ISCTE Business School
Instituto Universitário de Lisboa

CARDIOTOXICITY OF CANCER THERAPY – A COST-BENEFIT ANALYSIS OF A CARDIONCOLOGY ASSESSMENT IN PORTUGAL

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Resumo

Cardiotoxicidade é um efeito adverso da terapêutica do cancro e pode ser monitorizada através da avaliação da LVEF. Nesta dissertação desenvolveu-se um modelo de custo-benefício para analisar a LVEF na perspetiva do recetor de cuidados de saúde e num período de 5, 10 e 30 anos. O modelo Markov, assente na progressão clínica retrospetiva de 109 pacientes seguidos no Hospital de Santa Maria, Portugal e probabilidades de transição, foi desenvolvido para medir o custo-benefício da análise LVEF. Custos e utilidades foram monitorizados num período de 5, 10 e 30 anos, e foi elaborada uma análise de sensibilidade para as variáveis significativas.

Nos casos de referência de pacientes com 50 e 60 anos avaliados na monitorização da LVEF, o período de análise de 5 anos (4.23 QALYs e custo de €5,824) e (3.79 QALYs e custo de €13,657) respetivamente, destacou-se dos períodos de 10 e 30 anos. Durante o período de 5 anos e disposição a pagar de €375.000, a probabilidade de um QALY adicional em relação à média aumenta 53,6% e 50,3% para pacientes de 50 e 60 anos, respetivamente. A simulação Monte Carlo do modelo Markov não teve efeito sobre as conclusões do modelo. Para Portugal, a análise de custo-benefício sugere que os custos por QALY aumentam substancialmente com o período de análise e a idade. Adicionalmente, a probabilidade de um QALY adicional em relação à média na disposição a pagar de uma coorte hipotética de 1000 pacientes decresce com o aumento do período de análise e a idade.

Palavras Chave: *Economia da Saúde; Análise de Custo-Benefício; Cardiotoxicidade; Terapêutica do Cancro*

JEL Codes**:** *D61; I15*

Abstract

Cardiotoxicity caused by cancer therapy can be monitored using LVEF assessment. This dissertation aims to develop a cost-benefit model to analyze a LVEF assessment using a healthcare payer perspective and five, ten and thirty years time horizon. A Markov model, informed by the retrospective clinical course of 109 patients followed by Hospital de Santa Maria, Portugal on transitional probabilities, was built to assess the cost-benefit of LVEF assessment. Costs and utilities were assessed over a 5, 10 and 30-year range, with sensitivity analyses for significant variables.

In the reference cases of a 50 years old and 60 years old patients treated in LVEF assessment, the 5-year time horizon (4.23 QALYS and €5,824 cost over 5 years) and (3.79 QALYs and €13,657 cost over 5 years), respectively dominated the 10 and 30-year time horizon. Under a time horizon of 5 years at a Willingness to Pay threshold of €375.000, over 53,6% and 50,3% of simulation adds QALYs above average for patients starting treatment with 50 and 60 years old, respectively. Monte Carlo simulation of the Markov model had no effect on model conclusions. From a Portuguese health payer perspective, the analysis of cost-benefit in cardiotoxicity suggest that the costs per QALY increase substantially with the time horizon and with the starting age. Also, the probability of additional QALY relatively to the average QALY of the hypothetical cohort of 1000 patients at Willingness to pay decreases with the increase of the time horizon and with the starting age.

Keywords**:** *Health Economics; Cost-Benefit Analysis; Cardiotoxicity; Cancer Therapy*

JEL Codes**:** *D61; I15*

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List of Abbreviations

CBA – Cost-benefit analysis

CEA – Cost-effectiveness analysis

GLS – Global longitudinal strain

HF – Heart failure

HSM – Hospital Santa Maria

LV – Left ventricular

LVEF – Left ventricular ejection function

MUGA – Multi-gated acquisition scan

QALY – Quality adjusted life year

VBA – Visual Basic for Applications

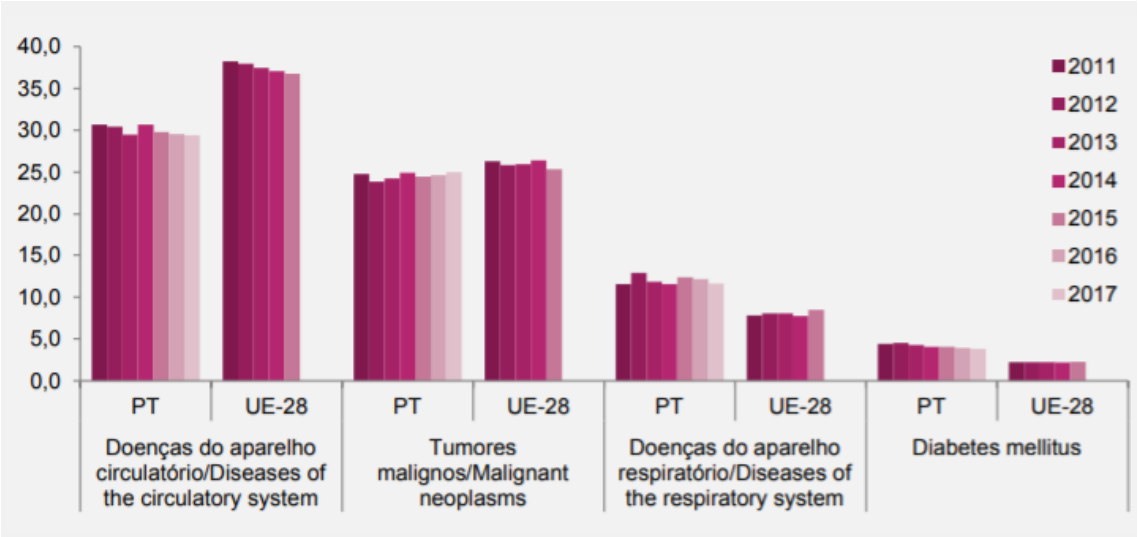
WTP – Willingness to Pay

1. Introduction

Cardiotoxicity is an adverse effect associated with various cancer therapies. Reports of cardiotoxicity, specifically heart failure (HF), from chemotherapy and radiation therapy have been described for several decades. Recent proliferation of new anti-cancer therapies improved substantially the prognosis of cancer patients. On the other hand, new anti-cancer targeted therapies demonstrated unanticipated effects on the cardiovascular system, leading to an increase of cancer survivors and a rise in the incidence of cardiotoxicity. (Yu *et al.*, 2017).

INE (2019) report on causes of death in 2017 determined that cardiovascular diseases are the most prevalent cause of death in Portugal and in Europe, corresponding to 29,8% and 36,7% of the total causes of death, respectively. The second most prevalent cause of death in Portugal and in Europe are malignant tumours, representing 24,5% and 25,4% of total deaths, respectively. Combined, cardiovascular and oncology diseases are the cause of more than half of total deaths, 54,2% in Portugal and 62,1% in Europe. Figure 1 shows the distributions of the most prevalent causes of death in Portugal and in Europe between 2011 and 2017.

Figure 1 - Deaths by some causes of death, Portugal 2011-2017 and EU-28[1] 2011-2015 (% of total)



Source: INE (2019)

[1] EU-28 is an acronym for European Union constituted by 28 countries.

The potential impact of cardiotoxicity on healthcare costs and health outcomes is substantial. Clinical practice recommendations made by cardiology and oncology organizations suggest cardiotoxicity monitoring, done by routine cardiac imaging with several clinical evaluations, including the left ventricular ejection function (LVEF). LVEF is the measurement of how much blood is being pumped out of the left ventricle of the heart. (Yu *et al.,* 2017).

The objective of this dissertation is to develop a cost-benefit model to analyze a LVEF assessment using a healthcare payer perspective and five, ten and thirty years time horizon. This cardiotoxicity monitoring cost-benefit analysis focuses on the impact of imaging-guided interventions to improve health outcomes in cancer patients. We use clinical data collected from the cardioncology medical appointment from Hospital Santa Maria, in Lisboa, Portugal. Hospital Santa Maria is a public hospital where the cardiology department has a cardioncology clinical speciality. Cardiac imaging interventions are prescribed in the medical appointment, according to the malignancy and type of cancer. LVEF was used to measure cardiotoxicity in this cost-benefit analysis. Given that the patients in the sample in this research have different type of cancers, anticancer therapies and cardioprotective medication standard monitoring care is recommended.

As for the structure of the dissertation, it is divided into 4 main chapters. In Chapter 2, literature review is made. Firstly, a review of the literature on cardiotoxicity, followed by an analysis of cardiac imaging techniques in the assessment of cardiotoxicity and analysis of the benefits and risks of cardiotoxicity monitoring. To conclude, a review of the research on cost-effectiveness analysis of cardiotoxicity monitoring in cancer patients.

In Chapter 3, it is presented the data and methodology used in the study. First, the data is described, followed by an analysis of the key assumptions. A Markov model was built to examine the costs and utilities of a cardioncology clinical assessment, assessed over a 5, 10 and 30-year range, with sensitivity analyses for significant variables.

In Chapter 4, the results showed that the earlier the assessment is done and the younger the patient starting the treatment, the lower is the cost per QALY. In Chapter 5, conclusion is presented as well as the study limitations and suggested future research.

2. Literature review

The objective of this Chapter is to review the literature on cost-effectiveness analysis of cardiotoxicity from cancer therapy. First, a review of the literature on cardiotoxicity, followed by an analysis of cardiac imaging techniques in the assessment of cardiotoxicity. Subsequently, we analyze the benefits and risks of cardiotoxicity monitoring. Finally, a review of the research on cost-effectiveness analysis of cardiotoxicity monitoring in cancer patients.

