Dual antiplatelet therapy versus oral anticoagulation plus dual antiplatelet therapy in patients with atrial fibrillation and low-to-moderate thromboembolic risk undergoing coronary stenting: Design of the MUSICA-2 randomized trial

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Background Oral anticoagulation (OAC) is the recommended therapy for patients with atrial fibrillation (AF) because it reduces the risk of stroke and other thromboembolic events. Dual antiplatelet therapy (DAPT) is required after percutaneous coronary intervention and stenting (PCI-S). In patients with AF requiring PCI-S, the association of DAPT and OAC carries an increased risk of bleeding, whereas OAC therapy or DAPT alone may not protect against the risk of developing new ischemic or thromboembolic events.

Objective The MUSICA-2 study will test the hypothesis that DAPT compared with triple therapy (TT) in patients with nonvalvular AF at low-to-moderate risk of stroke ($CHADS_2$ score ≤2) after PCI-S reduces the risk of bleeding and is not inferior to TT for preventing thromboembolic complications.

Design The MUSICA-2 is a multicenter, open-label randomized trial that will compare TT with DAPT in patients with AF and $CHADS_2$ score ≤2 undergoing PCI-S. The *primary end point* is the incidence of stroke or any systemic embolism or major adverse cardiac events: death, myocardial infarction, stent thrombosis, or target vessel revascularization at 1 year of PCI-S. The *secondary end point* is the combination of any cardiovascular event with major or minor bleeding at 1 year of PCI-S. The calculated sample size is 304 patients.

Conclusions The MUSICA-2 will attempt to determine the most effective and safe treatment in patients with nonvalvular AF and $CHADS_2$ score ≤2 after PCI-S. Restricting TT for AF patients at high risk for stroke may reduce the incidence of bleeding without increasing the risk of thromboembolic complications. (Am Heart J 2013;166:669-75.)

Atrial fibrillation (AF) portends an increased risk of systemic embolization, with cerebral embolism being the most catastrophic consequence. In patients with nonvalvular AF, oral anticoagulation (OAC) is recommended for those at medium or high risk for embolization, mainly to reduce the risk of stroke.[1] $CHADS_2$ score is widely used to assess the thromboembolic risk of patients with AF.[2]

Antithrombotic therapy is essential to prevent the risk of stent thrombosis or myocardial ischemic events in patients undergoing percutaneous coronary intervention (PCI) and stenting (PCI-S). Thus, dual antiplatelet therapy (DAPT) is recommended for PCI-S for at least 4 weeks in patients treated with bare-metal stents (BMS) or 6 to 12 months for those receiving drug-eluting stents (DES) or after an acute coronary syndrome (ACS).[3-6]

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Clinical trial registration: ClinicalTrials.gov no. NCT01141153.
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0002-8703/$ - see front matter

http://dx.doi.org/10.1016/j.ahj.2013.07.028

Approximately 5% of patients undergoing PCI-S are on OAC for AF.[1,5,6] The association of DAPT and OAC significantly increases the risk of bleeding to unacceptable rates (between 9% and 27% of major bleeding).[7-24] Therefore, management of patients on OAC who undergo PCI-S presents an unsolved clinical dilemma. The balance between reducing the risk of thromboembolic events and increasing major bleeding risk is the key point for therapeutic decision making in these patients.

For the management of patients with AF undergoing PCI-S, the current guidelines of the American College of Cardiology/American Heart Association have exercised caution in recommending triple therapy (TT), suggesting the combined therapy of lower OAC strictly to maintain an international normalized ratio (INR) between 2 and 3 using low-dose aspirin, with clopidogrel for 9 to 12 months and maintaining OAC monotherapy thereafter.[1] Dual antiplatelet therapy is reserved for patients in whom OAC is considered unsuitable owing to patient preference or inability to safely sustain anticoagulation (class IIb). On the other hand, the European Society of Cardiology clinical practice guidelines recommend treatment with TT for all patients with AF on OAC who undergo PCI-S, with its duration being established according to hemorrhagic risk, type of stent implanted, and clinical setting.[25] After discontinuation of TT, these guidelines recommended OAC plus a single antiplatelet agent for up to 12 months.

