PHARMACIA

Pharmacia 67(3): 115–120
DOI 10.3897/pharmacia.6.e52738

Research Article

Antithrombotic regimens in patients after coronary artery bypass grafting and coronary endarterectomy

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Received 30 March 2020 ♦ **Accepted** 10 June 2020 ♦ **Published** 25 August 2020

Citation: Kyuchukov D, Zheleva-Kyuchukova I, Nachev G (2020) Antithrombotic regimens in patients after coronary artery bypass grafting and coronary endarterectomy. Pharmacia 67(3): 115–120. https://doi.org/10.3897/pharmacia.67.e52738

Abstract

Background: Coronary artery bypass grafting (CABG) remains the gold standard in the treatment of complex chronic forms of coronary heart disease (CHD). Coronary endarterectomy (CEAE) is a useful adjunctive technique to CABG in patients with diffuse coronary artery disease. In order to maintain the patency of the coronary arteries and graft conduits, various antithrombotic protocols have been introduced over the years, combining various antiplatelet and anticoagulant drugs, but still there is no consensus.

Aim: The aim of the study is to compare results between two antithrombotic regimens after CEAE. The first one is a combination of acenocoumarol combined with acetylsalicylic acid (ASA), the second regimen is a dual antiplatelet therapy (DAPT) of clopidogrel combined with ASA.

Material and methods: We retrospectively reviewed 56 consecutive patients (60 ± 8.2 years) undergoing isolated CABG in association with CEAE between January 2018 and December 2019. In the postoperative period, patients were divided into two groups according to the antithrombotic regimens described above. Twenty-four were in the ASA and acenocoumarol group (AA) and 32 were in the ASA and clopidogrel group (AC). Patients were followed up to 30 days after the operation and we access the mortality rate, new ECG changes, levels of myocardial fraction of creatinine phosphokinase (CPK-MB), left ventricular systolic function, pericardial or pleural effusions requiring drainage or revision for bleeding.

Results: Operative mortality was 3,6 %. No differences in the antithrombotic efficacy of the two regimens. A significantly higher level of hemorrhagic complications was observed in the ASA + acenocoumarol treatment group.

Conclusion: Dual antiplatelet therapy (DAPT) after CABG and coronary endarterectomy is an effective pharmacological regimen in regard to 30-day postoperative outcomes and is considerably safety in terms of bleeding complications.

Keywords

dual antiplatelet therapy (DAPT), coronary endarterectomy (CEAE), coronary artery bypass grafting (CABG)

Introduction

Complete myocardial revascularization is a major goal in the treatment of coronary heart disease (CHD). Coronary artery bypass grafting (CABG) remains the gold standard in the treatment of complex chronic forms of CHD, despite the widespread entry and improved results of percutaneous coronary intervention (PCI). Coronary endarterectomy (CEAE) is a useful adjunctive technique to CABG in patients with diffuse coronary artery disease. It was introduced by Baeily in 1957 for the treatment of coronary occlusion and during the years his role in cardiac surgery has remained unclear and results remain controversial. Coronary endarterectomy can be performed by either closed or an open technique. The role of antithrombotic therapy to improve long-term graft patency after coronary surgery is well known in literature. It plays a crucial role in preventing postoperative myocardial infraction (MI) in a case of CEAE, though not uniform, has been less aggressive. In order to maintain the patency of the endarterectomized coronary arteries, various antithrombotic protocols have been introduced over the years, combining various antiaggregant and anticoagulant drugs, but still there is no consensus. Antithrombotic treatment with anticoagulants and platelet inhibitors reduces the risk for thromboembolic complications. Strategies to intensify antithrombotic regimens are limited by concomitant increases in clinically significant intraoperative or postoperative bleeding.

