

Worsening Clinical Outcome with Increasing Number of So-Called Off-Label or Unapproved Indications for Use of Drug Eluting Stents

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Abstract

Objective: We explored the impact of increasing number of off-label patient and lesion characteristics on 5-year clinical outcome following implantation of first generation drug eluting stents. Furthermore we tried to assess if stent performance might be improved if the off-label characteristics present were taken into account to guide the stent brand selection. **Design:** A total of 2888 coronary lesions treated with first generation drug eluting stents were classified for eventual presence of 18 different off-label characteristics and correlated to the 5-year clinical outcome by multiple stepwise Cox regression analysis. **Results:** The composite of cardiac death, myocardial infarction and target vessel revascularization (major adverse cardiac event, MACE) was 16.7% in cases with zero off-label characteristics and showed a stepwise increased rate up to 32.7% in cases with 5 off-label characteristics. The MACE rate for the sirolimus eluting stent appears to be 10% lower than the paclitaxel stent group and it may be further reduced by 10% - 18% if the off-label characteristics present in each case were taken into account to guide the stent brand selection. **Conclusion:** With increasing number of concomitantly appearing off-label characteristics there is a stepwise increase in MACE rate. The MACE rate may be reduced if the off-label characteristics were used to guide the stent brand selection.

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Keywords

Drug Eluting Stents

1. Introduction

New stent brands are continually developed in order to improve stent performance and clinical outcome. The improvement is obtained by changes in several factors in metal alloy, manufacturing technique, strut architecture, coating material, drug type and amount, medication release kinetics and stent balloon delivery systems.

The clinical outcome is not only determined by differences in these factors. It is also dependent on several patient and lesion characteristics like the so called “off-label” or unapproved indications for use of drug eluting. One stent brand may be particularly good when some off-label characteristics are present, but it may also be particularly bad in other cases. If the particularly bad cases for use of one stent brand could be identified then another and better stent could be selected and the clinical outcome for the population might thereby be improved without even manufacturing a new stent.

We explored the impact of increasing number of off-label lesions and patient characteristics on 5-year clinical outcome following implantation of first generation drug eluting stents. Furthermore we tried to assess the impact on outcome for each identifiable patient or lesion characteristic for each stent type. Finally, we attempted an estimation of the effect on outcome if the off-label characteristics present were taken into account to guide the stent brand selection.

2. Material

In the SORT OUT II trial 2098 patients with 2888 lesions were randomized to sirolimus- or paclitaxel-eluting stent implantation. The 18 months results and the 5 years results have been published [1] [2]. All patients were followed until emigration, death or five years of clinical observation. The SORT OUT II was the largest of the randomized studies that compared these first-generation drug-eluting stents [3]. The SORT OUT II trial was especially designed to reflect daily routine in clinical practice by including unselected all-comer patients and avoid preplanned repeat angiography. One third of the patients are treated for more than one lesion and most of the lesions have more than one off-label characteristic (**Table 1**) [1].

3. Methods

The clinical events were classified using definitions on acute myocardial infarction and definitions from ACC/AHA/SCAI as previously described [1] [4] [5]. The primary outcome measure was the MACE rate comprising cardiac death, acute myocardial infarction, and target vessel revascularization. The different off-label characteristics important to clinical outcome were deducted from the regulatory approval for sale and use of drug-eluting stents: “*The studies used to obtain regulatory approval were characterized by strict inclusion and exclusion criteria. The clinical outcome connected to the use of drug eluting stents only applied to these specific conditions. The FDA gave strict labeling for treatment with a drug eluting stent only to those specific lesions and patient characteristics for whom or which the safety and efficacy were proven to be suited*” [6] [7]. Furthermore, FDA explicitly mentioned certain lesion or patients characteristics in which the use of drug-eluting stents were not investigated and consequently considered to be an unsafe procedure [4] [6] [7]. We extracted 18 different off-label characteristics from the literature that we were able to account for in the SORT OUT II material (definitions and references in **Table 1**).

When off-label characteristics are used to guide stent brand selection it may be defined as an individualized stent brand selection approach. This is opposed to a so-called general stent brand selection approach in which one stent brand is used in all patients.

First we compared the two stent brands with the MACE rates for the 2888 lesions treated with sirolimus- or paclitaxel-eluting stents.

