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Management and prevention of thrombotic stent occlusion

We read with a great interest, the paper by Wenaweser *et al.*[1] who report the efficacy and outcome of emergency percutaneous coronary interventions in patients with stent thrombosis.

Recently, we published our data on 1519 consecutive patients who underwent 2020 stent implantations and were discharged on dual anti-platelet therapy. We compared the short- and long-term risks of thrombotic stent occlusion (TSO) and mortality in patients given clopidogrel or ticlopidine.[2,3]

The rates of TSO during the first year of follow-up, in our study, were 1.8, 0.7, and 2.8% in the whole group, the ticlopidine group and the clopidogrel group ($P < 0.01$). A multivariate model showed that clopidogrel (vs. ticlopidine) treatment was the sole predictor of TSO (OR = 5.4, 95% CI = 1.2–24.1, $P = 0.028$). Of even greater concern, clopidogrel treatment was associated with an increased risk of 1-year mortality (OR = 1.8, 95% CI = 1.2–2.8). Our data are in agreement with those published by Mueller *et al.*[4] who reported that the extended follow-up data of their initial randomized trial which compared clopidogrel with ticlopidine after stenting. Similar to our findings, these investigators reported a significantly higher rate of mortality, both overall and cardiovascular, in the clopidogrel arm.

Wenaweser *et al.*[1] report a prevalence of 1.6% of stent thrombosis, a rate that is similar to ours. Clopidogrel was used in many more of their TSO patients than ticlopidine (86 and 14%, respectively).

While the focus of the study of Wenaweser *et al.*[1] was on the treatment of TSO, we believe that in light of the previous findings, it would be of great interest to know whether Wenaweser *et al.*[1] could report the rates of TSO in their clopidogrel- and ticlopidine-treated patients, respectively. Such information from another well-studied cohort may shed further light on the potential role of ticlopidine vs. clopidogrel in the long-term prevention of TSO.

References

1. Wenaweser P, Rey C, Eberli FR, Togni M, Tuller D, Locher S, Remondino A, Seiler C, Hess OM, Meier B, Windecker S. Stent thrombosis following bare-metal stent implantation: success of emergency percutaneous coronary intervention and predictors of adverse outcome. *Eur Heart J* 2005;**26**(12):1180–1187.
2. Wolak A, Amit G, Cafri C, Gilutz H, Ilia R, Zahger D. Increased long term rates of stent thrombosis and mortality in patients given clopidogrel as compared to ticlopidine following coronary stent implantation. *Int J Cardiol* 2005;**103**(3):293–297.
3. Wolak A, Amit G, Cafri C, Gilutz H, Ilia R, Zahger D. Clopidogrel is associated with increased rates of 1-year stent thrombosis and mortality as compared with ticlopidine following coronary stent implantation. *Eur Heart J* 2004;August/September (suppl.).
4. Mueller C, Roskamm H, Neumann FJ, Hunziker P, Marsch S, Perruchoud A, Buettner HJ. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary artery stents. *J Am Coll Cardiol* 2003;**41**(6):969–973.

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The management and prevention of thrombotic stent occlusion: reply

Dual antiplatelet therapy with aspirin and thienopyridines has been shown superior to treatment with oral anticoagulation and aspirin alone in the prevention of major adverse cardiac events following coronary stent implantation.[1] The therapeutic benefit of ticlopidine was somewhat limited by rare but potentially serious adverse effects such as neutropenia and thrombocytopenia. The advent of clopidogrel was associated with a superior haematological safety profile but comparable efficacy in three randomized trials and has largely replaced the use of ticlopidine.[2–4]

Notwithstanding, the comparative studies had some limitations: (1) the trials were underpowered to detect small but potentially important differences in the incidence of stent thrombosis; (2) the studies differed with respect to the loading dose regimen; and (3) the follow-up period was limited to 30 days. In light of these limitations, the report of Dr Wolak and colleagues of a higher incidence of stent thrombosis with clopidogrel (2.8%) than ticlopidine (0.7%) in an all-comer population of 1519 consecutive patients undergoing bare metal stent implantation is of interest. Their observation is echoed by the extended follow-up data of the randomized trial reported by Mueller *et al.*[5] and our own experience. Thus, we have previously investigated the incidence of stent thrombosis following bare metal stent implantation in 4500 consecutive patients.[6] While the overall rate of stent thrombosis was 0.8%, thrombotic stent occlusion occurred in 1.9% of patients with clopidogrel and in 0.6% of patients with ticlopidine treatment ($P < 0.05$). The mechanism for the observed difference in efficacy between ticlopidine and clopidogrel remains unclear but has been related to differences in drug–drug interaction as well as dose and length of treatment with the respective thienopyridine. Stent thrombosis has gained even more importance in the era of drug eluting stents and future studies with long-term follow-up will have to determine the optimal antiplatelet therapy.