The ACTIVE-W study demonstrated that OAC is superior to DAPT in patients with AF and $CHADS_2$ score ≥ 1. However, this trial—using a daily aspirin dose of 100 mg—was not focused on patients with recent PCI in whom the benefit of warfarin against ischemic stroke might be counterbalanced by an excess of hemorrhagic complications by warfarin given in the setting of TT. On the other hand, although no data are available on the risk of stroke or systemic embolism in AF patients after PCI, it has been estimated, based on data from the same ACTIVE-W trial,[26] that this risk would be relatively low (0.2% per month) in AF patients at intermediate or high risk for stroke on DAPT alone.[27] In fact, although clinical practice guidelines recommend TT in AF patients undergoing PCI-S, this strategy significantly increases the incidence of bleeding events. The most devastating bleeding event is intracranial hemorrhage, which, in some series, accounted for 90% of the deaths associated with warfarin use in the first 30 days after initiation of therapy and was the main cause of disability among survivors. Major bleeding has been associated with a 3- to 7-fold higher mortality rate among ACS patients compared with patients without bleeding.[28-30] This higher mortality rate is not only due to the bleeding event itself but also because to its consequences such as discontinuation of antithrombotic treatment leading to thrombotic complications.[31,32]

In addition, the cumulative bleeding risk for both OAC and DAPT increases in direct relation to the duration of treatment. In a nationwide registry of 40,812 acute myocardial infarction patients in Denmark, the risk of bleeding during a mean follow-up of 476 days was 4.3% for DAPT and 12.3% for TT.[33] In meta-analyses of available trials, the risk of major bleeding with TT was estimated to be 2.2% at 1 month,[34] which increased to 4% to 12% at 1 year.[35] Finally, in AF patients with $CHADS_2 \geq 1$ treated with PCI-S, Faxon et al[27] estimated a rate of stent thrombosis on DAPT of 1.5% during the first year but a 5- to 36-fold higher risk for premature discontinuation within the first month. However, to date, the strategy of TT versus DAPT has not been prospectively compared in randomized trials.

Between 2007 and 2008, the Management and USe of antiagregants In antiCoagulated patients After coronary stenting registry, a multicenter registry to record the different antithrombotic strategies used in our country and to analyze their safety and efficacy according to stroke risk, was undertaken in 405 patients requiring OAC who underwent PCI-S. Triple therapy was associated with the highest incidence of bleeding events at all levels of stroke risk compared with OAC plus clopidogrel and DAPT, whereas the highest incidence of cardiovascular events was observed with the association of clopidogrel and OAC, particularly in patients at moderate to high risk for stroke. We also found that, in patients at low stroke risk, DAPT appeared to be as effective as TT in preventing thromboembolic events with a lower incidence of bleeding events, thereby suggesting that this could be the treatment of choice for this particular subgroup of patients.[12] Concurring with our results, Hansen et al,[13] in a large cohort study in 82,854 patients, found that strategies using OAC plus clopidogrel and TT were associated with the highest bleeding risk.

The recently published WOEST trial compared TT versus OAC plus clopidogrel in 573 chronically anticoagulated patients (69% for AF) treated with PCI-S. In that study, OAC plus clopidogrel was associated with a lower rate of bleeding events than TT, with no excess thrombotic/thromboembolic events after 1 year of follow-up.[24] Significant differences exist between WOEST and both our observational study and the current trial. First, only 21% of the WOEST population had an ACS, whereas 70% of patients included in MUSICA-1 study had an ACS. In this respect, it has been pointed out that the WOEST study was underpowered to confidently confirm that there is no excess of stent thrombosis when aspirin is omitted.[35] In this regard, the MUSICA-2 trial will include only patients with nonvalvular AF whereas, in WOEST,[24] almost one-third of patients had other indications for OAC including mechanical prostheses.