2.1 Cardiotoxicity

Cancer therapy increases the risk of cardiotoxicity, specifically heart failure. Cardiotoxicity is a recognized adverse effect associated with various cancer therapies. Chemotherapy and radiation therapy are related with cardiac dysfunction and symptomatic heart failure. The potential impact of cardiotoxicity on healthcare costs and health outcomes is substantial. The effects on cardiac function and prognosis are clear since this assessment can restrict the delivery of anticancer treatment, dropping cancer-related quality of life and survival. The discovery of new target anticancer therapies led to an increasing proportion of cancer survivors. The new target anticancer therapies allowed cancer patients to live longer and to be exposed to cardiovascular effects of cancer treatment latter than under previous treatments. Clinical practices and guidelines for cardiotoxicity monitoring, both during and after cancer treatment, have been proposed by cardiology organizations over the recent years. (Yu *et al.,* 2017).

Cardiotoxicity monitoring is usually done by routine cardiac imaging. The best treatment for chemotherapy-induced cardiotoxicity is prevention. Candidates for chemotherapy should be carefully selected and followed before, during and after treatment with several clinical evaluations, including the left ventricular (LV) function. Since cardiotoxicity can manifest during chemotherapy, soon after (weeks or months) or many years after the interruption of treatment, cardiac follow-up is needed beyond the limited period of chemotherapy. (Curigliano *et al.,* 2012).

Steinherz *et al.* (1991) made one of the first studies that demonstrated the left ventricular function was associated with cardiotoxicity. They showed that chronic LV dysfunction in 23% of children treated with anthracyclines, an anti-cancer medication widely used in chemotherapy, showed an increase in cardiac damage later in life. Other studies corroborated with Steinherz *et al.* (1991) findings. For example, a recent study by Wang

et al. (2015) with of over 5.000 patients receiving anthracycline-based chemotherapy suggested that left ventricular ejection function (LVEF) at baseline is predictive of major adverse cardiac events, including symptomatic heart failure and cardiac death.

Among several imaging techniques, echocardiography is the ideal method for evaluating the left ventricular function. (Todaro *et al.,* 2013). Cardiotoxicity guidelines, in general, defined cardiotoxicity as a reduction of the LVEF of 5% to 55% with symptoms of heart failure or an asymptomatic reduction of the LVEF of 10% to 55% (Martin *et al.,* 2009). Guidelines are not defined universally and there is no official standard care adopted cross-wide. Nolan *et al.* (2016) mentioned that both European and United States cardiovascular society guidelines recognized the need to monitor and manage cancer patients, although they do not make specific recommendations regarding strategies for targeting therapy.

Early detection of LV dysfunction can lead to early implementation of cardioprotective interventions such as interruption of cardiotoxic therapy and cardioprotective medicines. Identification of patients at higher risk is one key strategy to reduce the morbidity and mortality from cardiotoxicity. The need to monitor cardiotoxicity in cancer patients led to a new interdisciplinary specialty, cardioncology. (Yu *et al.,* 2017). Although LVEF assessment infrequently leads to deviations in the cancer treatment, it is still necessary to target patients who could benefit from closer cardiac monitoring and understand if the patient requires cardioprotective medication. The patients who may need cardioprotective medication can start medical therapy earlier when cardiotoxicity in being monitored properly. LVEF assessment can help to better adjust the anticancer therapeutic approach. (Sawaya *et al*., 2012).

Other cardiac imaging methods are available to check cardiotoxicity. Global longitudinal strain (GLS) monitoring is becoming a valuable approach alongside LVEF monitoring. GLS is used to evaluate the myocardial contractility. GLS is mostly used for breast cancer patients, since it can predict changes in the systolic function before LVEF drops. (Portugal *et al*., 2017).

Serial echocardiographic assessment of LVEF became the gold standard in screening for chemotherapy-induced cardiotoxicity since guidelines converge to the appropriateness of this method to monitor cardiotoxicity. GLS is not regularly used for all cancers because it is expensive and most times LVEF monitoring is adequate to assess cardiotoxicity.

Unnecessary cardiotoxicity monitoring can increase healthcare costs and cause scarcity of healthcare resources. (Yu *et al.,* 2017).

2.2 Cost-Benefit Analysis

Cost-Benefit Analysis is a process to organize clinical facts and to present data in a way that is useful for making policy decisions. CBA balances the advantages and disadvantages of a procedure. This method can help organize clinical decisions and contribute to a more informed debate on the allocation of health care resources. (Getzel, 2013).

Cost-utility analysis is a type of cost-effectiveness analysis where the incremental cost per some preference-based valuation of health outcome is estimated. Two alternative strategies are compared according to how many additional health benefits are gained and at what additional cost. To quantify health outcomes, health economists use a measurement called the "quality-adjusted life-year," or QALY ("qually"). The use of QALYs allows to establish comparisons across different health technology assessments and is mostly advantageous for resource allocation decision-making. The lower the ratio of a cost per QALY, the more cost–effective a health intervention is said to be. (YHEC, 2016).

Cost-effectiveness analysis (CEA) is a shortened form of CBA and provides valuable information to evaluate costs and health benefits for different technologies or strategies for a given health intervention. Although CEA does not express all elements of importance in health care decisions, we can determine which strategy is better to invest, with useful, timely and affordable information on the health outcomes of the different interventions. (WHO, 2003).

There are several key steps when performing and interpreting data on the economics of disease that are not part of usual patient-oriented research practice. These include (1) defining perspective and time horizon, (2) collecting data on health care utilization, (3) costing health care resources, (4) analyzing data on utilization and cost, (5) defining and measuring health effects, (6) adjusting costs and effects for inflation and discounting, (7) and evaluating uncertainty. The cost–effectiveness of a new intervention depends heavily on the choices by the researcher on the above-mentioned issues.

In evaluating uncertainty, a model commonly used in economic evaluation of healthcare interventions is the Markov model. The Markov model is a tool for sequential decision making that analyses the clinical and economic consequences of medical decisions over a time period. (Alagoz *et al.*, 2010). Until the end of the 80s decade, the most common methodology used to evaluate decision analysis problems was the standard decision tree. Since Beck *et al.* (1983) description of Markov methods their use has grown substantially in medical decision making, often replacing the standard decision tree in cases when outcomes or events occur, or may reoccur, over time.

Monte Carlo simulations are a statistical method used to model stochastic systems and establish the probabilities for a variety of outcomes. Monte Carlo simulation uses random inputs to model the system and produce probable outcomes. Repeating possible sequences of transitions for the Markov chain *N* times, allow us to estimate quantities with more confidence. (Brooks *et al.*, 2011).

Few studies have been conducted regarding the cost-effectiveness of cardiotoxicity monitoring itself. From a societal perspective, Yeh *et al.* (2014) developed a cost-effectiveness analysis comparing four strategies of cardiotoxicity monitoring in childhood cancer survivors. The monitoring alternatives were: 1) Echocardiogram every one year; 2) Echocardiogram every two years; 3) Echocardiogram every five years and 4) Echocardiogram every ten years. Yeh *et al.* (2014) concluded that for patients receiving a dose higher than 250mg/m^2 of anthracyclines, the preferred cardiotoxicity monitoring strategy at a 100.000$ per quality adjusted life year (QALY) cost-effectiveness threshold was the echocardiogram every two years.

Most studies that included cardiotoxicity monitoring and decision-making analysis use cost-effectiveness analysis to compare different anti-cancer therapies. Neyt *et al.* (2008) estimated the cost-effectiveness and budget impact of reimbursing trastuzumab, from a healthcare payer's perspective, evaluating the efficacy and safety of trastuzumab in the treatment of early stage breast cancer in HER2+[2] tumors. Neyt *et al.* (2008) CEA model considered long-term consequences of preventing the progress to metastatic breast cancer and averting side effects, for example heart failure. Patient characteristics where ordered according to age (years) and stage (I, II, III) of breast cancer. Due to the possible risk of heart failure, LVEF is measured using multi-gated acquisition scan (MUGA), preferred

[2] HER2+ is a protein that can promote the growth of breast cancer cells.

over the standard echocardiography, since MUGA is specific for borderline cases. In this research the authors considered two different scenarios: 1) HERA trial: one-year post-chemotherapy treatment and 2) FinHer: nine-week initial treatment. The HERA regimen is not cost saving due to the higher initial treatment costs. Both from a medical and an economic point of view, the FinHer initial treatment regimen with trastuzumab showed promising results and justified the initiation of a large comparative trial with a one-year regimen. Although this article studied two different options for transtuzumab treatment and not directly the cardiotoxicity monitoring, these results were obtained considering the cardiotoxicity or heart failure follow-up costs. Neyt *et al.* (2008) demonstrated that cardiotoxicity does not only causes incremental costs due to extra follow-up costs (MUGA) and the treatment of heart failure, but also has implications on life expectancy, considering these assumptions in the CEA model.

From a healthcare payer perspective, Nolan *et al.* (2016) focused on the cost-effectiveness comparing three different strategies of screening and cardioprotection. Selected patients with cancer receiving cardiotoxic chemotherapy had the following monitoring alternatives: 1) After the LVEF-defined cardiotoxicity diagnosis the patient starts cardioprotective medications; 2) All patients in chemotherapy start universal cardioprotective medication and 3) 2D echo strain-guided management with initiation of cardioprotective medications in patients with a decline in GLS. Nolan *et al.* (2016) developed a Markov model considering these three strategies. This study concluded that strain-guided cardioprotection provides more QALY's at lower cost than universal cardioprotection. However, they admitted that the differences that exist in cost-effectiveness of strain-guided and LVEF-guided strategies may depend on the malignancy involved and that strain echocardiography is limited to small subgroups of breast cancer patients and these findings must take in consideration the actual scenario.