References

1. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomeri A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 1998;**339**:1665–1671.
2. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators FT. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;**102**:624–629.
3. Muller C, Buttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. *Circulation* 2000;**101**:590–593.
4. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. *Circulation* 2001;**104**:539–543.

5. Mueller C, Roskamm H, Neumann FJ, Hunziker P, Marsch S, Perruchoud A, Buettner HJ. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary artery stents. *J Am Coll Cardiol* 2003;**41**:969–973.
6. Wenaweser P, Rotter M, Windecker S, Seiler C, Hess O, Meier B, Eberli F. The phenomenon of late stent thrombosis: differential effect of ticlopidine and clopidogrel. *Circulation* 2002; **106**(suppl.):II-517.

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Comment on pregnancy and aortic root growth in the Marfan syndrome

Meijboom and coworkers[1] reported on the aortic root growth rate of women with Marfan syndrome during pregnancy. They could not find a significant increase in the aortic root diameter in 31 pregnancies of 23 patients and concluded that 'Pregnancy in women with Marfan syndrome seems to be relatively safe up to an aortic root diameter of 45 mm'.

We believe that it is too early to draw such a conclusion. All statistical tests performed in this study were aimed to find any growth. These tests failed, but a power analysis to determine the case number necessary to find any differences was not performed. The authors even reported on one woman with an aortic dissection during pregnancy and on an increased growth of the aortic root during long-term follow-up in those patients with an aortic root diameter >40 mm at baseline in a subgroup analysis.

We recently lost one of our patients, a 36-year-old woman with aortic coarctation and bicuspid aortic valve. These patients usually have structural abnormalities in the aortic medial wall predisposing to dilatation, aneurysm, and rupture, which are similar but less pronounced than those described in Marfan syndrome.[2,3] This woman died from aortic rupture at the 36th week of her second pregnancy. Her ascending aorta measured 40–41 mm and did not show any progression of diameter assessed several times by echocardiography as well as by helical CT prior to her second pregnancy. Unfortunately, the patient was not seen in our centre during pregnancy, and no consecutive imaging was performed.

Summarizing, this study did not provide real evidence for the conclusion that 'Pregnancy in women with Marfan syndrome seems to be relatively safe up to an aortic root diameter of 45 mm'. We should recommend to monitor all pregnant women with Marfan syndrome very carefully and closely, as suggested in many previous studies,[4,5] because aortic dissection does not only depend on aortic diameter progression and may also occur in Marfan patients with a normal aortic diameter.[5]

References

1. Meijboom LJ, Vos FE, Timmermans J, Boers GH, Zwinderman AH, Mulder BJ. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. *Eur Heart J* 2005;**26**: 914–920.
2. Niwa K, Perloff JK, Bhuta SM, Laks H, Drinkwater DC, Child JS, Miner PD. Structural abnormalities of great arterial walls in congenital heart disease: light and electron microscopic analyses. *Circulation* 2001;**103**: 393–400.
3. Isner JM, Donaldson RF, Fulton D, Bhan I, Payne DD, Cleveland RJ. Cystic medial necrosis in coarctation of the aorta: a potential factor contributing to adverse consequences observed after percutaneous balloon angioplasty of coarctation sites. *Circulation* 1987; **75**:689–695.
4. Immer FF, Bansi AG, Immer-Bansi AS, McDougall J, Zehr KJ, Schaff HV, Carrel TP. Aortic dissection in pregnancy: analysis of risk factors and outcome. *Ann Thorac Surg* 2003; **76**:309–314.
5. Lipscomb KJ, Smith JC, Clarke B, Donnai P, Harris R. Outcome of pregnancy in women with Marfan's syndrome. *Br J Obstet Gynaecol* 1997;**104**: 201–206.

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Comment on pregnancy and aortic root growth in the Marfan syndrome: reply

Thank you for the opportunity to respond to the comment from Hager and co-workers. It is an immense tragedy when a young woman dies during pregnancy. We agree with Hager and co-workers that there is no definite safe aortic root diameter for women with Marfan syndrome to get pregnant. Dissections may occur at normal aortic diameters in patients with Marfan syndrome. Should we therefore advise all women with Marfan syndrome against pregnancy? During recent years, a panel of international experts has reached consensus that pregnancy can be tolerated in women with Marfan syndrome with a slightly dilated aortic root.[1] This expert consensus is being validated by our findings, which indicate that pregnancy is relatively safe in women with Marfan syndrome and an aortic root diameter up to 45 mm.[2] However, women with a previous dissection should not get pregnant. We agree with Hager *et al*. that all patients with Marfan syndrome deserve close and careful monitoring before, during, and after pregnancy. Before pregnancy, all women should undergo a magnetic resonance angiogram to investigate if there is dilatation in other parts of the aorta. Also, frequent echocardiographic imaging should be performed throughout pregnancy and the postpartum period to check for progressive aortic dilatation. In the future other risk factors for aortic dissection, such as aortic elasticity, might become available to