Second, we searched for a possible relation between the numbers of concomitantly appearing off-label characteristics and the MACE rate.

Table 1. Uniform definitions of on- and off-label characteristics for the use of a drug eluting stent.

	Sirolimus-eluting 1481	Paclitaxel-eluting 1407	Total 2888
On-label characteristics for use of a drug eluting stent			
0	74	64	138
Use of only one stent irrespective of length with nominal diameters ranging from 2.5 to 3.5 mm in de novo lesions in native vessels and none of the off-label lesion or patients characteristics below			
Off-label characteristics for use of a drug eluting stent			
1	25	48	75
Use of stent in a re-stenotic previously stent-treated lesion [8]-[18]			
2	10	13	25
Use of stent in a vein graft. This combines and replaces: “degenerated vein grafts with friable lesions” (C-lesion, Table 6 in [5]) and “use of stent in bypass grafts” be it arteries or veins [7]-[18]			
3	14	20	37
Use of stent in the left main coronary artery [6]-[8] [10]-[12] [14]-[19]. Irrespective of it is being protected by a previously performed CABG or by a fine arterialized collateral or whether it seems to be unprotected			
4	257	243	509
Use of stent within 5 mm from the ostium [6]-[8] [10] [12] [15] [16] LAD2, LAD3, CX2, CX3, RCA2, RCA3 have no ostium			
5	125	124	272
Use of stent in bifurcation lesion [6] [7] [9]-[19] (<i>i.e.</i> a lesion where a balloon has been inflated in each of the branches of the bifurcation)			
6	114	145	272
Use of stent in an occlusion excepting acute myocardial infarctions treated acutely. This combines and replaces “use of stent in total occlusions more than 3 months old and/or bridging collaterals” (C-lesion, Table 6 in [5]) and “use of stent in a chronic total occlusion” [9]-[12] [14]-[18]			
7	128	119	257
Use of nominal stent diameter < 2.5 mm—our own definition which replaces use of stent in reference vessel diameter < 2.5 mm [6] [7] [10] [13] [15]-[18]			
8	260	265	558
Use of more than one stent in the same lesion, which replaces use of stent in lesion lengths > 26 mm [16], >28 mm [7], >30 mm [6] [8] [10] [11] [15] [18] or >36 mm [19] and at least 2 overlapping stents [7] [8] [16]			
9	518	454	1025
Use of stent length > 20 mm, a high risk lesion (C-lesion, Table 6 in [5])			
10	277	254	535
Use of stent in angulated lesion, a high risk lesion (C-lesion, Table 6 in [5])—in this context > 45 degrees as was our own definition prior to publication of guideline [5] which defined > 90 degrees			
11	289	245	538
Use of stent in vessel with severe proximal tortuosity, a high risk lesion (C-lesion, Table 6 in [5])—replaces the “use of stent in a tortuous vessel (>60 degrees) in the region of the obstruction or proximal to the lesion” [6] [7]			
12	95	89	187
Use of stent in lesions with visible thrombus at lesion site [6] [7] or distal to lesion			
13	324	305	631
Inability to protect major side branches, a high risk lesion (C-lesion, Table 6 in [5]), here defined as side branch > 1 mm in reference diameter			
Patient characteristics for off-label use of stent			
14	205	185	422
Use of stent in patients with STEMI [6]-[9] [11]-[14] [16]-[19] in an acute/emergency setting			
15	531	462	1049
Use of stent in patients with non-STEMI [9] [11] or unstable angina in a sub-acute/urgent setting which replaces: “use of stent in patients with acute coronary syndromes” [18] and “use of stent in patients with a recent AMI where there is evidence of thrombus or poor flow” [6] [7]			
16	669	602	1385
Use of stents in more than one lesion [19] which also encompass use of stent in patients with multi-vessel disease [9] [14] [17] [18]			
17	248	234	509
Use of stent in patients with diabetes [11] [14]			
Of special interest—although not an off-label characteristic			
18	364	308	716
Use of DES in female gender			
Not included in the present analysis due to absent data			
19	“not available”	“not available”	“not available”
Use of stent in patients with left ventricular ejection fraction < 0.30 [12] (or <0.25 [19])			

Continued

20	Use of stent in patients with renal failure [12] [14] [19]	“not available”	“not available”	“not available”
21	Use of nominal stent diameter > 3.5 mm—our own definition which replaces use of stent in reference vessel diameter >3.5 mm [6] [10] [15] [19], >3.75 mm [7], >4.0 mm [19]. This item cannot be investigated in SORT OUT II because the sirolimus-eluting stent does not come >3.5 mm	“not available”	“not available”	79

Third, we investigated the impact of each off-label characteristic on MACE rates for each stent brand. This was estimated by a hazard ratio (HR) for MACE when off-label characteristics were present in proportion to zero off-label characteristics present.