In summary, the MUSICA-2 trial will test the hypothesis that DAPT is not inferior to TT for preventing thrombotic complications and reduces the risk of bleeding

Table. Inclusion and exclusion criteria for eligibility to the study

Inclusion criteria	Exclusion criteria
1. Patients of both sexes, aged ≥18 y	1. Patients who cannot be followed up by the research team during the 12-m follow-up
2. Patients with permanent, persistent, or paroxysmal nonvalvular AF (at least 1 episode), documented electrocardiographically	2. Patients with severe kidney failure (estimated creatinine clearance ≤30 mL/min), neurologic deficits, active ulcer, or dyspepsia
3. Patients with ACS or stable angina who undergo PCI-S	3. Patients with severe bronchial asthma or severe liver impairment
4. Patients who have previously given their informed consent for participation in the study	4. Patients on regular treatment with nonsteroidal anti-inflammatory drugs
5. Female patients, with childbearing potential who have committed to using adequate contraception	5. Patients with an increased risk of bleeding[32]
	6. Patients who should receive pharmacologic treatment other than that specified in this protocol during the study period
	7. Pregnant women and those of childbearing age not using contraception
	8. For the sake of homogeneity, the new P2Y12 receptor blockers will not be allowed in the active phase of the study
	9. No patients on a new oral anticoagulant will be not eligible for the study
	9. Patients with a history of allergy to study drugs or excipients
	10. Patients with severe valvular heart disease
	11. Patients with $CHADS_2$ score >2
	12. Patients unable to receive the study treatment orally

in patients with AF at low to moderate risk for stroke who undergo PCI-S.

Study design

MUSICA-2 is a multicenter (10 tertiary Spanish teaching centers), open-label, randomized clinical trial with blinded independent event adjudication comparing the efficacy and safety of 2 antithrombotic regimens: DAPT (aspirin 300 mg/d plus clopidogrel 75 mg/d) versus TT (acenocumarol at doses required to obtain an INR between 2 and 2.5 plus aspirin 100 mg plus clopidogrel 75 mg daily) in patients with AF and low to moderate risk of stroke ($CHADS_2$ score ≤2) who undergo PCI-S. The trial will target the enrollment of 304 patients, of whom 50% will be assigned to receive TT and 50% to DAPT after PCI-S. After providing their written informed consent, all trial participants will be assigned to 1 of the 2 aforementioned treatment arms.

Study patients

The study will include patients with nonvalvular AF at low to moderate risk for stroke ($CHADS_2$ score ≤2) undergoing PCI and stent implantation (BMS or DES) for ACS or stable angina. The indications for PCI-S are based on the ACCF/SCAI/STS/ATTS/AHA/ASNC and ESC guidelines.[36,37]

Patients must meet each of the inclusion and none of the exclusion criteria (see details in Table) to be eligible.

Randomization

Patients who meet all the inclusion criteria and none of the exclusion criteria and signing their written informed consent will be randomized in consecutive order of qualification. Randomization will be conducted in blocks through a dedicated Web-based system (computer-generated sequence allocation), which will also be used for electronic data capture throughout the study. At each participating center, treatment allocation will be stratified by the type of stent used (BMS or DES). *Time zero* is defined as the time of randomization. Randomization will occur after conclusion of a successful PCI with stent placement. Patients will be considered enrolled in the study and eligible for final intention-to-treat analysis.

