

1 **Impact of dual antiplatelet therapy after coronary artery bypass surgery on 1 year out-**
2 **comes in the Arterial Revascularization Trial (ART).**

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24

25 **Abstract**

26 **Objectives:** There is still little evidence to support routine dual antiplatelet therapy (DAPT)
27 with P₂Y₁₂ antagonists following coronary artery bypass grafting (CABG). The Arterial Revas-
28 cularization Trial (ART) was designed to compare 10-year survival after bilateral versus single
29 internal thoracic artery grafting. We aimed to get insights into the effect of DAPT (with
30 clopidogrel) following CABG on 1 year outcomes by performing a post-hoc ART analysis.

31 **Methods:** Among patients enrolled in the ART (n=3102), 609 (21%) and 2308 (79%) were
32 discharged on DAPT or aspirin alone respectively. The primary endpoint was the incidence of
33 major adverse cerebrovascular and cardiac events (MACCE) at 1 year including cardiac death,
34 myocardial infarction, cerebrovascular accident and reintervention; safety endpoint was bleed-
35 ing requiring hospitalization. Propensity score (PS) matching was used to create comparable
36 groups.

37 **Results:** Among 609-PS matched pairs, MACCE occurred in 34 (5.6%) and 34 (5.6%) in the
38 DAPT and aspirin alone groups respectively with no significant difference between the two
39 groups (HR 0.97; 95%CI 0.59-1.59; P=0.90). Only 188 (31%) subjects completed 1 year of
40 DAPT and in this subgroup, MACCE rate was 5.8% (HR 1.11; 95%CI 0.53-2.30; P=0.78). In
41 the overall sample, bleeding rate was higher in DAPT group (2.3% versus 1.1%; P=0.02) alt-
42 hough this difference was no longer significant after matching (2.3% vs 1.8%; P=0.54).

43 **Conclusions:** Based on these findings, when compared to aspirin alone, DAPT with
44 clopidogrel prescribed at discharge was not associated with a significant reduction of adverse
45 cardiac and cerebrovascular events at 1 year following CABG.

46 **Keywords:** *dual antiplatelet therapy; coronary artery bypass grafting; bleeding*

47 **Introduction**

48 Coronary artery bypass grafting (CABG) is widely regarded as the revascularisation strategy
49 of choice, particularly in patients with multivessel coronary artery disease [1]. However,
50 CABG patients still have a significant risk of subsequent major adverse cardiovascular events
51 (MACCE, including mortality, myocardial infarction (MI) stroke and repeat revacularization)
52 secondary to graft failure and atherosclerosis progression, particularly during the first 12
53 months. In fact, MACCE rates in the first year after CABG still exceed 12% [2]

54 The appropriate antiplatelet regimen after CABG remains an area of controversy [3]. Dual
55 antiplatelet therapy (DAPT) with the addition of an oral P₂Y₁₂ antagonist such as Clopidogrel
56 to aspirin for 1 year after surgery has been proposed to improve outcomes. Plaque stability,
57 prevention of graft closure, and secondary thrombosis form the basis for using a second an-
58 tiplatelet drug, whereas the increased risk of bleeding and lack of conclusive evidence should
59 also be considered.

60 Evidence for use of DAPT following CABG [4] is based mainly on a small proportion of pa-
61 tients undergoing surgical revascularization in landmark trials enrolling acute coronary syn-
62 drome (ACS) patients [5-7]. Whereas cardiac surgeons are very familiar with the guidelines
63 regarding discontinuation of DAPT prior to CABG to minimize bleeding risks [8,9], there is
64 considerable variability in DAPT resumption in post CABG [10,11].

65 The Arterial Revascularization Trial (ART) was designed to investigate whether bilateral in-
66 ternal thoracic artery (BITA) grafting is associated with improved 10-year survival when com-
67 pared to single internal thoracic artery (SITA) grafting in patients with multivessel disease
68 undergoing CABG [12] and final results will be available in 2018. We aimed to get insights
69 into the efficacy and safety of DAPT following CABG on 1 year outcomes by performing a
70 retrospective analysis of the ART trial.

