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Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial)

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KEYWORDS

- ACS/NSTE-ACS
- drug-eluting stent
- STEMI

Abstract

Aims: The optimal duration of DAPT in ACS patients treated with DES is still unclear. Therefore, the aim of the current study was to investigate a short versus a standard 12-month DAPT regimen in ACS patients undergoing new-generation DES implantation.

Methods and results: REDUCE was a prospective, open-label, multicentre, investigator-initiated study that randomised 1,496 ACS patients after treatment with the COMBO stent to either three (n=751) or 12 months (n=745) of DAPT. The primary study endpoint was a composite of all-cause mortality, myocardial infarction, stent thrombosis, stroke, target vessel revascularisation and bleeding at 12 months. No difference was observed in the demographic and clinical characteristics between the two groups, except for gender (p=0.01). At one-year follow-up, non-inferiority of three- versus 12-month DAPT in the primary endpoint was met (8.2% vs 8.4%, $p_{non\text{-}inferiority}$<0.001). The similar outcome between the two groups was confirmed at two-year follow-up (11.6% vs 12.1%, p=0.76), with no significant difference in overall mortality (3.1% vs 2.2%, p=0.27), cardiac mortality (1.8% vs 1.1%, p=0.28), stent thrombosis (1.6% vs 0.8%, p=0.16) and major bleeding (3.3% vs 4.0%, p=0.46).

Conclusions: The results show that, among ACS patients treated with the COMBO stent, three months is non-inferior to 12 months of DAPT. However, given the numerically higher rates of mortality and ST in the three-month DAPT group, one-year DAPT should still be recommended in ACS until more information becomes available. A three-month DAPT strategy should be considered only if clinically mandated.

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Abbreviations

ACS	acute coronary syndrome
ASA	aspirin
BARC	Bleeding Academic Research Consortium
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
MI	myocardial infarction
NSTEMI	non-ST-elevation myocardial infarction
PCI	percutaneous coronary intervention
REDUCE	Randomised Evaluation of short-term DUal antiplatelet therapy in patients with acute coronary syndrome treated with the COMBO dual-therapy stEnt
ST	stent thrombosis
STEMI	ST-elevation myocardial infarction
TVR	target vessel revascularisation

Introduction

Due to the significant improvement in antithrombotic therapies and stent technologies, percutaneous revascularisation is currently the most preferred therapy for the treatment of coronary artery disease (CAD), especially in the setting of acute coronary syndromes (ACS). However, the optimal duration of dual antiplatelet therapy (DAPT) remains under debate. In fact, first-generation drug-eluting stents (DES) were associated with higher rates of late stent thrombosis (ST) and mortality[1,2], leading to the recommendation of 12-month DAPT after DES implantation. However, robust evidence to support this antithrombotic strategy in ACS is still lacking, as it was adopted from old ACS trials on the impact of DAPT in populations with low rates of intervention[3]. Although prolonged DAPT may prevent thrombotic complications, this benefit may be counterbalanced by the subsequent increase in major bleeding complications, especially with newer antiplatelet agents (i.e., ticagrelor or prasugrel)[4,5]. However, efforts have recently been made in the search for new stent technologies to promote vascular healing and endothelial repair[6-9] that may justify a shorter DAPT duration. In a recent randomised trial including patients with non-ST-elevation myocardial infraction (NSTEMI), the COMBO™ dual-therapy stent (OrbusNeich, Hong Kong, China) was non-inferior in terms of target vessel failure to the XIENCE stent (Abbott Vascular, Santa Clara, CA, USA), with a better stent strut coverage, as shown by OCT (91.3% vs 74.8%) ($p<0.001$)[10]. The Randomised Evaluation of short-term DUal antiplatelet therapy in patients with acute coronary syndrome treated with the COMBO dual-therapy stEnt (REDUCE trial) is the first study conducted in ACS-only patients treated with a new-generation DES to test the hypothesis that treatment with DAPT for three months is non-inferior compared to standard 12-month DAPT with regard to a combined safety and efficacy endpoint. We report the final two-year results of the REDUCE trial.

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Methods

STUDY DESIGN AND RANDOMISATION

The REDUCE trial (NCT02118870) was an investigator-initiated, prospective, open-label, multicentre, randomised study with two groups, as previously described[11]. Briefly, ACS patients who were successfully treated with the COMBO stent were subsequently randomised, after obtaining informed consent, during index hospitalisation (before discharge), in a 1:1 ratio, to either three-month or 12-month DAPT. Patients requiring staged PCI received their secondary PCI during index hospitalisation prior to randomisation.

Treatment assignments were performed centrally through a dedicated website as part of the electronic case report form according to computer-generated random permuted blocks with stratification by site. The intervention (DAPT administration) was not blinded. The central ethics committee (Isala Hospital, Zwolle, the Netherlands) initially approved the study. The ethics committees and competent authorities of each participating centre **(Supplementary Table 1)** approved the study. The study complies with the Declaration of Helsinki.

TREATMENT AND FOLLOW-UP PROCEDURES

Eligible patients **(Supplementary Table 2)** were treated with aspirin (ASA) and a $P2Y_{12}$ inhibitor. Prasugrel and ticagrelor were preferred over clopidogrel. The final choice of $P2Y_{12}$ inhibitor was at the discretion of the treating physician. Patients received DAPT according to their randomisation and continued on ASA monotherapy afterwards. If contraindications for ASA emerged, monotherapy with $P2Y_{12}$ inhibition was allowed. In case additional coronary intervention was required, only patients in whom these procedures were performed with a COMBO stent, and before discharge, were eligible to be randomised. Physical follow-up visits to the outpatient clinic were performed at three and 12 months, whereas a telephone contact was planned at six months and 24 months.

STUDY ENDPOINTS

The primary endpoint was the composite occurrence of all-cause death, myocardial infarction (MI; based on the third universal definition[12]), stent thrombosis (ST; definite/probable, Academic Research Consortium [ARC] definition[13]), stroke, target vessel revascularisation (TVR) and bleeding (Bleeding Academic Research Consortium [BARC] 2/3/5[14]) within the 12-month follow-up. The independent clinical events committee, while blinded to the randomisation of the patients, adjudicated all serious adverse events and determined whether any revascularisation event was related to the index procedure target vessel. A detailed list of primary and all secondary endpoints is provided in **Supplementary Table 3**.

STATISTICAL ANALYSIS

Continuous data are expressed as median (25^{th}-75^{th} percentile) and categorical data as percentages. The analysis of variance was appropriately used for continuous variables. χ^2 testing or the Fisher's exact test was used for categorical variables.

The sample size calculation was based on a non-inferiority design, with a one-sided log-rank test for comparison of independent survival curves at the 2.5% significance level, a power of 80%, and a margin for non-inferiority of 5%. Based on a recent study including ACS patients treated with DES[15], we assumed an event

rate of the primary endpoint of 12% in both DAPT groups with a counterbalance of thrombotic and bleeding complications. On the basis of this assumption and an extension for dropouts, 750 patients per group were required to demonstrate non-inferiority.

The primary endpoint was evaluated after completion of the one-year follow-up. Statistical analyses were performed by an independent contract research organisation (Diagram BV, Zwolle, the Netherlands). Data acquisition and analyses were performed independently. Primary and secondary analyses were based on the intention-to-treat population. Additionally, a pre-specified landmark analysis of the primary endpoint without TVR was performed from three to 12 months, since treatment during the first three months was equal in both groups. Analyses based on the per protocol analysis populations were considered secondary and confirmatory. With the sole exception of the primary endpoint, all other analyses were tested for superiority. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

From June 2014 to May 2016, 1,500 eligible ACS patients undergoing successful COMBO stent implantation were included in the study, as described in the protocol. Four patients withdrew their informed consent soon after randomisation, leaving 1,496 patients randomised to three (n=751) or 12 months (n=745) of DAPT. The study flow chart is shown in **Supplementary Figure 1**. Baseline characteristics are shown in **Table 1**, **Table 2**, and **Supplementary Table 4**. No differences were observed between the groups, except for gender (17.4% vs 22.7%, p=0.01). STEMI was observed in almost 50% in both groups. Median DAPT duration in the two groups was 91 (89-96) vs 365 (363-369) days; p<0.001, respectively. Almost 60% of patients were discharged on new adenosine-diphosphate (ADP) antagonists (prasugrel or ticagrelor) **(Supplementary Table 5)**.

PRIMARY STUDY ENDPOINT

As detailed in **Supplementary Figure 1**, a total of 1,462 patients (729 in the three-month and 733 in the 12-month DAPT groups) were analysed. No difference was observed in the primary endpoint (8.2% vs 8.4%, risk difference –0.0022, upper limit 95% confidence interval [CI]: 0.027, p<0.001; HR 0.97, 95% CI: 0.68-1.39). The result was confirmed after adjustment for gender (adjusted HR 0.96, 95% CI: 0.67-1.36, p=0.80). Kaplan-Meier curves are shown in **Figure 1**.

No difference between three- and 12-month DAPT was observed in the occurrence of the primary endpoint in the per protocol (8.1% vs 6.8%, p<0.001; HR 1.19, 95% CI: 0.78-1.83) and actual treatment analyses (8.0% vs 7.3%, p<0.001; HR 1.10, 95% CI: 0.72-1.66).

SECONDARY STUDY ENDPOINTS

As detailed in **Supplementary Figure 1**, a total of 1,460 patients (733 in the three-month and 727 in the 12-month DAPT groups) were analysed. The composite occurrence of all-cause death,

Table 1. Baseline characteristics.

	3-month DAPT (N=751)	12-month DAPT (N=745)
Age, years (median, Q1-Q3, n)	61.0 (53.0-69.0) (n=751)	60.0 (52.0-68.0) (n=745)
Female gender, n/N (%)*	131/751 (17.4%)	169/745 (22.7%)
Diagnosis at admission, n/N (%)		
STEMI	370/751 (49.3%)	336/744 (45.2%)
Non-STEMI	267/751 (35.6%)	305/744 (41.0%)
Unstable angina	114/751 (15.2%)	103/744 (13.8%)
Diabetes mellitus, n/N (%)	162/750 (21.6%)	145/744 (19.5%)
Smoking, n/N (%)	313/744 (42.1%)	314/736 (42.7%)
Hypercholesterolaemia, n/N (%)	346/748 (46.3%)	333/742 (44.9%)
Hypertension, n/N (%)	379/748 (50.7%)	375/740 (50.7%)
Family history of CAD, n/N (%)	260/743 (35.0%)	265/737 (36.0%)
Previous ACS, n/N (%)	94/751 (12.5%)	88/744 (11.8%)
Previous PCI, n/N (%)	88/751 (11.7%)	73/745 (9.8%)
Previous CABG, n/N (%)	21/751 (2.8%)	21/745 (2.8%)
Previous CVA, n/N (%)	11/751 (1.5%)	15/745 (2.0%)
Killip class upon arrival at PCI centre >1, n/N (%)	75/735 (10.2%)	84/725 (11.6%)

All *p*-values=NS ($p>0.05$). *$p=0.01$. ACS: acute coronary syndromes; CABG: coronary artery bypass graft; CAD: coronary artery disease; CVA: cerebrovascular accident; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

Table 2. Angiographic and procedural characteristics.