This literature review highlights the lack of studies analysing the cost-benefit of cardiotoxicity monitoring and identifies the gaps in the understanding of cost-benefit of cardiotoxicity monitoring. The objective of this thesis is to analyse the cost-benefit of cardiotoxicity monitoring, focusing on the impact of imaging-guided interventions to improve health outcomes in cancer patients.

3. Methods

In this section it will be presented the data and methods used for the Cost-Benefit analysis. First, the data is described, followed by an analysis of the key assumptions. A decision-analytic model was built to examine the costs and utilities of a cardioncology clinical assessment.

3.1 Data

To analyse the utility of cardiotoxicity monitoring, focusing on the impact of imaging-guided interventions, it required a valuable set of clinical data. Hospital Santa Maria, in Lisbon is a public hospital in Portugal that offers a cardioncology medical appointment. The clinical dataset was maintained and provided by the department of Cardiology from Hospital Santa Maria in Lisboa.

The retrospective data was analysed between November 2015 and November 2016. The provided data contains the clinical course of 109 patients from the first visit to the end of one year of treatment. The dataset comprises patients' age, gender, type of cancer, day of first visit, cancer medication, heart medication, risk scores of heart failure, heart rates, and LVEF imaging-guided results. Patients in this study followed individual anticancer therapies and cardiac medication in reference to their cancer type. The average age of the patients was 66 years old. A summary of the dataset is shown in Table 1.

Table 1 – Summary of statistics of the dataset

Variables	Min	Max	Average	Variance
Age	19	97	65,94	191,45
Number of Visits	1	3	2,18	0,15
Heart failure risk score	1	7	5,78	3,05
Subsequent heart failure risk score	1	6	2,19	1,38
Heart rates	47	120	78,50	208,97
LVEF assessment	0,19	0,78	0,42	0,01
Subsequent LVEF assessment	0,21	0,66	0,51	0,01
Gender	Female(66%); Males (34%)			

Table 1 shows that the dataset has 66% females and 34% of males. The average age of the patients was 66 years old. Regarding the number of hospital visits, patients had around

2 medical appointments. LVEF assessment was done in 42% of the patients under analysis, and 51 % of them followed the treatment.

To develop the CBA some key assumptions were assumed. Given that the cardiac imaging interventions were prescribed in the medical appointment according to the malignancy and type of cancer, LVEF was used to measure cardiotoxicity; when LVEF is less or equal to 55% means the patient has cardiotoxicity. Additionally, risk scores of heart failure are between 0 and 10; a patient with a risk score higher or equal to 5 is assumed to have heart failure. Another key assumption is that patients with an age higher than 85 that stop being followed in this medical appointment are considered deceased. Finally, hospital visits were proxied by the number of imaging-guided interventions. If the patient has 1 imaging-guided intervention he must have been in at least 2 visits. If the patient has 2 imaging-guided intervention he must been in at least 3 hospital visits.

3.2 Methodology

Based on the data provided by the hospital and on previous literature, a Markov Model was constructed to evaluate the clinical and economic consequences of this cardiotoxicity assessment, using Monte Carlo simulation in a hypothetical cohort of 1000 patients. The patients progress in the model according to transition probabilities (Table 2), utilities (Table 3) and costs (Table 4).

The Markov Model intends to estimate the costs and benefits of the cardioncology assessment (QALY's gained) of a large cohort. The Monte Carlo simulation was codded in an Excel Macro using Visual Basic for Applications (VBA) and can be accessed in Appendix 1.

Transition states incorporated in the model can be represented by a diagram of transition states, as presented in Figure 2. Figure 2 shows that after the LVEF assessment, a patient can be in four health states: well, cardiotoxicity, heart failure or death. A healthy patient can become cardiotoxic, have heart failure or die. Once the patient is considered cardiotoxic, he can continue cardiotoxic, having heart failure or die. If the patient is considered to have heart failure, he can continue in that state or progress to death.

Figure 2 - Diagram of transition states incorporated in the model

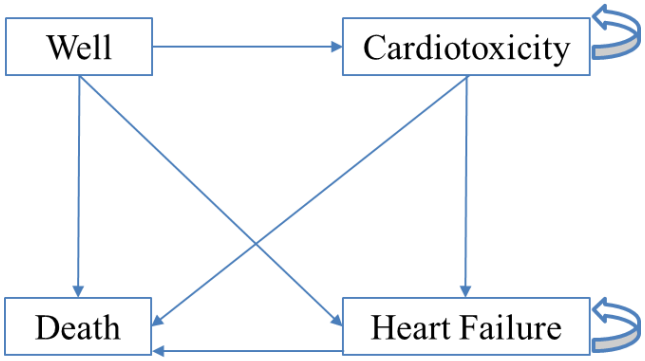


Table 2 presents the annual probabilities for each health state and captures the range of statistic information in the sample provided by the retrospective study of the patients under analysis. Cardioprotective medication probabilities and statistic information were obtained from Nolan *et al.* (2016). A Normal distribution was assigned for transition probabilities according to average and variance.

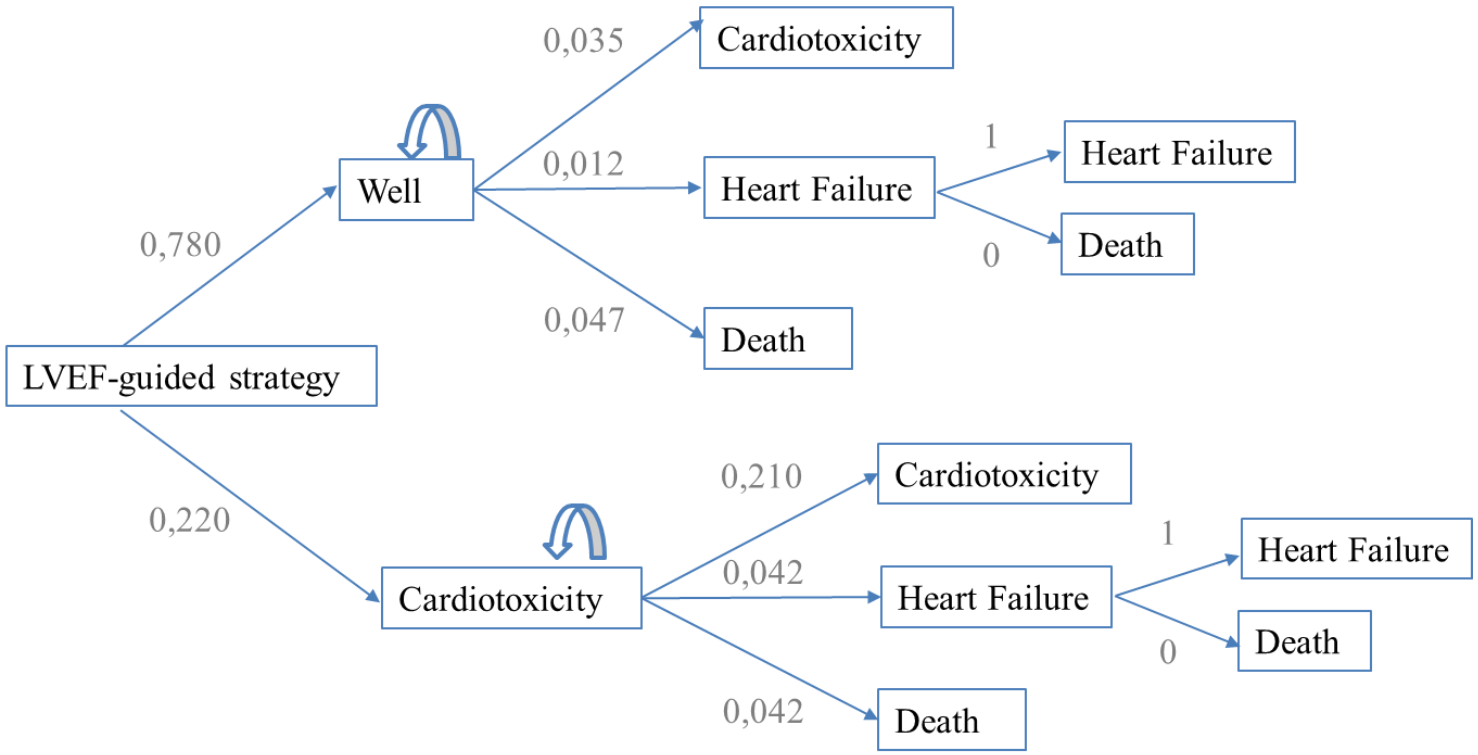
The decision tree with the transition probabilities for each health state in the Markov model, shown in Figure 3, relates the transition probabilities given in Table 2 and the diagram of transition states presented in Figure 2.

