

Different Measures to Determine Time in Therapeutic INR Range Among Warfarin-treated Patients Following Total Hip or Knee Replacement

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BACKGROUND

- The risk of venous thromboembolism (VTE) is high following total knee or hip replacement (THR/TKR); thromboprophylaxis with anticoagulants is recommended following such procedures^{1,2}
- Because all anticoagulants carry a risk of bleeding, the risk of thrombosis needs to be weighed against the risk of bleeding in patients undergoing THR/TKR
- Warfarin has variable pharmacokinetics among and between patients; international normalized ratio (INR) is used to monitor levels and therapeutic effect of warfarin³
 - An INR below target range can lead to an increased risk of thromboembolism, whereas an INR above target range can lead to an increased risk of bleeding⁴
- American College of Chest Physicians (ACCP) guidelines recommend a therapeutic INR range of 2.0–3.0¹
- American Academy of Orthopaedic Surgeons (AAOS) guidelines recommend maintaining INR ≤ 2.0 ^{2,5-6}

OBJECTIVE

- To assess trends in INR in patients receiving warfarin therapy after THR/TKR

METHODS

- Retrospective cohort study of an electronic medical record (EMR) database covering inpatient and outpatient care from a localized region in the US including patients who underwent a THR/TKR procedure (primary or revision) and who were treated with warfarin therapy from January 1, 2004 to January 31, 2009

Inclusion criteria

- At least 5 days of warfarin therapy starting on or within 3 days after the date of surgery, and ≥ 2 INR values available in the database from Days 5–90 of warfarin therapy

Exclusion criteria

- Use of warfarin within 30 days prior to THR/TKR surgery or first recorded visit in the EMR database <30 days prior to the index date

Analysis

- The index date was defined as the first day of warfarin use on or within 3 days after THR/TKR surgery
- INR results were categorized according to ACCP guidelines, from Day 5 post surgery (to allow for the lag in warfarin achieving therapeutic effect, on average, 3–5 days) and up to Day 90 post surgery
- Time in each INR category was estimated using the Rosendaal method (linear interpolation)⁷
- The percentage of INR levels within each patient that fell below (<2.0), in (≥ 2.0 –3.0), or above range (>3.0) were calculated
 - A similar approach was used to calculate within-patient percentage of time in each INR category
 - Median values of these within-patient percentages were calculated for all patients