Procedures

The protocol recommends continuing OAC treatment periprocedurally (the target INR is 2.0) when PCI-S is performed, whereas the decision to continue OAC or bridge the preprocedural and periprocedural period with low-molecular-weight heparins is at the discretion of the attending physician. Both radial and femoral accesses for angiography and PCI are permitted. In patients with femoral access, the access site is preferably closed by means of a closure device, although this is not mandatory. Oral anticoagulation is administered in an unblinded manner, in tablets of 1 or 4 mg, and adjusted locally to an INR of 2.0 to 2.5 measured at least monthly; INR measurement will be recorded at each follow-up visit.

Duration of the treatment depends on the type of stent implanted: in the case of BMS, it will be 6 weeks and up to 1 year at the discretion of the attending physician; in the case of DES, the assigned treatment duration is 12 months. No concern exists regarding concomitant therapies except for OAC or another antiplatelet regimen. Other cardiac medications will be prescribed at the discretion of the attending physician.

Follow-up

Monitoring of patients is planned for 12 months after inclusion in the study: physical follow-up visits at the center are scheduled for day 14 after inclusion and at 6 weeks and 3, 6, and 12 months. Visit 0 corresponds to enrollment of the patient in the study and includes checking the fulfillment of inclusion/exclusion criteria; signing of informed consent; and, subsequently, patient randomization to 1 of the 2 treatment arms.

During follow-up visits, basic vital signs (blood pressure and heart rate) will be monitored, occurrence of cardiovascular and/or bleeding events will be recorded, and treatment adherence will be checked by pill count.

Furthermore, the INR reached at each follow-up visit will be recorded together with any changes in acenocumarol dose for the group receiving TT.

All data collected during the follow-up visits will be recorded on an online case report form.

Primary and secondary end points

The *primary end point* is the incidence of stroke, systemic embolism, and any of the following major adverse cardiac events (MACE): death, myocardial infarction, stent thrombosis, or target vessel revascularization.

The *secondary end point* is the combination of any major adverse events, that is, the incidence of any clinical adverse event (bleeding and/or thrombotic) occurring during follow-up.

Response criteria

Stroke is defined as the sudden onset of a neurologic deficit in an area consistent with the territory of a major cerebral artery and is categorized as ischemic, hemorrhagic, or unspecified. Hemorrhagic transformation will not be considered as a hemorrhagic stroke. Intracranial hemorrhage will be considered if there is a hemorrhagic stroke or subarachnoid or subdural hemorrhage. Stroke may be diagnosed through techniques such as brain computed tomography and, if required, magnetic resonance imaging.[38]

Systemic embolism is an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina, or grafts) and must be documented by angiography, surgery, scintigraphy, or autopsy.

Acute myocardial infarction is defined following the criteria of the ESC/ACCF/AHA/WHF.[39]

Stent thrombosis is defined according to the criteria of the Academic Research Consortium.[40]

Bleeding (major and minor) will be assessed according to the classification scheme of the TIMI and PRISM-PLUS trials.[41,42]

Deaths will be classified as vascular (including bleeding), nonvascular due to other specified causes (eg, malignancy), or of unknown etiology.

Predefined clinical variables will be: MACE (stroke and/or systemic embolism, myocardial infarction, stent thrombosis, target vessel revascularization or death).

A data safety and monitoring board comprising the principal investigator and 3 independent members will meet every 3 months to review follow-up data. According to the clinical trial protocol, criteria for stopping the treatment are (1) appearance of a serious adverse event, (2) decision of the patient, (3) inability to continue follow-up, (4) lack of adherence to treatment, and (5) death of the patient.

Bleeding events will be managed at the discretion of the treating physicians. If a patient reports a bleeding event, a medically trained interviewer will contact the local investigator and collect all information available on the event. In all cases, the primary investigator will be contacted to obtain confirmation or any clarification of details regarding the identified event. All bleeding events will immediately be reported to the data safety and monitoring board of the study.

An independent adjudication committee will be established for the blinded adjudication of efficacy outcomes, death, and bleeding.

Ethics and informed consent

The study will be conducted according to Good Clinical Practice standards for clinical drug trials and following the current national and international standards of the Declaration of Helsinki.