Table 2 - Transition probabilities and statistic information

Variables	Probabilities	Min	Max	Average	Variance	Source	Distribution*
Initial Visit							
LVEF-guided strategy							
Cardiotoxicity	**0,220**	0,190	0,780	0,423	0,015	Dataset	Normal
Death	**0,000**	0,000	1,000	0,000	0,000	Dataset	Normal
Cardioprotective Medication							
Side-effects	**0,330**	0,250	0,640	0,330	0,083	Nolan *et al.* (2016)	Normal
Discontinuation	**0,100**	0,050	0,130	0,100	0,025	Nolan *et al.* (2016)	Normal
Subsequent Visits							
Clinically Well patients	**0,780**						
Cardiotoxicity	**0,035**	0,035	0,450	0,540	0,002	Dataset	Normal
Heart Failure	**0,012**	0,000	0,500	0,012	0,008	Dataset	Normal
Death	**0,047**	0,000	1,000	0,047	0,006	Dataset	Normal
Cardiotoxicity Patients							
Cardiotoxicity	**0,210**	1,000	0,425	0,016	0,004	Dataset	Normal
Heart Failure	**0,042**	0,000	0,600	0,042	0,011	Dataset	Normal
Death	**0,042**	0,000	1,000	0,042	0,011	Dataset	Normal
Cardioprotective Medication							
Side-effects	**0,200**	0,100	0,300	0,200	0,050	Nolan *et al.* (2016)	Normal
Discontinuation	**0,050**	0,020	0,080	0,050	0,013	Nolan *et al.* (2016)	Normal

*Distribution used for the sensitivity analysis

Figure 3 -Diagram of transition health states and corresponding probabilities



In respect to the utilities, the values were obtained from Gohler *et al.* (2009) and Lewis *et al.* (2001), resumed in Table 3. Gohler *et al.* (2009) studied utility estimates for decision-analytic modelling in heart failure, with health states based on New York Heart Association classes and number of rehospitalizations. Lewis *et al.* (2001) evaluated preferences for quality of life or survival expressed by patients with heart failure using Minnesota Living with Heart Failure questionnaires. The patients' utility for medication side-effects only refers to patients with heart failure.

Table 3 - Values for Utilities

Variable	Base Value	Min	Max	Average	Variance	Source	Distribution*
Cardiotoxicity	0,94	0,68	0,99	0,83	0,05	Gohler *et al.* (2009)	Beta
Heart Failure	0,60	0,52	0,74	0,63	0,04	Gohler *et al.* (2009)	Beta
Medication side-effects	0,96	0,92	1,00	0,96	0,01	Lewis *et al.* (2001)	Beta

*Distribution used for the sensitivity analysis

To test the robustness of our benefit analysis, sensitivity analysis was carried around the assumed utilities, as the utilities are from published literature for United States Citizens. Utility parameters were assigned a distribution according to the methodology suggested by Briggs *et al.* (2007). Those authors suggest using the Beta distribution for utilities.

Regarding cost analysis, this model was constructed from the perspective of the healthcare payer. Data on costs was obtained from several sources and represented in Table 4. Hospital visits and LVEF-guided echocardiographic screening costs were retrieved from Diário da República no. 63/2016 and calculated according to the key assumptions stated in section 3 regarding information on number of visits and image-guided interventions from the sample. For the LVEF-guided echocardiographic screening it was considered a 2-dimension transthoracic echocardiogram. Cardiotoxicity costs and statistic evaluation were obtained from Nolan *et al.* (2016). Cardiac Medication costs were obtained from and converted from 2015 US$ to 2019 EU€ using the Banco de Portugal currency convertor. Heart failure cost base value was obtained from Macedo *et al.* (2010) and the range values from Nolan *et al.* (2016). Cardiac Medication costs were obtained from Infarmed Reference Prices. Calculation of the medication costs considered the medication indicated on the data, the active substance and dose, the government reimbursement rate and the number of packages needed for one year of treatment.

Table 4 - Annual costs (2019 EU€)

Variable	Base Value	Min	Max	Average	Variance	Source	Distribution*
Hospital visit	15,3	7,0	21,0	15,3	7,4	(DRE) no. 63/2016	Gamma
LVEF screening	45,2	38,8	77,6	45,2	209,5	(DRE) no. 63/2016	Gamma
Cardiotoxicity	2670	890	4450	2670	890	Nolan *et al.* (2016)	Gamma
Heart Failure	10900	4450	17800	10900	3338	Macedo *et al.* (2010)	Gamma
Cardioprotective medications	64,7	5,0	335,1	64,7	4568,5	Infarmed	Gamma
Medication side-effects	44,5	44,5	667,5	44,5	156,0	Nolan *et al.* (2016)	Gamma

*Distribution used for the sensitivity analysis

To test the robustness of our cost analysis, sensitivity analysis was carried around the assumed costs, as some costs used are from published literature for United States Citizens. Parameters were assigned a distribution according to the methodology suggested by Briggs *et al.* (2007). Those authors suggest using the Gamma distribution for costs where parameters are non-negative.

In summary, patients progress in the Markov model according to the transition probabilities given in Table 2. The CBA uses the utilities presented in Table 3 and costs presented in Table 4. Data for this research came from several sources: literature, dataset from a cardioncology medical appointment in the department of Cardiology of Hospital Santa Maria, and Infarmed. The sensitive analysis of the decision-analytic model was performed using Monte Carlo simulation in a hypothetical cohort of 1000 patients with Excel VBA.

We followed Nolan *et al.* (2016) and assumed that interventions took place at the start of the time horizon. An annual discounted factor of 3% was applied for costs and benefits. Cycle length is the time of transition between health states where all information is held constant. Cycle length was assumed to be 1 year for the purposes of this analysis. The results will be presented in the next section.

4. Results and Discussion

In this section the Cost-Benefit Analyses derived from the Markov Model are presented and discussed. An internal model validation was performed using a Normal, Gamma and Beta distributions, with a hypothetical cohort of 1000 patients in order to calculate the mean probabilities, utilities and costs. For each simulation, the model calculated the costs and QALY.

The CBA results of the deterministic analysis are presented in Table 5.

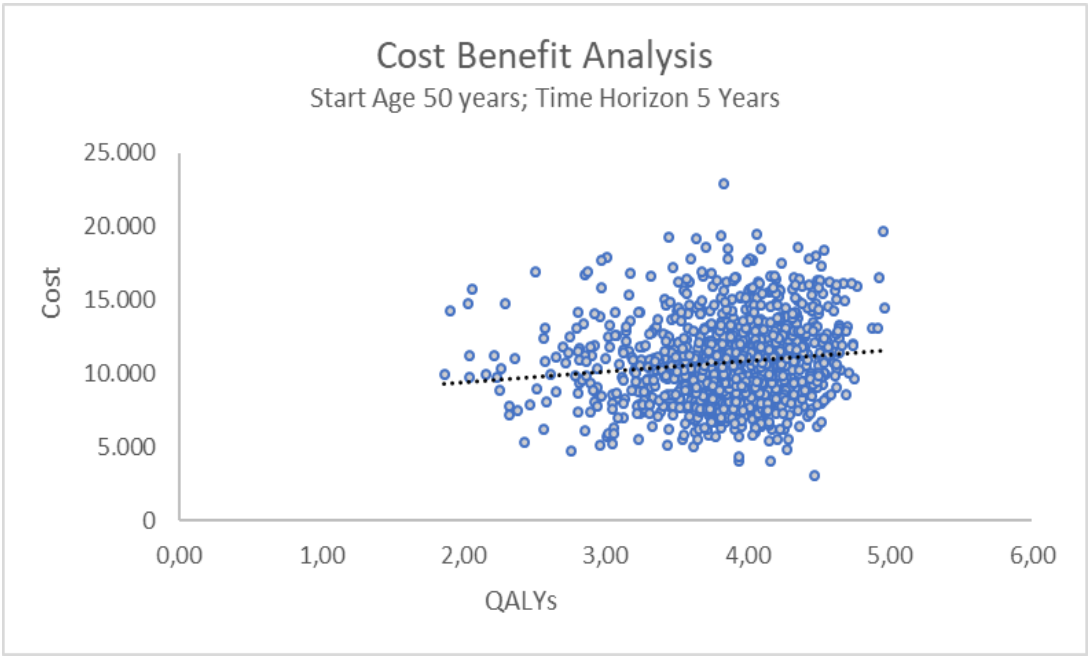
Table 5 - Cost-Benefit Deterministic Analysis

Time Horizon	Start Age	Deterministic Analysis		
		Cost	QALYs	Cost per QALY (€)
5 years	50 years	5 824	4,23	1 378
	60 years	13 657	3,79	3 600
10 years	50 years	18 678	6,93	2 695
	60 years	36 165	5,85	6 186
30 years	50 years	76 555	11,09	6 900
	60 years	106 939	9,93	10 773

Table 5 shows the CBA for 6 scenarios. Patients starting the treatment with 50 years old for a time horizon of 5, 10 and 30 years; and patients starting the treatment with 60 years old for a time horizon of 5, 10 and 30 years. As we may observe in Table 5, cost per QALY for patients starting LVEF-assessment with 50 years old is 1.378 euros for 5 years horizon, 2.695 euros for 10 years horizon, and 6.900 euros for 30 years horizon. For patients starting the treatment with 60 years old, the cost per QALY is 3.600 euros for 5 years horizon, 6.186 euros for 10 years horizon, and 10.773 euros for 30 years horizon. The cost per QALY of LVEF increases both with the starting age and with the time horizon.