	3-month DAPT (N=751)	12-month DAPT (N=745)
Multivessel disease, n/N (%)	271/750 (36.1%)	252/745 (33.8%)
LAD, n/N (%)	360/750 (48.0%)	329/745 (44.2%)
Initial TIMI flow 0 (culprit vessel), n/N (%)	199/740 (26.9%)	177/728 (24.3%)
Radial access, n/N (%)	564/741 (76.1%)	566/736 (76.9%)
Balloon predilatation, n/N (%)	524/748 (70.1%)	513/745 (68.9%)
TIMI 3 post (culprit lesion), n/N (%)	745/748 (99.6%)	743/743 (100.0%)
Number of stents used >2, n/N (%)	131/750 (17.4%)	135/745 (18.1%)
Total stent length, mm (median, Q1-Q3, n)	23.0 (18.0-28.0) (n=749)	23.0 (18.0-28.0) (n=744)
Post-dilatation, n/N (%)	430/749 (57.4%)	429/745 (57.6%)
PCI successful (culprit lesion), n/N (%)	745/750 (99.3%)	743/745 (99.7%)
Thrombosuction, n/N (%)	94/750 (12.5%)	101/745 (13.6%)
IABP, n/N (%)	1/750 (0.1%)	1/745 (0.1%)
Additional segments dilated during hospitalisation, n/N (%)	152/750 (20.3%)	163/745 (21.9%)

All differences are non-significant ($p>0.05$). IABP: intra-aortic balloon pump; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction

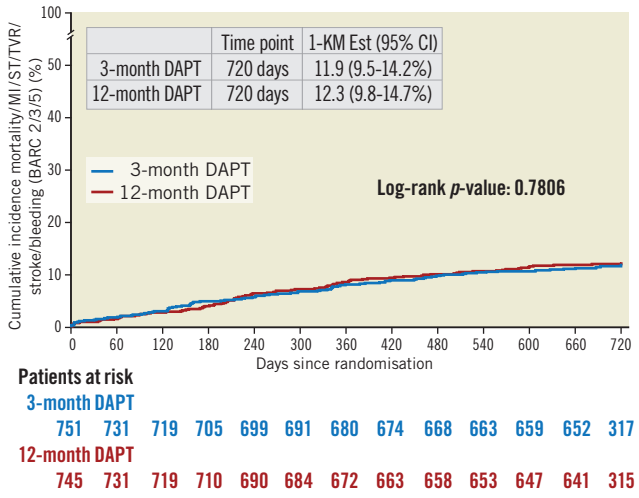


Figure 1. *Kaplan-Meier curves for the primary study endpoint.*

MI, ST, stroke, TVR and bleedings was observed in 173 patients (11.8%) at two-year follow-up, without any significant difference between three and 12 months of DAPT (11.6% vs 12.1%, HR 0.96, 95% CI: 0.71-1.29, p=0.76). The result was confirmed after adjustment for gender (adjusted HR 0.95, 95% CI: 0.70-1.28, p=0.81). Kaplan-Meier curves are shown in **Figure 1**.

At two-year follow-up, no difference between three and 12 months of DAPT was observed in the occurrence of the composite of all-cause death, MI, ST, stroke, TVR or bleeding in the per protocol (11.2% vs 10.8%, p=0.82, HR 1.05, 95% CI: 0.74-1.49) and actual treatment analyses (11.1% vs 11.2%, p=0.97; HR 1.0, 95% CI: 0.71-1.41).

As shown in **Table 3** and **Supplementary Table 6**, no statistically significant difference was observed between three- and 12-month DAPT in any secondary endpoint at one- and two-year follow-up. A total of 39 deaths (2.7%) were observed at two-year follow-up, with 21 of them (54%) classified as cardiovascular **(Supplementary Table 7)**. A non-significant difference in cardiac mortality was observed between the groups (1.8% vs 1.1%, p=0.28). An overall low rate of definite/probable ST was observed in our study (18 events, 1.2%), without any significant difference between the groups (1.6% vs 0.8%, p=0.16). Kaplan-Meier curves are shown in **Figure 2**. A non-significantly higher rate of major bleeding was observed with 12 months as compared to three months of DAPT (4% vs 3.3%, p=0.46) **(Supplementary Figure 2)**. No difference was observed in other secondary endpoints **(Supplementary Figure 3-Supplementary Figure 6)**.

As shown in **Supplementary Figure 7**, in a pre-specified landmark analysis no statistically significant difference in the occurrence of all-cause death, MI, definite or probable ST, stroke, or bleeding (BARC 2, 3, 5) was observed between the groups including only patients who were free from events at three-month follow-up (p=0.76).

SUBGROUP ANALYSES

The difference in primary outcome between three- and 12-month DAPT was explored (for superiority) in several high-risk subsets of patients, defined according to age, gender, diabetes, chronic kidney disease and clinical presentation (STEMI vs NSTEMI/unstable angina [UA]). Results were quite consistent across the subgroups, including gender, without any significant statistical interaction at one- **(Supplementary Figure 8)** and two-year follow-up **(Figure 3)**.

Discussion

The REDUCE trial is the first study restricted to ACS patients comparing a short (three-month) versus a standard 12-month DAPT strategy after successful stent implantation. In our study, among ACS patients treated with the COMBO stent, no difference was observed between three and 12 months of DAPT at one- and two-year follow-up.

OPTIMAL DAPT DURATION IN ACS

The optimal duration of DAPT after DES implantation in ACS is still a matter of debate, because thrombotic risk needs to be balanced with bleeding risk.

Table 3. Clinical outcome at two-year follow-up according to intention-to-treat analysis.

2-year follow-up	3-month DAPT (N=733)	12-month DAPT (N=727)	$p_{superiority}$ log-rank	HR [95% CI]
All-cause mortality, MI, stent thrombosis, stroke, TVR or bleeding (BARC 2/3/5)	85/733 (11.6%)	88/727 (12.1%)	0.764	0.96 [0.71-1.29]
Bleeding (BARC 2/3/5)	24/733 (3.3%)	29/727 (4.0%)	0.465	0.82 [0.48-1.41]
All-cause mortality, def/prob ST, stroke, MI, TVR	64/733 (8.7%)	66/727 (9.1%)	0.832	0.96 [0.68-1.36]
All-cause mortality, def/prob ST, stroke or MI	45/733 (6.1%)	41/727 (5.6%)	0.685	1.09 [0.72-1.67]
All-cause mortality	23/733 (3.1%)	16/727 (2.2%)	0.267	1.44 [0.76-2.72]
Cardiac mortality	13/733 (1.8%)	8/727 (1.1%)	0.280	1.62 [0.67-3.92]
MI	26/733 (3.5%)	22/727 (3.0%)	0.577	1.18 [0.67-2.08]
Definite/probable ST	12/733 (1.6%)	6/727 (0.8%)	0.160	2.00 [0.75-5.32]
TVR	36/733 (4.9%)	34/727 (4.7%)	0.834	1.06 [0.66-1.69]
Stroke	2/733 (0.3%)	4/727 (0.6%)	0.450	0.50 [0.09-2.71]

BARC: Bleeding Academic Research Consortium; MI: myocardial infarction; ST: stent thrombosis; TVR: target vessel revascularisation