Finally, we estimated the magnitude of the potential effect of an individualized stent brand selection approach. The optimal stent to use would be the stent brand with the lowest HR for MACE when $HR_{\text{sirolimus}}$ is compared to $HR_{\text{paclitaxel}}$ for each individual lesion.

Statistical Methods

All analyses were done according to the intention to treat principle and performed by use of SPSS 17.0 statistical package [1]. The different subgroups had different numbers of patients or lesions. The statistical power to detect different effects on MACE varied accordingly. The subgroup sizes were not necessarily large enough to obtain power to determine whether any characteristic was of statistical significance. Consequently, our backward stepwise multivariate Cox regression analysis was not based on statistical significance. Instead we included off label characteristics that was correlated to a relative change in hazard for MACE of at least 25% (*i.e.* a HR of ≥ 1.25 or ≤ 0.8). Afterwards we assessed the validity of the result by use of conventional stepwise regression now based upon significance levels.

Multivariate Cox regression analysis equations were developed for MACE. For each lesion we calculated the HR connected to the use of either the paclitaxel-eluting ($HR_{\text{paclitaxel}}$) or the sirolimus-eluting ($HR_{\text{sirolimus}}$) stent brand for the specific off-label combination. First all 18 off-labels were forced into the model. Then we identified that off-label characteristic with least clinical importance (identified by a HR closest to 1.0). This off-label characteristic was removed. The remaining 17 off-labels were forced into the model and a new off label closest to 1.0 was identified and removed. This stepwise regression was repeated until all HR were outside 0.8 - 1.25. The model was tested for statistically significant interaction by a correlation regression table. The assumption of constant proportional hazard was tested by log minus log plots. The same method was repeated in the group of patients with only one lesion in order to assure independent variables in the equations. Thereby the HR obtained in the total group of lesions could be checked for discrepancies.

$$HR_{\text{stent.brand}} = HR_{\text{off-1}} * HR_{\text{off-2}} * HR_{\text{off-3}} * \dots * HR_{\text{off-19}}$$

The equation above contain to the left a $HR_{\text{stent.brand}}$ being a proportional hazard with the hazard for MACE for a lesion with some off-label characteristics in the numerator divided by the hazard for MACE for a lesion with zero off-label characteristics in the denominator: If an off-label characteristic is not present the corresponding $HR_{\text{off-number}}$ is replaced by the factor 1. By calculating the $HR_{\text{stent.brand}}$ for a specific off-label combination for each stent brand two different HR's may be found. By example $HR_{\text{paclitaxel}} = 1.20$ and $HR_{\text{sirolimus}} = 1.60$. The two HR cannot be directly compared because the sirolimus eluting stent appears to hold a MACE rate of 90% of that of the paclitaxel eluting stent groups. Consequently the sirolimus eluting stent may possess a $HR_{\text{sirolimus}}$ that is a fraction higher than the $HR_{\text{paclitaxel}}$ and still be the better stent brand choice. A simple way to enable direct comparison is to multiply the $HR_{\text{sirolimus}}$ by 0.9 and achieve a corrected $HR_{\text{sirolimus}} = 1.60 \times 0.9 = 1.44$. In this example the paclitaxel eluting stent should be selected to use in that specific lesion because 1.20 is lower than 1.44.

These HR's were calculated from the Cox regression equations on off-label characteristics with an impact on MACE of at least 25%. The lesions treated by stent brands with the “lowest or at least equal” HR are defined to have been treated with the optimal stent brand. Lesions treated by stent brands with highest HR are defined to have been treated with the worst stent brand. The MACE rate for lesions treated by the optimal stent was compared to the MACE rate for the sirolimus eluting stent group. This stent was chosen because a meta-analysis has found the sirolimus eluting stent to be significantly better than the paclitaxel eluting stent [3]. The comparison would reflect the effect of an individualized stent brand selection approach versus a generalized stent brand se-

lection approach.