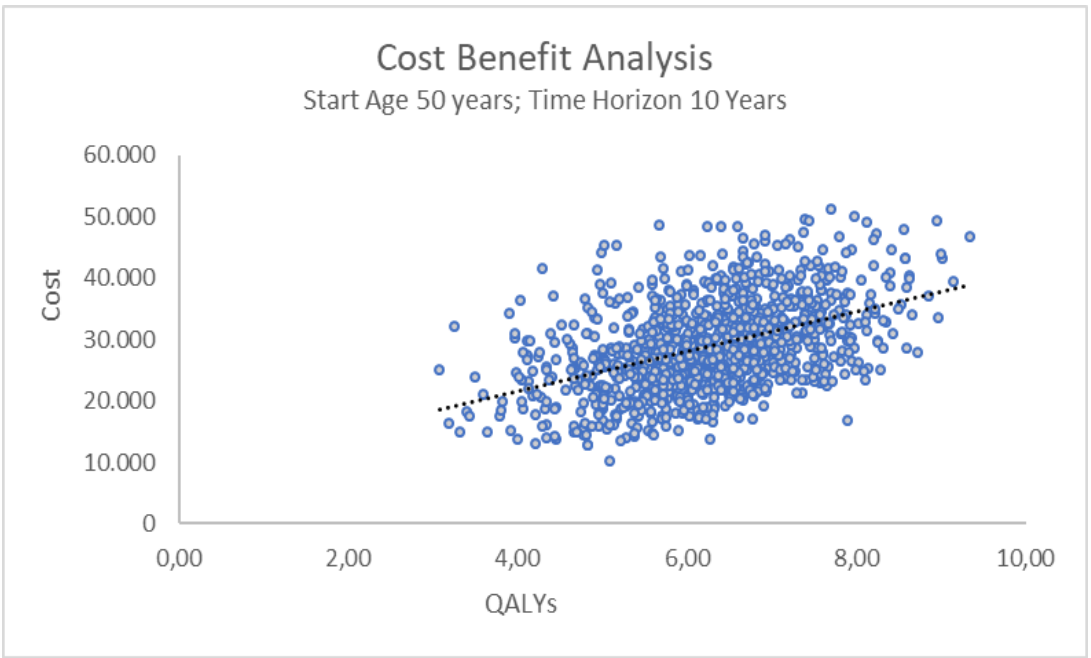
The CBA of the simulation of a hypothetical cohort of 1000 patients are shown in Figures 4 to 9. Figures 4, 5, and 6 show the CBA for a patient starting the treatment with 50 years old for 5, 10 and 30 years time horizon, respectively.

Figure 4 - Cost-Benefit Analysis for 5 years in patients with 50 years old



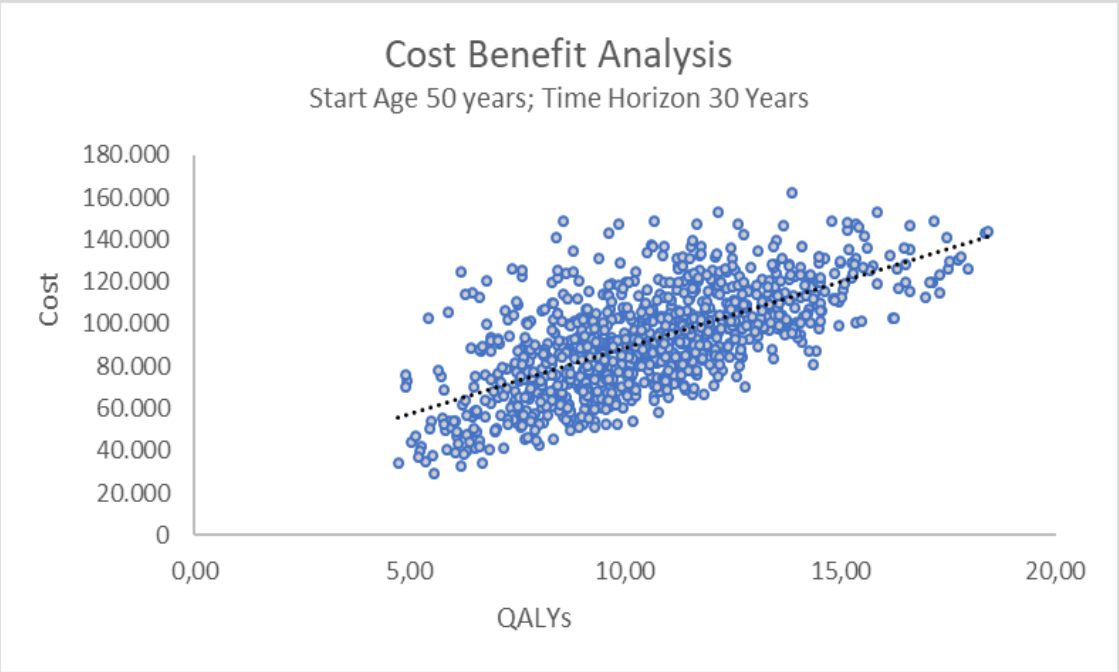
In Figure 4 the costs range between 5.000€ and 15.000€, and the QALYs range between 2 and 5 years.

Figure 5 - Cost-Benefit Analysis for 10 years in patients with 50 years old



In Figure 5 the cost range between 10.000 euros and 50.00 euros. The QALYs range between 3 and 10 years. When compared to Figure 4, Figure 5 shows a higher QALY variability a positive trend of the cost of the treatment.

Figure 6 - Cost-Benefit Analysis for 30 years in patients with 50 years old



In Figure 6, we may observe that the cost range between 20.00 and 150.000 euros. The heath benefit range between 5 and 18 QALYs. The trend of the cost per QALY, given by the black line in dots, increases with the time horizon of the treatment.

Figures 7, 8, and 9 show the CBA for a patient starting the treatment with 60 years old for 5, 10 and 30 years time horizon, respectively.

In Figure 7 the costs range between 12.000€ and 24.000€, and the QALYs range between 1,5 and 5 years. When compared to Figure 5, Figure 7 shows that the starting age affects positively the cost of the treatment. In Figure 8, the cost range between 25.000 euros and 60.00 euros. The QALYs range between 3 and 8 years. In Figure 9, we may observe that the cost range between 30.00 and 160.00 euros. The heath benefit range between 5 and 18 QALYs. In all figures we observed that the trend of the cost per QALY, given by the black line in dots, increases with the time horizon of the treatment.

