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Title: Composite Endpoints for Stent Cardiovascular Clinical Trials.

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COMPOSITE ENDPOINTS FOR STENT CARDIOVASCULAR CLINICAL TRIALS

Master Thesis in
Interuniversity Master in Statistics and Operations Research

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Summary

In clinical trials when comparing two treatment groups A and B it is common to use a composite event $\mathcal{E}_*$ consisting of the union of two or more distinct outcomes ($\mathcal{E}_* = \mathcal{E}_1 \cup \mathcal{E}_1$). For example, in cardiovascular studies it is usual to use a composite event consisting of Death ($\mathcal{E}_1$) and Target Vessel Revascularization ($\mathcal{E}_2$).

The advantages and drawbacks of using a composite event have been reported in several papers. Most of these papers focus the debate on the medical perspective rather than as a statistical problem. Based on Gómez and Lagakos (2011) paper we consider the asymptotic relative efficiency (ARE) of a logrank test for comparing treatment groups with respect to a primary endpoint versus the composite endpoint to decide when it should be better to use a composite endpoint.

We focus this master thesis on the cardiovascular area and more precisely on the cardiovascular device studies involving coronary stents. As Gómez and Lagakos show, the ARE depends basically on the correlation between the times until $\mathcal{E}_1$ and $\mathcal{E}_2$, on the hazard ratios and on the probability of occurrence of each endpoint. We have developed a literature search strategy on Pubmed database studies (randomized clinical trials, data from registries and observational studies) in order to gain knowledge about the distinct components used in the composite endpoints and to find real life parameters values used in that kind of studies. Finally, statistical recommendations to decide whether to expand a study primary endpoint from $\mathcal{E}_1$ to the composite of $\mathcal{E}_1$ and $\mathcal{E}_2$ have been analyzed from the ARE results.

Contents

Chapter 1

General Introduction to Composite Endpoints

In time-to-event analysis when comparing two treatment groups it is common to use a composite outcome, sometimes called combined outcomes, consisting of two or more distinct outcomes. For example, in cardiovascular studies we can construct a composite endpoint ($\mathcal{E}_*$) consisting of cardiac death ($\mathcal{E}_1$) and stroke ($\mathcal{E}_2$). When using a composite endpoint individuals are followed until the event of interest, $\mathcal{E}_1$ or $\mathcal{E}_2$, whichever occurs first.

Literature shows that there has been a great debate about the advantages and disadvantages about using a composite endpoint, but surprisingly there is very little discussion about statistical considerations about this issue.

1.1 Main objectives

The principal aim of this thesis is to develop recommendations to decide when it would be better to use a composite endpoint consisting in adding an extra endpoint to the primary endpoint in stent coronary clinical trials studies. This guide will be based on the statistical efficiency as a function of a small number of interpretable parameters.

In order to achieve this principal objective we have had to undertake many different tasks, from doing a systematic literature review, to learn how to use the Maple Software passing by a deeper understanding of the asymptotic survival theory, and last but not least, to learn how to use the Latex environment to write this thesis. In what follows we itemize some of the most important steps done for the achievement of this work:

1. State of the art on composite issues endpoints. Advantages and disadvantages of using composite outcomes.

2. Statistical theory needed to compute the relative efficiency of a composite endpoint vesus a primary endpoint.

3. Literature search on stent coronary clinical trials. Identification of a range of values for each relevant parameter involved in the computation of the asymptotic relative efficiency.

4. Adapt Maple computations following the Gómez and Lagakos's paper [16] to the specific set of values for stent cardiovascular clinical trials.

5. Execute the programs and analyze the results.

6. Propose guidelines for the use of composite endpoint in stent cardiovascular trials.

Chapter 2

The Composite Endpoint

2.1 Background about Clinical Trials

A clinical trial is a research study designed to provide extensive data that will allow for statistically valid evaluation of treatment or interventions on a group of individuals [20]. The study compares outcomes (or endpoints) in the group of participants receiving a new treatment with a comparable control group receiving either the standard treatment or a placebo (see Figure 2.1). A randomized clinical trial (RCT) is the optimal experimental method used to determine which of two treatments has the most favorable outcome. The main reason for using a RCT is to avoid bias in the allocating of the patients to each treatment and hence to make comparable treatment groups. A sophisticated allocation that permits removing bias and balancing prognostic factors can be an alternative method but randomization is the only method that balances both known and unknown factors.

We have two approaches for about clinical trials results: **evidence** and **decision** [8]. The first one is **Fisher's perspective**, since we obtain the quantity of information (evidence) that we have obtained in the test regarding the mean differences. For example, in a test of mean differences we may obtain a p-value of the statistic equal to 0.09. On the other hand, in **Neyman-Pearson's perspective**, investigators have to

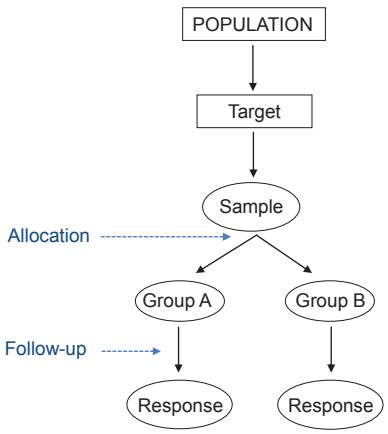

Figure 2.1: *Global scheme of a Clinical trial.*

decide and make yes/no decisions [27] based on whether or not a p-value obtained in the test lets us to reject a null hypothesis to the alternative by fixing (a priori) a boundary for the alpha level. That is, a researcher wants to achieve enough evidence to confirm that treatment B is more effective than treatment A (or placebo) and in these cases the power of the test (the probability of rejecting the null hypothesis when it is false) plays an important role.

It is important how we measure the values of the endpoints, since endpoints that require subjective judgment are subject to bias [23]. For example, death is easy to know (yes/not) but x-rays interpretation can be different depending on different doctor's evaluation. So the **validity** and **reliability** of the measure would be imperfect, making bias about systematic and proportional errors.

Nowadays, clinical trials are used frequently in many areas like oncological and cardiovascular studies [1, 15].

2.2 Definition of Composite Endpoint and Statistical Notation

Composite endpoints are defined as the occurrence of any event from among a given set of events after a certain period of follow-up [12].

Consider a two-arm randomized study with random assignment either to a control treatment (X=0) or to an active treatment (X=1). For instance, the control treatment group could be a placebo medicine or standard of care and the active treatment group corresponds to a new therapy or treatment. We follow patients from randomization until the occurrence of one set of clinical outcomes.

For a given clinical trial suppose that you only have two endpoints of interest that we denote by $\mathcal{E}_1$ or primary endpoint and $\mathcal{E}_2$ or secondary endpoint. For example, we could have *Cardiovascular Death* and *Stroke* as primary endpoints and Myocardial Infarction as secondary endpoint.

Individuals in the clinical trial are followed until the event occurs or until the study ends. The times to $\mathcal{E}_1$ and $\mathcal{E}_2$ are denoted respectively by T_1 and T_2 and they are assumed to be absolutely continuous so ties cannot occur. C represents the time from randomization to the end of the study and this administrative censoring is the only noninformative censoring cause.

Define the composite endpoint as $\mathcal{E}_* = \mathcal{E}_1 \cup \mathcal{E}_2$ and $T_* = \min\{T_1, T_2\}$ as the time to the occurrence of the earlier element of the composite $\mathcal{E}_1$ or $\mathcal{E}_2$. Note that T_* will be always observed if $T_* < C$. That is, with the composite we observe whichever occurs first of the $\mathcal{E}_1$ and $\mathcal{E}_2$ and then we always will see T_* except when we observe a censoring time before.

On the other hand, observations of endpoints $\mathcal{E}_1$ and $\mathcal{E}_2$ depend on whether or not they include a terminating event. For example, we will not always observe T_1, the time to event (*Stroke*) if $\mathcal{E}_2$ includes *Death*.

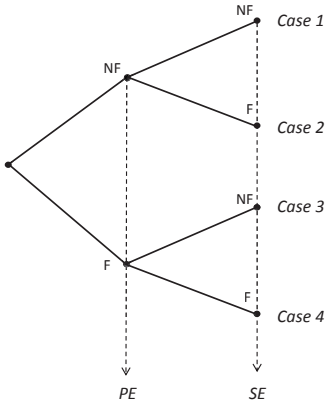

Figure 2.2: *Scheme for the 4 possible cases. PE stands for Primary Endpoint, F stands for Fatal event and NF for Non Fatal Event. The two endpoints could occur in either order.*

So, regarding the different combinations of $\mathcal{E}_1$ and $\mathcal{E}_2$ depending if they include a terminating event or not we can consider the following four cases (see Figure 2.2):

Case 1: Neither of the two endpoints ($\mathcal{E}_1$, $\mathcal{E}_2$) includes a terminating event. We observe T_j $(j = 1, 2)$ (time to event 1 or 2) if T_j occurs before the right-censoring time C. That is, we observe the time until the $\mathcal{E}_1$ if T_1 is not censored by C. And the same happens for T_2.

Case 2. The primary event does not include a terminating event while the secondary event includes a terminating event. Hence, we observe T_1 if $T_1 < \min\{T_2, C\}$. That is we observe T_1 if T_1 occurs before T_2 and C. And we observe T_2 if $T_2 < C$. So T_2 will be observed if T_2 occurs before the censoring.

Case 3. The primary endpoint includes a terminating event, but the secondary event does not include a terminating event. Then, we will observe T_1 if $T_1 < C$ and T_2 if $T_2 < \min\{T_1, C\}$. That is to say, we observe T_1 if T_1 occurs before the censoring, and we observe T_2 if T_2 occurs before T_1 and C.

Case 4. Both events ($\mathcal{E}_1$, $\mathcal{E}_2$) include a terminating event. We observe T_1 if $T_1 < \min\{T_2, C\}$ and observe T_2 if $T_2 < \min\{T_1, C\}$. That is, we observe T_1 if T_1 occurs before T_2 and C, and we observe T_2 if T_2 occurs before T_1 and C.

Note that in Cases 2 and 4 the secondary endpoint includes a terminating event which is competing with the censoring random variable C in the observation of $\mathcal{E}_1$ and the endpoint T_1 is right-censored by $\min\{T_2, C\}$. Thus, in cases 2 and 4 we have a competing risk situation with dependent censoring on T_1. This fact should be taken into account in the derivations.

The composite endpoint T_* is right-censored by C in all four cases and the observed outcome will be denoted as $U_* = \min\{T_*, C\}$.

2.3 Advantages and Disadvantages of Composite Endpoints

One advantage of using a composite endpoint is that we can reduce the problem of **multiple comparisons** (or multiplicity) to analyze the results [12, 14, 23, 37]. So if we take many events separately (and so many number of tests) it would require a stronger level of evidence to avoid spurious positive conclusions and hence we would have to modify the initial alpha error (the error of rejecting a null hypothesis when it is actually true) [13]. Moreover, using a composite endpoint we avoid bias associated with **competing risks** [37]. For example, if nonfatal myocardial infarction is the event of interest, death is a competing risk. So if death rate in the treatment group is higher than in the control group, the number of patients at risk of suffering myocardial infarction in the treatment group will be reduced. Thus, if we focus on the total rate of myocardial infarction, the estimated treatment effect would be biased suggesting that the treatment reduces myocardial infarction. But the use of the composite (death or myocardial infarction) may reveal that there is no overall benefit of treatment [12].

In some trials, studying nonfatal events without **including death** could be methodologically invalid [23], since death outcome would censor the rest of outcomes. It is important because a treatment may decrease the number of non-fatal events only because mortality is increased. For example, the effect of a composite of non-fatal infarctions and stroke can be reduced because a treatment effect increases the mortality. So with the composite endpoint we have the possibility to add a fatal event in our primary outcome.

The choice of a primary endpoint in some areas is not the ultimate clinical endpoint of interest, but rather some surrogate believed to be relevant for **predicting** the effect of the intervention on the clinical outcome of interest [37]. For example, in HIV field the pathogenesis is sufficiently understood so that the effect of a drug regimen on the viral load (CD4) is accepted as being relevant for understanding the contribution of the treatment to AIDS and death from AIDS. This choice is done because the clinical endpoint of interest may be rare and take many years to occur. So in HIV studies the composite outcomes used are usually a combination of surrogate markers (e.g. viral load) and true clinical endpoints (e.g. death or progression to AIDS).

However, there are some disadvantages when using a composite endpoint. When we create a composite we are analyzing somehow different than when using a single primary endpoint. So we should be aware of what is actually the **medical meaning of the composite endpoint**. Doctors can use a composite endpoint to measure the

differences of a global measure for drug efficacy defined about a disease process [27, 36, 37] or a complex disease (e.g., the assessment of skeletal-related events in trials for prevention or treatment of bone metastases [23]), but actually the global effect of a composite could also be confounding if the elements (events) are quite different between them due to its heterogeneity [12]. In short, we get greater uncertainly in interpretation of the composite endpoint results [14]. Moreover, when investigators report the primary endpoint as a composite it is important to take into account that we cannot attribute proof of efficacy (or lack) to each individual component of the composite [14, 12] and components should always be defined as secondary endpoints analyzing and reporting them separately [14, 34] and if possible classifying them by levels of clinical importance [12].

When doctors decide to use a composite endpoint they should recognize the relation of the elements included in the composite. So there are two main characteristics: **relevance and relationship with the objectives** and **potential effect for each endpoint** [14]. First, if we decide to use a composite endpoint, and then to include another endpoint apart from the primary, this extra endpoint should be relevant enough for the objectives of the study. For example, in a cardiovascular study with cardiac death as a primary endpoint may not be acceptable to add number of headaches or another endpoint with less importance to the patients [10] to increase the number of events. In this case, we could achieve to demonstrate statistical differences but not a credible and serious report. That is, we could have **enough statistical significance but not clinical importance** [27]. So clinical trialists should construct composite endpoints only when components endpoints are of similar patient-importance [14, 11, 26] [34, 37] and pharmaceutical regulators should have control on that [13]. Secondly, investigators could be tempted to add an endpoint that will give them high number of observed events (for example hospitalizations) [14] to increase the efficiency but, if this endpoint have a lower effect in each treatment they will not be able to reject the null hypothesis of equality of the treatment effects although the power has increased. So using of composite endpoint could be disadvantageous when the effect of the therapy on components diverges (different treatment effects) [12, 34] and, when large variations exist between components, the composite endpoint should be abandoned [26]. And obviously the clinically more important components of the composite endpoints should at least not be affected negatively [23]. Moreover, when clinician driven outcomes, such as revascularization or hospitalization are used, these appear generally to be more amenable to change, presenting further challenges for interpretation [14].

In cardiovascular device trials involving coronary stents, it is common to take the rare endpoints of cardiovascular death and myocardial infarction and combine with a more frequent endpoint. For example, considering cardiovascular death as a primary endpoint maybe we would not have enough number of events to see statistical differences. Making a composite of death and hospitalization (whichever occurs the first) we will probably increase the power but if the hospitalization endpoint is affected similarly by both treatments we will not be able to demonstrate the differences about the effects even if hospitalization has a lot of occurrences [9]. That is, the weight of the hospitalization endpoint will balance the effect of the composite endpoint for both treatments. So investigators could rise to see opposite conclusions than they estimated at the beginning.

The following questions should be answered before deciding whether to use a composite endpoint or not [23]:

- Does the composite endpoint really measure a disease?
- Does the use of a composite endpoint solve a medical problem or is it just for statistical convenience?
- Are the individual components of the composite endpoint valid, biologically plausible, and of importance for patients?
- Are the results clear and clinically meaningful? Do they provide a basis for therapeutic decisions? Does each single endpoint support the overall result?
- Is the statistical analysis adequate?

In summary, we see the existence of a debate about the main advantages and disadvantages that one can find in literature, but there is very little discussion about statistical solutions to decide whether to use a composite endpoint versus an endpoint that belongs to a subset of the components of the composite. Investigators have to evaluate the value for money and the cost-effectiveness [27] for each combination to optimize their resources. And the decision of using a composite should be based on investigators experience and medical framework recommendations but also, as we will see in this thesis, statistical guidelines should be taken into account.

Chapter 3

Introduction to the Cardiovascular Stents

We are focusing this Master Thesis on the cardiovascular area and in particularl in stent cardiovascular clinical trial studies. We give next a brief definition of stents and other related concepts.

3.1 Definition of a Coronary Stent

A stent is a tube placed inside a duct or canal to reopen it or keep it open. It may be a simple tube, usually plastic, or an expandable, usually sprung mesh metal tube (see Figure 3.1).

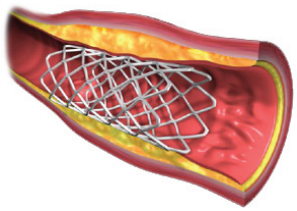

Figure 3.1: *Picture of a coronary stent.*

When a stent is placed into the body, the procedure is called stenting.

Most stents are made of a metal (bare stents) while other are of plastic mesh-like material. However, stent grafts (or covered stents) used in larger arteries are made of fabric which creates a stronger inner lining for the artery. Nowadays there are several bio-absorbable stents in development and these are the focus of many clinical trials. These stents are made from a variety of biodegradable polymer materials, such as organic biopolymers and corrodible metals.

There are different types of stents. An intraluminal coronary artery stent is a small, self-expanding, metal mesh tube that is placed inside a coronary artery after balloon angioplasty to prevent the artery from re-closing. A drug-eluting stent (DES) is coated with a medicine that helps further prevent the arteries from re-closing. Like other coronary stents, it is left permanently in the artery.

3.2 Why are Stents Used?

Coronary artery disease occurs when cholesterol plaque builds up (atherosclerosis) in the walls of the arteries to the heart (see Figure 3.2) and then the coronary artery (an artery feeding the heart muscle) is narrowed by a buildup of fatty deposits called plaque, and it can reduce the blood flow. If this occurs, chest pain can result and if a clot blocks the blood flow to part of the heart muscle, a heart attack results.

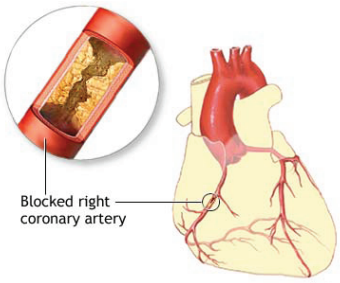

Figure 3.2: *Picture of a blocked artery.*

So stents help keep coronary arteries open and reduce the chance of a heart attack. And when it is necessary to open a narrowed artery, a doctor may do a procedure called angioplasty.

3.3 Definition of Coronary Angioplasty (PCI)

Coronary Angioplasty, also called percutaneous coronary intervention or PCI, is a minimally invasive procedure performed to improve blood flow in the body's arteries and veins and (with or without vascular stenting) is commonly used to treat conditions that involve a narrowing or blockage of arteries or veins throughout the body, including narrowing of large arteries (aorta and its branches) due to atherosclerosis.

In an **angioplasty procedure** using image guidance, an inflatable balloon mounted at the tip of a catheter is inserted through the skin into an artery (see Figure 3.3) and advanced to the site of an arterial blockage where the balloon is inflated and deflated.

In this process, the balloon expands the artery wall, increasing blood flow through the artery. The balloon is then deflated and removed.

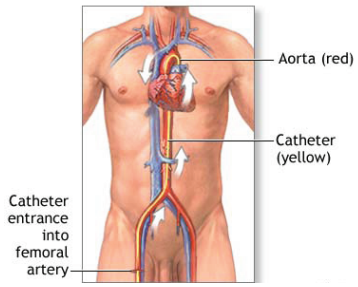

Figure 3.3: *Picture of an angioplasty procedure.*

When a stent is used, it's collapsed to a small diameter and put over the balloon catheter (see Figure 3.4). It's then moved into the area of the blockage. When the balloon is inflated, the stent expands, locks in place and forms a scaffold. The stent stays in the artery permanently and holds it open. This improves blood flow to the heart muscle and relieves symptoms (usually chest pain).

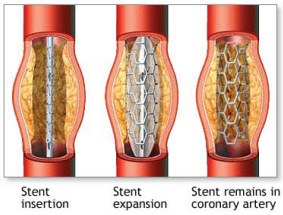

Figure 3.4: *Picture of a Stent insertion.*

Stenting has become fairly common and the majority of angioplasty procedures are done using stents.

3.4 Using Stents. The Benefits versus Risks

Using stents have benefits and also some risks compared to surgical interventions that we should take into account.