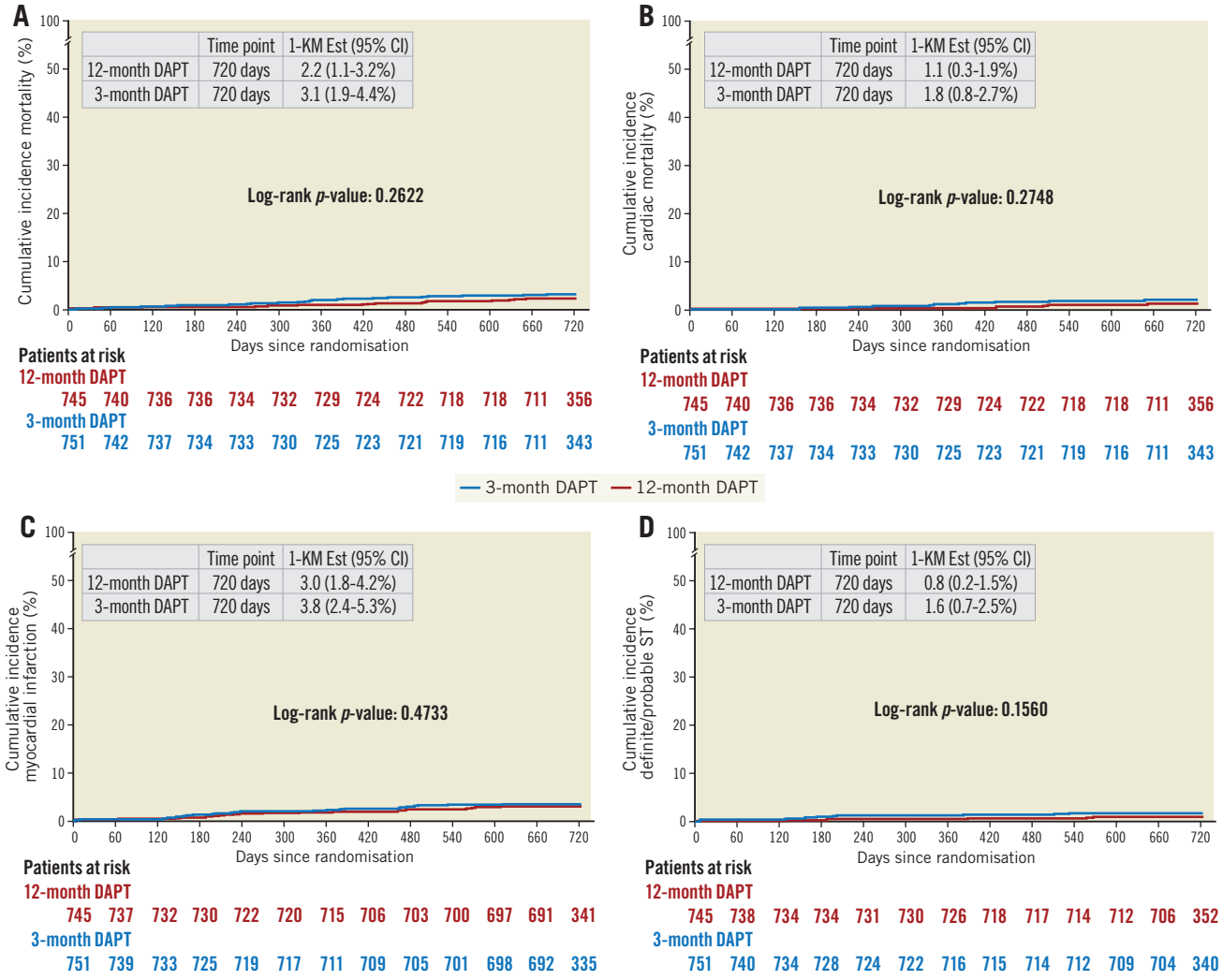


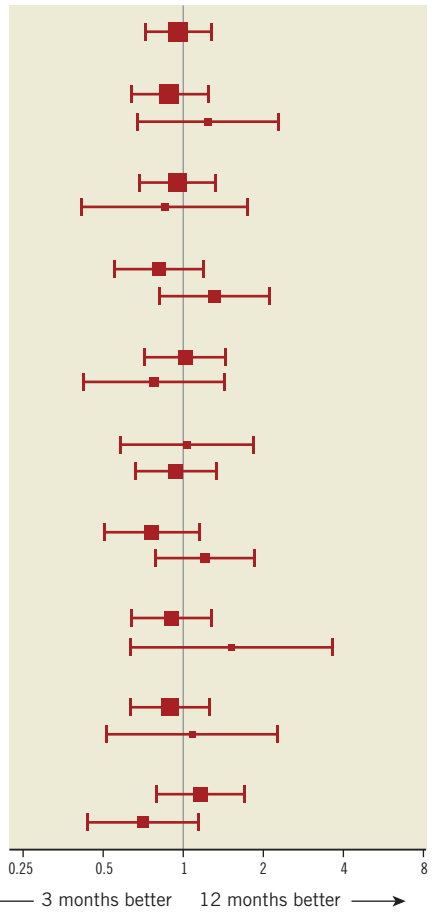
Figure 2. *Kaplan-Meier curves. A) Mortality. B) Cardiac mortality. C) Myocardial infarction. D) Definite/probable stent thrombosis.*

While protecting from thrombotic complications, a significant increase in bleedings may be expected in case of prolonged DAPT that may counterbalance the net benefit. This may be of relevance in consideration of the higher risk profile of current patients undergoing PCI, at higher risk of bleedings, which may impact on survival.

Based on the CURE trial[3], scientific societies have been in favour of DAPT after an ACS. However, this trial was conducted 20 years ago, whereas new-generation DES technologies have been shown to minimise the risk of ST.

So far, only a few dedicated trials have investigated this issue in ACS, especially in the era of new ADP antagonists and new-generation DES. In the multicentre DAPT STEMI trial[16] a total of 870 STEMI patients treated with primary angioplasty and the Resolute Onyx™ stent (Medtronic, Minneapolis, MN, USA) who were taking DAPT and were event-free at six months were randomised 1:1 to single antiplatelet therapy or to DAPT for an additional six months. New ADP antagonists were used similarly in both groups (58%). All patients who were randomised were then followed for another 18 months (i.e., 24 months after the primary PCI). The primary endpoint (a composite of all-cause mortality, any MI, any revascularisation, stroke, and Thrombolysis In Myocardial Infarction [TIMI] major bleeding at 18 months after randomisation) occurred in 4.8% of patients receiving single antiplatelet therapy versus 6.6% of patients receiving DAPT ($p_{non\text{-}inferiority}$=0.004). In the multicentre SMART-DATE trial[17], a total of 2,712 ACS patients treated with PCI and DES with permanent (XIENCE or Resolute Onyx) or bioresorbable (Orsiro; Biotronik, Bülach, Switzerland) polymer were randomly assigned to six-month (n=1,357) and 12-month or longer DAPT (n=1,355). Clopidogrel was used in 79.7% of patients in the six-month DAPT and in 81.8% of patients in the 12-month DAPT groups. The primary endpoint (a composite of all-cause death, MI, or stroke at 18 months) occurred in 4.7% with six-month DAPT and in 4.2% with 12-month DAPT ($p_{non\text{-}inferiority}$=0.03). Although all-cause mortality did not differ significantly between six-month DAPT and 12-month DAPT (2.6% vs 2.9%, p=0.90) and neither did stroke (0.8% vs 0.9%, p=0.84) or ST (1.1% vs 0.7%, p=0.32), MI occurred more frequently in the six-month DAPT group than in

Subgroup	3-month DAPT Events/N (%)	12-month DAPT Events/N (%)	HR (95% CI)	p-value*
All	85/733 (11.6)	88/727 (12.1)	0.96 (0.71-1.29)	
Age				0.37
<75 years	62/633 (9.8)	69/630 (11.0)	0.89 (0.63-1.25)	
≥75 years	23/100 (23.0)	19/97 (19.6)	1.23 (0.67-2.26)	
Gender				0.77
Male	73/605 (12.1)	70/563 (12.4)	0.96 (0.70-1.34)	
Female	12/128 (9.4)	18/164 (11.0)	0.85 (0.41-1.77)	
Diagnosis				0.13
Non-STEMI	45/371 (12.1)	59/394 (15.0)	0.81 (0.55-1.19)	
STEMI	40/362 (11.0)	28/332 (8.4)	1.31 (0.81-2.12)	
Geographic region				0.46
European site	67/510 (13.1)	65/505 (12.9)	1.02 (0.72-1.43)	
Asian site	18/223 (8.1)	23/222 (10.4)	0.78 (0.42-1.44)	
Diabetes				0.79
Yes	24/157 (15.3)	21/141 (14.9)	1.03 (0.57-1.84)	
No	61/575 (10.6)	66/585 (11.3)	0.94 (0.66-1.33)	
Vessel disease				0.13
Single	39/471 (8.3)	52/481 (10.8)	0.76 (0.50-1.15)	
Multi	46/262 (17.6)	36/246 (14.6)	1.20 (0.78-1.86)	
Zwolle risk score				0.27
≥3	58/531 (10.9)	63/522 (12.1)	0.90 (0.63-1.28)	
>3	12/80 (15.0)	9/88 (10.2)	1.52 (0.64-3.60)	
CKD				0.63
GFR ≥60	64/617 (10.4)	72/617 (11.7)	0.88 (0.63-1.24)	
GFR <60	15/92 (16.3)	13/86 (15.1)	1.08 (0.51-2.27)	
$P2Y_{12}$				0.12
New $P2Y_{12}$	56/430 (13.0)	49/433 (11.3)	1.16 (0.79-1.70)	
Clopidogrel	29/303 (9.6)	39/294 (13.3)	0.71 (0.44-1.15)	



*p-value is the test of interaction between treatment and each subgroup unadjusted for multiplicity

Figure 3. *Forest plot showing the composite occurrence of all-cause death, MI, ST, stroke, TVR and bleeding (BARC 2/3/5) at two-year follow-up across several major subgroups of patients. CKD: chronic kidney disease*

the 12-month DAPT group (1.8% vs 0.8%, p=0.02). No significant difference was observed in the rate of BARC type 2/3/5 bleeding between the two groups (2.7% vs 3.9%, p=0.09).

In a recent comprehensive meta-analysis restricted to ACS which included 17,941 patients[18], a shorter DAPT strategy was associated with a reduction in bleedings, whereas no difference in cardiovascular mortality, MI or ST was observed with shorter versus standard 12-month DAPT.

REDUCE TRIAL

REDUCE is the first trial comparing, in a total of 1,496 ACS patients, a very short DAPT strategy (three months) versus a standard 12-month DAPT strategy. The use of a new-generation DES, the large inclusion of STEMI patients (almost 50%), and the predominant use of new ADP antagonists in almost 60% of the population make this study contemporary. Differently from DAPT-STEMI but similarly to SMART-DATE, patients were randomised during initial hospitalisation.

Our study showed that three-month DAPT was non-inferior to 12-month DAPT with regard to the primary endpoint (a composite of mortality, MI, ST, stroke, TVR or bleeding [BARC 2/3/5]). A similar outcome between the two groups was observed at two-year follow-up (11.6% vs 12.1%, respectively), and also confirmed in the per-protocol analysis, actual treatment analysis, and for major subgroups such as age, diabetic status, gender, type of ACS (STEMI versus NSTEMI/ACS) and kidney function.

No significant differences were observed in secondary endpoints (mortality, MI, ST, TVR and bleedings). A numerically higher occurrence of (cardiac) mortality and definite/probable ST was observed in the three-month DAPT group. However, these findings must be interpreted with caution. In fact, this study was not powered for these very low event rates. In addition, about half of the deaths were non-cardiovascular, and some were even observed when patients were still on DAPT. Nevertheless, these outcomes do not justify a liberal use of the shorter DAPT therapy. In fact, short DAPT should be applied only when clinically indicated, for example due to high bleeding risk.

The overall low rates of definite/probable ST at one-year follow-up (0.8%), despite the short DAPT duration in half of the population, may be explained by the use of a new-generation DES

with faster re-endothelialisation, whereas in TRITON-TIMI 38 and PLATO most of the patients received either BMS (about 50%) or first-generation DES. In fact, our data are consistent with other STEMI trials with new-generation DES[19].

Even though we included BARC 2 bleedings, domination of the primary endpoint by minor bleeding was not observed. Similarly, in the DAPT trial[20] there was only a difference of 1.6% in BARC 2 bleeding incidence between 12 and 30 months (3.1% in the continued DAPT group versus 1.5% in the placebo group). Furthermore, the recent PEGASUS trial[21] has shown that prolonged three-year ticagrelor in patients with previous MI reduced the rate of thrombotic complications, that was, however, counterbalanced by a higher risk of bleedings. In fact, a similar mortality was observed between ticagrelor and placebo. These data on prolonged DAPT are in line with the large DAPT trial[20] even trending towards higher mortality with prolonged DAPT[22]. In fact, current guidelines provide a class 2B recommendation for prolonged DAPT after ACS[23,24].

Limitations

The lower than expected event rates observed in our study may be due to the randomisation strategy after successful stenting (freedom from in-hospital events) which may have led to selection bias of lower-risk ACS patients. Although the non-inferiority margin of 5% may appear relatively large, especially in comparison with an actual primary endpoint event rate of 8.3%, our study should be placed in the context of other non-inferiority stent studies, with comparable relative margins[16,17]. Furthermore, our sample size estimation was based on a postulated event rate of 12%, which was higher than the actual rate of 8.3% at one-year follow-up, but consistent with the rate observed at two-year follow-up showing a similar outcome between the groups (11.6% vs 12.1%).

We observed a significant difference in gender between the two groups. However, our results were confirmed after adjustment for gender and were consistent in both male and female gender, without significant interaction.

The study was performed unblinded, without placebo control. Furthermore, the use of $P2Y_{12}$ inhibitors was heterogeneous, reflecting real-world practice.

While most of the baseline characteristics of included patients were similar to those observed in other trials, the younger age (mean of 60 years), in addition to the use of new ADP antagonists in less than 60% of the population, the exclusion of patients at high risk of bleeding, such as those needing oral anticoagulation, may have contributed to minimising the benefits in bleeding complications expected with a shorter DAPT duration. In fact, shorter DAPT was associated with a numerically lower occurrence of bleeding complications, without reaching statistical significance. However, in addition to its prognostic impact and the costs related to bleeding complications, it must be recognised that a short-term DAPT strategy (especially in the era of new ADP antagonists) certainly provides advantages in terms of cost reduction (when applied on a large scale).

