazard rate is associated with the event rate or median survival time, the hazard rate itself is not sufficiently informative for interpreting clinical trial results. The hazard ratio however gives a measure of the treatment effect (i.e., the effect of an intervention / treatment on an outcome of interest over time compared to the control group). In this research, hazard ratios are a measure of probability of mortality. Subtracting this value from 1 gives the probability of mortality reduction (i.e. survival). This value is multiplied by 100 to express it as a percentage for better interpretation. For example for a hazard ratio of 0.505 the percentage survival is 49.5% (1 minus 0.505 = 0.495; 0.495 X 100 = 49.5%). Hazard ratio is reported most commonly in time-to-event analysis or survival analysis (i.e. when one wants to know how long it takes for a particular event / outcome to occur). Hazard ratio can be calculated from the Cox proportional hazard regression model.

Heterogeneity / Homogeneity

Heterogeneity in statistics means that populations, samples or results are different. It is the opposite of homogeneity, which means that the population, data, or results are the same. In clinical studies and meta-analysis, heterogeneity of results means that studies have widely varying outcomes. Some studies might show favorable results, while others show unfavorable results. In this research, heterogeneity is used to indicate variation in effect size and significance of results. Statistical heterogeneity only comes to light after results from studies are analyzed.

Mortality rate

Mortality rates are used instead of raw numbers for comparing mortality occurrence (i.e. frequency) in different populations because rates adjust for differences in population sizes. A mortality rate is a measure of the frequency with which death occurs in a population over a period of time and expresses the probability or risk of the event during that time. The numerator is the number of deaths and the denominator is the population at risk. The numerator of an event rate should reflect the deaths that occurred during the specified period. The denominator is the population at risk which may be adjusted for a specific demographic such as age or sex. When this event is qualified to be disease-specific, the persons included in the denominator should be able to die from the disease that is being described during the time period covered. For unspecified death, the persons who are included in the denominator are exposed to all-cause mortality. In practice, census population counts or estimates are taken for the midpoint of the time period under consideration. If the population being studied is small and very specific, exact denominator data should be used as is the case for this research. The denominator should represent the population from which the cases in the numerator arose. Since mortality rate is a measure of risk, when one population has a higher rate than another, one can say that the first population is at a higher risk of mortality than the second, all other factors being equal. Alternatively one can express the first population as a high-risk group relative to the second population. The mortality rate is like the velocity that indicates how quickly people die measured in people per year.

Mortality rate ratio

A mortality rate ratio (MRR) compares mortality rate between two different groups. The two groups are typically differentiated by demographic factors or by exposure to treatment. The rate for the group of primary interest (exposed group) is divided by the rate for the comparison group (unexposed or control group). A rate ratio of 1.0 indicates equal rates in

the two groups, a rate ratio greater than 1.0 indicates an increased risk for the group in the numerator, and a rate ratio less than 1.0 indicates a decreased risk for the group in the numerator. Mortality rate ratio is a useful metric because it is easy to interpret and it allows immediate understanding if exposure to something increases or decreases the rate. The larger the value for MRR, the greater the ratio of mortality rate in an exposed group compared to an unexposed group. Conversely, the closer MRR is to 1 the smaller the difference in the mortality rate between an exposed group and an unexposed group.

Incident diagnosis

First heart failure diagnosis confirmed with a reduced left ventricular ejection fraction ≤ 40%.

Instantaneous risk / survival

The probability of harm such as death (risk) or survival during any point in time after baseline as defined by a Kaplan-Meier plot. It is measured by the hazard function from the Cox proportional hazards model. If this probability remains constant than the assumption of proportionality in the model is respected. This means that the probability of any significant benefit or harm remains the same during the follow-up period of a study.

Intention-to-treat (ITT)

A method of data analysis based on the principle that once assigned to the arm, it remains assigned to the same arm. Participants who violate the protocol such as treatment switching are considered as belonging to the treatment arm they were originally assigned to. The main scope of the ITT analysis is to maintain the comparability of patients in the treatment arms at study entry for known and unknown prognostics factors, and to avoid selection bias resulting from treatment allocation based on prognosis, expected drug response or preference. This eliminates protocol violations that may dilute any potential differences between the treatment arms, favouring comparative effectiveness. The consequence of this strategy is that all enrolled patients are considered in the primary analysis of the study and maintains unchanged the study power because no patient is excluded from the analysis. In randomization it also preserves the balancing of risk factors between the study arms at baseline however this advantage is not applicable in this research as it was not based on randomization. The disadvantage is that this method may not capture the “true” exposure to treatment or its absence due to no censoring for treatment switching or cessation. Therefore, it is preferable for comparative effectiveness studies to be analysed according to other approaches including as-treated and per-protocol methods

Internal / external validity

In observational research, validity refers to a lack of systematic error as opposed to precision which is a lack of random error. Observational studies are evaluated in terms of both internal and external validity. Internal validity refers to the strength of the inferences from the study. That is, the difference in the outcome was caused by “exposure” or “intervention” (high internal validity) rather than by systematic error in the study (low internal validity). Therefore, assessing internal validity is whether observed changes can be attributed to the exposure and not to other possible causes. The internal validity of a study may be compromised by not having a control group or by having a control group that is not comparable to the exposed group in measurable or unmeasurable ways. External validity is the ability to generalize study results to a more universal population. Consequently, internal validity is a prerequisite for external validity. The study must demonstrate that the “exposure” in the study is the cause of variation in the outcome before one can generalize that the exposure more universally causes the outcome. One indication that a study lacks external validity is if the sample is not representative. The most common loss of external validity in observational research comes from the fact that studies often employ small samples obtained from a single geographic location or facility. Because of this, one cannot be sure that the conclusions drawn about cause-effect relationships apply to people in other geographic locations or at other facilities. The best way to demonstrate external validity of research results is to replicate results in different populations, places, and time periods.

Major risk factor

Factors that not only display the strongest association with cardiovascular disease but are also very common in the population. Hence, they account for an important proportion of cardiovascular disease cases in the population. They prevention strategies targeted at their control are potentially most effective. Major cardiovascular risk factors are hypertension, smoking, hypercholesterolaemia, lack of physical activity, and obesity.

Mean hospitalisation

In this research, hospitalisation refers to the number of HFrEF associated hospital admissions during the 3-year follow-up after incident diagnosis. The mean value of this number is the average for each group in the study cohort. This is used for comparison between groups.

Odds ratio

Odds of an event happening is defined as the likelihood that an even will occur, expressed as a proportion of the likelihood that the event will not occur. Therefore, if A is the probability of subjects affected and B is the probability of subjects not affected, then odds is A/B. The odds ratio (OR) represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. This gives a measure of association between exposure and outcome, and also informs how the presence or absence of exposure has an effect on the presence or absence of outcome. In fact the OR is used to determine if exposure is a risk factor for outcome. An odds ratio of 1.0 (or close to 1.0) indicates that the odds of exposure among case-patients are the same as, or similar to, the odds of exposure among controls. So exposure is not associated with the disease. Greater than 1.0 indicates that the odds of exposure among case-patients are greater than the odds of exposure among controls. In this case exposure might be a risk factor for the disease. Less than 1.0 indicates that the odds of exposure among case-patients are lower than the odds of exposure among controls. Therefore, exposure might be a protective factor against the disease. ORs are often associated with logistic regression. An adjusted OR is an odds ratio that has been calculated considering other predictor variables in a regression model. For example OR estimated for a specific age group is an odds ratio adjusted for age.

Per protocol (PP)

A method of data analysis that allows the investigation of effect of the actual, assigned treatment throughout the whole follow-up period, as specified in the protocol. Per protocol analysis does not consider patients who violate the protocol, including those who switched the allocation arm throughout the study. Therefore it captures the “true” exposure to treatment and its absence. However, the PP subpopulation eliminates patients for known and unknown factors that needed treatment switching and therefore introduces uncertainty of comparability in the two study arms at study inception. This method also reduces sample power from attrition of subjects.

Person-time (Person-years)

An estimate of the actual time at risk (in years, months, or days) that all participants contributed to a study. It is also a statistic for expressing incidence rates by incorporating time into the denominator. Typically, each person is observed from a set beginning point to an established end point (onset of disease, death, migration out of the study, or end of the study). The numerator is still the number of incident cases as in incidence rate, but the

denominator is different. While in incidence rate the denominator is the population at risk, in person-time it is the sum of the time each person is observed (i.e. the time at risk), totalled for all persons. All individuals will enter the study at the same moment in time. However, not all will exit at the same time. At the end of follow-up period, all person-years are summed up to represent the cumulative time at risk for disease. The time at risk for each person will be calculated from the time the individual entered the study until the time he/she exits the study. In chronic diseases, time is usually expressed in years. The calculation of events per patient-year(s) is the number of incident cases divided by the amount of person-time at risk. The calculation can be accomplished by adding the number of patients in the group and multiplying that number times the years that patients are in a study in order to calculate the patient-years (denominator). Then divide the number of events (numerator) by the denominator. For example, a person enrolled in a study who develops the disease of interest 5 years later contributes 5 person-years to the denominator. A person who is disease-free at one year and who is then lost to follow-up contributes just that 1 person-year to the denominator. A subject is eligible to contribute person-time to the study only so long as that person does not yet have the health outcome under study and, therefore, is still at risk of developing the health outcome of interest. Therefore the use of person-time is a way of considering the fact that subjects may be followed for varying amounts of time. This allows the researcher to account for those who dropped out of the study and no longer contribute to person-years at risk due to a variety of reasons (moved away, refused to participate, died from unrelated causes, etc.). Person-time rates are often used in cohort (follow-up) studies of diseases with long incubation or latency periods, such as some occupationally related diseases, AIDS, and chronic diseases. By knowing the number of new cases of the health outcome and the person-time-at-risk contributed to the study, an investigator can calculate the rate of the health outcome or disease, or how quickly people are acquiring the health outcome or disease.

Predisposing risk factor

Refers to distal factors in the causal chain of cardiovascular disease and includes factors such as obesity, sedentary lifestyle, or male sex, which exert their action through intermediate, causal, or conditional risk factors.

RAS inhibitor

Refers to ACEI or ARB as renin angiotensin system inhibitors. Note that the class of angiotensin receptor neprilysin inhibitors (ARNI) is not included since this did not exist at the time the study commenced.

Saturation

A prediction point in time when a population is expected to stop growing. This is mostly due to a decreasing number of children born almost worldwide. As fertility rate (birth rate) is projected to fall, a point will be reached where this rate will not be sufficient to sustain further population growth. At this point, fertility rate will be equal to the "replacement fertility rate," or the number of births per woman that would keep the population the same size, replacing people as they die. For this research the predicted saturation point is based on Eurostat data.

Superiority threshold

Comparison between treatments may need to answer the question whether one treatment is effective enough to justify its use instead of other treatment. This is determined if the difference in response exceeds a threshold that is accepted as a margin for superiority. In the final study of this research, this was set at a relative reduction of 16% in risk of all-cause mortality. Detection of superiority must produce a response greater than this value. This threshold is defined relative to the established benefits of standard treatment over placebo. When comparing an experimental drug with an active control as comparator as in this research, the traditional, comparative design is used with two-sided testing at the usual α significance level of 0.05. The alternative is the hypothesis for superiority whereas the null is the working hypothesis of comparative effectiveness. If the results of the study are not statistically significant, the null hypothesis that the new treatment is effective as standard treatment is accepted. Superiority is confirmed with a significant P value and with the 95% confidence interval limits excluding the value of 1 for hazard ratio.

“Regression analysis is the hydrogen bomb of the statistics arsenal.”
Charles Wheelan, Naked Statistics: Stripping the Dread from the Data.

1. Introduction

Heart failure with reduced ejection fraction (HFrEF) is becoming more common due to rapid aging of the population and the increased number of survivors of serious cardiovascular illness with recent advances in therapeutic strategies (1). Up to 80% of patients suffering from this chronic disease may be elderly from 70 years upwards (2). It is a recognized fact that patients aged over 70 years are under-represented in clinical trials that shaped current treatment and further research is required to establish facts instead of extrapolating results from younger study samples (3).

The aim of this research is to analyze trends of hospitalisation and mortality in HFrEF patients and study the relationship of these outcome measures with the use of Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) in patients aged ≥ 70 years at incident diagnosis. The study population is the segment of Maltese patients aged ≥ 50 years with a focus on patients aged ≥ 70 years with a reduced ejection fraction ≤ 40%.

2. Project Aims

Study 1

In patients aged 50 years or older, with left ventricular ejection fraction ≤ 40%, what is the epidemiology and predicted burden of morbidity and mortality, and what treatment patterns may be revealed with the use of ACEI and ARB?

Study 2

In patients aged 70 years or older, with left ventricular ejection fraction ≤ 40%, do ACEI, compared to no ACEI, reduce morbidity and mortality?

Study 3

In patients aged 70 years or older, with left ventricular ejection fraction ≤ 40%, do ARB compared to no ARB reduce morbidity and mortality?

Study 4

In patients aged 70 years or older, with left ventricular ejection fraction ≤ 40%, are ARB and ACEI comparable in reducing morbidity and mortality?

3. Background

3.1. Maltese Healthcare and Research Setting

Malta and Gozo form part of an archipelago in the Mediterranean Sea with the highest average population density in Europe (1325 persons per km^2). The Maltese population in 2017 was 475 701. People ≥ 50 years constituted 37.5% of the population. Health services are provided mainly by the state and to a lesser extent by the private sector. The public

health care system provides a comprehensive basket of health services to all persons residing in Malta who are covered by the Maltese social security legislation. The system is based on the Beveridge model as it is primarily state funded by tax revenues which represent two-thirds of the total health expenditure (4). The latter was 9.1% of the gross domestic product in 2012. There are five public hospitals, of which two are acute general hospitals (one on each island) and three are specialised. The acute public general hospital in Malta (Mater Dei hospital) is also a university teaching hospital. Health care service in Malta can be considered as essentially hospital based. Most secondary and tertiary care are provided through public owned hospitals. In addition, Mater Dei hospital takes the bulk of day and emergency care, where specialised ambulatory services, inpatient care and highly specialised care also take place. This hospital is the location of all four studies.

Primary healthcare is provided by both the state and the private sector, the latter mostly provided by general practitioners and private specialist clinics. The private sector accounts for approximately two-thirds of the workload in primary healthcare and functions independently from the state. Medicines listed on the Government Formulary List are given free of charge to patients entitled according to a list of chronic diseases identified in the Social Security Act including heart failure. The formulary contains all the necessary medicines to treat heart failure in line with current guidelines (4, 5, 6).

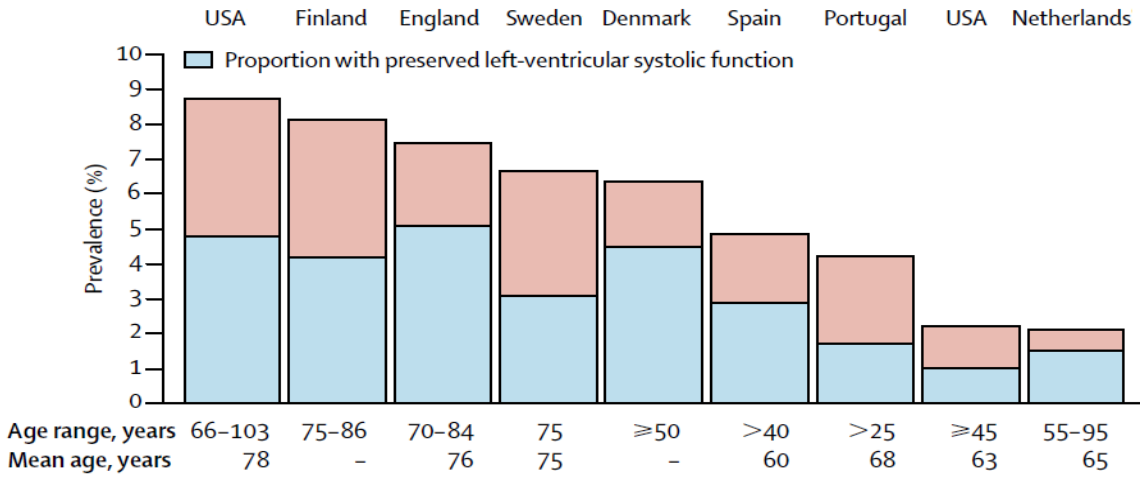
Accurate linkage of all individual data is possible using the unique identity number assigned by the Public Registry to each resident. The population of Malta is well suited for these studies because of the availability of comprehensive unique number-linked medical records for the residents, and centralized data accessibility through a standardized index of diagnoses.

3.2. The Burden of Heart Failure

Historically, studies of the epidemiology of heart failure have been complicated by the lack of universal agreement on a definition of heart failure. Initial studies adopted scoring methodologies based on symptoms and signs such as the Framingham study. However, these criteria are not pathognomonic of heart failure and may be related to common comorbidities associated with the disease (7). Other studies used algorithms and scores based on treatment, physical findings, cardiac imaging, and ICD-10 codes (8). Although the European Society of Cardiology (ESC) and American Heart Association (AHA) have published common guidelines for diagnosis since 2012, accuracy of diagnosis remains suboptimal with higher precision post hospital admission compared to ambulatory care. Contemporary studies on disease burden also persist in adopting different definitions to define the patient population depending on the setting (9). National and international

comparisons have therefore remained difficult with differences between studies possibly reflecting different diagnostic criteria and not necessarily different rates (10). This is exhibited by figure 1 with a comparison of several, cross-sectional, population based echocardiographic studies from the USA and Europe illustrating the relative proportions of heart failure cases with and without HFpEF.

Figure 1: Prevalence of heart failure and proportion of HFrEF and HFpEF from cross-sectional studies in different countries.



Source: McMurray JJ, Pfeffer MA. Heart failure. Lancet. 2005 May 28-Jun 3;365(9474):1877-89. Reproduced with permission.

Despite this drawback, a clear perspective on global trend and regional burden can still be drawn from the wealth of data available. The largest, population-based study in the USA was the Framingham Heart Study. This was also the earliest prevalence study considered to provide accurate estimates. The prevalence in men was 8 per 1000 at age 50 to 59 years, increasing to 66 per 1000 at age 80 t0 89 years. Similar values (8 increasing to 79 per 1000) were noted in women (11). The Rotterdam study was a European population-based study with ESC guidelines that reported higher prevalence in men (8% versus 6%). A sharp rise was also noted with age from 0.9% at age 55 – 64 years to 17.4% in those aged 85 years or over (12). Age-adjusted incidence from the Framingham study was 0.14% in women and 0.23% in men. Survival in women was better than men leading to the same point prevalence. It was also noted that incidence approximately doubled with each decade of aging, reaching 3% per year in those aged 85 – 94 years. Incidence was twice as high with hypertension compared to normotensive individuals, and five time greater post myocardial infarction than among those who have not (11). In the Rotterdam Study, the overall incidence rate was 14.4 / 1000 person-years and was significantly higher in men (17.6 /

1000 man-years) than in women (12.5 / 1000 woman-years). The incidence rate increased with age from 1.4 / 1000 person years at age 55 – 59 years to 47.5 / 1000 person-years in those aged 90 years or older. The increase with age was evident in both sexes but incidence rates were on average approximately two times higher in men than in women in each age category (12) (Table 1). Figure 2 gives a worldwide comparison of heart failure between regions and countries as reported in 2021.

Table 1: Incidence rates for heart failure from The Rotterdam Study.

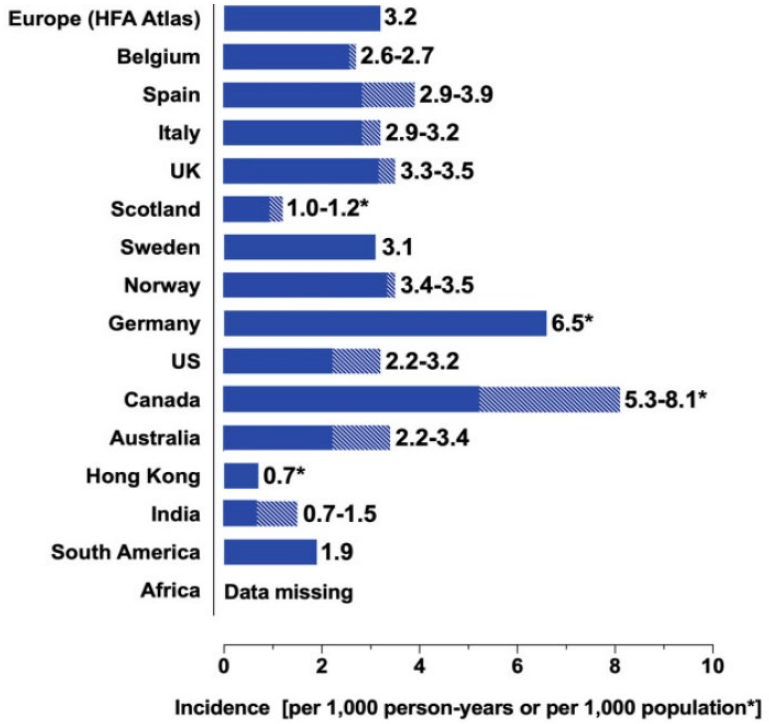
Incidence rates for heart failure per 5-year age category

Age category (years)	Number of incident cases	Person-years	Incidence rate[a] (95% CI)
55–59	4	2888.6	1.4 (0.5–3.3)
60–64	27	8713.6	3.1 (2.1–4.4)
65–69	56	10392.1	5.4 (4.1–6.9)
70–74	113	9665.6	11.7 (9.7–14.0)
75–79	136	8012.8	17.0 (14.3–20.0)
80–84	166	5513.5	30.1 (25.8–35.0)
85–89	137	3269.0	41.9 (35.3–49.4)
⩾ 90	86	1813.5	47.4 (38.6–58.2)

[a] Per 1000 person-years.

Source: Bleumink GS, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J. 2004. Reproduced with permission.

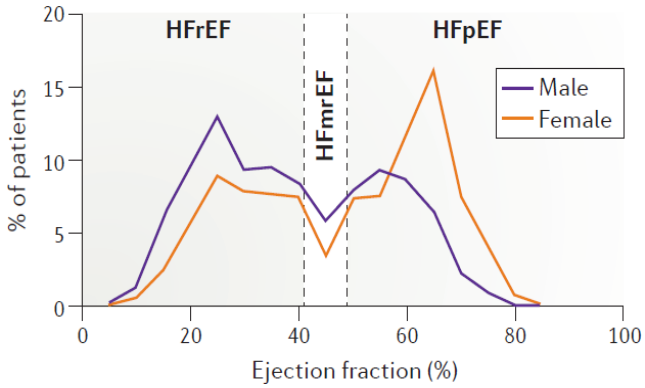
Figure 2: Incidence of heart failure worldwide



Source: Savarese G, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023 Jan 18;118(17):3272-3287. Reproduced with permission.

Few studies have evaluated the different trends in HFrEF versus HFpEF prevalence and there are currently no data on the emerging HFmrEF category (13, 14, 15). Data are heterogenous and also depend on the definition used for HFpEF and HFrEF. However it is estimated that about half of heart failure patients have HFrEF and half HFpEF, with the proportion of individuals with HFpEF increasing, particularly if more unselected populations are considered (Figure 3).

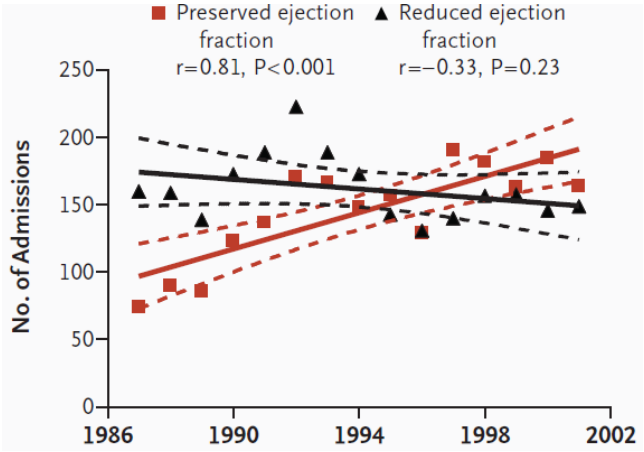
Figure 3: Bimodal distribution of LVEF in Olmsted County heart failure population



Source: Adapted from Dunlay SM. et al. Circ. Heart Fail. 5(6), 720 - 726 (2012). Reproduced with permission.

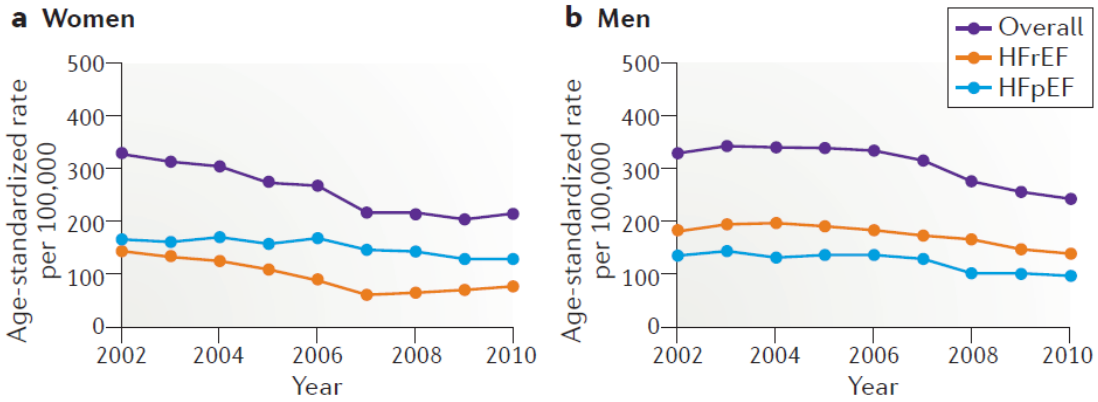
Over the last 20 years secular trends have reported an increasing proportion of HFpEF but relatively stable or even decreasing rates of HFrEF (figures 4 and 5). Women, the elderly, and those who are obese are more likely to have heart failure with preserved ejection fraction (figures 6 and table 2).

Figure 4: Trends in admissions rates for HFpEF and HFrEF



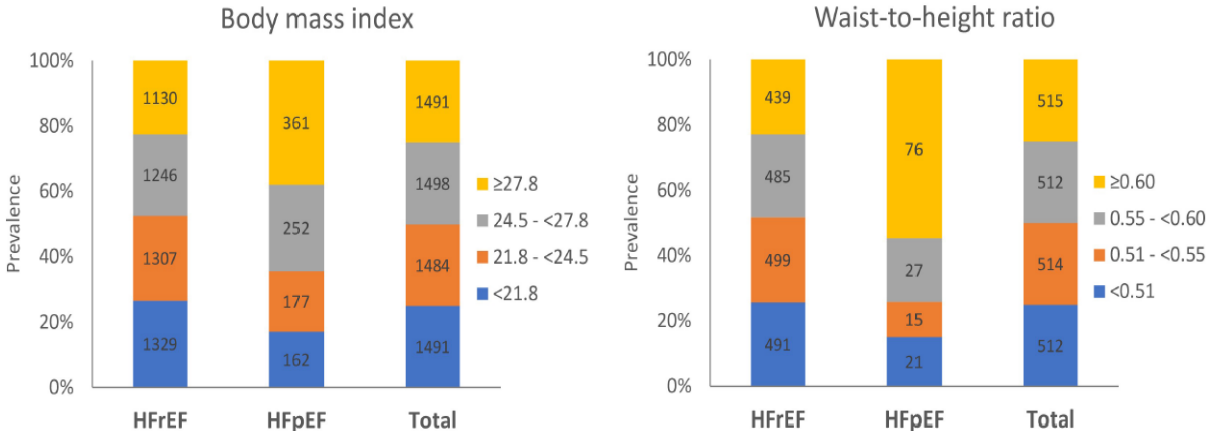
Solid lines are regression lines for the relation between years of admission and percentage of patients. Dashed lines indicate 95% CI. Source: Owan et al., N Engl J Med. 355(3):251-259 (2006). Reproduced with permission.

Figure 5: Secular trends in the rates of overall heart failure, HFpEF, and HFrEF



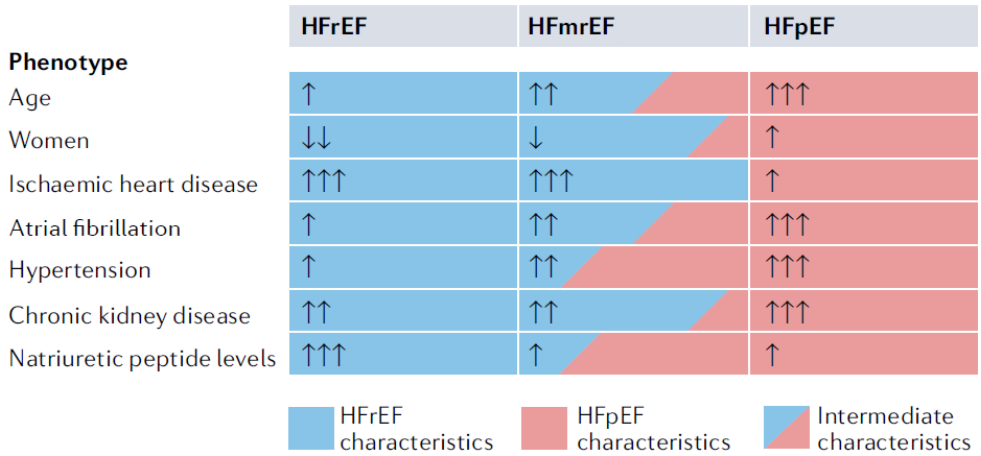
Source: Gerber, Y. et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern. Med. 175 (6), 996–1004 (2015). Reproduced with permission.

Figure 6: Prevalence of HFrEF and HFpEF stratified by BMI and waist-to-height ratio



Source: Chandramouli C, et al. Association of obesity with heart failure outcomes in 11 Asian regions: A cohort study. PLoS Med 16(9) (2019). Reproduced with permission.

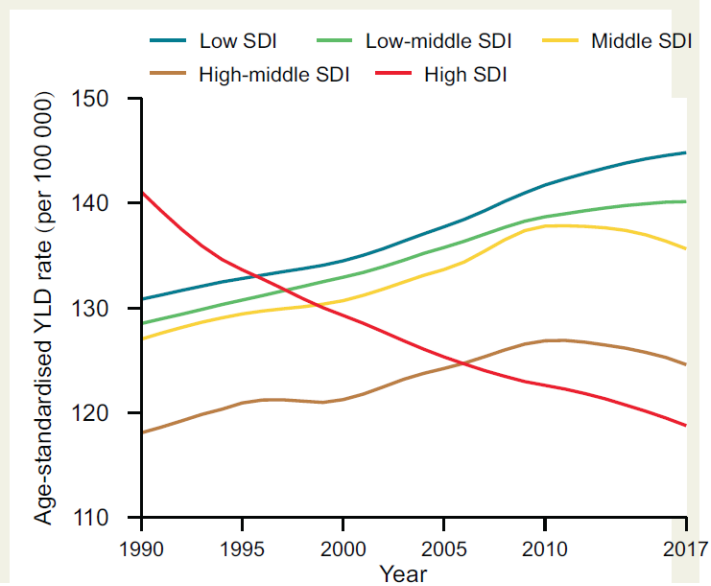
Table 2: Phenotype and risk of cause-specific outcomes in HFrEF, HFmrEF and HFpEF



Source: Savarese, G., et al. Heart failure with mid-range or mildly reduced ejection fraction. Nat Rev Cardiol 19, 100–116 (2022), Reproduced with permission.

Notably, heart failure incidence has been reported to be stable or even decreasing in various studies particularly in females. Therefore, the increase in prevalence observed worldwide may not necessarily be linked with an increase in incidence. In fact, the number of heart failure patients worldwide nearly doubled from 35.5 million in 1990 to 64.3 million in 2017. Nearly half of the global increase was in China (29.9%) and India (16.6%) (16). This challenges the common view that heart disease is under control. From analysis of global burden during the same period, age-standardised prevalence rate showed a slow downward trend, suggesting that population ageing and growth are responsible for most of the increase in prevalence. However, while there was a decrease of 20.3% in high socio-demographic index (SDI) countries, age-standardised prevalence rates increased in low, low-middle, and middle SDI countries (figure 7). The decrease in high SDI countries was attributed to better

Figure 7: Trends in age-standardised years lived with disability rates of heart failure by socio-demographic index quintiles

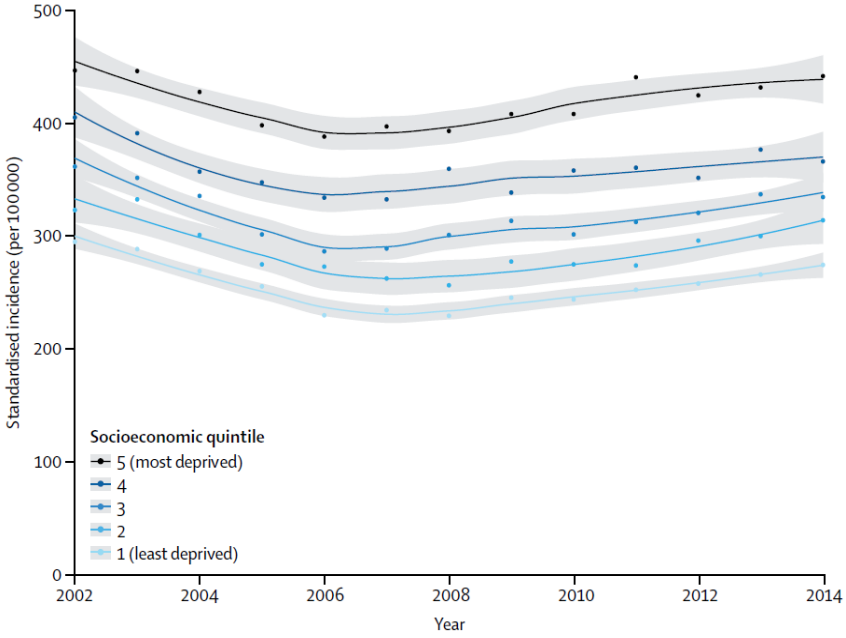


Source: Bragazzi NL, et al. Eur J Prev Cardiol. 2021 Dec 29;28(15):1682-1690. Reproduced with permission.

prevention and treatment particularly after 2010. Poor compliance to healthy diets, physical activity and smoking cessation led to continued rate deterioration in low and low and middle SDI countries. The top two causes of heart failure were ischaemic heart disease and hypertension accounting for approximately 60% of the age-standardised prevalence for heart failure. Both are also leading risk factors for HFrEF (17). Furthermore, affordable core treatment for ischaemic heart disease and heart failure were generally unavailable in low and middle-income countries leading to a worse burden of HF in these regions (18).
The crude incidence rate in the UK population was 1·3 cases per 1000 population per year

in the 1990s. The rate increased steadily with age to 11·6 in those aged 85 years or over and was higher in males than females. The single most common aetiology was ischaemic heart disease accounting for 36% of cases and often coexisting with hypertension (44% of cases) (7). Despite a moderate decline in age and sex standardised incidence from 2002 to 2014, the absolute number of cases increased by 23% reaching a prevalence of 1.6% in 2014 (19). This substantial increase in prevalence compared to incidence was possibly due to longer survival after HF diagnosis. In 2022, crude prevalence was estimated at 1.44% (9). The top 4 comorbidities reported were ischaemic heart disease (50%), Hypertension (64%), diabetes (24%) and atrial fibrillation (39%) with one in four cases identified as obese (20).

Figure 8: UK Temporal trends in heart failure incidence by socioeconomic status quintile

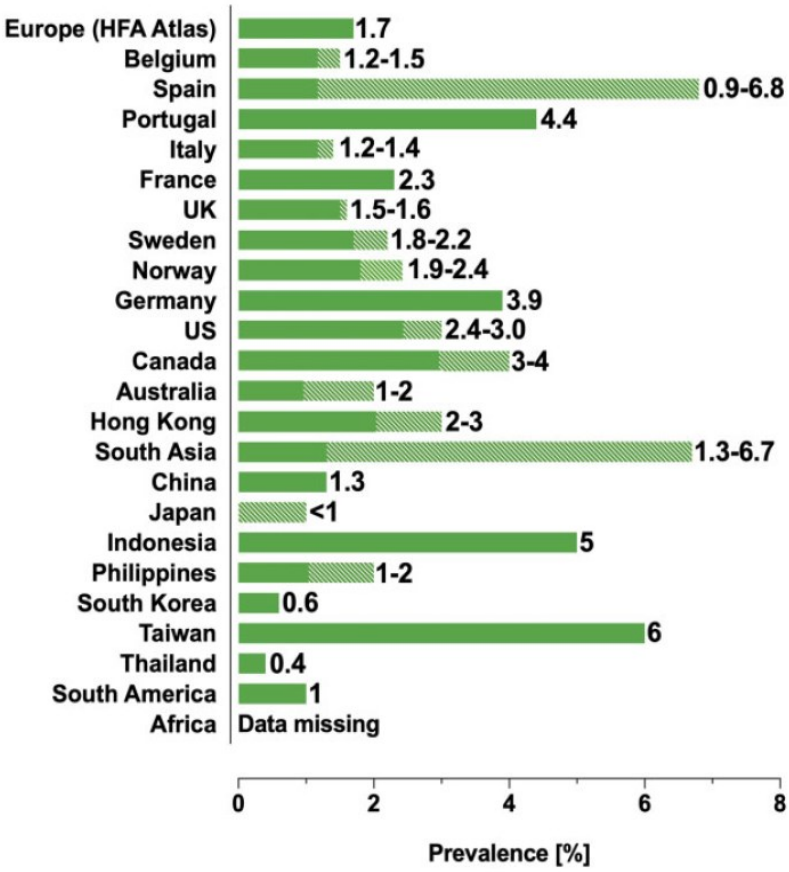


Age and sex-standardised incidence per 100 000 per year and socioeconomic quintile with 95% CI in grey. Source: Conrad N et al. Temporal trends and patterns in heart failure: a population-based study of 4 million individuals. Lancet 2018; 391: 572-80. With permission.

The number of comorbidities associated with HF increased parallel with increasing age at onset and was also probably influenced by population ageing, enhanced screening and diagnostics, physician awareness, and changes in risk factors (19). Patients with 3 or more comorbidities increased from 68% in 2002 to 87% in 2014. However socioeconomic inequalities were also determinant of disparities in disease incidence and age at onset. From 2002 to 2014 the socioeconomic gradient in age at onset widened, with deprived groups more likely to develop HF, earlier in life, and with higher comorbidities, compared to affluent individuals (figure 8) (19).

Malta is disadvantaged with the absence of a heart failure dedicated registry. However there is data that indicates an alarming trend. In 2017 age-standardised prevalence was reported at 850 – <900 per 100,000 (22). In 2020 it was estimated that 8000 patients suffered from HF out of an adult population of 355,075 and HF contributed 5.7% to mortality (23). This gives an age-adjusted prevalence higher than the European average and comparable to that of Sweden (Figure 9).

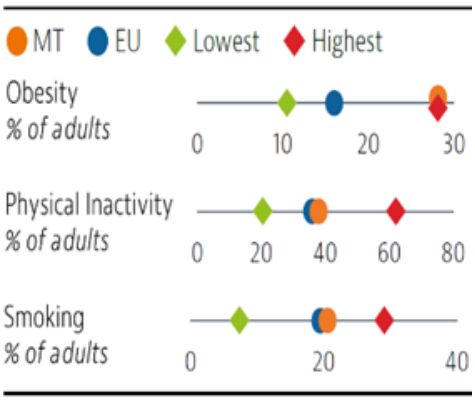
Figure 9: Prevalence of HF worldwide.



Source: Savarese et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardio Research 2022. 118; 3272-3287. Reproduced with permission.

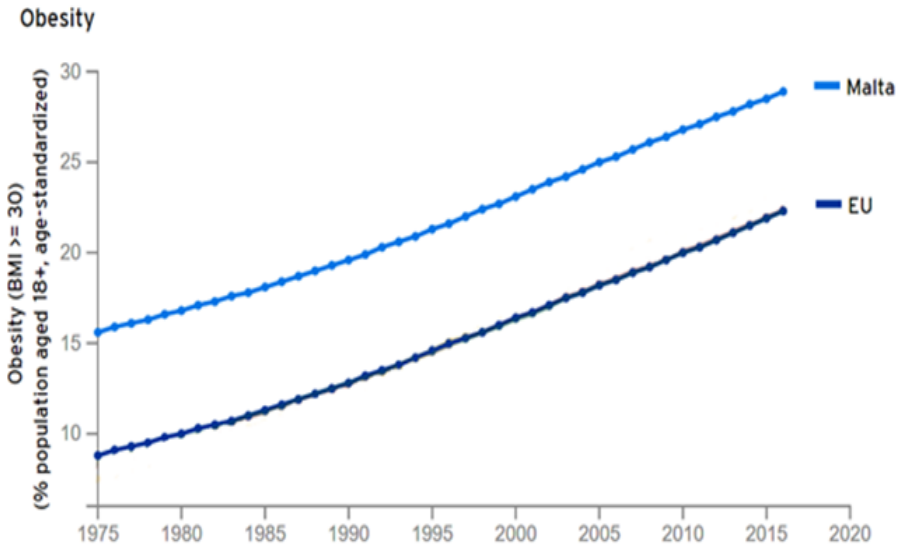
Considering risk factors, while smoking rates among adults are similar to the EU average, rates of obesity in Malta are the highest, with more than 25% of adults classified as obese (page 36, figures 10, 11). Poor diets and physical inactivity are both contributing factors. Ischaemic heart disease persists as the leading cause of treatable mortality with death rates remaining above the EU average despite a 15% decline in mortality rates from preventable causes since 2011. In 2018, the leading cause of death was ischaemic heart disease accounting for 17% of all deaths, followed by stroke (7%). Malta is also experiencing a rising

Figure 10: Risk factors in Malta compared to EU highest, mean, and lowest levels.



Source: OECD/European Observatory on Health Systems and Policies (2021), Malta: Country Health Profile 2021, State of Health in the EU, OECD Publishing, Paris/European Observatory on Health Systems and Policies, Brussels. Reproduced with permission.

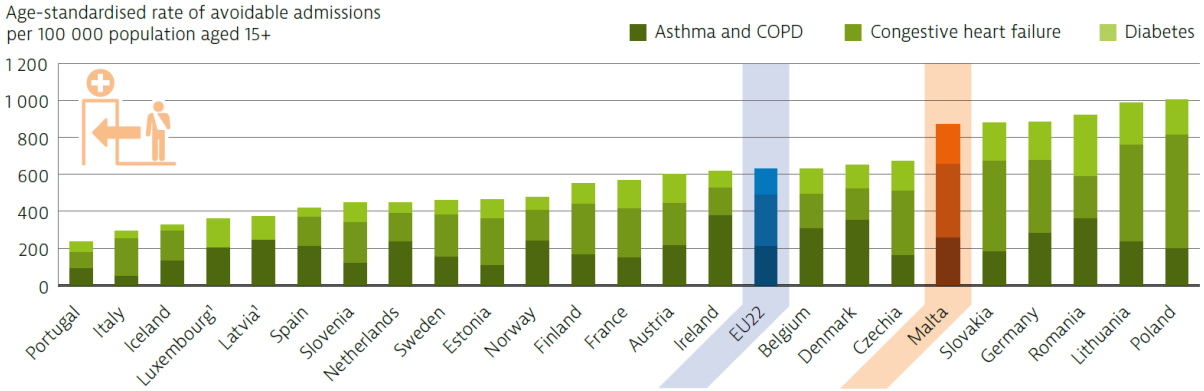
Figure 11: Prevalence trend of obesity for Malta compared to mean for WHO European Region.



Source: ESC atlas of cardiology (https://eatlas.escardio.org/Countries/Malta) Open access.

incidence in diabetes, hypertension, and elevated cholesterol. In many cases, this incidence compares negatively with analogous international indices as measured by Malta's Health Systems Performance Assessment in 2018 (24, 25). Deaths attributed to diabetes (50.8 per 100,000 population) were the third highest in the EU. These high levels of risk factors have translated into a rate of avoidable hospital admissions for chronic heart failure that is higher than in many other EU countries (page 37, figure 12). However, an above average prevalence of chronic heart failure was not the only reason attributed. High avoidable admission rates were also partially explained by inadequate coordination between

Figure 12: Rates of avoidable hospital admissions in Malta



Data refers to 2017 for Malta and 2019 for most other countries. Source: OECD/European Observatory on Health Systems and Policies (2021), Malta: Country Health Profile 2021, State of Health in the EU, OECD Publishing, Paris/European Observatory on Health Systems and Policies, Brussels. Reproduced with permission.

ambulatory and inpatient care settings and the need for improvement in the community healthcare system. In particular, interventions at outpatients and primary care level were considered insufficient with more timely diagnosis and effective treatment required (26). In parallel, age-standardised, preventable mortality rate for Malta was 49 per 100,000 population and lower than the EU average in 2018 but with more than 30% attributed to heart failure. At the same time, private out-of-pocket spending in 2018 was 34.3% of total health spending – the fourth highest proportion in the EU and more than twice the EU average, driven mostly by primary and outpatient care. Out-of-pocket spending on medicine alone was 8.3% of overall health spending which is more than double the EU average of 3.7% (26). It is not known how this influences morbidity and mortality of heart failure patients that are socioeconomically deprived in Malta. However, in 2019, 42% of the Maltese population in the lowest income quintile reported an absence of good health as opposed to 11% from the highest income quintile in a nation that had the tenth widest disparities in self-reported good health according to income – well above the EU average (26).

3.3. Why focus on ACE Inhibitors and Angiotensin Receptor Blockers?

At the time of protocol design and study implementation, angiotensin blockade was only achievable with two drug classes: ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB). The advent of angiotensin receptor neprilysin inhibitors (ARNI) was still two years away. Several large clinical trials and meta-analysis have demonstrated that effectiveness of angiotensin blockade is only second to β blockers in the reduction of morbidity and mortality in HFrEF (table 3).

Table 3: Relative risk reduction in mortality and heart failure hospitalisation by treatment

Treatment	%RRR in all-cause mortality in RCTs	%RRR in all-cause mortality in meta-analyses	%Absolute 2Yr mortality rate	NNT for mortality standar-dised / 5Yr)	%RRR for HF hospitali-sations	%Absolute 2Yr hospitali-sation rate
None	---	---	35	---	---	39
ACEI[1]	23	23	29	18	31	27
ARB[1]	20	13	31	37	29	20
β Blockers	34	31	16	8	41	13
ARNi[2]	16	15	24	11[3]	21	21
MRA	30	25	11	15	35	8
SGLT2i	21	17	9	16	30	6
Hydralazine / ISDN[4]	43	---	26	4	33	20
Cumulative	74% RRR	---	26% ARR	2	85 RRR	33 ARR

2 Incremental over ACEI/ARB 3 Imputed over placebo 4 Self-identified African Americans

Source: updated from Brownell et al. The Gap to Fill: Rationale for Rapid Initiation and Optimal Titration of Comprehensive Disease-modifying Medical Therapy for Heart Failure with Reduced Ejection Fraction. Card Fail Rev. 2021.

1: McMurray JJ. Angiotensin inhibition in heart failure. J Renin Angiotensin Aldosterone Syst. 2004 Sep;5 Suppl 1:S17-22.

3: Srivastava et al. Estimated 5-Year Number Needed to Treat to Prevent Cardiovascular Death or Heart Failure Hospitalization With Angiotensin Receptor-Neprilysin Inhibition vs Standard Therapy for Patients With Heart Failure With Reduced Ejection Fraction: An Analysis of Data From the PARADIGM-HF Trial. JAMA Cardiol. 2018 Dec 1;3(12):1226-1231.

Similar to β blockers, angiotensin blockade has additional benefits beyond its effects on the renin-angiotensin-aldosterone system. It can improve endothelial function, decrease oxidative stress, and reduce inflammation (27). By tradition and according to past guideline recommendations, an ACEI is usually initiated first, followed by a beta-blocker after a varying time period based on clinical judgement (28). This is because despite β blockers conferring

the largest survival benefit, pursuing a beta blocker during an acute event related to systolic dysfunction was suspected to be deleterious due to its negative inotropic effect (29). There was also no rationale for simultaneous up-titration of an ACEI or ARB with a β blocker during the period under study. Furthermore, robust evidence best supports early initiation and maintenance of angiotensin blockade therapy in symptomatic as well as acute HF during hospitalisation to prevent or delay the onset of adverse cardiac remodeling (30, 31, 32). ACEI and ARB have acute hemodynamic benefit of afterload reduction as opposed to other therapy (33). In fact, ACEI have long been considered to deserve early use in patients with dilated cardiomyopathy and symptomatic heart failure since they appear to improve both the efficacy and safety of diuretics over the long term (34). For these reasons, angiotensin blockade with ACEI has long been regarded as first-line therapy for initiation in the early course of HFrEF, with ARB as an immediate alternative started at current ACEI equivalent dose in case of intolerance. Moreover, the prescription of β blockers in daily practice remains an issue because it is known from registries that β blockers are still the last drug introduced, and the drug for which an increase in dosage is the most difficult so that dosage remains lower than recommended in daily practice (29). The crux of this research was the influence of HFrEF therapy on mortality and hospitalisation from the time of incident diagnosis. The latter was taken as the point of entry for the study from which measurement of primary and secondary endpoints started. Therefore, time to initiation of treatment from the moment of diagnosis was critical as it influenced validity and accuracy of hypothesis testing particularly for studies 2 to 4. The slower the pace of treatment initiation, the lower the accuracy of endpoint measurement from incident diagnosis and the validity of the of the data analyses in contextualising the real-world use of treatment in HFrEF. Since this study included in-hospital as well as outpatient settings, angiotensin blockade was considered the best choice of treatment for analyses. Landmark trials have associated this treatment with a strong survival benefit that is measurable albeit in a younger population. Traditionally it is also the most common treatment that is started as first-line therapy early in the course of HFrEF management including symptomatic and acute heart failure. It is important to note that the paradigm for treatment initiation has changed with evidence in favour of simultaneous starting of all pillars of treatment for early benefit of survival and reduction of HFrEF related events (35).

3.4. Differences between ACEI and ARB – the sex factor

Evidence is divided on the presence or magnitude of a sex related variable response to ACEI and ARB in HFrEF. A meta-analysis of randomized controlled trials published in 1990–2021 showed no differences between sex in treatment effect for RAS inhibition in HFrEF (36,

37). However, females were underrepresented in preclinical and clinical research due to a large discrepancy in the proportion of women represented in randomized landmark studies compared to real-world HF populations (38). The proportion of women in real-world populations with HFrEF is between 36–42% and in surveys or registries with a more selected patient population the proportion of women with HFrEF is between 21 and 23% (39). This discrepancy was highlighted in two studies where the proportion of women enrolled in HF trials from 2001 to 2016 were investigated (40, 41). These studies confirmed that HFrEF trials included only 24% women. Therefore, RCTs were far from being adequately powered to ascertain sex-related differences, while sex-specific analysis of drug efficacy was not taken into consideration when designing and reporting their results (42). Consequently, the mechanisms underlying established sex differences between males and females associated with the renin-angiotensin-aldosterone system and their interplay with HFrEF and treatment remain poorly understood (43).Emerging evidence suggests that differential activation of the renin-angiotensin system (RAS) contributes to sex differences in CVD (44, 45). While the RAS intrinsically regulates blood pressure and cardiovascular end organ function in both sexes, premenopausal females exhibit a shift in this hormone system towards cardioprotective counter-regulatory pathways modulated, in part, by interactions with oestrogen (43).

Angiotensin II (Ang II) acts at cell surface type I G protein-coupled receptors (AT1R) to elevate blood pressure via multiple mechanisms including vasoconstriction, sodium reabsorption, sympathetic and immune activation, impairment of arterial baroreceptor reflex sensitivity, and increases in aldosterone, fibrosis, and inflammation (46). To counteract AT1R actions, Ang II binds cell surface type II receptors (AT2R) to increase arterial baroreflex sensitivity and promote vasodilation, natriuresis, and NO production (47). A secondary, vasodilatory arm of the renin-angiotensin system is characterized by angiotensin-(1–7), angiotensin-converting enzyme 2, and Mas receptors (MasR). Emerging studies provide evidence for a shift towards these cardioprotective angiotensin-(1–7) and ATR2 pathways in females, with effects modulated by interactions with oestrogen (43).

Oestrogen decreases Ang II levels by suppression of formation of renin. It also reduces serum and tissue ACE expression and activity, AT1R expression and signalling in tissues (e.g. kidney, adrenal cortex, vasculature), as well as aldosterone production in animal models (44, 48, 49). In addition to reducing activation of Ang II-ACE-AT1R pathways, oestrogen upregulates protective Ang-(1–7)-ACE2-MasR-AT2R pathways (44, 49). These protective oestrogen-RAS interactions appear diminished during aging (43). Furthermore, loss of vasodilatory responses to Ang-(1–7) is observed with increasing age (50). In contrast to oestrogen, sex-specific differences in CVD pathophysiology are amplified by androgens

through stimulation of the Ang II-ACE-AT1R axis (43). Testosterone shifts the balance of the RAS towards Ang II-ACE-AT1R pathways to induce vasoconstriction, vascular dysfunction, cardiac hypertrophy and fibrosis. This strongly suggests differential roles for these pathways between the sexes, with the balance tipped toward depressor pathways in females (51, 52). This evidence suggests that the epidemiology and clinical characteristics of heart failure, as well as response to heart failure therapies including those inhibiting the RAS, are in part, sex dependent. Supporting this view is the finding of female rodents being more sensitive to Ang II in terms of susceptibility to heart failure, with increased susceptibility to dilated cardiomyopathy and higher mortality (53, 54). This is consistent with clinical findings showing that women are more susceptible to developing heart failure in response to hypertension compared with men (55). Clinically, pressure overload-induced hypertrophy is associated with a smaller left ventricular chamber and larger wall thickness in women than in men leading to concentric myocardial hypertrophy (56, 57). HFpEF is often characterised geometrically by concentric hypertrophy, and the increase in wall thickness compared with the volume of the left ventricle makes the ventricle less elastic (58). These findings may explain why older men are more likely than age-matched women to experience HFrEF (59). Response to ACEI and ARB in HFrEF also appears to have a sex-dependent variable element. ARBs appear more effective to improve survival in women with congestive heart failure compared with ACE inhibitors irrespective of hypertensive status (60). Early RCTs with ACEI reported that enalapril and captopril produced a significant reduction in mortality and/or heart failure hospitalisation in men (30–40%), but not in women (<5%). In the SOLVD studies, enalapril reduced total and HF mortality, heart failure hospitalisation and death or heart failure hospitalisation in both sexes, although the effect appeared significantly greater among men (61). In the CONSENSUS-1 trial a significant reduction in mortality was reported with enalapril in men but not in women (62). Similarly, in the SAVE trial, the early administration of captopril to patients with asymptomatic LV dysfunction post-MI reduced mortality and the composite endpoint of cardiovascular death and morbidity more in men than in women, but after adjustment for other variables, no sex related differences were observed (63). In a meta-analysis of 34 RCTs, ACEI significantly reduced total mortality and the combined endpoint of mortality or heart failure hospitalisation (HFH) in both men and women (64). However, on the combined outcome of death or HFH, the reduction was statistically significant in men (37%), but not in women (22%). In another meta-analysis of 6 RCTs, the pooled random effect estimates on mortality yielded HR values of 0.80 for men and 0.90 for women (P=0.07) (65). Men exhibited a clear benefit from ACEI in patients with symptomatic or asymptomatic LV systolic dysfunction. Women with symptomatic HF benefitted from ACEI, but less than men, while women with asymptomatic LV did not achieve

a benefit. Both meta-analysis suggested that there is a trend toward less benefit for women treated with ACEI.

In the case of ARB, a sex stratified subgroup analysis of the HEAAL trial, which compared two doses of losartan (50 or 150mg/day) in patients with HFrEF and intolerance to ACEIs, showed a reduction in death or heart failure hospitalisation in men at the highest dose of losartan, but no significant differences between the two doses in women (66). In a post-hoc analysis of the Val-HeFT trial, valsartan significantly reduced the RR for the combined mortality and morbidity end point in women, but not in men, and the risk of nonfatal morbidity and HFH in both sexes (67). Another study compared the clinical outcomes between sexes in the CHARM program (68). Compared to men, women obtained a significantly greater benefit from candesartan therapy in terms of reduction in all-cause mortality, sudden death, death from worsening, cardiovascular mortality, and heart failure hospitalisation. In a large, retrospective population-based study with chronic HF, women on ARB had better survival than those on ACEI. However, there was no difference in survival in men prescribed ARB compared to ACEI (60). Apart from responding better to ARB with improved survival in CHF when compared to ACEI, women tend to experience increased side effects with ACEI as well (69).

Enhanced effectiveness of ARB in females may be related to sex differences in AT2 receptor expression. Since the AT2 receptor gene is located on the X chromosome, it is to be expected that sex chromosomal complement influences AT2 receptor expression (70). The AT1/AT2 ratio in kidneys is less in females because of the presence of 17-estradiol (69). With ARBs selectively blocking AT1 receptors, there is an increased likelihood that Ang II will bind AT2 receptors. Because AT2 receptor activation stimulates vasodilation, improves renal blood flow, and enhances pressure natriuresis, an increase in AT2 receptor stimulation could contribute to increased ARB effectiveness in females. Indeed, Okumura et al. have shown that treatment with the ARB valsartan attenuates the degree of vascular injury induced by the placement of a polyethylene cuff around the femoral artery to a greater extent in arteries from females compared with males. This effect was likely due to an exaggerated increase in AT2 receptor expression in the femoral artery of female mice following the induction of vascular injury compared with arteries from males, as the effect of valsartan was markedly attenuated in AT2 receptor-null mice (71). Losartan treatment has also been shown to selectively increase AT2 mRNA expression in mesenteric arteries from female spontaneously hypertensive (SHR) and not in arteries from male SHR rats (72).

The review of evidence presented here collectively indicate that sex differences exist in susceptibility for developing myocardial hypertrophy and heart failure as well as responsiveness to therapies targeting Ang II for treatment of hypertensive cardiac

abnormalities. Current HF guidelines recommend ARB to reduce heart failure hospitalisation and death in symptomatic patients with HFrEF unable to tolerate an ACEI, but do not make any sex-specific recommendation regarding the use of ARB or ACEI in women (34, 73, 74, 75). Nevertheless, the possibility that women have a better survival with ARB compared to ACEI has not received the attention it deserves so far (38).

3.5. Study 1

Cardiovascular disease accounts for 37% of all deaths across the European Union and is the leading cause of mortality in nearly all EU member states (76). In particular, heart failure remains a major public health challenge worldwide because it is responsible for a tremendous burden on health care systems in terms of morbidity, mortality, and cost (77). It is associated with high mortality and frequent, prolonged hospitalisations with incidence and prevalence increasing with age (78). This disease is becoming more common owing to the rapid aging of the population and the increased number of survivors of serious cardiovascular illness due to recent advances in therapeutic strategies (79). Up to 80% of patients suffering from this chronic disease may be from the age group of 70 years upwards (80). Available data suggest that outcome is particularly poor in octogenarians and treatment is often complicated by the presence of multiple co-morbid factors (81). For these reasons heart failure has been labelled as the “last great battleground in cardiology” (82). Heart failure is prevalent in Malta and the prognosis is similarly poor as in other European countries (83). Despite these facts, published literature on Maltese heart failure patients is deficient while recent data specific to Mediterranean countries is absent (84, 85). It is imperative to understand past trends for heart failure to optimally plan for the challenges and pressures that lay ahead for healthcare systems. However, recent systematic projections for heart failure in Europe are unavailable.