4. Results

A total of 1065 patients with 1481 treated lesions were randomized to sirolimus-eluting and 1033 patients with 1407 treated lesions to paclitaxel-eluting stent implantation. The five year MACE rate was 20.8% for lesions treated by a sirolimus-eluting stents and was 22.9% for lesions treated by a paclitaxel-eluting stents (log rank test, HR 0.90, 95% confidence interval 0.77 - 1.05, Chi square 1.77, $p = 0.18$, **Figure 1**).

In lesions with zero off-label characteristics we found a MACE rate of 16.7%. With an increasing number of off-label characteristics in each lesion we found a statistically significant stepwise increase in MACE rate up to 32.7% in lesions with 5 off-label characteristics (log rank test for trend, Chi square = 44.32, $df = 1$, $p < 0.0001$, **Figure 2**). The HR's for MACE was estimated for all off-label characteristics as well as for the off-label characteristics with an impact on MACE of at least 25% (HR outside 0.8 - 1.25, **Table 2**). According to the study randomization a lesion could be classified to having been treated either by the optimal stent with the “lowest or at least equal HR” or by the worst stent with the “highest HR”. By comparison between those two groups the optimal stent group had a HR for MACE of 0.74 compared to the worst stent group (log rank test, Chi square 14.42, $p = 0.0001$, $df = 1$, 95% confidence interval 0.63 - 0.86). The MACE rate for the optimal stent group was 18.8% compared to 20.8% for the sirolimus treated lesions equal to a HR of 0.90 (log rank test, Chi square 1.75, $p = 0.20$, $df = 1$, 95% confidence interval 0.76 - 1.06).

The sum of all $HR_{paclitaxel}$ and $0.9 * HR_{sirolimus}$ according to the randomization amounted to 4266 and corresponded to 628 MACE. Those lesions that happened to be treated by the worst stent brand with a higher HR might have had a lower MACE rate if treated by the alternative stent. If the HR for these lesions were replaced by the HR for the alternative and better stent then the virtual sum of $HR_{paclitaxel}$ and $0.9 * HR_{sirolimus}$ would have been 3500. This sum is 0.82 times the above mentioned 4266 corresponding to an expected MACE rate of 515 instead of the real MACE rate of 628. This risk reduction would be to a value of 0.82.

5. Discussion

The comparison of MACE rates between the two stent brands showed as expected nearly the same result using a lesion perspective ($n = 2888$) as with a patient perspective ($n = 2098$) [2].

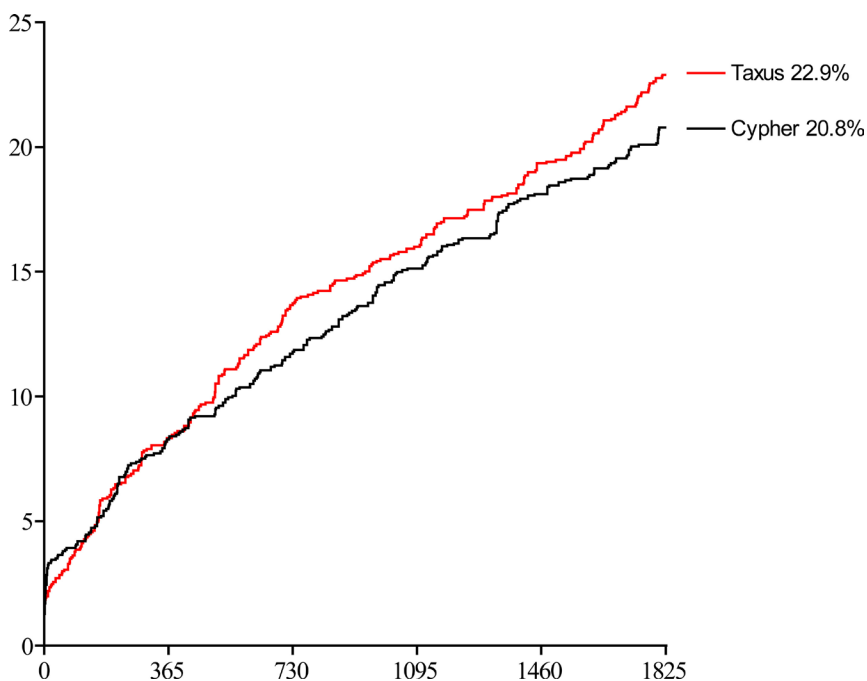


Figure 1. Cumulative proportions of lesions experiencing major adverse cardiac events during 5 years of follow up if treated by sirolimus(cypher)- or paclitaxel(taxus)-eluting stents. Abscissa: days. Ordinate: percentage.