Benefits

- Compared to surgical interventions such as bypass surgery, balloon angioplasty and stent placement are much less invasive and relatively low-risk and with low-cost procedures.
- These procedures are performed using local anesthesia. No general anesthetic is required in the majority of patients.
- No surgical incision is needed. Only a small nick in the skin that does not have to be stitched closed.
- Patients return to their normal activities shortly after the procedure and they have much less discomfort, too.

Risks

- Inserting the catheter can lead to injury of the artery. The balloon also poses a risk of blood clots or tearing the artery.
- When angioplasty is performed alone, blockages can recur, although most of these arteries can be opened again successfully. This can also occur when a stent is placed in the artery at the time of the angioplasty.
- Heavy bleeding from the catheter insertion site may require special medication or a blood transfusion.
- There is a risk of stroke when angioplasty and/or stenting are performed on the carotid artery.
- Other rare complications include heart attack and sudden cardiac death. Moreover, any procedure where the skin is penetrated carries a risk of infection and there is a very slight risk of an allergic reaction if contrast material is injected.

Chapter 4

Statistical Methodology

The following statistical methodology and technical procedures summarize Gómez and Lagakos findings developed in "Statistical Considerations in the Use of a Composite Time-to-Event Endpoint for Comparing Treatment Groups" (2011) [16].

As discussed before, there has been a great debate in the literature concerning the use of composite endpoints in time-to-events analysis but very little discussion about statistical considerations to elucidate whether to use a composite endpoint or one of its components endpoints.

The main goal is therefore to derive guidelines for deciding when it is recommended to expand a primary endpoint from $\mathcal{E}_1$ to the composite of $\mathcal{E}_1$ and $\mathcal{E}_2$ in stent cardiovascular studies.

We will follow the notation given in section 2.2 and review the main findings in Gómez and Lagakos (2011) focusing on the Case 3 situation (see Figure 4.1). In stent cardiovascular studies the primary endpoint always include cardiovascular death or death due to any cause, while the secondary endpoint to be added is not in general a terminating event.

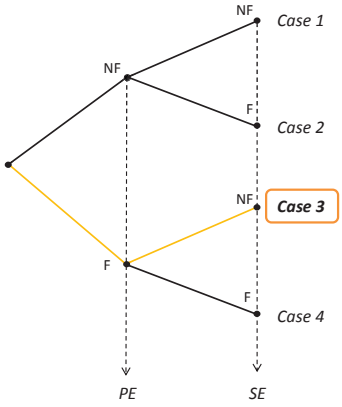

Figure 4.1: *Scheme for the 4 possible cases. PE stands for Primary Endpoint, F stands for Fatal event and NF for Non Fatal Event. The two endpoints could occur in either order.*

Assume that we have two independent samples and a total sample size of n individuals. The efficiency calculations will be evaluated based on a sequence of contiguous alternatives to the null and based on the following assumptions:

Assumption 1: For a total sample size of n individuals, let $\pi_n = \Pr_{H_0}\{X = 1\}$ denote the probability under the null of being allocated to group 1.

Assumption 2: End-of-study censoring at time τ (without loss of generality we take $\tau = 1$) is the only noninformative censoring cause, that is, $\Pr\{C > t\} = \mathbf{1}\{[0, \tau]\}(t) = \mathbf{1}\{[0, 1]\}(t)$.

Assumption 3: End-of-study censoring is identical across groups, that is, $\Pr\{C > t|X = 0\} = \Pr\{C > t|X = 1\} = \Pr\{C > t\} = \mathbf{1}\{[0, \tau]\}(t)$. This assumption facilitates computations and derivations although the general expressions could be analogously stated without it.

Assumption 4: Treatment groups have proportional hazards. The proportionality assumption is given by the hazard ratios $\frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)} = \mathrm{HR}_1$ and $\frac{\lambda_2^{(1)}(t)}{\lambda_2^{(0)}(t)} = \mathrm{HR}_2$ for all t.

4.1 Logrank Test for the Primary Endpoint

Recall that T_1 is the time to the primary event $\mathcal{E}_1$ and that individuals have been randomized to one of two groups.

When comparing two treatment groups we stablish the null hypothesis

$H_0 : S^{(0)}(\cdot) = S^{(1)}(\cdot)$, or equivalently by: $H_0 : \lambda_1^{(0)}(\cdot) = \lambda_1^{(1)}(\cdot)$

where $S^{(0)}(\cdot)$ and $S^{(1)}(\cdot)$ are the survival functions of T_1 for group 0 and 1 respectively, and $\lambda_1^{(0)}(\cdot)$ and $\lambda_1^{(1)}(\cdot)$ represent the hazard functions for each group. It is very common to use the logrank test statistic Z to test H_0.

The logrank test Z under the hypothesis of no treatment difference is asymptotically normally distributed $N(0,1)$. The large sample behavior of Z when H_0 does not hold is considered for a sequence of alternatives and under these conditions Z is asymptotically normal with unit variance and mean μ given by

$$\mu = \frac{\sqrt{n}\int_0^\infty \log\left\{\frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)}\right\} p(t)[1-p(t)]\Pr_{H_0}\{U \geq t\}\lambda_1^{(0)}(t)dt}{\sqrt{\int_0^\infty p(t)[1-p(t)]\Pr_{H_0}\{U \geq t\}\lambda_1^{(0)}(t)dt}} \tag{4.1}$$

where n is the total sample size, U is the observed outcome given by $U = min\{T_1, C\}$, $p(t) = \Pr_{H_0}\{X = 1 | U \geq t\}$ is the null probability that, someone at risk at time t, is in treatment group 1, $\Pr_{H_0}\{U \geq t\}$ is the null probability that someone is still at risk at time t and $\Pr_{H_0}\{U \geq t\}\lambda_1^{(0)}(t)$ corresponds to the probability, under the null, of observing event $\mathcal{E}_1$ by time t.

If we denote by T_2 the time to the secondary event $\mathcal{E}_2$ and by $T_* = min\{T_1, T_2\}$ the time to the composite endpoint, to test the null hypothesis of no treatment difference based on T_*, H_0^*: $\lambda_*^{(0)}(\cdot) = \lambda_*^{(1)}(\cdot)$ we use as well the logrank test statistic Z_*.

Analogously as above, under H_0 Z_* is is asymptotically $N(0,1)$, and when H_0 does not hold, Z_* is asymptotically normal with unit variance and mean μ_* given by

$$\mu_* = \frac{\sqrt{n}\int_0^\infty \log\left\{\frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)}\right\} p_*(t)[1-p_*(t)]\Pr_{H_0^*}\{U_* \geq t\}\lambda_*^{(0)}(t)dt}{\sqrt{\int_0^\infty p_*(t)[1-p_*(t)]\lambda_*^{(0)}(t)\Pr_{H_0^*}\{U_* \geq t\}dt}}, \tag{4.2}$$

where $p_*(t) = \Pr_{H_0}\{X = 1 | U_* \geq t\}$ is the null probability that, someone at risk at time t, is in treatment group 1 and $\Pr_{H_0^*}\{U_* \geq t\}$ is the null probability that someone is still at risk at time t.

4.2 The Asymptotic Relative Efficiency (ARE)

We use the asymptotic relative efficiency of Z_* versus Z to discriminate whether to use the composite endpoint or the primary endpoint.

Given that both tests Z and Z_* are asymptotically N(0,1) under H_0 and H_0^*, respectively, and are asymptotically Normal with variance 1 under a sequence of contiguous alternatives to the null, their asymptotic relative efficiency is given by:

$$\mathrm{ARE}(Z_*, Z) = \left(\frac{\mu_*}{\mu}\right)^2, \tag{4.3}$$

where μ and μ_* can be replaced by (4.1) and (4.2).

The rule to decide when will be recommended to use the composite or not will be as follows:

- When $ARE(Z_*, Z) > 1 \Rightarrow$ the composite endpoint should be used.
- When $ARE(Z_*, Z) \leq 1 \Rightarrow$ the primary endpoint should be used.

Gómez and Lagakos use a more flexible rule such that the composite endpoint is always used if $\mathrm{ARE}(Z_*, Z) > 1.25$, it is never used if $\mathrm{ARE}(Z_*, Z) < 1.1$, and whenever $1.1 < \mathrm{ARE}(Z_*, Z) < 1.25$ the benefits of using the composite endpoint over the primary endpoint on the particular setting are studied based on other grounds.

As it is developed in Gómez and Lagakos paper, the noncentrality parameter μ given in 4.1 can be expressed as:

$$\mu = \frac{\sqrt{n\pi_n(1-\pi_n)}\int_0^\infty \log\left\{\frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)}\right\}\frac{\Pr_{H_0}\{U\geq t|X=1\}\Pr_{H_0}\{U\geq t|X=0\}}{\Pr_{H_0}\{U\geq t\}}\lambda_1^{(0)}(t)dt}{\sqrt{\int_0^\infty \frac{\Pr_{H_0}\{U\geq t|X=1\}\Pr_{H_0}\{U\geq t|X=0\}}{\Pr_{H_0}\{U\geq t\}}\lambda_1^{(0)}(t)dt}}. \tag{4.4}$$

and the noncentrality parameter μ_* given in (4.2) becomes equal to

$$\mu_* = \frac{\sqrt{n\pi_n(1-\pi_n)}\int_0^\infty \frac{\log\left\{\frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)}\right\}\Pr_{H_0^*}\{U_*\geq t|X=1\}\Pr_{H_0^*}\{U_*\geq t|X=0\}}{\Pr_{H_0^*}\{U_*\geq t\}}\lambda_*^{(0)}(t)dt}{\sqrt{\int_0^\infty \frac{\Pr_{H_0^*}\{U_*\geq t|X=1\}\Pr_{H_0^*}\{U_*\geq t|X=0\}}{\Pr_{H_0^*}\{U_*\geq t\}}\lambda_*^{(0)}(t)dt}}.$$

Taking into account that the endpoint T_1 is right-censored by C and that the null hypothesis of no effect $H_0 : \lambda_1^{(0)}(\cdot) = \lambda_1^{(1)}(\cdot)$ implies the equality of the marginal survival functions $S_1^{(0)}(t) = S_1^{(1)}(t)$, the noncentrality parameter μ in 4.4 becomes equal to

$$\mu = \frac{\sqrt{n\pi_n(1-\pi_n)}\int_0^1 \log\left\{\frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)}\right\} f_1^{(0)}(t)dt}{\sqrt{\int_0^1 f_1^{(0)}(t)dt.}} \tag{4.5}$$

where $f_1^{(0)}(t)$ is the marginal density function for T_1 in group 0.

Following analogous derivations, denoting by $f_*^{(0)}(t)$ the marginal density function for T_* in group 0 and taking into account that under H_0^*: $\lambda_*^{(0)}(\cdot) = \lambda_*^{(1)}(\cdot)$, we have $S_*^{(0)}(t) = S_*^{(1)}(t)$, the expression for the noncentrality parameter μ_* becomes

$$\mu_* = \frac{\sqrt{n\pi_n(1-\pi_n)}\int_0^1 \log\left\{\frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)}\right\} f_*^{(0)}(t)dt}{\sqrt{\int_0^1 f_*^{(0)}(t)dt}}. \tag{4.6}$$

Replacing (4.5) and (4.6) in (4.3), the ARE is given by

$$\mathrm{ARE}(Z_*, Z) = \left(\frac{\mu_*}{\mu}\right)^2 = \frac{\left(\int_0^1 \log\left\{\frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)}\right\} f_*^{(0)}(t)dt\right)^2}{(\log \mathrm{HR}_1)^2(\int_0^1 f_*^{(0)}(t)dt)(\int_0^1 f_1^{(0)}(t)dt)} \tag{4.7}$$

where $\frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)}$ has been substituted by the constant hazard ratio, HR_1, established in Assumption 4.

4.3 The Asymptotic Relative Efficiency as a Function of Interpretable Parameters

The close study of $\mathrm{ARE}(Z_*, Z)$ reveals that it only depends on:

- The marginal law of T_1 ($f_1^{(0)}(t)$)
- The law for T_* in group 0 ($f_*^{(0)}(t)$) and the hazard functions $\lambda_*^{(0)}(t)$ and $\lambda_*^{(1)}(t)$
- The hazard ratio for the primary endpoint (HR_1)

The law for T_* for each group can be derived from the bivariate distribution of (T_1, T_2). The joint law of (T_1, T_2) is specified as a function of the marginal densities $f_1^{(0)}(t_1)$ and $f_2^{(0)}(t_2)$ and an association parameter θ via Frank's copula model.

If we assume equal association parameter θ for groups 0 and 1, the joint density and bivariate survival functions for (T_1, T_2) in group j ($j = 0, 1$) are given by:

$$f_{(1,2)}^{(j)}(t_1, t_2; \theta) = \frac{\theta e^{-\theta(S_1^{(j)}(t_1)+S_2^{(j)}(t_2))}}{e^{-2\theta S_{(1,2)}^{(j)}(t_1,t_2;\theta)}(e^{-\theta}-1)}[f_1^{(j)}(t_1)][f_2^{(j)}(t_2)] \tag{4.8}$$

$$S_{(1,2)}^{(j)}(t_1, t_2; \theta) = -\frac{1}{\theta}\log\left\{1 + \frac{(e^{-\theta S_1^{(j)}(t_1)}-1)(e^{-\theta S_2^{(j)}(t_2)}-1)}{e^{-\theta}-1}\right\} \tag{4.9}$$

The density survival and hazard functions of the minimum T_* are given by

$$\begin{aligned} f_*^{(j)}(t;\theta) &= \frac{e^{-\theta S_1^{(j)}(t)}(e^{-\theta S_2^{(j)}(t)}-1)}{e^{-\theta C^{(j)}(S_1^{(j)}(t), S_2^{(j)}(t);\theta)}(e^{-\theta^{(j)}}-1)} f_1^{(j)}(t) \\ &+ \frac{e^{-\theta S_2^{(j)}(t)}(e^{-\theta S_1^{(j)}(t)}-1)}{e^{-\theta C^{(j)}(S_1^{(j)}(t), S_2^{(j)}(t);\theta)}(e^{-\theta}-1)} f_2^{(j)}(t), \\ S_*^{(j)}(t;\theta) &= C(S_1^{(j)}(t), S_2^{(j)}(t)) = S_{(1,2)}^{(j)}(t, t; \theta) \end{aligned} \tag{4.10}$$

$$\lambda_*^{(j)}(t;\theta) = \frac{f_*^{(j)}(t;\theta)}{S_*^{(j)}(t;\theta)}$$

Hence, in order to compute $\mathrm{ARE}(Z_*, Z)$ we need to specify:

- $f_1^{(0)}(t)$ ($S_1^{(0)}(t)$): The marginal density (survival) function of T_1 for group 0.
- $f_2^{(0)}(t)$ ($S_2^{(0)}(t)$): The marginal density (survival) function of T_2 for group 0.
- θ: The copula association parameter between T_1 and T_2.
- HR_1: The constant hazard ratio $HR_1 = \lambda_1^{(1)}(t)/\lambda_1^{(0)}(t)$.
- $f_1^{(1)}(t)$ ($S_1^{(1)}(t)$): The marginal density (survival) function of T_1 for group 1.
- $f_2^{(1)}(t)$ ($S_2^{(1)}(t)$): The marginal density (survival) function of T_2 for group 1.

Regarding the marginal laws of T_1 and T_2, the Weibull distributions were chosen because they are widely used in Survival analysis due to its flexibility, allowing decreasing, constant and increasing hazard functions.

Hence, for both treatment groups ($j = 0, 1$) the survival function is given by:

$S_k^{(j)}(t) = \exp\{-(t/b_k^{(j)})^{\beta_k^{(j)}}\}$, ($k = 1, 2$ depending if we refer to T_1 or T_2)

where $b_1^{(j)}$, $b_2^{(j)}$ are the scale parameters and $\beta_1^{(j)}$, $\beta_2^{(j)}$ are the shape parameters.

The shape parameters are chosen equal for both groups, that is $\beta_1^{(0)} = \beta_1^{(1)} = \beta_1$ and $\beta_2^{(0)} = \beta_2^{(1)} = \beta_2$, so that the assumption of proportionality of the hazards holds.

Denoting by p_1 and p_2 the probabilities of observing $\mathcal{E}_1$ and $\mathcal{E}_2$ in group 0 (assuming that end-of-study censoring at time τ is the only censoring cause) they are related to the marginal law of T_1 and the bivariate law of (T_1, T_2) in group 0 as follows:

$$p_1 = 1 - S_1^{(0)}(1) \qquad (Fixing\ \tau = 1\ (Assumption\ 2))$$

$$p_2 = \int_0^\tau \int_v^\infty f_{(1,2)}^{(0)}(u, v; \theta) du dv$$

where $f_{(1,2)}^{(0)}(u, v; \theta)$ is the joint density of (T_1, T_2) in group 0 and has been defined in (4.8).

We can relate the scale parameters $b_1^{(0)}$ and $b_2^{(0)}$ to p_1 and p_2 as follows:

$$b_1^{(0)} = \frac{1}{(-\log(1-p_1))^{1/\beta_1}}.$$

and $b_2^{(0)}$ is a function of the joint density $f_{(1,2)}^{(0)}(\cdot, \cdot; \theta)$ and it is found as the solution of equation $p_2 = \int_0^1 \int_v^\infty f_{(1,2)}^{(0)}(u, v; \theta) du dv$.

On the other hand, the scale parameters $b_1^{(1)}$, $b_2^{(1)}$, for group 1 are computed so that the assumption of proportionality of the hazards holds, that is, $b_1^{(1)}$ and $b_2^{(1)}$ are such that:

$\mathrm{HR}_1 = \frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)}$ and $\mathrm{HR}_2 = \frac{\lambda_2^{(1)}(t)}{\lambda_2^{(0)}(t)}$.

Summarizing, in order to calculate the ARE in terms of interpretable parameters we will have to specify:

1. The marginal parametric laws for the time T_1 to the primary endpoint $\mathcal{E}_1$ and for the time T_2 to the secondary endpoint $\mathcal{E}_2$ for both treatment groups 0 and 1,
2. The probability p_1 of an uncensored T_1 from group 0,
3. The probability p_2 of an uncensored T_2 from group 0,
4. The treatment effect of $T_1|X = 1$ versus $T_1|X = 0$ given by the hazard ratio HR_1,
5. The treatment effect of $T_2|X = 1$ versus $T_2|X = 0$ given by the hazard ratio HR_2,
6. The association between T_1 and T_2 evaluated by means of Spearman's correlation parameter ρ (ρ is uniquely determined by the copula association parameter θ).

Note that the above parameters are all easily interpretable for physicians and investigators. Interpretability is important because investigators will have to decide a priori which are the most plausible values for p_1, p_2, HR_1, HR_2 and ρ and, based on those, the decision to adopt or not a composite endpoint will have to be made on ARE results.

In this Master Thesis we choose $\beta_1 = 1, 2$ and $\beta_2 = 1, 2$ representing constant and increasing hazard functions and ρ ranging from 0.15 to 0.75. Regarding the rest of the necessary parameters to compute ARE (p_1, p_2, HR_1 and HR_2) a literature search has been done to get a realistic range of values used in stent cardiovascular articles.

Chapter 5

Stent literature search

In order to know which is the range of the common values for the parameters needed to compute the ARE (as developed in chapter 4) for stent cardiovascular studies, we have followed a structured search. Online Pubmed database searcher was used to find current clinical trial articles submitted in the last three years and focused in the stenting clinical trials area.

Furthermore, a boolean strategy was necessary to enclose the results. The main logical strategy was:

(STENT *OR* STENTING) **AND**
("RISK RATIO" *OR* "RELATIVE RISK" *OR* RR *OR* "HAZARD RATIO" *OR* HR) **AND**
(MACE *OR* MACCE)

The two first keywords represent the specific medical area of the search. Since the parameters are related to time-to-event (survival) analysis, we included Hazard Ratio and its acronym (HR). Moreover, keywords about Relative Risk and its acronym (RR) were included in order to amplify the focus and get those articles that use relative risk or RR to refer to the hazard ratio.

We have followed the advise of an expert biostatistician in cardiovascular studies, Professor Sharon-Lise Normand from Harvard University, and use the acronyms MACE and MACCE to refer to the composite endpoints which are commonly used in stenting clinical trials. The main single endpoints included in MACE and MACCE are: Cardiac death, Target Vessel Revascularizatio (TVR), Myocardial Infarction (MI) and Stroke.

5.1 Papers Identified as Candidates for Application

A total of 27 papers from Pubmed searcher database were obtained (see Figure 5.1). Among these 27 papers, 5 of them have not been considered because they either were not based as a clinical trial or they were not a doing survival analysis.