Antiplatelet agents

Acenocoumarol

Acenocoumarol is a 4-hydroxycoumarin derivative with anticoagulant activity. As a vitamin K antagonist (VKA), acenocoumarol inhibits vitamin K epoxide reductase, thereby inhibiting the reduction of vitamin K and the availability of vitamin KH2 (2-Methyl-3-[(2E)-3,7,11,15-tetramethyl-2-hexadecenyl]-1,4-naphthalenediol). This prevents gamma carboxylation of glutamic acid residues near the N-terminals of the vitamin K-dependent clotting factors, including factor II, VII, IX, and X and anticoagulant proteins C and S. This prevents their activity and thus thrombin formation. Compared to other coumarin derivatives, acenocoumarol has a short half-life.

Acetylsalicylic acid (ASA)

ASA nonselectively and irreversibly acetylates a serine residue on the cyclooxygenase (COX) enzymes, suppressing the production of prostaglandins and thromboxane A2 (TxA2), a potent platelet activator ASA is one of the cornerstones for the treatment of acute and chronic cardiovascular disease. According to the landmark Antithrombotic Trialists' Collaboration meta-analysis of 287

studies including 212 000 patients ASA has been shown to reduce mortality, MI and cerebrovascular events in different subsets of patients with occlusive cardiovascular disease especially for secondary prevention. (Antithrombotic Trialists' Collaboration 2002) That's why ASA is at the foundation in most antithrombotic regimens, both as a single agent, and in combination with other antithrombotic agents, but should not be forgotten that increases the risk for bleeding complications.

Clopidogrel

Clopidogrel was released onto the market in 1997 in the United States, and in 1998 in Europe, and is a secondgeneration thienopyridine that exerts its anti-aggregating action by irreversibly inhibiting the bond between ADP and the P2Y12 surface purinergic receptors. This binding activates the inhibitory G protein, which results in a reduction of intra-platelet concentration of cyclic adenosine monophosphate (cAMP), which promotes the expression of GPIIb/IIIa aggregation receptors on the platelet surface. Thus, ADP is the P2Y12 receptor agonist, while adenosine triphosphate (ATP) is the receptor antagonist that increases the production of cAMP and therefore reduces platelet aggregation. (Gulizia et al. 2018) Clopidogrel has been widely studied and shown to reduce cardiovascular events among patients with atherosclerotic disease. Among high-risk patients with ischemic stroke, MI, or established PAD, clopidogrel monotherapy was associated with a 7.9% relative risk reduction in MI, ischemic stroke, vascular death, or rehospitalization compared with aspirin. (Bhatt et al. 2000)

Strategies to intensify antithrombotic regimens should be complemented by approaches that focus on targeting thrombosis while preserving hemostasis. Generally, as routine practice in patients with CABG / CE, it is recommended that vit K antagonist in combination with ASA should be continued until 3 months postoperatively and eventually ASA alone permanently.(Vafaey et al. 2018). The therapy with vit K antagonists has some serious potential side effects such as bleeding, tissue necrosis and hypersensitivity reactions. Patients must be evaluated weekly for International normalized ratio (INR) testing to keep it around 2–3. Current guidelines recommend DAPT for all patients with acute coronary syndrome (ACS) independently of revascularization treatment. This recommendation also applies to patients having CABG or other non-coronary cardiac operations. (Sousa-Uva et al. 2018) Furthermore, DAPT after CABG has been associated with reduced all-cause mortality (Verma et al. 2015) and better vein graft patency (OR 0.59; 95% CI 0.43–0.82) (Deo et al. 2013), although the evidence is conflicting. The potential benefits of DAPT after CABG are offset by an increased risk for bleeding complications. There is currently no evidence to support starting routine DAPT after CABG in patients not receiving DAPT preoperatively, although starting DAPT may be considered in patients with a higher ischaemic risk due to a coronary endarterectomy or off-pump surgery. (Sousa-Uva et al. 2018). Nowadays there is no unified guideline available regarding the use of antiplatelet or anticoagulation therapy in patients under-

going CEAE. Though most of the authors have followed different anticoagulation regimen as per their institute protocols, the overall reported difference in bleeding and mortality remains clinically insignificant.