Based on the data collected, we could not exactly identify patients at high risk of bleeding, with the exception of elderly patients who carry higher risk primarily due to their comorbidities.

Finally, the current results are pertinent to the COMBO stent, and therefore cannot be extrapolated to other DES.

Conclusions

The results of the REDUCE trial show that, among ACS patients treated with the COMBO stent, three months is non-inferior to 12 months of DAPT. However, given the numerically higher rates of mortality and ST in the three-month DAPT group, one-year DAPT should still be recommended in ACS until more information becomes available. A three-month DAPT strategy should be considered only if clinically mandated.

Impact on daily practice

Until more information becomes available, one-year DAPT should still be recommended in ACS patients. In case of intolerance to one-year DAPT, such as high bleeding risk, a shorter duration of DAPT, even for three months, should be safe, even for ACS patients.

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Appendix. Study collaborators

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Conflict of interest statement

A. van 't Hof reports grants from Medtronic, grants and personal fees from AstraZeneca, grants and personal fees from Abbott, outside the submitted work. J. Lalmand reports grants and personal fees from OrbusNeich, during the conduct of the study. The other authors and the other study collaborators have no conflicts of interest to declare.

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Supplementary data

Supplementary Figure 1. Study flow chart.

Supplementary Figure 2. Kaplan-Meier survival curve for bleeding (BARC 2/3/5) at two-year follow-up.

Supplementary Figure 3. Kaplan-Meier survival curve for all-cause mortality, MI, def/prob ST, stroke and TVR at two-year follow-up.

Supplementary Figure 4. Kaplan-Meier survival curve for all-cause mortality, MI, def/prob ST or stroke at two-year follow-up.

Supplementary Figure 5. Kaplan-Meier survival curve for TVR at two-year follow-up.

Supplementary Figure 6. Kaplan-Meier survival curve for stroke at two-year follow-up.

Supplementary Figure 7. Landmark analysis of composite of all-cause mortality, MI, ST, stroke, bleeding (BARC 2/3/5) from 3 to 12 months.

Supplementary Figure 8. Subgroup analysis at one-year follow-up.

Supplementary Table 1. List of enrolling centres.

Supplementary Table 2. Inclusion and exclusion criteria in the population.

Supplementary Table 3. Primary and secondary study outcomes.

Supplementary Table 4. Additional baseline and angiographic characteristics.

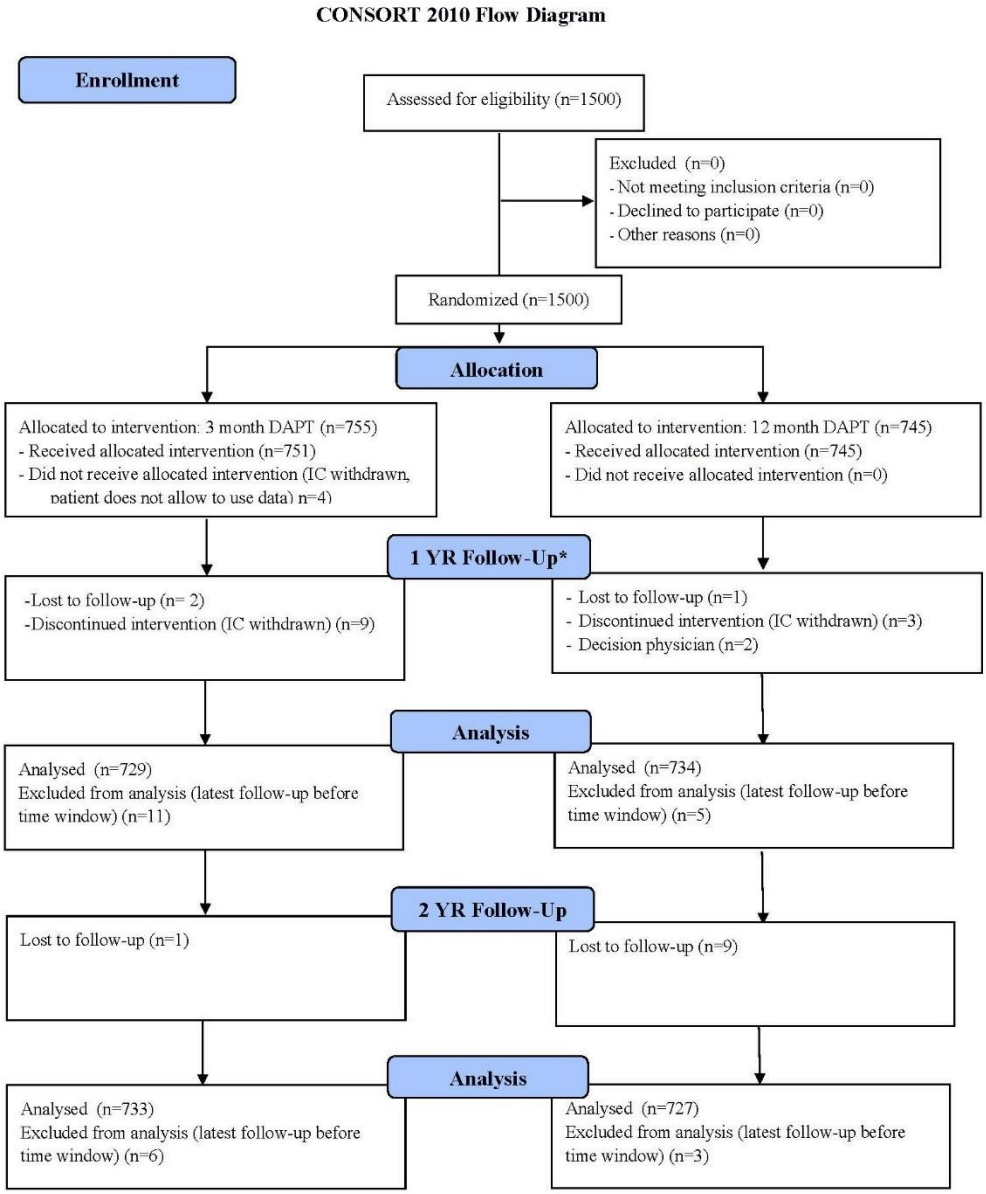
Supplementary Table 5. Hospital stay and discharge medication.

Supplementary Table 6. Clinical outcome at one-year follow-up according to intention-to-treat analysis.

Supplementary Table 7. Detailed causes of non-cardiac mortality.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00539

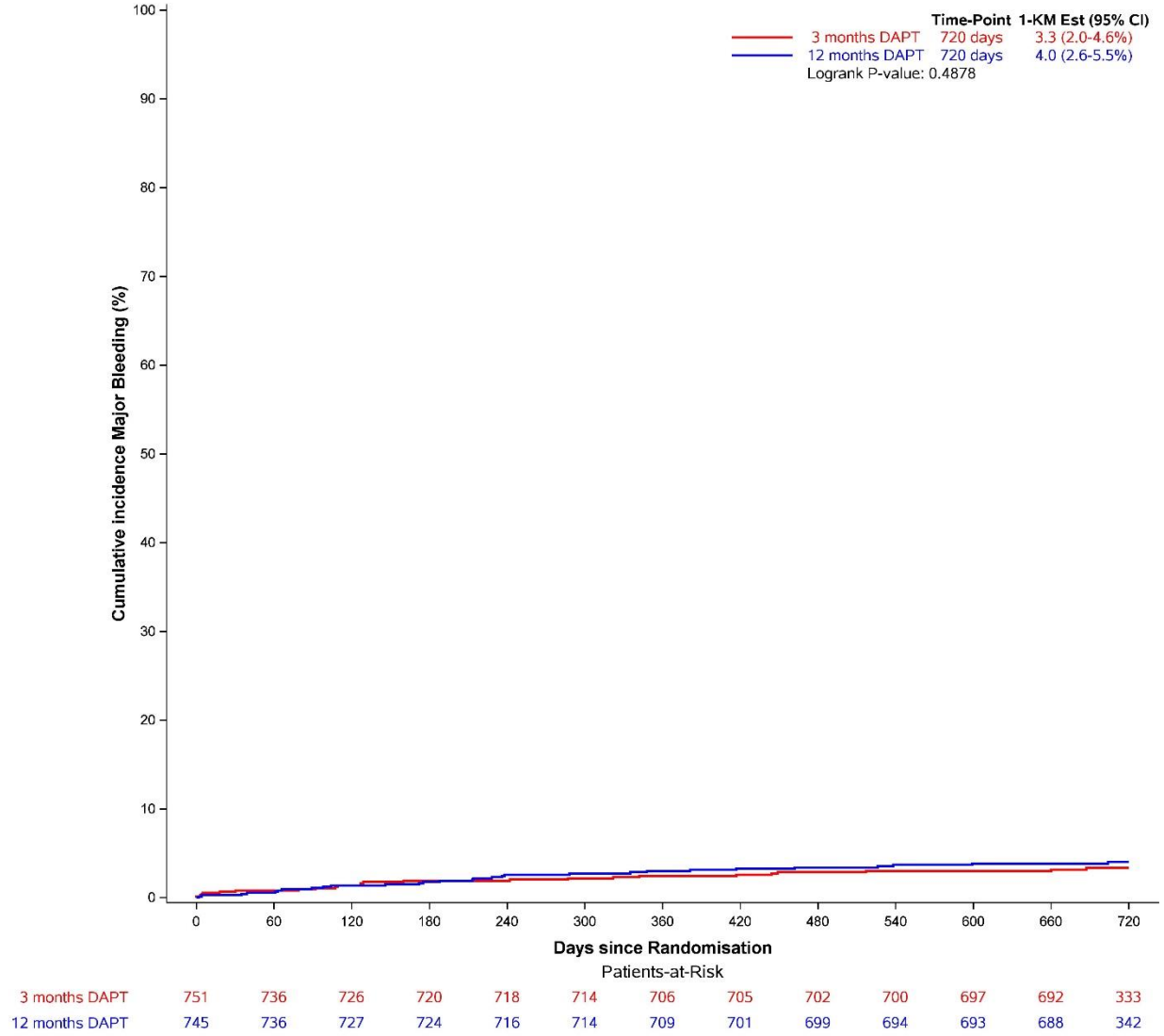
Supplementary data



Supplementary Figure 1. Study flow chart.