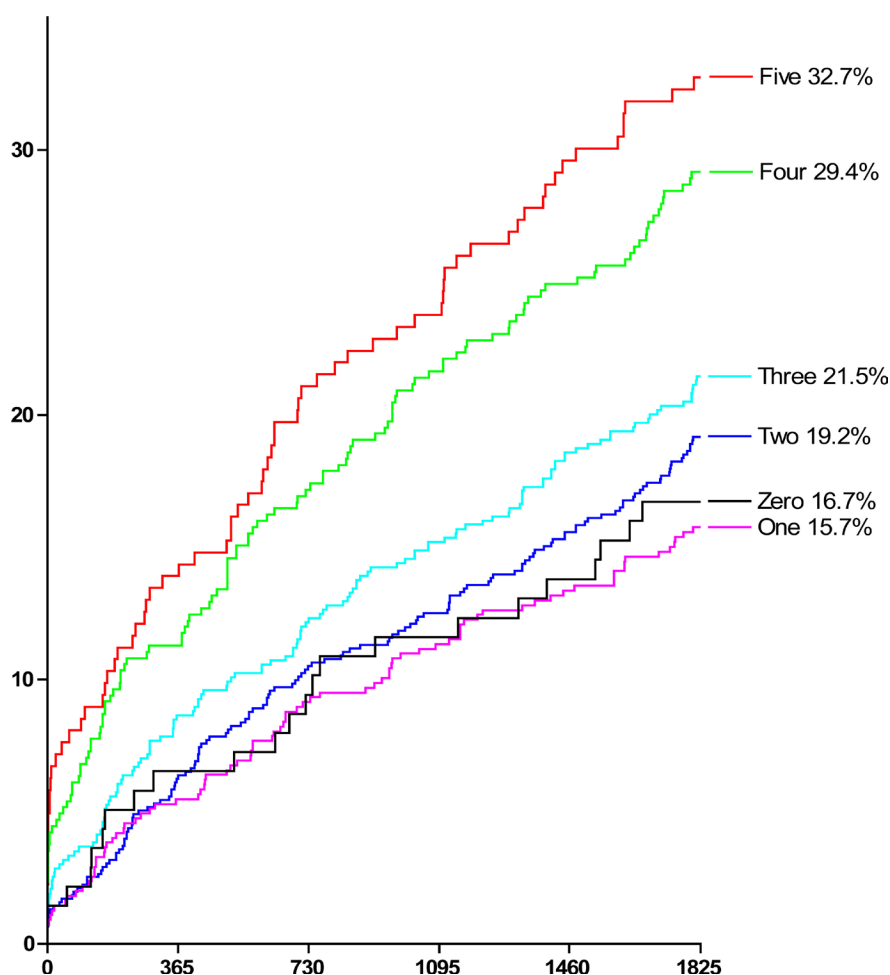


Figure 2. Cumulative proportions of lesions experiencing Major Adverse Cardiac Events during 5 years of follow up when grouped by Zero ($n = 138$), One ($n = 549$), Two ($n = 753$), Three ($n = 627$) and Four ($n = 427$) or Five ($n = 223$) concomitantly appearing off-label characteristics in each lesion. Abscissa: days. Ordinate: percentage.

In the present study of patients randomized in the SORT OUT II to one of the two first generation drug-eluting stents, we used 18 different off-label characteristics to show that MACE rates increased with an increasing number of off-label characteristics. This was also expected and has now been proven. The fact that the multiple stepwise regression analysis found some off-label characteristics connected to a HR < 1.0 may explain why the MACE curves for zero, 1, 2, 3, 4 and 5 concomitantly appearing off label characteristics are not just stacked lines in numerical order (Figure 2).

