Abbott

CLINICAL INSIGHTS

MASTERS SERIES AND REGENT AORTIC MECHANICAL HEART VALVES

Bileaflet Aortic Mechanical Heart Valves, Low INR Management For Low Risk Patients: A Class Effect?

Mechanical heart valves (MHVs) are a viable option for many heart valve disease patients. They have long-term durability, but necessitate life-long antithrombotic therapy, typically an oral vitamin K antagonist (VKA), to mitigate risk of thromboembolic (TE) complications.

- VKA levels need to reduce TE risk, but be at the same time low enough to manage anticoagulated-related hemorrhage risk
- Measured by patient's clotting prothrombin time expressed as the International Normalized Ratio (INR)

As valve prosthetics and thrombotic therapy management have improved over time, guideline INR levels have been reduced. The approach is to balance or reduce the risk of bleeding while not appreciably increasing the risk of TEs.

A significant number of studies have investigated the intensity of low oral anticoagulation with a low INR regimen (such as INR 1.5 to 2.5) in patients who undergo aortic valve replacement with a MHV. These efforts have included different MHV brands and designs.

META-ANALYSES REVIEW

A review of published meta-analyses provides evidence to be considered in the context of VKA regimens. (See Table 1).

Mohamed and colleagues analyzed 7 papers, 1 meta-analysis, 5 randomized clinical trials (RCT), and 1 prospective cohort study. They found growing evidence that support reducing the target INR range for patients with aortic MHVs. Several large RCT's reviewed concluded that reducing the target INR range for MHVs in patients with low risk produces less bleeding and does not increase TE events.[2]

Another meta-analysis by **Gupta et al**. showed that lower INRs reduce bleeding without significantly impacting TE's or mortality regardless of risk factors or valve position. The results of this review do not support the need for higher INR targets in MHV patients at higher thromboembolic risk as lower targets appeared to produce less bleeding without compromising efficacy.[3]

Table 1. Meta-Analyses and Subject Review

Study	Databases	Publications/Review
Mohamed, et al. 2020[8] (n = 5,923)	MEDLINE	• 5 randomized controlled trials, • 1 meta-analysis, • 1 prospective cohort
Gupta, et al. 2018[9] (n = 3,250)	Cochrane CENTRAL, MEDLINE, EMBASE	• 6 randomized controlled trials
Aikins, et al. 2020[10] (n = 5,517)	NA	• 6 randomized controlled trials • 2 prospective, nonrandomized trials

Aikins and colleagues review of evidence from RCTs and observational studies also demonstrated that lower INR targets reduce bleeding risk without increasing rates of TE's. They noted that VKAs are a mainstay but that recent evidence suggested a benefit to a lower INR target range and concomitant antiplatelet therapy for most patients.[4]

These publications agreed that the evidence supports lower INR targets for at least some aortic MHV patients and that the risk of bleeding for those patients could be lowered without increasing the risk of TEs.

The art of antithrombotic guidelines has always worked to balance the risks of bleeding and thromboembolic events, and has generally moved in the direction of lowering the target levels. Prof G. Van Nooten, in his 15 year paper on MHV anticoagulation implied that the aim should be to anticoagulate the patient, not the valve.[5] This recent data suggests that may be right.

LOW INR STUDIES

Five of those analyzed low INR studies are detailed here (See Figure 2 and Table 2). It is important to note the study design and endpoint definitions when applying their findings to clinical practice. **Koertke and colleagues** published two reports from RCTs with 2673 patients. The study employed home INR monitoring and management, and demonstrated good outcomes, especially in the lower target-INR groups.[6,7] The LOWERING-IT RCT, reported by **Torella, et al**. had a classic, simple design, included a well-defined low-risk aortic population who received a mix of valve brands, and very good outcomes with clearly different group results.[8] **Bove and colleagues** published the results of their very large observational study in 2017. The investigators closely followed patients' aortic experience with excellent follow up. Good outcomes were reported in both regular (n= 357) and low INR groups (n=552).[9]

See Important Safety Information referenced within.