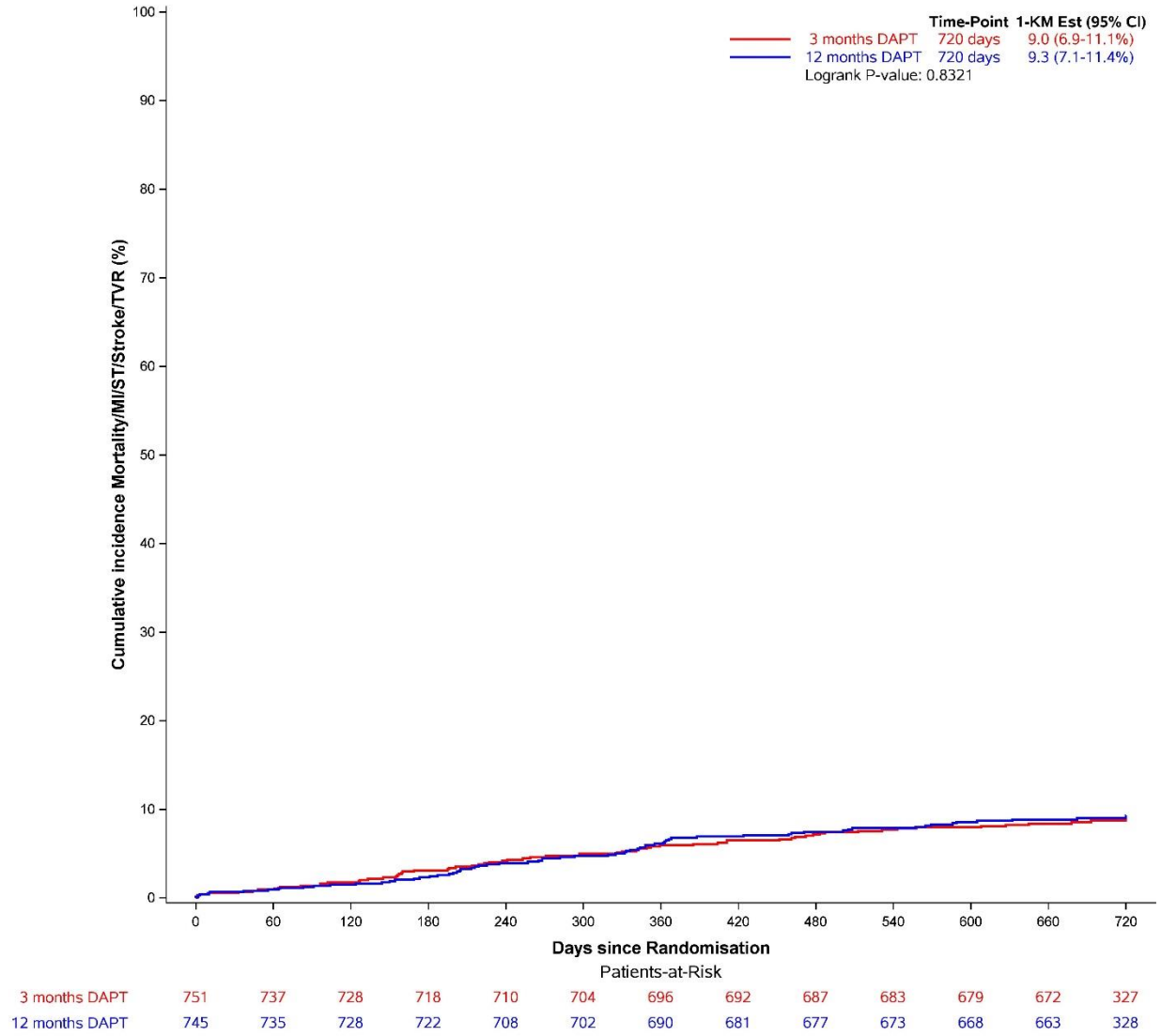
* In the 3-month group, DAPT was discontinued earlier (before 85 days) in 52 patients and continued longer (more than 95 days) in 194 patients, whereas 64 patients in the 12-month group discontinued DAPT early (before 330 days).

DAPT: dual antiplatelet therapy; IC: informed consent; YR: year



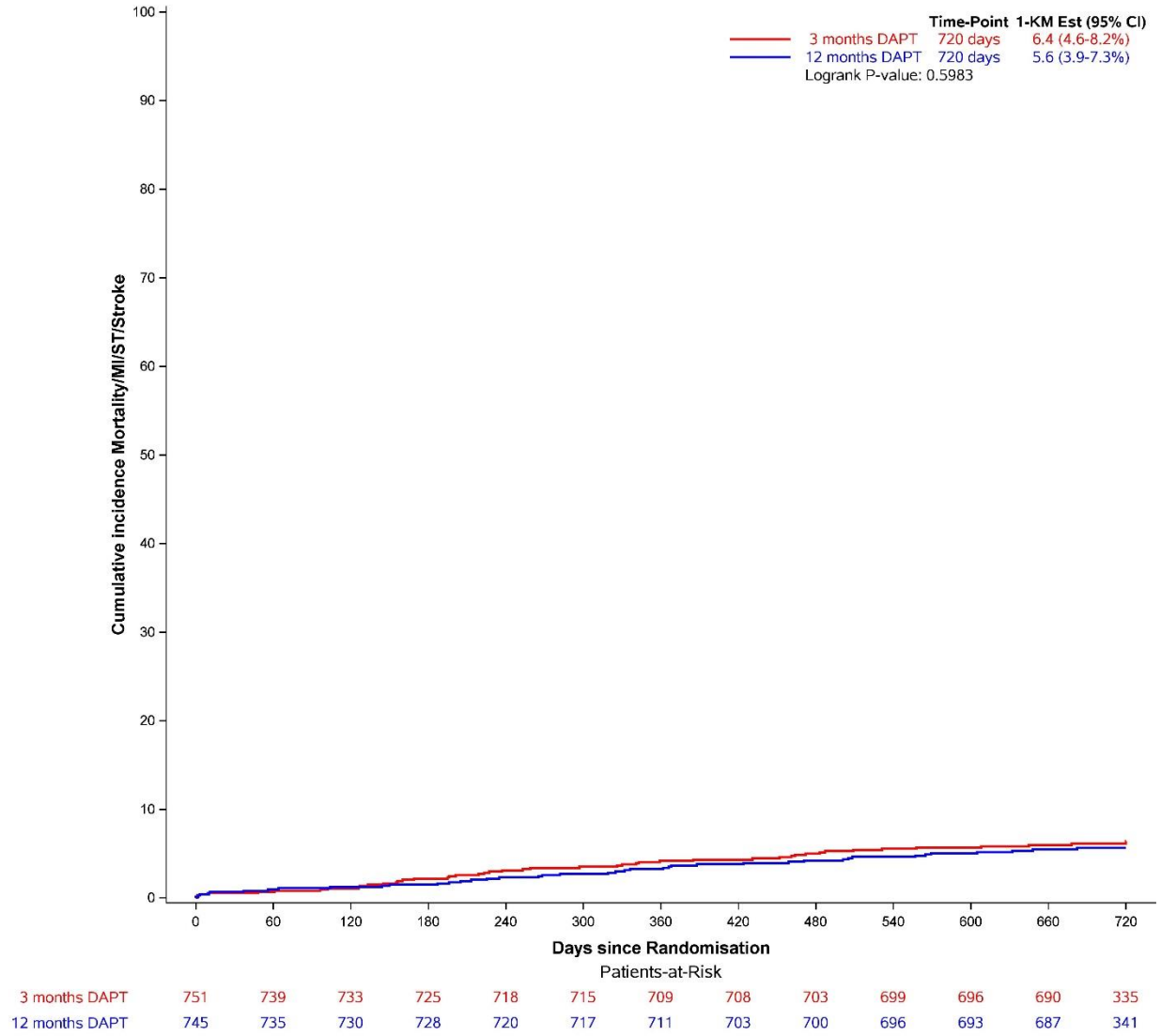
Supplementary Figure 2. Kaplan-Meier survival curve for bleeding (BARC 2/3/5) at two-year follow-up.

BARC: Bleeding Academic Research Consortium; CI: confidence interval; DAPT: dual antiplatelet therapy; YR: year



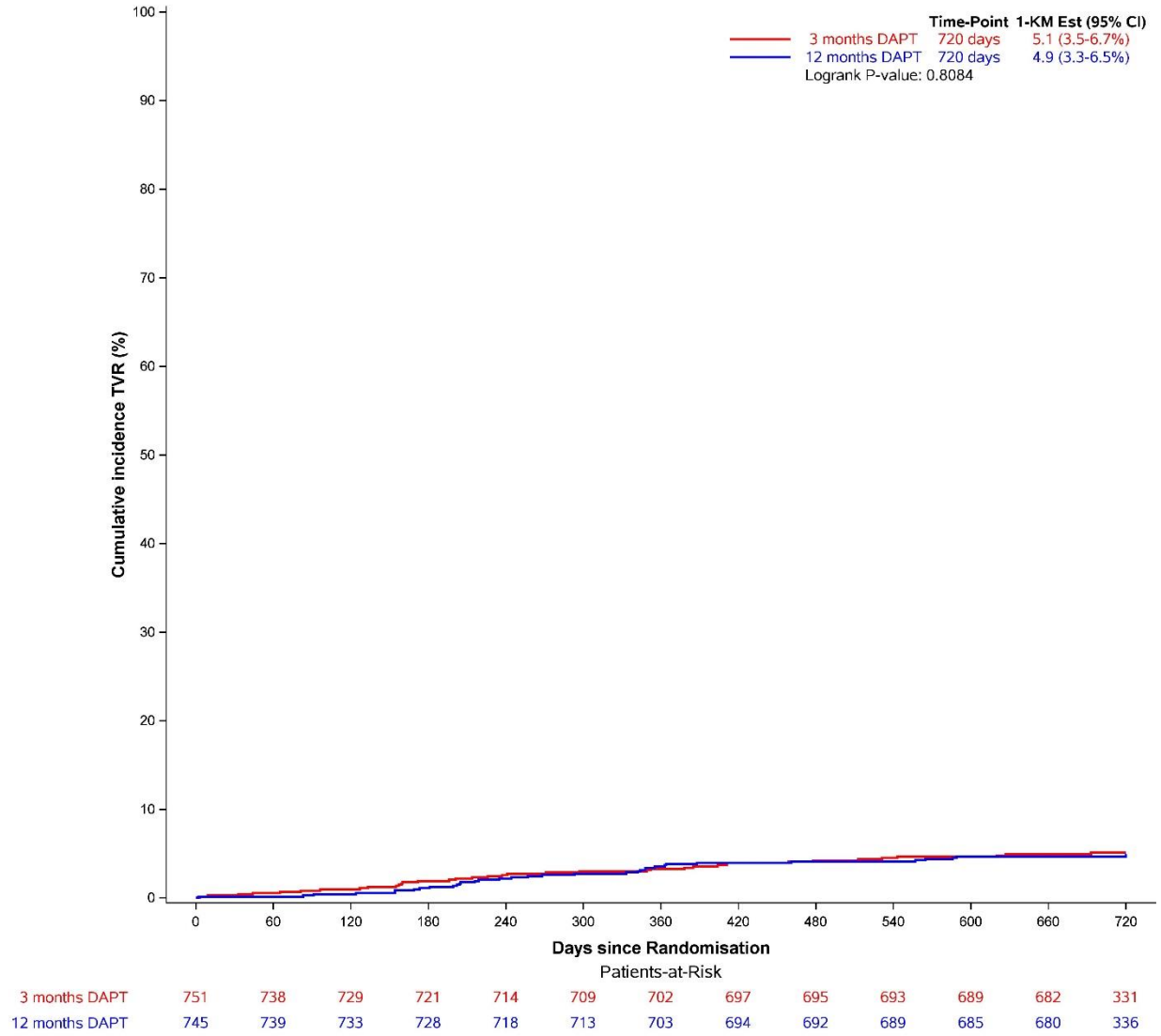
Supplementary Figure 3. Kaplan-Meier survival curve for all-cause mortality, MI, def/prob ST, stroke and TVR at two-year follow-up.