71 **Materials and Methods**

72 This research adheres to the principles set forth in the Declaration of Helsinki
73 (<http://www.wma.net/en/30publications/10policies/b3/index.html>). For the purpose of the pre-
74 sent analysis, patients enrolled in the ART (n=3102) were classified according to whether they
75 were discharge on DAPT (with clopidogrel) or aspirin alone following surgery. In the ART,
76 antiplatelet therapy prescribed at discharge was at discretion of responsible physicians. We
77 excluded those who met the following criteria: 1) Hospital death; 2) Withdrawn; 3) No infor-
78 mation on antiplatelet therapy at discharge; 4) Clopidogrel alone at discharge.

79 **Trial design**

80 The protocol for the ART has been published [13]. Briefly, the ART is a 2-arm, randomized
81 multicenter trial conducted in 28 hospitals in 7 countries, with patients being randomized
82 equally to SITA or BITA grafts. Eligible patients were those with multivessel coronary artery
83 disease undergoing CABG including urgent patients. Emergency patients (on-going myocar-
84 dial ischemia/cardiogenic shock) and those requiring single grafts or redo CABG were ex-
85 cluded.

86 **Follow-up and Study Endpoints**

87 Questionnaires were sent to study participants by post at 1 year after surgery. No clinic visits
88 were planned apart from the routine clinical 6-week post-operative visit. Participants were sent
89 stamped addressed envelopes to improve the return rates of postal questionnaires. Study co-
90 ordinators contacted participants by telephone to alert them to the questionnaire's arrival and
91 to ask them about medications, adverse events and health services resource use.

92 The primary endpoint was the incidence of major adverse cerebrovascular and cardiac events
93 (MACCE) at 1 year defined as the occurrence of cardiovascular death (CV-death), myocardial
94 infection (MI), either ST elevation or non ST elevation MI, cerebrovascular accident (CVA) or

95 repeat revascularization. We also investigated the composite endpoint of cardiac death, MI and
96 CVA and all-cause mortality. Safety endpoint was bleeding requiring re-hospitalization. Ad-
97 verse events were adjudicated blind to surgical procedure by a member of the Clinical Event
98 Review Committee. Follow-up at 1 year was available for all patients included in the analysis
99 (100%).

100 **Statistical analysis**

101 Multiple imputation was used to address missing data (<http://www.jstatsoft.org/v45/i07/>). Ex-
102 pectation-maximization with bootstrapping algorithm was used to generate 3 imputed datasets.
103 No prior information was used. Sets of estimates from different datasets were combined using
104 the Rubin rule: the central estimate corresponds to the mean of individual imputation estimates
105 and the variance is the weighted sum of two variances: the within imputation variance and the
106 between imputation variance [14]. Due to lack of randomization with regards to DAPT admin-
107 istration following surgery, a propensity score (PS) was generated for each patient from a mul-
108 tivariabile logistic regression model based on pre-treatment covariates as independent variables
109 with DAPT versus aspirin alone administration as a binary dependent variable [15]. Covariates
110 included in the PS model were: age, female gender, body mass index (BMI), creatinine, diabe-
111 tes mellitus (DM), smoking, chronic obstructive pulmonary disease (COPD), peripheral vas-
112 cular disease (PVD), left ventricular ejection fraction (LVEF), left main disease (LMD), myo-
113 cardial infarction (MI, including both ST elevation and non ST elevation MI), percutaneous
114 coronary intervention (PCI), unstable angina (UA), off-pump CABG (OPCAB), use of saph-
115 eous vein graft (SVG), other medication prescribed at discharge: vitamin K antagonist (VKA),
116 beta-blockers (BB), angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor
117 blocker (ARB).