Prescribing rates of evidence-based drugs also appear to vary according to age, sex and comorbidities with treatment gaps defined as the proportion of patients who received less than 50 % of the guideline recommended target doses. High percentages have been reported for both ACEI and ARB by a number of studies both in Europe and beyond with 60 to 72% for ACEI and from 34.6% to 51% for ARB (86, 87, 88, 89, 90). The importance of closing the treatment gap is highlighted by the finding that optimisation of treatment according to guidelines was associated with reduced mortality (86). Therefore, prescribing trends of anti-failure pharmacotherapy, particularly the frontline treatment of ACEI and ARB have a major influence on disease progression especially in patients predisposed to high risk of decompensation. However, information about the true impact of an evidence-based strategy in treating HFrEF patients ≥65 years is limited since only two studies reporting such

data were found (83, 89). Much less is known on HFrEF patients over the age of 75 years (87, 89). Furthermore, it was reported that hospitalized HF patients are a heterogeneous group with a wide range of 30-day mortality (1.7 – 7.2%) and a high post-discharge event rate, approaching 40% at 90 days (91). Consequently, both characteristics of prescribing rates and disease progression trends, characterized by diagnosis, hospitalisation and death rates remain uncertain in Maltese elderly patients with HFrEF.

Therefore it is essential to examine population-based analysis of temporal trends in incident cases, hospitalisation, and mortality and to look at prescribing rates for ACEI and ARB. It is also critical to do future projections that predict forthcoming disease burden with current heart failure policy considering the far-reaching consequences on future planning of healthcare, public health prevention, and impact of current strategy. These predictions serve as a baseline for gauging success of a future heart failure national plan.

3.6. Study 2

Target doses of ACEI for elderly with heart failure are not well established (92) and based on a meta-analysis published in 2000, the long-term benefit appears to decline after the age of 75 (93). The PEP-CHF study of 2006 (94) also expressed uncertainty on the long-term effect on morbidity and mortality in this population age group. Current evidence of treatment benefit is based on the inclusion of many elderly patients in all major randomized trials with ACEI (62) (95) (96) (97), and on several community based observational studies that support benefit of ACEI in elderly (98) (99). The latter showed benefit similar in magnitude seen in younger patients but this is based on data from 1998. In addition, landmark trials occurred between 1987 and 1999 and studies done specifically in elderly HFrEF patients are rare. The ATLAS study (100) explored the dose related benefit of lisinopril in a population sample from 19 countries with a mean age of 64 years (±10 years). Although it was not explicitly done on elderly patients, a large extent of the study sample was recruited from this age group though relatively younger than 75 years. The sex distribution of the sample was predominantly male (80%) and the study did not include a control. Subjects were followed for a minimum of 3 years and showed no significant difference in mortality or NYHA improvement between the low and high dose groups. A later study published in 2004 was more versatile (101). It was large with more than 16000 subjects, covered all ACEI, had a mean age of 79 and included a control sample with no ACEI treatment. The aim was to assess the dose-related benefits associated with use of ACEI therapies in a large population-based cohort of older patients surviving a new heart failure hospitalisation. The study demonstrated a mortality reduction of more than 20% for older adults receiving high-dose ACEI therapy relative to low-dose therapy. This survival benefit persisted for the

combined outcomes of mortality and heart failure hospitalisation. Findings also suggested that low-dose ACEI therapy still provided a survival benefit to older patients compared to not receiving any ACEI therapy. This is the only paper found that tackles properly the caveat in information for elderly patients with HFrEF. A final paper was published in 2008 on the effect of different ACEI on mortality in elderly with heart failure (102). Median age in this study was 78 years with a sample over 43000 subjects followed for 5 years post hospital admission. However, there were two major limitations. There was no control group and use of different ACEI was not balanced between various drug groups with 34% of the study sample on ramipril.

Since then, treatment guidelines have changed considerably and life expectancy has increased. We are now seeing heart failure patients living longer with chronic disease (103). Therefore, apart from limited literature on the subject, published papers are dated and results are not in agreement. This disagreement is best exhibited by two major, randomized, controlled trials with ACEI carried out during the same period – the HOPE study (104) that showed significant cardiovascular benefit with ramipril in elderly patients, and the PEACE trial where trandolapril was equivalent to placebo (105). Consequently, there is a need for research to identify how ACEI affects morbidity and mortality in the aging HFrEF population in the context of contemporary pharmacotherapy and interventional cardiology.

3.7. Studies 3 and 4

European surveys and primary care data from the UK demonstrated lower preference for ACEI for specific segments of the population (89, 106, 107, 108). While Malta follows guidelines from the European Society of Cardiology, there are anecdotal reports of ARB used extensively as first-line therapy. The only strong evidence supporting the use of ARB as reasonable first-line agents in heart failure (73, 109) comes from a single, large trial that was aimed at patients with a history of ACEI intolerance - the CHARM-alternative study (2003) (107). This was a multi-centre, double-blind, parallel-group, randomized, controlled trial of 2028 subjects with a median follow-up of almost 34 months on an intention-to-treat basis. Patients with HFrEF on Candesartan resulted in a 20% decrease in cardiovascular mortality as well as a 40% decrease in hospitalisation for heart failure versus placebo (110). These benefits rivalled those of the ACE inhibitor enalapril in the earlier SOLVD trial (96). However, the CHARM-alternative trial did not address the role of ARB as first line treatment in patients without a history of ACE inhibitor intolerance. Other trials gave mixed conclusions. Results from the ELITE I study were shot down by ELITE II and showed that ARB should not replace ACEI (111). The losartan/captopril hazard ratio for the primary end point of all-cause mortality was 1.13 (95% confidence interval 0.95 to 1.35), showing that

losartan was not superior to captopril. However this study was not designed to test for non-inferiority or equivalence. so this result did not mean that these two classes of drugs were not equally effective therapies. ELITE II further raised the question of whether ARB are more efficacious than placebo (112).

Two landmark trials studied the effect of ARB on heart failure post myocardial ischemia. The OPTIMAAL trial practically gave the same outcome results of ELITE II but within the context of a high risk older patient population with a mean age over 67 years (113). This was a multi-centre, randomized, double-blind controlled study of almost 5500 patients recruited during the acute phase of a confirmed infarct with heart failure. Losartan was compared to captopril, patients were followed for 2.7 years and analysis was by intention-to-treat. Results confirmed that ACEI should remain first choice and, even more important, failed to show conclusively that losartan is better than placebo. Concern was again reported that data suggested a possibility that losartan might increase mortality in some patients compared to captopril (114). These were critical conclusions since the population studied were high risk patients after experiencing myocardial infarction. High expectations fell on the VALIANT trial to address the questions from OPTIMAAL. This study was a multi-centre, double-blind, parallel-group, randomized, controlled trial of 14700 patients followed up for almost 25 months (115). VALIANT was designed and well powered to test the superiority of valsartan compared to captopril albeit at a much higher dose. The result was that valsartan was as effective as captopril in improving survival among patients with HF and/or LV dysfunction in the post-MI period.

Benefits and harms of ARB therapy for HFrEF were evaluated by a 2012 Cochrane systematic review (116). This review avoided the limitation of limiting analyses to total mortality and hospital admission for worsening HF by analyzing clinical outcomes. These included cardiovascular mortality, total hospitalisations, hospitalisations for other causes, stroke, MI, and withdrawals due to adverse effects to clarify the benefit and harm of ARB treatment in HF patients based on published data from large-scale clinical trials.

When ARB were compared to ACEI (16 studies; n=13463), there was no difference with regard to total mortality, cardiovascular mortality, or non-cardiovascular mortality. Total hospitalisations, heart failure hospitalisations, and other hospitalisations also did not differ between treatment groups. There was also no significant difference between treatment groups for MI or stroke. Withdrawals due to adverse effects were significantly lower in patients treated with ARB (RR 0.63 [95% CI 0.52, 0.76]; ARR=6.0%; NNT=17).

Benefit was less compelling when ARB were compared to placebo (116). This was based on nine randomized trials with a total of 4623 patients. The CHARM-alternative trial contributed most of the data in this meta-analysis. In these studies, the reduction in total mortality with

ARB therapy was of borderline statistical significance at the 5% error level (RR 0.87 [95% CI 0.76, 1.00]). When the analysis was limited to the 7 trials with full reporting, the difference between ARB and placebo was not statistically significant (RR 0.91 [95% CI 0.79 to 1.04]). There were also no differences between ARB and placebo for cardiovascular and non-cardiovascular mortality. All-cause hospitalisations from the 2 candesartan studies that reported this outcome were not reduced compared with placebo. When this outcome was divided according to cause, candesartan reduced the risk of hospital admissions for HF (RR 0.71 [95% CI 0.61, 0.82]; ARR = 8.0%; NNT = 13) but increased the risk of hospital admissions for other causes (RR 1.12 [95% CI 1.00, 1.25]). More patients in the ARB group discontinued therapy due to an adverse effect but the increase did not reach statistical significance (RR 1.14 [95%CI 0.97, 1.33]).

A meta-analysis was published in 2015 on the efficacy and safety of ARB from 16 randomized controlled trials with 113386 patients (117). It was aimed at older patients however the mean age of the pooled trials was 68 years. Analysis showed that ARB were associated with a marginal increase in all-cause mortality when compared to a beta blocker (RR: 1.03, 95% confidence interval (CI): 1.00–1.06, P = 0.05) but not when compared to placebo in older patients. There was also a non-significant decrease in heart failure hospitalisation.

All of the major randomized trials included many elderly patients and supported a benefit from ARB in elderly patients similar in magnitude to that seen with ACEI. For this reason the ACC/AHA guidelines suggest the use of ARB as a reasonable alternative to ACEI as first-line therapy for patients with HF and reduced LVEF, particularly in patients taking ARB for another indication (73, 109). However, the evidence supporting the use of ARB in the very elderly especially those with multiple comorbidities is limited. The mean age of trials used in the 2012 Cochrane review was 65 years with only 3 trials (ELITE, ELITE II and I-PRESERVE) with a mean age over 70 (116). Aronow in his review paper on drug treatment of systolic and of diastolic heart failure in elderly persons quoted only the ELITE II trial (118). While the ELITE II showed that ARB should not replace ACEI (44), the I-PRESERVE exhibited no significant difference in the composite outcome of all-cause mortality and hospitalisation for cardiovascular causes for irbesartan versus placebo (119).

The only study with a true population over the age of 70 was published in 2016 (120). This evaluated the association of ACEI or ARB dose level with long-term survival in stable patients aged over 70 years with HFrEF. The mean age of the trial was 78 years with 35% of the patients as octogenarians. The high dose was associated with a better survival than the low dose in the total population (HR = 0.35; 95 % CI0.19 – 0.67; p = 0.001). However, there were two drawbacks. The study conclusions were based on a very small sample size of 138

patients which renders results unsuitable for direct extrapolation to the intended population. Second, while the level of evidence supporting the use of ACEI and ARB is different, as explained by the above literature review, the authors of this study decided to report the outcome measures for both classes of drugs combined. This carried the automatic assumption that for each reference dose level (no dose, low, high) the ACEI and ARB effect on long-term survival was identical.

In the case of ACEI, current evidence of treatment benefit is based on the inclusion of many elderly patients in all major randomized trials with ACEI (2, 6, 121, 122). The CONSENSUS trial studied the addition of enalapril with other anti-failure therapy in 253 patients with advanced NYHA III or IV HF and demonstrated a reduction in the six-month mortality by 40 percent when compared to placebo (26 versus 44 percent) and the 12-month mortality by 31 percent (36 versus 52 percent). This benefit was sustained for at least four years and the risk reduction averaged over the 10-year duration of the trial was 30 percent. In addition to the mortality benefit, enalapril was associated with significant reductions in NYHA class and in the requirement for other heart failure therapies. The SOLVD treatment trial evaluated 2569 patients with symptomatic NYHA class II to III heart failure with LVEF ≤35 percent. When compared to placebo, enalapril resulted in a significant reduction in all-cause mortality (35 versus 40 percent, risk reduction 16 percent, 95% CI 5 to 26 percent). A subsequent analysis, called XSOLVD, followed the patients in the SOLVD treatment trial up to a median of 12 years and the outcome was determined in virtually all of the original participants. The reduction in all-cause mortality in the enalapril group narrowed over time and was no longer significant at 12 years, at which time 80 percent of patients in both groups had died (hazard ratio 0.93, 95% CI 0.85-1.01). Overall, enalapril significantly increased median life expectancy by 8.6 months. The SAVE trial investigated the effect of captopril in 2231 patients after myocardial infarction and subsequently reduced ejection fraction. At 42 months the reduction in risk for death from cardiovascular causes was 21% versus placebo and a reduction of 22% for heart failure requiring hospitalisation.

It is possible that some elderly patients with comorbidities were excluded from these trials. However, all of the major randomized trials included many elderly patients. Furthermore, community-based observational studies support a benefit from ACEI in elderly patients with HF that is similar in magnitude to that seen in younger patients (98, 99). Long-term benefit is seen even in those who have a perceived contraindication to ACEI (systolic pressure ≤90 mmHg, serum creatinine ≥ 2.5 mg/dL, serum potassium ≥ 5.5 mEq/L, and severe aortic stenosis) (123, 124). In addition, although benefit is greater with doses titrated up to those used in the clinical trials, lower doses are also associated with improved outcomes (100, 125).

In the UK, the average age at diagnosis of HF is 76 years (126). However, the average age of patients included in most landmark heart failure trials is 60 years (127). Apart from this, there is also a disagreement on the benefit of ARB. The need exists for research to look again at how ARB compare to ACEI at influencing associated morbidity and mortality in the aging HFrEF aging population in the context of contemporary pharmacotherapy and interventional cardiology.

4. Programme of Research

4.1. Scheme of Study

Study one surveyed the Maltese population aged 50 years or older at incident diagnosis from 2007 to 2017. The intention was to evaluate the extent of disease risk through measurement of incidence for diagnosis and mortality rate as outcome measures together with the frequency of hospital admission. This data provided a profile of how disease burden changed with time and was used for future predictions based on projected population growth. This gave an insight into the current and predicted national burden of the disease and revealed differences in the diseased population particularly for patients ≥ 70 years that may be investigated further. The study population demographics obtained from this study provide a background description of the setting used for the proceeding studies.

Study two and three tested the hypothesis of treatment associated potential differences in all-cause mortality and hospitalisation between treatment naïve and treatment exposed patients aged ≥ 70 years at incident diagnosis. Study two tested for association with ACEI while study 3 repeated the same hypothesis testing for ARB. A comparison arm of treatment exposed patients aged ≥ 50 and < 70 years was also included as a positive control. These studies aimed to reveal possible significant relationships between morbidity or mortality differences and ACEI or ARB in patients aged ≥ 70 year. Results obtained however were not comparable since both drug classes were tested separately. The comparison of ARB to ACEI was tested in the fourth study. Research four was a head-to-head study comparing ACEI and ARB with a goal of demonstrating comparative effectiveness. The aim was to investigate differences in morbidity and mortality in elderly heart failure patients aged ≥ 70 years at incident diagnosis and using ACEI or ARB.

4.2. Quantitative Research

The selection of the four study designs was based on the consideration of the intended outcome from the outset (128):

- A description of the study population
- Development of a model enabling predictions to be made about this population
- Test a hypothesis regarding potential differences and relationships

The methodology used to achieve these desired outcomes is typical of quantitative research in other contexts.

4.3. ≥

Each study was a national, single centre, retrospective, all inclusive, population based, cohort research of patients with HFrEF confirmed by echocardiogram registered at Mater Dei

Hospital. The lower age limit was ≥ 50 years at incident diagnosis with a focus on ≥ 70 years. The population cohort was identified from the hospital echocardiogram database to reveal patients with reduced ejection fraction ≤40%. Patients that received ACEI or ARB were identified from the patients' list for free medicine entitlement afforded by the Social Security Act. Since the studies were built on a population based cohort, and given the limited sample size available, all candidates identified retrospectively from 2007 to 2017 were included. Study 1 surveyed patients until December 2017 for hospitalisation and mortality. Studies 2 to 4 analyzed morbidity and mortality data for three years retrospectively from incident diagnosis until December 2020. Selection for each study arm followed a simple allocation based on ACEI or ARB use.

The primary endpoint for studies 2 to 4 was all-cause mortality, with the secondary endpoint of heart failure associated morbidity. The latter was defined as hospitalisation due to heart failure. A provisional secondary endpoint of cardiac mortality was also selected if all-cause mortality leads to positive bias towards the null hypothesis. This effect could have occurred when a difference in cardiac mortality was accompanied by no difference in noncardiac deaths between patient groups (129). However, this was not the case in all three studies. For studies 2 to 4, patients were followed historically for 3 years starting from the date of first diagnostic echo with outcome variables for primary and secondary endpoints measured at the end of the follow-up period or until death or censoring. A pilot study for internal feasibility was done to try out the procedure and to assist the preparation of the larger, more comprehensive study. This pilot study was monitored for design integrity, feasibility of procedure, data access and progress rate. The inclusion and exclusion criteria were adopted from previous studies to enable comparison of results with published literature.

4.4. Ethics

The primary ethical issues raised by the design of this protocol were related to access and handling of patient personal and medical data. The only personal data required was the patient identity number as the key link to identifying medical records, treatment entitlement and laboratory results. Through a series of protection measures for data collection, handling and disposal, an ethically acceptable balance between risks and benefits was established. Full confidentiality was safeguarded through EU and UK data protection regulations as well as hospital specific corporate procedures. The four studies were presented as a joint, single protocol and simultaneously reviewed and approved by an independent Ethics Board from the University of Malta on behalf of the national Maltese Office of the Data Protection Commissioner as well as the ethics board of Aston University as the institution running the doctorate programme.

5. STUDY 1

A survey of patients ≥ 50 years with heart failure and reduced ejection fraction for temporal trends of clinical outcomes and use of ACEI or ARB.

5.1. Aims and Objectives

The survey specifically studied patients aged 50 years or more at incident diagnosis with a focus on patients ≥ 70 years. Trends in HFrEF associated hospitalisation and mortality were examined as well as trends for treatment of HFrEF with ACEI or ARB.

Patients were enrolled if they were diagnosed with left ventricular ejection fraction ≤ 40% with echocardiography. Patients that changed drug class between ACEI / ARB, dose, or stopped treatment throughout the study period were retained in the treatment sample category that was dominant.

The study provided important insights into the trends for morbidity and mortality of patients with HFrEF, presented a basis for burden prediction, and revealed patterns of RAS inhibition treatment. Results were compared with those from published studies.

5.2. Inclusion / Exclusion Criteria

Subjects met the following inclusion and exclusion criteria:

Inclusion criteria

- Documented left ventricular systolic dysfunction defined as left ventricular ejection fraction ≤40%
- Age ≥ 50 years at incident diagnosis

Exclusion criteria

- left ventricular EF not available
- Diastolic heart failure (HFpEF)
- Myocardial infarction, cardiac surgery, or percutaneous transluminal coronary angioplasty (PTCA) within 8 weeks
- Need for cardiac surgery (e.g., severe valvular disease, planned coronary artery bypass graft surgery) or PTCA. (Such patients are eligible after surgery or PTCA.) Patients on heart transplant list were not eligible
- Intravenous Inotropic agents within 45 days
- Presence of cardiac implantable devices

5.3. Design

Interventions

The study involved surveying data of HFrEF patients and analyzing demographic trends of heart failure associated mortality and hospitalisation, all-cause mortality, and prescribing patterns of ACEI and ARB.

Data

Parameters collected were sex, age at diagnosis, date of diagnosis, treatment (ACEI / ARB), hospitalisation rate for worsening heart failure, date of hospitalisation, mortality age, mortality date, and cause of death. Nationwide data was obtained from five sources. Population census statistics by year and age group, and all-cause mortality rates were obtained from the National Statistics Office. Census forecasts for Malta were extracted from Eurostat (130). Patients diagnosed with HFrEF were identified via the hospital echocardiograms electronic database from 2007 to 2017. Echocardiogram records revealed the national identity number, sex, date of echocardiogram, age at echocardiogram, and LVEF fraction of eligible patients. The majority of this data was obtained from Mater Dei hospital and a small fraction (< 5%) was acquired from Gozo General Hospital. This exercise produced a master list of HFrEF patients as eligible candidates for study. The list was compiled on an Excel spreadsheet eliminating duplicates and retaining the first diagnostic echocardiogram by date with HFrEF ≤ 40%. The Department for Health Information and Research provided data on hospitalisation and mortality including dates, age at death and main cause of death by ICD 10 codes with heart failure code I50 (131). The Pharmacy Directorate provided data on prescribing. All records were available in Excel however extensive formatting was required to standardize data such as ID numbers into 8 digit codes and format of date. Patients with HFrEF were identified from these records using the HFrEF master list through MS Access using the relationship function for the national identity number as linkage factor. Age group and sex specific incidence was calculated according to the age group and sex census for the specific year. All data was clustered by age group and sex and entered in SPSS for analysis. The 2007 – 2017 data were presented as Study 1 for the PharmD qualifying report. Further data treatment utilisation was collected until 2020 towards studies 2 to 4 following the qualifying report and used for comparison in the thesis.

5.4. Statistical Considerations

5.4.1. Sample Size

All patients that qualified for the study were identified retrospectively from 2007 to 2017 and included in the database.

5.4.2. Statistical Analysis

Patients were characterized according to year of primary diagnostic echocardiogram, age at incident diagnosis, sex, hospital admission year, mortality year and age at death. A significance level of 0.05 and a 95% confidence interval were adopted.

The measure of burden associated with annual disease and mortality was analyzed by annual and mean incidence for the period under study. Incidence was calculated as the observed number of cases per year divided by the age group and sex specific population during the same year. The resulting proportion was expressed as incidence per 1000 in order to get the number of periodic new cases and associated deaths per 1000 population for each age group.

The Shapiro-Wilk test was used to determine whether the two dependent variables of mean incidence for age at diagnosis and mortality have a normal or skewed distribution by age group and sex. The null hypothesis specifies that distribution is normal and is accepted if the P value exceeds 0.05 level of significance. This indicates that parametric tests must be used. The alternative hypothesis specifies that distribution is skewed and is accepted if the P value is less than the 0.05 criterion. In such a case non-parametric tests are indicated. Since the alternative hypothesis was satisfied for both dependent variables the Wilcoxon-Mann-Whitney U test was selected for group comparisons. Bar graphs were generated by sex and age group to display trends in 2007 – 2017 mean incidence per 1000 population for diagnosis and disease associated mortality.

Logistic growth curve modelling was used to predict disease demographic changes using sex and age group specific incidence rates for incident cases of patients ≥ 50 years diagnosed annually and associated hospital admissions based on population projections and saturation points from Eurostat 2019 data (130). The following logistic growth equation was used for the plots:

$$Y = \frac{M}{1 + a\, e^{-bX}}$$

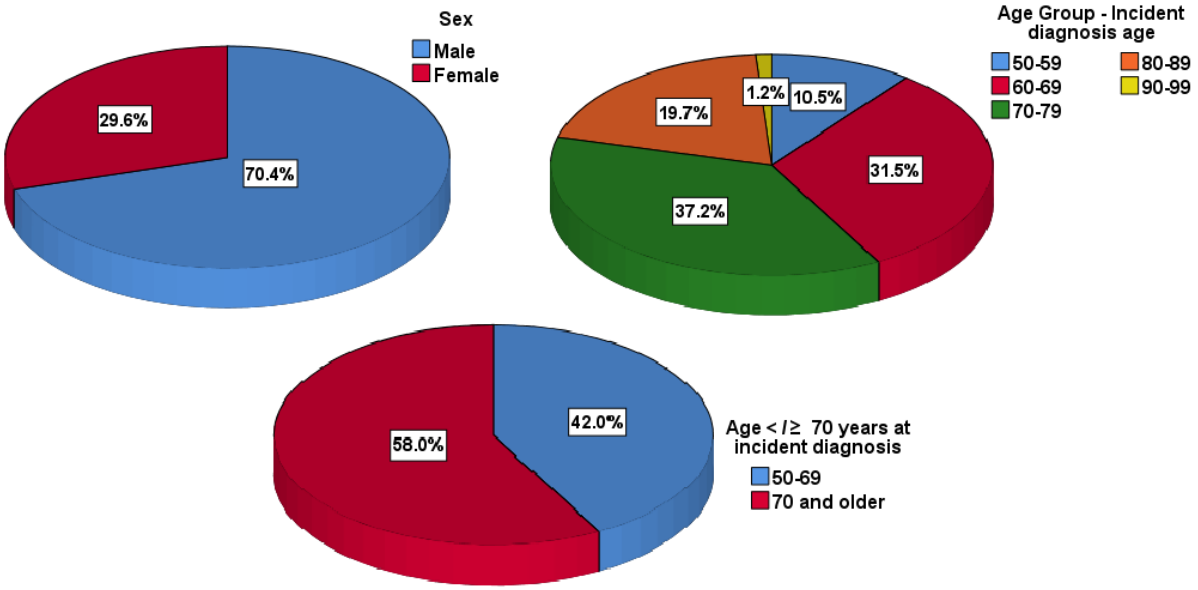
where Y = predicted value, M = saturation value, X = year where 2007 corresponds to X = 0; 2008 corresponds to X = 1, etc., and values *a* and *b* are unknown constants estimated by SPSS version 25.1 (132).

5.5. Results

5.5.1. Epidemiology

The total sample was 3340 heart failure patients with HFrEF composed of 70.4% males and 29.6% females. Two dominating age groups that emerged were the 70 to 79 years at 37.2% and the 60 to 69 years at 31.5% (Figure 13).

Figure 13: Cohort description by sex and age group (2007 – 2017)



The 90 years and older age group was the smallest (1.2%) and 58% were 70 years or older. Median age at diagnosis was 70 years (SD ± 8.95) for men and 74.19 years (SD ± 8.82) for women while the overall median age increased from 2007 (69.49 years, SD ± 8.39) to 2017 (73.09 years, SD ± 9.33).

Analysis of annual incident diagnosis distributed by age group exhibited higher annual percentages for patients within the 60 to 79 years age group mostly between 30 to 40% of annual total counts throughout 2007 – 2017 (page 57, Figure 14). The 50 to 59 years age group varied between 11 to 16%. However the annual percentage for 80 to 89 years group increased and peaked in 2015 as it increased by 10% over 2007. The percentage of annual incident diagnosis for the age group of 90 years and older remained lowest below 2.5% (page 57, Table 4).

Figure 14: Distribution of patients diagnosed with HFrEF by age group from 2007 to 2017

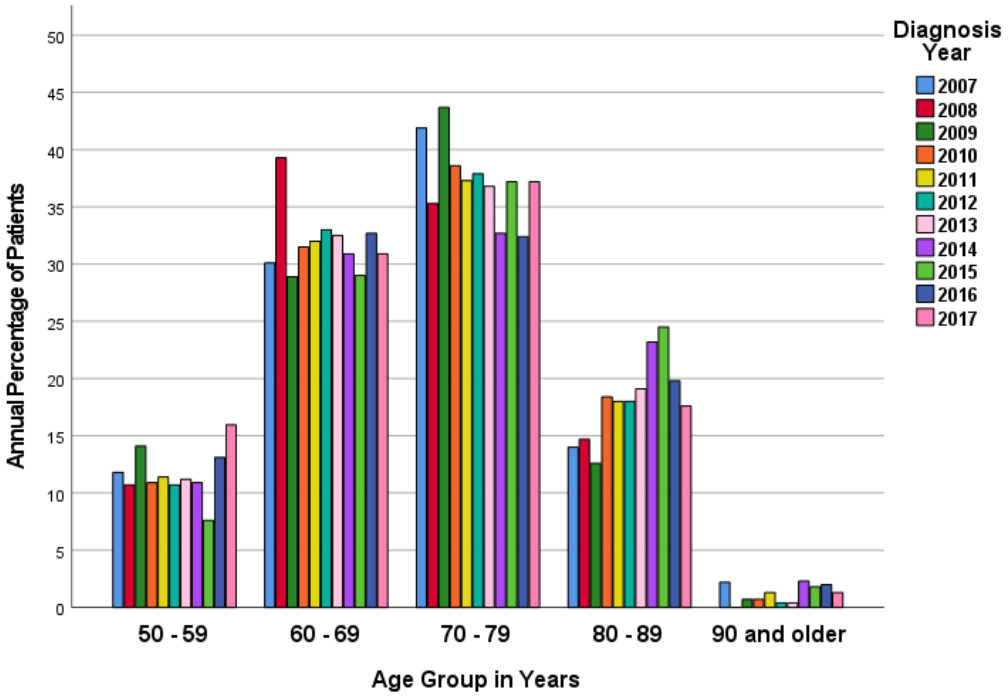


Table 4: Distribution of percentage values for Figure 14

Year	Age Group %				
	50 - 59	**60 - 69**	**70 - 79**	**80 - 89**	**90 and older**
2007	11.8	30.1	41.9	14	2.2
2008	10.7	39.3	35.3	14.7	0
2009	14.1	28.9	43.7	12.6	0.7
2010	10.9	31.5	38.6	18.4	0.7
2011	11.4	32	37.3	18	1.3
2012	10.7	33	37.9	18	0.4
2013	11.2	32.6	36.6	19.2	0.4
2014	10.9	30.9	32.7	23.2	2.3
2015	7.6	29	37.2	24.5	1.8
2016	12.5	28	38.2	19.5	1.7
2017	16.3	27.7	34.5	19.6	1.9

The annual rate of disease associated hospital admissions increased from 12 to 450 during the 11 years under study with a steady increase over the periods 2009 – 2011 and 2013 – 2017 (page 58, Figure 15). Analysis of this trend by age group based on age at incident diagnosis exhibited increasing rates across all age groups (page 58, Figure 16). Markedly

higher rates were displayed by the 60 to 89 years age groups that contributed most towards disease associated hospital admissions over the study period.

Figure 15: Annual total hospital admissions for HFrEF of patients ≥50 years from 2007 to 2017

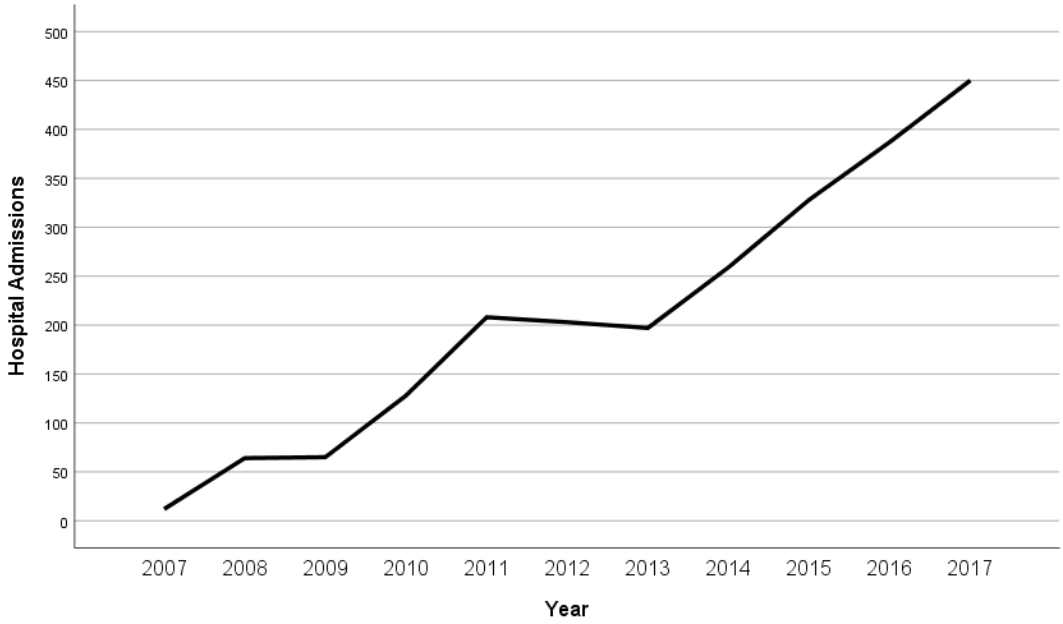
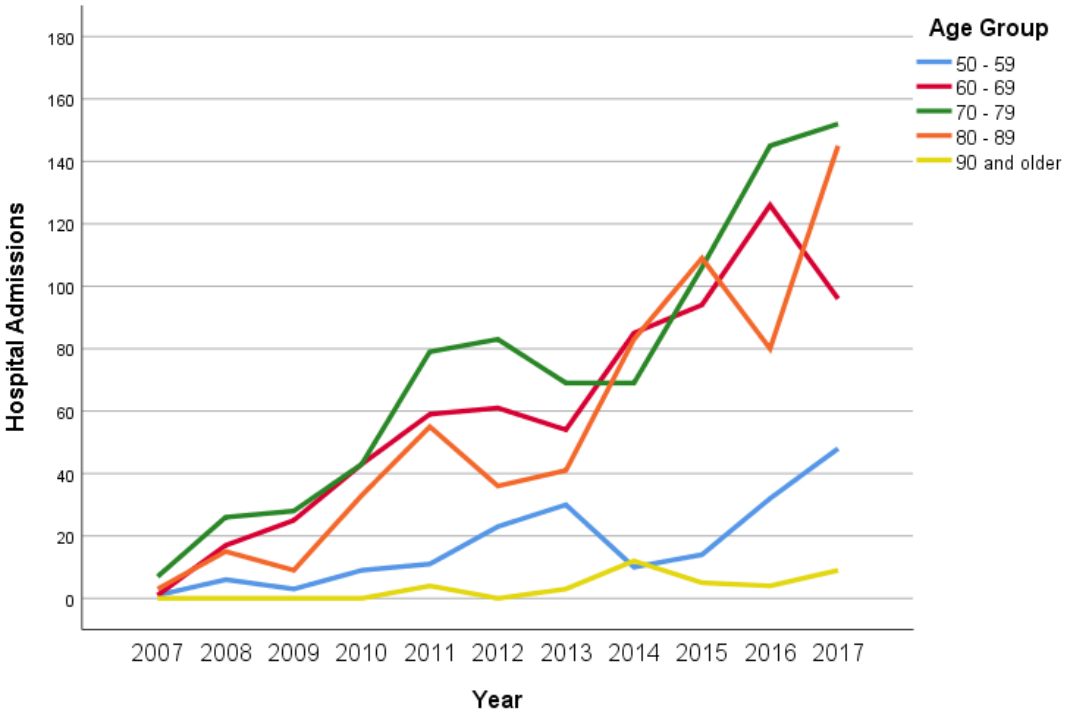
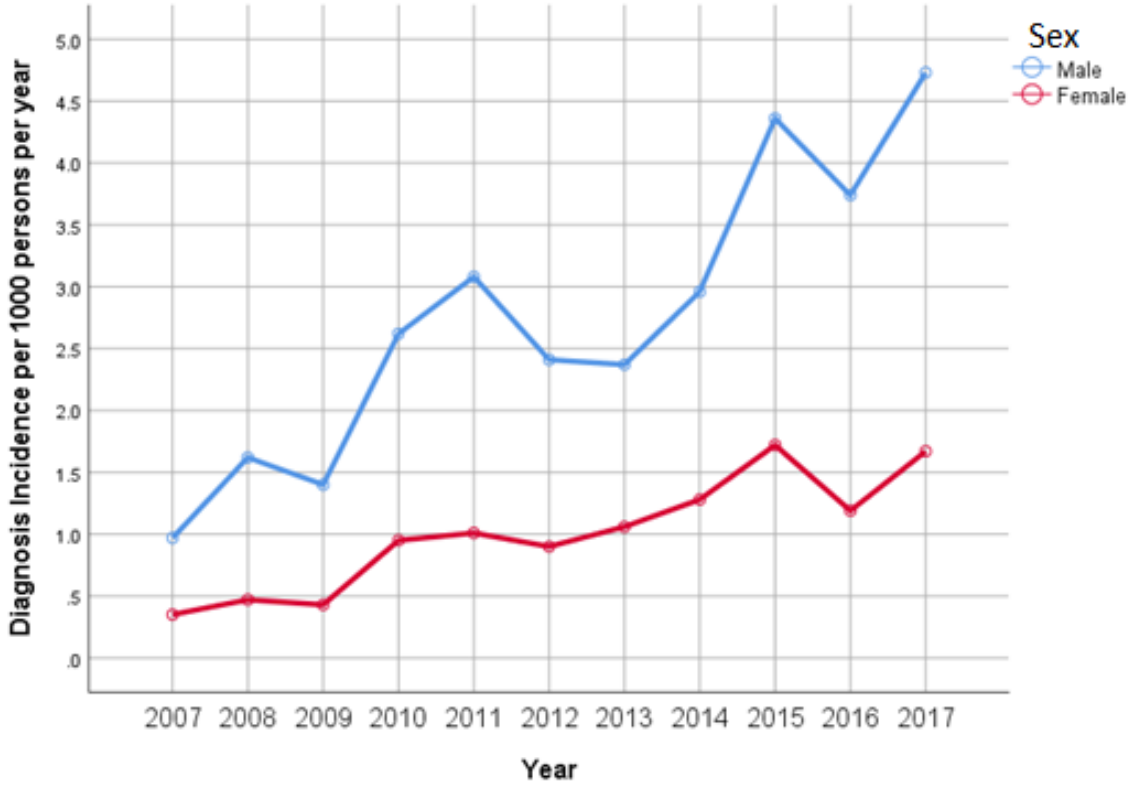


Figure 16: Distribution of annual hospital admissions by age group for HFrEF from 2007 to 2017



Annual incidence of new cases diagnosed per 1000 population from age ≥50 years increased for both sexes at different rates and patterns (Figure 17). The rise in male incidence was faster, erratic and characterised by two periods exhibiting rapid inclines for 2009 – 2011 and 2013 – 2017. Male rates remained consistently higher from 0.97 in 2007 to 4.73 in 2017. Female incidence climbed gradually at a slower rate from 0.35 in 2007 to 1.67 in 2017. The faster growth rate for male incidence translated into a 5 times increase in the difference between male and female incidence from 2007 to 2017.

Figure 17: Incidence rates by sex of patients diagnosed with HFrEF of patients ≥50 years from 2007 to 2017



Analysis of the 2007 – 2017 mean diagnosis incidence per 1000 population clustered by sex and age group revealed that males had a much higher incidence throughout all age groups compared to females (page 60, Figure 18). This sex difference in incidence for diagnosis increased with age up to 80 – 89 years where the highest mean diagnosis incidence for both sexes was also recorded. From 90 years upwards this difference in incidence between sexes decreased however this disparity was not significant in the 90 years and older age group (P-value 0.067) (page 60, Table 6). The difference in mean diagnosis incidence between males and females was highly significant for the rest of the groups (50 – 89 years) (P-value < 0.05).

Figure 18: Mean annual diagnosis incidence for 2007 – 2017 clustered by age group (for age at incident diagnosis) and sex

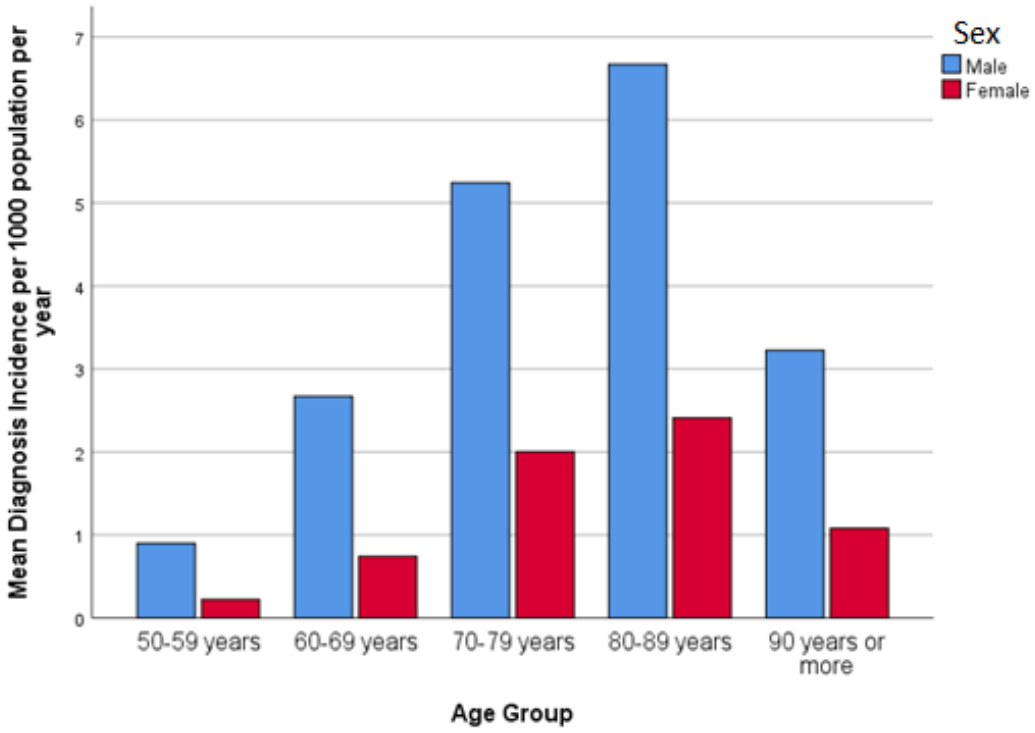


Table 5: Shapiro-Wilk test of normality for diagnosis incidence clustered by age group for age at incident diagnosis

Tests of Normality

		Statistic	Statistic	P-value
Diagnosis Incidence per 1000 population	50-59 years		0.912	0.051
	60-69 years		0.892	0.021
	70-79 years		0.901	0.031
	80-89 years		0.889	0.018
	≥ 90 years		0.824	0.001

Table 6: Mann-Whitney U test for mean annual diagnosis incidence clustered by age group (for age at incident diagnosis) and sex for Figure 18

Diagnosis Age Group	Sex	Mean diagnosis incidence	Std. Deviation	P-value
50-59 years	Male	0.90	0.410	0.000
	Female	0.22	0.177	
60-69 years	Male	2.67	1.069	0.000
	Female	0.74	0.347	
70-79 years	Male	5.24	1.924	0.000
	Female	2.00	0.752	
80-89 years	Male	6.67	3.534	0.002
	Female	2.41	1.348	
≥ 90 years	Male	3.23	2.998	0.067
	Female	1.08	1.139	

Annual rate of HFrEF associated mortality per 1000 population from age ≥ 50 years exhibited a rapid rise with time with similar trends for both sexes (Figure 19). Male mortality rate increased from 0.44 to 2 with female rate maintaining a lower rate throughout the 11-year period and increasing from 0.14 to 1.39. The higher rate for males resulted in a 3 times increase in the difference between males and females from 2007 to 2017. By comparison, all-cause mortality rate per 1000 population from age ≥ 50 years demonstrated a similar higher rate for males but a downward trend for both sexes rather than an increase over the same period (page 62, Figure 20).

Figure 19: Mortality rate for HFrEF by sex of patients aged ≥50 years from 2007 to 2017

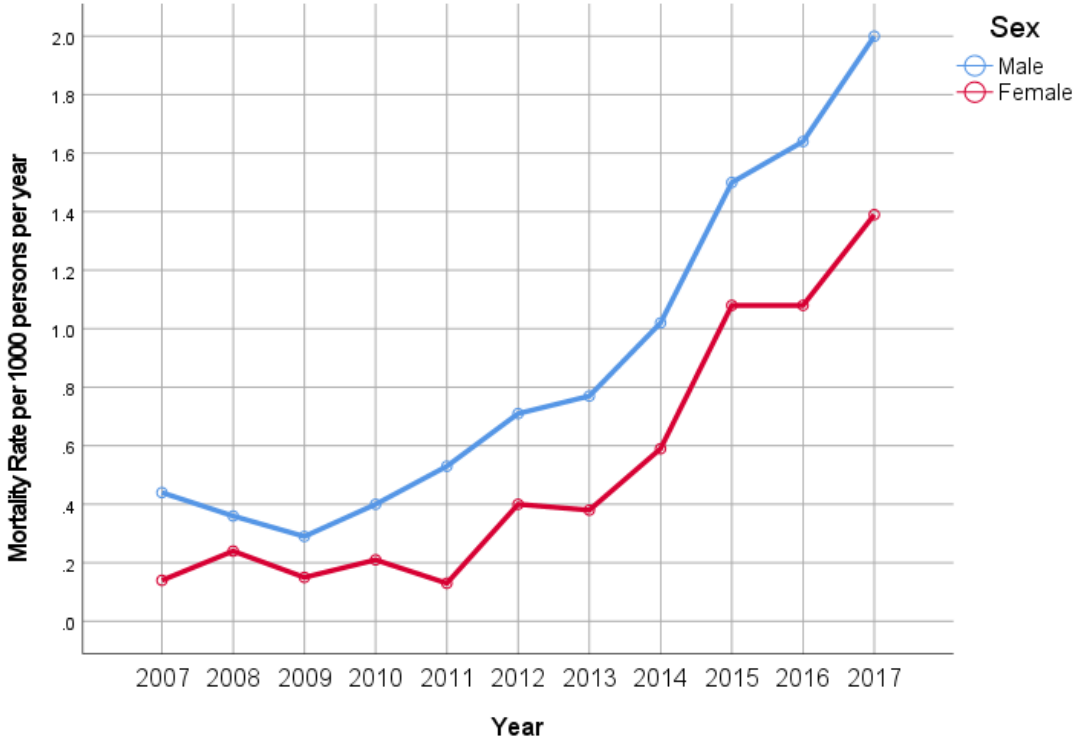
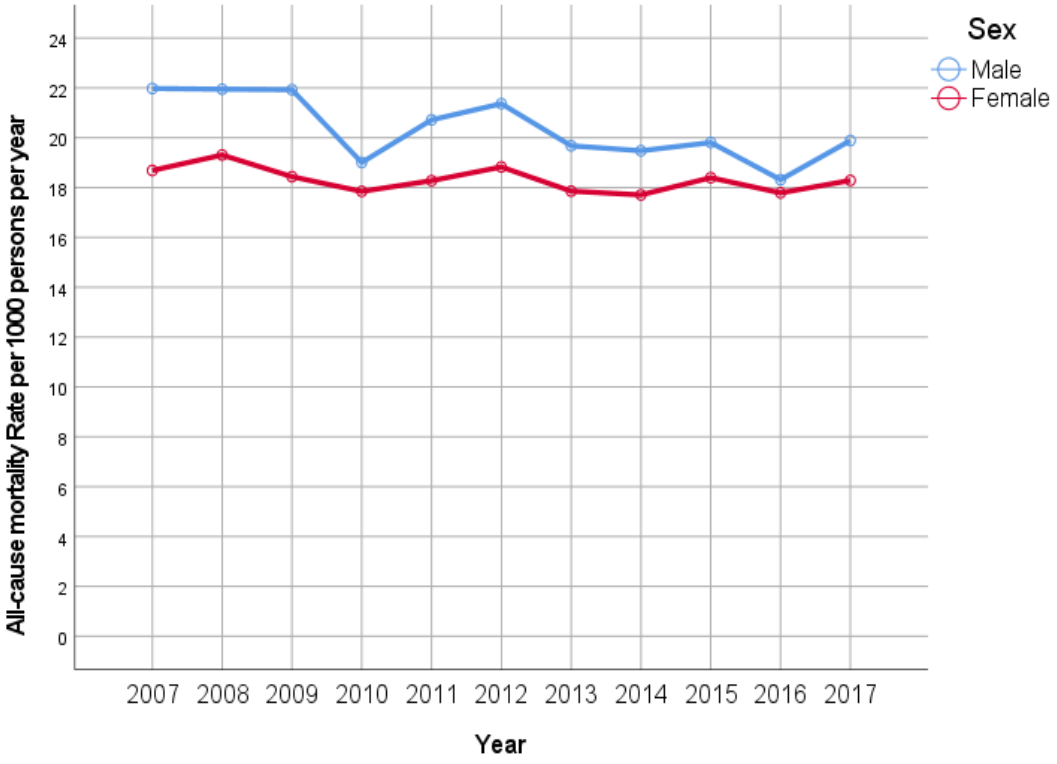


Figure 20: All-cause mortality rate by sex of patients ≥50 years from 2007 to 2017



Analysis of the mean annual mortality rate per 1000 population clustered by sex and age group across the period 2007 – 2017 revealed that males had a higher rate throughout all age groups compared to females (page 63, Figure 21). This difference between males and females increased with age but was only significant in the 60 to 79 years group where males had a significantly higher rate compared to females (P-value < 0.05) (page 63, Table 8). In the case of the age groups 50 to 59 years and from 80 years upwards the difference in mean rate between sexes was not significant (P-value > 0.05). The age group for 90 years and older of both sexes contained the highest mean rate for mortality for both sexes.

The mean age at diagnosis was compared between two independent groups clustered either by sex or survival outcome at 3 years after the index year of incident diagnosis (page 64, Table 10). The null hypothesis specifies that the mean age at diagnosis varies marginally between the two groups (male/female; alive/dead) and is accepted if the P-value exceeds the 0.05 level of significance. The alternative hypothesis specifies that the mean vary significantly between the two groups and is accepted if the P-value is less than the 0.05 criterion. The mean age at diagnosis for females (73.54 years) was significantly larger than for males (70.59 years) (P-value < 0.05). In the case of survival outcome, the mean age at diagnosis for patients that died (74.15 years) was significantly larger than the group that survived (69.42 years) (P-value < 0.05).

Figure 21: Mean annual mortality rate for HFrEF from 2007 – 2017 clustered by age group (for age at death) and sex

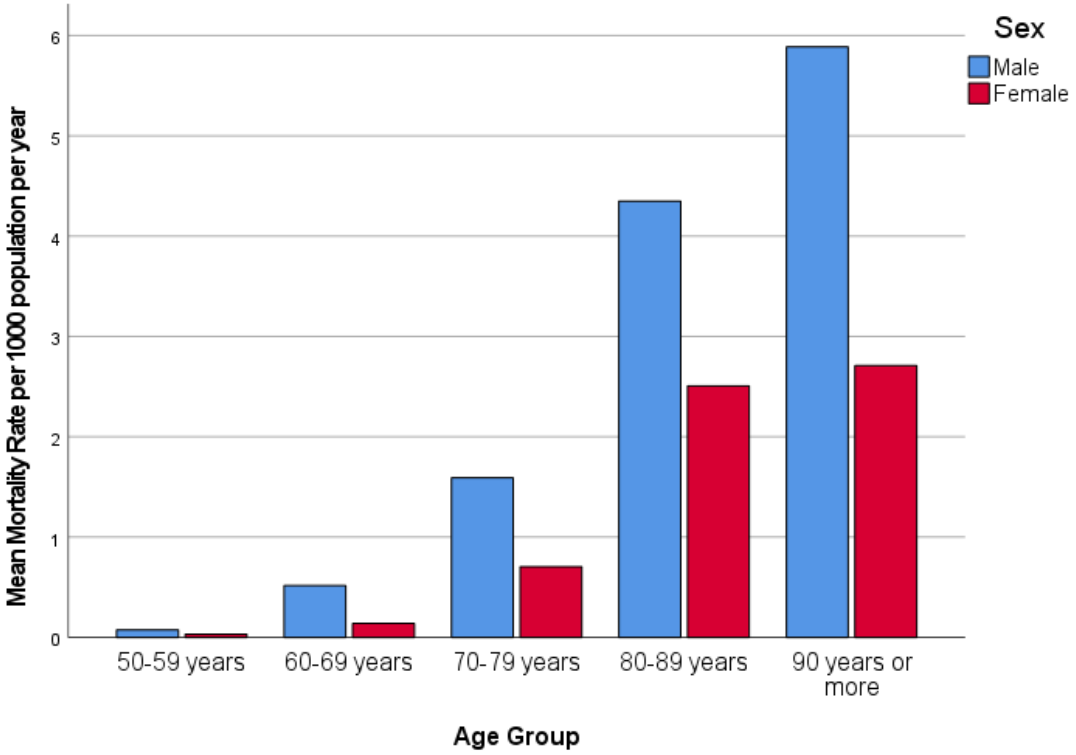


Table 7: Shapiro-Wilk test of normality for mortality rates clustered by groups for age at death

Tests of Normality

		Statistic	P-value
Mortality Rate per 1000	50-59 years	0.831	0.002
	60-69 years	0.919	0.052
	70-79 years	0.867	0.007
	80-89 years	0.871	0.008
	≥ 90 years	0.711	0.000

Table 8: Mann-Whitney U test for mean annual mortality rate clustered by group for age at death and sex for figure 21

Mortality Age Group	Sex	Mean Mortality Rate	Std. Deviation	P-value
50-59 years	Male	0.007	0.007	0.094
	Female	0.033	0.042	
60-69 years	Male	0.517	0.224	0.001
	Female	0.140	0.131	
70-79 years	Male	1.592	0.843	0.01
	Female	0.706	0.3801	
80-89 years	Male	4.350	3.363	0.094
	Female	2.508	2.325	
≥ 90 years	Male	5.888	7.671	0.469
	Female	2.710	2.668	

Table 9: Shapiro-Wilk test of normality for age at incident diagnosis with histogram

Tests of Normality

	Shapiro-Wilk		
	Statistic	df	Sig.
Age at Diagnosis	.988	3340	.000

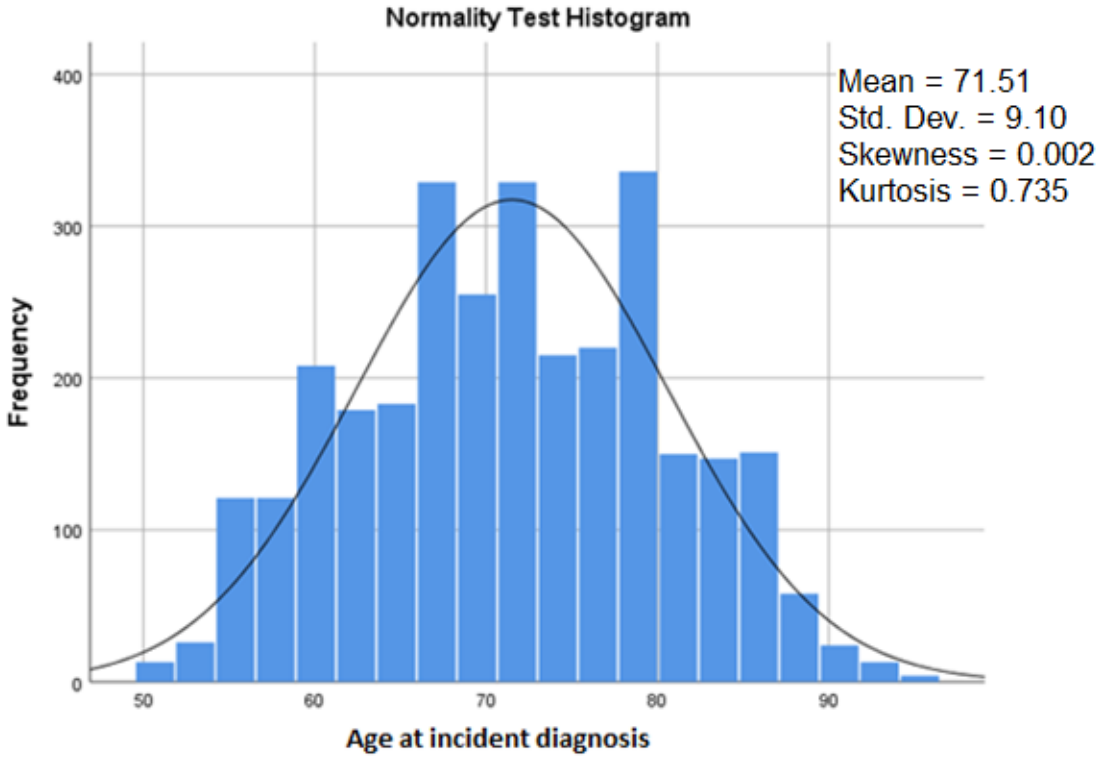


Table 10: Mann-Whitney U test P-values for mean age at incident diagnosis clustered separately by sex and survival for 2007 – 2015 data (N = 2362)

	Sex	*Sample size*	*Mean*	*Std. Deviation*	*Mean rank*	*P-value*
Age at incident Diagnosis	*Male*	*1663*	*70.59*	*8.952*	*1579.46*	*0.000*
	Female	*699*	*73.54*	*8.882*	*1899.53*	

	Survival	*Sample size*	*Mean*	*Std. Deviation*	*Mean rank*	*P-value*
Age at incident Diagnosis	*Dead*	*870*	*74.15*	*8.888*	*1958..56*	*0.000*
	Alive	*1492*	*69.42*	*8.601*	*1458.76*	

Logistic growth curve modelling was done for prediction of annual diagnosis of HFrEF incidence by sex, age group and annual total for patients ≥ 50 years. The same statistical model was used for prediction of annual incidence of associated hospital admissions clustered by two age groups of patients 50 - 69 years old, and ≥ 70 years, together with total hospital admissions of patients aged ≥ 50 years (Figures 22 to 24). The R^2 value shows how close the data is to the fitted growth line. An R^2 value of 0.9 means 90% of the variation in the Y-axis data (dependent variable) is due to variation in the X-axis data (independent variable). The value of R^2 is always between 0 and 1 and the closer it is to 1 the better the fit of the curve. All R^2 values expressed a high accuracy of curve fitting for this model except for the 90 years and older age group as a result of the relatively small sample size for this group.