Aim

The aim of this study is to compare results between two antithrombotic regimens. The first one is the combination of acenocoumarol (coumarin anticoagulant /VKA) and acetylsalicylic acid (ASA) - irreversible cyclooxygenase-1 inhibitor, which block the formation and release of thromboxane A2, a potent platelet activator. The second regimen is DAPT of clopidogrel - irreversible, competitive, thienopyridine P2Y12 receptor antagonist combined with ASA.

Material and methods

We analyzed 56 consecutive patients undergoing isolated CABG in association with CEAE between January 2018 and December 2019. Patients were not included in the analysis if they had one of the following: concomitant valve or aortic surgery; history of an allergic reaction to any of the medications used in the study; operation in a setting of acute coronary syndrome; prolonged intake of clopidogrel or acenocoumoral in the week before surgery; patients with more or less 3 bypass grafts and more than one vessel with CEAE. All patients had signed an informed consent and underwent standard CABG surgery, under conditions of cardiopulmonary bypass at moderate hypothermia 30–32 °C, aortic clamping, and myocardial protection with intermittent ante- and retrograde infusion of cold blood cardioplegic solution according to the protocol of the clinic. For revascularization of the anterior descending artery, the internal thoracic artery was always used as a "graft in situ" and the rest of the vessels were revascularized with segments of saphenous vein. In all cases, the decision for CEAE was made intraoperatively if the lumen of the coronary artery was completely obstructed and a large extension and a competent anastomosis was impossible. The CEAE itself was performed through a longitudinal arteriotomy measuring 8–20 mm, the so-called "closed method".

In the postoperative period, patients were divided into two groups according to two antithrombotic regimens. The first one is a combination of acenocoumarol and ASA . The second regimen is DAPT of clopidogrel combined with ASA. 24 pts operated in 2018 were included in the acenocoumarol and ASA group (AA) and 32, operated in 2019, were in the ASA and clopidogrel group (AC). Patients were followed up to 30 days after the operation and we access the mortality rate, new ECG changes (Q-waves and/or ST-T changes), levels of MB fraction of creatinine phosphokinase (CPK-MB), left ventricular systolic function, pericardial or pleural effusions requiring drainage or revision for bleeding. In the AA group in conjunction with intravenous heparin infusion started at the sixth postoperative hour, administration of 80 mg ASA and 6 mg acenocoumarol was initiated 6 hours later. The infusion was stopped when INR (International Normalized Ratio) values reached the range of 2–3. To maintain a stable therapeutic level of acenocoumarol daily INR testing was measured. In the AC group in conjunction with intravenous heparin infusion started at the sixth postoperative hour if there is no bleeding from the drainage on the 12th hour patient received a loading dose of 300 mg clopidogrel plus 80 mg ASA followed by daily therapy of 75 mg clopidogrel and 80 mg ASA.

Statistical analysis:

For all analyzes was used statistical analysis software (Version 18, SPSS). All continuous

values were expressed as mean plus or minus 1 standard deviation of the mean. For categorical

data were used chi-square test, Fisher exact test and t-test. A p-value less than 0.05 was considered significant.

Results

Data from 56 consecutive eligible patients was processed. The average age of patients was 60 ± 8.2 years**.** Table 1 presents the main preoperative patients' characteristics.

There was no significant difference in the distribution of reported preoperative demographic and risk factors, as well as in the calculated operative risk according to EuroScore system.

The comparison of anatomic and intraoperative data also showed no significance between groups (Table 2).

From all CEAE cases only 4 (7,14 %) were in left anterior descending (LAD) coronary artery (equally in both groups) and 50 (89,3%) cases in the right coronary artery (RCA) (including 21 cases in AA group and 29 cases in AC group). The mean ECC time was 74,2 ± 10,2 min in AA group and 77,2 ± 11,3 min in AC group. This difference was not statistically significant. The mean AoXclamping time also showed no difference. (44,6 ± 3,45 for AA group vs 46,7 ± 3,29 for AC group).