Unfortunately, even with the help of Professors Normand and Olga Julià (from the department of statistics, *Universitat de Barcelona*) we were not able to obtain 4 papers from *EuroIntervention* journal and we have restricted our study to the 18 papers left.

Id.	Authors	TITLE	Journal	Year of publication	Vol.	Pages
1	~~Tavasoli N. et al.~~	~~High maintenance dosage of clopidogrel is associated with a reduced risk of stent thrombosis in clopidogrel-resistant patients.~~	~~Am J Cardiovasc Drugs.~~	~~2010~~	~~10(1)~~	~~29-35~~
2	Buszman P. et al.	Percutaneous versus surgical revascularization for multivessel coronary artery disease: a single center 10 year follow-up of SOS trial patients.	Catheter Cardiovasc Interv.	2009	74(3)	420-6
3	~~Ge YG. et al.~~	~~Long-term efficacy of sirolimus-eluting stents (Cypher) versus bare-metal stents for patients with ST-segment elevation myocardial infarction~~	~~Zhonghua Xin Xue Guan Bing Za Zhi.~~	~~2008~~	~~36(2)~~	~~108-12~~
4	Okada T. et al.	One-year clinical outcomes of dialysis patients after implantation with sirolimus-eluting coronary stents.	Circ J.	2008	72(9)	1430-5
5	~~Chen SL. et al.~~	~~Comparison between the NERS (New Risk Stratification) score and the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score in outcome prediction for unprotected left main stenting.~~	~~JACC Cardiovasc Interv.~~	~~2010~~	~~3(6)~~	~~632-41~~
6	Song YB. et al.	Sirolimus- versus paclitaxel-eluting stents for the treatment of coronary bifurcations results: from the COBIS (Coronary Bifurcation Stenting) Registry.	J Am Coll Cardiol.	2010	55(16)	1743-50
7	Sheiban I. et al.	Sex-related differences in patients undergoing percutaneous unprotected left main stenting.	EuroIntervention.	2010	5(7)	795-800
8	Stojkovic S. et al.	Systemic rapamycin without loading dose for restenosis prevention after coronary bare metal stent implantation.	Catheter Cardiovasc Interv.	2010	75(3)	317-25
9	Palmerini T. et al.	Impact of bifurcation technique on 2-year clinical outcomes in 773 patients with distal unprotected left main coronary artery stenosis treated with drug-eluting stents.	Circ Cardiovasc Interv.	2008	1(3)	185-92
10	Balducelli M. et al.	Comparison of 2-year clinical outcomes with sirolimus and paclitaxel-eluting stents for patients with diabetes: results of the Registro Regionale AngioPLastiche Emilia-Romagna Registry.	Catheter Cardiovasc Interv.	2010	75(3)	327-34
11	Di Lorenzo E. et al.	Benefits of drug-eluting stents as compared to bare metal stent in ST-segment elevation myocardial infarction: four year results of the PaclitAxel or Sirolimus-Eluting stent vs bare metal stent in primary angiOplasty (PASEO) randomized trial.	Am Heart J.	2009	158(4)	e43-50
12	Wykrzykowska JJ. et al.	Impact of vessel size on angiographic and clinical outcomes of revascularization with biolimus-eluting stent with biodegradable polymer and sirolimus-eluting stent with durable polymer the LEADERS trial substudy.	JACC Cardiovasc Interv.	2009	2(9)	861-70
13	Wykrzykowska JJ. et al.	Biolimus-eluting biodegradable polymer versus sirolimus-eluting permanent polymer stent performance in long lesions: results from the LEADERS multicentre trial substudy.	EuroIntervention.	2009	5(3)	310-7
14	Katritsis DG. et al.	Comparison of long versus short ("spot") drug-eluting stenting for long coronary stenoses.	Am J Cardiol.	2009	104(6)	786-90
15	Mehran R. et al.	Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial.	Lancet.	2009	374(9696)	1149-59
16	~~Gyöngyösi M. et al.~~	~~2-year results of the AUTAX (Austrian Multivessel TAXUS Stent) registry beyond the SYNTAX (synergy between percutaneous coronary intervention with TAXUS and cardiac surgery) study.~~	~~JACC Cardiovasc Interv.~~	~~2009~~	~~2(8)~~	~~718-27~~
17	Saia F. et al.	Patient selection to enhance the long-term benefit of first generation drug-eluting stents for coronary revascularisation procedures. Insights from a large multicentre registry.	EuroIntervention.	2009	5(1)	57-66
18	Nfor T. et al.	Comparing long-term outcomes between drug-eluting and bare-metal stents in the treatment of cardiac allograft vasculopathy.	Catheter Cardiovasc Interv.	2009	74(4)	543-9
19	Umeda H. et al.	Safety and efficacy of 2.5-mm sirolimus-eluting stent implantation at lower deployment pressures in very small vessels (<2.5 mm).	Coron Artery Dis.	2009	20(2)	163-8
20	Novack V. et al.	Multivessel drug-eluting stenting and impact of diabetes mellitus--a report from the EVENT registry.	Catheter Cardiovasc Interv.	2009	73(7)	874-80
21	Garro N. et al.	Very late thrombosis in acute myocardial infarction: drug-eluting versus uncoated stents.	EuroIntervention.	2008	4(3)	324-30
22	~~Lee MS. et al.~~	~~Multicenter international registry of unprotected left main coronary artery percutaneous coronary intervention with drug-eluting stents in patients with myocardial infarction.~~	~~Catheter Cardiovasc Interv.~~	~~2009~~	~~73(1)~~	~~15-21~~
23	Kim JS. et al.	Comparison of sirolimus-eluting stent and paclitaxel-eluting stent for long-term cardiac adverse events in diabetic patients: the Korean Multicenter Angioplasty Team (KOMATE) Registry.	Catheter Cardiovasc Interv.	2008	72(5)	601-7
24	Bertrand OF. et al.	Effects of intracoronary compared to intravenous abciximab administration in patients undergoing transradial percutaneous coronary intervention: A sub-analysis of the EASY trial.	Int J Cardiol.	2009	136(2)	165-70
25	Bertrand OF. et al.	One-year clinical outcome after abciximab bolus-only compared with abciximab bolus and 12-hour infusion in the Randomized EArly Discharge after Transradial Stenting of CoronarY Arteries (EASY) Study.	Am Heart J.	2008	156(1)	135-40
26	Billinger M. et al.	Two-year clinical outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents in diabetic patients.	Eur Heart J.	2008	29(6)	718-25
27	Brodie BR. et al.	Outcomes with drug-eluting stents versus bare metal stents in acute ST-elevation myocardial infarction: results from the Strategic Transcatheter Evaluation of New Therapies (STENT) Group.	Catheter Cardiovasc Interv.	2008	72(7)	893-900

Figure 5.1: *Papers identified as candidates for application. Colored: available and selected articles. Crossed out: ruled out articles.*

5.2 Description of the Clinical Studies and their Endpoints

Since the main goal of this thesis is to recommend whether to add a *secondary* endpoint $\mathcal{E}_2$ to the already considered *primary* endpoint $\mathcal{E}_1$, we are interested in several plausible combinations of combined endpoints $\mathcal{E}_1 \cup \mathcal{E}_2$. We are therefore describing in Figure 5.2 the primary endpoints used in the chosen clinical trial together with the list of their individual components of the composite endpoints. Each row of the database is represented by one or several rows depending on whether or not sub-group analysis were considered in each paper or more than one primary endpoint was specified. The sample size of each treatment group were annotated. We also describe the time to follow-up in months and how is calculated in each paper (mean, median or minimum time for each patient).

Note that in half of the papers a Propensity-adjusted Cox regression were used to adjust the nonrandomized study with some possible confounding variables. However, since the aim of this thesis is to obtain a real world range of values for the different parameters in cardiovascular studies when using stents, we do not attempt to validate neither criticize the statistical analysis.

The last two columns include the reported p-values and whether or not statistical differences between treatments were found. We observe that the majority endpoints are composites, but not always statistical differences between treatments were achieved.

Article ident.	n_1 (control)	n_2	Time to follow-up (months)	Randomized	Subgroup (when applicable)	Primary endpoint in the article (and their components)	Type of endpoint	p-value	Significant (95% confidence)
2	50	50	115,2 (mean)	Yes		RR	Not a composite	<0,05	Yes
4	80	124	12 (min.)	Yes		*Cardiac death, MI, ST, TLR	Composite	<0,05	Yes
6	562	1033	22 (median)	No	Overall Population	*Cardiac death, MI, TLR	Composite	<0,05	Yes
6	562	1033	22 (median)	No	Propensity-matched population	*Cardiac death, MI, TLR	Composite	<0,05	Yes
8	40	40	6,8 (mean)	Yes		In-stent angiographic binary restensosis	Not a composite	<0,05	Yes
8	40	40	6,8 (mean)	Yes		In-segment angiographic binary restensosis	Not a composite	<0,05	Yes
9	456	317	24 (min.)	No		*Death, MI, TLR	Composite	<0,05	Yes
10	606	339	33,1 (median)	No		*AMI, Death, TVR	Composite	<0,05	Yes
11	90	90	12 (min.)	Yes	BMS vs PES (1 year outcome)	TLR	Not a composite	<0,05	Yes
11	90	90	41,1 (mean.)	Yes	BMS vs PES (4 years outcome)	TLR	Not a composite	<0,05	Yes
12	434	429	12 (min.)	Yes	Small vessell size	*Death, MI, TVR	Composite	0,89	No
12	272	267	12 (min.)	Yes	Large vessell size	*Death, MI, TVR	Composite	0,2	No
12	133	154	12 (min.)	Yes	Mixed vessell size	*Death, MI, TVR	Composite	0,57	No
14	90	89	36 (min.)	Yes		*Cardiac death, Ischemia, MI, ST, TLR	Composite	<0,05	Yes
15	1802	1800	12 (min.)	Yes		*Death, Major bleeding, MI, Stroke, TVR	Composite	<0,05	Yes
15	1802	1800	12 (min.)	Yes		*Death, MI, Stroke, TVR	Composite	>0,05	No
18	19	25	12 (min.)	No		ISR	Not a composite	<0,05	Yes
19	118	126	12 (min.)	No		*Death, MI, TLR	Composite	0,002	Yes
20	256	466	12 (min.)	Yes		*Death, MI, RR	Composite	>0,05	No
23	206	428	38 (mean)	No		*Cardiac death, MI, TVR	Composite	>0,05	No
24	208	797	1 (min.)	No	30 days of follow-up	*Death, MI, TVR	Composite	>0,05	No
24	208	797	6 (min.)	No	6 months of follow-up	*Death, MI, TVR	Composite	<0,05	Yes
24	208	797	12 (min.)		1 year of follow-up	*Death, MI, TVR	Composite	>0,05	No
25	504	501	12 (min.)	Yes		*Access site complication, Death, Major bleeding, MI, Rehospitalization, Severe thrombocytopenia, TVR	Composite	<0,05	Yes
26	509	503	24 (min.)	Yes	Diabetic patients	*Cardiac death, MI, TLR	Composite	>0,05	No
26	509	503	24 (min.)	Yes	Non-diabetic patients	*Cardiac death, MI, TLR	Composite	<0,05	Yes
27	548	1292	9 (min.)	No	Outcomes at 9 months	*Death, MI, TVR	Composite	>0,05	No
27	548	1292	24 (min.)	No	Outcomes at 2 years	*Death, MI, TVR	Composite	>0,05	No

Figure 5.2: *Primary endpoints used in the literature.* n_1 *and* n_2 *stands for the sample size for the control and treatment group respectively.*

No information about Spearman's correlation between time to events were found in literature. However, this information could be assessed, up to certain degree, from physicians in each study based on their medical experience. Furthermore, as we will see below, a large range of values were assigned to Spearman's ρ correlation coefficients in order to evaluate how the ARE computations depend upon them.

All the collected information has been analyzed and summarized with SPSS (v15) statistical program. For more detailed results, see some descriptives outputs about this database in Appendix A.

In the stent clinical trials many studies based their results on the comparison of a composite endpoint known as MACE (Major Adverse Cardiac Events). But when studying which are the components of MACE we find that there is not a unique definition. Most of the studies include Death, Myocardial Infarction and Target Vessel Revascularization in MACE. However, as wee see in Figure 5.3 other different combinations of events are used to define MACE for the study. Authors referred to the composite MACCE (Major Cardiac Cardiovascular and Cerebrovascular Events) as Death, Myocardial Infarction, Repeat Revascularization and Stroke, and they referred to the composite NACE (Net Adverse Clinical Events) as Death, Major bleeding, Myocardial Infarction, Stroke and Target Vessel Revascularization. And some authors did not use a particular name for other composites.

		COMPOSITE NAME				
		MACCE	MACE	NACE	NO NAME	Total
Endpoint	*Access site complication, Death, Major bleeding, MI, Rehospitalization, Severe thrombocytopenia, TVR	0	0	0	1	1
	*AMI, CHF,Death, ISR, Retransplantation, TVR	0	2	0	0	2
	*AMI, Death	0	0	0	3	3
	*AMI, Death, TVR	0	3	0	0	3
	*Cardiac death, Ischemia, MI, ST, TLR	0	2	0	0	2
	*Cardiac death, MI	0	0	0	2	2
	*Cardiac death, MI, ST, TLR	0	2	0	0	2
	*Cardiac death, MI, TLR	0	4	0	0	4
	*Cardiac death, MI, TVR	0	1	0	0	1
	*Death, Major bleeding, MI, Stroke, TVR	0	0	1	0	1
	*Death, MI	0	0	0	7	7
	*Death, MI, RR	0	1	0	0	1
	*Death, MI, RR, Stroke	1	0	0	0	1
	*Death, MI, ST	0	2	0	0	2
	*Death, MI, Stroke, TVR	0	2	0	0	2
	*Death, MI, TLR	0	2	0	0	2
	*Death, MI, TVR	0	13	0	0	13
	*MI, Death	0	0	0	1	1
Total		1	34	1	14	50

Figure 5.3: *Elements of composite endpoints and the names used in the literature.*

Hence, we have distinguished the following *single* endpoints as candidates for $\mathcal{E}_1$ (or $\mathcal{E}_2$) (in alphabetical order):

- Access site complication
- Acute Myocardial Infarction (AMI)
- Cardiac death
- Congestive heart failure
- Death (any cause)
- Ischemia
- In-Stent Restenosis
- Major bleeding
- Myocardial Infarction (MI)
- Rehospitalization
- Retransplantation
- Repeat Revascularization (RR)
- Severe Thrombocytopenia
- Stent Thrombosis (ST)
- Stroke
- Target Lesion Revascularization (TLR)
- Target Vessel Revascularization (TVR)

We remark that the composite endpoint that these studies are using as primary endpoint to test the efficacy of the given treatment can be quite different. However, as we see in Figure 5.4, Death (or cardiac death) is always included, Myocardial Infarction or Acute Myocardial Infarction are also always included and Target Lesion Revascularization and Target Vessel Revascularization are almost always included. Other events such as Stroke, Stent Thrombosis and Repeat Revascularization are only included as primary endpoints in some studies.

Which the aim of assessing the values of the parameters used to each single event we have combined Cardiovascular death and Death from any cause in a single event *Death* since based in our data we cannot split these two cases. Analogously we have combined Myocardial Infarction and Acute Myocardial Infarction.

Hence, based on the above, **Death (any cause) and Myocardial Infarction (including Acute Myocardial Infarction)** were considered as a unique primary endpoint of a general composite since they are common in all the composites found. And secondary endpoints of a general composite where set as (**Target Vessel Revascularization, Target Lesion Revascularization, Stent Thrombosis, Stroke and Repeat**

	Frequency
*Access site complication, Death, Major bleeding, MI, Rehospitalization, Severe thrombocytopenia, TVR	1
*AMI, Death, TVR	1
*Cardiac death, Ischemia, MI, ST, TLR	1
*Cardiac death, MI, ST, TLR	1
*Cardiac death, MI, TLR	4
*Cardiac death, MI, TVR	1
*Death, Major bleeding, MI, Stroke, TVR	1
*Death, MI, RR	1
*Death, MI, Stroke, TVR	1
*Death, MI, TLR	2
*Death, MI, TVR	8
Total	22

Figure 5.4: *Frequency of the composite primary endpoints and their elements.*

Revascularization). Since the primary endpoint of the composite includes a terminating event (Death) and any of the secondary endpoints does not, as we see in chapter 3 we are in the **Case 3 situation** (see Figure 4.1 in chapter 4).

5.3 Obtaining the Range Values for the Probabilities and Hazard Ratios

Taking into account the primaries and secondaries endpoints considered to set a general composite endpoint we need to specify their range of values for probabilities and hazard ratios. In Figure 5.5 we provide the probabilities of observing each endpoint found in literature together with their hazard ratios for the first articles (see in Appendix B the entire table).

Article ident.	Endpoint	Type of endpoint	Probability (x 100)	Hazard Ratio
2	RR	Primary Endp.	42,00	
2	*Death, MI, RR, Stroke	Composite and secondary endp.	72,00	
2	Death	Secondary Endp.	18,00	
2	MI	Secondary Endp.	10,00	
2	Stroke	Secondary Endp.	8,00	
2	Cardiac death	Secondary Endp.	8,00	
2	LVEF	Secondary Endp.	58,00	
4	*Cardiac death, MI, ST, TLR	Composite and primary endp.	38,20	0,7
4	Cardiac death	Secondary Endp.	11,90	
4	Sudden/unexplained death	Secondary Endp.	5,30	
4	MI	Secondary Endp.	0,00	
4	ST	Secondary Endp.	0,80	
4	TLR	Secondary Endp.	30,90	
4	Death	Secondary Endp.	19,80	
4	*Cardiac death, MI, ST, TLR	Composite and secondary endp.	4,10	
4	Cardiac death	Secondary Endp.	4,10	
4	Sudden/unexplained death	Secondary Endp.	0,80	
4	MI	Secondary Endp.	0,00	
4	ST	Secondary Endp.	0,80	
4	TLR	Secondary Endp.	0,80	
4	Death	Secondary Endp.	4,80	
6	*Cardiac death, MI, TLR	Composite and primary endp.	8,70	0,545
6	Cardiac death	Secondary Endp.	0,40	2,89
6	MI	Secondary Endp.		
6	TLR	Secondary Endp.	6,80	0,54
6	*Cardiac death, MI	Composite and secondary endp.	2,50	0,83
6	TVR	Secondary Endp.	8,40	0,57
6	Periprocedural enzyme elevation	Secondary Endp.	17,30	
6	ST	Secondary Endp.	0,70	
6	*Cardiac death, MI, TLR	Composite and primary endp.	8,60	0,52
6	Cardiac death	Secondary Endp.	0,50	2,675
6	MI	Secondary Endp.		
6	TLR	Secondary Endp.	7,10	0,47
6	TVR	Secondary Endp.	8,80	0,54
6	Periprocedural enzyme elevation	Secondary Endp.	16,50	
6	ST	Secondary Endp.	0,50	
8	In-stent angiographic binary restensosis	Primary Endp.	51,35	
8	In-segment angiographic binary restensosis	Primary Endp.	48,65	
8	TLR	Secondary Endp.	22,70	
8	TVR	Secondary Endp.	22,70	
8	*Death, MI, Stroke, TVR	Composite and secondary endp.	22,70	

Figure 5.5: *Sample table for the first four articles with their probabilities and hazard ratios of each endpoint.*

We see in Figure 5.6 that the probability values mixing both primary and secondary endpoints for the general composite ranges from 0% to 30% in 98% of cases. We provide the values of the hazard ratios in Figure 5.7.