Figure 22: Predictions of total and by sex of annual diagnosis incidence of patients ≥ 50 years

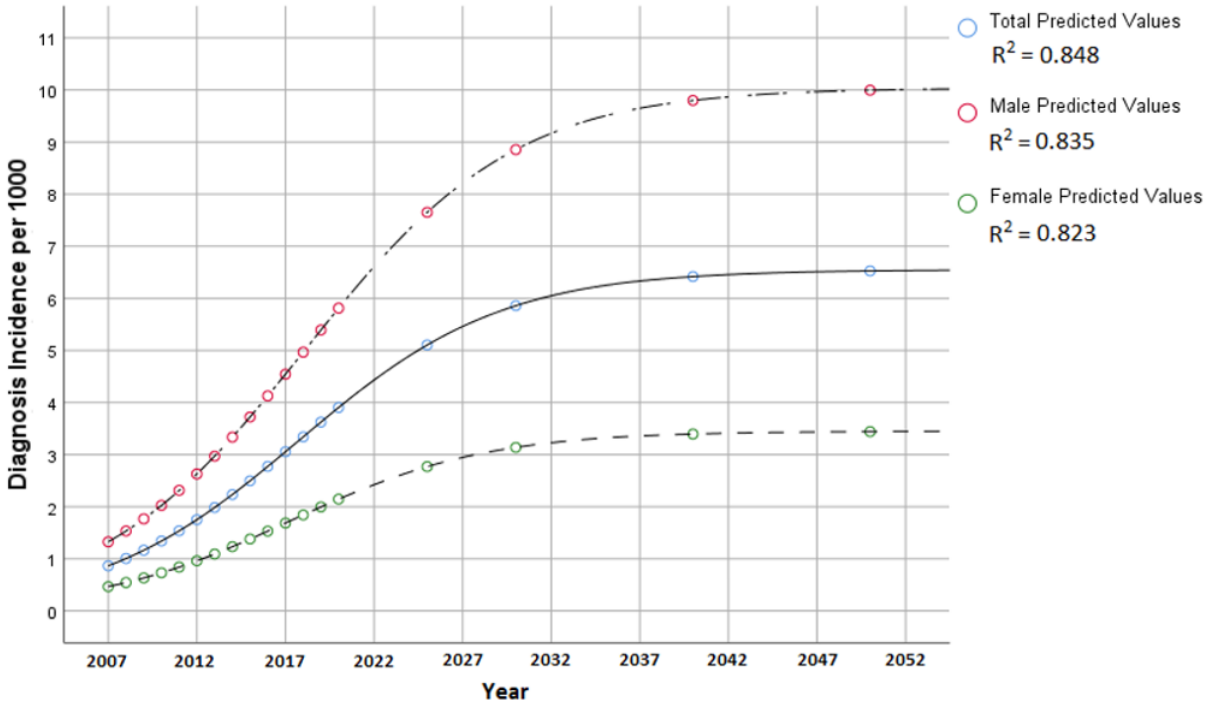


Figure 23: Predictions of annual diagnosis incidence by age group

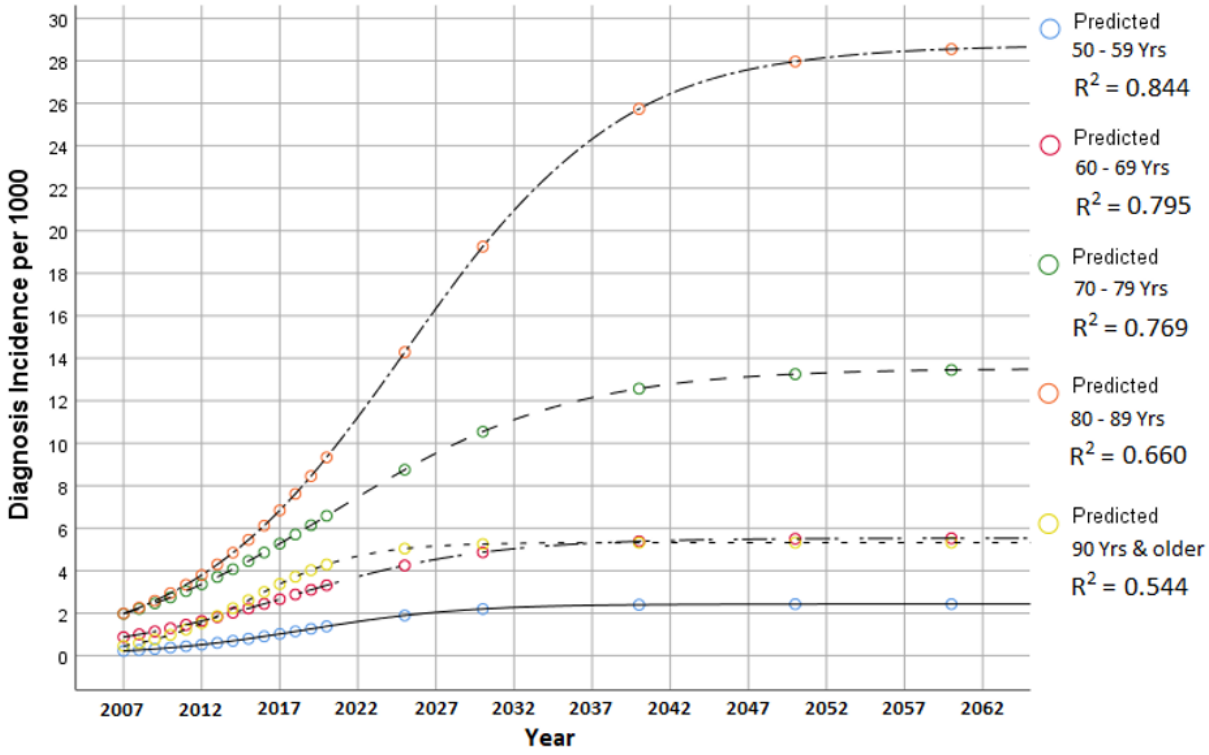
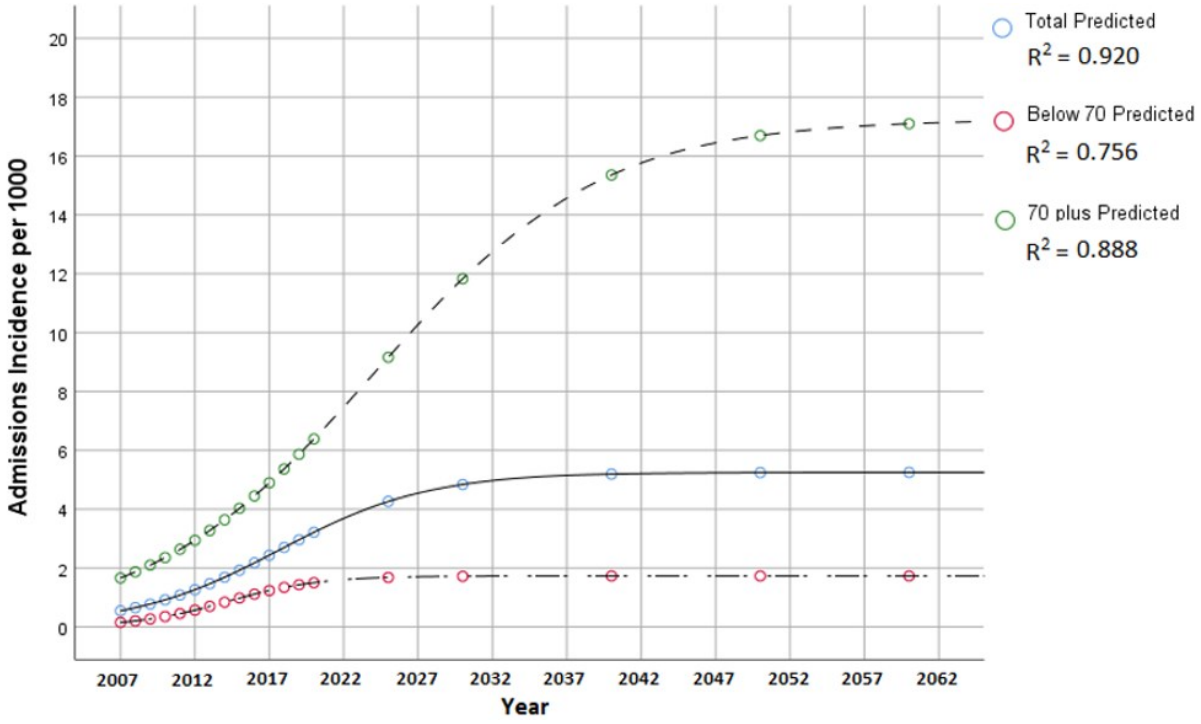


Figure 24: Predictions of annual hospital admissions incidence for HFrEF patients aged 50-69 years, ≥ 70 years, and total ≥ 50 years



5.5.2. Pharmacotherapy Trends

The final goal of this research was to identify trends in use of the two drug classes and reveal possible predictors of choice. ACEI/ARB treatment or absence thereof for 2 years or more during follow-up was taken as the predominant choice of HFrEF management throughout the study duration of 3 years post incident diagnosis. The absence of use any angiotensin blockade treatment dominated with more than half of the study population falling in this category until 2017 (figure 25). By 2020 this fraction reduced to 23% or 1 in 4 patients throughout the complete patient population. The least category of choice for management remained the use of ARB. Categorising treatment by sex, absence of treatment remained 4% higher for females despite the overall reduction in no treatment from 2017 to 2020. Males were treated with ACEI more than females (2007-2017: males 39%; females 29.9%) while more females were managed with ARB (2007-2017: males 10.8%; females 15.9%). The same pattern was observed in the 2007-2020 cohort for the subsequent 3 studies (Figure 26, table 11).

Figure 25: Study population distribution by angiotensin blockade management

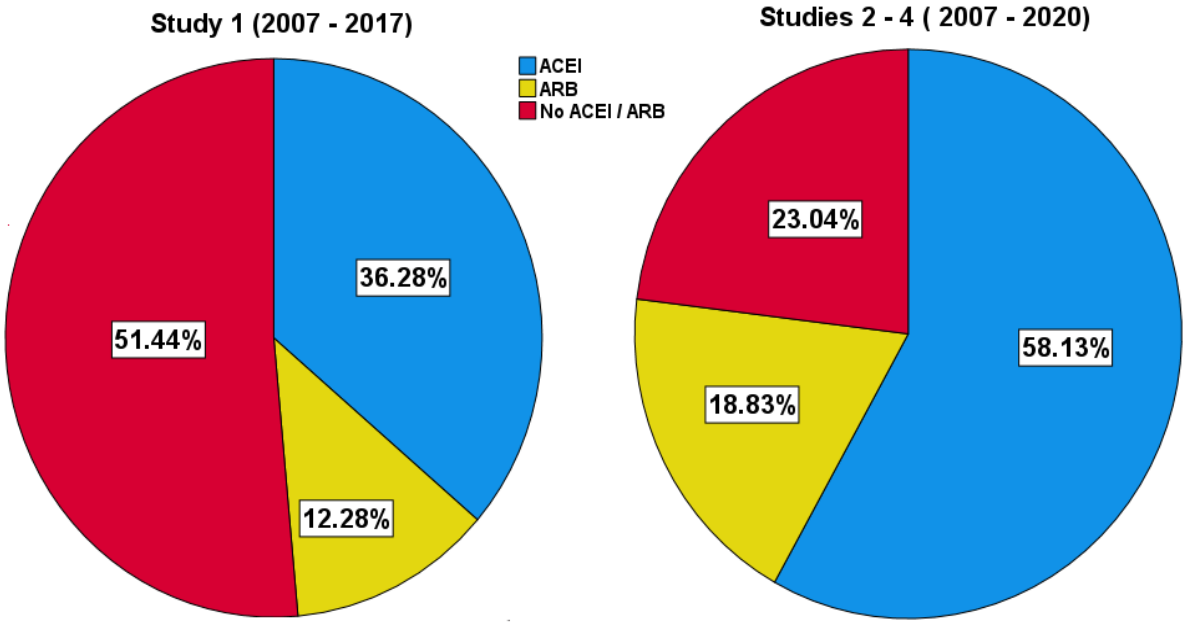


Figure 26: Study population distribution of angiotensin blockade management by sex

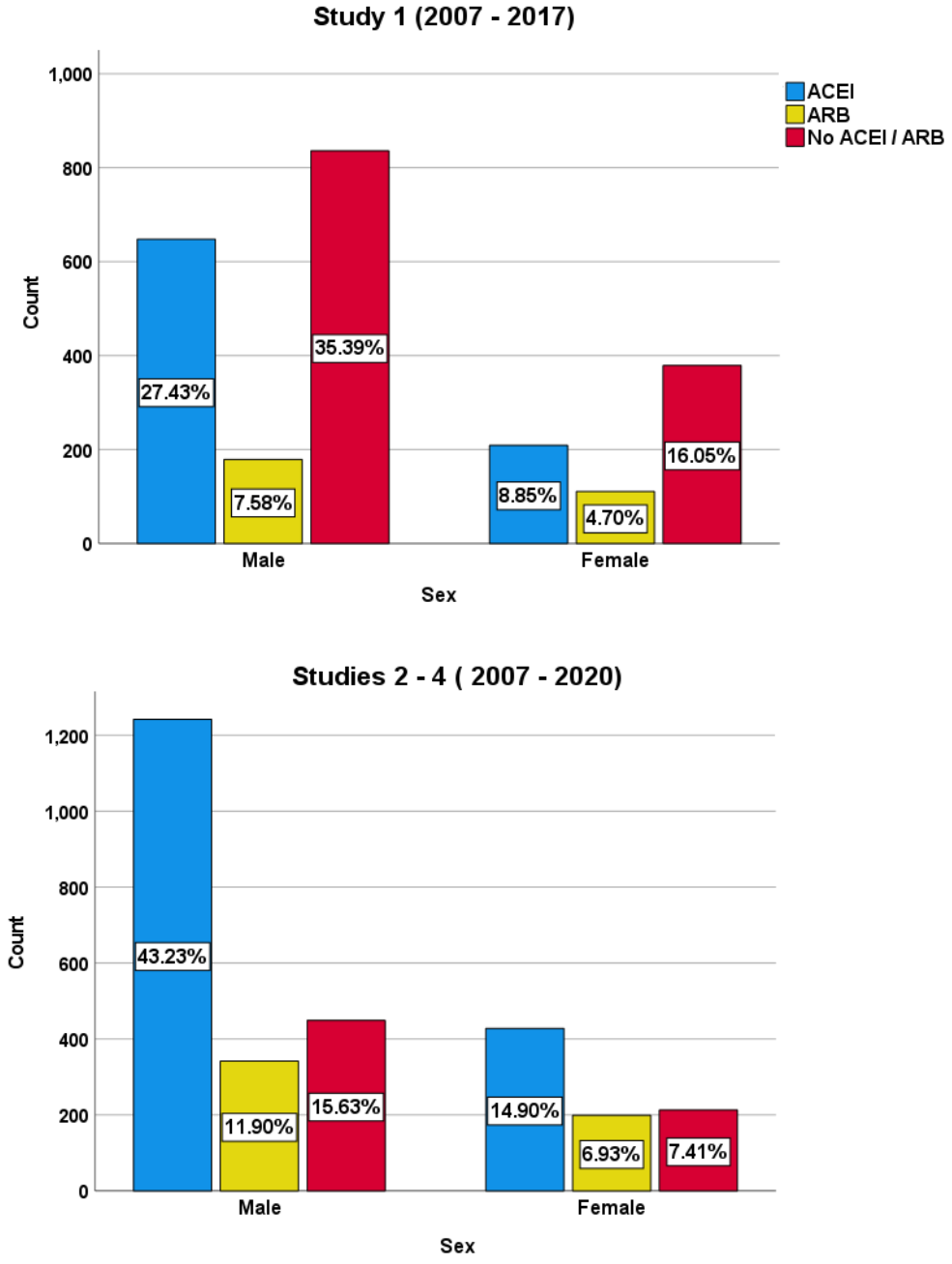


Table 11: Angiotensin blockade distribution within sex

	% within Sex			
	Study 1 (2007 – 2017)		Studies 2 – 4 (2007 – 2020)	
	Male	Female	Male	Female
ACEI	39	29.9	61.1	51
ARB	10.8	15.9	16.8	23.7
No ACEI / ARB	50.3	54.2	22.1	25.4

It is well known that a lone predictor could have a large impact on the dependent variable but would be rendered ineffective in the presence of other predictors. The aim was therefore to analyze the impact of all predictors collectively on treatment as the dependent variable. For this reason, multinomial logistic regression analysis was used to relate year of diagnosis, sex and diagnosis age group as joint predictors of ACEI treatment, or ARB treatment, or no treatment (Table 12).

Table 12: Logistic regression output for parameter estimates for ACEI, ARB, or no treatment versus predictor variables

Treatment[a]		B	Std. Error	P-value	Odds Ratio	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
ACEI	Intercept	-377.355	40.624	.000			
	Diagnosis Year	.186	.020	.000	1.205	1.158	1.253
	Male	.229	.106	.031	1.257	1.021	1.548
	Female	0[b]	.	.	.	.	.
	50 – 59 years	3.000	.753	.000	20.077	4.586	87.896
	60 – 69 years	2.716	.744	.000	15.122	3.518	65.003
	70 – 79 years	2.343	.743	.002	10.410	2.426	44.664
	80 – 89 years	1.531	.748	.041	4.621	1.067	20.001
	≥ 90 years	0[b]	.	.	.	.	.
ARB	Intercept	-366.811	59.206	.000			
	Diagnosis Year	.181	.029	.000	1.198	1.131	1.269
	Male	-.427	.141	.002	.652	.495	.859
	Female	0[b]	.	.	.	.	.
	50 – 59 years	2.638	1.044	.011	13.980	1.808	108.106
	60 – 69 years	2.458	1.030	.017	11.681	1.551	87.983
	70 – 79 years	1.931	1.030	.061	6.898	.917	51.891
	80 – 89 years	1.352	1.036	.192	3.866	.508	29.435
	≥ 90 years	0[b]	.	.	.	.	.

a. The reference category is: No Treatment. b. This parameter is set to zero because it is redundant.

For every one-year increase in the year of diagnosis, the odds of using ACEI rather than no treatment increases by 20.5% (OR 1.205). The same odds were observed for ARB (19.8%; OR 1.198). This means that the preference to include ACEI or ARB increased significantly with time over the option of leaving out both treatments from heart failure management. The

odds ratio for a male receiving ACEI treatment (OR 1.257) was larger than 1 indicating that this treatment was more prevalent with males (25.7% higher likelihood) than females. On the other hand the odds ratio for males to receive ARB treatment compared to females (OR 0.652) was less than 1 indicating that this treatment was less prevalent in males (35% less likelihood) than females. The effect of sex was significant for both ACEI and ARB.

The odds ratio of using ACEI decreased marginally as the age group got older but remained significantly higher than 1 which is the odds ratio for the reference age group of 90 years and older. In the case of a patient aged 50 – 59 years the likelihood of receiving ACEI was 20 times (OR 20.077) that of a patient aged 90 years and more. This likelihood decreased with increasing age but remained significantly higher compared to the oldest age group.

A similar trend was observed with the use of ARB. In the 50 – 59 years age group the use of ARB was 14 times more likely (OR 13.98) to receive ARB compared to the 90 years and older age group as reference. While the likelihood for the 60 – 69 years age group was almost 12 times more (OR 11.681) compared to the reference group. The odds ratio for ARB decreased with increasing age but remained significantly higher compared to the oldest age group.

The final test compared ACEI directly with ARB and looked at the likelihood of selecting either drug class against a panel of joint predictors including sex, age at incident diagnosis, year of diagnosis, age groups and age ≥ 70 at diagnosis (Table 13). The latter factor was tested separately as it is a sub-set of the age group factor (page 71, Table 14). Multinomial

Table 13: Logistic regression output for parameter estimates for ACEI or ARB versus predictor variables (excluding age groups < 70 and ≥ 70 years)

Dominant Treatment[a]		B	Std. Error	P-value	Odds Ratio	95% Confidence Interval	
						Lower Bound	Upper Bound
ACEI	Intercept	-13.142	65.570	.841			
	Male	.650	.148	.000	1.915	1.432	2.561
	Female	0[b]	.	.	.	.	.
	50 – 59 years	-.673	1.516	.657	.510	.026	9.961
	60 – 69 years	-.588	1.403	.675	.555	.036	8.684
	70 – 79 years	-.173	1.307	.895	.841	.065	10.897
	80 – 89 years	-.136	1.263	.914	.873	.073	10.376
	≥ 90 years	0[b]	.	.	.	.	.
	Diagnosis age	-.027	.026	.309	.974	.925	1.025
	Diagnosis year	.008	.033	.807	1.008	.946	1.075

a. The reference category is: ARB.

b. This parameter is set to zero because it is redundant.

logistic regression analysis was again used with treatment (ACEI / ARB) as the dependent categorical variable, and the other factors as the independent variables. This model tested the null hypothesis that in the population there is no difference in the logarithm of the odds of selecting an ACEI over ARB for males compared to females, or for patients aged ≥ 70 years compared to those aged below 70 years, or for patients compared by age at incident diagnosis or diagnosis age group, or by year of diagnosis. In this model the ACEI group was the determinant group.

Table 14: Logistic regression output for parameter estimates for ACEI or ARB versus age groups < 70 and ≥ 70 years as predictor variables

Dominant Treatment[a]		B	Std. Error	P-value	Odds Ratio	95% Confidence Interval	
						Lower Bound	Upper Bound
ACEI	Intercept	-13.486	65.530	.837			
	Diagnosis year	.008	.033	.809	1.008	.946	1.074
	Diagnosis age	-.022	.015	.151	.979	.950	1.008
	Age < 70	-.380	.252	.131	.684	.417	1.120
	Age ≥ 70	0[b]	.	.	.	.	.
	Male	.651	.148	.000	1.918	1.435	2.564
	Female	0[b]	.	.	.	.	.

a. The reference category is: ARB.

b. This parameter is set to zero because it is redundant.

The P-values obtained from this model rejected the null hypothesis only for sex. Therefore one may infer that controlling for all the other variables in this model, there was a significant relationship between sex and ACEI prescribing. Since the regression coefficient was positive and the model selected for males, the relationship with this sex is defined by an increased likelihood. In fact the odds ratio for a male receiving ACEI was significant both in the model for all age groups (OR 1.915) and in the model for age groups ≥ / < 70 (OR 1.918) years. Both odds ratios were greater than 1 indicating that this treatment was more prevalent with males than females. Both models estimated a higher likelihood of 92% for males to get ACEI over ARB compared to females.

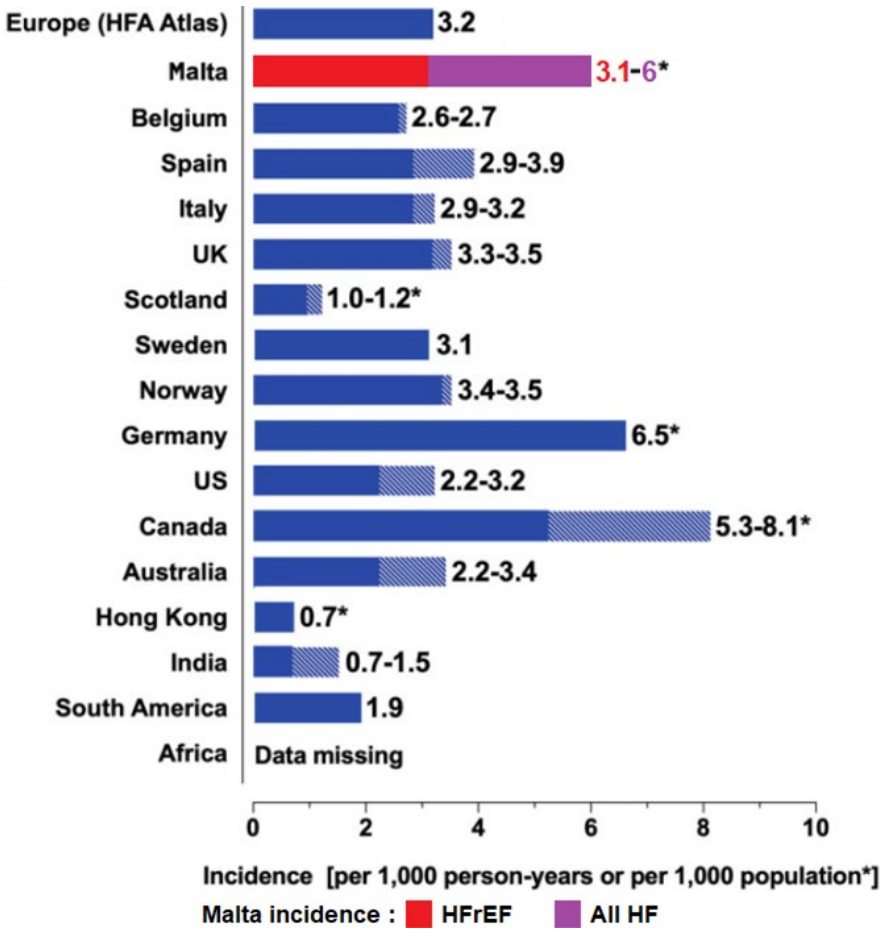
5.6. Discussion

5.6.1. Epidemiology

This national, all-inclusive, population-based cohort study provides several insights into the burden of heart failure in Malta and its variation with time, past and predicted, by age and sex.

The incidence of heart failure with reduced ejection in Malta was 3.14 per 1000 population adjusted for age ≥ 50 years in 2017 (Figure 22). Although the incidence of HFpEF and HFmrEF in Malta are not known, it can be assumed that distribution of heart failure across the left ventricular ejection fraction spectrum follows a modest bimodal distribution (133, 134, 135, 136). This gives an estimated, age-adjusted incidence for total HF of 6 per 1000 population aged ≥ 50 years for Malta (figure 27).

Figure 27: Incidence of heart failure in Malta compared globally



Maltese data is age-adjusted incidence for population aged ≥ 50 years. Worldwide data is for general heart failure incidence per full population. Source: adapted and updated from Savarese G, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023 Jan 18;118(17):3272-3287. Erratum in: Cardiovasc Res. 2023 Feb 09.

From 2007 to 2017 diagnosis of HFrEF increased from 0.87 to 3.14 per 1000 population aged ≥ 50 years (Figure 22). Reasons attributable to this increase are various. Mater Dei hospital is the national acute general hospital where all patients are referred including echocardiography and other imaging techniques. This hospital opened in 2007 however data capture was not complete before the end of 2009. A few years later two major improvements occurred in heart failure diagnostic elements at Mater Dei hospital. In 2014 the waiting time for outpatient echocardiograms went down from two years and nine months to one year with 6000 patients waiting for an echocardiogram appointment. This was further shortened in 2017 to three months (137, 138, 139). Also in 2016 the NT-proBNP test was introduced both as an emergency and as a routine test. Both measures increased immensely the rate of diagnosis of new cases (140). Malta has also been experiencing a rapidly aging population that involves accelerated growth of particular age segments of the population. From 2007 to 2017 the 60 – 89 age group increased by 39.7% representing the generation that has reached the age when heart failure risk increases (19). Also the Maltese population is characterised by a prevalence of cardiovascular risk factors that are higher than the EU average (5). Ischemic heart is the leading cause of death together with stroke and heart failure, accounting for 40% of all deaths in Malta. Diabetes accounts for nearly 9% of all deaths, 22.4% smoke regularly, 32.2% have hypertension and 25.2% are obese (5, 76). In particular, the incidence of diabetes and obesity are still increasing (26, 141) A rising incidence in risk factors coupled with accelerated aging of the population may also have contributed to the increase in diagnosis of HFrEF during the study period. Looking at individual causes of heart failure, ischaemic heart disease was the leading cause of mortality in 2018, accounting for 17 % of all deaths while (26). Deaths attributable to diabetes (50.8 per 100 000 population) were the third highest in the EU, and the death rate from ischaemic heart disease is also relatively high. Ischaemic heart disease is the leading cause of treatable mortality in Malta, and deaths rates remain above the EU average. Relatively high mortality rates from diabetes and ischaemic heart disease are partly attributable to the high prevalence of overweight and obesity among Malta's population (26). The importance of diabetes in the context of heart failure has long been recognised, more so in women (142). In the Framingham Health Study, diabetes was a more portent risk factor for the development of heart failure in women than in men (five-fold in women vs two-fold in men). Furthermore, women with diabetes had greater evidence of left ventricular remodelling that appeared earlier than men (142). Rates of obesity in Malta are the highest in the EU, with more than one in four adults classified obese in 2019. Men (28 %) were more likely to be obese than women (23 %) (26). However, there is increasing evidence that biological differences may impact the expression of cardiovascular risk factors and impart a differential

risk for women compared to men. When obesity is combined with female sex, HF with preserved ejection fraction (HFpEF) stands out as a special phenomenon (143). Hypertension, diabetes, and smoking are more potent risk factors for ischaemic heart disease in women than in men, with an odds ratio of 1.5, 1.6, and 1.3, respectively. Despite this, fewer women present with the classic symptoms of chest pain than men and instead exhibit more atypical symptoms such as dyspnoea, weakness, arm, back or jaw pain, lightheadedness, or loss of appetite. Current data suggest that in women, symptoms of chest pain are less discriminatory in predicting obstructive coronary artery disease (CAD) than in men.12 (144).The historic, limited interpretation of women's symptoms based on traditional approaches results from under-recognition of the sex-specific presentation of ischaemic heart disease. This contributes to misdiagnosis and delayed recognition of ischaemia (145). Young women with myocardial infarction are significantly more likely than men to be told by their health care provider that their prodromal symptoms are not cardiac (53% versus 37%, $P<0.001$) (146). Due to underestimation of risk by patients and by health care workers, significant sex differences persist for women in time to presentation and revascularization compared with men (146). A study of trends in cardiac surgery in the Maltese population between 1992 – 1994 found that the male to female rate ratios for CABG far exceeded the current mortality ratios for ischaemic heart disease. This difference may arise from inadequate referral of women for coronary angiography or different referral practices for men and women following coronary angiography. Revascularisation rates in men were 5.5 times higher than in women over the five years studied despite the fact that the male / female sex ratio for death from ischaemic heart disease in Malta was 1:1.1 between 1998 – 1999 (147, 148).

This study also found discordant trends between sex in age group specific incidence rates of heart failure diagnosis and associated mortality from 2007 to 2017. Despite the fact that incidence rates increased for both sexes, males had higher rates than females for diagnosis and associated mortality (Figures 17 and 19). This sex difference increased with time for both variables. The greater disparity occurred for incidence of annual diagnosis with male incidence increasing by 3.76 (range 0.97 – 4.73) compared to the 1.32 increase for females (range 0.35 – 1.67) per 1000 persons over 11 years. The mean incidence rates confirmed that this sex gap for diagnosis and mortality rates was not modest or random and was consistently observed across the majority of age groups (60 – 89 years) that contained the majority of patients throughout the period studied (Figure 18 and 21). Moreover, males developed heart failure at a significantly higher rate compared to females starting at 50 to 59 year (Table 6). Mortality followed a similar trend albeit the disparity was less between sexes when compared to diagnosis rate. However, males exhibited significantly higher mortality

incidence between 60 and 79 years (Table 8). This sex influence on mean incidence for diagnosis and mortality rate becomes insignificant from 90 year upwards. Significant deterioration in survival probability occurred if diagnosis happened after a mean age of 69 years (Table 10).

Ischemic heart disease is thought to be the most important risk factor for heart failure (149). However, the sex disparity in Maltese heart failure trends cannot be explained only by the higher rate of ischemic heart disease in Maltese males (male vs female deaths: 132 vs 85 per 100 000; years 2012) (5). Women are approximately 65% less likely to develop HFrEF than men (106, 150, 151, 152). Also women have better survival with HFrEF than men, although women with an ischaemic etiology for HFrEF may have a mortality similar to or worse than men with ischaemic HFrEF (5, 153). Diabetes and obesity significantly increase the risk of HFrEF in women compared to men. Women are less likely to achieve a glycated haemoglobin < 7 than men and obesity appears to have a worse outcome in women than in men (151, 154). The Framingham Heart Study reported that obesity increased the relative risk of coronary artery disease in women by 64% as opposed to 46% in men (151). Hypertension is also associated with a smaller relative risk but contributes more than ischemic heart disease to the population burden of heart failure because of its greater prevalence (150). Yet these findings do not add up to explain the Maltese context for HFrEF. Diabetes, obesity, and smoking rates of Maltese females are approaching those of males (5). Hypertension rates are also similar between sexes (149). A possible reason for this disparity in HFrEF associated morbidity and mortality trends between sexes is that heart failure with preserved systolic function is more common in women and this was excluded from the study (106, 155, 156, 157). Alternative explanations include less effective control of cardiovascular risk factors or better diagnosis rates of male patients (19). Women were less often admitted to cardiology wards or had an assessment of left ventricular function (154). Confounding from selection bias is not an issue here since the study design was all inclusive.

Evidence is divided on the influence of sex on heart failure incidence and inconsistent findings in the literature have left clinicians uncertain about the implications for clinical care (158, 158). A majority of previous studies have found that men with heart failure have worse survival than women, but other studies have been neutral or suggested that women are at higher risk (154, 155, 160, 161). In the USA the Framingham study reported higher incidence across all age groups for males rising highest in the 80 – 89 age group as reflected by this study (11). Higher incidence for males was again reported decades later by the American Heart Association (162) and by a recent major study in Australia (163). The United States National Health and Nutrition Epidemiologic Survey also supports the lower

mortality incidence for females (164). Other studies however point towards a different direction with equal incidence compared to males (165), or higher incidence in females attributed to more ischemic heart disease (106, 166). This difference in heart failure rates between sexes may be attributable to a complex interaction of differences in healthcare infrastructure or quality, genetics, environment, lifestyle, and social factors (73, 167).

The current higher annual male diagnosis incidence compared to females is expected to worsen and exacerbate the difference between sexes with future projections (Figure 10). Two factors appear to contribute towards the development of this pattern through time. Male diagnosis incidence will increase at a much higher rate compared to female incidence. Also, while female diagnosis incidence is expected to peak by the year 2037, male diagnosis incidence is predicted to keep rising for another 10 years before it almost saturates in 2047. This male trend shall be the main reason for a rising rate of total diagnosis incidence that starts saturating in 2042.

The demographics for annual diagnosis incidence by age group is also predicted to change considerably over the coming years (Figure 23). The age group for 90 years and older shall remain the least contributor towards rising incidence with a saturation year predicted in 2032. The same saturation year is predicted for the age groups from 50 to 69 years albeit with a modest increase in incidence. The incidence for the 70 – 79 years age group is predicted to increase considerably and peak in 2047. However the 80 to 89 years age group exhibits the most accelerated increase in predicted incidence and will become the major influence after 2022 when it will be the group with the highest incidence for diagnosis of incident cases. This age group shall dominate the rate for annual diagnosis of incident cases with 2057 as the predicted saturation year and will be the main force driving up the incidence of HFrEF. Prediction estimates show that HFrEF incidence will increase by 50% from 2017 to 2040 up to 5.2 per 1000 population aged ≥50 years under status-quo heart failure prevention and treatment trends.

Assuming no change in policy over the time, these projections may be explained by two reasons. An increase in associated risk factors coupled with the effect of accelerated aging of particular segments of the population intensify further the increasing rates of HFrEF in the affected age groups. In particular the 80 – 89 years age group was identified to be the most exposed to these influences (168). From 2007 to 2017 the 60 – 89 age group increased by 39.7% representing the post-war baby-boom generation that has reached the age when heart failure risk increases (19). This is a common demographic change seen in other countries (169, 170). However the incidence for all-cause mortality decreased for the population under study during the same period. This indicates that a rise in risk factors is the predominant factor for the increase in HFrEF incidence (168, 171). The National Health and

Nutrition Epidemiologic Survey suggested that coronary heart disease had the largest impact on the development of heart failure and may be responsible for more than 60% of cases (172). Diabetes mellitus increases the risk of heart failure by ≈2-fold in men and up to 5-fold in women. Smoking remains the single preventable cause. Obesity was associated with a doubled risk of heart failure while hypertension is also linked to heart failure development (171, 173). Smoking is decreasing in the Maltese population and hypertension is improving but diabetes is increasingly becoming a stronger issue for health systems while obesity is becoming more prevalent (5).

Furthermore, the age group for 70 years and older shall be largely responsible for hospital admissions incidence (Figure 24). This shall increase from 5.87 in 2019 to 17.25 per 1000 population aged ≥ 50 years in 2057 as the predicted saturation year. The age group below 70 years shall exert a substantially less effect on total incidence and saturate 30 years earlier in 2027. Total incidence for hospital admissions is expected to increase from 2.96 in 2019 to 5.25 in 2037 per 1000 population aged ≥ 50 years. This demographic forecast raises concern on the absence of suitable representation of the age group aged ≥ 70 years in clinical trials of therapeutic strategies that are now standard treatment (174). It is a recognized fact that patients aged over 70 years are under-represented in clinical trials that shaped current treatment and further research is required to establish facts instead of extrapolating results from younger study samples (175).

Current and predicted trends for Malta seem to share a similar trend observed in Spain which experienced markedly increasing hospitalisation rates for heart failure up to 2005 with a subsequent apparent levelling off (176). However Maltese trends for heart failure hospitalisation run counter to trends in other countries where hospitalisation rates for heart failure in Western populations appear to peak during the 1990's and decline thereafter. This trend was observed in Denmark (1983 – 2000), The Netherlands (1980 – 1999), Scotland (1986 – 2003), Sweden (1987 – 2006), New Zealand (1988 – 2008), Australia (1990 – 2007), Canada (1999 – 2007), France (2000 – 2012), and the USA (2001 - 2009) (177). Factors attributed to the decline in hospitalisation for heart failure include:

- Reductions in prevalence of smoking, sedentary lifestyle, and uncontrolled hypertension
- Declining incidence of myocardial infarction
- Optimized pharmacotherapy after myocardial infarction at tertiary medical care
- Increased diagnosis and treatment of heart failure at primary care (98).

The decline in hospitalisation rates for heart failure occurred with decreasing trends in AMI hospitalisation and mortality reported in the USA and despite an increasing prevalence of obesity and diabetes described in Denmark (177, 178).

The Maltese prevalence of hypertension is improving however rates of obesity in Malta are the highest in the EU, with more than a quarter of adults classified as obese (5, 26). Poor diets and physical inactivity contribute to high levels of obesity in the country. Smoking rates among adults are similar to the EU average and decreasing (26). Also obesity and smoking rates of females are approaching those of males (5, 26). From 2000 to 2018, age-standardised mortality rates per 100 000 population from cardiovascular diseases fell by more than 50 %. Cardiovascular diseases nevertheless remained the leading cause of death in 2018, accounting for 34 % of all deaths. Ischaemic heart disease was the leading cause of mortality in 2018, accounting for 17 % of all deaths, followed by stroke. As a primary risk factor for cardiovascular disease, mortality rate from diabetes is the third highest in the EU which are partly attributable to the high prevalence of overweight and obesity among Malta's population (26). To counter these risk factors a series of national initiatives were launched between 2012 and 2020. The National Health Promotion Unit increased engagement with the public to educate about obesity and lack of physical exercise. This included the implementation of two national strategies – one for a healthy weight for life and another as a food and nutritional policy / action plan (179, 180, 181). Additionally, recent legislation regulating advertising and food provision in schools, along with inter-sectoral investment to promote a culture of physical activity, aims to help tackle this major public health challenge. A national Quitline was also introduced for the general public wanting to seek support related to smoking cessation or to apply for smoking cessation classes (26). A national strategy for diabetes was adopted to improve prevention and access to innovative and quality treatment (182).

The increase in heart failure incidence shall be greatest in the older Maltese population particularly in those aged ≥ 70 years (Figure 23). If smoking and ischemic heart disease remain high, while diabetes and obesity continue to rise, we can see a much greater increase in heart failure incidence, associated hospital admissions and mortality. These risk factors in the Maltese population are already among the highest in Europe (5). Ischemic heart is the leading cause of death together with stroke and heart failure, accounting for 40% of all deaths in Malta. Diabetes accounts for nearly 9% of all deaths, 22.4% smoke regularly, 32.2% have hypertension and 25.2% are obese (5, 76).

5.6.2. Pharmacotherapy trends

The following observations can be concluded from the analysis of use of ACEI and ARB in HFrEF patients over the study period:

- There was a progressive increase in prescribing of ACEI and ARB with time at approximately equal rates (Table 12).
- The increasing preference for ACEI was driven by prescribing for males with ARB exhibiting an opposite trend of a small but significant decrease of ARB use with time for males. This indicates that the observed increase in ARB use was due to prescribing for females (Table 13 and 14).
- The preference for ACEI and ARB decreased with increasing age. However ARB reached nadir rates at age 70 years, that is 20 years earlier compared to ACEI which reached lowest rates at age 90 years. This indicates that the increase in guideline-directed medical therapy use of ACEI and ARB was mostly driven by prescribing for age groups between 50 – 69 years (Table 12).
- All of this indicates that females had a higher chance of receiving ARB compared to males but with increased likelihood of no treatment as they grew older. Females aged 70 years or older were at greatest disadvantage of receiving sub-optimal treatment.

The increasing preference to include ACEI or ARB in heart failure treatment with time may be explained by the sustained recommendation prevailing since 2005 of both drug classes as a cornerstone of management of heart failure with reduced ejection fraction even in the absence of associated symptoms (183). The CONSENSUS study demonstrated a 40% mortality reduction in patients with severe heart failure treated with enalapril (62). long-term follow-up data further suggested that ACEI therapy increased survival time by 50% (184). ARB exhibited similar survival benefit with the ELITE II trial (112). Therefore this trend in increased utilization of treatment is positive albeit protracted.

Meta-analysis subsequent to the CONSENSUS and SOLVD trials demonstrated comparable benefits of ACEI in survival and heart failure associated hospitalisation in both men and women with HFrEF (185). Landmark placebo-controlled trials with ARB used in HFrEF achieved similar benefit (66, 110, 153). Therefore treatment with ACEI or ARB is advocated in all patients with left ventricular dysfunction irrespective of sex (155). Unfortunately there is considerable evidence that supports the existence of treatment inequality between sexes in heart failure care. Several studies have suggested that women receive fewer guideline-directed heart failure therapies (158, 159, 186, 187). In particular, women were less likely to be treated with ACEI during hospitalisation, even when left ventricular systolic dysfunction was present (158, 159). This research goes one step further and extrapolates this bias in treatment to women post discharge and during follow-up. A European multi-centre survey of

primary care heart failure management observed that the odds of receiving an ACEI was significantly reduced for women in the 70 years and older age group (107). Primary care data from the UK also demonstrated that at all ages, women are less likely to receive ACEI for heart failure (108). This difference in ACEI use was more pronounced in elderly patients especially those aged over 80 years (157, 158). This was observed specifically in heart failure data from the General Practice Research Database (108) and reported by Mehta and Cowie (106). No plausible explanations were provided for this difference. However, it does not appear that less use of ACEI was the case since 72% of men aged 55–64 years were prescribed ACE inhibitors while overall, 80% were eligible for ACEI (188).

Lenzen et al. extended this sex bias to heart failure treatment including ARB by revealing that women were less likely to be treated with drugs proven to reduce mortality, preferring cardiac glycosides and diuretics. This difference in treatment was more pronounced in elderly patients (155).

Furthermore, the finding from this study that use of ACEI was driven by prescribing for males while prescribing for females exhibited a preference for ARB mirrors previous research that found the same pattern of persistency with treatment that was dependent on sex. Women were less persistent with ACEI than with ARB while men were more persistent with ACEI than with ARB (60). This observation is supported by further research where the odds of receiving ACEI was significantly higher in men than women (89). This sex bias in treatment appears to persist despite the substantial (> 40%) increase in treatment with ACEI during the 1990s (108).

Females present with heart failure at an older age and with a different clinical profile compared to males, including increased hypertension and less coronary artery disease (189). However this does not explain the observed sex difference in treatment. Furthermore, the teratogenic effects of both drug classes are not an issue since this study excluded women of childbearing age. One explanation may be that women are known to have more side effects when treated with ACEI leading to preferential treatment with ARB (190). This choice may actually be beneficial with better survival observed for women on ARB compared to ACEI (60). However Gustafsson et al. observed that translating evidence of sex differences in clinical outcome is challenged by the contradictory observation of increased male risk for mortality versus decreased likelihood for women to receive ACEI (159). This study substantiates this observation and shows that it remains an issue. Furthermore this research presents three new findings that give more detail about the problem. First, that males with HFrEF remain at a higher mortality even with decreasing use of ARB in females as they grow older. Second, this study redefines the age when inappropriate treatment becomes more probable and starts from 70 years upwards, that is 10 years earlier from

Gustafsson's study (159). Third, this age threshold is identified by this research to be specific for females.

5.6.3. Strengths

The all inclusive, population based design within the setting of a tax-supported universal healthcare system and with virtually complete follow-up of all patients reduced selection bias. This allowed this study to investigate true incidence rates and not to rely on hospitalisation rates as with previous studies (177). True incidence rates provide a real picture of severe and symptomatic heart failure and may differ with the magnitude of hospitalisation rates.

The primary diagnostic echo that led patient eligibility was interpreted in a dedicated hospital lab. This methodology combined with a follow-up of three years allowed for a fair assessment of the magnitude of the problem. The study enrolment period (2007 – 2017) supported assessment of differences in treatment, survival, and hospitalisation in the context of current heart failure care. This notion is further strengthened by the consideration of both in-hospital as well as chronic ambulatory treatment for assessment of therapy trends of ACEI and ARB. Therefore this study reflects previous research at addressing limitations associated with the availability of representative data and the length of follow-up (158, 159), but also goes further at defining the direction of the problem between sexes with contemporary care.

5.6.4. Limitations

The hospital opened in 2007 and data capture was not complete before 2009. Analysis of incidence for all-cause mortality included external harm related deaths apart from mortality caused by disease. However the rate of external harm related deaths was small (≈5%). Rates were fairly stable, and the majority of harm associated deaths occurred in the younger population. So the influence of including all-cause mortality instead of disease related mortality had little impact on the trend. The small size of the age group aged 90 years or older contributed towards a 54.4% accuracy for the logistic curve model. Research using hospitalisation records relied on the accuracy of clinical coding input without internal validation while mortality rates were dependent on subjective death certification. Patients were identified from hospital-based echocardiography records that leads to possible underestimation of the actual incidence in the community. Although the effect is expected to be minimal since the majority of heart failure patients are eventually referred for echocardiography. This study lacked detailed clinical data such as NYHA class, use of ICDs, ventricular assist devices, and heart transplantation as measures of disease severity.

However left ventricular ejection fraction is a core factor used for classifying heart failure by current guidelines and this was used for identifying patients in this study. Besides, this study was not designed to look into heart failure severity.

Malta is an island with an advanced aging population and may not be a representative European model. The population size also limited the size of the study cohort. However, the opportunity of an all-inclusive, population study owing to the island size and centrally accessible free hospital care is a research design advantage. The study cohort included only registered Maltese residents and did not take into consideration the influx of immigration particularly from sub-Saharan Africa. This group will also undergo an epidemiological transition that will influence future trends, however current numbers within the age groups studied are insufficient to measure effect (191).

In the case of treatment analysis, there was no validation of appropriateness of pharmacotherapy through consideration of contraindications or adverse reactions. This limits the ability to judge the importance of differences in treatment. Second, a number of patients were switched between ACEI and ARB. While this study considered the treatment with longer duration as the main treatment for consideration, it does not assess the significance of switching therapy in relation to clinical outcome. However there were 153 switching events that amount to less than 5% of the cohort. Finally, while this research aimed to capture all eligible patients in the Maltese population, the status remains a single-centre study with all associated limitations.

5.7. Conclusion

Findings from this research have implications for future planning of healthcare resources and preventive strategies. An older, heart failure population carries an increasing number of comorbidities and makes disease management more complex with a higher burden on healthcare services. Unfortunately there also seems to be sex bias in healthcare where women are less likely to receive pharmacotherapy with documented benefit. Men and women are still treated differently with a paradoxical situation of higher male morbidity and mortality despite lower ACEI and ARB prescribing for females. While ARB are more likely to be prescribed for females, they are also exposed to the highest levels of inadequate treatment with no ACEI or ARB from 70 years of age upwards, that is 20 years before males have the likelihood of the same level of treatment. Overall, increasing age for both sexes was associated with reduced therapy that can decrease morbidity and improves survival. This has consequences considering that predicted incidence increase for HFrEF diagnosis and hospitals admission shall be attributed mainly to patients aged ≥70 years by 2057. In

fact, forthcoming trends indicate surging proportions of HFrEF patients with a progressively aging population simulating a future epidemic.

Suboptimal therapy is an appealing explanation for the increasing morbidity and mortality throughout the 11 years studied as it implies the possibility of improvement if therapy use and adherence can be enhanced, but it may not be all there is to it. Evidence comes from this research were females failed to get optimal therapy with bias reaching highest at the age of 70 years. Suboptimal therapy was found highest in males aged 90 years. Yet mortality was significantly higher for males in the 60 to 79 years age group. There is circumstantial evidence coming from the PARADIGM-HF trial that substantiates this view where suboptimal therapy does not explain mortality trends in HFrEF in outpatients as in this study. All-cause mortality over 2 years remained high even in optimally treated patients at 17% in the ARNI group and 20% in the enalapril group (192). A more plausible reason for the deterioration in HFrEF related morbidity and mortality is the increase in prevalence of associated co-morbidities of which the highest is ischaemic heart disease. Associated hospitalisation rates increased from 1678 in 2009 to 2055 in 2017. This should not underestimate the fact that efforts remain essential in heart failure to improve treatment implementation and adherence as previously emphasized (193). However it appears even more important to redouble prevention efforts at controlling the growing burden of associated comorbidities of which ischemic heart disease ranks strikingly higher than the EU average (143 per 100 000 in Malta versus 80 per 100 000 in EU; 2012 data) (5).

These findings suggest that current policy for treatment and prevention is failing with the rapid increase in heart failure incidence and associated mortality, This demands a national strategy to reduce the expanding burden of heart failure. A combined improvement in environmental changes, public health measures and clinical care is urgent (19). Observed age and sex disparities and projected trends may point to potential opportunities for more targeted prevention strategies.

Finally, the seemingly contrary results between males and females highlight the importance of a greater understanding of underlying mechanisms for sex differences in heart failure before clinical care can be altered to address them. One essential hypothesis is the influence of ACEI and ARB prescribing on morbidity and mortality that may vary between males and females particularly in those aged ≥ 70 years where evidence is scant.

6. STUDY 2

6.1. Aims and Objectives

Are ACEI effective in a contemporary cohort of adults aged 70 years or older and diagnosed with heart failure and reduced ejection fraction?

The null hypothesis is that there is no difference between treatment and control. The primary endpoint for investigation is all-cause mortality with a separate secondary endpoint of heart failure associated hospitalisation.

6.2. Inclusion / Exclusion Criteria

Subjects met the following inclusion and exclusion criteria:

Inclusion criteria

- Documented left ventricular systolic dysfunction defined as left ventricular ejection fraction ≤ 40%
- Treatment with ACEI or no treatment with a renin angiotensin system blocker
- Age ≥ 50 years at incident diagnosis for the study; < 70 years for positive control arm

Exclusion criteria

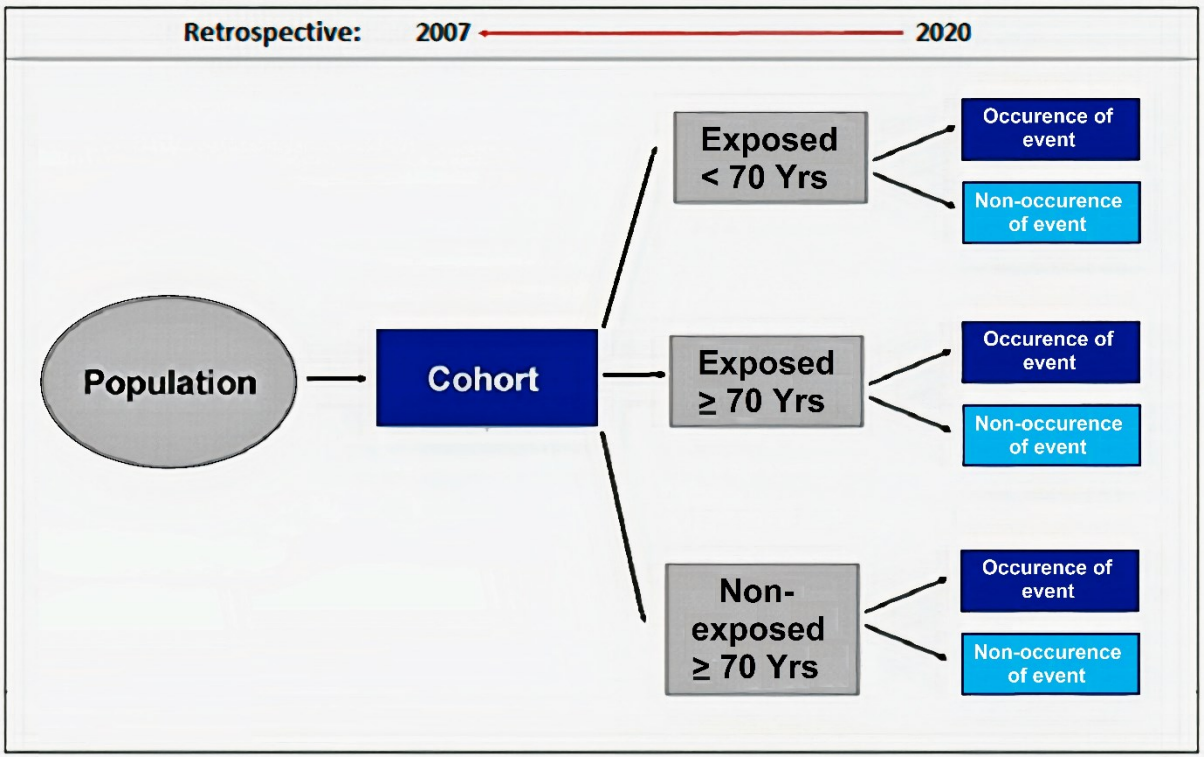
- Left ventricular EF not available
- Treatment with ARB or other non-ACEI RAS inhibitors
- Diastolic heart failure (HFpEF)
- Myocardial infarction, cardiac surgery, or percutaneous transluminal coronary angioplasty (PTCA) within 8 weeks
- Need for cardiac surgery (e.g. severe valvular disease, planned coronary artery bypass graft surgery) or PTCA in the near future. (Such patients are eligible after surgery or PTCA). Patients on heart transplant list were not eligible
- Intravenous inotropic agents within 45 days
- Potassium above 5.5 mmol/L
- Creatinine > 3.0 mg/dL
- Presence of cardiac implantable devices

6.3. Design

The cohort was made up two study arms, one with ACEI and another without RAS exposure. All patients diagnosed with a documented echocardiogram from 2007 to 2017 were included. The design was applied for the full cohort with an age limit of ≥ 50 years and a second cohort aged ≥ 70 years. The index age was the patient's age at incident diagnosis. A

comparison arm was also included for patients aged under 70 years and exposed to ACEI as a positive control to compare outcome with published trials. Patients were followed retrospectively for three years or until censored from time of incident diagnosis. The primary endpoint was all-cause mortality with a secondary endpoint of heart failure associated hospitalisation. The next schematic explains the stages of the study design (Figure 28).

Figure 28: Schematic of the study design – Study 2



The study involved testing ACEI in the active group against a control group with no RAS inhibitor on board. Baseline clinical descriptors collected were age and date for diagnosis and death, sex, ejection fraction, ACEI treatment duration, additional heart failure therapy, warfarin, and digoxin treatment, Charlson comorbidity score, and associated hospitalisation frequency. The inclusion of digoxin and warfarin was taken as an indication of the presence of significant additional cardiovascular morbidity that increase mortality risk and possibly lead to confounding of the primary endpoint of all-cause mortality. The majority of patients in the study population with substantial thromboembolic burden were on Warfarin. While patients on digoxin was indicative of atrial fibrillation coexisting with heart failure. Both comorbidities portent considerable additional mortality and inclusion of these two medicines allowed for atrial fibrillation and thromboembolic disease to be analysed as potential covariates for possible confounding of primary endpoint.

6.4. Statistical Considerations

6.4.1. Sample Size and Power

The SOLVD trial showed that enalapril reduced 4-year all-cause mortality from heart failure by 16% (RR 0.84; 95% CI 0.74 - 0.95; P=0.0036) when compared with placebo (95). Cardiovascular hospitalisation was also reduced by 10% (RR 0.90; P < 0.001). Mortality rate from heart failure extracted from North American and Scottish data was estimated at 28% adjusted for 1 year (194). Adjusting all-cause mortality reduction from the SOLVD trial for 1 year, and assuming a constant risk ratio, a two-sided P value of 0.05 and a sample size ratio of 1 for ACEI naïve to exposed groups, the study would need to recruit 1000 patients to have 85% power to detect a true change in all-cause mortality rate of 8% by ACEI treatment over one year (Appendix 12.8.2.).

6.4.2. Statistical Analysis

Baseline characteristics for ACEI exposed and unexposed patients at the first month of follow-up were compared using the mean and standard deviation for each group. Rates for all-cause death were calculated per 1000 person-years with associated 95% confidence limits.

The primary treatment comparisons between groups were performed according to the as-treated (AT) principle based on a time-to-event analysis. Patients were also censored for terminating ACEI and for switching to, or from another non-ACEI RAS inhibitor during the 3-year follow-up. Kaplan-Meier cumulative event rates were calculated for each group, with event or censored times measured from the time of incident diagnosis. These plots estimated probability for unadjusted all-cause mortality with and without ACEI exposure. Differences between curves were tested for significance by log-rank test. Kaplan-Meier plots were tested for the assumption of constant relative risk using log-minus-log plots. Relative risks were expressed as hazard ratios with associated 95% confidence intervals derived using the Cox proportional hazards model. The Cox models was also used for subgroup analysis to assess the consistency of treatment effect by testing for interactions between ACEI and the prespecified variables of background heart failure treatment, digoxin, warfarin and the Charlson comorbidity score (195). Each variable was tested individually for interaction using the enter method in SPSS. Hazard ratios from the main Cox regression model were adjusted for all prespecified variables together through simultaneous entry in a multivariable Cox model. This allowed analysis of the primary endpoint measure in a cohort that reflected a real-world population considering that these patients are typically on multiple medications for heart failure and have additional comorbidities. Two-sided significance testing was used with a conventional significance level of 0.05 and 95% confidence intervals.

The frequency of associated hospitalisation events during the 3-year follow-up period was checked as a dependent variable for normality distribution for each level of the independent variable of treatment with and without ACEI using the Shapiro-Wilk test. The null hypothesis for the Shapiro-Wilk test was that the scores in the dependent variable are normally distributed. Hospitalisation scores failed to meet the normality assumption for the t-test and a Mann-Whitney U test was conducted to analyse for differences in hospitalisation scores between the two groups in each cohort.

Four levels of sensitivity analysis were done to test for robustness of results. ACEI exposed and unexposed groups were compared for the values and proportions of missing laboratory values as well as the mean of plasma potassium, serum creatinine, eGFR, bilirubin and LVEF. The t-test or Mann-Whitney U test was used depending on the Shapiro-Wilk test for normality to identify potential confounding covariates leading to bias. Variables with significant P-values were tested with Cox regression interaction analysis to check for modification of effect of ACEI on mortality in the main Cox regression model.

Analysis using a falsification endpoint was performed for residual confounding (196, 197). Risk of outpatient pulmonary disease (asthma or chronic obstructive pulmonary disease) was selected as this was unlikely to be affected by treatment with or without the index drug. Unadjusted hazard ratios from the primary Cox regression model with AT analysis were compared with intention-to-treat and per-protocol analyses. This tested the robustness of association of ACEI exposed versus unexposed groups with mortality to measured and unmeasured confounding. The intention-to-treat analysis did not censor for patients at the time of discontinuation of ACEI or treatment switching and followed for 36 months post incident diagnosis. This preserved the baseline comparability and provided conservative estimates of differences between treatment groups. In the per-protocol analysis, patients with treatment switching involving ACEI were removed from the cohort (198).

Finally, follow-up analysis of post hoc sample power was done of the observed effect based on the actual cohort size and parameter estimates derived from the data set in view of the unequal patient allocation ratios between groups. (199).

All analysis was done for the two study arms for full cohort and independently for the cohort of patients aged ≥ 70 years at incident diagnosis which was taken as baseline. Additionally, unadjusted hazard ratios were determined for the positive control group of patients aged < 70 years at incident diagnosis. This control arm provided a direct comparison with the survival outcome of the other two study arms and allowed confirmation that the study still exhibited the same survival benefit as shown by landmark trials where mean age was below 70 years. Analysis included data of patients diagnosed between 2007 – 2017 and was done with SPSS version 26, Stata version 17, and PASS Pro 2021.

6.5. Results

6.5.1. Baseline Characteristics

Table 15 : Baseline comorbidities of full cohort – study 2

Disease	No ACEI %	ACEI %
Arrythmias	9.1	13.2
Cerebrovascular disease	4.5	2.8
Chronic kidney disease	6.6	5.1
Dementia	0.6	1
Diabetes	8.7	12.4
Hypertension	15.4	25
Genetic dyslipidaemia	3.3	6.9
Ischaemic heart disease	14.7	22.6
Malignant diseases	3	3.5
Peripheral vascular disease	2.1	2

Table 16 : Baseline comorbidities of cohort aged ≥ 70 years – study 2

Disease	No ACEI %	ACEI %
Arrythmias	9.5	13.9
Cerebrovascular disease	6.3	3.3
Chronic kidney disease	8.1	5.9
Dementia	0.9	1.5
Diabetes	10	12
Hypertension	16.7	25.3
Genetic dyslipidaemia	3.7	6.7
Ischaemic heart disease	16	22.8
Malignant diseases	3.7	4.2
Peripheral vascular disease	2.3	2.2

Table 17: Baseline characteristics for full cohort – study 2

Full cohort (N=2332) Characteristics	ACEI Arm (n=1670)	Unexposed Arm (n=662)
Diagnosis age (Yrs)		
Mean (Std. Deviation)	70.7 (9)	73.3 (9.7)
Median	70.6	74.2
Sex		
Males	1242 (74.4%)	449 (67.8%)
Females	428 (25.6%)	213 (32.2%)
LVEF %		
Mean (Std. Deviation)	33.9 (9.1)	34.5 (9)
Median	36.9	38.2
Charlson comorbidity score		
0	800 (47.9%)	331 (50%)
1	59 (3.5%)	21 (3.2%)
2 - 3	494 (29.6%)	194 (29.3%)
≥ 4	317 (19%)	116 (17.5%)
Background treatment		
Carvedilol	1004 (60.1%)	158 (23.9%)
Spironolactone	690 (41.3%)	121 (18.3%)
Nitrates + Hydralazine	18 (1.1%)	8 (1.2%)
Loop Diuretics	1364 (81.7%)	327 (49.4%)
Digoxin	341 (20.4%)	92 (13.9%)
Warfarin	653 (39.1%)	160 (24.2%)
HF Hospitalisation		
Total	2063	494
Mean (Std. Deviation)	1.24 (2.071)	0.75 (1.431)

Table 18: Baseline characteristics for cohort aged ≥ 70 years – study 2

Cohort aged ≥ 70 years (N=1312) Characteristics	ACEI Arm (n=882)	Unexposed Arm (n=430)
Diagnosis age (Yrs)		
Mean (Std. Deviation)	77.8 (7.8)	79.2 (5.6)
Median	77	79.5
Sex		
Males	615 (69.7%)	276 (64.2%)
Females	267 (30.3%)	154 (35.8%)
LVEF %		
Mean (Std. Deviation)	34.4 (8.7)	34.6 (8.9)
Median	37.7	38.3
Charlson comorbidity score		
0	436 (49.4%)	208 (48.4%)
1	28 (3.2%)	11 (2.6%)
2 - 3	245 (27.8%)	126 (29.3%)
≥ 4	173 (19.6%)	85 (19.8%)
Background treatment		
Carvedilol	486 (55.1%)	92 (21.4%)
Spironolactone	341 (38.7%)	75 (17.4%)
Nitrates + Hydralazine	11 (1.2%)	5 (1.2%)
Loop Diuretics	759 (86.1%)	222 (51.6%)
Digoxin	199 (22.6%)	65 (15.1%)
Warfarin	347 (39.3%)	103 (24%)
HF Hospitalisation		
Total	1134	352
Mean (Std. Deviation)	1.29 (2.010)	0.82 (1.448)

A total of 1670 patients (mean diagnosis age 70.7 ± 9 years) filling a prescription for an ACEI were identified while 662 patients (mean diagnosis age 73.3 ± 9.7 years) received no treatment for angiotensin blockade. The cohort for patients diagnosed at 70 years or more consisted of 882 patients (mean diagnosis age 77.8 ± 7.8 years) with ACEI therapy and 430 patients (mean diagnosis age 79.2 ± 5.6 years) without angiotensin blockade. The groups were balanced for most comorbidities at baseline except for diabetes, dyslipidaemia, hypertension and ischaemic heart disease. These were more common in the ACEI exposed group (Tables 15 and 16). Both groups were also balanced with respect to baseline characteristics including cardiac function except for background heart failure treatment and heart failure associated hospitalisation. Both characteristics were more common in the ACEI treatment groups for both cohorts (Tables 17 and 18).