IMPORTANCE OF STUDY DESIGN IN LOW INR TRIALS

A report from the PROACT trial by **Puskas, et al**. included 374 patients implanted with the On-X mechanical heart valve and who utilized prescriptive home INR management. This **non-inferiority study** met its low INR endpoint which was a composite of major bleeding, minor bleeding, TE events, and valve thrombosis – a mix of safety and efficacy measure which typically move in opposite directions.[10] There were significant reductions in both major and minor bleeding in the test group, while the **control group demonstrated major and total bleeding more than twice that of the objective performance criteria**. **In the test group TE events rose by 30% numerically, and the rate by more than 45% per patient year**, though due to the scope of this trial, these differences did not rise to statistical significance. Lastly, all participants in the trial were on home INR management which was reported 3 to 4 times per month, and they were largely on recommended brand name Coumadin, **which may not reflect the typical treatment course of a real-world patient population.**

"Limited statistical power, certain methodological concerns, the restriction to certain prostheses, and the use of INR self-management" led the European Society of Cardiology not to change recommendations for target INR in their 2017 guidelines.[11] Based on the PROACT Trial, the On-X valve does have an IFU target INR of 1.5 to 2.5, when used for isolated aortic valve replacement.

Figure 2. **With one exception, use of lower INR targets resulted in lower rates of major bleeding, major thrombolitic events, and the combination of the two in these studies.**

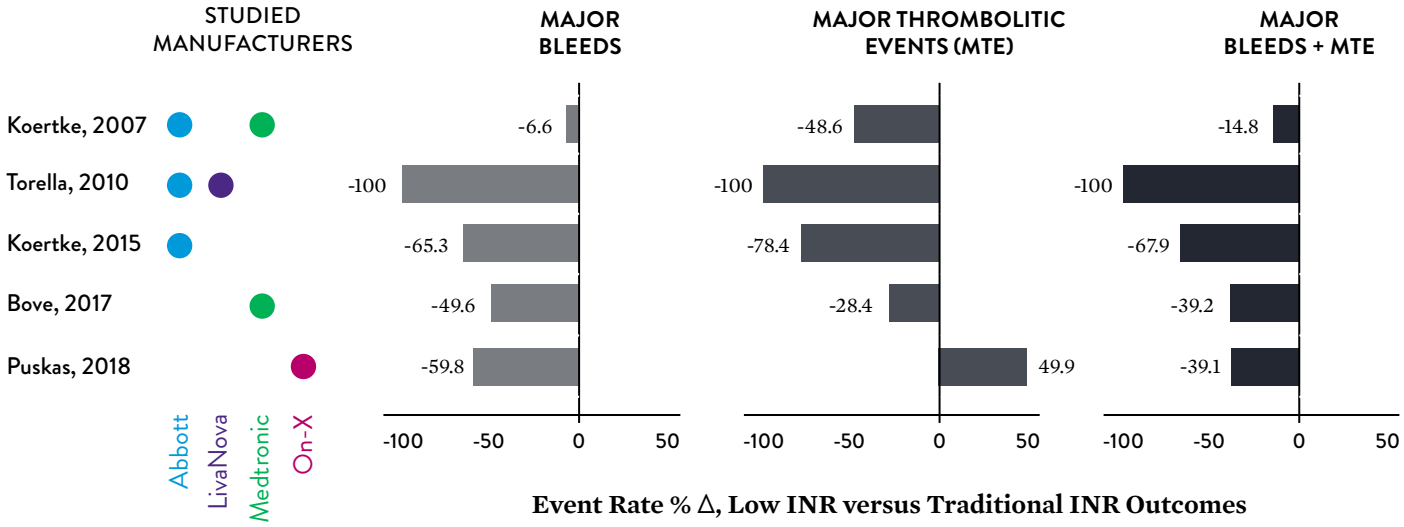

Table 2. Low INR Studies and Key Outcomes*

Study	INR Target Range	Major Bleeds per Patient Year	Major Thrombolitic Events (MTE+Thrombosis) per Patient Year	Major Event (MB + MTE + Thrombosis) per Patient Year
Koertke, 2007[6]	2.5–4.5 1.8–2.8 Δ	1.52% (n=33) 1.42% (n=30) **-6.58%**	0.37% (n=7) 0.19% (n=5) **-48.65%**	1.89% (n=40) 1.61% (n=35) **-14.81%**
Torella, 2010[8]	2.0–3.0 1.5–2.5 Δ	0.27% (n=3) 0% (n=0) **-100%**	0.18% (n=2) 0% (n=0) **-100%**	0.45% (n=5) 0% (n=0) **-100%**
Koertke, 2015[7]	1.8–2.8 1.5–2.1 Δ	1.93% (n=49) 0.67% (n=17) **-65.3%**	0.51% (n=13) 0.11% (n=3) **-78.4%**	2.43% (n=62) 0.78% (n=20) **-67.9%**
Bove, 2017[9]	2.5–3.5 1.5–2.5 Δ	1.21% (n=19) 0.61% (n=9) **-49.59%**	1.16 (n=18) 0.83% (n=13) **-28.45%**	2.37% (n=37) 1.44% (n=22) **-39.24%**
Puskas, 2018[10]	2.0–3.0 1.5–2.0 Δ	3.94% (n=43) 1.59% (n=15) **-59.77%**	0.92% (n=10) 1.38% (n=13) **49.92%**	4.86% (n=53) 2.96% (n=28) **-39.08%**
Zhang, 2020[1]	1.5-2.5	0.42% (n=54)	1.03% (n=131)	1.43% (n=182)