		Frecuencia	Porcentaje	Porcentaje válido	Porcentaje acumulado
Válidos	< 0.05 %	10	3,8	7,7	7,7
	0.05 - 1 %	11	4,2	8,5	16,2
	1 - 5%	43	16,4	33,1	49,2
	5 - 10%	36	13,7	27,7	76,9
	10 - 15%	17	6,5	13,1	90,0
	15 - 20%	4	1,5	3,1	93,1
	20 - 25%	4	1,5	3,1	96,2
	25 - 30%	2	,8	1,5	97,7
	>30%	3	1,1	2,3	100,0
	Total	130	49,6	100,0	
Perdidos	Sistema	132	50,4		
Total		262	100,0		

Figure 5.6: *Probabilities (by intervals) for both primary and secondary endpoints in the general composite.*

HR_T

		Frecuencia	Porcentaje	Porcentaje válido	Porcentaje acumulado
Válidos	,17	1	,4	1,7	1,7
	,21	1	,4	1,7	3,4
	,24	1	,4	1,7	5,2
	,27	1	,4	1,7	6,9
	,28	1	,4	1,7	8,6
	,29	2	,8	3,4	12,1
	,38	1	,4	1,7	13,8
	,39	1	,4	1,7	15,5
	,40	1	,4	1,7	17,2
	,42	1	,4	1,7	19,0
	,44	1	,4	1,7	20,7
	,45	1	,4	1,7	22,4
	,47	2	,8	3,4	25,9
	,48	2	,8	3,4	29,3
	,50	1	,4	1,7	31,0
	,54	2	,8	3,4	34,5
	,55	1	,4	1,7	36,2
	,57	4	1,5	6,9	43,1
	,57	1	,4	1,7	44,8
	,64	1	,4	1,7	46,6
	,67	2	,8	3,4	50,0
	,68	2	,8	3,4	53,4
	,71	1	,4	1,7	55,2
	,72	1	,4	1,7	56,9
	,75	2	,8	3,4	60,3
	,76	2	,8	3,4	63,8
	,80	1	,4	1,7	65,5
	,81	1	,4	1,7	67,2
	,83	1	,4	1,7	69,0
	,85	1	,4	1,7	70,7
	,85	1	,4	1,7	72,4
	,89	1	,4	1,7	74,1
	,92	2	,8	3,4	77,6
	,93	2	,8	3,4	81,0
	,98	1	,4	1,7	82,8
	1,01	1	,4	1,7	84,5
	1,02	1	,4	1,7	86,2
	1,06	2	,8	3,4	89,7
	1,08	1	,4	1,7	91,4
	1,21	2	,8	3,4	94,8
	1,26	1	,4	1,7	96,6
	1,31	1	,4	1,7	98,3
	1,61	1	,4	1,7	100,0
	Total	58	22,1	100,0	
Perdidos	Sistema	204	77,9		
Total		262	100,0		

Figure 5.7: *Hazard ratios for both primary and secondary endpoints in the general composite.*

In order to get a parsimonious analysis, we crossed the information between the probabilities of occurrence of the primary endpoint p_1 versus their Hazard Ratios HR_1 (see Figure 5.8). This information allows us to avoid unnecessary combinations that we will not see in real world studies. We observe that values of p_1 in the neighborhood of 0.035 act together with HR_1 around 0.5, while p_1 near 0.05 appear together with $HR_1 = 0.8$, p_1 near 0.09 appear together with $HR_1 = 0.9$ and p_1 near 0.125 appear together with $HR_1 = 0.7$. And this provides the combination of values for the primary endpoint given in Table 5.1.

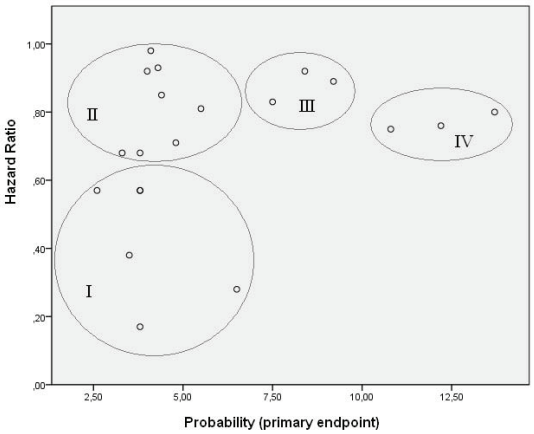

Figure 5.8: *Probability of the primary endpoint versus their Hazard Ratio. Outliers were ruled out.*

	p_1	HR_1
I	0.035	0.5
II	0.05	0.8
III	0.09	0.9
IV	0.125	0.7

Table 5.1: *Combinations of values for the primary endpoint. p_1 stands for the probability of occurrence of the primary endpoint and HR_1 stands for the hazard ratio of the primary endpoint.*

Parameters values for secondary endpoints of the composite were chosen in the same way (see Figure 5.9). See combinations for the secondary endpoint in table 5.2.

	p_2	HR_2
I	0.1	0.55
II	0.1	0.8
III	0.15	0.3
III	0.15	0.35
III	0.20	0.25

Table 5.2: *Combinations of values for the secondary endpoint. p_2 stands for the probability of occurrence of the secondary endpoint and HR_2 stands for the hazard ratio of the secondary endpoint.*

Observations of p_2 with lower percentage than 5% were ruled out since investigators may not be interested in an endpoint that adds so few observed events for the clinical trial.

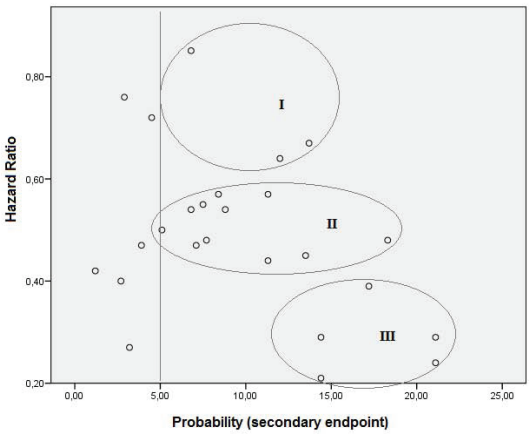

Figure 5.9: *Probability of the secondary endpoint versus their Hazard Ratio. Outliers were ruled out.*

The combination of values for (p_1, HR_1) and (p_2, HR_2) given in Tables 5.1 and 5.2, would yield 20 plausible combinations for the composite endpoint. However, to increase the scope of the present study we have combined all the possibilities for p_1, p_2, HR_1 and HR_2 as it is shown in Table 5.3.

p_1	0.035	0.05	0.09	0.125	
p_2	0.1	0.15	0.2		
HR_1	0.5	0.7	0.8	0.9	
HR_2	0.25	0.3	0.35	0.55	0.8

Table 5.3: *p_1 and p_2 stands for the probability of occurrence of the primary and secondary endpoint respectively. And HR_1 and HR_2 stands for the hazard ratio of the primary and secondary endpoint respectively.*

We are using the values given in Table 5.3 to feed the Maple programs and to obtain the ARE for each possible combination as it is presented in chapter 6.

Chapter 6

Specific Analysis for Stents

6.1 Setting for the Computations and execution with Maple

In chapter 5 we have described which are the more plausible values for p_1 and p_2, HR_1 and HR_2, consistent with those found in stent clinical trials. These values together with the chosen values for the shape parameters for the Weibull marginal laws ($\beta_j = 1$ representing constant hazards and $\beta_j = 2$ for increasing hazards) and an exhaustive election for Spearman's rank correlation between the primary and the secondary endpoint, form the bases of our first exploratory analysis and are given in Table 6.1.

β_1	1	2					
β_2	1	2					
p_1	0.035	0.05	0.09	0.125			
p_2	0.1	0.15	0.2				
ρ	0.15	0.25	0.35	0.45	0.55	0.65	0.75
HR_1	0.5	0.7	0.8	0.9			
HR_2	0.25	0.3	0.35	0.55	0.8		

Table 6.1: *Range of values chosen for each parameter. p_1 and p_2 stands for the probability of occurrence of the primary and secondary endpoint respectively. HR_1 and HR_2 stands for the hazard ratio of the primary and secondary endpoint respectively. β_1 and β_2 are the shape parameters and ρ the Spearman's rank correlation between T_1 and T_2.*

All the computations were done with Maple (v12) (see code in the Appendix C) and were based on Gómez and Lagakos method (2011) following the steps below:

- The the range of values of Spearman's rank correlation ρ are introduced and for each one the corresponding Frank's copula association parameter θ is calculated.
- Sets of values for $(\beta_1, \beta_2, p_1, p_2, HR_1, HR_2)$ as shown in Table 6.1 are provided. For each possible combination the ARE is computed following the method described in chapter 4.
- The resulting values of the ARE for each parameter combination are written in a

database and used for the analysis of the convenience of choosing the composite endpoint versus the primary endpoint.

6.2 Preliminary Results

Preliminary analysis of the ARE values show that the Asymptotic Relative Efficiency for a given combination ($p_1, p_2, HR_1, HR_2, \rho$) is analogous for the 4 different choices of (β_1, β_2). Thus, we concluded that the behavior of ARE is independent of whether or not the marginal hazard functions are constant or increasing. For the moment no other choices for β_1 and β_1 are considered.

We present the results for a particular combination of $\beta_1 = \beta_2 = 1$ and for each of the 48 scenarios that the possible values of p_1, p_2 and HR_1 yield. For each scenario we plot the 6 curves corresponding to the 6 different values of the relative treatment effect on $\mathcal{E}_2$ (HR_2) in cartesian axis. The abscissae is used for Spearman's ρ while the $ARE(Z_*, Z)$ are in a logarithmic scale in the ordinate. We use a logarithmic scale to faithfully represent the significance of the relative asymptotic efficiency, as, for example, an $ARE(Z_*, Z) = 2$ is as relevant as an $ARE(Z_*, Z) = 0.5$. That is, the distance from a point with $ARE(Z_*, Z) = 2$ to 1 is the same as the distance from a point with $ARE(Z_*, Z) = 0.5$.

One instance of these plots is given for scenario 25 in Figure 6.1. In this case the probability of observing a primary endpoint is 0.09 and of observing a secondary endpoint is 0.1 for a relative treatment effect on $\mathcal{E}_1$ equal to 0.5. We observe that irrespective of the degree of association between T_1 and T_2 we will always choose the composite endpoint when the effect on $\mathcal{E}_2$ is very low ($HR_2 \cong 0.8$).

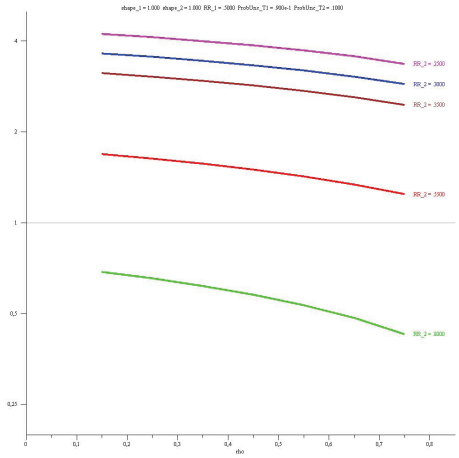

Figure 6.1: *Scenario 25: Values of the ARE depending on the Spearman's rank correlation between T_1 and T_2 and on the Hazard Ratios of the secondary endpoint HR_2. Fixed values: $\beta_1 = \beta_2 = 1, HR_1 = 0.5, p_1 = 0.09$ and $p_2 = 0.1$. HR_1 and HR_2 stands for the hazard ratios of the primary and secondary endpoints respectively and p_1 and p_2 stands for the probability of occurrence of the primary and secondary endpoints respectively.*

Close study of these 48 plots reveals that the composite endpoint should always be used if $HR_1 \geq 0.8$ and $HR_2 \leq 0.35$ irrespective of the values of (p_1, p_2, ρ). We observe as well that values of HR_1 chosen to 0.5 and of HR_2 larger than 0.55 provide often ARE values in the vicinity of 1, for this reason new values for HR_1 and HR_2 are established as shown in Table 6.2.

Hence, the new range of parameters were given by:

β_1	1						
β_2	1						
p_1	0.035	0.05	0.09	0.125			
p_2	0.1	0.15	0.2				
ρ	0.15	0.25	0.35	0.45	0.55	0.65	0.75
HR_1	0.5	0.6	0.7	0.8			
HR_2	0.4	0.5	0.6	0.7	0.8	0.9	

Table 6.2: *Range of values chosen for each parameter.*

6.3 Results and Guidelines

Regarding Gómez and Lagakos paper, the range of parameters values of the hazard ratios HR_1 and HR_2 used were similar to the hazard ratios used in this thesis, and the range of Spearman's rank correlation ρ was the same. However, probabilities p_1 and p_2 were higher (0.5 and 0.7 for both) compared to our probability parameters values (see table 6.2). As a general summary about the conclusions of Gómez and Lagakos obtained for the case 3, they observed that the ARE values decrease whenever the correlation between the two endpoints increases and when the relative effect on treatment on the secondary endpoint is smaller. The recommendation to use the composite endpoint is clear when the relative treatment effect HR_2 on the secondary

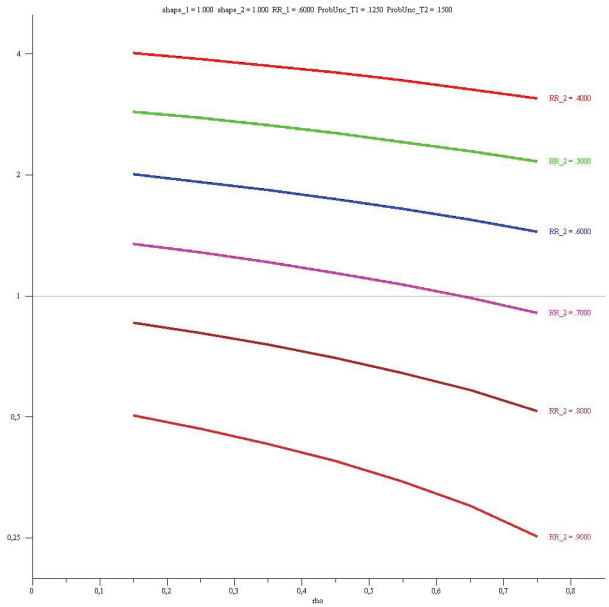

Figure 6.2: *Scenario 42: Values of the ARE depending on the Spearman's rank correlation between T_1 and T_2 and on the hazard ratios of the secondary endpoint. Fixed values: $\beta_1 = \beta_2 = 1, HR_1 = 0.6, p_1 = 0.125$ and $p_2 = 0.15$. HR_1 and HR_2 stands for the hazard ratios of the primary and secondary endpoints respectively and p_1 and p_2 stands for the probability of occurrence of the primary and secondary endpoints respectively.*

endpoint is smaller (higher beneficial effect) than on the primary endpoint. However, when the secondary endpoint has approximately the same relative treatment effect on treatment, or slightly larger (smaller beneficial effect), than the primary endpoint, the decision on whether or not to use the composite depends on the frequency of observing each endpoint together whit their correlation.

Regarding the choice of parameters we are studying, we observe a similar pattern in all 48 scenarios showing that the values of ARE decrease when the Spearman's rank correlation between the endpoints increases (see Figure 6.2 as an example). In Appendix D we present the plots for the 48 scenarios.

In Figure 6.3 we observe that the percentage of cases in which we should use the composite (ARE > 1) is higher when the Spearman's rank correlation value between the endpoints decreases. However, we observe that the amount of association between T_1 and T_2 is not enough on itself to elucidate whether or not to use the composite endpoint, hence the influence of other parameters in the ARE value is studied.

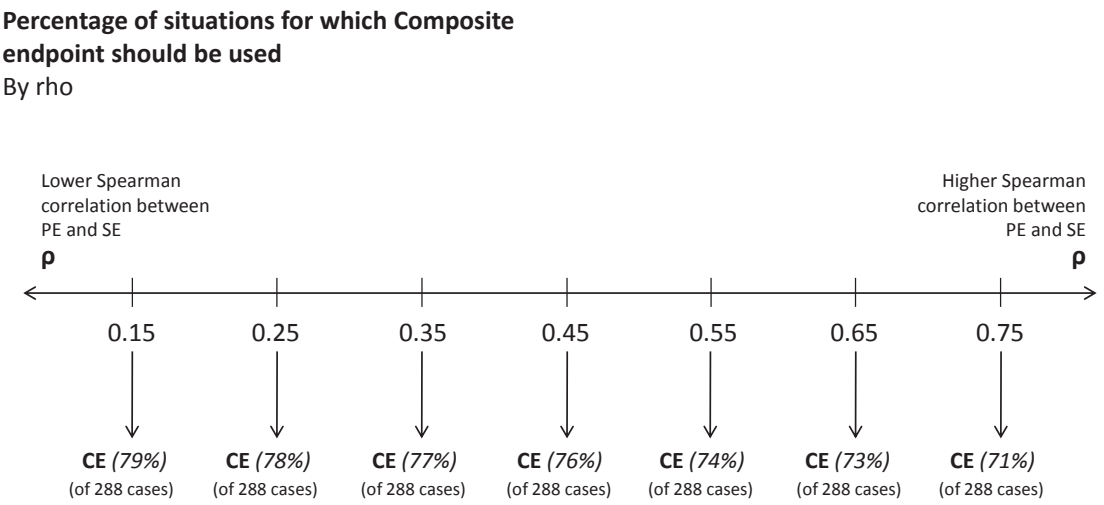

Figure 6.3: *CE stands for composite endpoint, PE for primary endpoint and SE for secondary endpoint.*

Figure 6.4 shows that as the probability of observing the primary endpoint gets larger, the need of adding a secondary endpoint and use the composite endpoint is less relevant, while the secondary endpoint tends to be more necessary when the probability of being observed gets larger. However, the frequency of observing either endpoint is not enough to recommend the composite endpoint over the primary endpoint.

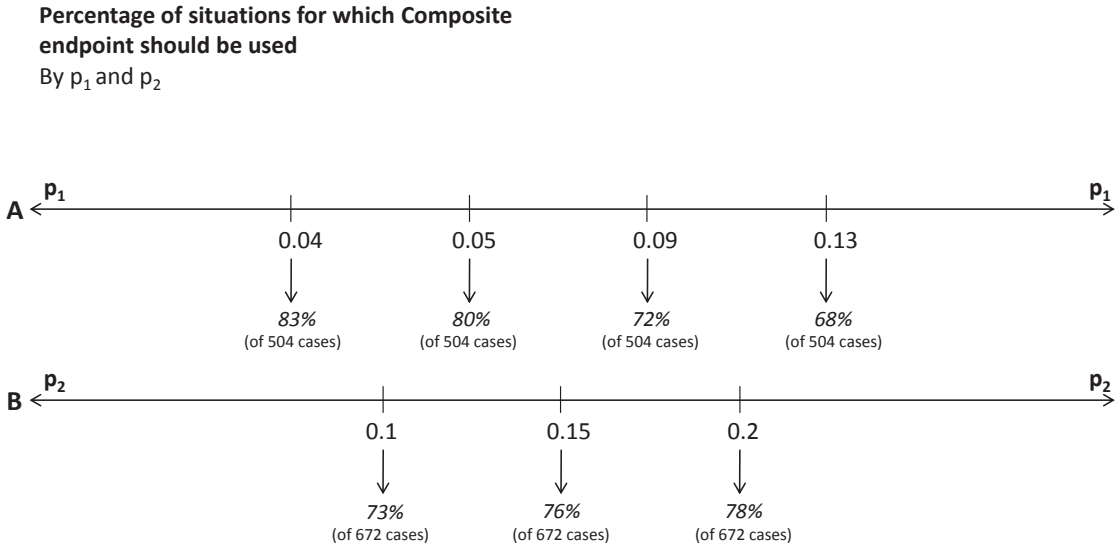

Figure 6.4: *p_1 and p_2 stands for the probability of occurrence of the primary and secondary endpoints respectively.*

We explore now how do the ARE values behave when combining the frequencies of observing $\mathcal{E}_1$ and $\mathcal{E}_2$. In Figure 6.5 we present 4 plots for the 4 possible values of p_1 as a function of p_2. We observe that when the probability of observing the primary endpoint gets larger, the need of adding a secondary endpoint is less relevant for all the possible values of p_2. Again, however we do not have a clear pattern which allow us to present a general recommendations in terms of (p_1, p_2) jointly.