Regarding the reported ECG changes, no new onset Q-waves and no significant ST-T changes were found in all

Table 1. Preoperative patients' characteristics.

	AA (N = 24)	AC (N = 32)	P
Male (%)	16(66,7%)	20 (62,5%)	NS
Age (years)	59,86 ± 9,88	61,68 ± 10,11	
Smoking %	20 (83,3%)	28 (87,5%)	
Arterial hypertension %	23 (95,8%)	31 (96,9%)	
Diabetes %	13 (54,2%)	18 (56,3%)	
Obesitas %	7 (29,2%)	10 (31,2%)	
Previous MI %	20 (83,3%)	25 (78,1%)	
CKD > 2 stage %	6 (25%)	9 (28,1%)	
COPD %	4 (16,6%)	4 (12,5%)	
EuroSCORE	3,9 ± 1,95	3,4 ± 2,21	

Abbreviations: MI – myocardial infarction, CKD – chronic kidney disease, COPD – chronic obstructive pulmonary disease.

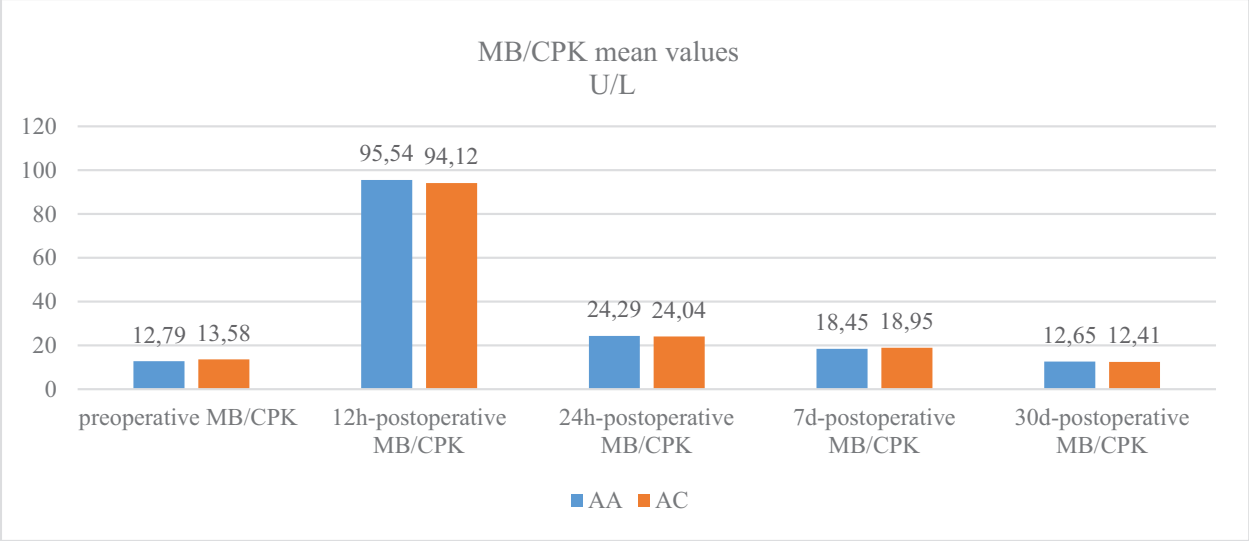

Figure1. MB/CPK mean values.

Table 2. Anatomic and intraoperative characteristics.

	AA (N = 24)	AC (N = 32)	P
RCA N (%)	21 (87,5%)	29 (90,4%)	NS
LCx N (%)	1 (4,2%)	1 (3,2%)	
LAD N (%)	2 (8,3%)	2 (6,4%)	
Distal anastomosis (average number ± SD)	2,9 ± 0,43	3,03 ± 0,49	
CPB (average time, min± SD)	74,2 ± 10,2	77,2 ± 11,3	
Ao X clamping (average time, min± SD)	44,6 ± 3,45	46,7 ± 3,29	

Abbreviations: RCA- Right Coronary Artery; LAD – Left Anterior Descending Coronary Artery; LCx- Circumflex Branch of Left Coronary Artery; CPB- Cardio-Pulmonary Bypass, time: AoXclamping- Cross clamping of Ascending Aorta.