CI: confidence interval; DAPT: dual antiplatelet therapy; MI: myocardial infarction; ST: stent thrombosis; TVR: target vessel revascularisation; YR: year



Supplementary Figure 4. Kaplan-Meier survival curve for all-cause mortality, MI, def/prob ST or stroke at two-year follow-up.

CI: confidence interval; DAPT: dual antiplatelet therapy; MI: myocardial infarction; ST: stent thrombosis; YR: year



Supplementary Figure 5. Kaplan-Meier survival curve for TVR at two-year follow-up.

CI: confidence interval; DAPT: dual antiplatelet therapy; TVR: target vessel revascularisation; YR: year

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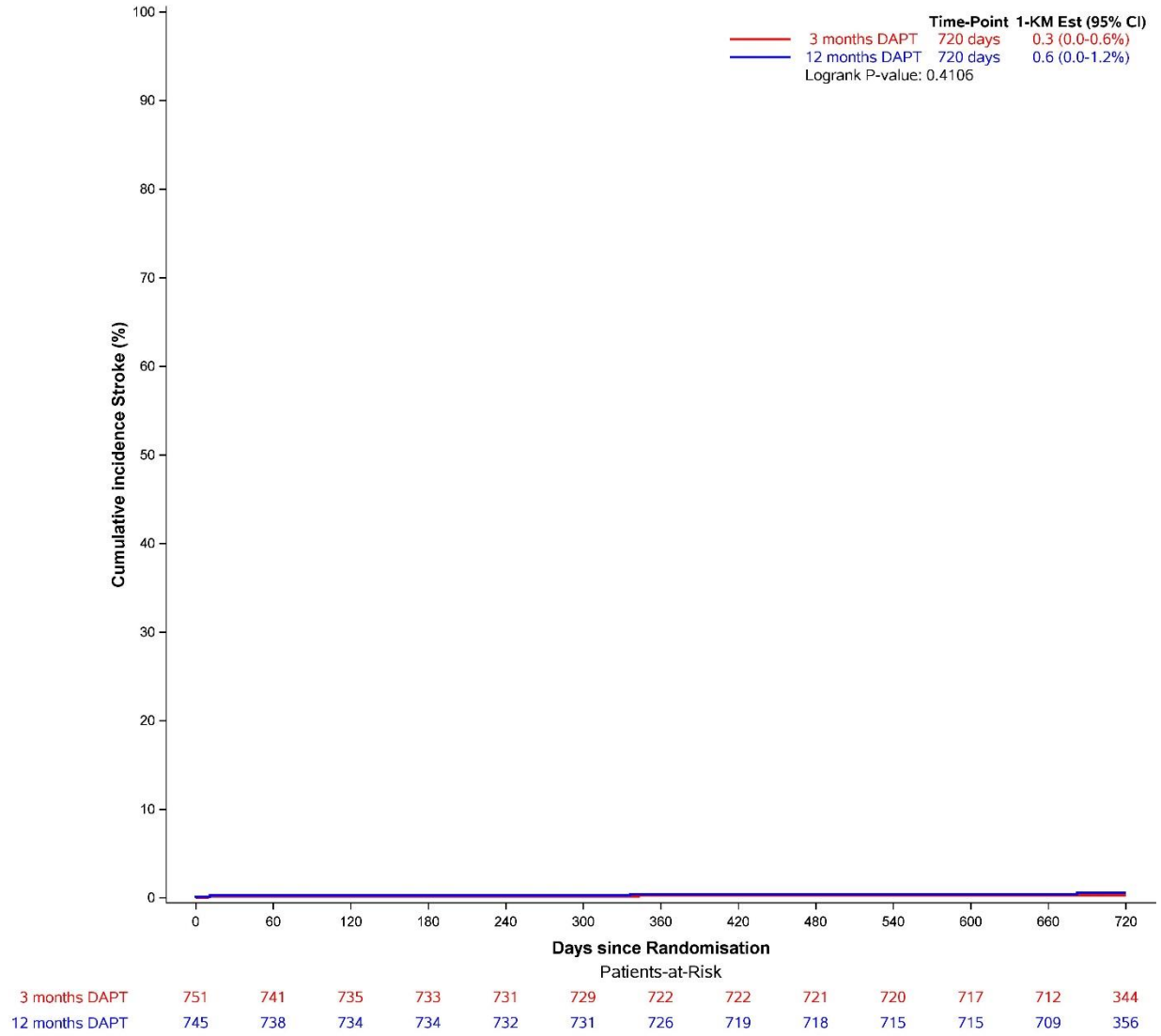
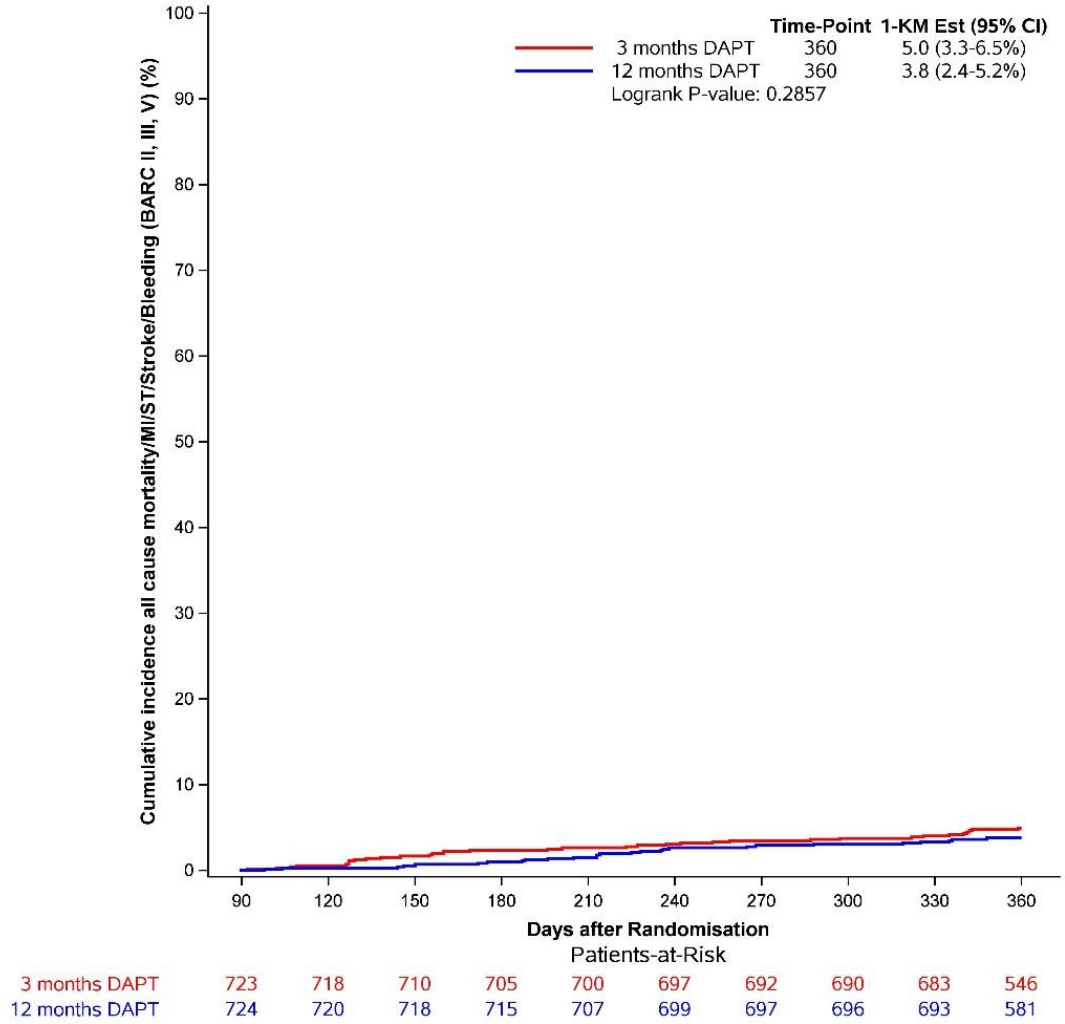


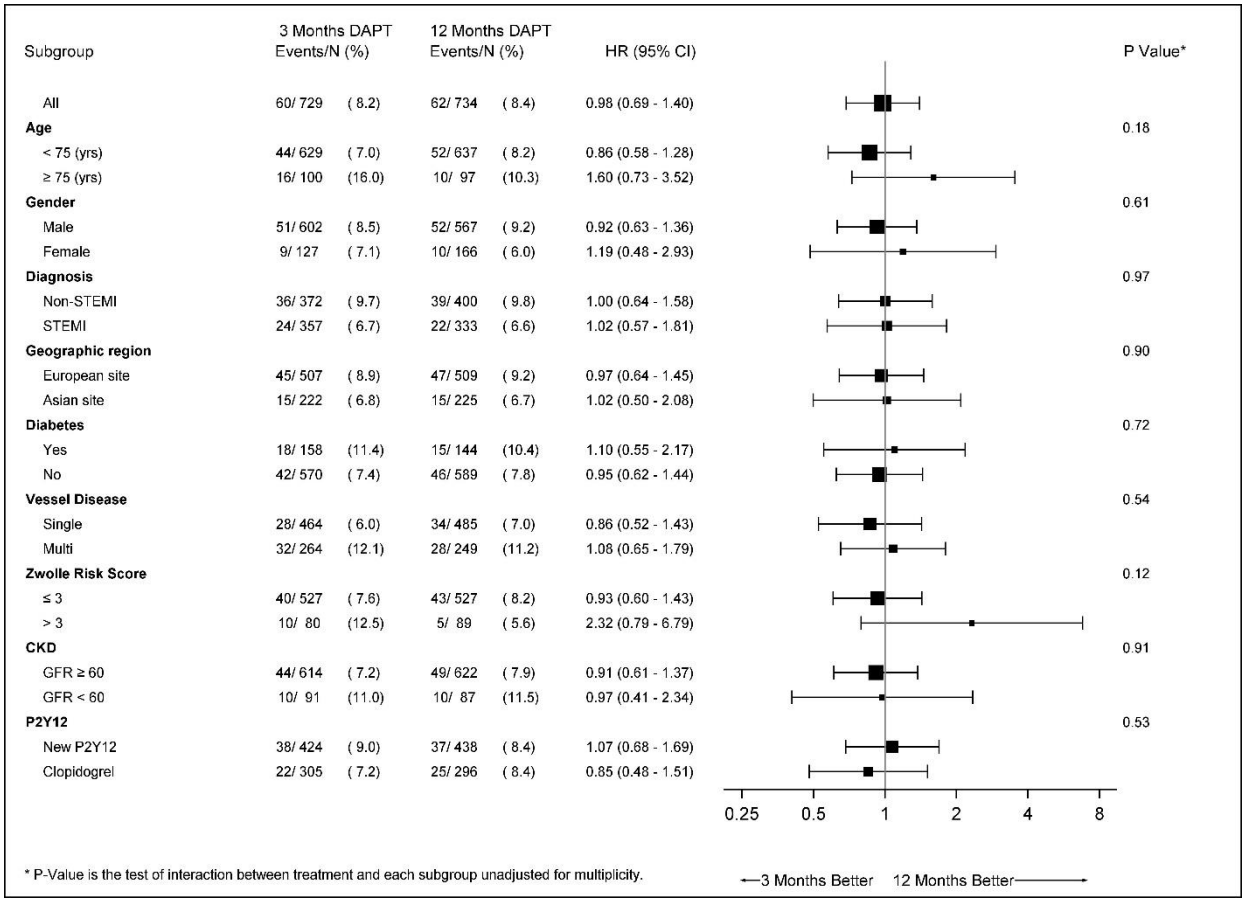
Supplementary Figure 6. Kaplan-Meier survival curve for stroke at two-year follow-up.