*NOTE: Data not from head-to-head studies. Data provided for informational purposes only.

See Important Safety Information referenced within.

DEEPER DIVE INTO AN IMPORTANT RECENT, MAJOR, ASIAN LOW INR TRIAL

Low-intensity Anticoagulation Experience in Chinese Patients Following Implantation of the Abbott/SJM Mechanical Valve[1]

TITLE

Optimal oral anticoagulant therapy in Chinese patients with mechanical heart valves

AUTHORS

Zhang H, Dong Y, Ao X, et al.

BACKGROUND

Oral anticoagulants are effective at preventing thromboembolic complications after mechanical heart valve implant, but introduce dose-dependent bleeding risk.

OBJECTIVE

This study aimed to better determine the ideal intensity of oral anticoagulant therapy in a cohort of Chinese patients after heart valve replacement with a mechanical valve.

METHODS

This was a single-center, observational study of patients implanted with a St. Jude Medical bileaflet mechanical valves since 2013. Patients were followed for 1 to 6 years. Study endpoints included instances of thromboembolism (TE) and major hemorrhage. The international normalized ratio (INR)-specific incidence of adverse events was calculated to determine optimal anticoagulant therapeutic intensity.

RESULTS

3017 patients were followed and 182 experienced an adverse events (AE), a 1.43% annual incidence rate. 54 had a major bleeding event (0.42% per patient-year, 95% CI, 0.31–0.53). 131 had a thromboembolism (1.03% per patient-year, 95% CI, 0.85–1.21). Optimal INR was between:

- 1.5 and 2.0 for aortic valve replacement (AVR) patients regardless of TE risk factors. (Note: 22 AVR pts. had A/F)
- 1.5 and 2.0 for mitral valve replacement (MVR) patients not at risk for TE
- 2.0 and 2.5 for MVR patients at risk of TE In patients undergoing both AVR and MVR (DVR), ideal anticoagulant intensity was the same as for those undergoing single MVR.

CONCLUSION

A target INR range between 1.5 and 2.5 was found to be optimal for patients in this study undergoing AVR, MVR, or DVR using an Abbott/SJM mechanical valve, with individual risk of thromboembolism informing the final anticoagulant regimen. Results in a Chinese patient population may not be generalized to a Western population.

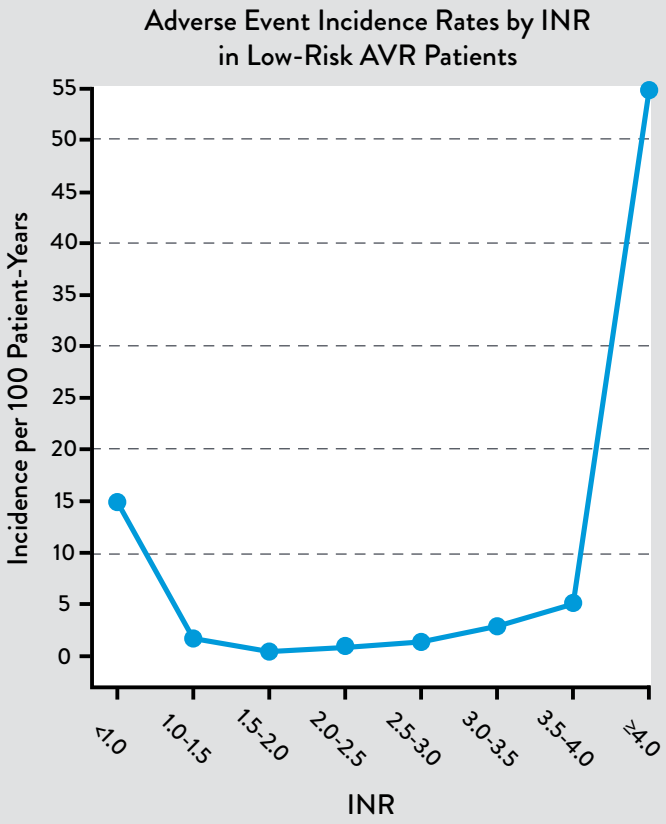

Figure 1. The optimal oral anticoagulant intensity was found to be an INR in the range of 1.5 to 2.0 in low-risk patients.