Table 3. Left ventricle systolic function.

	AA (N = 24) Mean ± SD	AC (N = 32) Mean ± SD
Preoperative LVEF	41,61 ± 9,87	42,56 ± 7,78
Postoperative LVEF	41,05 ± 10,54	44,73 ± 8,61
p - value	0,316	0,212

Abbreviations: LVEF – left ventricle ejection fraction
Pre and postoperative echocardiographic study of LVEF showed no significant difference between the two groups.

Table 4. Bleeding complications.

	Revisions for bleeding %	Pericardial effusions %	Pleural effusions %
AA (N = 24)	3 (12,5%)	4 (16,6%)	12 (50%)
AC (N = 32)	1 (3,1%)	1 (3,1%)	3 (9,3%)
p-value	0,004	0,004	0,0001

patients in the study. Serum MB/CPK levels were checked before surgery and immediately after surgery, in addition to 24 and 48h later. The following Figure 1 depicts the evolution of the average MB/CPK of patients in two groups during the perioperative and 30-day postoperative period.

No significant difference was found between groups. Point of interest is the early postoperative increasing of

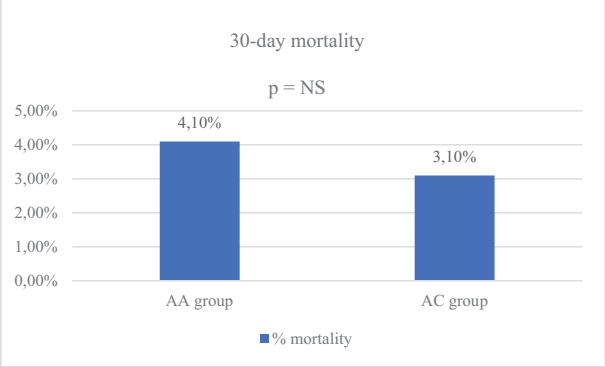

Figure 2. 30-day mortality.

MB/CPK levels, which rapidly dropped off to normal values after 24 hours and persists within these ranges through the whole follow up period.

The ejection fraction (EF) of left ventricle (LV) was recorded by transthoracic echocardiography using the Simpson method, and values were registered before surgery and on the 30-th postoperative day. (Table 3).

The overall mortality rate for all patients was 3.6% and was established in the early postoperative period. For the AA group it is 4.1% and for the AP group 3.1%, the difference is not statistically significant (p = NS) (Fig.2)

The mortality analysis showed no difference between the two groups within 30-y days. Patients died in the early postoperative period with a picture of low-debit syndrome, resistance to catecholamine and intra-aortic balloon pump therapy.

The percentages of bleeding and pericardial or pleural effusions indicated surgical treatment are presented on Table 4.

The differences between the groups are significant in terms of all three indicators and in favor of the group receiving dual antiplatelet therapy.