CI: confidence interval; DAPT: dual antiplatelet therapy; YR: year



Supplementary Figure 7. Landmark analysis of composite of all-cause mortality, MI, ST, stroke, bleeding (BARC 2/3/5) from 3 to 12 months.

BARC: Bleeding Academic Research Consortium; CI: confidence interval; DAPT: dual antiplatelet therapy; MI: myocardial infarction; ST: stent thrombosis



Supplementary Figure 8. Subgroup analysis at one-year follow-up.

CKD: chronic kidney disease; STEMI: ST-segment elevation myocardial infarction; YR: year

Supplementary Table 1. List of enrolling centres.

Site	Country	Principal investigator	First randomisation	Last randomisation	Total enrolment
Jessa Ziekenhuis (Hasselt)	BE	E. Benit	09-JAN-2015	29-APR-2016	159
Radboud University Medical Center (Nijmegen)	NL	C. Camaro	04-AUG-2014	28-APR-2016	157
Isala (Zwolle)	NL	E. Kedhi	05-JUN-2014	02-MAY-2016	152
Eastern Piedmont University (Novara)	IT	G. De Luca	27-MAR-2015	28-APR-2016	124
Atrium Medical Center (Heerlen)	NL	S. Rasoul	25-SEP-2014	28-APR-2016	121
Queen Elizabeth II Sabah (Sabah)	MY	H.B. Liew	09-OCT-2014	08-JAN-2016	98
Jeroen Bosch Ziekenhuis ('s Hertogenbosch)	NL	J. Polad	19-DEC-2014	25-APR-2016	86
University of Malaya (Kuala Lumpur)	MY	W.A.W. Ahmad	26-SEP-2014	21-APR-2016	70
National Heart Institute (Kuala Lumpur)	MY	R. Zambahari	27-OCT-2014	06-APR-2016	65
Centre Hospitalier Universitaire Charleroi (Charleroi)	BE	J. Lalmand	31-MAR-2015	28-APR-2016	61
Onze Lieve Vrouwe Gasthuis (Amsterdam)	NL	R.J. Van der Schaaf	24-AUG-2015	02-MAY-2016	57
National Heart Center (Singapore)	SG	T.H. Koh	19-NOV-2014	06-APR-2016	50
Queen Mary Hospital, University of Hong Kong (Hong Kong)	HK	F.C.C. Tan	05-AUG-2014	11-APR-2016	40
Hopital du Sart-Tilman (Liège)	BE	V. Legrand	09-FEB-2015	02-MAY-2016	33
Hasan Sadikin Hospital (Bandung)	ID	A.F. Yahya	25-NOV-2014	13-APR-2016	24
National University Heart Centre (Singapore)	SG	H.C. Tan	03-FEB-2015	21-APR-2016	24
Kariadi General Hospital (Semarang)	ID	S. Rifqi	16-JUN-2015	22-APR-2016	23
Hospital Besar Pulau Pinang (Penang)	MY	M.A.S.A. Kader	26-DEC-2014	27-APR-2016	19
Ospedale Generale Madre Giuseppina Vannini (Rome)	IT	B. Pironi	16-OCT-2015	13-APR-2016	17
Academic Medical Center (Amsterdam)	NL	R.J. De Winter	05-MAR-2015	29-APR-2016	16
Telogorejo Hospital (Semarang)	ID	S. Rifqi	06-JUL-2015	18-MAR-2016	13

Queen Elizabeth Hospital (Hong Kong)	HK	M.K.Y. Lee	27-JAN-2015	28-AUG-2015	12
Katholisches Krankenhaus St. Johann Nepomuk (Erfurt)	GE	H. Ebelt	30-SEP-2015	24-FEB-2016	11
Universitätsklinikum (Leipzig)	GE	M. Neef	29-MAY-2015	16-DEC-2015	10
Semmelweis University, Heart and Vascular Center (Budapest)	HU	B. Merkely	30-MAY-2015	02-MAR-2016	10
Medical University of Silezia (Katowice)	PL	W. Wojakowski	09-NOV-2015	22-APR-2016	9
Ospedaliera Universitaria 'Paola Giaccone' (Palermo)	IT	G. Andolina	02-MAR-2016	27-APR-2016	8
University Hospital (Krakow)	PL	D. Dudek	30-OCT-2015	01-FEB-2016	7
Tan Tock Seng Hospital (Singapore)	SG	J.K.B. Tan	06-MAY-2015	30-SEP-2015	7
Herz- und Diabeteszentrum NRW (Bad Oeynhausen)	GE	W. Scholtz	05-MAR-2015	07-DEC-2015	5
Pamela Youde Nethersole Eastern Hospital (Hong Kong)	HK	K.L. Tsui	30-MAR-2015	24-SEP-2015	4
Städtische Kliniken Lukaskrankenhaus (Neuss)	GE	M. Haude	21-DEC-2015	07-JAN-2016	3
Klinikum St.-Marien-Hospital Lünen GmbH (Lünen)	GE	C. Perings	12-JAN-2016	08-MAR-2016	2
San Bortolo Hospital (Vicenza)	IT	L. La Vecchia	26-OCT-2015	26-OCT-2015	1
Cliniques universitaires Saint-Luc (Brussels)	BE	J. Renkin	26-FEB-2015	26-FEB-2015	1
Princess Margaret Hospital (Hong Kong)	HK	P.T. Tsui	18-AUG-2015	18-AUG-2015	1
					1500

Supplementary Table 2. Inclusion and exclusion criteria in the population.

	Overall (N=1,496)	3-month DAPT (N=751)	12-month DAPT (N=745)
Male or female more than 18 years	1,496/1,496 (100.0%)	751/751 (100.0%)	745/745 (100.0%)
Diagnosed with acute coronary syndrome (STEMI, non-STEMI or unstable angina)	1,495/1,496 (99.9%)	751/751 (100.0%)	744/745 (99.9%)
Patient is willing to comply with specified follow-up evaluations	1,496/1,496 (100.0%)	751/751 (100.0%)	745/745 (100.0%)
Patient provided a written informed consent	1,496/1,496 (100.0%)	751/751 (100.0%)	745/745 (100.0%)
Successful COMBO stent implantation, with no clinical adverse event during hospitalisation	1,494/1,496 (99.9%)	750/751 (99.9%)	744/745 (99.9%)
Patient presenting with cardiogenic shock	0/1,496 (0.0%)	0/751 (0.0%)	0/745 (0.0%)
Patient with recent major bleeding complications or contraindication to DAPT*	3/1,496 (0.2%)	2/751 (0.3%)	1/745 (0.1%)
Planned need for concomitant cardiac surgery	0/1,496 (0.0%)	0/751 (0.0%)	0/745 (0.0%)
Planned intervention of another lesion after index hospital discharge	1/1,496 (0.1%)	0/751 (0.0%)	1/745 (0.1%)
Any revascularisation performed within index hospitalisation with stents other than COMBO	0/1,496 (0.0%)	0/751 (0.0%)	0/745 (0.0%)
Potential for non-compliance towards the requirements in the study protocol or follow-ups	0/1,496 (0.0%)	0/751 (0.0%)	0/745 (0.0%)
Patient requires permanent DAPT due to comorbidities	1/1,496 (0.1%)	1/751 (0.1%)	0/745 (0.0%)
Patient received any organ transplant or is on a waiting list for any organ transplant	0/1,496 (0.0%)	0/751 (0.0%)	0/745 (0.0%)
Life expectancy of less than 2 years	0/1,496 (0.0%)	0/751 (0.0%)	0/745 (0.0%)
Pregnancy or intention to become pregnant during the course of the study	0/1,496 (0.0%)	0/751 (0.0%)	0/745 (0.0%)
Any significant medical or mental condition which in the investigator's opinion may intervene with the patient's optimal participation in the study	0/1,496 (0.0%)	0/751 (0.0%)	0/745 (0.0%)
Currently participating in another investigational drug or device study	0/1,496 (0.0%)	0/751 (0.0%)	0/745 (0.0%)
Patient who has been treated with another DES within 9 months prior to the index procedure	0/1,496 (0.0%)	0/751 (0.0%)	0/745 (0.0%)
The subject has given written informed consent	1,496/1,496 (100.0%)	751/751 (100.0%)	745/745 (100.0%)

*

a) Hypersensitivity to aspirin, clopidogrel, prasugrel or ticagrelor
b) Need for oral anticoagulation
c) History of bleeding diathesis or known coagulopathy (including heparin-induced thrombocytopaenia) or refusal of blood transfusions
d) History of intracerebral mass, aneurysm, arteriovenous malformation, or haemorrhagic stroke
e) Stroke or transient ischaemic attack within the past 6 months or any permanent residual neurologic defect
f) Gastrointestinal or genitourinary bleeding within the last 2 months or major surgery within 6 weeks
g) Recent history (<3 months prior to randomisation) or known current platelet count <100,000 cells/mm^3 or haemoglobin <10 g/dL
h) An elective surgical procedure is planned that would necessitate interruption of thienopyridines during the first 12 months post enrolment

Supplementary Table 3. Primary and secondary study outcomes.

Primary outcome Composite of all-cause mortality, MI, ST, stroke, TVR or bleeding (BARC 2, 3, 5) within 12 months **Secondary outcomes**
1. Bleeding (BARC 2, 3, 5) at 12 months 2. All-cause mortality, MI, ST, stroke, TVR, bleeding (BARC 2, 3, 5) at 24 months 3. All-cause mortality, MI, ST, stroke, TVR at 12 and 24 months 4. Mortality at 12 and 24 months 5. Cardiac mortality at 12 and 24 months 6. Any MI at 12 and 24 months 7. ST at 12 and 24 months 8. Repeat revascularisation at 12 and 24 months 9. Time to event as defined by the occurrence of one of the following: all-cause mortality, MI, ST, stroke, TVR or bleeding (BARC 2, 3, 5) within 12 and 24 months 10. Pre-specified landmark analysis of the primary endpoint (without TVR) from 3 to 12 months

BARC: Bleeding Academic Research Consortium; MI: myocardial infarction, ST: stent thrombosis; TVR: target vessel revascularisation

Supplementary Table 4. Additional baseline and angiographic characteristics.

