Author`s Reply

To the Editor,

We would like to thank the authors of this letter for their interest in our recently published paper (1). We agree that antithrombotic management of patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) can be challenging, especially in the elderly population, due to the attendant bleeding risk. International guidelines have previously recommended triple therapy, including oral anticoagulation (OAC) and dual antiplatelet treatment, for one up to six months after PCI as the preferred strategy to prevent both coronary events and AF-related thromboembolic complications (2, 3). With the aim to reduce the risk of bleeding events, recent studies have investigated in this setting the use of dual antithrombotic therapy with a single antiplatelet agent, mainly a P2Y12 inhibitor, in combination with OAC (4-6). We have recently published a study-level meta-analysis of randomized trials on this topic, including approximately 6,000 patients with indication to chronic OAC, mostly because of AF; this meta-analysis showed that, compared to triple therapy, dual antithrombotic treatment with a single antiplatelet agent (essentially clopidogrel) plus OAC [warfarin or non-vitamin K antagonist anticoagulant (NOAC)] prevented 15 major bleeding and 39 minor bleeding events per 1,000 patients at one year, without any increase in the risk of myocardial infarction, definite stent thrombosis or stroke (7). Interestingly, our data might suggest a potential survival benefit with dual antithrombotic regimen that needs confirmation by larger studies. These data reinforce the concept that dual therapy may represent the preferable therapeutic option in patients with AF undergoing PCI, especially in the elderly and in presence of a high bleeding risk. Available evidence and logical considerations derived from the better safety profile of NOACs compared to warfarin, indicate that the optimal combination for dual therapy may be a P2Y12 inhibitor plus a NOAC.

Ilaria Cavallari, Giuseppe Patti
Department of Cardiovascular Science, Campus Bio-Medico University of Rome; Rome-*Italy*

References

1. Cavallari I, Patti G. Efficacy and safety of oral anticoagulation in elderly patients with atrial fibrillation. Anatol J Cardiol 2018; 19: 67-71.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37: 2893-62.
3. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al; ACC/AHA Task Force Members, Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130: 2354-94.
4. Dewilde WJM, Oirbans T, Verheugt FWA, Kelder JC, Smet BJGL De, Herrman JP, et al; WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013; 381: 1107-15.
5. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med 2016; 375: 2423-34.
6. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al; RE-DUAL PCI Steering Committee and Investigators. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med 2017; 377: 1513-24.
7. Cavallari I, Patti G. Meta-Analysis Comparing the Safety and Efficacy of Dual Versus Triple Antithrombotic Therapy in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention. Am J Cardiol 2017 Dec 25. doi: 10.1016/j.amjcard.2017.12.014. [Epub ahead of print]

Address for Correspondence: Giuseppe Patti, MD,
Campus Bio-Medico University of Rome,
Via Alvaro del Portillo, 200, 00128,
Rome-*Italy*
Phone: +39-06-225411612
E-mail: g.patti@unicampus.it

High anthracycline cumulative dose without cardiac toxicity: A possible protective role of morphine

To the Editor,

Improvements in global anticancer strategy have resulted in better outcomes for a large proportion of cancer patients. Anthracyclines (A) are the best studied anticancer drugs with an established clinically significant dose-dependent cardiotoxicity. One of the strategies developed to reduce their well-known dose-dependent toxicity is dose limitation to 400-450 mg/m^2 for doxorubicin (DOX) and 900 mg/m^2 for epirubicin (E) (1). Preclinical evidences have pointed out a possible role for morphine as a cardioprotective agent (2, 3). On the basis of these, we conducted a retrospective database search to determine patients receiving a higher E dose without cardiotoxicity so as to look for clinical or pharmacological protective factors while focusing on concomitant opioid use.