See Important Safety Information referenced within.

IMPORTANT SAFETY INFORMATION

MASTERS SERIES MECHANICAL HEART VALVE

Rx ONLY

INDICATIONS FOR USE

The SJM™ Masters Series Mechanical Heart Valve is intended for use as a replacement valve in patients with a diseased, damaged, or malfunctioning aortic or mitral heart valve. This device may also be used to replace a previously implanted prosthetic heart valve.

CONTRAINDICATIONS

The SJM™ Masters Series Mechanical Heart Valve is contraindicated for individuals unable to tolerate anticoagulation therapy.

WARNINGS

- For single use only. Attempts to reuse the valve may result in valve malfunction, inadequate sterilization, or patient harm.
- Do not use if:
  - The valve has been dropped, damaged, or mishandled in any way.
  - The expiration date has elapsed.
  - The tamper-evident container seal or inner/outer tray seals are damaged, broken or missing.
- Remove any residual tissue that may impair valve size selection, correct seating of the valve, rotation of the valve, or leaflet motion.
- Proper valve size selection is crucial. Do not oversize the valve. If the native annulus measurement falls between two SJM™ Masters Series Mechanical Heart Valve sizes, use the smaller size SJM™ Masters Series Mechanical Heart Valve.
- Use only St. Jude Medical™ mechanical heart valve sizers.
- The outer tray is not sterile, and should not be placed in the sterile field.
- To minimize direct handling of the valve during implantation, do not remove the holder/rotator until the valve has been seated in the annulus.
- Do not use hard or rigid instruments to test leaflet mobility, as this may result in structural damage to the valve or thromboembolic complications. Use a St. Jude Medical™ leaflet tester to gently test valve leaflet mobility.
- Place sutures in the outer half of the valve sewing cuff.
- Never apply force to the valve leaflets. Force may cause structural damage to the valve.
- Use only SJM™ Valve Holder/Rotators to perform valve rotation. Use of other instruments could result in structural damage. The valve holder/rotator is intended for single use only and should be discarded after surgery.
- The two retention sutures on the valve holder/rotator must be cut and removed before the SJM™ Masters Series Mechanical Heart Valve can be rotated.
- Do not pass catheters or other instruments through St. Jude Medical™ mechanical heart valves. This could result in scratched or damaged valve components, or leaflet fracture or dislodgment.
- Cut suture ends short, especially in the vicinity of the pivot guards, to prevent leaflet impingement.
- Three cases of impeded leaflet motion not satisfactorily explained were reported in a survey of 149 centers reporting on 4,934 patients implanted over a period of three (3) years. A number of other cases occurred early in the investigation of this prosthesis; however, the rates of occurrence are not statistically determinable.

PRECAUTIONS

- Do not touch the prosthetic valve unnecessarily, even with gloved hands. This may cause scratches or surface imperfections that may lead to thrombus formation.
- Be careful not to cut or tear the valve sewing cuff when removing the identification tag and the holder/rotator from the SJM™ Masters Series Mechanical Heart Valve.
- Before placing sutures in the valve sewing cuff, verify that the valve is mounted correctly on the valve holder/rotator.
- To avoid structural damage, the valve must be rotated in the fully closed position.
- To minimize rotational torque, verify that the valve holder/rotator is properly seated in the valve, and that the valve holder handle is perpendicular to the valve (Figures 15a and 15b).
- Remove any loose suture or thread, which may be a source of thrombus or thromboembolism.

POTENTIAL ADVERSE EVENTS

Complications associated with replacement mechanical heart valves include, but are not limited to:

hemolysis; infections; thrombus; or thromboembolism; valve dehiscence; unacceptable hemodynamic performance; hemorrhagic complications secondary to anticoagulation therapy; prosthetic failure; and heart failure or death.

Any of these complications may require reoperation or explantation of the device.

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