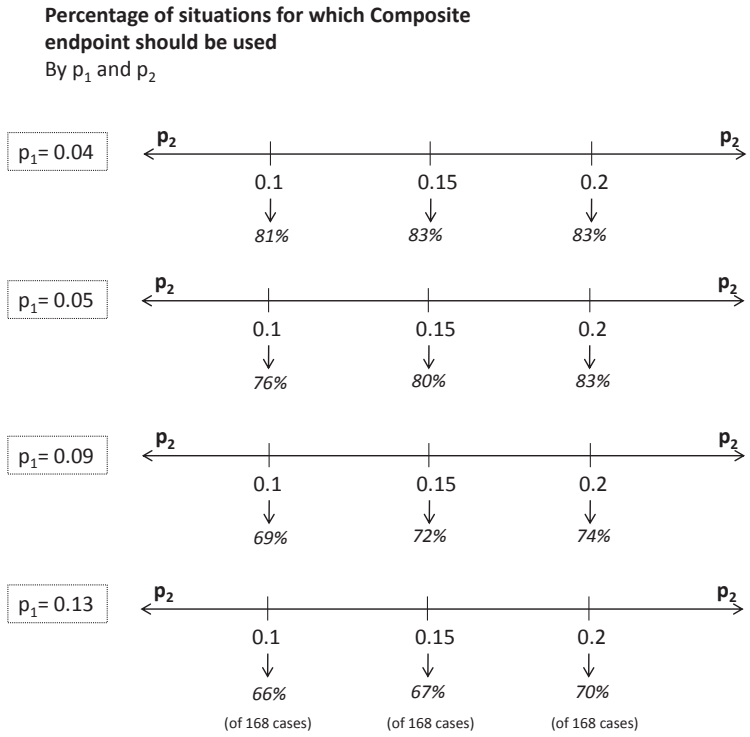

Figure 6.5: *p_1 and p_2 stands for the probability of occurrence of the primary and secondary endpoints respectively.*

Figure 6.6 presents the percentage of situations for which the composite endpoint should be used for the 4 different values of p_1 together with the 7 possible values of Spearman's rank correlation. We observe that the percentage of cases in which we should use the composite is higher when the Spearman's rank correlation value between the endpoints decreases for each value of the probability of observing the primary endpoint. Although it is clear that as p_1 and ρ get larger the composite endpoint is less convenient no conclusions results are achieved.

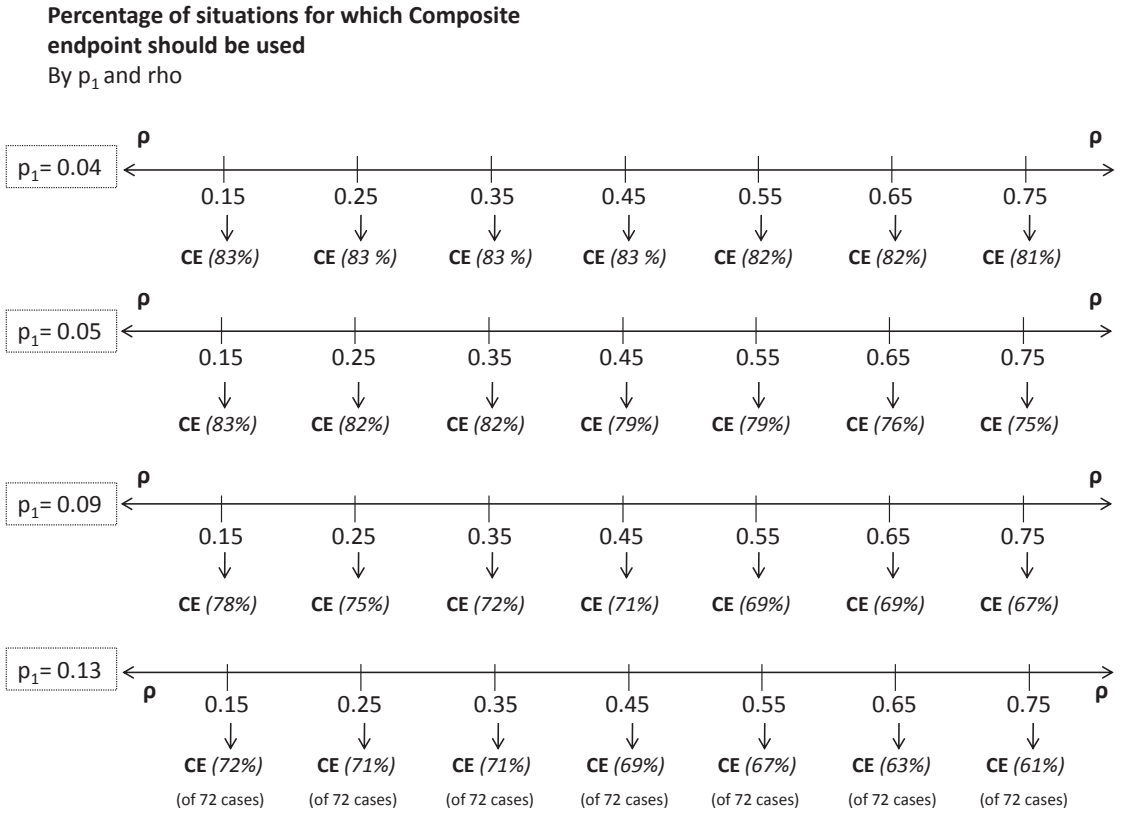

Figure 6.6: *CE stands for composite endpoint, p_1 stands for the probability of occurrence of the primary endpoint and rho (ρ) stands for the Spearman's rank correlation between T_1 and T_2.*

Regarding how the values of the relative treatment effect on the primary endpoint influence the ARE value, we observe that as it gets larger, hence having less beneficial effect, adding a secondary endpoint is more convenient (see Figure 6.7 A).

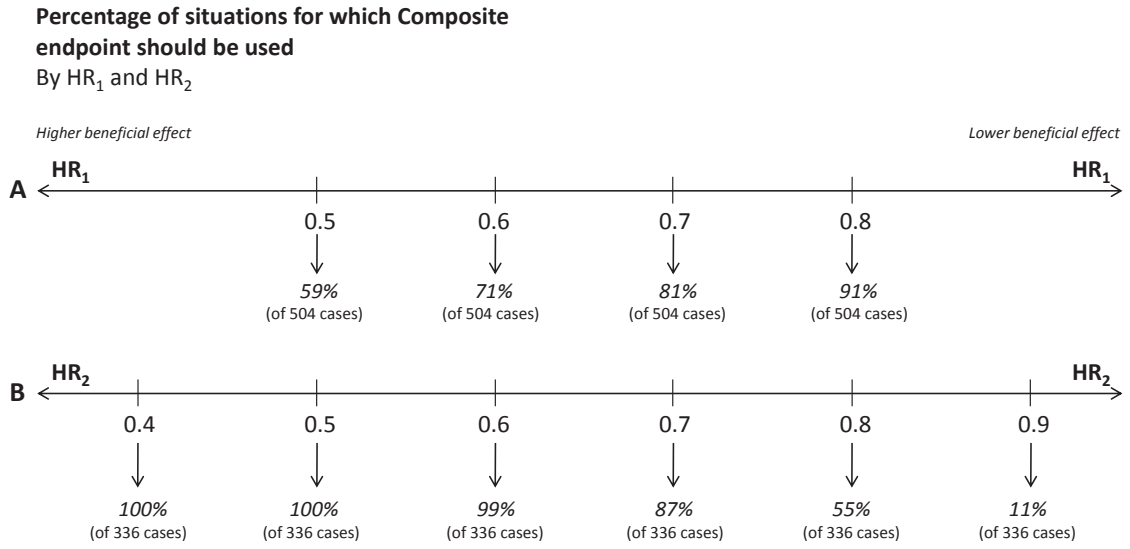

Figure 6.7: *HR_1 and HR_2 stands for the hazard ratios of the primary and the secondary endpoints respectively.*

The value of the hazard ratio of the secondary endpoint is by itself relevant (see Figure 6.7 B). Notice that if the relative treatment effect on $\mathcal{E}_2$ gets higher ($HR_2 \leq 0.5$) the composite endpoint should always be used irrespective of the effect that the treatment has on $\mathcal{E}_1$ and irrespective of the frequency of observing $\mathcal{E}_1$ or $\mathcal{E}_2$.

Figure 6.8 where the plots are presented for joint combinations of HR_1 and HR_2 present some conclusive results. We observe that irrespective of the correlation between T_1 and T_2 and of the frequencies p_1 and p_2, when the $HR_2 \leq HR_1$ the composite endpoint should always be used. That is, when the treatment effect on the secondary endpoint is higher or equal to the treatment effect on the primary, we always recommend to use the composite endpoint.

On the other hand, if the treatment effect on $\mathcal{E}_2$ is very low ($HR_2 = 0.9$) the composite endpoint should never be used unless perhaps if the effect on $\mathcal{E}_2$ is as well very low.

Finally, those situations where the effect on $\mathcal{E}_2$ is slightly lower than on $\mathcal{E}_1$ ($HR_2 - HR_1 = 0.1$) the recommendations is not clear and should be based on the values of other parameters and on other clinical considerations.

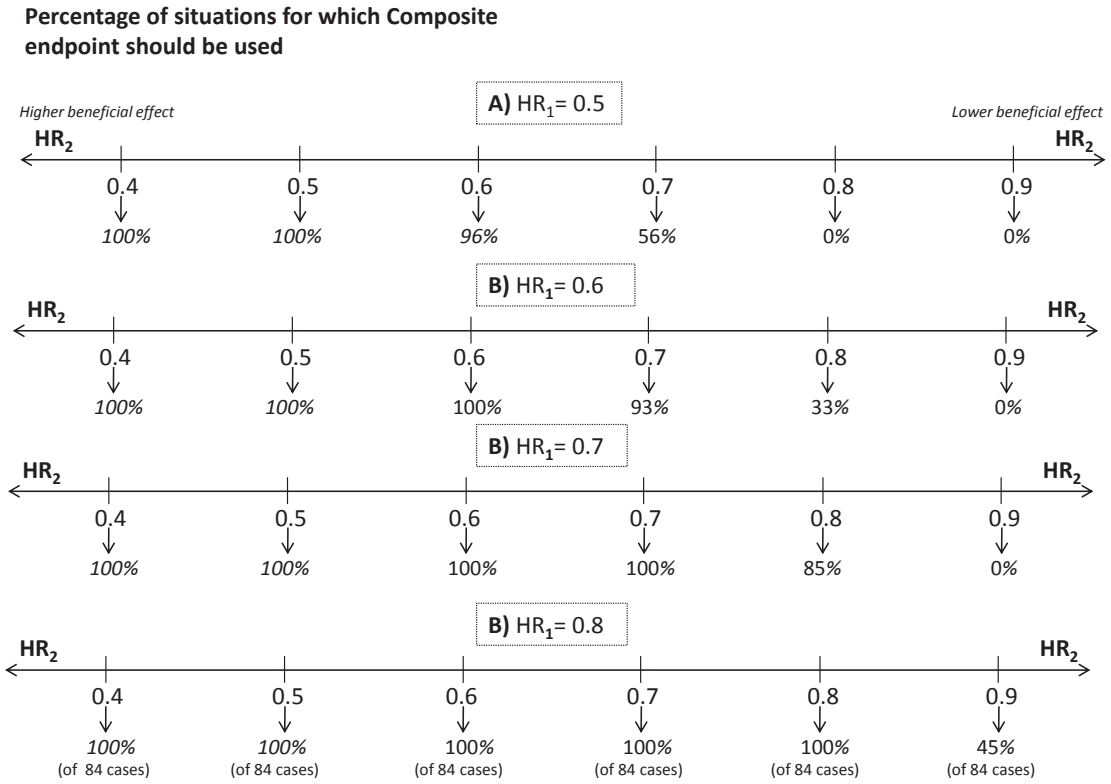

Figure 6.8: *HR_1 and HR_2 stands for the hazard ratios of the primary and the secondary endpoints respectively.*

6.4 Conclusions

We have obtained the Asymptotic Relative Efficiency for parameter values in agreement with those reported in stent cardiovascular clinical trials. We can conclude that the decision to use a composite endpoint, other than medical suitability and considerations, depends basically on the combinations of the hazard ratios of the primary and secondary endpoints. The following table summarizes these particular combinations:

Use the Primary endpoint when:	Use the Composite endpoint when:
$HR_1 = 0.5$ and $HR_2 \geq 0.8$	$HR_2 \leq HR_1$
$HR_1 = 0.6$ and $HR_2 \geq 0.9$	$HR_2 \leq 0.5$
$HR_1 = 0.7$ and $HR_2 \geq 0.9$	$HR_1 = 0.5$ and $HR_2 \leq 0.5$
$HR_2 \geq HR_1 + 0.3$	$HR_1 = 0.6$ and $HR_2 \leq 0.6$
	$HR_1 = 0.7$ and $HR_2 \leq 0.7$
	$HR_1 = 0.8$ and $HR_2 \leq 0.8$
	$HR_1 \geq 0.8$ and $HR_2 \leq 0.35$

Table 6.3: *Summary table to decide when it should be better to use a primary endpoint or a composite by the combinations of the hazard ratios HR_1 and HR_2.*

The main goal of this research is to specialize these findings for the stent cardiovascular clinical trials. We are now working on this and we hope to share our findings with experts in this field so that specific guidelines on when it is best to add stroke, say, to a primary endpoint consisting of Death and Myocardial Infarction are set for specific frequencies of observing each of the events and specific hazard ratio values. As an instance, we illustrate this with Brodie paper [5]. In this study they used a primary composite endpoint consisting of Death, Myocardial Infarction and Target Vessel Revascularization. The hazard ratios of Death and Myocardial Infarction were 0.92 and 0.81, respectively, while the hazard ratio of Target Vessel Revascularization was 0.55. We see in Figure 6.8 that for the combination $HR_1 = 0.8$ and $0.5 < HR_2 = 0.55 < 0.6$ the composite endpoint provides always a higher efficiency, hence in this particular situation the choice of Death, Myocardial Infarction and Target Vessel Revascularization as endpoint it was indeed preferable to the choice of, for instance, Death and Myocardial Infarction as endpoint.

However, ARE results show us that there are other cases where it is better to use a single endpoint depending on other parameter combinations and these guidelines could help physicians to decide whether or not use a composite in a particular clinical trial in the future.

Chapter 7

Concluding Remarks and Future Research

This master thesis has brought me a personal grateful experience and an opportunity to have a deeper understanding of the asymptotic survival theory and their applicability to the stent cardiovascular area. Moreover, I have learnt how to write this document in LaTeX and how to improve my writing in English. I have also learnt how to use Maple and refresh my knowledge of SPSS.

I want to remark that this master thesis is a first introductory study that will help to Professors Guadalupe Gómez, Urania Dafni and me to submit a contribution to the 6th EMR-IBS conference in Crete (Greece) on May 2011. In addition, a paper concerning the application of composite endpoints to the cardiovascular area is in mind. And this master thesis will be the prelude to develop my Doctoral Thesis research based in the following issues to carry out:

- Develop recommendations to decide when it is necessary to extend the primary endpoint to the composite based on the different parameter values amplifying the possibilities by different tests as weighted log-rank test and other from the Fleming-Harrington family.
- Study the behavior of the guidelines using other laws for the variable T different to the Weibull that incorpores other shapes for the risk function (e.g bath-tub curve).
- From a theoretical point of view, develop different hypothesis if the hazard ratios were not proportional.
- Analyze the better option by means of the relative efficiency in different areas, as oncology and HIV infection.
- Study the correspondence between the relative efficiency and the sample size related to the power of the test.
- Develop the statistical repercussions if we treat the T variable as a dicotomy (e.g. death/no death) rather than the time to an event. Analyze this for a single endpoint, or a composite endpoint, modeling the analysis with a log-logistic regression.

- Create a Web interface where institutions and companies could help them to decide whether or not to use a composite endpoint based on different parameters and their relative efficiency results.

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Appendix A

Descriptive Outputs

Descriptive outputs

	N	Minimum	Maximum	Mean	Standard deviation
Sample size	262	44	3602	1000,87	1006,143
n1 (control)	262	19	1802	452,40	499,230
n2	262	25	1800	548,47	537,226
Probability	247	,00	72,00	10,6478	11,24357
HR	126	,2	2,9	,766	,4243

Type of endpoint

	Frequency	Percentage	Valid percentage	Cumulative percentage
Composite and primary endp.	22	8,4	8,4	8,4
Composite and secondary endp.	28	10,7	10,7	19,1
Primary Endp.	6	2,3	2,3	21,4
Secondary Endp.	206	78,6	78,6	100,0
Total	262	100,0	100,0	

Significant

	Frequency	Percentage	Valid percentage	Cumulative percentage
	17	6,5	6,5	6,5
NO	183	69,8	69,8	76,3
YES	62	23,7	23,7	100,0
Total	262	100,0	100,0	

Figure A.1: *Descriptive outputs from stent cardiovascular literature search papers.*

Appendix B

Row data in Literature Search

Article ident.	Endpoint	Type of endpoint	Probability	HR
2	RR	Primary Endp.	42,00	
2	*Death, MI, RR, Stroke	Composite and secondary endp.	72,00	
2	Death	Secondary Endp.	18,00	
2	MI	Secondary Endp.	10,00	
2	Stroke	Secondary Endp.	8,00	
2	Cardiac death	Secondary Endp.	8,00	
2	LVEF	Secondary Endp.	58,00	
4	*Cardiac death, MI, ST, TLR	Composite and primary endp.	38,20	0,7
4	Cardiac death	Secondary Endp.	11,90	
4	Sudden/unexplained death	Secondary Endp.	5,30	
4	MI	Secondary Endp.	0,00	
4	ST	Secondary Endp.	0,80	
4	TLR	Secondary Endp.	30,90	
4	Death	Secondary Endp.	19,80	
4	*Cardiac death, MI, ST, TLR	Composite and secondary endp.	4,10	
4	Cardiac death	Secondary Endp.	4,10	
4	Sudden/unexplained death	Secondary Endp.	0,80	
4	MI	Secondary Endp.	0,00	
4	ST	Secondary Endp.	0,80	
4	TLR	Secondary Endp.	0,80	
4	Death	Secondary Endp.	4,80	
6	*Cardiac death, MI, TLR	Composite and primary endp.	8,70	0,545
6	Cardiac death	Secondary Endp.	0,40	2,89
6	MI	Secondary Endp.		
6	TLR	Secondary Endp.	6,80	0,54
6	*Cardiac death, MI	Composite and secondary endp.	2,50	0,83
6	TVR	Secondary Endp.	8,40	0,57
6	Periprocedural enzyme elevation	Secondary Endp.	17,30	
6	ST	Secondary Endp.	0,70	
6	*Cardiac death, MI, TLR	Composite and primary endp.	8,60	0,52
6	Cardiac death	Secondary Endp.	0,50	2,675
6	MI	Secondary Endp.		
6	TLR	Secondary Endp.	7,10	0,47
6	TVR	Secondary Endp.	8,80	0,54
6	Periprocedural enzyme elevation	Secondary Endp.	16,50	
6	ST	Secondary Endp.	0,50	
8	In-stent angiographic binary restensosis	Primary Endp.	51,35	
8	In-segment angiographic binary restensosis	Primary Endp.	48,65	
8	TLR	Secondary Endp.	22,70	
8	TVR	Secondary Endp.	22,70	
8	*Death, MI, Stroke, TVR	Composite and secondary endp.	22,70	
9	*Death, MI, TLR	Composite and primary endp.	24,70	0,505
9	Cardiac death	Secondary Endp.	7,70	
9	MI	Secondary Endp.	3,50	0,38
9	TLR	Secondary Endp.	13,00	
9	*MI, Death	Composite and secondary endp.		0,38
9	Death	Secondary Endp.	9,60	
9	Diabetes	Secondary Endp.		1,47
9	Acute coronary syndrome	Secondary Endp.		1,56
9	Renal dysfunction	Secondary Endp.		1,61
9	LVEF	Secondary Endp.		0,98
9	Multivessel disease	Secondary Endp.		0,8
9	Kissing balloon postdilation	Secondary Endp.		0,49
10	*AMI, Death, TVR	Composite and primary endp.	24,40	1,01
10	Death	Secondary Endp.	9,70	1,02
10	AMI	Secondary Endp.	9,20	0,89