118 Pairs of patients were derived using greedy 1:1 matching with a calliper of width of 0.2 stand-
119 ard deviation of the logit of the PS (<http://CRAN.Rproject.org/package=nonrandom>). The qual-
120 ity of the match was assessed by comparing selected pre-treatment variables in propensity
121 score-matched patients using the standardized mean difference (SMD), for which an absolute
122 standardized difference of greater than 10% is suggested to represent meaningful covariate
123 imbalance [16]. A Cox regression model, stratified on the matched pairs [14] and adjusted for
124 other medications at discharge, was used to estimate the treatment effect (i.e. DAPT vs aspirin
125 alone) on outcomes of interest (<http://CRAN.R-project.org/package=survival>). This approach
126 accounts for the within-pair homogeneity by allowing the baseline hazard function to vary
127 across matched sets. For competing risk adverse event (MI, CVA and repeat revascularization)
128 a competing risk framework was used (<https://CRAN.R-project.org/package=riskRegression>).
129 Potential effect modifiers (interaction terms) examined were: 1) unstable angina, 2) prior MI
130 within 1 year; 3) prior percutaneous coronary intervention (PCI) within 1 year; 4) off-pump
131 surgery; and 5) use of saphenous vein graft (SVG). Double robust method (multivariate adjust-
132 ment in the PS matched sample) was used to compute treatment effect estimates within sub-
133 groups. The proportional hazard assumption was tested by graphical inspection using log(-
134 log(S)) method with Kaplan Meier estimators from the PS matched sample. In this case, the
135 space between the two curves should be constant over time (Supplementary Figure 1 for the
136 primary endpoint). A goodness of fit test (Schoenfeld residuals) was used to confirm that re-
137 siduals for the treatment variable were not related to time (P=0.49 for the primary endpoint).
138 A generic binomial test was used for a post-hoc power calculation for the primary end-point.
139 Time to event analysis were graphically presented as cumulative incidence curves which show
140 the cumulative probabilities of experiencing the event of interest. Cumulative incidence was
141 computed as $1-S_t$ where S_t corresponds to the proportion surviving past interval t) obtained
142 from the life table using the Kaplan-Meier approach. All p-values <0.05 were considered to

143 indicate statistical significance. All statistical analysis were performed using R Statistical Soft-
144 ware (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

145 **Results**

146 The final study population consisted of 2917 patients. Of them 609 (21%) and 2308 (79%)
147 were discharged on DAPT or aspirin alone respectively. Baseline characteristics of the two
148 groups are reported in Table 1. In particular, patients receiving DAPT were more likely to have
149 unstable angina and to receive clopidogrel preoperatively. Patients discharged on DAPT were
150 more likely to have off-pump surgery, to receive SVG and to be discharged on statins and
151 ACEI/ARB. The use of vitamin K antagonists at discharge was higher in the aspirin group
152 (Figure 1). After PS matching the two groups were comparable for all pre-treatment variables
153 investigated (Figure 1).

154 **Efficacy endpoints**

155 Efficacy endpoints in the 609-PS matched pairs are reported in Table 2. The rate of MACCE
156 was 34 (5.6%) and 34 (5.6%) in the DAPT and aspirin alone groups respectively with no sig-
157 nificant difference between the two groups (HR 0.97; 95%CI 0.59-1.59; P=0.90; Figure 2 left).
158 The rate of the composite of CV death, MI and stroke was 21 (3.5%) and 29 (4.8%) in the
159 DAPT and aspirin alone groups (HR 0.71; 95%CI 0.40-1.27; P=0.20; Figure 2 right).

160 None of the possible effect modifiers showed a significant interaction with MACCE: unstable
161 angina ($\beta=-0.39\pm 0.70$; P=0.57); prior MI ($\beta=0.1 \pm 0.87$; P=0.98) or prior PCI within 1 year ($\beta=-$
162 0.04 ± 1.55 ; P=0.97), OPCAB ($\beta=-0.82\pm 0.69$; P=0.23) and use of saphenous vein grafts ($\beta=-$
163 0.35 ± 0.97 ; P=0.71). However, unstable angina, OPCAB and the use of SVG showed larger
164 coefficients in favor of a benefit from DAPT. In particular, in patients with unstable angina,
165 DAPT did not significantly influence the risk of MACCE (HR_{DR} 0.90; 95%CI 0.40-2.06;
166 P=0.81) but was associated with a lower risk for the composite of CV death, MI and CVA

167 (HR_{DR} 0.42; 95%CI 0.15-1.21; P=0.1). In patients undergoing off-pump surgery, DAPT did
168 not significantly influence the risk of MACCE (HR_{DR} 0.90; 95%CI 0.50-1.63; P=0.73) but was
169 associated with a lower risk for the composite of CV death, MI and CVA (HR_{DR} 0.53; 95%CI
170 0.25-1.11; P=0.09).