Disscussion

Coronary endarterectomy was introduced by Baeily in 1957 for the treatment of coronary occlusion and during the years his role in cardiac surgery has remained unclear and results remain debated. The operative mortality ranges from 2.0% to 6.5% and appears higher as compared with CABG without CEAE. (Byrne et al. 2003; Vohra et al. 2006) A recent meta-analysis of 54,440 patients (7,366 CE patients), enrolled in twenty observational studies by Soylu et al.(2014), showed an increased 30-day mortality (OR = 1.69; 95% CI: 1.49–1.92; $p < 0.00001$), perioperative (OR = 2.10; 95% CI: 1.82–2.43; $p < 0.00001$) and post-operative MI (OR = 3.34; 95% CI: 1.74–6.41; $p = 0.0003$) in the CABG plus CEAE group in comparison with CABG alone. As it is reported in literature, 30-days mortality in our study was 3,6%. Patients undergoing CEAE had a preoperative score from low to intermediate risk, (mean EuroSCORE value was 3,9 ± 1,95 for AA group and 3,4 ± 2,21 in AC group (p=NS)) and, as expected, operative mortality was higher than that observed in patients undergoing CABG alone operated in our institution - 2,5%. The late graft patency rates after CEAE range from 40% to 81.5%: Schwann et al. analyzed the results of 288 operated with CABG/ CEAE. (Schwann et al. 2007; Nishi et al. 2005). In order to reduce the incidence of thrombosis, several authors have recommended the use of aggressive postoperative antiplatelet and anticoagulant therapy, varying from dual antiplatelet to lifelong oral anticoagulant therapy. No standard anticoagulation protocol after CEAE exists. (Tiruvoipati et al. 2005) According to the so-called "classical regimen" introduced 40 years ago (long before the discovery of modern antiplatelet agents) postoperatively, 100 mg of ASA and warfarin administration to obtain an INR between 2 and 2.5 were recommended, and then, after 3 months, warfarin was discontinued based on the minimum period for neoendothelialization of the coronary artery.(Schwann et al. 2007; Nishi et al. 2005; Schmitto et al. 2009) In order to reduce morbidity, mortality and specific anticoagulant-related toxicity (total annual risk ≈ 4%), prolonged monitoring of serum activity is required through serial INR controls, which is associated with a number of patients' discomfort. Nishigawa et al. (2017) proposed the use of dual antiplatelet therapy in association with warfarin for the first 3 months after CEAE, following by ASA only continued indefinitely. Using this protocol, the patency rate of the internal thoracic artery on the endarterectomized LAD at 13 ±12 months was 96.6%.

Our study aims to determine whether dual antiplatelet therapy with clopidogrel and ASA is sufficient to prevent early (up to day 30) thrombosis of endarterectomy coronary arteries and to account for the level of additional risks, formulated as percentages of bleeding and follow-up revisions. Definitive assessment of the patency of the coronary graft requires coronary catheterization, which is not recommended in the absence of other clinical indications. For this reason, we used indirect patency assessment tools, including: postoperative ECG changes (new Q wave and / or ST-T segment changes); increased CPK/MB (excess of more than 5 times standard value); changes in LVEF assessed by ultrasound also considered as an indirect indicator of bypass patency. Most studies regarding patients with CEAE compare their results with those of patients undergoing conventional surgical revascularization, with controversial outcomes. Some authors declare that there are no significant differences in postoperative outcomes between two techniques, and thus substantiate the conclusion that CEAE is a competitive option allowing complete revascularization in patients with severely diffuse atherosclerosis. (Nemati et al. 2015) Quite the opposite are the results of almost the same number of studies published by other authors reporting elevated mortality rates and complications in endarterectomized versus conventionally revascularized patients, and recommend only a limited number of cases with severe restrictive indications. (Bernal-Aragón et al. 2015) Byrne et al. (2004) found that, because of the large area of destroyed endothelium of target vessel during CEAE, ASA monotherapy was not sufficient to provide long-term bypass patency. Article by Ferraris et al. (2000) 20 years ago, based on late angiographic outcomes of patients with single CEAE, published that the addition of coumarin anticoagulant to ASA therapy does not reduce the rate of bypass thrombosis but increases the hemorrhagic risk. Despite the lack of sufficient evidence, it can be suggested that the pathogenetic processes responsible for the development of thrombosis during coronary endarterectomy are similar to the changes that occur with percutaneous stenting. (Russo et al. 2016) DAPT with ASA and P2Y12-receptor inhibitor (clopidogrel) reduces the risk for thrombotic complications in patients with acute coronary syndrome (ACS) compared to treatment with ASA only (Verdoia et al. 2018) especially if they undergo percutaneous coronary intervention. ASA administration is Class I indication after CABG (Patrono et al.) and the benefit of concomitant clopidogrel is a controversial issue. Different studies have shown that DAPT increases saphenous vein graft patency and play a role to maintain the grafts patent after off-pump bypass surgery or after CABG performed in a setting of acute coronary syndrome. (Deo et al. 2013; Bomb et al. 2015) These results are limited to specific subgroups of patients and the majority of clinical trials have failed to demonstrate an improvement in graft patency with DAPT. Despite that, there are no evidence and no specific protocols regarding postoperative management of patients treated with CABG/ CEAE in term of antithrombotic specific regimen. We found significantly higher levels of hemorrhagic postoperative complications in the AA group (p=0,004). In a combination with impaired quality of life and risks associated with regular intake of oral anticoagulant, warranted us to recommend the use of DAPT as an effective and safer alternative for postoperative antithrombotic therapy in CEAE.