Figure 7 - Cost-Benefit Analysis for 5 years in patients with 60 years old

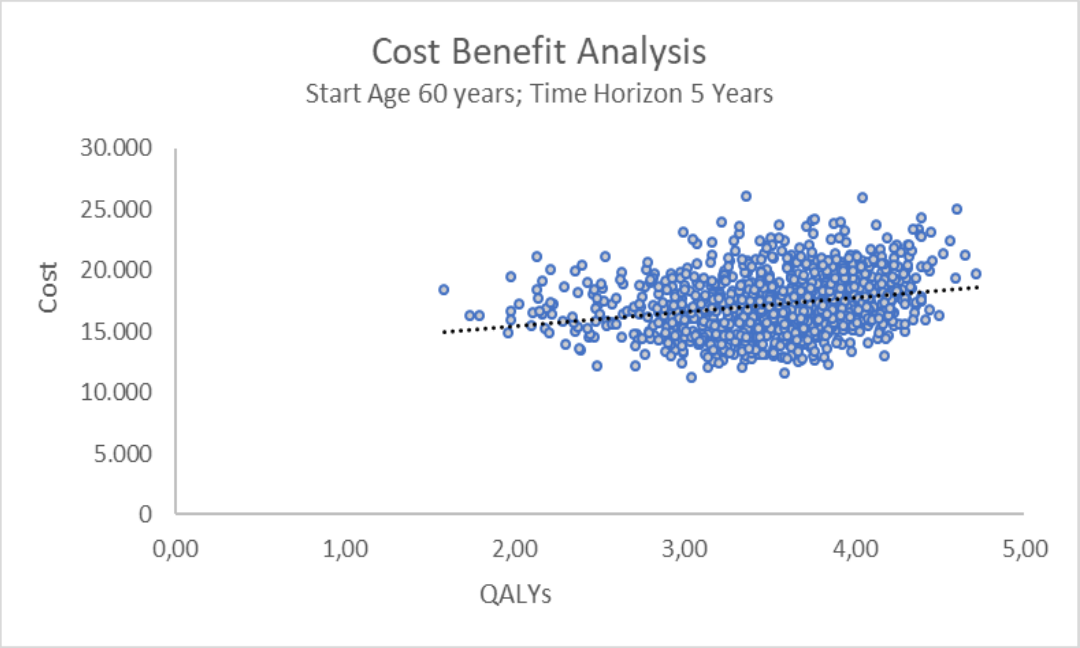


Figure 8 - Cost-Benefit Analysis for 10 years in patients with 60 years old

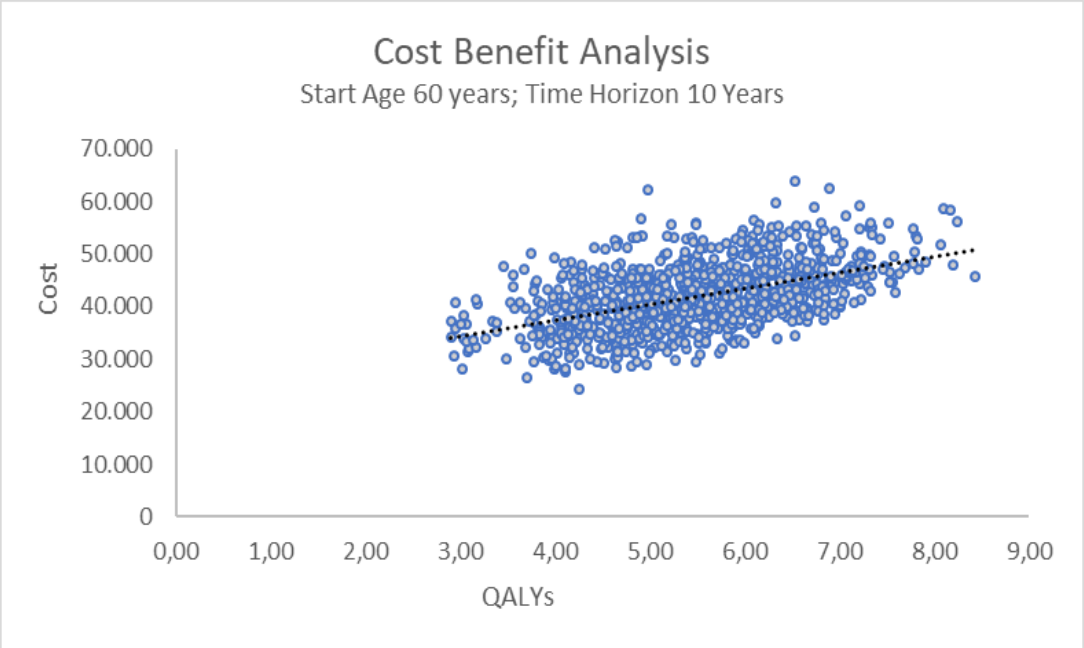
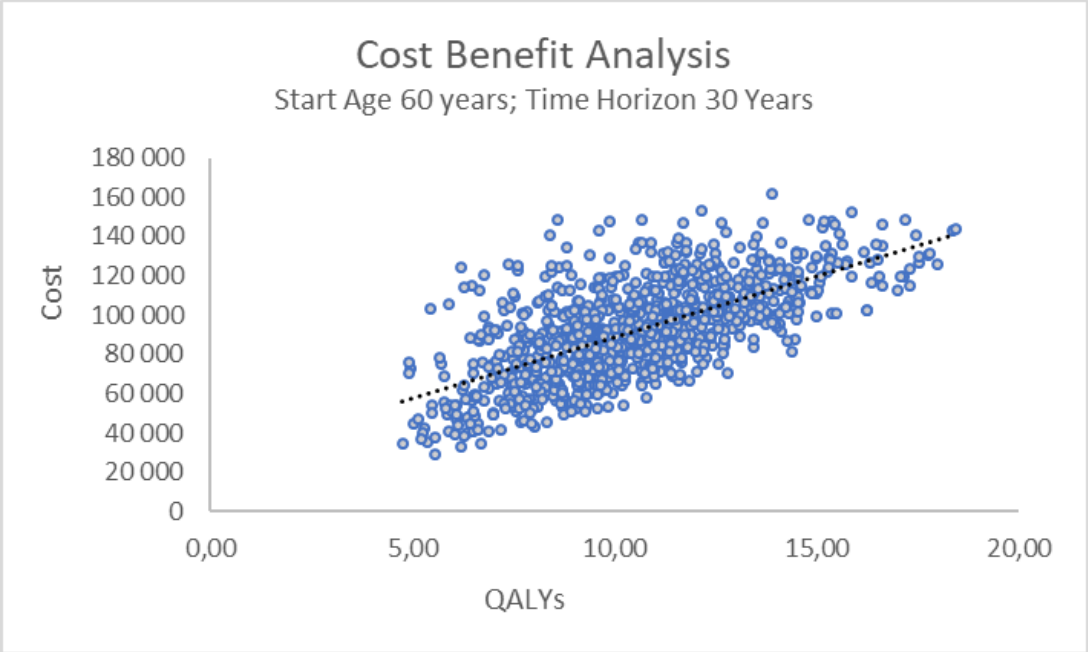


Figure 9 - Cost-Benefit Analysis for 30 years in patients with 60 years old



In the probabilistic analysis, we also simulate the probability of adding QALYs above the average of the 1000 cohort QALYs. The results of this probabilistic analysis are presented in Table 6. The average QALY for hypothetical cohort of 1000 patients with 50 years old is old is 3,83 for 5 years horizon, 6,22 for 10 years horizon, and 10,54 for 30 years horizon. The average QALY for hypothetical cohort of 1000 patients with 60 years old is 3,49 for 5 years horizon, 5,54 for 10 years horizon, and 10,07 for 30 years horizon. The probabilistic average QALY decreases slightly with the starting age. However, we observe that for both stating ages, in 30 year time horizon, the QALY decreases for one third of the life span.

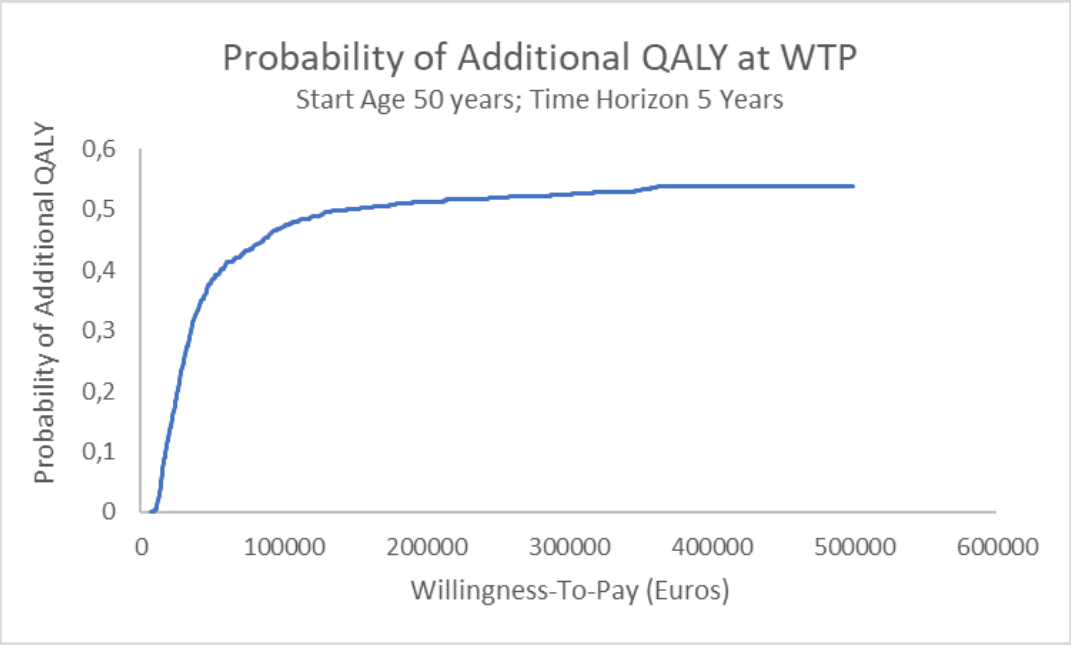
Table 6 - Probabilistic Cost-Benefit Analysis

Time Horizon	Start Age	Probability of Additional QALY at Willingness to Pay			
		Average QALY	25000	250000	375000
5 years	50 years	3,83	18,7%	36,5%	53,6%
	60 years	3,49	6,5%	26,7%	50,3%
10 years	50 years	6,22	12,9%	31,2%	48,4%
	60 years	5,54	3,3%	18,7%	45,1%
30 years	50 years	10,54	4,0%	21,0%	41,9%
	60 years	10,07	1,0%	15,6%	42,5%

The results presented in Table 6 are shown in Figures 10 to 15. Figures 10, 11, and 12 show the probability of Additional QALY for a given maximum Willingness to Pay (WTP) per QALY gained for a patient starting the treatment with 50 years old for 5, 10 and 30 years time horizon, respectively. According to Getzel (2013) the best measure for the value of the benefit you get is your "willingness to pay", since it is considered the mirror image of "opportunity cost". Thus, the total value of treatment is assumed to be the WTP times the QALYs one gets with the treatment.

All cost-benefit acceptability curves, shown in Figures 10 to 12, are consistent, increasing, and the flat of the curve starts at a Willingness to Pay threshold of around €375.0003. For a patient with 50 years old under a time horizon of 5 years at a Willingness to Pay threshold of €375.000, over 53,6% of simulation will add QALYs above average. This probability decreases with the time horizon, reaching 48,4% and 41,9% for 10 years and 30 years' time horizon, respectively.

Figure 10 - Probability of Additional QALY at WTP for 5 years in patients with 50 years old



[3] The flat of the curve means that there is very few patients having additional QALYs above the average after WTP threshold of €375.000.