Before participating in this study, each investigator must obtain local ethics committee approval until the study is completed, and the investigators will inform the ethics committee of the progress of the study on at least an annual basis. Patients will be identified only by a patient identification code and randomization number to maintain patient confidentiality.

Before obtaining written consent, the investigator or collaborator will provide the patient with a written explanation of the study, accompanied by a verbal explanation giving the patient the opportunity to ask questions about the study.

Patients must voluntarily sign the informed consent form to participate in the study before inclusion before any determination is made or before starting treatment other than that prescribed as part of standard care.

Statistical analysis

Sample size was calculated after examination of the rate of events in our previous prospective study consisting of the systematic analysis of case records.[12] According to these data, we foresee that 92.1% of patients assigned to TT will be free of cardiovascular events, whereas this percentage will be higher, approximately 96%, with DAPT, and a 3% difference will be considered clinically

significant. Sample size was increased by 5% to account for potential dropouts. According to these data, 152 patients per group will suffice, with a power of 80% and a $P \leq .05$ considered as significant to declare DAPT as not inferior to TT. The final sample size is estimated at 304 patients, of whom 50% will receive DAPT and 50% TT (152 patients per treatment arm). The study was designed as a noninferiority trial. Analysis will be performed via 2 approaches: intention to treat and per protocol. A confirmatory analysis will be made of the demographic balance in the treatment groups. Descriptive statistics (mean, SD, median, and interquartile range for continuous data, and frequency tables for categorical data) of the main variables will be performed categorical demographic variables will be compared using the χ^2 test. Continuous demographic variables including total body surface will be compared using the Student *t* tests. Primary and secondary end point analyses will be based on time to first event. Kaplan-Meier–based cumulative incidence rates will be calculated and compared by means of the log-rank test. Multivariate analyses will be made for these purpose end points: primary and secondary, MACE, major adverse events, and for the following single outcomes: stroke, myocardial infarct, major bleeding, and death.

Although patients will be included in the study based on the $CHADS_2$ score, the $CHADS_2$-VASC and HAS-BLED scores[25] will also be calculated in all patients to permit which will allow performing post hoc analyses once the study has been completed.

Discussion

The MUSICA-2 study is the first randomized trial to assess DAPT as an alternative to TT in patients with AF and low to moderate thromboembolic risk.

The choice of an open-label design with blinded event ascertainment instead of a conventional double-blind trial was based on several factors. An open-label design is more likely to be representative of true differences in the management of acenocumarol plus DAPT and DAPT alone in daily practice. In addition, an open design would also allow management of intercurrent events based on the characteristics of the anticoagulant agent rather than managing all patients as if they were on acenocumarol. A double-blind methodology is complex, requiring dummy INRs and management, assuming that patients are assigned to acenocumarol.

Therefore, MUSICA-2 will randomize patients at risk for stroke to a regimen that excludes OAC because, as mentioned previously, the thromboembolic risk of patients with an intermediate to high risk of stroke on DAPT is 0.2% per month (2.4% per year) based on ACTIVE-W results. Also in support of this strategy, Fosbol et al,[43] in 7,619 older non–ST-segment elevation myocardial infarction patients with AF treated with antithrombotic therapy, found that compared with aspirin alone, patients treated with TT had a cardiovascular risk similar to DAPT, whereas TT strategy presented a significantly higher risk than DAPT for postdischarge bleeding at 30 days.

The use of different aspirin doses used in MUSICA-2 in the 2 treatment arms merits consideration. In the DAPT-only arm, the dose of 300 mg/d of aspirin was chosen as the ACC/AHA Guidelines recommend 81 to 325 mg aspirin daily in AF patients as an alternative to vitamin K antagonist in low-risk patients or in those with contraindications to OAC.[44] In addition, we hope that the dose of 300 mg/d of aspirin will increase the benefit, reducing the incidence of stroke already seen in the ACTIVE-W study.[26] The use of a single antiplatelet agent in combination with warfarin is uncommon after PCI-S and is not recommended by current guidelines because, until WOEST, DAPT was considered essential to protect against stent thrombosis. Based on the increased bleeding risk with TT, DAPT (clopidogrel 75 mg/d plus aspirin 300 mg/d) for a reduced period might also be safer than TT in patients with $CHADS_2 \leq 2$.