10	TVR	Secondary Endp.	14,60	1,06
10	*AMI, Death	Composite and secondary endp.	16,30	
10	ST	Secondary Endp.	1,20	0,42
10	*AMI, Death, TVR	Composite and secondary endp.	19,60	
10	Death	Secondary Endp.	6,90	
10	AMI	Secondary Endp.	9,20	
10	TVR	Secondary Endp.	11,50	
10	*AMI, Death	Composite and secondary endp.	12,40	
10	ST	Secondary Endp.	1,00	
10	*AMI, Death, TVR	Composite and secondary endp.	11,40	
10	Death	Secondary Endp.	3,60	
10	AMI	Secondary Endp.	4,90	
10	TVR	Secondary Endp.	6,50	
10	*AMI, Death	Composite and secondary endp.	7,40	
10	ST	Secondary Endp.	0,70	
11	TLR	Primary Endp.	14,40	0,29
11	*Death, MI	Composite and secondary endp.	13,30	
11	Death	Secondary Endp.	6,70	
11	ReMI	Secondary Endp.	6,70	
11	ST	Secondary Endp.	1,10	
11	*Death, MI, TVR	Composite and secondary endp.	24,40	0,42
11	TLR	Secondary Endp.	21,10	0,29
11	*Death, MI	Composite and secondary endp.	21,10	
11	Death	Secondary Endp.	12,20	0,76
11	ReMI	Secondary Endp.	13,30	
11	ST	Secondary Endp.	2,20	
11	*Death, MI, TVR	Composite and secondary endp.	36,70	0,51
11	TLR	Primary Endp.	14,40	0,21
11	*Death, MI	Composite and secondary endp.	13,30	
11	Death	Secondary Endp.	6,70	
11	ReMI	Secondary Endp.	6,70	
11	ST	Secondary Endp.	1,10	
11	*Death, MI, TVR	Composite and secondary endp.	24,40	0,42
11	TLR	Secondary Endp.	21,10	0,24
11	*Death, MI	Composite and secondary endp.	21,10	0,7
11	Death	Secondary Endp.	12,20	
11	ReMI	Secondary Endp.	13,30	
11	ST	Secondary Endp.	2,20	
11	*Death, MI, TVR	Composite and secondary endp.	36,70	0,51
12	*Death, MI, TVR	Composite and primary endp.	11,80	1,03
12	Death	Secondary Endp.	2,30	1,21
12	Cardiac death	Secondary Endp.	1,80	1,26
12	MI	Secondary Endp.	4,60	1,21
12	TLR	Secondary Endp.	7,40	1,31
12	TVR	Secondary Endp.	9,90	1,08
12	ST	Secondary Endp.	2,80	1,61
12	Target Vessel Failure	Secondary Endp.	13,10	1,03
12	*Death, MI, TVR	Composite and primary endp.	10,30	0,68
12	Death	Secondary Endp.	4,40	0,85
12	Cardiac death	Secondary Endp.	3,30	0,68
12	MI	Secondary Endp.	4,00	0,92
12	TLR	Secondary Endp.	5,10	0,5
12	TVR	Secondary Endp.	7,70	0,48
12	ST	Secondary Endp.	2,90	0,76
12	Target Vessel Failure	Secondary Endp.	11,00	0,57
12	*Death, MI, TVR	Composite and primary endp.	14,30	0,83
12	Death	Secondary Endp.	3,80	0,68
12	Cardiac death	Secondary Endp.	3,80	0,17

12	MI	Secondary Endp.	5,30	2,02
12	TLR	Secondary Endp.	11,30	0,44
12	TVR	Secondary Endp.	13,50	0,45
12	ST	Secondary Endp.	4,50	0,72
12	Target Vessel Failure	Secondary Endp.	14,30	0,63
14	*Cardiac death, Ischemia, MI, ST, TLR	Composite and primary endp.	20,00	0,41
14	Death	Secondary Endp.	2,20	
14	MI	Secondary Endp.	1,10	
14	Restenosis	Secondary Endp.	8,90	
14	ST	Secondary Endp.	0,00	
14	Angina and positive dobutamine stress echocardiographic result	Secondary Endp.	7,80	
14	New lesion in same vessel	Secondary Endp.	4,40	
14	*Cardiac death, Ischemia, MI, ST, TLR	Composite and secondary endp.	15,60	
14	Death	Secondary Endp.	2,20	
14	MI	Secondary Endp.	1,10	
14	Restenosis	Secondary Endp.	8,90	
14	ST	Secondary Endp.	0,00	
14	Angina and positive dobutamine stress echocardiographic result	Secondary Endp.	7,80	
14	New lesion in same vessel	Secondary Endp.	4,40	
15	*Death, Major bleeding, MI, Stroke, TVR	Composite and primary endp.	18,30	0,83
15	*Death, MI, Stroke, TVR	Composite and primary endp.	11,90	1
15	Major bleeding	Secondary Endp.	9,20	0,61
15	Death	Secondary Endp.	3,80	0,57
15	Death	Secondary Endp.	4,80	0,71
15	Cardiac death	Secondary Endp.	3,80	0,57
15	Non cardiac death	Secondary Endp.	1,10	
15	ReMI	Secondary Endp.	4,40	
15	Qwave	Secondary Endp.	2,10	
15	Non-Q wave	Secondary Endp.	2,70	
15	*Death, MI	Composite and secondary endp.	8,50	
15	TVR	Secondary Endp.	5,90	
15	TLR	Secondary Endp.	4,50	
15	Ischaemic remote TVR	Secondary Endp.	2,00	
15	Stroke	Secondary Endp.	1,20	
15	ST	Secondary Endp.	3,20	
15	ST - definitive	Secondary Endp.	2,40	
15	ST - probable	Secondary Endp.	0,80	
15	Protocol major, non-CABG	Secondary Endp.	9,20	
15	Protocol major, all	Secondary Endp.	11,80	
15	Blood transfusion	Secondary Endp.	4,00	
15	TIMI (major or minor)	Secondary Endp.	10,20	
15	TIMI major	Secondary Endp.	5,50	
15	TIMI minor	Secondary Endp.	4,80	
15	GUSTO (life-threatening,severe or moderate)	Secondary Endp.	6,00	
15	GUSTO life-threatening or severe	Secondary Endp.	0,70	
15	GUSTO moderate	Secondary Endp.	5,40	
18	ISR	Primary Endp.	12,90	
18	In-segment restenosis	Secondary Endp.	16,10	
18	TVR	Secondary Endp.	9,70	
18	Death	Secondary Endp.	5,30	
18	*AMI, CHF,Death, ISR, Retransplantation, TVR	Composite and secondary endp.	21,10	
18	ISR	Secondary Endp.	38,00	0,4
18	ISR with vessels <= 3mm (5 years)	Secondary Endp.	55,00	0,37
18	ISR with vessels > 3mm (5 years)	Secondary Endp.	18,20	
18	ISR	Secondary Endp.	38,00	
18	In-segment restenosis	Secondary Endp.	38,10	0,9

18	TVR	Secondary Endp.	39,40	0,93
18	Death	Secondary Endp.	28,00	0,75
18	*AMI, CHF,Death, ISR, Retransplantation, TVR	Composite and secondary endp.	49,90	1,09
19	*Death, MI, TLR	Composite and primary endp.	27,10	0,32
19	Death	Secondary Endp.	0,80	
19	MI	Secondary Endp.	0,80	
19	ST	Secondary Endp.	0,80	
19	TLR	Secondary Endp.	26,30	
20	*Death, MI, RR	Composite and primary endp.	22,10	1
20	Death	Secondary Endp.	3,60	
20	MI	Secondary Endp.	12,40	
20	RR	Secondary Endp.	10,40	
20	Unrgent PCI	Secondary Endp.	8,00	
20	TLR	Secondary Endp.	6,40	
20	nonTLR	Secondary Endp.	4,00	
20	CABG	Secondary Endp.	2,40	
23	*Cardiac death, MI, TVR	Composite and primary endp.	14,10	0,858
23	ST (definitive)	Secondary Endp.	1,90	
23	ST (probable)	Secondary Endp.	1,50	
23	ST (possible)	Secondary Endp.	4,90	
23	Stent thrombosis (definitive and probable)	Secondary Endp.	2,80	0,96
23	Death	Secondary Endp.	5,80	
23	Cardiovascular death	Secondary Endp.	4,90	
23	*Cardiac death, MI	Composite and secondary endp.	8,30	
23	TVR	Secondary Endp.	6,80	0,851
23	MI	Secondary Endp.		0,67
24	*Death, MI, TVR	Composite and primary endp.	2,00	
24	Death	Secondary Endp.	0,00	
24	MI	Secondary Endp.	2,00	
24	TVR	Secondary Endp.	0,00	
24	*Death, MI, TVR	Composite and primary endp.	9,00	
24	Death	Secondary Endp.	0,00	
24	MI	Secondary Endp.	3,00	
24	TVR	Secondary Endp.	6,00	
24	*Death, MI, TVR	Composite and primary endp.	10,00	1,07
24	Death	Secondary Endp.	10,00	
24	MI	Secondary Endp.	1,00	
24	TVR	Secondary Endp.	3,00	
24	PCI	Secondary Endp.	7,00	
24	CABG	Secondary Endp.	2,00	
24	Bolus only	Secondary Endp.		1,07
24	Bolus+infusion	Secondary Endp.		1,1
24	Diabetes	Secondary Endp.		1
24	Unstable angina	Secondary Endp.		1,07
24	TnT> 0,03 microg/L	Secondary Endp.		1,15
25	*Access site complication, Death, Major bleeding, MI, Rehospitalization, Severe thrombocytopenia, TVR	Composite and primary endp.	11,10	
25	*Death, MI, TVR	Composite and secondary endp.	8,70	0,97
25	Death	Secondary Endp.	0,60	
25	MI	Secondary Endp.	2,40	
25	TVR	Secondary Endp.	6,50	
26	*Cardiac death, MI, TLR	Composite and primary endp.	25,80	0,52
26	Death	Secondary Endp.	10,80	0,75
26	Cardiac death	Secondary Endp.	7,50	0,83
26	MI	Secondary Endp.	6,50	0,28
26	MI (Q-wave)	Secondary Endp.	2,20	0,17

26	MI (Non-Q-wave)	Secondary Endp.	4,30	0,43
26	TLR	Secondary Endp.	17,20	0,39
26	TLR (Percutaneous)	Secondary Endp.	15,10	0,33
26	TLR (Surgical)	Secondary Endp.	4,30	0,41
26	TVR	Secondary Endp.	18,30	0,48
26	TVR (Percutaneous)	Secondary Endp.	16,10	0,41
26	TVR (Surgical)	Secondary Endp.	4,30	0,41
26	ST	Secondary Endp.	3,20	0,27
26	Target vessel failure	Secondary Endp.	26,90	0,57
26	*Death, MI, ST	Composite and secondary endp.	17,20	0,52
26	*Cardiac death, MI, TLR	Composite and primary endp.	15,10	0,65
26	Death	Secondary Endp.	4,10	0,98
26	Cardiac death	Secondary Endp.	2,60	0,57
26	MI	Secondary Endp.	4,30	0,93
26	MI (Q-wave)	Secondary Endp.	1,20	1,69
26	MI (Non-Q-wave)	Secondary Endp.	3,10	0,64
26	TLR	Secondary Endp.	12,00	0,64
26	TLR (Percutaneous)	Secondary Endp.	10,60	0,68
26	TLR (Surgical)	Secondary Endp.	2,40	0,31
26	TVR	Secondary Endp.	13,70	0,67
26	TVR (Percutaneous)	Secondary Endp.	12,30	0,7
26	TVR (Surgical)	Secondary Endp.	2,40	0,31
26	ST	Secondary Endp.	2,60	1,06
26	Target vessel failure	Secondary Endp.	16,80	0,64
26	*Death, MI, ST	Composite and secondary endp.	7,90	1,06
27	*Death, MI, TVR	Composite and primary endp.	17,20	0,77
27	Death	Secondary Endp.	8,40	0,92
27	MI	Secondary Endp.	5,50	0,81
27	*Death, MI	Composite and secondary endp.	12,80	0,83
27	TVR	Secondary Endp.	7,50	0,55
27	ST	Secondary Endp.	2,70	0,4
27	*Death, MI, TVR	Composite and primary endp.	25,70	0,74
27	Death	Secondary Endp.	13,70	0,8
27	MI	Secondary Endp.	6,90	1,01
27	*Death, MI	Composite and secondary endp.	19,10	0,82
27	TVR	Secondary Endp.	11,30	0,57
27	ST	Secondary Endp.	3,90	0,47

Appendix C

Maple Code

```
# CASE 3.

with(Statistics);

b10 := 'b10'; beta1 := 'beta1'; b20 := 'b20'; beta2 := 'beta2'; p2 := 'p2'; theta := 'theta';

listbeta1s := [1];
listbeta2s := [1];
listthetas := [.909887477, 1.547230858, 2.236162306, 3.010694328, 3.92618959, 5.086432004, 6.725813222];
listps := [[0.35e-1, .1], [0.35e-1, .15], [0.35e-1, .2], [0.5e-1, .1], [0.5e-1, .15], [0.5e-1, .2], [0.9e-1, .1], [0.9e-1, .15], [0.9e-1, .2], [.125,
.1], [.125, .15], [.125, .2]];
listRR := [[.5, [.4, .5, .6, .7, .8, .9]], [.6, [.4, .5, .6, .7, .8, .9]], [.7, [.4, .5, .6, .7, .8, .9]], [.8, [.4, .5, .6, .7, .8, .9]]];
OutFile := "CASE3Scenarios";

Escenari:=1:
b10 := 1/(-log(1-p1))^(1/beta1):
VL := proc (b20) options operator, arrow; exp(-1/b20^beta2) end proc:
UL := proc (v,b20) options operator, arrow; exp((b20*(-log(v))^(1/beta2))^beta1*log(1-p1)) end proc:
#g was named before fstar
g := proc (u, v) options operator, arrow; (1-exp(-theta))*theta*exp(-theta*(u+v))/(exp(-theta)+exp(-theta*(u+v))-exp(-theta*u)-exp(-
theta*v))^2 end proc:
f := proc(x) options operator, arrow; evalf(value(int(Int(g(u, v), u = 0 .. UL(v,x)), v = VL(x) .. 1))) end proc:

for beta1 in listbeta1s do
  for beta2 in listbeta2s do
      for probs in listps do
            p2:=probs[2]:
            p1:=probs[1]:
            listB20s:=[]:
            for theta in listthetas do
       g0:=0.5: g1:=10.0:
       v0:=f(g0):
       v1:=f(g1):vn:=v1:
       while (v1<p2 and v0>p2 and abs(g1-g0)>0.0001 and abs(vn-p2)>0.00001) do
         gn:=g0-(v0-p2)*(g0-g1)/(v0-v1):
         vn:=f(gn):
         if(vn<=p2) then g1:=gn: v1:=vn else g0:=gn: v0:=vn: end if:
       end do:
       listB20s:=[op(listB20s),[theta,gn]]
      end do:

# Got one list of Thetas/B20s...
      for descRRs in listRR do
        printf("%4d%c",Escenari,10);
        fprintf(OutFile,"%4d,%5.3f,%5.3f,%3.4f,[%3.4f",Escenari,beta1,beta2,descRRs[1],descRRs[2][1]);
        for RR2 in descRRs[2][2..] do
          fprintf(OutFile,",%3.4f",RR2):
        end do:
        fprintf(OutFile,"],%3.4f,%3.4f,[[%12.8f,%12.8f]",p1,p2,listB20s[1][1], listB20s[1][2]):
        for pair in listB20s[2..] do
          fprintf(OutFile,",[%12.8f,%12.8f]",pair[1],pair[2]):
        end do:
        fprintf(OutFile,"]%c",010); Escenari:=Escenari+1:
      end do:
    end do:
  end do:
end do:


fclose(OutFile);
```

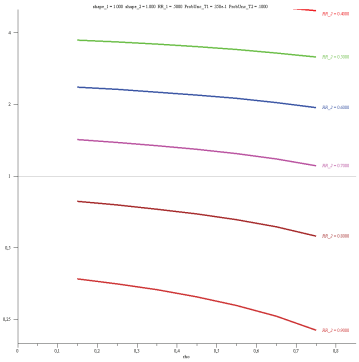
```
# ARE T* v T. CASE3

LOAD THE FOLLOWING:
with(Statistics);
with(plots);
with(ExcelTools);
with(StringTools);

COLOR FOR PLOTS, VALUES FOR RHO

colors := [red, green, blue, magenta, brown, orange]; i := 1; PLOTS := [];
assume(t > 0, t < 1, x > 0);
ValsRho := [seq(i, i = .15 .. .75, .1)];


ValsTheta:=[ ]:theta:='theta':numRhos:=0:
for rho in ValsRho do
  numRhos:=numRhos+1:
  auxtheta:=fsolve(1-12*(Int((theta*t-2*t^2)/((exp(t)-1)*theta), t = 0 .. theta))/theta^2 = rho, theta);
  ValsTheta:=[op(ValsTheta),auxtheta]:
end do:
print("ValsTheta := "): ValsTheta;


Tabulation of ARE for different parameters:
ScenariosFile := "C:/Users/Moi/Desktop/SOLVER/CASE3Scenarios.dat";
//This is the file that describes the desired scenarios

PrimeraLinea := 1;

FitxerExcel := "C:/Users/Moi/Desktop/SOLVER/Case3.xls";

Define procedures:

# Pressing this button (re)defines the computation procedures


toStr := proc (v) options operator, arrow; sprintf("%7.4f", v) end proc:

capcaleres := proc () options operator, arrow;
    global PrimeraLinea;FitxerExcel;
    Export(Vector[row](["Scenario", "Beta_1", "Beta_2", "p_1", "p_2", "RR_1", "Rho", "b20", "RR_2","ARE",
"RR_2","ARE","RR_2","ARE","RR_2","ARE","RR_2","ARE","RR_2","ARE", "RR_2","ARE"]),FitxerExcel,1,cat("A",PrimeraLinea)):
    PrimeraLinea:=PrimeraLinea+1;
end proc:

doOne:= proc (beta1,beta2,RR1,RR2,p1,p2,b20s)
global AREs,ARETTstar, ARETstarT;
local
v,nl,b11,b21,b10,b20,theta,T10,fT10,FT10,ST10,T11,fT11,FT11,ST11,T20,fT20,FT20,ST20,T21,fT21,FT21,ST21,C0,C1,AUX,fstar
0,fstar1,numlin,Sstar0,Lstar0,Sstar1,Lstar1,HRstar,logHRstar,tmp3,tmp4;
description "fills up AREs with the ARETstarT values for the ValsTheta for these params";
    nl := 10:numlin:=0:AREs:=[]:
    b10 := 1/(-log(1-p1))^(1/beta1):
    b11 := b10/RR1^(1/beta1):
  for v in b20s do
  theta:=v[1]: b20:=v[2]:
```

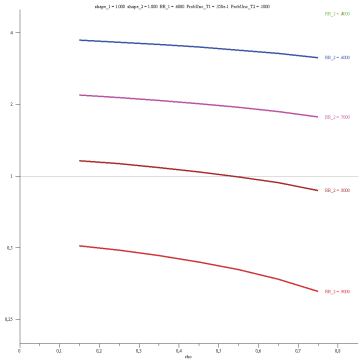
```
b21:=b20/RR2^(1/beta2):
      T10 := RandomVariable(Weibull(b10, beta1)):
      fT10:=(t)->PDF(T10,t): FT10:=(t)->CDF(T10,t): ST10:=(t)->1-FT10(t):
      T11 := RandomVariable(Weibull(b11, beta1)):
      fT11:=(t)->PDF(T11,t): FT11:=(t)->CDF(T11,t): ST11:=(t)->1-FT11(t):
      T20 := RandomVariable(Weibull(b20, beta2)):
      fT20:=(x)->PDF(T20,x): FT20:=(x)->CDF(T20,x): ST20:=(t)->1-FT20(t):
      T21 := RandomVariable(Weibull(b21, beta2)):
      fT21:=(x)->PDF(T21,x): FT21:=(x)->CDF(T21,x): ST21:=(t)->1-FT21(t):
      C0 := proc (t, x) options operator, arrow; -log(1+(exp(-theta*ST10(t))-1)*(exp(-theta*ST20(x))-1)/(exp(-theta)-1))/theta end
proc:
      AUX:=simplify((exp(-theta*ST10(t))*(exp(-theta*ST20(t))-1)*fT10(t)+exp(-theta*ST20(t))*(exp(-theta*ST10(t))-
1)*fT20(t))/(exp(-theta*C0(t, t))*(exp(-theta)-1)), exp):
      fstar0 := unapply(AUX, t):
      Sstar0 := proc (t) options operator, arrow; C0(t, t) end proc:
      Lstar0 := proc (t) options operator, arrow; simplify(fstar0(t)/Sstar0(t),exp) end proc:
      C1 := proc (t, x) options operator, arrow; -log(1+(exp(-theta*ST11(t))-1)*(exp(-theta*ST21(x))-1)/(exp(-theta)-1))/theta end
proc:
      AUX:=simplify((exp(-theta*ST11(t))*(exp(-theta*ST21(t))-1)*fT11(t)+exp(-theta*ST21(t))*(exp(-theta*ST11(t))-
1)*fT21(t))/(exp(-theta*C1(t, t))*(exp(-theta)-1)), exp):
      fstar1 := unapply(AUX,t):
      Sstar1 := proc (t) options operator, arrow; C1(t, t) end proc:
      Lstar1 := proc (t) options operator, arrow; evalf(fstar1(t)/Sstar1(t)) end proc:
      HRstar := proc (t) options operator, arrow; evalf(Lstar1(t)/Lstar0(t)) end proc:
      logHRstar := proc (t) options operator, arrow; evalf(log(Lstar1(t)/Lstar0(t))) end proc:


      tmp3 := proc (t) options operator, arrow; evalf(logHRstar(t)*fstar0(t)) end proc:
      tmp4 := evalf(Int(tmp3(t), t = 0. .. 1, method = _d01ajc)):
      #ARETTstar := log(RR1)^2*FT10(1)*(1-Sstar0(1))/tmp4^2:
      #ARETstarT:=evalf(1/ARETTstar):
      ARETstarT:=evalf(tmp4^2/(log(RR1)^2*FT10(1)*(1-Sstar0(1)))):
      AREs := [ op(AREs),evalf(ARETstarT)]:
   end do:
end proc:

doPlot:=proc(line)
description "parses line and produces plot defined within";
global scen,beta1,beta2,RR1,RR2,ValsLambda2,p1,p2,PLOTS,extrem,lbl,fitx,capt,AREs;
local i, b20s;
# vars for Excel export:
global ScenStart, PrimeraLinea, NxtCol, AREsStr, ExcelCol;

   if line=0 then return: end if:
   scen,beta1,beta2,RR1,ValsLambda2,p1,p2,b20s:=parse(line):

   # Export common parameters of this scenario to excel file:
   ScenStart:=PrimeraLinea: PrimeraLinea:=PrimeraLinea+nops(ValsRho):
   for i from ScenStart to PrimeraLinea-1 do
         Export(Vector[row]([scen,beta1,beta2,p1,p2,RR1]),FitxerExcel,1,"A"||i):
   od:
   Export(Vector(map(toStr,ValsRho)),FitxerExcel,1,"G"||ScenStart):
   Export(Vector(map(proc (i) options operator, arrow; b20s[i][2] end proc, [seq(j, j = 1 .. 7)])), FitxerExcel,1,"H"||ScenStart):
   NxtCol:="I":
   # End common parameters export
```

