Editorial comment

Oral anticoagulation and mechanical heart valves: the case of the elderly and pregnancy

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Life-long oral anticoagulation (OAC) is required after mechanical heart valve implantation to reduce the risk of thromboembolic complications. Over the last 10 years, guidelines for the management of patients with mechanical heart valves have been issued by the most authoritative Cardiology Associations[1-3] and a general consensus on how to carry out optimal OAC in these patients has been reached. In summary, for bileaflet or tilting disk valves in the aortic position the intensity of OAC must aim at an international normalized ratio (INR) of 2.5 (range 2.0-3.0), whereas in the vast majority of other situations including caged-ball valves, any mechanical prosthesis in the mitral position, more than one mechanical valve and the presence of additional risk factors for thrombosis (i.e. atrial fibrillation, left atrial enlargement, previous thromboembolism, severe left ventricular dysfunction), an INR of 3.0 (range 2.5-3.5) is recommended[2,3]. The addition of low-dose aspirin (75 to 100 mg/day) is recommended in patients at higher risk for thromboembolism (i.e. multiple risk factors for thrombosis or first-generation mechanical valves), although it should be considered for all other cases because of its beneficial effect in further reducing thromboembolic events, with only a small increase in the risk of hemorrhage[1-3].

Bleeding is, in fact, the major complication of long-term OAC. Established determinants of OAC-induced hemorrhage include the intensity of anticoagulation, the concomitant use of drugs interfering with hemostasis, the duration of therapy and patient characteristics[4]. Among these latter, age ≥ 75 years has been consistently recognized as an independent risk factor for major bleeding, including intracranial hemorrhage[4-6]. Among the explanations for that are the lower anticoagulant doses required in elderly patients, the higher prevalence of comorbid conditions, the higher likelihood of taking interacting drugs, and the tendency to mental impairment, which in turn, may lead to noncompliance to treatment[4-6]. Also, in older patients an increased vascular fragility has been reported, possibly accounting for the increased risk of intracranial bleeding[6]. Therefore, in order to obviate to the higher hemorrhagic risk associated with long-term OAC, for patients aged ≥ 60-65 years undergoing aortic valve replacement and ≥ 65-70 years undergoing mitral valve replacement, the choice of a biological prosthesis is generally suggested, provided that other indications for OAC are not present[2,7]. Low-dose aspirin (75-100 mg/day) is, in fact, considered sufficient as the antithrombotic treatment after the first 3 months of implantation of a bioprosthetic valve in the mitral position, and even immediately after surgery for bioprosthetic valves implanted in the aortic position[2,3]. Furthermore, the delayed appearance and slowed progression of structural deterioration occurring in the elderly to bioprosthetic heart valves, especially when implanted in the aortic position, accounts for the good long-term (≥ 10 to 15 years) patient outcomes, making therefore replacement of a heart valve with a bioprosthesis a suitable option when the patient's life expectancy is reduced[2,7].

Another important drawback of OAC is represented by the teratogenic effect of coumarins when administered during pregnancy[8]. Exposure to warfarin between the 6th and 12th week of gestation can cause a