Figure 11 - Probability of Additional QALY at WTP for 10 years in patients with 50 years old

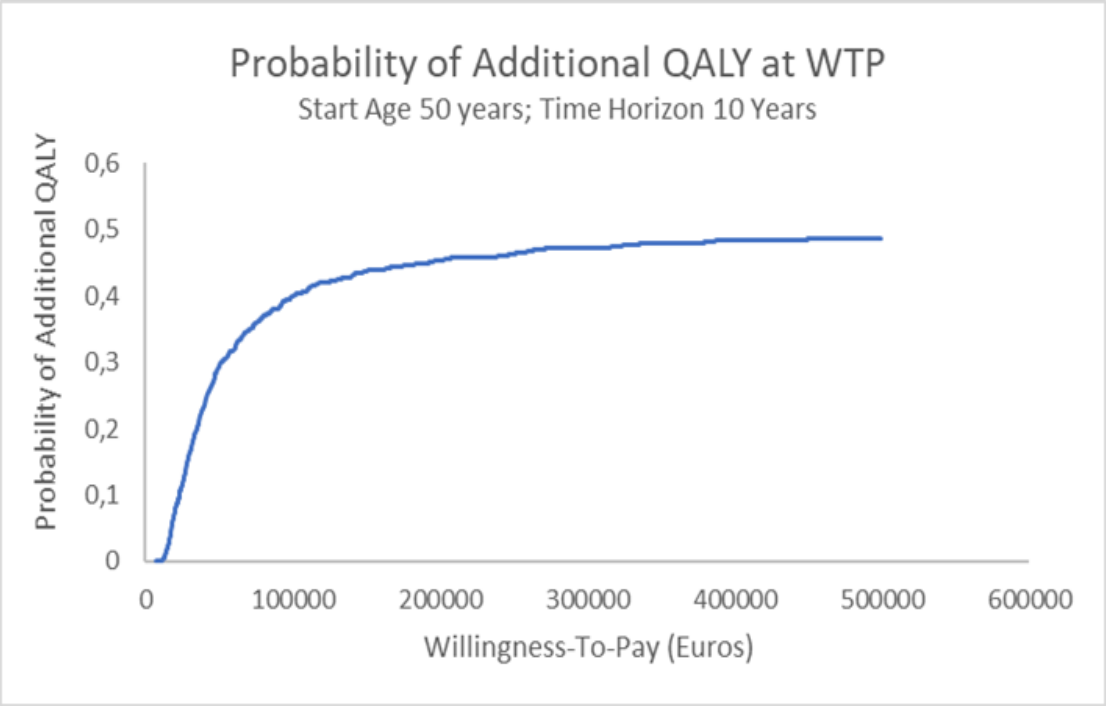
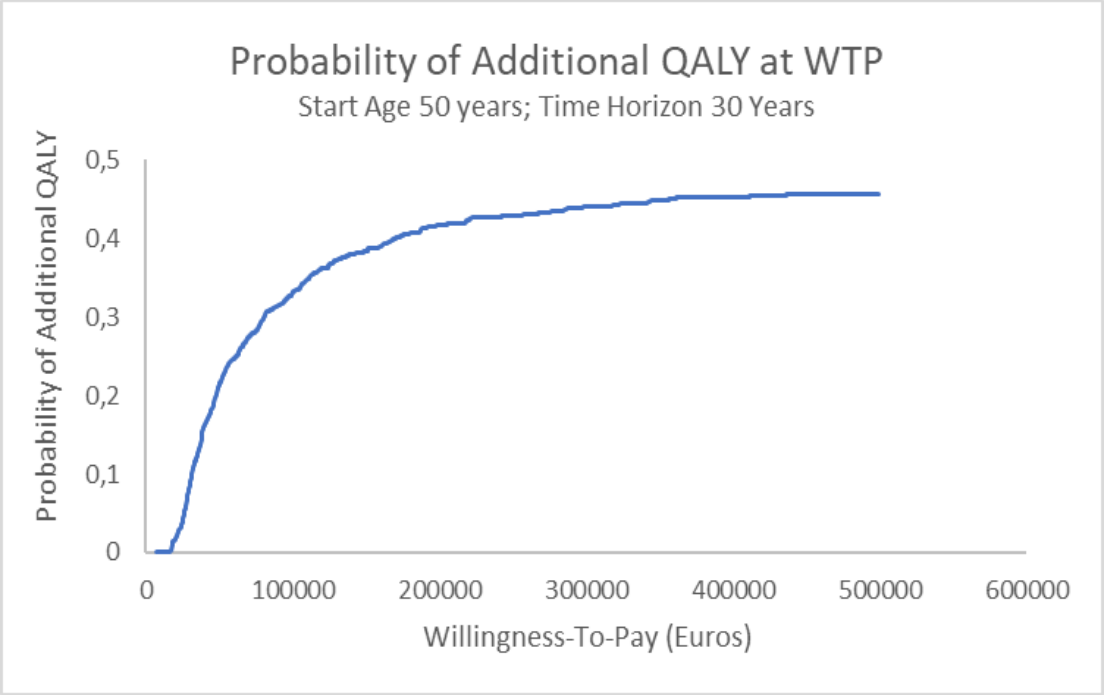


Figure 12 - Probability of Additional QALY at WTP for 30 years in patients with 50 years old



Figures 13, 14, and 15 show the probability of Additional QALY for a given maximum Willingness to Pay per QALY gained for a patient starting the treatment with 60 years old for 5, 10 and 30 years time horizon, respectively. The cost-benefit acceptability curves are consistent and increasing. For a patient with 60 years old under a time horizon of 5 years at a Willingness to Pay threshold of €375.000, over 50,3% of simulation will add QALYs above average. This probability decreases with the time horizon, reaching 45,1% and 42,5% for 10 years and 30 years' time horizon, respectively.

Figure 13 - Probability of Additional QALY at WTP for 5 years in patients with 60 years old

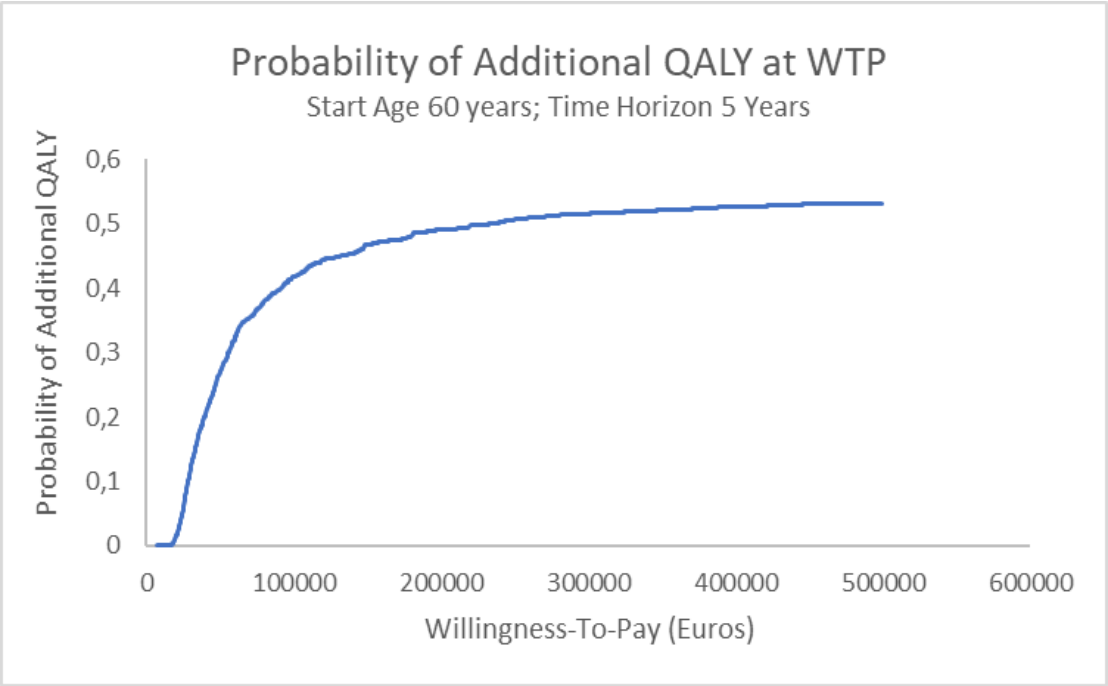


Figure 14 - Probability of Additional QALY at WTP for 10 years in patients with 60 years old