6.5.2. Epidemiology: All-Cause Mortality

Table 19: Mortality rate and mortality rate ratio – study 2

Study	MR ACEI	MR Unexposed	MRR	95% Confidence interval	Two-sided p-value
Full cohort	0.114	0.238	0.480	0.415 - 0.555	< 0.0001
Cohort aged ≥70 years	0.157	0.284	0.553	0.465 - 0.657	< 0.0001

MR: Mortality rate per person-years
MRR: Mortality rate ratio

Of the 2332 patients included in the full cohort study, 793 had a fatal all-cause event during the follow-up period of 36 months post incident diagnosis. The mortality rate per 1000 person-years was 114 for the ACEI exposed and 238 for the angiotensin blockade naïve group. In the cohort of 1312 patients aged ≥ 70 years at baseline, 549 had a fatal all-cause event during the 3-year follow-up. The mortality rate per 1000 person-years was 157 for ACEI exposed patients and 284 for the angiotensin blockade naïve group. The mortality rate ratio of all-cause mortality for the comparison of the ACEI group to the angiotensin blockade naïve group was 0.480 (95% CI 0.415 to 0.555, P < 0.0001) In the full cohort and 0.553 (95% CI 0.465 to 0.657, P < 0.0001) in the cohort aged ≥ 70 years at baseline (Table 19).

6.5.3. Survival Analysis

6.5.3.1. Kaplan – Meier Estimates

6.5.3.1.1. Kaplan-Meier Plots

Figure 29: Kaplan-Meier plot for full cohort – study 2

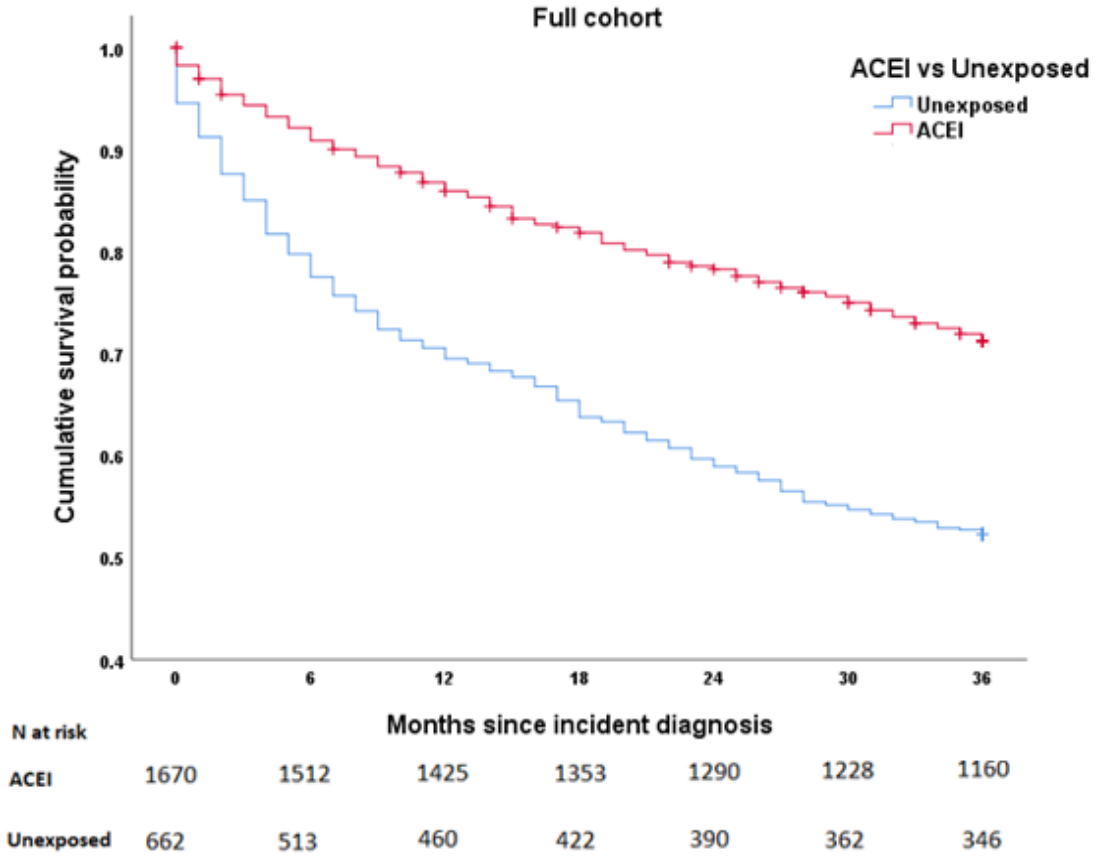


Table 20: Means for Survival Time (Months) for figure 29

ACEI vs Unexposed	Mean[a] Estimate	Std. Error	95% Confidence Interval Lower Bound	Upper Bound
Unexposed	24.029	.558	22.935	25.123
ACEI	29.885	.277	29.341	30.428

a. Estimation is limited to the largest survival time if it is censored.

Table 21: Log Rank test for figure 29

	Chi-Square	P-value
Log Rank (Mantel-Cox)	93.269	<0.0001

Figure 30: Kaplan-Meier plot for cohort aged ≥ 70 years – study 2

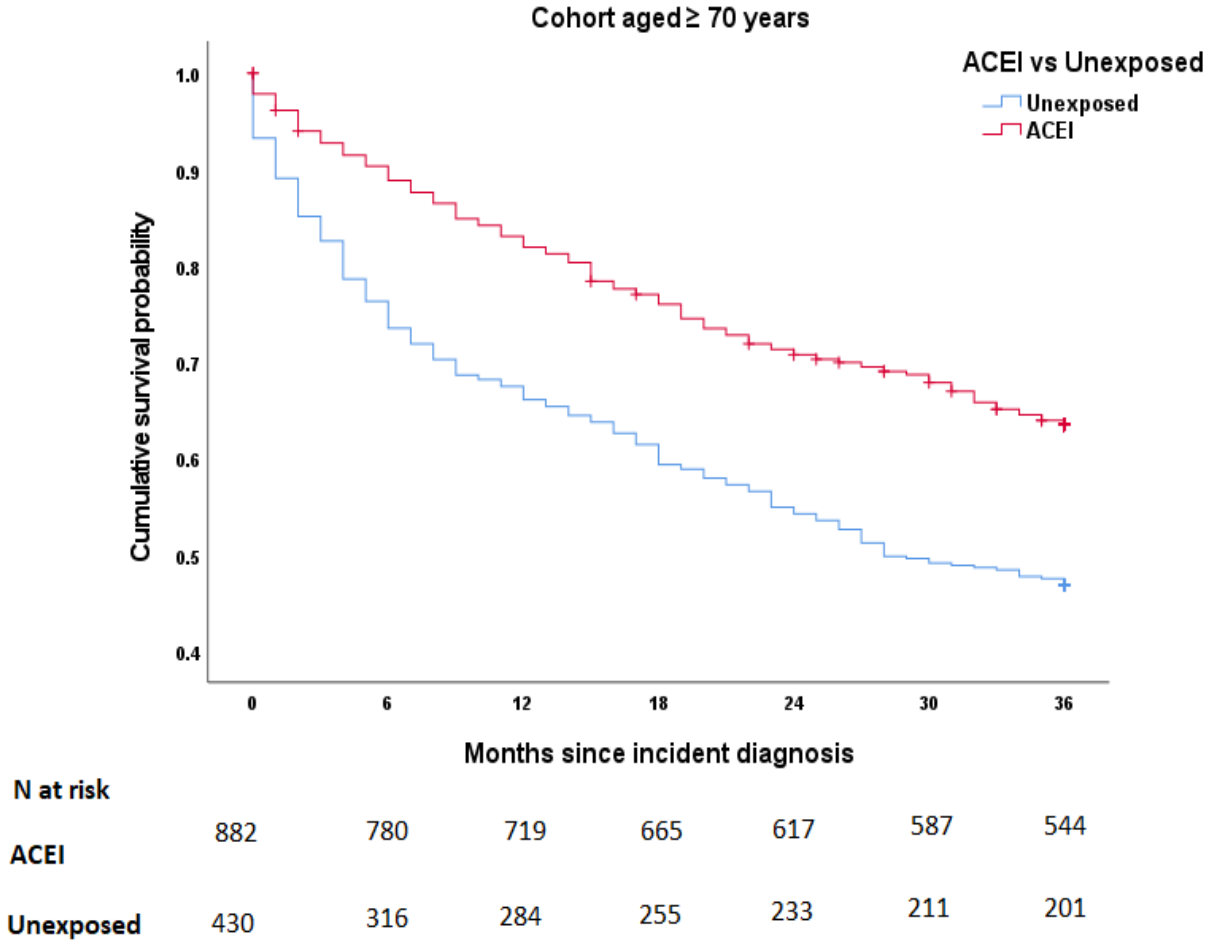


Table 22: Means for Survival Time (Months) for figure 30

ACEI vs Unexposed	Mean[a] Estimate	Std. Error	95% Confidence Interval Lower Bound	Upper Bound
Unexposed	22.535	.707	21.148	23.922
ACEI	28.057	.415	27.244	28.870

a. Estimation is limited to the largest survival time if it is censored.

Table 23: Log Rank test for figure 30

	Chi-Square	P-value.
Log Rank (Mantel-Cox)	43.061	<0.001

Figure 31: Full cohort composite Kaplan-Meier plot – study 2

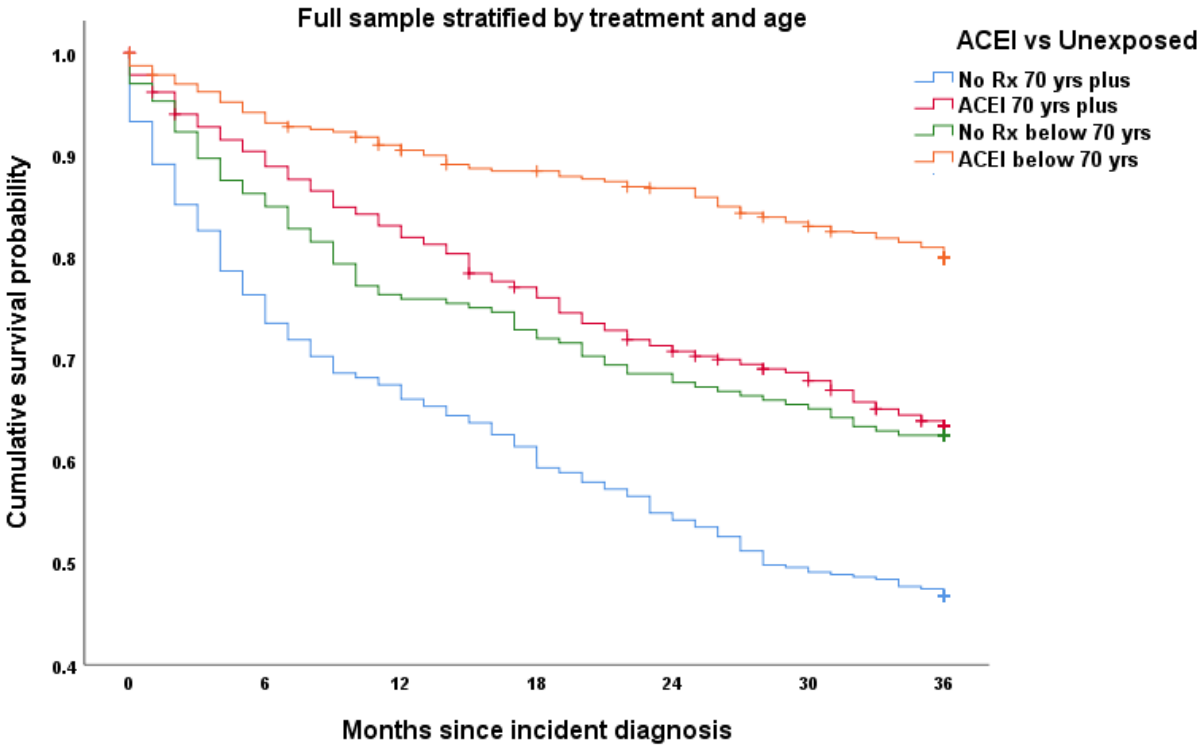


Table 24: Means for Survival Time (Months) for figure 31

Study Arm	Mean[a] Estimate	Std. Error	95% Confidence Interval Lower Bound	Upper Bound
Unexposed ≥ 70 years	22.535	.707	21.148	23.922
ACEI ≥ 70 years	28.057	.415	27.244	28.870
Unexposed below 70	26.797	.875	25.082	28.512
ACEI below 70	31.933	.347	31.252	32.613

a. Estimation is limited to the largest survival time if it is censored.

Table 25: Log Rank test with pairwise comparisons for figure 31

	Log Rank (Mantel-Cox)			
	ACEI exposed ≥ 70 years		ACEI exposed below 70 years	
Study Arm	Chi-Square	P-value	Chi-Square	P-value
Unexposed ≥ 70 years	43.061	<0.0001		
Unexposed below 70 years			34.865	<0.0001

The decrease in the probability of survival followed the same pattern with time for the ACEI exposed and unexposed group in the full cohort analysis and in the cohort aged ≥70 years at incident diagnosis but the rate of decline was much steeper for the unexposed group in both cohorts. This distinction became evident within the first 3 months of follow-up. The 3-year

cumulative survival probabilities were 71.4% in the ACEI exposed versus 52.3% in the unexposed group for the full cohort (P < 0.001) and 63.7% in the ACEI group versus 46.7% in the unexposed group for the cohort aged ≥70 years at incident diagnosis (P < 0.001) (Figures 29 and 30). The results of the log-rank tests indicated that the highly statistically significant difference in survival observed in the full cohort was also exhibited in the cohort aged ≥70 years at incident diagnosis. In patients with incident diagnosis age < 70 years the 3-year cumulative survival probability was 80.1% for ACEI exposed compared to 62.5% for unexposed patients (P < 0.001).

6.5.3.1.2. Log-minus-Log plots of Kaplan-Meier estimation

Figure 32: Log-minus-log plot for Kaplan-Meier estimation – full cohort – study 2

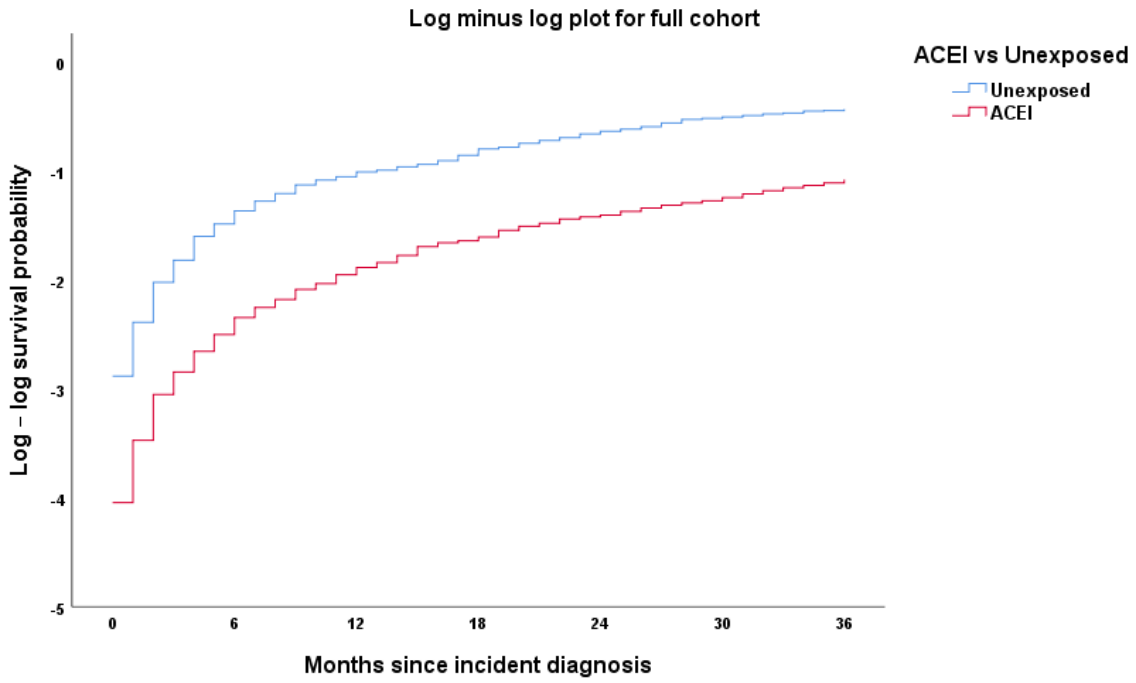
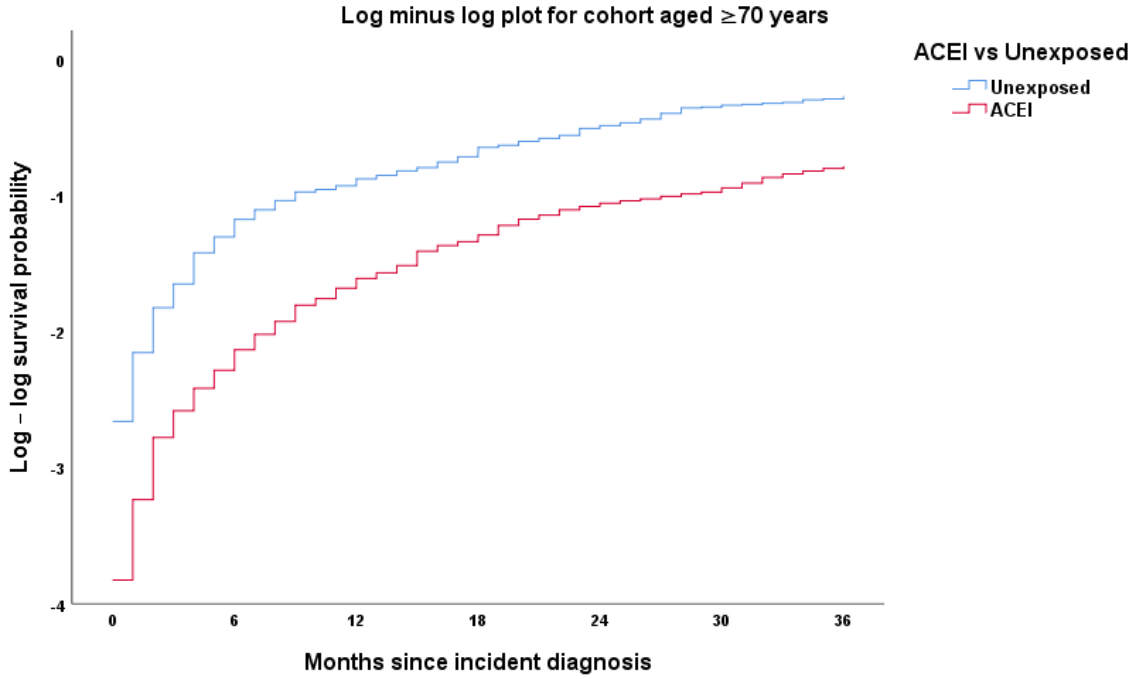


Figure 33: Log-minus-log plot for Kaplan-Meier estimation – cohort aged ≥ 70 years – study 2



Log-minus-log plots were used to test the assumption of constant relative risk. The log-rank test in Kaplan-Meier plots uses this assumption when comparing survival curves between two groups. This means that the risk of mortality in one group relative to the other does not change with time. Log-minus-log plots for full cohort analysis and for the cohort aged ≥ 70 years showed that the two curves do not meet and are parallel during the follow-up period. Therefore, in both cohorts the proportional hazards assumption was not violated. This means that the survival probabilities were the same for patients throughout the 3-year follow-up period (Figures 32 and 33).

6.5.3.2. Cox Proportional Hazards Regression Analysis

6.5.3.2.1. Main model

Table 26: Cox regression for full cohort and cohort aged ≥ 70 years – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
Full cohort	-.683	<0.001	.505	.438	.582
Cohort ≥ 70 years	-.556	<0.001	.573	.484	.679

Table 27: Cox regression for age ≥ 70 years exposed vs age < 70 years exposed – study 2

B	P-value	HR	95.0% CI for HR Lower	Upper
.707	<0.001	2.029	1.676	2.456

In the full cohort analysis, the hazard ratio of mortality in the ACEI exposed group was 0.505 compared to the unexposed group (P < 0.001, 95% CI = 0.438 – 0.582). In the cohort aged ≥ 70 years at baseline, the hazard ratio of mortality in the ACEI exposed group was 0.573 compared to the unexposed group (P < 0.001, 95% CI = 0.484 – 0.679) (Table 26). In the ACEI exposed group, the hazard ratio of mortality in patients aged ≥70 years at baseline was 2.029 compared to patients aged <70 years at incident diagnosis (P < 0.001, 95% CI = 1.676 – 2.456) (Table 27).

This means that in the full cohort analysis, ACEI lowered mortality by 49.5% compared to the unexposed group while in the cohort aged ≥ 70 years, ACEI lowered mortality by 42.7% compared to the unexposed group. Within the ACEI exposed group, the risk of mortality in patients aged ≥ 70 years at baseline doubled compared to patients with an incident diagnosis age < 70 years. All hazard ratios were highly statistically significant during the 3-year follow-up.

6.5.3.2.2 Positive Control Arm

Survival analysis was done for the cohort aged below 70 years at baseline. This group was analysed separately with and without treatment exposure.

Table 28: Cox regression for cohort aged < 70 years – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI vs Unexposed	-.768	< 0.001	.464	.357	.603

The Hazard ratio of mortality in the ACEI exposed group was 0.464 compared to the unexposed group (P < 0.001, 95% CI = 0.357 – 0.603) (Table 28). This means that in patients with a diagnosis age below 70 years, ACEI potentially lowered mortality by 53.6% compared to the unexposed group. The hazard ratio was highly statistically significant.

6.5.3.3. Cox Regression Interaction Analysis

The effect of ACEI versus unexposed on all-cause mortality was further analysed for statistical significance of interaction with various potential covariates that may lead to modification of the result obtained in the main Cox proportional hazard model. Selected variables were analysed separately to obtain hazard ratios of ACEI versus unexposed with each variable. Statistical significance of difference within these hazard ratios was analysed with the formation of interaction terms for each variable. The procedure was repeated for full cohort analysis and for patients aged ≥70 years at incident diagnosis.

Table 29: ACEI vs Unexposed layered by Carvedilol / Spironolactone – full cohort – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
No Carvedilol / Spironolactone	-.576	<0.001	.562	.468	.675
Carvedilol only	-.961	<0.001	.383	.251	.583
Spironolactone only	-.455	.041	.635	.410	.982
Carvedilol and Spironolactone	-1.086	<0.001	.338	.201	.568

Table 30: Interaction terms for Carvedilol / Spironolactone – full cohort – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI*No Carvedilol / Spironolactone		.134			
ACEI*Carvedilol only	-.354	.129	.702	.444	1.109
ACEI*Spironolactone only	.152	.529	1.164	.726	1.867
ACEI*Carvedilol and Spironolactone	-.468	.095	.626	.361	1.085

Table 31: ACEI vs Unexposed layered by Carvedilol / Spironolactone – age ≥ 70 years – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
No Carvedilol / Spironolactone	-.524	<0.001	.592	.477	.736
Carvedilol only	-.557	.032	.573	.345	.953
Spironolactone only	-.177	.506	.838	.496	1.413
Carvedilol and Spironolactone	-.917	.008	.400	.202	.791

Table 32: Interaction terms for Carvedilol / Spironolactone – age ≥ 70 years – study 2

	B	P-Value	HR	95.0% CI for HR Lower	Upper
ACEI*No Carvedilol / Spironolactone		.417			
ACEI*Carvedilol only	-.004	.990	.996	.574	1.731
ACEI*Spironolactone only	.360	.212	1.434	.814	2.525
ACEI*Carvedilol and Spironolactone	-.356	.329	.700	.343	1.432

Table 33: ACEI vs Unexposed layered by Digoxin– Full cohort – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
Digoxin	-.543	.006	.581	.395	.854
No Digoxin	-.692	<0.001	.501	.429	.584

Table 34: Interaction terms for Digoxin – Full cohort – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI*Digoxin	-.162	.444	.851	.562	1.287

Table 35: ACEI vs Unexposed layered by Digoxin – age ≥ 70 years – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
Digoxin	-.548	.013	.578	.375	.891
No Digoxin	-.538	<.001	.584	.485	.703

Table 36: Interaction terms for Digoxin – age ≥ 70 years – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI*Digoxin	-.009	.970	.991	.619	1.586

Table 37: ACEI vs Unexposed layered by Warfarin – Full cohort – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
No Warfarin	-.673	<0.001	.510	.434	.600
Warfarin	-.406	.013	.666	.483	.919

Table 38: Interaction terms for Warfarin – Full cohort – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI*Warfarin	.285	.120	1.330	.928	1.906

Table 39: ACEI vs Unexposed layered by Warfarin – age ≥ 70 years – study 2

	B	P-Value	HR	95.0% CI for HR Lower	Upper
No Warfarin	-.531	<0.001	.588	.484	.714
Warfarin	-.335	.079	.716	.492	1.040

Table 40: Interaction terms for Warfarin – age ≥ 70 years – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI*Warfarin	.214	.319	1.239	.813	1.887

Table 41: ACEI vs Unexposed layered by Charlson Score – Full cohort – study 2

Charlson Score	B	P-value	HR	95.0% CI for HR Lower	Upper
0	-.616	<0.001	.540	.441	.661
1	-1.139	.072	.320	.093	1.106
2 to 3	-.747	<0.001	.474	.355	.631
≥ 4	-.809	<0.001	.446	.333	.596

Table 42: Interaction terms for Charlson Score – Full cohort – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI*Charlson Score 0		.629			
ACEI*Charlson Score 1	-.552	.389	.576	.164	2.021
ACEI*Charlson Score 2 to 3	-.121	.498	.886	.624	1.258
ACEI*Charlson Score ≥ 4	-.184	.307	.832	.585	1.184

Table 43: ACEI vs Unexposed layered by Charlson Score – age ≥ 70 years – study 2

Charlson Score	B	P-value	HR	95.0% CI for HR Lower	Upper
0	-.471	<0.001	.625	.489	.798
1	-.565	.439	.568	.136	2.381
2 to 3	-.627	<0.001	.534	.381	.750
≥ 4	-.696	<0.001	.498	.354	.701

Table 44: Interaction terms for Charlson Score – age ≥ 70 years – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI*Charlson Score 0		.755			
ACEI*Charlson Score 1	-.116	.876	.891	.208	3.805
ACEI*Charlson Score 2 to 3	-.151	.477	.859	.566	1.305
ACEI*Charlson Score ≥ 4	-.218	.308	.804	.529	1.222

All hazard ratios for individual variables indicated different probabilities of significant reduction in mortality with ACEI except with a Charlson score of 1 for both cohorts and in the spironolactone and warfarin subgroups for the cohort aged ≥ 70 years at baseline (Tables 29, 31, 33, 35, 37, 39, 41, 43). The absence of statistical significance of hazard ratios for all interaction terms within each variable in both cohorts indicated that none of the selected variables exhibited evidence of interaction effect for modification of ACEI influence on all-cause mortality (Tables 30, 32, 34, 36, 38, 40, 42, 44) (page 102 Figures 34 and page 103 figure 35).

Figure 34: Endpoint subgroup analysis for interaction (as treated) full cohort – study 2

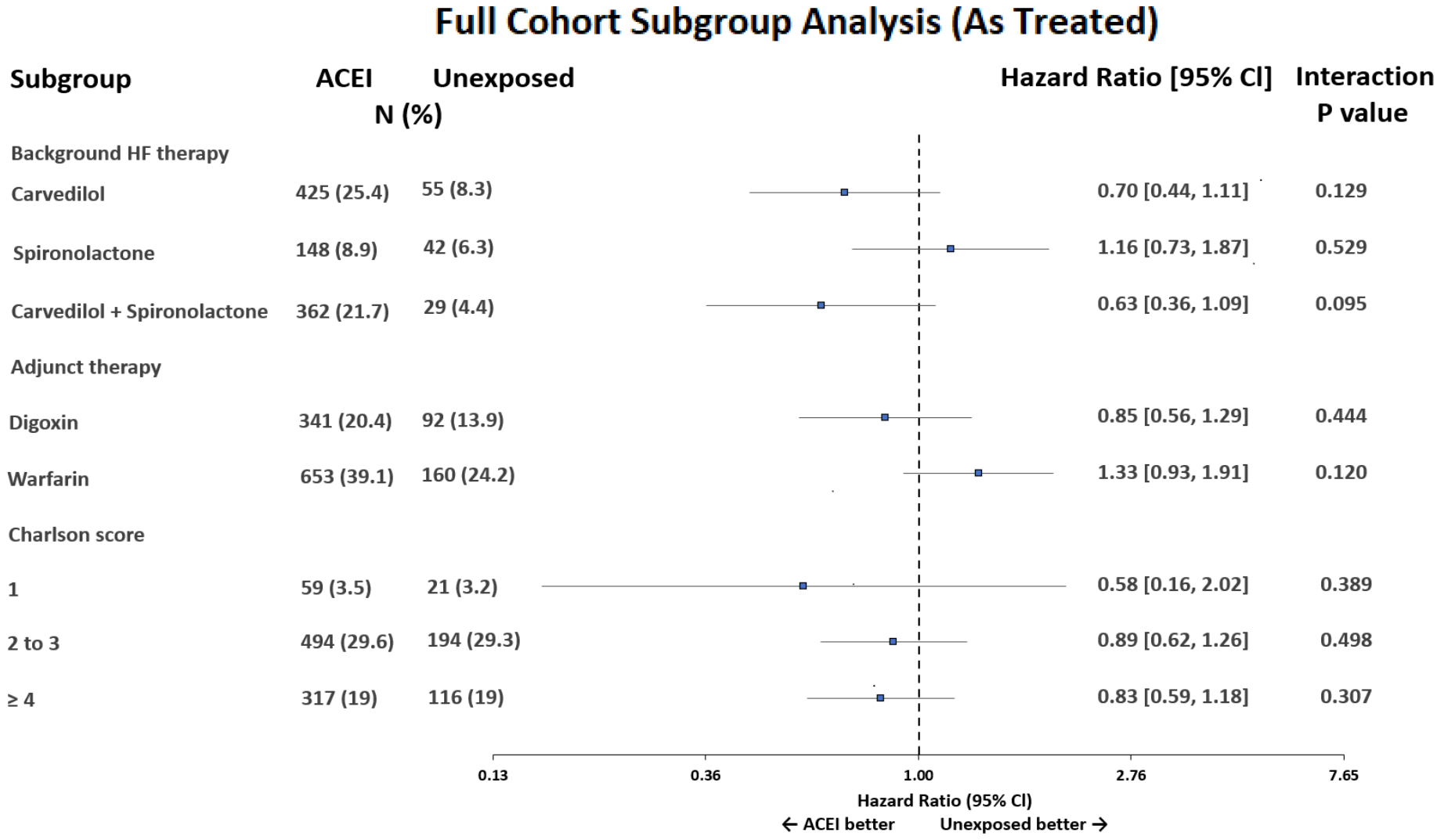
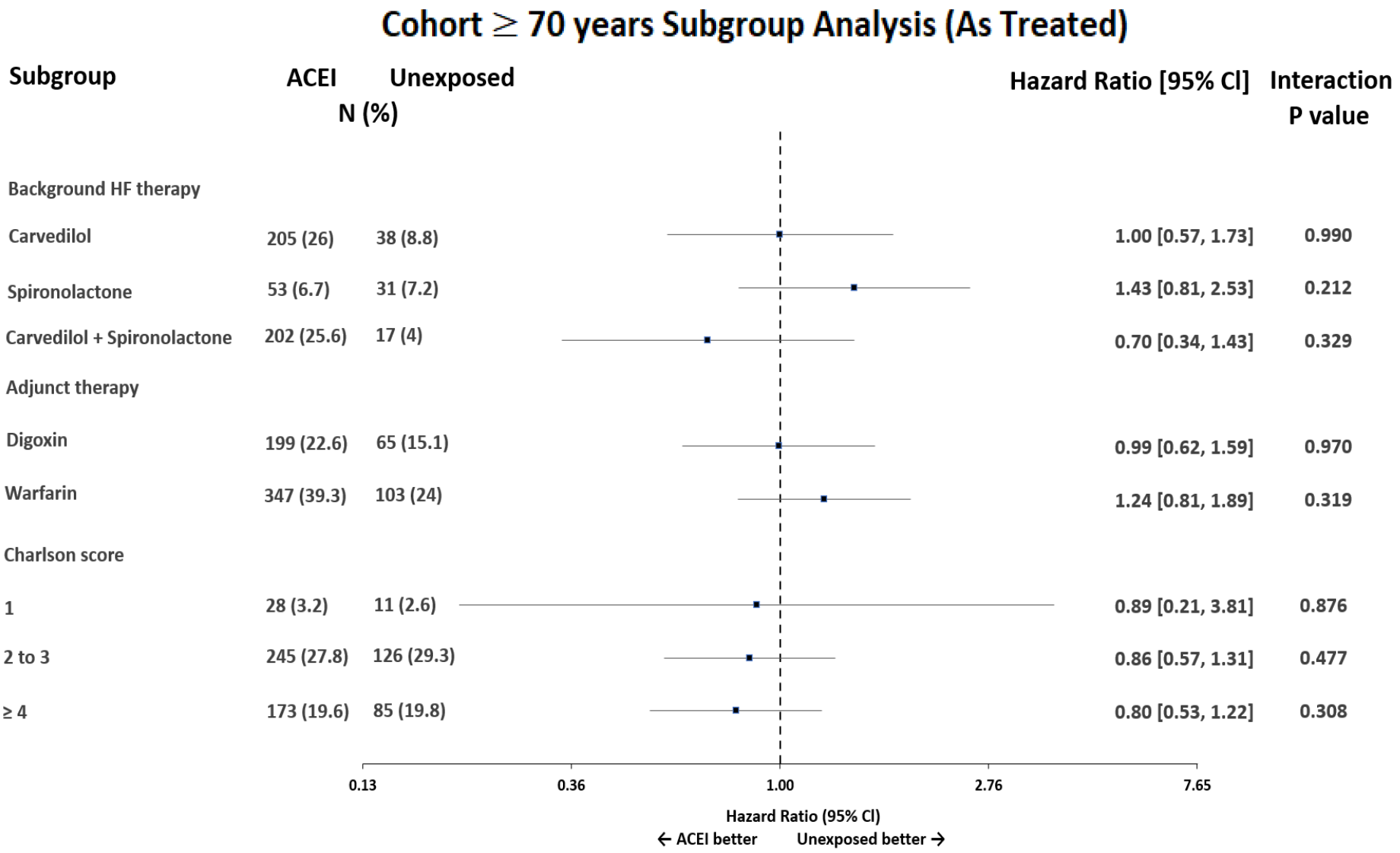


Figure 35: Endpoint subgroup analysis for interaction (as treated) cohort aged ≥ 70 years – study 2



The effect of ACEI was consistent across all subgroups for the two cohorts. Examination of prespecified subgroups based on background therapy and comorbidity characteristics across both cohorts did not identify a nominally significant interaction between any of the prespecified variables and the effect of ACEI on all-cause mortality (page 102 Figures 34 and page 103 figure 35). This excluded relative variations in the effect of ACEI, large enough to be clinically significant while also possessing sufficient precision to exclude the null effect (i.e., HR, 1). However, this does not completely exclude the prespecified variables as possible confounders by acting collectively to cause effect modification of ACEI on mortality. Therefore, multivariable Cox regression was used to investigate this effect through a model incorporating all potential covariates identified that may simultaneously influence all-cause mortality and hence require adjusted hazard ratios (Tables 45 and 46).

6.5.3.3.1. Multivariable Cox Regression Model with Adjusted Hazard Ratios

Table 45: Adjusted hazard ratio for ACEI vs Unexposed - Full cohort – study 2

	B	P-value	Adjusted HR	95.0% CI for HR Lower	Upper
ACEI vs Unexposed	-.611	<0.001	.543	.465	.633
No Carvedilol/Spironolactone		<.001			
Carvedilol only	-.195	.064	.823	.669	1.011
Spironolactone only	.677	<.001	1.967	1.577	2.454
Carvedilol and Spironolactone	-.099	.384	.906	.725	1.132
Digoxin	.015	.887	1.015	.826	1.248
Warfarin	-.572	<.001	.564	.474	.672
Charlson score 0		<.001			
Charlson score 1	-1.018	.002	.361	.193	.678
Charlson score 2 to 3	-.295	<.001	.745	.626	.886
Charlson score ≥ 4	.380	<.001	1.462	1.230	1.736

Table 46: Adjusted hazard ratio for ACEI vs Unexposed – age ≥ 70 years – study 2

	B	P-value	Adjusted HR	95.0% CI for HR Lower	Upper
ACEI vs Unexposed	-.463	<0.001	.629	.525	.755
No Carvedilol/Spironolactone		<0.001			
Carvedilol only	-.203	.104	.816	.639	1.042
Spironolactone only	.541	<.001	1.718	1.325	2.228
Carvedilol and Spironolactone	-.181	.223	.835	.624	1.116
Digoxin	.069	.569	1.072	.844	1.361
Warfarin	-.538	<.001	.584	.475	.719
Charlson score 0		<.001			
Charlson score 1	-.640	.075	.527	.260	1.067
Charlson score 2 to 3	-.217	.040	.805	.655	.991
Charlson score ≥ 4	.376	<.001	1.456	1.184	1.790

6.5.3.3.2. Summary of Hazard Ratios

Table 47: Summary of adjusted and unadjusted hazard ratios (as treated) – study 2

Study	Unadjusted HR	P-value	95.0% CI for Unadjusted HR Lower	Upper	Adjusted HR	P-value	95.0% CI for Adjusted HR Lower	Upper
ACEI vs Unexposed Full cohort	0.505	<0.001	0.438	0.582	0.543	<0.001	0.465	0.633
ACEI vs Unexposed Cohort aged ≥ 70 years	0.573	<0.001	0.484	0.679	0.629	<0.001	0.525	0.755

Adjusted hazard ratios for the full cohort and for patients aged ≥ 70 years at incident diagnosis were comparable with the original hazard ratios from the main survival model while all P-values did not change. This means that background heart failure treatment associated with improved survival in HFrEF (Carvedilol and Spironolactone), adjunct treatment (Digoxin, Warfarin) indicative of atrial fibrillation or thromboembolic burden, and additional comorbidities were not confounding effects in the full cohort analysis. This result persisted even when adjusting for age ≥ 70 years at incident diagnosis (Table 47).

6.5.4. Hospitalisation

The frequency of hospitalisation events during the 3-year follow-up period was checked as a dependent variable for normality distribution for each level of the independent variable of treatment with and without ACEI using the Shapiro-Wilk test. Analysis was done for the full cohort and for patients aged ≥70 years at incident diagnosis. The null hypothesis was that the scores in the dependent variable are normally distributed.

Table 48: Tests of Normality – Full cohort – study 2

ACEI vs Unexposed	P-value
Unexposed	<.0001
ACEI	<.0001

Table 49: Tests of Normality – Age ≥ 70 years – study 2

ACEI vs Unexposed	P-value
Unexposed	<.0001
ACEI	<.0001

In both cohorts the Shapiro-Wilk test was highly significant (P = < 0.0001) which rejected the null hypothesis (Tables 48 and 49). Therefore, hospitalisation scores failed to meet the normality assumption for the t-test and a Mann-Whitney U test was conducted to analyse for differences in hospitalisation scores between the two groups in each cohort.

Table 50: Ranks – Full cohort – study 2

ACEI vs Unexposed	N	Mean Rank	Sum of Ranks
Unexposed	662	1031.09	682578.50
ACEI	1670	1220.18	2037699.50

Table 51: Test Statistics[a] – Full cohort – study 2

	Hosp Admissions
Mann-Whitney U	463125.500
Wilcoxon W	682578.500
Z	-6.687
Asymp. Sig. (2-tailed)	<.0001

a. Grouping Variable: ACEI vs Unexposed

Table 52: Ranks – Age ≥ 70 years – study 2

ACEI vs Unexposed	N	Mean Rank	Sum of Ranks
Unexposed	430	585.71	251854.50
ACEI	882	691.01	609473.50

Table 53: Test Statistics – Age ≥ 70 years – study 2

	Hosp Admissions
Mann-Whitney U	159189.500
Wilcoxon W	251854.500
Z	-5.114
Asymp. Sig. (2-tailed)	<.0001

a. Grouping Variable: ACEI vs Unexposed

Table 54: ACEI Effect size statistic – study 2

	Z^2	N	R^2
Full cohort	44.716	2332	0.019
Cohort ≥ 70 years	26.153	1312	0.020

The ACEI exposed group in the full cohort exhibited a higher number of hospitalisation scores compared to the unexposed group and this result was consistent in the cohort aged ≥70 years at incident diagnosis (Tables 50 and 52). The difference of hospitalisation scores between ACEI exposed and unexposed groups was highly significant in the full cohort analysis (P < 0.0001) and in the cohort aged ≥ 70 years at incident diagnosis age (P < 0.0001) (Tables 51 and 53). However only 1.9% of variance in hospitalisation can be explained by the independent variable in the full cohort analysis. The effect size was also weak in the cohort aged ≥ 70 years at incident diagnosis where only 2% of variance in hospitalisation can be explained by the independent variable (Table 54).

6.5.5. Sensitivity Analysis

6.5.5.1. Comparison of Groups

Renal disease was the only factor that was significantly different between the ACEI exposed and unexposed groups as indicated by the eGFR and serum creatinine. This observation was consistent for the full cohort analysis (Cr: P= < 0.001; eGFR: P= < 0.001) and for the cohort aged ≥70 years at incident diagnosis (Cr: P= 0.001; eGFR: P= < 0.001) (page 108 Tables 55 and 56). The possibility of renal disease as a potential confounding covariate leading to bias was tested as part of the Charlson comorbidity score interaction analysis with a non-significant P value with no effect modification on all-cause mortality (page 102 Figures 34 and page 103 figure 35). The Charlson comorbidity score was also included in the Cox multivariable model and the adjusted hazard ratio did not change from the unadjusted hazard ratio that resulted from the main Cox regression model (Table 47).

Table 55: Comparison of groups for full cohort – study 2

Diagnostic test	(n) Missing values		(%) Missing values		Mean (Std. Deviation)		P value
	ACEI Arm (n=1670)	Unexposed Arm (n=662)	ACEI Arm (n=1670)	Unexposed Arm (n=662)	ACEI Arm (n=1670)	Unexposed Arm (n=662)	
Potassium mmol/L	1371	528	82.1	79.8	4.688 (0.587)	4.639 (0.601)	0.717
Creatinine umol/L	1371	528	82.1	79.8	108.02 (88.883)	129.56 (120.966)	<0.001
eGFR mL/min/1.73m2	1371	528	82.1	79.8	70.55 (25.844)	64.47 (29.467)	<0.001
Bilirubin umol/L	1371	528	82.1	79.8	14.48 (11.221)	16.71 (18.57)	0.541
LVEF %	N/A	N/A	N/A	N/A	33.9 (9.1)	34.5 (9)	0.024

Table 56: Comparison of groups for cohort aged ≥ 70 years – study 2

Diagnostic test	(n) Missing values		(%) Missing values		Mean (Std. Deviation)		P value
	ACEI Arm (n=882)	Unexposed Arm (n=430)	ACEI Arm (n=882)	Unexposed Arm (n=430)	ACEI Arm (n=882)	Unexposed Arm (n=430)	
Potassium mmol/L	742	349	84.1	81.2	4.633 (0.605)	4.607 (0.611)	0.059
Creatinine umol/L	742	349	84.1	81.2	110.436 (57.140)	111.79 (55.982)	0.001
eGFR mL/min/1.73m2	742	349	84.1	81.2	62.65 (22.622)	64.27 (30.043)	<0.001
Bilirubin umol/L	742	349	84.1	81.2	14.13 (10.609)	15.8 (17.571)	0.383
LVEF %	N/A	N/A	N/A	N/A	34.4 (8.7)	34.6 (8.9)	0.443

N/A: Not applicable

6.5.5.2. False Endpoint Analysis

Table 57: ACEI vs Unexposed – False endpoint analysis – study 2

	B	P-value	HR	95.0% CI for HR Lower	Upper
Full cohort	1.288	.080	3.625	.857	15.338
Cohort aged ≥ 70 years	.568	.261	1.765	.655	4.755

No difference in risk of pulmonary disease was observed in patients treated with ACEI versus the unexposed group both in the full cohort analysis (HR: 3.625, 95% CI: 0.857 to 15.338; P = 0.080) and in the cohort aged ≥70 years at incident diagnosis (HR: 1.765, 95% CI: 0.655 to 4.755; P = 0.261) (Table 57).

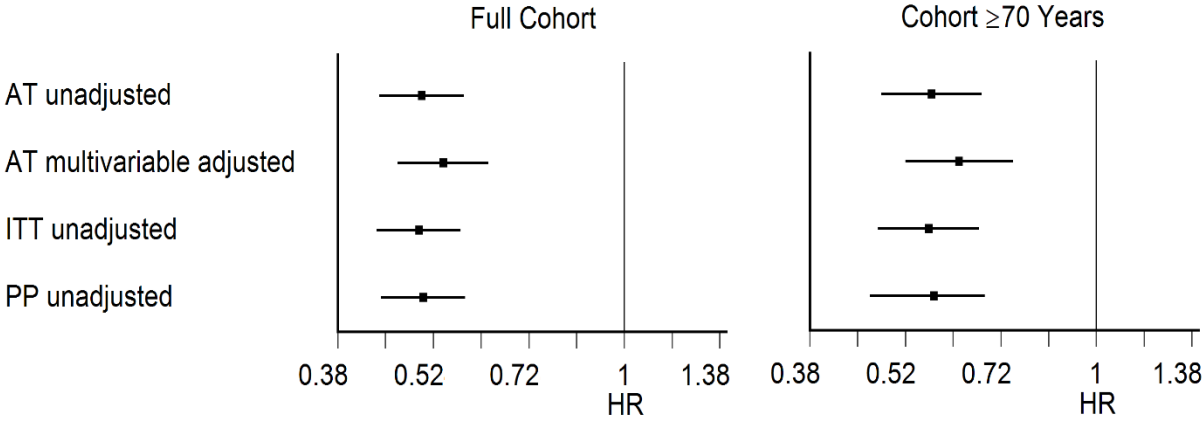
6.5.5.3. Comparison with Intention-to-Treat and Per Protocol designs

Table 58: Hazard ratios for as treated, intention-to-treat and per protocol analysis – study 2

Cox regression model	Full cohort			Cohort ≥70 years		
	HR	CI (95%)	P value	HR	CI (95%)	P value
AT Unadjusted	0.505	0.438 – 0.582	<0.001	0.573	0.484 – 0.679	<0.001
AT Multivariable Adjusted	0.543	0.465 – 0.633	<0.001	0.629	0.525 – 0.755	<0.001
ITT Unadjusted	0.500	0.434 – 0.576	<0.001	0.568	0.479 – 0.673	<0.001
PP Unadjusted	0.507	0.440 – 0.585	<0.001	0.578	0.466 – 0.686	<0.001

AT: As treated ITT: Intention-to-treat PP: Per protocol

Figure 36: Forest plots for table 58



Sensitivity analysis showed that hazard ratios under different analytical approaches were qualitatively consistent with the results of the primary Cox regression model of as-treated (AT) analysis. The hazard ratio estimates for the endpoint of all-cause mortality varied minimally under different study methods within the same cohort. The variations for the hazard ratio estimates were also similar and compared with the primary Cox regression model. All p-values remained highly significant and comparable as well. (page 109 Table 58 and Figure 36). This shows that the association of ACEI exposed versus unexposed groups with the outcome of reduced all-cause mortality was robust to most scenarios of measured and unmeasured confounding.

6.5.5.4. Post Hoc Sample Power Analysis

6.5.5.4.1. Survival Analysis

Post hoc power analysis for survival was done by applying study parameters including the cohort size and patient allocation ratio of ACEI group to unexposed group and using the two-sample comparison of the main Cox regression model (200, 201). The analysis was done for the full cohort and for the cohort aged ≥ 70 years at baseline.

Table 59: Post hoc sample power estimation for all-cause mortality – study 2

Cohort	alpha	N	n1	n2	n2/n1	HR	Power %
Full cohort	0.05	2332	662	1670	2.523	0.505	100
Cohort aged ≥ 70 years	0.05	1312	430	882	2.051	0.573	100

n1: Unexposed group n2: ACEI group

Analysis achieved 100% power at a 0.05 significance level to detect a minimum, true change in all-cause mortality where ACEI decreased mortality by 49.5% in the full cohort and 42.7% in the cohort aged ≥70 years at incident diagnosis compared to the unexposed group over 3 years (Table 59).

6.5.5.4.2. Hospitalisation Analysis

Post hoc power analysis for hospitalisation was done by applying study parameters including the cohort size and patient allocation ratio of ACEI group to unexposed group and using the two-sample comparison of the Mann-Whitney U test (202, 203, 204, 205). The analysis was done for the full cohort and the cohort aged ≥ 70 years at baseline.

Table 60: Post hoc sample power estimation for hospitalisation – study 2

Cohort	alpha	N	n1	n2	μ1	μ2	μ1 − μ2	Std. Dev.	Power %
Full cohort	0.05	2332	1670	662	1.24	0.75	0.49	0.05	100
Cohort aged ≥ 70 years	0.05	1312	882	430	1.29	0.82	0.47	0.07	100

n1: Unexposed group n2: ACEI group μ: Mean hospitalisation

The full cohort achieved 100% power to detect a true difference in observed mean hospitalisation of μ1 – μ2 = 1.24 – 0.75 = 0.49 using a two-sided Mann-Whitney U test assuming that the actual data distribution is logistic when the significance level (alpha) of the test is 0.05 and the population standard deviation is 0.05 in both groups (table 60).
The cohort aged ≥70 years at incident diagnosis achieved 100% power to detect a true difference in observed mean hospitalisation of μ1 – μ2 = 1.29 – 0.82 = 0.47 using a two-sided Mann-Whitney U test assuming that the actual data distribution is logistic when the significance level (alpha) of the test is 0.05 and the population standard deviation is 0.07 in both groups (Table 60).

6.6. Discussion

6.6.1. Main Findings

In this retrospective, all inclusive, population based research involving patients with heart failure and a reduced left ventricular ejection fraction, the risk of the primary outcome of all-cause mortality was lower in the ACEI group than in the unexposed group (Tables 26). In the full cohort, ACEI demonstrated a statistically significant improvement over the unexposed group, with a 49.5% reduction in risk of all-cause mortality (HR 0.505; 95% CI: 0.438 to 0.582; P < 0.001) and a 36-month improvement in mean survival post incident diagnosis (29.9 months; 95% CI 29.3 to 30.4) compared to the unexposed group (24 months; 95% CI 22.9 to 25.1). In the cohort aged ≥ 70 years at incident diagnosis, ACEI also demonstrated a statistically significant improvement over the unexposed group, with a 42.7% reduction in risk of all-cause mortality (HR 0.573; 95% CI: 0.484 to 0.679; P < 0.001) and a 36-month improvement in mean survival post incident diagnosis (28.1 months; 95% CI 27.2 to 28.9) compared to the unexposed group (22.5 months; 95% CI 21.1 to 23.9).
ACEI exposure was similarly effective in patients diagnosed at ≥ 70 years as in the general patient population with HFrEF including those diagnosed at < 70 years of age (Tables 26 and 28). This benefit was statistically highly significant and remained constant throughout the 3-year follow-up post first diagnostic echocardiogram. This demonstration of survival benefit of ACEI in patients diagnosed at ≥70 years provides support for prior suggestions that this treatment has survival benefit in geriatric heart failure patients with reduced ejection

fraction comparable to younger patients (64, 206).Therefore, this study provides evidence for the therapeutic role of ACEI in patients with HFrEF beyond the age of 70 years.

The lowering of all-cause mortality was generally homogenous across most of the prespecified subgroups for both cohorts, although three comparisons suggested possible heterogeneity with no benefit in the subgroups for Charlson score 1 subgroup for both cohorts and in the spironolactone and warfarin subgroups for the cohort aged ≥ 70 years at baseline (Tables 31, 39, 41, 43). However, it is inappropriate to assess the effects of treatment on a single subgroup by examination of the 95% CI for that subgroup and the general principle is that subgroup analysis should concentrate on differences from the average overall treatment effect via tests of interaction (207). Subgroup analysis showed no interaction between the reduction of all-cause mortality and the various prespecified variables in the full cohort (Figure 34). The absence of effect modification of ACEI on all-cause mortality persisted in patients aged ≥ 70 years at incident diagnosis including Charlson comorbidity scores (Figure 35). Geriatric patients are more susceptible to developing additional comorbidities and further compound the risks of heart failure that are enhanced with the onset of advanced age (208, 209). The presence of digoxin or warfarin was indicative of existing atrial fibrillation or substantial thromboembolic burden. Both conditions portend considerable additional mortality however ACEI still maintained a high beneficial effect (Tables 34, 36, 38, 40). Furthermore, the higher survival associated with ACEI was not influenced by prespecified background therapy that may have modified the beneficial effect size (Tables 30 and 32). The absence of effect modification suggests that the estimated hazard ratios indicated the true size of independent survival benefit inherent in ACEI therapy for both cohorts with respect to interaction with other heart failure therapy even for patients aged ≥70 years at diagnosis. This observation was further strengthened by the comparability of unadjusted to adjusted hazard ratios despite adjustment for all prespecified variables and for diagnosis age ≥ 70 years (Tables 47 and 58) (Figure 36). This study was highly powered to detect these differences in the primary endpoint of all-cause mortality outcome between the ACEI exposed and unexposed groups (Table 59). This validated the observation of informative differences between the groups across the entire cohort and also within the subgroup of patients with ≥70 years diagnosis age.

There is no dispute that ACEI are core RAS inhibitors for heart failure based on at least two landmark, randomized trials showing this treatment reduced mortality even when added to other heart failure therapy (62, 95). Since these trials occurred, new pharmacological approaches have demonstrated additional benefit when added to ACEI. Consequently, it is possible that the incremental benefit of ACEI might be modified when combined with other therapy associated with high survival benefit in heart failure. From a practical viewpoint, it is

of interest to know whether the presence of background therapy influences the benefit of ACEI as previously established by randomized, placebo-controlled trials. This caveat is more pronounced for geriatric patients particularly when diagnosed late in life, considering that patients are living longer with heart failure compared to the time when landmark trials occurred (210). Therefore this study also attempted to address this question by examining the effectiveness of ACEI in a real-world, outpatient scenario with current heart failure pharmacotherapy and with a focus on patients diagnosed ≥ 70 years.

This is, to the best of my knowledge, the first observational study to demonstrate indirectly on a large scale, consistent survival benefit with ACEI in a contemporary population with HFrEF regardless of whether patients are above 70 years of age. It also confirms that this benefit is incremental in this age group without effect modification by background heart failure therapy or increased comorbidity.

A key question is whether the survival benefit of ACEI in elderly heart failure patients with reduced ejection fraction remains incremental with the same level of benefit as established by landmark trials in a younger population with different background heart failure therapy. The observations from this research confirm that ACEI in heart failure patients aged ≥70 years have survival benefit as demonstrated by previous trials in younger patients and remains complimentary to contemporary heart failure pharmacotherapy. Therefore it is critical that these are prescribed in combination with other treatment to all appropriate patients in this age group who do not have demonstrable intolerance. This data also indicates that in patients aged ≥70 years with HFrEF, ACEI can be added irrespective of other therapies since the survival benefit is neither dependent upon specific treatment, nor modulated by any combination of disease-modifying therapies for HFrEF (Tables 32 and 36, Figure 35). So far, this evidence was missing from published data and this study potentially provides reassurance with the knowledge that ACEI work with different combinations of traditional heart failure treatment in patients aged ≥ 70 years. This observation is clinically critical considering that less than 2% of patients with chronic heart failure are receiving appropriate pharmacotherapy that prolong life, and that using guideline-directed, broad-based combination of heart failure-modifying drugs may reduce mortality by as much as 75% (211, 212). Furthermore, delaying initiation of life saving medication to patients in the outpatient setting carries a greater than 75% chance that therapy will not be started within the next year (213).

This study failed to demonstrate lower hospitalisation for heart failure with ACEI treatment both across the full cohort and in the cohort aged ≥ 70 years at incident diagnosis (Tables 50 and 52). In fact the ACEI group in both cohorts demonstrated significantly higher hospitalisation compared to the unexposed group (Table 51 and 53). Both cohorts were

highly powered to detect the reported variance as a true difference in the secondary endpoint between the ACEI exposed and unexposed groups (Table 60). However, the variance in heart failure associated hospitalisation could not be explained by ACEI therapy as demonstrated by a weak effect size attributed to ACEI exposure (Table 54). This indicates that the outcome of the secondary endpoint was influenced by other unmeasured factors in this study that reversed the expected direction of effect. A possible explanation may be the higher prevalence of cardiac comorbidity in the ACEI group that interfered with the detection of the true effect of ACEI on heart failure associated hospitalisation. In fact, the ACEI group carried a higher frequency of diuretics, digoxin and warfarin indicating greater cardiac comorbidity compared to the unexposed group.

The prevalence of diuretics in the ACEI group was 1.7 times that in the unexposed group across the full cohort and this ratio was consistent in the cohort aged ≥ 70 years diagnosis age (Tables 17 and 18). Increased use of diuretics correlates with higher severity of heart failure and more frequent rehospitalisation due to acute decompensation of heart failure (214). However with the absence in this research of a heart failure-specific, functional capacity score such as the NYHA classification, the influence of potentially higher cardiac comorbidity on the effect of ACEI cannot be tested. Despite the absence of a heart failure-specific, valid health status measure of functional capacity as an indicator, there is sufficient indication that the ACEI group carried greater cardiac comorbidity that translated into higher hospitalisation. In fact, the frequency of ischaemic heart disease in the treatment arm was twice that in the unexposed arm. The ICD 10 codes used to identify HF hospitalisation events also included erroneously other codes linked to a range of cardiovascular diseases where ischaemic heart disease is prominent. So the imbalance in ischaemic heart disease between arms led to a higher hospitalisation rate in the treatment arm that did not reflect true HF hospitalisation events. This disparity in disease distribution between groups introduced unmeasured confounding that led to selection bias for hospitalisation. This prevented the study from drawing a conclusion on the true effect of ACEI on heart failure associated hospitalisation in elderly patients with HFrEF.