specific embryopathy, consisting of nasal hypoplasia and/or stippled epiphyses, whereas the use of the drug during any trimester has been associated with the occurrence of central nervous system abnormalities, spontaneous abortions and fetal wastage[8]. Although a relationship between poor pregnancy outcomes and mean daily doses of warfarin has been reported[9], and the true occurrence of embryopathy might have been overestimated[8], OAC during pregnancy is generally believed contraindicated, and consideration of pregnancy termination has been recommended by the manufacturer in patients becoming pregnant while being treated with warfarin[8,10]. Unfractionated heparin (UFH) has been traditionally considered the anticoagulant of choice during pregnancy, since, as opposed to warfarin, it does not cross the placenta and therefore offers little direct risk to the fetus[8]. However, the occurrence of adverse effects, such as osteopenia (that may lead to symptomatic vertebral fracture in about 2-3% of cases) and thrombocytopenia[8], has been reported with long-term administration of UFH, which in pregnant patients with prosthetic heart valves has also been associated with a high incidence of thromboembolic complications, including valve thrombosis[10-12]. Because of the concerns relative to the use of both warfarin and UFH during pregnancy, low-molecular-weight heparins (LMWH) have recently gained considerable attention: the inability to cross the placental barrier, the highly predictable dose-response relationship and the lower occurrence of bleeding complications, as well as of osteopenia and thrombocytopenia[13], have made LMWH an attractive option for thromboprophylaxis in pregnant women with mechanical heart valves. However, data supporting their use in this clinical condition are at the present time sparse and inconsistent, since failures of treatment, also including valve thrombosis which led to maternal and fetal deaths, have been repeatedly reported[8,10-14]. As a result, the manufacturer has recently issued a warning where the use of enoxaparin is not recommended for thromboprophylaxis in patients with prosthetic heart valves[12]. Although most treatment failures with LMWH, as well as with UFH, might be related to inadequate dosing and/or use of an inappropriate target therapeutic range, the utilization of LMWH to prevent thromboembolism in pregnant patients with mechanical heart valves remains controversial[8,10-14]. Over the last decade, the Working Groups and Task Forces of the most prominent Cardiology Associations[1-3], as well as individual authorities[10,12,15], have released recommendations for the management of anticoagulation during pregnancy in patients with mechanical heart valves. Whereas in some of them the use of warfarin throughout pregnancy is contemplated[1,2,10], the most up-to-date guidelines recommend either: 1) aggressive adjusted-dose UFH throughout pregnancy, i.e. administered subcutaneously every 12 hours in doses adjusted to maintain the mid-interval activated partial thromboplastin time (aPTT) at least twice control or to attain an anti-factor Xa heparin level of 0.35-0.70 U/ml, or 2) adjusted-dose LMWH throughout pregnancy, i.e. administered subcutaneously every 12 hours in doses adjusted to maintain a 4- to 6-hour postinjection anti-factor Xa heparin level of 1.0-1.2 U/ml, or 3) UFH or LMWH (as above) until the 13th week of gestation, then warfarin with a target INR of 2.5-3.5 until the middle of the third trimester, followed by reinitiation of UFH or LMWH until delivery[8,12,15]. With any of the three above regimens, consideration of adjunctive low-dose aspirin (75 to 100 mg/day) is recommended, as well as resumption of long-term OAC *post-partum*[1-3,8,10,12,15].

In this issue of the *Italian Heart Journal*, Cotrufo et al.[16] report on their experience with OAC in patients with newer-generation mechanical heart valves, with special regard to the elderly and pregnancy. Both these latter conditions have long been a field of clinical investigation of this group, which has indeed provided a substantial amount of original data[16]. It is noteworthy, therefore, that their position with respect to OAC after mechanical heart valve implantation in elderly and pregnant patients is someway in contrast with what is generally accepted in current clinical practice.

Based on the results of a retrospective study in which the authors' group showed comparable thromboembolic and hemorrhagic OAC-related complications in both over-septuagenarians and patients aged < 50 years undergoing isolated aortic valve replacement with bileaflet mechanical prosthesis[17], Cotrufo et al.[16] support the use of mechanical rather than biological heart valves also in older patients. As correctly pointed out by the authors, these conclusions apply only to selected patients, without associated mitral valve disease or coronary artery disease (which are known to predispose to thromboembolism and/or hemorrhage)[2,3,6], in whom isolated aortic valve replacement with bileaflet mechanical prosthesis is performed. The very low incidence (< 1%) over the long-term of both thromboembolic and hemorrhagic complications observed by Cotrufo et al.[16] in such a setting, might be accounted for by the known low thrombogenicity of bileaflet valves in the aortic position, and the use of low-intensity OAC (which yielded in fact, a mean INR of about 2.0), respectively. Indeed, an INR of 1.8 to 2.5 has been shown to be both effective and safe in elderly patients with bileaflet mechanical valves in the aortic position, and is therefore considered for this setting in the most recent guidelines[3]. While acknowledging their appeal, the conclusions drawn by Cotrufo et al.[16], however, are hampered by several methodological limitations, such as the retrospective data collection and adjudication of hemorrhagic complications, as well as the relatively small size of the population evaluated. Furthermore, a true relationship between age and bleeding might have gone undetected since an increased hemorrhagic risk has generally been shown for a cut-off age higher than the 70 years adopted by Cotrufo et al.[16]. With the exception of a few studies in fact, age ≥ 75