In summary, the aim of MUSICA-2 is to compare 2 drug combinations in AF patients undergoing to PCI-S; the results may have a significant impact on health given the current uncertainty regarding the optimal management of these patients and severity of the potential complications associated with antithrombotic regimen.

Acknowledgements

We are indebted to Christine O'Hara for help with the English version of the manuscript.

Disclosures

This study will be supported by a research grant from the Spanish Government (Fondo de Investigación Sanitaria), the Instituto de Salud Carlos III, Reference TRA-2, EC11-473, Eudract 2009-NCT1141153. No additional external funding was received for this study.

References

1. Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2011;15(123):e269-367.
2. Gage BF, Waterman AD, Shennon W, et al. Validation of clinical classification schemes for predicting stroke results from the national registry of atrial fibrillation. JAMA 2001;282:2864-70.
3. Leon M, Baim D, Popma J, et al. Randomized trial comparing three drug regimens to prevent thrombosis following elective coronary stenting. N Engl J Med 1998;339:1665-71.
4. Mehta SR, Yusuf S, Peters RJ, et al. Clopidogrel in unstable angina to prevent recurrent events trial (CURE) investigators. Effects of

pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-33.
5. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guidelines for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011; 124:e574-651.
6. Wijns W, Kolh P, Danchin N, et al. Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI). Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501-55.
7. Orford JL, Fasseas P, Melby S, et al. Safety and efficacy of aspirin, clopidogrel, and warfarin after coronary stent placement in patients with an indication for anticoagulation. Am Heart J 2004; 147:463-7.
8. Karjalainen PP, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet warfarin therapy after coronary stenting. Eur Heart J 2007;28:726-32.
9. Nguyen M, Lim YL, Walton A, et al. Combining warfarin and antiplatelet therapy after coronary stenting in the Global Registry of Acute Coronary Events: is it safe and effective to use just one antiplatelet agent? Eur Heart J 2007;28:1717-22.
10. Manzano-Fernandez S, Pastor FJ, Marin F, et al. Increased major bleeding complications related to triple antithrombotic therapy usage in patients with atrial fibrillation undergoing percutaneous coronary artery stenting. Chest 2008;134(3):559-67.
11. Ruiz-Nodar JM, Marín F, Hurtado JA, et al. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation. JACC 2008;51:818-25.
12. Sambola A, Ferreira-Gonzalez I, Angel J, et al. Therapeutic strategies after coronary stenting in chronically anticoagulated patients: the MUSICA study. Heart 2009;95:1483-8.
13. Hansen ML, Sorensen R, Clausen MT, et al. Risk of bleeding with single, dual or triple therapy with warfarin, aspirin and clopidogrel in patients with atrial fibrillation. Arch Intern Med 2010;170: 1433-41.
14. Gao F, Zhou YJ, Wang ZJ, et al. Meta-analysis of the combination of warfarin and dual antiplatelet therapy after coronary stenting in patients with indications for chronic oral anticoagulation. Int J Cardiol 2011;148:96-101.
15. Persson J, Lindbäck J, Hofman-Bang C, et al. Efficacy and safety of clopidogrel after PCI with stenting in patients on oral anticoagulants with acute coronary syndrome. EuroIntervention 2011;6:1046-52.
16. Lamberts M, Olesen JB, Ruwald MH, et al. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nation-wide cohort study. Circulation 2012;126(10): 1185-93.
17. Nikolsky E, Mehran R, Dangas GD, et al. Outcomes of patients treated with triple antithrombotic therapy after primary percutaneous coronary intervention for ST-elevation myocardial infarction (from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI] trial). Am J Cardiol 2012; 109(6):831-8.
18. Chan W, Ajani AE, Clark DJ, et al. Melbourne impact of periprocedural atrial fibrillation on short-term clinical outcomes following percutaneous coronary intervention. Interventional Group Investigators. Am J Cardiol 2012;109:471-7.