However, these observations present a paradox in the treatment arm between increased ischaemic heart disease, lower all-cause mortality with ACEI, and the absence of interaction of background heart failure treatment with ACEI for all-cause mortality. A greater frequency of IHD was accompanied by lower all-cause mortality in the treatment arm compared to the unexposed arm. Patients in the ACEI exposed arm were also treated more intensely with carvedilol and spironolactone. Taken together, ACEI and carvedilol provide cumulative survival benefit in IHD and this may explain the reduced all-cause mortality in the treatment arm. If this cumulative survival benefit was sufficiently strong to neutralise the increased risk

from IHD and produce a net benefit of reduced mortality, one would expect a degree of interaction with ACEI in their reduction of all-cause mortality in HFrEF as well. But paradoxically, no combination of background heart failure therapy was found to influence the survival benefit of ACEI in HFrEF. The absence of a clear explanation for this observation puts more emphasis on repeating this research with propensity score matched groups to eliminate confounding biases from unmatched characteristics. Concerning this study, there is evidence of selection bias that prevents drawing a conclusion on the true effect of ACEI on heart failure associated hospitalisation in elderly patients with HFrEF. The main cause appears to lie in the selection of ICD10 codes that defined hospitalisation and this is explained in detail under limitations.

6.6.2. Strengths

Both cohorts were well powered to detect the identified variances as true differences in the primary endpoint for this study (Table 59). Apart from serving to validate the difference in effect between the main groups, the magnitude of the power was also sufficient to allow exploration for differences in prespecified subgroups and determine if overall survival benefit identified in the main Cox regression model persisted. The inclusion of subgroup analysis in the Cox regression model also determined the extent of stability of this benefit across key subgroups of concern particularly with various combinations of background heart failure therapy. The influence of background therapy on the impact of individual heart failure treatment is an evidence gap that only started being investigated recently (215, 216). To the extent of my knowledge this is the first study to gain an insight into the efficacy of ACEI in subgroups with varied treatment combinations in elderly patients with HFrEF. The use of log-minus-log plots confirmed that all Kaplan-Meir plots did not violate the assumption of constant benefit of survival against instantaneous risk of all-cause mortality throughout the 3-year follow-up (Figures 32 and 33). The exhaustive process of sensitivity analysis demonstrated a high degree of robustness for the primary endpoint of all-cause mortality. Due to the retrospective nature that limited control of confounding and the absence of propensity score matching of subjects, sensitivity analysis was performed using a falsification endpoint for residual confounding (196, 197). The absence of a difference in risk for pulmonary disease between the ACEI and unexposed group further validated the observations of this study for the primary endpoint (Table 57). Hazard ratios and their 95% confidence intervals remained consistent for as-treated, intention-to-treat and per protocol study approaches demonstrating an association of ACEI with survival in patients aged ≥70 years with HFrEF that was robust to most scenarios of measured and unmeasured confounding (Table 58, Figure 36).

6.6.3. Limitations

The ACEI exposed and unexposed groups were not balanced with regards to background heart failure treatment (Tables 17 and 18). While background treatment was not found to influence survival outcome, this imbalance between groups may have introduced an unmeasured, potential covariate with strong confounding that led to bias in the statistical tests for the secondary endpoint (217). In this respect, this study lacked information on other important prognostic indicators such as BMI, systolic blood pressure, smoking, and blood haemoglobin concentration at baseline. Consequently, it was not possible to test these factors as variables for confounding of the true outcome for the secondary endpoint attributed to ACEI exposure. Renal disease was also not balanced between groups although this variance was not found to be clinically meaningful for the primary endpoint of all-cause mortality (Tables 55 and 56). Mean LVEF for the two groups was balanced at baseline. However the ACEI exposed group contained more intense heart failure pharmacotherapy including higher use of diuretics. This may indicate that cardiac functional capacity in the ACEI group was worse hence requiring greater rehospitalisation compared to the unexposed group although this argument is paradoxical since the ACEI group had a significantly higher survival benefit**.** Another limitation was the unequal patient allocation with a ratio greater than 2 to 1 between the two study arms for both cohorts. Unequal ratio for patient allocation is associated with bias if the patients in the two arms of the study differed in important characteristics (218) and probably this reversed the expected direction of the effect of ACEI on hospitalisation (Tables 50, 51, 52, 53). This limitation also has consequences for statistical power. A 2 to 1 allocation ratio requires 12% more patients than a study using a 1 to 1 ratio to detect the same size effect with equivalent power (219). The post hoc power estimation took into consideration the unequal patient allocation between the study arms. While this does not appear to have affected the size effect on all-cause mortality as a result of a sufficiently sustained sample power, the reduction of size effect detection potentially underestimated the true effect size of ACEI on hospitalisation (Table 54). Issues of unequal patient allocation ratios and imbalance of baseline, prognostic variables are inherent to non-randomised studies and since this study was retrospective, reducing these limitations was restricted by the patients available historically.

A more potential reason for significantly higher readmissions in the treatment arm lies in the range of ICD10 codes used to identify the number of heart failure associated readmissions for analysis. A re-examination of the codes utilised by the data provider revealed that in addition to the ICD10 codes directly related to heart failure (I11, I25.5, I42.0, I42.6, I42.9, I50, I50.0, I50.1, I50.9), a series of other codes were used that are linked to a range cardiovascular diseases where ischaemic heart disease is prominent including myocardial

infarction (I10 to I79, I95, R06, and R07). These were included by the data provider in an effort to try to capture other admissions with incomplete or wrong coding at the Emergency Department and potentially related to heart failure. An analysis of disease characteristics revealed that the treatment arm contained almost twice the frequency of ischaemic heart disease confirmed at baseline compared to the unexposed arm as comparator (table 15). This disparity in disease distribution between groups introduced extensive unmeasured confounding that was sufficiently strong to cause bias in the statistical test for the secondary endpoint (217).

The evidence-based target doses of ACEI and background therapy are well defined with evidence of a dose-response relationship of reduction in all-cause mortality and heart failure hospitalisation (66, 100). Yet, target doses are infrequently achieved in clinical practice (211, 220). Therefore, it is possible that the incremental benefit of ACEI may be less if dosing for ACEI or any of the background therapy was not optimized. This study was not designed to demonstrate consistent benefit of ACEI irrespective of whether treatment was optimized. A related limitation is the presence of sacubitril valsartan that became available late in the study follow-up phase in 2016. These patients were not identified in this study. However, patients that switched to this treatment were censored at the time of stopping ACEI. From 2016 to December 2021 there were approximately 350 patients that received this treatment (personal communication, February 2022). So the number was minor compared to the large sample sizes of both cohorts. Additionally, the only renin angiotensin system inhibitor treatment for all patients in this study were ACEI during the 3-year follow-up or until censoring. Moreover, none of the background heart failure therapy modified the outcome of ACEI on all-cause mortality (Tables 30, 32) (Figures 34, 35). Therefore it is justified to assert that sacubitril-valsartan did not exert any influence on treatment or survival in this study albeit censoring was required.

Another limitation is the absence of comprehensive information on the cardiac functional capacity of patients. The original plan for the study protocol was to include data capture of the NYHA scores at baseline and upon completion of the 3-year follow-up. The pilot study revealed that in practice, functional scores for heart failure severity are rarely recorded. This prevented a complete description of the study population at baseline and precluded analysis of the effect of ACEI interaction with heart failure progression through follow-up. Similarly, the availability of NT-proBNP testing became available in 2016 when the protocol for the complete research programme was finalized for UREC approval and 9 years after the index year identified to start data capture that is in 2007. Therefore this prognostic data was also not part of the study design and research relied on LVEF from the primary diagnostic echocardiogram as the only clinical parameter of informative status.

Length of hospital-stay related to heart failure in conjunction with associated hospital readmission would have provided more reliable information to inform on the secondary outcome measure of HFrEF morbidity (221, 222). Extracting this data required identification of admission and discharge dates from electronic and physical records, with manual calculation of the in-hospital days. In view of the time constraints for this research, this exercise was not feasible.

Finally, since this research was a single centre study that was also retrospective and non-randomised, there were design limitations and statistical issues associated with limited sample size that led to unequal patient allocation, selection bias that introduced baseline imbalance, the inevitable presence of confounding variables, and the lack of generalizability to a broader population. For these reasons, this study lacked internal and external validity to provide indisputable evidence to clinical practice.

6.6.4. Comparisons

Comparison of this research with previous studies can be done at 3 levels – landmark placebo-controlled, randomised trials, community-based observational studies, and studies specific for patients aged over 70 years. The CONSENSUS trial demonstrated a 40% mortality reduction in patients with severe heart failure treated with enalapril (62). Long-term follow-up data suggested that ACEI therapy increased survival time by 50% (223). The SOLVD trial extended this benefit to patients with mild to moderate heart failure with a reduction of 4-year mortality by 16% and a decrease in hospitalisation for heart failure by 26% (95). In the V-HeFT II trial there was a 28% reduction in the risk of all-cause mortality with enalapril at 2 years of follow-up. Significantly, subgroup analyses revealed no interaction with background treatment. However these landmark trials were not representative of patients aged over 70 years especially with added comorbidities. Mean baseline age was 71 years for Consensus, and 61 years for SOLVD and V-HEFT II. A systematic review of these RCT's revealed that only 8.4% of patients aged ≥75 years were included although there were 5260 individuals aged ≥ 65 years (93). Despite this drawback, a parallel can be drawn with this research for high and sustained survival benefit that is not modified with other therapy for patients aged ≥70 years.

Subsequent community-based observational studies supported a benefit from ACEI in elderly patients with heart failure and additional comorbidity that was similar in magnitude or higher to that seen in younger patients in previous trials (93, 100, 224). This research compares with these observational studies on two criteria. The mortality reduction in elderly patients persisted even with additional comorbidity, and a higher survival benefit was also observed compared to most landmark trials. A meta-analysis of the trials of ACEI in heart

failure estimated a mortality risk reduction of 17% (225). This is smaller than the apparent mortality risk reduction in this research of 49% for the full cohort analysis and 42% in patients aged ≥ 70 years as baseline. Possible reasons for this discrepancy include failure to use ACEI due to poor overall care and impact of other heart failure treatment modalities or greater use of anticoagulants in the unexposed group (98). However this research does not support these claims. There are two other reasons that are considered more plausible for this research. The first is selection bias in view of the imbalance in baseline characteristics and second is the patient allocation ratio between the two study arms. These limitations can cause single-centre trials to provide inflated treatment effect estimates compared to multicentre trials (217). Furthermore, disease characteristics at baseline were not balanced between both study arms. This may have introduced covariates that lead to unmeasured biases. Additionally, the presence of non-comparable baseline characteristics due to selection bias coupled with unequal patient allocation may have introduced unmeasured comorbidity in the unexposed arm that led to poorer prognosis. Renal function was significantly poorer in the unexposed arm for the full cohort although this failed to be demonstrated in the cohort aged ≥ 70 years at baseline due to the high proportion of missing values for serum creatinine and eGFR. Another possibility is that real-world patients on treatment have better baseline prognosis than patients in landmark trials due to better use of treatment that reduce the incidence of sudden death in symptomatic HFrEF. This may explain the lower mortality in the ACEI treated group for this research compared to treated patients in randomised trials.

A limited number of studies of patients over 70 years with HFrEF also support the survival benefit observed in this research for the same age group albeit with lower mortality reductions. In a cohort including all elderly patients admitted to two community hospitals for heart failure, ACEI reduced mortality by 9% (21% with chronic renal failure) at 6-months after discharge (226). A second study of 17,456 older patients with LVSD from the same cohort demonstrated a 6% absolute reduction in 1-year mortality associated with ACEI (227). This benefit was consistent across all age groups, including patients over the age of 85 and was independent of a wide range of potential confounders. In another study of 11,854 elderly patients with LVSD, ACEI was associated with an 8% absolute reduction in mortality at 1 year (99). Several large cohort studies in elderly patients also indicated a large benefit on hospitalisation rate (98, 228). This research reversed this outcome observed in previous studies with higher hospitalisation demonstrated in the ACEI group. However the effect was not attributed to ACEI due to selection bias and an imbalance in the patient selection ratio. Although these studies were aimed at the elderly patients with heart failure, their purpose for comparison is inadequate since these occurred between 1996 and 2004 when heart failure

therapy was different. In 2016 a study was done on 138 patients >70 years that demonstrated an adjusted HR of 0.24 that increased to 0.27 with age ≥80 years. (229). However, the inclusion criteria included ACEI or ARB with results published collectively. So using this study for comparison is again limited. Besides the fact that there is limited data available concerning ACEI in patients aged ≥70 years, there is also the absence of data investigating continuous, lifelong therapy with ACEI (230).

One final comparison is the result demonstrated by this study where the risk of mortality in patients aged ≥ 70 years at baseline doubled compared to patients aged < 70 years at incident diagnosis within the ACEI exposed group (Table 27). Incident diagnosis in elderly patients raises the concern that many heart failure diagnoses are missed in the outpatients setting (231). Age was proven to be an independent predictor of 1-year mortality in patients with heart failure and increasing age at diagnosis was associated with increased mortality (228, 232). Earlier recognition and intervention can also mitigate heart failure morbidity (2). Furthermore, This observation confirms evidence from a smaller study where the presence of chronic heart failure in older patients resulted in an approximately 50% reduction in life expectancy (233).

6.7. Conclusions

1. ACEI reduced all-cause mortality substantially in patients aged ≥70 years with HFrEF.
2. This benefit is comparable to the general population with HFrEF.
3. The observed survival benefit was maintained during the 3-year follow-up.
4. This benefit was incremental and independent of other heart failure treatment and comorbidity.
5. Age reduced life expectancy with the risk of mortality in patients aged ≥70 years doubled compared to patients diagnosed <70 year.
6. These results were observed at 3-year follow-up post primary diagnosis with HFrEF.
7. The result obtained for hospitalisation is inconclusive and requires a more rigorous study design.
8. This research indicates critical areas for statistical improvement for future studies.

7. STUDY 3

7.1. Aims and Objectives

Are ARB effective in a contemporary cohort of adults aged 70 years or older and diagnosed with heart failure and reduced ejection fraction?

The null hypothesis is that there is no difference between treatment and control. The primary endpoint for investigation is all-cause mortality with a separate secondary endpoint of heart failure associated hospitalisation.

7.2. Inclusion / Exclusion Criteria

Subjects met the following inclusion and exclusion criteria:

Inclusion criteria

- Documented left ventricular systolic dysfunction defined as left ventricular ejection fraction ≤ 40%
- Treatment with ARB
- Age ≥ 50 years at incident diagnosis for the study; < 70 years for positive control arm

Exclusion criteria

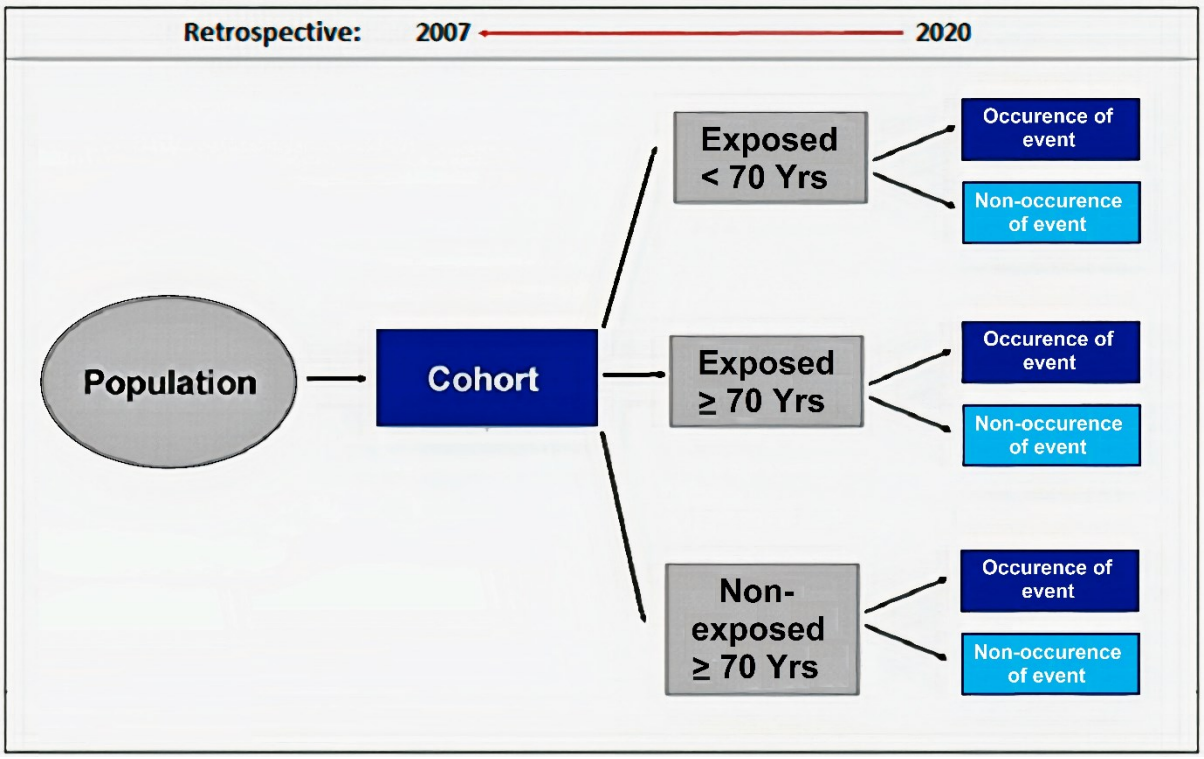
- Left ventricular EF not available
- Treatment with ACEI or other non-ARB RAS inhibitor
- Diastolic heart failure (HFpEF)
- Myocardial infarction, cardiac surgery, or percutaneous transluminal coronary angioplasty (PTCA) within 8 weeks
- Need for cardiac surgery (e.g. severe valvular disease, planned coronary artery bypass graft surgery) or PTCA in the near future. (Such patients are eligible after surgery or PTCA). Patients on heart transplant list are not eligible
- Intravenous inotropic agents within 45 days
- Potassium above 5.5 mmol/L
- Creatinine > 3.0 mg/dL
- Presence of cardiac implantable devices

7.3. Design

The cohort was made up two study arms, one with ARB and another without RAS exposure. All patients diagnosed with a documented echocardiogram from 2007 to 2017 were included. The design was applied for the full cohort with an age limit of ≥ 50 years and a second cohort aged ≥ 70 years. The index age was the patient's age at incident diagnosis. A

comparison arm was also included for patients aged under 70 years and exposed to ARB as a positive control to compare outcome with published trials. Patients were followed retrospectively for three years or until censored from time of incident diagnosis. The primary endpoint was all-cause mortality with a secondary endpoint of heart failure associated hospitalisation. The next schematic explains the stages of the study design (Figure 37).

Figure 37: Schematic of the study design – study 3



The study involved testing ARB in the active group against a control group with no RAS inhibitor on board. Baseline clinical descriptors collected were age and date for diagnosis and death, sex, ejection fraction, ARB treatment duration, additional heart failure therapy, warfarin and digoxin treatment, Charlson comorbidity score, and associated hospitalisation frequency. The inclusion of digoxin and warfarin was taken as an indication of the presence of significant additional cardiovascular morbidity that increase mortality risk and possibly lead to confounding of the primary endpoint of all-cause mortality. The majority of patients in the study population with substantial thromboembolic burden were on Warfarin. While patients on digoxin was indicative of atrial fibrillation coexisting with heart failure. Both comorbidities portent considerable additional mortality and inclusion of these two medicines allowed for atrial fibrillation and thromboembolic disease to be analysed as potential covariates for possible confounding of primary endpoint.

7.4. Statistical Considerations

7.4.1. Sample Size and Power

The CHARM-alternative trial showed that candesartan reduced cardiovascular mortality by 20% and hospitalisation for heart failure by 40% at 38 months (HR 0.80; 95% CI 0.66-0.97; P 0.02) when compared to placebo (110). Mortality rate from heart failure extracted from North American and Scottish data was estimated at 28% adjusted for 1 year (194). Adjusting cardiovascular mortality reduction from the CHARM-alternative trial for 1 year, and assuming a two-sided P value of 0.05 with a sample size ratio of 1 for ARB naïve to exposed groups, the study would need to recruit 1600 patients to have 85% power to detect a true change in cardiovascular mortality rate of 6.5% by ARB treatment over one year (Appendix 12.8.3.).

7.4.2. Statistical Analysis

Baseline characteristics for ARB exposed and unexposed patients at the first month of follow-up were compared using the mean and standard deviation for each group. Rates for all-cause death were calculated per 1000 person-years with associated 95% confidence limits.

The primary treatment comparisons between groups were performed according to the as-treated (AT) principle based on a time-to-event analysis. Patients were also censored for terminating ARB and for switching to, or from another non-ARB RAS inhibitor during the 3-year follow-up. Kaplan-Meier cumulative event rates were calculated for each group, with event or censored times measured from the time of incident diagnosis. These plots estimated the probability for unadjusted all-cause mortality with and without ARB exposure. Differences between curves were tested for significance by log-rank test. Kaplan-Meier plots were tested for the assumption of constant relative risk using log-minus-log plots. Relative risks were expressed as hazard ratios with associated 95% confidence intervals derived using the Cox proportional hazards model. The Cox models was also used for subgroup analysis to assess the consistency of treatment effect by testing for interactions between ARB and the prespecified variables of background heart failure treatment, digoxin, warfarin and the Charlson comorbidity score (195). Each variable was tested individually for interaction using the enter method in SPSS. Hazard ratios from the main Cox regression model were adjusted for all prespecified variables together through simultaneous entry in a multivariable Cox model. This allowed analysis of the primary endpoint measure in a cohort that reflected a real-world population considering that these patients are typically on multiple medications for heart failure and have additional comorbidities. Two-sided significance testing was used with a conventional significance level of 0.05 and 95% confidence intervals.

The frequency of associated hospitalisation events during the 3-year follow-up period was checked as a dependent variable for normality distribution for each level of the independent variable of treatment with and without ARB using the Shapiro-Wilk test. The null hypothesis for the Shapiro-Wilk test was that the scores in the dependent variable are normally distributed. Hospitalisation scores failed to meet the normality assumption for the t-test and a Mann-Whitney U test was conducted to analyse for differences in hospitalisation scores between the two groups in each cohort.

Four levels of sensitivity analysis were done to test for robustness of results. ARB exposed and unexposed groups were compared for the values and proportions of missing laboratory values as well as the mean of plasma potassium, serum creatinine, eGFR, bilirubin and LVEF. The t-test or Mann-Whitney U test was used depending on the Shapiro-Wilk test for normality to identify potential confounding covariates leading to bias. Variables with significant p-values were tested with Cox regression interaction analysis to check for modification of effect of ARB on mortality in the main Cox regression model.

Analysis using a falsification endpoint was performed for residual confounding (196, 197). Risk of outpatient pulmonary disease (asthma or chronic obstructive pulmonary disease) was selected as this was unlikely to be affected by treatment with or without the index drug. Unadjusted hazard ratios from the primary Cox regression model with AT analysis were compared with intention-to-treat and per-protocol analyses. This tested the robustness of association of ARB exposed versus unexposed groups with mortality to measured and unmeasured confounding. The intention-to-treat analysis did not censor for patients at the time of discontinuation of ARB or treatment switching and followed for 36 months post incident diagnosis. This preserved the baseline comparability and provided conservative estimates of differences between treatment groups. In the per-protocol analysis, patients with treatment switching involving ARB were removed from the cohort (198).

Finally, follow-up analysis of post hoc sample power was done of the observed effect based on the actual cohort size and parameter estimates derived from the data set in view of the unequal patient allocation ratios between groups. (199).

All analysis was done for the two study arms for full cohort and independently for the cohort of patients aged ≥ 70 years at incident diagnosis which was taken as baseline. Additionally, unadjusted hazard ratios were determined for the positive control group of patients aged < 70 years at incident diagnosis. This control arm provided a direct comparison with the survival outcome of the other two study arms and allowed confirmation that the study still exhibited the same survival benefit as shown by landmark trials where mean age was below 70 years. Analysis included data of patients diagnosed between 2007 – 2017 and was done with SPSS version 26, Stata version 17, and PASS Pro 2021

7.5. Results

7.5.1. Baseline Characteristics

Table 61: Baseline comorbidities of full cohort – study 3

Disease	No ARB %	ARB %
Arrythmias	9.1	15.3
Cerebrovascular disease	4.5	1.8
Chronic kidney disease	6.6	6.8
Dementia	0.6	1.3
Diabetes	8.7	16.4
Genetic dyslipidaemia	3.3	5.5
Hypertension	15.4	28.7
Ischaemic heart disease	14.7	25.3
Malignant diseases	3	3.9
Peripheral vascular disease	2.1	2

Table 62: Baseline comorbidities of cohort aged ≥ 70 years – study 3

Disease	No ARB %	ARB %
Arrythmias	9.5	16.3
Cerebrovascular disease	6.3	3.3
Chronic kidney disease	8.1	8.7
Dementia	0.9	2.2
Diabetes	10	13.8
Genetic dyslipidaemia	3.7	5.1
Hypertension	16.7	29.7
Ischaemic heart disease	16	24.6
Malignant diseases	3.7	4.3
Peripheral vascular disease	2.3	1.4

Table 63: Baseline characteristics for full cohort – study 3

Full cohort (N=1203) Characteristics	ARB Arm (n=541)	Unexposed Arm (n=662)
Diagnosis age (Yrs)		
Mean (Std. Deviation)	70.9 (8.7)	73.3 (9.7)
Median	70.2	74.2
Sex		
Males	342 (63.2%)	449 (67.8%)
Females	199 (38.8%)	213 (32.2%)
LVEF %		
Mean (Std. Deviation)	34.8 (7.7)	34.5 (9)
Median	37	38.2
Charlson comorbidity score		
0	253 (46.8%)	331 (50%)
1	24 (4.4%)	21 (3.2%)
2 - 3	148 (27.4%)	194 (29.3%)
≥ 4	116 (21.4%)	116 (17.5%)
Background treatment		
Carvedilol	324 (59.9%)	158 (23.9%)
Spironolactone	230 (42.5%)	121 (18.3%)
Nitrates + Hydralazine	9 (1.7%)	8 (1.2%)
Loop Diuretics	479 (88.5%)	327 (49.4%)
Digoxin	123 (22.7%)	92 (13.9%)
Warfarin	221 (40.9%)	160 (24.2%)
Hospitalisation		
Total	681	494
Mean (Std. Deviation)	1.26 (2.152)	0.75 (1.431)

Table 64: Baseline characteristics for cohort aged ≥ 70 years – study 3

Cohort aged ≥ 70 years (N=706) Characteristics	ARB Arm (n=276)	Unexposed Arm (n=430)
Diagnosis age (Yrs)		
Mean (Std. Deviation)	77.8 (5)	79.2 (5.6)
Median	77.6	78.5
Sex		
Males	144 (52.2%)	276 (64.2%)
Females	132 (47.8%)	154 (35.8%)
LVEF %		
Mean (Std. Deviation)	35.4 (7.1)	34.6 (8.9)
Median	38.1	38.3
Charlson comorbidity score		
0	135 (48.9%)	208 (48.5%)
1	13 (4.7%)	11 (2.6%)
2 - 3	72 (26.1%)	126 (29.3%)
≥ 4	56 (20.3%)	85 (19.8%)
Background treatment		
Carvedilol	151 (54.7%)	92 (21.4%)
Spironolactone	117 (42.4%)	75 (17.4%)
Nitrates + Hydralazine	5 (1.8%)	5 (1.2%)
Loop Diuretics	249 (90.2%)	222 (51.6%)
Digoxin	76 (27.5%)	65 (15.1%)
Warfarin	121 (43.8%)	103 (24%)
Hospitalisation		
Total	394	352
Mean (Std. Deviation)	1.43 (2.299)	0.82 (1.448)

A total of 541 patients (mean diagnosis age 70.9 ± 8.7 years) filling a prescription for an ARB were identified while 662 patients (mean diagnosis age 73.3 ± 9.7 years) received no treatment for angiotensin blockade. The cohort for patients diagnosed at 70 years or more consisted of 276 patients (mean diagnosis age 77.8 ± 5 years) with ARB therapy and 430 patients (mean diagnosis age 79.2 ± 5.6 years) without angiotensin blockade. The groups were balanced for most comorbidities at baseline except for arrhythmias, diabetes, hypertension, and ischaemic heart disease. These were more common in the ACEI exposed group (table 61 and 62). Both groups were also balanced with respect to baseline characteristics including cardiac function except for background heart failure treatment and heart failure associated hospitalisation. These was more common in the ARB treatment groups for both cohorts (Tables 63 and 64).

7.5.2. Epidemiology: All-Cause Mortality

Table 65: Mortality rate and mortality rate ratio - study 3

Cohort	MR ARB	MR Unexposed	MRR	95% Confidence interval	Two-sided p-value
Full cohort	0.094	0.238	0.395	0.318 - 0.483	< 0.0001
Cohort aged ≥ 70 years	0.139	0.284	0.489	0.380 - 0.628	< 0.0001

MR: Mortality rate per person-years
MRR: Mortality rate ratio

Of the 1203 patients included in the full cohort study, 448 had a fatal all-cause event during the follow-up period of 36 months post incident diagnosis. The mortality rate per 1000 person-years was 94 for the ARB exposed and 238 for the angiotensin blockade naïve group. In the cohort of 706 patients aged ≥ 70 years at baseline, 319 had a fatal all-cause event during the 3-year follow-up. The mortality rate per 1000 person-years was 139 for ARB exposed patients and 284 for the angiotensin blockade naïve group. The mortality rate ratio of all-cause mortality for the comparison of the ARB group to the angiotensin blockade naïve group was 0.395 (95% CI 0.415 to 0.318, $p < 0.0001$) In the full cohort and 0.489 (95% CI 0.380 to 0.628, $p<0.0001$) in the cohort aged ≥70 years at baseline (Table 65).

7.5.3. Survival Analysis

7.5.3.1. Kaplan – Meier Estimates

7.5.3.1.1. Kaplan-Meier Plots

Figure 38: Kaplan-Meier plot for full cohort – study 3

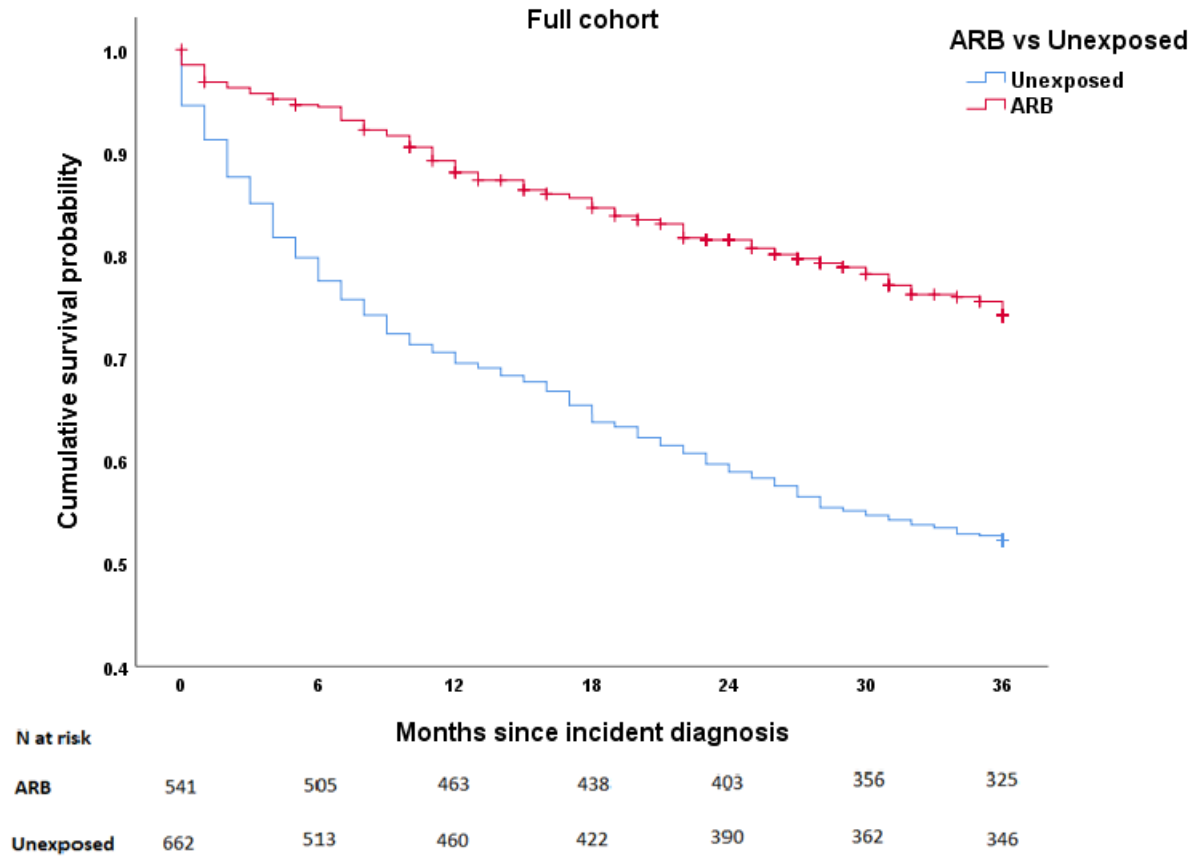


Table 66: Means for Survival Time (Months) for figure 38

	Mean[a]		95% Confidence Interval	
ARB vs Unexposed	Estimate	Std. Error	Lower Bound	Upper Bound
Unexposed	24.029	.558	22.935	25.123
ARB	30.859	.452	29.973	31.744

a. Estimation is limited to the largest survival time if it is censored.

Table 67: Log Rank test for figure 38

	Chi-Square	P-value
Log Rank (Mantel-Cox)	68.168	<0.0001

Test of equality of survival distributions for the different levels of ARB vs Unexposed.

Figure 39: Kaplan-Meier plot for cohort aged ≥ 70 years – study 3

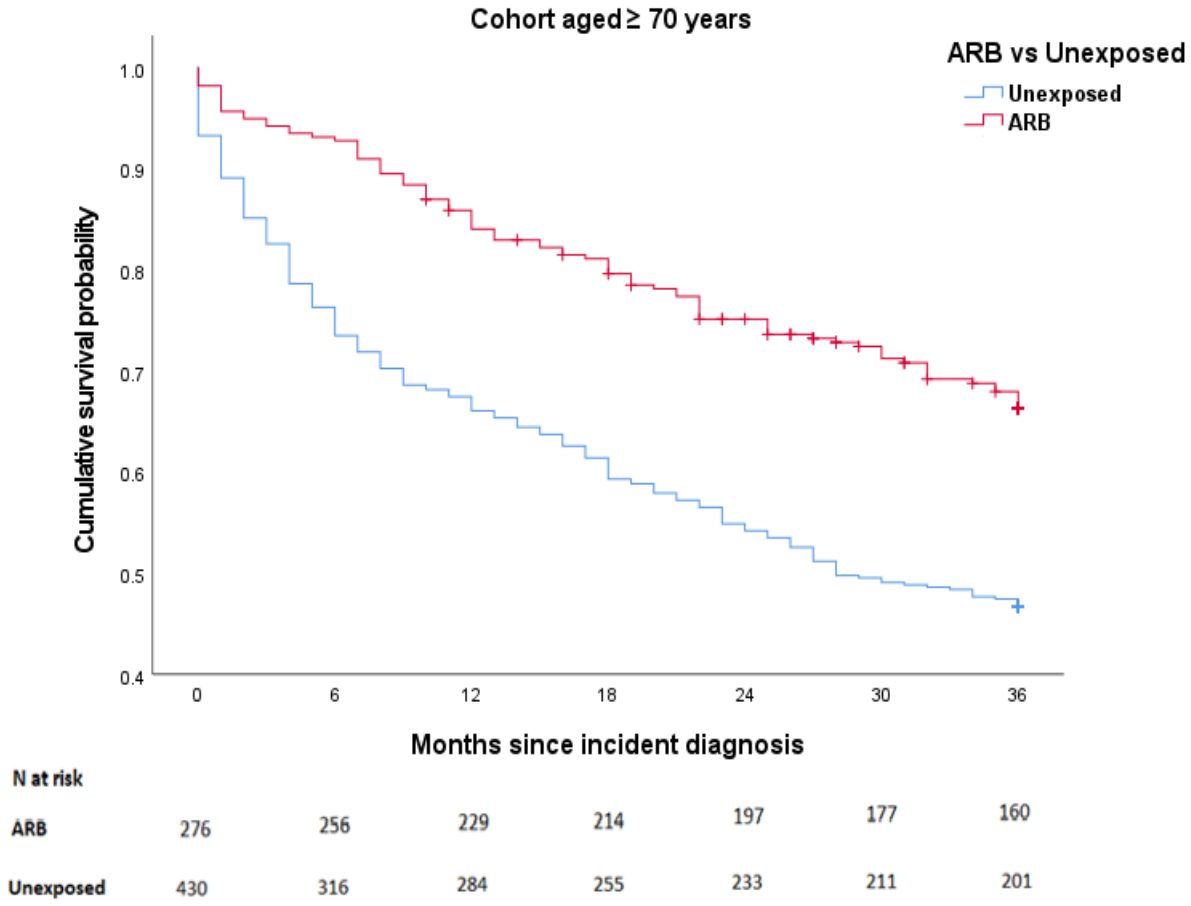


Table 68: Means for Survival Time (Months) for figure 39

	Mean[a]		95% Confidence Interval	
ARB vs Unexposed	Estimate	Std. Error	Lower Bound	Upper Bound
Unexposed	22.535	.707	21.148	23.922
ARB	29.202	.699	27.832	30.571

Table 69: Log Rank test for figure 39

	Chi-Square	P-value
Log Rank (Mantel-Cox)	30.859	<0.0001

Figure 40: Full cohort composite Kaplan-Meier plot – study 3

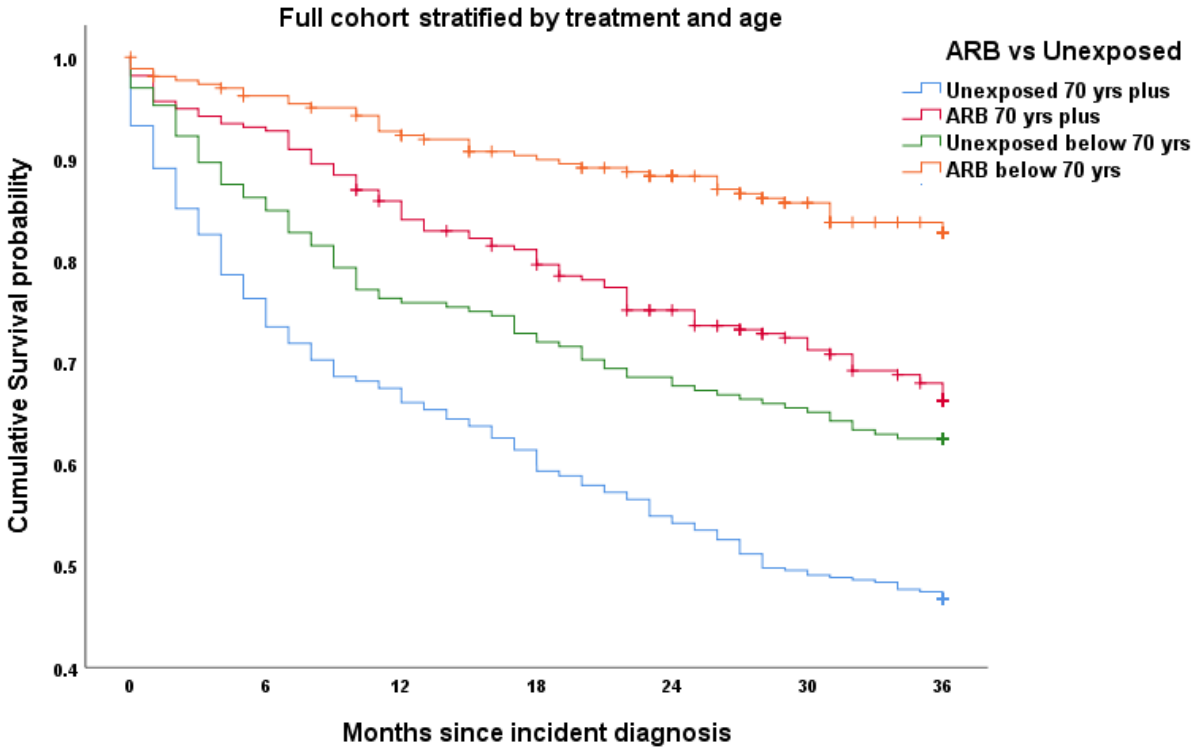


Table 70: Means for Survival Time (Months) for figure 40

	Mean[a]		95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound
Unexposed 70 plus	22.535	.707	21.148	23.922
ARB 70 plus	29.202	.699	27.832	30.571
Unexposed below 70	26.797	.875	25.082	28.512
ARB below 70	32.631	.548	31.557	33.705

a. Estimation is limited to the largest survival time if it is censored.

Table 71: Log Rank test with pairwise comparisons for figure 40

	Log Rank (Mantel-Cox)			
	ARB exposed 70 plus		ARB exposed below 70	
Study Arm	Chi-Square	P-value	Chi-Square	P-value
Unexposed 70 plus	30.859	<.0001		
Unexposed below 70			28.069	<.0001

The decrease in the probability of survival followed the same pattern with time for the ARB exposed and unexposed group in the full cohort analysis and also in the cohort aged ≥ 70 years at incident diagnosis but the rate of decline was much steeper for the unexposed

group in both cohorts. This distinction became evident within the first 3 months of follow-up. The 3-year cumulative survival probabilities were 60.1% in the ARB exposed versus 52.3% in the unexposed group for the full cohort (P < 0.001) and 58% in the ARB group versus 46.7% in the unexposed group for the cohort aged ≥70 years at incident diagnosis (P < 0.001) (Figures 38 and 39). The results of the log-rank tests indicated that the highly statistically significant difference in survival observed in the full cohort was also exhibited in the cohort aged ≥ 70 years at incident diagnosis. In patients with incident diagnosis age < 70 years the 3-year cumulative survival probability was 84.2% for ACEI exposed compared to 62.5% for unexposed patients (P < 0.001).

7.5.3.1.2. Log-minus-Log plots of Kaplan-Meier estimation

Figure 41: Log-minus-log plot for Kaplan-Meier estimation – full cohort – study 3

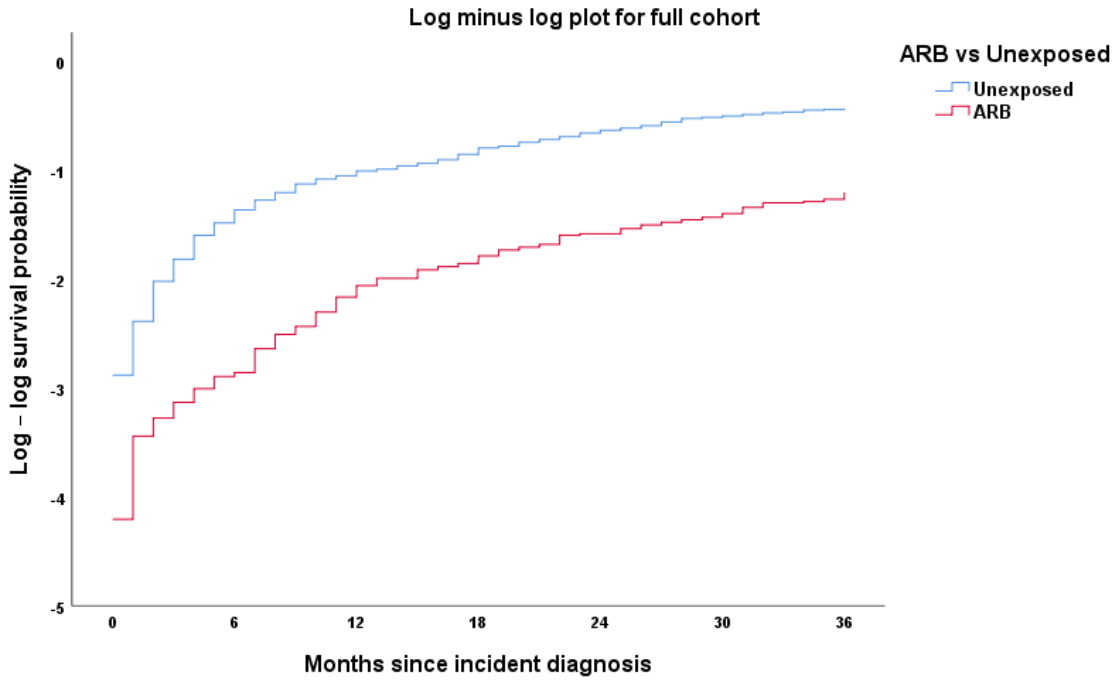
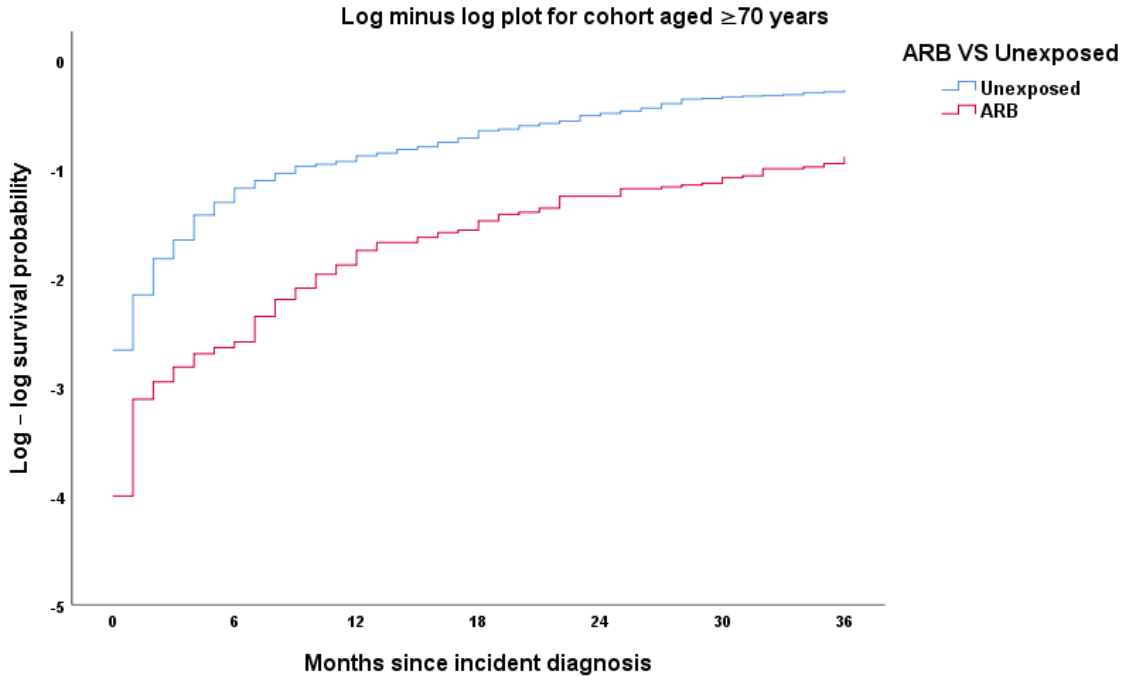


Figure 42: Log-minus-log plot for Kaplan-Meier estimation – cohort aged ≥ 70 years – study 3



Log-minus-log plots were used to test the assumption of constant relative risk. The log-rank test in Kaplan-Meier plots uses this assumption when comparing survival curves between two groups. This means that the risk of mortality in one group relative to the other does not change with time. Log-minus-log plots for full cohort analysis and for the cohort aged ≥70 years showed that the two curves do not meet and are parallel during the follow-up period. Therefore, in both cohorts the proportional hazards assumption was not violated. This means that the survival probabilities were the same for patients throughout the 3-year follow-up period (Figures 41 and 42).

7.5.3.2. Cox Proportional Hazards Regression Analysis

7.5.3.2.1. Main Model

Table 72: Cox regression for full cohort and cohort aged ≥ 70 years – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
Full cohort	-.826	<0.001	.438	.357	.537
Cohort ≥ 70 years	-.672	<0.001	.511	.400	.652

Table 73: Cox regression for age ≥ 70 years exposed vs age < 70 years exposed – study 3

	P-value	HR	95.0% CI for HR Lower	Upper
.770	<0.001	2.160	1.498	3.116

In the full cohort analysis, the hazard ratio of mortality in the ARB exposed group was 0.438 compared to the unexposed group (P < 0.001, 95%CI = 0.357 – 0.537). In the cohort aged ≥ 70 years at baseline, the hazard ratio of mortality in the ARB exposed group was 0.511 compared to the unexposed group (P < 0.001, 95% CI = 0.4 – 0.652) (Table 72). In the ARB exposed group, the hazard ratio of mortality in patients aged ≥ 70 years at baseline was 2.160 compared to patients aged < 70 years at incident diagnosis (P < 0.001, 95% CI = 1.498 – 3.116) (Table 73).

This means that in the full cohort analysis, ARB lowered mortality by 56.2% compared to the unexposed group while in the cohort aged ≥ 70 years group, ARB lowered mortality by 48.9% compared to the unexposed group. Within the ARB exposed group, the risk of mortality in patients with ≥ 70 years at baseline doubled compared to patients with an incident diagnosis age < 70 years. All hazard ratios were highly statistically significant during the 3-year follow-up.

7.5.3.2.2. Positive Control Arm

Survival analysis was done for the cohort aged below 70 years at baseline. This group was analysed separately with and without treatment exposure.

Table 74: Cox regression for cohort aged <70 years – study 3

	B	P-value.	HR	95.0% CI for HR Lower	Upper
ARB vs Unexposed	-.955	<0.001	.385	.266	.556

The hazard ratio of mortality in the ARB exposed group was 0.385 compared to the unexposed group (P < 0.001, 95% CI = 0.266 – 0.556) (Table 74). This means that in patients with a diagnosis age below 70 years, ARB lowered mortality potentially by 61.5% compared to the unexposed group. The hazard ratio was statistically highly significant.

7.5.3.3. Cox Regression Interaction Analysis

The effect of ARB versus unexposed on all-cause mortality was further analysed for statistical significance of interaction with various potential covariates that may lead to modification of the result obtained in the main Cox proportional hazard model. Selected variables were analysed separately to obtain hazard ratios of ARB versus unexposed with each variable. Statistical significance of the difference within these hazard ratios was analysed with the formation of interaction terms for each variable. The procedure was repeated for full cohort analysis and for patients aged ≥ 70 years at incident diagnosis.

Table 75: ARB vs Unexposed layered by Carvedilol / Spironolactone – full cohort – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
No Carvedilol / Spironolactone	-.828	<0.001	.437	.321	.596
Carvedilol Only	-.930	<0.001	.394	.238	.653
Spironolactone Only	-.642	.015	.526	.314	.882
Carvedilol plus Spironolactone	-1.436	<0.001	.238	.125	.452

Table 76: Interaction terms for Carvedilol / Spironolactone – full cohort – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
ARB*No Carvedilol / Spironolactone		.330			
ARB*Carvedilol only	-.038	.899	.962	.533	1.738
ARB*Spironolactone only	.224	.465	1.251	.686	2.282
ARB*Carvedilol and Spironolactone	-.542	.135	.582	.286	1.184

Table 77: ARB vs Unexposed layered by Carvedilol /Spironolactone – age ≥70 years – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
No Carvedilol / Spironolactone	-.715	<0.001	.489	.339	.706
Carvedilol Only	-.596	.060	.551	.296	1.025
Spironolactone Only	-.422	.183	.656	.352	1.221
Carvedilol plus Spironolactone	-1.072	.010	.342	.152	.774

Table 78: Interaction terms for Carvedilol / Spironolactone – age ≥70 years – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
ARB*No Carvedilol / Spironolactone		.465			
ARB*Carvedilol only	-.928	.129	.395	.119	1.310
ARB*Spironolactone only	-.505	.466	.603	.155	2.347
ARB*Carvedilol and Spironolactone	-.816	.252	.442	.109	1.788

Table 79: ARB vs Unexposed layered by Digoxin – full cohort – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
Digoxin	-.629	.011	.533	.328	.867
No Digoxin	-.845	<0.001	.430	.343	.539

Table 80: Interaction terms for Digoxin – Full cohort – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
ARB*Digoxin	-.232	.397	.793	.464	1.356

Table 81: ARB vs Unexposed layered by Digoxin – age ≥ 70 years – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
Digoxin	-.558	.043	.573	.334	.982
No Digoxin	-.669	<.001	.512	.388	.676

Table 82: Interaction terms for Digoxin – age ≥ 70 years – study 3

	B	P-Value	HR	95.0% CI for HR Lower	Upper
ARB*Digoxin	-.134	.664	.874	.477	1.603

Table 83: ARB vs Unexposed layered by Warfarin – full cohort – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
No Warfarin	-.823	<0.001	.439	.346	.558
Warfarin	-.521	.013	.594	.394	.895

Table 84: Interaction terms for Warfarin – full cohort – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
ARB*Warfarin	.312	.198	1.366	.849	2.196

Table 85: ARB vs Unexposed layered by Warfarin – age ≥ 70 years – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
No Warfarin	-.605	<0.001	.546	.409	.730
Warfarin	-.486	.047	.615	.381	.993

Table 86: Interaction terms for Warfarin – age ≥ 70 years – study 3

	B	P-value.	HR	95.0% CI for HR Lower	Upper
ARB*Warfarin	.141	.620	1.152	.658	2.016

Table 87: ARB vs Unexposed layered by Charlson Score – Full cohort – study 3

Charlson Score	B	P-value	HR	95.0% CI for HR Lower	Upper
0	-.904	<0.001	.405	.300	.548
1	-.720	.324	.487	.116	2.038
2 to 3	-.738	<0.001	.478	.317	.720
≥ 4	-.881	<0.001	.414	.281	.611

Table 88: Interaction terms for Charlson Score – Full cohort – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
ARB*Charlson Score 0		.920			
ARB*Charlson Score 1	-.155	.835	.856	.198	3.698
ARB*Charlson Score 2 to 3	-.173	.505	.841	.506	1.398
ARB*Charlson Score ≥ 4	-.020	.935	.980	.600	1.601

Table 89: ARB vs Unexposed layered by Charlson Score – age ≥ 70 years – study 3

Charlson Score	B	P-value	HR	95.0% CI for HR Lower	Upper
0	-.775	<0.001	.461	.319	.665
1	-.708	.439	.493	.082	2.957
2 to 3	-.680	.008	.507	.306	.839
≥ 4	-.493	.031	.611	.391	.955

Table 90: Interaction terms for Charlson Score – age ≥ 70 years – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
ARB*Charlson Score 0		.807			
ARB*Charlson Score 1	-.289	.327	.749	.421	1.335
ARB*Charlson Score 2 to 3	-.284	.763	.753	.119	4.758
ARB*Charlson Score ≥ 4	-.182	.596	.834	.425	1.634

All hazard ratios for individual variables indicated different probabilities of significant reduction in mortality with ARB except with a Charlson score of 1 for both cohorts and in the carvedilol and spironolactone subgroups for the cohort aged ≥ 70 years at baseline (Tables 75, 77, 79, 81, 83, 85 87, 89). The absence of statistical significance of hazard ratios for all interaction terms within each variable in both cohorts indicated that none of the selected variables exhibited evidence of interaction effect for modification of ARB influence on all-cause mortality (Tables 76, 78, 80, 82, 84, 86, 88, 90) (page 139 Figures 43 and page 140 figure 44).

Figure 43: Endpoint subgroup analysis for interaction (as treated) full cohort – study 3

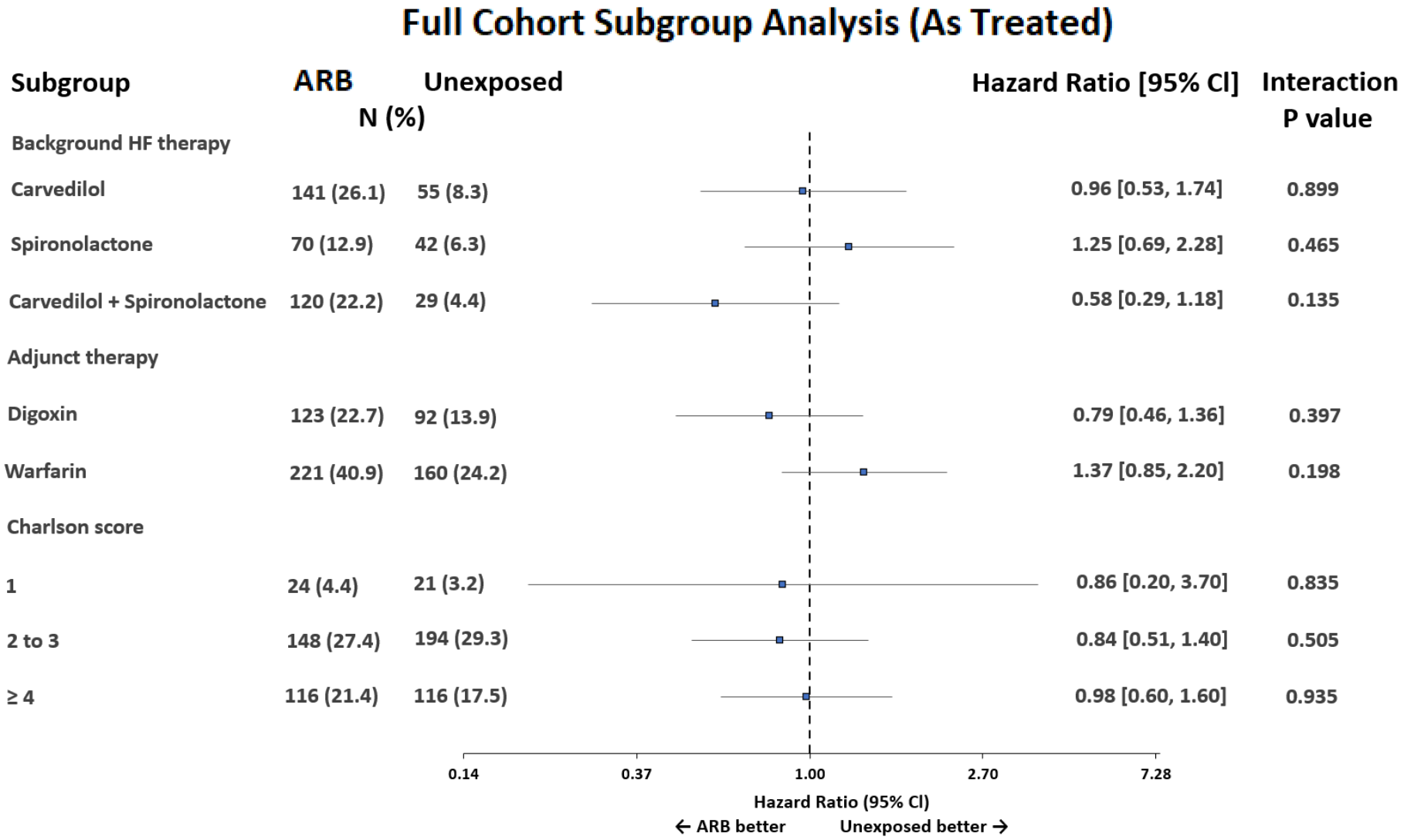
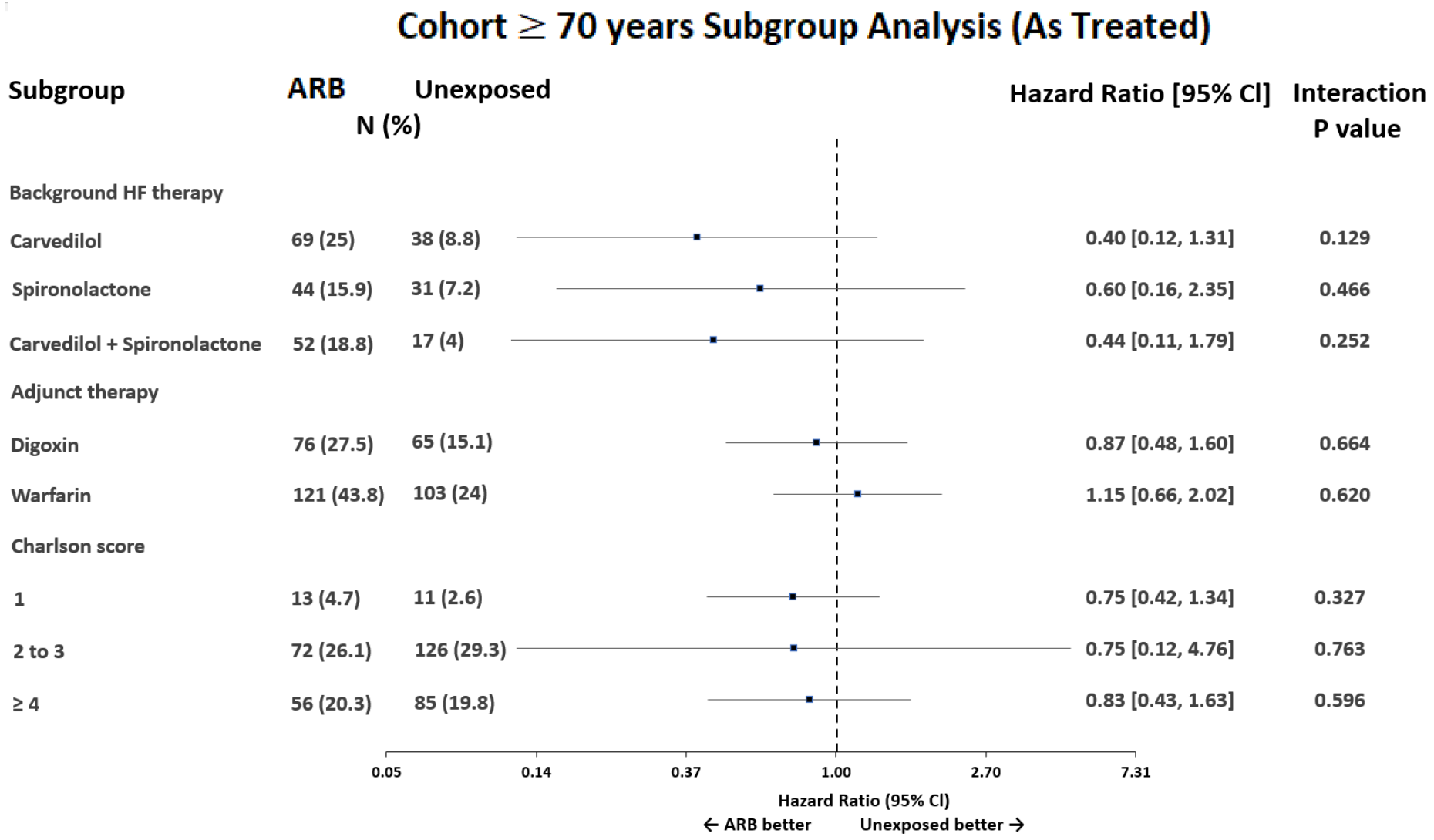


Figure 44: Endpoint subgroup analysis for interaction (as treated) cohort aged ≥ 70 years – study 3



The effect of ARB was consistent across all subgroups for the two cohorts. Examination of prespecified subgroups based on background therapy and comorbidity characteristics across both cohorts did not identify a nominally significant interaction between any of the prespecified variables and the effect of ARB on all-cause mortality (Figures 43 and 44). This excluded relative variations in the effect of ARB, large enough to be clinically significant while also possessing sufficient precision to exclude the null effect (i.e., HR, 1).
However, this does not completely exclude these variables as possible confounders by acting collectively to cause effect modification of ARB on mortality. Therefore, multivariable Cox regression was used to investigate this effect through a model incorporating all potential covariates identified that may simultaneously influence all-cause mortality and hence require adjusted hazard ratios (Tables 91 and 92).