years was found to be associated with a significantly higher risk of life-threatening or fatal (i.e. intracranial) hemorrhage[4-6], even when patients were closely monitored in specialized anticoagulation clinics[6]. And although the rate of bleeding markedly increases with INR values > 3.0, the occurrence of hemorrhagic complications appears not always related to the intensity of OAC, being more frequent during the initiation of treatment, when cryptic lesions are likely to be unmasked and poor anticoagulation control is common[5,6]. In the light of the above considerations, avoidance of long-term OAC and choice of biological rather than mechanical prostheses when heart valve replacement is needed, appear preferable in the elderly[2,7]. Since structural deterioration, which represents the major disadvantage with use of bioprostheses, begins later and progresses more slowly in this age group as compared to younger patients, it is estimated that the need for reoperation at 10-15 years is limited to only 15-30% of cases[7]. This means that, out of 100 patients undergoing mitral valve replacement at 65 years, in whom 20% probability of being alive and 30% probability of structural valve deterioration at 15 years are expected, only 6 will actually need reoperation. The choice of mechanical rather than biological prostheses even in elderly patients is recommended when other risk factors for thromboembolism (i.e. atrial fibrillation, left atrial enlargement, previous thromboembolism, severe left ventricular dysfunction) are present[2,7]. It should be pointed out, however, that even in these circumstances implantation of a bioprosthesis might still be preferable. As previously reported, in fact, elderly patients on long-term OAC are at increased risk of (major) hemorrhage[4-6], which upon occurrence pose a challenging dilemma to the clinician who must decide whether to discontinue warfarin for an extended period, thus putting the mechanical valve at risk of thrombosis, or continue OAC, thus putting the patient's life in jeopardy. Although limited available data suggest that withholding or reversing warfarin therapy in patients with prosthetic heart valves hospitalized with a major hemorrhage is safe[18], this issue is poorly defined at present. There is little doubt, however, that in the presence of a bioprosthetic heart valve the management of such a situation would be less cumbersome and safer. Similar considerations apply to patients undergoing coronary artery stenting, and therefore requiring prolonged dual antiplatelet therapy, in whom an indication for long-term OAC is also present. Again, little information is available about the optimal antithrombotic treatment for this patient subset[19,20]. Yet, because of the relevant incidence of major hemorrhage reported with the association of OAC, aspirin and a thienopyridine[20,21], the possibility of temporarily suspending OAC as long as dual antiplatelet therapy is required, appears highly desirable, especially in advanced age patients.