For each stent brand the HR connected to each off-label characteristics has now been estimated with up to 18 different off-label characteristics. This result is only applicable to the presently investigated stents and our Cox regression equations for the sirolimus- and the paclitaxel-eluting stent need further confirmation in other studies. These other studies have hardly tracked the same number or type of off-label characteristics as we have, and the extraction of the clinically most important ones (HR outside 0.8 - 1.25) are therefore specifically justified.

Multiple Cox regression analysis necessitates a lot of observations and a very large database to extract the equations from. If such a large database is non-existing it will be impossible to execute a stepwise exclusion based on statistical significance. But as sufficient data is often scarce, our way of selecting the variables after clinical importance in preference to statistical significance is a way to identify those parameters with important impact on health. Of course, statistical significance is the preferred method but in the present case it would have been at the cost of missed identification of characteristics of importance to clinical outcome, because the present study—despite its size—was not powered to investigate all subgroups. Our threshold for inclusion of a characteristic into the equations requires an impact on HR of at least 25% in MACE. It is reassuring, that 14 of the 18

Table 2. The impact on MACE from off-label use. First column is the off-label number. Second column is the description of the off-label item grouped for each stent brand. Third column is the hazard ratio (HR) for MACE with all 18 off-label characteristics forced into the model. Fourth and fifth columns contain the 95% confidence interval (CI) for the HR. Sixth column contains the p-value for the HR. The last columns are repetitions of column three through six but now only with the off-label characteristics that have an effect on MACE of at least 25% (HR outside the range 0.80 - 1.25).

		MACE			MACE change > 25%				
		HR	95% CI		P<	HR	95% CI		P<
Paclitaxel eluting stent group			Lower	Upper			Lower	Upper	
1	Use of stent in a restenotic lesion	2.12	1.37	3.30	0.001	2.31	1.52	3.50	0.001
2	Use of stent in a graft	6.28	3.53	11.20	0.001	6.21	3.58	10.75	0.001
3	Use of stent in the left main coronary artery	1.24	0.50	3.10	0.644				
4	Use of stent within 5 ostium	0.99	0.74	1.33	0.970				
5	Use of stent in bifurcation lesion	1.55	1.09	2.20	0.014	1.63	1.16	2.29	0.005
6	Use of a stent in an occlusion	0.73	0.50	1.08	0.114	0.72	0.49	1.05	0.087
7	Use of nominal stent diameter smaller than 2.5 mm	1.47	1.03	2.09	0.033	1.48	1.05	2.09	0.027
8	Use of more than one stent in the same lesion	1.94	1.38	2.73	0.001	1.93	1.50	2.50	0.001
9	Use of sum of stent length more than 20 mm	1.00	0.73	1.38	0.989				
10	Use of stent in angulated lesion > 45 degree	1.05	0.78	1.42	0.747				
11	Use of stent in lesion with severe proximal tortuosity	0.89	0.65	1.21	0.447				
12	Use of stent in lesion with visible trombus	0.73	0.44	1.21	0.217	0.79	0.50	1.26	0.317
13	Use of stent with inability to protect major side branches	0.82	0.61	1.09	0.173				
14	Use of stent in patients with STEMI	1.23	0.84	1.80	0.288				
15	Use of stent in patients with non-STEMI or unstable angina	1.05	0.82	1.36	0.684				
16	Use of stents in more than one lesion	1.18	0.92	1.52	0.189				
17	Use of stent in patients with diabetes	1.41	1.07	1.85	0.015	1.42	1.08	1.85	0.012
18	Use of stent in female gender	0.82	0.62	1.10	0.184				
Sirolimus eluting stent group									
1	Use of stent in a restenotic lesion	2.75	1.46	5.16	0.002	2.72	1.47	5.03	0.001
2	Use of stent in a graft	3.60	1.51	8.62	0.004	3.68	1.57	8.66	0.003
3	Use of stent in the left main coronary artery	1.78	0.78	4.07	0.173	1.98	0.88	4.42	0.098
4	Use of stent within 5 ostium	1.62	1.24	2.11	0.001	1.58	1.21	2.06	0.001
5	Use of stent in bifurcation lesion	1.72	1.23	2.42	0.002	1.67	1.20	2.34	0.003
6	Use of a stent in an occlusion	0.83	0.52	1.32	0.438				
7	Use of nominal stent diameter smaller than 2.5 mm	1.73	1.25	2.40	0.001	1.73	1.25	2.38	0.001
8	Use of more than one stent in the same lesion	0.96	0.68	1.38	0.838				
9	Use of sum of stent length more than 20 mm	1.20	0.89	1.63	0.234				
10	Use of stent in angulated lesion > 45 degree	1.28	0.95	1.73	0.102	1.42	1.08	1.86	0.011
11	Use of stent in lesion with severe proximal tortuosity	1.27	0.96	1.67	0.093				
12	Use of stent in lesion with visible trombus	0.86	0.52	1.40	0.539				
13	Use of stent with inability to protect major side branches	1.15	0.87	1.53	0.319				
14	Use of stent in patients with STEMI	1.42	1.01	2.01	0.046	1.29	0.95	1.75	0.105
15	Use of stent in patients with non-STEMI or unstable angina	1.19	0.92	1.53	0.192				
16	Use of stents in more than one lesion	1.36	1.06	1.74	0.014	1.37	1.07	1.74	0.012
17	Use of stent in patients with diabetes	1.11	0.82	1.49	0.497				
18	Use of stent in female gender	0.72	0.55	0.96	0.024	0.72	0.54	0.95	0.021