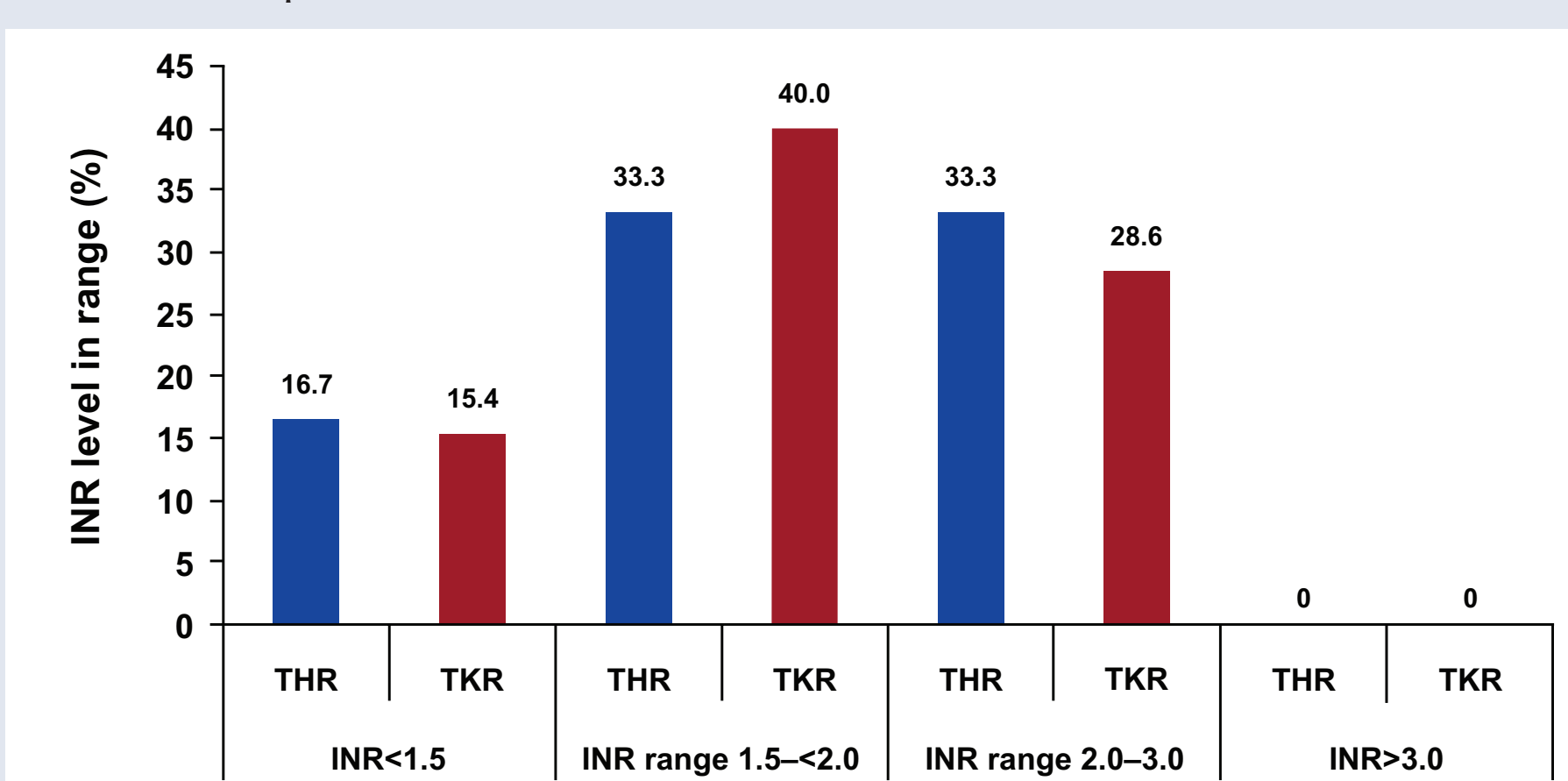
RESULTS

- Baseline characteristics of the study cohort are presented in **Table 1**
- Approximately 50% and 55.4% of INR values in patients who underwent THR or TKR, respectively, were below the ACCP-recommended therapeutic INR range of 2.0–3.0 (**Figure 1**)
 - 16.7% and 15.4% of INR levels in THR and TKR patients, respectively, were <1.5 (median values)
- Patients who underwent TKR or THR were within the ACCP-recommended therapeutic INR range for 27.6–28.6% of total days after Day 5 post surgery (median values; **Figure 2**)
 - INR values fell below the ACCP-recommended therapeutic range for both surgeries ~48% of the days
 - Patients had elevated INR levels >3.0 for 0 days (median)
- Over 90% of patients had INR <2.0, while fewer than 20% had INR values >3.0 (**Figure 3**)
 - Approximately 70% of patients had INR values within the recommended range of 2.0–3.0
 - Five times as many patients had INR levels below the ACCP-recommended range, compared with those who had levels above the guideline range