7.5.3.3.1. Multivariable Cox Regression Model with Adjusted Hazard Ratios

Table 91: Adjusted hazard ratio for ARB vs Unexposed – Full cohort – study 3

	B	P-value	Adjusted HR	95.0% CI for HR Lower	Upper
ARB vs Unexposed	-.867	<0.001	.420	.335	.526
No Carvedilol/Spironolactone		<0.001			
Carvedilol only	.139	.349	1.149	.859	1.537
Spironolactone only	.744	<.001	2.103	1.556	2.844
Carvedilol and Spironolactone	-.025	.891	.975	.681	1.396
Digoxin	.050	.732	1.051	.791	1.397
Warfarin	-.662	<.001	.516	.403	.661
Charlson score 0		<.001			
Charlson score 1	-.569	.116	.566	.279	1.151
Charlson score 2 to 3	-.200	.088	.819	.651	1.030
Charlson score ≥ 4	.453	<.001	1.574	1.251	1.979

Table 92: Adjusted hazard ratio for ARB vs Unexposed – age ≥ 70 years – study 3

	B	P-value	Adjusted HR	95.0% CI for HR Lower	Upper
ARB vs Unexposed	-.614	<0.001	.541	.414	.707
No Carvedilol/Spironolactone		.057			
Carvedilol only	-.062	.731	.940	.662	1.335
Spironolactone only	.464	.011	1.591	1.111	2.278
Carvedilol and Spironolactone	-.022	.921	.978	.626	1.527
Digoxin	.052	.750	1.053	.765	1.449
Warfarin	-.625	<.001	.535	.400	.716
Charlson score 0		<.001			
Charlson score 1	-.533	.244	.587	.239	1.440
Charlson score 2 to 3	-.076	.583	.927	.706	1.216
Charlson score ≥4	.547	<.001	1.728	1.323	2.257

7.5.3.3.2. Summary of Hazard Ratios

Table 93: Summary of adjusted and unadjusted hazard ratios (as treated) – study 3

Study	Unadjusted HR	P-value	95.0% CI for Unadjusted HR Lower	Upper	Adjusted HR	P-value	95.0% CI for Adjusted HR Lower	Upper
ARB vs Unexposed Full cohort	.438	<0.001	.357	.537	.420	<0.001	.335	.526
ARB vs Unexposed Cohort aged ≥ 70 years	.511	<0.001	.400	.652	.541	<0.001	.414	.707

Adjusted hazard ratios for the full cohort and for patients aged ≥ 70 years at incident diagnosis were comparable with the original hazard ratios from the main survival model while all P-values did not change. This means that background heart failure treatment associated with improved survival in HFrEF (Carvedilol and Spironolactone), adjunct treatment (Digoxin, Warfarin) indicative of atrial fibrillation or thromboembolic burden, and additional comorbidities were not confounding effects in the full cohort analysis. This result persisted even when adjusting for age ≥ 70 years at incident diagnosis (Table 93).

7.5.4. Hospitalisation

The frequency of hospitalisation events during the 3-year follow-up period was checked as a dependent variable for normality distribution for each level of the independent variable of treatment with and without ARB using the Shapiro-Wilk test. Analysis was done for the full cohort and for patients aged ≥ 70 years at incident diagnosis. The null hypothesis was that the scores in the dependent variable are normally distributed.

Table 94: Tests of Normality – Full cohort – study 3

ARB vs Unexposed	Shapiro-Wilk Sig.
Unexposed	<.0001
ARB	<.0001

Table 95: Tests of Normality – Age ≥ 70 years – study 3

ARB vs Unexposed	Shapiro-Wilk Sig.
Unexposed	<.0001
ARB	<.0001

In both cohorts the Shapiro-Wilk test was highly significant (P = < 0.0001) which rejected the null hypothesis (Tables 94 and 95). Therefore, hospitalisation scores failed to meet the normality assumption for the t-test and a Mann Whitney U test was conducted to analyse for differences in hospitalisation scores between the two groups in each cohort.

Table 96: Ranks – full cohort – study 3

ARB vs Unexposed	N	Mean Rank	Sum of Ranks
Unexposed	662	559.76	370561.50
ARB	541	653.69	353644.50

Table 97: Test Statistics[a] – Full cohort – study 3

	Hosp Admissions
Mann-Whitney U	151108.500
Wilcoxon W	370561.500
Z	-5.218
P-value (2-tailed)	.000

a. Grouping Variable: ARB vs Unexposed

Table 98: Ranks – Age ≥ 70 years – study 3

ARB vs Unexposed	N	Mean Rank	Sum of Ranks
Unexposed	430	328.83	141398.50
ARB	276	391.93	108172.50

Table 99: Test Statistics[a] – Age ≥ 70 years – study 3

	Hosp Admissions
Mann-Whitney U	48733.500
Wilcoxon W	141398.500
Z	-4.415
P-value (2-tailed)	.000

a. Grouping Variable: ARB vs Unexposed

Table 100: ARB Effect size statistic – study 3

	Z^2	N	R^2
Full cohort	27.228	662	0.041
Cohort ≥ 70 years	19.492	430	0.045

The ARB exposed group in the full cohort exhibited a higher number of hospitalisation scores compared to the unexposed group and this result was consistent in the cohort aged ≥ 70 years at incident diagnosis (Tables 96 and 98). The difference of hospitalisation scores between ARB exposed and unexposed groups was highly significant in the full cohort analysis (P = < 0.0001) and in the cohort aged ≥ 70 years at incident diagnosis (P = < 0.0001) (Tables 97 and 99). However only 4.1% of variance in hospitalisation can be explained by the independent variable in the full cohort analysis. The effect size was also weak in the cohort aged ≥ 70 years at incident diagnosis where only 4.5% of variance in hospitalisation can be explained by the independent variable (Table 100).

7.5.5. Sensitivity Analysis

7.5.5.1. Comparison of Groups

In the full cohort analysis, renal disease was the only factor that was significantly different between the ARB exposed and unexposed groups as indicated by the eGFR and serum creatinine (Cr P= < 0.001; eGFR P= < 0.001) (page 145 Table 101). However, there was no significant difference in the diagnostic tests analysed for the cohort aged ≥ 70 years at incident diagnosis (page 145 Table 102). The possibility of renal disease as a potential confounding covariate leading to bias was tested as part of the Charlson comorbidity score interaction analysis with a non-significant P value (Figures 43 and 44). The Charlson comorbidity score was also included in the Cox multivariable model and the adjusted hazard ratio did not change from the unadjusted hazard ratio that resulted from the main Cox regression model (Table 93).

Table 101: Comparison of groups for full cohort – study 3

Diagnostic test	(n) Missing values		(%) Missing values		Mean (Std. Deviation)		P value
	ARB Arm (n=541)	Unexposed Arm (n=662)	ARB Arm (n=541)	Unexposed Arm (n=662)	ARB Arm (n=541)	Unexposed Arm (n=662)	
Potassium mmol/L	455	528	84.1	79.8	4.616 (0.483)	4.639 (0.601)	0.661
Creatinine umol/L	455	528	84.1	79.8	104.62 (39.737)	129.56 (120.966)	<0.001
eGFR mL/min/1.73m2	455	528	84.1	79.8	68.12 (24.802)	64.47 (29.467)	<0.001
Bilirubin umol/L	455	528	84.1	79.8	15.12 (15.232)	16.71 (18.570)	0.12
LVEF %	N/A	N/A	N/A	N/A	34.8 (7.7)	34.5 (9)	0.505

Table 102: Comparison of groups for cohort aged ≥ 70 years – study 3

Diagnostic test	(n) Missing values		(%) Missing values		Mean (Std. Deviation)		P value
	ARB Arm (n=276)	Unexposed Arm (n=430)	ARB Arm (n=276)	Unexposed Arm (n=430)	ARB Arm (n=276)	Unexposed Arm (n=430)	
Potassium mmol/L	238	349	86.2	81.2	4.630 (0.504)	4.607 (0.611)	0.062
Creatinine umol/L	238	349	86.2	81.2	115.92 (42.815)	111.79 (55.982)	0.093
eGFR mL/min/1.73m2	238	349	86.2	81.2	58.5 (24.063)	64.27 (30.043)	0.366
Bilirubin umol/L	238	349	86.2	81.2	12.67 (8.571)	15.8 (17.571)	0.224
LVEF %	N/A	N/A	N/A	N/A	35.4 (7.1)	34.6 (8.9)	0.78

N/A: Not applicable

7.5.5.2. False Endpoint Analysis

Table 103: ARB vs Unexposed – False endpoint analysis – study 3

	B	P-value	HR	95.0% CI for HR Lower	Upper
Full cohort	.390	.783	1.127	.480	2.649
Cohort aged ≥ 70 years	-.072	.898	.930	.309	2.799

No difference in risk of pulmonary disease was observed in patients treated with ARB versus the unexposed group both in the full cohort analysis (HR: 1.127, 95% CI: 0.480 to 2.649; P = 0.783) and in the cohort aged ≥ 70 years at incident diagnosis (HR: 0.930, 95% CI: 0.309 to 1.367; P = 2.799) (Table 103).

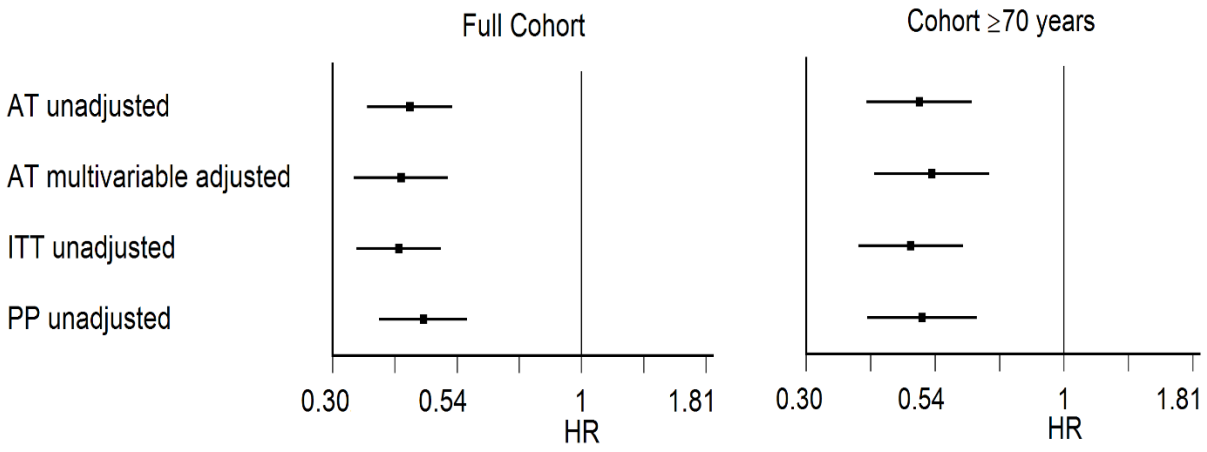
7.5.5.3. Comparison with Intention-to-Treat and Per Protocol designs

Table 104: hazard ratios for as treated, intention-to-treat and per protocol analysis – study 3

Cox regression model	Full cohort			Cohort ≥70 years		
	HR	CI (95%)	P value	HR	CI (95%)	P value
AT Unadjusted	0.438	0.357 – 0.537	<0.001	0.511	0.400 – 0 .652	<0.001
AT Multivariable Adjusted	0.420	0.335 – 0.526	<0.001	0.541	0.414 – 0.707	<0.001
ITT Unadjusted	0.415	0.339 – 0.509	<0.001	0.491	0.385 – 0.627	<0.001
PP Unadjusted	0.467	0.378 – 0.577	<0.001	0.517	0.401 – 0.667	<0.001

AT: As treated ITT: Intention-to-treat PP: Per protocol

Figure 45: Forest plots for table 104



Sensitivity analysis showed the HR analysis under different analytical scenarios were qualitatively consistent with the results of the primary Cox regression analysis of as-treated (AT) analysis. The HR estimates for the endpoint of all-cause mortality varied minimally under different study methods within the same cohort. The variations for the hazard ratio estimates were also similar and compared with the primary Cox regression model. All p-values remained highly significant and comparable as well (Table 104) (Figure 45). This shows that the association of ARB exposed versus unexposed groups with the outcome of reduced of all-cause mortality was robust to most scenarios of measured and unmeasured confounding.

7.5.5.4. Post Hoc Sample Power Analysis

7.5.5.4.1. Survival Analysis

Post hoc power analysis was done by applying study parameters including the cohort size and patient allocation ratio of ARB group to unexposed group and using the two-sample comparison of the main Cox regression model (200, 201). The analysis was done for the full cohort and for the cohort aged ≥ 70 at baseline.

Table 105: Post hoc sample power estimation for all-cause mortality – study 3

Cohort	alpha	N	N1	N2	N2/N1	HR	Power %
Full cohort	0.05	1203	662	541	0.817	.438	100
Cohort aged ≥ 70 years	0.05	706	430	276	0.642	.511	100

N1: Unexposed group
N2: ARB group

Analysis achieved 100% power at a 0.05 significance level to detect a minimum, true change in all-cause mortality where ARB decreased mortality by 56.2% in the full cohort and 48.9% in the cohort aged ≥ 70 years at incident diagnosis compared to the unexposed group over 3 years (Table 105).

7.5.5.4.2. Hospitalisation Analysis

Post hoc power analysis for hospitalisation was done by applying study parameters including the cohort size and patient allocation ratio of ARB group to unexposed group and using the two-sample comparison of the Mann-Whitney U test (201, 202, 203, 204). The analysis was done for the full cohort and the cohort aged ≥ 70 years at baseline.

Table 106: Post hoc sample power estimation for hospitalisation – study 3

Cohort	alpha	N	N1	N2	μ1	μ2	μ1 − μ2	Std. Dev.	Power %
Full cohort	0.05	1203	541	662	1.26	0.75	0.51	3.122	84
Cohort aged ≥ 70 years	0.05	706	276	430	1.43	0.82	0.61	3.667	62

N1: Unexposed group
N2: ARB group
μ: Mean hospitalisation

The full cohort achieved 84% power to detect a true difference in observed mean hospitalisation of μ1 – μ2 = 1.26 – 0.75 = 0.51 using a two-sided Mann-Whitney U test assuming that the actual data distribution is logistic when the significance level (alpha) of the test is 0.05 and the population standard deviation is 3.12 in both groups(Table 106).
The cohort aged ≥ 70 years at incident diagnosis achieved 62% power to detect a true difference in observed mean hospitalisation of μ1 – μ2 = 1.43 – 0.82 = 0.61 using a two-sided Mann-Whitney U test assuming that the actual data distribution is logistic when the significance level (alpha) of the test is 0.05 and the population standard deviation is 3.67 in both groups (Table 106).

7.6 Discussion

7.6.1. Main Findings

In this retrospective, all inclusive, population based research involving patients with heart failure and a reduced left ventricular ejection fraction, the risk of the primary outcome of all-cause mortality was lower in the ARB group than in the unexposed group (Table 72). In the full cohort, ARB demonstrated a statistically significant improvement over the unexposed group, with a 56.2% reduction in risk of all-cause mortality (HR 0.438; 95% CI: 0.357 to 0.537; P < 0.001) and a 36-month improvement in mean survival post incident diagnosis (30.9 months; 95% CI 30 to 31.7) compared to the unexposed group (24 months; 95% CI 22.9 to 25.1). In the cohort aged ≥ 70 years at incident diagnosis, ARB also demonstrated a statistically significant improvement over the unexposed group, with a 48.9% reduction in risk of all-cause mortality (HR 0.511; 95% CI: 0.400 to 0.652; P < 0.001) and a 36-month improvement in mean survival post incident diagnosis (29.2 months; 95% CI 27.8 to 30.5) compared to the unexposed group (22.5 months; 95% CI 21.1 to 23.9).

ARB exposure was similarly effective in patients diagnosed at ≥ 70 years as in the general patient population with HFrEF including those diagnosed at < 70 years of age (Tables 72, 74). This benefit was statistically highly significant and remained constant throughout the 3-year follow-up post first diagnostic echocardiogram. This demonstration of survival benefit of ARB in patients diagnosed at ≥ 70 years provides support for prior suggestions that this treatment has survival benefit in geriatric heart failure patients with reduced ejection fraction comparable to younger patients (224, 234, 235). Therefore this study provides evidence for the therapeutic role of ARB in patients with HFrEF beyond the age of 70 years.

The lowering of all-cause mortality was generally homogenous across most of the prespecified subgroups for both cohorts, although three comparisons suggested possible heterogeneity with no benefit in the Charlson score of 1 subgroup for both cohorts and in the carvedilol and spironolactone subgroups for the cohort aged ≥ 70 years at baseline (Tables 77, 87, 89). However, it is it is inappropriate to assess the effects of treatment on a single subgroup by examination of the 95% CI for that subgroup and the general principle is that subgroup analysis should concentrate on differences from the average overall treatment effect via tests of interaction (207). Subgroup analysis showed no interaction between the reduction of all-cause mortality and the various prespecified variables in the full cohort (Figure 43). The absence of effect modification of ARB on all-cause mortality persisted in patients aged ≥ 70 years at incident diagnosis including Charlson comorbidity scores (Figure 44). Elderly patients are more susceptible to developing additional comorbidities and further compound the risks of heart failure that are enhanced with the onset of advanced age (208, 209).

The presence of digoxin or warfarin was indicative of existing atrial fibrillation or substantial thromboembolic burden. Both conditions portend considerable additional mortality however ARB still maintained a high beneficial effect (Tables 80, 82, 84, 86). Furthermore, the higher survival associated with ARB was not influenced by prespecified background therapy that may have modified the beneficial effect size (Tables 76, 78). The absence of effect modification suggests that the estimated hazard ratios for all-cause mortality indicated the true size of independent survival benefit for in both cohorts inherent in ARB therapy with respect to interaction with other heart failure therapy even for patients aged ≥ 70 years at diagnosis. This observation was further strengthened by the comparability of unadjusted to adjusted hazard ratios despite adjustment for all prespecified variables and incident diagnosis age ≥ 70 years (Tables 93, 104) (Figure 45). This study was highly powered to detect these differences in the primary endpoint of all-cause mortality outcome between the ARB exposed and unexposed groups (Table 105). This validated the observation of informative differences between the groups across the entire cohort and also within the subgroup of patients with ≥70 years diagnosis age.

The use of ARB as core RAS inhibitors for heart failure is established by three landmark, randomized trials showing this treatment reduced mortality even when added to other heart failure therapy (224, 236, 237). Since these trials occurred, new pharmacological approaches have demonstrated additional benefit when added to ARB. Consequently, it is possible that the incremental benefit of ARB might be modified when combined with other therapy associated with high survival benefit in heart failure. From a practical viewpoint, it is of interest to know whether the presence of background therapy influences the benefit of ARB as previously established by randomized, placebo controlled trials. This caveat is more pronounced for geriatric patients particularly when diagnosed late in life, considering that patients are living longer with heart failure compared to the time when landmark trials occurred (210). Therefore this study also attempted to address this question by examining the effectiveness of ARB in a real-world outpatient scenario with current heart failure pharmacotherapy and with a focus on patients diagnosed ≥ 70 years.

This is, to the best of my knowledge, the first observational study to demonstrate indirectly on a large scale, consistent survival benefit with ARB in a contemporary population with HFrEF regardless of whether patients are above 70 years of age. It also confirms that this benefit is incremental in this age group without effect modification by background heart failure therapy or increased comorbidity.

A key question is whether the survival benefit of ARB in elderly heart failure patients with reduced ejection fraction remains incremental with the same level of benefit as established by landmark trials in a younger population with different background heart failure therapy.

The observations from this research confirm that ARB in heart failure patients aged ≥ 70 years have survival benefit consistent with younger patients as demonstrated by previous trials and complimentary to contemporary heart failure pharmacotherapy. Therefore it is critical that these are prescribed in combination with other treatment to all appropriate patients in this age group who do not have demonstrable intolerance. This data also indicates that in patients aged ≥ 70 years with HFrEF, ARB can be added irrespective of other therapies since the survival benefit is neither dependent upon specific treatment, nor modulated by any combination of disease-modifying therapies for HFrEF (Tables 78, 82) (Figure 44). So far, this evidence was missing from published data and this study potentially provides reassurance with the knowledge that ARB work with different combinations of traditional heart failure treatment in patients aged ≥ 70 years. This observation is clinically critical considering that less than 2% of patients with chronic heart failure are receiving appropriate pharmacotherapy that prolong life, and that using, guideline-directed, broad-based combination of heart failure-modifying drugs may reduce mortality by as much as 75% (211, 212). Furthermore, delaying initiation of life saving medication to patients in the outpatient setting carries a greater than 75% chance that therapy will not be started within the next year (213).

This study failed to demonstrate lower hospitalisation for heart failure with ARB treatment both across the full cohort and in the cohort aged ≥70 years at incident diagnosis (Tables 96 and 98). In fact the ARB group in both cohorts demonstrated significantly higher hospitalisation compared to the unexposed group (Tables 97, 99). Both cohorts were highly powered to detect the reported variance as a true difference in the secondary endpoint between the ARB exposed and unexposed groups (Table 106). However, the variance in heart failure associated hospitalisation could not be explained by ARB therapy as demonstrated by a weak effect size attributed to ARB exposure (Table 100). This indicates that the outcome of the secondary endpoint was influenced by other unmeasured factors in this study that reversed the expected direction of effect. A possible explanation may be the higher prevalence of cardiac comorbidity in the ARB group that interfered with the detection of the true effect of ARB on heart failure associated hospitalisation. In fact, the ARB group carried a higher frequency of diuretics, digoxin and warfarin indicating greater cardiac comorbidity compared to the unexposed group. The prevalence of diuretics in the ARB group was 1.8 times that in the unexposed group across the full cohort and this ratio was consistent in the cohort aged ≥ 70 years diagnosis age (Tables 63, 64). Increased use of diuretics correlates with higher severity of heart failure and more frequent rehospitalisation due to acute decompensation of heart failure (214). However with the absence in this research of a heart failure-specific, functional capacity score such as the NYHA

classification, the influence of potentially higher cardiac comorbidity on the effect of ARB cannot be tested. Despite the absence of a heart failure-specific, valid health status measure of functional capacity as an indicator, there is sufficient indication that the ARB group carried greater cardiac comorbidity that translated into higher hospitalisation. In fact, the frequency of ischaemic heart disease in the treatment arm was twice that in the unexposed arm. The ICD 10 codes used to identify HF hospitalisation events also included erroneously other codes linked to a range of cardiovascular diseases where ischaemic heart disease is prominent. So the imbalance in ischaemic heart disease between arms led to a higher hospitalisation rate in the treatment arm that did not reflect true HF hospitalisation events. This disparity in disease distribution between groups introduced unmeasured confounding that led to selection bias for hospitalisation. This prevented the study from drawing a conclusion on the true effect of ARB on heart failure associated hospitalisation in elderly patients with HFrEF.

However, these observations present a paradox in the treatment arm between increased ischaemic heart disease, lower all-cause mortality with ARB, and the absence of interaction of background heart failure treatment with ARB for all-cause mortality. A greater frequency of IHD was accompanied by lower all-cause mortality in the treatment arm compared to the unexposed arm. Patients in the ARB exposed arm were also treated more intensely with carvedilol and spironolactone. Taken together, ARB and carvedilol provide cumulative survival benefit in IHD and this may explain the reduced all-cause mortality in the treatment arm. If this cumulative survival benefit was sufficiently strong to neutralise the increased risk from IHD and produce a net benefit of reduced mortality, one would expect a degree of interaction with ARB in their reduction of all-cause mortality in HFrEF as well. But paradoxically, no combination of background heart failure therapy was found to influence the survival benefit of ARB in HFrEF. The absence of a clear explanation for this observation puts more emphasis on repeating this research with propensity score matched groups to eliminate confounding biases from unmatched characteristics. Concerning this study, there is evidence of selection bias that prevents drawing a conclusion on the true effect of ARB on heart failure associated hospitalisation in elderly patients with HFrEF. The main cause appears to lie in the selection of ICD10 codes that defined hospitalisation and this is explained in detail under limitations.

7.6.2. Strengths

Both cohorts were well powered to detect the identified variances as true differences in the primary endpoint for this study (Table 105). Apart from serving to validate the difference in effect between the main groups, the magnitude of the power was also sufficient to allow

exploration for differences in prespecified subgroups and determine if overall survival benefit identified in the main Cox regression model persisted. The inclusion of subgroup analysis in the Cox regression model also determined the extent of stability of this benefit across key subgroups of concern particularly with various combinations of background heart failure therapy. The influence of background therapy on the impact of individual heart failure treatment is an evidence gap that only started being investigated recently (215, 216). To the extent of my knowledge this is the first study to gain an insight into the efficacy of ARB in subgroups with varied treatment combinations in geriatric patients with HFrEF. The use of log-minus-log plots confirmed that all Kaplan-Meir plots did not violate the assumption of constant benefit of survival against instantaneous risk of all-cause mortality throughout the 3-year follow-up (Figures 41, 42). The exhaustive process of sensitivity analysis demonstrated a high degree of robustness for the primary endpoint of all-cause mortality. Due to the retrospective nature of the study that limited the control of confounding and the absence of propensity score matching of subjects, sensitivity analysis was performed using a falsification endpoint for residual confounding (196, 197). The absence of a difference in risk for pulmonary disease between the ARB and unexposed group further validated the observations of this study for the primary endpoint (Table 103). Hazard ratios and their 95% confidence intervals remained consistent for as-treated, intention-to-treat and per protocol study approaches demonstrating an association of ARB with survival in patients aged ≥ 70 years with HFrEF that was robust to most scenarios of measured and unmeasured confounding (Table 104) (Figure 45).

7.6.3. Limitations

The ARB exposed and unexposed groups were not balanced with regards to background heart failure treatment (Tables 63, 64). While background treatment was not found to influence survival outcome, this imbalance between groups may have introduced an unmeasured, potential covariate with strong confounding that led to bias in the statistical tests for the secondary endpoint (217). In this respect, this study lacked information on other important prognostic indicators such as BMI, systolic blood pressure, smoking, and blood haemoglobin concentration at baseline. Consequently, it was not possible to test these factors as variables for confounding of the true outcome for the secondary endpoint attributed to ARB exposure. Renal disease was also not balanced between groups in the full cohort although this variance was not found to be clinically meaningful for the primary endpoint of all-cause mortality (Table 101). Mean LVEF for the two groups was balanced at baseline. However the ARB exposed group required more intense heart failure pharmacotherapy including higher use of diuretics. This may indicate that cardiac functional

capacity in the ARB group was worse hence requiring greater rehospitalisation compared to the unexposed group although this argument is paradoxical since the ARB group had a significantly higher survival benefit. Another limitation was the unequal patient allocation with a ratio greater than 2 to 1 between the two study arms for both cohorts. Unequal ratio for patient allocation is associated with bias if the patients in the two arms of the study differed in important characteristics (218) and probably this reversed the expected direction of the effect of ARB on hospitalisation (Tables 96, 97, 98, 99). This limitation also has consequences for statistical power. A 2 to 1 allocation ratio requires 12% more patients than a study using a 1 to 1 ratio to detect the same size effect with equivalent power (219). The post hoc power estimation took into consideration the unequal patient allocation between the study arms. While this does not appear to have affected the size effect on all-cause mortality as a result of a sufficiently sustained sample power, the reduction of size effect detection potentially underestimated the true effect size of ARB on hospitalisation (Table 100). Issues of unequal patient allocation ratios and imbalance of baseline, prognostic variables are inherent to non-randomised studies and since this study was retrospective, reducing these limitations was restricted by the patients available historically (218).

A more potential reason for significantly higher readmissions in the treatment arm lies in the range of ICD10 codes used to identify the number of heart failure associated readmissions for analysis. A re-examination of the codes utilised by the data provider revealed that in addition to the ICD10 codes directly related to heart failure (I11, I25.5, I42.0, I42.6, I42.9, I50, I50.0, I50.1, I50.9), a series of other codes were used that are linked to a range cardiovascular diseases where ischaemic heart disease is prominent including myocardial infarction (I10 to I79, I95, R06, R07). These were included by the data provider in an effort to try to capture other admissions with incomplete or wrong coding at the Emergency Department and potentially related to heart failure. An analysis of disease characteristics revealed that the treatment arm contained almost twice the frequency of ischaemic heart disease confirmed at baseline compared to the unexposed arm as comparator. This disparity in disease distribution between groups introduced extensive unmeasured confounding that was sufficiently strong to cause bias in the statistical test for the secondary endpoint (217).

The evidence-based target doses of ARB and background therapy are well defined with evidence of a dose-response relationship of reduction in all-cause mortality and heart failure hospitalisation (66, 100). Yet, target doses are infrequently achieved in clinical practice (211, 220). Therefore, it is possible that the incremental benefit of ARB may be less if dosing for ARB or any of the background therapy was not optimized. This study was not designed to demonstrate consistent benefit of ARB irrespective of whether treatment was optimized. A related limitation is the presence of sacubitril valsartan that became available late in the

study follow-up phase in 2016. These patients were not identified in this study. However, patients that switched to this treatment were censored at the time of stopping ARB. From 2016 to December 2021 there were approximately 350 patients that received this treatment (personal communication, February 2022). So the number was minor compared to the large sample sizes of both cohorts. Additionally, the only renin angiotensin system blocker treatment for all patients in this study were ARB during the 3-year follow-up or until censoring. Moreover, none of the background heart failure therapy modified the outcome of ARB on all-cause mortality (Tables 76, 78) (Figures 43, 44). Therefore it is justified to assert that sacubitril-valsartan did not exert any influence on treatment or survival in this study albeit censoring was required.

Another limitation is the absence of comprehensive information on the cardiac functional capacity of patients. The original plan for the study protocol was to include data capture of the NYHA scores at baseline and upon completion of the 3-year follow-up. The pilot study revealed that in practice, functional scores for heart failure severity are rarely recorded. This prevented a complete description of the study population at baseline and precluded analysis of the effect of ARB interaction with heart failure progression through follow-up. Similarly, the availability of NT-proBNP testing became available in 2016 when the protocol for the complete research programme was finalized for UREC approval and 9 years after the index year identified to start data capture that is in 2007. Therefore this prognostic data was also not part of the study design and research relied on LVEF from the primary diagnostic echocardiogram as the only clinical parameter of informative status.

Length of hospital-stay related to heart failure in conjunction with associated hospital readmission would have provided more reliable information to inform on the secondary outcome measure of HFrEF morbidity (221, 222). Extracting this data required identification of admission and discharge dates from electronic and physical records, with manual calculation of the in-hospital days. In view of the time constraints for this research, this exercise was not feasible.

Finally, since this research was a single centre study that was also retrospective and non-randomised, there were design limitations and statistical issues associated with limited sample size that led to unequal patient allocation, selection bias that introduced baseline imbalance, the inevitable presence of confounding variables, and the lack of generalizability to a broader population. For these reasons, this study lacked internal and external validity to provide indisputable evidence to clinical practice.

7.6.4. Comparisons

Comparison of this research with previous studies can be done at 2 levels – landmark placebo-controlled, randomised trials in the general population with HFrEF and subgroup analysis of these studies specific for patients over 70 years. The CHARM-Added trial demonstrated a 37.9% reduction in cardiovascular mortality and a decrease in heart failure hospitalisation by 42.3% in HFrEF with NYHA class II to IV heart failure symptoms (237). Beneficial results were similarly found for both endpoints in symptomatic HFrEF by other trials including the Charm-Alternative study (237, 238). The CHARM-Overall programme established this survival benefit to be maintained over at least 37 months and persisted across all patients with LVEF of 40% or less. Similar risk reductions were observed among patients with and without diabetes at baseline. More importantly, the subset of patients aged 75 years or older showed as great a benefit with ARB as did younger patients (224). The beneficial effects of ARB in the CHARM programme were not altered by baseline heart failure therapy despite the fact that 55% of the patients recruited were receiving this treatment. Subgroup analysis of the CHARM-Overall trial also reported nonsignificant age-by-treatment interaction with significant mortality benefit with ARB in patients aged ≥70 years (224) Relative risk reduction in cardiovascular death or heart failure hospitalisation was similar across all age groups with ARB regardless of age (234). However the benefit increased with advancing age because of the higher morbidity and mortality in the elderly where the combined risk of cardiovascular death or heart failure hospitalisation was 46% in the oldest age group compared to 24% in the youngest age group. A post hoc analysis of Val-HeFT demonstrated similar risk reduction in the composite endpoint of the first morbid event (death, sudden death, heart failure hospitalisation or urgent heart failure treatment) regardless of age. Half of the patients recruited were aged > 65 years (235). Risk reduction in morbidity was 11.8% in patients aged > 65 years versus 14.6% in those aged < 65 years. Beneficial effects were also observed on left ventricular function and size, quality of life and levels of natriuretic peptides, regardless of age. Although the use of this trial for comparison is limited since 93% of patients also had ACEI.

Despite strong evidence about the benefits of ARB in the general population with HFrEF without evidence of age-related heterogeneity in major RCTs, none of the trials selectively enrolled patients with an inclusion criterion specific for age >70 years. Mean baseline age was 64 years for CHARM-Added, 66.8 years for CHARM-Alternative, 66 years for CHARM-Overall, and 62 years for Val-HeFT. The proportion of patients recruited aged ≥ 75 years was between 17% and 23% in the CHARM programme. Therefore these landmark trials were not representative of patients aged over 70 years especially with added comorbidities and data is limited in this age group with HFrEF (239).

Notwithstanding this drawback, a parallel can be drawn with this research for high and sustained survival benefit that is not modified with other therapy for patients aged ≥ 70 years. Significantly, subgroup analysis of this research revealed no interaction with background heart failure treatment indicating that benefit is independent and incremental in patients ≥70 years. Furthermore, the mortality reduction in elderly patients persisted in this research even with additional comorbidity, albeit with a higher survival benefit as observed in landmark trials. This research demonstrated a reduction in all-cause mortality of 48% in patients aged ≥ 70 years at baseline and 56% in the full cohort analysis, compared to the 10% reduction for the same outcome in the CHARM-Alternative trial (240). Possible reasons for this discrepancy include failure to use ARB due to poor overall care and impact of other heart failure treatment modalities or greater use of anticoagulants in the unexposed group (33, 98). However this research does not support these claims. There are two other reasons that are considered more plausible for this research. The first is selection bias in view of the imbalance in baseline characteristics and second is the patient allocation ratio between the two study arms. These limitations can cause single-centre trials to provide inflated treatment effect estimates compared to multicentre trials (217). Furthermore, disease characteristics at baseline were not balanced between both study arms. This may have introduced covariates that lead to unmeasured biases. Additionally, the presence of non-comparable baseline characteristics due to selection bias coupled with unequal patient allocation may have introduced unmeasured comorbidity in the unexposed arm that led to poorer prognosis. Renal function was significantly poorer in the unexposed arm for the full cohort analysis though this failed to be demonstrated in the cohort for ≥70 years at baseline due to the high proportion of missing values for serum creatinine and eGFR. Another possibility is that real-world patients on treatment have better baseline prognosis than patients in landmark trials due to better use of treatment that reduce the incidence of sudden death in symptomatic HFrEF. This may explain the lower mortality in the ARB treated group for this research compared to treated patients in randomised trials (210).

The CHARM-Alternative trial also indicated a large benefit of 48% reduction in heart failure hospitalisation. Although there was no subgroup analysis for patients aged ≥ 70 years, 23% of patients were aged ≥ 75 years (237). This research reversed the outcome for hospitalisation observed in previous studies with higher events demonstrated in the ARB group. However the effect was not attributed to ARB possibly due to selection bias and an imbalance in the patient selection ratio.

Apart from the absence of selective enrolment of patients aged ≥ 70 years, another drawback with using these trials and subgroup analysis for comparison is noncontemporary data since these trials occurred between 2001 and 2003 when heart failure therapy was

different. In 2016 a study was done on 138 patients aged > 70 years which demonstrated an adjusted HR of 0.24 that increased to 0.27 with age ≥ 80 years. (229). However, the inclusion criteria included ACEI or ARB with results published collectively. So using this study for comparison is again limited. Besides the fact that there is limited data available concerning ARB in patients aged ≥ 70 years, there is also the absence of data investigating continuous, lifelong therapy with ARB (225).

One final comparison is the result demonstrated by this study where the risk of mortality in patients aged ≥ 70 years at baseline doubled compared to patients aged < 70 years at incident diagnosis within the ARB exposed group (Table 65). Incident diagnosis in elderly patients raises the concern that many heart failure diagnoses are missed in the outpatients setting (231). Age was proven to be an independent predictor of 1-year mortality in patients with heart failure and increasing age at diagnosis was associated with increased mortality (228, 232). Earlier recognition and intervention can also mitigate heart failure morbidity (2). Furthermore, This observation confirms evidence from a smaller study where the presence of chronic heart failure in older patients resulted in an approximately 50% reduction in life expectancy (233).

The outcome of this research with the use of ARB was very similar to that obtained in the preceding study on the effect of ACEI. The results demonstrated by both studies were comparable for the outcome of hospitalisation and this indicated the same level of bias and study design deficiencies in attempting to measure the effect of treatment on the secondary endpoint. Even more significant was the overall result of the effect of treatment on all-cause mortality which is almost identical. These observations lead to the question of potential similarity of treatment effect on survival between ACEI and ARB particularly in HFrEF patients aged ≥70 years. The subsequent research attempted to test the hypothesis of comparative effectiveness between the two drug classes for the same primary and secondary endpoints. In view of lower incidence of HFrEF associated mortality observed in females, where ARB were also preferred, the possibility for superiority of ARB over ACEI was also investigated.

7.7 Conclusion

1. ARB reduced all-cause mortality substantially in patients aged ≥70 years with HFrEF.
2. This benefit is comparable to the general population with HFrEF.
3. The observed survival benefit was maintained during the 3-year follow-up.
4. This benefit was incremental and independent of other heart failure treatment and comorbidity.

5. Age reduced life expectancy with the risk of mortality in patients aged ≥70 years doubled compared to patients diagnosed <70 years.
6. These results were observed at 3-year follow-up post primary diagnosis with HFrEF.
7. This research demonstrates similar results to those observed in study 2 with ACEI.
8. The result obtained for hospitalisation is inconclusive and requires a more rigorous study design.
9. This research indicates critical areas for statistical improvement for future studies.

8. STUDY 4

8.1. Aims and Objectives

ARB versus ACEI in a contemporary cohort of adults aged 70 years or older and diagnosed with reduced ejection fraction

The null hypothesis was that there is no difference between both treatment modalities. The alternative hypothesis was that ARB are superior to ACEI. The primary endpoint for investigation was all-cause mortality with a separate secondary endpoint of heart failure associated hospitalisation.

8.2. Inclusion / Exclusion Criteria

Subjects met the following inclusion and exclusion criteria:

Inclusion criteria

- Documented left ventricular systolic dysfunction defined as left ventricular ejection fraction ≤40%
- Age ≥ 50 years at incident diagnosis for the study; < 70 years for positive control arm
- Treatment with ACEI or ARB

Exclusion criteria

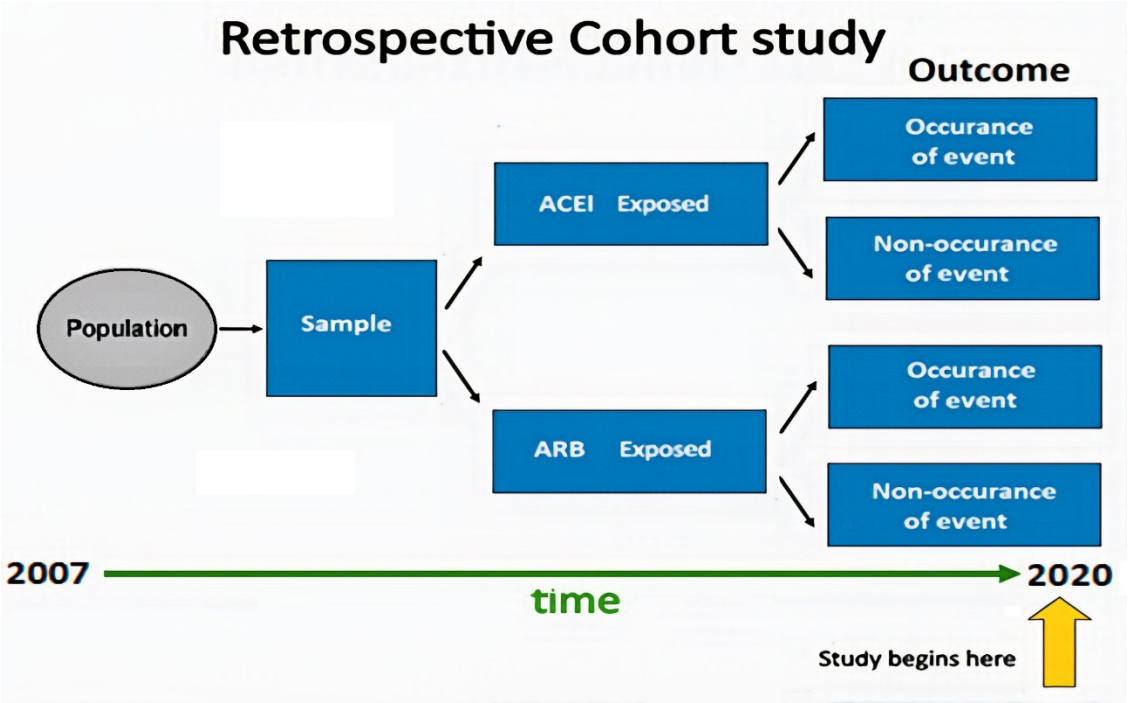
- Left ventricular EF not available
- Diastolic heart failure (HFpEF)
- Myocardial infarction, cardiac surgery, or percutaneous transluminal coronary angioplasty (PTCA) within 8 weeks
- Need for cardiac surgery (e.g., severe valvular disease, planned coronary artery bypass graft surgery) or PTCA in the near future. (Such patients are eligible after surgery or PTCA). Patients on heart transplant list are not eligible
- Intravenous inotropic agents within 45 days
- Potassium above 5.5 mmol/L
- Creatinine > 3.0 mg/dL
- Presence of cardiac implantable devices

8.3. Design

The cohort was made up two study arms, one with ACEI and another with ARB exposure. All patients diagnosed with a documented echocardiogram from 2007 to 2017 were included. The design was applied for the full cohort with an age limit of ≥ 50 years and a second cohort aged ≥ 70 years. The index age was the patient's age at incident diagnosis. A

comparison arm was also included for patients aged under 70 years and exposed to ACEI and ARB as a positive control to compare outcome with published trials. Patients were followed retrospectively for three years or until censored from time of incident diagnosis. The primary endpoint was all-cause mortality with a secondary endpoint of heart failure associated hospitalisation. The next schematic explains the stages of the study design (Figure 46).

Figure 46: Schematic of the study design – study 4



The study involved testing ARB in the active group against an active control group with ACEI as standard therapy. Baseline clinical descriptors collected were age and date for diagnosis and death, sex, ejection fraction, ACEI and ARB treatment duration, additional heart failure therapy, warfarin and digoxin treatment, Charlson comorbidity score, and associated hospitalisation frequency. The inclusion of digoxin and warfarin was taken as an indication of the presence of significant additional cardiovascular morbidity that increase mortality risk and possibly lead to confounding of the primary endpoint of all-cause mortality. The majority of patients in the study population with substantial thromboembolic burden were on Warfarin. While patients on digoxin was indicative of atrial fibrillation coexisting with heart failure. Both comorbidities portent considerable additional mortality and inclusion of these two medicines allowed for atrial fibrillation and thromboembolic disease to be analysed as potential covariates for possible confounding of the primary endpoint.

8.4. Statistical Considerations

8.4.1. Sample Size and Power

This study aimed to compare the survival functions of two active treatment groups as described by Chow et al. (2008) (202) and by Christensen (2007) (241). This was addressed by testing the null hypothesis that the effectiveness of ACEI and ARB are comparable in patients with HF and left ventricular ejection fraction ≤ 40% with no difference in the primary and secondary clinical endpoints. The alternative hypothesis holds that ARB are superior to ACEI with a difference in the clinical endpoints (Appendix 10.8.4).

The SOLVD trial showed that ACEI reduced 4-year all-cause mortality from heart failure by 16% (RR 0.84; 95% CI 0.74-0.95; P=0.0036) when compared with placebo (95). Cardiovascular hospitalisation was also reduced by 10% (RR 0.90; P < 0.001). Mortality rate from heart failure extracted from North American and Scottish data was estimated at 28% adjusted for 1 year (194). Assuming a constant risk ratio during SOLVD for the primary endpoint and a sample size ratio of 1 for ACEI to ARB exposed groups, the study needed to recruit 2902 subjects which would provide a power of 80% to detect a relative reduction of 16% in the risk of all-cause mortality in the ARB group at a two-sided alpha level of 0.05. The superiority threshold for hospitalisation was set to a limit of 20% decrease in mean hospitalisation for ARB compared to ACEI (Appendix 12.8.4.).

8.4.2. Statistical Analysis

Baseline characteristics for ARB and ACEI exposed patients at the first month of follow-up were compared using the mean and standard deviation for each group. Rates for all-cause death were calculated per 1000 person-years with associated 95% confidence limits.

The primary treatment comparisons between groups were performed according to the as-treated (AT) principle based on a time-to-event analysis. Patients were also censored for terminating ACEI or ARB and for switching between ACEI and ARB the 3-year follow-up. Kaplan-Meier cumulative event rates were calculated for each group, with event or censored times measured from the time of incident diagnosis. These plots estimated probability for unadjusted all-cause mortality with ACEI or ARB exposure. Differences between curves were tested for significance by log-rank test. Kaplan-Meier plots were tested for the assumption of constant relative risk using log-minus-log plots. Relative risks were expressed as hazard ratios with associated 95% confidence intervals derived using the Cox proportional hazards model. The Cox model was also used for subgroup analysis to assess the consistency of treatment effect by testing for interactions between index treatment (ACEI / ARB) and the prespecified variables of background heart failure treatment, digoxin,

warfarin and the Charlson comorbidity score (195). Each variable was tested individually for interaction using the enter method in SPSS. Hazard ratios from the main Cox regression model were adjusted for all prespecified variables together through simultaneous entry in a multivariable Cox model. This allowed analysis of the primary endpoint measure in a cohort that reflected a real-world population considering that these patients are typically on multiple medications for heart failure and have additional comorbidities. Two-sided significance testing was used with a conventional significance level of 0.05 and 95% confidence intervals.

The frequency of associated hospitalisation events during the 3-year follow-up period was checked as a dependent variable for normality distribution for each level of the independent variable of treatment with ACEI and ARB using the Shapiro-Wilk test. The null hypothesis for the Shapiro-Wilk test was that the scores in the dependent variable are normally distributed. Hospitalisation scores failed to meet the normality assumption for the t-test and a Mann-Whitney U test was conducted to analyse for differences in hospitalisation scores between the two groups in each cohort.

Four levels of sensitivity analysis were done to test for robustness of results. ACEI and ARB exposed groups were compared for the values and proportions of missing laboratory values as well as the mean of plasma potassium, serum creatinine, eGFR, bilirubin and LVEF. The t-test or Mann-Whitney U test was used depending on the Shapiro-Wilk test for normality to identify potential confounding covariates leading to bias. Variables with significant p-values were tested with Cox regression interaction analysis to check for modification of effect of index treatment on mortality in the main Cox regression model.

Analysis using a falsification endpoint was performed for residual confounding (196, 197). Risk of outpatient pulmonary disease (asthma or chronic obstructive pulmonary disease) was selected as this was unlikely to be affected by treatment with or without the index drug. Unadjusted hazard ratios from the primary Cox regression model with AT analysis were compared with intention-to-treat and per-protocol analyses. This tested the robustness of association of ARB versus ACEI exposed groups with mortality to measured and unmeasured confounding. The intention-to-treat analysis did not censor for patients at the time of discontinuation of index treatment or treatment class switching and followed for 36 months post incident diagnosis. This preserved the baseline comparability and provided conservative estimates of differences between treatment groups. In the per-protocol analysis, patients with treatment switching between drug classes were removed from the cohort (198).

Finally, follow-up analysis of post hoc sample power was done of the observed effect based on the actual sample size and parameter estimates derived from the data set in view of the unequal patient allocation ratios between groups. (199).

All analysis was done for the two study arms for full cohort and independently for the cohort of patients aged ≥70 years at incident diagnosis which was taken as baseline. Additionally, unadjusted hazard ratios were determined for the positive control group of patients aged < 70 years at incident diagnosis. This control arm provided a direct comparison with the survival outcome of the other two study arms and allowed confirmation that the study still exhibited the same survival benefit as shown by landmark trials where mean age was below 70 years. Analysis included data of patients diagnosed between 2007 – 2017 and was done with SPSS version 26, Stata version 17, and PASS Pro 2021.

8.5. Results

8.5.1. Baseline characteristics

Table 107: Baseline comorbidities of full cohort – study 4

Disease	ARB %	ACEI %
Arrythmias	15.6	13.2
Cerebrovascular disease	1.9	2.7
Chronic kidney disease	6.4	5.2
Dementia	1.3	1
Diabetes	15.6	13.4
Genetic dyslipidaemia	5.8	6.8
Hypertension	28.9	24.9
Ischaemic heart disease	25	22.7
Malignant diseases	3.9	3.5
Peripheral vascular disease	1.9	2.1

Table 108: Baseline characteristics for comorbidities of cohort aged ≥ 70 years – study 4

Disease	ARB %	ACEI %
Arrythmias	16.1	14
Cerebrovascular disease	2.9	3.4
Chronic kidney disease	8	6.1
Dementia	2.2	1.5
Diabetes	12.8	12.3
Genetic dyslipidaemia	5.5	6.6
Hypertension	29.9	25.2
Ischaemic heart disease	24.5	22.9
Malignant diseases	4.7	4.1
Peripheral vascular disease	1.1	2.3

Table 109: Baseline characteristics for full cohort – study 4

Full cohort (N=2211) Characteristics	ACEI Arm (n=1678)	ARB Arm (n=533)
Diagnosis age (Yrs)		
Mean (Std. Deviation)	70.7 (9.1)	71.1 (8.6)
Median	70.5	70.2
Sex		
Males	1245 (74.2%)	339 (63.6%)
Females	433 (25.8%)	194 (36.4%)
LVEF %		
Mean (Std. Deviation)	33.9 (9)	34.8 (7.5)
Median	37	37
Charlson comorbidity score		
0	802 (47.8%)	251 (47.1%)
1	59 (3.5%)	24 (4.5%)
2 - 3	498 (29.7%)	144 (27%)
≥ 4	319 (19%)	114 (21.4%)
Background treatment		
Carvedilol	1009 (60.1%)	319 (59.8%)
Spironolactone	688 (41%)	232 (43.5%)
Nitrates + Hydralazine	19 (1.1%)	8 (1.5%)
Loop Diuretics	1371 (81.7%)	472 (88.6%)
Digoxin	338 (20.1%)	126 (23.6%)
Warfarin	656 (39.1%)	218 (40.9%)
Hospitalisation		
Total	2063	685
Mean (Std. Deviation)	1.23 (2.058)	1.29 (2.190)

Table 110: Baseline characteristics for cohort aged ≥ 70 years – study 4

Cohort ≥ aged 70 years (N=1158) Characteristics	ACEI Arm (n=884)	ARB Arm (n=274)
Diagnosis age (Yrs)		
Mean (Std. Deviation)	77.8 (5.3)	78.1 (4.9)
Median	77	77.6
Sex		
Males	614 (69.5%)	145 (52.9%)
Females	270 (30.5%)	129 (47.1%)
LVEF %		
Mean (Std. Deviation)	34.5 (8.6)	35.1 (8.6)
Median	37.8	37.6
Charlson comorbidity score		
0	436 (49.3%)	135 (49.3%)
1	28 (3.2%)	13 (4.7%)
2 - 3	247 (27.9%)	70 (25.5%)
≥ 4	173 (19.6%)	56 (20.4%)
Background treatment		
Carvedilol	484 (54.8%)	153 (55.8%)
Spironolactone	341 (38.6%)	117 (42.7%)
Nitrates + Hydralazine	11 (1.2%)	5 (1.8%)
Loop Diuretics	762 (86.2%)	246 (89.8%)
Digoxin	199 (22.5%)	76 (27.7%)
Warfarin	347 (39.3%)	121 (44.2%)
Hospitalisation		
Total	1131	397
Mean (Std. Deviation)	1.28 (1.978)	1.45 (2.386)

A total of 1678 patients (mean diagnosis age 70.7 ± 9.1 years) filling a prescription for an ACEI were identified while 533 patients (mean diagnosis age 71.1 ± 8.6 years) received an ARB. The cohort for patients diagnosed at 70 years or more consisted of 884 patients (mean diagnosis age 77.8 ± 5.3 years) treated with ACEI and 274 patients (mean diagnosis age 78.1 ± 4.9 years) with ARB treatment. The groups were balanced with respect to baseline characteristics including cardiac function, Charlson comorbidity scores and background heart failure treatment as well as baseline comorbidities. This result was observed in the full cohort and in the cohort aged ≥ 70 years at incident diagnosis. (Tables 107, 108, 109, 110).

8.5.2. Epidemiology: All-Cause Mortality

Table 111: Mortality rate and mortality rate ratio - study 4

Cohort	MR ACEI Exposed	MR ARB exposed	MRR	95% Confidence interval	Two-sided p-value
Full cohort	0.114	0.100	0.878	0.719 - 1.065	0.183
Cohort aged ≥ 70 years	0.156	0.135	0.869	0.679 - 1.101	0.238

MR: Mortality rate per person-year
MRR: Mortality rate ratio

Of the 2211 patients included in the full cohort study, 609 had a fatal all-cause event during the follow-up period of 36 months post incident diagnosis. The mortality rate per 1000 person-years was 114 for the ACEI exposed and 100 for the ARB exposed group. In the cohort of 706 patients aged ≥ 70 years at baseline, 410 had a fatal all-cause event during the 3-year follow-up. The mortality rate per 1000 person-years was 156 for ACEI exposed patients and 135 for the ARB exposed group. The mortality rate ratio of all-cause mortality for the comparison of the ARB exposed group to the ACEI exposed group was 0.878 (95% CI 0.719 to 1.065, P = 0.183) in the full cohort, and 0.869 (95% CI 0.679 to 1.101, P = 0.238) in the cohort aged ≥ 70 years at baseline (Table 111).