included characteristics (14 of 18) in the two regression equations were in fact of statistical significance. Even smaller effects on MACE may be justified but it takes more observations than what the present investigation contain. A meta-analysis has found the sirolimus eluting stent to be significantly better than the paclitaxel eluting stent [3]. The sirolimus-eluting stent in our study was slightly superior with a relative MACE rate of 0.90 compared to that of the paclitaxel-eluting stent. Even though that result was ns the meta-analysis result justified that the HR concerning sirolimus-eluting stent should be multiplied by 0.9 to enable translation to a direct comparison of the expected hazard for MACE between the two stents. It was then possible to determine whether the initially randomized stent in fact happened to be the worst stent (posses the highest HR) or the presumed optimal stent (lower or at least equal HR).

Compared to a general use of only one stent brand the MACE rates may be reduced by 10% - 18% if the combination of off-label characteristics was used to guide stent selection in each individual case. Such effect size may be worth looking for in newer generation drug eluting stents.

Clinical Perspective of the Individualized Stent Brand Selection Approach

As drug-eluting stents are approaching maximal obtainable stent performance any new invention or improvement can only induce modest changes in clinical outcome. The traditional approach is to identify the best stent to use in a population—which unfortunately will include cases where an alternative stent would have been a better choice. Opposed to this general approach is an individualized stent brand selection approach where each individual patient's and lesions off-label characteristics are important and are used to determine which stent brand to select. Such an individualized approach may help to ensure, that we are in fact treating each case with the optimal stent brand for that particular off-label combination. As a consequence of an individualized stent brand selection approach we may potentially yield an outcome for the population which is superior to the outcome obtained by a general stent brand selection approach—even though one stent brand might have proven—at the average—to be generally the better stent brand (Figure 3).

Introduction of a new stent should be accompanied by clinical investigations with an intense characterization of both lesions and participating patients followed by recording of clinical events. From such a source the calculation of the HR-equation to use in the future may be extracted. If all new stents were characterized by an equa-