We collected data of patients who were receiving a cumulative dose of E >900 mg/m^2 (representing the threshold warning dose) and who had undergone regular appropriate cardiac monitoring (1) without any evidence of cardiotoxicity. All available clinical/pathological characteristics were recorded focusing on concomitant medication with known cardioprotective effects as well as concomitant opioid use. We identified 10 such patients [median age, 58 (range, 49-71) years, F/M=9/1]. Their cumulative epirubicin dose was 1600 (range, 1350-2220) mg. None of the clinical parameters (age, sex, body mass index, comorbidities,

and previous anticancer agent use) was associated with non-cardiotoxic effect. All patients concomitantly received opioids for long term for pain control [median morphine dose, 60 (range, 20-160) mg/die] started before weekly E therapy and kept after treatment stop . Only for the purpose of generating hypotheses, we compared the identified population with eight patients who had developed cardiotoxicity after or during A treatment. The two groups showed overlapping prevalences of cardiovascular risk factors and cardioprotective agent [β-blockers, sartans, and renin-angiotensin-aldosterone system (RAAS) inhibitors] use; however, those developing cardiotoxicity were slightly older [median age 67 (range, 59-82) yrs] and reported diabetes more frequently in their medical history; furthermore, only three of those eight patients received concomitant opioids.

Excessive reactive oxygen species (ROS) generation by A, together with iron complexes formation, is the most accepted hypothesis on anthracycline-induced cardiomyopathy (4). Morphine can exert a cardioprotective role in preclinical models. Molecular mechanisms underlying the cardioprotective effect of morphine are poorly understood; however, a theory on prevention of ROS-induced cell apoptosis in neuroblastoma cells has proposed inhibition of ROS generation as well as blockade of nuclear factor-kappa B transcription signaling pathway by morphine (5). Morphine inhibits ROS generation and prevents DOX-mediated caspase-3 activation, cytochrome-c release, and changes in Bax and Bcl-2 protein expression, leading to inhibition of cell apoptosis (5). We found that all patients receiving higher than usual cumulative dose of E without cardiotoxicity concomitantly received long-term morphine treatment for pain control. Interestingly, when checked for concomitant "cardioprotective" medications (β-blockers, sartans, and RAAS inhibitors) to exclude possible confounding factors, none but two were found to have received such agents, making a protective effect unlikely .

Keeping in mind study limitations (small sample size, selection bias, single-center experience, and descriptive hypothesis-generating only comparison), our results represent the first clinical data supporting the preclinical hypothesis of a cardioprotective effect of morphine pretreatment. A prospective confirmation of our results on a larger population is needed.

Maria Laura Canale, Andrea Camerini*, Massimo Magnacca, Jacopo Del Meglio, Alessio Lilli, Sara Donati*, Domenico Amoroso*, Giancarlo Casolo

Departments of Cardiology and *Medical Oncology, Versilia Hospital-Azienda USL Toscana Nord-Ovest; Lido di Camaiore-*Italy*

References

1. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al; ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 2768-2801. [CrossRef]
2. Kelishomi RB, Ejtemaeemehr S, Tavangar SM, Rahimian R, Mobarakeh JI, Dehpour AR. Morphine is protective against doxorubicin-induced cardiotoxicity in rat. Toxicology 2008; 243: 96-104. [CrossRef]
3. He SF, Jin SY, Wu H, Wang B, Wu YX, Zhang SJ, et al. Morphine preconditioning confers cardioprotection in doxorubicin-induced failing rat hearts via ERK/GSK-3β pathway independent of PI3K/Akt. Toxicol Appl Pharmacol 2015; 288: 349-58. [CrossRef]
4. Doroshow JH. Effect of anthracycline antibiotics on oxygen radical formation in rat heart. Cancer Res 1983; 43: 460-72.
5. Lin X, Li Q, Wang YJ, Ju YW, Chi ZQ, Wang MW, et al. Morphine inhibits doxorubicin-induced reactive oxygen species generation and nuclear factor κB transcriptional activation in neuroblastoma SH-SY5Y cells. Biochem J 2007; 406: 215-21. [CrossRef]

Address for Correspondence: Maria Laura Canale, MD,
Department of Cardiology,
Versilia Hospital-Azienda USL Toscana Nord-Ovest;
Lido di Camaiore-*Italy*
Phone: +39 0584 605 97 12
Fax: +39 0584 605 72 08
E-mail: marialaura.canale@uslnordovest.toscana.it

DOI:10.14744/AnatolJCardiol.2018.65481