8.5.3. Survival Analysis

8.5.3.1. Kaplan – Meier Estimates

8.5.3.1.1. Kaplan-Meier Plots

Figure 47: Kaplan-Meier plot for full cohort – study 4

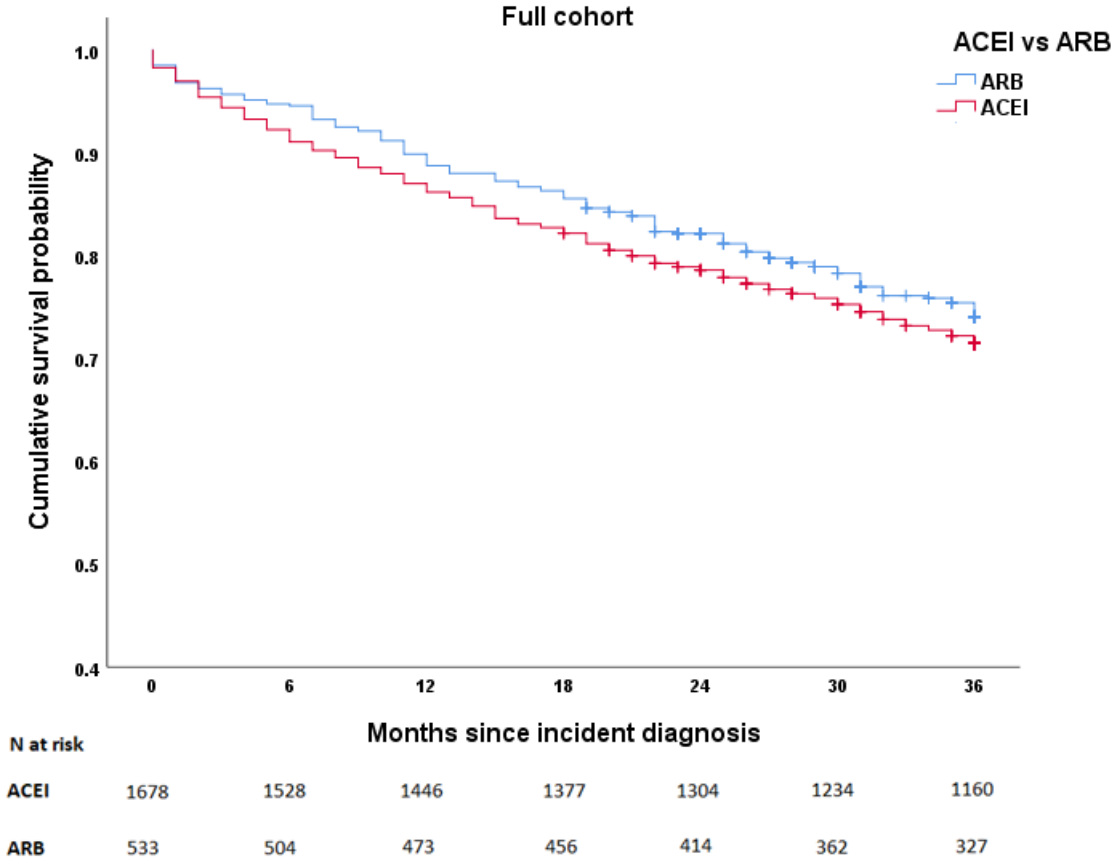


Table 112: Means for Survival Time (Months) for figure 47

	Mean[a]		95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound
ARB	30.987	.445	30.115	31.858
ACEI	29.972	.274	29.434	30.510

a. Estimation is limited to the largest survival time if it is censored.

Table 113: Log Rank test for figure 47

	Chi-Square	P-value
Log Rank (Mantel-Cox)	1.790	.181

Test of equality of survival distributions for the different levels of ACEI vs ARB.

Figure 48: Kaplan-Meier plot for cohort aged ≥ 70 years – study 4

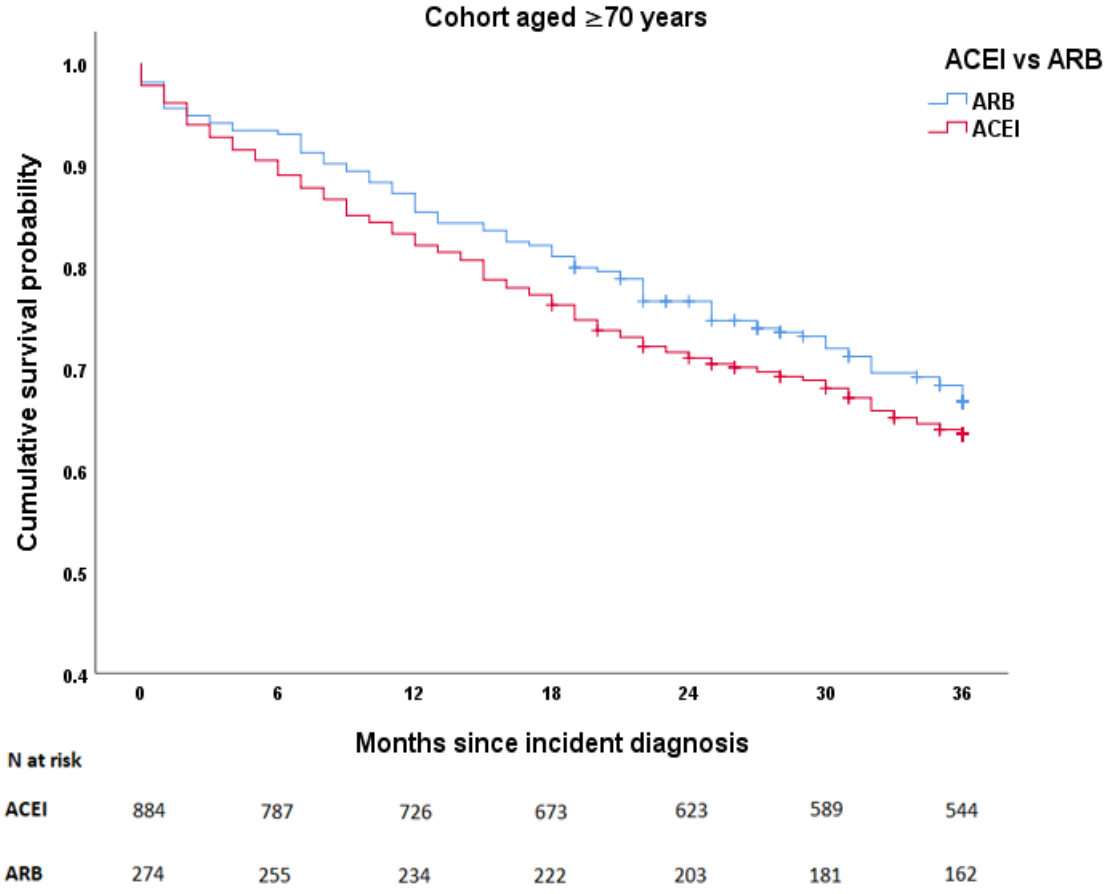


Table 114: Means for Survival Time (Months) for figure 48

	Mean[a]		95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound
ARB	29.503	.684	28.163	30.844
ACEI	28.127	.412	27.320	28.934

Table 115: Log Rank test for figure 48

DiagAgeMonth70		Chi-Square	P-value
70 plus	Log Rank (Mantel-Cox)	1.369	.242

Test of equality of survival distributions for the different levels of ACEI vs ARB.

Figure 49: Full cohort composite Kaplan-Meier plot – study 4

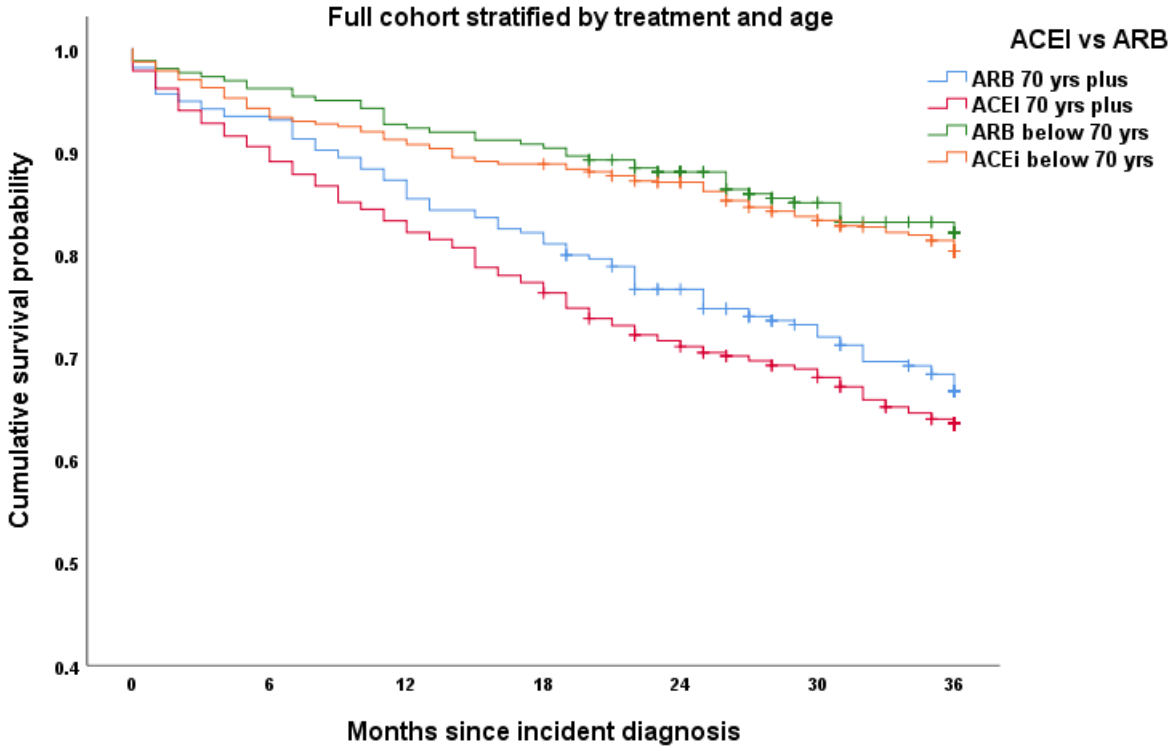


Table 116: Means for Survival Time (Months) for figure 49

	Mean[a]		95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound
ARB 70 plus	29.503	.684	28.163	30.844
ACEI 70 plus	28.127	.412	27.320	28.934
ARB below 70	32.565	.549	31.489	33.640
ACEI below 70	32.027	.342	31.357	32.697

a. Estimation is limited to the largest survival time if it is censored.

Table 117: Log Rank test with pairwise comparisons for figure 49

	Log Rank (Mantel-Cox)			
	ACEI exposed 70 plus		ACEI exposed below 70	
Study Arm	Chi-Square	P-value	Chi-Square	P-value.
ARB exposed ≥ 70 years	1.369	.242		
ARB exposed below 70			0.416	0.519

The decrease in the probability of survival followed the same pattern with time for the ACEI exposed and ARB exposed groups in the full cohort analysis and in the cohort age ≥ 70 years at incident diagnosis. The rate of decline was higher for the ACEI exposed group in both cohorts however this difference in survival was not significant throughout the follow-up period. The 3-year cumulative survival probabilities were 71.6% in the ACEI exposed versus

75% in the ARB exposed group for the full cohort (P = 0.181) and 63.7% in the ACEI group versus 67.5% in the ARB exposed group for the cohort aged ≥ 70 years at incident diagnosis (P = 0.242). In patients with diagnosis age < 70 years the 3-year cumulative survival probability was 80.5% for ACEI exposed compared to 83% for ARB exposed patients (P = 0.519) (Figures 47, 48). The results of the log-rank tests indicated that the absence of a statistically significant difference in survival between ACEI and ARB exposed groups as demonstrated in the full cohort was also exhibited in the cohort with incident diagnosis age ≥ 70 years and observed in the cohort aged < 70 years at baseline as well.

8.5.3.1.2. Log-minus-Log plots of Kaplan-Meier estimation

Figure 50: Log-minus-log plot for Kaplan-Meier estimation – full cohort – study 4

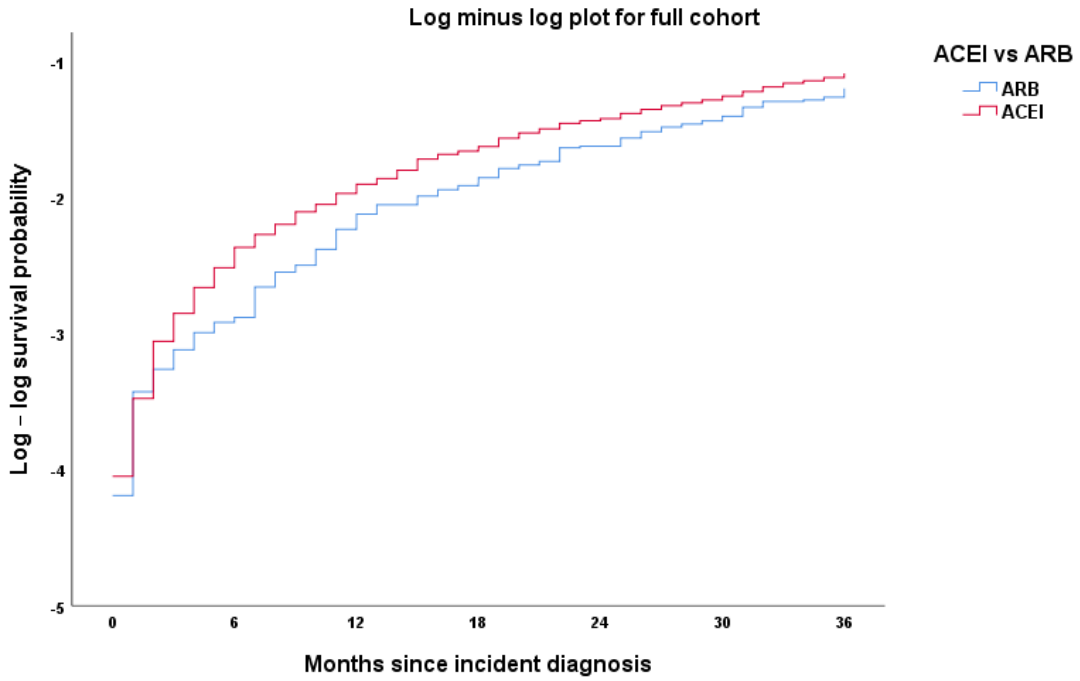
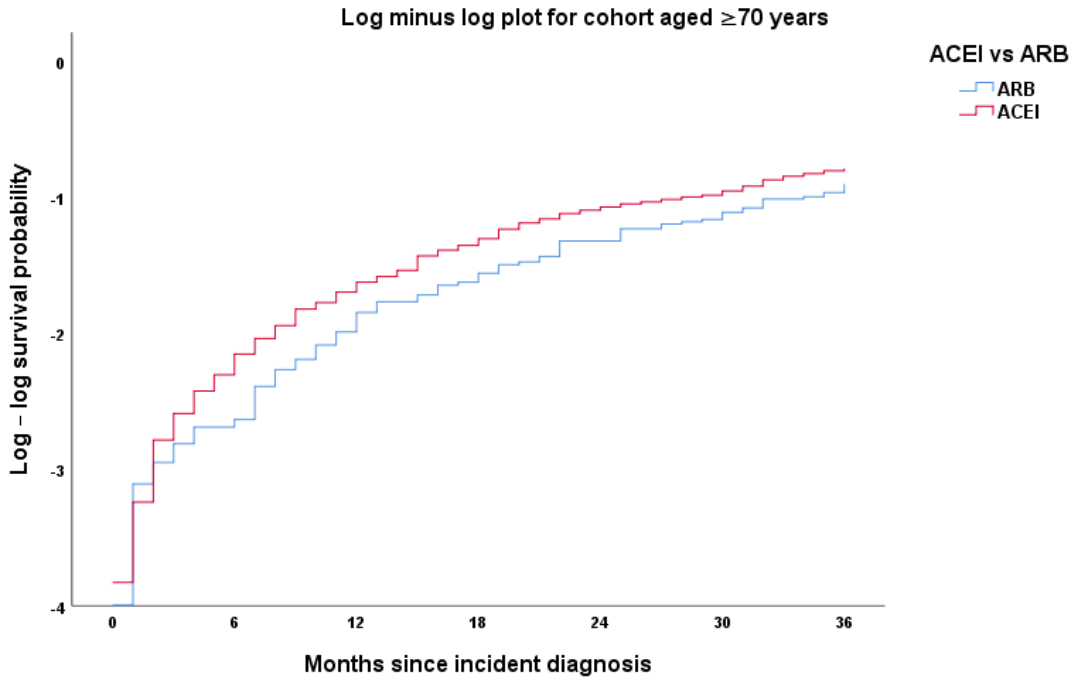


Figure 51: Log-minus-log plot for Kaplan-Meier estimation – cohort aged ≥ 70 years – study 4



Log-minus-log plots were used to test the assumption of constant relative risk. The log-rank test in Kaplan-Meier plots uses this assumption when comparing survival curves between two groups. This means that the risk of mortality in one group relative to the other does not change with time. Log minus log plots for full cohort analysis and for the cohort aged ≥ 70 years showed that the two curves do not meet and are parallel during the follow-up period. Therefore, in both cohort the proportional hazards assumption was not violated. This means that the survival probabilities were the same for patients throughout the 3-year follow-up period (Figures 50, 51).

8.5.3.2. Cox Proportional Hazards Regression Analysis

8.5.3.2.1. Main Model

Table 118: Cox regression for full cohort and cohort aged ≥ 70 years – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
Full cohort	-.131	.183	.878	.724	1.064
Cohort aged ≥ 70 years	-.139	.245	.870	.688	1.100

Table 119: Cox regression for age ≥ 70 years exposed vs age < 70 years exposed – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
ARB	.711	<0.001	2.037	1.419	2.923
ACEI	.729	<0.001	2.074	1.712	2.513

In the full cohort analysis, the hazard ratio of mortality in the ARB exposed group was 0.878 compared to the ACEI exposed group (P = 0.183, 95% CI = 0.724 – 1.064). In the cohort aged ≥ 70 years at baseline, the hazard ratio of mortality in the ARB exposed group was 0.870 compared to the ACEI exposed group (P = 0.245, 95% CI = 0.688 – 1.100) (Table 118).

Within the ARB exposed group, the hazard ratio of mortality in patients aged ≥ 70 years at baseline was 2.037 compared to patients aged < 70 years at baseline (P < 0.001, 95% CI = 1.712 – 2.513). While for the ACEI exposed group, the hazard ratio of mortality in patients aged ≥ 70 years at baseline was 2.074 compared to patients aged < 70 years at baseline (P < 0.001, 95%CI = 1.712 – 2.513) (Table 119).

This means that in the full cohort analysis and in the cohort aged ≥ 70 years, the hazard ratio of mortality for ARB versus ACEI exposed patients was not statistically significant during the 3-year follow-up. In patients exposed to ARB or ACEI, the hazard ratio of mortality in patients aged ≥ 70 years at incident diagnosis doubled compared to patients aged < 70 years at the same baseline with highly statistically significant P values during the 3-year follow-up period.

8.5.3.2.2. Positive Control Arm

Survival analysis was done for the cohort aged < 70 years at baseline. This group was analysed separately with ACEI and ARB treatment exposure.

Table 120: Cox regression for cohort aged < 70 years – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI vs ARB	-.110	.520	.896	.641	1.252

The hazard ratio of mortality in the ARB exposed group was 0.896 compared to the ACEI exposed group (P = 0.520, 95% CI = 0.641 – 1.252) (Table 120). This means that in patients aged below 70 years at incident diagnosis, the hazard ratio of mortality for ARB versus ACEI exposed patients was not statistically significant.

8.5.3.3. Cox Regression Interaction Analysis

The effect of ARB versus ACEI on all-cause mortality was further analysed for statistical significance of interaction with various potential covariates that may lead to modification of the result obtained in the main Cox proportional hazard model. Selected variables were analysed separately to obtain hazard ratios of ARB versus ACEI with each variable. Statistical significance of difference within these hazard ratios was analysed with the formation of interaction terms for each variable. The procedure was repeated for full cohort analysis and for patients aged ≥ 70 years at incident diagnosis.

Table 121: ACEI vs ARB layered by Carvedilol / Spironolactone – full cohort – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
No Carvedilol/Spironolactone	-.212	.178	.809	.595	1.101
Carvedilol only	.049	.811	1.050	.705	1.564
Spironolactone only	-.183	.399	.833	.544	1.274
Carvedilol and Spironolactone	-.338	.163	.713	.443	1.147

Table 122: Interaction terms for Carvedilol / Spironolactone – full cohort – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI vs ARB*No Carvedilol/Spironolactone		.633			
ACEI vs ARB*Carvedilol only	-.263	.307	.769	.465	1.272
ACEI vs ARB*Spironolactone only	-.023	.931	.977	.578	1.651
ACEI vs ARB*Carvedilol and Spironolactone	.123	.670	1.131	.642	1.993

Table 123: ACEI vs ARB layered by Carvedilol / Spironolactone – age ≥ 70 years – study 4

	B	P-value	HR	95.0% CI for OR Lower	Upper
No Carvedilol/Spironolactone	-.225	.236	.798	.550	1.159
Carvedilol only	-.086	.734	.917	.558	1.508
Spironolactone only	-.192	.455	.825	.498	1.366
Carvedilol and Spironolactone	-.120	.692	.886	.489	1.608

Table 124: Interaction terms for Carvedilol / Spironolactone – age ≥ 70 years – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI vs ARB*No Carvedilol/Spironolactone		.971			
ACEI vs ARB*Carvedilol only	-.145	.648	.865	.465	1.610
ACEI vs ARB*Spironolactone only	-.033	.917	.967	.517	1.811
ACEI vs ARB*Carvedilol and Spironolactone	-.101	.779	.904	.448	1.825

Table 125: ACEI vs ARB layered by Digoxin– Full cohort – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
Digoxin	-.114	.594	.892	.586	1.358
No Digoxin	-.128	.246	.880	.709	1.092

Table 126: Interaction terms for Digoxin– Full cohort – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
Digoxin*ACEI vs ARB	-.012	.962	.989	.616	1.586

Table 127: ACEI vs ARB layered by Digoxin – age ≥ 70 years – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
Digoxin	-.084	.736	.920	.565	1.496
No Digoxin	-.140	.306	.869	.664	1.137

Table 128: Interaction terms for Digoxin– age ≥ 70 years – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
Digoxin*ACEI vs ARB	-.054	.849	.947	.543	1.651

Table 129: ACEI vs ARB layered by Warfarin – Full cohort – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
Warfarin	-.053	.761	.949	.677	1.330
No Warfarin	-.159	.183	.853	.675	1.078

Table 130: Interaction terms for Warfarin – Full cohort – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
Warfarin*ACEI vs ARB	.102	.627	1.107	.734	1.670

Table 131: ACEI vs ARB layered by Warfarin – age ≥ 70 years – study 4

	B	P-Value	HR	95.0% CI for HR Lower	Upper
Warfarin	-.111	.591	.895	.598	1.340
No Warfarin	-.121	.413	.886	.664	1.183

Table 132: Interaction terms for Warfarin – age ≥ 70 years – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
Warfarin*ACEI vs ARB	.007	.979	1.007	.613	1.653

Table 133: ACEI vs ARB layered by Charlson Score – Full cohort – study 4

Charlson Score	B	P-value	HR	95.0% CI for HR Lower	Upper
0	-.246	.088	.782	.589	1.037
1	.416	.569	1.516	.362	6.347
2 to 3	-.028	.892	.973	.653	1.449
≥ 4	-.076	.680	.927	.646	1.330

Table 134: Interaction terms for Charlson Score – Full cohort – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI vs ARB*Charlson score 0		.671			
ACEI vs ARB*Charlson score 1	-.674	.365	.510	.119	2.193
ACEI vs ARB*Charlson score 2 to 3	-.218	.382	.804	.494	1.311
ACEI vs ARB*Charlson score ≥ 4	-.166	.479	.847	.536	1.341

Table 135: ACEI vs ARB layered by Charlson Score – age ≥ 70 years – study 4

Charlson Score	B	P-value	HR	95.0% CI for HR Lower	Upper
0	-.294	.096	.745	.527	1.053
1	-.179	.831	.836	.162	4.312
2 to 3	-.110	.670	.896	.541	1.484
≥ 4	.143	.516	1.154	.750	1.776

Table 136: Interaction terms for Charlson Score – age ≥ 70 years – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
ACEI vs ARB*Charlson Score 0		.516			
ACEI vs ARB*Charlson Score 1	-.425	.132	.654	.376	1.136
ACEI vs ARB*Charlson Score 2 to 3	-.323	.709	.724	.133	3.946
ACEI vs ARB* Charlson Score ≥ 4	-.242	.475	.785	.404	1.524

All hazard ratios for individual variables were not significant indicating comparable reduction in mortality between ACEI and ARB exposure across all the prespecified variables for both cohorts (Tables 121, 123, 125, 127, 129, 131, 133, 135). The absence of statistical significance for hazard ratios of all interaction terms within each variable in both cohorts indicated that none of the selected variables exhibited evidence of interaction effect for modification of ARB influence on all-cause mortality compared to ACEI (Tables 122, 124, 126, 128, 130, 132, 134, 136) (page 179 figure 52, page 180 figure and 53).

Figure 52: Endpoint subgroup analysis for interaction (as treated) full cohort – study 4

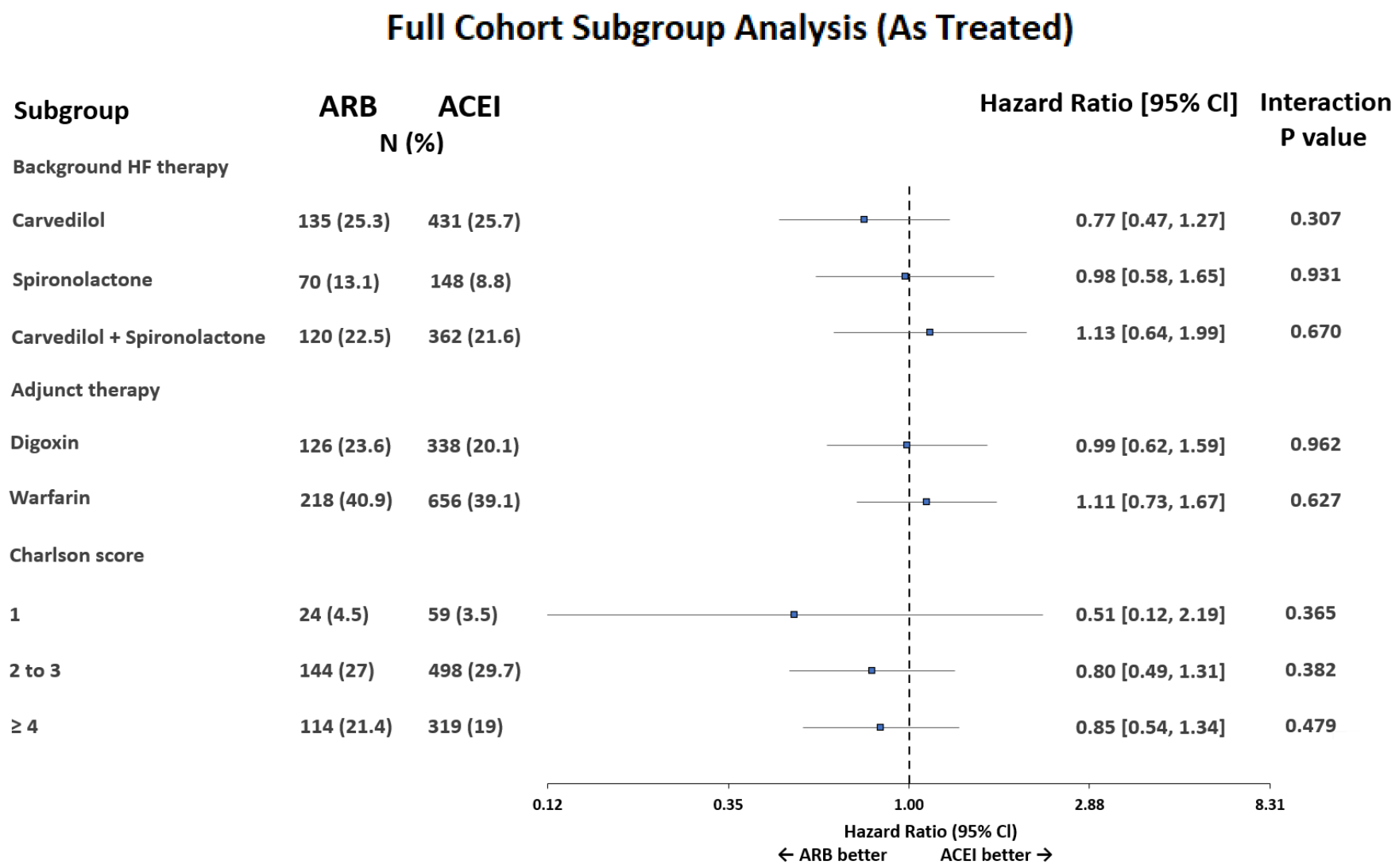
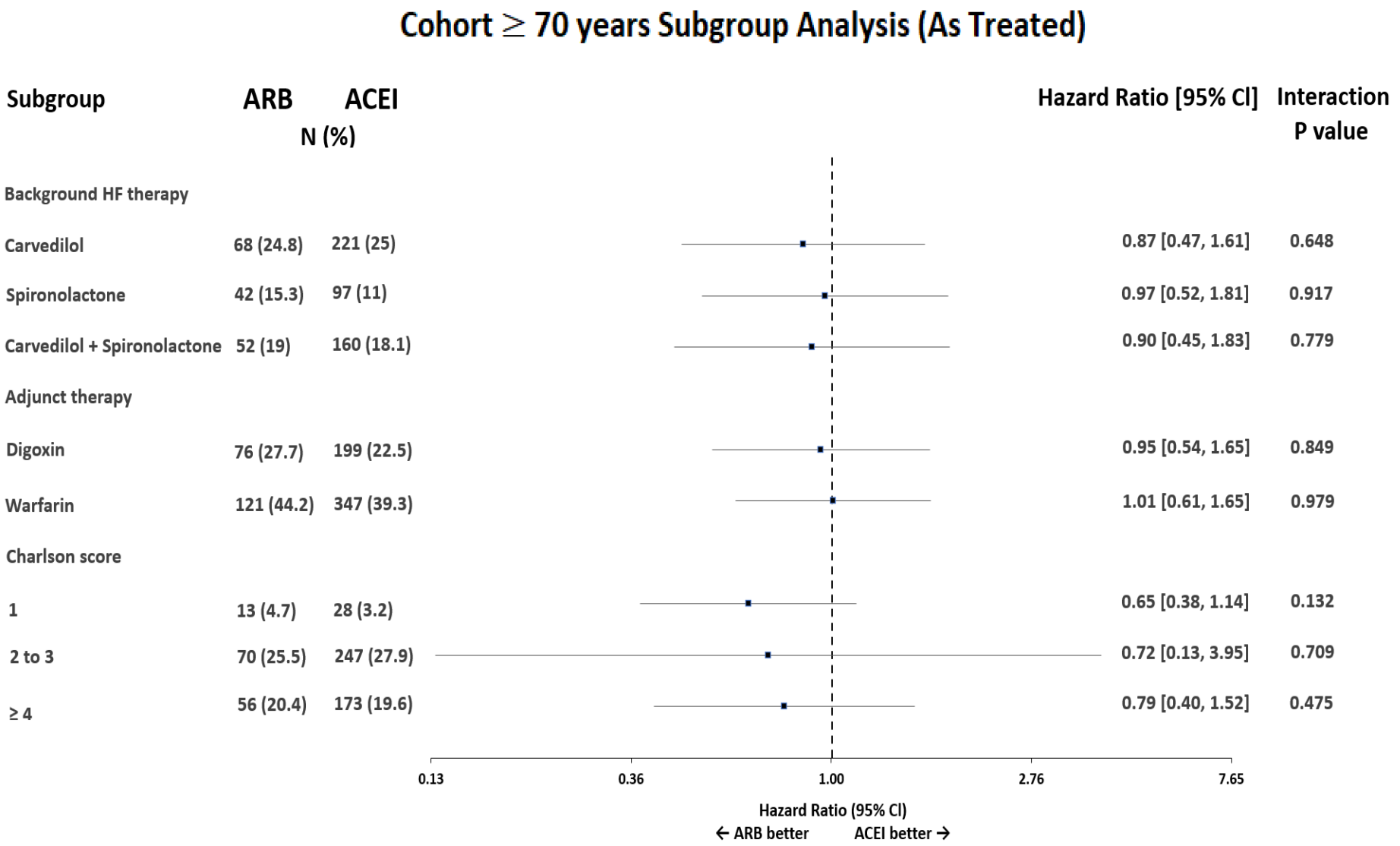


Figure 53: Endpoint subgroup analysis for interaction (as treated) cohort aged ≥ 70 years – study 4



ARB were comparable to ACEI across all subgroups for the two cohorts. Examination of prespecified subgroups based on background therapy and comorbidity characteristics across both cohorts did not identify a nominally significant interaction between any of the prespecified variables and the effect of ARB versus ACEI on all-cause mortality (Figures 52 and 53). This excluded relative variations in the effect of ARB compared to ACEI, large enough to be clinically significant while also possessing sufficient precision for the possibility to exclude the inferior effect of the alternative hypothesis (i.e. HR > 1).

However, this does not completely exclude these variables as possible confounders by acting collectively to cause effect modification of ARB versus ACEI on mortality. Therefore, multivariable Cox regression was used to investigate this effect through a model incorporating all potential covariates identified that may simultaneously influence all-cause mortality and therefore require adjusted hazard ratios (Tables 137 and 138).

8.5.3.3.1. Multivariable Cox Regression Model with Adjusted Hazard Ratios

Table 137: Adjusted hazard ratio for ACEI vs ARB – Full cohort – study 4

	B	P-value	Adjusted HR	95.0% CI for HR Lower	Upper
ACEI vs ARB	-.181	.066	.834	.688	1.012
No Carvedilol/Spironolactone		<.001			
Carvedilol only	-.234	.028	.791	.642	.976
Spironolactone only	.670	<.001	1.955	1.554	2.459
Carvedilol and Spironolactone	-.232	.042	.793	.634	.992
Digoxin	-.047	.676	.954	.766	1.189
Warfarin	-.492	<.001	.611	.507	.737
Charlson score 0		<.001			
Charlson score 1	-1.096	.002	.334	.166	.675
Charlson score 2 to 3	-.304	.003	.738	.604	.902
Charlson score ≥ 4	.333	<.001	1.396	1.151	1.692

Table 138: Adjusted hazard ratio for ACEI vs ARB – age ≥ 70 years – study 4

	B	P-value	Adjusted HR	95.0% CI for HR Lower	Upper
ACEI vs ARB	-.157	.193	.855	.675	1.082
No Carvedilol/Spironolactone		<.001			
Carvedilol only	-.192	.137	.825	.641	1.063
Spironolactone only	.583	<.001	1.792	1.367	2.349
Carvedilol and Spironolactone	-.233	.115	.792	.593	1.058
Digoxin	.049	.707	1.051	.812	1.360
Warfarin	-.491	<.001	.612	.490	.766
Charlson score 0		<.001			
Charlson score 1	-.698	.070	.497	.233	1.059
Charlson score 2 to 3	-.246	.050	.782	.612	1.000
Charlson score ≥ 4	.376	.002	1.457	1.153	1.842

8.5.3.3.2. Summary of Hazard Ratios

Table 139: Summary of adjusted and unadjusted hazard ratios (as treated) – study 4

Study	Unadjusted HR	P-value	95.0% CI for Unadjusted HR Lower	Upper	Adjusted HR	P-value	95.0% CI for Adjusted HR Lower	Upper
ARB vs ACEI Full cohort	0.878	0.183	0.724	1.064	0.834	0.066	0.688	1.102
ARB vs ACEI Cohort aged ≥ 70 years	0.870	0.245	0.688	1.100	0.855	0.193	0.675	1.082

Adjusted hazard ratios and associated P-values for the full cohort and for the cohort aged ≥70 years at incident diagnosis age were comparable with those from the main survival model. This means that background heart failure treatment associated with improved survival in HFrEF (Carvedilol and Spironolactone), adjunct treatment (Digoxin, Warfarin) indicative of atrial fibrillation or thromboembolic burden, and additional comorbidities were not confounding effects. This result persisted even when adjusting for age ≥70 years at incident diagnosis (Table 139).

8.5.4. Hospitalisation

The frequency of hospitalisation events during the 3-year follow-up period was checked as a dependent variable for normality distribution for each level of the independent variable of treatment with ACEI and ARB using the Shapiro-Wilk test. Analysis was done for the full

cohort and for patients aged ≥ 70 years at incident diagnosis age. The null hypothesis was that the scores in the dependent variable are normally distributed.

Table 140: Tests of Normality – Full cohort – study 4

	P-value
ARB	<.0001
ACEI	<.0001

Table 141: Tests of Normality – Age ≥ 70 years – study 4

	P-value.
ARB	<.0001
ACEI	<.0001

In both cohorts the Shapiro-Wilk test was highly significant (P = < 0.0001) which rejected the null hypothesis (Tables 140 and 141). Therefore, hospitalisation scores failed to meet the normality assumption for the t-test and a Mann-Whitney U test was conducted to analyse for differences in hospitalisation scores between the two groups in each cohort.

Table 142: Ranks – Full cohort – study 4

ACEI vs ARB	N	Mean Rank	Sum of Ranks
ARB	533	1104.89	588906.00
ACEI	1678	1106.35	1856460.00

Table 143: Test Statistics[a] – Full cohort – study 4

	Hosp Admissions
Mann-Whitney U	446595.000
Wilcoxon W	588906.000
Z	-.050
P-value (2-tailed)	.960

a. Grouping Variable: ACEI vs ARB

Table 144: Ranks – Age ≥ 70 years – study 4

ACEI vs ARB	N	Mean Rank	Sum of Ranks
ARB	274	586.11	160595.50
ACEI	884	577.45	510465.50

Table 145: Test Statistics[a] – Age ≥ 70 years – study 4

	Hosp Admissions
Mann-Whitney U	119295.500
Wilcoxon W	510465.500
Z	-.398
P-value (2-tailed)	.691

a. Grouping Variable: ACEI vs ARB

Hospitalisation scores were almost identical between the ACEI and ARB groups in the full cohort analysis and comparable in the cohort aged ≥70 years at incident diagnosis (Tables 142 and 144). The difference of hospitalisation scores between ACEI and ARB groups was not significant in the full cohort analysis (P = 0.960) and in the cohort aged ≥70 years (P = 0.691) (Tables 143 and 145). This means there was no significant variance in effect of the independent variable on hospitalisation scores between the ACEI and ARB groups.

8.5.5 Sensitivity Analysis

8.5.5.1. Comparison of Groups

Renal disease was the only factor that was significantly different between the ACEI exposed and ARB exposed groups as indicated by the eGFR. This observation was consistent for the full cohort (eGFR P= 0.018) and also for the cohort aged ≥70 years at baseline (eGFR P= 0.004) (page 185, tables 146 and 147). The possibility of renal disease as a potential confounding covariate leading to bias was tested as part of the Charlson comorbidity score interaction analysis with a non-significant P value (Figures 52 and 53). The Charlson comorbidity score was also included in the Cox multivariable regression and the adjusted hazard ratio did not change from the unadjusted hazard ratio that resulted from the main Cox regression model (Table 139).

Table 146: Comparison of groups for full cohort – study 4

Diagnostic test	(n) Missing values		(%) Missing values		Mean (Std. Deviation)		P value
	ACEI Arm (n=1678)	ARB Arm (n=533)	ACEI Arm (n=1678)	ARB Arm (n=533)	ACEI Arm (n=1678)	ARB Arm (n=533)	
Potassium mmol/L	1375	451	81.9	84.6	4.694 (0.591)	4.590 (0.453)	0.212
Creatinine umol/L	1375	451	81.9	84.6	107.726 (88.463)	105.537 (39.374)	0.182
eGFR mL/min/1.73m2	1375	451	81.9	84.6	70.89 (26.054)	66.72 (23.726)	0.018
Bilirubin umol/L	1375	451	81.9	84.6	14.42 (11.163)	15.36 (15.549)	0.268
LVEF %	N/A	N/A	N/A	N/A	33.9 (9)	34.8 (7.5)	0.342

Table 147: Comparison of groups for cohort aged ≥ 70 years – study 4

Diagnostic test	(n) Missing values		(%) Missing values		Mean (Std. Deviation)		P value
	ACEI Arm (n=884)	ARB Arm (n=274)	ACEI Arm (n=884)	ARB Arm (n=274)	ACEI Arm (n=884)	ARB Arm (n=274)	
Potassium mmol/L	743	237	84	86.5	4.632 (0.607)	4.635 (0.491)	0.279
Creatinine umol/L	743	237	84	86.5	110.61 (57.135)	115.405 (42.446)	0.095
eGFR mL/min/1.73m2	743	237	84	86.5	62.53 (22.76)	58.84 (23.657)	0.004
Bilirubin umol/L	743	237	84	86.5	14.12 (10.58)	12.69 (8.655)	0.753
LVEF %	N/A	N/A	N/A	N/A	34.5 (8.6)	35.1 (8.6)	0.646

N/A: Not applicable

8.5.5.2. False Endpoint Analysis

Table 148: ACEI vs ARB – False endpoint analysis – study 4

	B	P-value	HR	95.0% CI for HR Lower	Upper
Full cohort	-.250	.384	.779	.443	1.368
Cohort aged ≥ 70 years	-.487	.233	.614	.276	1.367

No difference in risk of pulmonary disease was observed in patients treated with ACEI versus ARB both in the full cohort analysis (HR: 0.779, 95% CI: 0.443 to 1.368; P = 0.384) and in the cohort aged ≥70 years at incident diagnosis (HR: 0.614, 95% CI: 0.276 to 1.367; P = 0.233) (Table 148).

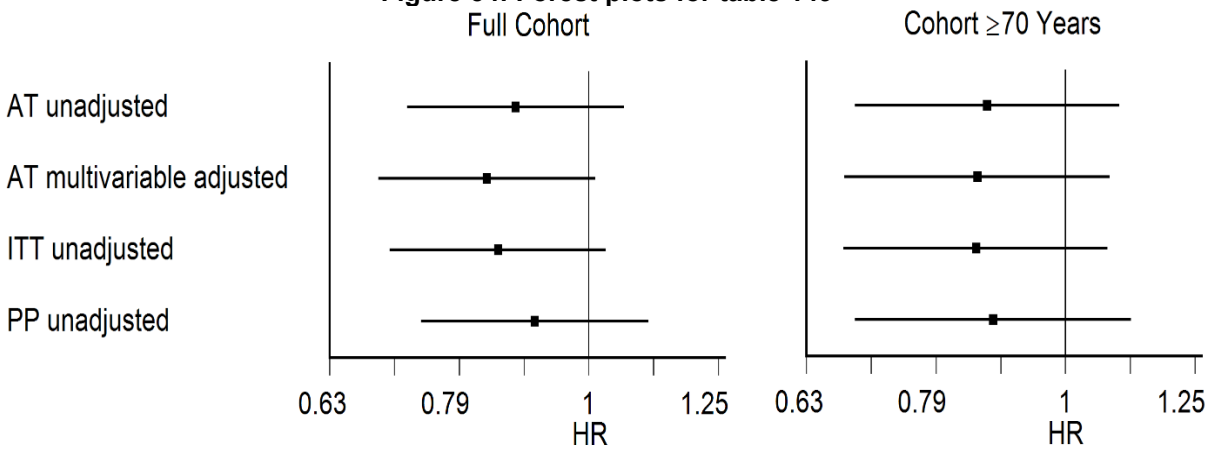
8.5.5.3. Comparison with Intention-to-Treat and Per Protocol designs

Table 149: hazard ratios for as treated, intention-to-treat and per protocol analysis – study 4

Cox regression model	Full cohort			Cohort ≥70 years		
	HR	CI (95%)	P value	HR	CI (95%)	P value
AT Unadjusted	0.878	0.724 – 1.064	0.183	0.870	0.688 – 1.100	0.245
AT Multivariable Adjusted	0.834	0.688 – 1.012	0.066	0.855	0.675 – 1.082	0.193
ITT Unadjusted	0.851	0.702 – 1.031	0.099	0.853	0.674 – 1.078	0.184
PP Unadjusted	0.908	0.742 – 1.112	0.351	0.879	0.688 – 1.124	0.304

AT: As treated ITT: Intention-to-treat PP: Per protocol

Figure 54: Forest plots for table 149



Sensitivity analysis showed that survival analyses under different analytical scenarios were qualitatively consistent with the results of the primary Cox regression analysis of as-treated (AT) analysis. The HR estimates for the endpoint of all-cause mortality varied minimally under different study methods within the same cohort. The variations for the hazard ratio estimates were also similar and compared with the primary Cox regression model. All p-values remained non-significant (Table 149) (Figure 54). This shows that the outcome of comparative effectiveness in the reduction of all-cause mortality by ARB compared to ACEI was robust to most scenarios of measured and unmeasured confounding.

8.5.5.4. Post Hoc Sample Power Analysis

8.5.5.4.1. Survival Analysis

Post hoc power analysis was done by applying study parameters including the cohort size and patient allocation ratio of ARB group to ACEI group and using the two-sample comparison of the main Cox regression model (202, 242). The analysis was done for the full cohort and for the cohort aged ≥ 70 years at baseline.

Table 150: Post hoc sample power estimation for all-cause mortality – study 4

Cohort	N	N1	N2	% Control N1	HR	HR_θ	P1	P2	Power %
Full cohort	2211	1678	533	75.893	0.505	0.84	0.284	0.249	99
Cohort aged ≥ 70 years	1158	884	274	76.339	0.573	0.84	0.362	0.325	95

N1: ACEI group (Control)
N2: ARB group (Experimental group)
HR: Assumed actual HR for ACEI (Control)
HR_θ : Superiority hazard ratio
P1 & P2: Event probability in ACEI & ARB respectively
% Control N1: % of total sample in ACEI group

The analysis for the full cohort achieved 99% power at a 0.05 significance level to detect a minimum, true change in all-cause mortality where ARB decreased mortality by 16% compared to the ACEI group. While the analysis for the cohort aged ≥ 70 years at baseline achieved 95% power at a 0.05 significance level to detect a minimum, true change in all-cause mortality where ARB decreased mortality by 16% compared to the ACEI group (Table 150). Actual hazard ratios from study 2 for ACEI exposed versus unexposed were applied as control and assumed to persist for ACEI in this cohort.

8.5.5.4.2. Hospitalisation Analysis

Post hoc power analysis for hospitalisation was done by applying study parameters including the cohort size and patient allocation ratio of ARB group to ACEI group and using the two-sample comparison of the Mann-Whitney U test (119, 120, 121, 122). The analysis was done for the full cohort and for the cohort aged ≥ 70 years at baseline.

Table 151: Post hoc sample power estimation for hospitalisation – Full cohort – study 4

Variance	alpha	N	N1	N2	μ1	μ2	μ1 − μ2	Std. Dev.	Power %
Actual	0.05	2211	533	1678	1.29	1.23	0.06	2.09	9.2
20% decrease	0.05	2211	533	1678	0.984	1.23	− 0.246	2.09	69.8

N1: ARB group (Experimental group)
N2: ACEI group
μ: Mean hospitalisation

The full cohort achieved 9.2% power to detect a true difference in observed mean hospitalisation of 0.06, and 69.8% power to detect a 20% decrease in mean hospitalisation by ARB compared to ACEI, with a population standard deviation of 2.09 assumed in both groups (table 151).

Table 152: Post hoc sample power estimation for hospitalisation – age ≥ 70 years – study 4

Variance	alpha	N	N1	N2	μ1	μ2	μ1 − μ2	Std. Dev.	Power %
Actual	0.05	1158	274	884	1.45	1.28	0.17	2.082	23.5
20% decrease	0.05	1158	274	884	1.024	1.28	− 0.256	2.082	46

N1: ARB group (Experimental group)
N2: ACEI group
μ: Mean hospitalisation

The cohort aged ≥ 70 years at incident diagnosis achieved 23.5% power to detect a true difference in observed mean hospitalisation of 0.17, and 46% power to detect a 20% decrease in mean hospitalisation by ARB compared to ACEI, with a population standard deviation of 2.082 assumed in both groups. Analysis of both cohorts was done using a two-sided Mann-Whitney U test assuming that the actual data distribution is logistic when the significance level (alpha) of the test is 0.05 (table 152).

8.6. Discussion

8.6.1. Main Findings

In this retrospective, all inclusive, population based research involving patients with heart failure and a reduced left ventricular ejection fraction, ACEI and ARB had comparative effectiveness for the primary efficacy outcome of reduced all-cause mortality (Table 118). In the full cohort, ARB demonstrated no statistically significant difference from ACEI in risk of all-cause mortality (HR 0.878; 95% CI: 0.724 to 1.064; P = 0.183) with similar 36-months mean survival post incident diagnosis (31 months; 95% CI 30.1 to 31.9) compared to the ACEI group (30 months; 95% CI 29.4 to 30.5). In the cohort aged ≥ 70 years at incident diagnosis, ARB also demonstrated no statistically significant difference from ACEI in risk of all-cause mortality (HR 0.870; 95% CI: 0.688 to 1.100; P = 0.245) and similar 36-months mean survival post incident diagnosis (29.5 months; 95% CI 28.2 to 30.8) compared to the ACEI group (28.1 months; 95% CI 27.3 to 28.9).

ARB exposure was similarly effective as ACEI for reduction in all-cause mortality in patients aged ≥ 70 years at incident diagnosis as well as in the cohort representing the general population with HFrEF and in patients aged < 70 years at incident diagnosis (Tables 118 and 120). This demonstration of comparative survival benefit in patients aged ≥ 70 years at incident diagnosis as well as in a large cohort with a high inclusion of these patients (> 52%) provides support for prior suggestions that ARB are comparable to ACEI in geriatric heart failure patients with a similar effect in younger patients (206).Therefore this study validates the therapeutic role of ARB as alternative first-line therapy instead of ACEI in patients with HFrEF including patients aged ≥ 70 years. The comparative effect of decreased all-cause mortality by ARB compared to ACEI was homogenous across all prespecified subgroups for the full cohort analysis (Tables 121, 125, 129, 133). The absence of significant difference in effect was also exhibited by patients with incident diagnosis at ≥ 70 years where survival benefit was comparable between ARB and ACEI across all prespecified subgroups (Tables 123, 127, 131, 135). This comparative effectiveness for survival benefit remained constant throughout the 3-year follow-up post incident diagnosis.

However, it is inappropriate to assess the effects of treatment on a single subgroup by examination of the 95% CI for that subgroup and the general principle is that subgroup analysis should concentrate on differences from the average overall treatment effect via tests of interaction (207). Subgroup analysis showed no interaction between the comparative reduction of all-cause mortality by ARB compared to ACEI and the various prespecified variables in the full cohort (Figure 52). The absence of modification of the comparative effect on all-cause mortality persisted in patients aged ≥70 years at incident diagnosis across all prespecified subgroups including Charlson comorbidity scores (Figure 53). Elderly patients

are more susceptible to developing additional comorbidities and further compound the risks of heart failure that are enhanced with the onset of advanced age (208, 209).
The presence of digoxin or warfarin was indicative of existing atrial fibrillation or substantial thromboembolic burden. Both conditions portend considerable additional mortality however ARB still maintained a comparative, beneficial effect compared to ACEI (Tables 126, 128, 130 and 132). Furthermore, this comparative result was not influenced by prespecified background therapy that may have modified the difference in beneficial effect size (Tables 122, 124). The absence of effect modification suggests that the estimated, non-significant hazard ratios indicated the true comparative effect of independent survival benefit inherent in ARB compared to ACEI with respect to interaction with other heart failure therapy even for patients aged ≥ 70 years at incident diagnosis. This observation was further strengthened by the comparability of unadjusted to adjusted hazard ratios despite adjustment for all prespecified variables including age ≥ 70 years at baseline for incident diagnosis (Tables 139, 149) (Figure 54). The cohort of patients aged ≥ 70 years at baseline as well as the full cohort achieved the sample power required for the purpose of testing the null hypothesis. The full cohort that represented the general population with HFrEF was powered at 99% to reject a false null hypothesis at a hazard ratio for a 16% decrease in mortality with ARB compared to ACEI while the cohort for patients aged ≥ 70 years at baseline was powered at 95% for the same purpose (Table 150). This supports the observation of informative differences between the groups across both cohorts where ARB superiority over ACEI was rejected and the null hypothesis of comparative effectiveness was accepted.
The use of ACEI as core RAS inhibitor in heart failure guidelines with ARB as an alternative with similar benefit is based on various landmark, randomized trials showing that both are valid, key agents to reduce mortality even when added to other heart failure therapies (62, 95, 232, 233). Since these trials occurred, new pharmacological approaches have demonstrated additional benefit when added to ACEI or ARB. Consequently, it is possible that the incremental benefit of ARB might be modified when combined with other therapy associated with high survival benefit in heart failure to the extent that a difference in mortality may exist when compared to ACEI. It is of interest to know whether the presence of background therapy influences the benefit of ACEI or ARB. However, there are limited head-to-head comparisons in the literature with reports of conflicting results from indirect comparative studies (206, 243, 244, 245) This caveat is more pronounced for geriatric patients particularly when diagnosed late in life, considering that patients are living longer with heart failure compared to the time when landmark trials occurred (210). With the gap of evidence on head-to-head comparison of ACEI and ARB particularly in geriatric heart failure patients, a key question is whether the established survival benefit of ARB and ACEI

remains comparable with different background heart failure therapy in a real-world patient population. Therefore this study also attempted to address this question by comparing the effectiveness of ARB with ACEI in a real-world outpatient scenario with current heart failure pharmacotherapy and with a focus on patients aged ≥ 70 years at incident diagnosis. This is, to the best of my knowledge, the first head-to-head, observational study to demonstrate indirectly on a large scale, a survival benefit with ARB that is comparable to ACEI in HFrEF within a contemporary study population for patients aged ≥ 70 years at incident diagnosis. The observations from this research confirm that ACEI and ARB are RAS inhibitors with comparative effectiveness in HFrEF patients. In addition, this research establishes the persistence of the observed comparative effectiveness in patients aged ≥ 70 years that is comparable to the result observed in younger patients as demonstrated by previous meta-analysis and large scale registry analysis (Table 118 and 120) (206, 245).

Results confirm that this comparative effectiveness persists over 3 years post incident diagnosis without effect modification by contemporary background heart failure therapy or increased comorbidity. This study also indicates that in patients ≥ 70 years with HFrEF, comparative effectiveness is maintained between ACEI and ARB irrespective of other therapies since the comparability of survival benefit is neither dependent upon specific treatment, nor modulated by any combination of disease-modifying therapies for HFrEF (Tables 124 and 128) (Figure 53). So far, support for this observation was based on community studies or indirectly from meta-analysis and evidence was missing from testing the hypothesis on a large scale in a real world scenario with an elderly population (206, 246, 247, 248, 248). Therefore this study indicates that ARB have comparative survival benefit to ACEI with different combinations of traditional heart failure treatment in patients ≥ 70 years. This observation is clinically critical considering that ARB are increasingly being preferred as first-line therapy over ACEI due to a significantly better safety profile particularly when hypertension is the underlying cause (249). This preference prevails in this research particularly in Maltese females with HFrEF despite uncertainty pertaining to the applicability of findings from randomised, clinical trials to the population of patients with heart failure encountered in routine clinical practice (Tables 13, 14) (206).

This study demonstrated no significant variance in hospitalisation for heart failure between ARB and ACEI treatment. This result was obtained across the full cohort and in the cohort of patients aged ≥70 years at baseline (Table 143 and 145). However both cohorts were underpowered to detect the observed variance as a true difference between study arms or for detecting the superiority threshold of 20% decrease in hospitalisation by ARB over ACEI (Tables 151 and 152). Furthermore, it is dubious whether the observed values of hospitalisation are true in view of the observed increase in associated hospitalisation with

ACEI and ARB from studies 2 and 3 in this research that was indicative of strong selection and confounding bias. The resulting bias and power limitations prevented this study from drawing a conclusion on the true effect of ARB versus ACEI on heart failure associated hospitalisation in geriatric patients with HFrEF.

8.6.2. Strengths

The ARB and ACEI exposed groups were balanced with regards to baseline comorbidities, background heart failure treatment, Charlson comorbidity score, mean LVEF% and age at incident diagnosis (Tables 107, 108, 109, 110). Although renal disease was not balanced between groups, this variance was not found to be clinically meaningful for the primary endpoint of all-cause mortality (Tables 146 and 147). The full cohort representing the general population and the smaller cohort representing patients aged ≥ 70 years with HFrEF exceeded the 80% power required to reject a false null hypothesis at a 16% decrease in all-cause mortality by ARB as a true difference in the primary endpoint for this study (Table 150). The selected superiority limit of 16% mortality reduction also compares well with variances observed in randomized, controlled trials as clinically meaningful differences in mortality (16% in SOLVD, 20% in CHARM-Alternative, 15% in PARADIGM-HF) (95, 107, 192). Apart from serving to validate the result on comparative effectiveness of ARB compared to ACEI in the main Cox regression model, the magnitude of the power also allowed exploration for differences in prespecified subgroups and determine if this result persisted. The inclusion of subgroup analysis in the Cox regression model also determined the extent of stability of this result across key subgroups of concern particularly with various combinations of background heart failure therapy (Figures 52, 53). The influence of background therapy on the impact of individual heart failure treatment is an evidence gap that only started being investigated recently (215).

This is, to the extent of my knowledge, the first study based on real-world data to gain an insight into the comparative effectiveness of ARB compared to ACEI in subgroups with varied treatment combinations for HFrEF where elderly patients are well represented with a high inclusion of patients aged ≥ 70 years (Table 118) (Figure 47). The use of log-minus-log plots confirmed that all Kaplan-Meir plots did not violate the assumption of constant, comparative benefit of survival against instantaneous risk of all-cause mortality throughout the 3-year follow-up (Figures 47, 48, 50, 51). The exhaustive process of sensitivity analysis demonstrated a high degree of robustness for the primary endpoint of all-cause mortality. Due to the retrospective nature of the study that limited control of confounding and the absence of propensity score matching of subjects, sensitivity analysis was performed using a falsification endpoint for residual confounding (196, 197). The absence of a difference in

risk for pulmonary disease between the ARB and ACEI groups further validated the observations of this study for the primary endpoint (Table 148).
Hazard ratios and their 95% confidence intervals remained consistent for various study approaches demonstrating robustness of the comparative effectiveness observed for ARB compared to ACEI for survival in both cohorts (Table 149, figure 54). The hazard ratios of all study approaches (AT, AT-adjusted, ITT and PP) for both cohorts were close and consistently not significant which confirmed the robustness of observations for all-cause mortality to measured and unmeasured confounding. (Table 149, figure 54). Furthermore, all confidence interval limits included a value of 1 and therefore superiority of ARB over ACEI cannot be declared. These observations indicate that the relative variance in all-cause mortality did not exceed the superiority threshold of 16% and further support the comparative effectiveness outcome particularly in the full cohort.

8.6.3. Limitations

Unequal patient allocation ratio between the two study arms was a major limitation for both cohorts (Tables 109 and 110). Unequal ratio for patient allocation is associated with selection bias if the patients in the two arms of the study differed in important characteristics (218, 250, 251). The imbalance between groups may have introduced bias by potential, unmeasured covariates with strong confounding for the secondary endpoint. In this respect, this study lacked information on other important prognostic indicators such as BMI, systolic blood pressure, smoking, and blood haemoglobin concentration at baseline. Consequently, it was not possible to test these factors as variables for confounding of the true outcome of comparative effectiveness for the secondary endpoint attributed to ARB compared to ACEI.
Unequal patient allocation between study arms also has consequences for statistical power. A 2 to 1 allocation ratio requires 12% more patients than a study using a 1 to 1 ratio to detect the same size effect with equivalent power (219). In this study the patient allocation ratio was 3 to 1 for both cohorts. This affected the analysis for secondary endpoint of HFrEF associated hospitalisation with extensive reduction of size effect detection in both cohorts (Tables 151 and 152). Both cohorts did not achieve 80% sample power to detect a 20% decrease in hospitalisation by ARB as the superiority threshold and also failed to reach the same power to detect the observed difference in hospitalisation as a true variance. Furthermore, failure to reach the required sample size reduced more the sample power. These limitations are therefore thought to be the main contributors towards the failure to reach the a priori sample power estimation to test the null hypothesis for the secondary endpoint in both cohorts. This power was estimated on the main assumption of a sample size ratio of 1 for ACEI to ARB exposed groups and on a greater sample estimation. Both

cohorts violated both assumptions and failed to reach the 80% power limit for the purpose of testing the null hypothesis at measured differences and superiority threshold for the secondary endpoint of HFrEF associated hospitalisation (Tables 151 and 152). Issues of unequal patient allocation ratios and imbalance in baseline, prognostic variables are inherent to non-randomised studies and since this study was retrospective, reducing these limitations was restricted by the patients available historically (218, 252, 253).

