# 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]

**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]

**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 |

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## 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.**
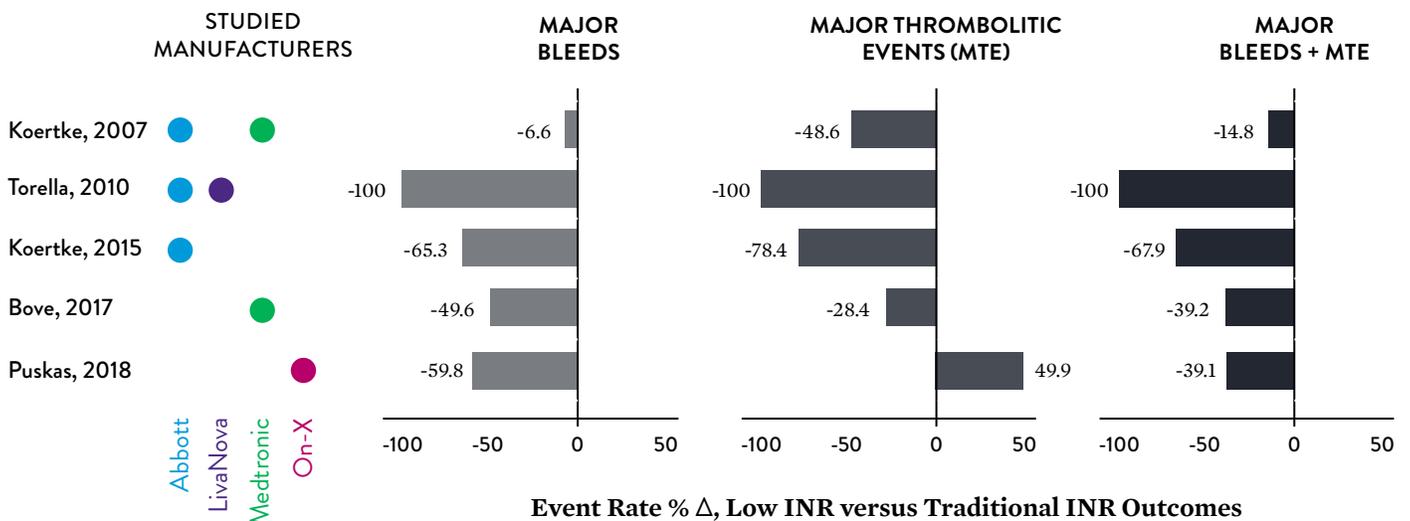


**Event Rate % Δ, Low INR versus Traditional INR Outcomes**

**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 <br> 1.8–2.8 <br> Δ | 1.52% (n=33) <br> 1.42% (n=30) <br> **-6.58%** | 0.37% (n=7) <br> 0.19% (n=5) <br> **-48.65%** | 1.89% (n=40) <br> 1.61% (n=35) <br> **-14.81%** |
| **Torella, 2010**[8] | 2.0–3.0 <br> 1.5–2.5 <br> Δ | 0.27% (n=3) <br> 0% (n=0) <br> **-100%** | 0.18% (n=2) <br> 0% (n=0) <br> **-100%** | 0.45% (n=5) <br> 0% (n=0) <br> **-100%** |
| **Koertke, 2015**[7] | 1.8–2.8 <br> 1.5–2.1 <br> Δ | 1.93% (n=49) <br> 0.67% (n=17) <br> **-65.3%** | 0.51% (n=13) <br> 0.11% (n=3) <br> **-78.4%** | 2.43% (n=62) <br> 0.78% (n=20) <br> **-67.9%** |
| **Bove, 2017**[9] | 2.5–3.5 <br> 1.5–2.5 <br> Δ | 1.21% (n=19) <br> 0.61% (n=9) <br> **-49.59%** | 1.16 (n=18) <br> 0.83% (n=13) <br> **-28.45%** | 2.37% (n=37) <br> 1.44% (n=22) <br> **-39.24%** |
| **Puskas, 2018**[10] | 2.0–3.0 <br> 1.5–2.0 <br> Δ | 3.94% (n=43) <br> 1.59% (n=15) <br> **-59.77%** | 0.92% (n=10) <br> 1.38% (n=13) <br> **49.92%** | 4.86% (n=53) <br> 2.96% (n=28) <br> **-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.

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# 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 thrombo-embolic 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.
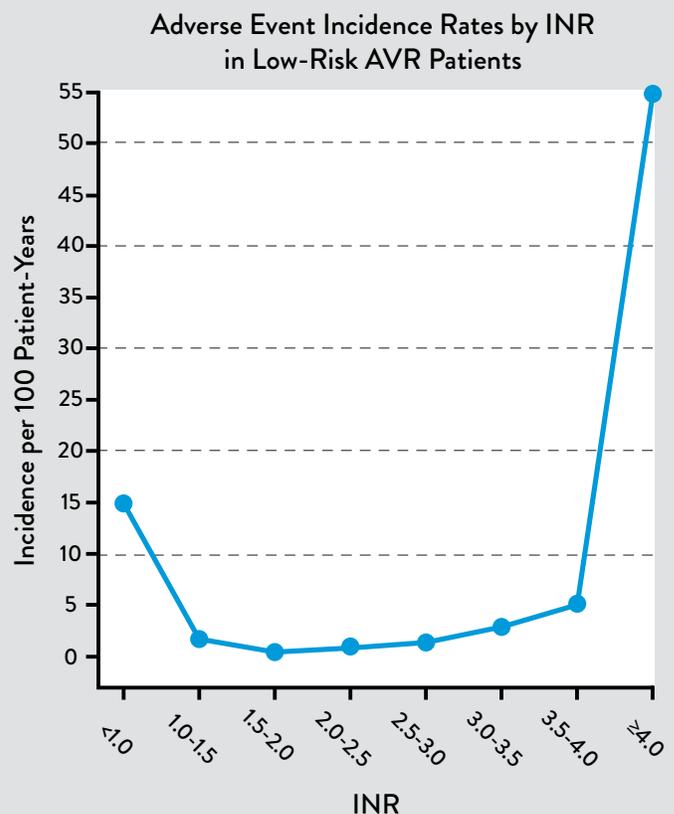


**Adverse Event Incidence Rates by INR in Low-Risk AVR Patients**

**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.

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