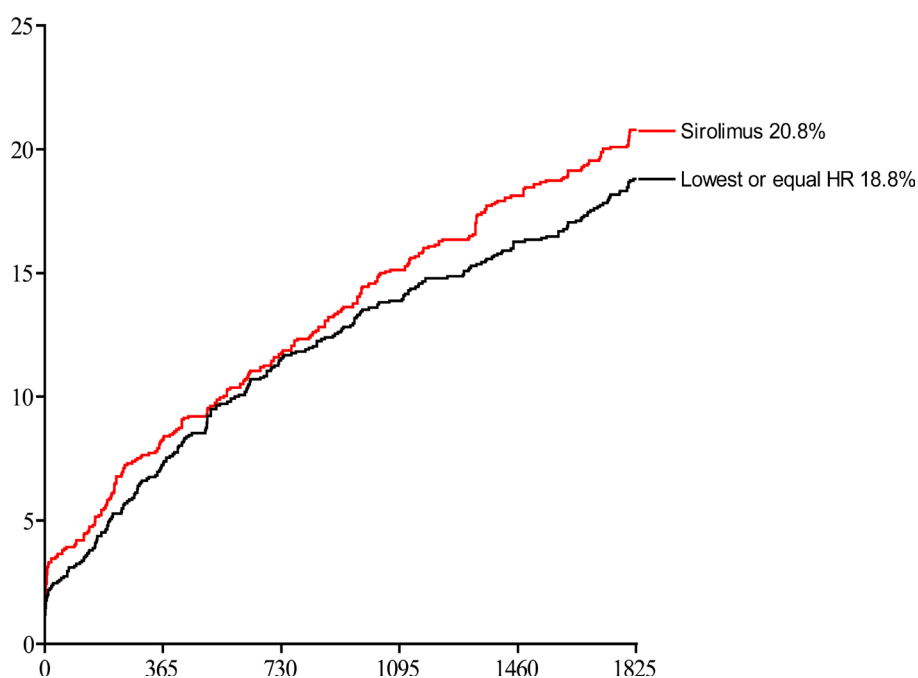


Figure 3. Cumulative proportions of lesions experiencing major adverse cardiac events during five years follow up. The lesions were grouped into one group that had received the optimal stent at the randomization time according to the individualized stent brand selection approach. The other group is the sirolimus(cypher)-eluting stent group representing the group treated in a generalized stent brand selection approach with the same stent brand to all lesions. Abscissa: days. Ordinate: percentage.

tion for individualized stent brand selection, then each individual with exactly those combinations of patient and lesion characteristics could be entered into the different equations, and eventually the stent brand with the lowest HR would be a fairly good choice.

6. Conclusion

There was no statistically significant difference in MACE rates between sirolimus and paclitaxel treated lesions. With increasing number of concomitantly appearing off-label characteristics we found a statistically significant stepwise increase in MACE rate from 16% to 32% in cases with 5 off-label characteristics. For each stent brand the HRs for MACE connected to 18 different off-label characteristics were estimated. If the clinically most important off-label characteristics are utilized to select the presumed better stent in each singular case then the populations MACE rate may be reduced by 10% - 18%. If introduction of all new stents was accompanied by HR for MACE for each off-label characteristic then the optimal stent brand to use in each case may be identified. This might increase stent performance and the clinical outcome for the population thereby would be optimized.

7. Study Limitation

The stents in the present study are no longer in use, and the exact HR for each off-label characteristic is now unimportant. Rather, the HR values serve to exemplify the impact of an individualized stent brand selection approach. It is therefore of no importance that the two stents are not in use anymore. Even a new study on the same matter, with present day stents would probably be outdated when the results of five years observation are ready. But present day stent performance may potentially be improved if the individualized stent brand selection approach were applied. The concept may therefore be important to investigate.

The MACE rate is not very lesion specific outcome measure. Multiple Cox regression with inclusion of 18 parameters requires a lot of events. The study sample should be much higher if the outcome parameter was focused to be lesion specific like a composite of proven re-stenosis and definite stent thrombosis. The present 2888 lesions observed for 5 years did not produce enough such events. The use of MACE is still justified because it merely serves to illustrate the impact of an individualized stent brand selection approach.

The Cox regression equations are drawn from the 2888 lesions, and are subsequently used to identify if a lesion in fact had been treated by an optimal or the worst stent brand. The correct approach would have been to use the equations in another sample of lesions, but this has not been possible because our lesion sample is the only sample with knowledge of 18 of-label characteristics. Being aware of this major drawback we still accept to commit such an error because it serves to illustrate the individualized stent selection principle. When comparing the MACE curve for lesions treated with sirolimus to the lesions treated with the presumed optimal stent brand we found 10% reduction in hazard for MACE among the latter group. When calculating the risk reduction we found an effect of 18%. Notably, the true effect among sirolimus- or paclitaxel-eluting stents remains unknown.

There is uncertainty of independence between lesions because some patients contributed with more than one lesion. The Cox regression analysis was consequently repeated in patients with only one lesion in order to assure that the HRs did not differ importantly from the ones deducted from the $n = 2888$ sample. If we had only utilized those patients the number of off-label characteristics had to be reduced due to insufficient number of events. As the HRs were only slightly changed we accepted to use the 2888 lesions—again simply because they merely serve to exemplify the individualized stent selection approach.

The correct proof of concept would necessitate a new randomized trial. Thus, **Figure 3** may only be used to visualize the concept. The magnitude of the maximally achievable effect of an individualized stent brand selection approach remains to be proven.

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Conflicts of Interest

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