Table 1. Baseline characteristics of study cohort

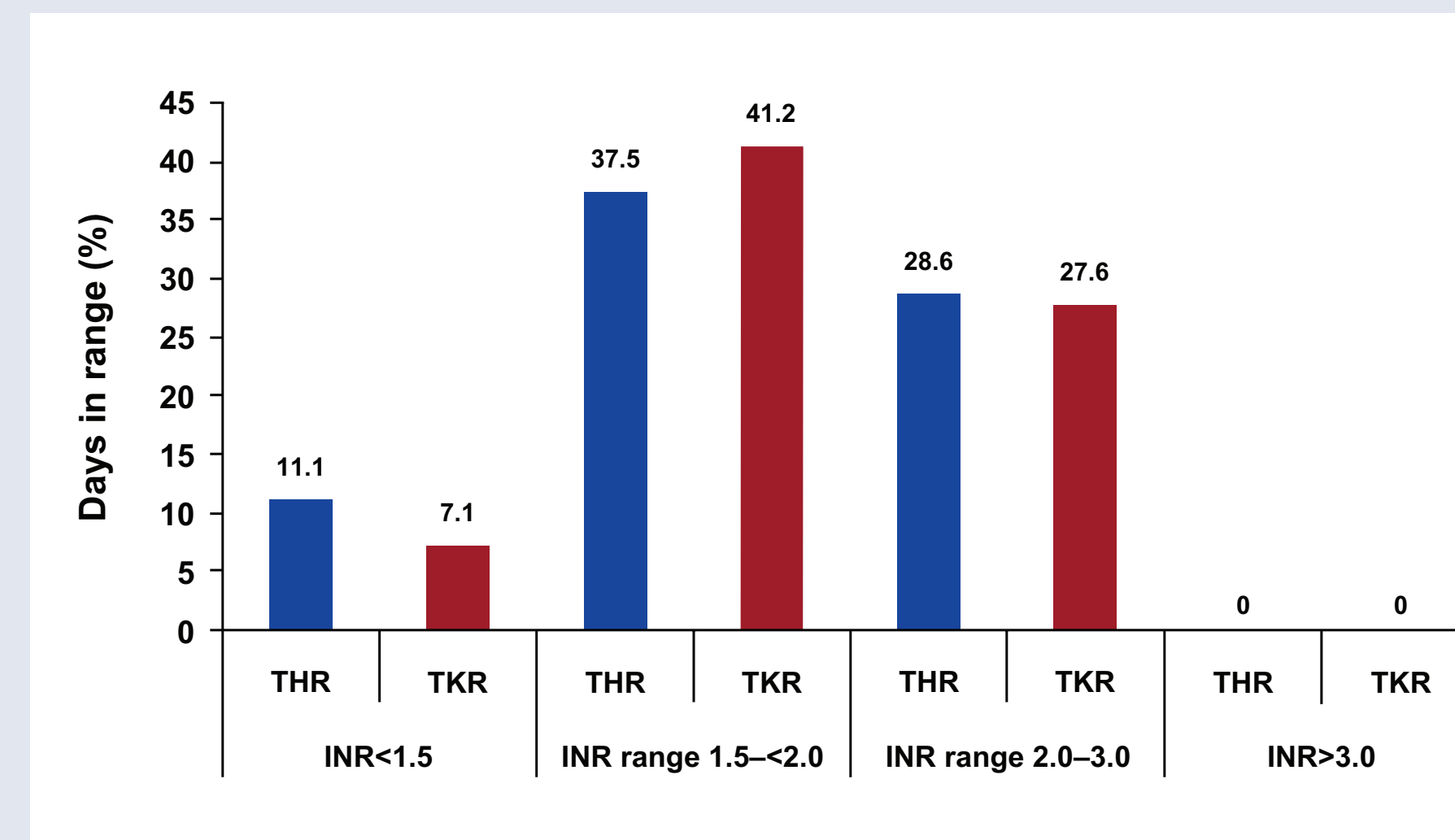
	THR	TKR
Patient characteristic	n=653	n=871
Days from surgery to warfarin start		
0	532 (81.5%)	701 (80.5%)
1	81 (12.4%)	114 (13.1%)
2	31 (4.7%)	43 (4.9%)
3	9 (1.4%)	13 (1.5%)
Duration of hospitalization, days		
Median	4	3
Mean (standard deviation)	4.5 (± 2.9)	3.7 (± 1.7)
Duration of warfarin therapy, days		
Median	69	62
Mean (standard deviation)	58.9 (± 33.3)	57.8 (± 33.7)

Figure 1. Median within-patient percentage of INR levels following total hip replacement and total knee replacement