The evidence-based target doses of ACEI, ARB and background therapy are well defined with evidence of a dose-response relationship of reduction in all-cause mortality and heart failure hospitalisation (66, 100). Yet, target doses are infrequently achieved in clinical practice (211, 220). Therefore, it is possible that the incremental benefit of ACEI may be less if dosing for ACEI or any of the background therapy in the ACEI arm was not optimized. The same argument also holds for the ARB arm. This study was not designed to analyse comparative effectiveness of the benefit of ARB versus ACEI according to the extent of treatment optimisation. A related limitation is the presence of sacubitril valsartan that became available late in the study follow-up phase in 2016. These patients were not identified in this study. However, patients that switched to this treatment were censored at the time of stopping ACEI or ARB. From 2016 to December 2021 there were approximately 350 patients that received this treatment (personal communication, February 2022). So the number was minor compared to the large sample sizes of both cohorts. Additionally, the only renin angiotensin system inhibitor treatment for all patients in this study were either ACEI or ARB during the 3-year follow-up or until censoring. Moreover, none of the background heart failure therapy modified the outcome of comparative effectiveness of ARB and ACEI on all-cause mortality (Tables 122, 124) (Figures 52, 53). Therefore it is justified to assert that sacubitril-valsartan did not exert any influence on treatment or survival in this study albeit censoring was required.

Another limitation is the absence of comprehensive information on the cardiac functional capacity of patients. The original plan for the study protocol was to include data capture of the NYHA scores at baseline and upon completion of the 3-year follow-up. The pilot study revealed that in practice, functional scores for heart failure severity are rarely recorded. This prevented a complete description of the study population at baseline and precluded analysis of the effect of ARB and ACEI interaction with heart failure progression through follow-up. Similarly, the availability of NT-proBNP testing became available in 2016 when the protocol for the complete research programme was finalized for UREC approval and 9 years after the index year identified to start data capture that is in 2007. Therefore this prognostic indicator was also not part of the study design and research relied on LVEF from the primary diagnostic echocardiogram as the only clinical parameter of informative status.

Length of hospital-stay related to heart failure in conjunction with associated hospital readmission would have provided more reliable information to inform on the secondary outcome measure of HFrEF morbidity (222). Extracting this data required identification of admission and discharge dates from electronic and physical records, with manual calculation of the in-hospital days. In view of the time constraints for this research, this exercise was not feasible.

Finally, since this research was a single centre study that was also retrospective and non-randomised, there were design limitations and statistical issues associated with limited sample size that led to unequal patient allocation, selection bias that introduced baseline imbalance, the inevitable presence of confounding variables, and the lack of generalizability to a broader population. For these reasons, this study lacked internal and external validity to provide indisputable evidence to clinical practice.

8.6.4. Comparisons

Findings from this work show no significant difference in all-cause mortality outcome in HFrEF between ACEI and ARB and this result is consistent with observations from previous systemic reviews or meta-analysis conducted from RCT's or from observational clinical studies (206, 245, 253, 254). This observation is further strengthened by prior studies that also demonstrated similar effects for ACEI and ARB on heart failure associated prognostic factors or risks including blood pressure, cardiovascular mortality, stroke, myocardial infarction, composite cardiovascular events, kidney disease, or diabetes (248, 255, 256, 257). Moreover, the results of this research run parallel to the findings of OPTIMAAL and VALIANT, two RCTs which established the non-inferiority of ARB compared with captopril in patients with LVSD or HF after acute myocardial infarction (115, 258). Despite this evidence, these randomised, controlled trials and most observational studies are recognised as unrepresentative of the general heart failure population encountered in general practice in terms of age and contemporary background therapy. The exception for age is the OPTIMAAL study that investigated the effects of losartan versus captopril in patients up to the age of 95 years. Furthermore, the question of clinically meaningful differences in the cardioprotective activity of ACEI and ARB has been long debated with studies finding differences between ACEI and ARB, claiming this might account for differences seen in mortality and morbidity reduction between the two classes of drugs in heart failure patients (243, 259, 260, 261). Therefore, uncertainty to the applicability of non-inferior findings to the population of patients with heart failure persists.

For the purpose of direct comparison, seven studies were found with results that provide robust support for the observations of comparative effectiveness obtained for all-cause

mortality in this research. The ELITE II study demonstrated no difference between losartan and captopril in reducing all-cause mortality in elderly heart failure patients (262, 263). This randomised controlled trial was done in 1998 in patients with a mean age of 65 years. This result was repeated by VALIANT in 2003, a randomised, controlled trial that compared valsartan with captopril post myocardial infarction complicated heart failure with reduced LVEF with a mean age of 65 years (115). These RCTs have comparative issues of noncontemporary background therapy and patients' age at baseline considering that heart failure patients are now living longer (17). However these still remain the only head-to-head, large scale RCTs comparing ACEI and ARB in heart failure patients. Comparative effectiveness in elderly patients was analysed by a nationwide, population based, cohort study in Taiwan in 2010 where mean age was > 78 years. This found no difference in major adverse cardiovascular events between ACEI and ARB (253). The extent of comorbidities that prevailed in the Taiwan study supports the finding of persisting comparative effectiveness in this research including elderly patients across a range of Charlson comorbidity scores. However this observational study focused on hypertensive patients although 30% were heart failure patients. Heart failure patients were specifically analysed in the Japanese cardiac registry study in 2007. Discharge use of ARB compared with ACEI for all-cause death after 2.2 years with consistent results across all clinically relevant subgroups including age, ejection fraction, hypertension, and diabetes (206). More than 50% of the patients were aged over 65 years. The extent of comorbidities in the Japanese study resembled those included in the Charlson comorbidity score and background heart failure therapy was identical for this research. The most recent meta-analysis comparing ACEI versus ARB for cardiovascular events was the study by Ricci et al. in 2015 (245). With 27 RCTs included, this meta-analysis demonstrated no significant differences in the prevention of cardiovascular death, myocardial infarction, or stroke as separate outcomes. The study focused on patients at high cardiovascular risk and found no statistical support for a difference between ACEI and ARB at preventing incident risk of new-onset heart failure after a maximum follow-up duration of 6.5 years. However this meta-analysis deliberately excluded patients with heart failure at baseline and maximum patient age was 69 years with a mean of 58 years. The study that best approaches this research for suitable comparison is the Alabama Heart Failure Project of 2011 that included the most senior cohort studied so far for ARB versus ACEI (3). This included a propensity-matched comparative effectiveness of 419 elderly patients with HFrEF and discharged on ARB or ACEI with a mean age of 78 years. In patients with HFrEF there was no significant difference in all-cause mortality during >8 years of follow-up. This result is consistent with the findings from this research where mean age was 70.8 years at baseline. This observational study included all of the medical

conditions in the Charlson comorbidity score for propensity-score matching. Background heart failure therapy also matched with this research. Therefore current evidence comparing ACEI and ARB in heart failure patients specifically with HFrEF is limited and comes mainly from indirect analysis. The paucity of evidence is even more pronounced for elderly patients aged ≥70 years. The ELITE II remains the only direct, head-to-head RCT that compared ACEI with ARB in heart failure and a straightforward comparison of published studies with this doctoral research is inaccurate.

With regards to heart failure hospitalisation, both ELITE II and the Japanese cardiovascular registry study demonstrated no difference between ACEI and ARB in the reduction of this endpoint in patients with symptomatic heart failure. (206, 263). This research also demonstrated a non-significant variance between the effect of ARB and ACEI on heart failure associated hospitalisation (Tables 143,145). This result was observed in the analysis representing the full HFrEF population and was repeated in patients ≥70 years at baseline. This outcome is indicative of comparative effectiveness between ARB and ACEI for reduction in heart failure hospitalisation. However, the presence of extensive selection bias as a result of an imbalance in the patient allocation ratio reduced the sample power required to reject a false null hypothesis and a meaningful measurement of this endpoint was not possible for this study (Tables 151, 152). This limitation precludes a comparison of observations from this research with published studies for heart failure hospitalisation.

One final comparison is the result demonstrated by this study where the risk of mortality in patients aged ≥ 70 years at baseline doubled compared to patients diagnosed < 70 years on the same RAS inhibitor. This result was observed regardless of treatment exposure to ARB or ACEI (Table 119). Incident diagnosis in elderly patients raises the concern that many heart failure diagnoses are missed in the outpatients setting (231). Age was proven to be an independent predictor of 1-year mortality in patients with heart failure and increasing age at diagnosis was associated with increased mortality (230, 232). Earlier recognition and intervention can also mitigate heart failure morbidity (231). Furthermore, This observation confirms evidence from a smaller study where the presence of chronic heart failure in older patients resulted in an approximately 50% reduction in life expectancy (233).

8.7. Conclusion

1. The result for survival benefit observed in patients with HFrEF indicate that ACEI and ARB have comparative effectiveness in patients aged ≥ 70 years.
2. This benefit was independent of other heart failure treatment and comorbidity.

3. Age reduced life expectancy regardless of ARB or ACEI treatment with the risk of mortality in patients aged ≥ 70 years doubled compared to patients diagnosed < 70 years.
4. These results were observed at 3-year follow-up post primary diagnosis with HFrEF.
5. The result obtained for hospitalisation is inconclusive and requires a more rigorous study design.
6. This research indicates critical areas for statistical improvement for future studies.

9. General Discussion and Programme Conclusions

9.1. Programme Discussion

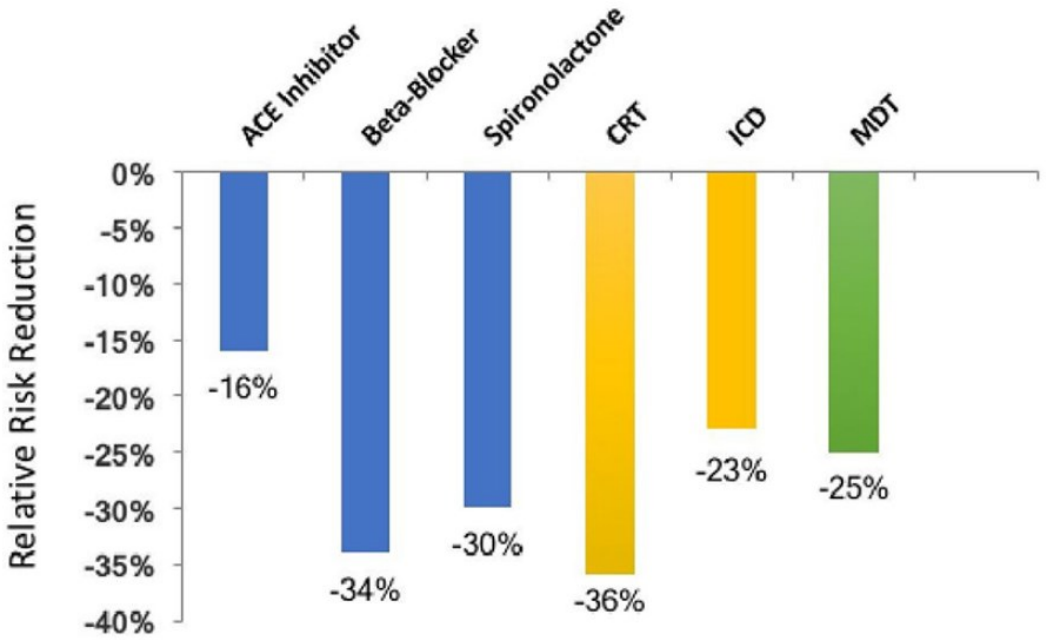
The work presented in this thesis achieved for the first time, a nationwide analysis of the state-of-health of the Maltese population suffering from heart failure with reduced ejection fraction. It has been known for several years that cardiac health in Malta was faring much worse than the EU average with heart failure at the forefront (26, 141). This clinical awareness was based on increasing annual figures for heart failure patients registered with the National Health Service, related drug expenditure, community nurse outreach demand, and heart failure palliative care support, plus rising incidence of risk factors particularly diabetes, and obesity (26, 141). A number of initiatives have been taken at national level to counter worsening trends however the effort and intensity were fragmented and based on primary observations that underrated the real urgency for sustained action and long term investment (179, 180, 181, 182). The results of these initiatives have so far been dismal as evidenced by the latest national figures for obesity and diabetes (26).

This research also revealed inadequate patient management with necessary laboratory tests done for less than 20% of patients at baseline year in each study and poor pharmacotherapy that is not aligned with international guidelines (Figure 25 and Tables 17, 18, 55, 56, 63, 64, 101, 102, 109, 110, 146, 147). The European Society of Cardiology and the American College of Cardiology both support multidisciplinary team involvement in the management of heart failure to reduced hospitalisations and/or mortality and identifies this effort as a key component in a heart failure management programme (evidence level IA) (264, 265, 266). These programmes are effective in improving quality of HF care and outcomes in the outpatient setting (267). Two meta-analyses showed a similar relative risk reduction in the order of 20%–25%. The most contemporary Cochrane review (268) on clinical service organisation for patients with HF reported an approximate risk reduction of 25% (OR 0.74; 95% CI 0.60 to 0.90, P=0.003) with significant reduction in mortality conferred by more intensive interventions. Although direct comparisons cannot be drawn, similar magnitudes of benefit have been demonstrated with other important medical and device interventions in HF (page 200, Figure 55) (269, 270, 271, 272, 273).

Despite this evidence, the care provided by Mater Dei hospital to heart failure patients is not through a multidisciplinary team. This was a service limitation for this research that denied patients immediate access to a multi-specialty care team with proven potential of additional survival benefit and reduced hospitalisations. The majority of Maltese heart failure patients in ambulatory and inpatient settings are managed by non-cardiologists mostly under the care of

renal or diabetes consultants. Patients under the care of cardiologists are seen mostly through physician referral from other specialties and the rest via direct emergency admission if severely decompensated (personal communication, March 2023). Furthermore, patients under the care of cardiologists had additional access to a nurse-led hospital-based clinic for medicine optimisation and further follow-up. Care of HFrEF patients by non-cardiologists is

Figure 55: Relative risk reduction associated with various interventions for heart failure



Source: Morton G, et al. Multidisciplinary team approach to heart failure management. Heart. 2018 Aug;104(16):1376-1382. CRT: cardiac resynchronization therapy; ICD: implantable cardioverter-defibrillator; MDT: multidisciplinary team. Reproduced with permission.

associated with lower use of GDMT and higher mortality versus cardiology care both at admission / discharge and also in ambulatory care (274, 275, 276). There are dedicated ECG technicians for cardiology clinics and the catheterisation suite. A specialist clinical pharmacist was also part of the cardiology team from 2010 to 2018 and shared responsibility for therapeutic interventions in the inpatient setting post admission including the intensive coronary care unit. Other allied healthcare professionals are called in through referral mostly prior to hospital discharge. So the absence of a single process to access a dedicated multidisciplinary, specialised team with a defined care pathway is partially compensated by a fragmented referral system where other healthcare professionals (HCPs) are utilised based on individual clinical judgement, and subject to waiting times, HCP availability and delayed communication. Such a system is prone to breakdown of treatment continuation and loss of follow-up. Following hospital discharge, community heart failure support falls mostly on a declining number of GPs, with support from two regional health centres and a hospice care

team for end-stage heart failure patients (277). Furthermore, meaningful therapeutic intervention by non-physicians is limited since only physicians are authorised to prescribe according to law. This drawback impacts most those patients requiring quick or radical changes in treatment where the immediate alternative is the GP. Often these cases entail changes in the free medicines entitlement and end up as a hospital referral to a Consultant who is the only HCP authorised to make amendments to this entitlement according to the Social Security Act. Alternatively patients can see the responsible Consultant during private practice to fill the necessary paperwork and prescriptions. This partly explains why out-of-pocket spending as a share of total health spending in Malta is the fourth highest proportion in the EU and more than twice the EU average. This is driven by a substantial proportion of the population opting to purchase private primary and outpatient specialist care to circumvent waiting lists (26). With 1500 new patients suffering from heart failure each year (278) a radical change in the treatment management of these patients is urgent otherwise well-timed access to good quality specialist care with early attainment of guideline-directed medical therapy (GDMT) will be unfeasible. Therefore broad-reaching strategies must be applied across multiple care settings for Maltese heart failure patients to benefit from the added risk reduction conferred by a multidisciplinary heart failure management programme. Shared decision-making with an interdisciplinary team coupled with proven strategies can help improve HF management (279). These include psychosocial and dietary consultation, early detection of clinical deterioration and prompt assessment for medication adjustment, intense patient education and counselling, compliance monitoring and tackling related barriers, early comprehensive discharge planning, and addressing nonclinical risk factors for readmission and disease progression (280) Social determinants of health, in particular, can complicate the short- and long-term management of HF so it is important to address these factors early (281). Other tested strategies include the implementation of evidence-based algorithms or clinical pathways, standardized encounter forms and utilisation of checklists that improve adherence to guideline recommendations (279). Multidisciplinary teams that include physicians, APPs, nurses, and pharmacists are best suited to address the many needs of the heart failure population (282). Non-physician prescribing with expanded access to the community can accelerate optimisation of GDMT for ambulatory patients including complex cases without added burden on hospital ambulatory clinics or consultant appointment lists. This can be part of a community HF team where discharged patients are referred with transfer of information. A hospital based multidisciplinary team can ensure a complete review with all baseline laboratory values taken and avoid omission of any GDMT either at discharge or during an outpatient clinic appointment. This research revealed that 80% of patients had missing values of lab investigations that are required as baseline at

incident diagnosis and also as routine during treatment. Also data in this study point towards a residual treatment gap in many eligible patients who fail to receive indicated therapies to improve patient outcomes resulting in poor level of treatment. From 2017 to 2020 there were 23% of patients without ACEI or ARB, 60% without an indicated beta blocker and 73% without a MRA for 2 years or more during the 3-year follow-up.

This research presents direct evidence of the situation and provides robust, prediction estimates of the magnitude of future stress expected on health systems from this disease. The results obtained by this research lends direct support for major process changes at hospital and community level that translate to reduced morbidity and mortality. It also exposes the real urgency to better meet the challenges of a rapidly expanding heart failure population over the next 15 years (Figure 23). The findings and conclusions can be used to develop workload and time benchmarks for healthcare systems as well as targeted community prevention aimed at this population. The finding that HFrEF is significantly less prevalent in females with males prevailing more particularly over the age of 65 years concurs with recent evidence (Figure 18) (151, 283). This observation runs parallel with the higher incidence of ischaemic heart disease in males compared to females. Interestingly, ACEI were prescribed more in males while females demonstrated a higher preference for ARB (Tables 12, 13, 14). The reasons for this difference are unknown however this research established a clear absence of association between selecting ACEI or ARB and all-cause mortality. Women had better survival with HFrEF than men but major differences between age groups indicate that there is more than sex to account for the significant differences in morbidity and mortality observed in this research (Figure 21). Variations in prevalence of risk factors by age and sex in the Maltese population appear to play a major role and this is a key area for patient-focused, intensive education (26, 284, 285). It was also unfortunate to find that use of ACEI and ARB declines in patients ≥ 70 years (Table 12). This is a critical gap in optimising heart failure therapy in view of the high survival benefit elderly heart failure patients can obtain at par with younger patients. Evidence from this work shows that inappropriate treatment becomes more common as patients age and females start experiencing this bias earlier than males. This adds another problem for elderly patients with heart failure on top of the deficiency of target doses that are infrequently achieved in clinical practice (211, 286). Clearly there is ample room for better implementation of treatment guidelines and optimisation of heart failure pharmacotherapy in elderly heart failure patients. Unless there are outright contraindications to avoid ACEI or ARB, denying this treatment to HFrEF patients aged ≥ 70 years denies them increased survival with the disease and the extent of survival benefit that can be gained is clinically meaningful and extensive. This observation came out clear from the two studies where patients on ACEI and ARB were

separately compared to those not on RAS inhibitor treatment (Tables 26, 72). Until now this observation was either based on analysis of risk factors and surrogate markers, or determined from studies with smaller cohorts, a younger patient population or non-contemporary background therapy (3, 206, 248, 249, 253, 257, 259, 260, 261). This thesis presents the first large scale, observational study that establishes significant and clinically meaningful reduction in all-cause mortality with ACEI and ARB from indirect evidence in a real-world scenario with an elderly population (Tables 58, 104). This survival benefit has the same hallmarks in elderly patients as that observed in younger patients: it is independent of other heart failure therapy hence it is incremental, and persists for at least three years post diagnosis, therefore it is not time-dependent (Tables 47, 93) (Figures 29, 30, 38, 39). The added bonus is that additional comorbidity does not appear to reduce this effect, at least those conditions identified by the Charlson comorbidity score (Tables 42, 44, 88, 90). The downside is that age remains an independent factor, with patients on treatment and aged ≥ 70 years at incident diagnosis dying twice the rate as those below this age threshold (Tables 27, 73). This means that with optimised heart failure therapy including ACEI or ARB as lifelong treatment, we can expect elderly HFrEF to keep gaining from the associated survival benefit and live longer until cardiac deterioration, worsening comorbidity or advancing age shift the balance towards mortality.

With results showing separate, significant reductions in all-cause mortality with both ACEI and ARB, it was logical to attempt a direct, head-to-head comparison taking advantage of the large sample size accessible to address the ultimate question. A comparative effectiveness design was selected after a pilot study confirmed feasibility for sample size. Despite an imbalanced allocation ratio with selection bias, and a sample size below the assumed estimate, the study still achieved good statistical power (> 80%) to demonstrate comparative effectiveness at the superiority threshold of 16% of ARB versus ACEI for reduction of all-cause mortality. This was achieved in a national, all-inclusive cohort representing the complete HFrEF population aged from 50 years upwards at baseline (Table 149). This research also accomplished its original aim to test this assumption in patients aged ≥ 70 years at baseline with a statistical power of 95% and confirmed that comparative effectiveness persists despite adjusting for age ≥ 70 years at baseline. (Table 150). This is, to my knowledge, the first head-to-head study to demonstrate indirectly on a large scale, comparative effectiveness in survival benefit between ACEI and ARB in HFrEF within a study sample that closely resembles the real-world population with this disease. It also confirmed that this comparative benefit persisted over 3 years post diagnosis regardless of other heart failure treatment on board with adjusted hazard ratios throughout follow-up

remaining unchanged (Figures 47, 50). So results are strongly indicative of comparative effectiveness of ARB compared to ACEI across all age groups.

The results for all-cause mortality from this work remain suggestive albeit significant for a multitude of reasons. A higher survival benefit was observed for ACEI in study 2 and for ARB in study 3, compared to landmark trials and meta-analyses (Table 153).

Table 153. Comparison of relative risk reduction in mortality and heart failure hospitalisation treatment from randomised control trials and meta-analyses with results from studies 2 to 4

	RCTs			Meta-Analyses			Studies (HR)	
Treatment	**All-Cause Death**	**CV Death**	**HFH**	**All-Cause Death**	**CV Death**	**HFH**	**All-Cause Death Full cohort**	**All-Cause Death ≥70yrs**
ACEI vs No treatment	0.84[1] RR	0.82[1] RR	0.63[5] OR	0.86[6] RR	0.83[6] RR	0.64[8]– 0.69[6] RR	0.54	0.63
ARB vs No treatment	0.90[2] HR	0.76[4] RR	0.47[4] RR	0.95[7] HR	0.88[7] HR	0.71[6]– 0.77[8] RR	0.42	0.54
ARB vs ACEI	1.12[3*] RR	1.15[3*] RR	0.92[3*] RR	1.07[6*] RR	1.08[6*] RR	1.02[6*/9*] RR	0.83*	0.86*

HR: hazard ratio OR: odds ratio HFH: heart failure hospitalisation RR: risk ratio * Not significant

1 SOLVD Investigators, 1991 (269).

2 CHARM Investigators and Committees, 2003 (224).

3 Losartan Heart Failure Survival Study ELITE II, 2000 (263).

4 Val-HeFT Investigators, 2002 (287).

5 ACE-Inhibitor Myocardial Infarction Collaborative Group, 2000 (91).

6 Park et al. 2023 (288).

7 Tromp et al. 2022 (289).

8 Hafkamp et al. 2022 (290).

9 Ohtsubo et al. 2019 (291).

Subgroup analysis of this research revealed no interaction with background heart failure treatment indicating that benefit was independent in both cohorts and not influenced by additional heart failure therapy. Two limitations were identified as plausible reasons for this effect and both are associated with the internal validity of studies. First is absence of a 1:1 patient allocation ratio between the two study arms and second is selection bias in view of the imbalance in baseline characteristics. These limitations can cause single-centre trials to provide inflated treatment effect estimates compared to multicentre trials (217, 292). Apart

from reducing the sample power for the study (219), unequal ratio for patient allocation is associated with bias if the patients in the two arms of the study differed in important characteristics (218). There is evidence of unequal distribution of baseline characteristics between active treatment exposed and exposed groups particularly in studies 2 and 3. This may have introduced unrecognised confounding factors that could have distorted the results. In fact, a factor that emerged later towards the end of these studies was that most of the patients identified for this research were managed by non-cardiologists, largely from the specialties of diabetes and nephrology (personal communication, March 2023). Furthermore, patients under the care of cardiologists had additional access to a nurse-led clinic for medicine optimisation and further follow-up. Care of HFrEF patients by cardiologists is associated with higher use of GDMT and lower mortality versus non-cardiology care both at admission / discharge and also in ambulatory care (274, 275, 276). This research also found that ACEI/ARB exposed groups exhibited higher survival benefit despite the presence of greater comorbidity associated with cardiac disease compared to the unexposed groups. Typically patients with higher cardiovascular risk/comorbidity are managed by cardiologists. The majority of these patients were in the ACEI/ARB exposed arms. This is indirect evidence of selection bias that may have selectively introduced cardiology-managed patients with superior GDMT, earlier ACEI/ARB optimisation and better HFrEF care in the ACEI/ARB arms of studies 2 and 3. This selection bias may have led to extensive reduction in sudden death in symptomatic HFrEF the resulted in a higher survival benefit compared to landmark trials and meta-analyses (293). Therefore the presence of non-comparable, unmeasured baseline characteristics due to selection bias that was further enhanced by unequal patient allocation may have introduced unknown variables that acted as covariates and led to poorer prognosis in the unexposed arm. The introduction of unrecognized confounding factors is a fundamental criticism of observational, post-hoc studies that is attributed to critical design issues of retrospective observation, non-randomisation, and adequate sample (294).

In the case of study 4, the result for the primary outcome of all-cause mortality agreed with that observed in trials and meta-analyses with a non-significant hazard ratio indicating comparable survival benefit between ACEI and ARB in HFrEF. While it is acknowledged that the majority of survival outcome in major trials and meta-analysis is expressed as risk ratio, this measure can still be taken as an estimate for comparison with hazard ratios (295).

The benefit of GDMT in HFrEF associated hospitalisation was consistent throughout all trials and meta-analyses. A direct comparison with this research cannot be done since different statistical methodology was used without applying risk ratio or hazard ratio as a standard measure of estimated relative risk. However it is clear that studies 2 and 3 reversed the outcome of benefit of reduced hospitalisation from previous studies with higher rates

demonstrated in the ACEI/ARB arms. Further analysis confirmed that other factors were influencing hospitalisation. In fact, the selected ICD10 codes introduced unrelated hospitalisation related to other cardiovascular disease with an imbalance in disease characteristics where treatment exposed arms were at a disadvantage. This selection bias was of sufficient concern to dismiss the result for hospitalisation in study 4 despite indications baseline disease characteristics were balanced between arms. Although the outcome in this final study reflected previous trials and meta-analyses.

Despite the exhaustive effort of complicated sensitivity analysis that confirmed robustness of results for the primary endpoint, this programme remains a retrospective, single centre investigation. So the internal and external validity of this research were completely dependent on the data available historically. This includes the presence of bias and confounding variables, a deficiency that was exhibited by the violation of the a priori assumption of a sample size ratio of 1 for ACEI to ARB exposed groups. The resulting selection bias undermined prespecified sample power and reproducibility to validate the observed effect size of the secondary endpoint. It is for these reasons that conclusive observations on the influence on heart failure hospitalisation by ARB compared to ACEI cannot be declared in elderly HFrEF patients from this research (Tables 143, 145, 151). However, the results of the primary endpoint for the study can be considered as strongly indicative of an outcome of comparative effectiveness in all-cause mortality reduction between ARB and ACEI across all age groups. This conclusion draws considerable support from a post hoc statistical power exceeding 90% in both cohorts to reject a false null hypothesis and with a strong representation of elderly patients aged over 70 years.

There were design limitations of failure to capture more comprehensive baseline characteristics such as BMI, systolic blood pressure, smoking and haemoglobin concentration. Time limitation precluded manual collection of this data from physical files and processing of further electronic data. Additionally, the research programme started before the routine availability of NT-proBMP while NYHA scores were almost inexistent in medical histories. This prevented more proper analysis for selection bias through testing of these variables as potential confounders especially in studies 2 and 3 comparing drug exposed and unexposed groups. In both studies there was clear evidence of more intensive heart failure treatment in the research arm for the index drug that was indicative of a more acute group and/or follow-up by a cardiologist. Finally, the Covid-19 pandemic impacted the timely availability of data. This research was originally planned to include patients with incident diagnosis in 2018 with a post-diagnosis follow-up until 2021. Mortality data including date and primary cause of date with ICD 10 codes was obtained from the Department of Public Health in July 2022 with a delay of 6 months based on previous schedules of data release.

The number of missing patients was 450 that would have increased the full sample closer to the required estimated size. Although this was not expected to improve sample power for reduction of HFrEF associated hospitalisation since the main limitation for this endpoint was the unequal patient allocation ratio between study arms.

9.2. Limitations of the Charlson Comorbidity Index

The Charlson comorbidity index (CCI) is a summed score of 17 comorbidities weighted according to severity (195) that was developed to objectively assess comorbid status and associated risk of death. The index has been validated in many countries for use with administrative registries and its performance compares favourably with other diagnosis-based indices (e.g., Elixhauser) and pharmacy-based indices (e.g. RxRisk-V and CDS) in mortality prediction, albeit with a simpler mode of calculation (296). After the introduction of the index, several updates and modifications of the index have been published to maintain and improve its applicability (296). During the evolution of the index, the number of included diseases and the score weighting have varied. The current index considers comorbidities that are coded according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (297). CCI is a well-established surrogate marker of comorbidity and it has been widely applied as a prognostic indicator for patients with colorectal cancer, advanced non-small cell lung carcinoma and acute myocardial infarction (298, 299). Despite being used for this purpose in heart failure, the Charlson Index has not been specifically validated for heart failure outcome studies with mixed correlations reported (300, 301, 302, 303). In particular, Lee et al. found that among patients hospitalised for heart failure, a subset of comorbid conditions had greater independent impact on mortality in community-based patients, and the relative contributions of the comorbid conditions to mortality differed substantially in comparison with the Charlson comorbidity index (304). In the case of elderly patients, the Charlson Comorbidity Index is the most extensively studied comorbidity index to assess the presence and the degree of comorbidity in this population (305). It has been reported to be reliable and to provide a good correlation with mortality and survival outcomes and, mainly, to account for the effect of age (306). However, no studies are available on the ability of CCI to predict mortality in elderly heart failure subjects (300). Other than 2 studies in this population addressing short-term (1-year) or long-term (12-year) mortality, the effect of comorbidity, as measured with the CCI, on the prognosis of heart failure has not been addressed (300, 307). Testa et al. also confirmed that the ability of CCI to predict mortality in elderly subjects but showed that this ability is lost in elderly subjects with CHF (300). These findings suggest that CHF within the CCI is probably underestimated and should be more heavily weighted. Unfortunately, the CCI also uses serum creatinine to

estimate renal function, rather than the glomerular filtration rate according to the Modification of Diet in Renal Disease study group equation, which is more accurate in elderly patients. Therefore, It is possible that the CCI underestimates the severity of renal dysfunction in elderly patients (308). Another limitation is that most studies on CCI have utilized specific subpopulations, for example cohorts selected from hospitalized patients, which ensures availability of health care data and hence feasibility of calculating the index (296). This limits the generalizability of the results to larger, less selective populations, such as the general population, where undocumented illnesses could reduce the predictive power of the index. Furthermore, the Charlson comorbidities and the derived CCI score are commonly used for risk-adjustment in several mortality prediction models constructed from administrative data (309). Reliance on administrative data for CCI may result in under-reporting of comorbidities and incomplete assessment of patient risk. Hua-Gen Li et al. found that administrative data significantly under-reported comorbidities present in the patient records in the majority of cases. Their findings are, in general, consistent with several previous reports (310). Also, any variation in reporting of comorbidities between institutions will lead to misleading comparative results. A health service that under-reports comorbidities will have lower CCI scores resulting in these patients appearing to be healthier (310). The optimal source from where not only the most accurate, but also the most efficient, CCI can be obtained also warrants further investigation (311). Using the CCI as a proxy for all comorbidity is problematic because it was developed to include only conditions predictive of higher mortality (312). Also the development of the index does not align with the commonly used definition of comorbidity or multimorbidity which does not specify that these health conditions have to confer an increased risk of death (313, 314, 315). Not all conditions are associated with negative outcomes, for example, lower rates of some solid tumours in people who have Down syndrome, schizophrenia, or anorexia nervosa (316). Consequently CCI requires further scrutiny for validation of content, convergence, and divergence in heart failure both in hospital and outpatient settings. Content validity indicates how well the index includes domains thought to be relevant to the condition. Convergent validity demonstrates whether the index that is thought to measure the same construct has a high correlation coefficient. Divergent validity demonstrates if the index thought to measure different constructs has a low correlation coefficient. In the case of heart failure, there is no “gold standard” measure of aggregate comorbidity for comparison, so these types of validity cannot be assessed.

9.3. Programme Conclusions

Should these design limitations undermine the significance of this work? Although observational studies have known limitations largely associated with unrecognized

confounding factors that may distort results, they could be used to exploit clinically rich data bases and usually do provide valid information (294). Observational research particularly that originating from single-centre studies is useful to generate hypotheses that can then be studied via large, prospective, multi-centre, cohort studies or randomised, placebo-controlled trials (317). Realizing these designs for this research is either ethically impossible to achieve from denial of treatment that prolongs life, or logistically extremely difficult to accomplish with increasing use of new treatment that extends survival significantly including ARNI, SGLT2 inhibitors, cardiac resynchronisation therapy, implantable cardioverter-defibrillators, and ventricular assist devices. This research recruited patients before this new treatment became widely available so potential confounding on survival outcome was prevented. While an appreciable sample size was still reached despite the exclusion of patients with implantable devices. Furthermore, the absence of heterogeneity in treatment effect on all-cause mortality across the prespecified subgroups, and the minimal variation in HRs with different analytical approaches, even when adjusting for age indicate that significant survival benefit was derived with ACEI and ARB by contemporary elderly patients with HFrEF. Furthermore this benefit was comparable and sustained over 3 years. The added efficacy on top of other therapy is also noteworthy since it remained incremental in patient aged over 70 years as with younger patients and justifies maintaining either treatment in elderly patients. The next best alternative is to repeat this work on a larger scale as a multi-centre study and this research lays the foundations for the sequential statistical methodology to be followed and the design improvements necessary to resolve the limitations identified. Maintaining a sample size ratio of 1 for ACEI to ARB exposed groups eliminates selection bias and obviates the need for post hoc power analysis. Capturing comprehensive data for baseline characteristics is crucial to allow for propensity score matching of patients that will work with balanced study arms at further minimising confounding considerably. Broader data on risk factors and prognostic indicators permits wider statistical testing for significant differences between study arms that may be analysed for bias. In particular NYHA class status and systolic blood pressure at baseline and mid-way shall give information on the cardiac functional condition at baseline and the rate of deterioration through the study. Inclusion of length of hospital-stay related to heart failure in conjunction with associated hospital readmission as a composite, secondary outcome measure will provide more reliable information to better inform on the secondary endpoint of reduced hospitalisation as a measure of HFrEF morbidity. Absence of residual confounding is better confirmed with multiple falsification endpoint analysis instead of a single endpoint as employed by this research. Finally, the generalisability of results is limited by the single-centre status of this research despite the relatively large sample sizes obtained. Expanding this research to a

multi-centre, international collaboration shall increase the representativeness of the study population and the applicability of the findings to other settings. While employing a non-inferiority trial requires a smaller sample compared to a study testing comparative effectiveness although it is more complicated for design and interpretation.
Notwithstanding these limitations resulting from the nature of the study designs, the epidemiological findings and treatment outcome for mortality from this work remain compelling for the Maltese population and noteworthy for the positive implications for elderly patients with heart failure. Knowledge of temporal trends in HFrEF and future burden in the Maltese population is crucial for major process changes in health systems and prevention strategies. The demonstrated positive impact of treatment on mortality is of benefit to patients who are hemodynamically unstable (SBP≥100 mmHg for at least 6 hours, no increase in dose of intravenous diuretics in the preceding 6 hours, and no intravenous inotropes in the preceding 24 hours) and are compelled to remain on ACEI or ARB instead of transitioning to ARNI. This risk is higher in elderly patients that may constitute up to 80% of the population suffering from the disease (318). Nonetheless, this research supports similar survival benefit of ACEI and ARB that persists in this group of patients with mortality reductions comparable to younger patients. Until more rigorous research is done with wider generalisability this work remains, to the best of my knowledge, the best evidence available on the positive influence of ACEI and ARB on survival in patients aged ≥ 70 years with HFrEF.
A summary of the conclusions of this research programme are shown below in relation to the study aims.

Study 1
To examine temporal trends of morbidity and mortality in patients aged 50 years with HFrEF and to investigate treatment patterns of use versus non-use of ACEI and ARB
Epidemiology:

- Males had higher rates than females for diagnosis and associated mortality. This difference increased with time for both variables.
- Males developed heart failure at a significantly higher rate compared to females starting at 50 to 59 year.
- Mortality followed a similar trend albeit the disparity was less between sexes when compared to diagnosis rate.
- Males exhibited significantly higher mortality incidence between 60 and 79 years.

- The sex gap for diagnosis and mortality rates was substantial and consistent across the majority of age groups (60 – 89 years).
- The influence of sex on mean incidence for diagnosis and mortality became insignificant from 90 year upwards.
- Significant deterioration in survival probability occurred if diagnosis happened after a mean age of 69 years.
- Male diagnosis incidence shall increase at a much higher rate compared to female incidence.
- Female diagnosis incidence is expected to peak by the year 2037 while male diagnosis incidence is predicted to peak 10 years later.
- The highest accelerated increase in predicted diagnosis incidence and will be within the 80 to 89 years age group.
- Rate of total diagnosis incidence shall peak in 2042 and will be mostly driven by males.
- HFrEF incidence will increase by 50% from 2017 to 2040 up to 5.2 per 1000 population aged ≥50 years under status-quo heart failure prevention and treatment trends.
- Pharmacotherapy trends:
- There was a progressive increase in prescribing of ACEI and ARB with time at approximately equal rates.
- The increasing preference for ACEI is driven by prescribing for males with ARB exhibiting an opposite trend of a small but significant decrease of ARB use with time for males. This indicates that the observed increase in ARB use is due to prescribing for females.
- The preference for ACEI and ARB decreases with increasing age. However ARB reach nadir rates at 70 years that is 20 years earlier compared to ACEI which reaches lowest rates at 90 years. This indicates that the increase in use of ACEI and ARB is driven by prescribing for age groups between 50 – 69 years.
- Females have a higher chance of receiving ARB compared to males but with increasing likelihood of no treatment as they grow older. Females from 70 years upwards are at greatest disadvantage of receiving sub-optimal treatment.

Study 2

To investigate the influence of ACEI on morbidity and mortality in patients aged ≥ 70 years with HFrEF

- ACEI reduced all-cause mortality substantially in patients aged ≥ 70 years with HFrEF.
- This benefit is comparable to the general population with HFrEF.
- The observed survival benefit was maintained during the 3-year follow-up.
- This benefit was incremental and independent of other heart failure treatment and comorbidity.
- Age reduced life expectancy with the risk of mortality in patients aged ≥70 years doubled compared to patients diagnosed <70 years.
- These results were observed at 3-year follow-up post primary diagnosis with HFrEF.
- The result obtained for hospitalisation is inconclusive and requires a more rigorous study design.
- This research indicates critical areas for statistical improvement for future studies.

Study 3

To investigate the influence of ARB on morbidity and mortality in patients aged ≥ 70 years with HFrEF

- ARB reduced all-cause mortality substantially in patients aged ≥70 years with HFrEF.
- This benefit is comparable to the general population with HFrEF.
- The observed survival benefit was maintained during the 3-year follow-up.
- This benefit was incremental and independent of other heart failure treatment and comorbidity.
- Age reduced life expectancy with the risk of mortality in patients aged ≥70 years doubled compared to patients diagnosed <70 years.
- These results were observed at 3-year follow-up post primary diagnosis with HFrEF.
- This research demonstrates similar results to those observed in study 2 with ACEI.
- The result obtained for hospitalisation is inconclusive and requires a more rigorous study design.
- This research indicates critical areas for statistical improvement for future studies.

Study 4

To investigate comparative effectiveness of ARB to ACEI in reducing morbidity and mortality in patients aged ≥ 70 years with HFrEF.

- The result for survival benefit observed in patients with HFrEF indicate that ACEI and ARB have comparative effectiveness in patients aged ≥ 70 years.
- This benefit was independent of other heart failure treatment and comorbidity.
- Age reduced life expectancy regardless of ARB or ACEI treatment with the risk of mortality in patients aged ≥ 70 years doubled compared to patients diagnosed < 70 years.
- These results were observed at 3-year follow-up post primary diagnosis with HFrEF.
- The result obtained for hospitalisation is inconclusive and requires a more rigorous study design.
- This research indicates critical areas for statistical improvement for future studies.

10. Future studies

Further studies are required to confirm the finding on all-cause mortality with better external validity and examine again the influence of treatment on heart failure hospitalisation. The following research questions have been identified during this study program employing a multicentre approach:

What is the effect of ACEI on HFrEF failure hospitalisation in patients aged ≥70 years at incident diagnosis?

What is the effect of ARB on HFrEF failure hospitalisation in patients aged ≥70 years at incident diagnosis?

Is comparative effectiveness of ARB compared to ACEI observed in the all-inclusive sample maintained in patients aged ≥70 years at incident diagnosis?

Are ARB non-inferior compared to ACEI in reducing all-cause mortality in HFrEF patients aged ≥70 years at incident diagnosis?

Are ARB non-inferior compared to ACEI in reducing HFrEF hospitalisation in patients aged ≥70 years at incident diagnosis?

These studies are planned with a greater sample and with propensity score matching of patients including a wider range of prognostic factors. Additionally, the non-inferior studies shall be carried out using the two one-sided test procedure at an α significance level of 0.025 for a 95% confidence interval. The possibility of these studies performed as multi-centre observational research is not excluded.

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[Articles Appendix [pages 253-329] removed for copyright reasons]

12.5. Risk Assessment

RISK ELIMINATION & CONTROL
Process / Activity / Area / Equipment

Business/Site Name	Mater Dei Hospital, Malta	Date	22 August, 2017	Dep	Pharmacy	RA Ref.	#1198	Issue 1

Describe Process/Activity/Equipment being assessed:
Retrieval and analysis of clinical data gathered in the process of medical management of this patient cohort and in accordance with local (Maltese) guidelines. The intended analysis has been approved by the local site and their Ethics and Governance oversight systems. Any clinically important findings for individual patients will be forwarded to the relevant clinical teams should any arise. Followed by publication of results.

Materials/Substances/Resources used
Study site electronic and paper records only (which include clinical details of patients in the course of their management) - further investigations will not be required for this study.

Are there clear work instructions/procedures: List document numbers below	Yes	No
One		

Is the process / activity included in the skills matrix:	Yes	No
Are you confident in your abilties	Yes	No

High risk if activity not in skills matrix, and user is not confident in abilities

What is the operator's level of competency?	Highly skilled and experienced	Trained or highly experieced	No training / some experience / supervised	Novice / inexperienced / unsupervised

TO INSERT RISK FIGURES FOR FREQUENCY PROBABILITY AND SEVERITY REFER TO THE TABLES BELOW

FREQUENCY

	FA - Freq. of Exposure		FB - Duration of Exp
1	Yearly	1	< 10 min's
2	Monthly	2	10min - 1hr
3	Weekly	3	1 - 4hrs
4	Daily	4	4 - 8 hrs
5	Continuously	5	Continuously

PROBABILITY

	PA - Likelihood of injury
1	Improbable
2	Less likely
3	Possible
4	Likely
5	Certainty

SEVERITY

	SA-Number exposed		SB - Who's Exposed		SC - Severity
1	0 - 1	1	Operator	1	Insignificant
2	2 - 5	2	Contractor	2	Minor
3	6 - 20	3	Visitor	3	1-3 days off
4	21 - 100	4	All in vicinity	4	+3 days off
5	>100	5	Public	5	Fatality

When choosing risk value for the 'F', 'P' or 'S' if you cannot distinguish between two values always choose the higher of the two.

Not necessary		Up to assessor		Assess further		Assess further	
1~10	I	11~20	L	21~60	M	> 60	H

No.	Hazard type	Control measures	(F) Frequency F-A	F-B	F	(P) Probability P-A	P	(S) Severity S-A	S-B	S-C	S	Total risk=F.P.S	I	L	M	H
1	Breach in privacy and confidentiality	Password protected data files held by operator only	4	3	3.5	1	1	1	1	2	1.333	4.6667				
2	Other work commitments	plan deadlines around projects, make arrangements to work schedule	4	3	3.5	3	3	1	1	2	1.333	14				
3	Access to materials	Plan list of files in advance, make arrangements with Records	4	3	3.5	3	3	1	1	2	1.333	14				
4	Method	Consult regularly on progress with supervisor	2	5	3.5	2	2	1	1	2	1.333	9.3333				
5	Illness	Ensure work involving travel and retrieval of data is carried out early in schedule, understand ruules for extensions	2	5	3.5	2	2	1	1	3	1.667	11.667				
6	Injury at work	Follow work related risk minimization procedures and safety protocols	5	5	5	1	1	1	1	4	2	10				
7	Data loss	Maintain multiple data files in separate databanks and update regularly according to set schedule	5	5	5	3	3	1	1	2	1.333	20				
8																
9																

Risk assessment continued:

RISK ELIMINATION & CONTROL
Process / Activity / Area / Equipment

Business/Site Name		Date		Dep		RA Ref. No.		Issue 1

ABNORMAL CONDITIONS

No.	Hazard type	Control measures	(F) Frequency			(P) Probability		(S) Severity				Total risk=F.P.S			
			F-A	F-B	F	P-A	P	S-A	S-B	S-C	S	I	L	M	H
1															
2															
3															
4															
5															

EMERGENCY CONDITIONS

No.	Hazard type	Control measures	(F) Frequency			(P) Probability		(S) Severity				Total risk=F.P.S			
			F-A	F-B	F	P-A	P	S-A	S-B	S-C	S	I	L	M	H
1															
2															
3															
4															
5															

NO further assessment required [redacted] **Further assessments required**

Comments & Notes

	Name	Signature	Date
Principal Investigator	Anthony Cutajar	[redacted]	18 July, 2017

12.6. Aston UREC Approvals

Aston University
Aston Triangle
Birmingham
B4 7ET
0121 204 3000

Date: 8th December 2017

School of Life and Health Sciences

Dear Anthony Cutajar (cc. Supervisor: Dr David Terry)

Study title:	An investigation in to ACE inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) in elderly patients 75 years and over with heart failure and reduced left ventricular ejection fraction (LVEF).
REC REF:	#1198

Confirmation of Ethical Opinion

On behalf of the Committee, I am pleased to confirm a favourable opinion for the above research based on the basis described in the application form, protocol and supporting documentation listed below.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Ethics application #1198		18/07/2017
University of Malta UREC approval letter		27/07/2017
Mater Dei Hospital Patient Data Letter		15/06/2017
Letter to Aston from Mater Dei re: sponsorship		28/07/2017
Risk Assessment form re: clinical data		22/08/2017
Response to UREC PO		28/11/2017

With the Committee's best wishes for the success of this project.
Yours sincerely

Dr Nichola Seare
Chair of the University Research Ethics Committee

Anthony Cutajar

PharmD Research Student Number 159219315

Principal Supervisor: Dr David Terry

28th May 2018

Chair

University Research Ethics Committee

Aston University

Petition to change criterion of age for analysis

Study title:	An investigation in to ACE inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) in elderly patients 75 years and over with heart failure and reduced left ventricular ejection fraction (LVEF).
REC REF:	#1198

This is a petition to change the criterion of age for analysis of research already sanction by Aston UREC. The original research proposal was approved, based on the age criterion set at ≥ 75 years. Through this petition, the researcher is requesting to change this criterion to ≥ 50 years of age for the preliminary survey and to ≥ 70 years for the subsequent three inferential studies.

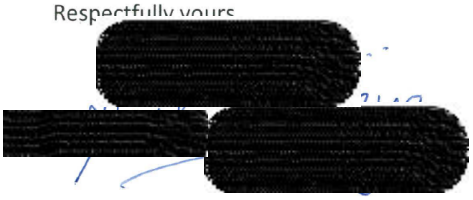
The extension of data analysis to 50 years of age will enable a direct comparison of the very elderly at ≥ 70 years of age with heart failure patients diagnosed at an earlier age starting at 50 years, when age becomes a male risk factor for cardiovascular disease. This shall allow a more comprehensive and meaningful research for the present population that that originally proposed, particularly the primary survey.

In the case of the subsequent three quantitative studies planned for inferential statistics after the survey, a preliminary full sample analysis showed that these studies may either be impossible to be done with the available study sample, or will struggle to achieve the necessary sample size. The latter was calculated at a set minimum power value of 85% to detect a meaningful change in primary outcome that is all cause mortality. Through this petition the researcher is requesting to decrease the age limit to ≥ 70 years as the age criterion for analysis for these three studies. This shall increase the study sample by approximately 400 patients, making all three studies possible.

UREC is respectfully asked to note that the extra data being requested is already available to the researcher. This occurred not by intent or design, but by the very nature of the electronic reports made available which are not restricted by age. However I confirm that further data analysis cannot

proceed pending a favourable decision by UREC. I can also confirm that this change in criterion was endorsed by the Principal Research Supervisor, Dr. David Terry, and approved by UREC from the University of Malta.

Respectfully yours



Anthony Cutajar

Additional documents:

Revised full protocol

Previous Aston UREC approval

Re-approval by University of Malta UREC

Aston University
Aston Triangle
Birmingham
B4 7ET
0121 204 3000

Date: 18/06/2016

Dr David Terry (cc Anthony Cutajar)
School of Life and Health Sciences

Study title:	An investigation in to ACE inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) in elderly patients 75 years and over with heart failure and reduced left ventricular ejection fraction (LVEF).
REC REF:	Ethics application #1198

Confirmation of Ethical Opinion

On behalf of the Committee, I am pleased to confirm a favourable opinion for the amendment to this research as described in your e-mail of 30th May 2018 *and subsequent e-mail corespondence dated 31st May and 1st June.*

Documents approved

Document	*Version*	*Date*
Aston UREC amendment request		28 May 2018
Malta ethics second approval		4 May 2018
Protocol	2	1 June 2018

With the Committee's best wishes for the success of this project.
Yours sincerely

Dr Nichola Seare
Chair of the University Research Ethics Committee

12.7. University of Malta UREC Approvals

L-UNIVERSITÀ TA' MALTA
Msida - Malta
KUMITAT TA' L-UNIVERSITA'
GHALL-ETIKA FIR-RIĊERKA

UNIVERSITY OF MALTA
Msida - Malta
UNIVERSITY RESEARCH
ETHICS COMMITTEE

27th July 2017

Mr Anthony Cutajar
Senior Principal Pharmacist
Clinical Pharmacy Practice Unit
Department of Pharmacy
Mater Dei Hospital

Dear Mr Cutajar,

Re: 1)A Survey of the Use of ACE Inhibitors or Angiotensin Receptor Blockers in Patients over 75 Years with Heart Failure and Reduced Ejection Fraction

2) Are ACE Inhibitors Effective and Safe in a Contemporary Cohort of Adults aged 75 years and over, and Diagnosed with Heart Failure and Reduced Ejection Fraction?

3) Efficacy and Safety of Angiotensin Receptor Blockers as Primary Therapy Versus no Angiotensin Blockade in a Contemporary Cohort of Adults aged 75 years and over, and Diagnosed with Reduced Ejection Fraction

4) Efficacy and Safety of Angiotensin Receptor Blockers as Primary Therapy Versus ACE Inhibitors in a Contemporary Cohort of Adults Aged 75 years and over, and Diagnosed with Reduced Ejection Fraction

As Chairperson of the University Research Ethics Committee, I am pleased to inform you that UREC has approved the research proposals listed above.

Yours sincerely,

[redacted]

Professor H Grech
Chairperson
University Research Ethics Committee

Re: Change in UREC approved research

University Research Ethics Committee [research-ethics.committee@um.edu.mt]
Sent: 04 May 2018 16:29
To: Cutajar Anthony J at Health-MDH
Cc: urec@um.edu.mt; charlene.bonello@um.edu.mt; patrick.j.schembri@um.edu.mt; Vassallo Mario J at Health-MDH; janet.mifsud@um.edu.mt; Cassar Andrew at Health-MDH

Dear Mr Cutajar,
We refer to your letter requesting a change in age criteria from >= 75, as originally approved, to >=55.
As this does not materially change any key considerations in your previously approved application, you may proceed with the change in age criteria.
Best wishes for your research,
UREC

12.8. A priori sample size and power estimation

12.8.1. Study 1

This is a nationwide survey of mortality and incident diagnosis where the full cohort identified from 2007 to 2017 was 3340 patients. This is estimated to represent at least 98% of all the patients aged ≥50 years at incident diagnosis during this period nationwide. Taking all-cause mortality as a measure, mean cumulative incidence during the 11-years period was 0.64 per 1000 with a standard deviation of 0.505.

$$\bar{x} \pm Z\frac{s}{\sqrt{n}}$$

Sample mean ($\bar{x}$)	0.64
Standard deviation (s)	0.505
Sample size (n)	3340
Confidence level	95 %
or Z-score (Z)	1.959964 σ

Your sample's confidence interval is **0.64 ± 0.01713**, or from **0.6229 to 0.6571**

Confidence interval	
Lower bound	0.62287
Upper bound	0.65713
Margin of error (E)	0.0171264

Assuming 95% confidence level this sample had a margin of error of 0.02 for mean cumulative incidence of all-cause mortality (319).

12.8.2. Study 2

Statistical Parameters

Anticipated Incidence

Group 1 (?) 28 %

Group 2 (?) 20 %

Incidence

Enrollment ratio (?) 1

Type I/II Error Rate

Alpha (?) 0.05

Power (?) 85%

RESULTS

Dichotomous Endpoint, Two Independent Sample Study

Sample Size	
Group 1	510
Group 2	510
Total	**1020**

Study Parameters	
Incidence, group 1	28%
Incidence, group 2	20%
Alpha	0.05
Beta	0.15
Power	0.85

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + kp_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$N_1 = \left\{ 1.96 * \sqrt{0.24 * 0.76 * (1 + \frac{1}{1})} + 1.04 * \sqrt{0.28 * 0.72 + (\frac{0.2 * 0.8}{1})} \right\}^2 / 0.08^2$$

$$N_1 = 510$$

$$N_2 = K * N_1 = 510$$

p_1, p_2 = proportion (incidence) of groups #1 and #2
$\Delta = |p_2 - p_1|$ = absolute difference between two proportions
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β
K = ratio of sample size for group #2 to group #1

Therefore the study would need to recruit 1000 patients to have 85% power to detect a true change in all-cause mortality rate of 8% by ACE inhibitor treatment over one year (95, 194, 319, 320)

12.8.3. Study 3

Statistical Parameters

Anticipated Incidence

Group 1 (?) 28 %

Group 2 (?) 21.5 %

Incidence

Enrollment ratio (?) 1

Type I/II Error Rate

Alpha (?) 0.05

Power (?) 85%

RESULTS

Dichotomous Endpoint, Two Independent Sample Study

Sample Size	
Group 1	790
Group 2	790
Total	**1580**

Study Parameters	
Incidence, group 1	28%
Incidence, group 2	21.5%
Alpha	0.05
Beta	0.15
Power	0.85

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + k p_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$N_1 = \left\{ 1.96 * \sqrt{0.248 * 0.752 * (1 + \frac{1}{1})} + 1.04 * \sqrt{0.28 * 0.72 + (\frac{0.215 * 0.785}{1})} \right\}^2 / 0.065^2$$

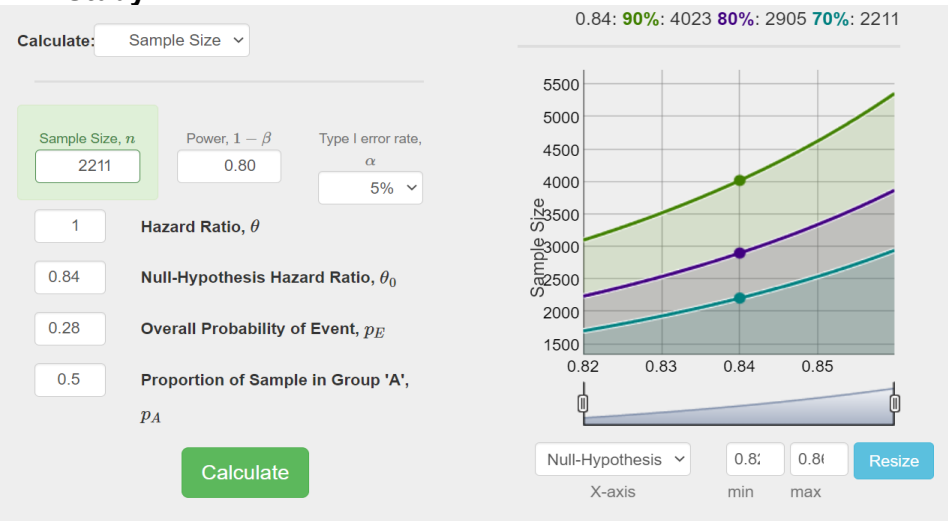
$$N_1 = 790$$

$$N_2 = K * N_1 = 790$$

p_1, p_2 = proportion (incidence) of groups #1 and #2
$\Delta = |p_2 - p_1|$ = absolute difference between two proportions
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β
K = ratio of sample size for group #2 to group #1

Therefore the study would need to recruit 1600 patients to have 85% power to detect a true change in cardiovascular mortality rate of 6.5% by ARB treatment over one year (110, 194, 320, 321).

12.8.4. Study 4



Calculate Sample Size Needed to Test Time-To-Event Data: Cox PH 1-Sided, non-inferiority, or superiority

You can use this calculator to perform power and sample size calculations for a time-to-event analysis, sometimes called survival analysis. A two-group time-to-event analysis involves comparing the time it takes for a certain event to occur between two groups.

For example, we may be interested in whether there is a difference in recovery time following two different medical treatments. Or, in a marketing analysis we may be interested in whether there is a difference between two marketing campaigns with regards to the time between impression and action, where the action may be, for example, buying a product.

Since 'time-to-event' methods were originally developed as 'survival' methods, the primary parameter of interest is called the hazard ratio. The *hazard* is the probability of the event occurring in the next instant given that it hasn't yet occurred. The *hazard ratio* is then the ratio of the hazards between two groups Letting θ represent the hazard ratio, the hypotheses of interest are

$$H_0 : \theta = \theta_0$$
$$H_1 : \theta > \theta_0$$

or

$$H_0 : \theta = \theta_0$$
$$H_1 : \theta < \theta_0$$

where θ_0 is the hazard ratio hypothesized under the null hypothesis; θ_0 can also be viewed as the non-inferiority/superiority margin, just like in the other non-inferiority/superiority calculators here. The calculator above and the formulas below use the notation that

θ is the hazard ratio
$\ln(\theta)$ is the natural logarithm of the hazard ratio, or the log-hazard ratio
p_E is the overall probability of the event occurring within the study period
p_A and p_B are the proportions of the sample size allotted to the two groups, named 'A' and 'B'
n is the total sample size
Notice that $p_B = 1 - p_A$.

Formulas

This calculator uses the following formulas to compute sample size and power, respectively:

$$n = \frac{1}{p_A\, p_B\, p_E}\left(\frac{z_{1-\alpha} + z_{1-\beta}}{\ln(\theta) - \ln(\theta_0)}\right)^2$$

$$1 - \beta = \Phi\left(z - z_{1-\alpha}\right) \quad , \quad z = \left(\ln(\theta) - \ln(\theta_0)\right)\sqrt{n\, p_A\, p_B\, p_E}$$

where

n is sample size
Φ is the standard Normal distribution function
Φ^{-1} is the standard Normal quantile function
α is Type I error
β is Type II error, meaning $1 - \beta$ is power

References (322)