171 Among 609 patients who received DAPT postoperatively, 188 (31%) completed 1 year of
172 DAPT, 362 (59%) switched to aspirin alone and other 24 (4%) switched to Clopidogrel alone
173 (unknown for the remaining 35 patients). The rate of MACCE and the composite of CV death,
174 MI and CVA was 5.8% and 2.7% respectively for those who continued DAPT for 1 year, 3.9%
175 and 1.7% respectively for those who switched to aspirin alone and 12.5% and 8.3% respec-
176 tively for those who switched to clopidogrel alone. We the analysis was restricted to subjects
177 who continued DAPT for 1 year (n=188), DAPT did not significantly influence MACCE
178 (HR_{DR} 1.11[0.53-2.30]; P=0.78) or the composite of death, MI and CVA (HR_{DR} 0.62; 95%CI
179 0.22-1.69; P=0.34).

180 Post-hoc power calculation was based on a 2.0 percentage point reduction in MACCE (3.5%
181 with DAPT vs 5.5% with Aspirin alone) accordingly to a pooled analysis recently published
182 [3]. The power achieved was 90% (sample size 1218, 5% significance, 2 tails; Supplementary
183 Figure 2).

184 **Safety endpoint**

185 The rate of major bleeding was significantly higher in patients discharged on DAPT (14/609,
186 2.3%) when compared to aspirin alone (25/2308, 1.1%) (HR 2.14[1.11-4.11]; P=0.02; Figure
187 3) although this difference was no longer significant after PS matching (14,2.3% vs 11,1.8%;
188 HR 1.30; 95%CI 0.58-2.8; P=0.54).

189 **Discussion**

190 Based on the present post-hoc analysis there is no evidence that DAPT with Clopidogrel can
191 significantly reduce the rate of MACCE following surgery. However, in subjects admitted with
192 unstable angina and undergoing off-pump surgery, we found a non-significant trend towards a
193 larger protective effect from DAPT. DAPT at discharge was associated with an increased risk
194 of bleeding but bleeding rates were particularly low in both groups.

195 Definitive guideline recommendations regarding use of DAPT after CABG are currently lack-
196 ing. Evidence for use of DAPT following CABG is based mainly on a small proportion of
197 patients in three landmark trials enrolling ACS patients [17-19]. Those trials were not ade-
198 quately powered to address the role of DAPT in the post-CABG cohort. Another limitation is
199 that they studied three different oral P₂Y₁₂ antagonists: Clopidogrel, Ticagrelor and Prasugrel.
200 Moreover these results are based on post-randomization subsets from single RCTs in which
201 DAPT was initiated prior to CABG. Therefore the decision to undergo CABG is a post ran-
202 domization event occurring at variable times post randomization. This decision can thus be
203 influenced by randomized group resulting in potential baseline imbalances between interven-
204 tion and control groups. On the other hand, available trials on DAPT enrolling CABG patients
205 only present limited design and are largely underpowered to detect significant differences [20-
206 25].

207 Patients were enrolled into ART from 2004 to 2007 and Clopidogrel was the only P₂Y₁₂ antag-
208 onist used in this trial. Prasugrel and Ticagrelor were approved for use in Europe 2009 and
209 2010 respectively and the question whether DAPT with newer P₂Y₁₂ antagonists is more effec-
210 tive remains to be determined. Of note, a recent meta-analysis [3] including 4 CABG-sub-
211 groups ACS RCTs [17-20] (n=3901) and 5 post-elective CABG trials [21-25] (n=986) con-
212 cluded that DAPT resumption with higher intensity P₂Y₁₂ antagonists (Prasugrel or Ticagre-
213 lor), but not Clopidogrel, reduces all-cause mortality in ACS patients who have undergone

214 CABG. In the ART trial the vast majority of patients with prior MI within 1 year were dis-
215 charged on aspirin alone in contrast with current recommendation to continue DAPT for one
216 year following ACS regardless of the treatment adopted [4]. This might be partially explained
217 by the fact that these recommendations have gained popularity after ART recruitment. We
218 observed that subjects with unstable angina showed a larger benefit from DAPT although this
219 result was not statistically significant. We also found that a non-significant trend toward better
220 outcomes with DAPT in subjects undergoing off-pump surgery and those who received SVG
221 but these subgroup analyses were largely underpowered to detect significant difference.