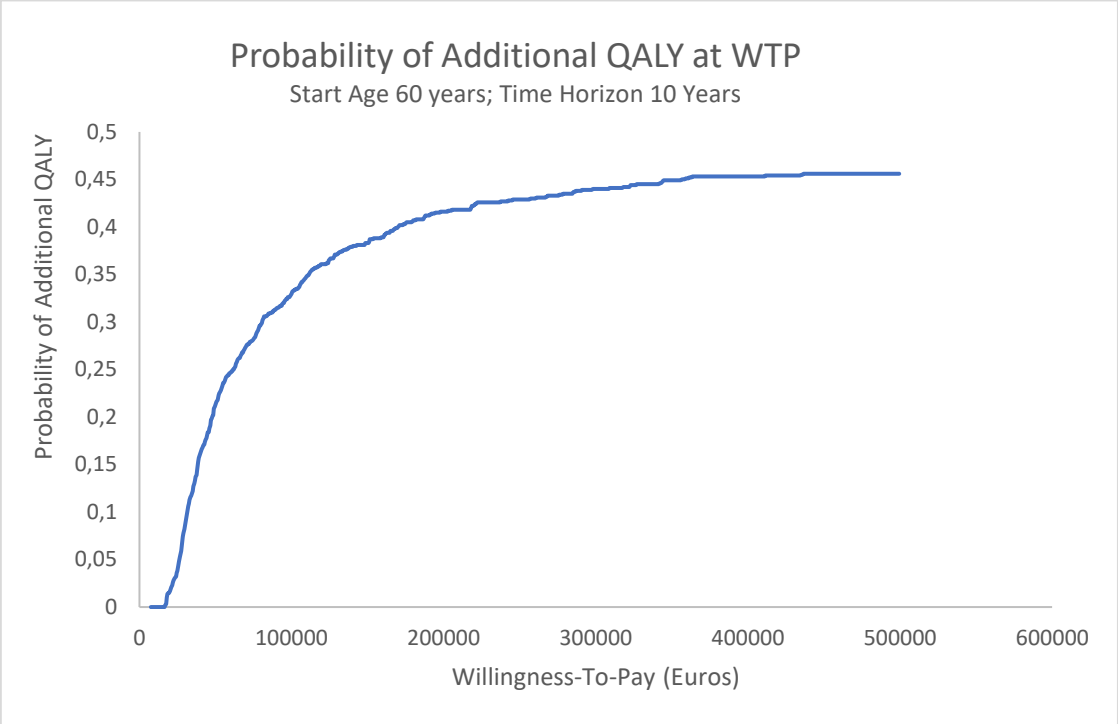
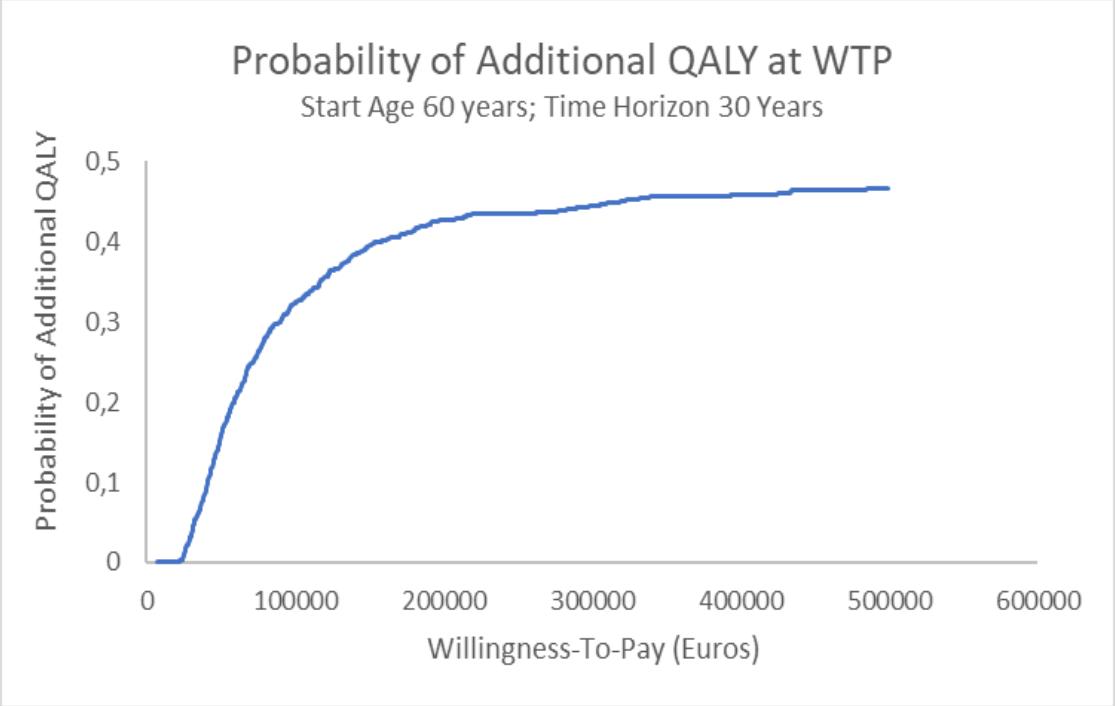


Figure 15 - Probability of Additional QALY at WTP for 30 years in patients with 60 years old



The sensitive analysis for patients starting the treatment with 50 years old was observed in Figures 4, 5 and 6. At a 5 years' time horizon the trend of the cost per QALY, given by the black line in dots, is almost flat. This result leads us to conclude that the cost is almost constant with the additional QALYs for a 5 year time horizon. On the other hand, at the time horizon 10 and 30 years the trend of the cost per QALY, given by the black line in dots has a positive slope, i.e. the cost increases with the benefit from treatment. Therefore, we may conclude that the best-case scenario is the 5 year time horizon.

The sensitive analysis for patients starting the treatment with 60 years old can be observed in Figures 7, 8 and 9. At a 5 year time horizon the trend of the cost per QALY, given by the black line in dots, is almost flat. On the other hand, at the time horizon 10 and 30 years the trend of the cost per QALY, given by the black line in dots has a positive slope, i.e. the cost increases with the benefit of the treatment over time. Therefore, we may conclude that the best-case scenario for a patient starting the treatment with 60 years old is the 5 year time horizon.

Regarding the probability of additional QALY at WTP, Table 6 shows that the probability of an additional QALY relatively to the simulated average QALY's decreases with the increase of the time horizon and starting age. The probabilistic analysis for patients starting the treatment with 50 years old can be observed in Figures 10, 11 and 12. Under a time horizon of 5 years at a Willingness to Pay threshold of €25.000, over 18,7% of simulation will add QALYs above average; at WTP threshold of €250.000, over 36,5% of simulation will add QALYs above average; and finally at threshold of €375.000, over 53,6% of simulation will add QALYs above average.

The probabilistic analysis for patients starting the treatment with 60 years old can be observed in Figures 13, 14 and 15. Under a time horizon of 5 years at a Willingness to Pay threshold of €25.000, over 6,5% of simulation will add QALYs above average; at WTP threshold of €250.000, over 26,7% of simulation will add QALYs above average; and finally at threshold of €375.000, over 50,3% of simulation will add QALYs above average.

Comparing the results for patients at starting age of 50 years old, we conclude that the best case scenario is the time horizon of 5 years since the cost doesn't significantly increase with the QALYs. The same conclusion applies for the scenarios for patients

starting the treatment with 60 years old. Comparing the probabilistic results between patients' starting the treatment with 50 and 60 years old, we may conclude that patients should start treatment as sooner as possible in order to get more QALYs at a lower cost.

5. Conclusion

This study focuses on a cost-benefit analysis of a cardioncology clinical assessment from a health payer perspective. With that aim, a decision-analytic model was built to evaluate the clinical and economic consequences of the LVEF cardiotoxicity assessment.

The Markov Model was simulated using Monte Carlo in a hypothetical cohort of 1000 patients to estimate the costs and benefits of a cardioncology assessment.

The analysis of cost-benefit in cardiotoxicity, suggest that the costs per QALY increase substantially with the time horizon and with the starting age. The average age of the patients was 66 years old, thus we analysed a scenario where the patient starts the treatment with 60 years old. Then we compare it with the scenario of a patient starting the treatment with 50 years old.

The probability of additional QALY relatively to the average QALY of the hypothetical cohort of 1000 patients at Willingness to pay decreases with the increase of the time horizon and with the increase of the starting age.

Finally, limitations in this study are related to the quality of data entered into the model. It is used a retrospective data of 109 patients provided by Hospital de Santa Maria from a cardioncology medical appointment. This study would benefit from the greater accuracy of data that a prospective study would afford. Another caveat of the data is that patients under analysis were followed for one year. Analysing the patients during one year can result in biased transitional probabilities.

Another limitation in this CBA is the use of utilities from the published literature. These utilities refer to a study that uses data on United States patients. This study would benefit greatly if there were utilities available for Portuguese patients. We had to use carditoxitity costs and medication side effects costs from a study applied to United States. The heart failure cost used in this study came from the results from published literature applied to the Portuguese patients. However, we could allocate to each patient under analysis, the Portuguese medications' costs, Hospital visits fees and LVEF ecogradiographic assessment fee, what makes our cost analysis more reliable. These data limitations were partially overcome by the internal model validation, that showed consistent results with the determinist analysis.

In future research this study would benefit from a cost-effectiveness analysis to evaluate if this cardioncology assessment is more effective than the standard care in central hospitals. This study can provide valuable information for health policy decision makers and to hospital administrations in Portugal. When cardiotoxicity in being monitored properly, the identification of higher risk patients can reduce the morbidity and mortality from cardiotoxicity. Also, the patients who may need cardioprotective medication can start medical therapy earlier. Furthermore, the cost-effectiveness analysis could contribute to the development of consensual guidelines for cardiotoxicity monitoring.

Cardiovascular toxicity has become a challenging problem during cancer therapy, and this research provides an analysis of the cost-benefit of a cardioncology assessment in Portugal. The results showed that the earlier the assessment is done and the younger the patient starting the treatment, the lower is the cost per QALY. This conclusion is expected to contribute to health policy decisions, especially to support on the possible implementation of this medical appointment in other portuguese hospitals.

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A. Appendix

Appendix 1 - VBA routine for the Markov Model

```
Sub PSA()
'declare variables
Dim total_cost_lvef(1000) As Double
Dim total_qaly_lvef(1000) As Double

' Delete old results
   Application.ScreenUpdating = False
   Sheets("simulation").Select
      Range("C4:H1003").Select
      Selection.ClearContents
      Range("p4:P1003").Select
      Selection.ClearContents
      Sheets("Evaluation").Select

   Application.ScreenUpdating = True


'probabilistic model
Range("model_type") = 2

'Store results
For i = 1 To 1000
   Range("D5") = "iteration" & i & "of 1000"

   Calculate 'random sampling

   total_cost_lvef(i) = Range("total_cost_lvef")
   total_qaly_lvef(i) = Range("total_qaly_lvef")


Next i 'loop 1000 times

'print results

For i = 1 To 1000

   Sheets("Evaluation").Select
   Application.ScreenUpdating = True
      Range("D5") = "Printing the results" & i & "of 1000"

   Application.ScreenUpdating = False
   Sheets("simulation").Select
```

```
    Cells(3 + i, 3).Value = total_cost_lvef(i)
    Cells(3 + i, 4).Value = total_qaly_lvef(i)

'CEAC----------------------------------------------------
Dim WTP As Double
Dim Prob_ce As Double

For i = 1 To 1000
WTP = Cells(3 + i, 15)
Range("WTP").Value = WTP
Prob_ce = Range("Prob_ce")
Cells(3 + i, 16).Value = Prob_ce


Next i

'reset to deterministic
Range("model_type") = 1
Sheets("Evaluation").Select
Range("D5").ClearContents
Range("b1").Select

End Sub
```