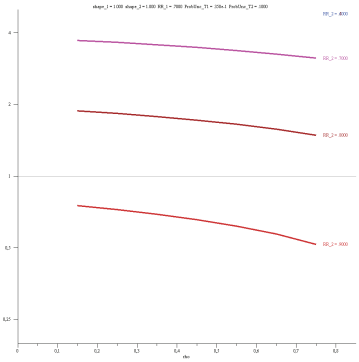
```
PLOTS := []: i := 1:
   for RR2 in ValsLambda2 do
      doOne(beta1,beta2,RR1,RR2,p1,p2,b20s):
      PLOTS := [op(PLOTS), plot(ValsRho, AREs, color = colors[i], thickness=4)]:
     # for extrem from numRhos by -1 to 1 while evalf(AREs[numRhos])>5 do; end do:
     # if extrem > 1 then
     extrem:=nops(ValsRho):
         lbl := textplot([ValsRho[extrem]+0.05, min(4.8,AREs[extrem]), typeset(RR_2 = RR2), color = colors[i]]):
         PLOTS:=[op(PLOTS), lbl]:
    #  end if:
      i:=i+1:
      # Export a column of AREs for this RR2 to excel file:
      AREsStr:=map(toStr, AREs);
      #ExcelCol:=map(proc (i) options operator, arrow;
       #               cat(toStr(RR2), ",", toStr(AREs[i])) end proc,
      #            [seq(i, i = 1 .. nops(AREs))]):
      ExcelCol:=map(proc(i) options operator, arrow;
           toStr(RR2) end proc, [seq(i, i=1..nops(AREs))]):
      Export(Vector(ExcelCol),FitxerExcel,1,cat(NxtCol,ScenStart)):
      NxtCol:=Char(Ord(NxtCol)+1):
      Export(Vector(AREsStr),FitxerExcel,1,cat(NxtCol,ScenStart)):
      NxtCol:=Char(Ord(NxtCol)+1):
      # END Export a column...

   end do:
   fitx:=sprintf("C:/Users/Moi/Desktop/SOLVER/Scenario_%03d",scen):
   plotsetup(png, plotoutput = fitx, plotoptions = "width=1000,height=1000,orientation=portrait");
   display(PLOTS, axis[2] = [gridlines = [1], mode = log, tickmarks = [.25, .5, 1, 2, 4]], labels = [typeset('rho'), "evalf(ARETstarT)"],
labeldirections = [horizontal, vertical], view = [0 .. .85, .2 .. 5],caption=typeset(shape_1=beta1,"  ",shape_2=beta2,"  ",RR_1=RR1,"
",ProbUnc_T1=p1,"  ",ProbUnc_T2=p2));
   #print(fitx," done.");
end proc:

capcaleres():

fclose(ScenariosFile);
for i to 48 do doPlot(readline(ScenariosFile)); fitx end do;
```

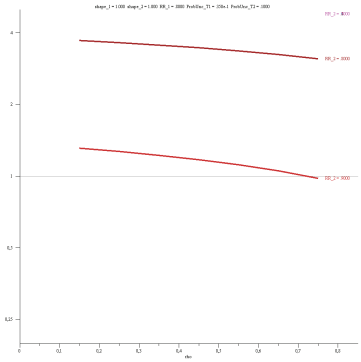
Appendix D

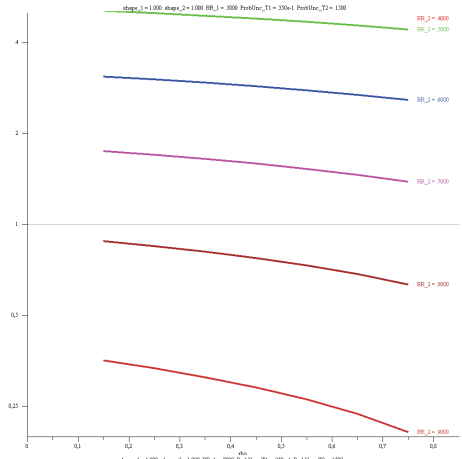
ARE Plots

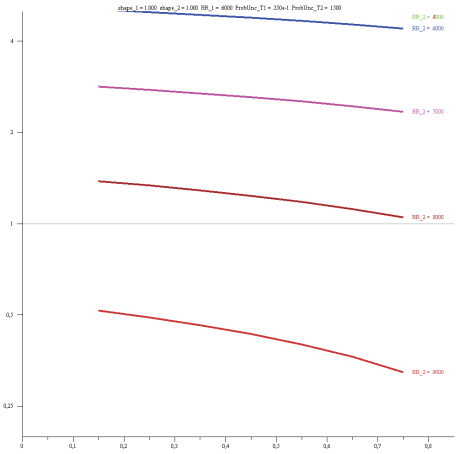


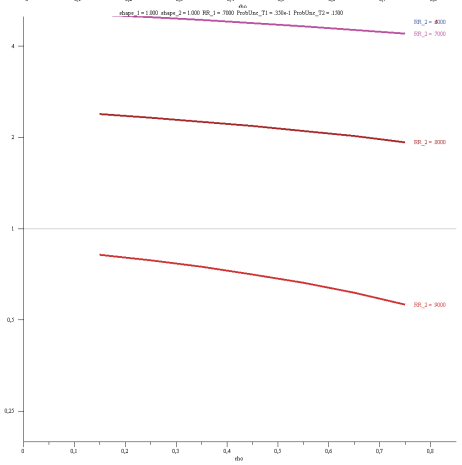


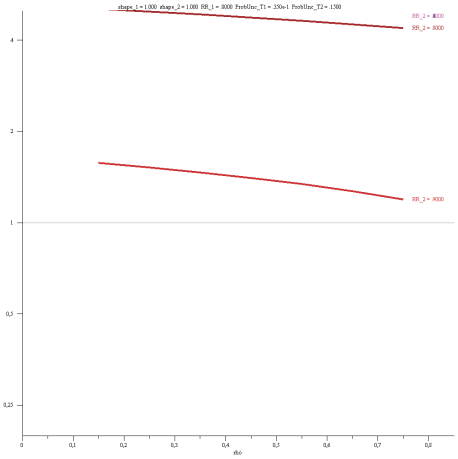


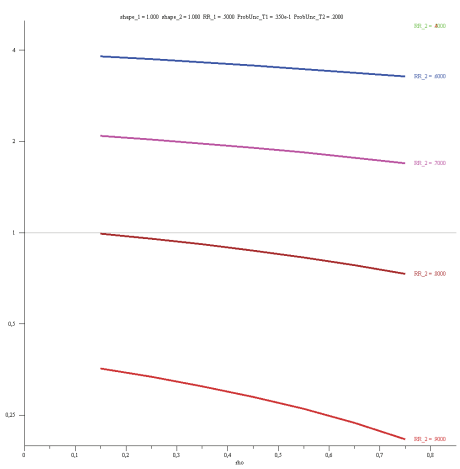


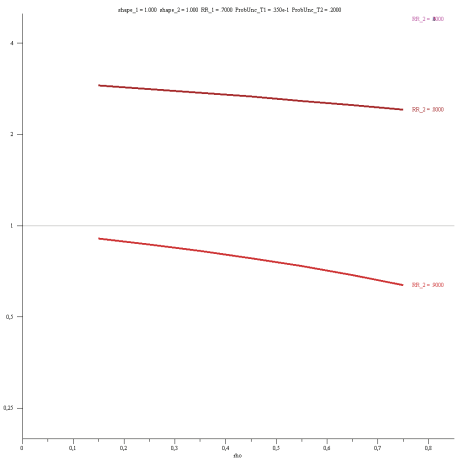

shape_1 = 1.000 shape_2 = 1.000 RR_1 = 3000 ProbUnc_T1 = 350e-1 ProbUnc_T2 = 1.500
RR_2 = 4000
RR_2 = 5000
RR_2 = 6000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000
rho

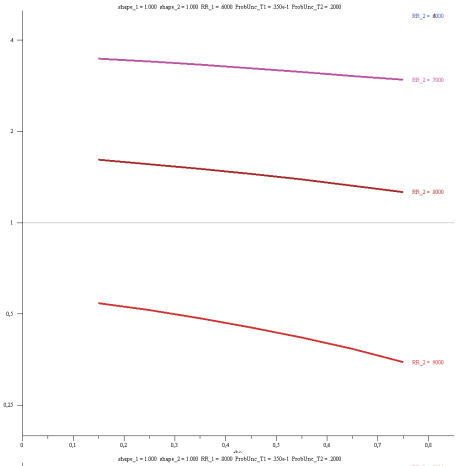

shape_1 = 1.000 shape_2 = 1.000 RR_1 = 6000 ProbUnc_T1 = 350e-1 ProbUnc_T2 = 1.500
RR_2 = 4000
RR_2 = 6000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000

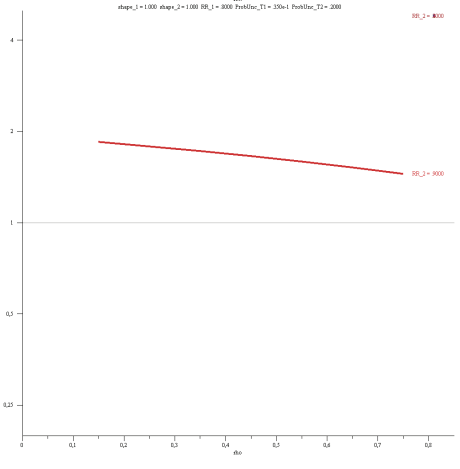

shape_1 = 1.000 shape_2 = 1.000 RR_1 = 7000 ProbUnc_T1 = 350e-1 ProbUnc_T2 = 1.500
RR_2 = 4000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000
rho

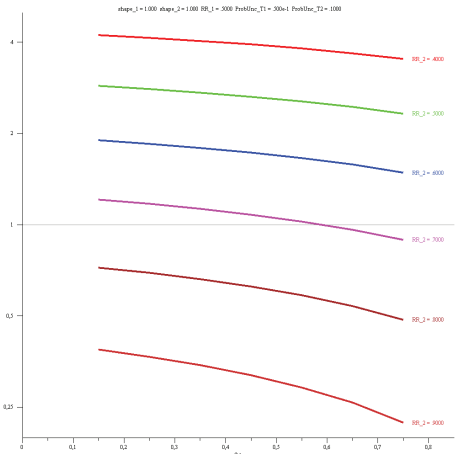

shape_1 = 1.000 shape_2 = 1.000 RR_1 = 8000 ProbUnc_T1 = 350e-1 ProbUnc_T2 = 1.500
RR_2 = 4000
RR_2 = 8000
RR_2 = 9000
rho


shape_1 = 1.000 shape_2 = 1.000 RR_1 = 5000 ProbUnc_T1 = 350e-1 ProbUnc_T2 = 2000
RR_2 = 6000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000
rho


shape_1 = 1.000 shape_2 = 1.000 RR_1 = 7000 ProbUnc_T1 = 350e-1 ProbUnc_T2 = 2000
RR_2 = 8000
RR_2 = 9000
rho


shape_1 = 1.000 shape_2 = 1.000 RR_1 = 6000 ProbUnc_T1 = 350e-1 ProbUnc_T2 = 2000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000
rho