222 It has been demonstrated that off-pump CABG is associated with hypercoagulability postop-
223 eratively [26] which can affect graft patency rate in particular with saphenous vein graft. These
224 patients may benefit more from DAPT than patients operated with conventional surgery alt-
225 hough there is still paucity of evidence with conflicting results reported [24,27].

226 There are several limitations of the present study. Although a post-hoc power calculation sug-
227 gested that the present analysis was sufficiently powered to detect a difference in the primary
228 endpoint (MACCE at 1 year) between the two groups. Subgroup analyses including subjects
229 presenting with unstable angina or receiving off-pump surgery or SVGs were largely under-
230 powered. Despite PS matching, a residual imbalance cannot be excluded. In particular, we no-
231 ticed that the rate of reintervention was higher in patients discharged on DAPT. This might
232 partially due to higher prevalence of risk factors for further coronary interventions in this
233 group. Finally only 31% of subjects initially prescribed on DAPT completed 1 year of treat-
234 ment and this aspect might have underestimated the effect of DAPT. No data were available
235 on DAPT duration in subjects who discontinued DAPT and therefore we were unable to dis-
236 criminate the effect of short (3-6 months) versus long (1 year) DAPT. We performed a sensi-
237 tivity analysis including only subjects who completed 1 year of DAPT and DAPT was con-

238 firmed to not be associated with better outcomes. We observed that the vast majority of bleed-
239 ing occurred during the first two months from discharge thus supporting the hypothesis that
240 also short term DAPT following CABG may increase the risk of bleeding.

241 In conclusion, based on these findings, there is no evidence of a significant benefit from DAPT
242 with clopidogrel over aspirin alone following CABG. However, the present analysis was un-
243 derpowered to investigate the effect of DAPT in high risk subgroups such as patients with
244 ACS. Large prospective RCTs evaluating the use of DAPT post-CABG with higher intensity
245 P₂Y₁₂ antagonists are urgently needed to provide more definitive guidance for clinicians.

246 **Funding statement:** None

247 **Conflict of interest:** none declared.

248 **Figures Legends**

249 Figure 1. Standardized mean difference (SMD) for baseline variables before and after pro-
250 propensity score matching. (DAPT: dual antiplatelet therapy; SMD: standardized mean differ-
251 ence; PS: propensity score; BMI: body mass index; DM: diabetes mellitus; COPD: chronic
252 obstructive pulmonary disease. PVD: peripheral vascular disease; MI: myocardial infarction;
253 PCI: percutaneous coronary intervention; UA: unstable angina; LVEF: left ventricular ejec-
254 tion fraction; AF: atrial fibrillation; SVG: saphenous vein graft; OPCAB: off-pump coronary
255 artery bypass; VKA: Vitamin K antagonist; BB: beta-blocker; ACEI: angiotensin converting
256 enzyme inhibitor; ARB: angiotensin receptor blocker)

257 Figure 2. Cumulative incidence with relative 95% confidence bands of major cerebrovascular
258 and cardiac events (MACCE, right) and of composite of cardiac death/myocardial infarction
259 (MI) and cerebrovascular accident (left) in patients discharged on dual antiplatelet therapy
260 (DAPT) or aspirin alone.

261 Figure 3. Cumulative incidence with relative 95% confidence bands of bleeding requiring
262 hospitalization in patients discharged on dual antiplatelet therapy (DAPT) or aspirin alone.

263 Supplementary Figure 1. Proportional hazard assumption tested by graphical inspection using
264 $\log(-\log(S))$ method with Kaplan Meier estimators from the matched sample.

265 Supplementary Figure 2. Graphical representation of post-hoc power calculation for the pri-
266 mary end-point.

267

268 Table 1. Baseline and operative characteristics of patients discharged on dual antiplatelet
 269 therapy (DAPT) or aspirin alone.