	3-month DAPT (N=751)	12-month DAPT (N=745)
Race, n/N (%)		
Caucasian	517/750 (68.9%)	509/745 (68.3%)
Black	2/750 (0.3%)	5/745 (0.7%)
Asian	228/750 (30.4%)	228/745 (30.6%)
Other	3/750 (0.4%)	3/745 (0.4%)
Enrolment at Asian sites, n/N (%)	223/751 (29.7%)	226/745 (30.3%)
Known angina before current ACS, n/N (%)	94/751 (12.5%)	97/744 (13.0%)
Systolic blood pressure (mmHg) (median, Q1-Q3, n)	134.0 (118.0-150.0) (n=749)	134.0 (118.0-151.0) (n=740)
Diastolic blood pressure (mmHg) (median, Q1-Q3, n)	79.0 (70.0-88.0) (n=749)	79.0 (69.0-90.0) (n=740)
Heart rate (beats/min) (median, Q1-Q3, n)	74.0 (64.0-83.0) (n=749)	73.0 (64.0-84.0) (n=741)
Killip class upon arrival at PCI centre, n/N (%)		
Class I	660/735 (89.8%)	643/727 (88.4%)
Class II	63/735 (8.6%)	67/727 (9.2%)
Class III	6/735 (0.8%)	8/727 (1.1%)
Class IV	6/735 (0.8%)	9/727 (1.2%)
Body mass index (kg/m²) (median, Q1-Q3, n)	26.6 (24.2-29.4) (n=723)	26.6 (24.3-29.4) (n=727)
Creatinine (µmol/l) (median, Q1-Q3, n)	81.0 (69.8-94.0) (n=725)	81.0 (70.7-95.5) (n=719)
Glucose (mmol/l) (median, Q1-Q3, n)	6.7 (5.8-8.5) (n=632)	6.7 (5.8-8.5) (n=637)
Haemoglobin (mmol/l) (median, Q1-Q3, n)	9.1 (8.4-9.6) (n=655)	9.1 (8.4-9.7) (n=641)
Vessel disease, n/N (%)		
One	479/750 (63.9%)	493/745 (66.2%)
Two	209/750 (27.9%)	184/745 (24.7%)
Three	62/750 (8.3%)	68/745 (9.1%)
LAD, n/N (%)	360/750 (48.0%)	329/745 (44.2%)
RCA, n/N (%)	234/750 (31.2%)	246/745 (33.0%)
CX, n/N (%)	146/750 (19.5%)	164/745 (22.0%)
Initial TIMI flow (culprit vessel), n/N (%)		

	3-month DAPT (N=751)	12-month DAPT (N=745)
0	199/740 (26.9%)	177/728 (24.3%)
1	80/740 (10.8%)	78/728 (10.7%)
2	116/740 (15.7%)	116/728 (15.9%)
3	345/740 (46.6%)	357/728 (49.0%)
Access site, n/N (%)		
Femoralis	175/741 (23.6%)	169/736 (23.0%)
Radialis	564/741 (76.1%)	566/736 (76.9%)
Brachialis	2/741 (0.3%)	1/736 (0.1%)
Balloon predilatation, n/N (%)	524/748 (70.1%)	513/745 (68.9%)
TIMI post (culprit lesion), n/N (%)		
0	0/748 (0.0%)	0/743 (0.0%)
1	0/748 (0.0%)	0/743 (0.0%)
2	3/748 (0.4%)	0/743 (0.0%)
3	745/748 (99.6%)	743/743 (100.0%)
Visual diameter stenosis post (culprit lesion), n/N (%)		
<20%	749/750 (99.9%)	744/745 (99.9%)
20-50%	1/750 (0.1%)	1/745 (0.1%)
>=50%	0/750 (0.0%)	0/745 (0.0%)
100%	0/750 (0.0%)	0/745 (0.0%)
Number of stents used, n/N (%)		
1	619/750 (82.5%)	610/745 (81.9%)
2	113/750 (15.1%)	112/745 (15.0%)
3	15/750 (2.0%)	21/745 (2.8%)
4	3/750 (0.4%)	2/745 (0.3%)

All p-values = NS (p>0.05).

ACS: acute coronary syndromes; CX: circumflex artery; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; RCA: right coronary artery; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 5. Hospital stay and discharge medication.

	Overall (N=1,496)	3-month DAPT (N=751)	12-month DAPT (N=745)
Hospital stay (median, IQR, n)	2.0 (1.0-4.0) (n=1,494)	2.0 (1.0-4.0) (n=750)	2.0 (1.0-4.0) (n=744)
$P2Y_{12}$ type, n/N (%)			
Prasugrel	155/1,494 (10.4%)	83/750 (11.1%)	72/744 (9.7%)
Ticagrelor	730/1,494 (48.9%)	359/750 (47.9%)	371/744 (49.9%)
Clopidogrel	609/1,494 (40.8%)	308/750 (41.1%)	301/744 (40.5%)
Statin, n/N (%)	1,415/1,494 (94.7%)	716/750 (95.5%)	699/744 (94.0%)
Calcium antagonist, n/N (%)	185/1,494 (12.4%)	98/750 (13.1%)	87/744 (11.7%)
Beta-blocker, n/N (%)	1,245/1,494 (83.3%)	619/750 (82.5%)	626/744 (84.1%)
Nitrate, n/N (%)	440/1,494 (29.5%)	221/750 (29.5%)	219/744 (29.4%)
ACE inhibitor, n/N (%)	942/1,494 (63.1%)	472/750 (62.9%)	470/744 (63.2%)
Digoxin, n/N (%)	5/1,494 (0.3%)	3/750 (0.4%)	2/744 (0.3%)
Diuretics, n/N (%)	196/1,494 (13.1%)	105/750 (14.0%)	91/744 (12.2%)
Spironolactone, n/N (%)	74/1,494 (5.0%)	45/750 (6.0%)	29/744 (3.9%)
ARB, n/N (%)	142/1,494 (9.5%)	73/750 (9.7%)	69/744 (9.3%)
Oral anticoagulant or NOAC, n/N (%)	27/1,494 (1.8%)	15/750 (2.0%)	12/744 (1.6%)
Insulin, n/N (%)	101/1,494 (6.8%)	56/750 (7.5%)	45/744 (6.0%)
Oral anti-diabetic, n/N (%)	230/1,494 (15.4%)	117/750 (15.6%)	113/744 (15.2%)
Proton pump inhibitor, n/N (%)	858/1,494 (57.4%)	429/750 (57.2%)	429/744 (57.7%)
Other medication at discharge, n/N (%)	661/1,494 (44.2%)	324/750 (43.2%)	337/744 (45.3%)

ACE: angiotensin-converting-enzyme; ARB: angiotensin II receptor blocker; NOAC: new oral anticoagulants; SD: standard deviation

Supplementary Table 6. Clinical outcome at one-year follow-up according to intention-to-treat analysis.

1-year follow-up	3-month DAPT (N=733)	12-month DAPT (N=727)	$p_{superiority}$ log-rank	HR [95% CI]
All-cause mortality, MI, def/prob ST, stroke, TVR or bleeding (BARC 2/3/5)	60/729 (8.2%)	62/734 (8.4%)	0.879	0.98 [0.69-1.40]
Bleeding (BARC 2/3/5)	18/729 (2.5%)	22/734 (3.0%)	0.540	0.83 [0.45-1.55]
All-cause mortality, MI, def/prob ST, stroke, TVR	43/729 (5.9%)	43/734 (5.9%)	0.974	1.01 [0.66-1.55]
All-cause mortality, MI, def/prob ST or stroke	30/729 (4.1%)	23/734 (3.1%)	0.325	1.32 [0.77-2.28]
All-cause mortality	14/729 (1.9%)	6/734 (0.8%)	0.070	2.37 [0.91-6.16]
Cardiac mortality	8/729 (1.1%)	3/734 (0.4%)	0.127	2.71 [0.72-10.2]
MI	17/729 (2.3%)	14/734 (1.9%)	0.575	1.23 [0.61-2.50]
Definite/probable ST	9/729 (1.2%)	3/734 (0.4%)	0.082	3.04 [0.82-11.2]
TVR	24/729 (3.3%)	25/734 (3.4%)	0.928	0.98 [0.56-1.72]
Stroke	2/729 (0.3%)	3/734 (0.4%)	0.666	0.68 [0.11-4.07]

BARC: Bleeding Academic Research Consortium; MI: myocardial infarction; ST: stent thrombosis; TVR: target vessel revascularisation

Supplementary Table 7. Detailed causes of non-cardiac mortality.

Randomised treatment	CEC adjudication	Reason death	Days till death	DAPT
3-month DAPT	Non-cardiac	Acute sepsis with acute renal failure and metabolic acidosis	138	off
3-month DAPT	Non-cardiac	Severe hepatic cancer	102	off
3-month DAPT	Non-cardiac	Gastroesophageal cancer	326	off
3-month DAPT	Non-cardiac	Sepsis of pulmonary origin and hyperkalaemia and desaturation	253	off
3-month DAPT	Non-cardiac	Peritonitis with an intra-abdominal abscess, systemic atherosclerosis with heart failure and cardiorespiratory failure	335	off
3-month DAPT	Non-cardiac	Sepsis secondary to cellulitis	61	on
12-month DAPT	Non-cardiac	Lung carcinoma and pneumonia	325	off
12-month DAPT	Non-cardiac	Bleeding left parieto-occipital (possible metastasis of a melanoma)	104	on
12-month DAPT	Non-cardiac	Dyspnoea and lung fibrosis	37	on
12-month DAPT	Non-cardiac	Intracranial bleeding	417	off
12-month DAPT	Non-cardiac	Lung cinoma	424	off
12-month DAPT	Non-cardiac	Pleural-pulmonary mass that was much advanced. Patient died at home from disease	505	off

12-month DAPT	Non-cardiac	Death due to leukaemia	625	off
12-month DAPT	Non-cardiac	Death due to neck cancer	600	off
3-month DAPT	Non-cardiac	Death due to lung cancer	678	off
3-month DAPT	Non-cardiac	Death due to pneumonia complicated by respiratory insufficiency	558	off
3-month DAPT	Non-cardiac	Exacerbation COPD with pneumonia	452	off
3-month DAPT	Non-cardiac	Diagnosed acute cholangitis and worsening of general condition, anorexia and cachectic status, pleural effusion on the left side; bad general conditions and cognitive impairment persisted, therefore the colleagues proposed indication to palliative treatment.	501	off

CEC: clinical events committee; DAPT: dual antiplatelet therapy