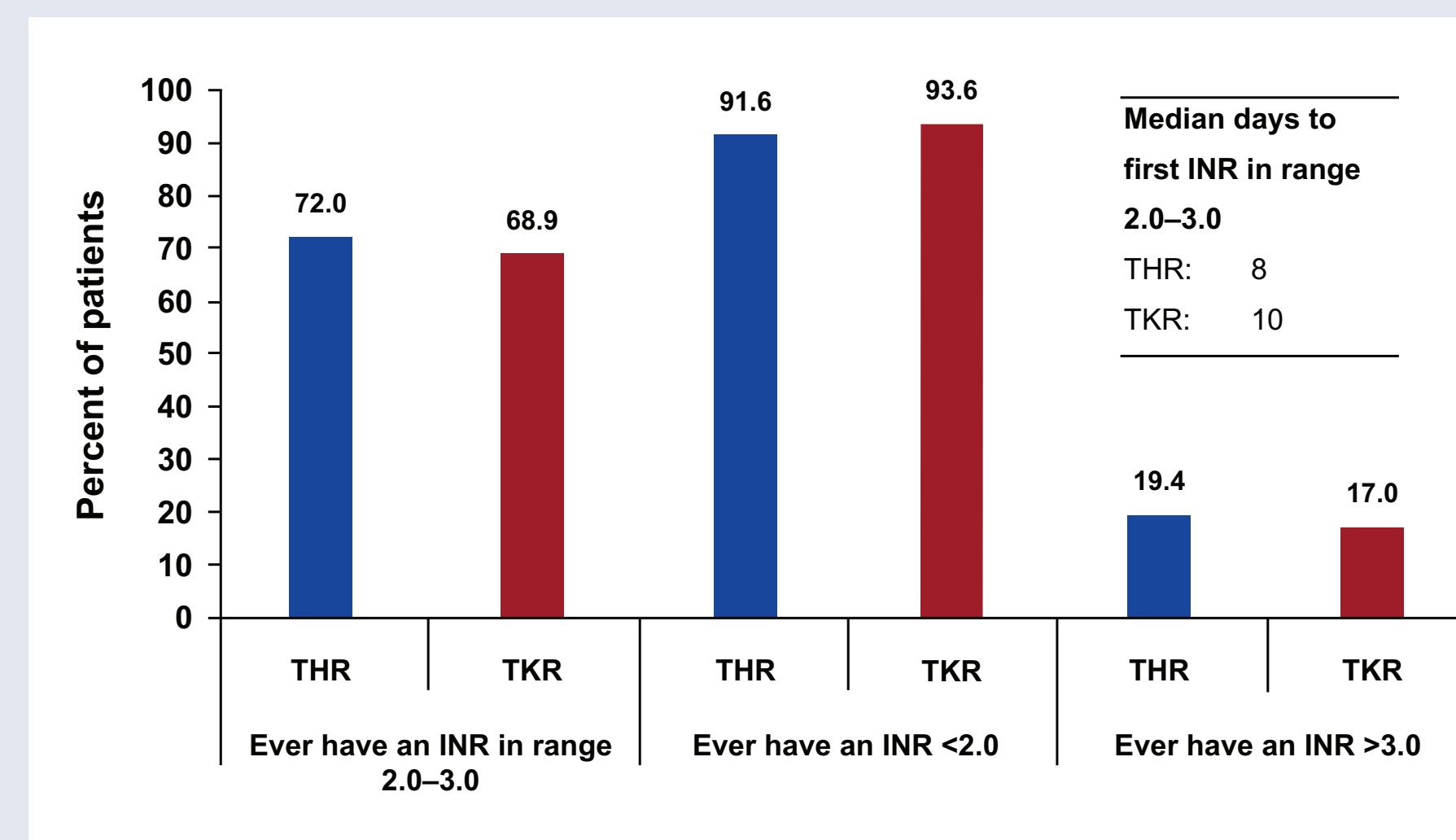
INR, international normalized ratio; THR, total hip replacement; TKR, total knee replacement

Figure 2. Median within-patient percentage of time in each INR category estimated using the Rosendaal method (linear interpolation)



INR, international normalized ratio; THR, total hip replacement; TKR, total knee replacement

Figure 3. INR values during post-surgery warfarin exposure from Day 5 post surgery



INR, international normalized ratio; THR, total hip replacement; TKR, total knee replacement

Study limitations

- INR levels were not measured per protocol, and many values may be unknown/missing
- The assumption in Rosendaal method of linear trend between INR measurements is an estimate
- Only patients who used warfarin were included in this analysis; use of other anticoagulants is unknown
- Level of adherence is unknown (i.e. patients may have been prescribed warfarin without ever taking it, or they may have taken it improperly)
- EMR system includes a relatively small geographic area, and care outside of the EMR health system is not represented

CONCLUSIONS

- Among all patients, a large proportion of INR values were below the ACCP-recommended therapeutic range of 2.0–3.0
 - Only one-third or fewer were within the therapeutic range
- Although the majority of patients had ≥ 1 INR within the 2.0–3.0 range, >90% of patients had ≥ 1 INR below that range
 - INR levels >3.0 were rare
- The risk of VTE is highest during the first 7–10 days post surgery in these types of patient populations⁸
 - Given that the average time to achieve therapeutic INR while administering warfarin is greater than a week for both TKR and THR, it is conceivable that the low INR levels generally attained during this period might represent inadequate thromboprophylaxis
- Targeting an INR lower than 2.0–3.0 to minimize bleeding risk may unnecessarily place patients at even higher risk for VTE

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- Edith Nutescu receives research funding from Ortho-McNeil Janssen Scientific Affairs, LLC
- Jeff Schein, Alan Fisher, and Brahim Bookhart are all employees of Ortho-McNeil Janssen Scientific Affairs, LLC and stockholders of Johnson & Johnson

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