19. Smith JG, Wieloch M, Koul S, et al. Triple antithrombotic therapy following an acute coronary syndrome: prevalence, outcomes and prognostic utility of the HAS-BLED score. EuroIntervention 2012;8: 672-8.
20. Annala AP, Karjalainen PP, Biancari F, et al. Long-term safety of drug-eluting stents in patients on warfarin treatment. Ann Med 2012; 44:271-8.
21. Andrade JG, Deyell MW, Khoo C, et al. Risk of bleeding on triple antithrombotic therapy after percutaneous coronary intervention/-stenting: a systematic review and meta-analysis. Can J Cardiol 2013; 29(2):204-12.
22. Denas G, Padayattil Jose S, Gresele P, et al. Major bleeding in patients undergoing PCI and triple or dual antithrombotic therapy: a parallel-cohort study. J Thromb Thrombolysis 2013;35(2):178-84.
23. Ho KW, Ivanov J, Freixa X, et al. Antithrombotic therapy after coronary stenting in patients with nonvalvular atrial fibrillation. Can J Cardiol 2013;29(2):213-8.
24. Dewilde WJ, Oirbans T, Verheugt FW, et al, for the 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.
25. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery. Eur Heart J 2010;31(19):2369-429.
26. Connolly S, Pogue J, Hart R, et al, ACTIVE writing Group on behalf on the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbersatan for prevention of vascular events (ACTIVE W): a randomised controlled trial. Lancet 2006;367: 1903-12.
27. Faxon DP, Eikelboom JW, Berger PB, et al. Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting: a North American perspective: executive summary. Circ Cardiovasc Interv 2011;4:522-34.
28. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol 2005;96:1200-6.
29. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. J Am Coll Cardiol 2007;49:1362-8.
30. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol 2010;55:2556-66.
31. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114(8):774-82.
32. Doyle BJ, Rihal CS, Gastineau DA, et al. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. J Am Coll Cardiol 2009;53: 2019-27.
33. Sørensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009;374:1967-74.

34. Paikin JS, Wright DS, Crowther MA, et al. Triple antithrombotic therapy in patients with atrial fibrillation and coronary artery stents. Circulation 2010;121(18):2067-70.
35. Fox KA. Dual or single antiplatelet therapy with anticoagulation? Lancet 2013;381(9872):1080-1.
36. Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS /AHA/ASNC 2009 Appropriateness
Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. Circulation 2009; 119(9):1330-52.
37. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2010;31(20):2501-55.
38. Whiteley WN, Slot KB, Fernandes P, et al. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies. Stroke 2012;43(11):2904-9.
39. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126(16):2020-35.
40. Cutlip DE, Windecker S, Mehran R. Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115(17):2344-51.
41. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987;76:142-54.
42. [No authors listed]Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. N Engl J Med 1998; 338(21):1488-97.
43. Fosbol EL, Wang TY, Li S, et al. Safety and effectiveness of antithrombotic strategies in older adult patients with atrial fibrillation and non–ST elevation myocardial infarction. Safety and effectiveness of antithrombotic strategies in older adult patients with atrial fibrillation and non-ST elevation myocardial infarction. Am Heart J 2012;163(4):720-8.
44. Anderson JL, Halperin JL, Albert NM, et al. Management of Patients With Atrial Fibrillation (Compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS Recommendations): A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Management of Patients With Atrial Fibrillation (Compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS Recommendations): A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127(18):1916-26.