Also noteworthy is the position of Cotrufo et al.[16] as regards OAC in pregnant patients with mechanical heart valves. Because of previous observations of the author's group that the risk of poor pregnancy outcomes is dependent on the warfarin mean daily dose[9], Cotrufo et al.[16] suggest to administer warfarin throughout pregnancy, provided that on a preliminary evaluation of the woman in childbearing age requiring heart valve replacement, it is found that therapeutic INR is achieved with a mean daily dose of warfarin < 5 mg. Warfarin should then be discontinued 48 hours prior to an elective cesarean section scheduled for the 37th week, and resumed 24 hours thereafter. The observed 10% risk of poor pregnancy outcomes (i.e. occurrence of spontaneous abortion, stillbirth, or congenital birth defects), and the reported poor efficacy of both UFH and LMWH regimens in this setting, are at the basis of the strategy supported, and adopted, by Cotrufo et al.[16]. Again, the limitations inherent in the retrospective study design, absence of a control group and small size of the population examined, need to be mentioned, as well as the failure to observe a similar relationship between warfarin dose and pregnancy outcomes in a larger cohort study[22]. Moreover, inadequate UFH or LMWH dosing and/or achievement of subtherapeutic anticoagulation levels have been consistently reported in most pregnant patients with mechanical heart valves experiencing thromboembolic complications while on these anticoagulation regimens[8,10-12,14]. Indeed, it appears that not only low doses of UFH (i.e. 5000 U every 8-12 hours subcutaneously) or LMWH (i.e. 4000 U every 24 hours subcutaneously) are ineffective for prevention of mechanical valve thrombosis, but also the common adjusted-dose regimens targeted to a minimum aPTT ratio of 1.5 the control or a minimum anti-factor Xa level of 0.3 U/ml may be inadequate, owing to the hypercoagulable state which is known to accompany pregnancy[8]. Whenever high initial doses of UFH (i.e. 17 500-20 000 U every 12 hours subcutaneously) or LMWH (i.e. 100 U/kg every 12 hours subcutaneously) are given, and aggressive monitoring with appropriate dose adjustments to ensure consistent anticoagulant effect is warranted[8,10-14], there is no plausible reason for these agents not to be as effective as they have been demonstrated in other clinical conditions (i.e. acute coronary syndromes, venous thromboembolism). Unfortunately, prospective controlled trials comparing the outcomes of treatment with UFH or LMWH, as well as with warfarin, are lacking and most of the available data derive from case series. Moreover, for two of the drugs (i.e. warfarin and LMWH) the use during pregnancy is formally contraindicated, as stated in the insert package[8]. Therefore, the clinician entrusted to care for a pregnant patient with mechanical heart valve is called to the challenging task of choosing among: 1) a contraindicated agent, such as warfarin, which carries a definite harm to the fetus, with no relevant side effects to the mother, 2) the "gold standard" for anticoagulation during pregnancy, such as UFH, which is safe to the fetus, while being associated with long-term adverse effect to the mother and apparently poor efficacy

in preventing thromboembolic complications, and 3) another contraindicated agent, such as LMWH, which is safe to both the fetus and mother, while having uncertain efficacy in preventing thromboembolic complications. Certainly, thorough discussion with the patient and her partner is indicated before conception, and the competing risks to the mother and to the fetus should be carefully weighed when choosing the anticoagulant strategy. All three anticoagulant options appear to be not fully protective, but undoubtedly, women with mechanical heart valves require anticoagulation during pregnancy. A 4-10% risk of embryopathy secondary to warfarin treatment during the first trimester, however, is substantial, and most women would probably not accept to take this risk, as well as that of giving birth to children with neurological dysfunction and low intelligence quotient, as it has been reported with warfarin administration at anytime during pregnancy[10]. In the light of these limitations, as well as of those presented by UFH, LMWH should be reasonably considered at present the best option of three suboptimal alternatives, although the lack of good quality data and the underinvestigation of all three anticoagulant strategies must be acknowledged[8]. The 29% rate of valve thrombosis reported in the only randomized trial comparing enoxaparin with UFH and warfarin, and prematurely discontinued after 2 of the 7 patients enrolled developed fatal prosthesis dysfunction, is in fact not realistic because of the small size of the population and the very wide confidence intervals (4-71%)[10]. Also, the potential for teratogenicity of LMWH, which recently led the manufacturer of enoxaparin to issue a precaution[12], lacks biologic plausibility since these agents have been shown to not cross the placental barrier[8,13].

In conclusion, the strategies proposed by Cotrufo et al.[16] for the management of elderly patients needing aortic valve replacement and pregnant patients requiring long-term OAC because of a mechanical heart valve, need to be substantiated by more information before their adoption in clinical practice is endorsed. While waiting for a prospective study addressing the safety and efficacy of these alternative strategies, optimal patient care is best accomplished at present by following up-to-date recommendations of the major Cardiology Associations.

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