	DAPT	Aspirin (unmatched)	SMD	Aspirin (PS-matched)	SMD
n	609	2308		609	
Age (mean (sd))	62.9 (9.4)	62.9 (8.7)	0.006	63.3(8.4)	0.052
Female n(%)	73 (12.0)	331 (14.3)	0.070	78 (12.8)	0.025
BMI (mean (sd))	27.9(4.4)	28.3(3.9)	0.110	28.0 (4.0)	0.027
Creatinine (mean (sd))	101.2 (19.3)	95.1 (21.3)	0.301	101.2 (23.1)	0.001
DM n(%)	164 (26.9)	531 (23.0)	0.091	158 (25.9)	0.022
Smoking n(%)	86 (14.1)	334 (14.5)	0.010	75 (12.3)	0.053
COPD n(%)	47 (7.7)	131 (5.7)	0.082	42 (6.9)	0.032
PVD n(%)	49 (8.0)	152 (6.6)	0.056	50 (8.2)	0.006
Prior stroke n(%)	13 (2.1)	68 (2.9)	0.052	12 (2.0)	0.012
LVEF<.50 n(%)	136 (22.3)	582 (25.2)	0.068	141 (23.2)	0.020
LMD n(%)	112 (18.4)	498 (21.6)	0.080	134 (22.0)	0.090
MI within 1Y n(%)	149 (24.5)	541 (23.4)	0.024	156 (25.6)	0.027
PCI within 1Y n(%)	28 (4.6)	265 (11.5)	0.255	32 (5.3)	0.030
UA n(%)	252 (41.4)	726 (31.5)	0.207	236 (38.8)	0.054
Preop aspirin n(%)	534 (87.7)	1989 (86.2)	0.045	539 (88.5)	0.025
Preop clopidogrel n(%)	236 (38.8)	462 (20.0)	0.420	210 (34.5)	0.089
OPCAB n(%)	430 (70.6)	760 (32.9)	0.814	423 (69.5)	0.025
SVG n(%)	496 (81.4)	1751 (75.9)	0.136	491 (80.6)	0.021
N grafts (mean (sd))	3.3 (0.9)	3.1 (0.8)	0.224	3.3 (0.9)	0.038
Postop VKA n(%)	6 (1.0)	87 (3.8)	0.184	10 (1.6)	0.058
Postop BB n(%)	501 (82.3)	1949 (84.4)	0.059	501 (82.3)	<0.001
Postop Statins n(%)	581 (95.4)	2118 (91.8)	0.149	578 (94.9)	0.023
Postop ACEI/ARB n(%)	359 (58.9)	1130 (49.0)	0.201	348 (57.1)	0.037

270 DAPT: dual antiplatelet therapy; SMD: standardized mean difference; PS: propensity score;
 271 BMI: body mass index; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease.
 272 PVD: peripheral vascular disease; MI: myocardial infarction; PCI: percutaneous coronary in-
 273 tervention; UA: unstable angina; LVEF: left ventricular ejection fraction; AF: atrial fibrillation;

274 SVG: saphenous vein graft; OPCAB: off-pump coronary artery bypass; VKA: Vitamin K an-
275 tagonist; BB: beta-blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin
276 receptor blocker

277 Table 2. Outcomes in matched patients discharged on dual antiplatelet therapy (DAPT) or as-
 278 pirin alone.

	DAPT	Aspirin (matched)	DAPT effect*
N	609	609	
MACCE n(%)	34(5.6)	34(5.6)	0.97[0.59-1.59]
CV death/MI/CVA n(%)	21(3.5)	29(4.8)	0.71[0.40-1.27]
Mortality n(%)	7(1.2)	9(1.5)	0.78[0.29-2.1]
CV mortality n(%)	5(0.8)	8(1.3)	0.63[0.21-1.91]
MI n(%)	11(1.8)	13(2.1)	0.84[0.37-1.90]
CVA n(%)	9(1.5)	12(2.0)	0.75[0.31-1.78]
Repeat revascularization n(%)	17(2.7)	9(1.5)	1.91[0.85-4.33]

279 *Estimates obtained with Cox models stratified by PS-matched pairs and competing risk frame-
 280 work for MI, CVA and repeat revascularization.

281 DAPT: dual antiplatelet therapy; MACCE: major cardiac and cerebrovascular events; CV-
 282 death: cardiovascular death; MI: myocardial infarction; CVA: cerebrovascular accident

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