shape_1 = 1.000 shape_2 = 1.000 RR_1 = 8000 ProbUnc_T1 = 350e-1 ProbUnc_T2 = 2000
RR_2 = 9000
rho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RR_2 = 4000
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RR_2 = 7000
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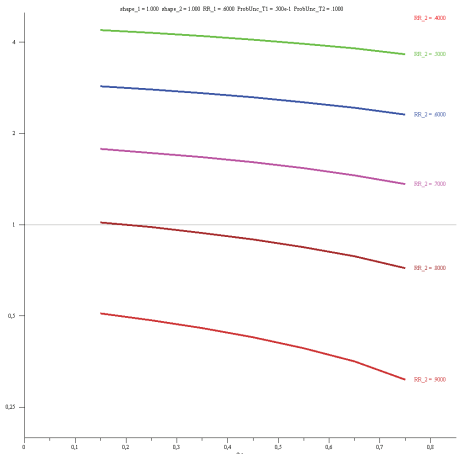
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RR_2 = 8000
RR_2 = 9000
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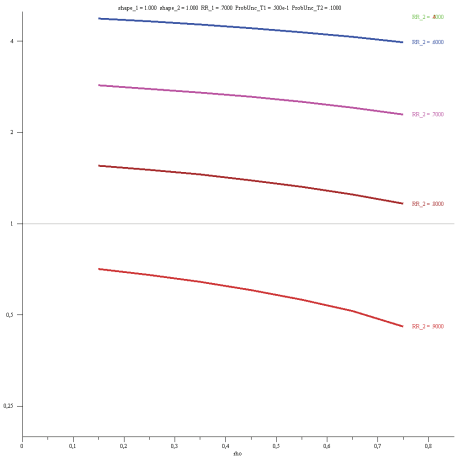
shape_1 = 1.000 shape_2 = 1.000 RR_1 = 7000 ProbUnc_T1 = 500e-1 ProbUnc_T2 = 1000
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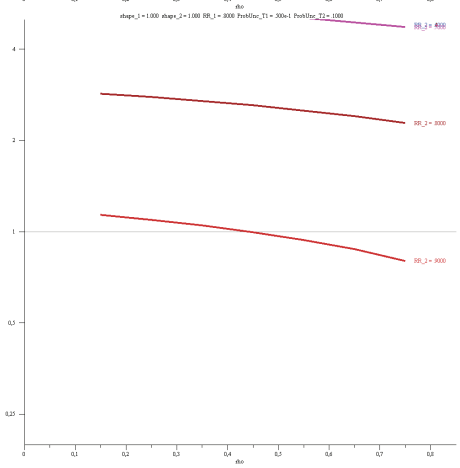
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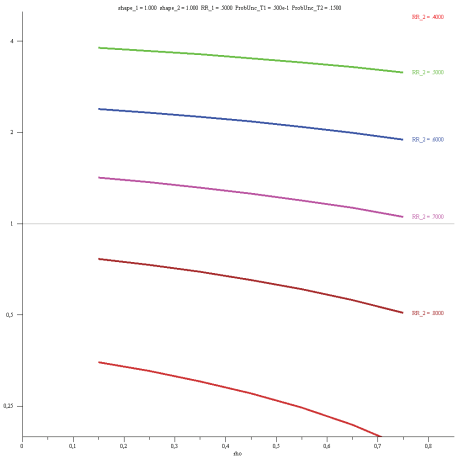
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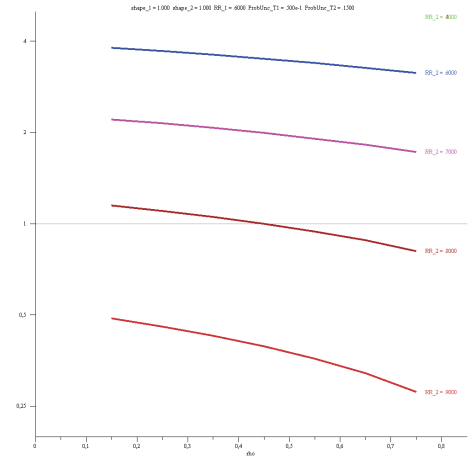
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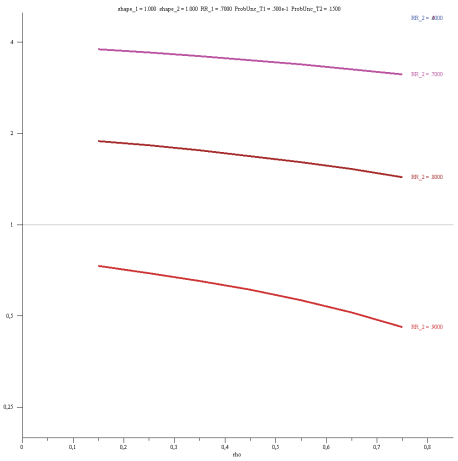
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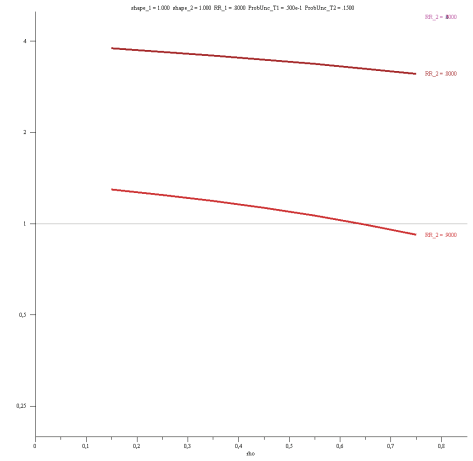
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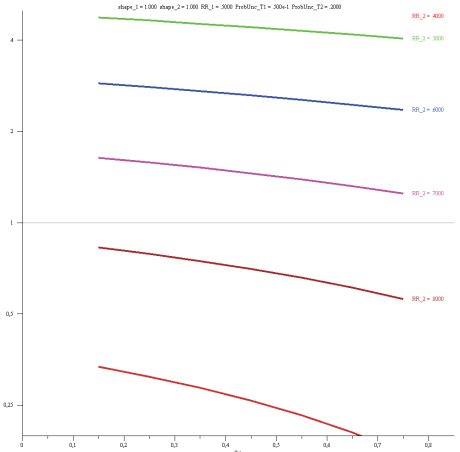
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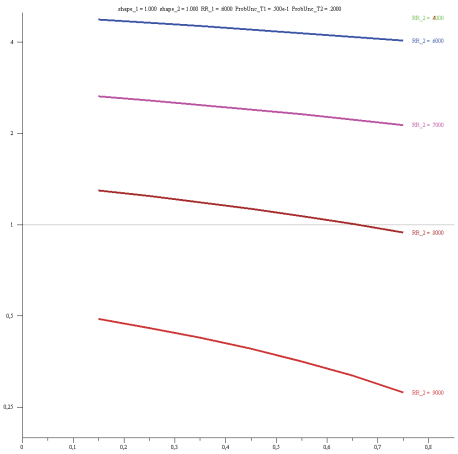
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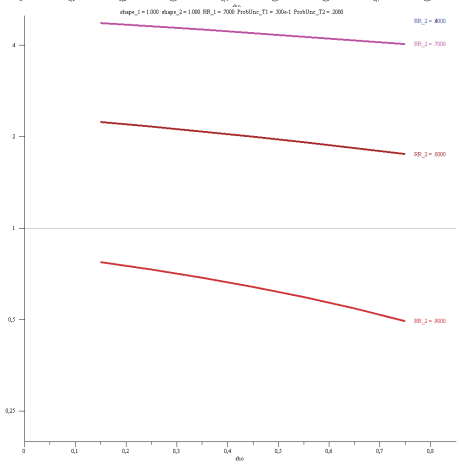
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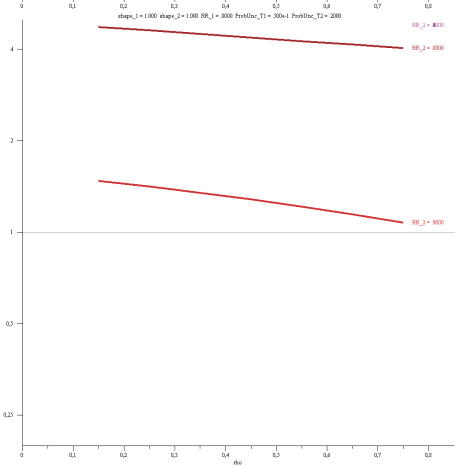
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RR_2 = 4000
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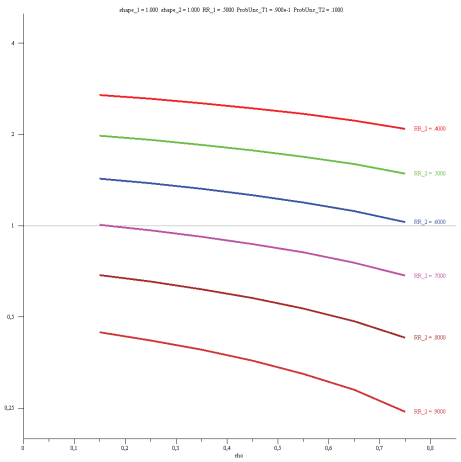
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RR_2 = 4000
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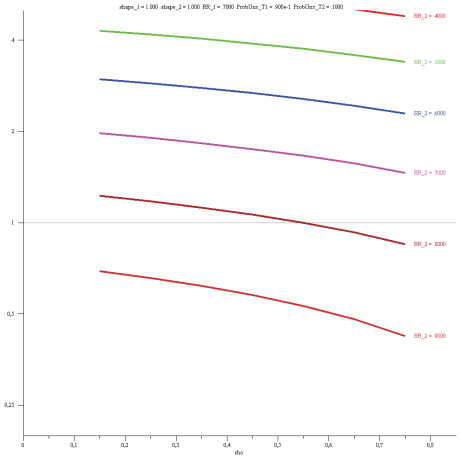
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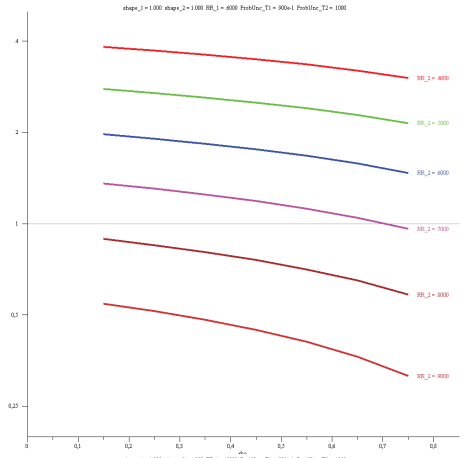
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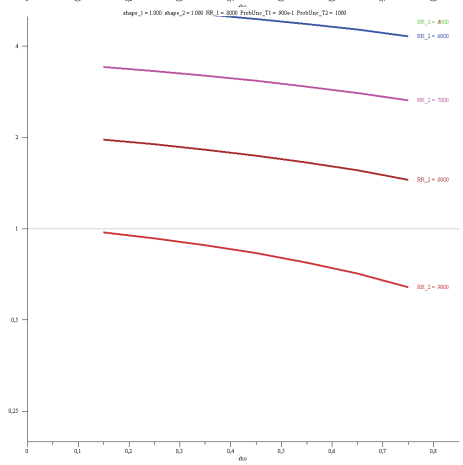
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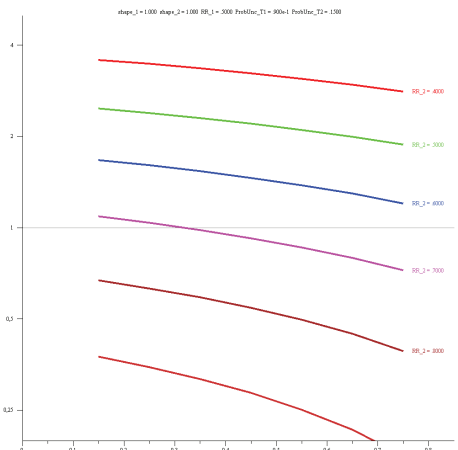
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RR_2 = 7000
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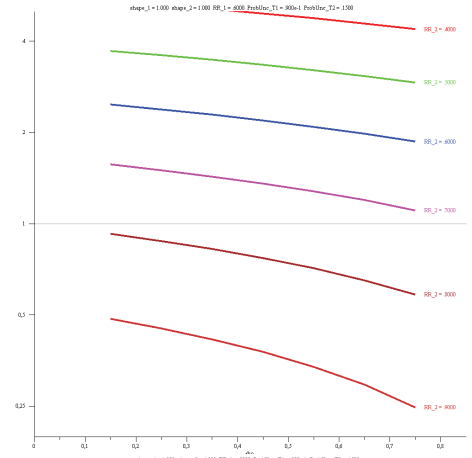
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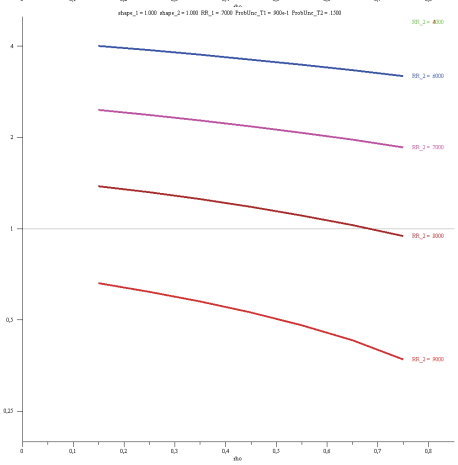
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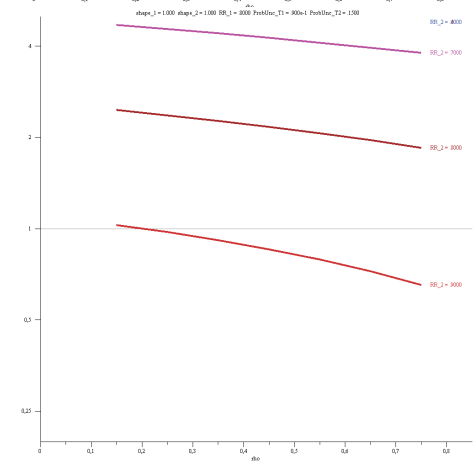
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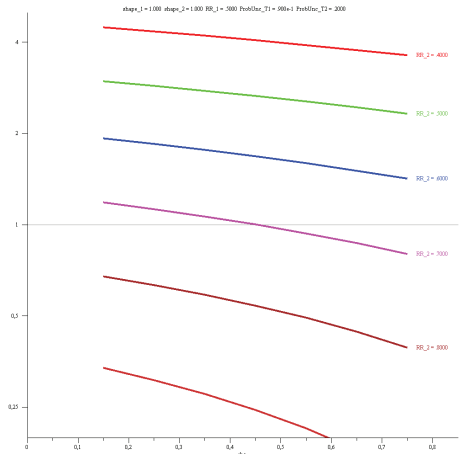
shape_1 = 1.000 shape_2 = 1.000 RR_1 = 5000 ProbUnc_T1 = 900e-1 ProbUnc_T2 = 2000
RR_2 = 4000
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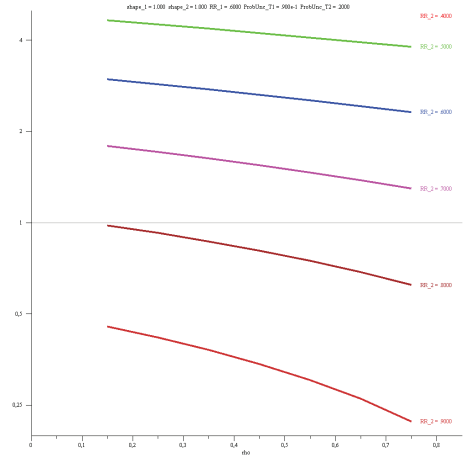
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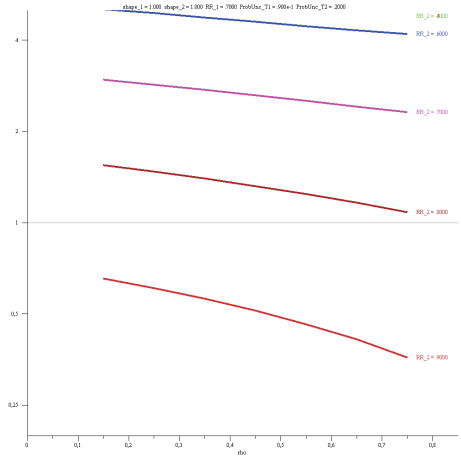
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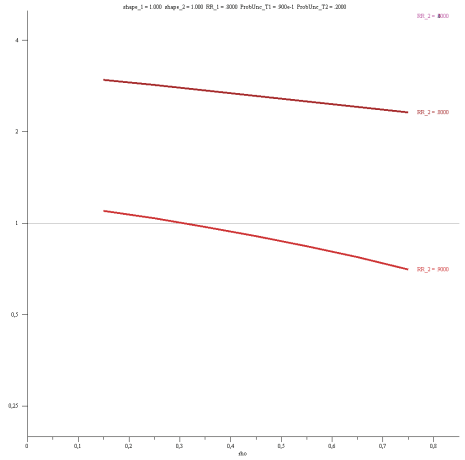
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RR_2 = 8000
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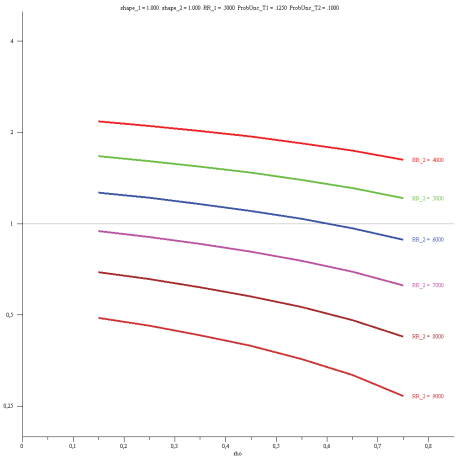
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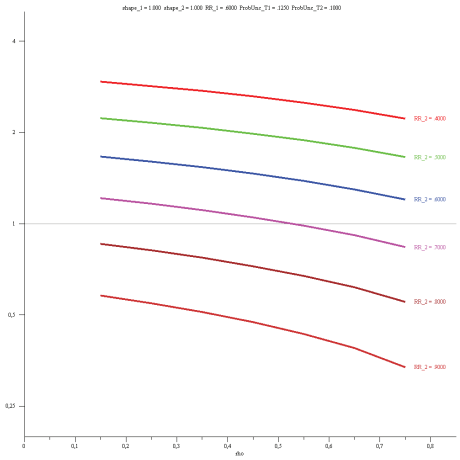
shape_1 = 1.000 shape_2 = 1.000 RR_1 = 6000 ProbUnr_T1 = .1250 ProbUnr_T2 = .1000
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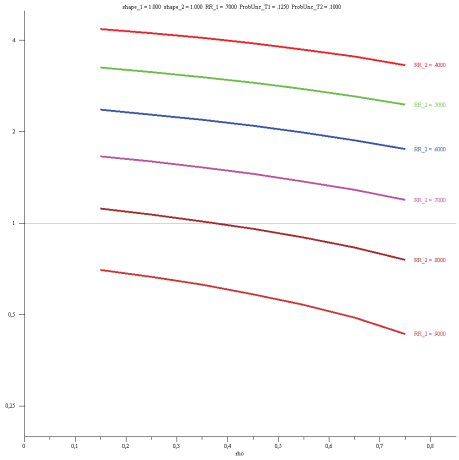
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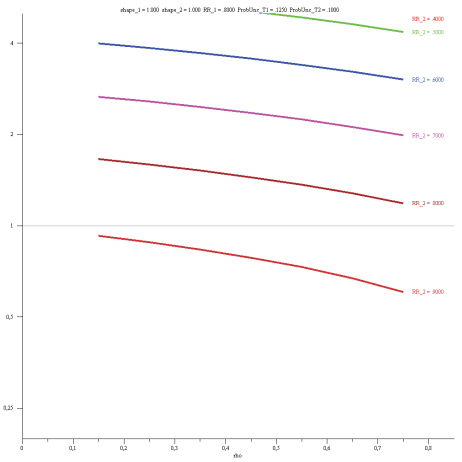
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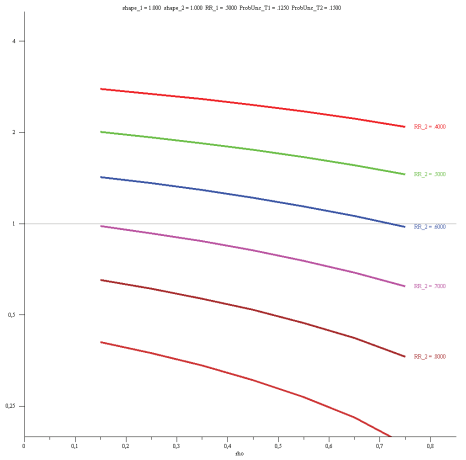
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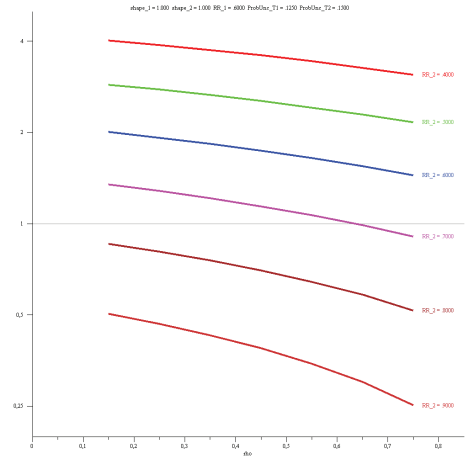
0,6
0,7
0,8
rho


shape_1 = 1.000 shape_2 = 1.000 RR_1 = 6000 ProbUnc_T1 = 1250 ProbUnc_T2 = 1500
RR_2 = 4000
RR_2 = 5000
RR_2 = 6000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000
4
2
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0,25
0
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0,2
0,3
0,4
0,5
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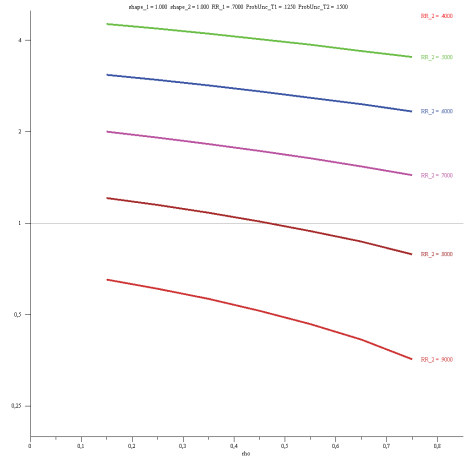
0,8
rho


shape_1 = 1.000 shape_2 = 1.000 RR_1 = 7000 ProbUnc_T1 = 1250 ProbUnc_T2 = 1500
RR_2 = 4000
RR_2 = 5000
RR_2 = 6000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000
4
2
1
0,5
0,25
0
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0,2
0,3
0,4
0,5
0,6
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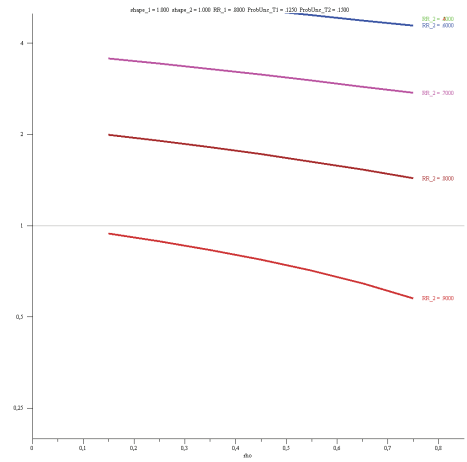
0,8
rho


shape_1 = 1.000 shape_2 = 1.000 RR_1 = 8000 ProbUnc_T1 = 1250 ProbUnc_T2 = 1500
RR_2 = 8000
RR_2 = 6000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000
4
2
1
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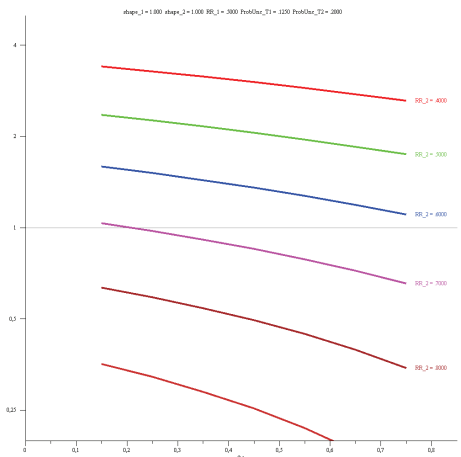
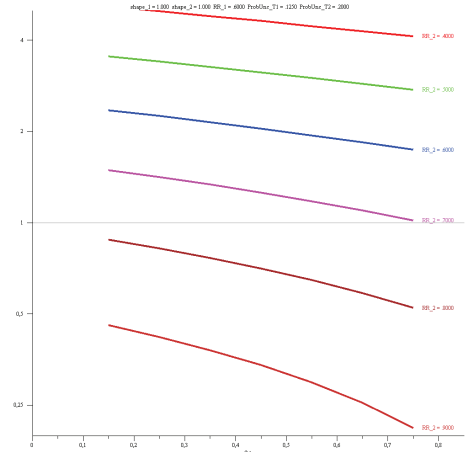
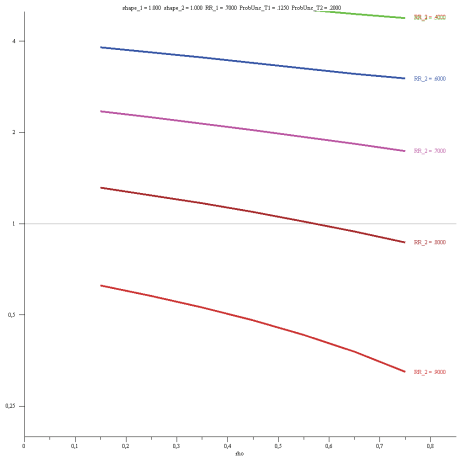
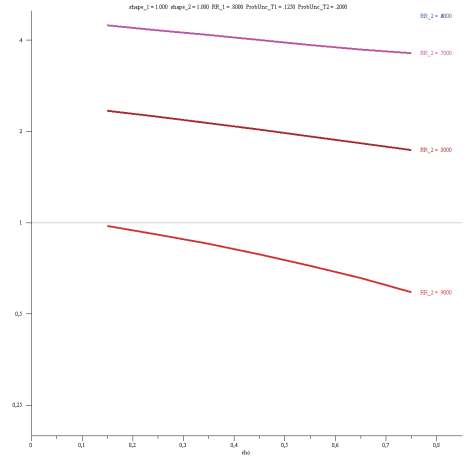
0,2
0,3
0,4
0,5
0,6
0,7
0,8
rho


shape_1 = 1.000 shape_2 = 1.000 RR_1 = 5000 ProbUnc_T1 = 1250 ProbUnc_T2 = 2000
RR_2 = 4000
RR_2 = 5000
RR_2 = 6000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000
rho


shape_1 = 1.000 shape_2 = 1.000 RR_1 = 6000 ProbUnc_T1 = 1250 ProbUnc_T2 = 2000
RR_2 = 4000
RR_2 = 5000
RR_2 = 6000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000
rho


shape_1 = 1.000 shape_2 = 1.000 RR_1 = 7000 ProbUnc_T1 = 1250 ProbUnc_T2 = 2000
RR_2 = 4000
RR_2 = 6000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000
rho


shape_1 = 1.000 shape_2 = 1.000 RR_1 = 8000 ProbUnc_T1 = 1250 ProbUnc_T2 = 2000
RR_2 = 4000
RR_2 = 7000
RR_2 = 8000
RR_2 = 9000
rho