The study has a lot of weak points, most notably the small number of patients, short follow-up, operations performed in one center, chronologically separated groups and lack of opportunity for randomization.

Conclusion

CEAE associated with CABG appears to be an important surgical tool for successful treatment of complex CHD with acceptable 30-day results, although the operative mortality is higher in comparison with CABG alone. In order to reduce the incidence of surgical bleeding, at equal efficiency with respect to graft patency, we recommend the use of DAPT (ASA and Clopidogrel) started early postoperatively.

References

Antithrombotic Trialists' Collaboration (2002) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 324(7329): 71–86. [published correction appears in BMJ 2002 Jan 19;324(7330):141]. https://doi.org/10.1136/bmj.324.7329.71

Bernal-Aragón R, Sáenz-Rodríguez R, Orozco-Hernández E, Guzmán-Delgado N, Aragón-Manjarrez R, Hernández-Alvídrez A (2015) Experiencia de la endarterectomía coronaria en cirugía de revascularización miocárdica [Coronary endarterectomy experience in myocardial revascularization]. Cirugía y Cirujanos 83(4): 273–278. https://doi.org/10.1016/j.circir.2015.05.049

Bhatt DL, Hirsch AT, Ringleb PA, Hacke W, Topol EJ (2000) Reduction in the need for hospitalization for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. CAPRIE investigators. American Heart Journal 140(1): 67–73. https://doi.org/10.1067/mhj.2000.108239

Bomb R, Oliphant CS, Khouzam RN (2015) Dual Antiplatelet Therapy After Coronary Artery Bypass Grafting in the Setting of Acute Coronary Syndrome. American Journal of Cardiology 116(1):148–154. https://doi.org/10.1016/j.amjcard.2015.03.050

Byrne JG, Karavas AN, Gudbjartson T, et al. (2004) Left anterior descending coronary endarterectomy: early and late results in 196 consecutive patients. The Annals of Thoracic Surgery 78(3): 867–874. https://doi.org/10.1016/j.athoracsur.2004.03.046

Deo SV, Dunlay SM, Shah IK, et al. (2013) Dual anti-platelet therapy after coronary artery bypass grafting: is there any benefit? A systematic review and meta-analysis. Journal of Cardiac Surgery 28(2): 109–116. https://doi.org/10.1111/jocs.12074

Ferraris VA, Harrah JD, Moritz DM, Striz M, Striz D, Ferraris SP (2000) Long-term angiographic results of coronary endarterectomy. The Annals of Thoracic Surgery 69(6): 1737–1743. https://doi.org/10.1016/S0003-4975(00)01293-5

Gulizia MM, Colivicchi F, Abrignani MG, et al. (2018) Consensus Document ANMCO/ANCE/ARCA/GICR-IACPR/GISE/SICOA: Long-term Antiplatelet Therapy in Patients with Coronary Artery Disease. European Heart Journal Supplements 20 (Suppl F): F1–F74. https://doi.org/10.1093/eurheartj/suy019

Nemati MH, Astaneh B, Khosropanah S (2015) Outcome and graft patency in coronary artery bypass grafting with coronary endarterectomy. The Korean Journal of Thoracic Cardiovascilar Surgery 48(1): 13–24. https://doi.org/10.5090/kjtcs.2015.48.1.13

Nishi H, Miyamoto S, Takanashi S, et al. (2005) Optimal method of coronary endarterectomy for diffusely diseased coronary arteries. The Annals of Thoracic Surgery 79(3): 846–853. https://doi.org/10.1016/j.athoracsur.2004.06.070

Nishigawa K, Fukui T, Yamazaki M, Takanashi S (2017) Ten-Year Experience of Coronary Endarterectomy for the Diffusely Diseased Left Anterior Descending Artery. The Annals of Thoracic Surgery 103(3): 710–716. https://doi.org/10.1016/j.athoracsur.2016.11.028

Patrono C, Bachmann F, Baigent C, et al. (2004) Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology. European Heart Journal 25(2): 166–181. https://doi.org/10.1016/j.ehj.2003.10.013

Russo M, Nardi P, Saitto G, Bovio E, Pellegrino A, et al. (2016) Coronary artery bypass grafting with adjunctive endarterectomy: A mandatory procedure in complex revascularizations. current results and postoperative considerations. Journal of Integrative Cardioloy 2. https://doi.org/10.15761/JIC.1000174

Schmitto JD, Kolat P, Ortmann P, et al. (2009) Early results of coronary artery bypass grafting with coronary endarterectomy for severe coronary artery disease. Journal of Cardiothoracic Surgery 4: 52. https://doi.org/10.1186/1749-8090-4-52 [Published 2009 Sep 22]

Schwann TA, Zacharias A, Riordan CJ, Durham SJ, Shah AS, Habib RH (2007) Survival and graft patency after coronary artery bypass grafting with coronary endarterectomy: role of arterial versus vein conduits. The Annals of Thoracic Surgery 84(1): 25–31. https://doi.org/10.1016/j.athoracsur.2007.02.053

Sousa-Uva M, Head SJ, Milojevic M, et al. (2018) 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. European Journal of Cardiothoracic Surgery 53(1): 5–33. https://doi.org/10.1093/ejcts/ezx314

Soylu E, Harling L, Ashrafian H, Casula R, Kokotsakis J, Athanasiou T (2014) Adjunct coronary endarterectomy increases myocardial infarction and early mortality after coronary artery bypass grafting: a meta-analysis. Interactive Cardiovascular and Thoracic Surgery 19(3): 462–473. https://doi.org/10.1093/icvts/ivu157

Tiruvoipati R, Loubani M, Lencioni M, Ghosh S, Jones PW, Patel RL (2005) Coronary endarterectomy: impact on morbidity and mortality when combined with coronary artery bypass surgery. The Annals of Thoracic Surgery 79(6): 1999–2003. https://doi.org/10.1016/j.athoracsur.2004.12.041

Vafaey HR, Salehi Omran MT, Abbaspour S, Banihashem N, Faghanzadeh Ganji G (2018) Anti-coagulation therapy following coronary endarterectomy in patient with coronary artery bypass graft. Caspian Journal of Internal Medicine 9(1): 27–31.

Verma S, Goodman SG, Mehta SR, et al. (2015) Should dual antiplatelet therapy be used in patients following coronary artery bypass surgery? A meta-analysis of randomized controlled trials. BMC Surgery 15: 112. https://doi.org/10.1186/s12893-015-0096-z [Published 2015 Oct 14]

Vohra HA, Kanwar R, Khan T, Dimitri WR (2006) Early and late outcome after off-pump coronary artery bypass graft surgery with coronary endarterectomy: a single-center 10-year experience. The Annals of Thoracic Surgery 81(5): 1691–1696. https://doi.org/10.1016/j.athoracsur.2005.12.028

Verdoia M, Khedi E, Ceccon C, Suryapranata H, De Luca G (2018) Duration of dual antiplatelet therapy and outcome in patients with acute coronary syndrome undergoing percutaneous revascularization: A meta-analysis of 11 randomized trials. International Journal of Cardiology 264: 30–38. [published correction appears in Int J Cardiol. 2018 Nov 15; 271: 407] https://doi.org/10.1016/j.ijcard.2018.06.016